



# EFFECTIVENESS OF ACETYLCHOLINESTERASE INHIBITORS AND MEMANTINE IN THE TREATMENT OF ALZHEIMER'S DISEASE: A SYSTEMATIC REVIEW AND COMPARATIVE ANALYSIS

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**Abstract:** *Introduction:* Many randomized throughout placebo-controlled trials have investigated the use of acetylcholinesterase inhibitors (AChEIs) and memantine in Alzheimer's disease (AD). However, few trials comparing different drugs have been conducted, meaning their relative effectiveness is not well-established. *Methods:* A systematic review of randomized controlled trials was conducted to identify the evidence base for donepezil, galantamine, rivastigmine, and memantine when used within European licensing limits. Literature databases (start to March 2010) and conference proceedings (2007 - 2010) were screened. Mixed treatment comparisons (MTC), were used to evaluate the comparative efficacy and safety. *Results:* Fifty-eight studies were identified; 48 were placebo comparisons, indicating the limited comparative evidence. Direct meta-analysis demonstrated that AChEIs are associated with significant advantage over placebo in cognitive outcomes at 3 months and 6 months ( $p < 0.05$ ); the pooled results of two studies did not indicate a significant advantage for memantine over placebo. An advantage for galantamine and donepezil over placebo in behavior at 6 months (NPI scale) was observed. MTC analysis identified no significant difference between AChEIs for cognition at 3 and 6 months, nor for behavior. A small increase in frequency of any adverse event was observed for AChEIs (approximate relative risk of 1.1) but not for memantine. Oral rivastigmine was associated with a higher risk of all and specific adverse events than other treatments. *Conclusions:* The benefits of AChEIs but not memantine on cognition in AD were established. No clear difference in cognition or behavior is apparent between AChEIs.

**Key words:** Alzheimer's disease, meta-analysis, mixed treatment comparison, acetylcholinesterase inhibitors, memantine.

**Abbreviations:** AChEIs: Acetylcholinesterase inhibitors; AD: Alzheimer's Disease; ADAS-cog: Alzheimer's Disease Assessment Scale-cognitive subscale; BEHAVE-AD: Behavioral pathology in Alzheimer's Disease rating scale; CI: Confidence interval; CONSORT: Consolidated Standards of Reporting Trials; CrI: Credible interval; CSR: Clinical Study Report; CTRS: Clinical Trial Report Summary; ITT: Intention to treat analysis; MMSE: Mini-mental state examination; MTC: Mixed Treatment Comparison; NMDA: N-methyl-D-aspartate; NPI: Neuropsychiatric Inventory; NPI-D: Neuropsychiatric Inventory - Distress subscale; RCT: Randomized Controlled Trial; RR: Risk ratio; SIB: Severe Impairment Battery; SMD: Standardized Mean Difference; WMD: Weighted Mean Difference.

## Background

Alzheimer's disease (AD) is the most common form of dementia. It is characterized by a progressive decline in cognition, consequent impairment in activities of daily living, and psycho-behavioral disturbances (1).

Evaluation of cognitive function in AD patients is commonly conducted in trials using the cognitive

subscale of the Alzheimer's Disease and Associated Disorders Scale (ADAS-cog) (2), while the Mini Mental State Examination (MMSE) (3) is more frequently used in clinical practice. The ADAS-cog and MMSE scales are both used to assess cognitive impairment, and interconvertibility of these scales has been demonstrated (4, 5). For the assessment of moderate to severe cognitive impairment, the Severe Impairment Battery (SIB) is frequently used since this measure is considered more capable of identifying differences in performance at the lower score region of the MMSE (6). Specific scales are used to assess behavioral symptoms, for example the Neuropsychiatric Inventory (NPI) and care giver distress scale (NPI-D), and the Behavioral Pathology in

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Alzheimer's disease Rating Scale (BEHAVE-AD).

Over the last decade, there has been established use of two types of pharmacological interventions, namely acetylcholinesterase inhibitors (AChEIs; donepezil, galantamine, and rivastigmine) and N-methyl D-aspartate (NMDA; memantine) receptor antagonists are currently available for the treatment of AD.

Multiple systematic reviews of AChEIs and memantine in AD have been conducted, including by the Cochrane Collaboration (7-9), as part of health technology assessments (10-12), and other published examples (13,14). All these reviews have used pooled direct comparisons to establish the efficacy and safety of these treatments compared to placebo. However, even where these comparisons have been reviewed, only qualitative comparisons of a limited number of trials comparing active treatments have been used to establish the relative efficacy and safety of active treatments.

Analysis by mixed treatment comparison (MTC) involves using data both from direct comparisons, and indirect evidence from comparisons against a common comparator (in this case placebo). It is a potentially valuable method to examine comparative effectiveness, especially when the amount of direct comparative evidence is restricted. This review aims to provide a comprehensive assessment of the evidence for the treatment of AD on cognitive, behavioral and safety outcomes through the use of systematic review, meta-analysis and MTC, comparing AChEIs and memantine both to placebo treatment and to each other.

## Methods

### *Study eligibility criteria*

Blinded and unblinded randomized controlled trials (RCTs) reported in English were included. Reflecting the 3- to 6- months recommendation for observation of response to therapy in clinical practice (15,16), the duration of the randomized phase was required to be at least 12 weeks. Studies were included that compared donepezil, galantamine, rivastigmine (oral or transdermal formulations) or memantine against each other, placebo/no treatment or best supportive care in patients with AD. Only treatment arms that considered assessed these interventions within European licensing limits with regard to dose (maintenance dose 5-10 mg/day for donepezil, 16-24 mg/day for galantamine, 3-6 mg twice daily for oral rivastigmine, 9.5 mg/24 h for rivastigmine patch, and 10 mg twice daily for memantine) and AD severity (mild to moderately severe for AChEIs and moderate to severe for memantine) were considered. The studies reporting data for a mixed population (with regard to dose and AD severity) were included only when subgroup data for the patient population of interest were reported in the publication.

### *Data sources*

MEDLINE®, Embase® and the Cochrane Central Register of Controlled Trials were searched from database start until 10 March 2010. In addition to the database searches, the following conferences were hand-searched, examining the last 3 years proceedings, since beyond this cut-off the majority of data have typically been published within a journal if this will occur (17): International Conference on Alzheimer's Disease (2007, 2008, 2009), International Psychogeriatric Association (2007, 2009), European Psychiatric Association (2008, 2009, 2010), and European Federation of Neurological Societies (2007, 2008, 2009). The bibliographies of recent systematic reviews in AD were reviewed to identify any studies not retrieved through the database search (7-10,12). Additionally, clinical study reports supplied by Janssen-Cilag provided supplementary data for the review and analysis.

