Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease (Review)

Rolinski M, Fox C, Maidment I, McShane R

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[Intervention Review]

Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease

Michal Rolinski[1], Chris Fox[2], Ian Maidment[3], Rupert McShane[4]

[1]Oxford University Hospitals NHS Trust, Oxford, UK. [2]Norwich Medical School, Norwich, UK. [3]Pharmacy Department, Kent and Medway NHS and Social Care Partnership Trust, Canterbury, UK. [4]Nuffield Department of Medicine, University of Oxford, Oxford, UK

Contact address: Michal Rolinski, Oxford University Hospitals NHS Trust, John Radcliffe Hospital, Headington, Oxford, OX3 9DU, UK. michal.rolinski@doctors.org.uk.

Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: New, published in Issue 3, 2012.
Review content assessed as up-to-date: 30 August 2011.

Citation: Rolinski M, Fox C, Maidment I, McShane R. Cholinesterase inhibitors for dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease. *Cochrane Database of Systematic Reviews* 2012, Issue 3. Art. No.: CD006504. DOI: 10.1002/14651858.CD006504.pub2.

ABSTRACT

Background

Previous Cochrane reviews have considered the use of cholinesterase inhibitors in both Parkinson's disease with dementia (PDD) and dementia with Lewy bodies (DLB). The clinical features of DLB and PDD have much in common and are distinguished primarily on the basis of whether or not parkinsonism precedes dementia by more than a year. Patients with both conditions have particularly severe deficits in cortical levels of the neurotransmitter acetylcholine. Therefore, blocking its breakdown using cholinesterase inhibitors may lead to clinical improvement.

Objectives

To assess the efficacy, safety and tolerability of cholinesterase inhibitors in dementia with Lewy bodies (DLB), Parkinson's disease with dementia (PDD), and cognitive impairment in Parkinson's disease falling short of dementia (CIND-PD) (considered as separate phenomena and also grouped together as Lewy body disease).

Search methods

The trials were identified from a search of ALOIS, the Specialised Register of the Cochrane Dementia and Cognitive Improvement Group (on 30 August 2011) using the search terms Lewy, Parkinson, PDD, DLB, LBD. This register consists of records from major healthcare databases (MEDLINE, EMBASE, PsycINFO, CINAHL) and many ongoing trial databases and is updated regularly.

Reference lists of relevant studies were searched for additional trials.

Selection criteria

Randomised, double-blind, placebo-controlled trials assessing the efficacy of treatment with cholinesterase inhibitors in DLB, PDD and cognitive impairment in Parkinson's disease (CIND-PD).

Data collection and analysis

Data were extracted from published reports by one review author (MR). The data for each 'condition' (that is DLB, PDD or CIND-PD) were considered separately and, where possible, also pooled together. Statistical analysis was conducted using Review Manager version 5.0.

Main results

Six trials met the inclusion criteria for this review, in which a total of 1236 participants were randomised. Four of the trials were of a parallel group design and two cross-over trials were included. Four of the trials included participants with a diagnosis of Parkinson's disease with dementia (Aarsland 2002a; Dubois 2007; Emre 2004; Ravina 2005), of which Dubois 2007 remains unpublished. Leroi 2004 included patients with cognitive impairment and Parkinson's disease (both with and without dementia). Patients with dementia with Lewy bodies (DLB) were included in only one of the trials (McKeith 2000).

For global assessment, three trials comparing cholinesterase inhibitor treatment to placebo in PDD (Aarsland 2002a; Emre 2004; Ravina 2005) reported a difference in the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change (ADCS-CGIC) score of -0.38, favouring the cholinesterase inhibitors (95% CI -0.56 to -0.24, P < 0.0001).

For cognitive function, a pooled estimate of the effect of cholinesterase inhibitors on cognitive function measures was consistent with the presence of a therapeutic benefit (standardised mean difference (SMD) -0.34, 95% CI -0.46 to -0.23, P < 0.00001). There was evidence of a positive effect of cholinesterase inhibitors on the Mini-Mental State Examination (MMSE) in patients with PDD (WMD 1.09, 95% CI 0.45 to 1.73, P = 0.0008) and in the single PDD and CIND-PD trial (WMD 1.05, 95% CI 0.42 to 1.68, P = 0.01) but not in the single DLB trial.

For behavioural disturbance, analysis of the pooled continuous data relating to behavioural disturbance rating scales favoured treatment with cholinesterase inhibitors (SMD -0.20, 95% CI -0.36 to -0.04, P = 0.01).

For activities of daily living, combined data for the ADCS and the Unified Parkinson's Disease Rating Scale (UPDRS) activities of daily living rating scales favoured treatment with cholinesterase inhibitors (SMD -0.20, 95% CI -0.38 to -0.02, P = 0.03).

For safety and tolerability, those taking a cholinesterase inhibitor were more likely to experience an adverse event (318/452 versus 668/842; odds ratio (OR) 1.64, 95% CI 1.26 to 2.15, P = 0.0003) and to drop out (128/465 versus 45/279; OR 1.94, 95% CI 1.33 to 2.84, P = 0.0006). Adverse events were more common amongst those taking rivastigmine (357/421 versus 173/240; OR 2.28, 95% CI 1.53 to 3.38, P < 0.0001) but not those taking donepezil (311/421 versus 145/212; OR 1.24, 95% CI 0.86 to 1.80, P = 0.25). Parkinsonian symptoms in particular tremor (64/739 versus 12/352; OR 2.71, 95% CI 1.44 to 5.09, P = 0.002), but not falls (P = 0.39), were reported more commonly in the treatment group but this did not have a significant impact on the UPDRS (total and motor) scores (P = 0.71). Fewer deaths occurred in the treatment group than in the placebo group (4/465 versus 9/279; OR 0.28, 95% CI 0.09 to 0.84, P = 0.03).

Authors' conclusions

The currently available evidence supports the use of cholinesterase inhibitors in patients with PDD, with a positive impact on global assessment, cognitive function, behavioural disturbance and activities of daily living rating scales. The effect in DLB remains unclear. There is no current disaggregated evidence to support their use in CIND-PD.

PLAIN LANGUAGE SUMMARY

Cholinesterase inhibitors are beneficial for people with Parkinson's disease and dementia

The clinical features of dementia with Lewy bodies (DLB) and Parkinson's disease with dementia (PDD) have much in common. As patients with DLB and PDD have particularly severe deficits in cortical levels of the neurotransmitter acetylcholine, blocking its breakdown using a group of chemicals known as cholinesterase inhibitors may lead to clinical improvement. Six trials showed a statistically significant improvement in global assessment, cognitive function, behavioural disturbance and activities of daily living rating scales in PDD and cognitive impairment in Parkinson's disease (CIND-PD) patients treated with cholinesterase inhibitors. There was no current disaggregated evidence to support their use in CIND-PD. No statistically significant improvement was observed in patients with DLB treated with cholinesterase inhibitors and further trials are necessary to clarify the effect of cholinesterase inhibitors in this patient group.

BACKGROUND

'When you've seen one patient with dementia, you've seen one patient with dementia'. This commonplace observation about the wide heterogeneity in the clinical presentation of dementia raises the possibility that there may be useful diagnostic subdivisions. The most common cause of dementia is Alzheimer's disease but there are several others, of which dementia with Lewy bodies is arguably the second most common.

Lewy bodies are the defining pathological feature of idiopathic Parkinson's disease. These inclusion bodies are found in the cytoplasm of cells of a wide variety of subcortical nuclei, including those of monoaminergic neurons. They are more likely to occur in cortical neurons in patients with Parkinson's disease when the patients also have dementia. A defining constituent is fibrillar aggregates of alpha-synuclein, a presynaptic protein involved in vesicle formation (Lee 2006). One current theory about why Lewy bodies form is that the cellular mechanisms for degrading and disposing of intracellular protein fragments (proteasomes) are dysfunctional (Olanow 2006). In epidemiological studies, up to 30% of those people with dementia have Lewy bodies (Zaccai 2005). The rate of dementia in clinical Parkinson's disease (24% to 31%) (Aarsland 2005) is at least two to five times that expected in age matched controls. Longitudinal studies suggest that most patients with Parkinson's disease who survive will eventually develop dementia (Aarsland 2003).

Scope of this review

Previous Cochrane reviews have considered the use of cholinesterase inhibitors in both Parkinson's disease with dementia (PDD) (Maidment 2006) and dementia with Lewy bodies (DLB) (Wild 2003). The clinical features of DLB and PDD have much in common. There is some convergence of opinion that DLB and PDD may be the same condition, but the matter is not fully resolved because DLB and PDD have slightly different neuropathological correlates (Ballard 2006; Burn 2006; McKeith 2005).

