Review Article

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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Keywords

Acetylcholinesterase inhibitor · Memantine · Alzheimer disease · Vascular dementia · Systematic review · Meta-analysis

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 subtype was a moderator of AChEI treatment effect, with the effect of treatment versus control twice as high for patients with Parkinson disease dementia/dementia with Lewy bodies (2.11 MMSE points at 6 months) as for patients with Alzheimer disease/vascular dementia (0.91 MMSE points at 6 months). **Key Messages:** AChEIs demonstrate a modest effect versus control on MMSE scores which is moderated by dementia subtype. For memantine the effect is smaller.

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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 a 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 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 on 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 most often used to monitor dementia severity and progression in routine clinical practice, and thus the advantage of reviewing 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 into 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, the 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. The searches were combinations of: (1) drug names (e.g., “donepezil,” “galantamine,” “rivastigmine,” and “memantine”); (2) diagnoses (e.g., “Alzheimer*,” “vascular dement*,” “lewy* bod*,” and “Parkinson* disease dement*”); and (3) “randomi?ed” and “trial.” A full list of the search terms used is provided in the online supplementary material (for all online suppl. material, see www.karger.com/doi/10.1159/000486546). Further searches were carried out using the International Clinical Trials Registry Platform (ICTRP) and industry trial registers to identify unpublished trials. References of the selected trials and articles which cited them were assessed to identify further trials for inclusion.

Study Selection Criteria and Data Extracted

Trials were included if they met the following criteria: (1) 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; (2) treatments compared to a control group receiving placebo or no treatment; (3) participants in the trial diagnosed with Alzheimer disease (AD),

vascular dementia (VaD), Parkinson disease dementia (PDD), dementia with Lewy bodies (DLB), or fronto-temporal dementia (FTD); (4) either the MMSE or the ADAS-cog or both used as an outcome; and (5) 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 differences in change score and differences in time point. In some cases, effect estimates and SEs had to be calculated from other statistics (e.g., confidence intervals).

From each trial, data were extracted on: (1) 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; (2) analytic approaches – analytic method, missing data methods, and effect size estimate used; and (3) trial parameters – baseline data, attrition and adherence rates, treatment effect estimates, and SEs.

Study selection and data extraction were conducted by one reviewer (R.K.), and a sample of each was checked by a second reviewer (N.M.). The reviewers agreed on study selection in 99% of the 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. The baseline measures from the 36 trials which measured both were used for translation. MMSE scores range from 0 to 30 and ADAS-cog scores from 0 to 70, and both an MMSE score of 30 and an ADAS-cog score of 0 represent healthy cognition. Thus, a linear regression of ADAS-cog on MMSE with the intercept fixed at 30 was fitted. The resulting model was: $MMSE = 30 - 0.42 \times ADAS\text{-}cog$, 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 $MMSE = -0.42 \times ADAS\text{-}cog$, and SEs using $MMSE = 0.42 \times ADAS\text{-}cog$.

Risk of Bias Assessment

The risk of bias in the 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 of the 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 3, 6, and 12 months (± 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 the Begg and Mazumdar rank correlation test [15]. 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 (1) the inclusion of translated results and (2) the risk of bias assessment overall rating. The hypothesised potential moderators were: (1) AChEI (donepezil, galantamine, or rivastigmine); (2) dementia diagnosis (AD, VaD, PDD/DLB, or FTD); (3) baseline MMSE score; and (4) date of publication (before or after 2000). All were categorical factors except baseline MMSE score, which was continuous. The Knapp and Hartung adjustment [18] 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 1,051 possible citations. After removal of duplicates,

Fig. 1. Flow diagram of the trials identified for inclusion in this review via a two-tier search strategy. RCT, randomised controlled trial; AChEI, acetylcholinesterase inhibitor.

title and abstract screening, and full-text screening, 84 references on 74 trials met the inclusion criteria. Searches in the 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 the Included Studies

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

The average baseline age in the AChEI trials was 73.8 years, and in the memantine trials it 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 score was higher in the AChEI trials (18.6 points) than in the memantine trials (16.5 points).

Risk of Bias Assessment

The Cochrane risk of bias tool was applied to each trial, and the final column of Table 1 records the 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 at high risk of bias was mainly due to missing data methods combined with relatively high volumes of missing data. The majority of the trials used observed case or last observation carried forward analyses, both of which 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 (Fig. 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. The Begg and Mazumdar rank test suggested some publication bias ($p = 0.01$) and the funnel plot supported this (Fig. 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 3–5 mg/day.

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; Fig. 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 the 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; Fig. 5). There was evidence of 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: by 4 trials at 3 months, by 8 trials at 6 months, and by 3 trials at 12 months after treatment initiation. The pooled

Table 1. Characteristics of the included studies

Study	Diagnosis	Duration, weeks	Cognitive measure	Trial arms (n)	Risk of bias
Donepezil					
Frölich et al. [29], 2011	AD	12	MMSE	5 or 10 mg/day (161) Placebo (164)	Unclear
Gault et al. [30], 2015	AD	12	ADAS-cog	10 mg/day (68) Placebo (68)	Low
Geldmacher et al. [31], 2000	AD	12	MMSE	Donepezil (6) Placebo (6)	Unclear
Marek et al. [32], 2014	AD	12	MMSE	10 mg/day (66) Placebo (66)	High
Peng et al. [33], 2005	AD	12	MMSE	5 mg/day (46) Placebo (43)	High
Rogers et al. [34], 1998a	AD	12	MMSE	5 mg/day (157) 10 mg/day (158) Placebo (153)	High
NCT00777608	AD	12	ADAS-cog	5 or 10 mg/day (53) Placebo (53)	High
Howard et al. [35], 2007	AD	12	MMSE	10 mg/day (128) Placebo (131)	Low
Moraes et al. [36], 2008	AD	13	ADAS-cog	5 mg/day (11) Placebo (12)	Unclear
Solé-Padullés et al. [37], 2013	AD	13	MMSE	10 mg/day (8) Placebo (7)	High
Haig et al. [38], 2014	AD	14	MMSE	10 mg/day (60) Placebo (63)	Low
Black et al. [39], 2007	AD	24	MMSE	10 mg/day (176) Placebo (167)	High
Burns et al. [40], 1999	AD	24	ADAS-cog	5 mg/day (271) 10 mg/day (273) Placebo (274)	Unclear
Feldman et al. [41], 2001	AD	24	MMSE	10 mg/day (144) Placebo (146)	Unclear
Gold et al. [42], 2010	AD	24	ADAS-cog	10 mg/day (84) Placebo (166)	High
Homma et al. [43], 2000	AD	24	ADAS-cog	5 mg/day (134) Placebo (129)	Unclear
Jia et al. [44], 2017	AD	24	MMSE	5 mg/day (156) Placebo (156)	Low
Maher-Edwards et al. [45], 2011	AD	24	ADAS-cog	10 mg/day (67) Placebo (63)	High
Mazza et al. [46], 2006	AD	24	MMSE	5 mg/day (25) Placebo (26)	High
Gault et al. [47], 2016	AD	24	MMSE	10 mg/day (76) Placebo (104)	Unclear
Rogers et al. [48], 1998b	AD	24	MMSE ADAS-cog	5 mg/day (154) 10 mg/day (157) Placebo (162)	High
Seltzer et al. [49], 2004	AD	24	MMSE ADAS-cog	10 mg/day (96) Placebo (57)	High
Tune et al. [50], 2003	AD	24	ADAS-cog	10 mg/day (14) Placebo (14)	Unclear
Maher-Edwards et al. [51], 2015	AD	24	MMSE	5 or 10 mg/day (152) Placebo (145)	High
dos Santos Moraes et al. [52], 2006	AD	26	ADAS-cog	10 mg/day (17) Placebo (18)	Low

Table 1 (continued)

Study	Diagnosis	Duration, weeks	Cognitive measure	Trial arms (n)	Risk of bias
Winblad et al. [53], 2006	AD	26	MMSE	10 mg/day (128) Placebo (121)	High
Winblad et al. [54], 2001	AD	52	MMSE	10 mg/day (142) Placebo (144)	Unclear
Mohs et al. [55], 2001	AD	54	MMSE	10 mg/day (214) Placebo (217)	High
Bentham et al. [56], 2004	AD or AD + VaD	12	MMSE	5 mg/day (282) Placebo (283)	High
Tariot et al. [57], 2001	AD or AD + CVD	24	MMSE	10 mg/day (103) Placebo (105)	High
Black et al. [58], 2003	VaD	24	MMSE ADAS-cog	5 mg/day (198) 10 mg/day (206) Placebo (199)	High
Román et al. [59], 2010	VaD	24	MMSE	5 mg/day (648) Placebo (326)	High
Wilkinson et al. [60], 2003	VaD	24	MMSE	5 mg/day (208) 10 mg/day (215) Placebo (193)	High
Dichgans et al. [61], 2008	CADASIL	18	MMSE	10 mg/day (86) Placebo (82)	Unclear
Aarsland et al. [62], 2002	PDD	10	MMSE	5 or 10 mg/day (8) Placebo (6)	High
Ravina et al. [63], 2005	PDD	10	ADAS-cog	5 mg/day (11) Placebo (11)	High
Leroi et al. [64], 2004	PDD	18	MMSE	10 mg/day (7) Placebo (9)	Unclear
Dubois et al. [65], 2012	PDD	24	MMSE ADAS-cog	5 mg/day (195) 10 mg/day (182) Placebo (173)	High
Ikeda et al. [66], 2015	DLB	12	MMSE	5 mg/day (46) 10 mg/day (47) Placebo (49)	High
Mori et al. [67], 2012	DLB	12	MMSE	3 mg/day (35) 5 mg/day (33) 10 mg/day (37) Placebo (35)	Low
Galantamine					
Wilkinson and Murray [68], 2001	AD	12	ADAS-cog	18 mg/day (88) 24 mg/day (56) 36 mg/day (54) Placebo (87)	High
Kadir et al. [69], 2008	AD	13	MMSE	8–16 mg/day (12) Placebo (6)	Unclear
Rockwood et al. [70], 2001	AD	13	ADAS-cog	24–32 mg/day (261) Placebo (125)	High
Rockwood et al. [71], 2006	AD	16	ADAS-cog	16–24 mg/day (64) Placebo (66)	Unclear
Tariot et al. [72], 2000	AD	22	ADAS-cog	8 mg/day (140) 16 mg/day (279) 24 mg/day (273) Placebo (286)	Unclear

Table 1 (continued)

Study	Diagnosis	Duration, weeks	Cognitive measure	Trial arms (n)	Risk of bias
Brodaty et al. [73], 2005	AD	26	ADAS-cog	16–24 mg/day (237) 16–24 mg/day PRC (320) Placebo (324)	High
Raskind et al. [74], 2000	AD	26	ADAS-cog	24 mg/day (212) 32 mg/day (211) Placebo (213)	High
Wilcock et al. [75], 2000	AD	26	ADAS-cog	24 mg/day (220) 32 mg/day (218) Placebo (215)	High
Likitjaroen et al. [76], 2012	AD	26	MMSE	16 mg/day (14) Placebo (11)	Unclear
Hager et al. [77], 2014	AD or AD + CVD	104	MMSE	18–24 mg/day (1,028) Placebo (1,023)	Low
Erkinjuntti et al. [78], 2002	VaD or AD + CVD	26	ADAS-cog	24 mg/day (396) Placebo (196)	High
Auchus et al. [79], 2007	VaD	26	ADAS-cog	24 mg/day (397) Placebo (391)	High
Litvinenko et al. [80], 2008	PDD	24	MMSE	16 mg/day (21) Placebo (20)	High
Rivastigmine					
Koch et al. [81], 2014	AD	4	MMSE	4.6 mg/day (10) Placebo (10)	Unclear
Mowla et al. [82], 2007	AD	12	MMSE	6–12 mg/day (41) Placebo (40)	Unclear
Iranmanesh et al. [83], 2012	AD	12	MMSE	3 mg/day (16) Placebo (16)	Unclear
Agid et al. [84], 1998	AD	13	MMSE	4 mg/day (136) 6 mg/day (133) Placebo (133)	High
Forette et al. [85], 1999	AD	18	ADAS-cog	12 mg/day BID (45) 12 mg/day TID (45) Placebo (24)	High
Winblad et al. [86], 2007	AD	24	MMSE	12 mg/day capsule (297) 9.5 mg/day patch (293) 17.4 mg/day patch (303) Placebo (302)	High
NCT00423085	AD	24	MMSE	9 mg/day patch (284) 18 mg/day patch (287) Placebo (288)	High
Rösler et al. [87], 1999	AD	26	MMSE	1–4 mg/day (243) 6–12 mg/day (243) Placebo (239)	High
Corey-Bloom et al. [88], 1998	AD	26	MMSE ADAS-cog	1–4 mg/day (233) 6–12 mg/day (231) Placebo (235)	High
Feldman and Lane [89], 2007	AD	26	MMSE ADAS-cog	2–12 mg/day BID (229) 2–12 mg/day TID (227) Placebo (222)	Unclear

Table 1 (continued)

Study	Diagnosis	Duration, weeks	Cognitive measure	Trial arms (n)	Risk of bias
Karaman et al. [90], 2005	AD	52	MMSE	12 mg/day (24) Placebo (20)	High
Ballard et al. [91], 2008	VaD	24	MMSE	3–12 mg/day (365) Placebo (345)	High
Mok et al. [92], 2007	VaD	26	MMSE	6 mg/day (20) Placebo (20)	Unclear
Emre et al. [93], 2004	PDD	24	MMSE	3–12 mg/day (362) Placebo (179)	High
Memantine					
Fox et al. [94], 2012	AD	12	MMSE	20 mg/day (74) Placebo (79)	Low
Bakchine and Loft [95], 2008	AD	24	ADAS-cog	20 mg/day (318) Placebo (152)	Low
Peskind et al. [96], 2006	AD	24	ADAS-cog	20 mg/day (201) Placebo (202)	Low
Wang et al. [97], 2013	AD	24	MMSE	20 mg/day (13) Placebo (13)	Unclear
Reisberg et al. [98], 2003	AD	28	MMSE	20 mg/day (126) Placebo (126)	High
Ashford et al. [99], 2011	AD	52	ADAS-cog	20 mg/day (7) Placebo (6)	High
Wilkinson et al. [100], 2012	AD	52	MMSE	20 mg/day (134) Placebo (144)	Low
Orgogozo et al. [101], 2002	VaD	28	MMSE	20 mg/day (165) Placebo (156)	High
Wilcock et al. [102], 2002	VaD	28	MMSE ADAS-cog	20 mg/day (295) Placebo (284)	Low
Leroi et al. [103], 2009	PDD	16	MMSE	20 mg/day (11) Placebo (14)	High
Aarsland et al. [104], 2009	PDD/DLB	24	MMSE	20 mg/day (35) Placebo (40)	Low
Boxer et al. [105], 2013	FTD	26	MMSE	20 mg/day (39) Placebo (42)	Low
Vercelletto et al. [106], 2011	FTD	52	MMSE	20 mg/day (26) Placebo (26)	High

AD, Alzheimer disease; VaD, vascular dementia; PDD, Parkinson disease dementia; DLB, dementia with Lewy bodies; FTD, frontotemporal dementia; CVD, cerebrovascular disease; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; PRC, prolonged-release capsule; BID, twice daily; TID, three times daily.

effect estimates at each time point were in favour of treatment, though they were much smaller than those for the AChEIs (Fig. 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

The high I^2 values observed for the AChEI meta-analyses at 3 and 6 months suggested considerable variability in the effect estimates; 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 the meta-regression coefficients, the associated p values, and the p value for the omnibus test of parameters at 3 and 6 months, respectively. For categorical factors, coefficients are the difference in average effect estimates

Fig. 2. Forest plot showing the treatment effects from the individual trials and meta-analysis results for acetylcholinesterase inhibitors at 3 months after treatment initiation. For the reference numbers of the studies, please refer to Table 1.

(Figure continued on next page.)

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Fig. 3. Funnel plot of treatment effects at 3 months after treatment initiation. All recorded effects at 3 months ± 14 days.

Fig. 4. Forest plot showing the treatment effects from the individual trials and meta-analysis results for acetylcholinesterase inhibitors at 6 months after treatment initiation. For the reference numbers of the studies, please refer to Table 1.

(Figure continued on next page.)

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Fig. 5. Forest plot showing the treatment effects from the individual trials and meta-analysis results for acetylcholinesterase inhibitors at 12 months after treatment initiation. For the reference numbers of the studies, please refer to Table 1.

Fig. 6. Forest plots showing the treatment effects from the individual trials and meta-analysis results for memantine at 3, 6, and 12 months after treatment initiation. For the reference numbers of the studies, please refer to Table 1.

for each category versus the reference category; for continuous factors, they are the relation between the factor and the effect estimate. Factors for which the omnibus test of parameters was 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 subtype diagnosis was the only factor significant at both 3 months ($p = 0.009$) and 6 months ($p = 0.007$). Examination of the 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 of the Diagnostic Subgroups

At 3 months, the pooled effect estimate was 0.97 MMSE points (95% CI 0.85–1.10) in the AD/VaD subgroup and 1.99 MMSE points (1.18–2.81) in the PDD/DLB subgroup. At 6 months, the effect was 0.91 MMSE points (0.77–1.05) in the AD/VaD subgroup and 2.11 MMSE points (0.61–3.61) in the PDD/DLB subgroup. All 4 trials providing an effect estimate at 12 months were in the AD/VaD subgroup. The memantine trials provided too few estimates for meta-regression to be conducted; however, at both 6 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).

Table 2. Meta-regressions of effects at 3 months

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

Coefficients, associated *p* values, and the *p* value for the omnibus test of parameters are provided. AD, Alzheimer disease; VaD, vascular dementia; PDD, Parkinson disease dementia; DLB, dementia with Lewy bodies. ** Significant at the 1% level.

Table 3. Meta-regressions of effects at 6 months

Factor	Levels	Number of trials	Coefficient (p value)	Omnibus test p value
Translation into MMSE	MMSE	35	Ref.	0.540
	ADAS-cog	17	0.117 (0.540)	
Risk of bias rating	Low	3	Ref.	0.735
	Unclear	9	0.269 (0.579)	
	High	40	0.329 (0.443)	
Medication	Donepezil	27	Ref.	0.033*
	Galantamine	11	0.320 (0.139)	
	Rivastigmine	14	−0.370 (0.133)	
Diagnosis	AD	39	Ref.	0.007*
	VaD	9	−0.134 (0.139)	
	PDD/DLB	4	0.970 (0.001)	
Baseline MMSE score	NA	52	−0.005 (0.869)	0.869
Date	Before 2000	17	Ref.	0.456
	2000 onwards	35	−0.141 (0.456)	

Coefficients, associated *p* values, and the *p* value for the omnibus test of parameters are provided. AD, Alzheimer disease; VaD, vascular dementia; PDD, Parkinson disease dementia; DLB, dementia with Lewy bodies. * Significant at the 5% level.

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 score, the outcome of interest, or the ADAS-cog score. Baseline measures from 36 trials which measured both were used to permit the translation of ADAS-cog results into MMSE scores. 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 through 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 subtype 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 for those diagnosed with PDD or DLB (1.99 MMSE points at 3 months and 2.11 points at 6 months). All reported effects at 12 months were for AD or VaD patients, and these indicated an effect similar 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 reported in a previous review of AChEIs for 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 effects [21, 22]; however, meta-regression indicated no significant differences between AD and VaD subgroups. Whilst these drugs are only licensed for 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 0.31 points at 12 months). Again, the effects in the PDD/DLB subgroup were greater (1.90 MMSE 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 regarding the MMSE, the scale most often used to monitor dementia in clinical practice. Estimation of effects on MMSE scores also potentially allows 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 1 MMSE point at 3, 6, and 12 months after treatment initiation. Since studies have suggested that the annual rate of decline in MMSE score amongst dementia patients is 4–5 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 the level of cognitive function as measured by the MMSE [25]. In addition, the length of time that these benefits continue may be of interest [23].

Use of the MMSE 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 subgroups in the meta-regressions.

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