### *Synthesis of evidence*

Data from studies identified in the systematic review were extracted, and each study critically appraised. A modified CONSORT checklist assessed quality of reporting (18) and the Jadad scoring system was used to evaluate adequacy of randomization, blinding and reporting of withdrawals (19). Descriptive assessment of each included study was also completed. Clinical heterogeneity with respect to the patient population and study methodology was judged qualitatively. Individual studies differing substantially from the group were excluded from the quantitative analyses. For a study to be included in the analysis of relative risk of an event, the number of patients with the event and the total number of patients evaluated were required to be reported. For analysis of change from baseline in an outcome measure, mean change and accompanying standard deviation were required. Where not available, the standard deviation was back-calculated from the standard error or 95% CI (confidence interval). Studies reporting data graphically were not included in the analysis. For the analyses of change from baseline, data from intent-to-treat (ITT) analysis were used where possible, otherwise last-observation carried forward, or observed data were substituted in this order of preference.

For analysis of efficacy outcomes, data reported at time points ranging between 12 weeks and 16 weeks were pooled as a 3- month time point. Similarly, data reported between 22 weeks and 28 weeks were pooled as a 6-month time point. If studies included more than one treatment arm with different doses (within the licensing limit) of the same treatment, data for the two arms were pooled. Similarly, the two formulations of galantamine (twice daily and prolonged release) were pooled together.





The oral and patch formulations of rivastigmine were analyzed separately due to their different modes of action and the differences in the AE profiles associated with these formulations.

### Direct meta-analysis

Pooled direct comparisons were made using conventional meta-analysis techniques using Stata® statistical software. The metan meta-analysis command was used, as written and described by Bradburn and colleagues (20). Both fixed-effects and random-effects estimates were calculated, using the inverse variance (for change from baseline outcomes) or Mantel-Haenszel (for relative risks) methods (21) for fixed-effects, and the DerSimonian and Laird (22) method for random-effects. Effect sizes were expressed as risk ratios (RR) with the associated 95% CI for dichotomous outcomes, and as weighted mean difference (WMD) or standardized mean difference (SMD) with the associated 95% CI for continuous outcomes. SMDs were used to combine the results of trials where different scales were used to measure cognitive outcomes (ADAS-cog, MMSE, and SIB) and behavioral outcomes (NPI-10 and NPI-12), whereas WMDs were used where trials reported results from the same scale. The Hedge's *g* method was used for deriving and pooling SMDs (23). The statistical heterogeneity within each analysis was assessed using the *I*<sup>2</sup> statistic (24).

### Indirect comparison and mixed treatment comparison

From the results of direct meta-analyses, evidence networks were produced to identify further comparative analyses that could be performed. Where networks included only indirect evidence, indirect treatment comparisons (ITCs) were performed according to the method described by Bucher and colleagues (25). If the networks included both direct and indirect evidence, Bayesian MTC analysis was conducted. Both these methodologies allow the comparison of treatments not otherwise available in head-to-head clinical trials, mediated via a common comparator. Further, MTC analysis combines this with available direct evidence. The key assumption behind MTC analysis is that the direct and indirect evidence for the same comparison does not disagree beyond chance (26). To provide further explanation of these techniques, the use of direct meta-analysis, indirect comparison and mixed treatment comparison are shown in Figure 1. The MTC analysis was conducted using a Bayesian technique with WinBUGS software. The results are reported as median values (effect sizes) with the corresponding 95% credible intervals (CrIs). Credible intervals are the Bayesian

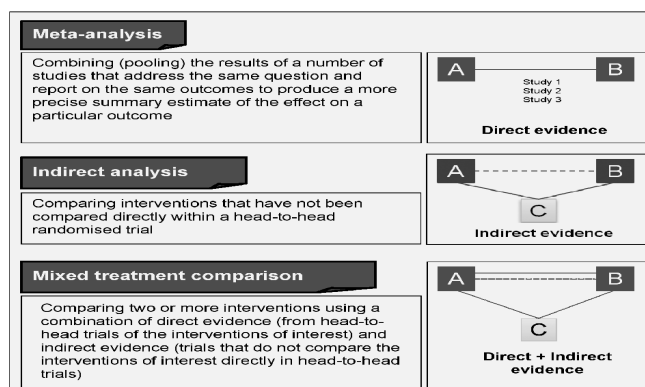
equivalent of classical confidence intervals. Statistical significance was assessed based on whether the CrI included the zero value. Also reported was the estimated probability that each treatment is the best treatment based on the number of iterations where the treatment came first, in line with the Bayesian approach. Further details of the MTC methods can be found elsewhere (27).

## Results

### Identified studies

After screening, 58 studies were identified that fulfilled the inclusion criteria (Table 1). After examining study populations and data reporting, 12 studies were excluded from the quantitative analysis (Figure 2). Five studies were excluded due to methodological issues including active pre-treatment and patient selection (28-31) and poor study design (double randomization in the study by Courtney et al. and inadequate method of randomization [based on patients' order of arrival at the center] in the study by Aguglia et al.) (32, 33). Another study was excluded due to the presentation of responder-only analysis (GAL ITA 2 Study). The remaining studies were excluded from the analysis because they either included a patient population not comparable to rest of the included studies (patients with Down's syndrome included in the study by Prasher et al.) (34) or reported data qualitatively, or graphically (35-39), or provided limited information in the English abstract (40).

**Figure 1**  
Evidence networks showing meta-analysis, indirect comparison and mixed treatment comparison



Plain line represents direct evidence; dashed line represents indirect evidence derived from network

Forty-eight of the studies identified were comparison with placebo; nine trials compared active treatments and the remaining study compared donepezil versus no treatment (44). Of the nine trials comparing active treatments, only certain of these were powered enough to





