Open access • Journal Article • DOI:10.1176/APPI.AJP.2015.14121582

Pharmacological Management of Lewy Body Dementia: A Systematic Review and Meta-Analysis — Source link

Chris Stinton, Ian G. McKeith, John-Paul Taylor, Louise Lafortune ...+6 more authors

Published on: 18 Jun 2015 - American Journal of Psychiatry (American Psychiatric AssociationArlington, VA)

Topics: Dementia with Lewy bodies, Lewy body, Dementia, Donepezil and Rivastigmine

Word count: 4975

Figures: 5

Tables: 0

Pharmacological management of Lewy body dementia: A systematic review and meta-analysis

Chris Stinton (PhD) Department of Psychiatry, University of Cambridge

Ian McKeith (FMedSci) Institute of Neuroscience, University of Newcastle

John-Paul Taylor (PhD) Institute of Neuroscience, University of Newcastle

Louise Lafortune (PhD) Department of Public Health and Primary Care, University of Cambridge

Eneida Mioshi (PhD) Department of Psychiatry, University of Cambridge

Elijah Mak (MSc) Department of Psychiatry, University of Cambridge

Victoria Cambridge (PhD) Department of Clinical Neurosciences, University of Cambridge

James Mason (DPhil) School of Medicine, Pharmacy and Health, University of Durham

Alan Thomas (PhD) Institute of Neuroscience, University of Newcastle

John T. O'Brien (DM) Department of Psychiatry, University of Cambridge

Correspondence to:

Dr Chris Stinton

Department of Psychiatry, University of Cambridge School of Clinical Medicine, Box 189, Level E4, Cambridge Biomedical Campus, Cambridge, England, CB2 2QQ

Study funding:

This article presents independent research funded by the National Institute for Health Research (NIHR) under its Programme Grants for Applied Research Programme (Reference Number DTC-RP-PG-0311-12001). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health.

Disclosure statement

Dr. Stinton reports no competing interests

Prof. McKeith has received speaker fees and research support from GE Healthcare

Dr. Taylor has received speaker fees from GE Healthcare and has consulted for Novartis

Dr. Lafortune reports no competing interests

Dr. Mioshi reports no competing interests

Mr. Mak reports no competing interests

Dr. Cambridge reports no competing interests

Prof. Mason reports no competing interests

Prof. Thomas has received research support from GE Healthcare

Prof. O'Brien has received speaker fees and research support from GE Healthcare and Avid/Lilly

Abstract

Objective: We examined effects, costs, and patient/carer views of pharmacological management strategies for Lewy body dementia. **Method:** Studies were identified through bibliographic databases, trials registers, grey literature, reference lists and experts. We searched the terms 'Lewy OR parkinson' AND 'dementia' until May 2015 using the following inclusion criteria: participant diagnoses of Lewy body dementia, dementia with Lewy bodies or Parkinson's disease dementia (or their carers); investigation of pharmacological management strategies; outcome measures and test scores reported. Data extraction and quality assessment were conducted by at least two authors. We undertook meta-analyses or provided summaries when studies could not be combined. **Results:** Forty-four studies were included in the review, examining 22 strategies. Meta-analysis indicated beneficial effects of donepezil and rivastigmine for cognitive and psychiatric symptoms. Rivastigmine, but not donepezil, was associated with greater risk of adverse events. Meta-analysis of memantine suggests it is well tolerated but with few benefits. Descriptive summaries provide some evidence for galantamine, modafinil, levodopa, rotigotine, clozapine, duloxetine, clonazepam, ramelteon, gabapentin, zonisamide, and yokukansan. Piracetam, amantadine, selegiline, olanzapine, quetiapine, risperidone, and citalopram do not appear to be effective. **Conclusions:** High level data regarding pharmacological strategies for managing Lewy body dementia is rare. Strategies for important areas of need in Lewy body dementia such as autonomic symptoms and carer burden have not been investigated, nor have the views of patients and carers about pharmacological strategies.

Introduction

Lewy body dementia is a common cause of degenerative dementia in older people, accounting for 3.2 – 15.4% of cases (1, 2). It is characterised by impairments and fluctuations in cognition, recurrent visual hallucinations, and motor features of parkinsonism. Other significant features include sleep disorders, depression, delusions, and autonomic dysfunction (3, 4). The term Lewy body dementia is used here to include two related disorders: dementia with Lewy bodies (DLB) and Parkinson's disease dementia (PDD). Comparisons suggest broad overlap clinically, though executive impairment, delusions, and hallucinations might be more common in DLB (5, 6). For diagnosis, PDD is applied when motor symptoms occur at least one year before dementia, and DLB when dementia precedes or is closely followed by motor symptoms (4).

While a range of pharmacological strategies are used in an attempt to ameliorate the symptoms of Lewy body dementia, and clinical guidelines have recommended cholinesterase inhibitors for cognitive and psychiatric symptoms, the current evidence for management options for the range of symptoms is limited and there remains no unified evidence-based management care pathway (7 – 10).

To develop effective approaches to care it is necessary to establish which strategies are effective and to determine whether DLB and PDD are amenable to the same treatments. In this paper we review pharmacological management strategies examining three questions: (1) what are their benefits, harms and costs in the disorders, (2) what views do patients and carers have of these strategies, (3) how, when and where should they be implemented?

Methods

The review protocol is registered at PROSPERO (registration number CRD42014007180, http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42014007180).

Search strategy

Studies were identified through bibliographic databases, trials registers and, grey literature (see published protocol for full details). Reference lists of relevant studies and previously systematic reviews were also examined and input sought from Lewy body dementia experts. We used the keywords “Lewy or parkinson” and “dementia”, conducting searches until May 2015, without restrictions on time or language.

Study selection

Titles and abstracts were screened independently by LL, EMa, EMi and CS, with non-English language papers screened by native speakers. Discrepancies were resolved through discussion between screeners. Potentially relevant studies were obtained in full and examined in detail by CS against the following criteria: (1) participants had a diagnosis of DLB, PDD, or Lewy body dementia (or were their carers), (2) studies examined pharmacological strategies, and (3) outcome measures and scores were specified. No restrictions were placed on study designs but opinion papers were excluded (see online supplementary figure S1 for study flowchart).

Data extraction

Data were extracted by EMi and CS and recorded in an Excel database. We collected information relating to participant demographics, selection criteria, study design, management strategies, outcome measures, adverse events, and withdrawals.

Data synthesis

Studies were grouped and analysed according to pharmacological strategy. For each strategy, studies of the highest level of evidence were included in the review. Classification of level of evidence was determined using guidelines from the Oxford Centre for Evidence-Based Medicine (11).

Methodological quality

Methodological quality was assessed by VC, EMi and CS using the Quality Assessment Tool for Quantitative Studies (QATQS, www.ephpp.ca/tools.html) (12). This tool examines selection bias, study design, confounders, blinding, data collection methods, withdrawals and dropouts. Domains are rated as weak, moderate or strong quality, which feed into an overall rating of study quality. Reliability and validity of the QATQS have been demonstrated (13). The tool was developed to assess quality across study designs, aiding consistency and clarity of reporting.

Statistical analysis

Meta-analysis was conducted using Revman 5.3 (Cochrane Collaboration, www.tech.cochrane.org/revman/download), employing the inverse variance method. Heterogeneity was assessed using chi-squared and I-squared (I^2) statistics and considered significant with chi-squared p value < .10 and I^2 > 40%. We employed random-effects

models when there was significant study heterogeneity and fixed-effect models when heterogeneity was not significant. Missing data were sought from study authors and estimated using methods outlined in the Cochrane Handbook for Systematic Reviews of Interventions if not obtainable (14). We estimated risk ratio with 95% confidence intervals (CI) for dichotomous outcomes and weighted mean difference or standardised mean difference with 95% CI for continuous outcomes. Descriptive summaries were provided when studies could not be combined.

Results

The titles and abstracts of 28,568 records were screened; 26,966 did not meet inclusion criteria. Assessment of 633 full articles was conducted; 197 met our inclusion criteria and 44 were included as the highest level of evidence for 22 pharmacological strategies (see online supplementary table S1 for characteristics of included studies).

MANAGEMENT STRATEGIES

Donepezil and Rivastigmine

Data from studies of donepezil and rivastigmine were combined and examined using meta-analysis to obtain an estimate of their combined and separate effects (no randomised controlled trials were identified for galantamine; discussed later). The highest level of evidence for donepezil was randomised controlled trials, two for DLB and four for PDD (15-20); for rivastigmine there was one randomised controlled trial each for DLB and PDD (21-22). The highest level of evidence of donepezil for visual hallucinations (a key symptom of Lewy body dementia) was an uncontrolled trial (23). The highest level of evidence for withdrawal of donepezil was an open label study (24). We identified three ongoing studies

examining donepezil for cognition, psychiatric symptoms, and functional ability (clinicaltrials.gov, trial numbers: NCT00776347, NCT01014858 umin.ac.jp, trial number: UMIN000010752, and one study to develop a predictive test to identify which cholinergic medication should be prescribed first (clinicaltrials.gov, trial number: NCT01944436).

Five studies examined clinician impression of change of global outcomes; four trials examined improvement figure 1a) (15 – 17, 22), three examined absence of deterioration (figure 1b) (15, 17, 22), and four trials examined impression of change as a continuous outcome measure (16, 17, 19, 22) (see online supplementary figure S2a). Scores were estimated for one trial (15). Analysis of improvement data indicated that participants treated with cholinesterase inhibitors were more frequently rated as improved than those receiving placebos (45% vs 34%; risk ratio 1.37, 95% CI 1.15, 1.62). Subgroup analyses indicated that compared to placebo improvement was more likely for donepezil in DLB (64% vs. 33%, risk ratio 1.93, 95% CI 1.08, 3.43) and PDD (49% vs. 38%, risk ratio 1.29, 95% CI 1.02, 1.63), and rivastigmine in PDD (40% vs. 29%, risk ratio 1.37, 95% CI 1.05, 1.79). Analysis of absence of deterioration data indicated that participants treated with cholinesterase inhibitors were more frequently rated as not deteriorating than those receiving placebos (71% vs 62%; risk ratio 1.26, 95% CI 1.01, 1.57), but with considerable heterogeneity (I^2 = 76%). Subgroup analyses indicated that absence of deterioration was more common in participants with DLB treated with donepezil (96% vs. 50%, risk ratio 1.93, 95% CI 1.34, 2.78), but with no between group difference in PDD for donepezil (p = 0.18) or rivastigmine (p = 0.07). Analysis of continuous data indicated that mean change scores were 0.55 points lower (suggesting improvements) in participants treated with cholinesterase inhibitors (95% CI -0.82, -0.28), but with significant heterogeneity (I^2 = 52%). Subgroup analysis indicated benefits of

donepezil in DLB (weighted mean difference -1.13, 95% CI -1.66, -0.60) and PDD (weighted mean difference -0.37, 95% CI -0.60, -0.14), and rivastigmine in PDD (weighted mean difference -0.50, 95% CI -0.77, -0.23).

Eight studies assessed cognition using the MMSE (15 – 22) (figure 1c). Standard deviations (SD) were estimated in three trials (17, 18, 21). Mean change scores were 1.26 points higher (suggesting improvements) in participants receiving cholinesterase inhibitors (95% CI 0.66, 1.86). In subgroup analysis benefits were seen for donepezil in DLB (weighted mean difference 1.93, 95% CI 1.01, 2.85) and rivastigmine in PDD (weighted mean difference 1.00, 95% CI 0.33, 1.67), but not for rivastigmine in DLB (p = 0.11) or donepezil in PDD p = 0.52).

Six studies used the Neuropsychiatric Inventory (NPI-10) to assess psychiatric symptoms (15, 17, 18, 20 - 22) (figure 1d). SD were estimated in two trials (17, 18). There were no significant between group differences (p = 0.46), but significant heterogeneity (i^2 = 79%). Subgroup analyses indicated benefits on total psychiatric symptoms in PDD of donepezil (weighted mean difference -1.17, 95% CI –2.26, -0.08) and rivastigmine (weighted mean difference -2.00, 95% CI -3.91, -0.09), but not for donepezil (p = 0.52) or rivastigmine (p = 0.17) in DLB. Two studies assessed psychiatric symptoms in DLB using the NPI-4 (the sum of scores of apathy, delusions, depression, and hallucinations) (15, 21). A significant effect, favouring cholinesterase inhibitors, was observed (weighted mean difference -3.36, 95% CI -8.63, -0.97). Subgroup analysis indicated a benefit for participants receiving donepezil (weighted mean difference -4.80, 95% CI -8.63, -0.97) but not rivastigmine (p = 0.17) (see online supplementary figure S2b). Generally, subscales scores for the NPI have not been reported. McKeith and colleagues and Mori and colleagues presented these graphically.

From 95% CI, rivastigmine does not appear to have beneficial effects on subscale items in DLB, but donepezil may be beneficial for delusions, hallucinations, and cognitive fluctuations. In PDD, donepezil was not beneficial in the treatment of hallucinations, hostility, suspiciousness, or unusual thought content (19). In an uncontrolled trial examining donepezil for hallucinations in DLB (n = 13), scores were 4.6 points lower on the BEHAVE-AD following treatment, suggesting improvements (23).

Three studies investigated activities of daily living in PDD using the Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory**,** Disability Assessment for Dementia**,** and Unified Parkinson's Disease Rating Scale – Activities of Daily Living (17, 18, 22) (see online supplementary figure S2c). SD were estimated in two trials (17, 18). A significant effect of cholinesterase inhibitors was observed (standardised mean difference 0.2, 95% CI 0.07, 0.34), with subgroup analysis indicating a benefit of rivastigmine (standardised mean difference 0.20, 95% CI 0.02, 0.40), but not donepezil (p = 0.06).

Eight studies reported adverse events and withdrawals (15 – 22; see online supplementary material S2d + e). Adverse events were more common in participants treated with cholinesterase inhibitors (80% vs 70%, risk ratio 1.13, 95% CI 1.06, 1.21). Subgroup analysis indicated a greater risk ratio in DLB (91% vs. 75%, risk ratio 1.21, 95% CI 1.03, 1.43) and PDD (83% vs. 70%, risk ratio 1.18, 95% CI 1.06, 1.31) for rivastigmine, but not for donepezil in DLB (p = 0.25) or PDD (p = 0.31). Adverse events reported more frequently in treatment than placebo groups were nausea (rivastigmine: DLB and PDD; donepezil: PDD), vomiting (rivastigmine: DLB and PDD), anorexia (rivastigmine: DLB), tremor (rivastigmine: PDD), somnolence (rivastigmine: DLB), dizziness (rivastigmine: PDD), and insomnia (donepezil:

PDD). Further, 25% of participants treated with cholinesterase inhibitors withdrew from studies compared to 17% of those receiving placebos (risk ratio 1.47, 95% CI 1.16, 1.85). Subgroup analysis indicated that the risk was significantly greater for participants with PDD treated with donepezil (23% vs. 15%, risk ratio 1.51, 95% CI 1.03, 2.23) and rivastigmine (27% vs. 17%, risk ratio 1.55, 95% CI 1.22, 1.97) but not for participants with DLB treated with donepezil (p = 0.68) or rivastigmine (p = 0.08). There were no between group differences in motor function (weighted mean difference -1.67, 95% CI -4.02, 0.69), as assessed by four studies using the Unified Parkinson's Disease Rating Scale -III (15, 16, 18, 19) (see online supplementary figure S2f), with SD estimated in one trial (18).

++ Figure 1 ++

Results of an uncontrolled trial suggest that sudden withdrawal of cholinesterase inhibitors might be associated with deteriorations in cognition in DLB and PDD (MMSE: -4.4 and -3.5 points, respectively), and increased psychiatric symptoms (NPI change = 22) for PDD (24).

Galantamine

The highest level of evidence for galantamine was an uncontrolled trial in DLB and a controlled trial in PDD (25, 26). In DLB (n = 50), improvements were reported for cognitive fluctuations (1-day fluctuations scale change = -1.8), sleep disturbances (Pittsburgh Sleep Quality Index change = -3.2), and psychiatric symptoms (NPI change = -8.2) (25). Inconsistent results were reported for cognition. In PDD (galantamine n = 21, treatment as usual n = 20) improvements were reported for cognition (MMSE change difference = 4.9), total psychiatric symptoms (NPI change difference = 8.9), hallucinations (NPI hallucinations change difference

= 4.1), anxiety (NPI anxiety change difference = 0.7), apathy (NPI apathy change difference = 3.9), and sleep (NPI sleep change difference = 1.4), that favoured treatment with galantamine (26).

Memantine

The highest level of evidence for memantine was one randomised controlled trial for PDD and two for mixed DLB and PDD samples (26-28). Three studies examined clinician impression of change; three examined improvement (figure 2a) (27 - 29), two absence of deterioration (27, 29) (see online supplementary figure S3a), and two continuous data see online supplementary figure S3b (27, 29). There were no between group differences for improvement (p = 0.09) or absence of deterioration (p = 0.07). Analysis of continuous data indicated mean change scores were significantly lower (0.40 points) in participants treated with memantine (95% CI -0.71, -0.10), suggesting improvements. Subgroup analysis indicated that this difference was significant for DLB (weighted mean difference -0.60, 95% CI -1.16, -0.04) but not PDD (p = 0.34).

Two studies assessed cognition using the MMSE (28, 29) (see online supplementary figure S3c, indicating no between group differences (p = 0.52). Three studies used the NPI to assess psychiatric symptoms (27 - 29) (see online supplementary figure S3d), with SD estimated in two trials (27, 28). There were no between group differences (p = 20). The effect of memantine on activities of daily living was investigated in two studies, one using the Alzheimer's Disease Co-operative Study - Activities of Daily Living Inventory and one the Disability Assessment for Dementia (see online supplementary figure S3e) (27, 28). There were no between group differences (p = 0.30). Three trials reported adverse events (see

online supplementary figure S3f) and withdrawals (see online supplementary figure S3g) (27 - 29). There were no between group differences for adverse events (p = 0.94) or withdrawals (p = 0.68). Further, there was no difference between the groups on the Unified Parkinson's Disease Rating Scale -III (p = 0.34) (see online supplementary S3h).

++ Figure 2 ++

Armodafinil/modafinil

The highest level of evidence for armodafinil was an uncontrolled trial (sleep) and a case series (global impression) in DLB, a case series (global impression) in PDD, and an uncontrolled trial (attention) in Lewy body dementia (30, 31). Results for DLB (n = 17) suggest that treatment with armodafinil is associated with increased wakefulness (30). Data from self-reports and computer-based reaction tasks in Lewy body dementia (n = 7) suggest improvements in subjective alertness and reflexive attention (31). In a retrospective review of treatment with modafinil or armodafinil (DLB n = 2, PDD n = 4) 50% of individuals were rated by clinicians as minimally improved, 33% as much improved and 17% as not improved (31).

Piracetam

The highest level of evidence for piracetam in PDD was a randomised controlled trial (n = 20) (32). No between group differences were observed in terms of cognition, motor function, or functional ability, except on a single subscale (engagement in recreational activities) which favoured the piracetam group. No studies of piracetam for DLB were identified.

Discontinued drugs

A small number of studies of metrifonate and tacrine were identified in our search. These drugs have been discontinued and are not discussed here.

Antiparkinsonian medications

Levodopa

The highest level of evidence for levodopa in DLB and PDD was four uncontrolled trials (33 - 36). The highest level of evidence for levodopa withdrawal in PDD was a randomised controlled trial (37). Examinations of acute and chronic effects of levodopa suggest improvements in motor functioning and reductions in tremor for individuals with DLB and PDD (33 - 35). Beneficial effects of levodopa (i.e. 10% or more improvement in Unified Parkinson's Disease Rating Scale -III score) were more common in PDD (65 – 70%) than DLB (32 – 50%) (33, 34, 36), though approximately one third of those who derive motor benefits experienced increases in psychotic symptoms (34).

A randomised controlled trial examined withdrawal of levodopa in PDD (n = 11) showing that removing levodopa did not result in worsening cognition, motor functioning or psychiatric symptoms (37).

Amantadine

The highest level of evidence for amantadine in PDD was an uncontrolled trial (PDD n = 10, Parkinson's disease and cognitive impairment n = 15) (38). For participants with dementia, no significant effects of amantadine were observed on 13 out of 15 cognitive tests. Statistically significant improvements were observed on total Frontal Assessment Battery

score (3 points) and the Inhibitory Control subscale (0.3 points). No studies of amantadine for DLB were identified.

Rotigotine

The highest levels of evidence for rotigotine in PDD were one uncontrolled trial (Parkinson's disease severity) and one case series (anxiety) (39, 40). Degree of disability due to Parkinson's disease (n = 9) and anxiety (n = 2) were rated as less severe after treatment (Unified Parkinson's Disease Rating Scale change = -12; Hamilton Anxiety Rating Scale change = -23). No studies of rotigotine for DLB were identified.

Selegiline

The highest level of evidence for selegiline in Parkinson's disease dementia was a cohort study (PDD n = 4, Parkinson's disease without dementia = 3) (41). No beneficial effects were observed for participants with dementia on measures of behaviour, cognition and motor function. No studies of selegiline for DLB were identified.

Antipsychotics

Clozapine

The highest level of evidence for clozapine in PDD was a chart review (PDD n = 8, 'other dementia' n = 8) (42). Scores on the Brief Agitation Rating Scale (-2.4) and Cohen-Mansfield Agitation Inventory (- 4.2) were significantly lower in the PDD group after treatment, with 62.5% of patients rated as much improved. Side effects included drooling, sedation, tremors, constipation and delirium. No studies of clozapine for DLB were identified.

Olanzapine

The highest level of evidence for olanzapine was a secondary analysis of a randomised controlled trial of Alzheimer's disease, with participants retrospectively identified as meeting DLB criteria, and an uncontrolled trial in PDD (43, 44). In participants with possible DLB (n = 29), those treated with 5mg (n = 10) of olanzapine showed greater reductions in scores on the NPI subscales of delusions (-3.8 points) and hallucinations (-5.9 points) than those receiving placebo (n = 10). No significant differences were observed between placebo, 10mg and 15mg groups (43). While no side effects were reported in this study, other authors have suggested that around 38% of people with DLB do not tolerate olanzapine even at low doses (2.5mg) (45). In a sample of participants with PDD (n = 3), reductions in NPI delusion (-3.2 points), NPI hallucination (-0.97) and total psychiatric symptoms (NPI: - 15.1 points, Behavioural Pathology in Alzheimer's Disease: -15 points) have been reported (44). Worsening of motor functioning and psychiatric symptoms are reported in 33 – 80% of individuals with PDD following olanzapine treatment (44, 46).

Quetiapine

The highest level of evidence for quetiapine was a case series in DLB, a retrospective chart review in PDD, and a randomised controlled trial in Lewy body dementia (47 - 49). Reductions in psychiatric symptoms were reported for 6 out of 9 individuals with DLB following treatment with quetiapine (change in sum of NPI delusions + hallucinations + agitation/aggression = 7.7) (47). However, 33% of participants withdrew due to adverse events. For individuals with PDD and drug-induced psychosis, quetiapine was associated with worsening cognition and motor functioning without improvements to psychiatric status (48). A randomised controlled trial of Lewy body dementia (DLB n = 23, PDD n = 9,

Alzheimer's disease with parkinsonian features n = 8) revealed no between group differences on measures of psychiatric symptoms, cognition, activities of daily living, motor function or clinician's impression of change (49).

Risperidone

The highest level of evidence for risperidone was a randomised trial in DLB and an uncontrolled trial in Parkinson's disease dementia (50, 51). In participants with PDD and psychosis (n = 9) significant reductions were observed on the total score of the Brief Psychiatric Rating Scale (-9.5 points) and Cohen-Mansfield Agitation Inventory (-9.6 points), and improvements in social, occupational and psychological functioning (Global Assessment of Functioning change = 17 points) (50). No side effects were reported. In DLB, risperidone does not appear to be well tolerated; results of a randomised controlled trial (n = 31) suggest deterioration in cognition (MMSE change = -2.3 points), worsening psychiatric symptoms (NPI change = 17.3 points) and study withdrawal (65%) (51).

Antidepressants

Citalopram/escitalopram, duloxetine and trazodone

The highest level of evidence for antidepressants was a randomised trial of citalopram in DLB (51) and an unpublished trial of duloxetine, escitalopram, and trazodone in PDD (52).Citalopram does not appear to be efficacious or well tolerated in DLB, with 10 out of 14 participants (71.4%) withdrawing due to adverse effects (51). In a trial of antidepressants for depression in PDD, participants treated with duloxetine (n = 8) experienced reductions in total Montgomery Asberg Depression Rating Scale score (-18.6 points) (52). Individuals

receiving escitalopram, (n = 7) and trazodone (n = 8) were reported to have reductions in depressive symptoms, but scores were not provided.

Sedatives

Clonazepam

The highest level of evidence for clonazepam in DLB was a case series in which two out of three participants experienced reductions in the number of nights on which episodes of sleep disturbance occurred (53). No studies of clonazepam for PDD were identified.

Ramelteon

The highest level of evidence for ramelteon in DLB was a case series (54). Descriptive statistics indicated reductions in neuropsychiatric symptoms, sleep disturbances and self-reported carer burden, with no adverse effects. No studies of ramelteon for PDD were identified.

Anticonvulsants

Gabapentin

The highest level of evidence for gabapentin was case reports, one for DLB (55) and one for PDD (56). Following treatment, reductions were reported in symptoms of restless leg syndrome (DLB) and agitation (PDD).

Zonisamide

The highest levels of evidence for zonisamide were case series for DLB (57) and PDD (58). Descriptive reports of DLB (n = 3) suggest improvements in daily living skills, motor, and

carer burden in mild dementia and a reduction in psychiatric symptoms in severe dementia (57). Similar results were reported in a single case of PDD (58). Randomised controlled trials of zonisamide for motor function (clinicaltrials.jp, trial number: JapicCTI-122040) and psychiatric symptoms (umin.ac.jp, trial number: UMIN000010631) are currently underway.

Herbal medicines

Yokukansan

The highest level of evidence for yokukansan was a randomised crossover trial in DLB and an uncontrolled trial in PDD (59, 60). In participants with DLB randomised to receive yokukansan followed by no treatment (group A, n = 9) or no treatment followed by yokukansan (group B, n = 6) reductions were reported in psychiatric symptoms in both groups (NPI change Group A = -10.1 points; Group B = -12.4 points); this was statistically significance in group A only (59). In a trial of participants with PDD (n = 7) there were significant difference in pre- and post-treatment scores for total psychiatric symptoms (-6 points) and visual hallucinations (-2.6 points), but no differences on any other NPI subscales (60).

PATIENT AND CARER VIEWS OF MANAGEMENT STRATEGIES

No studies were identified that examined the views of patients/carers about pharmacological strategies for Lewy body dementia.

COST-EFFECTIVENESS ANALYSIS

Two studies reported economic data (61, 62). Estimates of cost per quality of life year gained from treatment with cholinesterase inhibitors in Alzheimer's disease and DLB suggested

lower costs in the DLB group (61). However, in the DLB group there was considerable variability in the estimates of three models (micro-simulation = £2,706, Markov = £35,922, Southampton Health Technology Assessment Centre = £46,794). In a study of rivastigmine for PDD, no significant between group differences were reported for quality-adjusted life days or total costs (62).

Discussion

We conducted a systematic review of pharmacological strategies for Lewy body dementia, identifying 28,568 potentially relevant papers. Forty-four papers were included, examining 22 pharmacological strategies. High level evidence was rare, with only 17 randomised controlled trials. Methodological quality was rated as weak for 41% of included studies, moderate for 39%, and strong for 20%.

Data from controlled trials were available for donepezil, rivastigmine, galantamine, memantine, olanzapine, risperidone, piracetam, quetiapine, citalopram, and yokukansan. Meta-analyses indicated improvements with donepezil and rivastigmine for cognition, global psychiatric symptoms (PDD only), hallucinations, delusions, and activities of daily living (without worsening motor symptoms of parkinsonism) but with adverse events. This is consistent with prior reviews of cholinesterase inhibitors for Lewy body dementia (7, 9). Evidence for galantamine suggests potential benefits for psychiatric symptoms and possibly cognition, but data are limited. Memantine appears to be well tolerated, but with few benefits to participants. Consistent with previous meta-analyses, memantine was only superior to placebo in terms of impression of change when analysed as a continuous outcome measure; this advantage was not observed when analysed as categorical data in

terms of improvement or absence of deterioration. Recently published secondary analyses of memantine suggest some statistical advantages of memantine over placebo in relation to aspects of attention, sleep, carer burden, aspects of quality of life, and goal attainment (63 - 66). For olanzapine and quetiapine, reductions in psychiatric symptoms appear limited by high levels of adverse events. Citalopram, piracetam, and risperidone do not appear to be beneficial. Data regarding yokukansan for psychiatric symptoms is mixed.

There was weak evidence for potential efficacy of armodafinil/modafinil, levodopa, zonisamide, ramelteon, clonazepam, gabapentin, rotigotine, duloxetine, escitalopram, trazodone, and clozapine. These studies did not include controls so we can only conclude that there could be an association between interventions and benefits to participants. Amantadine and selegiline do not appear to be effective for managing symptoms of Lewy body dementia, but data are available from only single trials and/or small samples. Overall, we must be cautious not to overstate the apparent effects/lack of effects given how few high levels studies are available for each strategy.

Limited data are available about costs of pharmacological strategies. We identified two studies indicating that donepezil and rivastigmine might not be cost effective as treatment costs are not significantly different compared to placebo groups, and estimates are typically above the threshold of £30,000 per QALY for treatment, a cut-off often considered cost-effective. However, patents on these drugs have since expired and cheaper generic versions are now available.

Associations between strategy efficacy and participant characteristics have rarely been investigated. To date, only a small number of studies has investigated associations between treatment efficacy and participant characteristics. Results, which must be treated with caution, suggest a better response to levodopa for younger participants with DLB (36), a greater benefit from rivastigmine for cognition (global cognition, attention) in those who hallucinate (67, 68), and that participants with elevated plasma homocysteine experience a greater benefit of rivastigmine on aspects of cognition and global neuropsychiatric symptoms (69). In general, there is insufficient evidence about how, when and where management strategies should be implemented.

Differing treatment effects between DLB and PDD have received little attention, but some differences are apparent. For example, benefits of quetiapine on psychiatric symptoms for some people with DLB compared to a general lack of efficacy and adverse effects in PDD (47, 48), while levodopa appears to be more beneficial for PDD than DLB (36). Our meta-analyses suggest that the effects of donepezil and rivastigmine are comparable for DLB and PDD. Other studies suggest similar effects of donepezil in both groups (70). Overall, a lack of direct comparison hampers our ability to clarify differences in treatment effects. An additional caveat is the uncertainty about whether DLB and PDD are separate diseases; the one-year rule for distinguishing the diagnoses is provided only as a guide for clinical practice (4).

A notable outcome from our review is a potential disconnect between research trials and the reality of clinical practice and patients/carers preferences. For example, patient-related outcome and symptom-specific measures were rarely used, and apparent benefits of strategies were typically determined on the basis of statistical rather than clinical

significance. Further, no studies were identified concerning the views that people with Lewy body dementia /their carers have of management strategies. Future research that focuses on areas of need reported by people with Lewy body dementia and their families may provide useful information about which strategies to employ.

This review has a number of limitations. First, the evidence-base is small. Even for the most well researched management strategies there were few randomised controlled trials. Second, there was a range of issues relating to risks of bias and study quality including open label study designs, no control groups, small samples (which might affect the power of studies to detect differences), and concurrent use of medications that might obscured the effects of study drugs. Furthermore, the accuracy of diagnostic criteria for DLB and PDD is not clear, with diagnoses in some cases applied retrospectively (43). Third, research into the management strategies for Lewy body dementia has usually taken the form of efficacy studies. While these are important in establishing therapeutic effects under highly controlled circumstances, the results are not necessarily generalisable to clinical practice. For example, in research trials samples are often homogeneous, interventions are standardised without scope for flexibility, concurrent treatments or co-morbid conditions are not allowed, and those with more severe difficulties might be less likely to participate/be recruited. Effectiveness studies provide a way to address some of these concerns. Fifth, it was necessary to estimate missing information for our meta-analyses as we were not able to obtain original data from study authors. Sixth, studies of management strategies that are used in clinical practice, and have been recommended in expert opinion reviews, were not included as data for DLB/PDD groups were not available. For example, in Parkinson's disease

there is evidence from randomised controlled trials that pimavanserin and clozapine might be useful in treating psychotic symptoms in people with lower cognition (71).

Concluding remarks

In this comprehensive review of pharmacological strategies for DLB and PDD we have identified the current best evidence for many key areas of need. There remain substantial gaps in our knowledge of patient and carer experiences, cost effectiveness, how, when and with whom strategies should be implemented, and about how meaningfully the results of studies translate to clinical practice.

Acknowledgements

This work was supported by the NIHR Biomedical Research Unit in Dementia and the Biomedical Research Centre awarded to Cambridge University Hospitals NHS Foundation Trust and the University of Cambridge, and the NIHR Biomedical Research Unit in Lewy body dementia and Biomedical Research Centre awarded to Newcastle upon Tyne Hospitals NHS Foundation Trust and Newcastle University.

We would like to thank Isla Kuhn (Cambridge University, England) for her help in developing the protocol for the review and Keshani Jayaweera (Sydney University, Australia) for her assistance in screening abstracts and titles.

References

1. Aarsland D, Zaccai J Brayne C. A Systematic Review of Prevalence Studies of Dementia in Parkinson's Disease. Mov Disord 2005; 1255-1263.

2. Vann Jones SA, O'Brien JT. The prevalence and incidence of dementia with Lewy bodies: a systematic review of population and clinical studies. Psychol Med 2014; 44: 673–83.

3. Emre M, Aarsland D, Brown R, Burn DJ, Duyckaerts C., Mizuno Y, Broe GA, Cummings J, Dickson DW, Gauthier S, Goldman J, Goetz C, Korczyn A, Lees A, Levy R, Litvan I, McKeith I, Olanow W, Poewe W, Quinn N, Sampaio C, Tolosa E, Dubois B. Clinical Diagnostic Criteria for Dementia Associated with Parkinson's Disease. Mov Disord 2007; 22: 1689–1707.

4. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, Cummings J, Duda JE, Lippa C, Perry EK, Aarsland D, Arai H, Ballard CG, Boeve B, Burn DJ, Costa D, Del Ser T, Dubois B, Galasko D, Gauthier S, Goetz CG, Gomez-Tortosa E, Halliday G, Hansen LA, Hardy J, Iwatsubo T, Kalaria RN, Kaufer D, Kenny RA, Korczyn A, Kosaka K, Lee VM, Lees A, Litvan I, Londos E, Lopez OL, Minoshima S, Mizuno Y, Molina JA, Mukaetova-Ladinska EB, Pasquier F, Perry RH, Schulz JB, Trojanowski JQ, Yamada M. Diagnosis and management of dementia with Lewy bodies: Third report of the dementia with Lewy bodies Consortium. Neurology 2005; 65: 1863–1872.

5. Noe E, Marder K, Bell KL. Comparison of Dementia With Lewy Bodies to Alzheimer's Disease and Parkinson's Disease With Dementia. Mov Disord 2004; 19: 60–67.

6. Downes JJ, Priestley NM, Doran M, Ferran J, Ghadiali E, Cooper P. Intellectual, mnemonic, and frontal functions in dementia with Lewy bodies: a comparison with early and advanced Parkinson's disease. Behav Neurol 1998; 11: 173–183.

7. 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 Syst Rev 2012; 3.

8. Matsunaga S, Kishi T. Iwata N. Memantine for Lewy Body Disorders: Systematic Review and Meta-Analysis. Am J Geriatr Psychiatry 2013; Epub.

9. Wang H, Yu J, Tang S. Jiang T, Tan CC, Meng XF, Wang C, Tan MS, Tan L. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. J Neurol Neurosurg Psychiatry 2014; Epub.

10. NICE–SCIE. Guideline on Supporting People with Dementia and Their Carers in Health and Social Care, National Clinical Practice Guideline Number 42 (internet). 2011 (cited 2014 Nov 1). Available from http://www.scie.org.uk/publications/misc/dementia/dementia-guideline.pdf.

11. OCEBM Levels of Evidence Working Group. The Oxford 2011 Levels of Evidence. Oxford Centre for Evidence-Based Medicine. (cited 2013 Dec 1). Available from http://www.cebm.net/index.aspx?o=5653.

12. Thomas, BH, Ciliska, D, Dobbins, M, Micucci, S. A process for systematically reviewing the literature: Providing the research evidence for public health nursing interventions. Worldviews Evid Based Nurs 2004; 1: 176–184.

13. Armijo-Olivo S, Stiles CR, Hagen NA, Biondo PD, Cummings GG. Assessment of study quality for systematic reviews: a comparison of the Cochrane Collaboration Risk of Bias Tool and the Effective Public Health Practice Project Quality Assessment Tool: methodological research. J Eval Clin Pract 2012; 18: 12–18.

14. Julian PT Higgins and Jonathan J Deeks. Selecting studies and collecting data. In: Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (updated March 2011). The Cochrane Collaboration 2011. Available from www.cochrane-handbook.org.

15. Mori E, Ikeda M, Kosaka K. Donepezil for Dementia with Lewy Bodies: A Randomized, Placebo-Controlled Trial. Ann Neurol 2012; 72: 41–52.

16. Aarsland D, Laake K, Larsen JP, Janvin C. Donepezil for cognitive impairment in Parkinson's disease: A randomised controlled study. J Neurol Neurosurg Psychiatry 2002; 72: 708–712.

17. Dubois B, Tolosa E, Katzenschlager R, Emre M, Lees AJ, Schumann G, Pourcher E, Gray J, Thomas G, Swartz J, Hsu T, Moline ML. Donepezil in Parkinson's disease dementia: A randomized, double-blind efficacy and safety study. Mov Disord 2012; 27: 1230–1238.

18. Leroi I, Brandt J, Reich SG, Grill S, Thompson R, Marsh L. Randomized placebo-controlled trial of donepezil in cognitive impairment in Parkinson's disease. Int J Geriatr Psychiatry 2004; 19: 1–8.

19. Ravina B, Putt M, Siderowf A, Farrar JT, Gillespie M, Crawley A, Fernandez HH, Trieschmann MM, Reichwein S, Simuni T. Donepezil for dementia in Parkinson's disease: A randomised, double blind, placebo controlled, crossover study. J Neurol Neurosurg Psychiatry 2005; 76: 934-939.

20. Ikeda M, Mori E, Matsuo K, Nakagawa M and Kosaka K. Donepezil for dementia with Lewy bodies: a randomized placebo-controlled, confirmatory phase III trial. Alzheimer's Research & Therapy 2015: 7:4.

21. McKeith I, Del Ser T, Spano P, Emre M, Wesnes K, Anand R, Cicin-Sain A, Ferrara R, Spiegel R. Efficacy of rivastigmine in dementia with Lewy bodies: A randomised, double-blind, placebo-controlled international study. Lancet 2000; 356: 2031–2036.

22. Emre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, Durif F, Kulisevsky J, van Laar T, Lees A, Poewe W, Robillard A, Rosa MM, Wolters E, Quarg P, Tekin S, Lane R.

Rivastigmine for dementia associated with Parkinson's disease. N Engl J Med 2004; 351: 2509– 2518.

23. Satoh M, Ishikawa H, Meguro K, Kasuya M, Ishii H, Yamaguchi S. Improved visual hallucination by donepezil and occipital glucose metabolism in dementia with Lewy bodies: The Osaki-Tajiri project. Eur Neurol 2010; 64: 337 - 344

24. Minett TS, Thomas A, Wilkinson LM, Daniel SL, Sanders J, Richardson J, Littlewood E, Myint P, Newby J, McKeith IG. What happens when donepezil is suddenly withdrawn? An open label trial in dementia with Lewy bodies and Parkinson's disease with dementia. Int J Geriatr Psychiatry 2003; 18: 988 – 993.

25. Edwards K, Royall D, Hershey L, Lichter D, Hake A, Farlow M, Pasquier F, Johnson S. Efficacy and safety of galantamine in patients with dementia with Lewy bodies: A 24-week open-label study. Dement Geriatr Cogn Disord 2007; 23: 401–405.

26. Litvinenko IV, Odinak MM, Mogil'naya VI, Emelin AY. Efficacy and safety of Galantamine (Reminyl) for dementia in patients with Parkinson's disease (an open controlled trial). *Zh Nevrol Psikhiatr Im S S Korsakova* 2007; 107: 25–33.

27. Emre M, Tsolaki M, Bonuccelli U, Destée A, Tolosa E, Kutzelnigg A, Ceballos-Baumann A, Zdravkovic S, Bladström A, Jones R. Memantine in patients with Parkinson's disease dementia or dementia with Lewy bodies: A double-blind, placebo-controlled, multicentre trial. Lancet Neurol 2009; 8: 613–618.

28. Leroi I, Overshott R, Byrne EJ, Daniel E, Burns A. Randomized controlled trial of memantine in dementia associated with Parkinson's disease. Mov Disord 2009: 24: 1217 – 40.

29. Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, Ceballos-Baumann A, Zdravkovic S, Bladström A, Jones R. Memantine in patients with Parkinson's

disease dementia or dementia with Lewy bodies: A double-blind, placebo-controlled, multicentre trial. Lancet Neurology 2009: 8; 613-618.

30. Boeve, B. Pilot Study of Armodafinil in Patients With Dementia With Lewy Bodies. (cited 01.04.2014) Available from http://www.clinicaltrials.gov/ct2/show/NCT01023672 2009.

31. Varanese S, Perfetti B, Gilbertwolf R, Thomas A, Onofrj M, Di Rocco A. Modafinil and armodafinil improve attention and global mental status in Lewy bodies disorders: Preliminary evidence. Int J Geriatr Psychiatry 2013; 28: 1095-1098.

32. Sano M, Stern Y, Marder K, Mayeux R. A controlled trial of piracetam in intellectually impaired patients with Parkinson's disease. *Mov Disord* 1990, 5, 230-234.

33. Bonelli SB, Ransmayr G, Steffelbauer M, Lukas T, Lampl C, Deibl, M. L-Dopa responsiveness in dementia with Lewy bodies, Parkinson disease and with and without dementia. Neurology 2004; 63: 376-378.

34. Goldman J, Goetz CG, Brandabur M, Sanfilippo M, Stebbins GT. Effects of dopaminergic medications on psychosis and motor function in dementia with Lewy bodies. Mov Disord 2008; 23: 2248-2250.

35. Onofrj M, Varanese S, Bonanni L, Taylor JP, Antonini A, Valente EM, Petrucci S, Stocchi F, Thomas A, Perfetti B. Cohort study of prevalence and phenomenology of tremor in dementia with Lewy bodies. J Neurol 2013; 260: 1731–1742.

36. Molloy S, McKeith IG, O'Brien JT, Burn DJ. The role of levodopa in the management of dementia with Lewy bodies. J Neurol Neurosurg Psychiatry 2005; 76: 1200–1203.

37. Tse W, Frisina PG, Hälbig TD, Gracies JM, Liang L, Tarshish C, Lesser G, Neufeld R, Koller WC, Libow LS. The effects of withdrawal of dopaminergic medication in nursing home patients with advanced parkinsonism. J Am Med Dir Assoc 2008; 9: 670-675.

38. Yablonskaya AY, Fedorova NV, Belgusheva ME. Effects of amantadine sulfate on cognitive impairments in patients with Parkinson's disease. Neurosci Behav Physiol 2010; 40: 149-155.

39. Strothjohann MH. Fuchs GA. Rotigotine and demented Parkinson's disease patients: A therapeutic option. Movement Disorder Society Fifteenth International Congress of Parkinson's Disease and *Movement* Disorders; 2011 June 5 – 9; Toronto, Ontario, Canada

40. Fanciulli A. Assogna F. Caltagirone C. Spalletta G. Pontieri FE. Rotigotine for anxiety during wearing-off in Parkinson's disease with dementia. Aging 2013; 25: 601-603.

41. Portin R, Rinne UK. The effect of deprenyl (selegiline) on cognition and emotion in parkinsonian patients undergoing long-term levodopa treatment. Acta Neurol Scand 1983; 93: 135–144.

42. Lee HB, Hanner JA, Yokley JL, Appleby B, Hurowitz L, Lyketsos CG. Clozapine for treatment-resistant agitation in dementia. J Geriatr Psychiatry Neurol 2007; 20: 178–182.

43. Cummings JL, Street J, Masterman D, Clark WS. Efficacy of olanzapine in the treatment of psychosis in dementia with Lewy bodies. Dement Geriatr Cogn Disord 2002; 13: 67-73.

44. Moretti R, Torre P, Antonello RM, Cazzato G, Griggio S, Bava A. Olanzapine as a treatment of neuropsychiatric disorders of Alzheimer's disease and other dementias: A 24-month follow-up of 68 patients. Am J Alzheimers Dis Other Demen 2003, 18, 205–214.

45. Walker Z, Grace J, Overshot R, Satarasinghe S, Swan A, Katona CL, McKeith IG. Olanzapine in dementia with Lewy bodies: a clinical study. Int J Geriat Psychiatry 1999; 14: 459-466

46. Marsh, L., Lyketsos, C., & Reich, S.G. (2001). Olanzapine for the treatment of psychosis in patients with Parkinson's disease and dementia. Psychosomatics *2001;* 42: 477-481.

47. Takahashi H, Yoshidaa K, Sugitab T, Higuchic H, Shimizua T. Quetiapine treatment of psychotic symptoms and aggressive behavior in patients with dementia with Lewy bodies: A case series. Prog Neuropsychopharmacol Biol Psychiatry 2003; 27: 549-553.

48. Prohorov T, Klein C, Miniovitz A, Dobronevsky E, Rabey JM. The effect of quetiapine in psychotic Parkinsonian patients with and without dementia: An open-labeled study utilizing a structured interview. J Neurol 2006; 253: 171-175.

49. Kurlan R, Cummings J, Raman R, Thal L. Quetiapine for agitation or psychosis in patients with dementia and parkinsonism. Neurology 2007; 68: 1356–1363.

50. Workman RH, Orengo CA, Bakey AA, Molinari VA, Kunik ME. The use of risperidone for psychosis and agitation in demented patients with Parkinson's disease. J Neuropsychiatry Clin Neurosci 1997; 9: 594–597.

51. Culo S, Mulsant BH, Rosen J, Mazumdar S, Blakesley RE, Houck PR, Pollock BG. Treating neuropsychiatric symptoms in dementia with Lewy bodies: A randomized controlled-trial. ADAD 2010; 24: 360-364.

52. Vasile D, Vasiliu O, Vasile ML, et al. The efficacy of psychopharmacologic treatment in depressive disorders associated with Parkinson’s disease dementia. 18th European Congress of Psychiatry; 2010 February 27 - March 2, 2010; Munich, Germany.

53. Massironi G, Galluzzi S, Frisoni GB. Drug treatment of REM sleep behaviour disorders in dementia with Lewy bodies. Int Psychogeriatr 2003; 15: 377–383.

54. Kasanuki K, Iseki E, Nishida Y, Fujishiro H, Chiba Y, Sato K, Arai H. Effectiveness of Ramelteon for treatment of visual hallucinations in dementia with Lewy bodies: A report of four cases. *J Clin Psychopharmacol* 2013; 33: 581–582.

55. Fujishiro H. Effects of gabapentin enacarbil on restless legs syndrome and leg pain in dementia with Lewy bodies. Psychogeriatrics 2014; 14: 132-134.

56. Hawkins JW, Tinklenberg JR, Sheikh JI, Peyser CE, Yesavage JA. A retrospective chart review of gabapentin for the treatment of aggressive and agitated behavior in patients with dementias. Am J Geriatr Psychiatry 2000; 8: 221-225.

57. Odawara T, Shiozaki K, Togo T, Hirayasu Y. Adminsitration of zonisamide in three cases of dementia in Lewy bodies. Psychiatry Clin Neurosci 2010; 64: 327-329.

58. Tombini M, Pellegrino G, Di Pino G, Assenza G. Zonisamide for seizures in Parkinson's disease with dementia. Seizure 2013; 22: 324–325.

59. Mizukami K, Asada T, Kinoshita T, Tanaka K, Sonohara K, Nakai R, Yamaguchi K, Hanyu H, Kanaya K, Takao T, Okada M, Kudo S, Kotoku H, Iwakiri M, Kurita H, Miyamura T, Kawasaki Y, Omori K, Shiozaki K, Odawara T, Suzuki T, Yamada S, Nakamura Y, Toba K. A randomized cross-over study of a traditional Japanese medicine (kampo), yokukansan, in the treatment of the behavioural and psychological symptoms of dementia. *Int J Neuropsychopharmacol* 2009; 12: 191-199.

60. Kawanabe T, Yoritaka A, Shimura H, Oizumi H, Tanaka S, Hattori N. Successful treatment with Yokukansan for behavioral and psychological symptoms of Parkinsonian dementia. Prog Neuropsychopharmacol Biol Psychiatry 2010; 34: 284–287.

61. Gustavsson A, Van Der Putt R, Jönsson L, McShane R. Economic evaluation of cholinesterase inhibitor therapy for dementia: Comparison of Alzheimer's disease and dementia with Lewy bodies. Int J Geriatr Psychiatry 2009; 24: 1072-1078.

62. Willan AR, Goeree R, Pullenayegum EM, McBurney C, Blackhouse G. Economic evaluation of rivastigmine in patients with Parkinson's disease dementia. Pharmacoeconomics 2006; 41: 93–106.

63. Larsson V, Aarsland D, Ballard C, Minthon L, Londos E. The effect of memantine on sleep behaviour in dementia. Int J Geriatr Psychiatry 2010; 25: 1030–1038.

64. Larsson V, Engedal K, Aarsland D, Wattmo C, Minthon L, Londos E. Quality of Life and the Effect of Memantine in Dementia with Lewy Bodies and Parkinson's Disease Dementia. Dement Geriatr Cogn Disord 2011; 32: 227–234.

65. Leroi I, Atkinson R, Overshott R. Memantine improves goal attainment and reduces caregiver burden in Parkinson's disease with dementia. Int J Geriatr Psychiatry 2014; 29: 899–905.

66. Wesnes K., Aarsland D, Ballard C, Londos E. Memantine improves attention and episodic memory in Parkinson's disease dementia and dementia with Lewy bodies. Int. J. Geriat. Psychiatry 2014; doi: 10.1002/gps.4109

67. McKeith IG, Wesnes KA, Perry E, Ferrara R. Hallucinations predict attentional improvements with rivastigmine in dementia with Lewy bodies. Dement Geriatr Cogn Disord 2004; 18: 94–100.

68. Burn D, Emre M, McKeith I, De Deyn PP, Aarsland D, Hsu C, Lane R. Effects of rivastigmine in patients with and without visual hallucinations in dementia associated with Parkinson's disease. Mov Disord 2006; 21: 1899-1907.

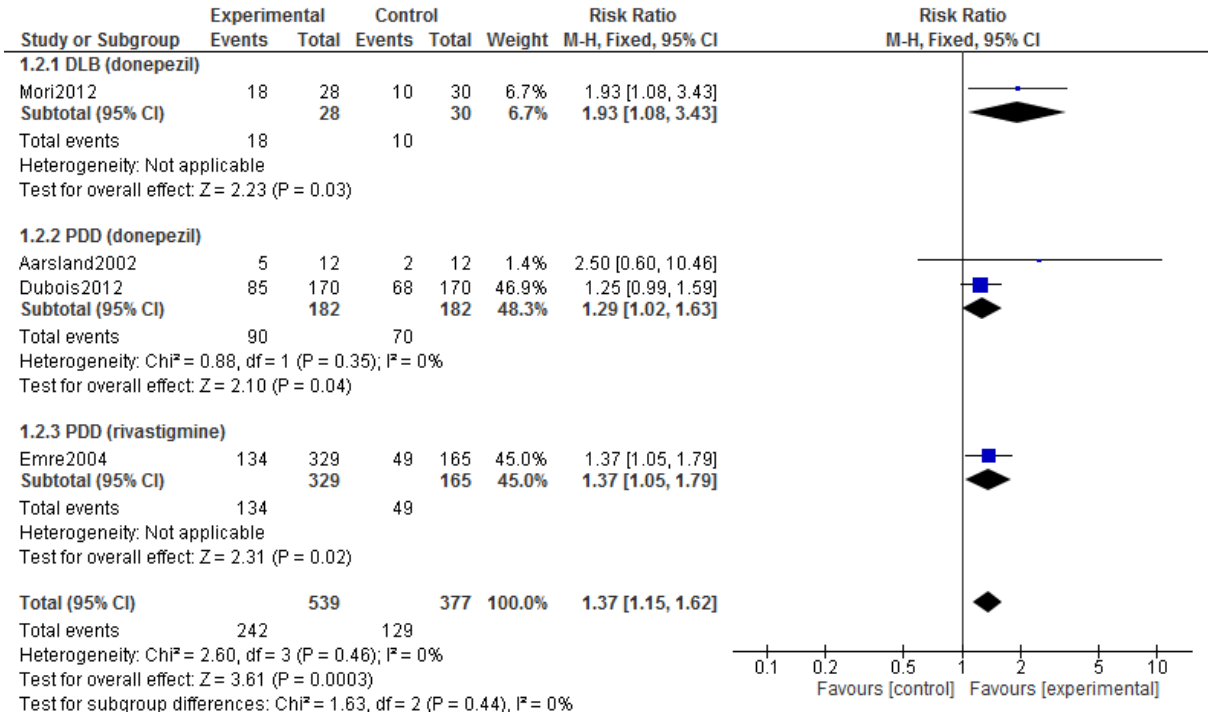
69. Barone P, Burn DJ, van Laar T, Hsu C, Poewe W, Lane RM. Rivastigmine Versus Placebo in Hyperhomocysteinemic Parkinson's Disease Dementia Patients. Mov Disord 2008; 23: 1532–1540.

70. Thomas AJ, Burn DJ, Rowan EN, Littlewood E, Newby J, Cousins D, Pakrasi S, Richardson J, Sanders J, McKeith IG. A comparison of the efficacy of donepezil in Parkinson's disease with dementia and dementia with Lewy bodies. Int J Geriatr Psychiatry 2005, 20, 928 – 44.

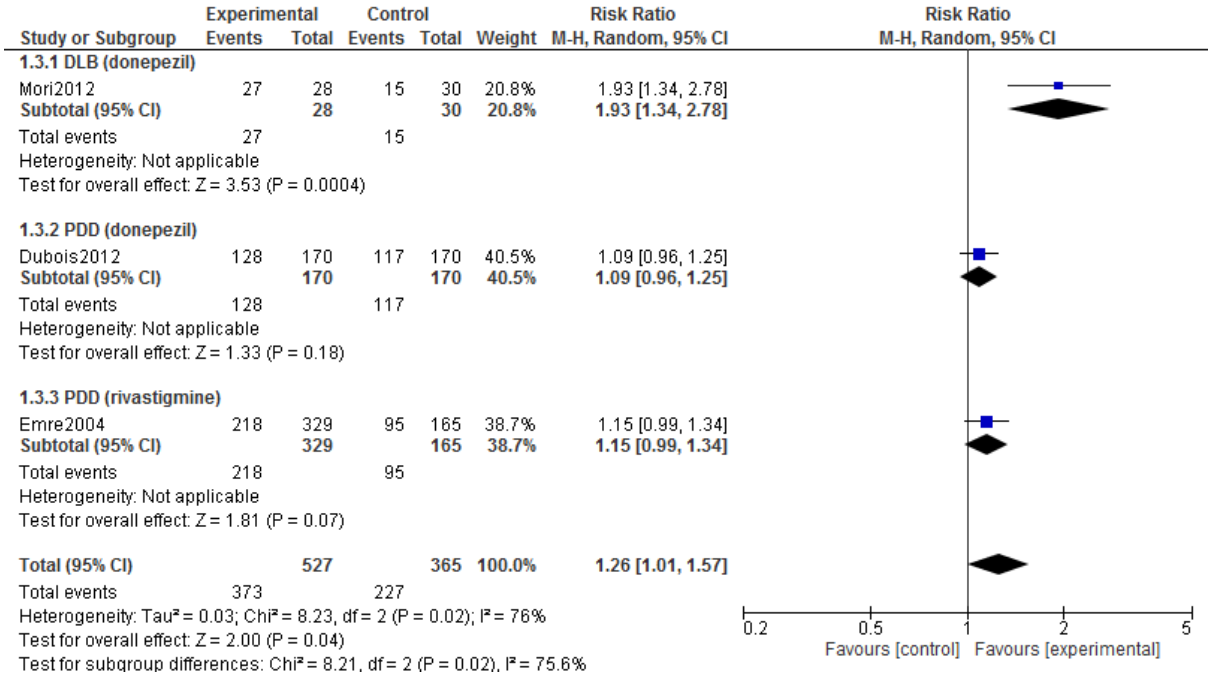
71. Connolly, B.S., & Lang, A.E. (2014). Pharmacological Treatment of Parkinson Disease: A Review. JAMA, 311, 1670 – 1863.

Figure 1. Forest plots for cholinesterase inhibitor trials

1a. Forest plot of global outcomes on the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (improvement): donepezil + rivastigmine vs. placebo. Four studies, n = 916

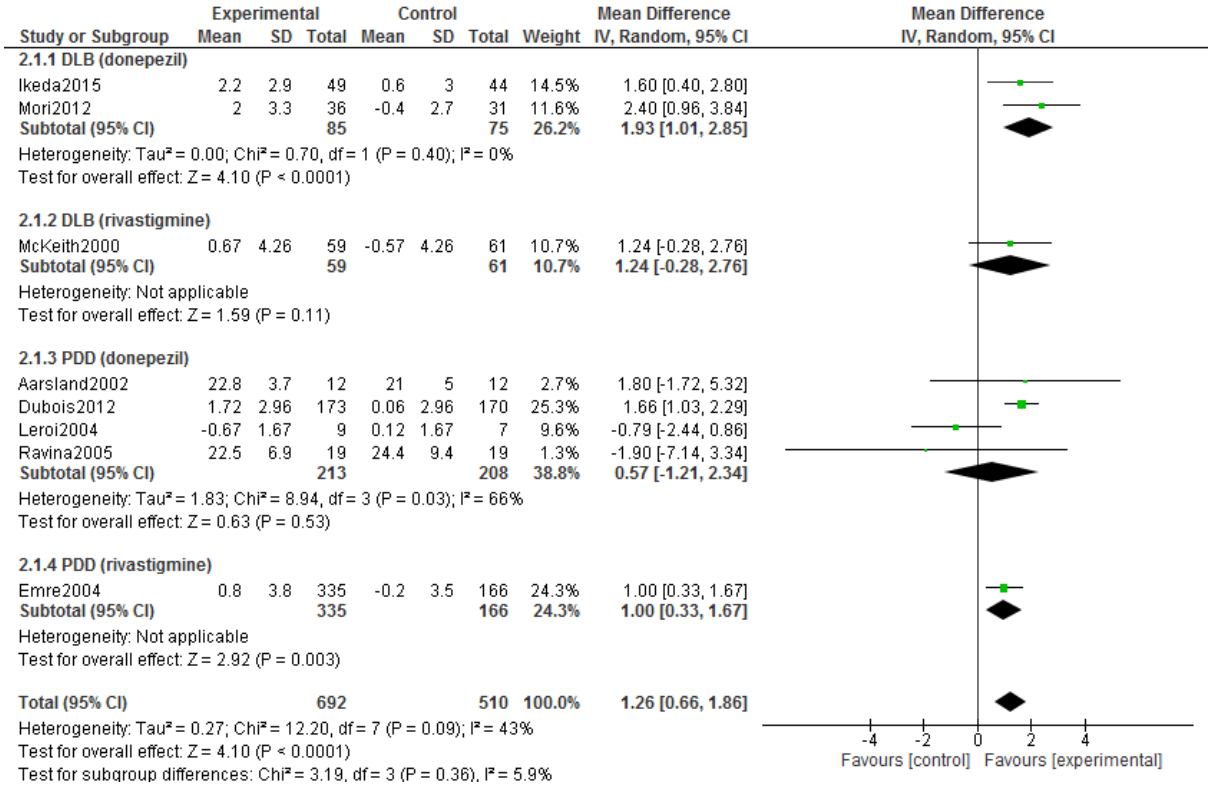


1b. Forest plot of global outcomes on the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (absence of deterioration): donepezil + rivastigmine vs. placebo. Three studies, n = 892



1c**.** Forest plot of cognitive functioning on the MMSE: donepezil + rivastgimine vs. placebo.

Eight studies, n = 1202



1d. Forest plot of neuropsychiatric symptoms on the NPI-10: donepezil + rivastigmine vs. placebo. Six studies, n = 1118

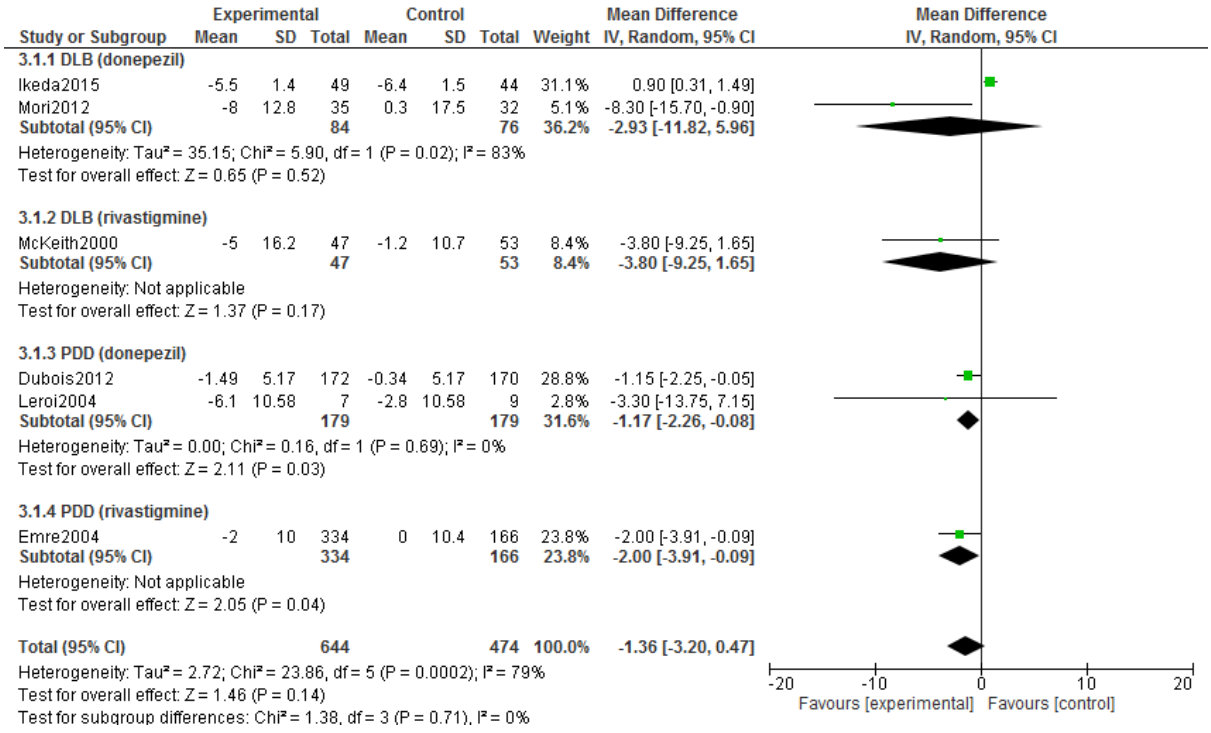


Figure 2. Forest plot of global outcomes on the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change (improvement): memantine vs. placebo. Three studies, n =277