The diagnosis of PDD rests on the occurrence of formally diagnosed Parkinson's disease followed at least 12 months later by dementia (with no other apparent cause identified). Most patients with Parkinson's disease have at least subtle deficits in neuropsychological function, typically affecting visuospatial and sometimes executive function. In many cases this does not cause problems and is only apparent on detailed specialist evaluation. Cognitive impairment that is clinically significant typically involves more clear-cut deficits in these areas but also tends to affect attention. These are also the three areas of function (visuospatial, executive, attention) prominently affected early in patients labelled DLB. Memory function may be affected late in the process. Dementia is more likely to occur in those in whom the Parkinson's disease develops later, tends to be of the postural instability-gait disorder subtype and to be associated with visual hallucinations when treated with L-dopamine (L-DOPA). The development of dementia associated with Parkinson's disease increases caregiver distress, nursing home requirements and mortality, twofold. It also reduces quality of life (Bedard 2003; Burn 2003). Similarly, parkinsonism in Alzheimer's disease increases the cost of care (Bostrom 2006).

The formal distinction between PDD and early cognitive impairment in Parkinson's disease rests on the definition of dementia. Dementia is defined as occurring when cognitive impairment is of a severity or type such that it interferes with day-to-day occupational and social functioning. However, it is particularly difficult to judge reliably whether any impairment in function in Parkinson's disease is due to cognitive decline or alternatively to the motor, mood or personality changes which may occur. In this review, we have therefore also included a further group of patients, patients who have Parkinson's disease and who have clinically significant cognitive impairment but in whom the diagnosis of dementia has not been formally established. This is analogous to the 'Cognitive Impairment, Not Dementia (CIND)' category and will be termed 'CIND-PD'. This approach is consistent with the current version of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-R) criteria (294.1x).

The diagnosis of 'probable DLB' is more complex than that for PDD. It depends on the presence of two of: persistent visual hallucinations; fluctuations in cognitive and functional ability; and parkinsonism. If parkinsonian symptoms are part of the picture, dementia should have occurred within 12 months of the onset of the parkinsonian symptoms. Additionally, 'probable DLB' can also be diagnosed if just one of these original features is present plus one of the following: severe sensitivity to neuroleptics; rapid eye movement (REM) sleep behaviour disorder; or evidence of striatal dopamine transporter protein loss on neuroimaging (McKeith 2005).

Other symptoms that support the diagnosis but are of less clear-cut diagnostic value are repeated falls, syncope, transient disturbances of consciousness, severe autonomic dysfunction (for example orthostatic hypotension), urinary incontinence, systematised delusions, non-visual hallucinations, depression, relative preservation of medial temporal lobe structures on a computed tomography (CT) or magnetic resonance imaging (MRI) scan, generalized low uptake on single-photon emission CT (SPECT) or positron emission tomography (PET) perfusion scan with reduced occipital activity, abnormal (low uptake) [123I]meta-iodobenzylguanidine (MIBG) myocardial scintigraphy and prominent slow wave activity on electroencephalography (EEG) with temporal lobe transient sharp waves. Olfactory function may also be impaired (Williams 2009).

The distinction between PDD and DLB was introduced in 1995 (McKeith 1996). It was recognised at the time that these conditions had much in common, and that the cut-off period of 12 months was arbitrary. The distinction was in part driven by the fact that, in some health systems, patients who develop Parkinson's disease first tend to see neurologists whereas those who develop cognitive impairment first tend to see psychiatrists. It also reflected in the fact that regulators can only issue licenses for drugs where a claim is

made for the drug in a clearly defined (and accepted) condition. In the third revision of the consensus statement (McKeith 2005), the DLB consortium has suggested that a generic term such as Lewy body disease (LB disease) may be helpful when PDD and DLB are considered together, but that in clinical situations the terms PDD and DLB should be retained as they differentiate between whether symptoms of dementia occur before or after those of Parkinson's disease.

By considering the results of treatment trials for PDD, DLB and CIND-PD, both separately and together, it may be possible to see whether there is any difference in the response to cholinesterase inhibitors in these conditions.

Rationale for cholinesterase inhibitors

Lewy bodies occur in the dopamine-producing cells of the substantia nigra, where their presence is associated with the movement problems of Parkinson's disease. However, alpha-synuclein aggregation occurs in many other brain areas too and the extent of this may correlate with dementia (Braak 2006). A broad correlation can also be made between the areas affected and specific clinical symptoms: cholinergic deficits and attention or memory (Nakano 1984); serotonergic deficits and depression (Jellinger 1994); dopaminergic deficits and visuospatial or executive symptoms (Dubois 1997); and cortical LBs and executive function impairment. In his original description, Frederick Lewy actually put more emphasis on the occurrence of LBs in the large cells of the substantia innominata (now named the nucleus basalis of Myenert). We now know that these cells synthesise acetylcholine and project widely to cortical areas. This nucleus is also affected by the neurofibrillary tangles of Alzheimer's disease. Patients with DLB or PDD have particularly severe deficits in cortical levels of acetylcholine and its enzyme for synthesis, even exceeding the deficits of patients with just Alzheimer's disease (AD) pathology (Perry 1994). The key neuropathological defect that is targeted by cholinesterase inhibitors is therefore present in AD, PDD and DLB. Moreover, the lower cholinergic functioning in DLB and PDD may indicate a greater potential improvement from these drugs than that seen in AD. Since there are fewer neurofibrillary tangles and neuritic plaques and less neuronal loss in DLB than AD (Lippa 1998), it is possible that cortical neurons in DLB are more viable than those in AD and could be more responsive to cholinergic stimulation. Similarly, because those patients with visual hallucinations and more profound deficits in attention tend to have worse cholinergic deficits, the presence of this symptom may be a predictor of treatment response.

The combination of psychotic features and parkinsonism which occur in DLB and PDD can be particularly difficult to manage. Antipsychotic drugs used to treat hallucinations, delusions and agitation can dramatically worsen cognitive and extrapyramidal symptoms and may lead to severe, and even fatal, neuroleptic sensitivity (McKeith 1992). Conversely, L-DOPA treatment of parkinsonism can exacerbate the psychosis. Given that anticholinergic agents are effective in reducing symptoms of tremor in PD, there are theoretical reasons why 'pro-cholinergic' interventions such as cholinesterase inhibitors, which act to reduce breakdown of acetylcholine, might worsen the motor symptoms of PD (Thomas 2005).

Drug licensing

To date, rivastigmine is the only cholinesterase inhibitor that is licensed for the treatment of mild to moderate dementia in Alzheimer's disease and Parkinson's disease in the UK (Medicines and Healthcare products Regulatory Agency) and the USA (Federal Drug Authority). The use of donepezil and galantamine is only licensed in mild to moderate Alzkeimer's disease.

OBJECTIVES

To assess the efficacy, safety and tolerability of cholinesterase inhibitors in patients with dementia with Lewy bodies (LB), Parkinson's disease with dementia and cognitive impairment in Parkinson's disease (considered as a separate phenomena and also grouped together as LB disease).

METHODS

Criteria for considering studies for this review

Types of studies

Randomised, double-blind, placebo-controlled trials assessing the efficacy of treatment with cholinesterase inhibitors in DLB, PDD and cognitive impairment in Parkinson's disease (CIND-PD).

Types of participants

All patients with either DLB or PDD or cognitive impairment in Parkinson's disease. Coexisting Alzheimer's disease was not an exclusion.

Types of interventions

Any studies comparing any of the current cholinesterase inhibitors (donepezil, galantamine, rivastigmine, tacrine) at any dose, taken over any length of time, against placebo.

Types of outcome measures

Outcome measures included the following.
1. Neuropsychiatric features (e.g. psychiatric symptoms, behavioural features); subgroup analysis of those with and without visual hallucinations.
2. Cognitive function; subgroup analysis of those with and without attentional deficits.
3. Activities of daily living.
4. Global assessments.
5. Quality of life, e.g. including maintenance of social functioning.
6. Effect on carers.
7. Institutionalization.
8. Effect on Parkinsonian features (e.g. tremor, rigidity).
9. Acceptability of treatment, as indicated by patient or carer assessment or by measurement of withdrawal from trials, or both.
10. Safety, as measured by severity and frequency of side effects and adverse events.
11. Deaths, including deaths during trials and time to death.
12. Heath economics.

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois), the Cochrane Dementia and Cognitive Improvement Group Specialised Register (on 30 August 2011). The search terms used were: PDD, parkinson, LBD, DLB, lewy.
ALOIS is maintained by the Trials Search Co-ordinator of the Cochrane Dementia and Cognitive Improvement Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy people. The studies are identified from:

1. monthly searches of a number of major healthcare databases: MEDLINE, EMBASE, CINAHL, PsycINFO and LILACS;
2. monthly searches of a number of trial registers: ISRCTN; UMIN (Japan's Trial Register); the WHO portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register plus others);
3. a quarterly search of *The Cochrane Library*'s Central Register of Controlled Trials (CENTRAL);
4. six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS website.
Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, CENTRAL and conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information about the Dementia and Cognitive Improvement Group.
Additional searches were performed in many of the sources listed above, to cover the timeframe from the last searches performed for ALOIS, to ensure that the search for the review was as up-to-date and as comprehensive as possible. The search strategies used can be seen in Appendix 1.
The latest search (August 2011) retrieved a total of 240 results. After a first assessment and de-duplication of these results the authors were left with 50 references to further assess.

Searching other resources

Reference lists of relevant studies were searched for additional trials.

Data collection and analysis

Selection of studies

Two review authors (MR, RMcS) independently selected trials for relevance using defined criteria in the current *Cochrane Handbook for Systematic Reviews of Interventions*.

Asessment of methodological quality

Review authors (MR, RMcS) independently assessed the quality of the trials according to the criteria given in the Cochrane Handbook. Where the review authors (MR, RMcS) identified bias and agreed that it was significant, trials were excluded from further analysis; reasons for such exclusion were given.

Data extraction

Data were extracted from the published reports (MR). Any uncertainty over inclusion or exclusion of a trial, methodological quality or data extraction were settled by discussion with a second review author (RMcS) who had previously extracted data in an earlier draft of this review.
The summary statistics required for each trial and each outcome for continuous data are the mean change from baseline, the standard error of the mean change, and the number of patients for each treatment group at each assessment. Where changes from baseline were not reported, the mean, standard deviation and the number of patients for each treatment group at the final time point were extracted, if available. Results from the donepezil groups in a study which compared two doses of donepezil were combined (Dubois 2007). For binary data the numbers in each treatment group and the numbers experiencing the outcome of interest were sought. The baseline assessment was defined as the latest available assessment prior to randomisation, but no longer than two months earlier. Data from titration phases prior to the randomised phase, or

from open-label follow-up periods, were not used to assess safety or efficacy because patients were not randomised or treatments concealed.

Analysis plan

Data for trials in each 'condition' (that is PDD, DLB, CIND-PD) were considered separately on each outcome measure. Data for the conditions were also combined. It was intended that data for the three conditions would be considered both separately and combined together. Results were also analysed according to the cholinesterase used and the duration of the trial. Results were examined to establish whether any heterogeneity was explicable on the basis of the condition. Where there was no heterogeneity, then the focus in the text was determined by the number and quality of trials. Where the heterogeneity of results was high, as indicated by $I^2 > 40\%$, this was reported in the text.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
Six trials met the inclusion criteria for this review and 1236 participants were randomised in total. Four of the trials were of a parallel group design and two were cross-over trials.

Participants

All participants were aged 18 years and over, with both males and females included in all of the trials. Four of the trials included participants with a diagnosis of Parkinson's disease with dementia (Aarsland 2002a; Dubois 2007; Emre 2004; Ravina 2005), of which Dubois 2007 remains unpublished. Leroi 2004 included patients with either Parkinson's disease with dementia or cognitive impairment in Parkinson's disease. Patients with dementia with Lewy Bodies were included in only one of the trials (McKeith 2000).

Setting

The trials were all conducted in the outpatient population. Three of the trials were multicenter studies (Dubois 2007; McKeith 2000; Emre 2004). Two of the trials took place in the United States of America (Leroi 2004; Ravina 2005), with the remaining trial taking place in Norway (Aarsland 2002a).

Intervention

Two of the trials compared the use of oral rivastigmine, up to 12 mg daily, with the use of placebo (Emre 2004; McKeith 2000). The remaining trials compared the use of oral donepezil to oral placebo. Three of the trials (Aarsland 2002a; Leroi 2004; Ravina 2005) studied donepezil at the highest tolerated dose (up to 10 mg daily). Dubois 2007 compared the use of donepezil at two different doses (either 5 mg or 10 mg) to placebo.

Duration

Four of the trials were 18 weeks or more in duration (Dubois 2007; Emre 2004; Leroi 2004; McKeith 2000). The remaining two trials lasted 10 weeks (Aarsland 2002a; Ravina 2005).

Outcome measures

- Global assessment

1. The Alzheimer's Disease Cooperative Study Clinician's Global Impression of Change (ADCS-CGIC) scale (Schneider 1997) is a 7-point scale providing a global rating of patient function in four areas: general, cognitive, behaviour and activities of daily living. Assessments should be performed by the same clinician with input from the patient and the caregiver.

- Cognitive function

1. Mini-Mental State Examination (MMSE) (Folstein 1975) evaluates cognition in five areas: orientation, immediate recall, attention and calculation, delayed recall, and language. Test scores range from 0 (severe impairment) to 30 (normal).
2. The cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-Cog) (Rosen 1984) comprises 11 individual sections testing spoken language, recall of test instructions, word finding difficulty, following commands, naming objects, construction drawing, ideational praxis, orientation, word recall and word recognition. The maximum score is 70, with higher scores representing greater impairment.
3. The Mattis Dementia Rating Scale (MDRS) (Mattis 1988) assesses cognitive function on five subscales: attention, initiation-perseveration, construction, conceptualisation and memory.
4. The Cognitive Drug Research (CDR) Computerized Assessment System (Simpson 1991) power of attention tests evaluate simple and complex reaction times and digit vigilance. Scores are measured in milliseconds with higher scores indicating a worse performance.
5. The Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency test (Delis 2001) requires patients to produce as many words starting with a particular letter as they can in one minute. Higher scores indicate better performance.
6. The Ten Point Clock-Drawing test (Manos 1994) is used as a measure of spatial dysfunction and neglect. Scores range from 0 to 10 with higher results indicating better performance.

7. Brief test of attention (BTA) (Schretlen 1997) is an auditory perception task that measures divided attention in the verbal-linguistic system. Raw scores range from 0 (severe impairment) to 20 (normal).
8. The Trail Making Test (TMT) (Reitan 1958) tests visual attention and task switching. It is divided into two parts: part A, containing only numbers; and part B, in which the participant must alternate between numbers and letters. The time to complete the test is used as the performance measure.
9. The Verbal Fluency test (Barr 1996) assesses the efficiency of verbal retrieval, short-term memory and cognitive flexibility by asking the participant to name as many animals as he or she can in 60 seconds.
10. Hopkins Verbal Learning Test (Brandt 2001) is a brief verbal learning and memory test.
11. Developmental Test of Visual-Motor Integration (VMI) (Beery 1989) consists of copying 24 geometric forms. A higher score indicates a better performance.

- Behavioural disturbance

1. The 10-item Neuropsychiatric Inventory (NPI) (Cummings 1994) is a relatively brief interview that assesses 10 types of behavioural disturbance: delusions, hallucinations, dysphoria, anxiety, agitation or aggression, euphoria, disinhibition, irritability or lability, apathy and aberrant motor behaviour. Scores range from 0 (normal) to 120 (severely disturbed).
2. The Brief Psychiatric Rating Scale (BPRS) (Overall 1962) is used to measure psychiatric symptoms such as depression, anxiety, hallucinations and unusual behaviour. Each symptom is rated 1 to 7 according to severity.

- Activities of daily living (ADL)

1. The Alzheimer's Disease Cooperative Study activities of daily living inventory (ADCS-ADL) (Galasko 1997) is a scale for basic and complex abilities that has been validated in patients with dementia. The highest score is 78 and implies no impairment.
2. Unfied Parkinson's Disease Rating Scale (UPDRS) - Activities of Daily Living is a subscale of the UPDRS (see below).

- Safety and tolerability

1. The Unified Parkinson's Disease Rating Scale (UPDRS) (Fahn 1987) is used to follow the longitudinal course of Parkinson's disease. It is divided into five sections: evaluation of mentation, behaviour and mood; self evaluation of activities of daily living; clinician-scored motor evaluation, severity of Parkinson's disease (Hoehn and Yahr); and the Schwab and England ADL scale. Higher scores imply more severe disease.

Risk of bias in included studies

Allocation

Aarsland 2002a and McKeith 2000 provided details of adequate sequence generation and concealment. Emre 2004 provided good details of sequence generation but did not specify methods used to maintain concealment of allocation, whilst Leroi 2004 did not discuss the randomisation procedures followed. Neither Dubois 2007 nor Ravina 2005 provided any details of the allocation procedure.

Blinding

All the trials described the use of 'double-blind' methods but none of them described how this was achieved.

Reporting of withdrawals or dropouts

Dubois 2007 did not disclose whether any of the participants withdrew or dropped out during the study. All other trials reported the numbers of withdrawals and dropouts but only McKeith 2000 included all of these in the final analysis. Aarsland 2002a, Emre 2004 and Leroi 2004 only included participants that received at least one dose of the study medication and had at least one measurement at baseline and at one other time point in the efficacy analysis, using the last observation carried forward. One study (Ravina 2005) specified that participants had to have at least one visit in the second period to be included in the efficacy analysis. Three participants were included in the safety but not the efficacy analysis as data from both periods were required for the cross-over analysis.