**Table 1**  
List of included studies

Study name	Sample size	Study design (RCT)	Study duration (weeks)	Location	Interventions Age, mean (SD)	Patient population Gender (% male)	Primary study outcome	Secondary study outcome
<i>Donepezil versus placebo</i> E2020 Study (71)	268	Double blind, multicenter	24	Japan	Donepezil 5 mg/day Placebo	70.1 (7.6) 69.4 (8.8)	ADAS-cog, J-CGIC	Safety, Withdrawals, CDR-SB, MENFIS, CMCS
Mazza 2006 (72)	76	Double blind, location unclear	24	-	Donepezil 5 mg/day Placebo	64.5 (6.0) 69.8 (3.0)	-	MMSE, Withdrawals, CGI, SKT
Peng 2005 (38,39)	89	Single blind, multicenter	12	China	Donepezil 5 mg/day Placebo	-	-	MMSE, Safety, CDR scale, ADL
Rogers 1996 (76)	161	Double blind, multicenter	12	USA	Donepezil 5 mg/day Placebo	72.9 70.6	ADAS-cog, CGIC	ADL, CDR-SB, Patient or caregiver (QoL-P and QoL-C), MMSE, Safety, Withdrawals
AD2000 Study (32)	566	Double blind, multicenter	114	UK	Donepezil 5-10 mg/day Placebo	76.0* (54.0 - 93.0)† 75.0* (46.0 - 90.0)†	Institutional care, BADLS	MMSE, NPI, GHQ-30, Safety, Withdrawals
Maier-Edwards 2008 (77)	197	Double blind, location unclear	24	-	Donepezil 5-10 mg/day Placebo	-	ADAS-cog, CIBIC-plus	Safety
312 Study (78,79)	431	Double blind, multicenter	54	USA	Donepezil 10 mg/day Placebo	75.4 (0.6) 75.3 (0.6)	Time to reach clinically evident functional decline	MMSE, Safety, Withdrawals, ADFACS, CDR
Alderton 2009 (80-82)	581	Double blind, location unclear	24	-	Donepezil 10 mg/day Placebo	72.9 72.5	ADAS-cog, CIBIC-plus	NPI, Safety, Withdrawals, DAD
AWARE Study (28,29)	202	Double blind, multicenter-international	12	Belgium, Denmark, Germany, Greece, Hungary, Iceland, The Netherlands, Poland and USA	Donepezil 10 mg/day Placebo	74.1 (7.6) 71.4 (9.3)	ADAS-cog	MMSE, NPI, Safety, Withdrawals, DAD
Donepezil 402 Study (83,84)	153	Double blind, multicenter	24	USA	Donepezil 10 mg/day Placebo	73.3 (9.6) 75.1 (8.8)	ADAS-cog	MMSE, CDR, CMBT, Apathy Scale, Patients Global Assessment Scale, HAM-D, Safety, Withdrawals
Frolich 2009 (35)	567	Double blind, multicenter	12	-	Donepezil 10 mg/day Placebo	73.0¶	ADAS-cog	MMSE, ADCS-CGIC, CDR computerized test battery, Patient reported outcomes (DAD, CMAI, ZBI, AAIQOL), Safety
Holmes 2004 (30)	96	Double blind, multicenter	12	UK	Donepezil 10 mg/day Placebo	78.6 (1.4)# 78.8 (1.2)#	NPI	NPI-D, MMSE, Safety, Withdrawals
Kemp 2003 (85)	12	Double blind, single center	17.3	UK	Donepezil 10 mg/day Placebo	75.0¶¶	-	Withdrawal, I-QNB imaging
Krishnan 2003 (86)	67	Double blind, multicenter	24	-	Donepezil 10 mg/day Placebo	74.4 (7) 72.4 (10.1)	Change in n-acetyl aspartate	ADAS-cog, Hippocampal volume, Brain myo inositol concentrations, Withdrawals, Safety
Moraes 2006 (36)	35	Double blind, multicenter	26	Brazil	Donepezil 10 mg/day Placebo	77.4 (6.6) 74.5 (9.8)	REM sleep	ADAS-cog, Safety
Moraes 2008 (37)	23	Double blind, single center	13	Brazil	Donepezil 10 mg/day Placebo	76.8 (6.2) 72.6 (11.0)	AHI	ADAS-cog, Safety
Prasher 2002 (34)	31	Double blind, single center	24	UK	Donepezil 10 mg/day Placebo	53.1 (8.0) 55.1 (4.6)	DMR	NPI, SIB, Safety, Withdrawals, ABS
Tartot 2001 (87)	208	Double blind, multicenter	24	USA	Donepezil 10 mg/day Placebo	85.4 85.9	NPI	MMSE, CDR-SB, PSMS, Safety, Withdrawals
Tune 2003 (56)	28	Double blind, single center	24	USA	Donepezil 10 mg/day Placebo	73.7 72.2	Change in relative AGMABS	ADAS-cog, NPI, Withdrawals
Winblad 2001 (88,89)	286	Double blind, multicenter-international	52	Denmark, Finland, Norway, Sweden, and The Netherlands	Donepezil 10 mg/day Placebo	72.1 (8.6) 72.9 (8.0)	GBS	MMSE, GDS, ADL, PDS, NPI, Safety, Withdrawals
MSAD Study (63-70)	291	Double blind, multicenter-international	24	Canada, Australia, and France	Donepezil 10 mg/day Placebo	74.3 (52 - 92)† 74.3 (40 - 90)†	CIBIC-plus	MMSE, SIB, DAD, IADL, PSMS, Safety, Withdrawals





**Table 1 (continued)**  
List of included studies

Study name	Sample size	Study design (RCT)	Study duration (weeks)	Location	Interventions	Patient population Age, mean (SD)	Gender (% male)	Primary study outcome	Secondary study outcome
Requena 2006 (44,45)	86	Blinding unclear, single center	104	Spain	Donepezil 10 mg/day No treatment	78.8 (6.6) 70.9 (8.1)	33.3 16.7	-	ADAS-cog, MMSE, GDS, FAST
Burns 1999 (90)	818	Double blind, multicenter-international	24	Australia, Belgium, Canada, France, Germany, Ireland, New Zealand, South Africa, and UK	Donepezil 10 mg/day Donepezil 5 mg/day Placebo	72.0 (0.5) 71.0 (0.5)#	43.0 45.0	ADAS-cog, CIBIC	CDR, IDDD, Patient related QoL, Safety, Withdrawals
Rogers 1998 (91,92)	468	Double blind, multicenter	12	USA	Donepezil 10 mg/day Donepezil 5 mg/day Placebo	73.4 (0.7)# 73.8 (0.7)# 74.0 (0.7)#	39.0 31.0 39.0	ADAS-cog, CIBIC-plus	MMSE, QoL, Safety, Withdrawals, CDR-SB
Rogers 1998a (93)	473	Double blind, multicenter	24	USA	Donepezil 10 mg/day Donepezil 5 mg/day Placebo	74.6 (0.6)# 72.9 (0.6)# 72.6 (0.6)#	38.0 37.0 39.0	ADAS-cog, CIBIC-plus	MMSE, CDR-SB, QoL, Safety, Withdrawals
<i>Galantamine versus placebo</i> Broday 2005 (53-55)	971	Double blind, multicenter-international	26	USA, Australia, Canada, South Africa, and New Zealand	Galantamine 16-24 mg/day Galantamine 16-24 mg/day (PRC) Placebo	76.5 (7.8) 76.6 (7.6) 76.3 (8.0)	36.0 36.0	ADAS-cog, CIBIC-plus	ADCS-ADL, percentage of responders, Safety, NPI, MMSE, withdrawals
GALITA 2 Study 2005\$	139	Double blind, multicenter	104	Italy	Galantamine 24 mg/day Placebo	74.2 (7.3)#	38.6#	ADAS-cog	MMSE, Safety, Withdrawals, CIBIC-plus, DAD
GAL-INT-6 Study (94-97)	592	Double blind, multicenter-international	26	Canada, Denmark, Finland, France, Germany, Israel, The Netherlands, Poland, and UK	Galantamine 24 mg/day Placebo	75.8 (6.8) 77.6 (5.9)	47.0 49.0	ADAS-cog/11, CIBIC-Plus	ADAS-cog/13, DAD, NPI, Safety, Withdrawals
Rockwood 2001 (98,99)	386	Double blind, multicenter-international	13	Australia, Canada, Great Britain, New Zealand, South Africa, and USA	Galantamine 24 mg/day Placebo	75.3 (7.5) 74.6 (7.6)	33.8 46.4	ADAS-cog/11, CIBIC-plus	ADAS-cog/13, NPI, DAD, Safety, Withdrawals
US-1 study group (100)	636	Double blind, multicenter	26	USA	Galantamine 24 mg/day Placebo	75.9 (0.5)# 75.3 (0.6)#	34.4 38.5	ADAS-cog, CIBIC-plus	DAD, Safety, Withdrawals
Wilcock 2000 (101-103)	653	Double blind, multicenter-international	26	Canada, Finland, France, Germany, Norway, Sweden, the Netherlands, and UK	Galantamine 24 mg/day Placebo	71.9 (8.3) 72.7 (7.6)	36.8 38.6	ADAS-cog	Safety, Withdrawals, DAD score
Kadir 2008 (104,105)	18	Double blind, multicenter	13	Sweden	Galantamine 16-24 mg/day Placebo	70.9 65.8	58.3 50.0	-	ADAS-cog, MMSE, Withdrawals
VISTA Study (106-110)	130	Double blind, multicenter	16	Canada	Galantamine 16-24 mg/day Placebo	77 (8.0) 78 (8.0)	36.0 38.0	GAS	ADAS-cog, CIBIC-plus, DAD, verbal repetition, misplacing, Safety, Withdrawals
GAL-JPN-3 2004\$	398	Double blind, multicenter	22	Japan	Galantamine 16 mg/day Galantamine 24 mg/day Placebo	74.6 (8.4) 75.5 (8.2) 74.4 (8.5)	26.4 27.4 29.2	ADAS-cog, CIBIC-plus J	DAD, BEHAVE-AD, MENFIS, Safety, Withdrawals
GAL-JPN-5 2006\$	580	Double blind, multicenter	24	Japan	Galantamine 16 mg/day Galantamine 24 mg/day Placebo	75.6 (8.4) 74.6 (8.8) 73.5 (7.6)	34.6 24.5 30.9	ADAS-cog, CIBIC plus-J	DAD, BEHAVE-AD, MENFIS, Safety, Withdrawals
Tariot 2000 (48-52)	978	Double blind, multicenter	21.7	USA	Galantamine 16 mg/day Galantamine 24 mg/day Placebo	76.3 (8.0) 77.7 (7.0) 77.1 (8.0)	37.6 33.0 37.8	ADAS-cog	CIBIC-plus, NPI, NPI-D, ADCS-ADL, Withdrawals, Safety

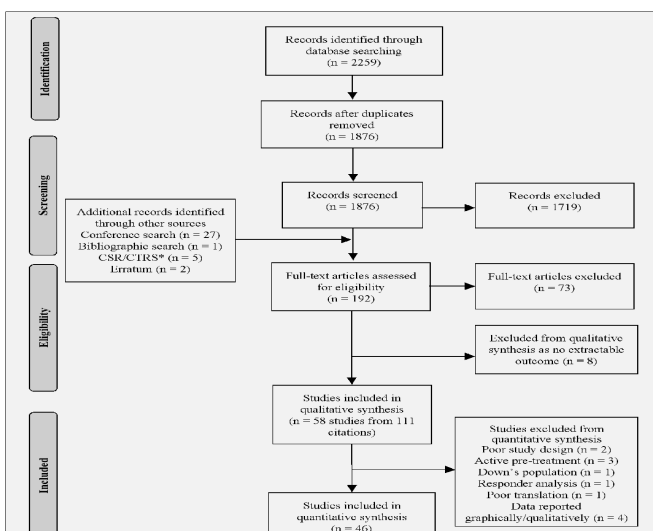






detect superiority of one active treatment over the other (41-43). One study compared donepezil versus no treatment (44). Treatment effects were generally evaluated over 3 months to 6 months, although nine studies measured treatment outcomes over a longer time period (up to 24 months). The quality of reporting of trials was generally judged to be adequate. Items on the CONSORT checklist with regard to baseline characteristics, participant flow, and reporting of adverse events were well answered. However, there were shortcomings with respect to reporting of methods of randomization and blinding. All placebo-controlled trials were double-blinded, apart from one trial that reported only to be single-blind (38, 39), and two trials where the blinding status was not reported (31, 44, 45). Six of the nine trials making active comparisons were open-label. Overall, the total number of items on the CONSORT checklist that were answered with "yes" did not differ according to year of study publication.

**Figure 2**  
Trial flow



\*CSR = Clinical Study Report; CTRS = Clinical Trial Report Summary

## Cognitive outcomes

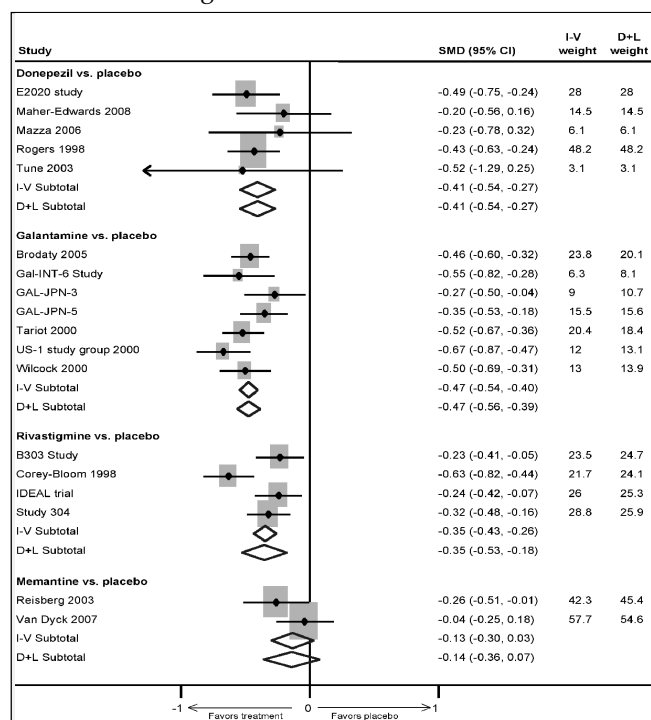
Cognition was assessed primarily using the ADAS-cog scale (39 studies), although the MMSE instrument alone was used in nine studies. Across studies reporting both ADAS-Cog and MMSE instrument, ADAS-Cog was preferred and MMSE was only used when ADAS-Cog was not available. All four trials examining memantine in moderate to severe patients used the SIB. For analysis, the standardized treatment effect SMD was calculated using all three instruments.

### Comparison versus placebo

Results of the meta-analysis indicated a statistically significant ( $p < 0.001$ ) improvement in cognitive function

compared with placebo for all three AChEIs after 6 months of treatment (Figure 3). Evidence for the efficacy of memantine is weaker; pooled results of two trials failed to demonstrate a statistically significant improvement in moderate to severe AD patients. A significant improvement in cognitive function at 6 months was also apparent with AChEI treatment compared to placebo for improvement of 4 points or more in ADAS-cog score ( $p = 0.01$ ; Figure 4). Ten trials (two, five, and three trials of donepezil, galantamine, and oral rivastigmine, respectively) reported 3-month data that could be included in meta-analysis: these meta-analyses identified significant efficacy of each AChEI also at this time point (data not shown). In agreement with previous reviews (7-9, 11, 12), our data set clearly shows that AChEIs have benefits for cognition.

**Figure 3**  
Meta-analysis results for ADAS-cog, MMSE or SIB change from baseline at 6 months



Pooled analyses of comparisons for donepezil, galantamine and placebo indicated significant efficacy compared with placebo in cognitive outcomes after six months of treatment. In this forest plot, each grey square is centered on the effect size (SMD: standardized mean difference) of a single study, while the size of the square is proportional to its weight in the pooled analysis. The 95% confidence interval for the effect size is represented by the horizontal line. The diamond represents the pooled analysis result and its 95% confidence interval, for either fixed effects (I-V: inverse variance) or random effects (D + L: Dersimonian and Laird) analysis. A confidence interval crossing the line of no difference (0) indicates no significant difference was seen.

### Comparison versus active

With limited and contradictory results arising from direct comparisons of active treatments (33, 40-42, 46, 47),





**Table 2**  
Long-term efficacy results

Study name	Treatment comparison	Study duration	Key results Cognitive outcomes	Behavioral outcomes
312 Study	Donepezil vs. placebo	1 year	Improved cognition with donepezil and deterioration with placebo ( $p < 0.001$ )	Not reported
Winblad 2001	Donepezil vs. placebo	1 year	Less deterioration with donepezil than with placebo ( $p < 0.001$ )	No significant difference between donepezil and placebo
Requena 2006	Donepezil vs. no treatment	2 years	Less deterioration with donepezil than with no treatment	Not reported
AD2000 Study	Donepezil vs. placebo	2 years	Less deterioration with donepezil than with placebo ( $p < 0.0001$ )	No significant difference between donepezil and placebo
GAL ITA 2 Study	Galantamine vs. placebo	2 years	Delayed cognitive deterioration with galantamine compared with placebo ( $p < 0.05$ )	Not reported
Karaman 2005	Rivastigmine (oral) vs. placebo	1 year	Improved cognition with rivastigmine and deterioration with placebo ( $p < 0.001$ )	Not reported
GAL-GBR-2 Study	Donepezil vs. galantamine	1 year	Significant differences favouring galantamine for the subgroup with MMSE score 12-18	No significant difference between galantamine and donepezil
Bullock 2005	Donepezil vs. rivastigmine (oral)	2 years	No significant difference between rivastigmine and donepezil	No significant difference between rivastigmine and donepezil
Cumbo 2005	Donepezil vs. galantamine vs. rivastigmine	1.5 years	Not reported	Better efficacy with rivastigmine than with donepezil and galantamine

MMSE: Mini-mental state examination

MTC analysis was the mainstay for assessing the comparative efficacy of active treatments. No significant difference between AChEIs was found for change in cognition at 3 months or 6 months when using all available evidence (Figure 5). The most evidence was available to examine the change in cognition at 6 months (19 placebo comparisons and one active comparison); here galantamine had the highest probability of being the best treatment for cognition ( $p=0.83$ ). At 3 months, oral rivastigmine had the highest probability of being the best treatment for cognition ( $p=0.78$ ). A trend for greater improvement was observed with the AChEIs compared to memantine, reaching significance for the galantamine versus memantine comparison at 6 months (absolute difference  $-0.29$ ; 95% CrI:  $-0.54, -0.03$ ). The difference in the severity of patients and instrument used for the assessments means this result must be interpreted with caution. No significant difference between AChEIs was observed for an improvement of 4 points or more in ADAS-cog at 6 months (Figure 6). It can be concluded that any differences in efficacy on cognition between AChEIs are non-significant.

### Behavioral outcomes

#### Comparison versus placebo

The effect of treatment on behavior is less well studied than cognition: only 23 of the 58 identified trials reported standard behavioral outcome measures (NPI, NPI-D and/or BEHAVE-AD). Meta-analysis of two studies indicated a significant advantage for galantamine over placebo in behavior using the NPI scale (SMD  $-0.16$ ; 95%

CI:  $-0.26, -0.05$ ) (48-55); pooled results for two other studies using BEHAVE-AD did not reach statistical significance for this comparison (WMD  $-0.36$ ; 95% CI:  $-0.85, 0.13$ ;  $p=0.15$ ) (unpublished data obtained from clinical study report). Single studies comparing donepezil (56) and rivastigmine (both formulations) (57-62) with placebo did not show significant advantage over placebo, nor did the combined results from two trials comparing memantine and placebo ( $p=0.28$ ) (63, 64). The MSAD study presenting data graphically reported a statistically significant clinical improvement at 6 months in donepezil-treated patients compared to placebo ( $p=0.0022$ ) (65-72). Evidence from single placebo-controlled trials of galantamine (48-52) and rivastigmine (both formulations) (57-62) indicated no significant improvement in carer distress at behavior (NPI-D scale) at the 6 months time point. One study identified significant improvement for donepezil patients compared with placebo at 12 weeks after randomization (preceded by a 12-week run-in period where all patients were actively treated) (30).

#### Comparison versus active

No studies directly compared behavioral outcomes between active treatments. Utilizing the available indirect data in MTC analysis, no significant difference between AChEIs was identified (Figure 7), although galantamine showed the highest probability of being best treatment for behavior (change from baseline in NPI score at 6 months;  $p=0.36$ ). Indirect comparison of two trials via placebo indicated a greater improvement in caregiver distress caused by behavioral symptoms (NPI-D) with

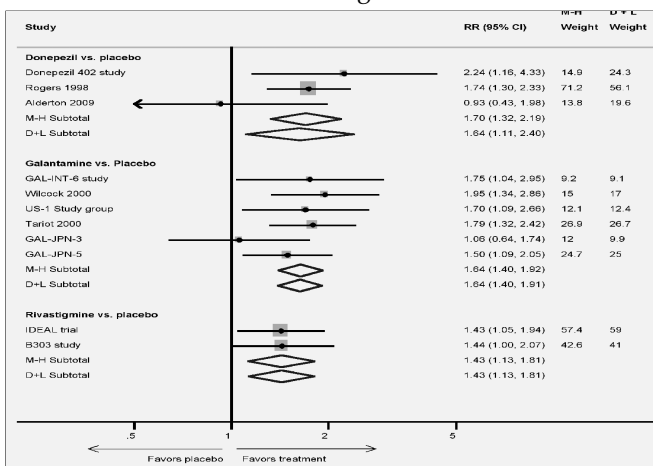




galantamine compared to oral rivastigmine (WMD: -0.17; 95% CI: -0.4, 0.07) and the transdermal formulation (WMD: -0.18; 95% CI: -0.42, 0.05), although the differences did not reach statistical significance.

**Figure 4**

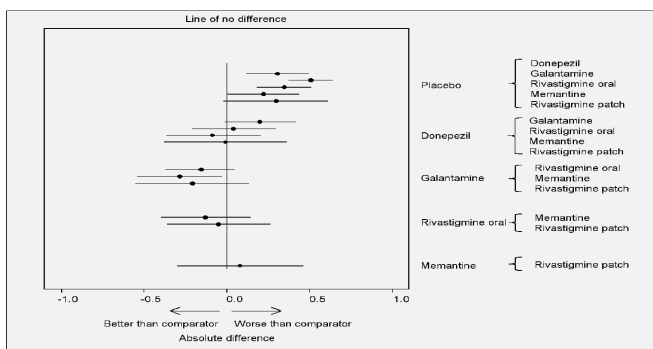
Meta-analysis results for improvement of 4 points or more in ADAS-cog at 6 months



Pooled analyses of comparisons for donepezil, galantamine and placebo indicated significant efficacy compared with placebo with regard to the relative risk (RR) of patients showing an improvement of 4 points on the ADAS-cog scale after six months of treatment. Fixed effects (M-H: Mantel-Haenzel) and random effects (D + L: Dersimonian and Laird) model results are shown.

**Figure 5**

Caterpillar plot of the absolute difference and 95% CrIs for MTC of ADAS-cog or MMSE or SIB change from baseline at 6 months



No significant difference between AChEIs for change in cognition at 6 months was seen when using direct and indirect evidence in MTC analysis. Galantamine showed a trend for being best treatment, and reached significance in comparison with memantine. This caterpillar plot shows a point estimate (central point) surrounded by the 95% credible interval for each comparison. Where this credible interval crosses the line of no difference (0), no significant difference between the two comparators is observed.

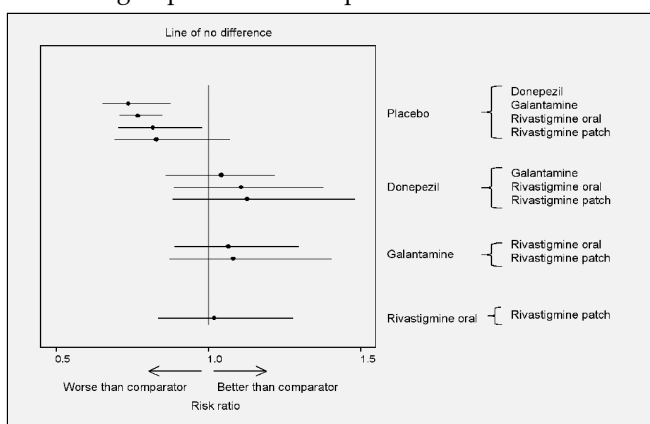
Given that in practice treatment is recommended to continue after the 3- to 6- month period examined by trials, this review also examined the RCT evidence of longer term efficacy. Table 2 summarizes the long-term efficacy results from the included studies.

## Safety and tolerability

Adverse events were frequently reported by trial participants: in 17 of the 23 placebo-controlled trials where this outcome was described, more than 60% of those receiving active treatment reported at least one adverse event. Meta-analysis results showed statistically significant increase in frequency of any adverse event for donepezil (RR: 1.12; 95% CI: 1.06, 1.19), galantamine (RR: 1.13; 95% CI: 1.08, 1.17) and oral rivastigmine (RR: 1.27; 95% CI: 1.17, 1.37) compared to placebo, but not for memantine (RR: 0.99; 95% CI: 0.91, 1.08). Approximately 20% of patients withdrew during 3- month to 6- month trials. Withdrawals were mainly due to adverse events and, compared with placebo, these occurred significantly more frequently with AChEIs ( $p < 0.05$ ; Figure 8), though not with memantine ( $p = 0.07$ ). Adverse events are clearly associated with AChEI treatment. However, there was no significant difference in frequency of any serious adverse events with AChEIs or memantine compared to placebo. Meta-analysis demonstrated no significant difference in treatment discontinuations due to death between AChEIs and placebo or between AChEIs.

**Figure 6**

Caterpillar plot of the risk ratio and 95% CrIs for MTC of ADAS-cog improvement of 4 points or more at 6 months



No significant difference between AChEIs was observed for improvement of 4 points or more in ADAS-cog score after 6 months of treatment.

MTC analysis demonstrated a significantly higher risk of any adverse event with oral rivastigmine compared to other AChEIs and memantine (Figure 9); specifically, oral rivastigmine was also significantly worse than all other active treatments for loss of appetite/anorexia, nausea, and vomiting (Figures 10A-C). However, based on one trial, the patch formulation did not show this disadvantage. Among other treatments, donepezil was significantly better than galantamine for the risk of nausea (RR: 0.91; 95% CrI: 0.83, 0.99) and vomiting (RR: 0.77; 95% CrI: 0.66, 0.88); the risks of diarrhea, weight loss, anorexia, and headache were not different between





**Table 3**  
Summary of existing reviews

Review	Interventions	Key sources	Search time frame	Number of included studies	Outcomes	Analysis type	Key results
Current review	Donepezil Galantamine Rivastigmine Memantine	MEDLINE, Embase, the Cochrane database, conference proceedings	Database start to March 2010	58	Cognition, behavior, safety, tolerability	Meta-analysis, indirect comparison, MTC	<ul style="list-style-type: none"> <li>• AChEIs but not memantine are more efficacious than placebo for cognition</li> <li>• MTC indicates no difference between AChEIs</li> <li>• AChEIs but not memantine reported higher AEs than placebo; AEs highest for oral rivastigmine</li> <li>• Donepezil is more efficacious than placebo</li> <li>• 10 mg/day dose has marginally better efficacy than 5 mg/day dose</li> </ul>
Birks 2006	Donepezil	The Cochrane Dementia and Cognitive Improvement Group's Specialized Register	Up to April 2006	26	Cognitive function, activities of daily living, behavior, global clinical state, safety, health care resource costs	Meta-analysis	<ul style="list-style-type: none"> <li>• AChEIs are more efficacious than placebo</li> <li>• No evidence of difference between AChEIs</li> <li>• Fewer AEs with donepezil than with rivastigmine</li> </ul>
Birks 2006a	Donepezil Galantamine Rivastigmine	The Cochrane Dementia and Cognitive Improvement Group's Specialized Register	Up to June 2005	14	Cognitive function, global impression, global disease activity, activities of daily living, behavior, QoL, effect on carer, dependency, death, safety, tolerability, health care resources, costs	Meta-analysis	<ul style="list-style-type: none"> <li>• Rivastigmine is more efficacious than placebo</li> <li>• Patch formulation is associated with fewer side effects</li> </ul>
Birks 2009	Rivastigmine	The Cochrane Dementia and Cognitive Improvement Group's Specialized Register	Up to March 2008	9	Cognitive function, behavior, global impression, dependency, functional performance, QoL, safety, tolerability, death, institutionalization, effect on carer	Meta-analysis	<ul style="list-style-type: none"> <li>• AChEIs are more efficacious than placebo</li> <li>• No clear difference is evident between AChEIs</li> </ul>
IQWiG Final report A05-19A	Donepezil Galantamine Rivastigmine	MEDLINE, Embase, the Cochrane database, Combined Health Information Database	Up to June 2006	27	Cognitive function, activities of daily living, psychopathological symptoms, QoL, mortality, safety institutionalization	Meta-analysis	<ul style="list-style-type: none"> <li>• No clear evidence for benefit of memantine</li> </ul>
IQWiG Final report A05-19C	Memantine	MEDLINE, Embase, the Cochrane database	Up to October 2008	7	Cognitive function, activities of daily living, psychopathological, symptoms, QoL mortality, safety, institutionalization	Meta-analysis	<ul style="list-style-type: none"> <li>• AChEIs are more efficacious than placebo, although the results are consistent across the outcomes</li> <li>• No clear difference is evident between AChEIs</li> <li>• Memantine shows benefit on functional and global measures; effects on cognition and behavior are less clear</li> </ul>
Loveman 2006	Donepezil Galantamine Rivastigmine Memantine	Cochrane database, NHS CRD DARE and NHS EED, Medline, PubMed, Embase, National Research Register, Current Controlled Trials	Database start to July 2004	31	Measures of global functioning, cognition, function, behavior and mood, QoL	Meta-analysis	<ul style="list-style-type: none"> <li>• AChEIs are more efficacious than placebo</li> <li>• Higher rates of AEs and treatment discontinuation with AChEIs than with placebo</li> </ul>
Lanctot 2003	Donepezil Galantamine Rivastigmine	MEDLINE, Embase, Cochrane database	1980 to May 2002	16	Global response, cognitive response, safety	Meta-analysis	<ul style="list-style-type: none"> <li>• AChEIs are more efficacious than placebo</li> <li>• AChEIs are more efficacious than placebo</li> <li>• Indirect comparison favored donepezil and rivastigmine over galantamine for some outcomes</li> <li>• AEs lowest for donepezil and highest for rivastigmine</li> </ul>
Hansen 2008	Donepezil Galantamine Rivastigmine	MEDLINE, Embase, Cochrane Library, the International Pharmaceutical Abstracts	1980 to July 2007	26	Cognition, function, behavior, global change, safety	Meta-analysis, indirect comparison	<ul style="list-style-type: none"> <li>• AChEIs are more efficacious than placebo</li> <li>• No clear evidence of difference between AChEIs</li> <li>• Indirect comparison favored donepezil and rivastigmine over galantamine for some outcomes</li> <li>• AEs lowest for donepezil and highest for rivastigmine</li> </ul>

AChEIs: Acetylcholinesterase inhibitors; AEs: Adverse events; QoL: Quality of life; MTC: Mixed Treatment Comparison

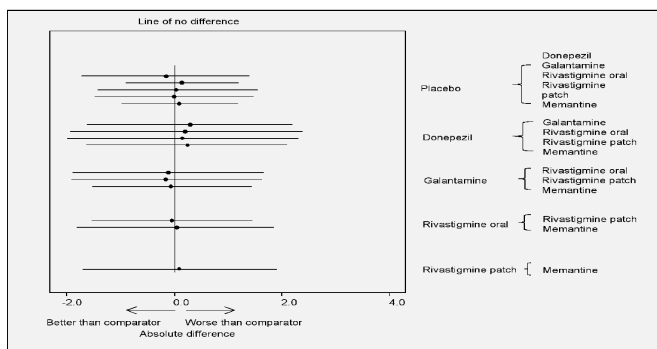




these interventions (data not shown). To note, despite these identified differences in risk of events, MTC results for treatment discontinuation due to adverse events and death showed no significant difference between treatments (data not shown).

**Figure 7**

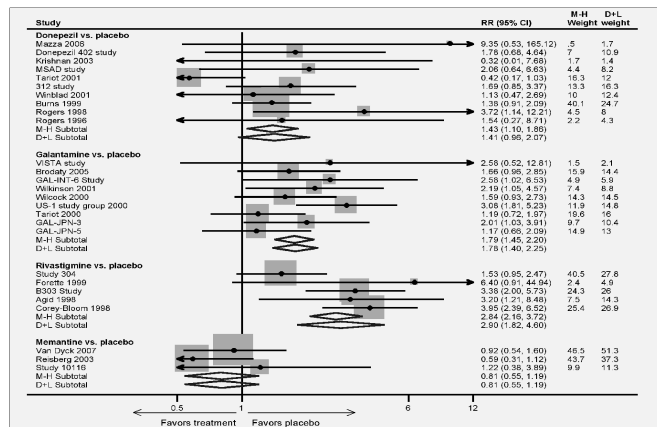
Caterpillar plot of the absolute difference and 95% CrIs for MTC of NPI change from baseline at 6 months



No significant difference between AChEIs was observed for the change in NPI after 6 months of treatment.

**Figure 8**

Meta-analysis results for treatment discontinuation due to adverse events



Pooled analyses of comparisons for rivastigmine, galantamine and placebo indicated significantly greater risk of discontinuation due to adverse events compared with placebo with regard to the relative risk (RR). Fixed effects (M-H: Mantel-Haenzel) and random effects (D + L: Dersimonian and Laird) model results are shown.

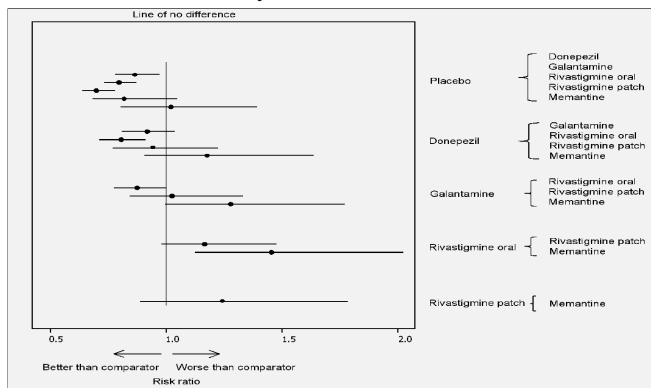
**Discussion**

This review identified sufficient evidence to support the use of AChEIs in mild to moderate AD. On the measures of cognition, the benefit of all three AChEIs over placebo was evident from the results of meta-analysis at 6 months, and longer-term benefit up to 2 years has also been shown. Advantage for memantine over placebo was observed in measures of cognition in the licensed population, although this difference failed to reach statistical significance. The results of these pooled direct comparisons align with the findings from previous

systematic reviews (Table 3). The evidence for behavioral outcomes is limited. The evidence of effect is most extensive for galantamine, with significant effect seen using the NPI instrument (NPI-10 and NPI-12). Results from using the NPI- distress or BEHAVE-AD instruments were infrequently reported, and generally no significant advantage was seen over placebo.

**Figure 9**

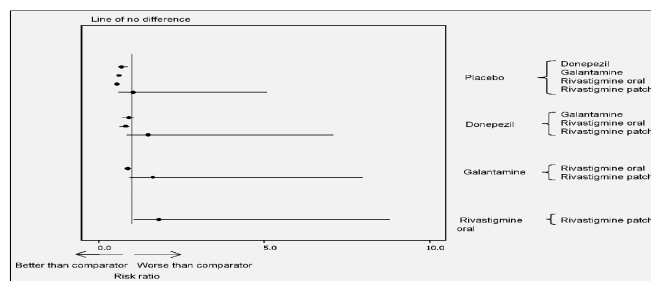
Caterpillar plot of the risk ratio and 95% CrIs for MTC of any adverse event



Oral rivastigmine was associated with a significantly higher risk of any adverse event compared to donepezil, galantamine or memantine. No significant difference was seen between donepezil and galantamine.

**Figure 10A**

Caterpillar plot of the risk ratio and 95% CrIs for MTC of loss of appetite

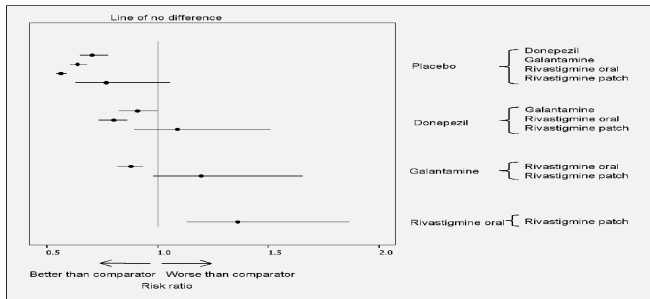


Distinct from previously published reviews, MTC analyses were conducted for this work, to combine direct and indirect evidence in order to evaluate the comparative effectiveness of these treatments. The use of this technique has allowed us to draw further conclusions in comparison with the reviews and analyses that have only used direct evidence. It should be noted that the results obtained from direct comparisons may not be similar to the results obtained in the MTC analysis for a particular comparison due to use of both direct and indirect evidence in latter. Our results are determined by the particular pre-defined methods we used for analysis and we recognize these may not be exactly replicated by other authors using a different methodology. Further, the studies included in the analysis varied in terms of the treatment duration which may have impacted the observed results.





**Figure 10B**  
Caterpillar plot of the risk ratio and 95% CrIs for MTC of nausea



Our results point to no significant difference between AChEIs across efficacy endpoints, although this does not discount the existence of minor differences. Data for comparison of memantine is more limited, given that different instruments have been used and the patient populations are not equivalent; however for cognition at 6 months, memantine showed a trend to be worse than other treatments. To note, one study demonstrated significantly greater improvement in cognition and behavior when memantine was added to ongoing donepezil therapy compared to placebo (73).

Only a small increase in risk of any adverse event was observed with AChEIs compared to placebo (RR around 1.1), although clearly the identified frequency of discontinuation due to adverse events in trials is of concern with regard to the persistence of patients using these drugs in clinical practice. Significant differences between AChEIs and placebo were apparent for the occurrence of specific adverse events. Particularly, donepezil and galantamine had a more favorable safety profile compared to oral rivastigmine, which was associated with a higher risk of any adverse events and specific adverse events.

A few limitations should be considered when interpreting the results. Lack of reporting of assessor blinding and limited reporting of method of randomization and blinding in the individual studies confer possible risk of outcome measurement bias and potentially increased risk of selection bias. In several publications, the efficacy data could not be accurately ascertained from graphical or qualitative presentation, or the measures of variance around the point estimate were not reported and authors were not contacted to maximize the data availability. Consequently, these trials could not contribute to the quantitative analyses of efficacy outcomes. If such data were available, the addition of results from these trials would have affected the overall strength and precision of results. Additionally, new data may have been made available since the review was undertaken in March 2010 but were not considered in the present work.

Prior published reviews in AD have mainly relied on

evidence from direct comparisons to establish the comparative effectiveness of available treatment options. Our review is a valuable addition to the existing literature in view of the use of available direct and indirect evidence (Table 3). Furthermore, we have included studies assessing the treatments within their licensed dosages which may be considered most relevant to clinical practice. We suggest this review will be informative for selection between pharmacological therapies and thus help in clinical decision-making for AD.

## Conclusions

In conclusion, the evidence base for AChEIs and memantine consisted chiefly of placebo-controlled trials. AChEIs but not memantine showed significant advantage over placebo for cognition. MTCs did not infer statistical significant differences between AChEIs in cognition and behavioral outcomes. Advantage for galantamine and donepezil over placebo in behavior at 6 months (NPI scale) was observed ( $p < 0.001$ ). No advantage over placebo was observed with rivastigmine (both formulations) for the behavioral outcomes. AChEIs but not memantine were associated with a slight but significant increase in reported adverse events compared with placebo. Oral rivastigmine has been shown to be associated with an increased risk of adverse events compared with other interventions; some other differences in frequency of specific adverse events between interventions were identified. This research informs clinical decision making by providing a summary of the comparative efficacy and safety of these interventions. Further research by including functional measures (for e.g. activities of daily living function) will add more insights into the benefits of the medications in AD.

*Competing interests:* RM and GP are employees of Heron Evidence Development Ltd, which received funding for this research and manuscript development from Janssen-Cilag GmbH who market galantamine. BS and MG are employees of Janssen-Cilag, a pharmaceutical company of Johnson & Johnson, and hold stock in Johnson & Johnson.

*Authors' contributions:* RM, GP and MG designed the study, and contributed to the review and analysis. All authors contributed to interpretation of the data, and read and approved the final manuscript.

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Under 'data sources, we state: "MEDLINE, Embase and the Cochrane Central Register of Controlled Trials were searched from database start until 10 March 2010.





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