Dementia
and Geriatric
Cognitive Disorders

Dement Geriatr Cogn Disord 2018;45:131–151
DOI: 10.1159/000486546
Accepted: December 29, 2017
Published online: May 7, 2018

Review Article

A Systematic Review and Meta-Analysis of the Effectiveness of Acetylcholinesterase Inhibitors and Memantine in Treating the Cognitive Symptoms of Dementia

Ruth Knight[a] Mizanur Khondoker[b] Nicholas Magill[a] Robert Stewart[c, d] Sabine Landau[a]

[a]Department of Biostatistics and Health Informatics, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [b]Norwich Medical School, University of East Anglia, Norwich, UK; [c]Department of Psychological Medicine, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK; [d]South London and Maudsley NHS Foundation Trust, London, UK

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.

Ruth Knight
Department of Biostatistics and Health Informatics
Institute of Psychiatry, Psychology and Neuroscience, King's College London
De Crespigny Park, London SE5 8AF (UK)
E-Mail ruth.s.young@kcl.ac.uk

Dement Geriatr Cogn Disord 2018;45:131–151
DOI: 10.1159/000486546

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),

Dement Geriatr Cogn Disord 2018;45:131–151
DOI: 10.1159/000486546

vascular dementia (VaD), Parkinson disease dementia (PDD), dementia with Lewy bodies (DLB), or frontotemporal 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 × 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 SEs using MMSE = 0.42 × ADAS-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,

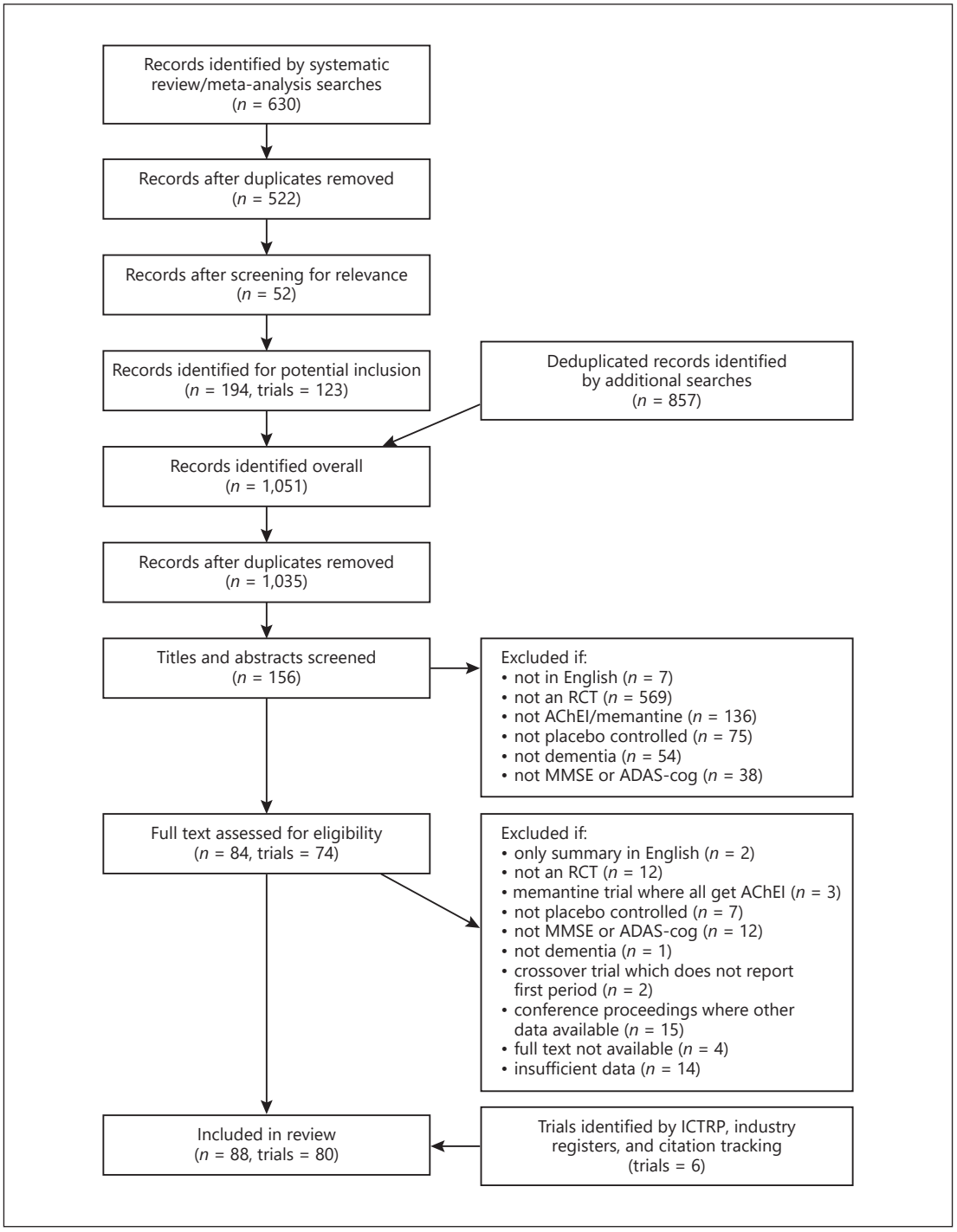


Fig. 1. Flow diagram of the trials identified for inclusion in this review via a two-tier search strategy. RCT, randomised controlled trial; AChEI, acetylcholinesterase inhibitor.

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.

Dement Geriatr Cogn Disord 2018;45:131–151
DOI: 10.1159/000486546

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 ADAS-cog	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

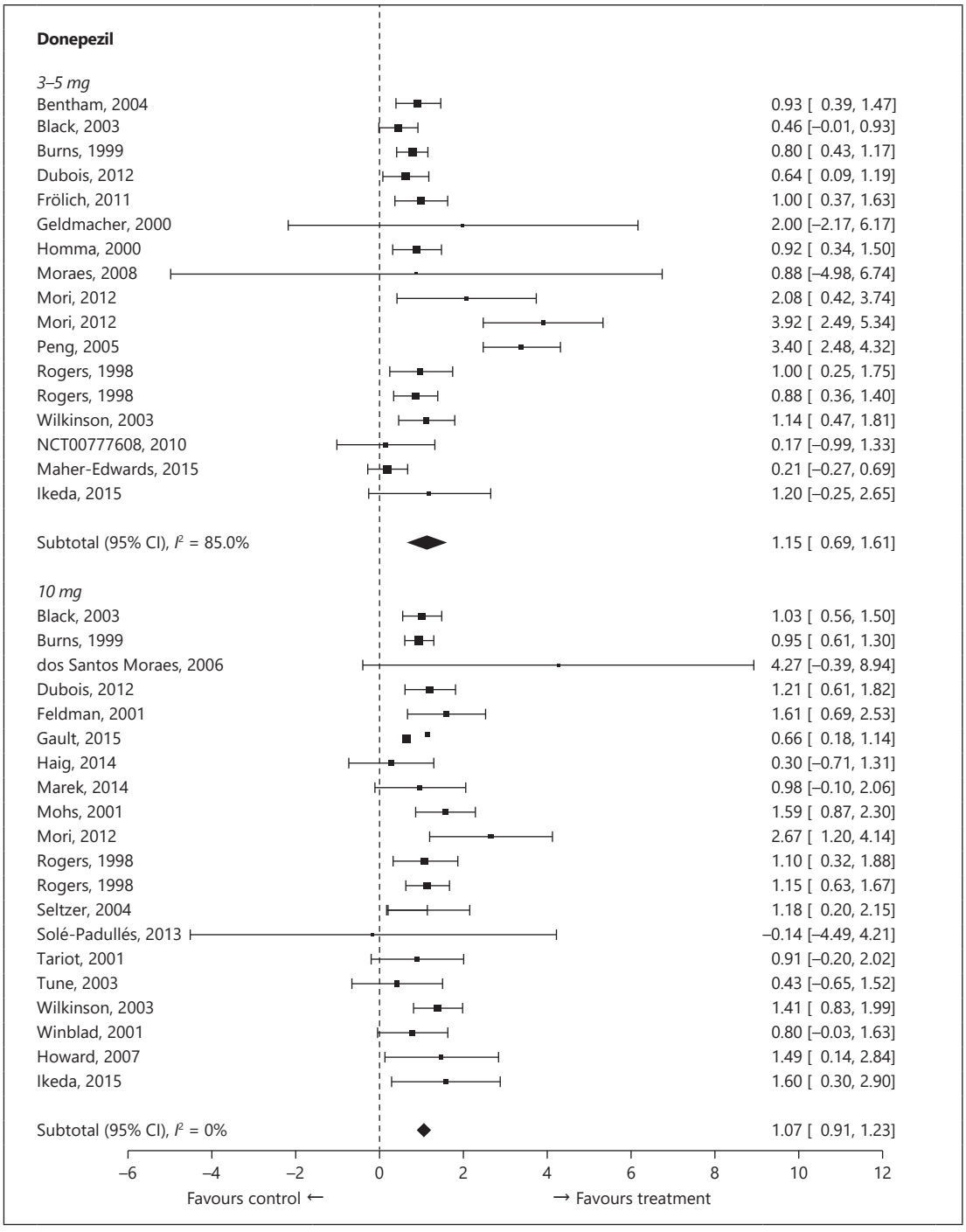
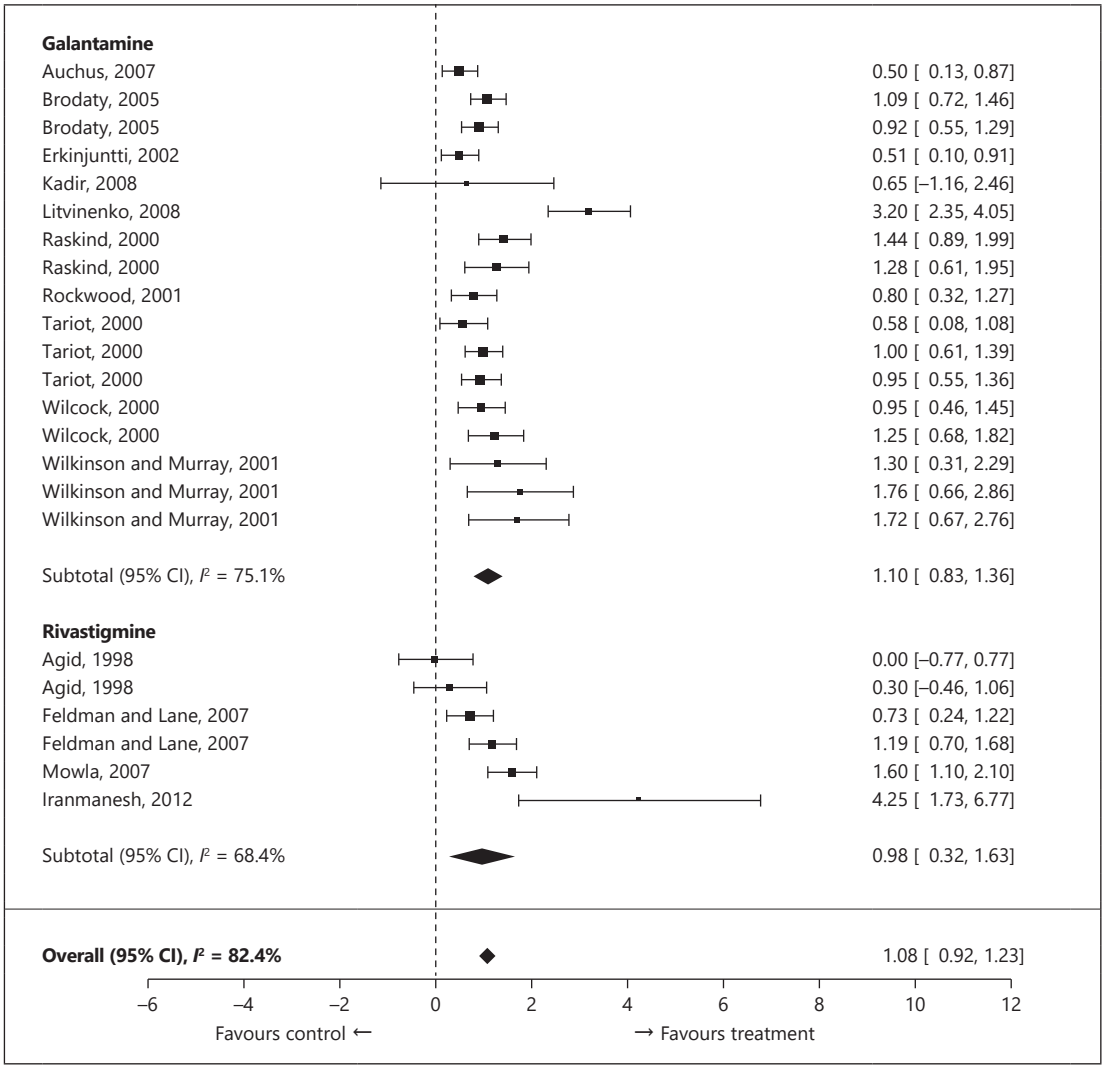


Fig. 2. Forest plot showing the treatment effects from the individual trials and meta-analysis results for acetylcholinesterase inhibitors at 3 months after treatment initiation. For the reference numbers of the studies, please refer to Table 1.

(Figure continued on next page.)



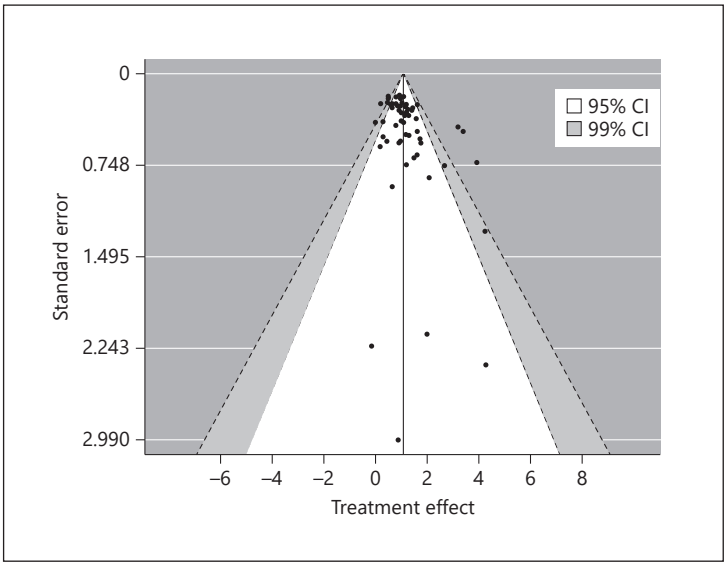


Fig. 3. Funnel plot of treatment effects at 3 months after treatment initiation. All recorded effects at 3 months ± 14 days.

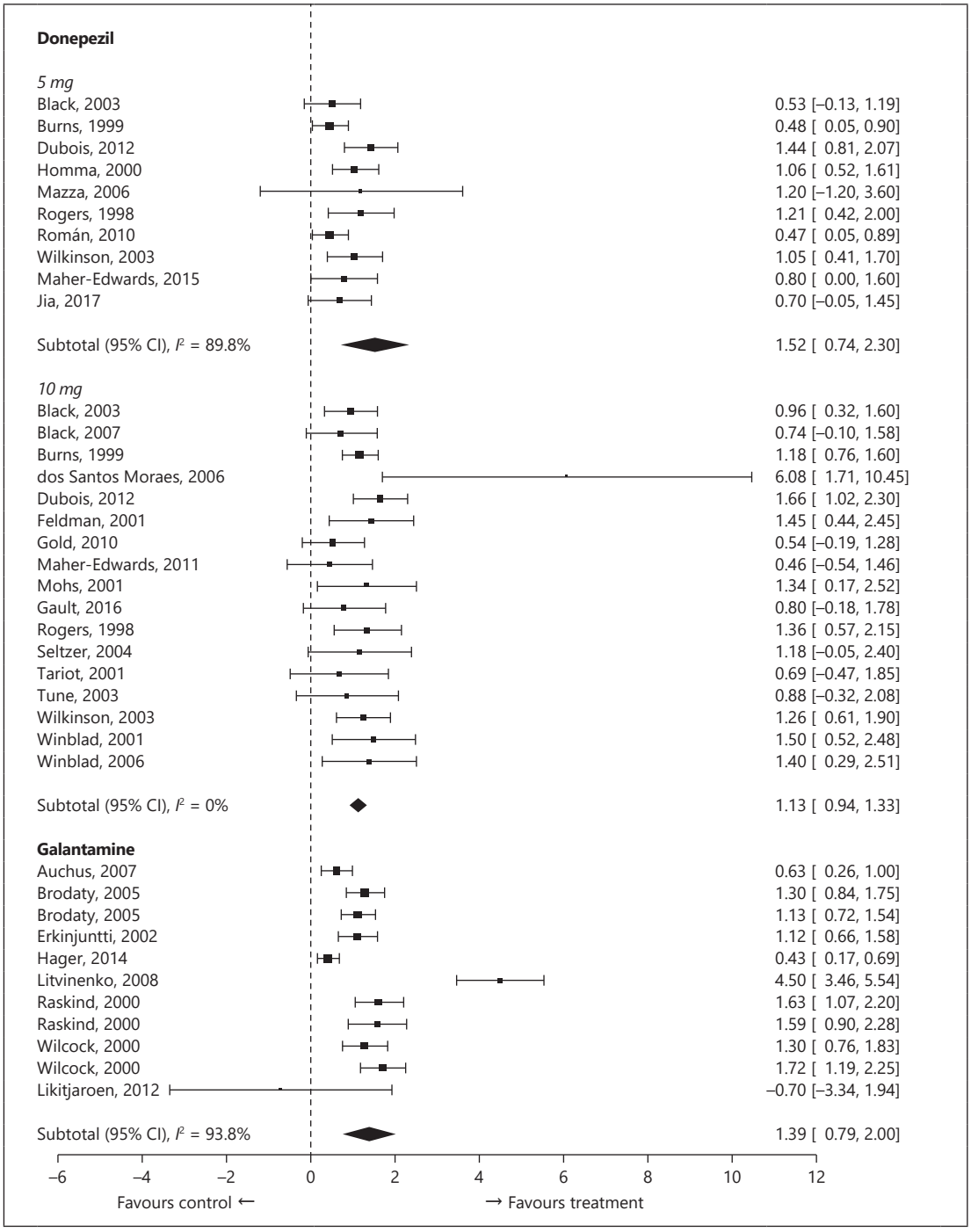
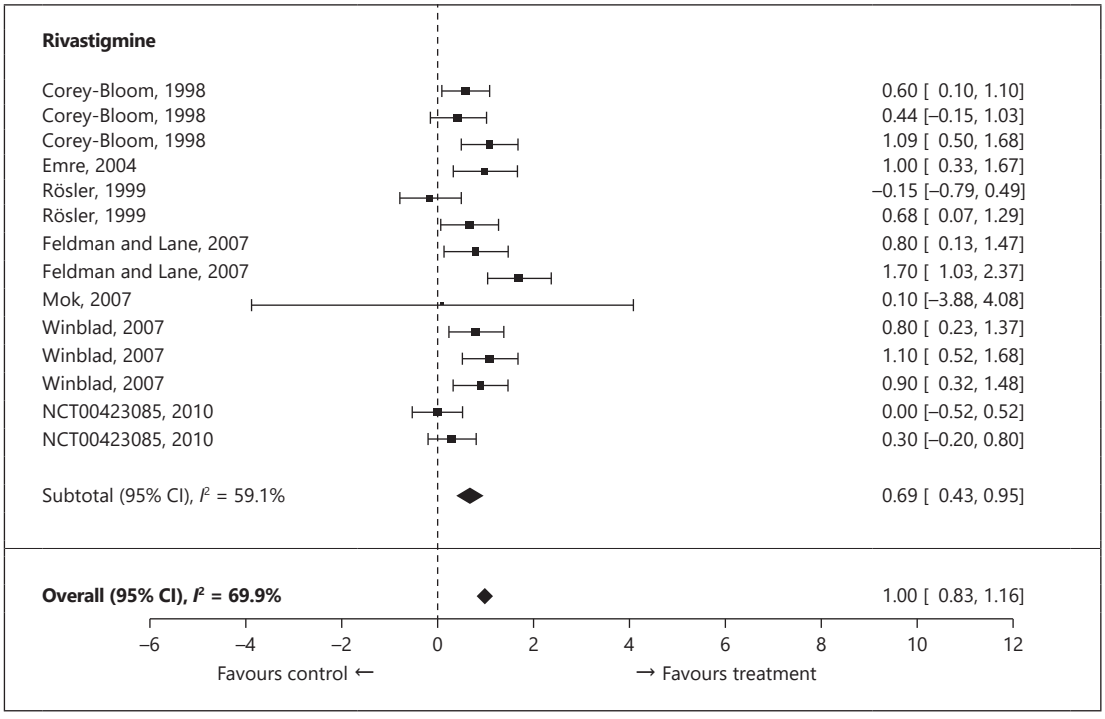


Fig. 4. Forest plot showing the treatment effects from the individual trials and meta-analysis results for acetylcholinesterase inhibitors at 6 months after treatment initiation. For the reference numbers of the studies, please refer to Table 1.

(Figure continued on next page.)



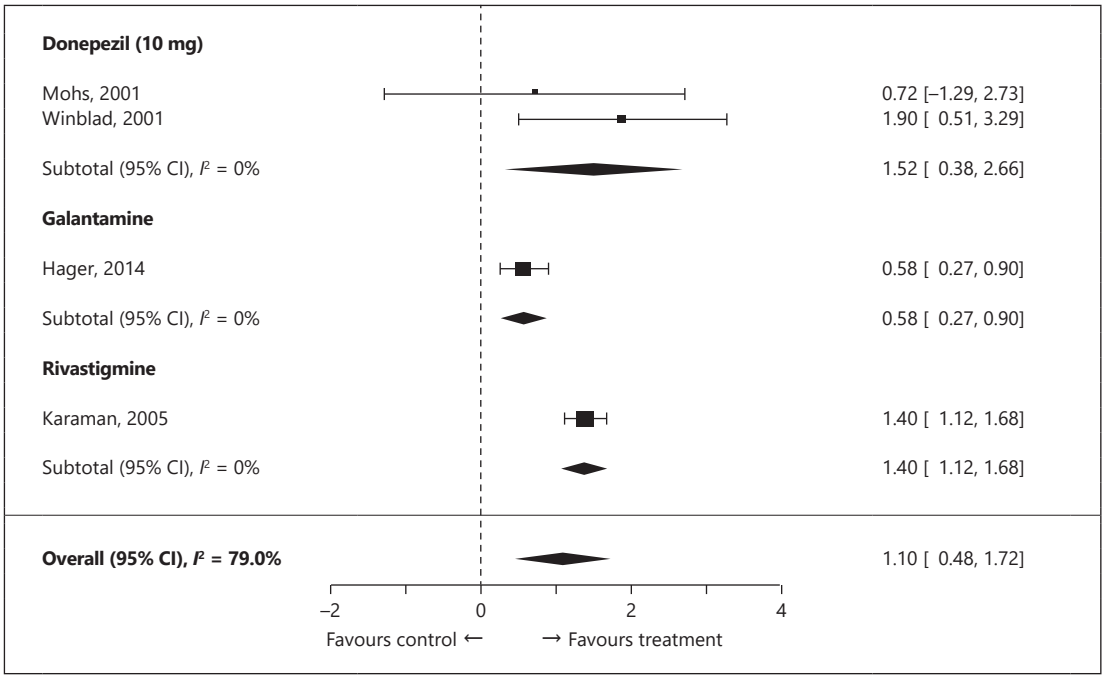


Fig. 5. Forest plot showing the treatment effects from the individual trials and meta-analysis results for acetylcholinesterase inhibitors at 12 months after treatment initiation. For the reference numbers of the studies, please refer to Table 1.

Dement Geriatr Cogn Disord 2018;45:131–151
DOI: 10.1159/000486546

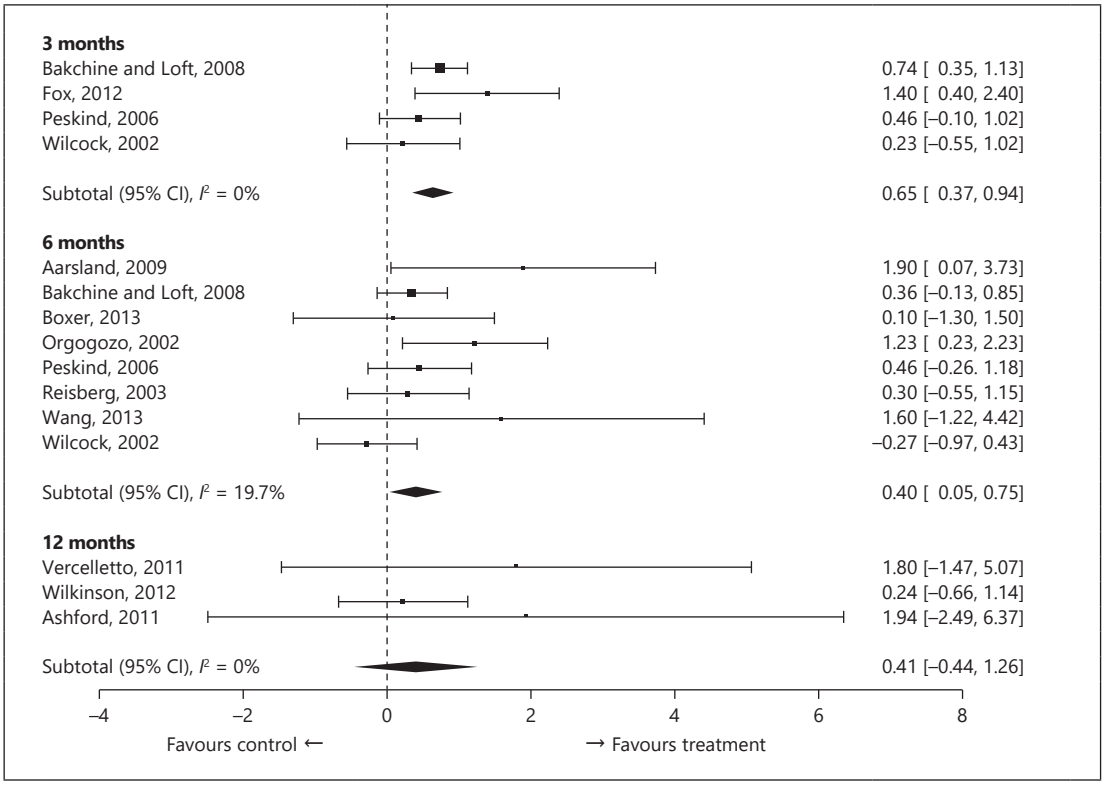


Fig. 6. Forest plots showing the treatment effects from the individual trials and meta-analysis results for memantine at 3, 6, and 12 months after treatment initiation. For the reference numbers of the studies, please refer to Table 1.

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.	
	ADAS-cog	32	–0.471 (0.007)	0.007**
Risk of bias rating	Low	8	Ref.	
	Unclear	13	–0.371 (0.307)	0.521
	High	39	–0.346 (0.269)	
Medication	Donepezil	37	Ref.	
	Galantamine	17	0.010 (0.961)	0.864
	Rivastigmine	6	–0.153 (0.612)	
Diagnosis	AD	46	Ref.	
	VaD	6	–0.211 (0.373)	0.009**
	PDD/DLB	8	0.806 (0.005)	
Baseline MMSE score	NA	55	–0.069 (0.092)	0.092
Date	Before 2000	26	Ref.	
	2000 onwards	34	0.068 (0.703)	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.	
	ADAS-cog	17	0.117 (0.540)	0.540
Risk of bias rating	Low	3	Ref.	
	Unclear	9	0.269 (0.579)	0.735
	High	40	0.329 (0.443)	
Medication	Donepezil	27	Ref.	
	Galantamine	11	0.320 (0.139)	0.033*
	Rivastigmine	14	–0.370 (0.133)	
Diagnosis	AD	39	Ref.	
	VaD	9	–0.134 (0.139)	0.007*
	PDD/DLB	4	0.970 (0.001)	
Baseline MMSE score	NA	52	–0.005 (0.869)	0.869
Date	Before 2000	17	Ref.	
	2000 onwards	35	–0.141 (0.456)	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.

Dement Geriatr Cogn Disord 2018;45:131–151
DOI: 10.1159/000486546

www.karger.com/dem

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

Dement Geriatr Cogn Disord 2018;45:131–151
DOI: 10.1159/000486546

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.

Disclosure Statement

The authors have no conflicts of interest to disclose.

Funding Sources

This paper represents independent research funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

References

1 Terry AV Jr, Buccafusco JJ: The cholinergic hypothesis of age and Alzheimer's disease-related cognitive deficits: recent challenges and their implications for novel drug development. J Pharmacol Exp Ther 2003;306:821–827.
2 Cacabelos R, Takeda M, Winblad B: The glutamatergic system and neurodegeneration in dementia: preventive strategies in Alzheimer's disease. Int J Geriatr Psychiatry 1999;14:3–47.
3 van de Glind EMM, van Enst WA, van Munster BC, Olde Rikkert MGM, Scheltens P, Scholten RJPM, Hooft L: Pharmacological treatment of dementia: a scoping review of systematic reviews. Dement Geriatr Cogn Disord 2013;36:211–228.
4 Winblad B, Jones RW, Wirth Y, Stöffler A, Möbius HJ: Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. Dement Geriatr Cogn Disord 2007;24:20–27.
5 Birks J: Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD005593.
6 Folstein MF, Folstein SE, McHugh PR: "Mini-mental state." A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
7 Rosen WG, Mohs RC, Davis KL: A new rating scale for Alzheimer's disease. Am J Psychiatry 1984;141:1356–1364.
8 Panisset M, Roudier M, Saxton J, Boiler F: Severe Impairment Battery. A neuropsychological test for severely demented patients. Arch Neurol 1994;51:41–45.
9 Tan C-C, Yu J-T, Wang H-F, Tan M-S, Meng X-F, Wang C, Jiang T, Zhu X-C, Tan L: Efficacy and safety of donepezil, galantamine, rivastigmine, and memantine for the treatment of Alzheimer's disease: a systematic review and meta-analysis. J Alzheimers Dis 2014;41:615–631.
10 Di Santo SG, Prinelli F, Adorni F, Caltagirone C, Musicco M: A meta-analysis of the efficacy of donepezil, rivastigmine, galantamine, and memantine in relation to severity of Alzheimer's disease. J Alzheimers Dis 2013;35:349–361.
11 Raina P, Santaguida P, Ismaila A, Patterson C, Cowan D, Levine M, Booker L, Oremus M: Effectiveness of cholinesterase inhibitors and memantine for treating dementia: evidence review for a clinical practice guideline. Ann Intern Med 2008;148:379–397.
12 Higgins J, Green S: Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0. The Cochrane Collaboration, 2011, 2013.
13 DerSimonian R, Laird N: Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–188.
14 Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–1558.
15 Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–1101.
16 R Core Team: R: A Language and Environment for Statistical Computing. Vienna, R Foundation for Statistical Computing, 2014.
17 Viechtbauer W: Conducting meta-analyses in R with the metafor package. J Stat Softw 2010;36:1–48.
18 Knapp G, Hartung J: Improved tests for a random effects meta-regression with a single covariate. Stat Med 2003;22:2693–2710.
19 Samuel W, Caligiuri M, Galasko D, Lacro J, Marini M, McClure FS, Warren K, Jeste DV: Better cognitive and psychopathologic response to donepezil in patients prospectively diagnosed as dementia with Lewy bodies: a preliminary study. Int J Geriatr Psychiatry 2000;15:794–802.

20 Tiraboschi P, Hansen LA, Alford M, Sabbagh MN, Schoos B, Masliah E, Thal LJ, Corey-Bloom J: Cholinergic dysfunction in diseases with Lewy bodies. Neurology 2000;54:407–411.
21 Birks J, McGuinness B, Craig D: Rivastigmine for vascular cognitive impairment. Cochrane Database Syst Rev 2013;5:CD004744.
22 Birks J, Harvey RJ: Donepezil for dementia due to Alzheimer's disease. Cochrane Database Syst Rev 2006; 1:CD001190.
23 Perera G, Khondoker M, Broadbent M, Breen G, Stewart R: Factors associated with response to acetylcholinesterase inhibition in dementia: a cohort study from a secondary mental health care case register in London. PLoS One 2014;9:e109484.
24 Ballard C, O'Brien J, Morris C, Barber R, Swann A, Neill D, McKeith I: The progression of cognitive impairment in dementia with Lewy bodies, vascular dementia and Alzheimer's disease. Int J Geriatr Psychiatry 2001;16: 499–503.
25 Knapp M, Chua K-C, Broadbent M, Chang C-K, Fernandez J-L, Milea D, Romeo R, Lovestone S, Spencer M, Thompson G: Predictors of care home and hospital admissions and their costs for older people with Alzheimer's disease: findings from a large London case register. BMJ Open 2016;6:e013591.
26 Franco-Marina F, García-González JJ, Wagner-Echeagaray F, Gallo J, Ugalde O, Sánchez-García S, Espinel-Bermúdez C, Juárez-Cedillo T, Rodríguez MÁV, García-Peña C: The Mini-Mental State Examination revisited: ceiling and floor effects after score adjustment for educational level in an aging Mexican population. Int Psychogeriatr 2010;22:72–81.
27 Dong Y, Sharma VK, Chan BP-L, Venketasubramanian N, Teoh HL, Seet RCS, Tanicala S, Chan YH, Chen C: The Montreal Cognitive Assessment (MoCA) is superior to the Mini-Mental State Examination (MMSE) for the detection of vascular cognitive impairment after acute stroke. J Neurol Sci 2010;299:15–18.
28 Osher JE, Wicklund AH, Rademaker A, Johnson N, Weintraub S: The Mini-Mental State Examination in behavioral variant frontotemporal dementia and primary progressive aphasia. Am J Alzheimers Dis Other Demen 2007;22:468–473.
29 Frölich L, Ashwood T, Nilsson J, Eckerwall G; Sirocco Investigators: Effects of AZD3480 on cognition in patients with mild-to-moderate Alzheimer's disease: a phase IIb dose-finding study. J Alzheimers Dis 2011;24:363–374.
30 Gault LM, Ritchie CW, Robieson WZ, Pritchett Y, Othman AA, Lenz RA: A phase 2 randomized, controlled trial of the α7 agonist ABT-126 in mild-to-moderate Alzheimer's dementia. Alzheimers Dement 2015;1:81–90.
31 Geldmacher DS, Perdomo C, Pratt R: Effect of donepezil treatment on visual attention/exploration tasks in patients with mild to moderately severe Alzheimer's disease: results of a pilot study. Neurobiol Aging 2000; 21:S169.
32 Marek GJ, Katz DA, Meier A, Greco N 4th, Zhang W, Liu W, Lenz RA: Efficacy and safety evaluation of HSD-1 inhibitor ABT-384 in Alzheimer's disease. Alzheimers Dement 2014;10(suppl):S364–S373.
33 Peng DT, Xu XH, Wang LN: Efficiency and safety assessment of donepezil for treating mild and moderate Alzheimer disease. Chin J Clin Rehabil 2005;9:170–172.
34 Rogers SL, Doody RS, Mohs RC, Friedhoff LT: Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebo-controlled study. Donepezil Study Group. Arch Intern Med 1998; 158:1021–1031.
35 Howard RJ, Juszczak E, Ballard CG, Bentham P, Brown RG, Bullock R, Burns AS, Holmes C, Jacoby R, Johnson T, Knapp M, Lindesay J, O'Brien JT, Wilcock G, Katona C, Jones RW, DeCesare J, Rodger M; CALM-AD Trial Group: Donepezil for the treatment of agitation in Alzheimer's disease. N Engl J Med 2007;357:1382–1392.
36 Moraes W, Poyares D, Sukys-Claudino L, Guilleminault C, Tufik S: Donepezil improves obstructive sleep apnea in Alzheimer disease: a double-blind, placebo-controlled study. Chest 2008;133:677–683.
37 Solé-Padullés C, Bartrés-Faz D, Lladó A, Bosch B, Peña-Gómez C, Castellví M, Rami L, Bargalló N, Sánchez-Valle R, Molinuevo JL: Donepezil treatment stabilizes functional connectivity during resting state and brain activity during memory encoding in Alzheimer's disease. J Clin Psychopharmacol 2013;33:199–205.
38 Haig GM, Pritchett Y, Meier A, Othman AA, Hall C, Gault LM, Lenz RA: A randomized study of H3 antagonist ABT-288 in mild-to-moderate Alzheimer's dementia. J Alzheimers Dis 2014;42:959–971.
39 Black SE, Doody R, Li H, McRae T, Jambor KM, Xu Y, Sun Y, Perdomo CA, Richardson S: Donepezil preserves cognition and global function in patients with severe Alzheimer disease. Neurology 2007;69:459–469.
40 Burns A, Rossor M, Hecker J, Gauthier S, Petit H, Möller HJ, Rogers SL, Friedhoff LT: The effects of donepezil in Alzheimer's disease – results from a multinational trial. Dement Geriatr Cogn Disord 1999;10:237–244.
41 Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E; Donepezil MSAD Study Investigators Group: A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001;57:613–620.
42 Gold M, Alderton C, Zvartau-Hind M, Egginton S, Saunders AM, Irizarry M, Craft S, Landreth G, Linnamägi U, Sawchak S: Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. Dement Geriatr Cogn Disord 2010;30:131–146.
43 Homma A, Takeda M, Imai Y, Udaka F, Hasegawa K, Kameyama M, Nishimura T: Clinical efficacy and safety of donepezil on cognitive and global function in patients with Alzheimer's disease. A 24-week, multicenter, double-blind, placebo-controlled study in Japan. E2020 Study Group. Dement Geriatr Cogn Disord 2000;11: 299–313.

44 Jia J, Wei C, Jia L, Tang Y, Liang J, Zhou A, Li F, Shi L, Doody RS: Efficacy and safety of donepezil in Chinese patients with severe Alzheimer's disease: a randomized controlled trial. J Alzheimers Dis 2017;56:1495–1504.
45 Maher-Edwards G, Dixon R, Hunter J, Gold M, Hopton G, Jacobs G, Hunter J, Williams P: SB-742457 and donepezil in Alzheimer disease: a randomized, placebo-controlled study. Int J Geriatr Psychiatry 2011;26:536–544.
46 Mazza M, Capuano A, Bria P, Mazza S: Ginkgo biloba and donepezil: a comparison in the treatment of Alzheimer's dementia in a randomized placebo-controlled double-blind study. Eur J Neurol 2006;13:981–985.
47 Gault LM, Lenz RA, Ritchie CW, Meier A, Othman AA, Tang Q, Berry S, Pritchett Y, Robieson WZ: ABT-126 monotherapy in mild-to-moderate Alzheimer's dementia: randomized double-blind, placebo and active controlled adaptive trial and open-label extension. Alzheimers Res Ther 2016;8:44.
48 Rogers SL, Farlow MR, Doody RS, Mohs R, Friedhoff LT; Donepezil Study Group: A 24-week, double-blind, placebo-controlled trial of donepezil in patients with Alzheimer's disease. Donepezil Study Group. Neurology 1998;50:136–145.
49 Seltzer B, Zolnouni P, Nunez M, Goldman R, Kumar D, Ieni J, Richardson S; Donepezil "402" Study Group: Efficacy of donepezil in early-stage Alzheimer disease: a randomized placebo-controlled trial. Arch Neurol 2004;61:1852–1856.
50 Tune L, Tiseo PJ, Ieni J, Perdomo C, Pratt RD, Votaw JR, Jewart RD, Hoffman JM: Donepezil HCl (E2020) maintains functional brain activity in patients with Alzheimer disease: results of a 24-week, double-blind, placebo-controlled study. Am J Geriatr Psychiatry 2003;11:169–177.
51 Maher-Edwards G, Watson C, Ascher J, Barnett C, Boswell D, Davies J, Fernandez M, Kurz A, Zanetti O, Safirstein B, Schronen JP, Zvartau-Hind M, Gold M: Two randomized controlled trials of SB742457 in mild-to-moderate Alzheimer's disease. Alzheimers Dement 2015;1:23–36.
52 dos Santos Moraes WA, Poyares DR, Guilleminault C, Ramos LR, Bertolucci PH, Tufik S: The effect of donepezil on sleep and REM sleep EEG in patients with Alzheimer disease: a double-blind placebo-controlled study. Sleep 2006;29:199–205.
53 Winblad B, Kilander L, Eriksson S, Minthon L, Båtsman S, Wetterholm AL, Jarisson-Blixt C, Haglund A; Severe Alzheimer's Disease Study Group: Donepezil in patients with severe Alzheimer's disease: double-blind, parallel-group, placebo-controlled study. Lancet 2006;367:1057–1065.
54 Winblad B, Engedal K, Soininen H, Verhey F, Waldemar G, Wimo A, Wetterholm AL, Zhang R, Haglund A, Subbiah P; Donepezil Nordic Study Group: A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. Neurology 2001;57:489–495.
55 Mohs RC, Doody RS, Morris JC, Ieni JR, Rogers SL, Perdomo CA, Pratt RD; "312" Study Group: A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. Neurology 2001;57:481–488.
56 Bentham P, Gray R, Raftery J, Hills R, Sellwood E, Courtney C, Farrell D, Hardyman W, Crome P, Edwards S, Lendon C, Lynch L; AD2000 Collaborative Group: Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004;363:2105–2115.
57 Tariot PN, Cummings JL, Katz IR, Mintzer J, Perdomo CA, Schwam EM, Whalen E: A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc 2001;49:1590–1599.
58 Black S, Román GC, Geldmacher DS, Salloway S, Hecker J, Burns A, Perdomo C, Kumar D, Pratt R; Donepezil 307 Vascular Dementia Study Group: Efficacy and tolerability of donepezil in vascular dementia: positive results of a 24-week, multicenter, international, randomized, placebo-controlled clinical trial. Stroke 2003;34:2323–2330.
59 Román GC, Salloway S, Black SE, Royall DR, DeCarli C, Weiner MW, Moline M, Kumar D, Schindler R, Posner H: Randomized, placebo-controlled, clinical trial of donepezil in vascular dementia: differential effects by hippocampal size. Stroke 2010;41:1213–1221.
60 Wilkinson D, Doody R, Helme R, Taubman K, Mintzer J, Kertesz A, Pratt RD; Donepezil 308 Study Group: Donepezil in vascular dementia: a randomized, placebo-controlled study. Neurology 2003;61:479–486.
61 Dichgans M, Markus HS, Salloway S, Verkkoniemi A, Moline M, Wang Q, Posner H, Chabriat HS: Donepezil in patients with subcortical vascular cognitive impairment: a randomised double-blind trial in CADASIL. Lancet Neurol 2008;7:310–318.
62 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.
63 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.
64 Leroi I, Brandt J, Reich SG, Lyketsos CG, 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.
65 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.
66 Ikeda M, Mori E, Matsuo K, Nakagawa M, Kosaka K: Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled, confirmatory phase III trial. Alzheimers Res Ther 2015;7:4.
67 Mori E, Ikeda M, Kosaka K; Donepezil-DLB Study Investigators: Donepezil for dementia with Lewy bodies: a randomized, placebo-controlled trial. Ann Neurol 2012;72:41–52.

68 Wilkinson D, Murray J: Galantamine: a randomized, double-blind, dose comparison in patients with Alzheimer's disease. Int J Geriatr Psychiatry 2001;16:852–857.
69 Kadir A, Darreh-Shori T, Almkvist O, Wall A, Grut M, Strandberg B, Ringheim A, Eriksson B, Blomquist G, Långström B, Nordberg A: PET imaging of the in vivo brain acetylcholinesterase activity and nicotine binding in galantamine-treated patients with AD. Neurobiol Aging 2008;29:1204–1217.
70 Rockwood K, Mintzer J, Truyen L, Wessel T, Wilkinson D: Effects of a flexible galantamine dose in Alzheimer's disease: a randomised, controlled trial. J Neurol Neurosurg Psychiatry 2001;71:589–595.
71 Rockwood K, Fay S, Song X, MacKnight C, Gorman M; Video-Imaging Synthesis of Treating Alzheimer's Disease (VISTA) Investigators: Attainment of treatment goals by people with Alzheimer's disease receiving galantamine: a randomized controlled trial. CMAJ 2006;174:1099–1105.
72 Tariot PN, Solomon PR, Morris JC, Kershaw P, Lilienfeld S, Ding C: A 5-month, randomized, placebo-controlled trial of galantamine in AD. The Galantamine USA-10 Study Group. Neurology 2000;54:2269–2276.
73 Brodaty H, Corey-Bloom J, Potocnik FCV, Truyen L, Gold M, Damaraju CRV: Galantamine prolonged-release formulation in the treatment of mild to moderate Alzheimer's disease. Dement Geriatr Cogn Disord 2005;20:120–132.
74 Raskind MA, Peskind ER, Wessel T, Yuan W: Galantamine in AD: a 6-month randomized, placebo-controlled trial with a 6-month extension. The Galantamine USA-1 Study Group. Neurology 2000;54:2261–2268.
75 Wilcock GK, Lilienfeld S, Gaens E: Efficacy and safety of galantamine in patients with mild to moderate Alzheimer's disease: multicentre randomised controlled trial. Galantamine International-1 Study Group. BMJ 2000;321:1445–1449.
76 Likitjaroen Y, Meindl T, Friese U, Wagner M, Buerger K, Hampel H, Teipel SJ: Longitudinal changes of fractional anisotropy in Alzheimer's disease patients treated with galantamine: a 12-month randomized, placebo-controlled, double-blinded study. Eur Arch Psych Clin Neurosci 2012;262:341–350.
77 Hager K, Baseman AS, Nye JS, Brashear HR, Han J, Sano M, Davis B, Richards HM: Effects of galantamine in a 2-year, randomized, placebo-controlled study in Alzheimer's disease. Neuropsychiatr Dis Treat 2014;10:391–401.
78 Erkinjuntti T, Kurz A, Gauthier S, Bullock R, Lilienfeld S, Damaraju CV: Efficacy of galantamine in probable vascular dementia and Alzheimer's disease combined with cerebrovascular disease: a randomised trial. Lancet 2002;359:1283–1290.
79 Auchus AP, Brashear HR, Salloway S, Korczyn AD, De Deyn PP, Gassmann-Mayer C; GAL-INT-26 Study Group: Galantamine treatment of vascular dementia: a randomized trial. Neurology 2007;69:448–458.
80 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). Neurosci Behav Physiol 2008;38:937–945.
81 Koch G, Di Lorenzo F, Bonni S, Giacobbe V, Bozzali M, Caltagirone C, Martorana A: Dopaminergic modulation of cortical plasticity in Alzheimer's disease patients. Neuropsychopharmacology 2014;39:2654–2661.
82 Mowla A, Mosavinasab M, Haghshenas H, Borhani Haghighi A: Does serotonin augmentation have any effect on cognition and activities of daily living in Alzheimer's dementia? A double-blind, placebo-controlled clinical trial. J Clin Psychopharmacol 2007;27:484–487.
83 Iranmanesh F, Vakilian A, Gadari F, Syadi A, Mehrabian M, Moradi M, Raesy E: Piracetam, rivastigmine and their joint consumption effects on MMSE score status in patients with Alzheimer's disease. IJPT 2012;11:60–63.
84 Agid Y, Dubois B, Anand R, Gharabawi G; International Rivastigmine Investigators: Efficacy and tolerability of rivastigmine in patients with dementia of the Alzheimer type. Curr Ther Res Clin Exp 1998;59:837–845.
85 Forette F, Anand R, Gharabawi G: A phase II study in patients with Alzheimer's disease to assess the preliminary efficacy and maximum tolerated dose of rivastigmine (Exelon). Eur J Neurol 1999;6:423–429.
86 Winblad B, Cummings J, Andreasen N, Grossberg G, Onofrj M, Sadowsky C, Zechner S, Nagel J, Lane R: A six-month double-blind, randomized, placebo-controlled study of a transdermal patch in Alzheimer's disease – rivastigmine patch versus capsule. Int J Geriatr Psychiatry 2007;22:456–467.
87 Rösler M, Anand R, Cicin-Sain A, Gauthier S, Agid Y, Dal-Bianco P, Stähelin HB, Hartman R, Gharabawi M: Efficacy and safety of rivastigmine in patients with Alzheimer's disease: international randomised controlled trial. BMJ 1999;318:633–638.
88 Corey-Bloom J, Anand R, Veach J: A randomized trial evaluating the efficacy and safety of ENA 713 (rivastigmine tartrate), a new acetylcholinesterase inhibitor, in patients with mild to moderately severe Alzheimer's disease. Int J Geriatr Psychopharmacol 1998;1:55–65.
89 Feldman HH, Lane R: Rivastigmine: a placebo controlled trial of twice daily and three times daily regimens in patients with Alzheimer's disease. J Neurol Neurosurg Psychiatry 2007;78:1056–1063.
90 Karaman Y, Erdoğan F, Köseoğlu E, Turan T, Ersoy AO: A 12-month study of the efficacy of rivastigmine in patients with advanced moderate Alzheimer's disease. Dement Geriatr Cogn Disord 2005;19:51–56.
91 Ballard C, Sauter M, Scheltens P, He Y, Barkhof F, van Straaten ECW, van der Flier WM, Hsu C, Wu S, Lane R: Efficacy, safety and tolerability of rivastigmine capsules in patients with probable vascular dementia: the VantagE study. Curr Med Res Opin 2008;24:2561–2574.
92 Mok V, Wong A, Ho S, Leung T, Lam WWM, Wong KS: Rivastigmine in Chinese patients with subcortical vascular dementia. Neuropsychiatr Dis Treat 2007;3:943–948.

Dement Geriatr Cogn Disord 2018;45:131–151
DOI: 10.1159/000486546

93 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.
94 Fox C, Crugel M, Maidment I, Auestad BH, Coulton S, Treloar A, Ballard C, Boustani M, Katona C, Livingston G: Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. PLoS One 2012;7:e35185.
95 Bakchine S, Loft H: Memantine treatment in patients with mild to moderate Alzheimer's disease: results of a randomised, double-blind, placebo-controlled 6-month study. J Alzheimers Dis 2008;13:97–107.
96 Peskind ER, Potkin SG, Pomara N, Ott BR, Graham SM, Olin JT, McDonald S: Memantine treatment in mild to moderate Alzheimer disease: a 24-week randomized, controlled trial. Am J Geriatr Psychiatry 2006;14:704–715.
97 Wang T, Huang Q, Reiman EM, Chen K, Li X, Li G, Lin Z, Li C, Xiao S: Effects of memantine on clinical ratings, fluorodeoxyglucose positron emission tomography measurements, and cerebrospinal fluid assays in patients with moderate to severe Alzheimer dementia: a 24-week, randomized, clinical trial. J Clin Psychopharmacol 2013;33:636–642.
98 Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ; Memantine Study Group: Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333–1341.
99 Ashford JW, Adamson M, Beale T, La D, Hernandez B, Noda A, Rosen A, O'Hara R, Fairchild JK, Spielman D, Yesavage JA: MR spectroscopy for assessment of memantine treatment in mild to moderate Alzheimer dementia. J Alzheimers Dis 2011;26(suppl 3):331–336.
100 Wilkinson D, Fox NC, Barkhof F, Phul R, Lemming O, Scheltens P: Memantine and brain atrophy in Alzheimer's disease: a 1-year randomized controlled trial. J Alzheimers Dis 2012;29:459–469.
101 Orgogozo JM, Rigaud AS, Stöffler A, Möbius HJ, Forette F: Efficacy and safety of memantine in patients with mild to moderate vascular dementia: a randomized, placebo-controlled trial (MMM 300). Stroke 2002;33:1834–1839.
102 Wilcock G, Möbius HJ, Stöffler A; MMM 500 Group: A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia (MMM500). Int Clin Psychopharmacol 2002;17:297–305.
103 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;24:1217–1221.
104 Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, Leroi I, Pozo-Rodriguez F, Minthon L, Londos E: 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.
105 Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, Mendez M, Kerwin D, Lerner A, Wu CK, Koestler M, Shapira J, Sullivan K, Klepac K, Lipowski K, Ullah J, Fields S, Kramer JH, Merrilees J, Neuhaus J, Mesulam MM, Miller BL: Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. Lancet Neurol 2013;12:149–156.
106 Vercelletto M, Boutoleau-Bretonnière C, Volteau C, Puel M, Auriacombe S, Sarazin M, Michel BF, Couratier P, Thomas-Antérion C, Verpillat P, Gabelle A, Golfier V, Cerato E, Lacomblez L; French Research Network on Frontotemporal Dementia: Memantine in behavioral variant frontotemporal dementia: negative results. J Alzheimers Dis 2011;23:749–759.