Selective reporting

Aarsland 2002a only published primary outcomes of the study and the publication of the secondary outcome measures is still pending. The results of one trial (Dubois 2007) are only available in poster format and, due to the very limited details provided, only one of the efficacy variables could be included in this meta-analysis. Despite numerous attempts to contact the authors, no further details of the trial have been made available.

Other sources of bias

Two trials (Aarsland 2002a; Ravina 2005) were cross-over in design and were considered in accordance with the guidance of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2008). Although dementia is a neuro-degenerative condition, the duration of the trials was considered to be too short for any significant disease progression to have occurred in that period. Neither of the two studies demonstrated a significant carry-over effect between the two phases of the trial.

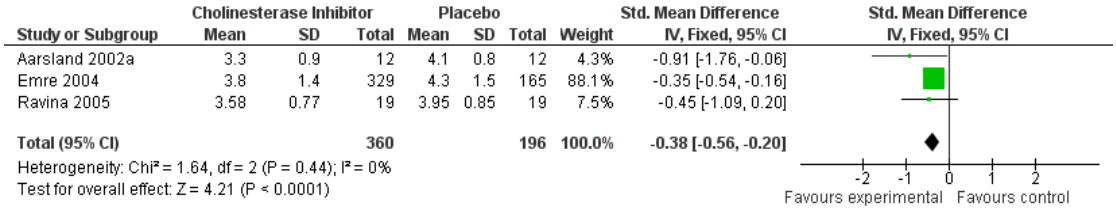
Effects of interventions

Table 1

Global assessment

Three trials comparing cholinesterase inhibitor treatment to placebo in PDD (Aarsland 2002a; Emre 2004; Ravina 2005) reported a difference in the ADCS-CGIC score of -0.38, favouring the cholinesterase inhibitors (95% CI -0.56 to -0.24, P < 0.0001) (Figure 1). A therapeutic benefit of cholinesterase inhibitors was observed irrespective of the agent used and the duration of the trial (weighted mean difference (WMD) -0.62, 95% CI -1.13 to -0.10, P = 0.02 for donepezil used for 10 weeks or less; and WMD -0.35, 95% CI -0.54 to -0.16, P = 0.0003 for rivastigmine used for 18 weeks or more).

Figure 1. Forest plot of comparison: 1 Global Assessment, outcome: 1.1 Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change (ADCS-CGIC).



Three trials reported response rates (Aarsland 2002a; Dubois 2007; Emre 2004). These favoured the cholinesterase inhibitor (OR 2.26, 95% CI 1.04 to 4.91, P = 0.04) but with high heterogeneity (I^2 = 78%).

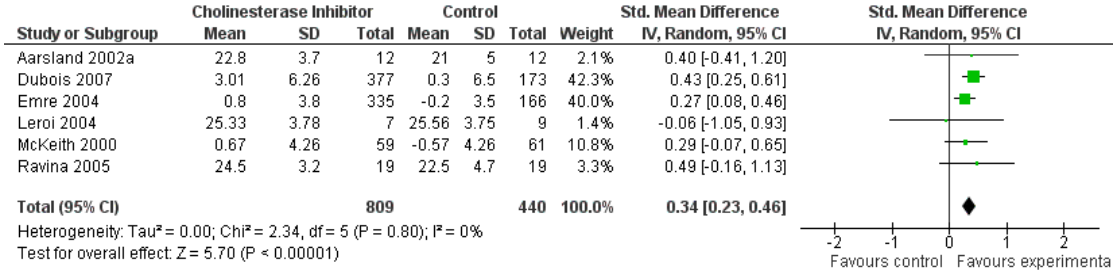
Cognitive function

Although there was no statistically significant difference in the MMSE between the control and treatment group for patients with DLB (McKeith 2000) (WMD 1.24, 95% CI 0.28 to 2.76, P = 0.11), a beneficial treatment effect was seen in PDD patients (Aarsland 2002a; Emre 2004; Ravina 2005) (WMD 1.09, 95% CI 0.45 to 1.73, P = 0.0008) and in PDD and CIND-PD patients (Aarsland 2002a; Emre 2004; Leroi 2004; Ravina 2005) (WMD 1.05, 95% CI 0.42 to 1.68, P = 0.001). Pooling all available data showed an improvement in the MMSE favouring treatment with cholinesterase inhibitors (WMD 1.08, 95% CI 0.50 to 1.66, P = 0.0003). Furthermore, cholinesterase inhibitors lead to an improvement in cognitive function in patients with PDD, as measured by the ADAS-Cog (Dubois 2007; Emre 2004; Ravina 2005) (WMD -2.72, 95% CI -3.61 to -1.83, P < 0.00001) and the Delis-Kaplan Executive Function System (Emre 2004) (WMD 2.80, 95% CI 1.47 to 4.13, P < 0.0001). There was also a statistically significant improvement in the Trail Making Test A in patients with PDD or CIND-PD (Leroi 2004) (WMD -71.68, 95% CI -108.44 to -34.92, P = 0.0001). Cholinesterase inhibitor use had no statistically significant impact on the Mattis Dementia Rating Scale (MDRS) when used in patients with PDD alone (Emre 2004; Ravina 2005) (WMD 3.39, CI 95% -4.06 to 10.84, P = 0.37) or in patients with PDD or CIND-PD (Emre 2004; Leroi 2004; Ravina 2005) (WMD 3.70, 95% CI -1.13 to 8.54, P = 0.30). No significant difference between the two groups was observed using the Cognitive Drug Research Computerized Assessment system power of attention scale (Emre 2004) (WMD -173.70, 95% CI -471.23 to 123.83, P = 0.25), the Ten Point Clock Drawing Test (Emre 2004) (WMD 1.10, 95% CI -0.01 to 2.21, P = 0.05), Brief Test of Attention (Leroi 2004) (WMD 1.65, 95% CI -0.82 to 4.12, P = 0.19), Trail Making Test B (Leroi 2004) (WMD -87.24, 95% CI -202.89 to 28.41, P = 0.14), Verbal Fluency Test (Leroi 2004) (WMD 6.63, 95% CI -2.33 to 15.59, P = 0.15), Hopkins Verbal Learning Test (Leroi 2004) (WMD 1.72, 95% CI -2.93

to 6.37, P = 0.47) and the Developmental Test of Visual-Motor Integration (Leroi 2004) (WMD 0.03, 95% CI -3.28 to 3.34, P = 0.99).

In an overall assessment of the cognitive function domain, combining MMSE scores where available, and ADASCog scores where not, the pooled estimate of the effect of cholinesterase inhibitors on cognitive function measures was consistent with the presence of a therapeutic benefit (standardised mean difference (SMD) -0.34, 95% CI -0.46 to -0.23, P < 0.00001) (Figure 2). The beneficial effect of cholinesterase inhibitors on cognitive function was observed in both the donepezil and rivastigmine groups (SMD -0.42, 95% CI -0.58 to -0.25, P < 0.00001; SMD -0.27, 95% CI -0.44 to -0.11, P < 0.001, respectively).

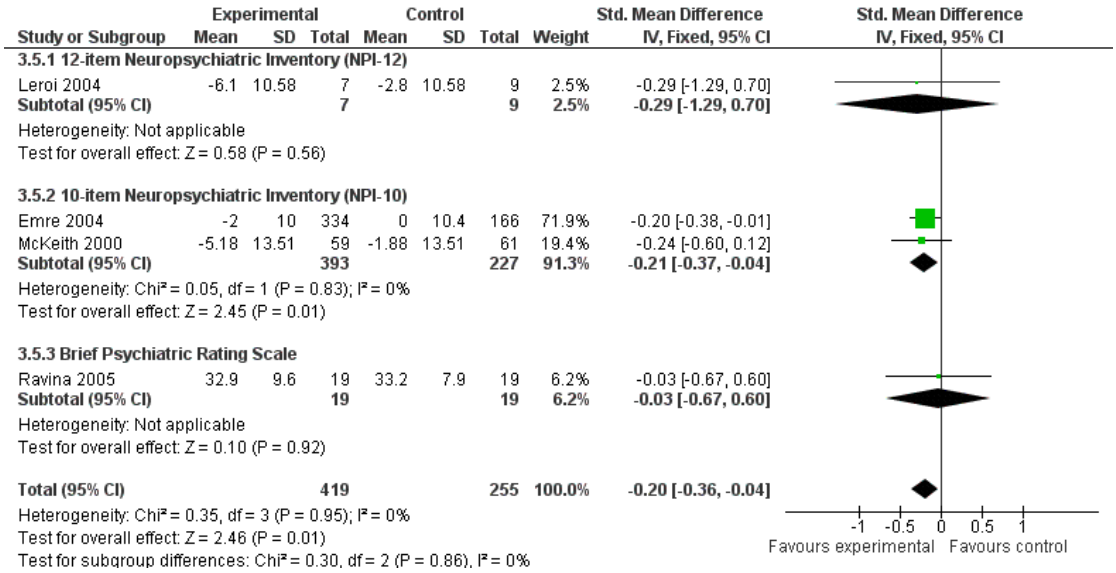
Figure 2. Forest plot of comparison: 2 Cognitive function, outcome: 2.3 Combined: MMSE or ADASCog.



Behavioural disturbance

Analysis of the pooled continuous data relating to behavioural disturbance rating scales once again favoured treatment with cholinesterase inhibitors (SMD -0.20, 95% CI -0.36 to -0.04, P = 0.01) (Figure 3). This effect was only seen in trials using rivastigmine (SMD -0.21, 95% CI -0.36 to -0.06, P = 0.006) and those lasting 18 weeks or longer (SMD -0.21, 95% CI -0.36 to -0.06, P = 0.005). Breakdown of the individual rating scales did not reveal any effect of the treatment on the Brief Psychiatric Rating Scale (Ravina 2005) (WMD -0.30, 95% CI -5.89 to 5.25, P = 0.92) or the 12-item Neuropsychiatric Inventory (Leroi 2004) (WMD -3.30, 95% CI -13.75 to 7.15, P = 0.54). Patients with DLB failed to improve their NPI-4 (McKeith 2000) (WMD -1.65, 95% CI -4.33 to 1.03, P = 0.23) or NPI-10 (McKeith 2000) (WMD -3.30, 95% CI -8.14 to 1.54, P = 0.18) scores on active treatment. Emre 2004 showed an improvement of -2.00 (95% CI -3.91 to -0.09, P = 0.04) in NPI-10 in PDD patients treated with cholinesterase inhibitors. Hallucinations were less frequently reported in the active treatment group than the placebo group, however this was not statistically significant (Dubois 2007; Emre 2004) (46/739 versus 33/352; OR 0.64, 95% CI 0.40 to 1.02, P = 0.06). There was a risk of bias due to selective reporting of this outcome, which was not available from the large Dubois 2007 study and Aarsland 2002a.

Figure 3. Forest plot of comparison: 3 Behavioural Disturbance, outcome: 3.5 Combined.



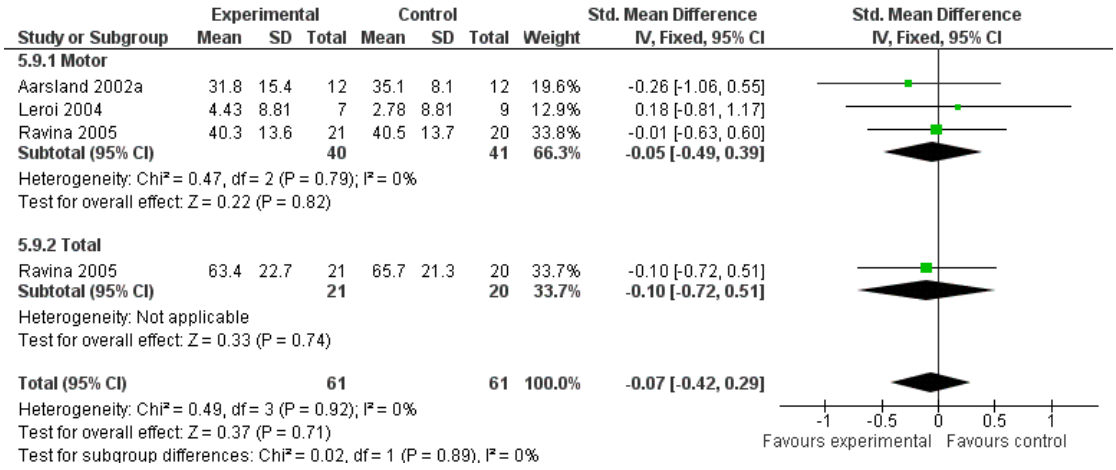
Activities of daily living

There was an improvement in the Alzheimer's Disease Cooperative Study activities of daily living rating scale (Emre 2004) (WMD 2.50, 95% CI 0.43 to 4.57, P = 0.02), with no difference observed using the UPDRS activities of daily living rating scale (Leroi 2004) (WMD 0.84, 95% CI -6.24 to 7.92, P = 0.82). Combined data favoured treatment with cholinesterase inhibitors (SMD -0.20, 95% CI -0.38 to -0.02, P = 0.03).

Safety and tolerability

Both the total number of dropouts and the number of dropouts due to adverse events were significantly higher in the treatment group as compared to the patients receiving placebo (128/465 versus 45/279; OR 1.94, 95% CI 1.33 to 2.84, P = 0.0006 and 73/430 versus 22/247; OR 2.12, 95% CI 1.27 to 3.55, P = 0.004). The placebo group experienced significantly fewer adverse events (668/842 versus 318/452; OR 1.64, 95% CI 1.26 to 2.15, P = 0.0003), although the number of adverse events that were judged to be severe was not significantly different between the two groups (21/73 versus 15/73; OR 1.60, 95% CI 0.68 to 3.81, P = 0.28). Interestingly, the increase in the number of dropouts and adverse events in the treatment group were significant in studies using rivastigmine (117/421 versus 42/240; OR 1.82, 95% CI 1.22 to 2.71, P = 0.003 and 357/421 versus 173/240; OR 2.28, 95% CI 1.53 to 3.38, P < 0.0001, respectively) but not in the studies using donepezil (11/44 versus 3/39; OR 3.64, 95% CI 0.99 to 13.46, P = 0.05 and 311/421 versus 145/212; OR 1.24, 95% CI 0.86 to 1.80, P = 0.25, respectively). Parkinsonian symptoms were reported more commonly in the treatment group (139/739 versus 40/352; OR 1.88, 95% CI 1.28 to 2.75, P = 0.001), however this did not have a significant impact on the UPDRS (total and motor) scores (SMD -0.07, 95% CI -0.42 to 0.29, P = 0.71) (Figure 4). Although tremor was more commonly reported in the treatment groups (64/739 versus 12/352; OR 2.71, 95% CI 1.44 to 5.09, P = 0.002), the same was not true of falls (43/739 versus 16/352; OR 1.29, 95% CI 0.72 to 2.33, P = 0.39). Fewer deaths occurred in the treatment group when compared to the placebo group (4/465 versus 9/279; OR 0.28, 95% CI 0.09 to 0.84, P = 0.03).

Figure 4. Forest plot of comparison: 5 Safety and Tolerability, outcome: 5.9 Unified Parkinson's Disease Rating Scale (UPDRS).



DISCUSSION

We identified six trials to help us to assess the efficacy, safety and tolerability of cholinesterase inhibitors in dementia with Lewy bodies (DLB), Parkinson's disease with dementia (PDD) and cognitive impairment in Parkinson's disease (CIND-PD). Where possible, we considered outcome measures for the separate diseases as well as combining the data available to estimate the general effect of cholinesterase inhibitors on Lewy body disease.

Currently available evidence suggests that cholinesterase inhibitors improve global assessment measures in patients with PDD, with no data for DLB and CIND-PD being available. As there was no evidence of a positive impact of cholinesterase inhibitors on cognitive function and behavioural disturbance rating scales in patients with DLB, the overall response in favour of using cholinesterase inhibitors is likely to be due to the effect seen in patients with PDD. As only one of the six trials included in this meta-analysis randomised patients with DLB, the over-representation of patents with PDD could have a substantial effect on the overall effects. The effect of cholinesterase inhibitors on measures of activities of daily living was not assessed in the DLB population but was statistically significant in the very small trial which included both patients with PDD and CIND-PD.

The trials that were included provided evidence that cholinesterase inhibitors were not as well tolerated as placebo, with significantly more adverse effects and dropouts seen in the active treatment group. Reassuringly, the frequency of severe adverse effects was the same in both groups. Indeed, death rates were lower amongst those taking the active drug than placebo, though this is based on small numbers. Although parkinsonian symptoms, and tremor in particular, were reported more frequently as adverse effects in patients receiving cholinesterase inhibitors, this did not seem to have an impact on the Parkinson's disease severity rating scales.

An important limitation of the current study lies in the incomplete public presentation of data from the important Dubois 2007 study, which was sponsored by Pfizer. The study was completed prior to current US legislation on trial registration.

AUTHORS' CONCLUSIONS

Implications for practice

The currently available evidence supports the use of cholinesterase inhibitors in patient with PDD and CIND-PD, with a positive impact on global assessment, cognitive function, behavioural disturbance and activities of daily living rating scales. The effect of cholinesterase inhibitors on patients with DLB has only been investigated in one small study and, therefore, evidence for their use in this patient group is less clear.

Implications for research

Patients with DLB were under-represented in this meta-analysis and further randomised evidence is required to reduce the uncertainty of the effects that cholinesterase inhibitors have in this patient group. A large trial of donepezil in patients with CIND-PD is due to commence in 2012 (Burn 2009).

ACKNOWLEDGEMENTS

The authors gratefully acknowledge the contributions of the consumer editor, Margaret Bullard. We are also grateful to David Beversdorf for sharing the data from his study with us.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aarsland 2002a

Methods	Randomised, single centre, double-blind, cross-over, placebo-controlled. Duration: 10 weeks.
Participants	Country: Norway No. of centres: 1 Diagnosis: definite or probable PD as per Larsen (Clinical diagnosis of Parkinson's disease. Proposal of diagnostic subgroups classified at different levels of confidence) AND dementia due to PD by DSM-IV criteria. Inclusions: age 41-95 years, mild-severe Parkinsonism (Hoehn and Yahr stage <5), clinical evidence of decline in memory AND at least one other category of cognitive function (starting at least 1 year after onset of parkinsonism), MMSE 16-26, on stable regimen anti-Parkinsonian mediation for at least 1 month immediately preceding study and throughout its duration, patient accompanied by care-giver (= informant). Exclusions: brain disease except PD, other severe medical disorders, use of anticholinergic drugs or psychtropic drugs with anticholinergic effects, use benzodiazepine medication (except short-acting) in 24 hours before testing Number of patients: 14
Interventions	Route: oral Treatment: donepezil started at 5mg once daily for 6 weeks and increased to 10mg daily for 4 weeks if tolerated
Outcomes	Primary outcome measures: mini-mental state examination (MMSE), the clinician's interview based global impression of change (CIBIC+), the motor subscale of the unified Parkinson's disease rating scale (UPDRS) Secondary measures: Neuropsychiatric Inventory (NPI) and the severity of parkinsonism (rated by patient and informer)
Notes	Details of secondary outcome measures are currently unpublished

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "a randomisation list was computer generated according to a random block design"
Allocation concealment (selection bias)	Low risk	Quote: "the principal investigator was given a sealed envelope containing the individual treatment regimens of each patient"
Blinding (performance bias and detection bias) All outcomes	Low risk	'The initial dose was donepezil 5 mg or identically appearing placebo tablets taken once a day in the evening. The dose was

Aarsland 2002a (*Continued*)

		increased to 10 mg after six weeks if well tolerated.'
Incomplete outcome data (attrition bias) All outcomes	High risk	Imputation of missing data using LOCF. Too small to be able to say whether there was differential dropout in drug arm. The lack of a published behavioural outcome increases the risk that there is selective reporting bias
Other bias	High risk	Small pilot studies such as this are inherently at high risk of bias

Dubois 2007

Methods	Randomised, multi-centre, double-blind, placebo-controlled, 3-arm parallel group Duration: 24 weeks
Participants	Countries: Details not available No. of centres: Details not available Diagnosis: PD by UK Brain Bank Criteria AND dementia by DSM-IV Inclusions: Mild-moderately severe dementia , MMSE 10-26, present at least 1 year after onset of PD Exclusions: Details not available Number of patients: 550 (377 on active treatment)
Interventions	Route: oral Treatment: donepezil 5mg or 10mg for 24 weeks
Outcomes	Primary outcome measures: Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog); Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change (ADCS-CGIC) Secondary outcome measures: executive function tests, working memory, attention and visuospatial function tests
Notes	Tolerability and safety assessed Treatment-related motor impairment assessed by motor subscale of UPDSRS Treatment-by-country interaction investigated

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details of randomisation process available
Allocation concealment (selection bias)	Unclear risk	No details of available

Dubois 2007 (*Continued*)

Blinding (performance bias and detection bias) All outcomes	Unclear risk	No details available
Incomplete outcome data (attrition bias) All outcomes	High risk	Only available as a poster. High risk of selective reporting of data, especially given that remains unpublished

Emre 2004

Methods	Randomised, multicenter, double-blind, placebo-controlled. Duration: 24 weeks
Participants	Countries: Austria, Belgium, Canada, France, Germany, Italy, Holland, Norway, Portugal, Spain, Turkey, UK. No. of centres: not stated. Diagnosis: PD by UK Parkinson's Disease Society Brain Bank criteria; Dementia by DSM-IV (dementia due to Parkinson's disease code 294.1) Inclusions: MMSE 10 to 24; onset of symptoms of dementia more than 2 years after diagnosis of PD; regular caregiver. Exclusions: primary neurodegenerative disease other than PD or dementia; history major depression; presence of active uncontrolled seizure disorder; disability or unstable disease unrelated to PD; hypersensitivity rivastigmine or similar drugs; use cholinesterase inhibitor or anticholinergic drug. Number of patients (Randomised/ITT/completers): rivastigmine: 362/329/263; placebo:179/161/147
Interventions	Route: oral Treatment: rivastigmine commenced at 1.5mg twice daily and increased according to tolerability by 3mg daily at intervals of at least 4 weeks over a 16 week period
Outcomes	Primary outcome measures: Intention to treat analysis with LOCF Alzheimer's Disease Assessment Scale - Cognitive sub-scale (ADAS-Cog); Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change (ADCS-CGIC) Secondary measures: Mini-Mental State Examination (MMSE); Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL); Neuropsychiatric Inventory (NPI); Cognitive Drug Research (CDR) Computerized Assessment System power of attention tests; Delis-Kaplan Executive Function System (D-KEFS) Verbal Fluency test; Ten Point Clock-Drawing test; Unified Parkinson's Disease Rating Scale (UPDRS)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Emre 2004 (*Continued*)

Random sequence generation (selection bias)	Low risk	Quote: "automated random assignment of treatment was performed with the use of a validated system, managed by Novartis Drug Supply Managment"
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis with LOCF. About half those who discontinued drug continued to attend for ITT evaluations, thereby reducing the attrition bias towards a positive effect of drug which would be associated with the greater discontinuation rate amongst those taking drug which occurred
Other bias	Low risk	Comment: The study appears to be free of other sources of bias

Leroi 2004

Methods	Randomized, multicenter, double-blind, placebo-controlled. Duration: 18 weeks
Participants	Country: USA No. of centres: 2 Diagnosis: PD by UK Parkinson's Disease Brain Bank Criteria AND either dementia or cognitive impairment secondary to PD by DSM IV Inclusions: on stable regimens of anti-Parkinsonian medications. Exclusions: MMSE<10, substance abuse or dependence (by DSM IV criteria), severe cardiac disease, severe renal disease, severe vascular disease, non-ambulatory, known inability to tolerate donepezil Number of patient: 16 (9 on active treatment)
Interventions	Route: oral Treatment: donepezil started at 2.5mg daily for 5 days then 5mg daily for 30 days then 7.5 mg daily for 5 days then 10mg daily for 91 days (total 18 weeks), study medication could be reduced in 2.5 mg decrements in response to adverse effects
Outcomes	LOCF analysis. Primary outcome measure: Mini Mental State Examination (MMSE); Dementia Rating Scale (DRS) - total score, attention subscore, initiation-perseveration subscore, conceptualisation subscore, memory subscore; Brief Test of Attention (BTA) ;Trail Making Test-Part A and B (TMT-A and TMT-B); Verbal Fluency; Hopkins Verbal Learning Test-Revised (HVLT); Developmental Test of Visual-motor Integration (VMI) Secondary measures: Neuropsychiatric Inventory (NPI); Cornell Scale for Depression in Dementia (CSDD); UPDRS-Activities of Daily Living (ADL) and Complications of

Leroi 2004 (*Continued*)

	Therapy subscales Safety measures: Unified Parkinson's Disease Rating Scale (UPDRS) motor subscale; Hoehn and Yahr stage	
Notes		

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Allocation concealment (selection bias)	Low risk	Quote: "the pharmacy maintained the randomisation code"
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	High risk	The high dropout rate (>30%), which was due to more adverse effects in the drug arm, and LOCF analysis, combine to create a high risk of bias towards finding a positive effect of drug
Other bias	High risk	This was a small pilot study. Such studies are inherently at risk of bias

McKeith 2000

Methods	Randomised, multicenter, double-blind, placebo-controlled. Duration: 23 weeks - 20 weeks treatment followed by 3 weeks 'rest'
Participants	Countries: Spain, UK and Italy No. of centres: details not available Diagnosis: clinical diagnosis of probable Lewy body dementia Inclusion: MMSE >9, regular caregiver Exclusion: severe extrapyramidal symptoms, asthma, taking neuroleptics, anticholinergics, selegiline or similar drugs Number of patients (Randomised/ITT/Completers): RVS: 59/n_1/41 Placebo: 61/n_2/51 (n_1+n_2=117)
Interventions	Route: oral Treatment: rivastigmine started at 1.5 mg twice daily, titrated to 6mg twice daily (or maximum tolerated) over 8 weeks maximum
Outcomes	ITT Neuropsychiatric Inventory, 10 and 4 item versions (NPI-10 & NPI-4); speed of response to selected tests; Clinician's Global Impression of Change (ADCS-CGIC); Mini Mental State Examination (MMSE); Unified Parkinson's Disease Rating Scale (UPDRS)

McKeith 2000 (*Continued*)

Notes	Data on speed of response was not used in this Cochrane review, as we viewed it as a proxy measure rather than a direct measure of a clinically important feature of DLB. We were unable to include the UPDRS, as data was not presented in the published paper

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "randomisation list was computer generated with a proprietary computer application, according to a randomised block design"
Allocation concealment (selection bias)	Low risk	Quote: "envelopes were to be opened only in case of emergency and were collected after unblinding and verified for code breaks"
Blinding (performance bias and detection bias) All outcomes	Low risk	
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	The presentation of ITT, LOCF and OC data is commendable. However, it is not reported how many of those in the ITT dataset were providing data for the final time point despite having discontinued medication and whether there was an imbalance in this. It is not clear whether outcome reporting was selective
Other bias	Low risk	Comment: The study appears to be free of other sources of bias

Ravina 2005

Methods	Randomized, multicenter, double-blind, crossover, placebo-controlled. Duration: 10 weeks
Participants	Country: USA No. of centres: 4 Diagnosis: PD by Movement Disorders Society Scientific issues Committee Parkinsonian disorders (diagnosis made by movement disorder specialists) Inclusions: age >40 years, mild-moderate dementia according to DSM IV criteria for dementia AND MMSE 17-26 Exclusions: clinical diagnosis of DLB, other causes of dementia (e.g. stoke), use of cholinergic or anticholinergic agents except amantadine or tolterodine within 2 weeks before screening, medical conditions or uncontrolled psychosis which were thought by investigator to interfere with the safe conduct of study, pregnancy or lactation.

Ravina 2005 (*Continued*)

	Number of patients: 22
Interventions	Route: oral Treatment: donepezil started at 5mg once daily and increased according to tolerability to donepezil 5mg twice daily after 3 weeks, then continued at that dose (if tolerated, otherwise reduced back to 5mg once daily) for 6 weeks
Outcomes	Primary outcome measure: Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) Secondary measures: Mini Mental State Examination (MMSE); Mattis Dementia Rating Scale (MDRS); Brief Psychiatric Rating Scale (BPRS); Unified Parkinson's Disease Rating Scale (UPDRS); Clinician's Global Impression of Change (ADCS-CGIC)
Notes	Data from first 10 week period was analysed for this review BPRS is a measure of psychosis

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	'Drug distribution to the sites and randomisation were performed by the University of Pennsylvania Investigational Drug Services Unit. Subjects were randomised in blocks of four to receive either donepezil in period I and placebo in period II or placebo in period I and donepezil in period II.'
Allocation concealment (selection bias)	Low risk	
Blinding (performance bias and detection bias) All outcomes	Low risk	'matching placebo'
Incomplete outcome data (attrition bias) All outcomes	High risk	LOCF imputation of missing data
Other bias	High risk	This was a very small study. Such studies are at inherent risk of bias

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

Study	Reason for exclusion
Aarsland 2002	Open label study
Adler 2011	Non-interventional trial
Anand 2000	Conference presentation. Review, not a clinical trial
Barone 2008	Only hyperhomocysteinemic Parkinson's disease dementia patients included
Barone 2010	Open label study
Bergman 2002	Open label study
Bergman 2003	Open label study; trial of people with Alzheimer's disease, not Parkinson's
Beversdorf 2004	Data kindly provided by the author, judged unsuitable for meta-analysis as a small double cross-over study without a wash-out period and no carry-over effect analysis
Brashear 2004	Data limited, details not available
Chung 2010	Trial of people with Parkinson's disease with advanced postural instability
Cummings 2010	Trial of people with Alzheimer's disease, not Parkinson's
De Deyn 2011	Open label study
Fabbrini 2002	Open label study
Fogelson 2003	Open label study; non-standard outcome measures
Foy 2000	Diagnostic criteria outside specification
Fujita 2010	Case report
Giladi 2003	Open label study
Gustavsson 2009	Open label study
Hutchinson 1996	Open label study
Korczyn 2001	Open label study
Lanctot 2000	Case series
Linsarazo 2005	Open label study

(*Continued*)

Litvinenko 2008	Open label study
McKeith 2000a	Open label exploratory trial; 20 weeks active treatment then 6 weeks of withdrawal
McLaren 2003	Open label study
Minett 2003	Open label study
Mori 2006	Open label study
Olin 2010a	Open label study, rivastigmine and memantine used
Pakrasi 2006	Open label study
Reading 2001	Open label study
Rektorova 2004	Open label study
Rosengarten 2010	Investigation of pathophysiological changes
Samuel 2000	Lewy body dementia patients compared with Alzheimer's disease patients regarding response to donepezil
Satoh 2010	Investigation of pathophysiological changes
Thomas 2005	Open label study
Touchon 2006a	Retrospective study
Touchon 2006b	as Touchon 2006a
Van Laar 2001	Open label study
Vasile 2010a	Comparative efficacy of cholinesterase inhibitors, no placebo group
Vasile 2010b	Comparative efficacy of cholinesterase inhibitors, no placebo group
Walker 2000b	Investigation of pathophysiological changes
Werber 2001	Open label study
Wilcock 2000	Project abandoned

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

Anon 2004a

Trial name or title	Donepezil for dementia in Parkinson's disease: A randomised double blinded placebo controlled crossover trial
Methods	RCT
Participants	N = 28 Country = USA Duration = 26 weeks
Interventions	Donepezil + Placebos
Outcomes	-ADAS/cog -cognitive function -activities of daily living -mood -quality of life -side effects -motor performance
Starting date	February 2002
Contact information	
Notes	Study ID numbers 020115; 02-N-0115//NLM identifier NCT00030979

Anon 2007a

Trial name or title	Double-blind study of E2020 in patients with dementia with Lewy bodies - Phase II
Methods	RCT
Participants	N = 160 Country = Japan Duration = 12 weeks
Interventions	Donepezil (E2020), Dosage of drug, Placebo
Outcomes	Primary outcome measures: Cognitive function, psychiatric symptoms, and global clinical function, burden on caregiver at 12 weeks
Starting date	November 2007
Contact information	
Notes	Study ID(s) and Acronym(s): NCT00543855 // E2020-J081-431

Anon 2011

Trial name or title	A study of E2020 in patients with dementia with Lewy bodies (DLB), followed by a long-term extension phase - Phase III
Methods	RTC
Participants	N = 141 Country = Japan Duration = 52 weeks
Interventions	Donepezil (E2020), Dosage of drug, Placebo
Outcomes	Primary Outcome Measures: Change from baseline in Mini Mental State Examination and Neuropsychiatric Inventory after 12 weeks
Starting date	February 2011
Contact information	
Notes	Study ID(s) and Acronym(s): NCT01278407 // E2020-J081-341

Burn 2009

Trial name or title	Multi-centre UK study of the acetylcholinesterase inhibitor donepezil in early dementia associated with Parkinson's disease (MUSTARDD-PD)
Methods	- RCT - 1. Donepezil: Experimental - 5mg of Donepezil for the first 8 weeks raising to 10mg thereafter if patient adjusted to 5mg dose. 10mg does continues for the remainder of the study; 2. Placebo: Placebo Comparator - Patient commences medication to match appearance of 5mg donepezil for first 8 weeks then 10mg for the remainder of the study
Participants	N = 500 Country = UK Duration = 24 months
Interventions	Donepezil, Placebo
Outcomes	Primary Outcome Measures: To demonstrate the superiority of donepezil over placebo in improving cognitive function, neuropsychiatric burden and functional ability in people with Parkinson's disease and mild dementia after 24 months of treatment Secondary Outcome Measures: To demonstrate the superiority of donepezil over placebo in improving patient and carer quality of life and to establish the cost-effectiveness of donepezil
Starting date	March 2010
Contact information	
Notes	Study ID(s) and Acronym(s): NCT01014858 // MUSTARDD-PD // 5137 // 08/13/14

Kurlan 2003

Trial name or title	Treatment of agitation/psychosis in dementia/parkinsonism
Methods	
Participants	N = Unknown Country = USA Duration = Unknown
Interventions	Donepezil, Quetiapine, Dosage of drug
Outcomes	Unknown
Starting date	
Contact information	Kurlan R Treatment of agitation/psychosis in dementia/parkinsonism Alzheimer's Disease Education and Referral Center (ADEAR) 2003
Notes	

Marion 2003

Trial name or title	An open 24 week prospective, randomised, double-blind placebo controlled parallel group study of efficacy, tolerability and safety of 3-12mg/day of Exelon and Exelon (rivastigmine) capsules in patients with Parkinson's disease dementia
Methods	
Participants	N = 10 Country = UK Duration = 24 weeks
Interventions	Rivastigmine + Dosage of Drug + Placebos
Outcomes	Unclear
Starting date	
Contact information	Marie-Helene.Marion@stgeorges.nhs.uk
Notes	

DATA AND ANALYSES

Comparison 1. Global assessment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alzheimer's Disease Cooperative Study - Clinician's Global Impression of Change (ADCS-CGIC)	3	556	Std. Mean Difference (IV, Fixed, 95% CI)	-0.38 [-0.56, -0.20]
2 Clinical Global Responder - at least minimal improvement	3	785	Odds Ratio (M-H, Random, 95% CI)	2.26 [1.04, 4.91]

Comparison 2. Cognitive function

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mini Mental State Examination	5	699	Mean Difference (IV, Fixed, 95% CI)	1.08 [0.50, 1.66]
2 Alzheimer's Disease Assessment Scale (ADAS-cog)	3	1078	Mean Difference (IV, Fixed, 95% CI)	-2.72 [-3.61, -1.83]
3 Combined: MMSE or ADASCog	6	1249	Std. Mean Difference (IV, Random, 95% CI)	0.34 [0.23, 0.46]
4 Mattis Dementia Rating Scale (MDRS)	3	82	Mean Difference (IV, Fixed, 95% CI)	3.70 [-1.13, 8.54]
5 Cognitive Drug Research (CDR) computerised assessment system power of attention	1	486	Mean Difference (IV, Fixed, 95% CI)	-173.7 [-471.23, 123.83]
6 Delis-Kaplan Executive Function System (D-KEFS)	1	402	Mean Difference (IV, Fixed, 95% CI)	2.8 [1.47, 4.13]
7 Ten Point Clock Drawing Test	1	79	Mean Difference (IV, Fixed, 95% CI)	1.1 [-0.01, 2.21]
8 Brief Test of Attention (BTA)	1	16	Mean Difference (IV, Fixed, 95% CI)	1.65 [-0.82, 4.12]
9 Trail Making Test (TMT) A	1	16	Mean Difference (IV, Fixed, 95% CI)	-71.68 [-108.44, -34.92]
10 Trail Making Test (TMT) B	1	16	Mean Difference (IV, Fixed, 95% CI)	-87.24 [-202.89, 28.41]
11 Verbal Fluency Test	1	16	Mean Difference (IV, Fixed, 95% CI)	6.63 [-2.33, 15.59]
12 Hopkins Verbal Learning Test	1	16	Mean Difference (IV, Fixed, 95% CI)	1.72 [-2.93, 6.37]
13 Developmental Test of Visual-Motor Integration (VMI)	1	16	Mean Difference (IV, Fixed, 95% CI)	0.03 [-3.28, 3.34]

Comparison 3. Behavioural disturbance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 12-item Neuropsychiatric Inventory (NPI-12)	1	16	Mean Difference (IV, Fixed, 95% CI)	-3.3 [-13.75, 7.15]
2 10-item Neuropsychiatric Inventory (NPI-10)	2	620	Mean Difference (IV, Fixed, 95% CI)	-2.18 [-3.95, -0.40]
3 4-item Neuropsychiatric Inventory (NPI-4)	1	120	Mean Difference (IV, Fixed, 95% CI)	-1.66 [-4.34, 1.02]
4 Brief Psychiatric Rating Scale	1	38	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-5.89, 5.29]
5 Combined	4	674	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.36, -0.04]
5.1 12-item Neuropsychiatric Inventory (NPI-12)	1	16	Std. Mean Difference (IV, Fixed, 95% CI)	-0.29 [-1.29, 0.70]
5.2 10-item Neuropsychiatric Inventory (NPI-10)	2	620	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.37, -0.04]
5.3 Brief Psychiatric Rating Scale	1	38	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.67, 0.60]

Comparison 4. Activities of daily living

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)	1	498	Mean Difference (IV, Fixed, 95% CI)	2.5 [0.43, 4.57]
2 Unified Parkinson's Disease Rating Scale (UPDRS) - Activities of Daily Living	1	16	Mean Difference (IV, Fixed, 95% CI)	0.84 [-6.24, 7.92]
3 Combined	2	514	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.38, -0.02]
3.1 Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)	1	498	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.40, -0.02]
3.2 Unified Parkinson's Disease Rating Scale (UPDRS) - Activities of Daily Living	1	16	Std. Mean Difference (IV, Fixed, 95% CI)	0.11 [-0.88, 1.10]

Comparison 5. Safety and tolerability

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropouts	5	744	Odds Ratio (M-H, Fixed, 95% CI)	1.94 [1.33, 2.84]
2 Dropouts due to Adverse Events	3	677	Odds Ratio (M-H, Fixed, 95% CI)	2.12 [1.27, 3.55]
3 Adverse Events	6	1294	Odds Ratio (M-H, Fixed, 95% CI)	1.64 [1.26, 2.15]
4 Severe Adverse Events	2	146	Odds Ratio (M-H, Fixed, 95% CI)	1.60 [0.68, 3.81]
5 Parkinsonian symptoms reported as adverse effects	2	1091	Odds Ratio (M-H, Fixed, 95% CI)	1.88 [1.28, 2.75]
6 Tremor	2	1091	Odds Ratio (M-H, Fixed, 95% CI)	2.71 [1.44, 5.09]
7 Falls	2	1091	Odds Ratio (M-H, Fixed, 95% CI)	1.29 [0.72, 2.33]
8 Hallucinations	2	1091	Odds Ratio (M-H, Fixed, 95% CI)	0.64 [0.40, 1.02]
9 Unified Parkinson's Disease Rating Scale (UPDRS)	3	122	Std. Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.42, 0.29]
9.1 Motor	3	81	Std. Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.49, 0.39]
9.2 Total	1	41	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.72, 0.51]
10 Deaths	5	744	Odds Ratio (M-H, Fixed, 95% CI)	0.28 [0.09, 0.84]

ADDITIONAL TABLES

Table 1. Effect of cholinesterase inhibitors on dementia with Lewy bodies, Parkinson's disease dementia and cognitive impairment in Parkinson's disease

	Dementia with Lewy Bodies(DLB)	Parkinson's Disease with dementia (PDD)	Parkinson's Disease with dementia (PDD) and cognitive impairment in Parkinson's Disease (CIND-PD)	Pooled results for DLB/PDD/CIND-PD
Global Assessment	N/A	**Favours treatment** (SMD -0.38, 95% CI -0.56, -0.24, P<0.00001)	N/A	N/A
Cognitive Function	**No effect** (SMD -0.29, 95% CI -0.65, 0.07, P=0.12)	**Favours treatment** (SMD -0.36, 95% CI -0.48, -0.23, P<0.00001)	**Favours treatment** (SMD -0.36, 95% CI -0.48, -0.23, P<0.00001)	**Favours treatment** (SMD -0.34, 95% CI -0.46, -0.23, P<0.00001)
Behavioural Disturbance	**No effect** (SMD -0.24, 95% CI -0.60, 0.12, P=0.19)	**Favours treatment** (SMD -0.18, 95% CI -0.36, -0.01, P=0.04)	**Favours treatment** (SMD -0.19, 95% CI -0.36, -0.01, P=0.04)	**Favours treatment** (SMD -0.20, 95% CI -0.36, -0.04, P=0.01)
Activities of Daily Living	N/A	**Favours treatment** (SMD -0.21, 95% CI -0.40, -0.02, P=0.03)	**Favours treatment** (SMD -0.20, 95% CI -0.39, -0.02, P=0.03)	N/A

WHAT'S NEW

Last assessed as up-to-date: 30 August 2011.

Date	Event	Description
30 August 2011	Amended	A pre-publication search was performed for this review on 30 August 2011 to ensure the review was as up-to-date as possible before publication

HISTORY

Protocol first published: Issue 2, 2007

Review first published: Issue 3, 2012

Date	Event	Description
8 February 2007	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

MR extracted the data, did the analysis and wrote the current draft. CF and IM contributed to previous versions of the review and commented on the current draft. RM wrote the first draft of this new title, was responsible for design and contributed to data extraction, interpretation, analysis and redrafting.

DECLARATIONS OF INTEREST

RMcS has received financial support to attend conferences from Eisai, Shire and Novartis, all marketers of cholinesterase inhibitors, more than five years ago. Within the last two years, his institution has received funding for his activities as a local PL for a Novartis study of rivastigmine patch versus tablets in Parkinson's disease dementia.

SOURCES OF SUPPORT

Internal sources

- Oxfordshire and Buckinghamshire Mental Health Partnership NHS Trust, UK.
- Nuffield Department of Medicine, University of Oxford, UK.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Cholinesterase Inhibitors [adverse effects; *therapeutic use]; Cognition Disorders [*drug therapy; etiology]; Dementia [*drug therapy; etiology]; Indans [adverse effects; therapeutic use]; Lewy Body Disease [*drug therapy]; Neuroprotective Agents [adverse effects; therapeutic use]; Parkinson Disease [*complications]; Phenylcarbamates [adverse effects; therapeutic use]; Piperidines [adverse effects; therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans