A systematic review and meta-analysis of the effectiveness of acetylcholinesterase inhibitors and memantine in treating the cognitive symptoms of dementia

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Abstract

Background: Acetylcholinesterase inhibitors (AChEIs) and memantine are commonly used in the management of dementia. In routine clinical practice dementia is often monitored via the mini-mental state examination (MMSE). We conducted a systematic review and meta-analysis of the effects of these drugs on MMSE scores. **Summary:** Eighty trials were identified. Pooled effect estimates were in favour of both AChEIs and memantine at 6 months. Meta-regression indicated that dementia sub-type was a moderator of AChEI treatment effect with the effect of treatment versus control twice as high for PDD/DLB patients (2.11 MMSE points at 6 months) as for AD/VaD patients (0.91 MMSE points at 6 months). **Key messages:** AChEIs demonstrate a modest effect versus control on MMSE scores which is moderated by dementia sub-type. For memantine the effect is smaller.

Introduction

Dementia is a major health concern in elderly populations worldwide which can affect many aspects of a person's life and functioning. There is currently no cure for most forms of dementia but several drugs are used in its management. The acetylcholinesterase inhibitors (AChEIs) were developed as a consequence of the cholinergic hypothesis of cognitive decline [1] and the NMDA receptor agonist memantine as a consequence of an hypothesised role of the glutamatergic system in neurodegeneration [2]. The effectiveness of these treatments has been evaluated in a large number of randomised controlled trials (RCTs) across functional, global, cognitive and neuropsychiatric domains [3-5]. This review focuses on their effects on cognition.

Measures of global cognition include the mini-mental state examination (MMSE) [6], the Alzheimer's disease assessment scale - cognitive subscale (ADAS-cog) [7], and the Severe Impairment Battery (SIB) [8], which focuses on those with severe cognitive impairment. Existing meta-analyses tend either to consider cognitive outcomes on the ADAS-cog or SIB [9] or to use standardised mean differences to combine results from several scales [10]. In this review results are analysed relating to the MMSE scale specifically. A small number of existing meta-analyses combine cognitive outcomes on the MMSE; however, these are mainly focused in diagnostic and medication subgroups and do not cover all available trials. The largest of these includes only 21 MMSE effect estimates [11], less than half of the number included in this review.

The MMSE is the scale which is most often used in routine clinical practice to monitor dementia severity and progression and thus the advantage of reviewed outcomes on this scale is better clinical interpretability and relevance to routine care. In addition the volume of evidence can be substantially increased by the inclusion of ADAS-cog results translated to MMSE scale equivalents.

Methods

A protocol for this systematic review was prospectively registered on PROSPERO and can be found at https://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42015025892.

Search strategy

A two-tier search strategy was employed to identify relevant trials for inclusion in this review. First, existing systematic reviews and meta-analyses assessing the drugs of interest were identified and citations to included trials extracted. Following this, additional searches subdivided by dementia diagnosis and, where necessary, drug received, were conducted to identify trials published since the date of the most recent review.

Searches were conducted using the Web of Science, MEDLINE, PsycINFO, EMBASE and CINAHL databases. Final searches were conducted in March 2017. Searches were combinations of; (i) drug names e.g. “donepezil”, “galantamine”, “rivastigmine”, “memantine”; (ii) diagnoses e.g. “Alzheimer*”, “vascular dement*”, “lewy* bod*”, “Parkinson* disease dement*”; and (iii) “randomi?ed” and “trial”. A full list of search terms used is provided in the supplementary material. Further searches were carried out using the International Clinical Trials Registry Platform (ICTRP) and industry trial registers to identify unpublished trials, and references and citing articles of selected trials were assessed to identify further trials for inclusion.

Study selection criteria and data extracted

Trials were included if they met the following criteria: (i) a randomised trial designed to evaluate the effectiveness of AChEI monotherapy, memantine monotherapy or memantine treatment in a group of patients some, but not all, of whom received a concurrent AChEI; (ii) treatments compared to a control group receiving placebo or no treatment; (iii) participants in the trial diagnosed with Alzheimer’s disease (AD), vascular dementia (VaD), Parkinson's disease dementia (PDD), dementia with Lewy bodies (DLB) or frontotemporal dementia (FTD); (iv) at least one of the MMSE or ADAS-cog used as an outcome; and (v) sufficient data provided, defined as at least one treatment effect estimate and associated standard error (SE) on either the MMSE or ADAS-cog. Treatment effect estimates used included change score differences and time point differences. In some cases, effect estimates and SEs had to be calculated from other statistics (for example, confidence intervals).

From each trial data were extracted on: (i) Trial design – duration, inclusion and exclusion criteria, numbers of patients randomised to each arm, intervention and control conditions, type of randomisation, details on blinding, cognitive assessments and measurement times; (ii) Analysis approaches – analysis method, missing data methods and effect size estimate used; and (iii) Trial data – baseline data, attrition and adherence rates, treatment effect estimates and SEs.

Study selection and data extraction were conducted by one reviewer (RK) and a sample of each was checked by a second reviewer (NM). Reviewers agreed on study selection in 99% of cases and agreement regarding data extraction was also high: 87.5% for risk of bias assessment, 82.8% for baseline measures and 75% for effect estimates. Most effect estimate discrepancies were due to miscommunication on how these were extracted. All discrepancies were discussed and resolved.

ADAS-cog translation

The objective of the meta-analysis was to estimate the treatment effect on the MMSE; however, effect estimates on the ADAS-cog were also collected and translated, since both scales measure global cognition. Baseline measures from the 36 trials which measured both were used to translate. MMSE scores range from 0 to 30 and ADAS-cog scores from 0 to 70 and both MMSE=30 and ADAS-cog=0 represent healthy cognition. Thus a linear regression of ADAS-cog on MMSE with intercept fixed at 30 was fitted. The resulting model was: MMSE=30-0.42*ADAS-cog, with a squared multiple correlation of 0.679 suggesting fairly good fit. Translation of both treatment effect estimates and SEs required only the coefficient. Treatment effect estimates were translated using MMSE=-0.42*ADAS-cog, and the SEs using MMSE=0.42*ADAS-cog.

Risk of bias assessment

The risk of bias in included studies was assessed using the Cochrane risk of bias tool [12]. This determines whether the risk of internal bias under a series of domains is low, high or unclear. These were combined so that a trial rated low in all domains was at low risk of bias. One domain, reporting bias, was excluded from the combination since trial protocols were required to assess it but were not available for most included trials due to their age.

Statistical analyses

Random-effects meta-analysis [13] was used to combine trial results. This was conducted separately for AChEIs and memantine. Pooled effects were estimated at 3, 6 and 12 months ($\pm$14 days) after treatment initiation. Effect estimates were also considered in AChEI drug subgroups. Heterogeneity was assessed using the I^2 statistic [14] and publication bias using funnel plots and Begg and Mazumdar's [15] rank correlation test. All statistical analyses were conducted using R [16] and the metafor package [17].

Meta-regressions were conducted to assess the impact of data quality on effect size estimates and test potential moderators. The data quality factors were: (i) the inclusion of translated results; and (ii) the risk of bias assessment overall rating. The hypothesised potential moderators were: (i) AChEI (donepezil, galantamine or rivastigmine); (ii) dementia diagnosis (AD, VaD, PDD/DLB or FTD); (iii) baseline MMSE score; and (iv) date of publication (before or after 2000). All were categorical factors except baseline MMSE which was continuous. The Knapp and Hartung [18] adjustment was used to account for uncertainty in the assessment of residual heterogeneity. The omnibus test of coefficients was used to identify factors significant at the 5% and 1% levels.

Results

Literature search results

The search for systematic reviews identified 522 citations of which 52 were relevant, and these included 194 citations to trials. An additional 857 citations were identified by further searches for trials resulting in 1051 possible citations. After removal of duplicates, title and abstract screening, and full text screening, 84 references about 74 trials met the inclusion criteria. Searches in ICTRP and industry

registers and citation tracking identified a further 6 trials for inclusion. In total, 80 trials met the inclusion criteria. The process of identifying these is detailed in Figure 1.

Characteristics of included studies

Of the included trials summarised in Table 1, half (40) investigated donepezil and the others were evenly split amongst galantamine (13), rivastigmine (14) and memantine (13). The majority of the trials (55) were conducted in patients with AD. Other diagnoses were VaD (9), AD and VaD (4), PDD or DLB (10) and FTD (2). Dementia severity ranged from mild in some trials to severe in others. The trials lasted between 4 and 104 weeks and many recorded outcome measures at intermediate time points. Forty eight trials provided MMSE outcomes, 24 ADAS-cog and the remainder reported a mixture of the two.

The average baseline age in AChEI trials was 73.8 years and in memantine trials was 75.9 years. The proportion of women was slightly more than half in the AChEI trials (mean 57.5%; range 7.1%-84.6%), and the memantine trials (mean 56.3%; range 25%-73.8%). The mean baseline MMSE was higher in the AChEI trials (18.6 points) than the memantine trials (16.5).

Risk of bias assessment

The Cochrane risk of bias tool was applied to each trial and the final column of Table 1 records overall ratings. Risk of bias was low in 14 trials, high in 45 trials and unclear in 21 trials. The large number of trials rated high risk was mainly due to missing data methods combined with relatively high volumes of missing data. The majority of trials used observed case or last observation carried forward analyses which both introduce a significant risk of bias in the presence of missing data.

Meta-analysis results

AChEIs – 3 months

At 3 months (±14 days) after treatment initiation, 42 trials provided 60 estimates of treatment effect. The pooled effect estimate (Figure 2) was 1.08 MMSE points (95% CI 0.92-1.23). There was evidence of heterogeneity (I^2=68.2%) and this was later explored via meta-regression. Begg and Mazumdar's rank test suggested some publication bias (p=0.01) and the funnel plot supported this (Figure 3), however the patterns did not seem overly concerning. In the drug subgroups the treatment effects ranged from 0.98 (95% CI 0.32-1.63) for rivastigmine to 1.15 (95% CI 0.69-1.61) for donepezil 3-5mg/d.

AChEIs – 6 months

At 6 months (±14 days) after treatment initiation, 38 trials provided 52 estimates of treatment effect. The pooled effect estimate was 1.00 (95% CI 0.83-1.16; Figure 4), and there was evidence of heterogeneity (I^2=69.9%). Neither the funnel plot nor the rank correlation test (p=0.385) suggested publication bias. The effect estimates in treatment subgroups ranged from 0.69 (95% CI 0.43-0.95) for rivastigmine to 1.39 (95% CI 0.79-2.00) for galantamine.

AChEIs – 12 months

At 12 months (±14 days) after treatment initiation, 4 trials provided estimates of treatment effect. The pooled effect estimate was 1.10 (95% CI 0.48-1.72; Figure 5). There was evidence for heterogeneity (I^2=79%); however, the funnel plot did not suggest any obvious publication bias and there were too few estimates for a formal test.

Memantine – 3, 6 and 12 months

Treatment effect estimates were provided by 12 memantine trials: 4 at 3 months; 8 at 6 months; and 3 at 12 months after treatment initiation. The pooled effect estimates at each time point were in favour of treatment though were much smaller than those for the AChEIs (Figure 6). At 12 months the pooled effect did not reach significance (0.41, 95% CI -0.44 to 1.26). At all 3 time points the I^2 values were small suggesting little heterogeneity.

Meta-regressions

High I^2 values observed for the AChEI meta-analyses at 3 and 6 months suggested considerable variability in the effect estimates and this was investigated further via meta-regression. Factors investigated were data quality measures and potential moderators as listed in the methods section. Tables 2 and 3 provide meta-regression coefficients, associated p-values and the p-value for the omnibus test of parameters at 3 and 6 months respectively. Coefficients are the difference in average effect estimates for each category versus the reference category for categorical factors and the relation between the factor and effect estimate for continuous factors. Factors for which the omnibus test of parameters is significant at the 5% and 1% levels are highlighted.

A true moderator of treatment effect would be expected to last over time, thus only factors significant at both 3 and 6 months were considered. Dementia sub-type diagnosis was the only factor significant at both 3 months (p=0.009) and 6 months (p=0.007). Examination of diagnostic subgroup results suggested that the effects in the AD and VaD subgroups were the same but those in the PDD/DLB subgroup were different.

Meta-analyses in diagnosis subgroups

At 3 months the pooled effect estimate in the AD/VaD subgroup was 0.97 MMSE points (95% CI 0.85-1.10) and in the PDD/DLB subgroup 1.99 (1.18-2.81). At 6 months the effect in the AD/VaD subgroup was 0.91 (0.77-1.05) and in the PDD/DLB subgroup was 2.11 (0.61-3.61). All four trials providing an effect estimate at 12 months were in the AD/VaD subgroup. The memantine trials provided too few trials for meta-regression to be conducted; however, at both 6 months and 12 months the effects in the PDD/DLB subgroup were significantly higher (1.90 points at 6 months and 1.80 points at 12 months) than those in the AD/VaD subgroup (0.36 points at 6 months and 0.31 points at 12 months).

Discussion

This review identified 80 trials evaluating the effects of donepezil, galantamine, rivastigmine and memantine on cognitive function in dementia, more than in any previous review. Cognitive effects were extracted on the MMSE, the outcome of interest, or the ADAS-cog. Baseline measures from 36 trials

which measured both were used to enable translation of ADAS-cog results to the MMSE scale. This allowed the inclusion of 24 additional trials and results at additional time points from a further 8 trials. The large number of studies included in this review is one of its strengths and this number is increased by the translation of ADAS-cog results. The translation relationship has good R^2; however, this relationship has not been used elsewhere and should therefore be treated as preliminary and requiring confirmation.

Meta-regressions of the AChEI results at 3 and 6 months identified one moderator of treatment effect, dementia sub-type diagnosis. Treatment effects were smaller for those patients diagnosed with AD or VaD (0.97 MMSE points at 3 months and 0.91 points at 6 months) than those diagnosed with PDD or DLB (1.99 points at 3 months and 2.11 points at 6 months). All trials reporting effects at 12 months were for AD or VaD patients and these indicated a similar effect to those at 3 and 6 months (1.10 points). The higher response seen in the PDD/DLB group is consistent with previous results [19] and may be due to the greater cholinergic deficit seen in these conditions [20]. The effects observed in the AD/VaD subgroup are somewhat smaller than those in a previous review of AChEIs in AD only [5]. This may be due to the inclusion of VaD results which evidence suggests may give rise to more mixed findings on AChEI effect [21, 22], although meta-regression indicated no significant differences between AD and VaD subgroups. Whilst these drugs are only licensed for the use in AD or PDD there is evidence that they are widely used for patients with DLB and VaD in routine clinical practice [23] and thus the inclusion of these trial results was felt to be appropriate.

The number of trials providing estimates of memantine treatment effects was much smaller and it was not possible to conduct meta-regression analyses; however, results were calculated for the previously identified subgroups. In the AD/VaD subgroup the effects were small and in favour of treatment (0.65 MMSE points at 3 months, 0.36 points at 6 months and 0.41 points at 12 months). Again the effects in the PDD/DLB subgroup were higher (1.90 points at 6 months and 1.80 points at 12 months). Few of these effects were significantly different from zero.

Through the results of this review, we sought to increase clinical interpretability and relevance to routine care since they are estimated on the MMSE, the scale most often used to monitor dementia in clinical practice. Estimation of MMSE effects also potentially enables results to be compared, contrasted and in future combined with observational findings from routine clinical practice. The AChEI results suggest a treatment effect of around one MMSE point at 3, 6 and 12 months after treatment initiation. Since studies have suggested that the annual rate of MMSE decline amongst dementia patients is 4 to 5 MMSE points [24] such an effect estimate is modest: equivalent to an approximately 3 month delay in cognitive decline. However, while the effect sizes are small, they could have a significant impact in terms of costs and hospital or nursing home admissions which have both been shown to be linked to level of cognitive function as measured by the MMSE score [25]. In addition the length of time for which these benefits continue may be of interest [23].

Use of the MMSE scale makes the results of this review more clinically applicable, however, there are several limitations to this scale. It suffers from both floor and ceiling effects [26], though these should not be of particular concern for the trials included in this study. In addition, it is particularly suitable for

measuring the cognitive deficits observed in AD and may be less sensitive to those in VaD [27] or FTD [28]. However, the latter has little impact in the current review since only one included trial concerned FTD and, as mentioned, no significant differences were found between AD and VaD sub-groups in meta-regressions.

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Table 1: Characteristics of included studies (CVD=cerebrovascular disease, CADASIL=Cerebral Autosomal-Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy, PRC=prolonged-release capsule, BID=twice daily, TID=three-times daily)

Study	Diagnosis	Duration (weeks)	Cognitive measure	Trial arms (n)	Risk of bias
Donepezil					
Frolich et al., 2011[29]	AD	12	MMSE	5 or 10mg/d (161) Placebo (164)	Unclear
Gault et al., 2015[30]	AD	12	ADAS-cog	10mg/d (68) Placebo (68)	Low
Gelmacher et al., 2000[31]	AD	12	MMSE	Donepezil (6) Placebo (6)	Unclear
Marek et al., 2014[32]	AD	12	MMSE	10mg/d (66) Placebo (66)	High
Peng et al., 2005[33]	AD	12	MMSE	5mg/d (46) Placebo (43)	High
Rogers et al., 1998a[34]	AD	12	MMSE	5mg/d (157) 10mg/d (158) Placebo (153)	High
NCT00777608	AD	12	ADAS-cog	5 or 10mg/d (53) Placebo (53)	High
Howard et al., 2007[35]	AD	12	MMSE	10mg/d (128) Placebo (131)	Low
Moraes et al., 2008[36]	AD	13	ADAS-cog	5mg/d (11) Placebo (12)	Unclear
Sole-Padulles et al., 2013[37]	AD	13	MMSE	10mg/d (8) Placebo (7)	High
Haig et al., 2014[38]	AD	14	MMSE	10mg/d (60) Placebo (63)	Low
Black et al., 2007[39]	AD	24	MMSE	10mg/d (176) Placebo (167)	High
Burns et al., 1999[40]	AD	24	ADAS-cog	5mg/d (271) 10mg/d (273) Placebo (274)	Unclear
Feldman et al., 2000[41]	AD	24	MMSE	10mg/d (144) Placebo (146)	Unclear
Gold et al., 2010[42]	AD	24	ADAS-cog	10mg/d (84) Placebo (166)	High
Homma et al., 2000[43]	AD	24	ADAS-cog	5mg/d (134) Placebo (129)	Unclear
Jia et al., 2017[44]	AD	24	MMSE	5mg/d (156) Placebo (156)	Low
Maher-Edwards et al., 2011[45]	AD	24	ADAS-cog	10mg/d (67) Placebo (63)	High
Mazza et al., 2006[46]	AD	24	MMSE	5mg/d (25) Placebo (26)	High

Gault et al., 2016[47]	AD	24	MMSE	10mg/d (76) Placebo (104)	Unclear
Rogers et al., 1998b[48]	AD	24	MMSE ADAS-cog	5mg/d (154) 10mg/d (157) Placebo (162)	High
Seltzer et al., 2004[49]	AD	24	MMSE ADAS-cog	10mg/d (96) Placebo (57)	High
Tune et al., 2003[50]	AD	24	ADAS-cog	10mg/d (14) Placebo (14)	Unclear
Maher-Edwards et al., 2015[51]	AD	24	MMSE ADAS-cog	5 or 10mg/d (152) Placebo (145)	High
dos Santos Moraes et al., 2006[52]	AD	26	ADAS-cog	10mg/d (17) Placebo (18)	Low
Winblad et al., 2006[53]	AD	26	MMSE	10mg/d (128) Placebo (121)	High
Winblad et al., 2001[54]	AD	52	MMSE	10mg/d (142) Placebo (144)	Unclear
Mohs et al., 2001[55]	AD	54	MMSE	10mg/d (214) Placebo (217)	High
Bentham et al., 2004[56]	AD or AD+VaD	12	MMSE	5mg/d (282) Placebo (283)	High
Tariot et al., 2001[57]	AD or AD+CVD	24	MMSE	10mg/d (103) Placebo (105)	High
Black et al., 2003[58]	VaD	24	MMSE ADAS-cog	5mg/d (198) 10mg/d (206) Placebo (199)	High
Roman et al., 2010[59]	VaD	24	MMSE	5mg/d (648) Placebo (326)	High
Wilkinson et al., 2003[60]	VaD	24	MMSE	5mg/d (208) 10mg/d (215) Placebo (193)	High
Dichgans et al., 2008[61]	CADASIL	18	MMSE	10mg/d (86) Placebo (82)	Unclear
Aarsland et al., 2002[62]	PDD	10	MMSE	5 or 10mg/d (8) Placebo (6)	High
Ravina et al., 2005[63]	PDD	10	ADAS-cog	5mg/d (11) Placebo (11)	High
Leroi et al., 2004[64]	PDD	18	MMSE	10mg/d (7) Placebo (9)	Unclear
Dubois et al., 2012[65]	PDD	24	MMSE ADAS-cog	5mg/d (195) 10mg/d (182) Placebo (173)	High
Ikeda et al., 2015[66]	DLB	12	MMSE	5mg/d (46) 10mg/d (47) Placebo (49)	High
Mori et al., 2012[67]	DLB	12	MMSE	3mg/d (35) 5mg/d (33)	Low

				10mg/d (37) Placebo (35)	
Galantamine					
Wilkinson and Murray, 2001[68]	AD	12	ADAS-cog	18mg/d (88) 24mg/d (56) 36mg/d (54) Placebo (87)	High
Kadir et al., 2008[69]	AD	13	MMSE	8-16mg/d (12) Placebo (6)	Unclear
Rockwood et al., 2001[70]	AD	13	ADAS-cog	24-32mg/d (261) Placebo (125)	High
Rockwood et al., 2006[71]	AD	16	ADAS-cog	16-24mg/d (64) Placebo (66)	Unclear
Tariot et al., 2000[72]	AD	22	ADAS-cog	8mg/d (140) 16mg/d (279) 24mg/d (273) Placebo (286)	Unclear
Brodaty et al., 2005[73]	AD	26	ADAS-cog	16-24mg/d (237) 16-24mg/d PRC (320) Placebo (324)	High
Raskind et al., 2000[74]	AD	26	ADAS-cog	24mg/d (212) 32mg/d (211) Placebo (213)	High
Wilcock et al., 2000[75]	AD	26	ADAS-cog	24mg/d (220) 32mg/d (218) Placebo (215)	High
Likitjaroen et al., 2011[76]	AD	26	MMSE	16mg/d (14) Placebo (11)	Unclear
Hager et al., 2014[77]	AD or AD+CVD	104	MMSE	18-24mg/d (1028) Placebo (1023)	Low
Erkinjuntti et al., 2002[78]	VaD or AD+CVD	26	ADAS-cog	24mg/d (396) Placebo (196)	High
Auchus et al., 2007[79]	VaD	26	ADAS-cog	24mg/d (397) Placebo (391)	High
Litvinenko et al., 2008[80]	PDD	24	MMSE	16mg/d (21) Placebo (20)	High
Rivastigmine					
Koch et al., 2014[81]	AD	4	MMSE	4.6mg/d (10) Placebo (10)	Unclear
Mowla et al., 2007[82]	AD	12	MMSE	6-12mg/d (41) Placebo (40)	Unclear
Iranmanesh et al., 2012[83]	AD	12	MMSE	3mg/d (16) Placebo (16)	Unclear
Agid et al., 1998[84]	AD	13	MMSE	4mg/d (136) 6mg/d (133) Placebo (133)	High
Forette et al., 1999[85]	AD	18	ADAS-cog	12mg/d BID (45) 12mg/d TID (45)	High

				Placebo (24)	
Winblad et al., 2007[86]	AD	24	MMSE	12mg/d capsule (297) 9.5mg/d patch (293) 17.4mg/d patch (303) Placebo (302)	High
NCT00423085	AD	24	MMSE	9mg/d patch (284) 18mg/d patch (287) Placebo (288)	High
Rosler et al., 1999[87]	AD	26	MMSE	1-4mg/d (243) 6-12 mg/d (243) Placebo (239)	High
Corey-Bloom et al., 1998[88]	AD	26	MMSE ADAS-cog	1-4mg/d (233) 6-12 mg/d (231) Placebo (235)	High
Feldman and Lane, 2007[89]	AD	26	MMSE ADAS-cog	2-12mg/d BID (229) 2-12mg/d TID (227) Placebo (222)	Unclear
Karaman et al., 2005[90]	AD	52	MMSE	12mg/d (24) Placebo (20)	High
Ballard et al., 2008[91]	VaD	24	MMSE	3-12mg/d (365) Placebo (345)	High
Mok et al., 2007[92]	VaD	26	MMSE	6mg/d (20) Placebo (20)	Unclear
Emre et al., 2004[93]	PDD	24	MMSE	3-12mg/d (362) Placebo (179)	High
Memantine					
Fox et al., 2012[94]	AD	12	MMSE	20mg/d (74) Placebo (79)	Low
Bakchine and Loft, 2007[95]	AD	24	ADAS-cog	20mg/d (318) Placebo (152)	Low
Peskind et al., 2006[96]	AD	24	ADAS-cog	20mg/d (201) Placebo (202)	Low
Wang et al., 2013[97]	AD	24	MMSE	20mg/d (13) Placebo (13)	Unclear
Reisberg et al., 2003[98]	AD	28	MMSE	20mg/d (126) Placebo (126)	High
Ashford et al., 2011[99]	AD	52	ADAS-cog	20mg/d (7) Placebo (6)	High
Wilkinson et al., 2012[100]	AD	52	MMSE	20mg/d (134) Placebo (144)	Low
Orgogozo et al., 2002[101]	VaD	28	MMSE	20mg/d (165) Placebo (156)	High
Wilcock et al., 2002[102]	VaD	28	MMSE ADAS-cog	20mg/d (295) Placebo (284)	Low
Leroi et al., 2009[103]	PDD	16	MMSE	20mg/d (11) Placebo (14)	High
Aarsland et al., 2009[104]	PDD/DLB	24	MMSE	20mg/d (35) Placebo (40)	Low

Boxer et al., 2013[105]	FTD	26	MMSE	20mg/d (39) Placebo (42)	Low
Vercelletto et al., 2011[106]	FTD	52	MMSE	20mg/d (26) Placebo (26)	High

Table 2: Meta-regressions of effects at 3 months. Coefficients, associated p-values and omnibus test of parameters p-value provided. *=significant at 5% level. **=significant at 1% level. ref=reference category.

Factor	**Levels**	**Number of trials**	**Coefficient (p-value)**	**Omnibus test p-value**
Translation to MMSE	MMSE ADAS-cog	28 32	ref -0.471 (0.007)	0.007**
Risk of bias rating	Low Unclear High	8 13 39	ref -0.371 (0.307) -0.346 (0.269)	0.521
Medication	Donepezil Galantamine Rivastigmine	37 17 6	ref 0.010 (0.961) -0.153 (0.612)	0.864
Diagnosis	AD VaD PDD/DLB	46 6 8	ref -0.211 (0.373) 0.806 (0.005)	0.009**
Baseline MMSE	NA	55	-0.069 (0.092)	0.092
Date	Pre 2000 2000 onwards	26 34	ref 0.068 (0.703)	0.703

Table 3: Meta-regressions of effects at 6 months. Coefficients, associated p-values and omnibus test of parameters p-value provided. *=significant at 5% level. **=significant at 1% level. ref=reference category.

Factor	**Levels**	**Number of trials**	**Coefficient (p-value)**	**Omnibus test p-value**
Translation to MMSE	MMSE ADAS-cog	35 17	ref 0.117 (0.540)	0.540
Risk of bias rating	Low Unclear High	3 9 40	ref 0.269 (0.579) 0.329 (0.443)	0.735
Medication	Donepezil Galantamine Rivastigmine	27 11 14	ref 0.320 (0.139) -0.370 (0.133)	0.033*
Diagnosis	AD	39	ref	

	VaD PDD/DLB	9 4	-0.134 (0.139) 0.970 (0.001)	0.007*
Baseline MMSE	NA	52	-0.005 (0.869)	0.869
Date	Pre 2000 2000 onwards	17 35	ref -0.141 (0.456)	 0.456

Figure 1: Flow diagram of trials identified for inclusion in this review through two-tier search strategy.

Figure 2: Forest plot showing treatment effects from individual trials and meta-analysis results for AChEIs at 3 months after treatment initiation

Figure 3: Funnel plot of treatment effects at 3 months after treatment initiation.

Figure 4: Forest plot showing treatment effects from individual trials and meta-analysis results for AChEIs at 6 months after treatment initiation

Figure 5: Forest plot showing treatment effects from individual trials and meta-analysis results for AChEIs at 12 months after treatment initiation

Figure 6: Forest plots showing treatment effects from individual trials and meta-analysis results for memantine at 3, 6 and 12 months after treatment initiation.