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Mohan M, Carpenter PK, Bennett C

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[Intervention Review]

Donepezil 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]. Acetylcholine is a chemical found in the brain that has an important role in memory, attention, reason and language. Donepezil a reversible inhibitor of acetylcholinesterase, which is thought to maintain levels of acetylcholine, and is reported to have some benefits for people with AD in the general population. 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 This review was superseded by a new review titled *' Pharmacological interventions for cognitive decline in people with Down syndrome'* in the *Cochrane Database of Systematic Reviews*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 donepezil 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 We contacted the manufacturers of donepezil as well as experts in the field, to ask about reports of unpublished or ongoing trials.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 donepezil was administered compared with a placebo group.

Data collection and analysis

Data were extracted from the published reports of the one relevant study identified.

Main results

The one study included in this review is a small (n=30) randomised controlled trial lasting 24 weeks. It was followed-up by an open label study with a crossover design.

No significant differences were found on any four validated outcomes including global functioning and three measures of cognitive abilities and behavioural problems. 6 out of 16 carers (37%) of participants on donepezil and 2 out of 15 (13%) on placebo reported improvement. No data were available for day to day skills, institutionalisation, reduction in carers' stress or economic outcomes. Half the intervention group and 20% of the placebo group reported adverse events; two participants left because of adverse events.

Authors' conclusions

To date there is only one small randomised controlled study on the effect of donepezil. This shows, at best, a modest, non statistically significant trend in favour of people with Down syndrome and Alzheimer's dementia who are able to tolerate donepezil (this drug is currently only dispensed in relatively large doses and is contraindicated for those with cardiac and respiratory problems).This study does not provide good evidence on which to base practice. Findings in an open-label follow up to this study suggest possible benefit in some individuals. Further, larger randomised controlled studies with longer-term follow up are required.

PLAIN LANGUAGE SUMMARY

Donepezil for dementia in people with Down Syndrome

Donepezil is a drug which is thought to discourage the breakdown of acetylcholine, which is a neurotransmitter in the brain that is important to how memory functions. Acetylcholine is lacking in people with Alzheimer's disease (AD). The drug donepezil 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 one randomised controlled trial of donepezil in people with Down syndrome. This shows, at best, a modest, non statistically significant trend in favour of people with Down syndrome and Alzheimer's dementia who are able to tolerate donepezil. The trial was of good quality, but small. It is important to note that people with Down syndrome may often have other conditions which mean that the drug is not suitable for all. Further research is needed.

This review was superseded by a new review titled *'P harmacological 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 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 similarities between DS and AD because of the extra chromosome 21 (Wisniewski 1985; 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 as 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 the 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. One of these drugs is donepezil, a reversible inhibitor of acetylcholinesterase (ACH) and this drug is the subject of this review.

How the intervention might work

Donepezil is thought to work by inhibiting the enzyme acetylcholinesterase from breaking down acetylcholine in the brain. Adverse effects of older ACE inhibitors such as physostigmine and tacrine (including liver damage) led to the development of donepezil. Chemically, donepezil is unrelated to other ACHs inhibitors, and is piperidine-based. It is highly selective for acetylcholinesterase. In long-term clinical trials, according to Shigeta and Homma, donepezil maintains cognitive and global function for 'up to one year prior to the resumption of gradual deterioration' (Shigeta 2001). Donepezil is reported to be generally well tolerated in the general population although it is not clear as to how it affects the learning disabled population; most of the adverse events reported for it have been classified as mild, transient and cholinergic in nature (Cipriani 2003; Kishnani 2001; Kondoh 2005a) although more serious adverse effects have been reported (Hemingway 1999; Prasher 2004a). It is thought that donepezil has the tendency of reducing the heart rate, hence it would be especially important to assess its affects in this population, as people with DS appear to have an increased incidence of cardiovascular disease, including ventro-septal defects and slow heart rates.

One report suggests that the optimum dose in patients with DS may be lower than the recommended regular dose (Kondoh 2005b) for this reason; however, currently the smallest dose available on the market, is 5 mg (tablet form). This is in contrast to other ACE inhibitors which have been provided in liquid and or transdermal patch form, making them easier to use in smaller doses.

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 2004a).

Given that donepezil has the potential to improve symptoms of dementia in individuals with Down syndrome in the general population (Birks 2006), 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: galantamine (Mohan 2009a), a reversible inhibitor of acetylcholinesterase that also has nicotinic receptor agonist properties; rivastigmine (Mohan 2009b), a reversible non-competitive inhibitor of acetylcholinesterases; and memantine, a NMDA-receptor antagonist that affects glutamate transmission, which is licensed for treating moderate to severe Alzheimer's disease (Mohan 2009c). The protocol for this review served as the template for the whole suite of reviews.

OBJECTIVES

To determine the effectiveness and safety of donepezil 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 donepezil was administered for more than a day and compared with a placebo group were included, with the intention that only first-period data would be taken from crossover studies.

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 donepezil 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 acetylcholinesterase inhibitors 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 contacted the manufacturers of donepezil as well as experts in the field, to ask about reports of unpublished or ongoing trials (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. The authors then extracted data from included trials and assessed trial quality independently. There was no disagreement between the authors and therefore no necessity for approaching the editorial base of the Cochrane Developmental, Psychosocial and Learning Problems Group (CDPLPG) for adjudication.

Data extraction and management

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

Study procedures

1. Recruitment

2. Diagnosis

3. Dosage (including issues of titration / escalation)

4. Duration

5. Setting

Study methods

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 was sought for:

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

Data were entered into Review Manager (RevMan 5) by one author (MM) and then checked by the second author (CB).

Assessment of risk of bias in included studies

Review authors independently assessed 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) (Higgins 2008):

Sequence generation

Description: the method used to generate the allocation sequence was assessed to determine if it produced comparable groups.

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

Allocation concealment

Description: Was the method used to conceal allocation sequence described in sufficient detail to assess whether intervention schedules could have been foreseen in advance of, or during, recruitment. In the 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: Were any measures used to blind participants, personnel and outcome assessors described so as to assess knowledge of any group as to which intervention a given participant might have received In the 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:

a) If studies did not report intention-to-treat analyses, we planned to make attempts to obtain missing data by contacting the study authors.

b) In the review authors' judgment: were incomplete data dealt with adequately by the reviewers? (See also 'Dealing with missing data', Appendix 10).

Data on attrition and exclusions reported were extracted (compared with total randomised), and reasons for attrition/ exclusion were obtained from investigators where not reported in publications.

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

Selective outcome reporting

Description: were attempts made to assess the possibility of selective outcome reporting by investigators. In the 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

Was the study apparently free of other problems that could put it at a high risk of bias?

Measures of treatment effect

No meta-analysis was possible as there is only one included trial (Prasher 2002). Due to differences at baseline, investigators adjusted their data and presented change scores. Endpoint data, change scores and investigators' tests for statistical significance (adjusted for differences in baseline between groups in this small study) are reported below. Full data appear in Table 1.

Methods planned in the protocol and archived for future updates in the review can be found in Appendix 10.

RESULTS

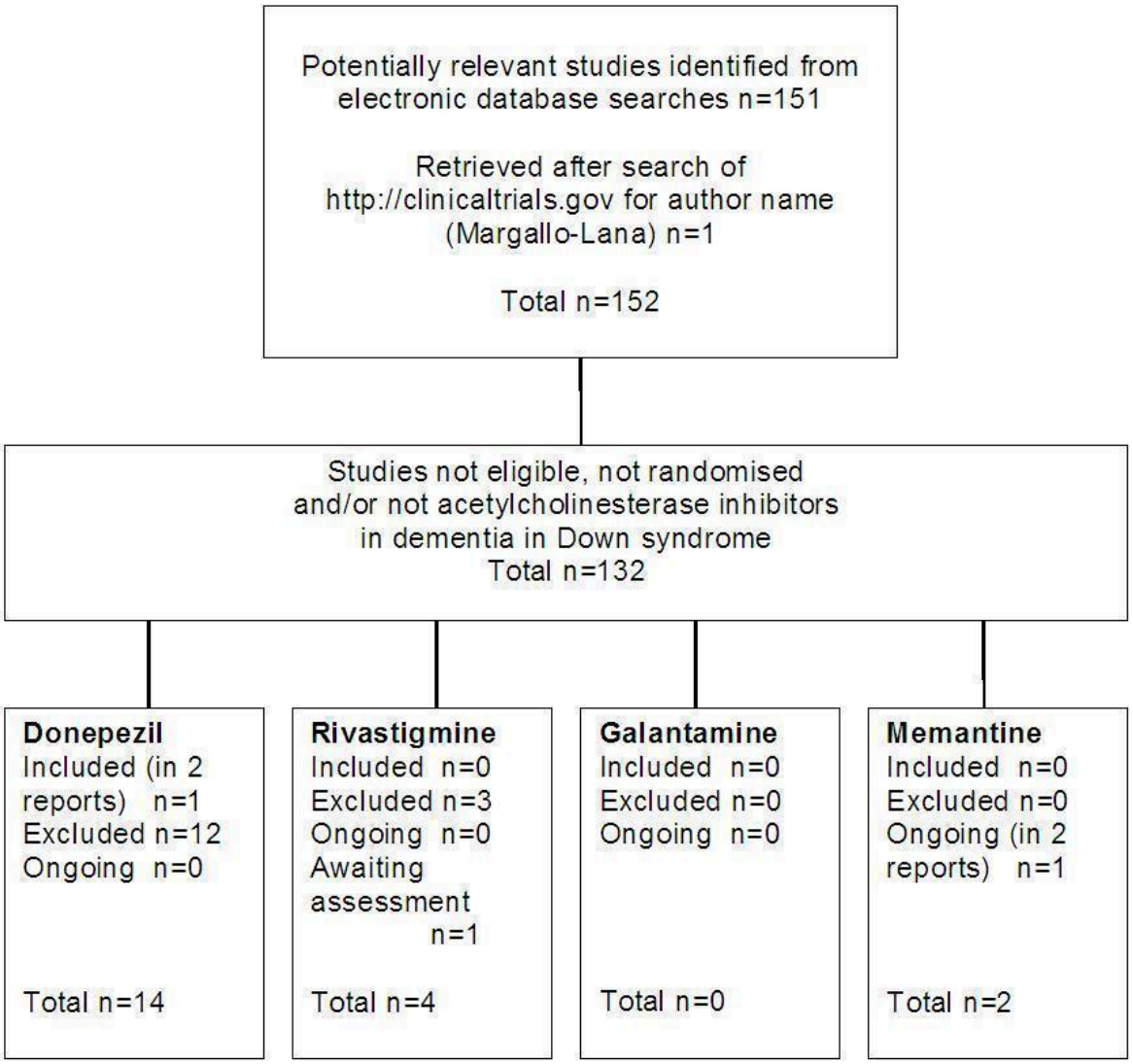
Description of studies

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. From these, one double-blind, placebo randomised controlled trial (full details are given in Figure 1) met our inclusion criteria for studies of donepezil for dementia in Down's syndrome and was included (Prasher 2002).

Figure 1. Quorom flowchart



Included studies

The included study (Prasher 2002) was conducted in the UK. 30 trial participants (adults having Down syndrome and dementia) were recruited from participants known to the learning disability services in the West Midlands, UK. Consultants treating people with Down syndrome were contacted in order to recruit participants (Prasher 2002). Participants had a mean age of 53.6 (SD 4.60) in the donepezil group and 55.7 (SD 8.03) in the placebo group. Inclusion criteria included "genetically karyotyped DS, mild to moderate AD according to Diagnostic Research Criteria (DCR-10 WHO 1993) and living with a carer who could administer and monitor the medication" (page 271, Prasher 2002).The diagnosis of AD was a clinical diagnosis made according to recommended international guidelines (Aylward 1997) using the ICD checklist along with a review of the medical records, a physical examination (including an assessment of hearing and vision), haematological, biochemical, and thyroid status screening, review of medication and a mental state examination for other possible causes of intellectual decline." 'Significant' medical conditions were grounds for exclusion (examples include "insulin diabetes or another untreated endocrine disorder, asthma, obstructive pulmonary disease, significant uncontrolled neurological, gastrointestinal, hepatic, cardiovascular disease, vitamin B 12 or folate deficiency"' page 271, Prasher 2002).

16 participants received donepezil and 14 received placebo. The dosage was 5mg donepezil per day for the first four weeks of the study, then 10mg per day thereafter. The medication and placebo were in tablet form and similar in appearance. The duration of the study was 24 weeks. A follow up open label study to this trial was conducted using a cross over design, from which data are available for six participants who received donepezil in the randomised study and the first phase of the follow up study and for seven participants

who received placebo only in the randomised trials and the first phase of the open label follow up (Prasher 2002). We have not analysed data for the follow up period because this study was carried out on an open label basis. Please see 'Characteristics of included studies'.

Excluded studies

12 studies which appeared potentially relevant by title and abstract were excluded from this review following closer inspection.

One was an RCT (Johnson 2003) which was excluded because adult DS participants did not have a diagnosis of dementia (this study, like others of younger people with DS, considered general language and cognition outcomes).

Three studies (Boada-Rovira 2005; Kondoh 2005b and Lott 2002) were excluded because they were not randomised and they did not have a placebo control group.

The eight remaining studies did not have control groups at all (Castane 2004; Cipriani 2003; Heller 2003; Heller 2004; Hemingway-Eltomy 1999; Kishnani 1999; Kishnani 2001; Kondoh 2005a).

Please see 'Characteristics of excluded studies'.

Risk of bias in included studies

Only one study met the inclusion criteria (Prasher 2002). We contacted the principal investigator of this trial for clarification about allocation concealment and number of participants (Prasher April - May 2008), and as a result we have assessed the risk of bias overall for this study to be low. The details of our assessment and the results are given below .

Allocation

In terms of sequence generation, we assessed this study as being at low risk of bias as the randomisation process was adequate. The principal investigator (VP) confirmed that clarified the method used to generate allocation sequence as names in sealed envelopes shuffled (Prasher April - May 2008)

The principal trial investigator also clarified that the pharmacist concealed medication type from participants and clinicians. Initial allocation was independent of the authors. We therefore assessed this trial as having complete allocation concealment and low risk of bias (Prasher 2002).

Blinding

We assessed blinding as adequate. Participants, carers and the researchers undertaking the data collection were blind to treatment status throughout the study period. After the first few weeks it became apparent carer concerns about some participants' experiencing side effects could only be appropriately responded to by the code being broken by the principal researcher (VP). This was felt not to significantly affect the study result, as VP was not involved either in patient assessments or in data analysis. The other researchers, patients, carers and data analysts remained 'blind' until the study was completed. We assessed this trial as having adequate blinding and low risk of bias.

Incomplete outcome data

The trial investigator confirmed that of 55 people who were, or appeared eligible, 24 were excluded for reasons including: lack of consent by carers; participants having very late stage AD or not fulfilling DCR-10 criteria in the first place; having co-morbid physical illness (see list above); living alone; marked brachycardia on ECG or no compliance with ECG/blood tests; and in one case, death prior to allocation. At time of randomisation, there were 31 participants (personal communication; Prasher April - May 2008). At the point of randomisation, one participant was hospitalised and then excluded, so the total number of participants at the beginning of the intervention period was 30. All participants were accounted for at post-treatment and we thus assessed this element of the trial design as having a low risk of bias.

Selective reporting

According to the paper and discussion with the primary investigator of the one included study (personal communication; Prasher April - May 2008) all outcomes measured were reported, and therefore there is low risk of bias for this criterion.

Other potential sources of bias

As noted above, in order to address carer concerns, the code was broken by the principal researcher (VP) but because this researcher was not was not involved in patient assessment or data analysis, we consider the risk of bias to be low.

Effects of interventions

As only one study met the inclusion criteria, we could not perform a meta-analysis. All outcome data below are reported are continuous.

Results were presented by the primary investigator in the form of endpoint data and change scores. Investigators presented p values for change scores, but not endpoint data. Investigators adjusted data to account for (sometimes large) differences at baseline in this small sample. Full baseline, endpoint data and change score data are presented in Table 1. We have also calculated p values for those endpoint data which are not skewed, and report them below.

Primary outcomes

1. Global functioning

Dementia Questionnaire for Persons with Mental Retardation [DMR]

Global functioning was measured by Prasher 2002 using DMR (Evenhuis 1996) (an increase in score equates to a deterioration in dementia). Investigators considered this the "primary efficacy parameter" for this study.

Mean post-treatment DMR scores were 55.1 (SD=17.9) for the 14 intervention group participants and 64.4 (SD=14.2) for the 13 placebo participants (t=1.49, df 25, p=0.15, not significant). Investigators reported a 0.8 (1.5%) mean deterioration in score as compared to a 6.2 point (10.7%) mean deterioration in the placebo group; however, investigators reported that this difference was not statistically significant ($F_{1,78}$=1.5, p=0.22).

The study investigators also commented that the "number of patients in each group with poorer performance on the DMR at the end point relative to baseline were placebo 9 of 13 (69%), and

donepezil 7 of 14 (50%). This suggests that at least 50% of patients treated with donepezil did not experience deterioration associated with AD as compared to 31% of placebo patients over the 24 week treatment period. As no decline in clinical psychopathology is considered to be a clinical benefit in a progressive condition such as AD donepezil does have some limited benefit." They also expressed the view that "an improvement of 5% or more in the total DMR score at endpoint as compared to baseline was seen in 21% (n= 3) of patients treated with donepezil as compared to 0% of patients given placebo" (Prasher 2002). However, the validity of this 5% threshold is not discussed further in the study report.

Cognitive abilities and behavioural problems

Cognitive abilities and behavioural problems were all considered "secondary efficacy parameters" by the investigators (Prasher 2002). They were measured by validated scales including the Adaptive Behavior Scale [ABS] (Nihira 1974) (where a reduction in score indicates deterioration), the Neuropsychiatric Inventory [NPI] (where an increase in scores indicates deterioration) (Cummings 1994), and the Severe Impairment Battery [SIB] (where reduction in score indicates deterioration) (Saxton 1993).

Adaptive Behavior Scale [ABS]

There was a large difference at baseline between groups for the ABS in favour of the donepezil group (baseline for intervention group was 121.4 (SD=36.9) compared to 93.0 (SD=19.2) for the control group). Endpoint data alone therefore appear to favour the treatment group dramatically (120.5 (SD=44.1); 84.5 (SD=22.4)) (t=2.64, df 25, p=0.014, significant). The trial investigators adjusted for the baseline differences and report a change of 0.7% in the treated group and 9.1% in the control. Although this difference is still generally favourable to the donepezil group, it is not statistically significant and the investigators report this as follows: "For the placebo group there was a a gradual decline (deterioration of dementia) in the mean total ABS scores over the study period. For the donepezil group the mean total ABS scores remained generally at baseline level during the 24 weeks. However the difference in decline for the two groups was not statistically significant ($F_{1,77}$=0.45, p=0.51)" (Prasher 2002).

Neuropsychiatric Inventory [NPI]

For the NPI score, endpoint data indicate that the treatment group (whose mean score was 5.7 (SD=7.6)) appeared to have improved less than the placebo group (whose mean score was 3.6 (SD=5.0)) (skewed data). These data represent improvements for both groups over the period of the study; however, in the first six weeks of the study, the intervention group actually deteriorated before recovering to a level just over baseline at the end of the study period. Overall, the placebo group reported significantly greater improvement (55%) than did the intervention group (27.8%). The investigators conclude: "difference in change in total NPI scores over the 24 week period were statistically significant for the two groups (analysis of variance $F_{1,78}$=5.1, p=0.03)" (Prasher 2002).

Severe Impairment Battery [SIB]

Investigators report that both groups performed poorly on the SIB at baseline and that groups differed significantly (donepezil group = mean 36.8 (SD=21.9); placebo mean 27.2 (SD=13.6). Deterioration in the mean total SIB score was seen for both the donepezil (31.6 (SD=28.2)) and placebo groups (11.2 (SD=8.7)) (skewed data), with a greater decline being observed in the placebo group. Confidence intervals were very wide and the investigators report this difference as not being quite statistically significant at the 5% level ($F_{1,77}$=3.6, p=0.06).

Carer report

Data for the carer assessment of improvement in the participant (delay of deterioration of AD or improvement) were reported. 6 out of 16 (37%) participants on donepezil were thought to have improved and 2 out of 15 (13%) on placebo were also thought to have improved; it is unclear from the paper whether this assessment was made before or after dropouts.

No data were available for the remaining primary outcomes of day to day skills (as measured by carer report)

Adverse events

Data on adverse effects of the medications and drop outs were collected (Table 2). Two participants in the donepezil group were withdrawn from the study due to severe diarrhoea; acute cholecystitis (possibly unrelated to the medication) and were excluded from data analysis. Fifty percent of participants in the donepezil group, and 20% in the placebo group experienced a serious adverse event. Adverse events which occurred more often in the donepezil group were diarrhoea, insomnia, nausea, and fatigue.

Institutionalisation and Death

No data were available on institutionalisation during the study period. There were no participant deaths during the treatment phase of the study in either the donepezil or the placebo group.

Secondary outcomes

No data were available on the secondary outcomes of reduction in carers' stress or economic outcomes.

DISCUSSION

Summary of main results

After an extensive search only one study was identified that was eligible for inclusion. This study (Prasher 2002) was conducted in the UK for 24 weeks, and employed strict inclusion and exclusion criteria, and used validated scales for measuring change.

No results were statistically significant for any outcomes (DMR, ABS, SIB or NPI). Trends favoured the intervention group overall, but results for the NPI actually favoured the control group. However as mentioned in 'Results', above, investigators argued that for the study's primary outcome (mean DMR score) results in percentages showing "improvement" (p. 270, Abstract, Prasher 2002) or simply "no decline" (p. 273, Prasher 2002) at least suggest some "limited benefit" of the intervention.

As Alzheimer's disease generally progresses slowly, with a mean of 5 to 10 years survival period, the duration of treatment in a 24 week RCT cannot provide evidence for the effects in long term use (Prasher 2002). Prasher and colleagues conducted a two year, open-label extension of their original RCT in which 27 of the participants who completed the randomised phase were eligible for entry to the open-label phase, of whom 25 entered the second phase.

In the open-label study, six participants from the original study remained on donepezil; eight previously on donepezil crossed over to placebo; four on placebo crossed over to donepezil and seven previously on placebo discontinued all intervention. Although data from this phase of the study could not be used for analysis due to the risk of bias of the open label design, it is interesting to note that at two years, participants who continued on donepezil demonstrated significantly less deterioration in Global Functioning and Adaptive Behaviour than those not receiving the drug. This suggests the possible benefit of longer-term use.

Donepezil was generally well tolerated in this study but did cause some adverse events with a higher incidence of fatigue, diarrhoea, insomnia, nausea, vomiting, muscle cramps, seizures, dizziness, agitation, low mood and acute abdominal discomfort (significant risk associated with treatment) reported in the donepezil group compared with placebo. Two participants were excluded from analysis due to side effects. The side effect profile is comparable to that in the general population (Birks 2006); the advisability of adjusting dosage downwards (if treatment is given) is discussed below.

Overall completeness and applicability of evidence

A comprehensive search for randomised controlled trials for pharmacological therapies for people with DS who have AD, our searches revealed one, small UK based study of relatively high quality (Prasher 2002) which met inclusion criteria. This one study examined the use of a specific anticholinesterase inhibitor in people with AD who had learning disabilities due to a specific syndrome that predisposes to AD. A further 12 studies (Hemingway-Eltomy 1999; Kishnani 1999; Kishnani 2001; Lott 2002; Johnson 2003; Cipriani 2003;Castane 2004; Heller 2003; Heller 2004;Boada-Rovira 2005; Kondoh 2005a; Kondoh 2005b;) were excluded, largely for reasons of weak design.

The included trial studied people who had Down syndrome proven by karyotyping, and it was reported that 'ICD-10 criteria' were used for diagnosis. It is possible therefore that though the study group accurately reflects the group who clinicians in daily practice diagnose as having AD, a significant number of study participants may have had other forms of dementia. In addition the study included only patients referred by local clinicians as being medically suitable for the trial, so it is unclear how many patients with DS and clinical dementia were felt to be medically unsuitable for the trial by their clinicians.

As people with DS appear to have an increased incidence of cardiovascular disease, including ventro-septal defects and also slow heart rates (Greenwood 1976; Carpenter 1995), it is unclear from the study what proportion of people with DS and AD would be suitable for a trial of donepezil. Donepezil is known to cause adverse effects including gastrointestinal disturbance (Cipriani 2003), urinary incontinence and muscle weakness (Kondoh 2005a; Kondoh 2005b) in people who had DS and arrhythmias, syncope, and bradycardia have been documented in people who are treated with ACE inhibitors for Alzheimer's disease (Anon 2004) as well as in patients with asthma and obstructive pulmonary disorders.

In addition, in this review we only included data on people with DS and mild or moderate AD. There is therefore no evidence for the effectiveness of donepezil in people with DS and severe AD.

Some have recommended that the optimum dose in patients with DS may be lower than the dose regularly recommended for those without DS (Kondoh 2005b) given the pharmodynamic and pharmakinetic presentation of this population. This is consistent with suggestions from clinical practice that lower dosage of other pharmaceutical preparations is required for most disorders in people with learning disabilities (Stanton 2004; Kondoh 2005a).

Quality of the evidence

The one included study by Prasher 2002 is of relatively high quality, considering the problems of research in this area, and is the first of its kind.

However, the unclear cohort population size, low sample size (and associated differences at baseline on key variables) as well as relatively short duration and small sample size mean it is difficult to interpret its conclusions. Current best practice also advises use of tools like the DC-LD for people with learning disabilities rather than ICD-10 as used by investigators, to whom it was not available at the time (DC-LD 2001).

The investigators themselves discuss the fact that given recruitment/power, statistical significance was never likely. However, as investigators say, "anything that has the potential to improve quality of life for people with DS and their carers should be investigated" (page 278, Prasher 2002). Further research is clearly needed.

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 (Margallo-Lana 2003), and hardships regarding recruitment of both participants and their families, remain problematic.

Potential biases in the review process

Whilst every attempt was made to identify studies which met inclusion criteria for this review, only one was identified.

Agreements and disagreements with other studies or reviews

No systematic review of this topic has been identified.

Studies excluded from this review because of concerns about methodological rigour tend to provide more encouraging results than Prasher 2002. We will report their details here briefly, to set context.

One small study (case control) conducted by Boada-Rovira et al reported that donepezil appears to be effective in the treatment of cognitive and behavioural disturbances associated with the progressive dementia syndrome in DS (Boada-Rovira 2005). Another small study by Kishnani et al was an open trial of donepezil on four adults with Down syndrome treated with up to 10mg donepezil and used the Vineland Adaptive Behavioural Scales. This study suggested improvement in communication,

language, attention and mood stability without significant side-effects (Kishnani 1999).

Heller et al conducted a 24 week open trial, which reported the effect of donepezil in the treatment of language and other cognitive domains in people with DS but without AD (Heller 2003); one other report from this investigator studied donepezil effects of language in children with DS (Heller 2004), also without AD. Hemingway-Eltomy et al described three patients with DS and AD on donepezil. Two developed urinary incontinence and all three developed aggression and agitation which reduced on stopping donepezil. Similar side effects have been described in the general adult population taking donepezil (Hemingway-Eltomy 1999). Cipriani also discontinued treatment for three patients (Cipriani 2003). Kondoh et al with his case summaries suggested donepezil may benefit patients with DS and AD although investigators also reported that such patients may experience adverse effects more frequently (Kondoh 2005a; Kondoh 2005b). Lott et al reported the use of donepezil in a small open label non-randomised pilot trial and found a lower score on the DSDS which suggested an significant improvement (Lott 2002). A 12-week double blind placebo controlled study of the effects of donepezil on cognitive functioning in Down syndrome in the absence of dementia (Johnson 2003) found some improvement on language scores for participants, but no benefit was found for cognition, behaviour, or caregiver ratings. Results from studies above must be treated with caution for methodological weaknesses stated.

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; Yoo 2007). 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

Limited data on the impact of donepezil for people with DS who develop mild, moderate or severe dementia were available from only one study that met the methodological standards for this review. This one small study highlights the need to weigh even the few potentially encouraging trends (e.g. in the DMR scores) in the balance against potential side effects. This is an insufficient basis to conclude that donepezil can slow the progression of dementia, and it must be noted that it cannot alter the course of the disorder.

Current use of donepezil 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 any conclusions can be drawn about the effectiveness of donepezil in treating people with Down syndrome and AD. Collaborative work between patients, carers and clinicians/researchers in order to produce large studies providing 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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CHARACTERISTICS OF STUDIES

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

Prasher 2002

Study characteristics	
Methods	Double blinded, placebo-controlled trial
Participants	31 randomised, but 1 did not progress to follow up in placebo group, and text states that only n = 30 participated of which16 in donepezil group, 14 in placebo group
Interventions	5mg per day during the fist 4 weeks and then 10mg per day thereafter. After an initial four week period drug treatment was increased for the remainder of the study to 10 mg/d donepezil and the equivalent placebo increase for the two groups.
Outcomes	**Primary outcomes** Improvement of: * global functioning (DMR recorded) see Table 1. * behavioural problems (SIB, ABA, NPI all recorded.) see Table 1. Day to day skills (as measured by carers report): A semi-structured questionnaire used while the main carers were still blind to which intervention was given, as a qualitative measure of carers perception. Adverse events: These were reported see Table 2. Institutionalisation: not reported. Death: (none died during the treatment phase of the study). **Secondary outcomes** Reduction in carer stress: not reported Economic outcomes: Discussed briefly, “Whether benefits seen in this study in DS patients treated with donepezil leads to significant improvement in a 'quality of life' and delays admission to nursing home type placements and reduces financial costs still requires further investigation (Melzer, 1998; Max, 1999; Neumann *et al.,* 1999).” (page 277 Prasher 2002)
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**

Prasher 2002 *(Continued)*

Random sequence generation (selection bias)	Low risk	VP clarified the method used to generate allocation sequence as names in sealed envelopes shuffled and drawn at randomisation into a bag alternatively to treatment and placebo group which produced comparable groups.
Allocation concealment (selection bias)	Low risk	VP clarified that the pharmacist concealed medication type from participants and clinicians. Initially allocation was independent of the authors. However, after the first few weeks it became apparent that with subjects experiencing side-effects, carer concerns could only be appropriately responded to by the code being broken by the principal researcher (VP). This was felt not to significantly affect the study result, as VP was not involved either in patient assessments or in data analysis. The other researchers, patients, carers and data analysts remained blind until the study was completed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Patients, carers and the researchers undertaking the data collection were blind throughout the study period, except for VP. Completeness of blinding was not assessed in any way.
Incomplete outcome data (attrition bias) All outcomes	Low risk	VP clarified 55 people were eligible of which 24 were excluded, making 31 who were randomised. At the point of randomisation one participant went into hospital so that participant was excluded so 30 ended up in groups. All the participants were accounted for.
Selective reporting (reporting bias)	Low risk	According to the paper and discussion with author there is no apparent selective reporting.
Other bias	Low risk	To address carer concerns, the code was broken by the principal researcher (VP). VP was not involved in patient assessment or data analysis.

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

Study	Reason for exclusion
Boada-Rovira 2005	Not randomised, no placebo group. Case control pilot experimental study using donepezil.
Castane 2004	No control group. Study of 12 of a group of 49 people older than 40 with Down syndrome, 12 of whom had diagnosed dementia and who were given donepezil. Experimental cohort study.
Cipriani 2003	No control group. Correspondence article refers to Lott 2002, not a report of a randomised controlled trial, reports 3 cases of donepezil use in dementia in Down syndrome.
Heller 2003	No control group. Open label study of donepezil for the treatment of language deficits, in adults with Down syndrome, no dementia.
Heller 2004	No control group, open label pilot study of donepezil effects on language in children with Down syndrome.
Hemingway-Eltomy 1999	No control group, case report of 3 cases of Down syndrome patients with dementia, treated with donepezil, report of adverse effects requiring discontinuation of therapy.
Johnson 2003	RCT. 12-week double blind, placebo controlled study of effects of donepezil on cognitive functioning in Down syndrome but no dementia.
Kishnani 1999	No control group, case report studying donepezil in 4 patients with Down syndrome, 2 having dementia.

Study	Reason for exclusion
Kishnani 2001	No control group, expands on results of case report published previously (Kishnani 1999) and comments on (Hemingway-Eltomy 1999).
Kondoh 2005a	No control group, case report of 2 cases with Down syndrome treated with donepezil, only one case had dementia.
Kondoh 2005b	Not randomised, no placebo group. Two groups (one with Down syndrome, one comprised of healthy volunteers, none with dementia) received donepezil. Experimental study (pharmacokinetics of donepezil).
Lott 2002	Not randomised, no placebo group. Donepezil was tested versus no treatment in people with Down syndrome who had dementia in a pilot study format.

ADDITIONAL TABLES

Table 1. Prasher 2002 data: baseline, endpoint, change scores, percentages

Prasher 2002 **data**	**Baseline**			
Donepezil (n= 14) vs placebo (n=13)	**Donepezil (Mean)**	**(SD)**	**Placebo**	**(SD)**
Global functioning - DMR	54.3	16.1	58.2	16.9
Behavioural scores - ABS	121.4	36.9	93	19.2
Behavioural scores - NPI	7.9	5.8	8	7.6
Behavioural outcomes - SIB	36.8	21.9	27.2	13.6

Donepezil (n= 14) vs placebo (n=13)	**Post-treatment**			
	Donepezil (Mean)	**(SD)**	**Placebo**	**(SD)**
Global functioning - DMR	55.1	17.9	64.4	14.2
Behavioural scores - ABS	120.5	44.1	84.5	22.4
Behavioural scores - NPI	5.7	7.6	3.6	5
Behavioural outcomes - SIB	31.6	28.2	11.2	8.7

Donepezil (n= 14) vs placebo (n=13)	**Change scores**		**Percentage**	
	Donepezil	**Placebo**	**Donepezil**	**Placebo**
Global functioning - DMR	0.8	6.2	1.5	10.7
Behavioural changes - ABS	-0.9	-8.5	0.7	9.1

Table 1. Prasher 2002 data: baseline, endpoint, change scores, percentages *(Continued)*

Behavioural changes - NPI	-2.2	-4.4	27.8	55
Behavioural outcomes - SIB	-5.2	-16	14.1	58.8

Table 2. Adverse events

Adverse event	Intervention group, n=16	Placebo group, n=14
Fatigue	7(44%)	2 (14%)
Diarrhoea	6 (38%)	3 (21%)
Insomnia	4 (25%)	2 (14%)
Nausea	4 (25%)	1 (7%)
Vomiting	2 (13%)	1 (7%)
Muscle cramps	2 (13%)	2 (14%)
Seizures	1 (6%)	4 (29%)
Dizziness	2 (13%)	2 (14%)
Anorexia	3 (19%)	0
Agitation	3 (19%)	0
Low mood	1 (6%)	0
Acute abdominal discomfort	1 (6%)	0

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 searched 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 October 2008

#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

8 Priory Road, Bristol, BS8 1TZ
T: +44 (0) 117 954 6755
F: +44 (0) 117 954 6756
W: http://www.bristol.ac.uk/Depts/SPS
J.Dennis@bristol.ac.uk
Medical Information
Pfizer Ltd
Walton Oaks, IPC 5F,
Dorking Road, Tadworth
Surrey KT20 7NS
April 22, 2008
Dear Sir or Madam
I am writing on behalf of a group of Cochrane systematic review authors (Dr Cathy Bennett, Dr Monica Mohan and Dr Peter Carpenter), all based in the UK, who are conducting a suite of systematic reviews researching the effectiveness of drug therapies for dementia in people with Down's syndrome. The therapies that will be reviewed subsequently in a series of linked reviews will include: donepezil, galantamine, rivastigmine and memantine. A copy of the protocol for donepezil, published electronically in The Cochrane Library, is enclosed.
To date, despite extensive electronic searches, we have only identified a few studies that potentially are randomised controlled trials and may meet our criteria for inclusion in the reviews. These are as follows:
1. Margallo-Lana, Dr Maria Luisa, lana@onetel.com (Northgate and Prudhoe NHS Trust and King's College London, Northgate Hospital, Morpeth, Northumberland, NE61 3BP, United Kingdom). 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 OLDER PEOPLE WITH DOWN'S SYNDROME, WITH AND WITHOUT DEMENTIA. Wolverhampton City Primary Care Trust. 2005 Jan 7; 1/7/2006 Comparing Memantine to placebo:):Complete; ISSN: N0281175554.
1a. Study ID Numbers: KCL/DS/MEM/1, EUDRACT-2005 000381 39, ISRCTN47562898
Study Design: Treatment, Randomized, Double-Blind, Placebo Control, Parallel Assignment, Safety/Efficacy Study
Official Title: 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

ClinicalTrials.gov Identifier: NCT00240760, Health Authority: United Kingdom: Medicines and Healthcare Products Regulatory Agency, Contact: Maria Luisa Margallo-Lana, PhD lana@onetel.com, contact: Verinder Prasher, PhD vprasher@compuserve.com
2. Prasher, Dr Vee (Department of Psychiatry, Queen Elizabeth Psychiatric Hospital, Mindelsohn Way, Off Vincent Drive, Edgbaston, Birmingham, B15 2QZ, England). Research study investigating the use of Aricept in the treatment of dementia in adults with Down's Syndrome. Birmingham and Solihull Mental Health NHS Trust. 1998 Jan 6; 2/7/2001(DMR, clinical change):Complete; ISSN: N0222095161.
3. Prasher, Dr Verinder, vprasher(a)compuserve.com (Birmingham Specialist Community Health NHS Trust, PO BOX 7041, Birmingham, B30 3QQ, England). Double blind placebo controlled trial of Donepezil (Aricept) in-patients with Down's Syndrome and Alzheimer's disease. R&D for Birmingham and Solihull Consortium. 1999 Jan 1; 1/1/2002 (Priority outcome will be change in neuropsychological and adaptive behaviour scores.):Complete; ISSN: N0233101497.
4. Prasher, V. P; Adams, C; Holder, R, and The-Down-Syndrome-Research-Group. Long term safety and efficacy of donepezil in the treatment of dementia in Alzheimer's disease in adults with Down syndrome: Open label study. International-Journal-of-Geriatric-Psychiatry. 2003; Vol 18(6):549-551.
5. Prasher, V. P; Fung, N, and Adams, C. Rivastigmine in the treatment of dementia in Alzheimer's disease in adults with Down syndrome. International-Journal-of-Geriatric-Psychiatry. 2005; Vol 20(5):496-497.
6. Prasher, V. P.; Huxley, A.; Haque, M. S., and Down syndrome Ageing Study Group (Monyhull Hospital, Monyhull Hall Road, Kings Norton, Birmingham, B30 3QB, UK. vprasher@compuserve.com). A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Down syndrome and Alzheimer's disease--pilot study. International Journal of Geriatric Psychiatry. 2002 Mar; 17(3):270-8.
I am writing to you in case you are willing to share information about, or even data from, any relevant unpublished or ongoing studies on donepezil. We would be most grateful to hear of any studies even if incomplete at present, in order to give readers the most complete picture possible of the current state of research in this important area. Please respond by email or post to me at the address above.
For information, all review authors are part of the Cochrane Developmental, Psychosocial and Learning Problems Group (CDPLPG). The CDPLPG, based in Bristol, England is just one of 50 Cochrane review groups worldwide which belong to the Cochrane Collaboration. The mission statement of the Collaboration is to "prepare, maintain and disseminate systematic reviews of the results of healthcare interventions."
More information about the Cochrane Collaboration is available at www.cochrane.org
We look forward to any assistance you can give us.
Yours faithfully,
Jane Dennis
Review Group Co-ordinator, Cochrane Developmental, Psychosocial and Learning Problems Group

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

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 analysed 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 may be conducted to assess the risk of bias.

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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 '*Pharmacological interventions for cognitive decline in people with Down syndrome*', in the *CDSR* in 2015, see www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD011546.pub2/full. See also 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 *Cochrane Database of Systematic Reviews* (*CDSR*) in 2015.

HISTORY

Protocol first published: Issue 2, 2008
Review first published: Issue 1, 2009

Date	Event	Description
25 April 2008	Amended	Converted to new review format.
20 December 2007	New citation required and major changes	Substantive amendment

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, entered the data, drafted some of the text (Methods and Results), and corrected and edited the text.

MM wrote the text of the background, carried out the eligibility assessments, double-entered the data into RevMan and contributed to writing up 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.

Following helpful comments by peer reviewer, issues of escalation and titration were added to data extraction.

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]; Cholinesterase Inhibitors [*therapeutic use]; Donepezil; Down Syndrome [*complications]; Indans [*therapeutic use]; Piperidines [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans