Cochrane Library

Cochrane Database of Systematic Reviews

Memantine for dementia (Review)

McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, Maayan N, Ware J, Debarros J

McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, Maayan N, Ware J, Debarros J.
Memantine for dementia.
Cochrane Database of Systematic Reviews 2019, Issue 3. Art. No.: CD003154.
DOI: 10.1002/14651858.CD003154.pub6.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Memantine for dementia

Rupert McShane[1a], Maggie J Westby[2b], Emmert Roberts[3], Neda Minakaran[4], Lon Schneider[5], Lucy E Farrimond[6], Nicola Maayan[7], Jennifer Ware[8], Jean Debarros[9]

[1]Radcliffe Department of Medicine, University of Oxford, Oxford, UK. [2]Division of Nursing, Midwifery and Social Work, School of Health Sciences, Faculty of Biology, Medicine and Health, University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. [3]Department of Psychological Medicine and National Addiction Centre, King's College London, London, UK. [4]Department of Ophthalmology, Moorfields Eye Hospital NHS Foundation Trust, London, UK. [5]Keck School of Medicine of the University of Southern California, Los Angeles, CA, USA. [6]Neurosciences Department, Oxford University Hospitals NHS Foundation Trust, Oxford, UK. [7]Cochrane Response, Cochrane, London, UK. [8]Cochrane Dementia and Cognitive Improvement Group, University of Oxford, Oxford, UK. [9]Nuffield Department of Clinical Neurosciences (NDCN), University of Oxford, Oxford, UK

[a]This author contributed equally to this work. [b]This author contributed equally to this work

Contact address: Rupert McShane, Radcliffe Department of Medicine, University of Oxford, John Radcliffe Hospital, Level 4, Main Hospital, Room 4401C, Oxford, Oxfordshire, OX3 9DU, UK. rupert.mcshane@oxfordhealth.nhs.uk.

Editorial group: Cochrane Dementia and Cognitive Improvement Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 3, 2019.

Citation: McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, Maayan N, Ware J, Debarros J. Memantine for dementia. *Cochrane Database of Systematic Reviews* 2019, Issue 3. Art. No.: CD003154. DOI: 10.1002/14651858.CD003154.pub6.

ABSTRACT

Background

Memantine is a moderate affinity uncompetitive antagonist of glutamate NMDA receptors. It is licensed for use in moderate and severe Alzheimer's disease (AD); in the USA, it is also widely used off-label for mild AD.

Objectives

To determine efficacy and safety of memantine for people with dementia. To assess whether memantine adds benefit for people already taking cholinesterase inhibitors (ChEIs).

Search methods

We searched ALOIS, the Cochrane Dementia and Cognitive Improvement Group's register of trials (http://www.medicine.ox.ac.uk/alois/) up to 25 March 2018. We examined clinical trials registries, press releases and posters of memantine manufacturers; and the web sites of the FDA, EMEA and NICE. We contacted authors and companies for missing information.

Selection criteria

Double-blind, parallel group, placebo-controlled, randomised trials of memantine in people with dementia.

Data collection and analysis

We pooled and analysed data from four clinical domains across different aetiologies and severities of dementia and for AD with agitation. We assessed the impact of study duration, severity and concomitant use of ChEIs. Consequently, we restricted analyses to the licensed dose (20 mg/day or 28 mg extended release) and data at six to seven months duration of follow-up, and analysed separately results for mild and moderate-to-severe AD.

We transformed results for efficacy outcomes into the difference in points on particular outcome scales.

Main results

Across all types of dementia, data were available from almost 10,000 participants in 44 included trials, most of which were at low or unclear risk of bias. For nearly half the studies, relevant data were obtained from unpublished sources. The majority of trials (29 in 7885 participants) were conducted in people with AD.

1. Moderate-to-severe AD (with or without concomitant ChEIs). High-certainty evidence from up to 14 studies in around 3700 participants consistently shows a small clinical benefit for memantine versus placebo: clinical global rating (CGR): 0.21 CIBIC+ points (95% confidence interval (CI) 0.14 to 0.30); cognitive function (CF): 3.11 Severe Impairment Battery (SIB) points (95% CI 2.42 to 3.92); performance on activities of daily living (ADL): 1.09 ADL19 points (95% CI 0.62 to 1.64); and behaviour and mood (BM): 1.84 Neuropsychiatric Inventory (NPI) points (95% CI 1.05 to 2.76). There may be no difference in the number of people discontinuing memantine compared to placebo: risk ratio (RR) 0.93 (95% CI 0.83 to 1.04) corresponding to 13 fewer people per 1000 (95% CI 31 fewer to 7 more). Although there is moderate-certainty evidence that fewer people taking memantine experience agitation as an adverse event: RR 0.81 (95% CI 0.66 to 0.99) (25 fewer people per 1000, 95% CI 1 to 44 fewer), there is also moderate-certainty evidence, from three additional studies, suggesting that memantine is not beneficial as a *treatment* for agitation (e.g. Cohen Mansfield Agitation Inventory: clinical benefit of 0.50 CMAI points, 95% CI -3.71 to 4.71) .

The presence of concomitant ChEI does not impact on the difference between memantine and placebo, with the possible exceptions of the BM outcome (larger effect in people taking ChEIs) and the CF outcome (smaller effect).

2. Mild AD (Mini Mental State Examination (MMSE) 20 to 23): mainly moderate-certainty evidence based on post-hoc subgroups from up to four studies in around 600 participants suggests there is probably no difference between memantine and placebo for CF: 0.21 ADAS-Cog points (95% CI -0.95 to 1.38); performance on ADL: -0.07 ADL 23 points (95% CI -1.80 to 1.66); and BM: -0.29 NPI points (95% CI -2.16 to 1.58). There is less certainty in the CGR evidence, which also suggests there may be no difference: 0.09 CIBIC+ points (95% CI -0.12 to 0.30). Memantine (compared with placebo) may increase the numbers of people discontinuing treatment because of adverse events (RR 2.12, 95% CI 1.03 to 4.39).

3. Mild-to-moderate vascular dementia. Moderate- and low-certainty evidence from two studies in around 750 participants indicates there is probably a small clinical benefit for CF: 2.15 ADAS-Cog points (95% CI 1.05 to 3.25); there may be a small clinical benefit for BM: 0.47 NOSGER disturbing behaviour points (95% CI 0.07 to 0.87); there is probably no difference in CGR: 0.03 CIBIC+ points (95% CI -0.28 to 0.34); and there may be no difference in ADL: 0.11 NOSGER II self-care subscale points (95% CI -0.35 to 0.54) or in the numbers of people discontinuing treatment: RR 1.05 (95% CI 0.83 to 1.34).

There is limited, mainly low- or very low-certainty efficacy evidence for other types of dementia (Parkinson's disease and dementia Lewy bodies (for which CGR may show a small clinical benefit; four studies in 319 people); frontotemporal dementia (two studies in 133 people); and AIDS-related Dementia Complex (one study in 140 people)).

There is high-certainty evidence showing no difference between memantine and placebo in the proportion experiencing at least one adverse event: RR 1.03 (95% CI 1.00 to 1.06); the RR does not differ between aetiologies or severities of dementia. Combining available data from all trials, there is moderate-certainty evidence that memantine is 1.6 times more likely than placebo to result in dizziness (6.1% versus 3.9%), low-certainty evidence of a 1.3-fold increased risk of headache (5.5% versus 4.3%), but high-certainty evidence of no difference in falls.

Authors' conclusions

We found important differences in the efficacy of memantine in mild AD compared to that in moderate-to-severe AD. There is a small clinical benefit of memantine in people with moderate-to-severe AD, which occurs irrespective of whether they are also taking a ChEI, but no benefit in people with mild AD.

Clinical heterogeneity in AD makes it unlikely that any single drug will have a large effect size, and means that the optimal drug treatment may involve multiple drugs, each having an effect size that may be less than the minimum clinically important difference.

A definitive long-duration trial in mild AD is needed to establish whether starting memantine earlier would be beneficial over the long term and safe: at present the evidence is against this, despite it being common practice. A long-duration trial in moderate-to-severe AD is needed to establish whether the benefit persists beyond six months.

PLAIN LANGUAGE SUMMARY

Memantine as a treatment for dementia

Review question

We reviewed the evidence on memantine, which is one of the main drugs for treating people with dementia. We wanted to find out if memantine can slow down the course of dementia and if it is harmful in any way. We also wanted to know if adding memantine to other dementia drugs gives an extra effect.

Background

The commonest type of dementia is Alzheimer's disease (AD), followed by vascular dementia. About one or two people in 100 have AD at age 65, and this rate doubles every five years. Dementia involves loss of memory, difficulty thinking and often changes in mood and behaviour.

There are two main types of treatment: acetyl cholinesterase inhibitor (ChEI) drugs and memantine. These drugs work differently and we wanted to find out whether giving the two drug types together would work better than the ChEI drugs on their own.

Study characteristics

We searched for as many relevant studies as we could find that had a reliable design (randomised controlled trials) and had compared memantine with placebo for each type of dementia. We found 44 studies involving about 10,000 people. Most studies (29 in 7885 people) were in people with AD. Most studies were well conducted, but some were not well reported and we got extra information from the drug companies. We analysed the results separately for people with mild dementia and those with moderate-to-severe dementia.

Key results

Memantine has a small beneficial effect in people with moderate-to-severe AD. This benefit affects thinking, the ability to carry on normal daily activities, and the severity of behaviour and mood problems. Overall, it is well tolerated in those with moderate--to-severe AD, but it may cause dizziness in a few of the people taking it.

An important result is that adding memantine to established ChEI treatment also results in less deterioration than placebo.

However, in people with mild AD, memantine is probably no better than placebo. This is mainly moderate-quality evidence.

In vascular dementia, two studies in about 750 people indicated there is probably a small benefit for thinking difficulties, behaviour and mood, and there may be less agitation for memantine compared with placebo. This is moderate- or low-quality evidence.

Quality of the evidence
Overall, the evidence on memantine for AD is high quality, and comes from many trials in thousands of people. We can be confident in the findings for AD, but less so in people with other types of dementia.

This plain language summary is up to date as of March 2018.

Summary of findings for the main comparison. Moderate-to-severe AD, six to seven months

Memantine 20 mg or equivalent compared to placebo for moderate-to-severe Alzheimer's disease (AD) 24- to 30-week data. OC

Population: Alzheimer's disease (AD), moderate-to-severe
Intervention: memantine 20 mg or equivalent
Comparison: placebo

Continuous outcomes	Score with placebo (median)	Mean improvement in change score between memantine and placebo	SMD (95% CI) meta-analysis findings	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Clinical Global (CIBIC+) 7-point Likert scale	Median CIBIC+ score was 4.60 [3] (i.e. deterioration with time)	MD: 0.21 (0.14 to 0.30)	-0.20 (-0.28 to -0.13)	2797 (10 RCTs)	⊕⊕⊕⊕ HIGH	SMD as a negative outcome (Analysis 1.1) Converted to CIBIC+ scale; median SD(pooled) = 1.06.
Cognitive Function (SIB) 100-point scale	Median SIB score at baseline: 75.2. Median change from baseline (positive scale): -2.4 [4] (i.e. deterioration with time)	MD: 3.11 (2.42 to 3.92)	-0.27 (-0.34 to -0.21)	3337 (13 RCTs)	⊕⊕⊕⊕ HIGH	SMD as a negative outcome (Analysis 1.2). Converted to SIB scale (and scale direction inverted); median SD (pooled) = 11.53.
Functional performance on activities of daily living: ADCS-ADL19 54-point scale	Median ADCS-ADL19 score at baseline: 33.2 Median change from baseline (positive scale): -2.8 [5] (i.e. deterioration with time)	MD: 1.09 (0.62 to 1.64)	-0.16 (-0.24 to -0.09)	2687 (11 RCTs)	⊕⊕⊕⊕ HIGH [1]	SMD for decline in ADL (a negative outcome) (Analysis 1.3). Converted to ADCS-ADL19 scale (and scale direction inverted); median SD(pooled) = 6.84.
Behaviour and Mood (NPI) 144-point scale	The median baseline NPI score was 17.0. Median change from baseline (negative scale): 2.80 [6] (i.e. deterioration with time)	MD: 1.84 (1.05 to 2.76)	-0.14 (-0.21 to -0.08)	3674 (14 RCTs)	⊕⊕⊕⊕ HIGH	SMD as a negative outcome (Analysis 1.4) Converted to NPI scale; median SD(pooled) = 13.15.

Binary outcomes	Anticipated absolute effects		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo (median)	Risk with memantine				
All-cause discontinuation	182 per 1000	169 per 1000 (151 to 189)	RR 0.93 (0.83 to 1.04)	5087 (17 RCTs) 924 events	⊕⊕⊕⊕ HIGH	RR and median control group risk in people with moderate-to-severe AD without agitation (Analysis 16.5).
	Difference: 13 fewer people per 1000 discontinued treatment for any cause (95% CI 31 fewer to 7 more)					
Number suffering at least one adverse event	716 per 1000	737 per 1000 (716 to 759)	RR 1.03 (1.00 to 1.06)	8033 (29 RCTs) 5371 events	⊕⊕⊕⊕ HIGH	RR from all studies (Analysis 9.3). Median control group risk for moderate-to-severe AD studies (Analysis 1.7).
	Difference: 21 more people per 1000 suffered adverse events (95% CI 0 to 43 more)					
Number suffering at least one serious adverse event	114 per 1000	104 per 1000 (93 to 116)	RR 0.91 (0.82 to 1.02)	6482 (19 RCTs) 918 events	⊕⊕⊕⊕ HIGH	RR and median control risk from all AD studies (except those with agitation) (from Analysis 8.10)
	Difference: 10 fewer people per 1000 suffered serious adverse events (95% CI 21 fewer to 2 more)					
Number suffering agitation as an adverse event	129 per 1000	104 per 1000 (85 to 128)	RR 0.81 (0.66 to 0.99)	4395 (12 RCTs) 321 events	⊕⊕⊕⊖ MODERATE [2]	RR from all AD studies (apart from those in people with agitation) (Analysis 8.11). Median control group risk for moderate-to-severe AD studies (Analysis 1.9).
	Difference: 25 fewer people per 1000 suffered agitation as an adverse event (95% CI 44 to 1 fewer)					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** Risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Some inconsistency in point estimates, but not enough to downgrade
[2] Some inconsistency in point estimates (downgrade once)
[3] Median control group values for 8 studies reporting CIBIC+ (Asada 2011a (IE3501); Bakchine 2008 (99679) SG; Grossberg 2008 (MD-50); Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S; Reisberg 2003 (9605); Tariot 2004 (MD-02); van Dyck 2007 (MD-01))
[4] Median control group baseline scores and median control group change from baseline for 5 studies reporting SIB (Grossberg 2008 (MD-50); Reisberg 2003 (9605); Tariot 2004 (MD-02); van Dyck 2007 (MD-01); Wang 2013)
[5] Median control group baseline scores and median control group change from baseline for the 4 studies reporting ADCS-ADL19 (Grossberg 2008 (MD-50); Reisberg 2003 (9605);Tariot 2004 (MD-02); van Dyck 2007 (MD-01))
[6] Median control group baseline scores and median control group change from baseline for the 10 studies reporting NPI (Bakchine 2008 (99679) SG; Dysken 2014 SG; Grossberg 2008 (MD-50); Howard 2012 (DOMINO-AD); Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S; Reisberg 2003 (9605); Tariot 2004 (MD-02); van Dyck 2007 (MD-01); Wang 2013)

Summary of findings 2. Vascular dementia - mild-to-moderate severity. six months

Memantine 20 mg compared to placebo for mild-to-moderate vascular dementia. six-month studies

Population: vascular dementia, mild-to-moderate severity
Intervention: memantine 20 mg
Comparison: placebo

Continuous outcomes	Score with placebo (mean)	Mean improvement in change score between memantine and placebo	SMD (95% CI) meta-analysis findings	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Clinical Global: (CIBIC+) 7-point Likert scale	CIBIC+ score (Orgogozo 2002 (9408)) was 4.19 (i.e. no change with time)	MD: 0.03 (-0,28 to 0.34)	-0.02 (-0.23 to 0.19)	757 (2 RCTs)	⊕⊕⊕⊖ MODERATE [1]	SMD as a negative outcome; random effects (Analysis 5.1). Converted to CIBIC+ scale; SD(pooled) = 1.46.
Cognitive function: ADAS-Cog 70-point scale	Mean ADAS-Cog score at baseline was 23.6. Mean change from baseline (negative scale) was 1.68 (i.e. deterioration with time)	MD: 2.15 (1.05 to 3.25)	-0.32 (-0.48 to -0.15)	569 (2 RCTs)	⊕⊕⊕⊖ MODERATE [2]	Analysed as mean difference (Analysis 5.2) [SMD as a negative outcome Analysis 8.2]
Performance on ADL (NOSGER self care subscale)	Baseline scores not reported. Change from baseline for the NOSGER II self care subscale	MD: 0.11 (-0.35 to 0.54)	-0.04 (-0.20 to 0.13)	542 (2 RCTs)	⊕⊕⊖⊖ LOW [3]	SMD for decline in ADL (a negative outcome) (Analysis 5.3).

Subscale 5 points	(negative scale) was 0.40 (one study) i.e. deterioration with time					Converted to NOSGER II self-care subscale (Wilcock 2002 (9202)) SD(pooled) = 2.69.
Behaviour: NOSGER disturbing behaviour subscale Subscale 5 points	Baseline scores not reported. Change from baseline for the NOSGER disturbing behaviour subscale (negative scale) was 0.57 (one study) i.e. deterioration with time	MD: 0.47 (0.07 to 0.87)	-0.20 (-0.37 to -0.03)	542 (2 RCTs)	⊕⊕⊖⊖ LOW [3]	SMD as a negative outcome (Analysis 5.4). Converted to NOSGER II disturbing behaviour subscale (Wilcock 2002 (9202)) SD(pooled) = 2.34.

Binary outcomes	**Anticipated absolute effects**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo (median)	**Risk with memantine**				
All-cause discontinuation	218 per 1000	229 per 1000 (181 to 292)	RR 1.05 (0.83 to 1.34)	900 (2 RCTs) 678 events	⊕⊕⊖⊖ LOW [4]	RR and control group risk for studies in people with vascular dementia (Analysis 5.6.)
	Difference: 11 more people per 1000 discontinued treatment for any cause (95% CI 37 fewer to 74 more)					
Number suffering at least one adverse event	742 per 1000	764 per 1000 (742 to 787)	RR 1.03 (1.00 to 1.06)	8033 (29 RCTs) 5371 events	⊕⊕⊕⊕ HIGH	RR from all studies (Analysis 9.3). Control group risk taken from studies in vascular dementia (Analysis 5.8)
	Difference: 22 more people per 1000 suffered adverse events (95% CI 0 to 45 more)					
Number suffering at least one serious adverse event	211 per 1000	173 per 1000 (95% CI 131 to 230)	RR 0.82 (0.62 to 1.09)	900 (2 RCTs) 162 events	⊕⊕⊖⊖ LOW [5]	RR and control group risk from vascular dementia studies (Analysis 8.10)
	Difference: 38 fewer people per 1000 suffered serious adverse events (95% CI 80 fewer to 19 more)					
Number suffering agitation as an adverse event	77 per 1000	44 per 1000 (26 to 75)	RR 0.57 (0.33 to 0.97)	900 (2 RCTs) 54 events	⊕⊕⊖⊖ LOW [6]	RR and control group risk from vascular dementia studies (Analysis 5.9); random effects
	Difference: 33 fewer people per 1000 suffered agitation as an adverse event					

		(95% CI 52 to 2 fewer)			

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** Risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Inconsistency in point estimates (and I^2 = 48%); some imprecision (95% CI crossed null and was consistent with benefit and no difference) but may be consequence of inconsistency (downgraded once overall)
[2] Majority of the information at high risk of bias (downgrade once). Some inconsistency (but insufficient to downgrade)
[3] Majority of the information at high risk of bias for 2 domains (downgrade twice)
[4] Majority of the information at high risk of bias (downgrade once); some inconsistency and some imprecision (crossed null and 1.25) (downgrade once)
[5] Majority of the information at high risk of bias (downgrade once); imprecision (162 events and crossed both 0.75 and null)) (downgrade once)
[6] Majority of the information at high risk of bias (downgrade once); imprecision (only 54 events) (downgrade once)

BACKGROUND

Description of the condition

This review covers the effect of memantine in dementia of all aetiologies.

Alzheimer's disease (AD) is the commonest cause of dementia, and is found in approximately 70% of autopsies of people with dementia. The prevalence of the disease is approximately 1% to 2% at the age of 65, but doubles every five years to at least the age of 90 (Qiu 2009). The disease is progressive. For the purposes of drug trials, people with AD who have a score on the brief mini mental state examination (MMSE) of more than 20 have come to be labelled as having 'mild' AD. However, the combination of loss of memory, disorientation and frequent loss of insight which accompanies this stage means that the impact on caregivers is often very far from 'mild'. It is not uncommon for patients to need admission to care homes in this stage. 'Moderate' AD has come to be defined as those with an MMSE score of 20 to 10. In this range, patients decline more rapidly. The impairment in patients' ability to manage everyday tasks becomes marked and is obvious during even brief conversation. By the time patients have progressed to an MMSE score of 10 or less ('severe' dementia), the deficits are profound and 24-hour supervision is required. Approximately 70% of people with AD require admission to care homes.

Aside from age, the biggest risk factor for developing AD is possession of the ApoE4 gene, which is present in 17% to 30% of the population. Other risk factors include all vascular risks (diabetes, hypertension, high cholesterol, lack of exercise), any cerebral injury (trauma or stroke), and being female (Patterson 2007; Sibbett 2017).

Cellular and animal models, genetic, neuroimaging, clinical and postmortem brain studies have all been important in advancing understanding of the many changes which occur in the brains of people with AD. Nerve cell loss and disruption of neurotransmitter systems becomes widespread throughout many brain areas, particularly the hippocampus and cerebral cortex. Aggregation of peptide fragments of the amyloid precursor protein, which probably holds nerve cells close enough together for signals to be transmitted between them, causes malfunction of processes within cells. Large deposits of these fragments, amyloid plaques, develop outside neurones and are associated with a mild inflammatory response. However, removal of existing plaques does not appear to result in improvement in symptoms so it is unclear to what extent the amyloid plaques are a cause of AD or a consequence of some other, more fundamental, disturbance. Within the neurons, the transport of cellular components becomes disrupted because tau, which helps to keep the microtubule scaffolding together, becomes hyperphosphorylated and itself forms into paired helical filament 'tangles'. No drugs affecting this process have been proven to benefit symptoms. Cholinergic function, which mediates attention, tends to be impaired in people with AD. This can be partially corrected by cholinesterase inhibitors (ChEIs) which reduce the breakdown of acetylcholine.

Vascular dementia, in which cognitive decline is attributed to some form of vascular injury, typically ischaemic, is the second most common cause of dementia in Western societies. Developing a valid definition, distinct from AD, has been problematic. It is a heterogeneous condition and clinical manifestations differ depending on the size and location of the cerebrovascular lesions. In autopsy studies, 'mixed' AD and vascular dementia has been reported as accounting for between 0% and 55% of cases of dementia. In addition to co-occurrence due simply to chance, AD and vascular dementia may have aetiological or pathogenetic factors in common (Kalaria 1999). In comparison with sufferers from AD, people with mixed dementia show higher frequencies of depressed mood, focal motor or sensory findings and gait disturbances, but the neuropsychological pattern is not distinctive. Using criteria which demand imaging evidence of discrete vascular lesions and a clinical event associated with cognitive decline, or evidence of marked small vessel disease, vascular dementia affects 1% to 20% of people aged 65 years or older.

Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) are closely related. The main clinical distinction is one of definition: those with PDD have had parkinsonism a year or more before developing dementia, whereas in DLB the onsets of dementia and any parkinsonism are closer in time. Some people with DLB show no signs of parkinsonism. Both groups are more likely to experience visual hallucinations, marked fluctuations in functional ability, and REM (rapid eye movement) sleep behaviour disorder.

Description of the intervention

Memantine was first synthesised at Eli Lilly as an agent to lower elevated blood sugar levels, but was ineffective. It has since been tested in over 100 randomised controlled trials in a wide variety of neurological and psychiatric conditions, including dementia of different sorts, depression, neuropathic pain, Parkinson's disease and autism.

In 1972, Merz applied for a German patent for memantine as a potential treatment for a wide range of cerebrovascular conditions, citing evidence of reduced degeneration and nerve cell loss following experimentally induced ischaemia in animal models. In 1975 and 1978, patents were granted in Germany and the USA, respectively (Parsons 1999). This basis for the original patent for memantine (Bormann 1991), which was due to expire in April 2010, was contested by manufacturers of generics (Forest 2007). Forest and Merz settled an agreement to provide licenses to each of Amneal, Cobalt, Dr. Reddy’s, Lupin, Orchid, Sun, Teva, Upsher −Smith, and Wockhardt that permitted these companies to launch their generic versions of 'Namenda' within three months prior to the expiration of the original patent (Forest 2010a). However, in March 2009, the U.S. Patent and Trademark Office issued a Notice of Final Determination that, after review of the regulatory timeline for approval, Namenda was entitled to a patent term extension until April 2015 and the patent finally expired in October 2015. Generic memantine is now available, but in 2010 the US Food and Drug Administration (FDA) awarded a license for an extended release, once daily preparation Namenda XR 28 mg (Forest 2010b). The patent for this expires in September 2029.

Memantine was approved in February 2002 by the European Agency for the Evaluation of Medical Products (EMEA) for the treatment of "moderately severe to severe Alzheimer's disease" (EMEA 2004) and in 2003 by the FDA for the treatment of moderate-to-severe AD (MMSE up to 14) (Anonymous 2003; Forest 2003). In 2006, the EMEA expanded its indication to 'moderate-to-severe AD' (MMSE up to 19) (EMEA 2006). In June 2008, the EMEA granted a license for a once daily 20 mg dosing schedule (EMEA 2008). Applications to the FDA

and EMEA for licenses for the treatment of mild-to-moderate AD have been unsuccessful (Forest 2005b; Lundbeck 2005).

Memantine has not been approved for vascular dementia or earlier stages of AD in any jurisdiction.

Memantine is marketed as Axura by Merz, as Ebixa by Lundbeck in Europe, as Namenda by Forest in North America and as Mamary by Daiichi Asubio in Japan. In 2010, memantine had 34.8% share of the US market for drugs for AD (Forest 2010a). Annual global sales exceed 1 billion USD. In 2015, the UK price of memantine to the NHS decreased by 94%. Prescribing rates in England increased from approximately 100,000 items dispensed in 2011 to 784,000 (at a cost of £5.4m) in 2015 (Prescriptions England 2016).

In May 2015, Actavis launched Namzaric (a fixed-dose combination of 28 mg extended-release memantine and the ChEI, donepezil 10 mg) for people with moderate-to-severe AD, following FDA approval in December 2014.

How the intervention might work

Memantine is a low affinity antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor. L-glutamate is the main excitatory neurotransmitter in the central nervous system and is implicated in neural transmission, learning, memory processes and neuronal plasticity (Sucher 1996). Physiological glutamate activity is required for normal brain activity and so cannot be abolished completely (Kornhuber 1997). The hippocampus and other brain regions which are affected in AD, are rich in glutamate receptors of the NMDA class. Consolidation of new memories is also mediated through these receptors.

Excessive glutamate-induced excitation, which results in excessive flow of calcium into neurons through NMDA receptors, plays a role in the pathogenesis of AD and in the damage due to an ischaemic stroke (Cacabelos 1999). The clinical actions of memantine may be mediated by preventing this excitotoxicity.

NMDA receptor-induced responses may depend on the receptor location. Stimulation of synaptic NMDA receptors, acting primarily through nuclear Ca(2+) signalling, leads to the build-up of a neuroprotective 'shield', whereas stimulation of extrasynaptic NMDA receptors promotes cell death (Hardingham 2010) and increases amyloid production (Bordji 2010). The differing pharmacodynamics of memantine at synaptic and extrasynaptic NMDA receptors may mean that there is a 'therapeutic window' for memantine at doses where inhibition of extrasynaptic receptors is greater than for synaptic receptors (Hardingham 2010). Inhibition of both subtypes occurs at higher doses.

It is possible that the effect of memantine is related to reduction of tau phosphorylation (Degerman Gunnarsson 2007) or of amyloid toxicity (Song 2008).

Memantine also preserves cerebral energy status during experimentally induced hypoglycaemia in healthy people (Willenborg 2011). Although this effect could be related to its actions in dementia, this has yet to be established.

Why it is important to do this review

First, since the last update of our review in 2006, the UK National Institute for Health and Care Excellence (NICE) has, on the basis of its 2011 appraisal (TA 217) revised an earlier recommendation that memantine was insufficiently cost-effective to warrant prescription on the UK's National Health Service (NHS), and produced new recommendations outlining its use (NICE 2011). In a further update in 2015, NICE stated that they "identified nothing new that affects recommendations 1.1, 1.2" (those concerning memantine). Concurrent with the update of our Cochrane Review, NICE's clinical guideline on dementia (CG 42) has been partially updated, to review further the effect of two topics relevant to this memantine review: concurrent treatment with memantine and cholinesterase inhibitors (ChEIs), and memantine for non-AD dementias. The guideline has not updated recommendations 1.1 and 1.2 (NICE 2018). The Cochrane Dementia and Cognitive Improvement review group is a stakeholder for this guideline and the authors of this review have shared data and evidence synthesis with NICE.

The UK recommendations regarding memantine monotherapy (TA 217 recommendations 1.1 and 1.2) therefore remain unchanged: that is, that memantine should be available at public expense for people who either (a) have moderate AD and are intolerant of, or have a contraindication to ChEIs or (b) have severe AD. The Appraisal Committee also concluded that "if cognitive scales are not appropriate for assessing the need for treatment, or whether to continue treatment, then clinicians should use another appropriate method of assessment".

NICE's 2011 updated decision was based on consideration of data from four studies, with emphasis on statistical significance. Their analysis showed a significant benefit on cognitive function assessed by the Severe Impairment Battery (SIB) at three months, but not at six months. Two studies provided data for assessment of activities of daily living (ADL) using the Alzheimer's Disease Cooperative Study - Activities of Daily Living (ADCS-ADL)19 scale, showing marginal significance at six months. No statistically significant effect was seen on behaviour. NICE's model suggested that memantine delayed time to institutional care by 0.8 months. Thus, NICE's 2015 decision to transfer recommendations 1.1 and 1.2 to their 'static list of technology appraisals' was taken on the basis of relatively few studies for clinical effectiveness. Memantine is now off-patent so cost-effectiveness will be affected.

NICE's original 2011 guidance also concluded that there was a "lack of evidence of additional clinical efficacy (of concurrent therapy with ChEIs) compared with memantine monotherapy" (NICE 2011). However, this aspect of the TA has now been updated in the newly published 2018 guideline (NICE 2018), which recommends that for people with an established diagnosis of AD who are already taking a ChEI, memantine should be additionally considered in moderate disease and additionally offered in severe disease (NICE 2018). A lack of clarity still remains because of the decision not to update the monotherapy recommendations, and there is potential confusion arising from conflating the old and new recommendations. The British Association for Psychopharmacology guideline suggests that there is "type I evidence [ie based on meta-analysis of RCTs] for adding memantine to a cholinesterase inhibitor" (O'Brien 2017).

Second, the German Institute for Quality and Efficiency in Healthcare (IQWIG) has revised its conclusions on memantine. In 2009, they concluded that "there is no scientific proof that patients with moderate or severe Alzheimer's disease benefit from drugs containing the agent memantine". Their last search of registries for studies was in January 2009. Data from nine studies of 16 to 28 weeks duration were eventually included. IQWIG pointed to a lack

of 'reliable responder analysis', which prevents an understanding of whether 'more patients in the memantine group notice a perceptible improvement in their symptoms than in the placebo group' and argued that it was "not possible to deduce a proof of a relevant effect" on clinical global because, although showing a significant benefit (standardised mean difference (SMD) 0.18, 95% confidence interval (CI) 0.05 to 0.3), the lower confidence limit fell below a threshold of 0.2. The majority of included studies collected data on the amount of care required ('resource utilisation') but this was not made available. However, in response, in 2011 Merz submitted post-hoc findings on responder analyses which led to changes to IQWIG's conclusions (IQWIG 2011), "The data provide proof of a benefit of memantine in patients with Alzheimer's disease with regard to the prevention of a relevant deterioration in cognitive function. For activities of daily living, taking into account the uncertain response criteria, as well as the concurrent minor size of the effect, the data provide an indication of a benefit of memantine."

Third, France's Minister for Health de-listed all drugs routinely used for AD from August 2018 (memantine and the ChEIs, donepezil, galantamine and rivastigmine), stating, "The drugs available in early 2018 for Alzheimer's disease have only minimal and transient efficacy. They are also difficult to use because of their disproportionate adverse effects and many interactions with other drugs. None of the available drugs has been shown to slow down progression toward dependence, yet all carry a risk of life-threatening adverse effects and severe drug interactions". De-listing means the drugs are no longer reimbursed by the national health insurance system (Prescrire 2018). The French dementia guideline was updated at the same time and indicated that the 'medical service' was insufficient to justify national support, although noting the marketing authorisation and stating that drugs can be prescribed in line with their summary of product characteristics (HAS 2018).

Fourth, many patients in North America are taking memantine outside the terms of its license, perhaps in the belief that 'if it works for moderate AD it must work in mild AD'. In 2006, it was prescribed to 19% of people with mild AD, despite the fact that, in 2005 the FDA did not approve a supplemental new drug application (sNDA) by Forest Labs which sought specific marketing approval for a mild AD indication (McManus 2006). In the mainly academic centres that comprise the Alzheimer Disease Neuroimaging Initiative (ADNI) 45.7% of people with mild AD were receiving memantine (Schneider 2011a). Nearly 40% of US neurologists report prescribing memantine at least sometimes to people with mild cognitive impairment (Roberts 2010).

Fifth, the regulations governing publication of trial results have changed since the last update of this review in 2006. Trials conducted by US sponsors now have to be reported on clinical registries within a year of the last data being collected from the last participant in the trial. This greater transparency has led to data becoming available which is not subject to peer review, and to the possibility of identifying data which was collected but remains unavailable ('known unknowns'). The inclusion of non peer-reviewed registry data in meta-analysis reduces the risk of bias due to selective publication. It also helps to restore the breach of ethical contract with trial participants and their families which occurs when data remain unpublished: they usually agree to participate in the belief that the experience will contribute to publicly available knowledge.

Sixth, pharmacological strategies for managing some of the behavioural changes associated with dementia are of low benefit, often have side effects, and are overused. Considerable marketing activity, especially in the 2000s, asserted that memantine might be an alternative.

Seventh, there may be a therapeutic window for memantine that impacts on the timing of when memantine is prescribed. Trials in cognitive impairment in multiple sclerosis have consistently found a dose-related worsening of neurological and psychiatric symptoms (Lovera 2010; Peyro-Saint-Paul 2016; Villoslada 2009), consistent with preclinical work suggesting the possibility of a therapeutic window (Hardingham 2010). In the ADNI, Schneider 2011a and colleagues found that people taking memantine and ChEIs declined faster on the MMSE and Clinical Dementia Rating (CDR) scales (but not Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) or a functional questionnaire) than those taking ChEIs alone. Whilst this was probably because memantine was started early by clinicians faced with patients who were declining more rapidly, and the results of the two cognitive scales are not wholly consistent, the result is also consistent with an adverse effect of memantine in early AD.

It is therefore important to conduct this review to investigate these unanswered questions and inconsistencies, in order to give clear information.

OBJECTIVES

The primary aim of the review is to assess the efficacy and safety of memantine for the treatment of dementia, as revealed in clinical trials involving people with Alzheimer's, vascular, mixed or other forms of dementia. Additionally, the review aims to assess whether memantine adds benefit for people already taking cholinesterase inhibitors (ChEIs).

METHODS

Criteria for considering studies for this review

Types of studies

We included studies for analysis in this review if they fulfilled the following criteria.

1. Double-blind, parallel-group, placebo-controlled, with randomised and unconfounded treatment assignment to memantine or placebo
2. Sample selection criteria were specified and diagnosis used established criteria (e.g. Diagnostic and Statistical Manual of Mental Disorders (DSM) or International Classification of Diseases (ICD) criteria)
3. Outcome instruments were specified
4. Duration was specified

We also included studies for which data were known to exist but were not available in published reports, in order that the potential impact of publication bias could be assessed.

Double-blind randomised trials of memantine for cognitive impairment which did not meet the inclusion criteria (e.g. in

participants with mild cognitive impairment, or head-to-head studies) are briefly discussed in 'Excluded studies'.

Types of participants

People with Alzheimer's, vascular, mixed or other types dementia of all degrees of severity, treated as in- or out-patients.

Types of interventions

Memantine at any dose and by any route of administration. Although there is evidence that 20 mg once daily is as well tolerated as 10 mg twice daily, an extended release formulation is now also available at an 'equivalent' dose (28 mg). Given this equivalence, and that it has a licence, it was included in analyses of the licensed dose and indication.

Types of outcome measures

The primary outcomes of interest included the following.

1. Clinical global rating
2. Cognitive function
3. Functional performance in activities of daily living (ADL)
4. Behavioural disturbance
5. Incidence of dropout and adverse events

We also sought data on the following pragmatic outcomes.

1. Effect on carer burden
2. Quality of Life
3. Institutionalisation
4. Costs

Search methods for identification of studies

Electronic searches

We searched ALOIS (www.medicine.ox.ac.uk/alois) - the Cochrane Dementia and Cognitive Improvement Group's Specialized Register on 25 March 2018. We used the Advanced search, with the following search terms: memantine, D-145, DMAA, DRG-0267, ebixa, abixa, axura, akatinol, memox and namenda.

ALOIS is maintained by the Information Specialists of the Cochrane Dementia Group and contains studies in the areas of dementia prevention, dementia treatment and cognitive enhancement in healthy people. The studies are identified from:

1. monthly searches of a number of major healthcare databases: MEDLINE, Embase, CINAHL, PsycINFO and LILACS;
2. monthly searches of a number of national and international trial registers: ISRCTN; UMIN (Japan's Trial Registry); ICTRP / WHO portal (which covers ClinicalTrials.gov; ISRCTN; the Chinese Clinical Trials Register; the German Clinical Trials Register; the Iranian Registry of Clinical Trials and the Netherlands National Trials Register, plus others);
3. quarterly search of the Cochrane Library's Central Register of Controlled Trials (CENTRAL)
4. six-monthly searches of a number of grey literature sources: ISI Web of Knowledge Conference Proceedings; Index to Theses; Australasian Digital Theses.

To view a list of all sources searched for ALOIS see About ALOIS on the ALOIS web site.

Details of the search strategies used for the retrieval of reports of trials from the healthcare databases, from Cochrane CENTRAL and from conference proceedings can be viewed in the 'methods used in reviews' section within the editorial information section of the Dementia and Cognitive Improvement Group.

We carried out additional searches in many of the sources listed above to cover the timeframe from the last searches performed for ALOIS to ensure that the search for the review was as up-to-date as possible. The search strategies used can be seen in Appendix 1.

We searched press releases from Merz, Lundbeck and Forest Laboratories (April 2017) and examined all releases pertaining to memantine.

The Forest, Lundbeck and JAPIC clinical trials registry and ClinicalTrials.gov were re-examined for the final time in April 2017.

Searching other resources

All conference posters sponsored by Forest Laboratories, Merz or Lundbeck presented before end 2009 were provided through the medical information department of Merz..

We wrote to authors, Lundbeck, Forest, Merz and Daiichi Asubio for details about various studies as detailed in Characteristics of included studies.

Additionally, we were aware of conference posters reporting data from the Fox 2012 (MAGD) study. Review author RMcS had access to additional data from the Howard 2012 (DOMINO-AD) study - therefore we also included this information.

Data collection and analysis

Selection of studies

For this update, the abstracts of references newly retrieved by the search since the search conducted for the previously published version of this review were read by review authors MW, ER, JD or LF and checked by RMcS. Any disparity in the final lists was resolved by discussion in order to arrive at the final list of included studies.

Assessment of risk of bias in included studies

For all studies conducted since the introduction of ICH-GCP (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice), we assumed that sequence generation, allocation concealment and blinding were all adequate and carried a low risk of bias. This was informed by prior findings, which were confirmed in the current review, of a low incidence of side-effects which could potentially unmask allocation.

Incomplete outcome data due to participant dropout is a very common problem in dementia trials. We recorded the number of participants in each arm who did not have outcome data at the measurement point, alongside the reasons for 'missingness', and we calculated for each arm the proportion missing of those randomised. We used this approach to missing data, regardless of the method of analysis (see Dealing with missing data). In assessing risk of attrition bias for the continuous efficacy outcomes, we considered the following factors: the level of missing data, the

difference between groups and the reasons for missingness. We also took into account whether the approach to missing data (e.g. observed case (OC) or last observation carried forward (LOCF)) gave different effect estimates. For the adverse events dichotomous outcome, we compared the proportions missing in each group with each other and with the adverse event risk. If there were substantial differential missing data or the missing data proportion was comparable with the adverse events risk, we rated the risk of attrition bias as high.

A further common problem is reporting bias, in which positive trials, or positive results within trials, are preferentially reported. We used funnel plots to assess whether results reported solely in trial registries were more likely to be positive than those published in peer review literature, or whether there were likely to be 'unknown unknowns': trials whose existence was not apparent despite the systematic searching. We noted in the 'Risk of bias' tables when outcomes had not been reported at all, but did not assign high risk of outcome reporting bias. Instead, we presented the results in forest plots for those studies that were known to exist, but for which no data were available. This approach did not alter estimates of effect size but was designed to show the extent of the 'known unknowns'. In the absence of definitive information, we assumed that the numbers in the placebo and drug arms were the same. Then, for GRADE assessment, we considered downgrading on risk of bias if the potential contribution from missing studies could affect the summary statistics for studies with available data for that outcome.

Measures of treatment effect

As described in Types of outcome measures, the analysis is focused on the five domains of clinical global, cognitive function, performance on activities of daily living (ADL) function, behaviour and adverse events. The measures used are described in more detail in Appendix 2. Table 1 details which measures were used in the AD and vascular dementia studies. For data on adverse events, we sought the numbers in each treatment group and the numbers experiencing the outcome of interest.

For analysis, we transformed the data so that all outcomes were treated as negative (i.e. a higher score indicating a worse result), as is usual in the dementia field. We transformed data for individual scales for some outcomes, but for the outcome, functional performance on ADL - a positive outcome - we converted the positive emphasis into a negative one, analysing the outcome as a 'lack of functional performance on ADL' and reversing the sign of the change scores. For the purposes of analysis, we have described the outcome as a 'decline in ADL'.

For interpretation of this outcome, however, we discuss the clinical effect in terms of the functionality itself, reporting the performance on ADL (so, a mean difference of 1.07 points between memantine and placebo is a clinical *benefit*).

Dealing with missing data

People with dementia often drop out from studies. The treatment of such missing data is controversial. The options include: (1) ignore participants who drop out and present data only on those who complete the trial and the final assessment ('completers' - closely related to 'observed case' (people who had an observation at the end point) and 'per protocol' analyses); (2) impute a value of 'no change from baseline' for those who were randomised but dropped out; (3) carry forward the last value obtained from whatever time point, as if it were the value for the final time point (last observation carried forward (LOCF)); (4) include people who have dropped out of the trial but have been encouraged to return for scheduled assessments ('retrieved dropouts'); or (5) use mixed methods to take into account the data at several time points.

In dementia, which is characterised by progressive decline, the final (latest) scores for participants who drop out early will, on average, be closer to the baseline values (i.e.less severe) than for those who do not. The use of LOCF in ChEI trials has been criticised because the higher dropout rates on drug meant that it inflated estimates of the drug effect. However, when dropout rates are lower in those taking the active drug than amongst those taking placebo, the LOCF technique yields a more conservative estimate of the size of the effect of the drug than analysis of 'observed cases'. Given that a lower dropout rate on drug probably reflects a beneficial effect of the drug, this is illogical and suggests that preference for the LOCF strategy in such cases reflects either misunderstanding or mere conservatism. The 'retrieved dropout' approach may reflect better the effectiveness of the drug, but large amounts of missing data, especially differential missing data, can still lead to more conservative results. Imputation of 'no change from baseline' is the most conservative analytical strategy. The high rates of dropout in dementia trials due to factors such as caregiver and patient physical ill health mean that the use of any of these strategies reduces the power of studies to show any effect, even if real. If these results are applied in cost-effectiveness modelling, the benefit of a drug will be underestimated because of underestimated efficacy, and also because the costs incurred by those who do not continue the drug or placebo will be less.

Because of this controversy, peer reviewed publications typically present both OC and LOCF analyses. This is not the case with summary results presented in trial registries, and in the memantine trials, registries usually, but not invariably, present OC data.

In this review, we planned to use OC analyses wherever possible, but in some analyses, we had to pool trials reporting OC and LOCF data. This is made explicit in the footnotes of the relevant forest plots. We assessed the impact of this OC approach in a sensitivity analysis, which compared the results of analyses based on the two main approaches (OC and LOCF). The sensitivity analysis supported our strategy of using OC analyses in the rest of the review. We reported explicitly the degree of missing data in the Characteristics of included studies. Where mixed methods or area-under-the curve methods were reported by study authors, we extracted results from these analyses only if OC results were unavailable. For the Howard 2012 (DOMINO-AD) study, a per protocol analysis was conducted (this excluded participants who received less than 70% of their treatment) and we used this analysis in preference to retrieved dropout, mixed-methods analysis or imputation methods, as being the closest to OC.

Data synthesis

We used standard Cochrane meta-analysis methods through RevMan 5.3. Data for the meta-analyses were the reported raw data for each study. The data required for each trial and each outcome for continuous data were the mean change from baseline, the standard deviation of the mean change, and the number of participants for each treatment group. Where changes from baseline were not reported, we extracted the mean, standard

deviation and the number of participants for each treatment group at study end. For the global impression of change outcome, the endpoint itself is of clinical relevance as all participants are by definition at the same baseline score. For some studies, we calculated th standard deviation (same for each group) using the P value for the mean difference (MD); this allowed analysis of the data using the standardised mean difference (SMD).

The summary statistics calculated by meta-analysis of the continuous outcomes were (i) the MD, with its 95% confidence interval (CI), used when the pooled trials had the same rating scale or test, and (ii) the SMD - the absolute MD divided by the standard deviation - when the trials used different rating scales to assess a particular domain. Where different scales had different directions, we reversed the signs for the mean change from baseline values before conducting meta-analysis (for example, in the ADAS-Cog and SIB scales for cognitive impairment, higher values indicate greater and less impairment, respectively - see Appendix 2 - so we reversed the signs for results on the SIB scale).

At the outset, we conducted separate analyses for dementia of different aetiologies (AD; vascular dementia; Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB); Frontotemporal dementia (FTD) and AIDS Dementia Complex).

As described in the section Dealing with missing data, we used the OC approach to missing data, wherever possible, but otherwise used what was reported by the study authors.

We initially combined all trials in AD, regardless of trial duration, severity of dementia or the presence of concomitant cholinesterase inhibitor (ChEI), and then examined these factors in pre-specified subgroup analyses.

Subgroup analysis and investigation of heterogeneity

We assessed heterogeneity using the I^2 statistic (Higgins 2011) and by inspecting forest plots. An I^2 of more than 50% suggests that studies within an analysis may not be sufficiently similar for pooling to be valid. In such circumstances, we conducted sensitivity and subgroup analyses to examine the cause of the heterogeneity. We also examined the variability of the point estimates and the overlap of the confidence intervals, when I^2 values were less than 50%. Where there was evidence of heterogeneity we explored this further. Where heterogeneity could not be explained and an I^2 exceeded 35%, we used a random-effects model instead of a fixed-effect model.

For this update of the review, we explored, in subgroup analyses, the influence of the following characteristics, which were not specified in the original protocol.

1. Trial duration (< six months; six to seven months; > seven months)
2. Severity or stage of AD (mild versus moderate-to-severe)
3. Effect of concomitant ChEI

We also conducted meta-regression using STATA (STATA 2013), considering the factors severity and presence of concomitant ChEIs.

Methods for subgroup analysis: mild versus moderate-to-severe disease

Only one study in AD investigated the effects of memantine solely in people with mild dementia, but, of our primary outcomes, only cognitive function at 12 months follow-up was reported (Holland 2013). Some other studies randomised people with mild-to-moderate AD (MMSE 10-23) but data were also available for separate subgroups of participants, either in the published study report or in a published industry-produced meta-analysis (Winblad 2007). The latter reported OC results separately for the subgroup of participants with moderate dementia, giving results for three mild-to-moderate AD studies (Bakchine 2008 (99679); Peskind 2004 (MD-10); Porsteinsson 2008 (MD-12). Comparison of these results with the full mild-to-moderate OC results allowed us to estimate the effect of memantine in mild AD. OC data for the three mild-to-moderate trials were kindly provided by Forest Laboratories.

To obtain the sample sizes and mean effects for the mild AD subgroup (MMSE from 20 to 23), we subtracted values for the moderate AD subgroup (MMSE 11 to 19), weighted by sample size, from the measures for all participants (MMSE from 11 to 23) (Schneider 2011b). We calculated standard deviations of the change scores for the mild subgroup using a standard formula for pooling standard deviations (Higgins 2011). We also obtained separate results for the Dysken 2014 study for six-month data for the mild and moderate subgroups (author communication).

None of these four trials in people with mild-to-moderate dementia stratified the participants by severity before randomising and therefore there may be imbalance in the patient characteristics across the intervention groups for a particular subpopulation (i.e. risk of selection bias). We noted this post-hoc splitting in the 'Risk of bias' assessments.

Sensitivity analysis

We conducted three sensitivity analyses, either to examine assumptions or to investigate risk of bias.

1. We assessed the impact of using an OC approach, by comparing the results of analyses based on the two main approaches (OC and LOCF).
2. We also examined the effect of high risk of bias, by conducting a sensitivity analysis in which we excluded from the analysis studies with high risk of bias for at least one domain.
3. We also examined the effect of using the results from post-hoc subgroups for moderate severity AD, investigating the removal of such studies from the analysis of memantine versus placebo in moderate-to-severe AD.

'Summary of findings' table

We present the main results of the review in 'Summary of findings' tables. These tables present key information concerning the certainty of the evidence and the magnitude of the effects of the interventions examined for the main outcomes (Schünemann 2011a). 'Summary of findings' tables also include an overall grading of the evidence related to each of the main outcomes using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach. The GRADE approach defines the certainty (formerly 'quality') of a body of evidence as the extent to which one can be confident that an estimate of effect or association is close to the true quantity of specific interest. The certainty of a

body of evidence involves consideration of within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias (Schünemann 2011b). We present the following outcomes in the 'Summary of findings' tables, with a separate table for each key comparison or population group.

1. Clinical global rating
2. Cognitive function
3. Performance on activities of daily living (ADL)
4. Behaviour and mood
5. Discontinuation (all-cause)
6. Adverse events and serious adverse events
7. Agitation

'Back transformation' for continuous outcomes

Where an SMD analysis was conducted for continuous outcomes, we presented 'back transformed' effect estimates as the MD with its 95% CI: we transformed the overall standardised effect size to an approximate equivalent score on a particular scale for ease of interpretation (Higgins 2011). This involved multiplying the SMD by the median standard deviation for studies using a particular scale, calculated using the method of Hedges adjusted 'g'. We did this separately for each population and outcome.

In some cases (for example, ADL), the most appropriate scale was positive (i.e. the maximum score represented a better result), which potentially led to interpretation difficulties, so in the summary tables we report the baseline scores and the change from baseline on the original scales, but give the back-transformed MD as absolute values representing improvement; the summary statistics from the analyses are also given (as negative outcomes, see Measures of treatment effect).

We analysed all continuous outcomes except clinical global rating using change scores, so for the 'Summary of Findings' Tables, we presented the control group value in two ways: firstly, as the median of the control group baseline scores for studies reporting that scale; and, secondly, as the median change from baseline for the control group.

For dichotomous outcomes, we calculated the absolute risk difference (RD) for the appropriate population using the median control group risk for those studies and the risk ratio (RR) for the analysis. For some outcomes (e.g. adverse events), we calculated the RR across studies in all populations because there were no differences between types or severities of dementia; this maximised the precision.

Assessing imprecision

Most of the efficacy outcomes are continuous variables, often reported on different scales. Effect estimates are generally small, but in the dementia field even a small improvement is considered important. Therefore, when assessing imprecision, we used a 'default' value of 400 participants as the optimal information size (OIS) (Guyatt 2011). If the evidence was based on fewer than 400 participants, we considered downgrading for imprecision. If there were more than 400 participants, we downgraded only if the 95% CI crossed the null (zero for MD or SMD) and if the CI included what might be an important benefit or harm or both. This decision was made by agreement between two review authors.

For assessing imprecision for dichotomous outcomes, we took into account the number of participants, the number of events, whether the CI crossed a risk ratio of 0.75 or 1.25 (GRADE 'default' values) and the CI around the absolute RD (Guyatt 2011).

RESULTS

Description of studies

Studies are described in detail in Characteristics of included studies; Characteristics of excluded studies. In the former table, we report one four-arm study four times: as two comparisons of memantine versus placebo (with or without vitamin E in both arms), and as post-hoc subgroups for moderate and mild Alzheimer's disease (AD) for each of these comparisons (Dysken 2014). Four other studies reported results for severity subgroups and for these studies we have also extracted data and assessed risk of bias separately for the subgroups (Bakchine 2008 (99679); Peskind 2004 (MD-10); Porsteinsson 2008 (MD-12); Winblad 1999 (9403)). Summary details of the participants at baseline are given in Table 2 for the AD studies. Only three studies had fewer than 50% females ((Dysken 2014 - 3%; Holland 2013 - 35%; Ashford 2011 (95722) - 38%). Most studies had a mean age between 70 and 80 years, exceptions were older participants in the Forest 2006 (MD-22) study (mean 85 years) and the Fox 2012 (MAGD) study (mean 84 years) and younger participants in the Wang 2013 study (mean 65 years).

Results of the search

The searches generated a total of 3262 results. After de-duplication and first assessment based on title and abstract screening, we obtained 264 in full text (Figure 1). We excluded 113 studies (see Characteristics of excluded studies). We added 32 new randomised controlled trials (RCTs) to the 12 studies in the previous 2006 update. Overall, these 44 studies were described in 148 reports. We are also aware of three ongoing studies (see Characteristics of ongoing studies).

Figure 1. Study flow diagram of studies identified

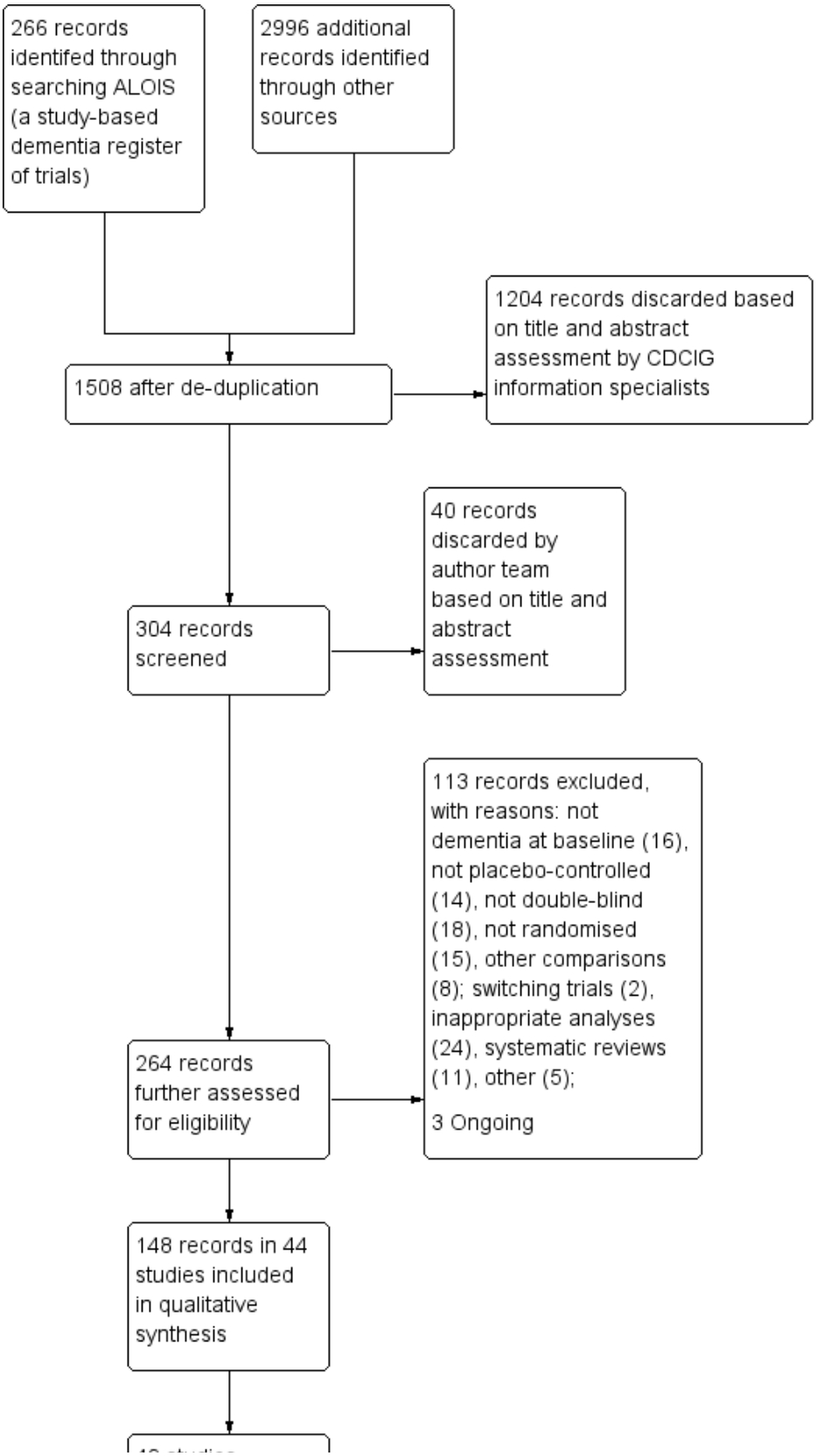
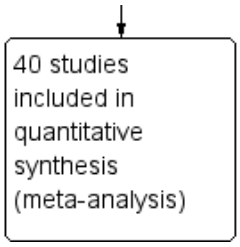


Figure 1. (Continued)



Included studies

Forty-four studies fulfilled the inclusion criteria, comprising 9811 participants (Aarsland 2009; Asada 2011 (MA3301); Asada 2011a (IE3501); Ashford 2011 (95722); Bakchine 2008 (99679); Boxer 2013; Ditzler 1991; Dysken 2014; Emre 2010 (11018); Forest 2006 (MD-22); Forest 2006 (MD-23); Fox 2012 (MAGD); Herrmann 2012 (10158); Gortelmeyer 1992; Grossberg 2008 (MD-50); Hofbauer 2009 (MD-71); Holland 2013; Homma 2007 (IE2101); Howard 2012 (DOMINO-AD); Leroi 2009; Lorenzi 2011 (SC05-03); Lundbeck 2006 (10116); Lundbeck 2006 (99817); Marsh 2009 PDD; Medina 2011; Merz 2003 (MRZ-9104); Merz 2003 (MRZ-9105); Merz 2003 (MRZ-9206); Nakamura 2016; Orgogozo 2002 (9408); Pantev 1993; Peskind 2004 (MD-10); Peters 2015 (MEGACOMBI2); Porsteinsson 2008 (MD-12); Reisberg 2003 (9605); Schifitto 2007; Schmidt 2008; Tariot 2004 (MD-02); van Dyck 2007 (MD-01); Vercelletto 2011; Wang 2013; Wilcock 2002 (9202); Wilkinson 2012 (10112); Winblad 1999 (9403)). The mean sample size was 223 and the median and range were 182.5 (13 to 677); 20 studies had more than 200 participants. Seven studies were reported solely as registry data or via author communication (Asada 2011 (MA3301); Forest 2006 (MD-22); Forest 2006 (MD-23); Lundbeck 2006 (99817); Marsh 2009 PDD; Merz 2003 (MRZ-9105); Merz 2003 (MRZ-9206)); and we obtained responses to requests for further information from the authors (or companies) of 16 studies (Asada 2011a (IE3501); Asada 2011 (MA3301); Bakchine 2008 (99679); Herrmann 2012 (10158); Grossberg 2008 (MD-50); Homma 2007 (IE2101); Howard 2012 (DOMINO-AD); Lundbeck 2006 (10116); Lundbeck 2006 (99817); Merz 2003 (MRZ-9104); Merz 2003 (MRZ-9105); Merz 2003 (MRZ-9206); Peskind 2004 (MD-10); Porsteinsson 2008 (MD-12); Schmidt 2008; Wilkinson 2012 (10112)).

We have not been able to identify the results or any associated publications or announcements belonging to four studies: Lundbeck 2006 (99817) was a 12-week study in Taiwan of 47 people with AD; Merz 2003 (MRZ-9105) was a 12-week study in Portugal of 27 people with 'primary dementia'; Merz 2003 (MRZ-9104) was a 13-week study in France of 56 people with AD; and Merz 2003 (MRZ-9206) was a 14-week study in Sweden of 56 people with vascular dementia.

Trial duration varied from six weeks to 2.27 years (mean), with the majority of studies having a duration of six months. Fourteen studies had a duration of less than six months (Ditzler 1991; Forest 2006 (MD-23); Fox 2012 (MAGD); Gortelmeyer 1992; Hofbauer 2009 (MD-71); Leroi 2009; Lundbeck 2006 (10116); Lundbeck 2006 (99817); Merz 2003 (MRZ-9104); Merz 2003 (MRZ-9105); Merz 2003 (MRZ-9206); Pantev 1993; Schifitto 2007; Winblad 1999 (9403)). Eight studies reported results at 12 months or longer (Ashford 2011 (95722); Dysken 2014; Holland 2013; Howard 2012 (DOMINO-AD); Peters 2015 (MEGACOMBI2); Schmidt 2008; Vercelletto 2011; Wilkinson 2012 (10112)), and of these, one provided interim results at 30 weeks (Howard 2012 (DOMINO-AD)); and three at six months (Dysken 2014; Peters 2015 (MEGACOMBI2); Schmidt 2008).

Fifteen trials were conducted in North America: including 14 in the USA (Ashford 2011 (95722); Boxer 2013; Dysken 2014; Forest 2006 (MD-22); Forest 2006 (MD-23), Holland 2013; Marsh 2009 PDD; Medina 2011; Peskind 2004 (MD-10); Porsteinsson 2008 (MD-12); Reisberg 2003 (9605); Schifitto 2007; Tariot 2004 (MD-02); van Dyck 2007 (MD-01)), and one in Canada (Herrmann 2012 (10158)). Twenty trials were conducted in Europe, including four in the UK (Fox 2012 (MAGD); Howard 2012 (DOMINO-AD); Leroi 2009; Wilcock 2002 (9202)); four in Germany (Ditzler 1991; Gortelmeyer 1992; Pantev 1993; Peters 2015 (MEGACOMBI2)); two in France (Merz 2003 (MRZ-9104); Vercelletto 2011); one each in Austria (Schmidt 2008); Italy (Lorenzi 2011 (SC05-03)); Latvia (Winblad 1999 (9403)); Portugal (Merz 2003 (MRZ-9105)); Sweden (Merz 2003 (MRZ-9206)); and five in more than one European country (Aarsland 2009; Bakchine 2008 (99679); Emre 2010 (11018); Orgogozo 2002 (9408); Wilkinson 2012 (10112)). Four trials were conducted in Japan (Asada 2011 (MA3301); Asada 2011a (IE3501); Homma 2007 (IE2101); Nakamura 2016); two in China (Lundbeck 2006 (10116); Wang 2013); and one in Taiwan (Lundbeck 2006 (99817)). The other two studies were international trials (Grossberg 2008 (MD-50); Hofbauer 2009 (MD-71)).

Funding

All studies had some funding from industry, with one exception (Schifitto 2007), although in three trials the only input was the provision of drugs and the main sponsors were the UK Medical Research Council; the US Veterans Affairs Co-operative Studies Program and the Bundesministerium fűr Bildung und Forschung (respectively, Howard 2012 (DOMINO-AD) Dysken 2014 and Peters 2015 (MEGACOMBI2)).

Eleven trials were sponsored by Merz Pharmaceuticals GmbH, Germany (Ditzler 1991; Gortelmeyer 1992; Merz 2003 (MRZ-9104); Merz 2003 (MRZ-9105); Merz 2003 (MRZ-9206); Orgogozo 2002 (9408); Pantev 1993; Reisberg 2003 (9605); Schmidt 2008; Wilcock 2002 (9202); Winblad 1999 (9403). Fourteen trials were sponsored by Forest Laboratories Inc, US (Ashford 2011 (95722); Boxer 2013; Forest 2006 (MD-22); Forest 2006 (MD-23); Grossberg 2008 (MD-50); Hofbauer 2009 (MD-71); Holland 2013; Marsh 2009 PDD; Medina 2011; Peskind 2004 (MD-10); Porsteinsson 2008 (MD-12); Tariot 2004 (MD-02); van Dyck 2007 (MD-01)); and this company also provided drugs for one trial (Dysken 2014).

Twelve trials were sponsored by H. Lundbeck A/S, Denmark (Aarsland 2009; Bakchine 2008 (99679); Emre 2010 (11018); Fox 2012 (MAGD); Herrmann 2012 (10158); Leroi 2009; Lorenzi 2011 (SC05-03); Lundbeck 2006 (10116); Lundbeck 2006 (99817); Vercelletto 2011; Wang 2013); and this company also provided

drugs for one trial (Howard 2012 (DOMINO-AD)). One trial was sponsored by both Merz and Lundbeck (Wilkinson 2012 (10112)).

Four trials were sponsored by Daiichi Sankyo Co. Ltd, Japan (Asada 2011 (MA3301); Asada 2011a (IE3501); Homma 2007 (IE2101); Nakamura 2016).

Patient characteristics

Diagnosis

The diagnosis of dementia was established using the latest versions of the Diagnostic and Statistical Manual of Mental Disorders (DSM III-R; DSM IV) in 17 studies (Aarsland 2009; Asada 2011a (IE3501); Ashford 2011 (95722); Bakchine 2008 (99679); Emre 2010 (11018); Gortelmeyer 1992; Grossberg 2008 (MD-50); Homma 2007 (IE2101); Leroi 2009; Marsh 2009 PDD; Orgogozo 2002 (9408); Pantev 1993; Reisberg 2003 (9605); Schmidt 2008; Wang 2013; Wilcock 2002 (9202); Winblad 1999 (9403)). Eleven other studies included people diagnosed with probable AD (McKhann 1984), according to the criteria of the National Institute of Neurologic, Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) (Asada 2011 (MA3301); Fox 2012 (MAGD); Herrmann 2012 (10158); Lorenzi 2011 (SC05-03); Nakamura 2016; Peskind 2004 (MD-10); Peters 2015 (MEGACOMBI2); Porsteinsson 2008 (MD-12); Tariot 2004 (MD-02); van Dyck 2007 (MD-01); Wilkinson 2012 (10112)); and two studies included people diagnosed with probable or possible AD according to the same criteria (Dysken 2014; Howard 2012 (DOMINO-AD)). The other studies did not report diagnosis by these criteria.

Type and severity of dementia

Almost all the studies measured severity of dementia as defined by scores on the Mini Mental State Examination (MMSE) (Folstein 1975). Three exceptions used the Sandoz Clinical Assessment Geriatric Scale (SCAG) (Ditzler 1991; Gortelmeyer 1992; Pantev 1993).

Twenty-eight studies were in people with AD (Asada 2011 (MA3301); Asada 2011a (IE3501); Ashford 2011 (95722); Bakchine 2008 (99679); Dysken 2014; Forest 2006 (MD-22); Forest 2006 (MD-23); Fox 2012 (MAGD); Herrmann 2012 (10158); Grossberg 2008 (MD-50); Hofbauer 2009 (MD-71); Holland 2013; Homma 2007 (IE2101); Howard 2012 (DOMINO-AD); Lorenzi 2011 (SC05-03); Lundbeck 2006 (10116); Lundbeck 2006 (99817); Merz 2003 (MRZ-9104); Nakamura 2016; Peskind 2004 (MD-10); Peters 2015 (MEGACOMBI2); Porsteinsson 2008 (MD-12); Reisberg 2003 (9605); Schmidt 2008; Tariot 2004 (MD-02); van Dyck 2007 (MD-01); Wang 2013; Wilkinson 2012 (10112)). We also included a subpopulation from a further study (Winblad 1999 (9403) AD), which reported an AD subgroup from the study Winblad 1999 (9403). These studies randomised a total of 7885 participants with AD.

Of these AD studies, one was in people with mild AD (Holland 2013); nine were in people with mild-to-moderate AD (Asada 2011 (MA3301); Ashford 2011 (95722); Bakchine 2008 (99679); Dysken 2014; Lundbeck 2006 (99817); Peskind 2004 (MD-10); Peters 2015 (MEGACOMBI2); Porsteinsson 2008 (MD-12); Schmidt 2008); two were in people with moderate AD (Hofbauer 2009 (MD-71); Wilkinson 2012 (10112)); 15 were in people with moderate-to-severe AD (Asada 2011a (IE3501); Forest 2006 (MD-22); Forest 2006 (MD-23); Fox 2012 (MAGD); Herrmann 2012 (10158); Grossberg 2008 (MD-50); Homma 2007 (IE2101); Howard 2012 (DOMINO-AD); Lorenzi 2011 (SC05-03); Lundbeck 2006 (10116); Nakamura 2016; Reisberg 2003 (9605); Tariot 2004 (MD-02); van Dyck 2007 (MD-01); Wang 2013); and we were unable to establish the severity in one study (Merz 2003 (MRZ-9104)). Three of these studies reporting mean MMSE scores at baseline had a mean score of less than 10, suggesting that at least 50% of participants had severe AD (Fox 2012 (MAGD); Howard 2012 (DOMINO-AD); Reisberg 2003 (9605)); the Winblad 1999 (9403) AD subgroup was selected to have a MMSE score below 10. One of the mild-to-moderate AD studies had a mean MMSE score of 22, so most people had mild dementia (Peters 2015 (MEGACOMBI2)).

Three studies involved **people with vascular dementia**, defined by the NINDS-AIREN criteria (Merz 2003 (MRZ-9206); Orgogozo 2002 (9408); Wilcock 2002 (9202)); 956 participants were randomised. One of these studies was in people with 'moderately severe' dementia (but reported no results) (Merz 2003 (MRZ-9206)) and the other two studies recruited people with mild-to-moderate dementia.

Three short, phase II trials of four to six weeks in 213 participants included **both AD and vascular dementia i**n various proportions (Ditzler 1991; Gortelmeyer 1992; Winblad 1999 (9403)); the Hachinski score was used to differentiate between AD and vascular dementia. Two further studies included both AD and vascular dementia, but there is no record of an attempt to distinguish the different types of dementia (Merz 2003 (MRZ-9105); Pantev 1993). Two studies included people with mild-to-moderate dementia (Ditzler 1991; Gortelmeyer 1992); participants in one study had severe dementia (Winblad 1999 (9403)); participants in one study were equally divided between mild, moderate and severe disease (Pantev 1993); and one study reported "mild to-moderate severe stages of primary dementia" (Merz 2003 (MRZ-9105)).

The remaining studies included participants with other types of dementia: four studies in 319 participants with **Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB)** (Aarsland 2009; Emre 2010 (11018), Leroi 2009; Marsh 2009 PDD); two studies in 133 participants with **frontotemporal dementia (FTD)** (Boxer 2013; Vercelletto 2011); one study in 140 participants with **HIV AIDS dementia complex** (Schifitto 2007); and one study in 50 participants with **Huntingdon's Disease** (this study, however, presented no useable data) (Medina 2011).

Three studies stated they selectively included patients with agitation (Forest 2006 (MD-23); Fox 2012 (MAGD); Herrmann 2012 (10158)); 556 participants were randomised. One of these studies investigated treatment for those with agitation living in the community (Forest 2006 (MD-23)); this study was terminated after recruiting only 34 participants, but reported these results. A second study recruited participants living in the community, who were specifically selected for the presence of agitation and aggression at baseline (Herrmann 2012 (10158)); the trial was prematurely terminated because of difficulty in recruitment (only recruiting 82% of the planned participants), but reported results. The third study of institutionalised patients with agitation specified a primary outcome of Cohen-Mansfield Agitation Index (CMAI) score at six weeks (Fox 2012 (MAGD)).

Interventions assessed

The majority of studies randomised participants to memantine at its licensed dose of 20 mg daily (or placebo). One study used an

extended release preparation of 28 mg/day, equivalent to 20 mg daily (Grossberg 2008 (MD-50)). Two studies investigated a dose of 10 mg/day memantine versus placebo (Ashford 2011 (95722); Winblad 1999 (9403)); and two other studies included a 10 mg/day arm, alongside 20 mg/day and placebo (Asada 2011 (MA3301); Homma 2007 (IE2101)).

Seven studies compared the efficacy and safety of memantine (versus placebo) in people who were already receiving stable treatment with donepezil (Dysken 2014; Herrmann 2012 (10158); Grossberg 2008 (MD-50); Lorenzi 2011 (SC05-03); Nakamura 2016; Porsteinsson 2008 (MD-12);Tariot 2004 (MD-02)). Five other studies included some participants who were already on cholinesterase inhibitors (ChEIs): 72% (Wilkinson 2012 (10112)); 50% (Marsh 2009 PDD); 86% for memantine and 67% for placebo (Ashford 2011 (95722)); 19% and 23% (Fox 2012 (MAGD)); and 18% and 14% (Leroi 2009). Two other studies allowed the continuation of stable ChEIs, but did not state the proportions involved (Hofbauer 2009 (MD-71); Holland 2013). One study was in people who were anti-dementia drug naive at baseline and were randomised to memantine plus galantamine (a ChEI) versus placebo plus galantamine (Peters 2015 (MEGACOMBI2)).

One study actively discontinued ChEIs before starting memantine or placebo (Bakchine 2008 (99679); another had participants who had ChEIs discontinued because of a lack of efficacy (Schmidt 2008). One four-arm study included 295 participants who were on stable ChEIs, but were being considered for a change of drug treatment; the participants were randomised to discontinue or continue donepezil, as well as randomising to memantine or placebo (Howard 2012 (DOMINO-AD)). One study did not permit ChEIs within 30 days of the trial, although 55% had prior use of donepezil (Peskind 2004 (MD-10)). Another study reported previous use of drugs for dementia by the participants, but without specifying types (Winblad 1999 (9403)).

One four-arm study randomised 613 participants to concurrent vitamin E or placebo, as well as randomising to memantine or placebo (Dysken 2014).

Outcome measures

The range of outcome measures used in the studies is summarised in Table 1.

Adverse events (AEs) were reported in various ways: the number of people with any AE (at least one per person); the number with at least one serious AE (SAE) and results were also given separately for the number of people with specific AEs (agitation, insomnia, confusion (as an AE), depression, headache, hypertension, dizziness, fall, accidental injury, urinary incontinence, diarrhoea and influenza-like symptoms). For these specific AEs, registry data were commonly presented separately for AEs and SAEs, but it was unclear whether there was overlap between the set of participants with a specific outcome recorded as an AE and the set of participants with that outcome recorded as an SAE. Therefore, we used results for the AE set only unless the outcome was solely reported as SAEs.

Adverse events across all diagnoses and durations are reported in Effects of interventions, section 5 and also separately for each diagnosis. These analyses were restricted to the 20 mg/day or equivalent dose of memantine.

Excluded studies

We excluded 115 studies (Figure 1) at the full-text stage. Details are given in the Characteristics of excluded studies table, but the main reasons for exclusion were: 15 were not RCTs; 18 were not double-blinded; the population in 16 studies did not have dementia (or not solely dementia participants); 16 studies were not placebo controlled; 24 were post-hoc analyses or had inappropriate ways of combining data; and eight studies compared memantine with other interventions. We obtained the full papers for 11 systematic reviews in order to check the references, but there was no new information found (systematic reviews that did provide additional information were added as references to the included studies).

Risk of bias in included studies

A detailed analysis of the risks of bias for each study can be found in Characteristics of included studies. 'Risk of bias' domain ratings are shown per study in Figure 2 and percentage contributions for each domain are shown in Figure 3.

Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

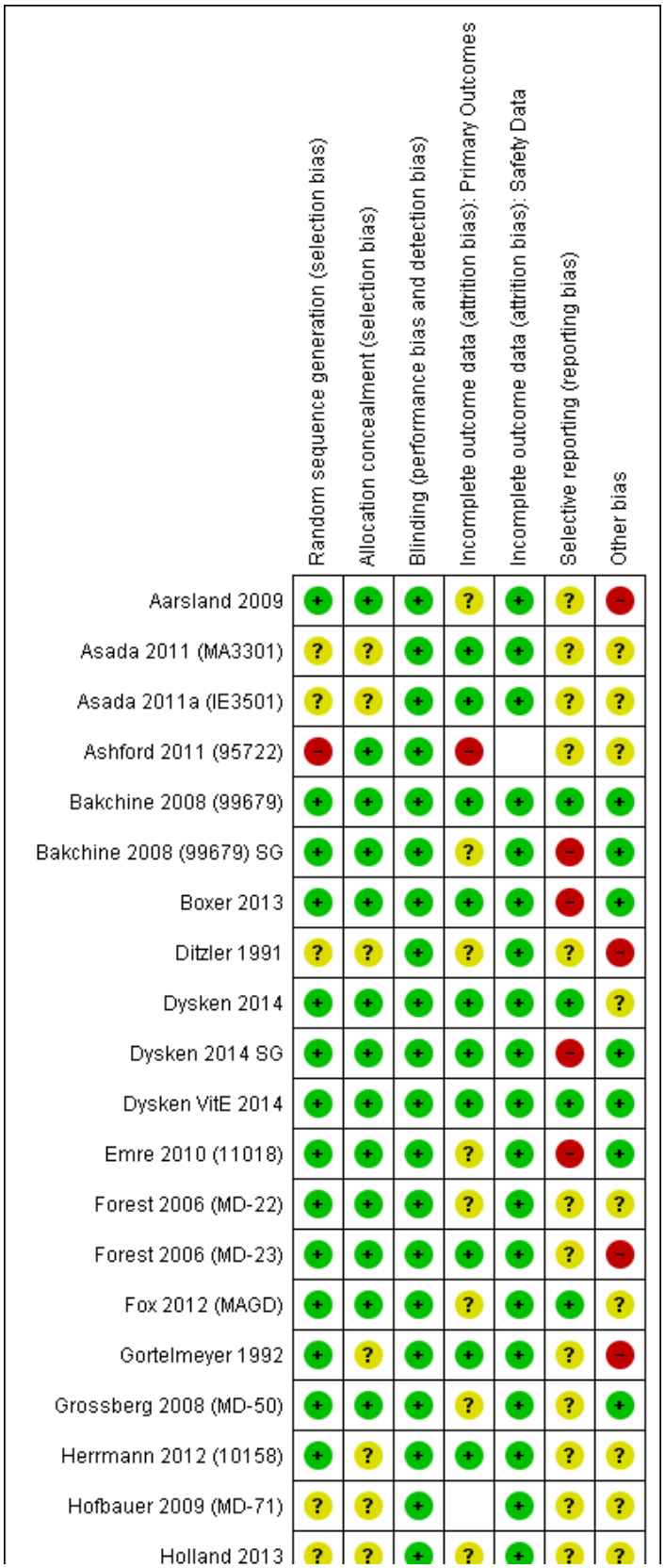


Figure 2. (Continued)

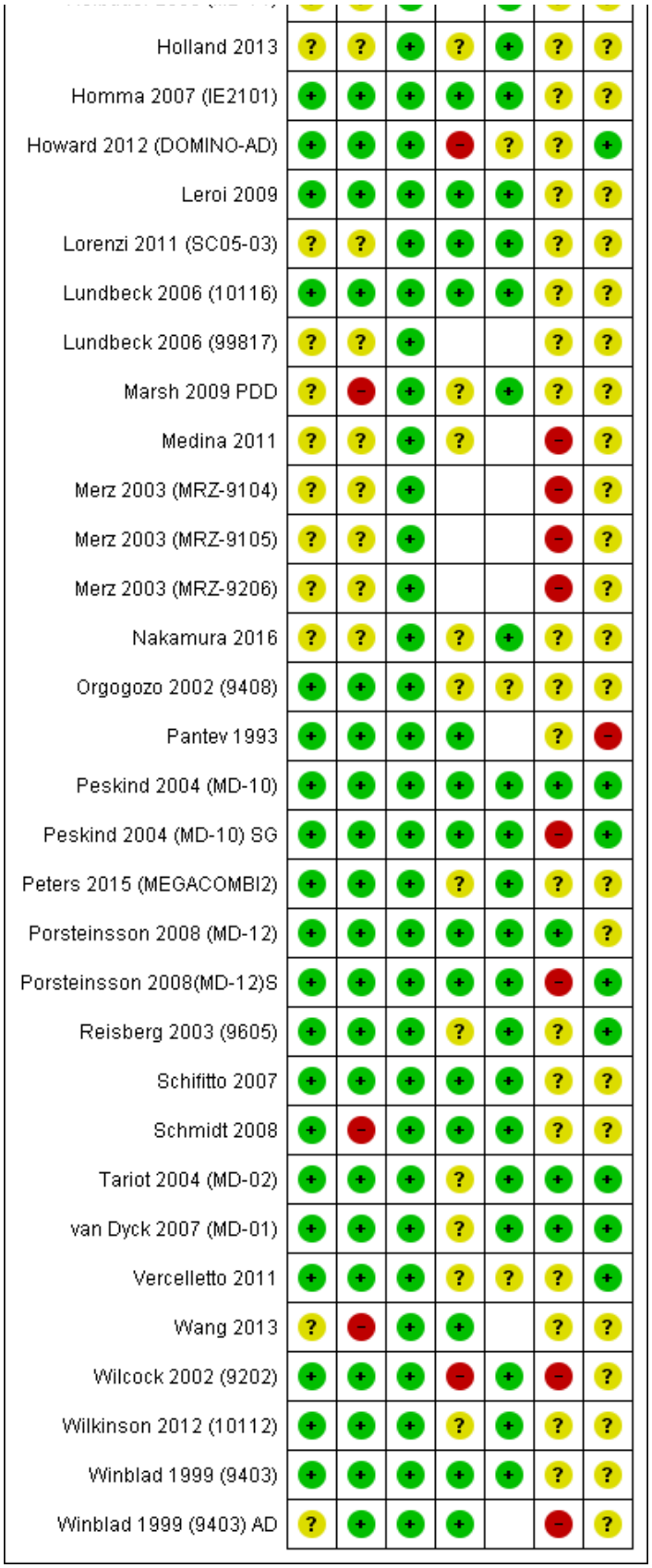
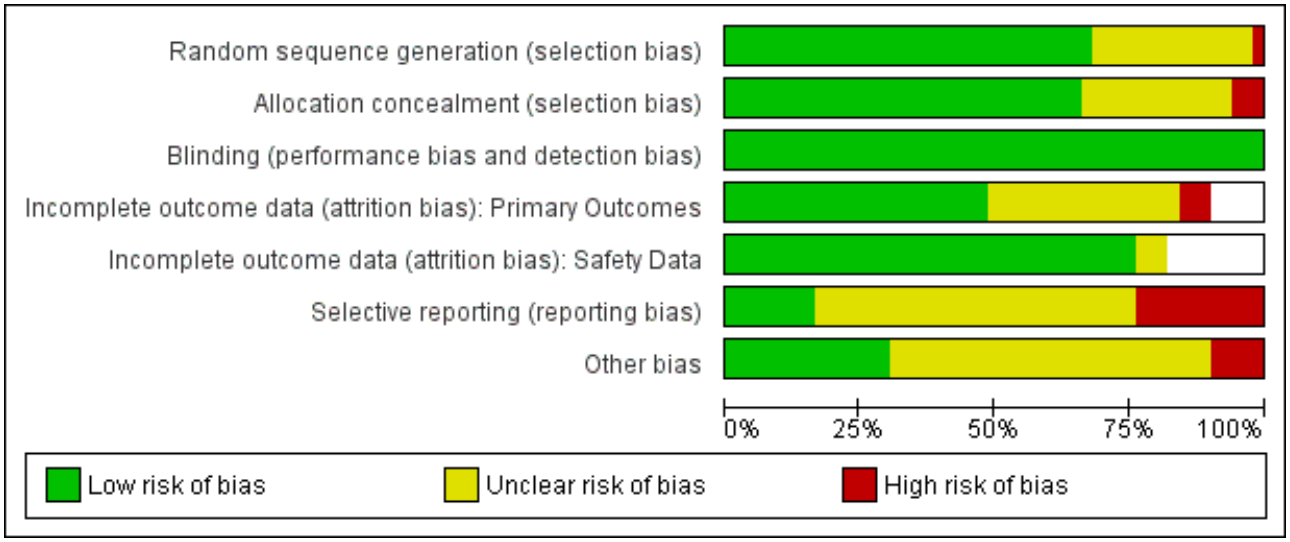


Figure 3. 'Risk of bia's graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

We assessed four studies to be at high risk of selection bias because of large differences in outcome at baseline that were as large or larger than the effect size for most outcomes (Aarsland 2009; Ashford 2011 (95722); Marsh 2009 PDD; Wang 2013); e.g. in one study (Wang 2013), 15.3 points baseline difference in Severe Impairment Battery (SIB), four points for MMSE, three points for Neuropsychiatric Inventory (NPI). The Aarsland 2009 study had baseline differences despite adequate methods of sequence generation and allocation concealment, and this is recorded as 'other' risk of bias. We considered one study to be at high risk of bias because of differences in the levels of concurrent neuroleptic medications: 33% in the placebo group and 28% in the memantine group, and because of a 10-point difference in activities of daily living (ADL) at baseline (Schmidt 2008).

Other studies reporting differences at baseline for particular outcomes that are comparable with the effect estimate are considered in the results sections for those outcomes.

Blinding

All studies were double blinded - this was an inclusion criterion - and all were at low risk of bias for this domain.

Incomplete outcome data

We considered three studies to have a high risk of attrition bias for the efficacy outcomes of the review: one very small study had missing data of 43% (memantine) and 0% (placebo) (Ashford 2011 (95722)); a second study reported a per protocol analysis at 30 weeks for which excluded data were: 45% (memantine), 60% (placebo); 30% (memantine + donepezil) and 32% (placebo + donepezil); sensitivity analyses comparing the per protocol analysis with a 'completed follow-up' analysis showed some differences in effect estimate (Howard 2012 (DOMINO-AD)). The third study also reported a per protocol analysis for which excluded data were 35% (memantine) and 43% (placebo) (Wilcock 2002 (9202)).

Selective reporting

We considered four studies to be at high risk of bias for selective reporting of outcomes: one study decided post hoc to reduce the Clinical Global Impression of Change (CGIC) values to three categories (Boxer 2013); the second did not report the numbers of participants for the observed case (OC) analysis and we had to make assumptions (Emre 2010 (11018)); and the third reported missing scores for some participants that were not explained (Nurse's Observational Scale for Geriatric Patients (NOSGER) outcomes) (Wilcock 2002 (9202)). Where other studies did not report outcomes or did not provide sufficient data to analyse, we included these studies in the appropriate forest plots and estimated their contribution to the whole meta-analysis, as described in the Assessment of risk of bias in included studies section.

We also assessed the five studies that reported post-hoc subgroups to be at high risk of outcome reporting bias for those subpopulations (Bakchine 2008 (99679) SG; Dysken 2014 SG; Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S; Winblad 1999 (9403) AD).

Other potential sources of bias

We recorded three other studies as having high risk of bias because they had an outdated diagnosis of AD (Ditzler 1991; Gortelmeyer 1992; Pantev 1993). We considered one study to be at high risk of bias because the trial was terminated early without explanation given (Forest 2006 (MD-23)).

Overall risk of bias

The overall risk of bias for most studies was either unclear or low (Figure 2). We considered three studies to have low risk of bias for all domains (Bakchine 2008 (99679); Dysken VitE 2014; Peskind 2004 (MD-10)).

We assessed two studies to be at high risk of bias for at least two domains (Ashford 2011 (95722); Wilcock 2002 (9202) for NOSGER outcomes), and 11 other studies to be at high risk of bias for

one domain (Aarsland 2009; Boxer 2013; Ditzler 1991; Emre 2010 (11018); Forest 2006 (MD-23); Gortelmeyer 1992; Howard 2012 (DOMINO-AD); Marsh 2009 PDD; Pantev 1993; Schmidt 2008; Wang 2013). We considered post-hoc subgroups of five studies to be at high risk of bias for one domain (Bakchine 2008 (99679) SG; Dysken 2014 SG; Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S; Winblad 1999 (9403) AD).

Effects of interventions

See: **Summary of findings for the main comparison** Moderate-to-severe AD, six to seven months; **Summary of findings 2** Vascular dementia - mild-to-moderate severity. six months

We present the efficacy results according to the aetiology of the dementia in sections 1 to 3 below. We compare effects across different types of dementia in section 4. We describe safety data, including discontinuation (all-cause and that due to adverse events) and adverse events outcomes in section 5 for all aetiologies of dementia, represented on the same forest plots, with analyses featuring separate subgroups.

We conducted the main analyses as observed case (OC), for the reasons discussed in the Dealing with missing data section, and also tested the OC approach in sensitivity analyses in comparison with the last observation carried forward (LOCF) approach (Appendix 3).

We produce a 'Summary of findings' table for most sections (Summary of findings for the main comparison; Summary of findings 2; Table 3; Table 4; Table 5; Table 6; Table 7; Table 8). We generally analysed the efficacy outcomes as standardised mean difference (SMD), but back-transformed to a common scale. Similarly, for dichotomous (safety) outcomes, we calculated the absolute risk difference (RD) for the relevant population. In doing so, we reported safety outcomes either for all trials of memantine (across all aetiologies) or for separate sub-populations, depending on the safety outcome concerned.

1. Alzheimer's disease (AD)

1.1. Results for all studies in people with AD: trial selection

Twenty-nine studies reported the effect of memantine in people with AD, however, we did not include five of these studies in the main analyses: three studies concerned participants selected for agitation or aggression and we treated this group separately because we considered this to be a different sub-population (see section 1.4) (Forest 2006 (MD-23); Fox 2012 (MAGD); Herrmann 2012 (10158). Secondly, it was necessary to analyse the main efficacy outcomes using the SMD because the studies employed different scales; therefore, we had to exclude from the efficacy analyses two studies reporting only final values (Ashford 2011 (95722); Lorenzi 2011 (SC05-03)). In addition, in a post-hoc decision, we excluded from the analyses results for two of the four arms in one study: the comparison of memantine versus placebo, in the presence of vitamin E (Dysken VitE 2014). This was because a negative interaction between memantine and vitamin E was identified by the authors for their primary outcome (decline in activities of daily living (ADL), P = 0.03), which persisted at all time points in the four-arm study. Finally, for one study, there was a discrepancy in the one-year results between the unpublished poster (which reported standard deviations) and the full paper (which did not) for their ADL outcome, so we also omitted this study for the outcome, decline in ADL (Schmidt 2008).

We therefore included data from 24 trials in 7102 randomised participants with AD, using the OC approach to missing data, whenever possible. For most outcomes, there was too much heterogeneity to make overall statements of effect, therefore we investigated the heterogeneity in sensitivity and subgroup analyses, examining risk of bias, trial duration, memantine dose, concomitant cholinesterase inhibitors (ChEIs) and severity of AD. Details are reported in Appendix 4 .

In a sensitivity analysis, we found that exclusion of the trials at high risk of bias for one or more domains generally made little difference to the heterogeneity, so all 24 studies were included in subgroup analyses (Appendix 4.1).

Following subgroup analyses (Appendix 4), we firstly restricted the main analyses (below) to those with the licensed memantine dose of 20 mg per day or a daily 28 mg extended release tablet, and to a duration of six to seven months. This meant that some studies were excluded from the analyses: four short-term studies in 658 participants (Hofbauer 2009 (MD-71); Lundbeck 2006 (10116); Merz 2003 (MRZ-9104); Winblad 1999 (9403) AD); and three longer-term studies in 334 participants that did not report interim results at six to seven months (Ashford 2011 (95722); Holland 2013; Wilkinson 2012 (10112)); these studies only reported results for the cognitive function outcome. Additionally, we did not include in the main analyses the 10 mg/day arms from two studies (Asada 2011 (MA3301); Homma 2007 (IE2101)). This left 17 studies in 5813 randomised participants.

Secondly, on the basis of subgroup analyses and meta-regression addressing both severity and the presence or absence of ChEIs, we concluded that it was necessary to stratify the studies by severity of AD, and to later investigate residual heterogeneity in the moderate-to-severe population (Appendix 4; Appendix 5; Appendix 6). In the test for subgroup differences, there were large differences relating to disease severity, both between mild-to-moderate and moderate-to-severe AD and between mild and moderate-to-severe AD. We analysed and reported separately results for mild dementia and moderate-to-severe dementia because these represent the categories for the licensed indications. These analyses include post-hoc subgroups for mild and moderate AD obtained from studies in people with mild-to-moderate AD. We had to omit from the main analyses three studies in 468 participants with mild-to-moderate AD because they did not report separately results for mild and moderate populations (Asada 2011 (MA3301); Peters 2015 (MEGACOMBI2); Schmidt 2008). Subgroup analyses also showed that any impact from the presence of ChEIs was small.

All subgroup analyses investigated the impact of different study factors on the effect estimate (i.e. the difference in mean change-from-baseline scores between memantine and placebo). However, we also observed differences according to severity in the change from baseline for the placebo group alone; this was found for all outcomes except clinical global (which appeared to be independent of severity). There was increased efficacy of memantine (versus placebo) with increasing severity of disease, but this occurred alongside deterioration in the placebo group for the moderate and severe populations and improvement for the mild population.

In the rest of this section, we report results for the following sub-populations: Section 1.2 reports the results for all participants with moderate-to-severe AD, with the exception of studies in patients selected for agitation. Section 1.3 examines the effect of concomitant ChEIs in people with moderate-to-severe AD. Section 1.4 covers the effect of memantine versus placebo in patients with agitation (who also had moderate-to-severe AD). Finally, section 1.5 summarises the evidence for people with mild dementia. We do not discuss separately results for moderate and severe AD in the main section, but analyses based on post-hoc subgroups are given in Appendix 4. Each sub-section includes the individual results for the efficacy outcomes, GRADE certainty ratings and a summary.

1.2. Effect of memantine in people with moderate-to-severe AD at six to seven months; OC

1.2.1. Effect of memantine (20 mg to 28 mg/day) versus placebo (irrespective of whether additionally taking a cholinesterase inhibitor)

Fifteen studies met the inclusion criteria and contributed data from approximately 3700 analysed participants (Asada 2011a (IE3501); Bakchine 2008 (99679) SG; Dysken 2014 SG; Forest 2006 (MD-22); Grossberg 2008 (MD-50); Homma 2007 (IE2101); Howard 2012 (DOMINO-AD); Lorenzi 2011 (SC05-03); Nakamura 2016; Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S; Reisberg 2003 (9605); Tariot 2004 (MD-02); van Dyck 2007 (MD-01); Wang 2013). Four of these studies provided post-hoc data for moderate severity AD participants (Bakchine 2008 (99679) SG; Dysken 2014 SG; Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S).

Not all studies reported all the outcomes: for the efficacy outcomes,10 studies contributed data to the clinical global outcome, 13 to cognitive function, 11 to decline in ADL and 14 to the behaviour and mood outcome. Thirteen studies reported all-cause discontinuation and 12 withdrawal due to adverse events, but considerably fewer studies reported adverse events: nine studies (72% of all participants) reported the proportion of participants with at least one adverse event; nine studies (77% of all participants) reported the proportion with serious adverse events and six studies (61% of all participants) reported the proportion with agitation.

The evidence for this section is summarised in Summary of findings for the main comparison, which covers both efficacy and safety outcomes; a negative SMD (or MD value means that the effect favours memantine.

- Clinical global rating (Analysis 1.1): high-certainty evidence: meta-analysis of 10 studies in 2797 participants gave an SMD of -0.20 (95% CI -0.28 to -0.13), favouring memantine.
- Cognitive function (Analysis 1.2): high-certainty evidence: meta-analysis of 13 studies in 3337 participants gave an SMD of -0.27 (95% CI -0.34 to -0.21); there was some variation in the point estimates (I^2 = 30%, P = 0.14).
- Decline in ADL (Analysis 1.3): high-certainty evidence: meta-analysis of 11 studies in 2687 participants gave an SMD -0.16 (95% CI -0.24 to -0.09).
- Behaviour and mood (Analysis 1.4) high-certainty evidence: meta-analysis of 14 studies in 3674 participants gave an SMD of -0.14 (95% CI -0.21 to -0.08); there was some variability in the point estimates (but I^2 = 8%, P = 0.36).
- All-cause discontinuation, discontinuation due to adverse events, adverse events and serious adverse events are reported in section 5.

Funnel plots for the primary outcomes are shown in Figure 4; Figure 5; Figure 6; Figure 7 and for all-cause discontinuation in Figure 8. There appeared to be no suggestion of publication bias. There may be some asymmetry in the funnel plot for the number of people with at least one adverse event (Figure 9), but probably not sufficient to downgrade the evidence on the basis of publication bias.

Figure 4. Funnel plot of comparison: 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease. 24-30 week data. OC, outcome: 1.1 Clinical Global.

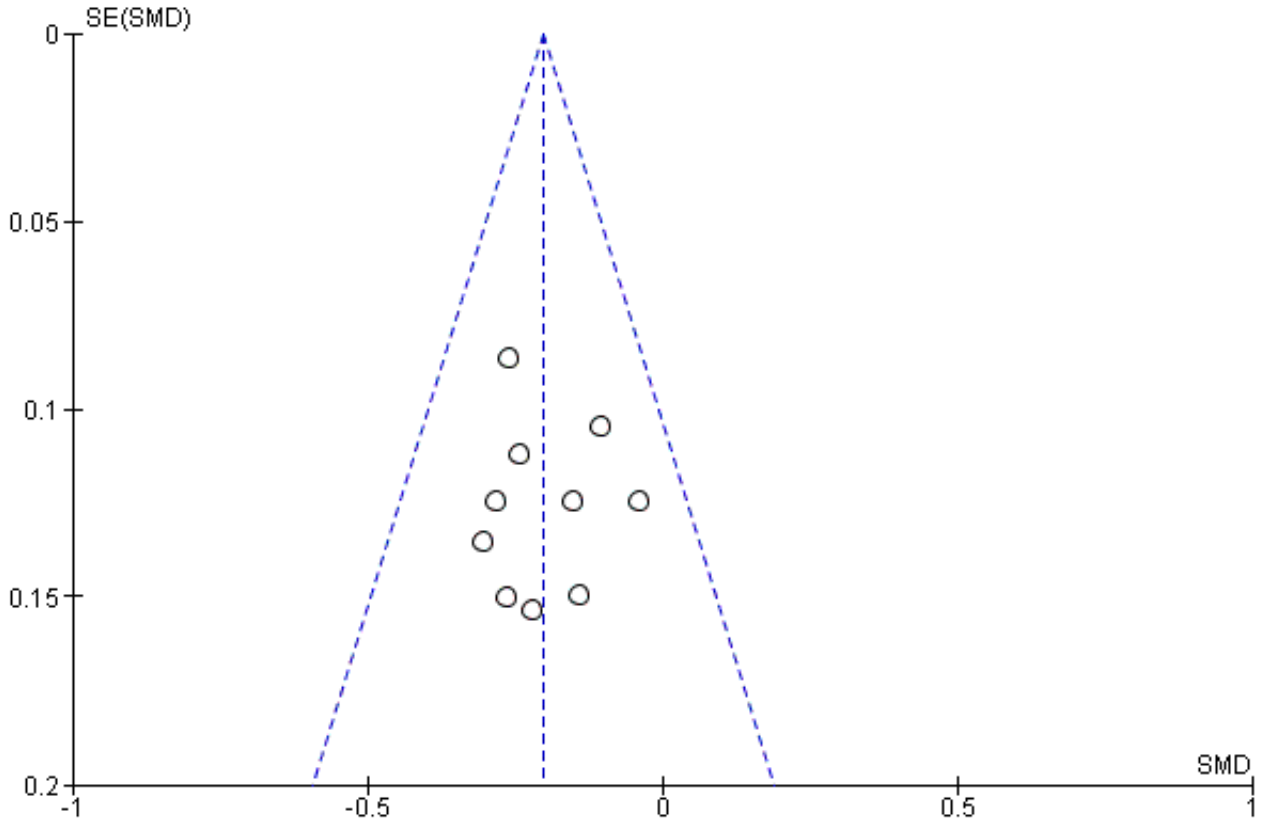


Figure 5. Funnel plot of comparison: 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease. 24-30 week data. OC, outcome: 1.2 Cognitive Function.

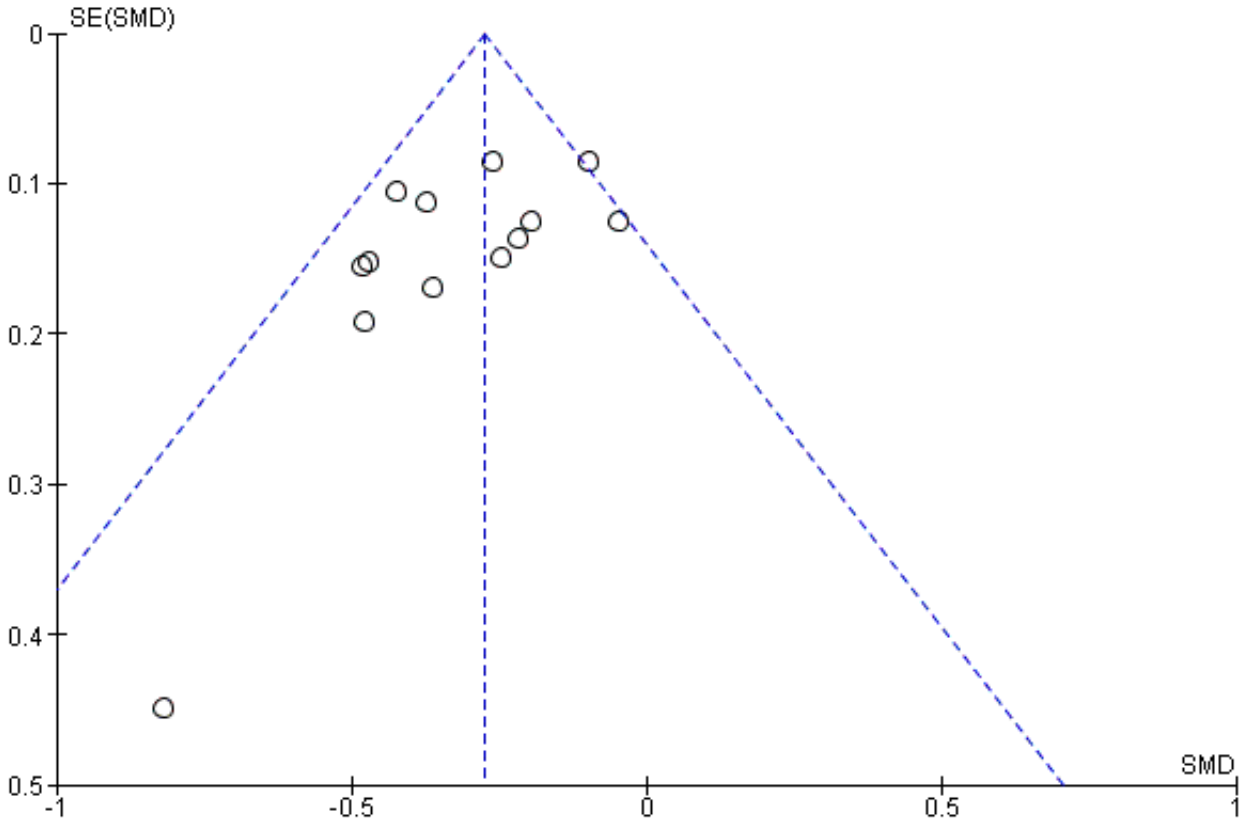


Figure 6. Funnel plot of comparison: 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease. 24-30 week data. OC, outcome: 1.3 Decline in ADL.

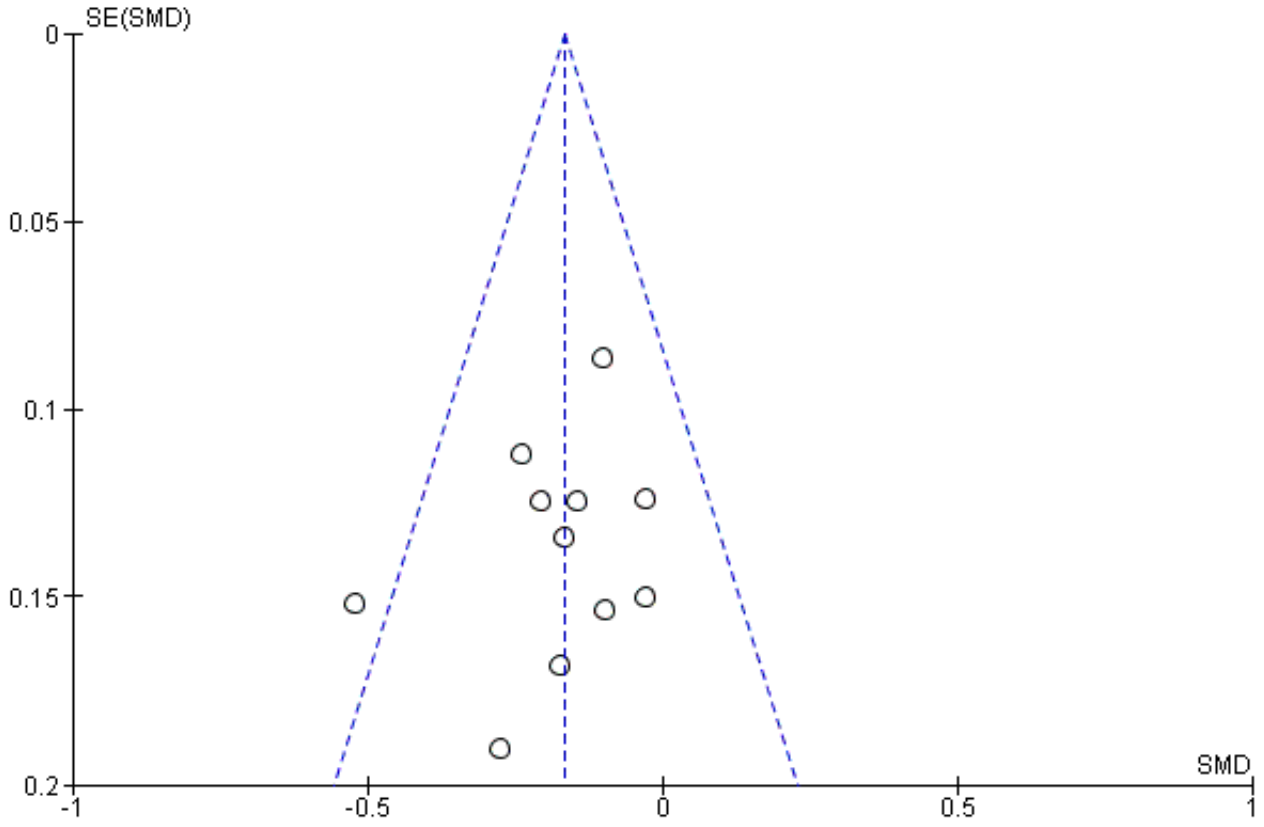


Figure 7. Funnel plot of comparison: 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease. 24-30 week data. OC, outcome: 1.4 Behaviour and Mood.

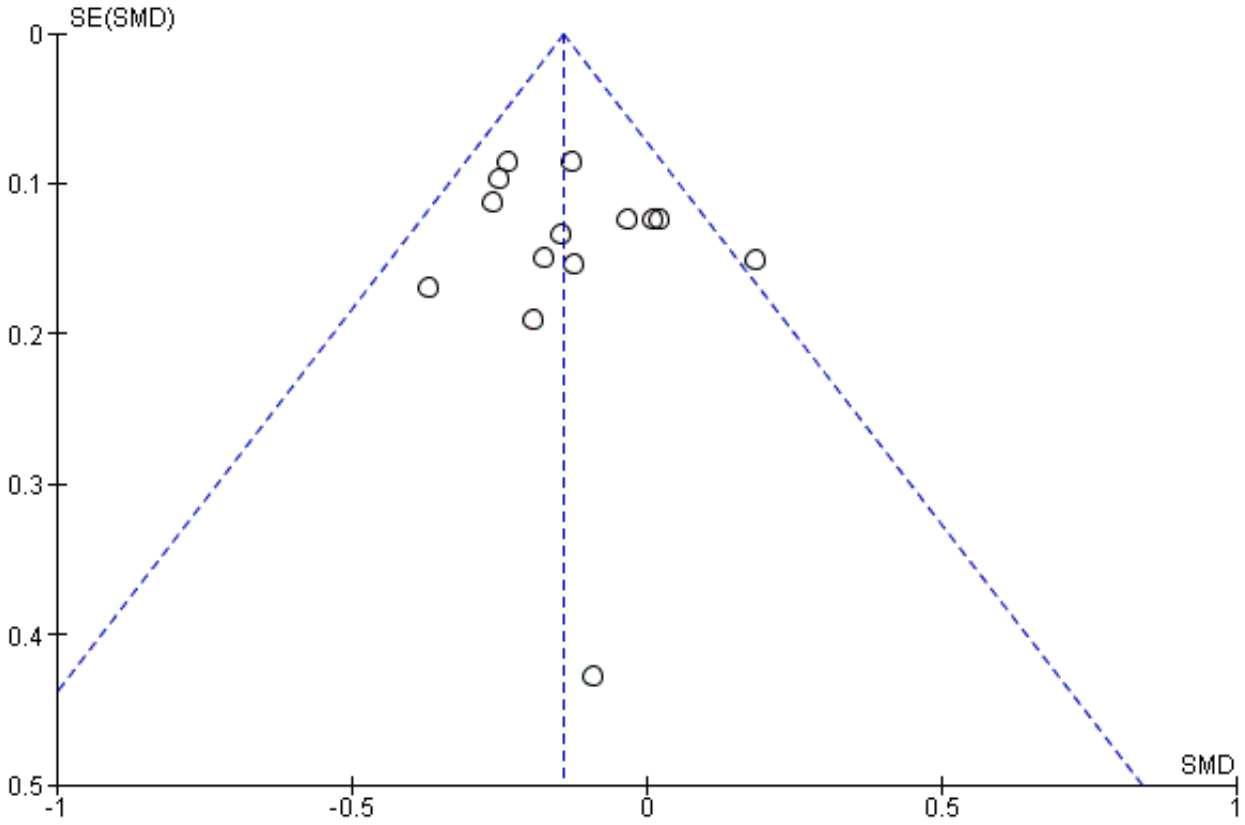


Figure 8. Funnel plot of comparison: 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease. 24-30 week data. OC, outcome: 1.5 All-cause discontinuation.

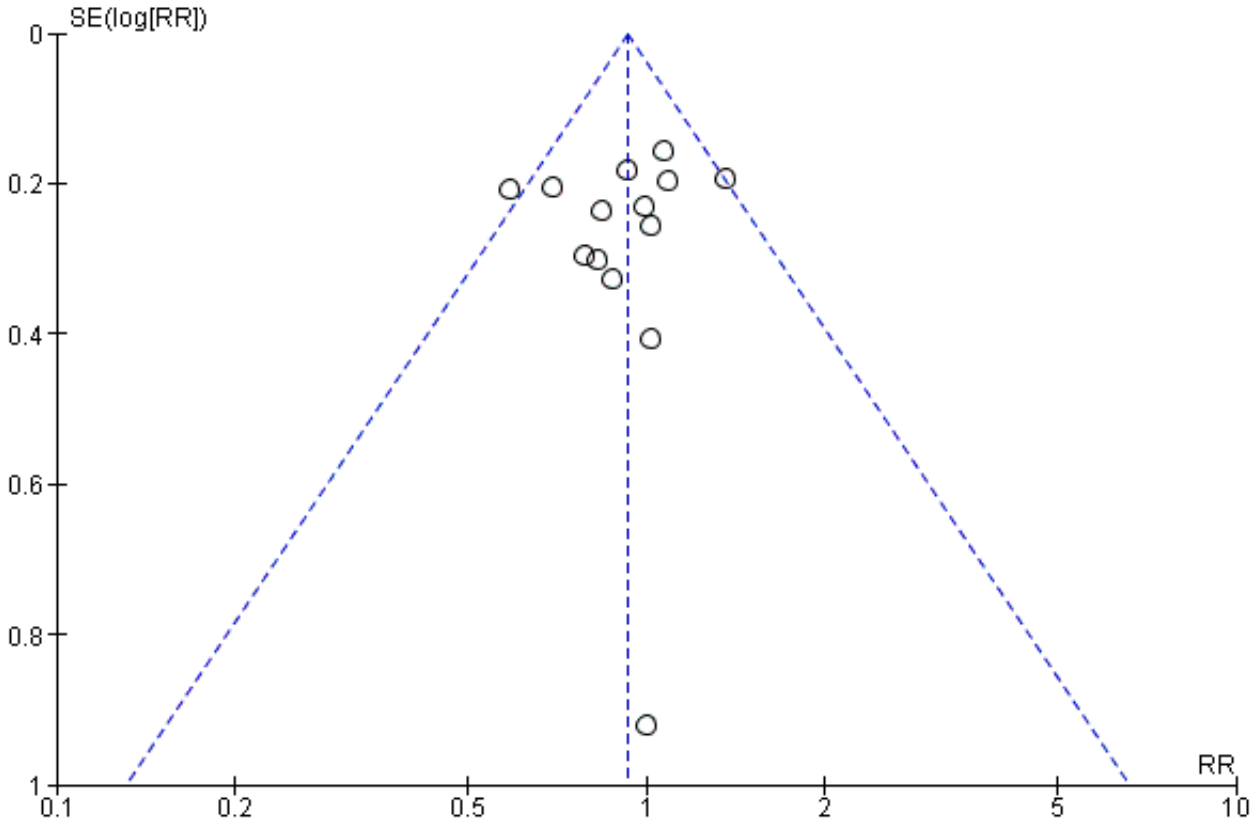
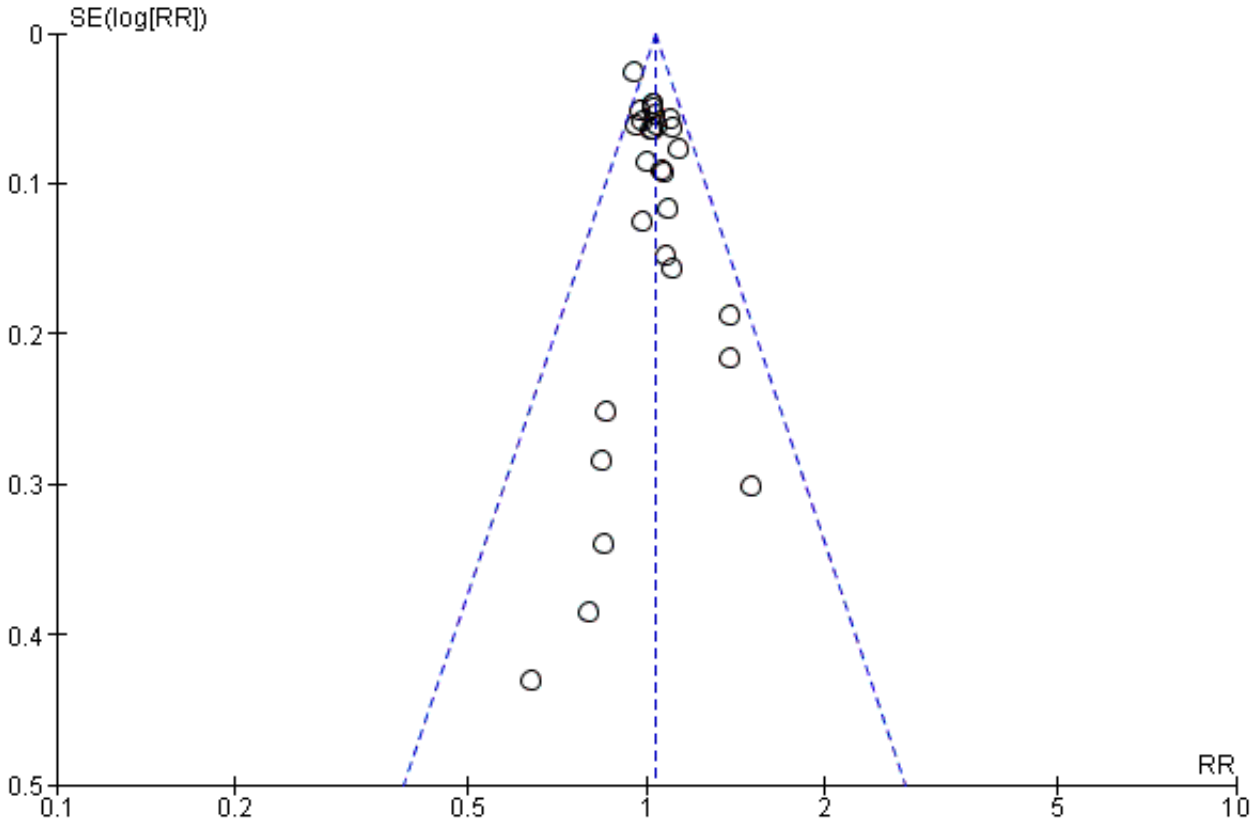


Figure 9. Funnel plot of comparison: 12 Adverse reactions - Memantine vs placebo for mild to severe dementia. All diagnoses, all durations, outcome: 12.3 Number suffering at least one adverse event.



1.2.2. Summary of results transformed to an appropriate scale

High-certainty evidence from up to 14 studies in around 3700 participants shows a small clinical benefit for memantine versus placebo in each of the following outcomes: clinical global rating (MD benefit: 0.21 Clinician's Interview-Based Impression of Change (CIBIC)+ points, 95% CI 0.14 to 0.30); cognitive function (MD benefit: 3.11 SIB points, 95% CI 2.42 to 3.92); performance on ADL (MD benefit: 1.09 ADL19 points, 95% CI 0.62 to 1.64); and behaviour and mood (MD benefit: 1.84 NPI points, 95% CI 1.05 to 2.76). (Summary of findings for the main comparison).

There are similar numbers of people with adverse events in both groups, and memantine (compared with placebo) shows little difference in the number of people discontinuing treatment: RR 0.93 (95% CI 0.83 to 1.04), which corresponds to 13 fewer people discontinuing per 1000, 95% CI 31 fewer to 7 more. There is probably a reduction in the number with agitation as an adverse event (25 fewer per 1000; 95% CI 1 to 44 fewer).

1.3. Effect of memantine 20 mg or equivalent versus placebo in people with moderate-to-severe AD six to seven months, receiving concomitant ChEI or receiving monotherapy

An important objective of this review was to determine whether memantine (versus placebo) gave additional benefits for people already on ChEIs. In this section, firstly, we report the results of pre-specified subgroup analyses by concomitant ChEI for the moderate-to-severe AD population. Statistically, there were no significant differences between the results for the two subgroups (with and without ChEI) - see section 1.3.1, but, for the interested reader, we also report results separately for the population receiving ChEIs in section 1.3.2 and results for the monotherapy subgroup in section 1.3.3.

1.3.1. Effect of memantine 20 mg or equivalent: subgroup analysis according to the presence or absence of concomitant ChEI

We conducted subgroup analyses for the four efficacy outcomes to investigate any differences in the effect of memantine (versus placebo) between memantine as monotherapy or with concomitant ChEI. We examined both between-trial and within-trial subgroup analyses (see Appendix 6). The results for patients receiving monotherapy and for those receiving concomitant ChEI are summarised in Table 9 for all outcomes (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4; Analysis 2.5; Analysis 2.6; Analysis 2.7).

The test for subgroup differences showed no significant difference between memantine monotherapy and memantine with concomitant ChEI (for the comparison of memantine versus placebo) for any of the primary efficacy outcomes, although there was a non-significant difference between subgroups for the behaviour and mood outcome (I^2 = 35.2%, P = 0.21), and for the cognitive function outcome (I^2 = 44.2%, P = 0.18). For the behaviour and mood outcome, the subgroup results suggested a slightly larger effect of memantine versus placebo in the presence of concomitant ChEI (SMD -0.18, 95% CI -0.27 to -0.09) than in

its absence (SMD -0.10, 95% CI -0.19 to -0.01), whereas for the cognitive function outcome, there was a slightly smaller effect in the presence of ChEI (SMD -0.24, 95% CI -0.33 to -0.14) compared with monotherapy (SMD -0.33, 95% CI -0.43 to -0,23). The forest plots for these analyses (Analysis 2.1; Analysis 2.2; Analysis 2.3; Analysis 2.4) are ordered within subgroups in decreasing order of mean study severity (MMSE) and we note that for the behaviour and mood outcome, an alternative explanation for the heterogeneity could be severity of disease (Appendix 4.5).

The safety outcomes showed no significant impact of concomitant ChEI (Analysis 2.9; Analysis 2.10; Analysis 2.11; Analysis 2.12; Analysis 2.13). There was a non-significant result in the test for subgroup differences for adverse events overall (I^2 = 46% and P = 0.17), however, this is likely to occur because the confidence intervals for the subgroups are small; the numerical difference is minimal: the ChEI subgroup is RR 1.05 (95% CI 0.98 to 1.12) and monotherapy is RR 0.99 (95%CI 0.94 to 1.04), both indicating no difference between memantine and placebo. For agitation as an adverse event, the test for subgroup differences was I^2 = 20.9% and P = 0.26, there was probably no difference between memantine and placebo for the ChEI subgroup (RR 0.92, 95% CI 0.60 to 1.40), but for the monotherapy subgroup there was probably a reduction in agitation (RR 0.68, 95% CI 0.51 to 0.91).

The within-trial subgroup analyses suffered from large and differential levels of missing data and it was uncertain whether there was a difference between subgroups with and without ChEIs (Howard 2012 (DOMINO-AD)). Low-certainty evidence (downgraded for risk of bias and imprecision) from one study, which randomised 149 participants to memantine plus continued donepezil versus memantine plus placebo and donepezil discontinued, suggested there may be a larger effect for the two drugs together compared with memantine monotherapy for cognitive function: MD benefit: 1.34 MMSE points (95% CI 0.19 to 2.49), i.e. it may be better to add memantine than to switch to memantine (Howard 2012 (DOMINO-AD)).

1.3.2. Effect of memantine versus placebo in people with moderate-to-severe AD, receiving concomitant ChEIs

We report results of analyses restricted to studies in participants receiving ChEIs. Six studies analysed results from 1855 participants (Dysken 2014 SG; Grossberg 2008 (MD-50); Howard 2012 (DOMINO-AD); Nakamura 2016; Porsteinsson 2008(MD-12)S; Tariot 2004 (MD-02)). Two of these studies were reported as post-hoc subgroups for moderate AD, taken from trials in people with mild-to-moderate AD (Dysken 2014 SG; Porsteinsson 2008(MD-12)S).

The evidence for this section is summarised in the additional 'Summary of findings' Table 3, which covers both efficacy and safety outcomes.

Results were as follows. We analysed one outcome (clinical global) as the mean difference (MD) (rather than SMD) because all studies used the same scale; a negative SMD (or MD) value means that the effect favours memantine. In the forest plots, studies are shown in decreasing order of severity (MMSE).

- Clinical global rating, CIBIC+ (Analysis 2.8): moderate-certainty evidence (downgraded for inconsistency): meta-analysis of three studies in 1125 participants gave an MD (random effects) of -0.21 (95% CI -0.36 to -0.06), favouring memantine. There was some heterogeneity in the point estimates (and I^2 = 32%, P = 0.23).
- Cognitive function (Analysis 2.2): high-certainty evidence: meta-analysis of 6 studies in 1852 participants gave an SMD of -0.24 (95% CI -0.33 to -0.14).
- Decline in ADL (Analysis 2.3): high-certainty evidence: meta-analysis of 5 studies in 1319 participants gave an SMD of -0.13 (95% CI -0.24 to -0.03).
- Behaviour and mood (Analysis 2.4): high-certainty evidence : meta-analysis of 6 studies in 1855 participants gave an SMD of -0.18 (-0.27 to -0.09). There was unimportant heterogeneity (I^2 = 10%, P = 0.35).
- All-cause discontinuation, discontinuation due to adverse events, adverse events and serious adverse events are reported in section 5 and Table 3.

1.3.3. Effect of memantine versus placebo in people with moderate-to-severe AD, receiving monotherapy

In this section, we report results of analyses restricted to studies in participants receiving monotherapy. Nine studies analysed results from 2215 participants (Asada 2011a (IE3501); Bakchine 2008 (99679) SG; Forest 2006 (MD-22); Homma 2007 (IE2101); Howard 2012 (DOMINO-AD); Peskind 2004 (MD-10) SG; Reisberg 2003 (9605); van Dyck 2007 (MD-01); Wang 2013). Two of these studies were reported as post-hoc subgroups for moderate AD, taken from trials in people with mild-to-moderate AD (Bakchine 2008 (99679) SG; Peskind 2004 (MD-10) SG).

The evidence for this section is summarised in the additional 'Summary of findings' Table 4, which covers both efficacy and safety outcomes. Results were as follows. Forest plots show studies in decreasing order of severity; a negative SMD (or MD) value means that the effect favours memantine.

- Clinical global rating, CIBIC+ (Analysis 2.1): high-certainty evidence: meta-analysis of 7 studies in 1672 participants gave an SMD of -0.20 (95% CI -0.30 to -0.10), favouring memantine.
- Cognitive function (Analysis 2.2): high-certainty evidence: meta-analysis of 8 studies in 1485 participants gave an SMD of -0.33 (95% CI -0.43 to -0.23). There is some heterogeneity in the point estimates, but apart from one study, the results are consistent with a benefit for memantine and were not downgraded for inconsistency (I^2 = 41%, P = 0.11).
- Decline in ADL (Analysis 2.3): high-certainty evidence: meta-analysis of 7 studies in 1368 participants gave an SMD of -0.20 (95% CI -0.30 to -0.09).
- Behaviour and mood, NPI (Analysis 2.9): high-certainty evidence: meta-analysis of 9 studies in 1819 participants gave an SMD of -0.10 (95% CI -0.19 to -0.01).
- All-cause discontinuation, discontinuation due to adverse events, adverse events and serious adverse events are reported in section 5 and Table 4.

1.3.4. Summary of results transformed to an appropriate scale

For people receiving concomitant ChEI

Mainly high-, and moderate-certainty evidence from up to six studies in around 1850 participants taking cholinesterase inhibitors shows a small clinical benefit for memantine versus placebo in cognitive function (MD benefit: 2.48 SIB points, 95% CI 1.45 to 3.41), performance on ADL (MD benefit: 0.95 ADL19 points, 95% CI 0.22 to

1.76) and behaviour and mood (MD benefit: 2.20 NPI points, 95% CI 1.10 to 3.29); and probably a small clinical benefit in clinical global rating (MD benefit: 0.21 CIBIC+ points, 95% CI 0.06 to 0.36) (Table 3).

There are similar numbers of people with adverse events in both groups. Memantine (compared with placebo) shows little difference in the number of people discontinuing treatment for any cause (12 fewer per 1000, 95% CI 29 fewer to 7 more), and there is probably no difference between interventions in the number with agitation as an adverse event (4 fewer per 1000, 95% CI 18 more to 18 fewer).

For people receiving monotherapy

High-certainty evidence from up to nine studies in around 1800 participants shows a small clinical benefit for memantine versus placebo in all efficacy outcomes: clinical global rating (MD benefit:0.22 CIBIC+ points, 95% CI 0.11 to 0.33); cognitive function (MD benefit: 3.97 SIB points, 95% CI 2.77 to 5.18); performance on ADL (MD benefit:1.33 ADL19 points, 95% CI 0.20 to 2.00) and behaviour and mood (MD benefit:1.57 NPI points, 95% CI 0.16 to 2.98) (Table 4).

There are similar numbers of people with adverse events in both groups. Memantine (compared with placebo) shows little difference in the number of people discontinuing treatment for any cause (13 fewer per 1000, 95% CI 32 fewer to 8 more), and there is probably also a reduction in the number with agitation as an adverse event (52 fewer per 1000, 95% CI 15 to 80 fewer) (compare agitation in people receiving concomitant ChEI).

Test for subgroup differences

The test for subgroup differences between trials in which participants did and did not receive concomitant ChEI showed no significant differences, but three outcomes had non-significant differences: cognitive function (I^2 = 44%), behaviour and mood (I^2 = 35%), and agitation as an adverse event (I^2 = 21%). For behaviour and mood, the effect of memantine appeared to be larger in people receiving ChEI, and for cognitive function the effect appeared larger in the monotherapy group. However, it was not clear that these differences could be attributed to concomitant ChEI, and severity may still play a role. For agitation as an adverse event, memantine monotherapy appeared to effect a reduction in the number of people with agitation, but memantine did not appear to add anything to existing effects with cholinesterase inhibitors.

1.4. Effect of memantine in people with moderate-to-severe AD with agitation; OC

1.4.1. Effect of memantine versus placebo in people with moderate-to-severe AD, with agitation

Three studies investigated the effect of memantine versus placebo in 556 randomised participants with agitation (Forest 2006 (MD-23); Fox 2012 (MAGD); Herrmann 2012 (10158)); one study was unpublished (Forest 2006 (MD-23)). Agitation was defined variously as: NPI > 12 with a score on the NPI agitation–aggression item of at least 1 (Herrmann 2012 (10158)); at least two weeks history of behavioural disturbance, and agitation judged by their clinical team to require intervention, with a Cohen Mansfield Agitation Inventory (CMAI) score ≥ 45 (Fox 2012 (MAGD)); and a score on the NPI agitation–aggression item of at least 4 (Forest 2006 (MD-23)). All studies recruited people with moderate-to-severe AD, although the mean MMSE scores differed: one study had a mean score of 7.5 (inclusion ≤ 19) (Fox 2012 (MAGD)); the second had a mean of 11.9 (range 5 to 15) (Herrmann 2012 (10158)); and the third did not state the mean, but the range was 3 to 18 (Forest 2006 (MD-23)). Two studies included participants on ChEIs (Forest 2006 (MD-23); Herrmann 2012 (10158)); and the other had about 20% participants on ChEIs (Fox 2012 (MAGD)). One of the three studies was in institutionalised patients (Fox 2012 (MAGD)).

Two studies had a duration of 12 weeks (Forest 2006 (MD-23); Fox 2012 (MAGD)); and the other was 24 weeks. Two of these studies were terminated prematurely, one after recruiting only 34 participants (Forest 2006 (MD-23)); and the other because of difficulties in recruitment (the 369 participants formed 82% of the planned recruited sample) (Herrmann 2012 (10158)). One study had the primary aim of reducing agitation (Fox 2012 (MAGD)), and the other two aimed to investigate the efficacy of memantine in an agitated population (Forest 2006 (MD-23); Herrmann 2012 (10158)). All three studies reported the effect of memantine on agitation using the CMAI, but one used the community version (Forest 2006 (MD-23)).

We did not extract data from two reviews reporting on post-hoc agitated subgroups because the data for individual trials were not available in a useful format (Gaultier 2005; Wilcock Post-Hoc 3RCTs 2008). However, we discuss the findings from these studies in the Agreements and disagreements with other studies or reviews) and note the disagreement.

We analysed all efficacy outcomes except clinical global rating as the mean difference (rather than SMD) because all studies used the same scale; a negative SMD (or MD) value means that the effect favours memantine (Table 5).

Two main outcome measures were used to investigate agitation: the CMAI score (range 29 to 203) (or the CMAI-community score in the Forest 2006 (MD-23)) study; and the agitation–aggression subscale of the NPI. Analyses were subgrouped by time point (12 weeks and 24 weeks); we reported both the results for the pooled analysis and the 24-week study alone, in order both to be consistent with the approach to duration in AD, and also to avoid reducing the analysis to only one study; a negative SMD (or MD) value means that the effect favours memantine.

- CMAI: the three studies varied in the CMAI scale used and how they reported the results (one only reported final values), so we did not combine all studies in either an SMD analysis or as the MD. Instead, we meta-analysed the two CMAI studies using the MD (Fox 2012 (MAGD); Herrmann 2012 (10158)) (Analysis 3.1) and also carried out meta-analysis for the two studies reporting change scores using the SMD (Forest 2006 (MD-23); Herrmann 2012 (10158)) (Analysis 3.2).
  - Meta-analysis of 2 studies in 306 participants: moderate-certainty evidence (downgraded once for imprecision) gave an SMD of 0.11 (-0.12 to 0.33).
  - Meta-analysis of 2 studies in 422 participants: moderate-certainty evidence (downgraded once for inconsistency; I^2 = 48% and P = 0.16) gave a mean difference of -0.50 (-4.71 to 3.71) (random effects).
  - The 24-week study (1 study in 273 participants): low-certainty evidence (downgraded once for imprecision and once for inconsistency with the other studies) gave an MD of 0.90 (95% CI -1.29 to 3.09) on the CMAI long form scale (range 29 - 203,

with a clinically important difference of about 40), i.e. no difference between interventions (Herrmann 2012 (10158)).
  * Baseline levels were: 43.3 and 41.3 (Forest 2006 (MD-23)); 68.3 for both groups (Fox 2012 (MAGD)); and 46.8 and 47.0 (Herrmann 2012 (10158)).
  * There was no inconsistency between the two studies in people receiving concomitant ChEI.
- NPI subscale for agitation–aggression (Analysis 3.3); this outcome was only reported for the short-term studies - very low-certainty evidence (downgraded once each for risk of bias, imprecision and indirectness): meta-analysis of 2 studies in 146 participants gave an MD of -0.39 (95% CI -1.90 to 1.13) (Forest 2006 (MD-23); Fox 2012 (MAGD)).

Two studies also reported the proportion with agitation as a treatment emergent adverse event (TEAE); a risk ratio (RR) less than 1 means the effect favours memantine.

- Proportion with agitation as a TEAE (Analysis 3.4).
  * Meta-analysis of 2 studies in 403 participants, 24 events, participants in both studies receiving concomitant ChEI: low-certainty evidence (downgraded for imprecision twice) gave a RR of 2.39 (95% CI 1.04 to 5.50). This effect was consistent across the two studies (I^2 = 0%, P = 0.60).
  * The 24-week study (369 participants, 22 events): low-certainty evidence (downgraded on imprecision twice) gave a RR of 2.20 (95% CI 0.92 to 5.27), i.e. about twice as many participants on memantine and ChEI had agitation compared with participants on ChEI plus placebo.

Results for the four other efficacy outcomes are shown below. All are reported as negative outcomes; a negative SMD (or MD) value means that the effect favours memantine.

- Clinical global rating (Analysis 3.5).
  * Meta-analysis of 3 studies in 443 participants: low-certainty evidence (downgraded for inconsistency and imprecision) gave an SMD (random effects) of -0.11 (95% CI -0.34 to 0.13). There is heterogeneity in the point estimates between the 12-week and 24-week studies (although I^2 = 25%, P = 0.26).
  * The 24-week study (275 participants): low-certainty evidence (downgraded on inconsistency with other studies and imprecision) gave an MD of 0.05 (95% CI -0.25 to 0.35) for the CIBIC+ scale.
- Cognitive function; SIB (Analysis 3.6).
  * The two studies gave very different results.There is substantial heterogeneity (I^2 = 90%, P = 0.002), and therefore results are reported separately.
  * At 12 weeks (1 study, 129 participants): the MD is -10.00 (95% CI -16.15 to -3.85).
  * The 24-week study (324 participants): very low-certainty evidence (downgraded twice on inconsistency with the other study and imprecision) gave an MD of 0.48 (95% CI -1.61 to 2.57).
- Decline in ADL; ADCS-ADL19 (Analysis 3.7).
  * Meta-analysis of 2 studies in 309 participants receiving ChEI: low-certainty evidence (downgraded once for imprecision and once overall for some inconsistency and risk of bias (baseline difference)): gave an MD of 1.48 (95% CI -0.19 to 3.15). There was heterogeneity in the point estimates (although I^2 = 0%, P = 0.40).
  * The 24-week study (276 participants): low-certainty evidence (downgraded for risk of bias and imprecision) gave an MD of 1.80 (95% CI -0.03 to 3.63). The difference at baseline for that study (276 participants) was 1.10 units lower for memantine (i.e. memantine more severe) (Herrmann 2012 (10158)),
- Behaviour and mood, NPI total (Analysis 3.8).
  * Meta-analysis of 3 studies in 470 participants: very low-certainty evidence (downgraded once each for risk of bias (baseline difference), inconsistency and imprecision): gave a random effects MD of -1.51 (95% CI -8.05 to 5.03). There was heterogeneity in both the 12-week studies' subgroup (I^2 = 57%, P = 0.13) and overall (I^2 = 62%, P = 0.07), but no differences between durations. In each study there were large baseline differences between the values for memantine and placebo, which for two studies were comparable with the effect estimate.
  * The 24-week study (324 participants): very low-certainty evidence (downgraded on imprecision, inconsistency and risk of bias) gave an MD of 1.23 (95% CI -2.19 to 4.65). The difference in NPI at baseline for that study was 1.70 units higher for memantine (i.e. more severe), which is larger than the effect estimate.
- All-cause discontinuation, discontinuation due to adverse events, adverse events and serious adverse events are reported in section 5.

The results for studies with and without patients with agitation are compared in Table 10.

1.4.2. Summary of results transformed to an appropriate scale

The evidence was mainly of low or very low certainty for this patient group. Three studies in around 550 participants compared memantine and placebo in people with moderate-to-severe disease with agitation, but only one of these studies had a duration of six to seven months (Herrmann 2012 (10158)). One of the short-term studies had more severe agitation at baseline compared with the other two studies, and this same study only had 20% of participants on ChEIs (Fox 2012 (MAGD)), whereas the other two studies had all on ChEIs. For the outcomes of CMAI, clinical global and cognitive function, there is inconsistency between the 24-week and 12-week studies. For these outcomes, we reported the meta-analysis results and also gave the results for the 24-week study alone, with the evidence for the latter downgraded due to inconsistency with the other study results. The results are summarised below in terms of relative improvement for memantine versus placebo for consistency with the other summary sections.

Low-certainty evidence from one study in 275 people suggested there may have been no difference between memantine and placebo, either for clinical global rating: MD (relative improvement) = -0.05 CIBIC+ points, 95% CI -0.35 to 0.25; or for cognitive function: MD (relative improvement) = -0.48, 95% CI -2.57 to 1.61. For performance on ADL, there may be no difference between memantine (with ChEI) and placebo (with ChEI): MD (relative improvement) = -1.48 ADL19 points, 95% CI -3.15 to 0.19 (2 studies in 309 people). It is very uncertain whether there is a difference between memantine and placebo for the behaviour and mood

outcome: MD (relative improvement) = +1.51 NPI points, 95% CI -5.03 to 8.05.

Regarding agitation, there is moderate-certainty evidence from two studies (422 participants) to suggest there is probably no difference between memantine and placebo on the agitation CMAI scale: MD (relative improvement) = 0.50 CMAI points, 95% CI -3.71 to 4.71: this is a very small change for the CMAI scale. The evidence on the NPI agitation–aggression subscale was not reported (although measured) for the 24 week study and the remaining evidence is of very low certainty.

The proportion reporting agitation as a TEAE in two studies (403 participants) may be doubled in those receiving memantine (plus ChEI) compared with placebo (plus ChEI) (RR 2.39, 95% CI 1.04 to 5.50). We assume that the proportion with agitation reflects increases in the severity of agitation in this patient group; baseline levels were not reported, but the proportions at 24 weeks in the two groups in the larger study were relatively small (8% for memantine and 4% placebo) (Herrmann 2012 (10158)). These proportions are similar to the ranges for the moderate-to-severe AD groups (0% to18% memantine and 3% to 22% placebo). Additionally, the larger study reported differences at baseline - the memantine group had higher levels of antipsychotic medication (24% versus 20%) and there was a centre effect (Herrmann 2012 (10158)).

There are similar numbers of people with adverse events in both groups, and memantine (compared with placebo) probably shows little difference in the number of people discontinuing treatment (RR 1.10, 95% CI 0.79 to 1.52, which corresponds to 17 fewer per 1000, 95% CI 36 fewer to 89 more).

1.5. Effect of memantine 20 mg in people with mild AD at six months

1.5.1. Effect of memantine versus placebo in people with mild AD

Four studies contributed data from post-hoc subgroups (Bakchine 2008 (99679) SG; Dysken 2014 SG; Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S); (see section Subgroup analysis and investigation of heterogeneity). Of the 1396 participants analysed in the four mild-to-moderate AD trials, 621 (44%) had mild AD. Two studies gave concomitant ChEIs (Dysken 2014 SG, Porsteinsson 2008(MD-12)S). One additional study recruited 26 participants with mild AD and reported cognitive function at 12 months ((Holland 2013)). One further study in 195 participants was considered in sensitivity analyses because it had a mean MMSE score of around 22 and the participants were anti-dementia treatment naive (Peters 2015 (MEGACOMBI2)). The addition of this study reinforced the efficacy results (see Appendix 4.5.2).

The evidence for this section is summarised in the additional summary of findings Table 6. Results are shown below; a negative SMD (or MD) value means that the effect favours memantine.

- Clinical global rating, CIBIC+ (Analysis 4.1): low-certainty evidence (downgraded once on risk of bias because post-hoc subgroups and once on imprecision): meta-analysis of 3 studies in 427 participants gave an MD of -0.09 (95% CI -0.30 to 0.12).
- Cognitive function, ADAS-Cog (Analysis 4.2): moderate-certainty evidence (downgraded once on risk of bias): meta-analysis of 4 studies in 619 participants gave an MD of -0.21 (95% CI -1.38 to 0.95).
- Decline in ADL, ADCS-ADL23 (Analysis 4.3): moderate-certainty evidence (downgraded once on risk of bias): meta-analysis of 4 studies in 621 participants gave an MD of 0.07 (95% CI -1.66 to 1.80). There was some heterogeneity in point estimates (but I^2 = 3%, P = 0.38).
- Behaviour and mood, NPI (Analysis 4.4): moderate-certainty evidence (downgraded once on risk of bias): meta-analysis of 4 studies in 621 participants gave an MD of 0.29 (95% CI -1.58 to 2.16).

One additional trial was conducted in 26 participants with mild AD, but only gave data for MMSE - and only final values were reported at 12 months (Holland 2013). Very low-certainty evidence (downgraded for imprecision (twice) and indirectness) gave an MD (negative outcome) of -1.15 (95% CI -3.47 to 1.17), favouring memantine, however, the baseline difference was -0.46. Addition of the Peters 2015 (MEGACOMBI2) study to the meta-analyses for cognitive function and decline in ADL showed very similar SMD results, but narrower CIs (Appendix 4.5.2).

All-cause discontinuation, discontinuation due to adverse events and adverse events are reported in section 5. Serious adverse events were not reported separately for people with mild dementia.

1.5.2. Summary of results transformed to an appropriate scale

The results are summarised in terms of the relative improvement for memantine versus placebo, for consistency with the other summary sections. Mainly moderate-certainty evidence based on post-hoc subgroups from up to four studies in around 600 participants suggests there is probably no difference between memantine and placebo for three of the efficacy outcomes: cognitive function: MD (relative improvement) = 0.21 ADAS-Cog points, 95% CI -0.95 to 1.38; performance on ADL: MD (relative improvement): -0.07 ADL 23 points, 95% CI -1.80 to 1.66; and behaviour and mood: MD (relative improvement) = -0.29 NPI points, 95% CI -2.16 to 1.58, and there may be no difference for clinical global rating: MD (relative improvement) = 0.09 CIBIC+ points, 95% CI -0.12 to 0.30 (low-certainty evidence) (Table 6).

For the cognitive function and behaviour and mood outcomes, we observed an average *improvement* over time for the placebo groups, but little or no change over time for the decline in ADL and clinical global outcomes (Appendix 4.5.2.2): for placebo, the median of the standardised mean change from baseline was: cognitive function -0.20, range -0.38 to 0.11 and behaviour and mood -0.16, range -0.33 to -0.10). This improvement with placebo is in contrast to the results for people with moderate-to-severe disease (see section 1.2.2 and Appendix 4.5.2.2).

There are similar numbers of people with adverse events in both groups, but memantine (compared with placebo) may give an increase in the number of people discontinuing treatment because of adverse events: RR 2.12 (95% CI 1.03 to 4.39), which corresponds to 33 more per 1000 (95% CI 1 to 100 more). The evidence is of very low certainty regarding all-cause discontinuation (74 more people per 1000 discontinued treatment, 95% CI 8 to 181 more), and agitation was not reported in these studies.

2. Vascular dementia

2.1. Effect of memantine in people with mild-to-moderate vascular dementia at six to seven months; OC or per protocol

2.1.1 Effect of memantine (20 mg/day) versus placebo

Three studies randomised 956 participants with vascular dementia (Merz 2003 (MRZ-9206); Orgogozo 2002 (9408); Wilcock 2002 (9202)); but only two of these contributed data (Orgogozo 2002 (9408); Wilcock 2002 (9202); 900 randomised participants). Both studies were in people with mild-to-moderate dementia, and neither study appeared to allow concurrent ChEIs. Participants were randomised to 20 mg/day memantine versus placebo for 28 weeks. The two studies used different scales for each outcome except cognitive function (for which both studies used ADAS-Cog). The decline in ADL, and the behaviour and mood outcomes used the Nurse's Observational Scale for Geriatric Patients (NOSGER) subscales (Appendix 2), but one study used the revised version (NOSGER II) and were presented as per protocol analyses (Wilcock 2002 (9202)). Consequently, we analysed all outcomes as SMD, with the exception of cognitive function.

The evidence for this section is summarised in Summary of findings 2, which covers both efficacy and safety outcomes.

Results are shown below; a negative SMD (or MD) value means that the effect favours memantine.

- Clinical Global (Analysis 5.1): moderate-certainty evidence (downgraded for inconsistency): meta-analysis of 2 studies in 757 analysed participants gave a random effects SMD of -0.02 (95% CI -0.23 to 0.19). There is some heterogeneity (I^2 = 48%, P = 0.16).
- Cognitive function, ADAS-Cog (Analysis 5.2): moderate-certainty evidence (downgraded for risk of bias): meta-analysis of 2 studies in 569 participants gave an MD of -2.15 (95% CI -3.25 to -1.05). There is some heterogeneity in the point estimates (and I^2 = 12%, P = 0.29), but this was insufficient to downgrade on inconsistency.
- Decline in ADL on the NOSGER self-care subscale (Analysis 5.3): low-certainty evidence (downgraded twice overall for risk of bias and unclear scale direction for one study): meta-analysis of 2 studies in 542 participants gave an SMD of -0.04 (95% CI -0.20 to 0.13).
- Behaviour and mood on the NOSGER disturbing behaviour subscale (Analysis 5.4): low-certainty evidence (downgraded twice for risk of bias): meta-analysis of 2 studies in 541 participants gave an SMD of -0.20 (95% CI -0.37 to -0.03).

Post-hoc subgroup analyses by severity were also conducted for an FDA report for the cognitive function outcome: results were reported for both trials, separated at an MMSE score of 14 into mild-to-moderate and moderate-to-severe. Analysis 5.5 (fixed effect) shows the test for subgroup differences to be significant (I^2 = 72.5, P = 0.06), with a bigger effect in the moderate-to-severe subgroup (ADAS-Cog MD -4.51, 95% CI -7.21 to -1.81) than in the mild-to-moderate subgroup (MD -1.64, 95% CI -2.83 to -0.45).

2.1.2. Summary of results transformed to an appropriate scale

Moderate- and low-certainty evidence from two studies in around 750 participants with vascular dementia gave mixed results for the comparison of memantine and placebo. There is probably a small clinical benefit for cognitive function: MD benefit = 2.15 ADAS-Cog points, 95% CI 1.05 to 3.25, and there may be a small clinical benefit on the NOSGER disturbing behaviour outcome: MD benefit = 0.47 NOSGER points, 95% CI 0.07 to 0.87. However, there is probably no difference between memantine and placebo in clinical global rating: MD benefit = 0.03 CIBIC+ points, 95% CI -0.28 to 0.34, and there may be no difference in performance on ADL: MD benefit = 0.11 NOSGER II self-care subscale points, 95% CI -0.35 to 0.54.

There are similar numbers of people with adverse events in both groups, and there may be no difference in the numbers of people discontinuing treatment RR 1.05 (95% CI 0.83 to 1.34), which corresponds to 11 fewer people per 1000 (95% CI 37 fewer to 74 more). There may be fewer people with agitation as an adverse event for memantine compared with placebo RR 0.57 (95% CI 0.33 to 0.97) (i.e., 33 fewer per 1000, 95% CI 2 to 52 fewer).

A post-hoc subgroup analysis by severity suggested that memantine (versus placebo) may have had a bigger effect for cognitive function in people with moderate-to- severe vascular dementia (MMSE ≥14) than in people with mild-to-moderate vascular dementia. The test for subgroup differences was significant (I^2 = 72.5%, P = 0.06), although this was a post-hoc analysis.

3. Other forms of dementia

3.1. Effect of memantine in people with Parkinson's disease dementia (PDD) or dementia Lewy bodies (DLB)

3.1.1. Effect of memantine (20 mg/day) versus placebo

Four studies in 319 randomised participants with PDD or DLB met the inclusion criteria (Aarsland 2009; Emre 2010 (11018); Leroi 2009; Marsh 2009 PDD); two studies were solely in participants with PDD (Leroi 2009; Marsh 2009 PDD); and the other two were in a mixed PDD–DLB population: one study had more PDD participants (memantine group 50%, placebo 61%) (Aarsland 2009); and the other had 65% with PDD in the memantine group and 59% in the placebo group (Emre 2010 (11018)). The severity of dementia was mild-to-moderate, with mean MMSE scores of ˜22 (Marsh 2009 PDD); ˜21 (Emre 2010 (11018)); ˜20 (Aarsland 2009); and ˜19 (Leroi 2009). Some studies gave the participants concomitant ChEIs: one study had 47% in the memantine group and 63% for placebo (Aarsland 2009); one did not permit ChEIs (Emre 2010 (11018)); one had 18.2% (memantine) and 14.2% (placebo) (Leroi 2009); and the other did not state the proportions (Marsh 2009 PDD). Only one study reported OC results (Emre 2010 (11018)). All outcomes were analysed as SMD apart from cognitive function and behaviour–mood. One study reported results at 16 weeks (Leroi 2009); the others were at 24 weeks. We report results for the 24-week studies, unless there was only one 24-week study, in which case the 16-week study was considered.

The evidence for this section is summarised in 'Summary of findings' Table 7, which covers both efficacy and safety outcomes. Results are shown below; a negative SMD (or MD) value means that the effect favours memantine.

- Clinical Global (Analysis 6.1): low-certainty evidence (downgraded once each for risk of bias and imprecision): meta-analysis of 3 studies in 243 participants gave an SMD of -0.35 (95% CI -0.60 to -0.09). There was a little heterogeneity in the point estimates (I^2 = 15%, P = 0.31).

- Cognitive function, MMSE (Analysis 6.2): very low-certainty evidence (downgraded once each for risk of bias, inconsistency with the 16-week study and imprecision): one study in 63 participants gave an MD of -1.90 (95% CI -3.73 to -0.07). There was substantial heterogeneity between this study and the study reporting results at 16 weeks (I^2 = 75%, P = 0.05).
- Decline in ADL (Analysis 6.3): very low-certainty evidence (downgraded once each on risk of bias, inconsistency and imprecision): meta-analysis of 3 studies in 243 participants gave a random effects SMD of -0.27 (95% CI -0.65 to 0.11). There was some heterogeneity (I^2 = 40%, P = 0.19).
- Behaviour and mood, NPI (Analysis 6.4): low-certainty evidence (downgraded once on each of risk of bias and imprecision or inconsistency): meta-analysis of 3 studies in 242 participants) gave a random effects MD of -2.18 (95% CI -5.57 to 1.21). There was some heterogeneity in the point estimates (I^2 = 20%, P = 0.29).
- All-cause discontinuation, discontinuation due to adverse events, adverse events and serious adverse events are reported in section 5.

3.1.2. Summary of results transformed to an appropriate scale

Low- and very low-certainty evidence from up to 3 studies in around 250 participants suggested that, for memantine versus placebo in people with PDD or DLB, there may be a small clinical benefit in clinical global rating (MD benefit: 0.49 CIBIC+ points, 95% CI 0.13 to 0.83) and in behaviour and mood (although the confidence interval was consistent with both no effect and benefit) (MD benefit: 2.18 NPI points, 95% CI -1.21 to 5.57). Evidence for all other efficacy outcomes is of very low certainty. There may be fewer people discontinuing treatment RR 0.84 (95% CI 0.55 to 1.28), which corresponds to 32 fewer per 1000 (95% CI 90 fewer to 56 more).

3.2. Effect of memantine in people with frontotemporal dementia (FTD)

3.2.1. Effect of memantine (20 mg/day) versus placebo in people with FTD

Two studies in 133 randomised participants with FTD were included (Boxer 2013; Vercelletto 2011). Both studies were in people with mild dementia and both prohibited the use of ChEIs. One study (52 participants) reported at 52 weeks (Vercelletto 2011), and the other (81 participants) at 26 weeks (Boxer 2013); both are included in the meta-analyses, but where there was heterogeneity, we reported only the 26-week (single study) results.

The evidence for this section is summarised in 'Summary of findings' Table 8, which covers both efficacy and safety outcomes. Results are shown below; a negative SMD (or MD) value means that the effect favours memantine.

- Clinical global rating (Analysis 7.1): low-certainty evidence (downgraded once each for risk of bias and imprecision): meta-analysis of 2 studies in 117 participants gave an SMD of -0.31 (95% CI -0.67 to 0.06). The single study at 26 weeks (76 participants) had an MD (CGIC) of -0.40 (95% CI -1.23 to 0.43) (low-certainty evidence).
- Cognitive function, MMSE (Analysis 7.2): very low-certainty evidence (downgraded twice for imprecision and once for inconsistency): meta-analysis of 2 studies in 122 participants gave a random effects MD (negative outcome is an improvement) of -0.23 (95% CI -2.03 to 1.56). The single study at 26 weeks (81 participants) had an MD of 0.30 (95% CI -1.23 to 1.83), low-certainty evidence (downgraded twice for imprecision).
- Decline in ADL - outcome reported only for one study (Vercelletto 2011), as the percentage DAD score = yes
- Behaviour and mood, NPI (Analysis 7.3): low-certainty evidence (downgraded twice overall for imprecision and some inconsistency): meta-analysis of 2 studies in 115 participants gave an MD of -3.16 (95% CI -8.06 to 1.74). For the single study at 26 weeks: MD (NPI) = -2.20 (95% CI -8.01 to 3.61) (low-certainty evidence (downgraded twice on imprecision)).
- All-cause discontinuation, discontinuation due to adverse events, adverse events and serious adverse events are reported in section 5.

3.2.2 Summary of results transformed to an appropriate scale

Mainly low-certainty evidence from 2 studies in around 120 participants suggests there may be a small clinical benefit in clinical global rating (MD benefit: 0.56 CGIC points, 95% CI -1.21 to 0.11) and in behaviour and mood (MD benefit: 3.16 NPI points, 95% CI -3.61 to 8.01) for memantine versus placebo in people with FTD. There may be no difference in cognitive function (MD benefit for one study: -0.30 MMSE points, 95% CI -1.83 to 1.23). However, for all of the efficacy outcomes, there is uncertainty and the confidence interval is consistent with more than one conclusion. There may be more discontinuation in the memantine group (compared with placebo) for this population (RR 1.54, 95% CI 0.54 to 4.06).

3.3. Effect of memantine in people with AIDS-related dementia complex (ADC)

Only one study currently fulfilled the inclusion criteria of this review with regard to the use of memantine in ADC ((Schifitto 2007)). The study randomised a total of 140 participants to 40 mg/day memantine or placebo. Only the cognitive function outcome was reported for 48 and 45 participants, respectively, as measured by a summary neuropsychological test score, averaged over eight measures (NPZ-8). The authors reported the percentage improvement from baseline at 16 weeks: MD 43.0% (95% CI -19.2 to 105.2), in favour of memantine (low-certainty evidence because of imprecision).

The number of adverse events (not the number of participants with adverse events) were similar in each arm: 116 in the memantine arm and 106 in the placebo arm. low-certainty evidence (downgraded twice for imprecision) suggested that for all-cause discontinuation, there may be no difference between memantine and placebo (1 study 140 participants, 28 events) RR 1.00 (95% CI 0.52 to 1.94). Similarly for discontinuation due to adverse events (1 study 140 participants, 14 events) RR 1.00 (95% CI 0.37 to 2.70). Further investigation into the use of memantine in ADC would be warranted.

4. Comparison of effects in different types of dementia

4.1 Memantine versus placebo, all severities - efficacy analyses at six-seven months

The results of the efficacy analyses for six to seven months for each type of dementia, separated by severity are summarised in Analysis 8.1; Analysis 8.2; Analysis 8.3; Analysis 8.4. These analyses only include studies with a duration of six to seven months, so some types of dementia are represented only by single studies: AD

with agitation (Herrmann 2012 (10158)); FTD (Boxer 2013); and, for cognitive function, PDD or DLB (Aarsland 2009).

The evidence for AD (apart from the studies in people with agitation) was mainly of high certainty and moderate for the mild subpopulation. The evidence certainty was moderate to low for vascular dementia and mainly low for FTD. For PDD or DLB and AD participants with agitation, the evidence certainty was low or very low.

Within these limitations, the following observations can be made for the efficacy outcomes; this section does not further address evidence certainty.

Clinical global rating (Analysis 8.1): memantine (versus placebo) gives a small improvement in clinical global rating in all types and severities of dementia, with the exception of AD with agitation (single study) and vascular dementia. In the latter two types, there seems to be no difference between memantine and placebo. There may be a smaller effect in people with mild AD than in people with moderate-to-severe AD, but severity does not seem very important for this outcome.

Cognitive function: memantine (versus placebo) gives an improvement in cognitive function for AD (moderate-to-severe), vascular dementia and PDD or DLB (single study). Single studies in people with AD plus agitation and FTD suggested there may have been no difference between interventions. There is a significantly larger effect of memantine (versus placebo) in the moderate-to-severe AD population compared with that in mild AD - such that memantine probably has no effect on cognitive function in people with mild AD, whereas an effect is observed in the moderate-to-severe population. The effect size in *mild-to-moderate* DLB or PDD (single study) and in *mild-to-moderate* vascular dementia appears to be similar to that in *moderate-severe AD* (Analysis 8.2). Further trends towards increased efficacy with severity are indicated in Analysis 5.5 for vascular dementia and (Appendix 4) for AD.

Decline in ADL (Analysis 8.3): memantine (versus placebo) gives an improvement in performance on ADL in AD (moderate-to-severe) and PDD or DLB, but there may be no effect in vascular dementia and a deterioration in ADL performance for AD with agitation (single study). There is a significantly larger effect of memantine (versus placebo) in participants with moderate-to-severe AD compared with mild AD - such that memantine probably has no effect on ADL in people with mild AD, but a small effect in people with moderate-to-severe AD. The effect in *mild-to-moderate* DLB or PDD again appears to be similar to that in *moderate-to-severe AD*.

Behaviour and mood (Analysis 8.4): memantine (versus placebo) appears to give an improvement in behaviour and mood for all types of dementia, with the exception of mild AD and AD with agitation (single study), for which there may be no difference between interventions. There is a significantly larger effect of memantine (versus placebo) in participants with moderate-to-severe AD versus mild AD - such that memantine probably has no effect on behaviour and mood in people with mild AD. The effect in each of the other types of dementia (vascular dementia, DLB or PDD and FTD (one study) for *mild-to-moderate* dementia appears to be similar to that in *moderate-to-severe AD* (Analysis 8.4). There appears to be a trend towards increased efficacy with increased severity (Appendix 4), but this was an aggregate level subgroup analysis.

Agitation: the CMAI score has been compared in a limited way between AD patients, with versus without agitation at baseline (Table 10). Memantine (versus placebo) appears to result in fewer people with agitation in most types of dementia, with the exception of AD patients with agitation, for which memantine may give more severe agitation (Analysis 8.5) (see section 5.2.3 below). The effect on agitation of memantine versus placebo appears to be larger in people with moderate-to-severe AD compared with mild-to-moderate AD (Analysis 8.5), and also seems more effective in monotherapy compared with concomitant ChEI (Analysis 8.6). Results for this outcome were not given for the mild post-hoc subgroup.

5. Adverse effects

We report results for all types of dementia and all durations for the 20 mg/day dose or equivalent. Forty-one studies met these dose inclusion criteria in 8960 randomised participants. However, not all studies reported all outcomes and four of these remaining studies did not report any safety outcomes (Lundbeck 2006 (99817); Merz 2003 (MRZ-9104); Merz 2003 (MRZ-9105); Merz 2003 (MRZ-9206)).

5.1. All-cause discontinuation and discontinuation due to adverse events

The results of the discontinuation analyses for all studies are shown in Analysis 9.1 and Analysis 9.2, regardless of study duration, but split by dementia type and severity in Analysis 8.7 and Analysis 8.8 (three studies in mild-to-moderate disease were excluded from this analysis: Asada 2011 (MA3301); Peters 2015 (MEGACOMBI2); Schmidt 2008. Differences between studies in participants with or without ChEI are shown in Analysis 2.9 and Analysis 2.10 (for which three studies were excluded from the analysis because a proportion of participants were treated with ChEI - Hofbauer 2009 (MD-71); Holland 2013; Wilkinson 2012 (10112)); all study durations were permitted.

5.1.1. All-cause discontinuation

All-cause discontinuation was reported in 36 studies that included 8752 participants (1600 events). Overall, there is no difference between memantine and placebo: RR 0.99 (95% CI 0.91 to 1.08) (Analysis 9.1). There may be slight heterogeneity in the point estimates, but $I^2 = 0\%$, P = 0.79. However, Analysis 8.7 suggests there are differences across dementia types and severities, and this is reinforced in AD, which shows a highly significant result in the test for subgroup differences ($I^2 = 83.8\%$ and P = 0.01) when comparing mild disease (RR 1.74, 95% CI 1.08 to 2.81) and moderate-to-severe disease (RR 0.93, 0.83 to 1.04).

We therefore report the results for this outcome separately for each dementia type and severity in the 'Summary of findings' tables for sections 1 to 3. For the moderate-to-severe AD group, there was no significant difference between the results for monotherapy and those for concomitant ChEI (Analysis 2.9) and so we report the combined moderate-to-severe results (test for subgroup differences $I^2 = 0\%$, P = 0.83).

5.1.2. Discontinuation due to adverse events

Discontinuation due to adverse events was reported in 32 studies that included 8271 participants (779 events). Overall, there is little difference between memantine and placebo: RR 1.06 (95% CI 0.92 to 1.21) (Analysis 9.2). There is some heterogeneity in the point estimates, but $I^2 = 0\%$, P = 0.64. Analysis 8.8 suggests there may

be differences in discontinuation due to adverse events across dementia types and severities, and for AD there is a significant result in the test for subgroup differences between mild and moderate-to-severe disease (I^2 = 78.5% and P = 0.03). For the moderate-to-severe subgroup, there is no difference between the results for monotherapy and those for concomitant ChEI (Analysis 2.10; test for subgroup differences: I^2 = 0%, P = 0.65).

A previous finding of this review was that all-cause discontinuation appeared to be less in participants taking memantine. This is only partially supported in this update by the six-month trials of moderate-to-severe AD, which suggest a slight benefit (Analysis 1.5). However, for populations in which memantine has little effectiveness, there may be more people discontinuing the drug compared with placebo.

5.2. Adverse events

The adverse effects profile and tolerability were good.

5.2.1. Number with at least one adverse event

Twenty-nine studies (of 41 possible) in 8033 participants reported the number of participants with at least one adverse event (Analysis 9.3); this is 90% of the available participants. Meta-analysis showed no difference between memantine and placebo, which appeared consistent across studies: RR 1.03 (95% CI 1.00 to 1.06), I^2 = 0%, P = 0.60 (5371 events).

Analysis 8.9 shows a subgroup analysis by severity (mild-to-moderate and moderate-to-severe) and type of dementia and there are no significant differences between subgroups. Sensitivity analysis, excluding studies at overall high risk of bias had little effect. An analysis of studies in AD patients with moderate-to-severe disease and without agitation at baseline showed there is no significant difference between the results for monotherapy (RR 0.99, 95% CI 0.94 to 1.04) and those for concomitant ChEI (RR 1.05, 95% CI 0.98 to 1.12). (Analysis 2.11). The test for subgroup differences was I^2 = 46.0%, P = 0.17), but this is probably due to the narrow confidence intervals as a consequence of a large number of participants, On the basis of the similarity of the different subgroup findings, we used AE results for the full dataset for every type and severity of dementia.

5.2.2. Number with at least one serious adverse event

Twenty-seven studies in 8138 participants reported the number with at least one serious adverse event (Analysis 9.4); this was 93% of all available participants. Meta-analysis shows little difference between memantine and placebo: RR 0.92 (95% CI 0.83 to 1.02), I^2 = 0%, P = 0.71 (1157 events). Analysis 8.10 shows subgroups by both type and severity of dementia. There appear to be some differences by type of dementia, but no dependence on severity amongst the AD studies without agitation. Additionally, there is no significant difference between the results for monotherapy and those for concomitant ChEI in people with moderate-to-severe disease (Analysis 2.12). Therefore, in sections 1 to 4 we report this outcome separately for the different types of dementia, but combine the results for the AD studies (apart from those with agitation).

5.2.3. Number with agitation as an adverse event

Nineteen studies in 5933 participants reported the number of participants with agitation (Analysis 9.5); this was 68% of all available participants. Data on agitation were mainly reported as 'serious adverse events' or 'adverse events' in ClinicalTrials.gov or as registry data (see footnotes to the forest plots). Meta-analysis suggests that fewer participants have agitation if they are taking memantine compared with placebo: RR 0.84 (95% CI 0.71 to 1.01) (424 events). There is some heterogeneity, I^2 = 32%, P = 0.09. Subgrouping by severity and type of dementia in Analysis 8.5 showed there were some differences by type of dementia, but the subdivision into mild-to-moderate and moderate-to-severe AD is not warranted, particularly because it was dependent on one study in people with moderate AD ((Wilkinson 2012 (10112)). There are no agitation data for the post-hoc subgroups of mild and moderate AD.

In the AD population with agitation at baseline, there may be twice as many participants with agitation as a treatment emergent adverse event at six months for memantine compared with those on placebo, whereas memantine appears to be protective for agitation in people with AD without agitation at baseline (test for subgroup differences I^2 = 84%, P = 0.01) (Analysis 8.5) (low-certainty evidence).

There may be different effects in the presence compared with the absence of ChEIs (Analysis 2.13; test for subgroup differences: I^2 = 20.9, P = 0.26). The results suggest less agitation for memantine (versus placebo) for the monotherapy subgroup (RR 0.68, 95% CI 0.51 to 0.91) and some heterogeneity, but little difference for concurrent therapy with ChEI (RR 0.92, 95% CI 0.60 to 1.40). Therefore, we reported this outcome separately in the summary of findings tables for sections 1 to 3 for other types of dementia; we combined the results for the AD studies across all severities (apart from those with agitation), but reported separately the results for studies in people receiving concomitant ChEI.

The collection of 'agitation as an adverse event' is not a good way to assess the impact of interventions on incident agitation, particularly for the studies in patients with agitation at baseline. Nevertheless, we have included these results in Analysis 8.11 for completeness, but have reported agitation as an efficacy outcome in section 1.4.

5.2.4. Number with specific adverse events

Results for other adverse events are shown in Table 11 and in Analysis 9.6 (insomnia); Analysis 9.7 (confusion); Analysis 9.8 (depression); Analysis 9.9 (headache); Analysis 9.10 (hypertension); Analysis 9.11 (dizziness); Analysis 9.12 (falls); Analysis 9.13 (accidental injury); Analysis 9.14 (urinary incontinence); Analysis 9.15 (diarrhoea) and Analysis 9.16 (influenza-type symptoms).

The evidence on specific adverse events was generally of low- or very low-certainty, mainly because relatively few studies reported the outcomes and we felt there was risk of reporting bias (Table 11).

Memantine is probably 1.6 times more likely than placebo to result in dizziness (RR 1.59, 95% CI 1.28 to 1.98) (moderate-certainty) and may be 1.2 times more likely to result in confusion (RR 1.23, 95% CI 0.91 to 1.65) and 1.3 times more likely to give headache (RR 1.29, 95% CI 1.00 to 1.66) (low certainty). Memantine may be 1.2 times less likely than placebo to result in diarrhoea (RR 0.82, 95% CI 0.66 to 1.02) (low certainty). There is no difference between interventions for the incidence of falls (RR 0.98, 95% CI 0.84 to 1.13) (high-certainty evidence). There is uncertainty about the other adverse events recorded.

DISCUSSION

Summary of main results

We discuss in this section the findings in relation to the two objectives of the review: to assess the efficacy and safety of memantine for the treatment of dementia of different aetiologies, and secondly, to assess whether memantine adds benefit for people already taking cholinesterase inhibitors (ChEIs).

A) Efficacy and safety of memantine

Memantine shows a small important clinical benefit over placebo in some populations, but not others. In particular, there is benefit for moderate-to-severe Alzheimer's disease (AD) for the four efficacy outcomes, and for some outcomes for vascular dementia. There is probably no benefit in mild AD and it is uncertain whether there is any effect in people with agitation in moderate-to-severe disease. A summary of the efficacy results are given below.

Throughout the review, we found no difference between memantine and placebo in the number of people with at least one adverse event, regardless of aetiology of dementia or severity (risk ratio (RR) 1.03, 95% confidence interval (CI) 1.00 to 1.06). The evidence on specific adverse events is generally of low- or very low-certainty, mainly because relatively few studies reported the outcomes and we felt there was risk of reporting bias. That said, memantine is probably 1.59 (95% CI 1.28 to 1.98) times more likely than placebo to result in dizziness (6.1% versus 3.9%) and may be 1.29 (95% CI 1.00 to 1.66) times more likely to result in headache (5.5% versus 4.3%). Memantine may be 1.2 times less likely than placebo to result in diarrhoea (RR 0.82, 95% CI 0.66 to 1.02) . There is no difference between interventions for the incidence of falls.

Discontinuation (all-cause) varies according to severity of disease and may have an inverse relationship with effectiveness. For example, discontinuation in mild AD participants (RR 1.74, 95% CI 1.08 to 2.81) is very different from that in moderate-to-severe AD: (RR 0.93, 95% CI 0.83 to 1.04).

1. Alzheimer's disease (AD)

The efficacy of memantine varies according to the severity of disease.

For moderate-to-severe AD, evidence from up to 14 studies in around 3700 participants shows there is a small clinical benefit for memantine relative to placebo in each of the main efficacy outcomes. Approximately similar numbers of people taking memantine and placebo discontinue treatment and there is probably a reduction in the number with agitation as an adverse event. These differences between memantine and placebo are small but important benefits and we know them with confidence (see Quality of the evidence). They are accompanied by similar numbers of people discontinuing treatment and there is probably a reduction in those with agitation.

For people with mild AD, we used evidence from post-hoc subgroups within four studies in people with mild-to-moderate disease. Although the trials were conducted in the mild-to-moderate population, licensing and treatment of AD is stratified into mild and moderate-to-severe categories, and we had to isolate evidence on the mild population in this way. There was one small study conducted solely in people with mild disease, but this did not give sufficient information to investigate the effect of memantine in this population (and was concerned with driving abilities). Evidence from up to four studies in around 600 participants suggested there may be no difference between memantine and placebo for clinical global rating and there is probably no difference for the other three efficacy outcomes. There may be an increase in the number of people discontinuing treatment because of adverse events, which may not be surprising given the lack of efficacy. For the population with mild AD, we observed an average improvement over time in cognitive function and in behaviour and mood for the placebo groups (median change from baseline). We are uncertain whether this improvement is a real effect or a statistical regression to the mean; it is possible that the improvement could be related to participants being in a trial.

We also investigated separately the effect of memantine in people with moderate-to-severe AD, who were selected for agitation. Only one study had results at six months, but we also analysed two other studies with three months' follow-up, in order to probe whether the six-month study was an outlier. This evidence was mainly of low or very low certainty, and within these limitations, suggested there may be little or no effect of memantine in this population for the outcomes of clinical global rating, cognitive function and performance on activities of daily living (ADL); the evidence for behaviour and mood was of very low certainty. There was moderate-certainty evidence for the Cohen-Mansfield Agitation Index (CMAI) score for agitation, which suggested there was probably no difference between memantine and placebo. The proportion reporting agitation as a treatment emergent adverse events (AEs) in two studies (403 participants) may be doubled in patients selected for agitation receiving memantine (plus ChEI) compared with placebo (plus ChEI). This is in contrast with AD patients with moderate-to-severe disease who were not selected for agitation, and in whom the proportion reporting agitation is reduced by memantine. We do not generally have confidence in these results, but consider that further research is needed to determine if memantine is indeed ineffective in an agitation population, appreciating that trials in this agitated population are difficult to conduct.

2. Vascular dementia

Moderate- and low-certainty evidence from two studies in around 750 participants with vascular dementia gave mixed results for the comparison of memantine and placebo. There is probably a small clinical benefit for cognitive function and there may be a small clinical benefit on the Nurse's Observational Scale for Geriatric Patients (NOSGER) disturbing behaviour outcome. However, there is probably no difference between memantine and placebo in clinical global rating and there may be no difference in performance on ADL. There may be no difference in the numbers of people discontinuing treatment and there may be fewer people with agitation as an adverse event for memantine compared with placebo.

A post-hoc subgroup analysis by severity suggested that memantine (versus placebo) may have a bigger effect for cognitive function in people with moderate-to-severe vascular dementia (Mini Mental State Examination (MMSE) ≥14) than in people with mild-to-moderate vascular dementia. The test for subgroup differences was significant (I^2 = 72.5%, P = 0.06), although this was a post-hoc analysis.

3. Other forms of dementia

Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB): low- and very low-certainty evidence from up to three studies in around 250 participants suggests that, for memantine versus placebo in people with PDD or DLB, there may be a small clinical benefit in clinical global rating and in behaviour and mood (although the confidence interval was consistent with both no effect and benefit). Evidence for all other efficacy outcomes was of very low certainty. There may be fewer people discontinuing treatment.

Frontotemporal dementia (FTD): mainly low-certainty evidence from two studies in around 120 participants suggests there may be a small clinical benefit in clinical global function and in behaviour and mood for memantine versus placebo in people with FTD. There may be no difference in cognitive function. However, for all of the efficacy outcomes, there is uncertainty and the confidence interval is consistent with more than one conclusion. There may be more discontinuation in the memantine group (compared with placebo) for this population, but again the CI is wide.

AIDS-related Dementia Complex (ADC): only one study in 140 participants was identified and suggested there may be an improvement in cognitive score (Neuropsychological Z score (NPZ)-8) at 16 weeks and that all-cause discontinuation may be similar for memantine and placebo.

B) Benefit of memantine for those already taking cholinesterase inhibitors (ChEIs)

For our second objective, we examined whether memantine could give incremental benefit for people already taking ChEIs. We examined this by investigating whether there were different effects according to the presence or absence of concomitant ChEIs in those for whom memantine was more efficacious than placebo (i.e. moderate-to-severe AD).

Moderate-to-severe AD, with concomitant ChEIs: six trials in around 1850 people showed a small clinical benefit for memantine versus placebo in cognitive function, performance on ADL and behaviour and mood; and there is probably a small clinical benefit in clinical global rating. There are similar numbers of people with adverse events in both groups (RR 1.03, 95% CI 1.00 to 1.06). Similar numbers of people taking memantine and a ChEI discontinue their treatment compared to those taking placebo and a ChEI, and there may be little or no difference between interventions in the number with agitation as an adverse event.

There were similar efficacy findings for people receiving memantine monotherapy, except that the benefit compared with placebo is smaller in monotherapy for the behaviour and mood outcome and larger for the cognitive function outcome (Table 10). In contrast to people receiving concomitant ChEI, people receiving memantine monotherapy probably have less agitation than those receiving placebo.

Between-trial subgroup analyses comparing the presence and absence of concomitant ChEIs suggest there is no significant difference between monotherapy and concurrent therapy with concomitant ChEI (for the comparison of memantine versus placebo) for any of the primary efficacy outcomes, although there is a non-significant difference between subgroups for the cognitive function outcome (I^2 = 44%, P = 0.18) and for the behaviour and mood outcome (I^2 = 35%, P = 0.21). These subgroup analyses are non-randomised comparisons between different groups of studies and do not investigate possible confounding factors, such as severity of disease. The only head-to-head randomised evidence was of low certainty: one study randomised 149 participants to memantine plus continued donepezil versus memantine plus placebo and donepezil discontinued. The study suffered from differential missing data, but there may be a benefit in using both drugs compared with memantine monotherapy for cognitive function, i.e. it may be better to add memantine than to switch to memantine.

Overall completeness and applicability of evidence

People with dementia who are recruited into drugs trials are often not representative of typical clinical populations. Those recruited typically lack physical comorbidities, have better psychosocial support, and are less likely to have neuropsychiatric symptoms, all of which may mitigate against decline and its functional impact.

The studies were too short and small to be expected to show any effect of memantine on life expectancy. It is possible that the drug extends the total time of deterioration without reducing the personal or social burden of the disease (Dresser 2000).The benefits of slowing Alzheimer's disease progression in the later stages can be controversial (Post 1997).

The reliability of the distinction between vascular and Alzheimer's dementia is not high: most patients with vascular dementia, especially those with severe dementia have additional Alzheimer's pathology. This limits the applicability of results from trials of mild-to-moderate vascular dementia to those with severe vascular dementia.

Responder analyses are not routinely presented although the data are available from all trials. However, a meta-analysis of responders based on six trials found that 10% more placebo-treated than memantine-treated patients showed any clinical worsening (Wilkinson Post-Hoc 6RCTs 2007). There was a similar difference in rates of marked clinical worsening.

Measures of executive function are difficult to assess in those with more advanced dementia and in general are not well covered in AD trials which use the Alzheimer's Disease Assessment Scale - Cognitive subscale (ADAS-Cog) and were not included in the vascular dementia trials (Roman 1999).

Comprehensive lists of adverse drug reactions are infrequently reported so there is a theoretical possibility of publication bias. Regulators require comprehensive reporting. Whilst the details of these reports to regulators remain confidential, changes in the 'Summary of Product Characteristics' are likely to be a more reliable source of information on rare adverse effects than pooled data in systematic reviews.

Quality of the evidence

The evidence for AD is mainly of high certainty (with the exception of studies in people selected for agitation), which means we can be very confident of the results, which we summarised across many studies in large numbers of participants. The evidence for mild AD was obtained from within-trial post-hoc subgroups, with data provided by drug companies, but this evidence is still of moderate certainty.

The evidence certainty is moderate to low for vascular dementia and mainly low for FTD. For PDD or DLB and AD participants with agitation, the evidence certainty is mainly low or very low.

The authors of this review have gone to great lengths to obtain data for studies that have not been fully published, or for which there have been delays in publication. This work has much increased the volume of evidence available, nevertheless the results of some studies are still not in the public domain and there could be publication bias. Funnel plots for the main efficacy outcomes and for all-cause discontinuation did not appear to suggest small studies' bias. There may be some asymmetry found for the adverse events outcome. Nearly all the trials were funded by drug companies.

Potential biases in the review process

In analysing the data, we have carried out a series of subgroup analyses and stratifications. At the outset, we stratified the studies by type of dementia, but later compared across aetiologies as a check. Stratification seemed appropriate for the efficacy outcomes and some safety outcomes, but we combined the results for adverse events across all studies because we found no differences in adverse events between diagnostic subgroups. We investigated duration of study, dose of memantine and type of analysis (observed case (OC) versus last observation carried forward (LOCF)) and restricted the main analyses to a duration of six months and licensed dose, also preferring to analyse OC data. We have documented our reasoning for all these decisions, but they could be a source of bias.

We split the data by severity into mild and moderate-to-severe AD, on the basis of subgroup analyses and pragmatism connected with current licensing requirements. These subgroup analyses seemed to provide convincing evidence, but are still non-randomised comparisons, and there could have been confounding by some other factor. We then split the moderate-to-severe dataset further in our investigation of the effect of concomitant ChEI, and this further splitting could have led to random error. For this reason (and the lack of evidence of a difference between monotherapy and dual therapy), we prefer to use results for all studies regardless of their use of ChEI.

We calculated data for mild AD from published trial data in people with mild-to-moderate disease and drug company-provided subgroup data for people with moderate disease. These data are from post-hoc subgroups and so there may be differences between intervention groups in baseline characteristics. It would have been preferable to stratify patients by severity and then randomise to treatments, but this was not done by the trialists. Having said this, there are large numbers of participants and the split into mild and moderate disease is pre-defined, so this is probably a minor limitation.

We also made some post-hoc decisions, namely to treat separately studies in AD patients selected for agitation and to exclude from the analysis two randomised arms from one study because of a study-reported interaction of memantine with Vitamin E. In the first instance, we considered the patients selected for agitation to be sufficiently dissimilar from other AD patients that they should not be included in the same analyses, and in the second case we thought the effect modification could have introduced unwarranted heterogeneity. These decisions could have meant that our findings for AD were overestimated.

We have been transparent about the approaches taken in this review, and do not consider the potential for bias is high.

Agreements and disagreements with other studies or reviews

This updated Cochrane Review has mainly similarities, but some differences with previous work. We focus here on clinical guidelines or technology appraisals for dementia, and recent systematic reviews of memantine. We mainly focus on AD, considering the number of studies included, the approach to monotherapy and concurrent therapy, ways of dealing with missing data, the effects of severity and the impact of agitation.

We have included 32 new studies (in comparison with 2006), several of which had unpublished data provided by the study authors or drug companies. We also included results for post-hoc subgroups, which have informed analyses for both the mild and moderate-to-severe AD categories. We have meta-analysed results from considerably more AD studies than were included in the NICE technology appraisal, which had four monotherapy and two dual therapy trials (NICE 2011); and consequently our review has more precise summary statistics. For moderate-to-severe AD, this has meant that all the main efficacy outcomes show small benefits that are statistically significant, in contrast to the largely non-significant findings of TA 217 - which were equated with no effect (see Why it is important to do this review).

Our analyses have shown that the benefit obtained for monotherapy versus placebo in moderate-to-severe AD is very similar to that obtained in dual therapy trials, and the test for subgroup differences is not significant. Therefore, we have included all trials in the meta-analyses, regardless of the presence or absence of ChEIs. This conclusion about the efficacy of dual therapy contrasts with the conclusion of the NICE appraisal, which stated there was a lack of evidence of additional clinical efficacy (of concurrent therapy with ChEIs) compared with memantine monotherapy (NICE 2011). Since 2011, there have been many new studies of memantine in AD, leading to more up-to-date systematic reviews, and NICE has now published an update to its dementia guideline in June 2018 (NICE 2018). We discuss this recent literature below.

Three systematic reviews in AD have been published in the past three years, two of memantine monotherapy (Chen 2017; Matsunaga 2015, and one of dual therapy (Matsunaga 2015b). These gave similar conclusions to our review for most outcomes, even though the authors included studies reporting participants with mild AD and studies that did not have a placebo comparator, and also used LOCF approaches for missing data. A further systematic review included three studies of dual therapy and showed significant benefits when the analysis was restricted to moderate-to-severe AD (Muayqil 2012). We also identified a recent review of predominantly Chinese studies, which compared concurrent therapy with donepezil, however the majority of studies did not include a placebo (Chen 2017). We note that the FDA granted a license for combination therapy in patients stabilised on 10 mg donepezil once daily in December 2014 and a combined formulation product was launched in 2015.

The effect of severity was also identified in two other systematic reviews (Di Santo 2013; Kishi 2017): one of these showed greater efficacy as severity increased in a similar way to our review, but only included six trials (Di Santo 2013). The other review of 30 AD studies (including those without a placebo comparator) reached similar conclusions to ours regarding severity, but did not probe the effect of memantine in mild AD disease (Kishi 2017).

The NICE dementia guideline has been updated concurrently with the update of this Cochrane Review (NICE 2018); we have shared data with the guideline developers and the Cochrane Dementia and Cognitive Improvement review group is a registered stakeholder for the guideline. The guideline is a major update of the original guideline and updates some aspects of TA 217. The guideline preserved the TA's original stratification for analyses of monotherapy and dual therapy, and has updated the dual therapy analyses by including additional studies; however, the monotherapy analyses have not been updated (NICE 2018). The update has revised recommendations for 'people who are already taking a ChEI', for whom clinicians should now consider adding memantine to ChEIs for people with moderate disease and offer memantine in addition to ChEI to people with severe disease (NICE 2018). The evidence in this Cochrane Review supports (and indeed has informed) recommendations to offer dual therapy, but we consider that the monotherapy recommendations should also have been examined, especially because there are many new studies and memantine is now off-patent. We are also concerned that the conflation of the old and new recommendations in the new guideline may lead to confusion for clinicians. For example, in severe disease, the unchanged monotherapy recommendation is to offer memantine (and not ChEIs), yet the new dual therapy recommendation is for people who are 'already taking a ChEI'. Additionally, the 2018 guideline is not explicit on whether combination therapy should be offered as first line therapy for people presenting with moderate or severe disease.

A systematic review of clinical guidelines reported the recommendations from 12 moderate- to high-quality guidelines (Ngo 2015). The authors noted there was disagreement between two guidelines on the benefit of memantine in mild AD, but agreement in its use in moderate-to-severe dementia.They noted conflicting recommendations amongst four guidelines to support combining ChEI therapy with memantine in moderate–to-severe dementia.

France's Minister for Health has recently de-listed memantine and the ChEIs, donepezil, galantamine and rivastigmine (HAS 2018), stating that "it is better to concentrate on helping to organise daily activities, maintain activity, support and help from those around you", This de-listing was based on work by the Haute Autorité de Santé (HAS), which stated in 2016 following evidence review, "The new data confirms that the efficacy of drugs for the symptomatic treatment of Alzheimer's disease is, at best, modest. It is established only in the short term, mainly on cognitive disorders, in placebo controlled clinical studies whose clinical relevance and transposability in real life are not ensured. Patients in these studies are indeed younger than those who are managed in real practice, and unlike these they have no comorbidities, nor risks of drug interactions. In addition, the effects on behavioral disorders, quality of life, time to enter an institution, mortality, burden of illness for carers are still not established... However, the data accumulated since the commercialization of the drugs confirm the risk of occurrence of undesirable side effects (digestive, cardiovascular or neuropsychiatric disorders for the most notable) potentially serious, which can alter the quality of life" (HAS 2016, translation). The 2018 statement was less measured, stating that, "None of the available drugs has been shown to slow down progression toward dependence, yet all carry a risk of life-threatening adverse effects and severe drug interactions" (Prescrire 2018) (see Why it is important to do this review).

The HAS based its conclusions for the efficacy of memantine on the Matsunaga 2015 review for monotherapy and an earlier review authored by some of us for dual therapy (Farrimond 2012), both of which broadly agree with the conclusions of our memantine review, but there are differences for ADL for both reviews (HAS Annexe 2016). The HAS considered the benefits to be 'clinically irrelevant' and stated there is no difference in ADL for dual therapy. These conclusions are not supported either by our current memantine review or by the review and cost-effectiveness analysis of the NICE guideline (NICE 2018). We consider that the small incremental benefits from each of ChEI and memantine for all outcomes at six months follow-up, each having an effect size that may be less than the minimum clinically important difference, do not equate to clinical irrelevance. As stated above, we do agree that participants recruited into drugs trials are often not representative of typical clinical populations.

Second, the French authorities examined adverse effect data in detail for the ChEIs and memantine, using meta-analyses of clinical trials, summary of products characteristics (SPC) and (for uncommon AEs) observational studies and analyses of pharmacovigilance databases (HAS Annexe 2016). The HAS reported that in placebo-controlled clinical trials, more people discontinued donepezil 10 mg than placebo due to adverse effects, but the HAS did not report this for other ChEIs or memantine. In our current memantine review, however, we have noted a significant subgroup difference for this outcome between people with mild disease (greater discontinuation on memantine) and those with moderate-to-severe disease (no difference compared with placebo) (see section A above). The HAS report included some observational studies, one of which compared memantine and the three ChEIs (but had no data on untreated patients) (Fosbøl 2012). This very large study in the USA and Denmark reported for the Danish cohort a greater risk (in adjusted analyses) of myocardial infarction and cardiac death for memantine (compared with donepezil) and a smaller risk for syncope and atrioventricular block, but no differences in the USA cohort on hospitalisation for cardiac events. In both cohorts, all-cause mortality was greater for patients receiving memantine. The authors concluded that the greater risk of cardiovascular events in the Danish cohort in users of memantine and dual therapy is probably related to selection of sicker participants, because these therapies are reserved for individuals with more severe dementia in Denmark. They also noted the lack of comparative data (with placebo/no treatment) and stated that "no clinical studies has found cardiovascular signals of clinical concern" (Fosbøl 2012). The HAS also gives pharmacovigilance data (as case reports) and indicates changes made to the SPCs of the various drugs: data on donepezil versus placebo was inconsistent for mortality in people with vascular dementia; there may be an increased risk of QT interval prolongation for galantamine and there may be an increased risk of myocardial infarction, stroke and torsade de pointes for rivastigmine. A very large pharmacovigilance study

of the WHO database, VigiBase, over 58 countries, investigated all ChEIs and noted that serious cardiovascular events were frequently reported, suggesting that their significance has probably been previously underestimated, and encouraging caution when prescribing these drugs, especially as patients with Alzheimer's disease are frequently frail and receive other drugs (Kröger 2015). The HAS has little to say about memantine pharmacovigilance except that hepatitis has been added to the SPC, but does agree with our review on the results for adverse effects from clinical trials. Instead of treating memantine separately from ChEIs, the HAS statements on safety apply to the dementia drugs as a whole (HAS Annexe 2016). Overall, we consider there is insufficient evidence to support the strong statement on adverse events (HAS 2016) and think that memantine, which has a different mode of action from ChEIs, should be considered separately.

The HAS recommends care and support for the individual *instead* of the drug treatments, rather than including drug treatments as a part of a general care package. They do not appear to have reviewed the evidence on this.

Overall, our view is that the evidence in our review and our examination of the French adverse effects data raises questions about the appropriateness of the de-listing policy taken by the French government. We note that de-listing means the drugs are no longer reimbursed by the national health insurance system (Prescrire 2018), but that the drugs can be prescribed in line with their summary of product characteristics (HAS 2018). This may mean confusion for clinicians and potential for inequalities in the healthcare system.

Our review of the evidence on the effect on memantine in people with moderate-to-severe AD selected for agitation suggested that memantine may be ineffective in this population, but this is low- or very low-certainty evidence. Our findings contrast with two post-hoc analyses (Gaultier 2005; Wilcock Post-Hoc 3RCTs 2008); the latter analysed individual participant data (IPD) from three randomised controlled trials (RCTs) in our review (Reisberg 2003 (9605); Tariot 2004 (MD-02); van Dyck 2007 (MD-01)); selecting only those from a 'behaviourally disturbed population', defined as a score > 0 on any of the three NPI symptoms of agitation–aggression, delusion, and hallucinations at baseline. Data were integrated in a single dataset and then analysed; meta-analysis was not reported and the data were said to be 'pooled', indicating that the randomisation was not maintained. The study found a significant benefit for memantine for each of the efficacy outcomes at six months, but its reliability is unclear. A second review (Gaultier 2005); reported separately data from two RCTs in our review (Reisberg 2003 (9605); Tariot 2004 (MD-02)), and, for one of the studies with memantine monotherapy (Reisberg 2003 (9605)) gave results for post-hoc subgroups of participants with agitation and no agitation at baseline. Results were not reported for the other study (which had dual therapy). The review stated that for people with agitation at baseline (defined as in Wilcock Post-Hoc 3RCTs 2008, and comprising about 60% of the population); there was a significant improvement in agitation symptoms for memantine compared with placebo, which does not agree with our review's findings, but we note this is a different outcome to that in our review (improvement versus worsening of symptoms). In people without agitation at baseline, there were stated to be significantly fewer emergent agitation symptoms for memantine. Overall, there may be some differences with earlier findings, but all the efficacy evidence is of low or very low certainty and there is a need for further research of alternative therapies in this important patient group.

Finally, we note some differences between this Cochrane Review and the 2018 NICE guideline for types of dementia other than AD (NICE 2018). For people with vascular dementia, the NICE guideline recommends that ChEIs or memantine should be considered only if they have comorbid AD or PDD/DLB. However, this Cochrane Review has identified small clinical benefits in cognitive function and in behaviour and mood in people diagnosed with vascular dementia, and there is a post-hoc analysis indicating there may be greater benefits in people with more severe disease. For people with FTD, the guideline recommends that ChEIs and memantine should not be offered (a strong recommendation), stating that there is not usually a cholinergic deficit in people with FTD, that there was no evidence of benefit and also citing the potential for adverse effects, whilst noting no difference between memantine and placebo. It may be that the guideline has conflated the findings for ChEIs with those for memantine, and we note that memantine has a non-cholinergic mechanism of action and may have potential for benefit, albeit from low- or very low-certainty evidence. For people with PDD or DLB, the guideline reviewed the evidence for PDD and DLB separately, and appeared to draw conclusions on the basis of a lack of statistical significance. The guideline recommended that memantine should be considered only if ChEIs are not tolerated or contraindicated, which, while consistent with our review findings of low- or very lo- certainty evidence in this patient group, has a strength which goes beyond the evidence.

AUTHORS' CONCLUSIONS

Implications for practice

A substantial volume of high-certainty evidence shows that memantine has a small, beneficial, clinically detectable effect in people with moderate-to-severe Alzheimer's disease (AD) at six months. The additional benefit is also apparent in those taking cholinesterase inhibitors (ChEIs).

Clinical heterogeneity in AD means that optimal drug treatment may involve multiple drugs, each having an effect size that may be less than the minimum clinically important difference.

There is moderate-certainty evidence that memantine is of no benefit in mild AD over six months and that there is a possibility of increased discontinuation due to adverse events. There is no clinical trial evidence to support the suggestion that memantine reduces disease progression any more than placebo. Current practice should more closely reflect this evidence.

The timely release of data remains problematic. Meta-analyses that attempt to avoid bias by restricting included studies to published data, or which over-rate the risk of bias due to last observation carried forward (LOCF) or observed case (OC) methods of analysis, incur a risk of bias due to selective publication.

Implications for research

A large trial of at least two to three years duration in mild AD is needed to definitively rule out benefit of long duration treatment in earlier dementia. Similarly, a three-year study in moderate-to-severe AD would establish whether there are any continuing effects beyond six months.

ACKNOWLEDGEMENTS

We thank Anna Noel Storr for running the searches and creating and maintaining ALOIS, Sue Marcus for guiding this so patiently to publication.

We thank Merz for providing an unpublished breakdown of global ratings of change and NOSGER scores from Wilcock 2002 (9202), Lundbeck for providing unpublished details of Lundbeck 2006 (10116).

We are grateful to the anonymous peer reviewers of previous versions of the review and to Elizabeta Mukaetova-Ladinska and Gad A Marshall who peer reviewed this update.

We also thank Dr Kiyomi Shinohara for her translation of the Japanese paper, Nakamura 2016.

REFERENCES

References to studies included in this review

Aarsland 2009 *{published data only}*

* Aarsland D, Ballard C, Walker Z, Bostrom F, Alves G, Kossakowski K, et al. Memantine in patients with Parkinson's Disease dementia or dementia with Lewy Bodies: a double-blind, placebo-controlled, multicentre trial. *Lancet Neurology* 2009;**8**(7):613-8.

Larsson V, Aarsland D, Ballard C, Minthon L, Londos E. The effect of memantine on sleep behaviour in dementia with Lewy bodies and Parkinson's disease dementia. *International Journal of Geriatric Psychiatry* 2010;**25(10)**:1030-8.

Stubendorff K, Larsson V, Ballard C, Minthon L, Aarsland D, Londos E. Treatment effect of memantine on survival in dementia with Lewy bodies and Parkinson's disease with dementia: a prospective study. *BMJ Open* 2014;**4**(7):e005158. [DOI: 10.1136/bmjopen-2014-005158]

Wesnes K, Aarsland D, Ballard C, Londos E. Memantine improves attention and verbal episodic memory in Parkinson's Disease dementia and dementia with Lewy Bodies: a double-blind, placebo-controlled multicentre trial. *Alzheimer's & Dementia* 2013;**9**(4):890. [DOI: 10.1016/j.jalz.2013.08.252]

Wesnes KA, Aarsland D, Ballard C, Londos E. Improvements to attention and verbal episodic memory with memantine in Parkinson's Disease dementia and dementia with Lewy Bodies. *Journal of Nutrition, Health & Aging* 2013;**17**(9):781-2. [DOI: 10.1007/s12603-013-0399-7]

Wesnes KA, Aarsland D, Ballard C, Londos E. Memantine improves attention and episodic memory in Parkinson's Disease dementia and dementia with Lewy Bodies. *International Journal of Geriatric Psychiatry* 2015;**30**(1):46-54. [DOI: http://dx.doi.org/10.1002/gps.4109]

Asada 2011 (MA3301) *{unpublished data only}*

* JAPIC trials registry. http://www.clinicaltrials.jp/user/ctiMain_e.jsp 14 Feb 2011; Vol. JapicCTI-R110144. [JapicCTI-R110144]

JAPIC trials registry. http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-050079.

Asada 2011a (IE3501) *{published and unpublished data}*

* JAPIC trials registry. http://www.clinicaltrials.jp/user/ctiMain_e.jsp 14 Feb 2011. [JapicCTI-R110143]

JAPIC trials registry. http://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-050078.

Report on the deliberation results: Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare. https://www.pmda.go.jp/files/000207435.pdf (accessed 5 April 2018). Pharmaceuticals and Medical Devices Agency, 2010:65-9.

Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's Disease: a systematic review and meta-analysis. *PLOS One* 2015;**10**(4):e0123289. [DOI: 10.1016/j.jagp.2013.11.007]

Nakamura Y, Homma A, Kitamura S, Yoshimura I. Phase III study of memantine hydrochloride, a new NMDA receptor antagonist, in patients with moderate to severe Alzheimer's disease. *Japanese Journal of Geriatric Psychiatry* 2011;**22**(4):464-73.

Nakamura Y, Kitamura S, Homma A. Efficacy and safety of memantine in people with moderate-to-severe Alzheimer's disease: results of a pooled analysis of randomized, double-blind placebo-controlled trials in Japan. *Alzheimer's & Dementia* 2013;**9**(4):297. [DOI: 10.1016/j.jalz.2013.05.605]

Ashford 2011 (95722) *{published data only}*

Ashford JW, Adamson M, Beale T, La D, Hernandex B, Noda A, et al. MR spectroscopy for assessment of memantine treatment in mild to moderate Alzheimer Dementia. *Journal of Alzheimer's Disease* 2011;**26**:331-6. [DOI: 10.3233/JAD-2011-0021]

Bakchine 2008 (99679) *{published and unpublished data}*

Anonymous. Forest press release. http://ir.frx.com/phoenix.zhtml?c=83198&p=irol-newsArticle&ID=482107&highlight= (Accesed 5 April 2018) 7 Jan 2003.

* 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. *Journal of Alzheimer's Disease* 2008;**13**(1):97-107.

Bakchine S, Loft H (Replaced by Bakchine 2008). Memantine treatment in patients with mild to moderate Alzheimer's Disease: results of a randomised, double-blind, placebo-controlled 6-month study ((study 99679) [Corrected and republished in: J Alzheimers Dis. 2008 Feb;13(1):97-107]. *Journal of Alzheimer's Disease* 2007;**11**(4):471-9.

Bakchine S, Pascual-Gangnant L, Hefting N, Loft H. Results of a randomised, placebo-controlled 6-month study of memantine in the treatment of mild to moderate Alzheimer's disease in Europe. *European Neuropsychopharmacology* 2005;**15**(3):S567–8. [DOI: 10.1016/S0924-977X(05)81189-7]

Doody RS, Tariot PN, Pfeiffer E, Olin JT, Graham SM, Bell JM. Meta-analysis of six month memantine clinical trials. Conference Proceeding: New Clinical Drug Evaluation Unit 45 Annual Meeting. Boca Raton, Florida, June 6-9 2005. 2005.

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. *Dementia and Geriatric Cognitive Disorders* 2007;**24**(1):20-7.

Bakchine 2008 (99679) SG *{published data only}*

* 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. *Journal of Alzheimer's Disease* 2008;**13**(1):97-107.

Bakchine S, Loft H (Replaced by Bakchine 2008). Memantine treatment in patients with mild to moderate Alzheimer's Disease: results of a randomised, double-blind, placebo-controlled 6-month study ((study 99679) [Corrected and republished in: J Alzheimers Dis. 2008 Feb;13(1):97-107]. *Journal of Alzheimer's Disease* 2007;**11**(4):471-9.

Olin J. Personal communication 2015.

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. *Dementia and Geriatric Cognitive Disorders* 2007;**24**(1):20-7.

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. 10th International Conference on Alzheimer's disease and related disorders. Madrid 15th - 20th July 2006 [poster]. 2006.

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. European Federation of Neurological Societies, 10th Congress Glasgow 2nd-5th September 2006 [poster]. 2006.

Boxer 2013 *{published and unpublished data}*

* Boxer AL, Knopman DS, Kaufer DI, Grossman M, Onyike C, Graf-Radford N, et al. Memantine in patients with frontotemporal lobar degeneration: a multicentre, randomised, double-blind, placebo-controlled trial. *Lancet Neurology* 2013;**12**(2):149-56. [DOI: 10.1016/S1474-4422(12)70320-4]

Forest Laboratories. Memantine (10mg BID) for the Frontal and Temporal Subtypes of Frontotemporal Dementia. https://clinicaltrials.gov/ct2/show/NCT00545974 2007.

Ditzler 1991 *{published data only}*

Ditzler K. Efficacy and tolerability of memantine in patients with dementia syndrome. *Arzneimittelforschung* 1991;**41**(8):773-80.

Dysken 2014 *{published and unpublished data}*

Dysken MW, Guarino PD, Vertrees JE, Asthana S, Sano M, Llorente M, et al. Vitamin E and memantine in Alzheimer's disease: clinical trial methods and baseline data. *Alzheimer's & Dementia* 2014;**10**(1):36-44. [DOI: 10.1016/j.jalz.2013.01.014]

* Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial [erratum appears in JAMA 2014 Mar 19;311(11):1161]. *JAMA* 2014;**311**(1):33-44. [DOI: 10.1001/jama.2013.282834.]

Dysken 2014 SG *{published and unpublished data}*

Dysken MW, Guarino PD, Vertrees JE, Asthana S, Sano M, Llorente M, et al. Vitamin E and memantine in Alzheimer's disease: clinical trial methods and baseline data. *Alzheimer's & Dementia* 2014;**10**(1):36-44. [DOI: 10.1016/j.jalz.2013.01.014]

* Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial [erratum appears in JAMA. 2014 Mar 19;311(11):1161]. *JAMA* 2014;**311**(1):33-44.

Dysken VitE 2014 *{published and unpublished data}*

Dysken MW, Guarino PD, Vertrees JE, Asthana S, Sano M, Llorente M, et al. Vitamin E and memantine in Alzheimer's disease: clinical trial methods and baseline data. *Alzheimer's & Dementia* 2014;**10**(1):36-44. [DOI: 10.1016/j.jalz.2013.01.014]

* Dysken MW, Sano M, Asthana S, Vertrees JE, Pallaki M, Llorente M, et al. Effect of vitamin E and memantine on functional decline in Alzheimer disease: the TEAM-AD VA cooperative randomized trial [erratum appears in JAMA 2014 Mar 19;311(11):1161]. *JAMA* 2014;**311**(1):33-44. [DOI: 10.1001/jama.2013.282834.]

Emre 2010 (11018) *{published and unpublished data}*

Emre M. A randomised, double-blind, placebo-controlled 6 month study of the efficacy and safety of memantine in patients with Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB). 13th Congress of European Federation of Neurological Societies (EFNS). 12-15 September 2009.

Emre M and 11018 study investigators. A randomised, double-blind, placebo-controlled, 6-month study of the efficacy and safety of memantine in patients with PDD or DLB. 9th International conference on Alzheimer's and Parkinson's disease. Prague. 11-15 March 2009.

* Emre M, Tsolaki M, Bonucelli U, Destée A, Tolosa E, Kutzelnigg A, et al. Memantine for patients with Parkinson's disease or dementia with Lewy bodies: a randomised, double-blind, placebo-controlled trial. *Lancet Neurology* 2010 August 20;**9**(10):969-77.

Forest 2006 (MD-22) *{unpublished data only}*

* Forest Laboratories Inc Clinical Trials Registry. A randomised, double-blind, placebo-controlled evaluation of the effectiveness and safety of memantine in nursing home residents with moderate to severe Alzheimer's disease. http://www.forestclinicaltrials.com 2006.

Forest 2006 (MD-23) *{unpublished data only}*

* Forest Laboratories Inc. A randomised, double-blind, placebo-controlled evaluation of the effectiveness and safety of memantine in non-institutionalised agitated patients with moderate to severe Alzheimr's disease. http://www.forestclinicaltrials.com 2006.

NCT00097916. An evaluation of the safety and efficacy of memantine in agitated patients with moderate to severe Alzheimer's Disease [A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of memantine in non-institutionalized agitated patients with moderate to severe Alzheimer's disease]. ClinicalTrials.gov NCT00097916 April 2006.

Fox 2012 (MAGD) *{published and unpublished data}*

Fox C, Crugel M, Maidment I, Auestad BH, Coulton S, Treloar A, et al. Efficacy of memantine for agitation in Alzheimer's dementia: a randomised double-blind placebo controlled trial. *PLOS One* 2012;**7**(5):e35185. [DOI: 10.1371/journal.pone.0035185]

Gortelmeyer 1992 *{published data only}*

Gortelmeyer R, Erbler H. Memantine in the treatment of mild to moderate dementia syndrome: a double-blind placebo-controlled study. *Arzneimittelforschung* 1992;**42**(7):904-13.

Grossberg 2008 (MD-50) *{published and unpublished data}*

Forest Laboratories, Inc. announces positive results of memantine study of once-daily formulation. Press release 5 Feb 08.

Alva G, Grossberg G, Hendrix S, Ellison N, Andersen KA, Edwards J. Efficacy of memantine ER on activities of daily living: a post hoc responder analysis from a randomized trial in patients with moderate-to-severe Alzheimer's disease. *Neurology* 2017;**88**(16 Suppl 1):P3.087.

Atri A, Cummings JL, Hendrix S, Ellison N, Andersen KA, Edwards J. Maintenance of cognitive improvement treatment response with memantine and donepezil: post hoc analyses from a placebo controlled study in patients with moderate to severe Alzheimer's disease. *Alzheimer's & Dementia* 2017;**13**(7):1232. [DOI: 10.1016/j.jalz.2017.07.430]

Atri A, Hendrix S, Pejovic V, Graham S. Extended-release daily memantine provides increasing cumulative benefits across clinical domains over 24 weeks in patients with moderate to severe Alzheimer's disease: an analysis of area under the curve. *Neurology* 2014;**82**(10):P1.006.

Atri A, Tocco M, Hendrix S, Pejovic V, Graham SM. Cumulative benefits of extended-release memantine (28 mg, once daily) across clinical domains in patients with moderate to severe alzheimer's disease: an area under the curve analysis. *American Journal of Geriatric Psychiatry* 2014;**22**(3):S120-21. [DOI: 10.1016/j.jagp.2013.12.138]

Forest Laboratories Inc. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of memantine in patients with moderate-to-severe dementia of the Alzheimer's Type. http://www.forestclinicaltrials.com 2005.

Graham S, Hendrix S, Miller M, Pejovic V, Tocco M. Efficacy of high-dose, extended-release memantine (28 mg, once daily): post hoc responder analysis from a randomized trial in patients with moderate to severe Alzheimer's disease. *Alzheimer's & Dementia* 2011;**7**(4):S782. [DOI: 10.1016/j.jalz.2011.05.2245]

Graham S, Hendrix S, Miller M, Pejovic V, Tocco M. Response across multiple outcome measures in a randomized trial of extended-release memantine (28 mg once daily) in patients with moderate-to-severe Alzheimer's disease. *Alzheimer's Dementia* 2012;**8**(4):P591. [DOI: 10.1016/j.jalz.2012.05.1611]

Graham SM, Hendrix S, Miller ML, Pejovic V, Tocco M. Extended-release memantine (28 mg, once daily) provides behavioral benefits across a wide range of disease severity in patients with moderate to severe Alzheimer's disease: post hoc analysis from a randomized trial. *American Journal of Geriatric Psychiatry* 2013;**21**(3):S139. [DOI: 10.1016/j.jagp.2012.12.184]

Graham SM, Hendrix S, Miller ML, Pejovic V, Tocco M. Responder analysis in a trial of once-daily, extended-release memantine (28 mg) in patients with moderate to severe Alzheimer's disease. American Society of Consultant Pharmacists, ASCP Annual Meeting and Exhibition; 2011 11 16-18; Phoenix, AZ United States. 2011.

Graham SM, Hendrix S, Miller ML, Pejovic V, Tocco M. Response across multiple outcome measures in patients with moderate to severe Alzheimer's disease taking extended-release memantine (28 mg, once daily). *Annals of Neurology* 2012;**72**:S42.

Graham SM, Tocco M, Hsu H-A, Xie L, Perhach JL. The effect of extended-release memantine on behavioral domains in patients with moderate to severe Alzheimer's disease. American Psychiatric Association; 163rd Annual Meeting; New Research Abstracts; 2010 May 22-26; New Orleans (LA). 2010.

Grossberg G, Alva G, Hendrix S, Hofbauer R, Pejovic V, Graham S. Efficacy and tolerability of memantine extended release added to stable donepezil regimen in individuals with moderate to severe alzheimer's disease: subset analysis of a randomized clinical trial. *Neurology* 2015;**84**(14 Suppl):P7.101.

Grossberg G, Alva G, Hendrix S, Hofbauer R, Pejovic V, Graham SM. Efficacy and tolerability of memantine extended release added to stable donepezil regimen in individuals with moderate to severe Alzheimer's disease: subset analysis of a randomized clinical trial. *Alzheimer's & Dementia* 2014;**10**(4):P450. [DOI: 10.1016/j.jalz.2014.05.612]

Grossberg GT, Manes F, Allegri R, Gutierrez-Robledo LM, Gloger S, Xie L, et al. A multinational, randomized, double-blind, placebo-controlled, parallel-group trial of memantine extended-release capsule (28 mg, once daily) in patients with moderate to severe Alzheimers disease. *Alzheimer's & Dementia* 2008;**4**(4):T793. [DOI: 10.1016/j.jalz.2008.05.2476]

* Grossberg GT, Manes F, Allegri RF, Gutiérrez-Robledo LM, Gloger S, Xie L, et al. The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. *CNS Drugs* 2013;**27**(6):469-78. [DOI: 10.1007/s40263-013-0077-7]

Thibault CS-L, Stillman IO, Chen S, Getsios D, Proskorovsky I, Hernandez L, et al. Cost-effectiveness of memantine extended release for treatment of moderate-to-severe Alzheimer's disease in the United States. *Alzheimer's & Dementia* 2014;**Conference: Alzheimer's Association International Conference 2014 Copenhagen Denmark. Conference Start: 20140712 Conference End: 20140717. Conference Publication**:P596-7.

Tocco M, Hendrix S, Miller M, Pejovic V, Graham S. Behavioral effects of extended-release memantine (28 mg, once daily) across a wide range of disease severity in patients with moderate to severe alzheimer's disease: Post hoc analysis from a randomized trial. Neurology 2013; Vol. 80, issue Meeting Abstracts 1:P01.012.

Tocco M, Hendrix S, Miller M, Pejovic V, Graham S. Benefits of extended-release memantine in moderate-to-severe Alzheimer's Disease as a function of disease severity: post hoc analysis from a randomized trial. *Annals of Neurology* 2013;**Conference: 138th Annual Meeting of the American**

Neurological Association, ANA 2013 New Orleans, LA United States. Conference Start: 20131013 Conference End: 20131015. Conference Publication:S92-3.

Tocco M, Hendrix S, Miller M, Pejovic V, Graham S. Clinical benefits of extended-release memantine (28 mg, once daily) as a function of disease severity in people with moderate to severe Alzheimer's disease: Post hoc analysis from a randomized trial. *Alzheimer's & Dementia* 2013;**Conference: Alzheimer's Association International Conference 2013 Boston, MA United States. Conference Start: 20130713 Conference End: 20130718. Conference Publication**:P655.

Tocco M, Hendrix S, Miller M, Pejovic V, Graham S. Effects of once-daily, extended-release memantine (28 mg/day) on cognitive domains in patients with moderate to severe alzheimer's disease. *Annals of Neurology* 2011;**70 Suppl 15**:S54.

Tocco M, Hendrix S, Miller M, Pejovic V, Graham S. Sustained cognitive improvement with extended-release memantine (28 mg, once daily) in moderate to severe Alzheimer's disease. *Annals of Neurology* 2012;**Conference: 137th Annual Meeting of the American Neurological Association Boston, MA United States. Conference Start: 20121007 Conference End: 20121010. Conference Publication:**(var.pagings):S42.

Tocco M, Hendrix S, Miller M, Pejovic V, Graham S. Sustained cognitive improvement with extended-release memantine (28 mg, once daily) in moderate to severe alzheimer's disease. *Consultant Pharmacist* 2012;**Conference: American Society of Consultant Pharmacists Fall 2012 National Harbor, MD United States. Conference Start: 20121106 Conference End: 20121109. Conference Publication:**(var.pagings):717.

Herrmann 2012 (10158) *{published and unpublished data}*

* Herrmann N, Gauthier S, Boneva N, Lemming OM, 10158 Investigators. A randomized, double-blind, placebo-controlled trial of memantine in a behaviorally enriched sample of patients with moderate-to-severe Alzheimer's disease. *International Psychogeriatrics* 2013;**25**(6):1-9. [DOI: 10.1017/S1041610213000239]

NCT00857649. Efficacy and safety of Memantine in moderate to severe Alzheimer's disease. ClinicalTrials.gov NCT00857649 17 January 2012.

Hofbauer 2009 (MD-71) *{published and unpublished data}*

* Hofbauer RK, Saxton J, Woodward M, et al. Effects of memantine on functional communication in patients with moderate AD: results of 12-week placebo controlled trial. Alzheimers & Dementia. Data posted on Forest clinical trials register, 2009; Vol. 5(4 suppl 1):P256-7. [NCT00469456]

Holland 2013 *{published and unpublished data}*

Holland P, Tappen R, Fisher L, Curtis AL. Effect of memantine on the progression of driving impairment in mild Alzheimer's disease. *Alzheimer's & Dementia* 2013;**Conference: Alzheimer's Association International Conference 2013 Boston, MA United States. Conference Start: 20130713 Conference End: 20130718. Conference Publication**:P886-7.

* Holland PJ, Tappen RM, Fisher L, Curtis AL, Apter J. Effect of memantine on the progression of driving impairment in patients with mild Alzheimer's disease. *Journal of Nutrition, Health and Aging* 2013;**Conference: 6th Conference Clinical Trials on Alzheimer's Disease San Diego, CA United States. Conference Start: 20131114 Conference End: 20131116. Conference Publication:**(var.pagings):823-4.

NCT00476008. Delaying the progression of driving impairment in individuals with mild Alzheimer's disease [Delaying the progression of driving impairment in individuals with mild Alzheimer's disease]. https://clinicaltrials.gov/ct2/show/NCT00476008 2013.

Homma 2007 (IE2101) *{published and unpublished data}*

Report on the deliberation results. Evaluation and licensing division, pharmaceutical and food safety bureau, ministry of health, labour and welfare (2010). https://www.pmda.go.jp/files/000207435.pdf (accessed 16 January 2016) 60-5.

Forest Laboratories. Powerpoint presentation for FDA Advisory Committee 23 September 2004. Slide 28 http://www.fda.gov/ohrms/dockets/ac/03/slides/3979S1_01_F-Forest-Backup.ppt 2004.

* Homma A, Kitamura S, Yoshimura I. Efficacy of memantine in patients with moderately severe to severe Alzheimer's Disease in Japan - dose-finding study. Poster at European Federation of Neurological Societies, 11th Congress Brussles 25th - 28th August 2007. 2007.

Kitamura S, Homma A, Nakamura Y. Late phase II study of memantine hydrochloride, a new NMDA receptor antagonist, in patients with moderate to severe Alzheimer's disease. *Jpn J Geriatr Psychiat.2011* 2011;**22**(4):453-63.

Matsunaga S, Kishi T, Iwata N. Memantine monotherapy for Alzheimer's Disease: a systematic review and meta-analysis. *PLoS ONE* 2015;**10**(4):e0123289. doi:10.1371/journal.pone.0123289. [DOI: http://dx.doi.org/10.1016/j.jagp.2013.11.007]

Nakamura Y, Kitamura S, Homma A. Efficacy and safety of memantine in people with moderate-to-severe Alzheimer's disease: results of a pooled analysis of randomized, double-blind placebo-controlled trials in Japan. *Alzheimer's & Dementia* 2013;**Conference: Alzheimer's Association International Conference 2013 Boston, MA United States. Conference Start: 20130713 Conference End: 20130718. Conference Publication:**(var.pagings):P297.

Howard 2012 (DOMINO-AD) *{published and unpublished data}*

* Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, et al. Donepezil and memantine in moderate to severe Alzheimer's Disease. *New England Journal of Medicine* 2012;**366**:893-903. [ISRCTN49545035]

Jones R, Sheehan B, Phillips P, Juszczak E, Adams J, Baldwin A, et al. DOMINO-AD team. DOMINO-AD protocol: donepezil and memantine in moderate to severe Alzheimer's disease - a multicentre RCT. *Trials* 2009;**10**:57.

Knapp M, King D, Romeo R, Adams J, Baldwin A, Ballard C, et al. Cost-effectiveness of donepezil and memantine in moderate to

severe Alzheimer's disease (the DOMINO-AD trial). *International Journal of Geriatric Psychiatry* 2017;**32**(12):1205-16.

Leroi 2009 *{published data only (unpublished sought but not used)}*

Leroi I, Atkinson R, Overshott R. Memantine improves goal attainment and reduces caregiver burden in Parkinson's disease with dementia. *International Journal of Geriatric Psychiatry* 2014;**29**(9):899-905. [DOI: 10.1002/gps.4077]

* Leroi I, Overshott R, Byrne J, Daniel E, Burns A. Randomized controlled trial of memantine in dementia associated with Parkinson's disease. *Movement Disorders* 2009;**24**(8):1217-21.

Lorenzi 2011 (SC05-03) *{published data only}*

Lorenzi M, Beltramello A, Mercuri NB, et al. Effect of memantine on resting state default mode network activity in Alzheimer's disease. Drugs & aging Vol. 28, issue 3:205-17.

Lundbeck 2006 (10116) *{published and unpublished data}*

* Completed memantine efficacy study: moderate to severe Alzheimers dementia - China. http://www.lundbecktrials.com October 2006.

Li W, Zhao JH, Sun SG, Zhang JW, Suo AQ, Ma MM. [Clinical rehabilitative effect of memantine on cognitive and motor disorders in patients with Parkinson's disease]. *Zhonghua yi xue za zhi* 2011;**91**(5):301-3.

Phul R. Clinical Trial Report Summary. Kindly supplied on 17 January 2008.

Lundbeck 2006 (99817) *{unpublished data only}*

Lundbeck. Personal communication 21 June 2006.

Marsh 2009 PDD *{unpublished data only}*

Marsh L, Biglan K, Williams JR. Randomised, placebo-controlled trial of memantine for dementia in Parkinson's disease. Poster at World PD Congress, Miami, FLorida. 14 December 2009.

Medina 2011 *{published data only}*

Medina LD, Gilbert P, Pirogovsky EV, et al. Memantine in Huntington's disease: a randomized, double blind, placebo-controlled pilot study. Neurology Vol. 76, issue 9:A544.

Merz 2003 (MRZ-9104) *{unpublished data only}*

* Boehm G. FDA new drug application 21-487: safety review. http://www.fda.gov/ohrms/dockets/ac/03/briefing/3979B1_04_FDA-Safety%20Review.pdf August 2003:71.

Merz 2003 (MRZ-9105) *{unpublished data only}*

Boehm G. FDA new drug application 21-487: safety review. http://www.fda.gov/ohrms/dockets/ac/03/briefing/3979B1_04_FDA-Safety%20Review.pdf August 2003:71.

Merz 2003 (MRZ-9206) *{unpublished data only}*

Boehm G. FDA new drug application 21-487: safety review. http://www.fda.gov/ohrms/dockets/ac/03/briefing/3979B1_04_FDA-Safety%20Review.pdf August 2003:71.

Nakamura 2016 *{published data only}*

Kishi T, Matsunaga S, Oya K, Nomura I, Ikutaban T, Iwata N. Memantine for Alzheimer's Disease: an updated systematic review and meta-analysis. *Journal of Alzheimer's Disease* 2017;**60**:401-25.

* Nakamura Y, Kitamura S, Nagakubo T, Kobayashi M, Homma A. Study of memantine hydrochloride in combination with donepezil hydrochloride in patients with moderate to severe Alzheimer's disease - Efficacy and safety. *Japanese Journal of Geriatric Medicine* 2016;**54**:1147-58.

Orgogozo 2002 (9408) *{published and unpublished data}*

Orgogozo JM, Forette F. Efficacy of memantine in mild to moderate vascular dementia (The MMM300 Trial). 6th International Stockholm/ Springfield Symposium on Advances in Alzheimer Therapy; 2000 April 5-8, Stockholm. 2000.

* Orgogozo JM, Rigaud AS, Stöffler A, Möbius HJ, Forettte F. Efficacy and safety of memantine in patients with mild to moderate vascular dementia. A randomised, placebo-controlled trial (MMM300 Trial Group). *Stroke* 2002;**33**:1834-9.

Pantev 1993 *{published data only}*

Pantev M, Ritter R, Gortelmeyer R. Clinical and behavioural evaluation in long-term care patients with mild to moderate dementia under memantine treatment. *Zeitschrift fuer Gerontopsychologie und Psychiatrie* 1993;**6**(2):103-17.

Peskind 2004 (MD-10) *{published and unpublished data}*

Bakchine S, Pascual-Gangnant L, Loft H. Results of a randomised, placebo-controlled 6-month study of memantine in the treatment of mild to moderate Alzheimer's disease in Europe. Results of a randomised, placebo-controlled 6-month study of memantine in the treatment of mild to moderate Alzheimer's disease in Europe. 2005.

Cummings JL, Schneider E, Peskind E, Tariot P, Graham SM, Bell JM. Effect of memantine on behavioral outcomes in Alzheimer's disease. In: IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005. 2005.

Peskind ER, Potkin SG, Pomara N, McDonald S, Xie Y, Gergel I. Memantine monotherapy is effective and safe for the treatment of mild to moderate Alzheimer's disease: A randomized controlled trial. American Association for Geriatric Psychiatry 17th Annual Meeting, Baltimore MD, February 21-24. 2004.

* Peskind ER, Potkin SG, Pomara N, Ott BR, Graham SM, Olin JT, et al. Memantine treatment in mild to moderate Alzheimer Disease: A 24-week randomized, controlled trial. *American Journal of Geriatric Psychiatry* 2006;**14**:704-15.

Peskind ER, Potkin SG, Pomara N, Ott BR, McDonal S, Gergel I. Memantine monotherapy is effective and safe for the treatment of mild to moderate Alzheimer's disease: A randomized controlled trial. CINP Cogress, Paris. June 2-24. 2004.

Pomara N, Ott B, Peskind E, Resnick EM. Efficacy of memantine for cognition in mild to moderate Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005. 2005.

Pomara N, Ott BR, Peskind E, Resnick EM. Memantine treatment of cognitive symptoms in mild to moderate Alzheimer disease:

secondary analyses from a placebo-controlled randomized trial.. *Alzheimer Dis Assoc Disord* 2007;**21**:60-4.

Potkin SG, Peskind ER, Pomara N, McDonald S, Xie Y, Gergel I. Memantine monotherapy is effective and safe for the treatment of mild to moderate Alzheimer's disease: a randomized controlled trial. 56th Annual meeting of the American Academy of Neurology,San Francisco CA, April 24-May 1. 2004.

Peskind 2004 (MD-10) SG *{published and unpublished data}*

* Peskind ER, Potkin SG, Pomara N, Ott BR, Graham SM, Olin JT, et al. Memantine treatment in mild to moderate Alzheimer Disease: A 24-week randomized, controlled trial. *American Journal of Geriatric Psychiatry* 2006;**14**:704-15.

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. Poster at 10th International Conference on Alzheimer's disease and related disorders. Madrid 15th - 20th July 2006. 2006.

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. *Dementia and Geriatric Cognitive Disorders* 2007;**24**:20-7.

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. Poster at European Federation of Neurological Societies, 10th Congress Glasgow 2nd-5th September 2006. 2006.

Peters 2015 (MEGACOMBI2) *{published data only (unpublished sought but not used)}*

Peters O, Fuentes M, Joachim LK, Jessen F, Luckhaus C, Kornhuber J. Combined treatment with memantine and galantamine-CR compared with galantamine-CR only in antidementia drug naive patients with mild-to-moderate Alzheimer's disease. *Alzheimer's & Dementia: Translational Research & Clinical Interventions* 2015;**1**:198-204.

Porsteinsson 2008 (MD-12) *{published and unpublished data}*

Completed memantine efficacy study: mild to moderate Alzheimer's dementia. http://www.lundbecktrials.com 2005.

Doody RS, Tariot PN, Pfeiffer E, Olin JT, Graham SM, Bell JM. Meta-analysis of six month memantine clinical trials. New Clinical Drug Evaluation Unit 45 Annual Meeting. Boca Raton, Florida, June 6-9 2005 .. 2005.

* Porsteinsson AP, Grossberg GT, Mintzer J, Olin JT. Memantine treatment in patients with mild-to-moderate Alzheimer's disease already receiving a cholinesterase inhibitor: a randomized, controlled trial. *Current Alzheimer Research* 2008;**5**:83-9.

Porsteinsson 2008(MD-12)S *{published and unpublished data}*

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. Poster at European Federation of Neurological Societies, 10th Congress Glasgow 2nd-5th September 2006. 2006.

Winblad B, Jones RW, Wirth Y, Stöffler A, Möbius HJ. English Title: Memantine in moderate to severe Alzheimer's Disease: a meta-analysis of randomised clinical trials. Poster at 10th International Conference on Alzheimer's disease and related disorders. Madrid 15th - 20th July 2006. 2006.

* 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. *Dementia and Geriatric Cognitive Disorders* 2007;**24**:20-7.

Reisberg 2003 (9605) *{published and unpublished data}*

Doody R, Wirth Y, Schmitt F, Mobius HJ. Specific functional effects of memantine treatment in patients with moderate to severe Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders* 2004;**18**(2):227-32.

Doody R, Wirth Y, Schmitt F, Moebius HJ. Functional benefits of memantine treatment for patients with moderate to severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005. 2005.

Feldman H, Schmitt FA, Doraiswamy PM, Graham SM, Bell JM. Memantine and individual activities of daily living in moderate to severe Alzheimer's Disease. In: 57th Annual Meeting of the American Academy of Neurology, Miami Beach, April 2005. 2005.

Feldman H, Schmitt FA, PFeiffer E, Graham SM, Bell JM. Memantine and individual activities of daily living in moderate to severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005. 2005.

Ferris S. Clinical trial of memantine in severe Alzheimer disease: rationale and design. Proceedings of the 9th Congress of the International Psychogeriatric Association, Aug 15-20 1999, Vancouver. 1999.

Gauthier S, Wirth Y, Mobius HJ. Effects of memantine on behavioural symptoms in Alzheimer's Disease patients: an analysis of the neuropsychiatric inventory (npi) data of two randomised, controlled studies. *International Journal of Geriatric Psychiatry* 2005;**20**(5):459-64.

Gauthier S, Wirth Y, Moebius HJ. Positive behavioural effects of memantine treatment in patients with Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005. 2005.

Moebius HJ, Wirth Y, Gauthier S. Memantine: behavioral benefits for moderate to severe Alzheimer's patients. 57th Annual Meeting of the American Academy of Neurology, Miami Beach, April 2005. 2005:P02.095.

* Reisberg B, Doody R, Stöffler A, Schimitt F, Ferris S, Möbius HJ for the Memantine Study group. Memantine in moderate to severe Alzheimer´s Disease. *New England Journal of Medicine* 2003;**348**:1333-41.

Reisberg B, Ferris S. Experimental therapeutic shows promise for people with moderately severe to severe Alzheimer's disease. World Alzheimer Congress 2000. 2000.

Reisberg B, Ferris S, Sahin K, Windscheif U, Möbius HJ. Results of a placebo-controlled 6 month trial with memantine in

moderate to severe Alzheimer's disease. *Journal of the European College of Neuropsychopharmacology* 2000;**10**(suppl 3):S363-4.

Reisberg B, Möbius HJ, Stöffler A, Schmitt F, Doody R, Ferris S. Long treatment with the NMDA antagonist memantine results of a 24 week open label extension study in moderately severe to severe Alzheimer's disease. The 8th Conference on Alzheimer's disease and related disorders, July 20-25, 2002, Stockholm, Sweden. 2002.

Reisberg B, Stöffler A, Ferris SH, Schmitt F, Doody RS. A placebo controlled study of memantine in advanced Alzheimer's disease. Proceedings of the 15th Annual Meeting of the American Psychiatric Association; 2001 May 5-10, New Orleans. 2001.

Reisberg B, Windscheif U, Ferris SH, Hingorani VN, Stöffler A, Möbius HJ. Memantine in moderately severe to severe Alzheimer's disease: Results of a placebo-controlled 6 month trial. Conference proceedings Worl Alzheimer Congress; 9-13 July, 2000. Washington. 2000.

Reisberg B, Windscheif U, Ferris SH, Stöffler A, Möbius HJ and the Memantine Study Group. Treatment of advanced Alzheimer's disease with memantine, an NMDA antagonist: results of a 6 month multicenter randomized controlled trial. Proceedings of the 39th Annual Meeting of the American College of Neuropsychopharmacology; Dec 10-14, 2000. San Juan, Puerto Rico. 2000.

Wimo A, Winblad B, Stoeffler A, Wirth Y, Moebius HJ. Effect of long term treatment with memantine, an NMDA antagonist, on costs associated with advanced Alzheimer's disease: results of a 28-week randomized double-blind, placebo-controlled study. Proceedings of the 8th International Conference on Alzheimer's Disease and Related Disorders; 2002 July 20-25, Stockholm, Sweden. 2002:Abstract No 167.

Wimo A, Winblad B, Stoeffler A, Wirth Y, Moebius HJ. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics* 2003;**21**(5):327-40.

Schifitto 2007 *{published data only}*

* Schifitto G, Navia BA, Yiannoutsos CT, Marra CM, Chang L, Ernst T, et al. Memantine and HIV-associated cognitive impairment: a neuropsychological and proton magnetic resonance spectroscopy study. *AIDS* 12 Sep 2007;**21**(14):1877-86.

Zhao Y, Navia BA, Marra CM, Singer EJ, Chang L, Berger J, et al. Memantine for AIDS dementia complex: open-label report of ACTG 301. HIV clinical trials 2010; Vol. 11, issue 1:59-67.

Schmidt 2008 *{published and unpublished data}*

Schmidt R, Ropele S, Ebenbauer B, Windisch M, Stoeffler A, Fazekas F. Memantine effects on brain volume, glucose metabolism and cognition in AD patients - a randomized, double-blind, placebo-controlled neuroimaging pilot study. 11th Congress of European Federation of Neurological Societies. Brussels. 25th-28th August 2007. 2007.

* Schmidt R, Ropele S, Pendl B, Ofner P, Enzinger C, Schmidt H, et al. Longitudinal multimodal imaging in mild to moderate Alzheimer's disease: a pilot study with memantine. *Journal of Neurology, Neurosurgery Psychiatry* 2008;**79**(12):1312-7.

Tariot 2004 (MD-02) *{published and unpublished data}*

Cummings JL, Schneider E, Peskind E, Tariot P, Graham SM, Bell JM. Effect of memantine on behavioral outcomes in Alzheimer's disease. In: IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005. 2005.

Cummings JL, Schneider E, Tariot PN, Graham SM, Memantine MEM-MD-02 Study Group. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology* 2006;**67**:57-63.

Feldman H, Schmitt FA, Doraiswamy PM, Graham SM, Bell JM. Memantine and individual activities of daily living in moderate to severe Alzheimer's Disease. In: 57th Annual Meeting of the American Academy of Neurology, Miami Beach, April 2005. 2005.

Feldman H, Schmitt FA, PFeiffer E, Graham SM, Bell JM. Memantine and individual activities of daily living in moderate to severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005. 2005.

Feldman HH, Schmitt FA, Olin JT, Memantine MEM-MD-02 Study Group. Activities of daily living in moderate-to-severe Alzheimer disease: an analysis of the treatment effects of memantine in patients receiving stable donepezil treatment. *Alzheimer Dis Assoc Disord* 2006;**20**:263-8.

Finucane TE. Memantine for patients with Alzheimer Disease. *JAMA* 2004;**291**(14):1695.

Forest Laboratories I. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of memantine in patients with moderate to severe dementia of the Alzheimer's type. http://www.forestclinicaltrials.com/CTR/CTRController/CTRCompletedListStudies 2005.

Gauthier S, Wirth Y, Mobius HJ. Effects of memantine on behavioural symptoms in Alzheimer's Disease patients: an analysis of the neuropsychiatric inventory (npi) data of two randomised, controlled studies. *International Journal of Geriatric Psychiatry* 2005;**20**(5):459-64.

Schmitt FA, van Dyck CH, Wichems CH, Olin JT, for the Memantine MEM-MD-02 Study Group. Cognitive response to memantine in moderate to severe Alzheimer disease patients already receiving donepezil: an exploratory reanalysis. *Alzheimer Disease and Associated Disorders* 2006;**20**(4):255-62.

* Tariot P, Farlow M, Grossberg T, Graham S, McDonald S, Gergel I, for the memantine study group. Memantine treatment in patients with moderate to severe Alzheimer Disease already receiving donepezil. A randomized controlled trial. *JAMA* 2004;**291**:317-24.

Tariot PN. Memantine for patients with Alzheimer Disease: reply to Funicane. *JAMA* 2004;**291**(14):1695.

van Dyck CH, Schmitt FA, Olin JT, Memantine MEM-MD-02 Study Group. A responder analysis of memantine treatment

in patients with Alzheimer disease maintained on donepezil. *American Journal of Geriatric Psychiatry* 2006;**14**:428-37.

van Dyck 2007 (MD-01) *{published and unpublished data}*

FDA. Peripheral and Central Nervous System Drugs Advisory Committee September 24, 2003. Presentation by Forest, Slide 28.. http://www.fda.gov/ohrms/dockets/ac/03/slides/3979S1_01_F-Forest-Backup.ppt.

Forest Laboratories I. A randomized, double-blind, placebo-controlled evaluation of the safety and efficacy of memantine in patients with moderate to severe dementia of the Alzheimer's type. http://www.forestclinicaltrials.com/CTR/CTRController/CTRCompletedListStudies 2005.

Peterson L. American Neurological Association. November 2003. http://www.trends-in-medicine.com/Nov2003/AmNeuro113p.pdf.

* van Dyck CH, Tariot PN, Meyers B, Resnick EM, Memantine MEM-MD01 Study Group. A 24-week randomized, controlled trial of memantine in patients with moderate-to-severe Alzheimer Disease. *Alzheimer Disease and Associated Disorders* 2007;**21**(12):136-43.

Vercelletto 2011 *{published data only}*

Vercelletto M, Boutoleau-Bretonnièrea C, Volteaub C, Puelc M, Auriacombed S, Sarazine M, et al. English title not available. [Etude contrôlée, en double aveugle, en groupe parallèle,de l'efficacité et de la tolérance de la mémantine (20 mg)versus placebo chez des patients présentant une variante comportementale de démence frontotemporale]. *Revue Neurologique* 2010;**166**:S46-8.

* Vercelletto M, Boutoleau-Bretonnièrea C, Volteaub C, Puelc M, Auriacombed S, Sarazine M, et al. Memantine in behavioral variant frontotemporal dementia: negative results. *Journal of Alzheimer's Disease* 2011;**23**:749-59.

Vercelletto MM, Boutoleau-Bretonniere CJ, Volteau C, Puel M, Auriacombe S, Sarazin M, et al. Efficacy and tolerability of memantine (20 mg) in behavioral variant of frontotemporal dementia: double-blind, parallel group, placebo-controlled trial. *Neurology* 2009;**72**(11):A12.

Wang 2013 *{published and unpublished data}*

* Wang T, Huang Q, Reiman EM, Chen K, Tan C-C, Meng X-F, et al. 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. *Journal of Clinical Psychopharmacology* 2013;**33**(5):636-42. [DOI: 10.1097/JCP.0b013e31829a876a]

Xiao S, Wang T, Huang Q, Chen K, Reiman E. Change of biological marker and brain PET imaging and clinical effects of memantine for patients with moderate to severe Alzheimer's disease: A 24-week double-blind, randomized, placebo-controlled study. *Alzheimer's & Dementia* 2011;**7**(4):S298.

Xiao S, Wang T, Huang Q, Chen K, Reiman E. Changes of biological markers and brain pet imaging and clinical effects of memantine for patients with moderate to severe Alzheimer's disease: a 24 week double-blind, randomized, placebo-controlled study. *Journal of Nutrition, Health & Aging* 2012;**Conference: 5th Conference Clinical Trials on Alzheimer's Disease Monte Carlo Monaco. Conference Start: 20121029 Conference End: 20121031. Conference Publication:**(var.pagings):855.

Wilcock 2002 (9202) *{published and unpublished data}*

Orgogozo J, Forette F, Wilcock HG, Moebius HG, Stoeffler A. Memantine in vascular dementia. Journal of the Neurological Sciences. Papers from the 2nd Congress on Vascular Dementia, Salzburg, Austria, 24-27 January 2002. 2002; Vol. 203-4:318.

Wilcock G. Cognitive improvement by memantine in a placebo-controlled trial in mild to moderate vascular dementia (The MMM 500 trial). 6th International Stockholm/Sprinfield symposium on advances in Alzheimer Therapy. April 5-8, 2000. Stockholm. 2000.

Wilcock G. Efficacy of memantine has been verified by two double-blind studies [Wirkssamkeit von Memantine durch zwei Doppelblindstudien belegt]. *Neurologie und Rehabilitation* 2000;**6**(4):226-7.

* Wilcock G, Möbius HJ, Stöffler A on behalf of the MM 500 group. A double-blind, placebo-controlled multicentre study of memantine in mild to moderate vascular dementia. *International Clinical Psychopharmacology* 2002;**17**:297-305.

Wilcock G, Stöffler A, Sahin K, Möbius HJ. Neuroradiological findings and the magnitude of cognitive benefit by memantine treatment. A subgroup analysis of two placebo controlled clinical trials. Proceedings of the 13th European College of Neuropsychopharmacology. 2000a; Vol. 10, issue suppl 3:S360.

Wilkinson 2012 (10112) *{published and unpublished data}*

Anonymous. Clinical trial report summary 10112. http://www.lundbecktrials.com/ 28 May 2010.

Wilkinson D, Fox N, Barkhof F, Phul R, Scheltens P. Evaluating the effect of memantine on the rate of brain atrophy in patients with Alzheimer's disease: a multicentre imaging study using a patient enrichment strategy. 14th InternationalCongress of the International Psychogeriatric Conference,Montreal. 1-5th September 2009.

* 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. *Journal of Alzheimers Disease* 2012;**29**(2):459-9.

Winblad 1999 (9403) *{published and unpublished data}*

Doody R, Wirth Y, Schmitt F, Mobius HJ. Specific functional effects of memantine treatment in patients with moderate to severe Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders* 2004;**18**(2):227-32.

Doody R, Wirth Y, Schmitt F, Moebius HJ. Functional benefits of memantine treatment for patients with moderate to severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005. 2005.

* Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-BEST study (Benefit and Efficacy in Severely demented patients during Treatment with memantine). *International Journal of Geriatric Psychiatry* 1999;**14**(2):135-46.

Winblad B, Poritis N, Möbius HJ. Clinical improvement in a placebo-controlled trial with memantine in care-dependent patients with severe dementia (M-BEST). In: Iqbal K, Swaab DF, Wisniewski HM editor(s). Alzheimer's Disease and Related Disorders Etiology, Pathogenesis and Therapeutics. Chichester, New York, Weinheim, Brisbane, Singapore, Toronto: John Wiley and Sons, 1999:633-40.

Winblad 1999 (9403) AD *{published and unpublished data}*

European Medicines Evaluation Agency (EMEA). Scientific Discussion. http://www.emea.europa.eu/humandocs/PDFs/EPAR/axura/094802en6.pdf 2004:16.

* Winblad B, Graham SM, Lees GS, Mobiüs HJ, Ruby J, McDonald S. Efficacy and tolerability of memantine in nursing home patients with severe dementia of the Alzheimer's type. American Association for Geriatric Psychiatry 17th Annual Meeting, Baltimor. Feb 21-24, 2004. 2004.

Winblad B, Poritis N. Memantine in severe dementia: results of the 9M-BEST study (Benefit and Efficacy in Severely demented patients during Treatment with memantine). *International Journal of Geriatric Psychiatry* 1999;**14**(2):135-46.

References to studies excluded from this review

10114/Waldemar *{unpublished data only}*

Safety and tolerability of memantine after switch from other Alzheimer's treatment. Completed.. http://www.lundbecktrials.com.

Waldemar G, Korner A, Hyvarinen M, Wetterberg P, Lehto H, Krog Josiassen M. Tolerability of switching from Donepezil to Memantine treatment in patients with moderate to severe Alzheimer's disease. 7th International Conference on Alzheimer's and Parkinson's disease, Sorrento. 2005.

Abe 2011 *{published data only}*

Abe S, Sakai M, Fujii H, Koizumi K, Iwamoto T. Changes in cerebral blood flow following administration of memantine hydrochloride in Alzheimer's dementia (DAT) patients - comparative study of SPECT scan findings using SPM8. Alzheimer's & Dementia 2011; Vol. 7, issue 4 supplement:S378.

Alva 2015 *{published data only}*

Alva G, Ellison N, Hendrix S, Pejovic V, Otcheretko V. Adding memantine to stable cholinesterase inhibitor therapy in patients with moderate to severe Alzheimer's disease is associated with improvement in various neuropsychiatric symptoms: a pooled analysis. *Neurology* 2015;**84**(14 supplement):P7.106.

Ambrozi 1988 *{published data only}*

Ambrozi L, Danielczyk W. Treatment of impaired cerebral function in psychogeriatric patients with memantine. Results of a Phase II double-blind study. *Pharmacopsychiatry* 1988;**21**(3):144-6.

Amidfar 2017 *{published data only}*

Amidfar M, Khiabany M, Kohi A, Salardini E, Arbabi M, Roohi Azizi M, et al. Effect of memantine combination therapy on symptoms in patients with moderate-to-severe depressive disorder: randomized, double-blind, placebo-controlled study. *Journal of Clinical Pharmacy and Therapeutics* 2017;**42**(1):44-50.

Anon 2008 *{published data only}*

NCT00652457. Study of memantine to treat Huntington's disease or a pilot study of memantine for cognitive and behavioral dysfunction in Huntington's disease [A Pilot Study of Memantine for Cognitive and Behavioral Dysfunction in Huntington's Disease]. clinicaltrials.gov/ct2/show/NCT00652457 2008.

Anon 2009 *{published data only}*

NCT00933608. Effects of memantine on magnetic resonance (MR) spectroscopy in subjects at risk for Alzheimer's disease [Effects of memantine on the magnetic resonance spectroscopy (MRS) measures of neuronal integrity in subjects at risk for Alzheimer's disease]. clinicaltrials.gov/ct2/show/NCT00933608 2009.

Araki 2014 *{published data only}*

Araki T, Wake R, Miyaoka T, Kawakami K, Nagahama M, Furuya M, et al. The effects of combine treatment of memantine and donepezil on Alzheimer's disease patients and its relationship with cerebral blood flow in the prefrontal area. *International Journal of Geriatric Psychiatry* 2014;**29**(9):881-9. [DOI: 10.1002/gps.4074]

Atri 2008 *{published data only}*

Atri A, Shaughnessy LW, Locascio JJ, Growdon JH. Long-term course and effectiveness of combination therapy in Alzheimer disease. *Alzheimer Disease and Associated Disorders* July/September 2008;**22**(3):209-21.

Atri 2013 *{published data only}*

Atri A, Molinuevo JL, Lemming O, Wirth Y, Pulte I, Wilkinson D. Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for combination therapy. *Alzheimer's Research & Therapy* 2013;**5**(1):6. [DOI: 10.1186/alzrt160]

Atri 2014c *{published data only}*

Atri A, Hendrix S, Pejovic V, Hofbauer RK, Edwards J, Graham SM. Area under the curve (AUC) pooled analysis of four randomized clinical trials shows cumulative benefits of memantine-donepezil combination over component monotherapies across clinical domains in Alzheimer's dementia. *Alzheimer's & Dementia* 2014;**Conference: Alzheimer's Association International Conference 2014 Copenhagen Denmark. Conference Start: 20140712 Conference End: 20140717. Conference Publication**:P917.

Atri 2015 *{published data only}*

Atri A, Hendrix SB, Pejovic V, Hofbauer RK, Edwards J, Luis MJ, et al. Cumulative, additive benefits of memantine-donepezil combination over component monotherapies in moderate to severe Alzheimer's dementia: a pooled area under the curve

analysis. *Alzheimer's Research & Therapy* 2015;**7**(1):28. [DOI: 10.1186/s13195-015-0109-2]

Atri 2017 *{published data only}*

Atri A, Grossberg G, Hendrix S, Ellison N, Johnstone MR, Edwards J. Memantine added to background cholinesterase-inhibitors reduces agitation and neuropsychiatric symptoms in Alzheimer's disease. *Neurology* 2017;**88**(16 Suppl 1):P3.082.

Aupperle 2007 *{published data only}*

Aupperle PM, Tariot PN, Safirstein B, Graham SM, Lee G, Tocco M. Long-term safety and efficacy of memantine treatment in moderate to severe Alzheimer's Disease: results from a three-year trial. *European Journal of Neurology* 2007;**14**:54.

Ballard 2015 (MAIN-AD) *{unpublished data only}*

Ballard C, Thomas A, Gerry S, Yu LM, Aarsland D, Merritt C, et al. A double-blind randomized placebo-controlled withdrawal trial comparing memantine and antipsychotics for the long-term treatment of function and neuropsychiatric symptoms in people with Alzheimer's disease (MAIN-AD). *Journal of the American Medical Directors Association* 2015;**16**(4):316-22.

Beauchet 2011 *{published data only}*

Beauchet O, Allali G, Launay C, Fantino B, Annweiler C. Does memantine improve the gait of individuals with Alzheimer's disease? [Erratum appears in J Am Geriatr Soc. 2012 Oct;60(10):2001]. *Journal of the American Geriatrics Society* 2011;**59**(11):2181-2.

Bernal-Pacheco 2010 *{published data only}*

Bernal-Pacheco O, Rodriguez RL, Haq IU, Wu SS, Okun MS, Malaty IA, et al. Memantine improves ''off periods'' in patients with advanced Parkinson's disease. *Movement Disorders* 2010;**25 Suppl 2**:S290.

Berthier 2009 *{published data only}*

Berthier ML Green C, Lara JP, Higueras C, Barbancho MA, Dávila G, et al. Memantine and constraint-induced aphasia therapy in chronic poststroke aphasia. *Annals of Neurology* 2009;**65**(5):577-85.

Boxer 2009 *{published data only}*

Boxer AL, Lipton AM, Womack K, Merrilees J, Neuhaus J, Pavlic D, et al. An open-label study of memantine treatment in 3 subtypes of frontotemporal lobar degeneration. *Alzheimer Disease and Associated Disorders* July/September 2009;**23**(3):211-7.

Burke 2012 *{published data only}*

Burke D. ACP Journal Club. Donepezil or memantine improved cognitive functioning in moderate-to-severe Alzheimer disease. Annals of Internal Medicine 2012; Vol. 156, issue 12:JC6-10.

Calabrese 2007 *{published data only}*

Calabrese P, Essner U, Forstl H. Memantine (EBIXA) in clinical practice - results of an observational study. *Dementia & Geriatric Cognitive Disorders* 2007;**24**(2):111-7.

Cerullo 2007 *{published data only}*

Cerullo MA, Adler CM, Strakowski SM, Eliassen JC, Nasrallah HA, Nasrallah AT. Memantine normalizes brain activity in the inferior frontal gyrus: a controlled pilot fMRI study. Schizophrenia Research 2007; Vol. 97, issue 1-3:294-6.

Chen 2017 *{published data only}*

Chen R, Chan PT, Chu H, Lin YC, Chang PC, Chen CY, et al. Treatment effects between monotherapy of donepezil versus combination with memantine for Alzheimer disease: a metaanalysis. *PLOS One* 2017;**12**(8):e0183586. doi: 10.1371/journal.pone.0183586. eCollection 2017.

Cheon 2008 *{published data only}*

Cheon YH, Hong EJ, Choi JH, Park JW, Lee HJ, Kim DJ. The improvement of deteriorated behavior and quality of lfe in alcohol related dementia after 12 weeks of open-label memantine clinical trial.. *Alcoholism-Clinical and Experimental Research* 2008;**32**(6):181A.

Cretu 2008 *{published data only}*

Cretu O. Szalontay AS. Chirita R. Chirita V. Effect of memantine treatment on patients with moderate-to-severe Alzheimer's disease treated with donepezil [Romanian]. *Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi* July/September 2008;**112**(3):641-5.

Cumbo 2014 *{published data only}*

Cumbo E, Ligori LD. Differential effects of current specific treatments on behavioral and psychological symptoms in patients with Alzheimer's disease: A 12-month, randomized, open-label trial. *Journal of Alzheimer's Disease* 2014;**39**(3):477-85. [DOI: http://dx.doi.org/10.3233/JAD-131190]

Cummings 2012 *{published data only}*

Cummings J, Hendrix S, Miller M, Pejovic V, Graham S, Tocco M. Extended-release memantine (28 mg, once daily) and sustained behavioral improvement: post hoc responder analysis from a randomized trial in patients with moderate to severe Alzheimer's disease. *Neurology* 2012;**78**(1 Suppl):P04.197.

Defer 2013 *{published data only}*

Defer G, Creveuil C, Derache N. Long term treatment with memantine failed to improve cognitive function in relapsing remitting multiple sclerosis: A placebo-controlled, double-blinded, randomized study. *Multiple Sclerosis (Houndmills, Basingstoke, England)* 2013;**Conference: 29th Congress of the European Committee for Treatment and Research in Multiple Sclerosis, ECTRIMS, 18th Annual Conference of Rehabilitation in MS, RIMS Copenhagen Denmark. Conference Start: 20131002 Conference End: 20131005. Conference Publica**(var.pagings):279.

Diehl-Schmid 2008 *{published data only}*

Diehl-Schmid J, Forstl H, Perneczky R, Pohl C, Kurz A. A 6-month, open-label study of memantine in patients with frontotemporal dementia. *International Journal of Geriatric Psychiatry* 2008;**23**(7):754-9.

Doody 2012 *{published data only}*

Doody RS, Geldmacher DS, Farlow MR, Sun Y, Moline M, Mackell J. Efficacy and safety of donepezil 23 mg versus donepezil 10 mg for moderate-to-severe Alzheimer's disease: a subgroup analysis in patients already taking or not taking concomitant memantine. Dementia and Geriatric Cognitive Disorders 2012; Vol. 33, issue 2:164–73.

Emaldeldin 2017 *{published data only}*

Emaldeldin D, Ramadan A, Fala SY, Sadik M, Sadik F, Bahbah EI, et al. Disease modifying efficacy of memantine in Alzheimer's disease; a pooled analysis of 13 randomized controlled trials. *Journal of the neurological sciences 2017 Conference: 23rd World Congress of Neurology, WCN 2017. Japan.* 2017;**381**(Supplement 1):767.

Evans 2014 *{published data only}*

Evans DA, Morris MC, Rajan KB. Vitamin E, memantine, and Alzheimer disease. *JAMA* 2014;**311**(1):29-30.

Feldman 2006 *{published data only}*

Feldman HH, Schmitt FA, Olin JT. Activities of daily living in moderate-to-severe Alzheimer disease: an analysis of the treatment effects of memantine in patients receiving stable donepezil treatment. Alzheimer Disease and Associated Disorders 2006; Vol. 20, issue 4:263-8.

Ferris 2007 *{published data only}*

* Ferris S, Schneider L, Farmer M, Kay G, Crook T. A double-blind, placebo-controlled trial of memantine in age-associated memory impairment (memantine in AAMI). *International Journal of Geriatric Psychiatry* 2007;**22**(5):448-55.

Kavirajan H, Schneider LS. Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials. *Lancet Neurol* 2007;**6**(9):782-92.

Ferris 2010 *{published data only}*

Ferris S, Ihl R, Robert P, Winblad B, Gauthier S, Tennigkeit F. Memantine treatment benefits the language function in patients with moderate to severe Alzheimer's disease. *European Journal of Neurology* 2010;**17 Suppl 3**:357.

Fleischhacker 1986 *{published data only}*

Fleischhacker WW, Buchgeher A, Schubert H. Memantine in the treatment of senile dementia of the Alzheimer type. *Progress Neuro-Psychopharmacology and Biological Psychiatry* 1986;**10**:87-93.

Gauthie 2010 *{published data only}*

Gauthie S. Benefits of combination treatment in Alzheimer's disease. *European Journal of Neurology* 2010;**17 Suppl 3**:354.

Gavrilova 1995 *{published data only}*

Gavrilova S, Selezneva N, Kolykhalov I, Mikhailova N, Kalyn Y, Roschina I. Glutaminergic approach to the treatment of Alzheimer type dementia. Xth World Congress of Psychiatry. Vol 2; 1996 Aug 23-28, Madrid. 1996.

Gavrilova S, Seleznyova N, Kolykhalov I. [Heterogeneity of anti-dementia drug response in Alzheimer type dementia]. Proceedings of the 8th European College of Neuropharmacology Congress (ECNP); 1995 Sep 30- 0ct 4, Venice. 1995.

Glodzik 2008 *{published data only}*

Glodzik L, King KG, Gonen O, Liu S, De Santi S, de Leon MJ. Memantine decreases hippocampal glutamate levels: a magnetic resonance spectroscopy study. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* May 2008;**32**(4):1005-12.

Graham 2009 *{published data only}*

Graham S, Saxton J, Woodward M, Gilchrist N, Potocnik F, Hofbauer RK, et al. Effects of memantine on functional communication in moderate Alzheimer's Disease: results of a 12-week placebo-controlled trial. *European Neuropsychopharmacology* 2009;**19**:S624.

Graham 2010a *{published data only}*

Graham S Tocco M, Hendrix S, Hofbauer RK, Perhach JL. Functional communication in patients with moderate Alzheimer's disease treated with memantine. *European Neuropsychopharmacology* 2010;**20**(Suppl 3):S557-8.

Graham 2010b *{published data only}*

Graham S, Tocco M, Hendrix S, Hofbauer RK, Miller ML, Perhach JL. Memantine prevents worsening across multiple domains in a trial of patients with moderate Alzheimer's disease. *European Neuropsychopharmacology* 2010;**20 Suppl 3**:S557.

Graham 2010c *{published data only}*

Hofbauer RK, Hendirx S, Tocco M, Graham S, Perhach JL. Memantine and prevention of worsening in functional communication: Post hoc analysis of a randomized, placebo controlled trial in patients with moderate Alzheimer's disease. *Alzheimer's & Dementia: Journal of the Alzheimer's Association* 2010;**6**(4):S312.

Graham 2013 *{published data only}*

Graham S, Hendrix S, Miller M, Pejovic V, Tocco M. Efficacy of memantine in people with moderate to severe Alzheimer's disease with and without background donepezil therapy: Pooled analysis of four randomized trials. *Alzheimer's & Dementia* 2013;**Conference: Alzheimer's Association International Conference 2013 Boston, MA United States. Conference Start: 20130713 Conference End: 20130718. Conference Publication:**(var.pagings):P656.

Graham 2013a *{published data only}*

Graham SM, Hendrix S, Miller ML, Pejovio V, Tocco M. Efficacy of memantine with and without donepezil in moderate-to-severe Alzheimer's disease: pooled analysis of four randomized trials. *Annals of Neurology* 2013s;**Conference: 138th Annual Meeting of the American Neurological Association, ANA 2013 New Orleans, LA United States. Conference Start: 20131013 Conference End: 20131015. Conference Publication:**:S88.

Graham 2014 *{published data only}*

Graham SM, Hendrix S, Pejovic V, Hofbauer RK, Otcheretko VB. Benefits of early versus delayed memantine addition to donepezil monotherapy in patients with moderate to severe Alzheimer's disease: A pooled analysis of two randomized trials. *Alzheimer's & Dementia* 2014;**Conference: Alzheimer's Association International Conference 2014 Copenhagen Denmark. Conference Start: 20140712 Conference End: 20140717. Conference Publication:**(var.pagings):P919.

Grossberg 2010 *{published data only}*

Grossberg GT, Manes F, Allegri R, Robledo LMG. Benefits of once-daily, extended-release memantine on caregiver distress in patients with moderate to severe Alzheimer's disease. *Annals of Neurology* 2010;**68**(Suppl 14):S47-8.

Grossberg 2010a *{published data only}*

Grossberg GT, Manes F, Allegri R, Robledo LMG. Benefits of extended-release memantine (28 mg, once daily) on caregiver distress: results of a multinational, double-blind, placebo-controlled trial in moderate to severe Alzheimer's disease. American Journal of Geriatric Psychiatry 2010; Vol. 18, issue 3 Suppl 1:S73-4.

Han 2012 *{published data only}*

Han HJ, C Kim CB, Lee J-Y, Ryu S-H, Hae RN, Soo JY, et al. Response to rivastigmine transdermal patch or memantine plus rivastigmine patch is affected by apolipoprotein E genotype in Alzheimer patients. Dementia and Geriatric Cognitive Disorders 2012; Vol. 34, issue 3-4:167-73.

Hellweg 2011 *{published data only}*

Hellweg R, Wirth Y, Janetzky W, Hartmann S. Efficacy of memantine in delaying clinical worsening: responder analyses in patients with moderate to severe Alzheimer's disease. Alzheimer's & Dementia: Journal of the Alzheimer's Association 2011; Vol. 7, issue 4:S782.

Hellweg 2012 *{published data only}*

Hellweg R, Wirth Y, Janetzky W, Hartmann S. Efficacy of memantine in delaying clinical worsening in Alzheimer's disease (AD): responder analyses of nine clinical trials with patients with moderate to severe AD. International Journal of Geriatric Psychiatry 2012; Vol. 27:651-6.

Hendrix 2015 *{published data only}*

Hendrix S, Ellison N, Pejovic V, Otcheretko V. Effects of add-on memantine on daily functioning in patients with moderate to severe Alzheimer's disease receiving stable donepezil treatment. *Neuro-degenerative Diseases* 2015;**Conference: 12th International Conference Alzheimer's and Parkinson's Diseases, AD/PD 2015 Nice France. Conference Start: 20150318 Conference End: 20150322. Conference Publication:**(var.pagings):839.

Hu 2006 *{unpublished data only}*

Hu HT, Zhang ZX, Yao JL, Yu HZ, Wang YH, Tang HC, et al. Clinical efficacy and safety of akatinol memantine in treatment of mild to moderate Alzheimer disease: a donepezil-controlled, randomized trial. *Zhonghua Nei Ke Za Zhi* 2006;**45**:277-80.

IE 2201/Daiichi *{unpublished data only}*

Forest Laboratories. Powerpoint presentation for FDA Advisory Committee 23 September 2004. Slide 28 http://www.fda.gov/ohrms/dockets/ac/03/slides/3979S1_01_F-Forest-Backup.ppt 2004.

Jiang 2015 *{published data only}*

Jiang J, Jiang H. Efficacy and adverse effects of memantine treatment for Alzheimer's disease from randomized controlled trials. *Neurological Sciences* 2015;**36**(9):1633-41. [DOI: 10.1007/s10072-015-2221-2]

Johnson 2010 *{published data only}*

Johnson NA, Rademaker A, Weintraub S, Gitelman D, Wienecke C, Mesulam M. Pilot trial of memantine in primary progressive aphasia. Alzheimer Disease and Associated Disorders 2010; Vol. 24, issue 3:308.

Jones 2005 *{published data only}*

Jones R, Bayer A, Inglis F, Phul R. Once-daily dosing of memantine found to be as safe and tolerable as twice-daily dosing in a 12-week, double-blind study in moderate to severe Alzheimer's disease. IPA 12th International Congress, Stockholm, Sweden, 20-24 September 2005. 2005; Vol. 17, issue Suppl 2:223.

Jones 2007 *{published data only}*

Jones RW, Bayer A, Inglis F, Barker A, Phul R. Safety and tolerability of once-daily versus twice-daily memantine: a randomised, double-blind study in moderate to severe Alzheimer's disease. *International Journal of Geriatric Psychiatry* March 2007;**22**(3):258-62.

Jones 2011 *{published data only}*

Jones R, O Lemming, JL Molinuevo. Effect of memantine on key domains in patients with moderate to severe Alzheimer's disease receiving stable doses of donepezil: a pooled analysis. *European Journal of Neurology* 2011;**18**(Suppl 2):78.

JPRN UMIN000011392 2013 *{published data only}*

JPRN-UMIN000011392. Investigation on efficacy of memantine in patients with Alzheimer's disease [Investigation on efficacy of memantine in patients with Alzheimer's disease]. https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr.cgi?function=brows&action=brows&type=summary&language=E&recptno=R000 2013.

Kano 2013 *{published data only}*

Kano O, Ito H, Takazawa T, Kawase Y, Murata K, Iwamoto K, et al. Clinically meaningful treatmentresponses after switching to galantamine and with addition of memantine in patients with Alzheimer's disease receiving donepezil. *Neuropsychiatric Disease and Treatment* 2013;**9**:ArtID 259±265.2013;9. https://doi.org/10.2147/NDT.S40682 PMID: 23431041.

Kolykhalov 2012 *{published data only}*

Kolykhalov IV, Gavrilova SI, Kalyn IaB, Selezneva ND, Fedorova IaB. [Efficacy, safety and tolerability of a single dose of akatinol memantine in comparison to two-doses in patients with moderately expressed and moderately severe dementia in

Alzheimer's disease]. [Russian]. Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova 2012; Vol. 112, issue 1:35-9.

Kurz 2014 *{published data only}*

Kurz A, Grimmer T. Efficacy of memantine hydrochloride once-daily in Alzheimer's disease. *Expert Opinion on Pharmacotherapy* 2014;**15**(13):1955-60. [DOI: 10.1517/14656566.2014.945907]

Ladea 2010 *{published data only}*

Ladea M, Sinca M, Bran CM. The benefits of memantine treatment on behavioral and psychotic symptoms in mild to moderate Alzheimer's disease. International Journal of Neuropsychopharmacology 2010; Vol. 13, issue Supplement S1:138.

Levin 2008 108(12) *{published data only}*

Levin OS, Batukaeva LA. Efficacy of memantine in Parkinson's disease with dementia. *Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova* 2008;**108**(12):16-23.

Levin 2008 108(5) *{published data only}*

Levin OS, Batukaeva LA, Smolentseva IG, Amosova NA. Efficacy and safety of memantine in dementia with Lewy bodies. *Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova* 2008;**108**(5):39-46.

Li 2011 *{published data only}*

Li G-J, Xiao S-F, Li X, Yang Q-M, Feng L-Y, Xu X-F, et al. Memantine oral solution in treatment of moderate to severe Alzheimer's disease: a multicenter, randomized, double-blind, parallel-group controlled study. Chinese Journal of New Drugs and Clinical Remedies 2011; Vol. 30:184-8.

Litvinenko 2008 *{published data only}*

Litvinenko IV, Odinak MM, Mogil'naia VI, Perstenev SV. [Memantine (akatinol) therapy of cognitive impairment in Parkinson's disease complicated by dementia] [Russian]. *Zhurnal Nevrologii i Psikhiatrii imeni S.S. Korsakova* 2008;**108**(10):37-42.

Litvinenko 2010 *{published data only}*

Litvinenko IV, Odinak MM, Mogil'naya VI, Perstnev SV. Use of memantine (akatinol) for the correction of cognitive impairments in Parkinson's disease complicated by dementia. Neuroscience and Behavioral Physiology 2010; Vol. 40, issue 2:149-55.

Lovera 2010 *{published data only}*

Lovera JF, Frohman E, Brown T. Randomized double-blind placebo-controlled trial of memantine 10mg twice a day for three months as a treatment for cognitive impairment in multiple sclerosis. Neurology 2009; Vol. 72, issue 11 Suppl 3:A112.

* Lovera JF, Frohman E, Brown TR, Bandari D, Nguyen L, Yadav V, et al. Memantine for cognitive impairment in multiple sclerosis: a randomized placebo-controlled trial. Multiple Sclerosis 2010; Vol. 16, issue 6:715-23.

NCT00300716. Trial of memantine for cognitive impairment in multiple sclerosis [Double blind placebo controlled pilot trial of memantine for cognitive impairment in multiple sclerosis]. https://clinicaltrials.gov/ct2/show/NCT00300716 2004.

MD-51 *{published data only}*

Forest Laboratories Inc. An open-label evaluation of the safety of memantine in patients with moderate-to-severe dementia of the Alzheimer's type. http://www.forestclinicaltrials.com 2005.

MEADOWS/Lana /Downs/2006 *{unpublished data only}*

Hanney M, Prasher V, Williams N, Jones EL, Aarsland D, Corbett A, et al. Memantine for dementia in adults older than 40 years with Down's syndrome (MEADOWS): a randomised, double-blind, placebo-controlled trial. Lancet 2012; Vol. 379:528-36.

Mecocci 2009 *{published data only}*

Mecocci P, Bladstrom K, Stender A. Effects of memantine on cognition in patients with moderate to severe Alzheimer's disease: post-hoc analyses of ADAS-cog and SIB total and single-item scores from six randomized, double-blind, placebo-controlled studies. International Journal of Geriatric Psychiatry 2009; Vol. 24:532-8.

Modrego/MRS *{published and unpublished data}*

Modrego PJ, Fayed N, Errea JM, Rios C, Pina MA, Sarasa M. Memantine versus donepezil in mild to moderate Alzheimer's disease: a randomized trial with magnetic resonance spectroscopy. *European Journal of Neurology* March 2010;**17**(3):405-12.

Molinuevo 2011 *{published data only}*

Molinuevo JL, Lemming O. Effects of memantine in patients with moderate Alzheimer's disease receiving stable doses of donepezil. *Alzheimer's and Dementia* 2012;**8**(4 Suppl 1):P601.

* Molinuevo JL, O Lemming, D Wilkinson. Effect of memantine in reducing the worsening of clinical symptoms in patients with moderate to severe Alzheimer's disease receiving stable doses of donepezil. *European Journal of Neurology* 2011;**18**(Suppl 2):79.

Moreau 2013 *{published data only}*

Moreau C, Delval A, Tiffreau V, Defebvre L, Dujardin K, Duhamel A, et al. Memantine for axial signs in Parkinson's disease: A randomised, double-blind, placebo-controlled pilot study. *Journal of Neurology, Neurosurgery & Psychiatry* 2013;**84**(5):552-5.

Nakamura 2014 *{published data only}*

Nakamura Y, Kitamura S, Homma A, Shiosakai K, Matsui D. Efficacy and safety of memantine in patients with moderate-to-severe Alzheimer's disease: results of a pooled analysis of two randomized, double-blind, placebo-controlled trials in Japan. *Expert Opinion on Pharmacotherapy* 2014;**15**(7):913-25. [DOI: 10.1517/14656566.2014.902446]

NCT01921972 2004 *{published data only}*

NCT01921972. Competence network - dementia (BMBF) "Pharmacological and psychosocial treatment" (Modul E.2) Part II: The efficacy of a combination regimen in patients with mild

to moderate probable Alzheimer's disease. clinicaltrials.gov/show/NCT01921972 2004.

NCT02080364 2015 *{published data only}*

NCT02080364. Randomized, double-blind, placebo controlled, multi-center registration trial to evaluate the efficacy and safety of Azeliragon (TTP488) in patients with mild Alzheimer's Disease receiving acetylcholinesterase inhibitors and/or memantine. clinicaltrials.gov/show/NCT02080364 2015.

Ondo 2007 *{published data only}*

Ondo WG, Mejia NI, Hunter CB. A pilot study of the clinical efficacy and safety of memantine for Huntington's disease. *Parkinsonism & Related Disorders* 2007;**13**(7):453-4.

Ondo 2011 *{published data only}*

Ondo WG, Shinawi L, Davidson A, Lai D. Memantine for non-motor features of Parkinson's disease: a double-blind placebo controlled exploratory pilot trial. Parkinsonism & Related Disorders 2011; Vol. 17, issue 3:156-9.

Peng 2015 *{published data only}*

Peng L, Chen F, Jiang X. The clinical research of the combination use of memantine and donepezil in the treatment of moderate to severe Alzheimer's disease. *Chinese Journal of Geriatric Care* 2015;**13**(2):75–7.

Peters 2012 *{published data only}*

Peters O, Lorenz D, Fesche A, Schmidtke K, Hull M, Perneczky R, et al. A combination of galantamine and memantine modifies cognitive function in subjects with amnestic MCI. Journal of Nutrition, Health & Aging 2012; Vol. 16, issue 6:544-8.

Peyro-Saint-Paul 2016 *{published data only}*

Peyro SP, Creveuil C, Heinzlef O, De Seze J, Vermersch P, Castelnovo G, et al. Efficacy and safety profile of memantine in patients with cognitive impairment in multiple sclerosis: a randomized, placebo-controlled study. *Journal of the Neurological Sciences* 2016;**363**:69-76.

Reisberg 2005 *{unpublished data only}*

Riepe 2005 *{published data only}*

Riepe MW, Adler G, Ibach B, Weinkauf B, Tracik F. Adding memantine to therapy with rivastigmine in patients with mild to moderate Alzheimer's Disease: results of a 12-week pilot study. 57th Annual Meeting of the American Academy of neurology, Miami Beach, April 2005. 2005, issue P06.081.

Rodriguez 2010 *{published data only}*

Rodriguez RL, Haq IU, Wu S. Memantine for the treatment of levodopa induced dyskinesias in demented and non-demented patients with Parkinson's disease. Movement Disorders. Conference: 14th International Congress of Parkinson's Disease and Movement Disorders Buenos Aires Argentina. Conference Start: 20100613 Conference End: 20100617. Conference Publication: (var.pagings).

Rustembegović 2003 *{published data only}*

Rustembegović A, Kundurović Z, Sapcanin A, Sofic E. A placebo-controlled study of memantine (Ebixa) in dementia of Wernicke-Korsakoff syndrome. *Medicinski arhiv* 2003;**57**(3):149-50.

Rustembegovic 2009 *{published data only}*

Rustembegovic A, Sofic E, Sapcanin A. A placebo-controlled study of memantine in dementia of Wernicke-Korsakoff syndrome, Alzheimer's disease and in vascular dementia. *Journal of the Neurological Sciences* 2009;**283**(1-2):283.

Saxton 2009 *{published data only}*

Saxton J, Hofbauer RK, Graham S, Yu SY, Li S, Hsu HA, et al. Memantine treatment in patients with Alzheimer's Disease: neuropsychological results from an open-label, multi-center brain imaging trial. *Neurology* 2009;**72**(11):A382-3.

Scharre 2005 *{published data only}*

Scharre DW, Warner JL, Knick JA, Davis RA, Theado-Miller N. Memantine in frontotemporal dementia. 57th Annual Meeting of the American Academy of Neurology, Miami Beach, April 2005. 2005, issue P02.078.

Schmidt 2015 *{published data only}*

Schmidt R, Hofer E, Bouwman FH, Buerger K, Cordonnier C, Fladby T, et al. EFNS-ENS/EAN Guideline on concomitant use of cholinesterase inhibitors and memantine in moderate to severe Alzheimer's disease. *European Journal of Neurology* 2015;**22**(6):889-98. [DOI: 10.1111/ene.12707]

Smart 2011 *{published data only}*

Smart KA, Herrmann N, Lanctôt KL. Validity and responsiveness to change of clinically derived MDS scales in Alzheimer disease outcomes research. Journal of Geriatric Psychiatry and Neurology 2011; Vol. 24, issue 2:67-72.

Sultzer 2010 *{published data only}*

Sultzer DL, Melrose RJ, Harwood DG, Campa O, Mandelkern MA. Effect of memantine treatment on regional cortical metabolism in Alzheimer's disease. American Journal of Geriatric Psychiatry 2010; Vol. 18, issue 7:606-14.

Tabaton 2010 *{published data only}*

Tabaton M, Perry G, Zhu X, Lee H-G, Casadesus G, Smith MA. Memantine "hypothesis testing" not "disease modifying" in Alzheimer's disease. American Journal of Pathology 2010; Vol. 176:540-1.

Tocco 2010 *{published data only}*

Tocco M, Graham SM, Hsu H-A, Xie L, Perhach JL. Effect of extended-release memantine on behavioral domains in patients with moderate to severe Alzheimer's disease. Alzheimer's & Dementia 2010; Vol. 68:S49.

Tocco 2010a *{published data only}*

Tocco M, Graham SM. Effects of memantine on language and functional communication in patients with moderate to severe Alzheimer's disease. Alzheimer's & Dementia 2010; Vol. 20:S559.

Tocco 2010b *{published data only}*

Tocco M, Graham SM. Effects of memantine treatment on language abilities and functional communication in patients with moderate to severe Alzheimer's disease: a review of data. *European Journal of Neurology* 2010;**17 Suppl 3**:357.

Tocco 2011 *{published data only}*

Tocco M, Hendrix S, Miller ML, Pejovic V, Graham SM. Efficacy of memantine by baseline disease severity: post-hoc analysis of pooled trials in patients with mild to moderate Alzheimer's disease. Journal of the American Medical Directors Association 2011; Vol. 12, issue 3:B10.

Tocco 2011a *{published data only}*

Tocco M, Hendrix S, Miller ML, Pejovic V, Graham SM. Efficacy of memantine in moderate to severe Alzheimer's disease: time-to-event analysis in a pooled population. *Neurodegenerative Diseases* 2011;**8 Suppl 1**:A621.

Tocco 2011b *{published data only}*

Tocco M, Hendrix S, Miller LM, Pejovic V, Graham SM. Efficacy of memantine by baseline disease severity: a pooled post-hoc analysis of trials in mild to moderate Alzheimer's disease. Journal of Post-acute and Long-term Care Medicine 2011; Vol. 12, issue 3:B10.

Tocco 2012 *{published data only}*

* Tocco M, Hendrix S, Miller M, Pejovic V, Graham S. Effects of extended-release memantine (28 mg, once daily) on language and communication abilities in a randomized trial of patients with moderate-to-severe Alzheimer's disease. *Consultant Pharmacist* 2012;**27**(10):718.

Tocco M, Hendrix S, Miller ML, Pejovic V, Graham SM. Extended-release memantine (28 mg, once daily) and sustained cognitive improvement: post hoc responder analysis from a randomized trial in patients with moderate to severe Alzheimer's disease. *Journal of the American Geriatrics Society* 2012;**60**(Suppl 4):S197.

Villoslada 2009 *{published data only}*

Villoslada P, Arrondo G, Sepulcre J, Alegre M, Artieda J. Memantine induces reversible neurologic impairment in patients with MS. *Neurology* 2009;**72**(19):1630-3.

Waldemar 2008 *{published data only}*

Waldemar G, Hyvarinen M, Josiassen MK, Korner A, Lehto H, Wetterberg P. Tolerability of switching from donepezil to memantine treatment in patients with moderate to severe Alzheimer's disease. *International Journal of Geriatric Psychiatry* 2008;**23**(9):979-81.

Wang 2015 *{published data only}*

Wang H-F, Yu J-T, Tang S-W, Jiang T, Tan C-C, Meng X-F, et al. Efficacy and safety of cholinesterase inhibitors and memantine in cognitive impairment in Parkinson's disease, Parkinson's disease dementia, and dementia with Lewy bodies: systematic review with meta-analysis and trial sequential analysis. *Journal of Neurology, Neurosurgery, and Psychiatry* 2015;**86**(2):135-43. [DOI: 10.1136/jnnp-2014-307659]

Wang 2015b *{published data only}*

Wang X. Clinical study of donepezil and memantine hydrochloride in the treatment of Alzheimer's disease. *China Continuing Medical Education* 2015;**7**(14):271.

Weiner 2009 *{published data only}*

Weiner MW, Graham SM, Holbatter RK, Yu SY, Li SY, Hsu HA, et al. Memantine treatment in patients with Alzheimer's Disease is associated with a slower right hippocampal volume loss: an open-label, multi-center trial. *Neurology* 2009;**172**(11):A150.

Weschules 2008 *{published data only}*

Weschules DJ, Maxwell TL, Shega JW. Acetylcholinesterase inhibitor and N-methyl-D-aspartic acid receptor antagonist use among hospice enrollees with a primary diagnosis of dementia. *Journal of Palliative Medicine* 2008;**11**(5):738-45.

Wilcock 2008 *{published data only}*

Wilcock GK, Ballard CG, Cooper JA, Loft H. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *Journal of Clinical Psychiatry* 2008;**69**(3):341-8.

Wilkinson 2010 *{published data only}*

Wilkinson D. Short- and long-term treatment with memantine in Alzheimer's disease. *Neurobiology of Aging* 2010;**31 Suppl 1**:S33.

Winblad 2010 *{published data only}*

Winblad B, Gauthier S, Astrom D, Stender K. Memantine benefits functional abilities in moderate to severe Alzheimer's disease. Journal of Nutrition, Health & Aging 2010; Vol. 14, issue 9:770-4.

Wirth 2012 *{published data only}*

Wirth Y, Rive B. Memantine enhances autonomy in moderate to severe Alzheimer's disease patients already receiving donepezil. *European Journal of Neurology* 2012;**19**(Suppl 1):474.

Zheng 2011 *{published data only}*

Zheng Y, Yu J. The efficacy and safety of combination therapy of memantine and donepezil among old Alzheimer's disease patients (Translated from Chinese) [Mei jin gang lian he duo nai zuo qi zhi liao gao ling a er ci hai mo bing de liao xiao ji an quan xing]. *Modern Practical Medicine* 2011;**4**:415-6.

References to ongoing studies

Lundbeck 11830A_Aker *{unpublished data only}*

Aker T. Investigating the effect of treatment on neurotrophic factors by means of functional magnetic resonance imaging (FMRI) in patients with Alzheimer's disease. https://www.nice.org.uk/guidance/ta217/documents/alzheimers-disease-donepezil-galantamine-rivastigmine-and-memantine-review-a-systematic-review-and-economic-model-b2 (accessed 15 March 2019) 2010.

Lundbeck 13143A/_Peng *{unpublished data only}*

Peng D. A randomized, double-blind, placebo-controlled study to Investigate the Improvement of language function in Chinese AD patients with memantine. https://www.nice.org.uk/

guidance/ta217/documents/alzheimers-disease-donepezil-galantamine-rivastigmine-and-memantine-review-a-systematic-review-and-economic-model-b2 (accessed 15 March 2019) 2010.

MEDUSA/Bullock/2005 *{published data only}*

Bullock R. Making evidence-based decisions using Alzheimer therapy (MEDUSA therapy). https://doi.org/10.1186/ISRCTN55568578 2005 trial, remains unpublished, last edited 2016.

Additional references

Anonymous 2003

Anonymous. FDA approves memantine drug for treating AD. *American Journal of Alzheimer's Disease and other Dementias* 2003;**18**(6):329-30.

Bordji 2010

Bordji K, Becerril-Ortega J, Nicole O, Buisson A. Activation of extrasynaptic, but not synaptic, NMDA receptors modifies amyloid precursor protein expression pattern and increases amyloid-ss production. Journal of Neuroscience 2010; Vol. 30, issue 47:15927-42.

Bormann 1991

Bormann J, Gold MR, Schatton W, inventors. Adamantane derivatives in the prevention and treatment of cerebral ischemia. United States Patent 5061703 1991 Oct 29.

Cacabelos 1999

Cacabelos R, Takeda M, Winblad B. The glutamatergic system and neurodegeneration in dementia: Preventive strategies in Alzheimer's disease. *International Journal of Geriatric Psychiatry* 1999;**14**:3-47.

Cohen Mansfield 1989

Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *Journal of Gerontology* 1989;**44**(3):M77-84.

Cummings 1994

Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gorrnbein J. The Neuropsychiatric inventory: comprehensive assessment of psychopathology in dementia. *Neurology* 1994;**44**:2308-14.

Degerman Gunnarsson 2007

Degerman Gunnarsson M, Kilander L, Basun H, Lannfelt L. Reduction of phosphorylated tau during memantine treatment of Alzheimer's disease. *Dementia and Geriatric Cognitive Disorders* 2007;**24**:247-52.

Di Santo 2013

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. *Journal of Alzheimer's Disease* 2013;**35**:349–61.

Dresser 2000

Dresser R. Weighing the benefits of new Alzheimer's treatments. *Science* 2000;**289**:869.

DSM III-R

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 3th edition revised. Washington D.C.: American Psychiatric Association, 1987.

DSM IV

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th Edition. Washington D.C.: American Psychiatric Association, 1994.

EMEA 2004

European Medicines Agency. Ebixa. European Public Assessment Report. www.emea.eu.int/humandocs/Humans/EPAR/ebixa/ebixa.htm 2004.

EMEA 2006

EMEA Committee for Medicinal products for Human Use. Plenary meeting monthly report. 17-11-2005. October 2005 Vol. http://www.emea.europa.eu/pdfs/human/press/pr/36234805en.pdf.

EMEA 2008

European Commission. Memantine receives European-wide approval for once-daily dosing. http://www.alzheimer-europe.org/?content=shnw&shnwid=5976E167EBBA.

Farrimond 2012

Farrimond LE, Roberts E, McShane R. Memantine and cholinesterase inhibitor combination therapy for Alzheimer's disease: a systematic review. *BMJ Open* 2012;**2**:e000917.doi:10.1136/bmjopen-2012-000917.

Folstein 1975

Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive state of patients for the clinician. *Journal of Psychiatry Research* 1975;**12**:189-98.

Forest 2003

FDA approves Namenda(TM)(Memantine HCl) for the treatment of moderate to severe Alzheimer's disease. http://ir.frx.com/phoenix.zhtml?c=83198&p=irol-newsArticle&ID=459801&highlight=..

Forest 2005b

Forest Laboratories announces FDA decision on supplemental new drug application for Namenda. http://www.frx.com/news/PressRelease.aspx?ID=734345.

Forest 2007

Forest Laboratories. Forest Laboratories receives notification of ANDA filings for generic equivalents of Namenda(R). http://www.frx.com/news/PressRelease.aspx?ID=1087334 13-12-2007.

Forest 2010a

Annual report pursuant to section 13 and 15(d). http://ir.frx.com/phoenix.zhtml?c=83198&p=irol-sec&control_symbol=Vol. 26 May 2010.

Forest 2010b

Forest Laboratories. Forest and Merz announce FDA approval of NAMENDA XR for the treatment of moderate to severe dementia of the Alzheimer's type. http://www.frx.com/news/PressRelease.aspx?ID=1440385 21 June 2010.

Fosbøl 2012

Fosbøl EL, Peterson ED, Holm E, Gislason GH, Zhang Y, Curtis LH, et al. Comparative cardiovascular safety of dementia medications: a cross-national study. *Journal of the American Geriatric Society* 2012;**60**:2283–9.

Galasko 1997

Galasko D, Benett D, Sano M, Ernesto C, Thomas R, Grundman M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer's Disease and Associated Disorders* 1997;**11**:S33-9.

Gaultier 2005

Gauthier S, Wirth Y, Möbius HJ. Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. *International Journal of Geriatric Psychiatry* 2005;**20**:459-64.

Gottfries 1982

Gottfries CG, Brane G, Gullberg B, Steen G. A new rating scale for dementia syndromes. *Archives of Gerontology and Geriatrics* 1982;**1**:311-30.

Guy 1976

Guy W. CGI: Clinical global impressions. In: Guy W editor(s). ECDEU Assessment Manual for Psychopharmacology. Rev. Rockville: National Institutes of Health, 1976:217-20.

Guyatt 2011

Guyatt GH, Oxman AD, Kunz R, Brozeka J, Alonso-Coello P, Rind D, et al. GRADE guidelines 6. Rating the quality of evidence - imprecision. *Journal of Clinical Epidemiology* 2011;**64**(12):1283–93.

Gélinas 1994

Gélinas I, Gauthier L. Disability assessment for dementia. User's guide 1994; Vol. https://www.inesss.qc.ca/fileadmin/doc/INESSS/Rapports/Geriatrie/MA_TNC_DAD_manual.pdf:accessed 12 March 2019.

Hardingham 2010

Hardingham GE, Bading H. Synaptic versus extrasynaptic NMDA receptor signalling: implications for neurodegenerative disorders. Nature reviews. Neuroscience 2010; Vol. 11, issue 10:682-96.

HAS 2016

Haute Autorité de Santé. Drugs of Alzheimer's disease: insufficient medical interest to justify their support by national solidarity. https://translate.google.com/translate?hl=en&sl=fr&u=https://www.has-sante.fr/portail/jcms/c_2679466/fr/medicaments-de-la-maladie-d-alzheimer-un-interet-medical-insuffisant-pour-justifier-leur-prise-en-charge-par-la-solidarite-nationale&prev=search (accessed 8 November 2018) 2016.

HAS 2018

Haute Autorité de Santé. Care Pathway Guide for Patients with Neurocognitive Disorders Associated with Alzheimer's Disease or Related Disease [Guide parcours de soins des patients présentant un trouble neurocognitif associé à la maladie d'Alzheimer ou à une maladie apparentée]. https://www.has-sante.fr/portail/upload/docs/application/pdf/2018-05/parcours_de_soins_alzheimer.pdf (accessed 28 October 2018).

HAS Annexe 2016

Haute Autorité de Santé. Assessment report of drugs indicated in the symptomatic treatment of Alzheimer's disease [Rapport d'évaluation des médicaments indiqués dans le traitement symptomatique de la maladie d'Alzheimer]. http://docreader.readspeaker.com/docreader/?jsmode=1&cid=brvzc&lang=fr_fr&voice=Thomas&url=https%3A%2F%2Fwww.has-sante.fr%2Fportail%2Fupload%2Fdocs%2Fapplication%2Fpdf%2F2016-10%2Fannexe_-_rapport_devaluation_des_medicaments.pdf&v= 2016 (accessed 8 November 2018).

Higgins 2011

Higgins JP, Green S (editors). Cochrane Handbook of Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Honigfeld 1974

Honigfeld G, NOSIE 30. History and current status of its use in pharmaco-psychiatric research. In: Pichot P editor(s). Modern Problems of Pharmacopsychiatry. Vol. **7 Psychological Measurements in Psychopharmacology**, Germany: Karger, 1974:238.

IQWIG 2009

IQWIG Insitute for Quality and Efficiency in Healthcare. Memantine in Alzheimer's Disease. https://www.iqwig.de/download/A05-19C_Executive_Summary_Memantine_in_Alzheimers_disease.pdf 10.09.2009.

IQWIG 2011

Institute for Quality and Efficiency in Health Care. Responder analyses on memantine in Alzheimer's disease. https://www.iqwig.de/download/A10-06_Executive-summary_Responder_analyses_on_memantine_in_Alzheimers_disease.pd (accessed 6 January 2018).

Kalaria 1999

Kalaria RN, Ballard C. Overlap between pathology of Alzheimer disease and vascular dementia. *Alzheimer Disease and Associated Disorders* 1999;**13**(suppl 3):S115-23.

Kim 1993

Kim YS, Nibbelink DW, Overall JE. Factor structure and scoring of the SKT battery. *Journal of Clinical Psychology* 1993;**49**(1):61-71.

Kishi 2017

Kishi T, Matsunaga S, Oya K, Nomura I, Ikutaban T, Iwata N. Memantine for Alzheimer's Disease: an updated systematic review and meta-analysis. *Journal of Alzheimer's Disease* 2017;**60**:401-25.

Kornhuber 1997

Kornhuber J, Weller M. Psychotogenicity and N-methyl-D-aspartate receptor antagonism: implications for neuroprotective pharmacotherapy. *Biological Psychiatry* 1997;**41**:135-44.

Kröger 2015

Kröger E, Mouls M, Wilchesky M, Berkers M, Carmichael P-H, van Marum R, et al. Adverse drug reactions reported with cholinesterase Inhibitors: an analysis of 16 years of individual case safety reports from VigiBase. *Annals of Pharmacotherapy* 2015;**49**(11):1197-206.

Lundbeck 2005

Ebixa extended approval for the treatment of moderate Alzheimer's disease. http://www.lunbeck.com/investor/releases/ReleaseDetails/Release_173_EN.asp.

Matsunaga 2015

Matsunaga S, Kishi T, Iwata N. Memantine for Alzheimer's Disease: systematic review and meta-analysis. *PLOS One* 2015;**10**(4):e0123289. doi:10.1371/journal.pone.0123289.

Matsunaga 2015b

Matsunaga S, Kishi T, Iwata N. Combination therapy with cholinesterase inhibitors and memantine for Alzheimer's disease: a systematic review and meta-analysis. *International Journal of Neuropsychopharmacology* 2015;**18**(5):pyu115. doi:10.1093/ijnp/pyu115.

McKhann 1984

McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM. Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA work group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 1994;**34**:939-44.

McManus 2006

McManus T. Stakeholder Insight: Alzheimer's Disease - prescribing trends indicate that neurologists are not adhering to guidelines. Datamonitor December 2006.

Muayqil 2012

Muayqil T, Camicioli R. Systematic review and meta-analysis of combination therapy with cholinesterase inhibitors and memantine in Alzheimer's disease and other dementias. *Dementia and Geriatric Cognitive Disorders Extra* 2012;**2**(1):546-72.

Ngo 2015

Ngo J, Holroyd-Leduc JM. Systematic review of recent dementia practice guidelines. *Age and Ageing (https://doi.org/10.1093/ageing/afu143)* 2015;**44**(1):25-33.

NICE 2011

National Institute for Clinical Excellence. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. Technology appraisal guidance 217 (Review of NICE technology appraisal guidance 111). http://guidance.nice.org.uk/TA217/Guidance/pdf/English 2011.

NICE 2018

Dementia: assessment, management and support for people living with dementia and their carers. https://www.nice.org.uk/guidance/ng97 (accessed 10 September 2018).

O'Brien 2017

O'Brien JT, Holmes C, Jones M, Jones R, Livingston G, McKeith I, et al. Clinical practice with anti-dementia drugs: A revised (third) consensus statement from the British Association for Psychopharmacology. *Journal of Psychopharmacology* 2017;**31**(2):1-22.

Parsons 1999

Parsons CG, Danysz W, Quack G. Memantine is a clinically well tolerated N-methhyl-D-aspartate (NMDA) receptor antagonist- a review of preclinical data. *Neuropharmacology* 1999;**38**:735-67.

Patterson 2007

Patterson C, Feightner J, Garcia A, MacKnight C. General risk factors for dementia: a systematic evidence review. *Alzheimer's & Dementia* 2007;**3**:341-7.

Post 1997

Post SG. Slowing the progression of Alzheimer disease: ethical issues. *Alzheimer Disease and Associated Disorders* 1997;**11**(suppl 5):S34-9.

Prescriptions England 2016

Prescribing and Medicines Team, Health and Social Care Information Centre. Prescriptions dispensed in the community: England 2005-2015. http://content.digital.nhs.uk/catalogue/PUB20664/pres-disp-com-eng-2005-15-rep.pdf accessed 10 May 2017.

Prescrire 2018

Drugs for Alzheimer's disease: finally delisted in France. http://english.prescrire.org/en/81/168/55126/0/NewsDetails.aspx (accessed 28 October 2018).

Qiu 2009

Qiu C, Kivipelto M, von Strauss E. Epidemiology of Alzheimer's disease: occurrence, determinants, and strategies toward intervention. *Dialogues in Clinical Neuroscience* 2009;**11**(2):111-28.

Reisberg 1997

Reisberg B, Schneider L, Doody R, Anand R, Feldman H, Haraguchi H, Kumar R, Lucca U, Mangone CA, Mohr E, Morris JC, Rogers S, Sawada T. Clinical global measures of dementia: position paper from the International Working group on Harmonization of Dementia Drug Guidelines. *Alzheimer Disease and Associated Disorders* 1997;**11 (suppl 3)**:8-18.

Roberts 2010

Roberts JS, Karlawish JH, Uhlmann WR, Petersen RC, Green RC. Mild cognitive impairment in clinical care: a survey of American Academy of Neurology members. *Neurology* 2010;**75(5)**:425-31.

Roman 1999

Roman GC, Royall DR. Executive control function: a rational basis for the diagnosis of vascular dementia. *Alzheimer Disease and Associated Disorders* 1999;**13**(suppl 3):S69-S80.

Rosen 1984

Rosen WG, Mohs RC, Davis KL. A new rating scale for Alzheimer's disease. *American Journal of Psychiatry* 1984;**11**:1356-64.

Schmitt 1997

Schmitt FA, Ashford W, Ernesto C, Saxton J, Schneider LS, Clark CM, et al. The Severe Impairment Battery: concurrent validity and the assessment of longitudinal change in Alzheimer's disease. *Alzheimer Disease and Associated Disorders* 1997;**11**(2):S51-6.

Schneider 1997

Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg B, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study - Clinical Global Impression of Change. *Alzheimer Disease and Associated disorders* 1997;**11**(suppl 2):S22-32.

Schneider 2011a

Schneider LS, Insel P, Weiner MW, Alzheimer's Disease Neuroimaging Initiative. Treatment with Cholinesterase inhibitors and memantine of patients in the Alzheimer Disease Neuroimaging Initiative. *Archives of Neurology* 2011;**68**(1):58-66.

Schneider 2011b

Schneider LS, Dagerman KS, Higgins JP, McShane R. Lack of evidence for the efficacy of memantine in mild Alzheimer Disease. *Archives Neurology* 2011;**68**(8):991-8.

Schünemann 2011a

Schünemann HJ, Oxman AD, Higgins JP, Vist GE, Glasziou P, Guyatt GH. Chapter 11: Presenting results and 'Summary of findings' tables. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Schünemann 2011b

Schünemann HJ, Oxman AD, Higgins JP, Deeks JJ, Glasziou P, Guyatt GH. Chapter 12: Interpreting results and drawing conclusions. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Shader 1974

Shader RL, Harmatz JS, Salzman C. A new scale for assessment in geriatric population: Sandoz Clinical Assessment Geriatric (scag). *Journal of the American Geriatrics Society* 1974;**22**:107-13.

Sibbett 2017

Sibbett RA, Russ TC, Deary IJ, Starr JM. Risk factors for dementia in the ninth decade of life and beyond: a study of the Lothian birth cohort 1921. *BMC Psychiatry* 2017;**17**:205 DOI 10.1186/s12888-017-1366-3.

Song 2008

Song MS, Rauw G, Baker GB, Kar S. Memantine protects rat cortical cultured neurons against beta-amyloid-induced toxicity by attenuating tau phosphorylation. *European Journal of Neuroscience* 2008;**28**:1989-2002.

Spiegel 1991

Spiegel R, Brunner C, Ermini-Funfschilling D, Monsch A, Notter M, Puxty J, et al. New behavioural assessment scale for geriatric out and inpatients: The NOSGER (Nurse's Observational Scale for Geriatric Patients). *Journal of the American Geriatrics Society* 1991;**39**:339-47.

STATA 2013 [Computer program]

StataCorp LLC. Stata data analysis and statistical software. Version 13. College Station, TX: StataCorp LLC, 2013.

Sucher 1996

Sucher NJ, Awobuluyi M, Choi YB, Lipton SA. NMDA receptors: from genes to channels. *Trends in Pharmacological Science* 1996;**17**:348-55.

Van der Kam 1989

Van der Kam P, Hoeksma BH. ADL and behaviour rating scales for the evaluation of nurses' workload in psychogeriatric nursing homes [De bruikbaarheid van BOP en SIVIS voor het schatten van de werklast in het psychogeriatrisch verpleeghuis]. *Tijdschrift voor Gerontologie en Geriatrie* 1989;**20**:159-66.

Wilcock Post-Hoc 3RCTs 2008

Wilcock GK, Ballard CG, Cooper JA, Loft H. Memantine for agitation/aggression and psychosis in moderately severe to severe Alzheimer's disease: a pooled analysis of 3 studies. *Journal of Clinical Psychiatry* 2008;**69**(3):341-8.

Wilkinson Post-Hoc 6RCTs 2007

Wilkinson D, Andersen HF. Analysis of the effect of memantine in reducing the worsening of clinical symptoms in patients with moderate to severe Alzheimer's disease. *Dementia & Geriatric Cognitive Disorders* 2007;**24**(2):138-45.

Willenborg 2011

Willenborg B, Schmoller A, Caspary J, Melchert UH, Scholand-Engler HG, Jauch-Chara K, et al. Memantine prevents hypoglycemia-induced decrements of the cerebral energy status in healthy subjects. Journal of Clinical and Endocrinology Metabolism 2011; Vol. 96, issue 2:E384-8.

Wimo 1988

Wimo A, Wetterholm AL, Mastey V, Vinblad B. Evaluation of the resource utilisation and caregiver time in anti-dementia drug trials: a quantitative battery. In: Wimo A, Jonxon B, Karlsson G editor(s). The Health Economics of Dementia. London: John Wiley & sons, 1988:465-99.

Winblad 2007

Winblad B, Jones R, Wirth Y, Stöffler A, Möbius HJ. Memantine in moderate to severe Alzheimer's disease: a meta-analysis of randomised clinical trials. *Dementia and Geriatric Cognitve Disorders* 2007;**24**(1):20-7.

References to other published versions of this review

Areosa 2003

Areosa Sastre A, Sherriff F. Memantine for dementia. *Cochrane Database of Systematic Reviews* 2003, Issue 3. [DOI: 10.1002/14651858.CD003154]

Areosa 2004

Areosa Sastre A, Sherriff F, McShane R. Memantine for dementia. *Cochrane Database of Systematic Reviews* 2004, Issue 4. [DOI: 10.1002/14651858.CD003154.pub2]

Areosa 2005a

Areosa Sastre A, Sherriff F, McShane R. Memantine for dementia. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD003154.pub3]

Areosa 2005b

Areosa Sastre A, Sherriff F, McShane R. Memantine for dementia. *Cochrane Database of Systematic Reviews* 2005, Issue 3. [DOI: 10.1002/14651858.CD003154.pub4]

McShane 2006

McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD003154.pub5]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Aarsland 2009

Methods	Randomised, double-blind, parallel-group, placebo-controlled, multicentre trial Duration: 24 weeks
Participants	Country: Norway, Sweden, and the UK Number of centres: four psychiatric and neurological outpatient clinics Diagnosis: PDD or DLB - memantine group 50% PDD and placebo 61% Some patients had ChEIs: 47% (memantine) and 63% (placebo) Inclusion: patients were included if they fulfilled the UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria for Parkinson's disease (PD) and developed dementia according to DSM IV criteria at least 1 year after the onset of motor symptoms (PDD) or met the revised consensus operationalised criteria for DLB. Mild or moderate PDD or DLB MMSE 12 or higher. Exclusion: other brain disease, recent major changes in health status, major depression, moderate-to-severe renal impairment, heart disease, pulmonary disease, hepatic impairment, results of laboratory tests deemed to be clinically relevant by the study physician that were higher than the normal values, or a known allergy to memantine Total number of patients: 75
Interventions	Route: oral Treatment: the initial dose was 5 mg memantine, with a planned gradual increase to the maintenance dose of 20 mg (10 mg in the morning and 10 mg in the evening) from week 4 (N = 35); placebo (N = 40)
Outcomes	Primary outcome: clinical global impression of change (CGIC) Secondary outcomes: MMSE, Cognitive Speed AQT, NPI, DAD, modified UPDRS motor subscale. Adverse events. Not reported: agitation
Severity (MMSE mean)	Mean˜20.0 (SD 4.0)
Notes	ITT population: 63/75. Funding: West Norway Regional Health Authority and H. Lundbeck A/S. The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report

Aarsland 2009 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The randomisation lists were generated by the study statistician in the statistical program package R". Comment: low risk of bias: computer-generated randomisation
Allocation concealment (selection bias)	Low risk	Quote: "A randomisation list was forwarded to the study pharmacist at each centre. The pharmacist assigned each participant to a treatment group on the basis of the generated randomisation list. Randomisation data were kept strictly blinded; access was restricted to only authorised individuals (e.g., the study pharmacist) who had no contact with patients before unblinding." Comment: pharmacist was an independent 3rd party
Blinding (performance bias and detection bias) All outcomes	Low risk	Quotes: "The drug codes were broken and made available for data analysis only when the study was completed" and (in Larsson 2010) "Patients were randomly assigned to receive either the active substance memantine, or the identically looking placebo." Comment: blinding implied. Study likely to have been conducted in compliance with the principles of good clinical practice (GCP)
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	75 patients initially randomised. Analysis based on LOCF dataset, N = 63. Three patients were excluded before start of trial (1 memantine arm, 2 placebo arm). Nine patients withdrew due to worsening disease (4 memantine arm, 5 placebo arm). 16 patients dropped out due to adverse events (7 memantine arm, 9 placebo arm).Thus, missing data were: 12/35 (34%) and 16/40 (40%). Comment: fairly high level of missing data, but similar in each arm, so assigned unclear risk of bias.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data (excluding those due to adverse events): 5/35 (14%) and 7/40 (18%), which compares with 15/35 and 20/40 event rates Comment: missing data low compared with event rate, so low risk of bias assigned
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk.
Other bias	High risk	Differential use of cholinesterase inhibitors (47% memantine and 63% placebo). Baseline differences comparable or larger than effect estimate for primary outcomes

Asada 2011 (MA3301)

Methods	Phase 3, confirmatory randomised, double-blind, parallel group, placebo-controlled trial
Participants	Country: Japan Safety 564; Efficacy 557 Mild-to-moderate AD: MMSE 10-23

Asada 2011 (MA3301) *(Continued)*

	Inclusion: patients whose age is 50 or higher and with a probable diagnosis of mild-to-moderate dementia of the Alzheimer's type according to the NINCDS-ADRDA diagnostic criteria. Patients with an MMSE score between 10 and 23. Patients with a CDR (Clinical Dementia Rating) score of "1 = mild dementia" or "2 = moderate dementia". Exclusion: patients with neurodegenerative disorder with dementia of any other type than AD, patients with systemic disease or with significant psychological disease determined according to DSM-IV. Patients with a history of severe drug allergy or with drug dependence or alcoholism.
Interventions	Memantine 10 mg once daily (N = 190), or 20 mg once daily (N = 188), or placebo (N = 186) (1:1:1) 24 weeks
Outcomes	Primary endpoints: ADAS-J cog, CIBIC-plus (ADCS-CGIC) Secondary endpoints: DAD, Caregiver-rated Crichton Scale , MMSE, CDR. Adverse events reported narratively. Not reported: decline in ADL, NPI and agitation
Severity (MMSE mean)	Inclusion criteria range 10-23; mean not reported
Notes	Recruitment: October 11, 2003 to December 5, 2007 Licencing approval NDA submitted: 8 February 2010 Preliminary trial registration on JAPIC: 19 April 2010 Results posted: 14 February 2011 Primary sponsor: Daiichi Sankyo Co.,Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Confirmatory randomised.. trial" Comment: unclear sequence generation
Allocation concealment (selection bias)	Unclear risk	Not specified; method of concealment is not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group.
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	High dose memantine: 1/188 (0.5%), low dose 0%, placebo: 6/186 (3%)
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data (excluding those due to adverse events): 1/188 and 6/186, which compares with 150/188 and 143/186 event rates
Selective reporting (reporting bias)	Unclear risk	Comment: incomplete reporting of some outcomes. MMSE reported only as a P value
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Asada 2011a (IE3501)

Methods	Phase 3 double-blind, parallel-group, placebo-controlled trial
Participants	74 centres Safety 432; Efficacy 426 Moderately severe to severe AD: MMSE 5-14 (mean 10.1 and 9.6) Monotherapy (concomitant use of donepezil was prohibited). Inclusion: patients diagnosed with dementia of the Alzheimer's type according to the DSM-IV criteria, and probable Alzheimer's Disease according to the NINCDS-ADRDA criteria. Patients diagnosed with dementia of the Alzheimer's type based on a brain CT or MRI scan. Patients fulfilling both the following requirements: MMSE score between 5 and 14; FAST stage between 6a and 7a. Patients aged 50 or over at the time of consent. Exclusion: patients with dementia of any other type than AD, patients with significant neurological disease or history of psychiatric disease not associated with AD. Patients with a history of severe drug allergy or with a history of alcoholism or drug abuse
Interventions	20 mg memantine (N = 221) or placebo (N = 211), once daily, 24 weeks
Outcomes	Primary: OC: SIB-J, Modified CIBIC plus-J. BEHAVE-AD. Safety: adverse events, adverse drug reactions. Not reported: decline in ADL, NPI, agitation
Severity (MMSE mean)	9.9
Notes	Recruitment: August 23, 2005 to September 12, 2008 Preliminary registration with JAPIC:19 April 2010 Results post: 14 Febuary 2011 Additional details from "Report on the Deliberation Results", and also Matsunaga 2015 and Nakamura 2014 systematic reviews Sponsor: Daiichi Sankyo Co., Ltd

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Randomized, double-blind parallel group, comparative study" Comment: sequence generation not specified - but licensing study (JAPIC Clinical Trials Information)
Allocation concealment (selection bias)	Unclear risk	Quote: "Randomized, double-blind parallel group, comparative study" Comment: allocation concealment not specified - but licensing study (JAPIC Clinical Trials Information)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled.
Incomplete outcome data (attrition bias)	Low risk	Data from "Report on the Deliberation Results" - Missing data: memantine 32/221 (14%) and placebo 36/211 (17%). Reasons included: 14 (6%) and 13

Asada 2011a (IE3501) *(Continued)*

Primary Outcomes		(6%) withdrawals for adverse events and 14 and 17 patients requested withdrawal
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data apart from adverse events: 8% and 4%. These levels are low compared with the rate of adverse events (81% and 79%)
Selective reporting (reporting bias)	Unclear risk	Publication was much delayed pending licensure. Minimal results posted but some results taken from a licensing report.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Ashford 2011 (95722)

Methods	Randomized, double-blind, placebo-controlled, parallel assignment, pharmacokinetics–dynamics study Duration: 1 Year
Participants	Country: USA Number of centres: not reported Diagnosis: probable AD diagnosis, DSM-IV Mild-to-moderate AD (mean 19.9 and 21.8) N = 13 Mean age: 76 years 38% females Inclusion criteria: mild-to-moderately demented patients with a probable AD diagnosis Exclusion criteria: Parkinson's disease, any MRI contraindications, certain neurologic or psychiatric conditions (e.g. seizures, clinically significant stroke, head trauma, major psychiatric disorder) or other medical or laboratory findings or medications rendering them unsuitable for an investigational trial
Interventions	Route: oral Treatment: memantine 10 mg (N = 7) Control: placebo 10 mg (N = 6) Titrated from 5 mg medication or placebo tablets each morning with increments of 5 mg every week to reach 10 mg tablets twice per day at the third week. 86% (memantine) and 67% (placebo) of patients were already on donepezil at the time of entry to the study
Outcomes	Primary outcome: change in NAA/Cr ratio MRS scan Secondary outcomes: change in cognitive state (ADAS-cog, MMSE, Verbal fluency), change in functioning (decline in ADL) - but no results at year 1 for decline in ADL Not reported: clinical global, NPI, agitation
Severity (MMSE mean)	˜21
Notes	For the outcome "discontinuations due to adverse events", the three losses to follow-up due to patients not being able to tolerate the study medication were assumed to be due to adverse events. Funding: unrestricted grant from Forest Research Institute, a subsidiary of Forest Labs, Inc

Risk of bias

Bias	Authors' judgement	Support for judgement

Ashford 2011 (95722) *(Continued)*

Random sequence generation (selection bias)	High risk	"Randomized", no further details reported. Comment: additionally, large difference at baseline (4.50) for ADAS-cog (the only outcome). Final values only reported and the difference in these was 4.64 (which is comparable with the baseline difference). This affects the effect estimate, therefore high risk of bias assigned.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomized to memantine or placebo arms by the unblinded pharmacist" and "the pharmacist randomized subjects into one of two groups: Treatment (T; target dose 10 mg memantine), or control (C; matching placebo), balancing the order of selection. Comment: randomisation by independent third party.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Subjects and all study staff, except the pharmacist, were blind to the treatment group".
Incomplete outcome data (attrition bias) Primary Outcomes	High risk	Quote: "Three subjects could not tolerate the study medication; two discontinued the study pills entirely and the third took a reduced dose but pill-count monitoring showed subject remained non-compliant with protocol". Missing data 3/7 (43%) memantine and 0/6 (0%) placebo. Comment: three patients receiving memantine were excluded prior to randomisation. High levels of differential missing data
Selective reporting (reporting bias)	Unclear risk	No data reported for the MMSE, verbal fluency and decline in ADL after 12 months - only at baseline. ADAS-Cog reported as final values rather than change from baseline
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Bakchine 2008 (99679)

Methods	Randomised, double-blind, parallel-group, placebo-controlled study Duration: 26 weeks
Participants	Mild-to-moderate AD, MMSE 11-23 Number of centres: 65 primary care centres in 12 countries (Austria, Belgium, Denmark, Finland, France, Greece, Lithuania, the Netherlands, Poland, Spain, Sweden and the UK).
Interventions	20 mg monotherapy (N = 318); placebo (N = 152)
Outcomes	Primary end points: CIBIC+, ADAS-Cog; secondary: ADCS-ADL23, NPI. Adverse events, agitation
Severity (MMSE mean)	18.7 (SD 3.2)
Notes	ITT population: 461/470 2:1 memantine to placebo allocation First patient, first visit: 6 May 2002 Last patient, last visit: 3 September 2003 Funding: H. Lundbeck A/S funded the study and was involved in planning the design, the protocol and data analysis along with the author
Risk of bias	

Bakchine 2008 (99679) *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At each study centre, sequentially enrolled patients were assigned the lowest randomisation number available". "The study was conducted in accordance with the principles of Good Clinical Practice" Comment: probably adequate sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "The details of the randomisation series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes. At each study centre, sequentially enrolled patients were assigned the lowest randomisation number available".
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The rater who scored the CIBIC-plus was blinded to the results of the other efficacy assessment", "The study products were tablets of identical appearance, taste and smell". "The study was conducted in accordance with the principles of Good Clinical Practice".
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	OC results are presented, although LOCF analysis was also conducted. OC analysis is more conservative than LOCF in trials such as this, where dropouts are higher in the treatment arm. Missing data (OC): memantine 50/318 (16%) and placebo 17/152 (11%). 9% and 4% were missing because of adverse events.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Quote: "A patient was withdrawn from the study if the randomisation code for that patient was broken, or if consent to participate was withdrawn for the patient or caregiver. A patient could also be withdrawn from the study if: they had a serious adverse event (SAE: death, life-threatening condition, hospitalisation), the caregiver became unavailable, the patient was lost to follow-up, or the patient was placed in a nursing home". Comment: remaining missing data 22/318 (7%) and 11/152 (7%); this is small compared with the rate of adverse events (56% and 52.6%).
Selective reporting (reporting bias)	Low risk	All patient outcome data presented. Four-year delay between study completion and publication or registry posting.
Other bias	Low risk	Appears to be free of other sources of bias.

Bakchine 2008 (99679) SG

Methods	As for LU-99679 (Bakchine 2007) Data drawn from Winblad 2007b meta-analysis (for moderate severity Alzheimer's patients) or calculated using these data (for mild severity Alzheimer's patients).
Participants	Post-hoc subgroups (moderate and mild); moderate subgroup: memantine 169 (53% of all patients), placebo 77 (51%)
Interventions	
Outcomes	
Severity (MMSE mean)	Not stated for subgroup; all patient mean 18.7

Bakchine 2008 (99679) SG *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "At each study centre, sequentially enrolled patients were assigned the lowest randomisation number available". "The study was conducted in accordance with the principles of Good Clinical Practice" Comment: probably adequate sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "The details of the randomisation series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes. At each study centre, sequentially enrolled patients were assigned the lowest randomisation number available". Comment: adequate allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The rater who scored the CIBIC-plus was blinded to the results of the other efficacy assessment", "The study products were tablets of identical appearance, taste and smell". "The study was conducted in accordance with the principles of Good Clinical Practice". Comment: adequate blinding.
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Missing data: memantine 50/318 (16%) and placebo 17/152 (11%). 9% and 4% were missing because of adverse events. However, the distribution of severity differed in the remaining data: memantine 54% moderate and placebo 47%. This difference could have affected the outcome.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Quote: "A patient was withdrawn from the study if the randomisation code for that patient was broken, or if consent to participate was withdrawn for the patient or caregiver. A patient could also be withdrawn from the study if: they had a serious adverse event (SAE: death, life-threatening condition, hospitalisation), the caregiver became unavailable, the patient was lost to follow-up, or the patient was placed in a nursing home". Comment: remaining missing data 22/318 (7%) and 11/152 (7%) this is small compared with the rate of adverse events (56% and 52.6%).
Selective reporting (reporting bias)	High risk	Subgroup of patients selected, post-hoc and not stratified by severity and then randomised
Other bias	Low risk	Appears to be free of other sources of bias.

Boxer 2013

Methods	Randomised, double-blind, parallel-group, placebo-controlled, multicentre study Duration: 26 weeks
Participants	Country: USA No. of centres: nine US academic dementia research centres with expertise in the diagnosis of frontotemporal lobar degeneration (FTD)

Boxer 2013 *(Continued)*

	Diagnosis: behavioural variant frontotemporal dementia (bvFTD) or semantic dementia, diagnosed with a CT or MRI scan of the brain within 24 months before randomisation Mild dementia: MMSE mean 24.3 Inclusion: patients were included if they had bvFTD or semantic dementia. Individuals with FTD-motor neuron disease were included if motor impairments did not interfere with study procedures. Individuals had to be aged between 40 and 80 years and have an MMSE score of 15 or higher at screening. Exclusion: patients with a diagnosis of progressive non-fluent aphasia, and use of memantine, acetylcholinesterase inhibitors, antipsychotic drugs, valproate, lithium, or benzodiazepines within 4 weeks before randomisation; evidence of disorders that preclude diagnosis of FTD Total number of patients: 81
Interventions	Route: oral Treatment: the initial dose was 5 mg memantine, increasing by 5 mg each week to the maintenance dose of 20 mg (10 mg twice per day) from week 4 (N = 39; 31 bvFTD and 8 semantic dementia); placebo (N = 42; 33 bvFTD; 9 SD)
Outcomes	Primary outcome: CGIC, NPI; Secondary outcomes: MMSE, CDR-SB-FTD, functional activities questionnaire (FAQ), Texas functional living scale (TFLS), executive interview (EXIT25); modified unified Parkinson's disease rating scale (UPDRS); the time to initiation of antipsychotic therapy; and a neuropsychological battery, including a California verbal learning test, category fluency, phonemic fluency, a 15-item Boston naming test (BNT), a modified trails set-shifting task, backward digit span Tertiary outcomes: Zarit burden interview (ZBI 22), and weight in kg Adverse events, agitation Not reported: decline in ADL
Severity (MMSE mean)	24.3
Notes	Funding: the study was funded by Forest Research Institute (FRI), the research arm of Forest Laboratories. FRI had no role in study design, data collection, analysis or interpretation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomisation codes were generated by an unmasked UCSF pharmacist (SF) with the Excel (Microsoft Office) random number generator in blocks of two and four patients."
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation codes were generated by an unmasked UCSF pharmacist (SF) ... Kits were given sequential numbers that corresponded to the randomisation key that was maintained in a secure location by the UCSF Investigational Pharmacy. When randomised, each successive participant was assigned by the electronic Clinical Trial Management System to the next numbered kit in sequence at each site."
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Tablets containing memantine 10 mg or placebo with no memantine (identical tablets) were packaged into kits (one per patient) of several blister packs (1 week of treatment per pack). All patients and study personnel were masked to treatment assignment"
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Missing data: 2/39 (5%) and 3/42 (7%). Reasons for 'missingness' were: memantine - 2 discontinuations because of adverse events; placebo - 3 discontinuations, 1 for adverse events, the other 2 for starting excluded medications.

Boxer 2013 *(Continued)*

		Comment: low levels - unlikely to affect the effect estimate.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Adverse events reported as the number of events and not the number of people with AEs. However, more than 7%, so low risk of attrition bias. For individual adverse events, 2 and 3 discontinued treatment (so high risk of bias for agitation).
Selective reporting (reporting bias)	High risk	Quote: "It was decided post hoc to reduce the CGIC values to “improved, no change, or worsened” because of the very few responses outside the middle three values." Comment: in addition, adverse events reported as the number of events and not the number of people with AEs.
Other bias	Low risk	Appears to be free from other types of bias

Ditzler 1991

Methods	Randomised, double-blind, parallel-group, placebo-controlled study Duration: 6 weeks
Participants	Country: Germany No. of centres: not stated Diagnosis: dementia syndrome. No stated criteria. Inclusion: mild-to-moderate dementia according to the Lausanne scale and SCAG score of 50 or more. Exclusion: kidney function disturbances, cholestasis, uncompensated congestive heart failure, stroke or head trauma 6 months before the study, brain tumours, endogenous psychoses, drugs or alcohol abuse, Parkinson's disease, intolerance to the test product. Not permitted: nootropics, neuroleptics, drugs for promoting cerebral blood flow, antidepressants, sleeping agents (except chloral hydrate or in exceptional cases a short-acting benzodiazepine), antiparkinsonians, myotonolytics, reserpine, ergot alkaloids or their derivatives. Total No. of patients: 66 Age: 72.2 (60-84) Sex (% females): 65% MMSE: indicates 'mild dementia'
Interventions	Route: oral Treatment: memantine: 30 mg. Treatment commenced at 10 mg/day and in 2 weeks increased to 30 mg/day (N = 32); placebo (N = 34)
Outcomes	Physician's global impression, SCAG, The Syndrom- Kurtztest, decline in ADL.
Severity (MMSE mean)	"mild"
Notes	As the study recruits those patients with "dementia syndrome", this leads to diagnostic uncertainty as to the underlying cause

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No method of sequence generation described. As study deemed unlikely to have been conducted in compliance with the principles of good clinical practice, no judgement on risk of bias can be made.

Ditzler 1991 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "The randomisation was performed by the statistician. The code for each patient was contained in a sealed envelope." Comment: unclear as unspecified as to whether envelopes were opaque and sequentially numbered.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "The pharmaceutical formulations of placebo and active substance were externally identical and not identifiable by doctor or patient."
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Dataset used of "only patients who completed the study", N = 59/66 (89%). Missing data: 2/32 (6%) memantine and 5/34 (15%) placebo. Quote: "Six patients withdrew from the study for undisclosed reasons and one placebo patient due to agitation" Comment: differential missing data could affect the effect estimate. Unclear risk of bias assigned.
Incomplete outcome data (attrition bias) Safety Data	Low risk	All patient outcome data presented. But reported as the number of events rather than the number of patients
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk. Adverse events reported as the number of events rather than the number of patients.
Other bias	High risk	Outdated diagnosis of AD

Dysken 2014

Methods	Design: random permuted block design with randomly varying block sizes, double-blind, placebo-controlled, parallel-group; 4 arms Duration: 5 years
Participants	Country: USA Number of centres: 14 Veterans Affairs Medical Centers Diagnosis: possible or probable mild-to-moderate AD diagnosis (NINCDS-ADRDA) (MMSE 12-26, mean 20.8) N = 613 (all 4 arms) Age, mean (SD) [range]: memantine: 78.8 (7.2) [53-92] years; placebo: 79.4 (7.0) [61-96] years % females: memantine: 4%; placebo: 2% Moderate severity (baseline MMSE 12-19, mean 20.8): memantine 32%; placebo 41% Inclusion criteria: possible or probable mild-to-moderate AD diagnosis and MMSE between 12˜26 inclusive Exclusion criteria: a) MMSE score outside the inclusion range
Interventions	Route: oral Treatment (2 arms of a 4-arm trial - see also Dysken VitE 2014 below): 1. memantine (N = 155): memantine plus a matching placebo for alpha tocopherol 2. placebo (N = 152): matching placebos for both memantine and alpha tocopherol Mode: a) Alpha tocopherol or matching placebo: dose of 1000 IU twice/day; b) Memantine or matching placebo: titrated over 4 weeks to maintenance dosage of 10 mg twice/day and reduced to 5 mg twice/day for individuals with estimated creatinine clearance less than 30 mL/minute

Dysken 2014 *(Continued)*

	c) Dosage adjustments for memantine and alpha tocopherol based on patient tolerability
Outcomes	Primary outcomes: Alzheimer's Disease Cooperative Study/Activities of Daily Living (ADCS-ADL23) Inventory score Secondary outcomes: a) MMSE - b) Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-cog) - c) Neuropsychiatric Inventory (NPI) - d) Caregiver Activity Survey (CAS) Not reported: clinical global, agitation Analysis for primary outcome used a longitudinal repeated-measures mixed-effects model assuming missing at random, adjusted for medical centre as a random effect and for the baseline ADCS-ADL
Severity (MMSE mean)	20.8
Notes	VA TEAM-AD was funded by the Veterans Affairs Cooperative Studies Program, Forest Research Institute (Forest Laboratories), donated the memantine and matching placebo tablets. DSM Nutritional Products donated the DL-alpha-tocopheryl acetate oil and funding for the purchase of the soybean oil from Arista Industries. The Veterans Affairs Cooperative Studies Program, Forest Research Institute, and DSM Nutritional Products had no input into data collection, management, analysis, and interpretation of the data or preparation, review, or approval of the manuscript. Data for 6 months taken from clinicaltrials.gov website; the number of patients at 6 months is taken as the number of patients with at least one reading. Data provided by M Dysken for mild and moderate severity separately.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Eligible participants were randomized centrally by the coordinating center to 1 of the 4 treatment groups stratified by site using a random permuted block design with randomly varying block sizes"
Allocation concealment (selection bias)	Low risk	Quote: "Eligible participants were randomized centrally by the coordinating center"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group, randomised clinical trial. Quote "Patients, caregivers, and site investigators were blinded to treatment assignment"
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Additional data from author communication: Missing data at end of trial (mean follow-up 2.27 years): memantine: 67/155 (43%; 39 died during follow-up, 19 withdrew, 9 lost to follow-up); 142 analysed. Placebo: 62/152 (41%; 31 died during follow-up, 18 withdrew, 13 lost to follow-up); 140 analysed. Quote: "Longitudinal repeated-measures mixed-effects model assuming missing at random, adjusted for medical center as a random effect and for the baseline ADCS-ADL Inventory score using all available data". Comment: missing data at 6 months from main paper (study figure 2): memantine 16/155 (10%; but 142 analysed) and placebo 17/152 (11%; but 140 analysed). These levels suggest a low risk of attrition bias at 6 months, with minimal imputation.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data levels are 10% in each group. Adverse events rates are around 60%, so this level of missing data is unlikely to affect the effect estimate.

Dysken 2014 *(Continued)*

Selective reporting (reporting bias)	Low risk	All patient outcome data presented. However, intermediate time point data were requested from the authors.
Other bias	Unclear risk	Proportion of patients with moderate AD was different in the two groups: memantine 32% and placebo 41%

Dysken 2014 SG

Methods	As for Dyksen 2014 Separate data were provided by the author for subgroups of patients with mild and moderate Alzheimer's disease.
Participants	Post-hoc subgroups (moderate and mild)
Interventions	Moderate severity: memantine, N = 50 (32%); placebo, N = 63 (41%) - from OC data Mild severity: memantine, N = 105; placebo 89
Outcomes	
Severity (MMSE mean)	Not stated for subgroup (all 20.8)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Quote: "Eligible participants were randomized centrally by the coordinating center to 1 of the 4 treatment groups stratified by site using a random permuted block design with randomly varying block sizes"
Allocation concealment (selection bias)	Low risk	Quote: "Eligible participants were randomized centrally by the coordinating center"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group, randomised clinical trial. Quote "Patients, caregivers, and site investigators were blinded to treatment assignment"
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Quote: "Longitudinal repeated-measures mixed-effects model assuming missing at random, adjusted for medical center as a random effect and for the baseline ADCS-ADL Inventory score using all available data". Comment: missing data at 6 months from main paper (study figure 2): memantine 16/155 (10%) and placebo 17/152 (11%). These levels suggest a low risk of attrition bias at 6 months, with minimal imputation.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data levels are 10% in each group. Adverse events rates are around 60%, so this level of missing data is unlikely to affect the effect estimate
Selective reporting (reporting bias)	High risk	Subgroup of patients selected post-hoc
Other bias	Low risk	The study appears to be free of other sources of bias

Dysken VitE 2014

Methods	Design: random permuted block design with randomly varying block sizes, Double-blind, placebo-controlled, parallel-group; 4-arm trial Duration: 5 Years
Participants	Country: USA Number of centres: 14 Veterans Affairs Medical Ccenters Diagnosis: possible/probable mild-to-moderate AD diagnosis N = 613 (for all 4 arms) Age, mean (SD) [range]: vitamin E: 78.6 (7.2) [55-93]; vitamin E + memantine: 78.3 (7.0) [54 to 94] years % females: vitamin E: 4%; vitamin E + memantine: 3% Moderate severity (baseline MMSE 12-19): memantine + vitamin E 29%; vitamin E 30% Inclusion criteria: possible or probable mild-to-moderate AD diagnosis and MMSE between 12˜26 inclusive Exclusion criteria: a) MMSE score outside the inclusion range
Interventions	Route: oral Treatment (2 arms of a 4-arm trial - see Dysken 2014 above) Placebo plus vitamin E (N = 152): alpha tocopherol plus matching placebo for memantine. Memantine plus vitamin E (N = 154): memantine plus alpha tocopherol. Mode: a) Alpha tocopherol or matching placebo: dose of 1000 IU twice/day b) Memantine or matching placebo: titrated over 4 weeks to maintenance dosage of 10 mg twice/day and reduced to 5 mg twice/day for individuals with estimated creatinine clearance less than 30 mL/minute c) Dosage adjustments for memantine and alpha tocopherol based on patient tolerability
Outcomes	Primary outcomes: Alzheimer's Disease Cooperative Study–Activities of Daily Living (ADCS-ADL) Inventory score Secondary outcomes: a) MMSE - b) Alzheimer Disease Assessment Scale–Cognitive Subscale (ADAS-cog) - c) Neuropsychiatric Inventory (NPI) - d) Caregiver Activity Survey (CAS) Not reported: clinical global, agitation Analysis for primary outcome used a longitudinal repeated-measures mixed-effects model assuming missing at random, adjusted for medical centre as a random effect and for the baseline ADCS-ADL
Severity (MMSE mean)	
Notes	VA TEAM-AD was funded by the Veterans Affairs Cooperative Studies Program, Forest Research Institute (Forest Laboratories), donated the memantine and matching placebo tablets. DSM Nutritional Products donated the DL-alpha-tocopheryl acetate oil and funding for the purchase of the soybean oil from Arista Industries. The Veterans Affairs Cooperative Studies Program, Forest Research Institute, and DSM Nutritional Products had no input into data collection, management, analysis, and interpretation of the data or preparation, review, or approval of the manuscript. Data for 6 months taken from clinicaltrials.gov web site; the number of patients at 6 months is taken as the number of patients with at least one reading. Data provided by M Dysken for mild and moderate severity separately.

Risk of bias

Bias	Authors' judgement	Support for judgement

Dysken VitE 2014 *(Continued)*

Random sequence generation (selection bias)	Low risk	Quote: "Eligible participants were randomized centrally by the coordinating center to 1 of the 4 treatment groups stratified by site using a random permuted block design with randomly varying block sizes"
Allocation concealment (selection bias)	Low risk	Quote: "Eligible participants were randomized centrally by the coordinating center"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group, randomised clinical trial. Quote "Patients, caregivers, and site investigators were blinded to treatment assignment"
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Additional data from author communication Missing data: vitamin E plus memantine: 65/154 (42%; 32 died during follow-up, 17 withdrew, 16 lost to follow-up); 139 analysed. Vitamin E: 62/152 (41%; 26 died during follow-up, 23 withdrew, 13 lost to follow-up); 140 analysed. Quote: "Longitudinal repeated-measures mixed-effects model assuming missing at random, adjusted for medical center as a random effect and for the baseline ADCS-ADL Inventory score using all available data". Comment: missing data at 6 months from main paper (figure 2): memantine + vitamin E: 23/154 (15%; but 139 analysed) and vitamin E: 18/152 (12%; but 140 analysed). Remaining patients had different proportions of moderate severity: memantine 32% and placebo 41%; this may have affected the effect estimate. These levels suggest a low risk of attrition bias at 6 months.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data levels are 15% in each group at 6 months. Adverse events rates are around 60%, so this level of missing data is unlikely to affect the effect estimate
Selective reporting (reporting bias)	Low risk	All patient outcome data presented. However, intermediate time point data were requested from the authors
Other bias	Low risk	The study appears to be free of other sources of bias

Emre 2010 (11018)

Methods	Randomised, double-blind, placebo-controlled 6-month study
Participants	Diagnosis of PDD (N = 62 on memantine, 58 on placebo) or DLB (N = 34 on memantine, 41 on placebo); i.e. memantine 65% PDD, placebo 59%) MMSE 10-24. (mean in PDD˜21.0 and in DLB˜20.0) Not taking ChEI. Hoehn and Yahr ≤ 3 when 'on'. Number of centres: 30 specialist centres in Austria, France, Germany, UK, Greece, Italy, Spain and Turkey. ChEIs.and the initiation of antipsychotic, antidepressant, or benzodiazepine drugs were not allowed during the study. Total number of patients: 199
Interventions	20 mg memantine once daily (N = 98); placebo (N = 101). 20 mg once daily in the morning (titrated in 5 mg increments over 4 weeks)
Outcomes	Cognitive function: executive function, attention, memory, language, visuospatial function.

Emre 2010 (11018) *(Continued)*

	Behaviour: NPI; Clinical Global: ADCS-CGIC; ADCS-ADL; UPDRS; Caregiver burden: Zarit
Severity (MMSE mean)	˜21
Notes	Lundbeck sponsored the study and Pär Thored, an employee of Lundbeck, provided medical writing assistance in the preparation of the report.The sponsor was involved in the study design, data collection, data analysis, and interpretation of the data, but not in the decision to submit the report for publication

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly assigned ...according to lists that were computer generated"
Allocation concealment (selection bias)	Low risk	Quote: "The details of the randomisation lists were contained in two sets of sealed opaque envelopes, and one was kept by the International Safety and Pharmacovigilance Department, Lundbeck, and the other by the investigator or pharmacist"
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "All study personnel and participants were unaware of treatment assignment for the duration of the study". Double-blind, placebo-controlled, parallel-group study.
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Withdrawals from the study: memantine 18/98 (18%) and placebo 22/101 (22%). Reasons for withdrawal: memantine - 11 adverse events, 4 withdrew consent, 1 lack of efficacy, 2 pre-start of trial; placebo - 12 adverse events, 6 withdrew consent, 1 lack of efficacy, 1 non-compliance, 2 pre-start of trial. Comment: unclear if this level of missing data would have affected the effect estimate
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data (other than adverse events): memantine 7/98 (7%), placebo 10/101 (10%). This level is low compared with the adverse event rate (40% to 50%), so low risk of attrition bias assigned
Selective reporting (reporting bias)	High risk	All patient outcome data presented, for both conditions (DLB and PDD) combined (and separately, although not stratified randomisation). OC data not reported in full paper (but in the poster), for which the number of patients is not stated explicitly
Other bias	Low risk	The study appears to be free of other sources of bias

Forest 2006 (MD-22)

Methods	Randomised double-blind parallel group placebo-controlled effectiveness study
Participants	Country: USA 30 centres Nursing home residents with moderate-to-severe AD MMSE 5-18 (mean 11.5 and 11.1) 85% female Total number of patients: 265
Interventions	Route: oral

Forest 2006 (MD-22) *(Continued)*

	Treatment: 20 mg memantine daily (N = 133), placebo (N = 132); monotherapy 24 weeks
Outcomes	NPI-NH MOSES CMAI BGP PANSS-EC ADCS-CGI-C and CGI-S MDS
Severity (MMSE mean)	11.3
Notes	ITT population: 263 Completers: 207 (79%) First patient, first visit: 4 November 2004 Last patient, last visit: 15 March 2006 Funding: Forest Laboratories Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised - but no method of sequence generation described. However, study likely to have been conducted according to the principles of good clinical practice. Comment: probably done.
Allocation concealment (selection bias)	Low risk	Method of concealment not described. However, study likely to have been conducted according to the principles of good clinical practice. Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group.
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	ITT-LOCF analysis used. 265 patients randomised, 263 included in ITT-LOCF analyses. Dropout rates identical across both arms of trial, 29/133 (21.8%) in treatment arm and 29/132 (22.0%) in placebo arm. Reasons for dropouts broadly similar across groups (19 due to adverse events in treatment arm compared to 24 in placebo arm). Comment: proportion missing around 22% in each group, and values imputed by LOCF model. This level of missing data could have affected the results, so unclear risk of bias assigned.
Incomplete outcome data (attrition bias) Safety Data	Low risk	All patient outcome data presented. Levels of missing data, other than adverse events were: memantine 10/133 (8%) and placebo 5/132 (4%). This is low compared with the adverse event rate (93% to 98%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk.

Forest 2006 (MD-22) *(Continued)*

Other bias	Unclear risk	Insufficient rationale or evidence that an identified problem will introduce bias.

Forest 2006 (MD-23)

Methods	Randomised, double-blind, placebo-controlled trial of the effectiveness and safety of memantine in non-institutionalised agitated patients with moderate-to-severe AD
Participants	Non-institutionalised agitated patients with moderate-to-severe AD USA N = 34 On stable donepezil MMSE 3-18 NPI score on agitation–aggression domain ≥4
Interventions	Oral memantine 10 mg twice daily (N = 17), placebo (N = 17) 12 weeks
Outcomes	NPI and NPI agitation subscale CMAI CGI-I ADCS-ADL19
Severity (MMSE mean)	not stated
Notes	Planned population: 150 Randomised:34 Completers:30 First patient, first visit: 11 January 2005 Last patient, last visit: 10 April 2006 Study terminated early - reasons not stated Funding: Forest Laboratories Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised - but no method of sequence generation described. However, study likely to have been conducted according to the principles of good clinical practice. Comment: probably done.
Allocation concealment (selection bias)	Low risk	Method of concealment not described. However, study likely to have been conducted according to the principles of good clinical practice. Comment: probably done.
Blinding (performance bias and detection bias)	Low risk	Double-blind, placebo-controlled; no methods described.

Forest 2006 (MD-23) *(Continued)*

All outcomes		Comment: sufficient for assignment of low risk of bias.
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	2/17 (12%) withdrawn in each group; 2 memantine and 1 placebo patients were withdrawn because of adverse events. This level is unlikely to affect the effect estimates
Incomplete outcome data (attrition bias) Safety Data	Low risk	Quote: "The pertinent safety findings are displayed". Adverse event data from all randomised participants displayed. Level of missing data, apart from adverse events: memantine 0%; placebo 1/17 (6%). This is low compared to the adverse events risk (71 and 47%) Comment: low risk of bias in data presented.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk.
Other bias	High risk	Termination prior to completion, reasons not stated

Fox 2012 (MAGD)

Methods	Randomised, double-blind, placebo-controlled, efficacy study
Participants	Randomised N = 153, started medication N = 149, completers = 117 Moderate-to-severe AD baseline MMSE ≤19, mean 7.5 Diagnosis: probable AD according to NINCDS-ADRDA criteria Institutionalised patients with at least 2-week history of behavioural disturbance, and agitation judged by their clinical team to require intervention CMAI ≥ 45 Exclusion: use of a cholinesterase inhibitor for less than 3 months; 19% memantine and 23% placebo patients were on ChEIs. Country: UK
Interventions	10 mg BD memantine (N = 74) versus placebo (N = 79) Duration: 12 weeks
Outcomes	Primary: CMAI at 6 weeks (and also reported at 12 weeks) Secondary: NPI, CGI-C, SIB, quality of life, co-medications, use of rescue protocol, incidents of agitation. 6/52 + 12/52
Severity (MMSE mean)	7.5
Notes	Funding: Lundbeck 11232

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Minimisation was adopted to maintain balance on key confounding variables; centre; age group; sex; dementia (moderate, moderately severe, severe and very severe); and agitation severity (CMAI score ,50, 51–55, 56–60, 61–65, 66–70, 71–75 and .75). Since participants, study personnel, clinicians and

Fox 2012 (MAGD) *(Continued)*

		carers were blind to allocation, no probabilistic element was introduced into the minimisation procedure" Comment: minimisation is an adequate method of sequence generation.
Allocation concealment (selection bias)	Low risk	Quote: "Randomisation used a secure internet-based randomisation service independent of the study team.". Comment: adequate allocation concealment method.
Blinding (performance bias and detection bias) All outcomes	Low risk	Quote: "Study personnel, clinicians and carers were blind to allocation". Comment: double-blind, placebo-controlled.
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Missing data: memantine 25/74 (34%), placebo 21/79 (27%). Reasons: memantine - 19 adverse events, 2 medical contraindication, 1 concomitant medication, 1 withdrawn consent, 2 other; placebo - 16 adverse events, 2 withdrawn consent, 3 other. For NPI outcome, missing data 34% and 19% Comment: fairly high level of missing data over 12 weeks. Slightly higher dropout in memantine arm.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data apart from adverse events: 6/74 (8%) and 5/79 (6%). This is low in comparison to the level of adverse events (but not reported as the number of patients with AEs).
Selective reporting (reporting bias)	Low risk	Primary and secondary outcomes all reported
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Gortelmeyer 1992

Methods	Randomised, double-blind, parallel-group, placebo-controlled study Duration: 6 weeks
Participants	Country: Germany No. of centres: 2 Diagnosis: dementia defined by DSM-III. Mild-to-moderate dementia (SCAG score > 50) Inclusion: SCAG score > 50. Exclusion: participation in a study the last 4 weeks, impaired renal function, cholestasis, decompensated heart failure, stroke or cerebral trauma in the last 6 months, brain tumour, endogenous psychoses, drug and alcohol abuse, Parkinson's disease, intolerance to the test product. Not permitted: nootropics, antidepressants, neuroleptics, hypnotics (except chloral hydrate and in exceptional cases benzodiazepine with a short half-life), antiparkinsonian drugs, myotonolytics, reserpine containing drugs, ergot alkaloids and their derivatives. Total No: 88 Age: 71,52 (59-96). Sex (% female): 75% MMSE 24.06 (11-30)
Interventions	Route: oral Treatment: memantine 20 mg/day. Treatment commenced at 10 mg/day and after 3 days was increased to 20 mg/day. (N = 45) Control: placebo 1 tablet the first 3 days and after 2 tablets/day (N = 43)

Gortelmeyer 1992 *(Continued)*

Outcomes	SCAG, CGI, GBS, modified ADL behaviour investigation, Tapping test, trace test.
Severity (MMSE mean)	Not stated
Notes	Funding: the study appeared to be supported by Merz. The study recruited patients with "dementia syndrome", this leads to diagnostic uncertainty with regard to an underlying cause.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The patients were assigned to medication groups on the basis of a random list covering both study centres, which was drawn up by the biometrician for a total of 100 patients (including possible technical dropouts) in blocks of 4 with the aid of the RANCODE (IDV) program". Comment: computer generated.
Allocation concealment (selection bias)	Unclear risk	Quote: "The patients were assigned to the medication groups on the basis of a random list covering both study centres, which was drawn up by the biometrician" Comment: insufficient information to assign low risk of bias. Study preceded ICH-GCP
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group. Quote: "Placebo tablets identical in appearance to those containing memantine", "Blinding was carried out by the department of pharmaceutical technology of the manufacturing company".
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Six patients dropped out in total; 4/45 (8.9%; 3 AEs) in the treatment arm and 2/43 (4.7%; 0 AEs) in the placebo arm. This small proportion of dropouts is unlikely to have biased results much.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data in the absence of adverse events was 1/45 (2%) and 2/43 (5%).This low level was much lower than the adverse event rate (56% and 42%).
Selective reporting (reporting bias)	Unclear risk	Data not reported in appropriate format for CGI and decline in ADL
Other bias	High risk	Outdated diagnosis of AD

Grossberg 2008 (MD-50)

Methods	Double-blind, placebo-controlled, RCT
Participants	Moderate-to-severe AD N = 677 Diagnosis: probable AD DSM-IV-TR and NINCDS–ADRDA) criteria Multiple sites in Argentina, Chile, Mexico, and the USA MMSE 3-14 (mean 10.6 and 10.9)

Grossberg 2008 (MD-50) *(Continued)*

	Participants were required to complete 4-14 days of single-blind placebo before baseline measurements
Interventions	28 mg memantine extended release, once daily (N = 342); placebo (N = 335) Patients assigned to memantine initially received 7 mg/day (once daily), and were up-titrated weekly in 7 mg/day increments, reaching the target dose of 28 mg at the beginning of week 4. 24 weeks Both groups had ChEI
Outcomes	Primary: NPI, SIB Secondary: CIBIC-plus, ADCS-ADL19 at week 24. OC data extracted from graphs
Severity (MMSE mean)	10.8
Notes	Start: June 2005. Completed October 2007. Funding: Forest Laboratories, Inc. sponsored this trial and provided financial, material, and statistical support.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The Statistical Programming department at Forest Research Institute generated (using SAS, v. 9.1.3; SAS Institute Inc., Cary, NC, USA) and maintained a list of randomization codes in a secure area." Comment: computer generated (SAS).
Allocation concealment (selection bias)	Low risk	Quote: "The Statistical Programming department at Forest Research Institute generated (using SAS, v. 9.1.3; SAS Institute Inc., Cary, NC, USA) and maintained a list of randomization codes in a secure area. At baseline, each patient was sequentially assigned a randomization number corresponding to treatment assignment. Medication corresponding to the randomization numbers was provided to each study site by Forest Laboratories." Comment: sufficient evidence for adequate allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled. Quote: "Study drug and placebo were administered in identically appearing blister packs, either in the morning or evening"
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Drop out rates similar across both arms of trial: 69/342 (20.2%) in treatment arm and 63/335 (18.8%) in placebo arm. Reasons for dropouts broadly similar across groups (but 34 due to adverse events in treatment arm compared to 21 in placebo arm). Comment: 20% missing data could have affected the outcome.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data apart from the adverse events were: memantine 35/342 (10%) and placebo 42/335 (13%). This is low in comparison with the adverse event rate of around 63%)
Selective reporting (reporting bias)	Unclear risk	OC data extracted from a graph and not reported otherwise

Grossberg 2008 (MD-50) *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Herrmann 2012 (10158)

Methods	Double-blind, placebo-controlled, RCT. Phase 3 efficacy
Participants	Country: Canada; 32 sites Outpatients diagnosed with moderate-to-severe AD and significant psychopathology. Diagnosis: probable AD according to the NINCDS–ADRDA criteria Taking a ChEI. MMSE 5-15 (mean 11.9 and 11.8) Mean age: memantine 74.7 (SD 7.9), placebo 75.1 (SD 6.9) Female 57.7% and 58.8% NPI > 12 with score on the NPI agitation–aggression item of at least 1 Hachinski < 5 Total number of patients: 369
Interventions	Memantine titrated up to 20 mg once daily (N = 182); placebo (N = 187) 24 weeks Plus stable ChEI
Outcomes	Cognitive and behavioural symptoms Primary: NPI, SIB Secondary: CIBIC-plus, ADCS-ADL19, CMAI (long form - max 203)
Severity (MMSE mean)	11.9
Notes	Start date Dec 2003 Last patient last visit: September 2010 Caveats: long recruitment, premature termination due to difficulties in recruiting patients, substantial protocol changes; baseline imbalances (concomitant medication and severity of agitation). Variability across sites in reported events frequency (50% of agitation reports from a single site) Funding for this study was provided by H. Lundbeck A/S

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were randomly and equally allocated to one of the two treatment groups in accordance with a randomization list generated by the sponsor following a standard routine" Comment: computer generation.

Herrmann 2012 (10158) *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "Patients were randomly and equally allocated to one of the two treatment groups in accordance with a randomization list generated by the sponsor... Enrollment of participants and assignment of participants to the study treatment was carried out by the investigators." Comment: insufficient information to show that the investigators knew nothing of the randomisation list, so unclear allocation concealment assigned.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled.
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Missing data (discontinued): memantine: 31/182 (17%; adverse event 15, withdrawal of consent 10, protocol violation 2, nursing home placement 2), placebo: 32/187 (17%; adverse event 10, withdrawal of consent 7, nursing home placement 9, protocol violation 2). This level would probably not have affected the results. However, for the outcome CMAI, results were missing for 134/182 (26%; memantine) and 48/187 (26%; placebo) participants (reasons not stated), which was quite high.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data in the absence of adverse events: memantine 16/182 (9%), placebo 22/187 (12%). These are low levels in comparison with the adverse event rate (73% to 76%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk.
Other bias	Unclear risk	Quote: "patients in the memantine group were more severely agitated compared with the patients in the placebo group, as measured by the CMAI Physical agitation subscore (16.6 (SD 6.8) versus 15.8 (SD 6.4)). At baseline, patients in the placebo group had greater exposure to ChEI treatment (97 versus 95%), and a lower proportion were receiving psychoactive medication treatment compared with the memantine group". (44% versus 54%) Comment: differences in concomitant medication could have affected some outcomes. ClinicalTrials.gov reports that the overall agitation scores were 46.8 (memantine) and 47.0 (placebo), so there may not be important differences.

Hofbauer 2009 (MD-71)

Methods	Randomised, double-blind, placebo-controlled, parallel assignment, safety–efficacy study Duration: 12 weeks Total randomised: 265
Participants	Randomised: memantine 136, placebo 129; ITT: memantine 133, placebo 124; completers memantine 131, placebo Moderate AD MMSE 10-19
Interventions	Memantine twice daily versus placebo twice daily Stable ChEIs permitted but not required; proportion not stated
Outcomes	Primary: Functional Linguistic Communication Inventory (FLCI) at Week 12

Hofbauer 2009 (MD-71) *(Continued)*

	Secondary: American Speech-Language-Hearing Association Functional Assessment of Communication Skills for Adults (ASHA FACS) at Week 12. Adverse events, agitation Not reported: clinical global, cognitive function, decline in ADL, NPI
Severity (MMSE mean)	Not stated
Notes	Funding: first author worked for Forest Research Institute

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised allocation, although method of sequence generation not described
Allocation concealment (selection bias)	Unclear risk	Method of concealment not described
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel assignment
Incomplete outcome data (attrition bias) Safety Data	Low risk	9/129 (7%) and 5/136 (4%) non-completers. This is low in comparison with the adverse event rate (49%)
Selective reporting (reporting bias)	Unclear risk	Only 2 outcomes reported on registry. Seems unlikely that no others were collected.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Holland 2013

Methods	Randomised, double-blind, placebo-controlled study Duration: 12 months Purpose of the study - to investigate whether memantine delays the progression of driving impairment Country: USA
Participants	Otherwise healthy men and women with mild AD ChEls permitted if on a stable dose for > 3 months prior to baseline. No initiation of ChEls permitted; discontinuation and dose reduction were permitted Diagnosis: either be previously diagnosed with mild Alzheimer's disease (AD) by a neurologist, psychiatrist, geriatrician, or be evaluated at a Memory Disorders Center prior to entry into the study MMSE ≥ 23 (mean 28.1 (SD 2.0) memantine and 27.7 (SD 1.6) placebo) Mean age 79.3 (SD 6.2). Female 15/43 (35%) Inclusion: ≥ 60 years; participants must receive a passing score on the DriveABLE test; females at least 2 years post-menopausal or surgically sterile

Holland 2013 *(Continued)*

	Exclusion: treatment with a depot neuroleptic within 6 months; failure on OPTEC vision test; Hachinski test score > 7. Participants with evidence of other psychiatric or neurologic disorders including vascular dementia, LBD, PD,any psychotic disorder, or bipolar disorder
Interventions	Memantine 20 mg (N = 22); placebo (N = 21) One tablet, 10 mg morning and evening (twice daily) for 12 months
Outcomes	Primary: number of patients able to pass the DriveABLE On-Road Test at month 12 Secondary: Fuld Object Memory Evaluation, Rey Complex Figure Test, Trail Making Test - Part A and Part B, MMSE, Useful Field of View, Motor Free Visual Perception Test - Visual Closure Subtest, CDR, ADAS-Cog - all at 12 months (although "6-month testing" stated, with numbers at that time)
Severity (MMSE mean)	~27.9
Notes	Registry data and conference abstracts only Funding: Florida Atlantic University and Forest Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "43 subjects met eligibility criteria and were randomized at a 1:1 ratio in a double-blind,12 month trial" Comment: no details on method of randomisation.
Allocation concealment (selection bias)	Unclear risk	Quote: "43 subjects met eligibility criteria and were randomized at a 1:1 ratio in a double-blind,12 month trial" Comment: no information on allocation concealment.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind trial Comment: probably low risk of bias
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	At 6 month testing, missing data: memantine 7/22 (32%); placebo 7/21 (33%). At 12 months, memantine 9/22 (41%), placebo 8/21 (38%). Reasons: memantine - 4 adverse events, 2 placebo concerns, 2 non-compliance, death 1; placebo - 4 adverse events, 2 placebo concerns, 1 non-compliance, withdrawal 1. This may have affected the outcomes.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data in the absence of adverse events: memantine 3/22 (14%) and 4/21 (19%). This is lower than the adverse event rate 8/22 (36%) and 12/21 (57%) and is considered unlikely to greatly affect the effect estimate
Selective reporting (reporting bias)	Unclear risk	Results not reported at first time point (6 months), which is mentioned in one report. Additionally, only subscales reported for ADAS-Cog and final values reported for MMSE
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Homma 2007 (IE2101)

Methods	Double-blind, randomised, parallel-group, placebo-controlled trial of SUN Y7017, 'Phase 2b'; 3-arm trial

Homma 2007 (IE2101) *(Continued)*

	Duration 24 weeks N = 315
Participants	Country: Japan Number of centres: 53 Diagnosis: moderately severe to severe AD N = 108,107, 100 (20 mg,10 mg, placebo) MMSE 5-14 (mean 10.1 and 10.4); FAST 6a-7a Concomitant use of donepezil was prohibited
Interventions	Memantine 10 mg (N = 107); memantine 20 mg (N = 108); placebo (N = 100). Memantine was started from 5 mg/day to 10 or 20 mg/day by up-titration weekly
Outcomes	Japanese versions of SIB, CIBIC+, ADCS-ADL, NPI, MMSE, FAST, BEHAVE-AD Not reported: agitation
Severity (MMSE mean)	10.3
Notes	Not registered on JAPIC. Funding: Daiichi Sankyo Co. Additional details from "Report on the Deliberation Results", and also Matsunaga 2015 and Nakamura 2014 systematic reviews

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised - but no method of sequence generation described. However, study likely to have been done according to the principles of good clinical practice. Comment: probably done.
Allocation concealment (selection bias)	Low risk	Method of concealment not described. However, study likely to have been done according to the principles of good clinical practice. Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled; no blinding methods described. However, study likely to have been done according to the principles of good clinical practice. Comment: probably done.
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	FAS-OC analysis conducted. Missing data: memantine 20 mg 16/100 (16%); memantine 10 mg 14/107 (13%) and placebo 21/108 (19%). Most were due to adverse events (8, 6 and 15 respectively). Unlikely to affect the effect estimate.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data, apart from adverse events: memantine 20 mg 8/100 (8%); memantine 10 mg 8/107 (7%) and placebo 6/108 (6%). This is low compared with the adverse event rate of 72%
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk.

Homma 2007 (IE2101) *(Continued)*

Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

Howard 2012 (DOMINO-AD)

Methods	Pragmatic randomised, double-blind, parallel-group, placebo-controlled (double-dummy), 4-arm trial Multi-centre Duration: one year
Participants	Country: UK No. of centres: 15 Moderate-to-severe AD; MMSE 5 to 13 (mean 9.1, proportion severe (5-9) 52%) Mean age 77.1 (SD 8.4). 65% female Inclusion: patients with probable or possible AD meeting standardised clinical McKhann criteria, have been continuously prescribed donepezil for at least 3 months and continuously prescribed 10 mg donepezil for the previous 6 weeks. They must have had no changes in prescription of any psychotropic drugs (antipsychotic, antidepressant, benzodiazepine) in the previous 6 weeks, currently living at home, receiving donepezil 10 mg daily, and with Standardized Mini-Mental State Examination (SMMSE) scores between 5 and 13. weeks, The prescribing clinician must have considered (based on NICE guidance, discussions with patient and carer and clinical judgement) that change of drug treatment (i.e. stop donepezil or introduce memantine) may have been appropriate. Exclusion: these include severe, unstable or poorly controlled medical conditions apparent from physical examination or clinical history, current prescription of memantine, contra-indications or previous adverse or allergic reactions to trial drugs, involvement in another clinical trial or that the clinician considers the patient would not be compliant Total number of patients: 295
Interventions	One of four treatment options. 1. Continuation of donepezil with memantine placebo added (N = 73); 2. Switch to memantine 10 mg twice daily with donepezil placebo added; active donepezil tapered and discontinued (N = 76); 3. Donepezil and memantine 10 mg twice daily together (N = 73); 4. Donepezil placebo with memantine placebo (N = 73); active donepezil tapered and discontinued
Outcomes	Primary outcomes: cognitive function (sMMSE), decline in ADL (Bristol Activities of Daily Living Scale (BADLS)) Secondary Outcomes: NPI, EQ-5D, DEMQOL-proxy, GHQ-12, Client service receipt inventory cost-effectiveness, institutionalisation. Adverse events Not reported: clinical global, agitation
Severity (MMSE mean)	9.1
Notes	Methods paper published. NCT00866060. Updated May 2010 Funding: UK Medical Research Council (MRC) and the Alzheimer's Society. Pfizer-Eisai and Lundbeck donated supplies of the drugs and placebo but had no involvement in the design or conduct of the study or the analysis or reporting of the data
Risk of bias	

Howard 2012 (DOMINO-AD) *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Pragmatic randomised, multicentre. Quote: "Treatment (1/4 treatment groups) assignments were made by telephone, by the U.K. Medical Research Council Clinical Trials Unit with the use of randomised minimisation".
Allocation concealment (selection bias)	Low risk	Quote: "...to maintain concealment of the treatment assignments, the first 80 participants were assigned with the use of a prepared list of simple randomised assignments. Treatment (1/4 treatment groups) assignments were made by telephone, by the U.K. Medical Research Council Clinical Trials Unit "
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled (double-dummy), parallel-group. Donepezil, memantine and placebo provided by the manufacturers. Quote: "Patients, caregivers, clinicians, outcome assessors and investigators were unaware of the treatment assignments".
Incomplete outcome data (attrition bias) Primary Outcomes	High risk	Per protocol data were used in the analyses. At 30 weeks, missing data: memantine 25/76 (10 died, 15 withdrew; 33%); placebo 18/73 (9 died, 8 withdrew, 1 loss to follow-up; 25%); memantine + donepezil 15/73 (7 died, 8 withdrew; 21%); donepezil 19/73 (13 died, 6 withdrew; 13%). Results not reported for the completers. However, excluded from the per protocol analysis were: memantine 34/76 (45%; 31 had < 70% adherence); placebo 44/73 (60%; 43 < 70% adherence); memantine + donepezil 22/73 (30%; 19 had < 70% adherence); Donepezil 23/73 (32%). These are high levels of missing data, and there are differential missing data for memantine versus placebo
Incomplete outcome data (attrition bias) Safety Data	Unclear risk	All patients included in the analysis for adverse events. Missing data as above. These levels are relatively low compared with the adverse event rates of around 60%.
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk. Clinical global not reported but not mentioned in methods section either
Other bias	Low risk	The study appears to be free of other sources of bias

Leroi 2009

Methods	Randomised, double-blind, parallel-group, placebo-controlled study Duration: 16 weeks (on drug), plus 22 weeks (off drug) analysis
Participants	Country: UK 25 patients PDD. Diagnosis: 25 Patients with idiopathic PD and dementia due to PD; as defined by DSM-IV with onset of cognitive symptoms at least 1 year after the onset of motor symptoms; Inclusion: MMSE: 10-27,motor aspects unchanged for 4 weeks prior to study entry; stable medical history and general health; and able to consent to study procedures (or have a suitable legal substitute to give consent). Those on cholinesterase inhibitors had to have been stable on the medications for at least 6 months prior to study entry and no recorded improvement in cognitive or behavioral symptoms for at least four weeks prior to randomisation. Population: memantine 11 (44%); placebo 14 (56%) Age: memantine: 74.7 (SD 7.9); placebo: 76.7 (SD 7.8) Sex (% males): memantine: 36.4%; placebo: 64.3% Mean MMSE ˜19.1 (SD 6.0)

Leroi 2009 *(Continued)*

	ChEI: memantine 18.2%, placebo 14.3%.
Interventions	Route: oral Treatment: fixed dose 20 mg memantine daily (N = 11) Control: placebo (N = 14) The study drug was discontinued without taper at week 16, with the final evaluation (off drug) at week 22
Outcomes	Primary outcomes: Dementia Rating Scale (DRS) Secondary outcomes: NPI, MMSE, CIBIC+, GAS, PDQ-8, ZBI Safety outcomes: Orthostatic Vital Signs, UPDRS motor score (UPDRS-III), adverse events, compliance checks
Severity (MMSE mean)	19.1
Notes	Concomitant cholinesterase inhibitor treatment, n (%) placebo: 2 (14.3%), memantine: 2 (18.2%) Funding: unrestricted grant from H. Lundbeck A/S, which in part supported this study. The funders of the study had no role in the study design, data collection, data analysis, data interpretation or the writing of the report

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	RCT - but no method of sequence generation described. However, study likely to have been done according to the principles of good clinical practice. Comment: probably done.
Allocation concealment (selection bias)	Low risk	Method of concealment not described. However, study likely to have been done according to the principles of good clinical practice. Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group; no blinding methods detailed. However, study likely to have been done according to the principles of good clinical practice. Comment: probably done.
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	ITT-LOCF population used for analysis. 25 patients randomised, all included in the analyses. One patient in the memantine arm (9%) failed to complete the trial due to hospital admission for pneumonia, classed as a SAE.
Incomplete outcome data (attrition bias) Safety Data	Low risk	All data presented. No missing data in the absence of adverse events
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk.
Other bias	Unclear risk	Disproportionate randomisation to trial arms (N = 14 placebo versus N = 11 memantine). Baseline characteristics were generally comparable, apart from the proportion of men (64.3% versus 36.4%)

Lorenzi 2011 (SC05-03)

Methods	Randomised, double-blind, placebo-controlled, parallel-assignment study Duration: 6 months
Participants	Country: Italy Number of centres: 1 Diagnosis: Alzheimer's disease (NINCDS-ADRDA) Moderate-to-severe disease; MMSE 15.6 (SD 4.9) memantine; 13.1 (SD 3.5) placebo N = 15 Mean age: 76.5 years 87% females Inclusion criteria: diagnosis of probable Alzheimer's disease, Clinical Dementia Rating scale score of ≥2, and treatment with ChEIs for at least 6 months Exclusion criteria: history of transient ischaemic attack or stroke, head trauma, alcohol or substance abuse, corticosteroid therapy, recent weight loss and a modified Hachinski ischaemic scale score of ≥4
Interventions	Route: not reported Treatment: memantine 5 mg once daily, increasing by 5 mg/day to a final dose of 20 mg/day for 6 months (N = 8). Control: placebo (N = 7).
Outcomes	Primary outcome: change in DMN activity (Resting state fMRIs) Secondary outcomes: cognitive assessment: MMSE; non-verbal reasoning: Raven's Coloured Progressive Matrices; constructional ability: Rey-Osterrieth complex figure copy; Attention and executive functions: Trail Making Test A, Trail Making Test B, Trail Making Test B-A; language: verbal fluency (phonemic, semantic), Token Test; Memory: story recall, Rey-Osterrieth complex figure recall, Digit span, Spatial span
Severity (MMSE mean)	˜14.4
Notes	Co-funded by Italian Ministry of Health, Ricerca Finalizzata and Lundbeck Italia SpA Pharmaceutical Other drugs permitted at stable doses for at least 2 weeks before recruitment were antidepressant, anti-inflammatory and antihypertensive agents, anticoagulants, diuretics, hypnotics and high-dose vitamin E

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised", no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information given.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel assignment, blinding methods not described
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	All enrolled participants completed the study; no missing data.
Incomplete outcome data (attrition bias) Safety Data	Low risk	No missing data

Lorenzi 2011 (SC05-03) *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All stated outcomes reported, but insufficient information to permit judgement of 'Low' or 'High' risk. MMSE results reported as final values only
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Lundbeck 2006 (10116)

Methods	Randomised, double-blind, parallel-group, placebo-controlled study
Participants	Country: China MMSE 5-18 (mean 11.8 SD 4.1) Probable AD Age 72, F:M = 3:2 Number of patients randomised: 258
Interventions	Route: oral Treatment: memantine 10 mg twice daily (N = 128); placebo (N = 130) 16 weeks No patients were receiving cholinesterase inhibitors (and patients were not allowed in the study if they had received treatment with a ChEI within 30 days prior to screening - personal communication)
Outcomes	SIB, ADCS-ADL19 , NPI , MMSE. Adverse events Not reported: clinical global, agitation
Severity (MMSE mean)	11.8
Notes	ITT Population: 249 (97%) Completer: 236 (95%) First patient, first visit: 7th Jan 2004 Last patient, last visit: 5th April 2005 Trial report approval: 11th October 2006 Posted: 23rd October 2006 Funding: Lundbeck A/S

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomised - but no method of sequence generation described. However, study was "conducted in compliance with the principles of *Good Clinical Practice*". Comment: probably done.
Allocation concealment (selection bias)	Low risk	Method of concealment not described. However, study was "conducted in compliance with the principles of *Good Clinical Practice*" Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group; no blinding methods described. However, study was "conducted in compliance with the principles of *Good Clinical Practice*".

Lundbeck 2006 (10116) *(Continued)*

Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Missing data: memantine 11/128 (9%) and placebo 11/130(8%) analysed. Reasons for dropouts broadly similar across groups; 6 due to adverse events in treatment arm, compared with 5 in the placebo arm. Comment: with an identical and low dropout rate between trial arms, low risk of bias is assumed.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data, apart from adverse events: 5/128 (4%) and 6/130 (5%). This is low compared to the adverse event rates of 15 and 18%
Selective reporting (reporting bias)	Unclear risk	Clinical global not reported, but possibly not done
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Lundbeck 2006 (99817)

Methods	Randomised, double-blind, placebo-controlled trial
Participants	Mild-to-moderate Alzheimer's disease 47 participants 16 with MMSE < 15. Taiwan.
Interventions	Memantine 12 weeks
Outcomes	Not known
Severity (MMSE mean)	not stated
Notes	Conducted by HatCo Ltd. Dr Pei-Ning Wang, Dr Sui- Hing Yan Last patient last visit: Aug 04 Was 'in write up phase' in June 06 (personal communication: Lundbeck)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised - but method of sequence generation not described.
Allocation concealment (selection bias)	Unclear risk	Method of concealment not detailed.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled. Comment: probably done.
Selective reporting (reporting bias)	Unclear risk	Insufficient reporting overall
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Marsh 2009 PDD

Methods	Randomised, double-blind, placebo-controlled, parallel assignment, safety–efficacy study Duration: 24 Weeks
Participants	Country: USA N = 20 (10 on ChEI, 5 in each arm) 10 completers in memantine arm, 8 in placebo arm Dementia secondary to PD, as defined by DSM-IV Participants taking ChEIs were included provided they had been on ChEIs for at least 6 months Stable dose of anti-PD medications for at least 2 months before randomisation. MMSE: placebo: 21.4 (SD 6.0); memantine: 23.2 (SD 3.7)
Interventions	Active memantine (N = 10) and placebo (N = 10), taken by mouth, titrated from 5 mg per day to 20 mg per day over 4 weeks. Five in each group continued cholinesterase inhibitors
Outcomes	Primary outcomes: cognitive efficacy; paper and pencil tests of memory, CGI, DRS Secondary outcomes: ADAS-cog, Lawton ADL, NPI, Safety–Tolerability
Severity (MMSE mean)	~22 (23.2 memantine and 21.4 placebo)
Notes	Sponsors: Forest, Johns Hopkins Estimated Primary Completion Date:September 2008 (Final data collection date for primary outcome measure). Data on total ADL score, total DRS score not available from poster - but likely to be available in submitted paper.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised allocation - but sequence generation process not described.
Allocation concealment (selection bias)	High risk	Concealment method not detailed. Baseline differences comparable or larger than effect estimate for primary outcomes, especially.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind (participant, caregiver, investigator, outcomes assessor), placebo-controlled, parallel assignment
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	2/10 (20%) in placebo withdrew (1 because of agitation; 1 because of 'subject preference'), 0/10 in memantine arm. Bias likely to favour placebo, but the difference in the number of patients is only 2 between arms, so unclear risk of bias assigned
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data apart from AEs: 0/10 memantine and 1/10
Selective reporting (reporting bias)	Unclear risk	Available as poster only

Marsh 2009 PDD *(Continued)*

Other bias	Unclear risk	Differences at baseline in MMSE

Medina 2011

Methods	Randomised, double-blind, placebo-controlled, parallel assignment study Duration: 6 months
Participants	Country: USA Number of centres: 3 medical centres Diagnosis: Huntingdon's Disease (criteria not reported) N = 50 Mean age: 47.25 years 62% females Inclusion criteria: mild-to-moderate Huntington's disease
Interventions	Route: not reported Treatment: memantine 10 mg (N not reported). Control: placebo (N not reported).
Outcomes	Attention (Brief Test of Attention), working memory (Digit Ordering Test), executive function (Stroop Inhibition, Verbal Fluency Switching), verbal fluency (Animals, Boys' Names, Fruits), and memory (Hopkins Verbal Learning Test); Neuropsychiatric Inventory (NPI), daily functioning: Alzheimer's Disease Cooperative Study (ADCS)-Activities of Daily Living (ADL) Scale; Quantified Neurological state: Quantified Neurological Exam (QNE)
Severity (MMSE mean)	Not stated
Notes	Supported by Forest Pharmaceuticals

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomised", no further details reported.
Allocation concealment (selection bias)	Unclear risk	No information given on process.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind; placebo-controlled, although insufficient detail "identical-appearing placebo"; parallel assignment.
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	No data reported on losses to follow-up
Selective reporting (reporting bias)	High risk	No means and SDs reported.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Merz 2003 (MRZ-9104)

Methods	Randomised, double-blind, parallel-group, placebo-controlled study
Participants	Country: France Prof Derouesne 56 patients AD of unknown severity
Interventions	13 weeks 20 mg memantine monotherapy
Outcomes	
Severity (MMSE mean)	
Notes	No results available. Quote "You have kindly requested data on memantine studies MRZ 9104, MRZ9105, MRZ9206. These studies were small studies of an exploratory nature and were conducted in the early 1990's in various types and severity stages of dementia. As the studies are very small in patients numbers, present a very heterogeneous patient population and none of these studies has been designed to evaluate Alzheimer's disease patients according to the current label, these studies are not suitable to understand or assess the risk/benefit ratio of memantine with respect to the treatment of Alzheimer patients. The safety data of all studies have of course been communicated to the authorities and are part of the integrated safety data base all safety analyses are based on and are therefore public knowledge. Dr. Ursula Windscheif, Head CNS Medical Communications, Central Strategic Marketing CNS, Merz Pharmaceuticals GmbH 20th March 2008"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized" only.
Allocation concealment (selection bias)	Unclear risk	Concealment process not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group - no further details
Selective reporting (reporting bias)	High risk	Incomplete knowledge of trial protocol or data. Quote from e-mail correspondence: "These studies were small studies of an exploratory nature and were conducted in the early 1990s in various types and severity stages of dementia. As the studies are very small in patient numbers, they present a very heterogeneous patient population"
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Merz 2003 (MRZ-9105)

Methods	Randomised, double-blind, parallel-group, placebo-controlled study
Participants	Country: Portugal 27 patients Mild-to-moderate severe stages of primary dementia
Interventions	12 weeks monotherapy 20 mg memantine
Outcomes	
Severity (MMSE mean)	not stated
Notes	No results available. Quote "You have kindly requested data on memantine studies MRZ 9104, MRZ9105, MRZ9206. These studies were small studies of an exploratory nature and were conducted in the early 1990's in various types and severity stages of dementia. As the studies are very small in patients numbers, present a very heterogeneous patient population and none of these studies has been designed to evaluate Alzheimer's disease patients according to the current label, these studies are not suitable to understand or assess the risk/benefit ratio of memantine with respect to the treatment of Alzheimer patients. The safety data of all studies have of course been communicated to the authorities and are part of the integrated safety data base all safety analyses are based on and are therefore public knowledge. Dr. Ursula Windscheif, Head CNS Medical Communications, Central Strategic Marketing CNS, Merz Pharmaceuticals GmbH 20th March 2008"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized" only.
Allocation concealment (selection bias)	Unclear risk	Concealment process not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group - no further details.
Selective reporting (reporting bias)	High risk	Incomplete knowledge of trial protocol or data. Quote from e-mail correspondence: "These studies were small studies of an exploratory nature and were conducted in the early 1990s in various types and severity stages of dementia. As the studies are very small in patient numbers, they present a very heterogeneous patient population"
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Merz 2003 (MRZ-9206)

Methods	Randomised, double-blind, parallel-group, placebo-controlled study

Merz 2003 (MRZ-9206) *(Continued)*

Participants	Country: Sweden 56 patients Moderately severe vascular dementia
Interventions	Monotherapy 20 mg memantine 14 weeks
Outcomes	
Severity (MMSE mean)	not stated
Notes	No results available. Quote "You have kindly requested data on memantine studies MRZ 9104, MRZ9105, MRZ9206. These studies were small studies of an exploratory nature and were conducted in the early 1990's in various types and severity stages of dementia. As the studies are very small in patients numbers, present a very heterogeneous patient population and none of these studies has been designed to evaluate Alzheimer's disease patients according to the current label, these studies are not suitable to understand or assess the risk/benefit ratio of memantine with respect to the treatment of Alzheimer patients. The safety data of all studies have of course been communicated to the authorities and are part of the integrated safety data base all safety analyses are based on and are therefore public knowledge. Dr. Ursula Windscheif, Head CNS Medical Communications, Central Strategic Marketing CNS, Merz Pharmaceuticals GmbH 20th March 2008"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomized" only.
Allocation concealment (selection bias)	Unclear risk	Concealment process not described.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group - no further details.
Selective reporting (reporting bias)	High risk	Incomplete knowledge of trial protocol or data. Quote from e-mail correspondence: "These studies were small studies of an exploratory nature and were conducted in the early 1990s in various types and severity stages of dementia. As the studies are very small in patient numbers, they present a very heterogeneous patient population"
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Nakamura 2016

Methods	Randomized, double-blind, parallel-group, placebo-controlled study
Participants	Country: Japan 546 patients AD

Nakamura 2016 *(Continued)*

	Diagnosis: probable Alzheimer's disease by NINCDS-ADRDA Moderate-to-severe AD Inclusion: MMSE: 1-14, people had been on donepezil for ≥ 4 weeks when recruited, then 12 weeks single blind observation period on donepezil (5 mg or 10 mg); only those stable (SIB) continued to the double-blind period. Population: memantine+donepezil 273 (50%); placebo 273 (50%) Age: memantine + donepezil: 78.4 (SD 8.1); placebo + donepezil: 78.6 (SD 7.6) years Sex: memantine + donepezil: 71.6%; placebo + donepezil: 74.0% Mean MMSE at start of double blind period: memantine + donepezil: 10.9 (SD 3.7); placebo + donepezil: 10.7 (SD 3.7)
Interventions	Memantine 20 mg + donepezil (167 at 5 mg and 101 at 10 mg) 24 weeks (N = 268) Placebo + donepezil (165 at 5 mg and 104 at 10 mg) 24 weeks (N = 269)
Outcomes	SIB-J, BEHAVE-AD (total and components, including aggression), Crichton Geriatric Behavioural Rating, Adverse events, discontinuation Not reported: clinical global, NPI
Severity (MMSE mean)	~10.8
Notes	Translated from Japanese. Supported by Sankyo Co. Ltd. LOCF Additionally results reported for SIB for a post-hoc subgroup with MMSE 5-14 to align with other studies

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Unclear
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Loss to follow-up: Memantine + donepezil group: 53/268 (20%); Placebo + donepezil: 39/269 (14%). Differential missing data but unclear how important this is
Incomplete outcome data (attrition bias) Safety Data	Low risk	Data reported for all participants
Selective reporting (reporting bias)	Unclear risk	Clinical global and ADL not reported, but possibly not done
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

Orgogozo 2002 (9408)

Methods	Randomized, double-blind, parallel-group, placebo-controlled Duration: 28 weeks
Participants	Country: France, Belgium and Switzerland No of centres: 50 Diagnosis: probable vascular dementia by NINDS-AIREN and HIS ≥ 5; dementia by DSM IIIR Inclusion: MMSE: 12-20 (˜16.9 SD 2.5) - mild-to-moderate dementia Exclusion criteria: Alzheimer's disease and secondary types of dementia. History of seizures, alcoholism, drug abuse, chronic users of medications with the potential to interfere with the outcomes, psychotic episodes. Concomitant use of anticonvulsants, anti-Parkinson medications, hypnotics, anxiolytics, antipsychotics, centrally- acting antihypertensives and cognition enhancers. Total number of patients: 321 Age: placebo: 76.1 (SD 8.68); memantine: 76.6 (SD 6.6) Sex (%females): memantine: 52,5%; placebo: 43%.
Interventions	Route: oral Treatment: memantine 20 mg/day (N = 165) Treatment started at 5 mg/day and increased in three weeks to 20 mg/day Control: placebo once per day (N = 156)
Outcomes	Primary endpoints: ADAS-Cog (Alzheimer's Disease Assessment Scale, cognitive subscale; 11 items); CIBIC-Plus (Clinician's Interview Based Impression of Change) Secondary efficacy variables: MMSE (Mini Mental State Examination); Gottsfries-Brane-Steen (GBS) scale; Clinical Global Impression of Change; Nurse's Observational Scale for Geriatric Patients (NOSGER) Safety and tolerability
Severity (MMSE mean)	˜16.9
Notes	ITT population: 288 (90%) PP Population: 188 (59%) Trial conducted between June 1996 and Janurary 1999 Funding: trial sponsored by Merz Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised - but no method of sequence generation described. However, Quote: "The study was conducted according to Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki". Comment: probably done.
Allocation concealment (selection bias)	Low risk	Method of concealment not described. However, Quote: "The study was conducted according to Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki". Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group; blinding method not detailed. However,Quote: "The study was conducted according to Good Clinical Practice Guidelines and the principles of the Declaration of Helsinki". Comment: probably done.

Orgogozo 2002 (9408) *(Continued)*

Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	OC data included in FDA report. Missing data varied with outcome: ADAS-Cog memantine 51/165 (31%), placebo 42/156 (27%). NOSGER: memantine - 72/165 (44%); placebo 61/156 (39%) Reasons for dropouts were broadly similar across groups: 20 due to adverse events in treatment arm compared to 19 in placebo arm. It is unclear whether this level of missing data could affect the effect estimates
Incomplete outcome data (attrition bias) Safety Data	Unclear risk	Missing data apart from adverse events: 41/165 (25%) and 36/156 (23%). This is rate is comparable with the serious adverse event rate (23% and 26%), so unclear risk of bias
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk. Published paper did not report SDs for the subscales of the NOSGER outcome. Calculated using P values for the mean difference
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists

Pantev 1993

Methods	Randomised, double-blind, parallel-group, placebo-controlled study Duration: 6 weeks
Participants	Country: Germany No. of centres: not stated. Diagnosis: DSM III-R. Inclusion: Lausanne scale and SCAG ≥ 80. Exclusion: participation in a study within the preceding 4 weeks, drug and alcohol abuse, known intolerance, severe chronic or terminal disease, decompensated hypertension, relevant heart disease, stroke in the last 3 months, impairment of liver or kidney function, secondary dementia, Parkinson's disease, seizures. No. of patients: 60 Age: 72.4 Sex (% female): 75%
Interventions	Route: oral Treatment: memantine 30 mg/day. Treatment commenced at 10 mg/day, increased by 10 mg/day at 2 and 7 days. Control: placebo (the same regime)
Outcomes	Global assessment of clinical efficacy, SCAG, BGP, NOSIE-Index, Physician's global rating of tolerability
Severity (MMSE mean)	not stated
Notes	Funding: Merz

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomised" - sequence generation process not detailed, but: "...carried out in accordance with the German guidelines on the proper performance of clinical trials (Bundesanzeiger, 1987)".

Pantev 1993 *(Continued)*

		Comment: probably done.
Allocation concealment (selection bias)	Low risk	Concealment method not sufficiently described, but: Quote: "...carried out in accordance with the German guidelines on the proper performance of clinical trials (Bundesanzeiger, 1987)". Comment: probably done
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group. Quote: "The blinding of the drugs was performed in the Dept. of Pharmaceutical Technology of the manufacturing company".
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	No missing outcome data. Absolute frequencies reported.
Selective reporting (reporting bias)	Unclear risk	Adverse event data discussed but not reported
Other bias	High risk	Outdated diagnosis of AD

Peskind 2004 (MD-10)

Methods	Randomised, double-blind, parallel-group, placebo-controlled study Duration: 24 weeks
Participants	Country: USA No. of Centres: 42 Diagnosis: probable Alzheimer's disease by NINCDS-ADRDA Mild-to-moderate AD: MMSE mean 17.4 and 17.2 Inclusion: MMSE: 10-22; age≥ 50 years; brain imaging (CT scan or MRI) within 12 months consistent with a diagnosis of probable AD; a knowledgeable and reliable caregiver to accompany the patient to all study visits and supervise administration of the study drug; Montgomery-Asberg Depression Rating Scale (MADRS)12 score < 22; ability to ambulate; vision and hearing capabilities allowing compliance with testing procedures; and medically stable condition. Stable doses of non-excluded concomitant medications allowed, including antihypertensives, antiinflammatories, diuretics, antidepressants, risperidone, olanzapine, Ginkgo biloba, ginseng, and tocopherol Exclusion: clinically significant and active pulmonary, gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease; clinically significant B12 or folate deficiency; evidence of any psychiatric or neurologic disorder other than probable AD; Hachinski Ischemia Score > 4; delusions or delirium (as defined by DSM–IV); oncology diagnosis and recent or ongoing treatment or evidence of active disease; treatment with a depot neuroleptic within 6 months of screening; positive urine test for prohibited medications; known or suspected history of alcoholism or drug abuse within the past 10 years; previous treatment with memantine; treatment within 30 days of screening with a ChEI or any investigational drug. Females at least 2 years postmenopausal or surgically sterile. Total No of patients: 403 Age: memantine:78 (SD 7.3); placebo: 77 (SD 8.2) Sex (%females): memantine: 60.2%, placebo: 57.4%
Interventions	Route: oral Treatment: memantine 20 mg/day (10 mg twice daily titrated over a 4-week period) (N = 201) Control: placebo (N = 202)
Outcomes	Primary end points: ADAS-Cog, CIBIC-plus Secondary outcomes: ADCS-ADL23, NPI, Safety, Agitation

Peskind 2004 (MD-10) *(Continued)*

Severity (MMSE mean)	17.3
Notes	First patient, first visit: 8 October 2001 Last patient, last visit: 16 June 2003 Funding: Forest labs Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomised to memantine or placebo in permuted blocks of four in accordance with the randomisation list generated and retained by Forest Research Institute, Department of Statistical Programming." Comment: computer generated
Allocation concealment (selection bias)	Low risk	Quote "Participants were randomised to memantine or placebo in permuted blocks of four in accordance with the randomisation list generated and retained by Forest Research Institute, Department of Statistical Programming".
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group. Quote: "Placebo and memantine tablets were visually identical", and study likely to have been conducted according to the principles of good clinical practice.
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Dropout rates similar across both arms of trial: 36/201 (18%) in treatment arm compared to 35/202 (17%) in placebo arm, however reason for dropouts not similar across groups (19 due to adverse events in treatment arm compared to 10 in placebo arm)
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data apart from adverse events: 17/201 (8%) and 25/202 (12%). This is low in comparison with the adverse events rate of 71% and 74%
Selective reporting (reporting bias)	Low risk	All outcome data presented
Other bias	Low risk	The study appears to be free of other sources of bias

Peskind 2004 (MD-10) SG

Methods	As for MD-10 (Peskind 2004) Data drawn from Winblad 2007b meta-analysis
Participants	Mild and moderate AD post-hoc data. Moderate: memantine 130 (65%); placebo 143 (71%)
Interventions	
Outcomes	
Severity (MMSE mean)	Not stated for subgroup (all 17.3)
Notes	

Risk of bias

Peskind 2004 (MD-10) SG *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomised to memantine or placebo in permuted blocks of four in accordance with the randomisation list generated and retained by Forest Research Institute, Department of Statistical Programming." Comment: computer generated
Allocation concealment (selection bias)	Low risk	Quote "Participants were randomised to memantine or placebo in permuted blocks of four in accordance with the randomisation list generated and retained by Forest Research Institute, Department of Statistical Programming".
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group. Quote: "Placebo and memantine tablets were visually identical", and study likely to have been conducted according to the principles of good clinical practice.
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Dropout rates similar across both arms of trial: 36/201 (18%) in treatment arm compared to 35/202 (17%) in placebo arm, however reason for dropouts not similar across groups (19 due to adverse events in treatment arm compared to 10 in placebo arm). Small differences in proportion with moderate severity in remaining patients: memantine 65% and placebo 70%
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data apart from adverse events: 17/201 (8%) and 25/202 (12%). This is low in comparison with the adverse events rate of 71% and 74%
Selective reporting (reporting bias)	High risk	Subgroup of patients selected, post-hoc and not stratified by severity and then randomised
Other bias	Low risk	The study appears to be free of other sources of bias

Peters 2015 (MEGACOMBI2)

Methods	Randomised, double-blind, placebo-controlled study Duration: 52 weeks
Participants	Country: Germany No. of Centres: 12 Diagnosis: probable Alzheimer's disease by NINCDS-ADRDA and the German Dementia Competence Network, and results of an MRI or CT within the past 12 months consistent with a diagnosis of probable AD. Mild-to-moderate AD: MMSE mean memantine + galantamine: 21.7 (SD 3.2); galantamine only: 22.6 (SD 3.1); significant difference between groups (P = 0.029) Inclusion: MMSE: 15-26; age ≥ 50 years; brain imaging (CT scan or MRI) within 12 months consistent with a diagnosis of probable AD; an informed and reliable caregiver to accompany the patient to all study visits and supervise administration of the study drug; vision and hearing capabilities allowing compliance with assessment; absence of previous treatments with ChEIs or memantine. Exclusion: clinically significant medical, psychiatric, neurodegenerative, or intracerebral diseases; specifically active pulmonary, gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease; clinically significant vitamin D or folate deficiency. Total No of patients: 232 recruited, 6 did not meet inclusion criteria, so 226 randomised Age: memantine + galantamine:72.1 (SD 8.5); placebo + galantamine: 72.6 (SD 8.5) years Sex (% females): memantine + galantamine: 58.9%, placebo + galantamine: 68.4%

Peters 2015 (MEGACOMBI2) *(Continued)*

Interventions	Memantine (10 mg twice daily; dose titration over 16 weeks) + galantamine-CR (24 mg / day; dose titration over 12 weeks, maintenance phase starting week 9); 50 % received galantamine first, 50 % memantine first to allow for differential qualitative evaluation of tolerability; 52 weeks (N = 112) Placebo + galantamine-CR 52 weeks (N = 114) Four weeks washout. All patients were ChEI naive
Outcomes	ADAS-Cog, CDR sum of boxes, ADCS-ADL23, NPI, safety and tolerability
Severity (MMSE mean)	˜22.2
Notes	(MRZ 10001-0207) NCT01921972 Funding: Bundesministerium fűr Bildung und Forschung. Drugs provided by Janssen-Cilag and Merz

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote "The randomization was performed in blocks with a block length of six." and "conducted in accordance with the current ICH-GCP-guidelines" Comment: computer randomisation
Allocation concealment (selection bias)	Low risk	Quote: "conducted in accordance with the current ICH-GCP-guidelines" Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled trial. Quote, "Memantine and placebo pills were equal with regard to shape, color, and size"
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Missing data at 52 weeks similar across both arms of trial: 30/112 (27%) in treatment arm compared to 27/114 (24%) in control arm; reason for dropouts similar (19 due to adverse events in treatment arm compared to 14 in placebo arm; 2 versus 3 for insufficient therapeutic response). At 26 weeks for ADAS-Cog outcome, missing data (per protocol): 24/114 (21%) 27/112 (24%). At 26 weeks for ADL outcome: 42/114 (37%) and 35/112 (31%). Unclear whether this would affect the outcome.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data apart from adverse events: 11/112 (10%) and 13/114 (11%). This is low in comparison with the adverse events rate of 79% and 70%
Selective reporting (reporting bias)	Unclear risk	Data extracted from graph, which is incorrectly labelled as SD. Statistics section states SE and P-values equate to SE. Discrepancy between PRISMA and number of patients in the ADAS-Cog graph. Error that might lead to high risk of bias. Results for NPI not reported fully
Other bias	Unclear risk	Significant difference in MMSE at baseline: combination: 21.7 (SD 3.2); galantamine only: 22.6 (SD 3.1)

Porsteinsson 2008 (MD-12)

Methods	Randomised, double-blind. parallel-group. placebo-controlled study

Porsteinsson 2008 (MD-12) *(Continued)*

	Duration: 24 weeks
Participants	Country: USA 432 patients Diagnosis: probable AD using NINCDS-ADRDA criteria Mild-to-moderate AD on ChEI MMSE 10-22 Mean 16.7 and 17.0
Interventions	Route: oral Treatment: memantine 20 mg/day (10 mg twice daily titrated over a 4-week period; N = 217). On stable dose of ChEI. Control: placebo plus continued ChEI (N = 216)
Outcomes	ADAS-Cog, CIBIC+; Secondary: ADCS-ADL23, NPI
Severity (MMSE mean)	16.9
Notes	ITT population: 427/433 First patient, first visit: 5 June 2002 Last patient, last visit: 25 March 2003 Funding: Forest Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomised to memantine or placebo in permuted blocks of four in accordance with the randomisation list generated and retained by Forest Research Institute, Department of Statistical Programming."
Allocation concealment (selection bias)	Low risk	"Participants were randomised to memantine or placebo in permuted blocks of four in accordance with the randomisation list generated and retained by Forest Research Institute, Department of Statistical Programming."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group and quote: "Site staff remained blinded to study medication during the trial"
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Missing data similar across both arms of trial: 23/217 (10.6%) in treatment arm compared to 25/216 (11.6%) in placebo arm; reason for dropouts broadly similar across groups (13 due to adverse events in treatment arm compared to 17 in placebo arm). Small differences in the proportion with moderate severity in remaining patients: memantine 70% and placebo 66%
Incomplete outcome data (attrition bias) Safety Data	Low risk	All patient outcome data presented. Missing data, apart from adverse events: 10/217 and 8/216. This is low in comparison with the adverse events rate of 27/217 and 30/216
Selective reporting (reporting bias)	Low risk	All outcome data reported
Other bias	Unclear risk	The study appears to be free of other sources of bias

Porsteinsson 2008(MD-12)S

Methods	As for MD-12. Data drawn from Winblad 2007b meta-analysis
Participants	Post-hoc subgroup analyses for mild and moderate AD. Moderate: memantine 154 (71%) and placebo 148 (69%)
Interventions	
Outcomes	
Severity (MMSE mean)	Not stated for the subgroup (all 16.9)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Participants were randomised to memantine or placebo in permuted blocks of four in accordance with the randomisation list generated and retained by Forest Research Institute, Department of Statistical Programming."
Allocation concealment (selection bias)	Low risk	"Participants were randomised to memantine or placebo in permuted blocks of four in accordance with the randomisation list generated and retained by Forest Research Institute, Department of Statistical Programming."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group and quote: "Site staff remained blinded to study medication during the trial"
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Missing data similar across both arms of trial: 23/217 (10.6%) in treatment arm compared to 25/216 (11.6%) in placebo arm; reason for dropouts broadly similar across groups (13 due to adverse events in treatment arm compared to 17 in placebo arm).
Incomplete outcome data (attrition bias) Safety Data	Low risk	All patient outcome data presented. Missing data, apart from adverse events: 10/217 and 8/216. This is low in comparison with the adverse events rate of 27/217 and 30/216
Selective reporting (reporting bias)	High risk	Subgroup of patients selected, post-hoc and not stratified by severity and then randomised.
Other bias	Low risk	The study appears to be free of other sources of bias

Reisberg 2003 (9605)

Methods	Randomised, double-blind, parallel-group, placebo-controlled study Duration: 28 weeks
Participants	Country: USA No of centres: 32 Diagnosis: probable Alzheimer's disease by DSM-IV and NINCDS-ADRDA Moderate-to-severe AD: MMSE mean 7.9 (SD 3.64) Inclusion: MMSE:3-14; GDS: 6; FAST: 6

Reisberg 2003 (9605) *(Continued)*

	Exclusion: vascular dementia, or other clinically significant neurological disease, major depressive disorder, or a score greater than 4 on the Modified Hachinski Ischaemia Rating Scale. Total No of patients: 252 Age: 76.1 (SD 8.07) Sex (females%): memantine: 72,2; placebo: 65,5. Baseline SIB ˜ 67
Interventions	Route: oral Treatment: memantine 20 mg /day (N = 126) Control: placebo (N = 126)
Outcomes	Primary end points: CIBIC-plus; ADCS-ADL19 Inventory, modified for severe dementia Secondary outcomes: Severe Impairment Battery (SIB); FAST, NPI
Severity (MMSE mean)	7.9
Notes	LOCF Population: 236 (94%). PP Population: 181 (72%) First patient, first visit: August 1998 Last patient, last visit: October 1999 Funding: Merz Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Randomization was stratified according to site with the use of RanCode (version 3.1)". Comment: computer generated.
Allocation concealment (selection bias)	Low risk	Quote: "Randomization was stratified according to site with the use of RanCode (version 3.1) and in blocks of four, with staff at the individual sites blinded to the randomization process."
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group. Quote: "Experienced clinicians, blinded to adverse events and other study assessments, conducted separate interviews with study patients and caregivers to assess overall change on the CIBIC-Plus." Also, as a licensing study, likely to have been conducted in compliance with the principles of good clinical practice.
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Quote: "Seventy-one of the patients (42 of the 126 assigned to placebo and 29 of the 126 assigned to memantine) discontinued their assigned treatment before week 28". Reasons for dropouts were described in detail as follows. Quote: "Premature discontinuations were due to adverse events in 22 of the patients in the placebo group and 13 of the patients in the memantine group". Other major reasons for discontinuation included the patients' refusal of ongoing participation (14 placebo and 12 memantine), death (4 placebo and 1 memantine), protocol violation (3 placebo and 3 memantine) and change of caregiver (2 placebo and 0 memantine). Reasons broadly similar across arms of trial, despite higher dropout rate for placebo (42/126 = 33%) than memantine (29/126 = 23%). Comment: differential dropout mainly due to adverse events - small differences between LOCF and OC for decline in ADL.

Reisberg 2003 (9605) *(Continued)*

Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data, apart from adverse events: 16/126 memantine (13%) and 20/126 (16%) placebo. This is low compared to the adverse events rate (84%)
Selective reporting (reporting bias)	Unclear risk	Quote "A subgroup of 19 individually validated items (the ADCS-ADLsev) was used". Unclear if this could have constituted risk of bias
Other bias	Low risk	The study appears to be free of other sources of bias

Schifitto 2007

Methods	Multi-centre, randomised, double-blind, parallel-group, placebo-controlled Duration: 16 weeks
Participants	Number of centres: 21 centres Diagnosis: AIDS Dementia Complex (ADC) stage 1 or greater with a neuropsychological impairment defined as: at least two standard deviations below the normative value on one or more neuropsychological tests, or one standard deviation below the normative on at least two tests. Inclusion: participants on stable anti-retroviral therapy for six weeks prior to trial entry, Exclusion: participants with a history of focal brain lesions, chronic seizures, active psychiatric disorders, or active alcohol or drug abuse. No. of patients: 140 Age: 43 years Sex (% male): 90%
Interventions	Route: oral Treatment: memantine 40 mg/day. Memantine was initiated at 10 mg daily and escalated to 40 mg daily, or up to the maximum tolerated dose (N = 70) Control: placebo (N = 70) All patients were receiving concurrent stable anti-retroviral therapy.
Outcomes	Primary : cognitive performance (NPZ-8) Secondary: brain metabolism changes measured by magnetic resonance spectroscopy (subgroup)
Severity (MMSE mean)	Not stated
Notes	Funding: National Institute of Allergy and Infectious Diseases and supplemental funding from the National Cancer Institute.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised, multicentre. Quote: "[Patients were] randomized via a central computer system (www.fstrf.org)". Comment: computer randomisation
Allocation concealment (selection bias)	Low risk	Quote: "[Patients were] randomized via a central computer system (www.fstrf.org)".Study also likely to have been conducted according to the principles of good clinical practice.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group - but blinding method not described. However, study likely to have been conducted according to the principles of good clinical practice.

Schifitto 2007 *(Continued)*

		Comment: probably done.
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	Quote: "Primary efficacy analyses were conducted using available data". Discontinuation reasons were similar across groups (6/70 (9%) memantine arm, 7/70 (10%) placebo arm). These were due to adverse events.
Incomplete outcome data (attrition bias) Safety Data	Low risk	No missing data other than because of adverse events
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk.
Other bias	Unclear risk	Insufficient information to assess if an important risk of bias exists.

Schmidt 2008

Methods	Double-blind, randomised controlled pilot study Duration: 52 weeks
Participants	Country: Austria 37 patients with mild-to-moderate AD. MMSE 14-22 (mean 19.0 SD 2.9) Diagnosis: probable Alzheimer's disease by DSM-IV and NINCDS-ADRDA Failed to respond to, or developed side effects leading to withdrawal of cholinesterase inhibitor Stratified by ApoE4
Interventions	Memantine 20 mg daily (N = 18) Placebo (N = 18)
Outcomes	Weeks 12, 26 and 52: ADAS-cog, Clinical Dementia Rating, ADCS-ADL Change in total brain and hippocampal volumes at 26 and 52 weeks: MRI volumetry using the automated Structural Image Evaluation with the Normalization of Atrophy (SIENA) method . Regional change in cerebral NAA and Ml levels at 26 and 52 weeks: chemical shift imaging. Global and regional change in cerebral glucose metabolism at 26 and 52 weeks: FDG-PET
Severity (MMSE mean)	19
Notes	Funding: Merz Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer randomised. Quote: "Patients were randomly assigned by a computerized randomization schedule to either placebo or memantine".
Allocation concealment (selection bias)	High risk	Method of concealment not described. However, study likely to have been conducted according to the principles of good clinical practice.

Schmidt 2008 *(Continued)*

		However, there were baseline differences: different levels of neuroleptic medications: 33% in placebo group and 28% in memantine group. Also the score for the decline in ADL at baseline memantine was very different 48.3 (SD 19.4), placebo 58.8 (SD 10.8)
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled. Quote: "Daily dose consisted of two identical tablets so as not to reveal the titration scheme: two placebo tablets throughout the study for patients treated with placebo and two tablets containing either 5 mg or 10 mg memantine depending on the titration stage for patients treated with memantine"
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	No definitive description is given of the analysed patient group contributing to clinical variables at 26 (or 52) weeks. Original group included 36 randomised patients. At 26 weeks, this set suffers from 4 dropouts: 2/18 (11%) from the treatment arm, 2/18 from the placebo arm; details of the reasons not given, and no alternative values imputed.
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data levels are low compared with adverse events rate (94% and 87%)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk.
Other bias	Unclear risk	Pilot study

Tariot 2004 (MD-02)

Methods	Randomised, double-blind, parallel-group placebo-controlled. Duration: 24 weeks
Participants	Country: USA No of centres: 37 Diagnosis: probable Alzheimer's disease by NINCDS-ADRDA; Moderate-to-severe AD: MMSE mean 9.9 and 10.2 Inclusion: MMSE: 5-14; older than 50 years; ongoing donepezil therapy for more than 6 months before entrance into the trial and at a stable dose for at least 3 months, a knowledgeable and reliable caregiver, ambulatory ability and stable medical condition and medications. Excluded: clinically significant B12 or folate deficiency; active pulmonary, gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease; other psychiatric or central nervous system disorders other than AD, HIS more than 4. Baseline SIB ˜79 Mean age 75.5 years Total number randomised: 404
Interventions	Route: oral Treatment: memantine 20 mg/day and donepezil 5 or 10 mg/day (N = 203). Control: placebo and donepezil 5-10 mg/day (N = 201).
Outcomes	Primary end points: SIB, ADCS-ADL19. Secondary outcomes: CIBIC-Plus, NPI, BGP.
Severity (MMSE mean)	10.1
Notes	LOCF Population: 395 (98%)

Tariot 2004 (MD-02) *(Continued)*

PP Population: 322 (80%)
First patient, first visit: 11 June 2001
Last patient, last visit: 3 June 2002

Funding: Forest Laboratories

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised. Quote: "Patients were randomly allocated to 1 of the 2 treatment groups in permuted blocks of 4 in accordance with the randomisation list generated and retained by the Department of Biostatistics at Forest laboratories". Comment: probably done.
Allocation concealment (selection bias)	Low risk	Quote: "Patients were randomly allocated to 1 of the 2 treatment groups in permuted blocks of 4 in accordance with the randomisation list generated and retained by the Department of Biostatistics at Forest laboratories". Study likely to have been conducted according to the principles of good clinical practice. Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group. Quote: "Masked study medication was supplied to each site for dispensation... Drug and placebo tablets were visually identical"
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Differential dropout rate: 30/203 (14.8%) in treatment arm compared to 51/201 (25.4%) in placebo arm, however reason for dropouts proportionally similar across groups (15 adverse events and 8 withdrawal of consent in treatment arm compared to 25 AEs and 16 withdrawals of consent in placebo arm). There was, however, little difference between LOCF and OC analyses
Incomplete outcome data (attrition bias) Safety Data	Low risk	All patient safety outcome data presented. Dropouts apart from adverse events: 15/203 (7%) and 43/201 (21%). This is a low level compared with the rate of adverse events (78% and 72%)
Selective reporting (reporting bias)	Low risk	All outcomes reported Comment: reporting bias unlikely.
Other bias	Low risk	The study appears to be free of other sources of bias

van Dyck 2007 (MD-01)

Methods	Randomised, double-blind, parallel-group, placebo-controlled study Duration: 24 weeks
Participants	Country: UA 350 patients Moderate-to-severe AD: MMSE mean 10.0 and 10.3 Diagnosis: probable Alzheimer´s disease by NINCDS-ADRDA; Inclusion: MMSE: 5-14. Age at least 50. Exclusions: clinically significant and active pulmonary, gastrointestinal, renal, hepatic, endocrine, or cardiovascular disease; clinically significant B12 or folate deficiency; evidence of any psychiatric or neurologic disorder other than probable AD; Hachinski Ischemia Score > 4; delusions or delirium (as defined by DSM–IV); active malignancy; history of drug abuse within the past 10 years; previous treat-

van Dyck 2007 (MD-01) *(Continued)*

	ment with memantine; treatment within 30 days of screening with a ChEI or any investigational drug. Females at least 2 years postmenopausal or surgically sterile. Age: placebo: 78 (SD 7.6), memantine:78 (SD 8.2) years Sex (% females)
Interventions	Route: oral Treatment: 20 mg memantine daily (N = 178) Control: placebo (N = 172)
Outcomes	Primary end points: SIB, ADCS-ADL19. Secondary outcomes: CIBIC-Plus, NPI, BGP, FAST, NPI agitation subscale
Severity (MMSE mean)	10.2
Notes	ITT Population: 336 (96%) PP Population: 260 (74%) First patient, first visit: 20 June 2001 Last patient, last visit: 23 April 2003 Supported by Forest Laboratories Inc

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised - but no method of sequence generation described. However, study likely to have been done according to the principles of good clinical practice. Comment: probably done.
Allocation concealment (selection bias)	Low risk	Method of concealment not described. However, study likely to have been done according to the principles of good clinical practice. Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group; method of blinding not detailed. However, study likely to have been done according to the principles of good clinical practice. Comment: probably done.
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Dropout rates similar: in the treatment arm, 44/178 (24.7%), compared to placebo arm, 46/172 (26.7%). Reasons for dropouts similar across groups (dropouts due to adverse events of 22 and 23 respectively). This level of missing data could have affected the effect estimate, so unclear risk of bias is assumed
Incomplete outcome data (attrition bias) Safety Data	Low risk	Missing data apart from adverse events: 22/178 (12%) and 23/172 (13%). This is a low level compared to the adverse events rate (73%)
Selective reporting (reporting bias)	Low risk	All outcomes reported. However, a number of post-hoc analyses were also included in an attempt to explain "anomalous data". This was unlikely to lead to risk of outcome reporting bias
Other bias	Low risk	The study appears to be free of other sources of bias

Vercelletto 2011

Methods	Randomised, double-blind, parallel-group, placebo-controlled Duration: 52 Weeks
Participants	Country: France No. of centres: Nantes, Paris, Bordeaux, Toulouse, Montpellier, Marseille, Saint Etienne, Limoges, Rennes Diagnosis: behavioural Variant (bv) - Fronto Temporal Dementia Inclusion: patients with FTD-bv, lasting for at least 1 year based on the scale of frontal dysfunction of Lebert and Pasquier (≥ 3), MMSE score ≥ 19; Aged 45-75 years, Presence of a caregiver, signed informed consent, psychotropic medication absent or stable for three months Exclusion: temporal variation (vt) Fronto Temporal Dementia (semantic dementia or aphasia or progressive non-fluent); Motor neurone Impairment; Patients treated with cholinesterase inhibitors Total No. of patients: 52 randomised, 4 excluded
Interventions	Route: oral Treatment: memantine 20 mg (N = 26; 3 patients did not receive memantine); initiated gradually during the first 3 weeks Placebo (N = 26)
Outcomes	Primary outcome: clinical global impression of change (CGIC) Secondary Outcomes: Neuropsychiatric Inventory (NPI), Frontal Behavioral Inventory (FBI), Mattis Dementia Rating Scale (MDRS), Disability Assessment and Dementia (DAD), Zarit Burden Inventory (ZBI)
Severity (MMSE mean)	24.8
Notes	Funding: Lundbeck

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised. Quote: "Patients were randomly allocated to treatment, using a list of random numbers"
Allocation concealment (selection bias)	Low risk	Quote: "On receipt of a faxed notification of a patient's inclusion in the study, the appropriate treatment was sent to the pharmacy department of the center concerned"
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group Quote: "Memantine (10 mg) and placebo were prepared as identical tablets (H Lundbeck A/S). Packaging and labeling (LC2, Lentilly-France) and treatment management were performed so as to safeguard blinding to treatment allocation throughout the duration of the trial"
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Missing data: memantine 8/26 (31%) and placebo 3/26 (11%). For memantine, 3 patients did not start the drug, 1 had worsening of dementia, 2 died, 1 withdrew consent, 1 had AE. For placebo, 3 had AEs. This differential dropout rate could have affected the effect estimate, but small numbers, so unclear risk of bias assigned
Incomplete outcome data (attrition bias) Safety Data	Unclear risk	All safety data presented. Missing data without adverse events were 5/26 (19%) and 3/26 (11%), and this level is almost comparable with the number of patients with AEs (8 and 10)

Vercelletto 2011 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	All expected outcomes included, however, data at 6 months not reported (apart from CIBIC+ on a graph), although measured
Other bias	Low risk	The study appears to be free of other sources of bias

Wang 2013

Methods	Randomised, double-blind, placebo-controlled, parallel assignment, bio-availability study Duration: 24 weeks
Participants	Country: China Number of centres: single centre Diagnosis: probable AD (DSM-IV and NINCD-ADRDA criteria) Moderate-to-severe AD: MMSE mean 14.1 and 10.1 N = 26 Mean age: placebo group 64.7 ± 11.5 years; treatment group 65.7 ± 12.5 years 64% female Inclusion criteria: clinical diagnosis of AD using DSM-IV or probable AD, moderate-to-severe AD, MMSE 4 - 20, Hachinski Ischemia Score < 4, absence of any approved or investigational anti-dementia drug in the previous 3 months
Interventions	Route: oral Treatment: memantine: initially memantine 5 mg/day, titrated within the first month to a maintenance dose of 20 mg/day (N = 13) Control: placebo (N = 13)
Outcomes	Primary: plasma and cerebrospinal fluid (CSF) interleukin-10 (IL-10), amyloid ß-40 (Aß-40), total tau protein AD Assessment Scale-Cognitive Subscale (ADAS-cog), the Mini-Mental State Exam (MMSE) and the Severe Impairment Battery (SIB), FDG-PET Secondary: behaviour; short-term memory No safety data reported or clinical global, or decline in ADL
Severity (MMSE mean)	14.1 & 10.1
Notes	Last patient last visit: October 2010 Funding: Lundbeck A/S provided an unrestricted research grant, and non-industry grants

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"Randomised", no further details reported.
Allocation concealment (selection bias)	High risk	No information given on allocation concealment. There was some evidence of risk of selection bias in baseline differences: ADAS-cog had a difference of -13.1 (versus effect estimate of 3.1); SIB was 15.3 (versus 5.6); NPI was -3 (versus -1). Baseline MMSE 14.1 and 10.1. So high risk of bias assigned
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel assignment; details of blinding method not provided

Wang 2013 *(Continued)*

Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	2/13 (15%) patients missing in each group, reasons not given. This low level is unlikely to affect the effect estimate
Selective reporting (reporting bias)	Unclear risk	Some outcomes not reported
Other bias	Unclear risk	Insufficient information to assess if an important risk of bias exists

Wilcock 2002 (9202)

Methods	Randomised, double-blind, parallel-group, placebo-controlled study Duration: 28 weeks
Participants	Country: UK No of Centres: 57 Diagnosis: vascular dementia according to the NICDS-AIREN criteria and dementia using DSM IIIR. Inclusion: MMSE: 10-22. (Mean 17.6 SD 3.26) Exclusion: secondary dementia, depressive pseudodementia, psychotic episodes, history of epilepsy or acute or poorly controlled illness. Other investigational drugs, psychotropic drugs, drugs with psychiatric side effects and oral anticoagulants were not allowed. Total No: 579 Age (years (SD)): memantine: 77.2 (SD 6.9); placebo: 77.6 (SD 7) Sex (female%): memantine: 48%; placebo: 49%
Interventions	Route: oral Treatment: memantine: 20 mg/day (N = 295) Control: placebo (N = 284)
Outcomes	Primary end points: ADAS-cog, CGI-C Secondary outcomes: NOSGER
Severity (MMSE mean)	17.6
Notes	ITT Population: 548 (95%). PP Population: 368 (64%) First patient, first visit: February 1994 Last patient, last visit: October 1998 Funding:Merz Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Multicentre, randomised. Quote: "Balanced randomization generated by SAS statistical software (SAS Institute Inc., Cary, NC, USA)". Comment: computer randomisation
Allocation concealment (selection bias)	Low risk	Quote: "Balanced randomization was carried out .. by a statistician with no access to information on the patients or physicians". And, "The trial was conducted in full compliance with the International Committee of Harmonization (ICH) guidelines on Good Clinical Practice (GCP)". Comment: adequate allocation concealment.

Wilcock 2002 (9202) *(Continued)*

Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group. Quote: "All trial medication was supplied by Merz Pharmaceuticals (Frankfurt, Germany). Memantine hydrochloride tablets (5mg or 10mg) were used. Placebo tablets were of identical taste and appearance", and "Patients, investigating staff, and the Merz study team were blinded to treatment allocation until data base lock."
Incomplete outcome data (attrition bias) Primary Outcomes	High risk	OC analysis used for ADAS-cog and CGIC, and per protocol used for NOSGER. Missing data per group is memantine 57/295 (19%) and placebo 58/284 (20%) for clinical global; and 118/295 (40%) and 117/284 (41%) for ADAS-Cog, For the per protocol analyses (NOSGER), the data excluded were: 103/295 (35%) and 122/284 (43%). These are high levels of missing data Comment: unclear risk of bias for CGIC
Incomplete outcome data (attrition bias) Safety Data	Low risk	Evaluable-for-safety (EFS) population used, N = 579. All patient safety outcome data presented. The drop-out rates due to adverse events were stated to be 9% and 7%, so missing data, apart from adverse events were 10% and 13%; this is low compared to the adverse event rates of 77% and 75%
Selective reporting (reporting bias)	High risk	Errors and discrepancies in reporting in published paper (e.g. quote: for ADAS-cog (change from baseline) "negative values indicate worsening". Primary outcome of the study, CGIC was not fully reported in published paper; quote, "CGI-C was not statistically significantly different between treatment groups in both the ITT and TPP populations (P1 = 0.29245; P2 = 0.3773; P1 P2 = 0.1103 > 0.0038)". However, values were obtained from the FDA submission, for which SDs were calculated from the P values 548 defined as ITT population. However, in the study's primary outcome ADAS-Cog score table (Table 3), only 527 patients were scored in the LOCF population. No explanation given, or alternative values imputed. OC values from FDA submission, with calculation of SD from P value Treated-per-protocol (TPP) population used N = 368 patients. NOSGER analysis only scores 341 patients at baseline, and 320 patients at 28 weeks. No explanation given, or alternative values imputed Comment: unclear risk of bias for CIBIC+, ADAS-Cog; high risk of bias for NOSGER
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

Wilkinson 2012 (10112)

Methods	Multinational, randomised, double-blind, parallel group, placebo-controlled, fixed dose study Duration: 1 year
Participants	Country: France, Germany, Switzerland, and the UK Probable AD NINCDS-ADRDA enriched for medial temporal lobe atrophy N = 278 randomised, 277 received interventions, 217 completed MMSE 12-20, Mean ˜17.0 (SD 2.5)
Interventions	Memantine 20 mg daily oral dose (N = 134) placebo (N = 144)

Wilkinson 2012 (10112) *(Continued)*

	Stratification by cholinesterase inhibitor and then randomisation; memantine 72% and placebo 73% ChEI
Outcomes	Primary: change in total brain volume from baseline using serial MRI scans Secondary: change in hippocampal brain volume. Cognitive and behavioural measures (MMSE and NPI)
Severity (MMSE mean)	17
Notes	Last patient Last visit: 12 February 2009 Funding: H Lundbeck A/S and Merz Pharmaceuticals GmbH July 2010: correspondence with Lundbeck: Quote: "Our understanding of US Public Law 110-85 is that we are not obligated to post the results of this study on CT.gov as we are not the marketing authorisation holder of memantine in the United States. We do, however, intend to do so, and the draft posting is almost ready for internal review. However, as I am sure you appreciate, CT.gov is set up for a particular type of study, and Study 10112 really does not fit the mould. For this reason, we have spent considerable time in trying to get the data onto CT.gov without compromising the actual results of the study. It is also for this reason that we have posted the study on our own web site using the synopsis format we use for our regulatory documents, as we see this as the most comprehensive way of presenting the results of this study. With regards to manuscript ..... we do not have an exact timeline for when the final manuscript will be submitted, as it is in draft, but once this is done we can surely consider availability of the data tables for inclusion in meta-analyses etc.. .....resource will be primarily focused on getting the clinical report written and finalised for submission to the Competent Authority."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Multinational, randomised. Quote: "...computer-generated randomization list".
Allocation concealment (selection bias)	Low risk	Quote: "The details of the randomization series were unknown to any of the investigators and were contained in a set of sealed opaque envelopes".
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group. Quote: "All study personnel and participants were blinded to treatment assignment for the duration of the entire study", "The randomisation code was broken for 2 patients: 1 for an AE and only data collected from this patient until the time of code break were kept in the analysis sets. The code for the second patient was broken by mistake after study completion, and since this code break had no impact on the blinding of either the patient or the investigator during the study, the patient's data were kept in the study".
Incomplete outcome data (attrition bias) Primary Outcomes	Unclear risk	Quote: "A total of 60 patients (22%) withdrew during the study, with 30 in each treatment group... Approximately half of the withdrawals in each treatment group were due to adverse events (AEs)". Missing data: memantine 30/133 (23%) and 30/143 (21%) withdrawals (adverse events: 15 memantine, 12 placebo)
Incomplete outcome data (attrition bias) Safety Data	Low risk	Withdrawals apart from AEs: memantine 15/133 (11%) and placebo 18/143 (13%). This is a low level compared with the adverse events rate of about 50%

Wilkinson 2012 (10112) *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Methods section unclear on review outcomes to be reported.ADAS-cog reported only as the orientation test subscale; MMSE also reported. 26-week data not reported. NPI data not reported in useable format
Other bias	Unclear risk	Insufficient information to assess if an important risk of bias exists

Winblad 1999 (9403)

Methods	Randomised, double-blind, parallel-group, placebo-controlled study
Participants	Country: Latvia No of centres: 7 Diagnosis: DSM-III-R for the diagnosis of dementia (mixed types) Severe dementia (MMSE <10) Total No: 166; AD subgroup 79 Age: females: 73.9 males: 68.4; memantine 73.4 placebo 74.9 Females: 70.7% (memantine) 63.2% (placebo) ITT population: 166 (98%) Per protocol population: 151 (90%)
Interventions	Treatment: oral memantine 10 mg/day (N = 82) or placebo (N = 84) Treatment started at 5 mg/day and increased in one week to 10 mg/day Duration: 12 weeks
Outcomes	Primary end points: Clinical Global Impression of Change (CGI-C), Behavioural Rating Scale for Geriatric Patients (BGP) Secondary efficacy variables: D-scale Adverse events
Severity (MMSE mean)	<10
Notes	AD subgroup listed as Winblad 1999 (9403) AD Funding: Merz Pharmaceuticals

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised - but no method of sequence generation described. However, as a licensing study, likely to have been conducted in compliance with the principles of good clinical practice. Comment: probably done.
Allocation concealment (selection bias)	Low risk	Method of concealment not described. However, as a licensing study, likely to have been conducted in compliance with the principles of good clinical practice. Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group; method of blinding not detailed. However, as a licensing study, likely to have been conducted in compliance with the principles of good clinical practice.

Winblad 1999 (9403) *(Continued)*

		Comment: probably done.
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	LOCF analysis used. All patients included in LOCF analysis. Quote: "Seven patients of the memantine and eight patients of the placebo group were excluded from the treated per protocol (TPP) sample because of discontinuation of therapy or protocol violations." Comment: this is a fairly low missing data rate (7/82 and 8/84).
Incomplete outcome data (attrition bias) Safety Data	Low risk	All patient safety outcome data presented. Missing data levels low in comparison with adverse events rate (18/82 and 18/84)
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'Low' or 'High' risk.
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists.

Winblad 1999 (9403) AD

Methods	As per 9403 (Winblad 1999) Randomised, double-blind, parallel-group, placebo-controlled study
Participants	Country: Latvia No of centres: 7 Diagnosis: DSM-III-R for the diagnosis of dementia. Hachinski ischaemia score (HIS) modified by Rosen to separate into subgroups with AD and vascular dementia. N = 79 with AD MMSE < 10 (mean 6.7 (range 0-9) and 6.3 (range 0-9)) Age: ˜74
Interventions	Treatment: oral memantine 10 mg/day or placebo Treatment started at 5 mg/day and increased in one week to 10 mg/day Duration: 12 weeks
Outcomes	Primary end points: Clinical Global Impression of Change (CGI-C), Behavioural Rating Scale for Geriatric Patients (BGP) Secondary efficacy variables: D-scale Adverse events
Severity (MMSE mean)	6.5
Notes	Original trial did not stratify into dementia type before randomisation

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised - but no method of sequence generation described. However, as a licensing study, likely to have been conducted in compliance with the principles of good clinical practice.

Winblad 1999 (9403) AD *(Continued)*

		Not stratified into AD and other dementia before randomisation and small study, so risk of selection bias. Baseline differences in BGP care dependency of about 1 point - could be important.
Allocation concealment (selection bias)	Low risk	Method of concealment not described. However, as a licensing study, likely to have been conducted in compliance with the principles of good clinical practice. Comment: probably done.
Blinding (performance bias and detection bias) All outcomes	Low risk	Double-blind, placebo-controlled, parallel-group - but method of blinding not detailed. However, as a licensing study, likely to have been conducted in compliance with the principles of good clinical practice. Comment: probably done.
Incomplete outcome data (attrition bias) Primary Outcomes	Low risk	LOCF analysis used. 79 patients randomised. All patients included in LOCF analysis. Dropout rates low (2/41 (5%) in treatment arm compared to 1/38 in placebo arm), although no reasons for missing data given.
Selective reporting (reporting bias)	High risk	Post hoc subgroup of AD patients analysed
Other bias	Unclear risk	Insufficient information to assess whether an important risk of bias exists. Data extracted from a graph.

AD: Alzheimer's disease; **ADAS-cog:** Alzheimer's Disease Assessment Scale - Cognitive subscale; **ADCS-ADL:** Alzheimer's Disease Cooperative Study Activities of Daily Living; **ADL:** activities of daily living; **AE:** adverse event; **AQT:** A Quick Test of Cognitive Speed; **BGP:** Behavioural rating scale for Geriatric Patients; **CDR:** Clinical Dementia Rating; **CGI-C:** Clinical Global Impression of Change; **CGI-I:** Clinical Global Impression Improvement; **CGI-S:** Clinical Global Impression – Severity scale; **ChEI:** cholinesterase inhibitor; **CIBIC:** Clinician's Interview-Based Impression of Change; **CMAI:** Cohen-Mansfield Agitation Index; **CT:** computed tomography;**DAD:** Disability Assesment for Dementia; **DEMQOL:** quality of life assessment in dementia; **DLB:** dementia Lewy bodies; **DRS**: Dementia Rating Scale; **DSM-IV:** Diagnostic and Statistical Manual of Mental Disorders IV; **EQ-5D:** EuroQuol 5D; **FAST:** Functional Assessment Staging Tool; **FDA:** Food and Drug Administration; **FDG-PET:** Positron Emission Tomography with fluorodeoxyglucose; **FTD:** Frontotemporal lobar degeneration;**GAS:** Goal Attainment Scaling; **GBS:** Gottsfries-Brane-Steen scale; **GDS:** Global Deterioration Scale; **GHQ:** General Health Questionnaire; **HIS:** Hachinski Ischemic Score; **ICH-GCP:** International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use - Good Clinical Practice; **ITT:** intention to treat; **LOCF:** last observation carried forward; **MADRS:** Montgomery-Asberg Depression Rating Scale; **MMSE:** Mini Mental State Examination; **MOSES:** Multidimensional Observation Scale for Elderly Subjects; **MRI:** magnetic resonance imaging; **MRS:** magnetic resonance spectroscopy; **NAA/Cr:** ratio of N-acetyl aspartate to creatinine; **NICE:** National Institute for Health and Care Excellence; **NOSGER:** Nurse's Observational Scale for Geriatric Patients; **NPI:** Neuropsychiatric Inventory; **NPZ:** Neuropsychological Z score; **OC:** observed case; **PANSS-EC:** Excited Component of the Positive and Negative Syndrome Scale; **PDQ:** Personhood in Dementia Questionnaire; **PP:** per protocol; **PDD**: Parkinson's disease dementia; **SAE:** serious adverse event; **SCAG:** Sandoz Clinical Assessment Geriatric; **SD:** standard deviation; **SE: standard error; SIB**: Severe Impairment Battery; **SMMSE:** Standardized Mini-Mental State Examination; **TPP:** treated-per-protocol population; **UPDRS:** Unified Parkinson's Disease Rating Scale; **ZBI:** Zarit Burden Interview

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
10114/Waldemar	Trial of switching from donepezil to memantine N = 47. Study completed 25-09-2004
Abe 2011	No reference to randomisation
Alva 2015	Systematic review
Ambrozi 1988	Included patients suffering from any severe chronic disease of the central nervous system.

Study	Reason for exclusion
Amidfar 2017	Not dementia
Anon 2008	Not placebo controlled
Anon 2009	Participants presymptomatic individuals at risk (subjective memory complaints and family history of Alzheimer's disease)
Araki 2014	Comparison of memantine + donepezil versus donepezil alone - no placebo used
Atri 2008	Not placebo controlled
Atri 2013	Ineligible patient population
Atri 2014c	Incorrect analysis
Atri 2015	Incorrect analysis
Atri 2017	Post-hoc analysis of 3 trials
Aupperle 2007	Three open-label extension periods
Ballard 2015 (MAIN-AD)	Comparison of memantine and antipsychotic
Beauchet 2011	Prospective cohort study
Bernal-Pacheco 2010	No reference to randomisation
Berthier 2009	Not dementia treatment, post stroke aphasia
Boxer 2009	Open-label study
Burke 2012	Commentary
Calabrese 2007	Open-label study
Cerullo 2007	Included participants with schizophrenia
Chen 2017	Review with extra studies (excluded)
Cheon 2008	Open-label study
Cretu 2008	Not placebo controlled
Cumbo 2014	Ineligible comparator
Cummings 2012	Post-hoc analysis
Defer 2013	Ineligible patient population
Diehl-Schmid 2008	Open-label study
Doody 2012	Participants were not randomised to memantine
Emaldeldin 2017	Systematic review in a conference abstract. Insufficient details.

Study	Reason for exclusion
Evans 2014	Ineligible study design
Feldman 2006	Post-hoc analysis
Ferris 2007	Trial in Age-Associated Memory Impairment (AAMI) not dementia
Ferris 2010	Post-hoc analysis
Fleischhacker 1986	Single-blind trial
Gauthie 2010	Review article
Gavrilova 1995	Open-label clinical trial
Glodzik 2008	Not placebo controlled
Graham 2009	No protocol-specified outcomes
Graham 2010a	Post-hoc analysis
Graham 2010b	Post-hoc analysis
Graham 2010c	Post-hoc analysis
Graham 2013	Incorrect analysis
Graham 2013a	Incorrect analysis
Graham 2014	Systematic review
Grossberg 2010	Post-hoc analysis
Grossberg 2010a	Post-hoc analysis
Han 2012	Open-label study
Hellweg 2011	Post-hoc analysis
Hellweg 2012	Post-hoc analysis
Hendrix 2015	Systematic review
Hu 2006	Compares memantine with donepezil not placebo
IE 2201/Daiichi	Clinical pharmacology study. Personal Communication: Not intending to release results.
Jiang 2015	Systematic review
Johnson 2010	Cross-over study and no first period results given.
Jones 2005	Not placebo controlled
Jones 2007	Not placebo controlled
Jones 2011	Meta-analysis

Study	Reason for exclusion
JPRN UMIN000011392 2013	Ineligible comparator
Kano 2013	Addition to donepezil of memantine versus additional donepezil (no placebo)
Kolykhalov 2012	Comparison of single dose memantine versus twice daily dose; not compared with placebo.
Kurz 2014	Ineligible study design
Ladea 2010	Not randomised
Levin 2008 108(12)	Not placebo controlled
Levin 2008 108(5)	Not placebo controlled open 16-week trial
Li 2011	Memantine solution versus memantine tablet; no comparison with placebo.
Litvinenko 2008	Not placebo controlled
Litvinenko 2010	Not placebo controlled
Lovera 2010	Multiple sclerosis and cognitive impairment - not clearly dementia
MD-51	Open-label study
MEADOWS/Lana /Downs/2006	Participants with Down's Syndrome and dementia or Down's Syndrome and aged over 40. The published report does not report data separately for those with dementia and those without.
Mecocci 2009	Post-hoc analysis
Modrego/MRS	Donepezil versus memantine - no placebo arm
Molinuevo 2011	Meta-analysis
Moreau 2013	Ineligible patient population (dementia excluded)
Nakamura 2014	Systematic review
NCT01921972 2004	Ineligible patient population
NCT02080364 2015	Wrong intervention
Ondo 2007	Open-label study
Ondo 2011	Participants with Parkinson's disease and dementia were excluded
Peng 2015	Memantine plus donepezil versus donepezil alone (no placebo)
Peters 2012	Included participants with amnestic mild cognitive impairment
Peyro-Saint-Paul 2016	Multiple sclerosis and cognitive impairment - not clearly dementia
Reisberg 2005	Comparison of memantine plus individual management and caregiver training versus memantine alone
Riepe 2005	Open-label study

Study	Reason for exclusion
Rodriguez 2010	Patients with Parkinson's disease suffering from levodopa induced dyskinesias, regardless of their cognitive status
Rustembegovic 2009	No reference to randomisation
Rustembegović 2003	No reference to randomisation
Saxton 2009	Open-label study
Scharre 2005	Open-label study
Schmidt 2015	Systematic review
Smart 2011	Assessment of rating scales used for Alzheimer's disease
Sultzer 2010	Not randomised
Tabaton 2010	Commentary
Tocco 2010	Post-hoc analysis
Tocco 2010a	Post-hoc analysis
Tocco 2010b	Post-hoc analysis
Tocco 2011	Post-hoc analysis
Tocco 2011a	Post-hoc analysis
Tocco 2011b	Post-hoc analysis
Tocco 2012	Post-hoc analysis
Villoslada 2009	Multiple sclerosis and cognitive impairment - not clearly dementia
Waldemar 2008	Trial of switching donepezil to memantine
Wang 2015	Systematic review - check references
Wang 2015b	Memantine plus donepezil versus donepezil alone (no placebo)
Weiner 2009	Open label study
Weschules 2008	Retrospective cross-sectional study
Wilcock 2008	Post-hoc analysis
Wilkinson 2010	Post-hoc analysis
Winblad 2010	Post-hoc analysis
Wirth 2012	Post-hoc analysis
Zheng 2011	Memantine plus donepezil versus donepezil alone (no placebo)

Characteristics of ongoing studies *[ordered by study ID]*

Lundbeck 11830A_Aker

Trial name or title	Investigating the effect of treatment on neurotrophic factors by means of functional magnetic resonance imaging (FMRI) in patients with Alzheimer's disease
Methods	Design: double-blind, prospective randomised
Participants	
Interventions	
Outcomes	
Starting date	Not initiated - included in PenTAG report for NICE Technology Appraisal of 2010
Contact information	
Notes	

Lundbeck 13143A/_Peng

Trial name or title	A randomized, double-blind, placebo-controlled study to Investigate the Improvement of language function in Chinese AD patients with memantine
Methods	
Participants	
Interventions	
Outcomes	
Starting date	included in PenTAG report for NICE Technology Appraisal of 2010
Contact information	
Notes	

MEDUSA/Bullock/2005

Trial name or title	MEDUSA: randomized controlled trial in patients with AD
Methods	
Participants	N = 75 (15 in each arm of the trial) Country: UK
Interventions	1.ChEi as usual 2. Increased dose of ChEi 3. Rivastigmine 4. Memantine

MEDUSA/Bullock/2005 *(Continued)*	5. ChEi as usual, plus memantine
Outcomes	Primary: CGIC, MMSE, decline in ADL, NPI GAS
Starting date	Date of first enrolment: September 30 2003
Contact information	ISRCTN55568578
Notes	COMPLETED Last refreshed on:19 May 2009

AD: Alzheimer's Disease; **ADL:** activities of daily living; **CGI-C:** clinical global impression of change; **ChEi:** cholinesterase inhibitors; **GAS:** Goal Attainment Scaling; **MMSE:** Mini Mental State Examination; **NI:** Neuropsychiatric Inventory

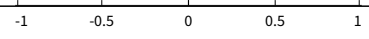
DATA AND ANALYSES

Comparison 1. Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease 24- to 30-week data. OC

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global	13	3079	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.28, -0.13]
2 Cognitive Function	14	3600	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.34, -0.21]
3 Decline in ADL	13	3077	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.24, -0.09]
4 Behaviour and Mood	14	3674	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.21, -0.08]
5 All-cause discontinuation	16	4661	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.82, 1.05]
6 Discontinuations due to adverse events	16	4661	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.13]
7 Number suffering at least one adverse event	17	4708	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.97, 1.06]
8 Number suffering serious adverse events	16	4449	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.75, 1.07]
9 Number suffering agitation as an adverse event	15	3904	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.60, 0.96]

Analysis 1.1. Comparison 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease 24- to 30-week data. OC, Outcome 1 Clinical Global.

Study or subgroup	Memantine		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		13.33%	-0.11[-0.31,0.1]
Bakchine 2008 (99679) SG	145	4.2 (1.1)	65	4.4 (1.2)		6.52%	-0.14[-0.43,0.15]
Dysken 2014 SG	50	0 (0)	63	0 (0)			Not estimable
Forest 2006 (MD-22)	131	3.6 (1.4)	129	3.8 (1.3)		9.44%	-0.15[-0.4,0.09]
Grossberg 2008 (MD-50)	269	3.8 (1.1)	272	4.1 (1.2)		19.53%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	4.4 (1.6)	87	4.7 (1.3)		6.19%	-0.22[-0.52,0.08]
Howard 2012 (DOMINO-AD)	77	0 (0)	66	0 (0)			Not estimable
Peskind 2004 (MD-10) SG	106	4.4 (1)	116	4.7 (1.1)		7.97%	-0.31[-0.57,-0.04]
Porsteinsson 2008(MD-12)S	135	4.5 (1)	125	4.5 (1)		9.45%	-0.04[-0.28,0.2]
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		6.5%	-0.27[-0.56,0.03]
Tariot 2004 (MD-02)	172	4.4 (1.1)	152	4.6 (1.1)		11.67%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	134	4.3 (1.1)	127	4.6 (1)		9.4%	-0.28[-0.53,-0.04]
Wang 2013	13	0 (0)	13	0 (0)			Not estimable
Total ***	**1603**		**1476**			**100%**	**-0.2[-0.28,-0.13]**
Heterogeneity: Tau²=0; Chi²=4.7, df=9(P=0.86); I²=0%							
Test for overall effect: Z=5.32(P<0.0001)							



Analysis 1.2. Comparison 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease 24- to 30-week data. OC, Outcome 2 Cognitive Function.

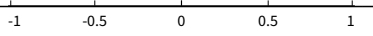
Study or subgroup	Memantine		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		11.02%	-0.42[-0.63,-0.22]
Bakchine 2008 (99679) SG	146	-0.9 (6.4)	65	0.7 (6.4)		5.48%	-0.25[-0.54,0.05]
Dysken 2014 SG	50	3.1 (7.6)	63	6.6 (7.3)		3.32%	-0.48[-0.86,-0.1]
Forest 2006 (MD-22)	132	0 (0)	131	0 (0)			Not estimable
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		16.46%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		5.09%	-0.48[-0.78,-0.18]
Howard 2012 (DOMINO-AD)	77	1.2 (2.6)	66	2.4 (3.8)		4.29%	-0.36[-0.69,-0.03]
Nakamura 2016	268	1.3 (8.2)	269	2.2 (8.1)		16.45%	-0.1[-0.27,0.07]
Peskind 2004 (MD-10) SG	101	0.8 (5.9)	114	2.2 (7)		6.53%	-0.22[-0.48,0.05]
Porsteinsson 2008(MD-12)S	133	0.9 (6)	123	2 (5.8)		7.8%	-0.19[-0.44,0.05]
Reisberg 2003 (9605)	96	4.5 (11.5)	83	10.2 (12.7)		5.31%	-0.47[-0.77,-0.17]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		9.74%	-0.37[-0.59,-0.15]
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		7.88%	-0.05[-0.29,0.2]
Wang 2013	11	0 (7.2)	11	5.6 (5.9)		0.61%	-0.82[-1.7,0.06]
Total ***	**1863**		**1737**			**100%**	**-0.27[-0.34,-0.21]**
Heterogeneity: Tau²=0; Chi²=17.17, df=12(P=0.14); I²=30.1%							
Test for overall effect: Z=7.83(P<0.0001)							

Analysis 1.3. Comparison 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease 24- to 30-week data. OC, Outcome 3 Decline in ADL.

Study or subgroup	Memantine		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Asada 2011a (IE3501)	193	0 (0)	175	0 (0)			Not estimable
Bakchine 2008 (99679) SG	146	2.6 (8.2)	64	2.8 (7.4)		6.75%	-0.03[-0.32,0.27]
Dysken 2014 SG	50	3.6 (11.2)	63	6.7 (10.9)		4.19%	-0.27[-0.65,0.1]
Forest 2006 (MD-22)	130	1.9 (6)	129	3.3 (7.4)		9.77%	-0.21[-0.45,0.04]
Grossberg 2008 (MD-50)	268	0.3 (8.1)	272	1.1 (7.8)		20.46%	-0.1[-0.27,0.07]
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		6.48%	-0.1[-0.4,0.2]
Howard 2012 (DOMINO-AD)	77	3.8 (6.9)	66	5 (7.1)		5.37%	-0.17[-0.5,0.16]
Peskind 2004 (MD-10) SG	107	4 (8.8)	118	5.3 (7)		8.49%	-0.17[-0.43,0.09]
Porsteinsson 2008(MD-12)S	136	3.6 (7)	125	3.9 (8)		9.88%	-0.03[-0.27,0.21]
Reisberg 2003 (9605)	97	2.5 (6.3)	84	5.9 (6.8)		6.61%	-0.52[-0.82,-0.22]
Tariot 2004 (MD-02)	172	1.7 (6.7)	152	3.3 (6.8)		12.16%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	133	1.3 (6.9)	127	2.3 (6.8)		9.83%	-0.15[-0.39,0.1]
Wang 2013	11	0 (0)	11	0 (0)			Not estimable
Total ***	**1604**		**1473**			**100%**	**-0.16[-0.24,-0.09]**
Heterogeneity: Tau^2=0; Chi^2=9.14, df=10(P=0.52); I^2=0%							
Test for overall effect: Z=4.23(P<0.0001)							

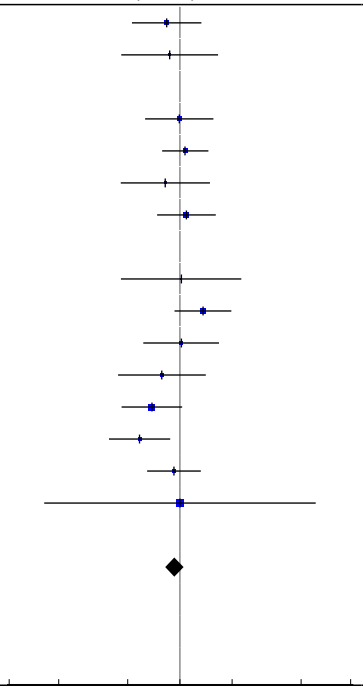
Analysis 1.4. Comparison 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease 24- to 30-week data. OC, Outcome 4 Behaviour and Mood.

Study or subgroup	Favours memantine		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Asada 2011a (IE3501)	217	-0.2 (4.2)	208	0.9 (5.1)		11.64%	-0.25[-0.44,-0.06]
Bakchine 2008 (99679) SG	146	-0.4 (10.4)	64	-2.2 (9.6)		4.9%	0.18[-0.11,0.48]
Dysken 2014 SG	50	0.4 (12.4)	63	2.8 (12.1)		3.07%	-0.19[-0.57,0.18]
Forest 2006 (MD-22)	132	-2.8 (15.5)	131	-3.1 (14.1)		7.26%	0.02[-0.22,0.26]
Grossberg 2008 (MD-50)	268	-4.9 (13.4)	272	-1.8 (13.2)		14.81%	-0.24[-0.4,-0.07]
Homma 2007 (IE2101)	84	-2.1 (9.4)	87	-0.9 (9.1)		4.71%	-0.12[-0.42,0.18]
Howard 2012 (DOMINO-AD)	77	-3.4 (15.8)	66	2.7 (17.2)		3.86%	-0.37[-0.7,-0.04]
Nakamura 2016	268	-0.2 (3.8)	269	0.3 (3.8)		14.8%	-0.13[-0.29,0.04]
Peskind 2004 (MD-10) SG	107	0.8 (12.1)	118	2.8 (15.7)		6.18%	-0.15[-0.41,0.12]
Porsteinsson 2008(MD-12)S	136	1 (11.3)	125	0.9 (11.1)		7.2%	0.01[-0.23,0.25]
Reisberg 2003 (9605)	97	0.1 (15.9)	84	2.9 (16.1)		4.96%	-0.17[-0.47,0.12]
Tariot 2004 (MD-02)	171	-0.5 (13)	152	2.9 (13.1)		8.82%	-0.26[-0.48,-0.04]
van Dyck 2007 (MD-01)	133	0.5 (15)	127	1 (15.8)		7.18%	-0.03[-0.28,0.21]
Wang 2013	11	5 (10)	11	6 (11.5)		0.61%	-0.09[-0.93,0.75]
Total ***	**1897**		**1777**			**100%**	**-0.14[-0.21,-0.08]**
Heterogeneity: Tau^2=0; Chi^2=14.2, df=13(P=0.36); I^2=8.43%							
Test for overall effect: Z=4.23(P<0.0001)							



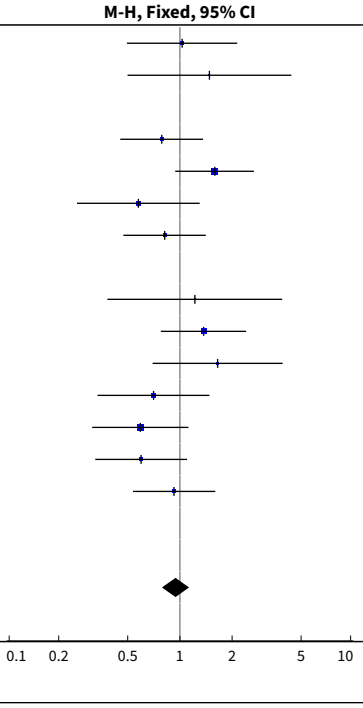
Analysis 1.5. Comparison 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease 24- to 30-week data. OC, Outcome 5 All-cause discontinuation.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asada 2011a (IE3501)	29/221	33/211		7.7%	0.84[0.53,1.33]
Bakchine 2008 (99679) SG	23/169	12/77		3.76%	0.87[0.46,1.66]
Dysken 2014 SG	0/50	0/63			Not estimable
Forest 2006 (MD-22)	29/133	29/132		6.64%	0.99[0.63,1.56]
Grossberg 2008 (MD-50)	69/342	63/335		14.51%	1.07[0.79,1.46]
Homma 2007 (IE2101)	16/100	21/108		4.6%	0.82[0.46,1.49]
Howard 2012 (DOMINO-AD)	40/149	36/146		8.29%	1.09[0.74,1.61]
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Lundbeck 2006 (10116)	11/128	11/130		2.49%	1.02[0.46,2.26]
Nakamura 2016	53/273	39/273		8.89%	1.36[0.93,1.98]
Peskind 2004 (MD-10) SG	24/130	26/143		5.65%	1.02[0.62,1.68]
Porsteinsson 2008(MD-12)S	18/154	22/148		5.12%	0.79[0.44,1.41]
Reisberg 2003 (9605)	29/126	42/126		9.58%	0.69[0.46,1.03]
Tariot 2004 (MD-02)	30/202	51/201		11.66%	0.59[0.39,0.88]
van Dyck 2007 (MD-01)	44/178	46/172		10.67%	0.92[0.65,1.32]
Wang 2013	2/13	2/13		0.46%	1[0.16,6.07]
Total (95% CI)	**2375**	**2286**		**100%**	**0.93[0.82,1.05]**
Total events: 417 (Memantine), 433 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=13.37, df=13(P=0.42); I^2=2.8%					
Test for overall effect: Z=1.21(P=0.23)					

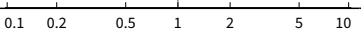


Analysis 1.6. Comparison 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease 24- to 30-week data. OC, Outcome 6 Discontinuations due to adverse events.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asada 2011a (IE3501)	14/221	13/211		6.04%	1.03[0.5,2.14]
Bakchine 2008 (99679) SG	13/169	4/77		2.5%	1.48[0.5,4.39]
Dysken 2014 SG	0/50	0/63			Not estimable
Forest 2006 (MD-22)	19/133	24/132		10.94%	0.79[0.45,1.36]
Grossberg 2008 (MD-50)	34/342	21/335		9.64%	1.59[0.94,2.67]
Homma 2007 (IE2101)	8/100	15/108		6.55%	0.58[0.26,1.3]
Howard 2012 (DOMINO-AD)	20/149	24/146		11.01%	0.82[0.47,1.41]
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Lundbeck 2006 (10116)	6/128	5/130		2.25%	1.22[0.38,3.89]
Nakamura 2016	26/273	19/273		8.63%	1.37[0.78,2.41]
Peskind 2004 (MD-10) SG	12/130	8/143		3.46%	1.65[0.7,3.91]
Porsteinsson 2008(MD-12)S	11/154	15/148		6.95%	0.7[0.33,1.48]
Reisberg 2003 (9605)	13/126	22/126		10%	0.59[0.31,1.12]
Tariot 2004 (MD-02)	15/202	25/201		11.39%	0.6[0.32,1.1]
van Dyck 2007 (MD-01)	22/178	23/172		10.63%	0.92[0.54,1.6]
Wang 2013	0/13	0/13			Not estimable
Total (95% CI)	**2375**	**2286**		**100%**	**0.94[0.79,1.13]**
Total events: 213 (Memantine), 218 (Placebo)					

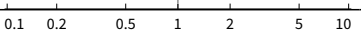


Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=14.87, df=12(P=0.25); I²=19.31%					
Test for overall effect: Z=0.64(P=0.52)					



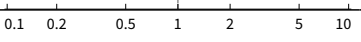
Analysis 1.7. Comparison 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease 24- to 30-week data. OC, Outcome 7 Number suffering at least one adverse event.

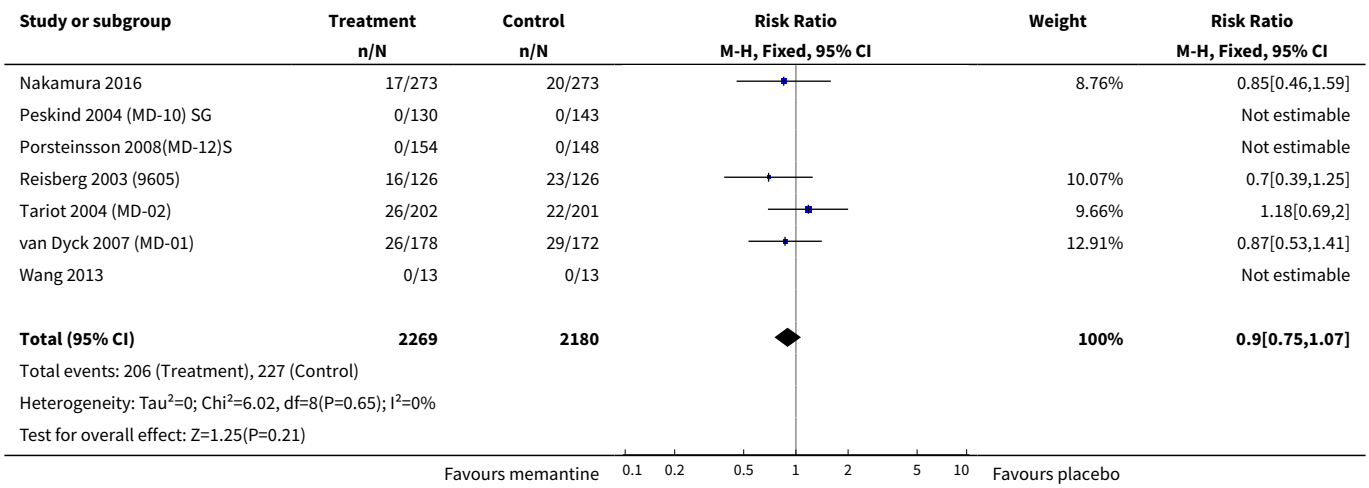
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asada 2011a (IE3501)	180/221	167/211		14.67%	1.03[0.94,1.13]
Bakchine 2008 (99679) SG	0/169	0/77			Not estimable
Dysken 2014 SG	0/50	0/63			Not estimable
Forest 2006 (MD-22)	124/133	129/132		11.12%	0.95[0.91,1.01]
Grossberg 2008 (MD-50)	214/342	214/335		18.56%	0.98[0.87,1.1]
Homma 2007 (IE2101)	72/100	78/108		6.44%	1[0.84,1.18]
Howard 2012 (DOMINO-AD)	0/149	0/146			Not estimable
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Lundbeck 2006 (10116)	19/128	23/130		1.96%	0.84[0.48,1.46]
Lundbeck 2006 (99817)	0/23	0/24			Not estimable
Nakamura 2016	186/273	169/273		14.51%	1.1[0.97,1.25]
Peskind 2004 (MD-10) SG	0/130	0/143			Not estimable
Porsteinsson 2008(MD-12)S	0/154	0/148			Not estimable
Reisberg 2003 (9605)	106/126	109/126		9.36%	0.97[0.88,1.08]
Tariot 2004 (MD-02)	158/202	145/201		12.48%	1.08[0.97,1.21]
van Dyck 2007 (MD-01)	131/178	125/172		10.91%	1.01[0.89,1.15]
Wang 2013	0/13	0/13			Not estimable
Total (95% CI)	**2398**	**2310**		**100%**	**1.02[0.97,1.06]**
Total events: 1190 (Treatment), 1159 (Control)					
Heterogeneity: Tau²=0; Chi²=10.04, df=8(P=0.26); I²=20.3%					
Test for overall effect: Z=0.75(P=0.45)					



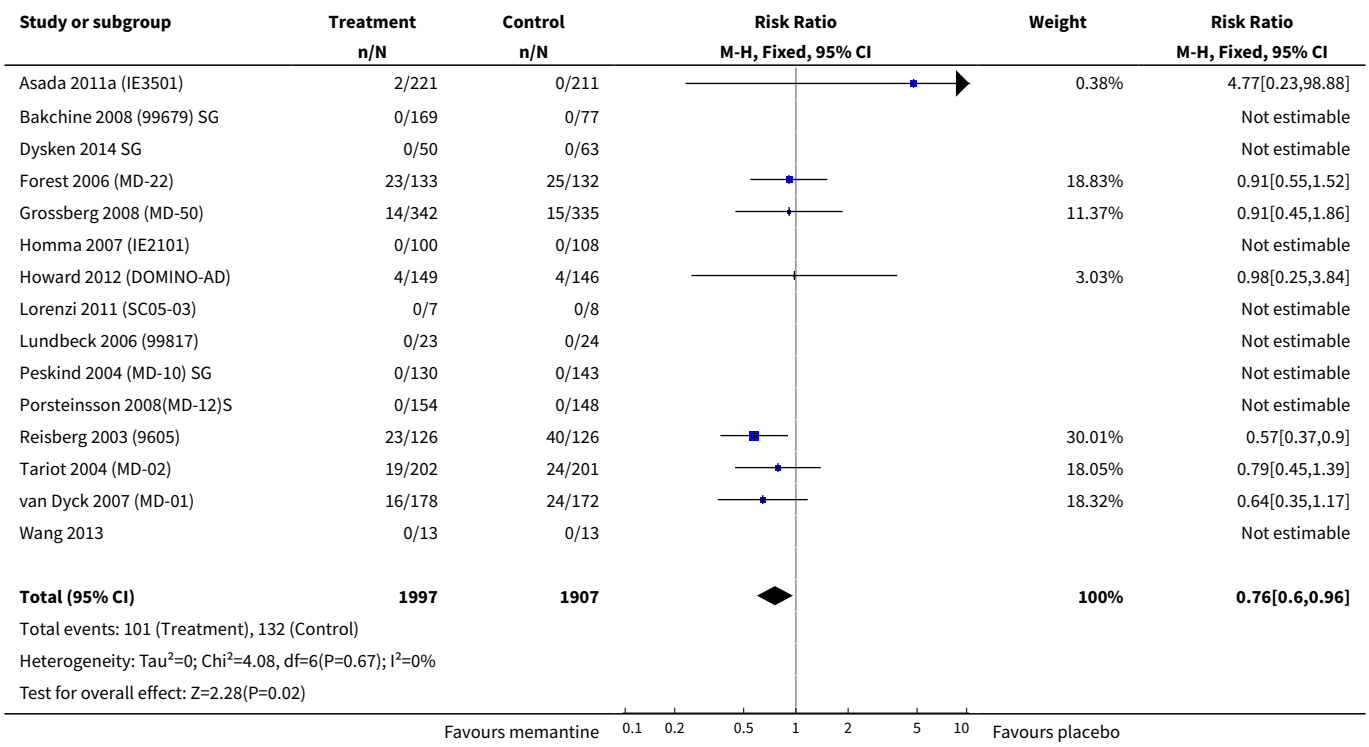
Analysis 1.8. Comparison 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease 24- to 30-week data. OC, Outcome 8 Number suffering serious adverse events.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asada 2011a (IE3501)	26/221	24/211		10.75%	1.03[0.61,1.74]
Bakchine 2008 (99679) SG	0/169	0/77			Not estimable
Dysken 2014 SG	0/50	0/63			Not estimable
Forest 2006 (MD-22)	24/133	38/132		16.7%	0.63[0.4,0.98]
Grossberg 2008 (MD-50)	28/341	23/335		10.16%	1.2[0.7,2.03]
Homma 2007 (IE2101)	7/100	11/108		4.63%	0.69[0.28,1.7]
Howard 2012 (DOMINO-AD)	36/149	37/146		16.36%	0.95[0.64,1.42]
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Lundbeck 2006 (99817)	0/23	0/24			Not estimable





Analysis 1.9. Comparison 1 Memantine 20 mg or equivalent vs placebo for moderate-to-severe Alzheimer's disease 24- to 30-week data. OC, Outcome 9 Number suffering agitation as an adverse event.



Comparison 2. Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data

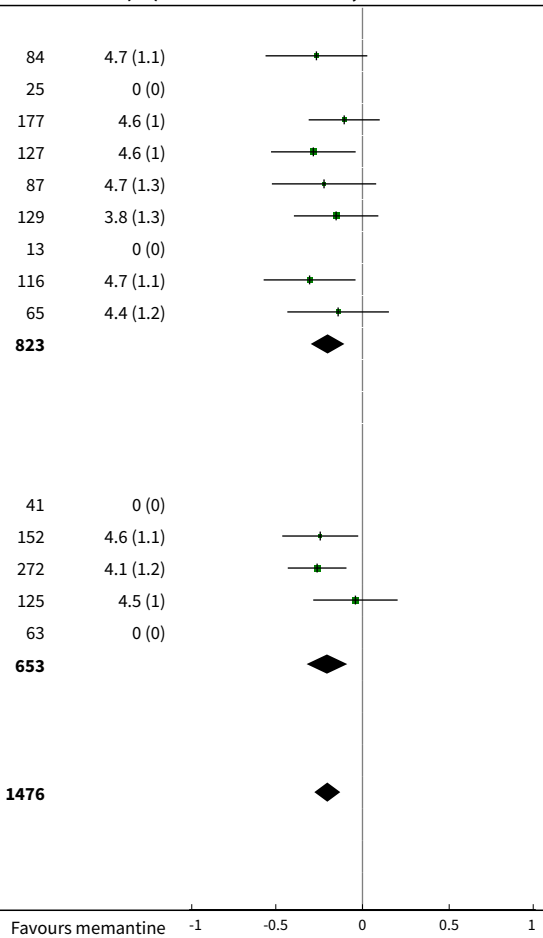
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global: subgroup analysis by +/- ChEI	13	3079	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.28, -0.13]
1.1 Monotherapy	9	1760	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.30, -0.10]
1.2 With concomitant cholinesterase inhibitors	5	1319	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.32, -0.09]
2 Cognitive Function subgroup analysis by +/- ChEI	14	3600	Std. Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.35, -0.21]
2.1 Monotherapy	9	1748	Std. Mean Difference (IV, Fixed, 95% CI)	-0.33 [-0.43, -0.23]
2.2 With concomitant cholinesterase inhibitors	6	1852	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.33, -0.14]
3 Decline in ADL: subgroup analysis by +/- ChEI	13	3077	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.24, -0.09]
3.1 Monotherapy	9	1758	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.30, -0.09]
3.2 With concomitant cholinesterase inhibitors	5	1319	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.24, -0.03]
4 Behaviour and Mood: subgroup analysis by +/- ChEI	14	3674	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.21, -0.08]
4.1 Monotherapy	9	1819	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.19, -0.01]
4.2 With concomitant cholinesterase inhibitors	6	1855	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.27, -0.09]
5 Cognitive function (sMMSE):subgroup analysis within randomised study - per protocol	1	143	Mean Difference (IV, Fixed, 95% CI)	-1.35 [-2.39, -0.31]
5.1 Monotherapy	1	62	Mean Difference (IV, Fixed, 95% CI)	-2.11 [-3.74, -0.48]
5.2 With concomitant cholinesterase inhibitor	1	81	Mean Difference (IV, Fixed, 95% CI)	-0.82 [-2.18, 0.54]
6 Decline in ADL (BADL): subgroup analysis within randomised study - per protocol	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 Monotherapy	1	62	Mean Difference (IV, Fixed, 95% CI)	-2.46 [-6.45, 1.53]
6.2 With concomitant cholinesterase inhibitor	1	81	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-3.21, 2.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 NPI: subgroup analysis within randomised study - per protocol	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
7.1 Monotherapy	1	62	Mean Difference (IV, Fixed, 95% CI)	-4.23 [-14.08, 5.62]
7.2 With concomitant cholinesterase inhibitor	1	81	Mean Difference (IV, Fixed, 95% CI)	-6.99 [-13.13, -0.85]
8 Clinical Global: CIBIC+ mean difference; ChEI subgroup	4	1238	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.33, -0.08]
9 All-cause discontinuation - by ChEI	16	4661	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.82, 1.05]
9.1 Monotherapy	10	2459	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.78, 1.08]
9.2 with concomitant ChEI	7	2202	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.13]
10 Discontinuations due to adverse events - by ChEI	16	4661	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.13]
10.1 Monotherapy	10	2459	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.72, 1.15]
10.2 With concomitant ChEI	7	2202	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.75, 1.30]
11 Adverse events - by ChEI	13	4324	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.06]
11.1 Monotherapy	8	2284	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.94, 1.04]
11.2 with concomitant ChEI	5	2040	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.98, 1.12]
12 Serious adverse events - by ChEI	15	5672	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.06]
12.1 Monotherapy	10	3161	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.74, 1.08]
12.2 With concomitant ChEI	6	2511	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.15]
13 Number suffering agitation as an adverse event - by ChEI	10	3175	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.60, 0.96]
13.1 Monotherapy	6	1535	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.51, 0.91]
13.2 with concomitant ChEI	5	1640	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.60, 1.40]
14 Memantine + donepezil vs memantine + placebo	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
14.1 Cognitive function (sMMSE)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.2 Decline in ADL (BADLS scale)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
14.3 Behaviour and mood (NPI)	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

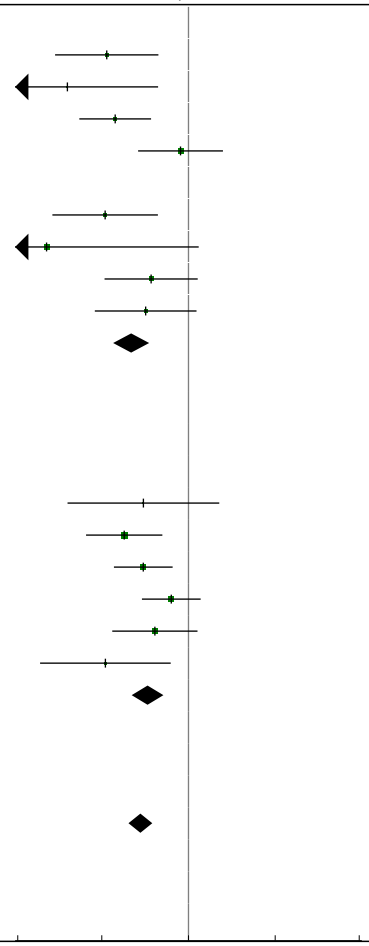
Analysis 2.1. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 1 Clinical Global: subgroup analysis by +/- ChEI.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.1.1 Monotherapy							
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		6.5%	-0.27[-0.56,0.03]
Howard 2012 (DOMINO-AD)	37	0 (0)	25	0 (0)			Not estimable
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		13.33%	-0.11[-0.31,0.1]
van Dyck 2007 (MD-01)	134	4.3 (1.1)	127	4.6 (1)		9.4%	-0.28[-0.53,-0.04]
Homma 2007 (IE2101)	84	4.4 (1.6)	87	4.7 (1.3)		6.19%	-0.22[-0.52,0.08]
Forest 2006 (MD-22)	131	3.6 (1.4)	129	3.8 (1.3)		9.44%	-0.15[-0.4,0.09]
Wang 2013	13	0 (0)	13	0 (0)			Not estimable
Peskind 2004 (MD-10) SG	106	4.4 (1)	116	4.7 (1.1)		7.97%	-0.31[-0.57,-0.04]
Bakchine 2008 (99679) SG	145	4.2 (1.1)	65	4.4 (1.2)		6.52%	-0.14[-0.43,0.15]
Subtotal ***	**937**		**823**			**59.35%**	**-0.2[-0.3,-0.1]**
Heterogeneity: Tau^2=0; Chi^2=2.39, df=6(P=0.88); I^2=0%							
Test for overall effect: Z=4.06(P<0.0001)							
2.1.2 With concomitant cholinesterase inhibitors							
Howard 2012 (DOMINO-AD)	40	0 (0)	41	0 (0)			Not estimable
Tariot 2004 (MD-02)	172	4.4 (1.1)	152	4.6 (1.1)		11.67%	-0.24[-0.46,-0.02]
Grossberg 2008 (MD-50)	269	3.8 (1.1)	272	4.1 (1.2)		19.53%	-0.26[-0.43,-0.09]
Porsteinsson 2008(MD-12)S	135	4.5 (1)	125	4.5 (1)		9.45%	-0.04[-0.28,0.2]
Dysken 2014 SG	50	0 (0)	63	0 (0)			Not estimable
Subtotal ***	**666**		**653**			**40.65%**	**-0.21[-0.32,-0.09]**
Heterogeneity: Tau^2=0; Chi^2=2.3, df=2(P=0.32); I^2=13.09%							
Test for overall effect: Z=3.43(P=0)							
Total ***	**1603**		**1476**			**100%**	**-0.2[-0.28,-0.13]**
Heterogeneity: Tau^2=0; Chi^2=4.7, df=9(P=0.86); I^2=0%							
Test for overall effect: Z=5.32(P<0.0001)							
Test for subgroup differences: Chi^2=0, df=1 (P=0.96), I^2=0%							



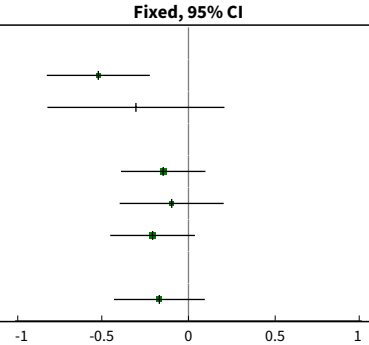
Analysis 2.2. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 2 Cognitive Function subgroup analysis by +/- ChEI.

Study or subgroup	Favours memantine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.2.1 Monotherapy							
Reisberg 2003 (9605)	96	4.5 (11.5)	83	10.2 (12.7)		5.32%	-0.47[-0.77,-0.17]
Howard 2012 (DOMINO-AD)	37	1.9 (2.5)	25	4 (3.6)		1.72%	-0.7[-1.22,-0.18]
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		11.03%	-0.42[-0.63,-0.22]
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		7.89%	-0.05[-0.29,0.2]
Forest 2006 (MD-22)	132	0 (0)	131	0 (0)			Not estimable
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		5.1%	-0.48[-0.78,-0.18]
Wang 2013	11	0 (7.2)	11	5.6 (5.9)		0.61%	-0.82[-1.7,0.06]
Peskind 2004 (MD-10) SG	101	0.8 (5.9)	114	2.2 (7)		6.54%	-0.22[-0.48,0.05]
Bakchine 2008 (99679) SG	146	-0.9 (6.4)	65	0.7 (6.4)		5.49%	-0.25[-0.54,0.05]
Subtotal ***	**931**		**817**			**43.7%**	**-0.33[-0.43,-0.23]**
Heterogeneity: Tau^2=0; Chi^2=11.86, df=7(P=0.11); I^2=40.98%							
Test for overall effect: Z=6.24(P<0.0001)							
2.2.2 With concomitant cholinesterase inhibitors							
Howard 2012 (DOMINO-AD)	40	0.6 (2.7)	41	1.4 (3.5)		2.47%	-0.26[-0.7,0.18]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		9.75%	-0.37[-0.59,-0.15]
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		16.47%	-0.26[-0.43,-0.09]
Nakamura 2016	268	1.3 (8.2)	269	2.2 (8.1)		16.47%	-0.1[-0.27,0.07]
Porsteinsson 2008(MD-12)S	133	0.9 (6)	123	2 (5.8)		7.81%	-0.19[-0.44,0.05]
Dysken 2014 SG	50	3.1 (7.6)	63	6.6 (7.3)		3.33%	-0.48[-0.86,-0.1]
Subtotal ***	**932**		**920**			**56.3%**	**-0.24[-0.33,-0.14]**
Heterogeneity: Tau^2=0; Chi^2=5.76, df=5(P=0.33); I^2=13.17%							
Test for overall effect: Z=5.05(P<0.0001)							
Total ***	**1863**		**1737**			**100%**	**-0.28[-0.35,-0.21]**
Heterogeneity: Tau^2=0; Chi^2=19.41, df=13(P=0.11); I^2=33.03%							
Test for overall effect: Z=7.92(P<0.0001)							
Test for subgroup differences: Chi^2=1.79, df=1 (P=0.18), I^2=44.21%							



Analysis 2.3. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 3 Decline in ADL: subgroup analysis by +/- ChEI.

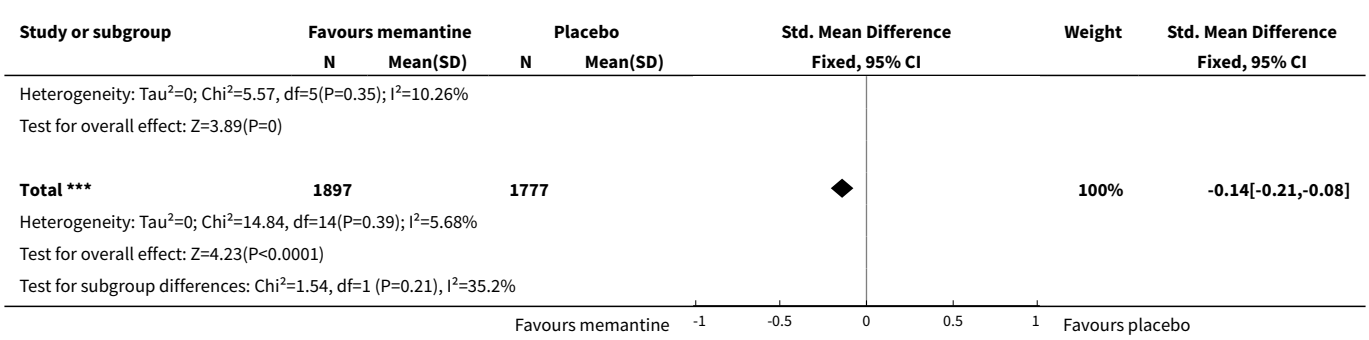
Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.3.1 Monotherapy							
Reisberg 2003 (9605)	97	2.5 (6.3)	84	5.9 (6.8)		6.61%	-0.52[-0.82,-0.22]
Howard 2012 (DOMINO-AD)	37	4.2 (8.3)	25	6.7 (7.6)		2.24%	-0.3[-0.81,0.21]
Asada 2011a (IE3501)	193	0 (0)	175	0 (0)			Not estimable
van Dyck 2007 (MD-01)	133	1.3 (6.9)	127	2.3 (6.8)		9.84%	-0.15[-0.39,0.1]
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		6.48%	-0.1[-0.4,0.2]
Forest 2006 (MD-22)	130	1.9 (6)	129	3.3 (7.4)		9.78%	-0.21[-0.45,0.04]
Wang 2013	11	0 (0)	11	0 (0)			Not estimable
Peskind 2004 (MD-10) SG	107	4 (8.8)	118	5.3 (7)		8.49%	-0.17[-0.43,0.09]



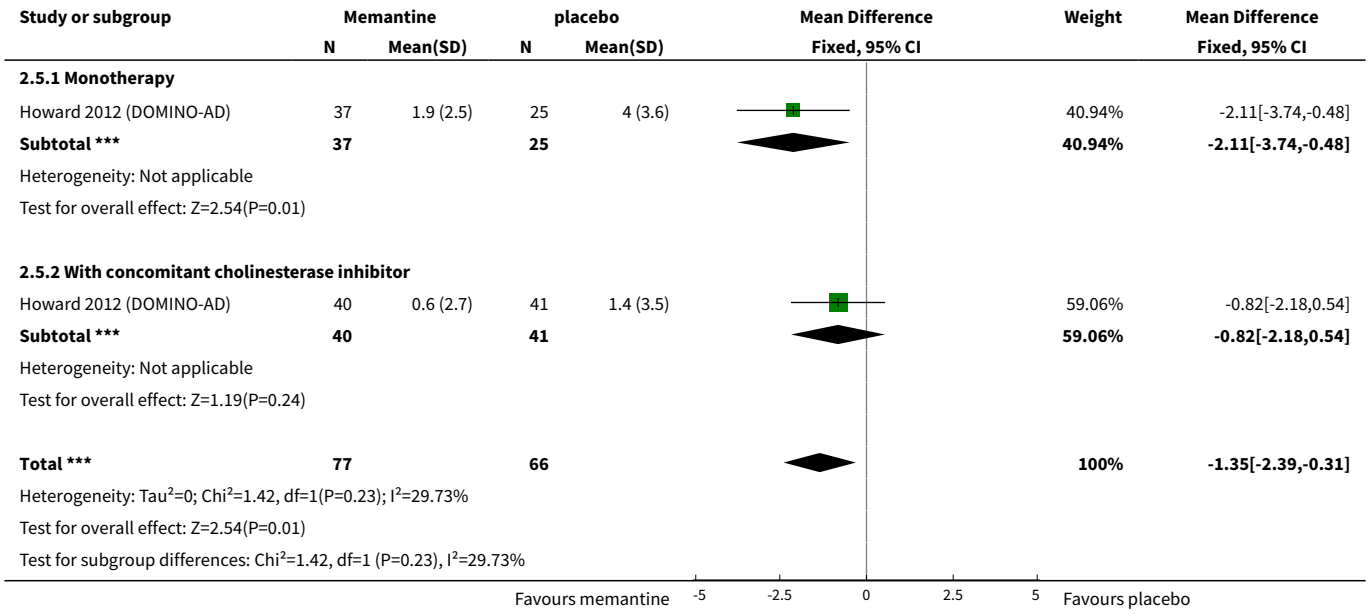
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Bakchine 2008 (99679) SG	146	2.6 (8.2)	64	2.8 (7.4)		6.76%	-0.03[-0.32,0.27]
Subtotal ***	**938**		**820**			**50.2%**	**-0.2[-0.3,-0.09]**
Heterogeneity: Tau²=0; Chi²=6.63, df=6(P=0.36); I²=9.54%							
Test for overall effect: Z=3.55(P=0)							
2.3.2 With concomitant cholinesterase inhibitors							
Howard 2012 (DOMINO-AD)	40	3.4 (5.3)	41	4 (6.7)		3.07%	-0.1[-0.53,0.34]
Tariot 2004 (MD-02)	172	1.7 (6.7)	152	3.3 (6.8)		12.17%	-0.24[-0.46,-0.02]
Grossberg 2008 (MD-50)	268	0.3 (8.1)	272	1.1 (7.8)		20.48%	-0.1[-0.27,0.07]
Porsteinsson 2008(MD-12)S	136	3.6 (7)	125	3.9 (8)		9.89%	-0.03[-0.27,0.21]
Dysken 2014 SG	50	3.6 (11.2)	63	6.7 (10.9)		4.19%	-0.27[-0.65,0.1]
Subtotal ***	**666**		**653**			**49.8%**	**-0.13[-0.24,-0.03]**
Heterogeneity: Tau²=0; Chi²=2.26, df=4(P=0.69); I²=0%							
Test for overall effect: Z=2.44(P=0.01)							
Total ***	**1604**		**1473**			**100%**	**-0.17[-0.24,-0.09]**
Heterogeneity: Tau²=0; Chi²=9.51, df=11(P=0.58); I²=0%							
Test for overall effect: Z=4.24(P<0.0001)							
Test for subgroup differences: Chi²=0.61, df=1 (P=0.43), I²=0%							

Analysis 2.4. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 4 Behaviour and Mood: subgroup analysis by +/- ChEI.

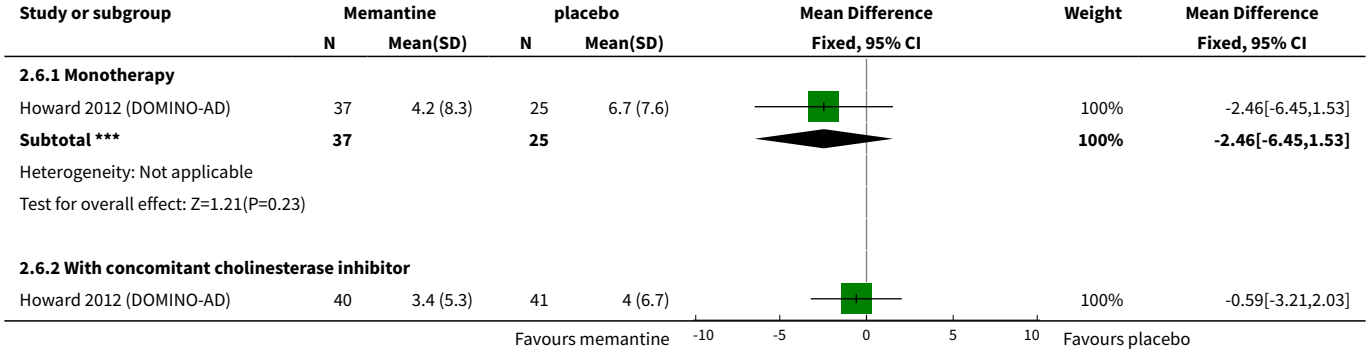
Study or subgroup	Favours memantine N	Favours memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
2.4.1 Monotherapy							
Reisberg 2003 (9605)	97	0.1 (15.9)	84	2.9 (16.1)		4.96%	-0.17[-0.47,0.12]
Howard 2012 (DOMINO-AD)	37	-4.3 (18.5)	25	-0.1 (20)		1.64%	-0.22[-0.73,0.29]
Asada 2011a (IE3501)	217	-0.2 (4.2)	208	0.9 (5.1)		11.65%	-0.25[-0.44,-0.06]
van Dyck 2007 (MD-01)	133	0.5 (15)	127	1 (15.8)		7.18%	-0.03[-0.28,0.21]
Homma 2007 (IE2101)	84	-2.1 (9.4)	87	-0.9 (9.1)		4.72%	-0.12[-0.42,0.18]
Forest 2006 (MD-22)	132	-2.8 (15.5)	131	-3.1 (14.1)		7.27%	0.02[-0.22,0.26]
Wang 2013	11	5 (10)	11	6 (11.5)		0.61%	-0.09[-0.93,0.75]
Peskind 2004 (MD-10) SG	107	0.8 (12.1)	118	2.8 (15.7)		6.19%	-0.15[-0.41,0.12]
Bakchine 2008 (99679) SG	146	-0.4 (10.4)	64	-2.2 (9.6)		4.9%	0.18[-0.11,0.48]
Subtotal ***	**964**		**855**			**49.11%**	**-0.1[-0.19,-0.01]**
Heterogeneity: Tau²=0; Chi²=7.73, df=8(P=0.46); I²=0%							
Test for overall effect: Z=2.08(P=0.04)							
2.4.2 With concomitant cholinesterase inhibitors							
Howard 2012 (DOMINO-AD)	40	-2.5 (13)	41	4.4 (15.2)		2.17%	-0.49[-0.93,-0.05]
Tariot 2004 (MD-02)	171	-0.5 (13)	152	2.9 (13.1)		8.82%	-0.26[-0.48,-0.04]
Grossberg 2008 (MD-50)	268	-4.9 (13.4)	272	-1.8 (13.2)		14.82%	-0.24[-0.4,-0.07]
Nakamura 2016	268	-0.2 (3.8)	269	0.3 (3.8)		14.81%	-0.13[-0.29,0.04]
Porsteinsson 2008(MD-12)S	136	1 (11.3)	125	0.9 (11.1)		7.2%	0.01[-0.23,0.25]
Dysken 2014 SG	50	0.4 (12.4)	63	2.8 (12.1)		3.07%	-0.19[-0.57,0.18]
Subtotal ***	**933**		**922**			**50.89%**	**-0.18[-0.27,-0.09]**

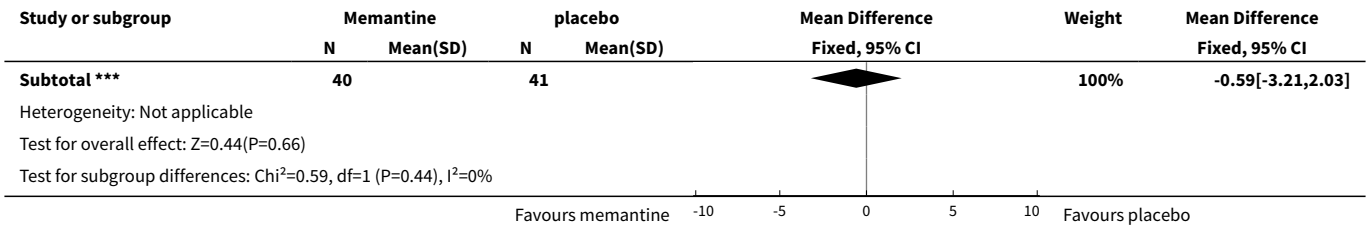


Analysis 2.5. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 5 Cognitive function (sMMSE):subgroup analysis within randomised study - per protocol.

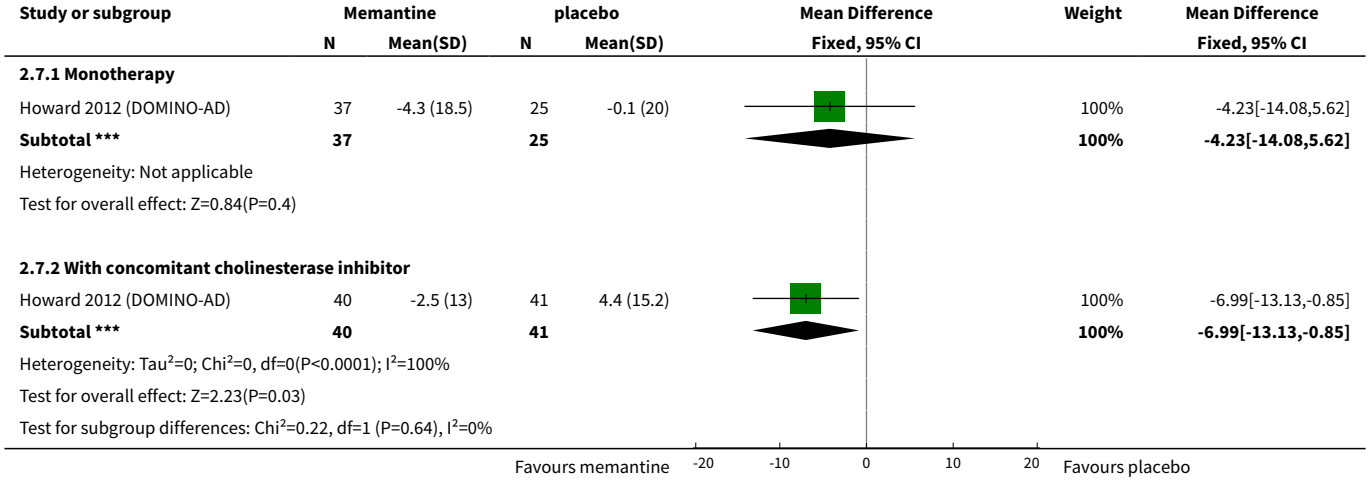


Analysis 2.6. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 6 Decline in ADL (BADL): subgroup analysis within randomised study - per protocol.

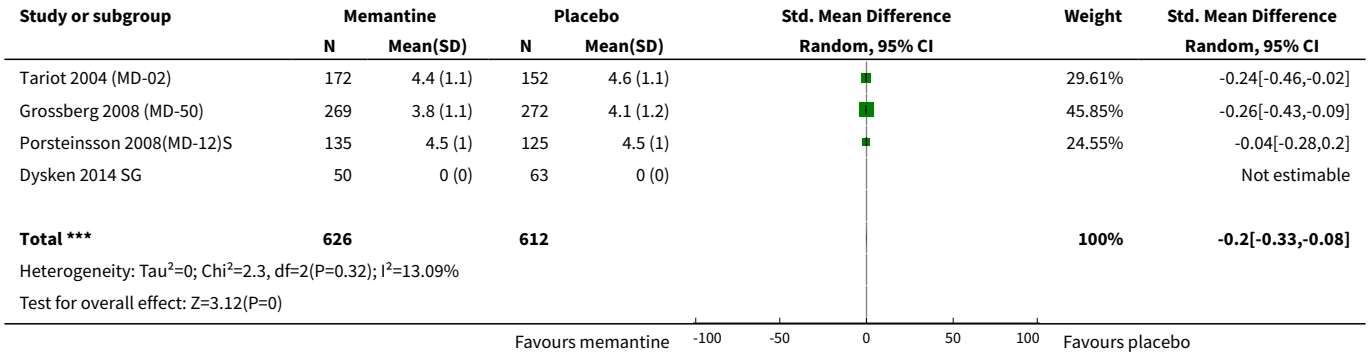




Analysis 2.7. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 7 NPI: subgroup analysis within randomised study - per protocol.



Analysis 2.8. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 8 Clinical Global: CIBIC+ mean difference; ChEI subgroup.



Analysis 2.9. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 9 All-cause discontinuation - by ChEI.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.9.1 Monotherapy					
Asada 2011a (IE3501)	29/221	33/211		7.7%	0.84[0.53,1.33]
Bakchine 2008 (99679) SG	23/169	12/77		3.76%	0.87[0.46,1.66]
Forest 2006 (MD-22)	29/133	29/132		6.64%	0.99[0.63,1.56]
Homma 2007 (IE2101)	16/100	21/108		4.6%	0.82[0.46,1.49]
Howard 2012 (DOMINO-AD)	25/76	17/73		3.95%	1.41[0.83,2.39]
Lundbeck 2006 (10116)	11/128	11/130		2.49%	1.02[0.46,2.26]
Peskind 2004 (MD-10) SG	24/130	26/143		5.65%	1.02[0.62,1.68]
Reisberg 2003 (9605)	29/126	42/126		9.58%	0.69[0.46,1.03]
van Dyck 2007 (MD-01)	44/178	46/172		10.67%	0.92[0.65,1.32]
Wang 2013	2/13	2/13		0.46%	1[0.16,6.07]
Subtotal (95% CI)	**1274**	**1185**		**55.49%**	**0.92[0.78,1.08]**
Total events: 232 (Memantine), 239 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.13, df=9(P=0.82); I^2=0%					
Test for overall effect: Z=1.05(P=0.29)					
2.9.2 with concomitant ChEI					
Dysken 2014 SG	0/50	0/63			Not estimable
Grossberg 2008 (MD-50)	69/342	63/335		14.51%	1.07[0.79,1.46]
Howard 2012 (DOMINO-AD)	15/73	19/73		4.33%	0.79[0.44,1.43]
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Nakamura 2016	53/273	39/273		8.89%	1.36[0.93,1.98]
Porsteinsson 2008(MD-12)S	18/154	22/148		5.12%	0.79[0.44,1.41]
Tariot 2004 (MD-02)	30/202	51/201		11.66%	0.59[0.39,0.88]
Subtotal (95% CI)	**1101**	**1101**		**44.51%**	**0.94[0.78,1.13]**
Total events: 185 (Memantine), 194 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=10.28, df=4(P=0.04); I^2=61.08%					
Test for overall effect: Z=0.65(P=0.52)					
Total (95% CI)	**2375**	**2286**		**100%**	**0.93[0.82,1.05]**
Total events: 417 (Memantine), 433 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=15.46, df=14(P=0.35); I^2=9.45%					
Test for overall effect: Z=1.21(P=0.23)					
Test for subgroup differences: Chi^2=0.05, df=1 (P=0.83), I^2=0%					

Analysis 2.10. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 10 Discontinuations due to adverse events - by ChEI.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.10.1 Monotherapy					
Asada 2011a (IE3501)	14/221	13/211		6.04%	1.03[0.5,2.14]
Bakchine 2008 (99679) SG	13/169	4/77		2.5%	1.48[0.5,4.39]
Forest 2006 (MD-22)	19/133	24/132		10.95%	0.79[0.45,1.36]

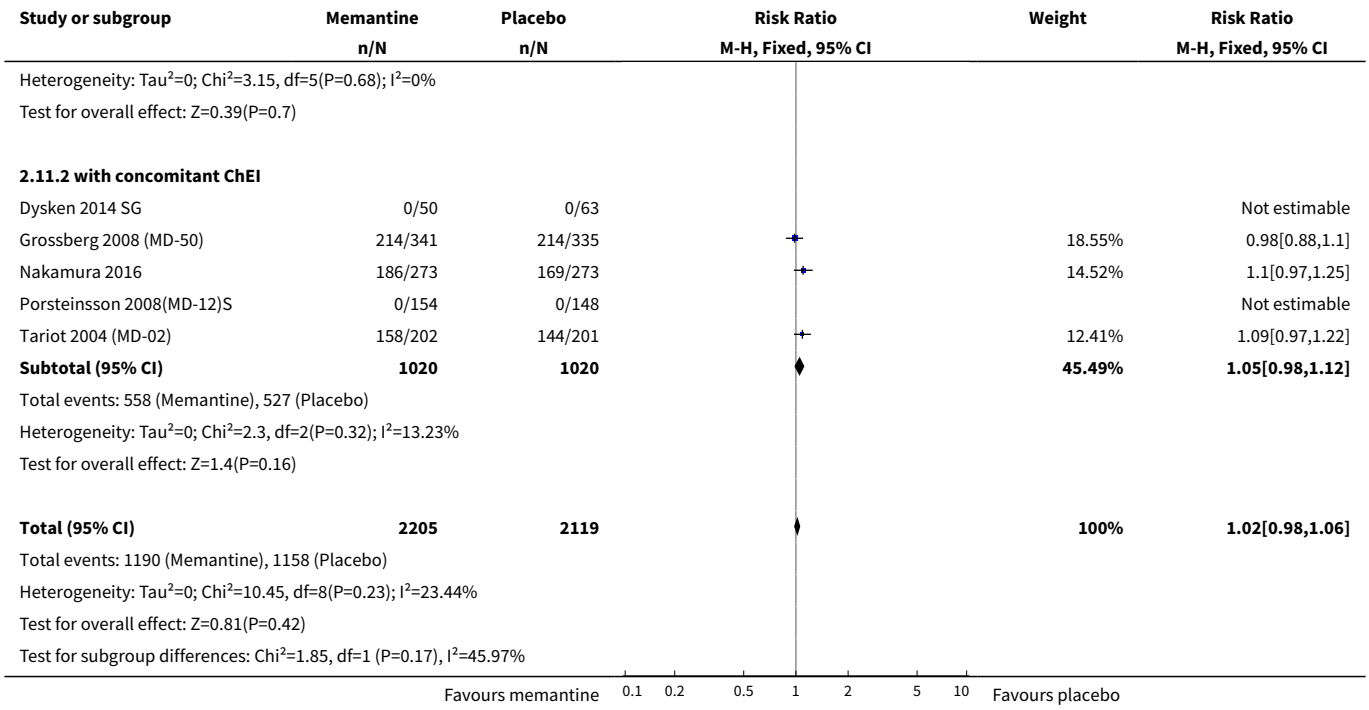
Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Homma 2007 (IE2101)	8/100	15/108		6.55%	0.58[0.26,1.3]
Howard 2012 (DOMINO-AD)	12/76	10/73		4.64%	1.15[0.53,2.5]
Lundbeck 2006 (10116)	6/128	5/130		2.25%	1.22[0.38,3.89]
Peskind 2004 (MD-10) SG	12/130	8/143		3.46%	1.65[0.7,3.91]
Reisberg 2003 (9605)	13/126	22/126		10%	0.59[0.31,1.12]
van Dyck 2007 (MD-01)	22/178	23/172		10.63%	0.92[0.54,1.6]
Wang 2013	0/13	0/13			Not estimable
Subtotal (95% CI)	**1274**	**1185**		**57.02%**	**0.91[0.72,1.15]**
Total events: 119 (Memantine), 124 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=6.54, df=8(P=0.59); I^2=0%					
Test for overall effect: Z=0.78(P=0.43)					
2.10.2 With concomitant ChEI					
Dysken 2014 SG	0/50	0/63			Not estimable
Grossberg 2008 (MD-50)	34/342	21/335		9.64%	1.59[0.94,2.67]
Howard 2012 (DOMINO-AD)	8/73	14/73		6.36%	0.57[0.26,1.28]
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Nakamura 2016	26/273	19/273		8.63%	1.37[0.78,2.41]
Porsteinsson 2008(MD-12)S	11/154	15/148		6.95%	0.7[0.33,1.48]
Tariot 2004 (MD-02)	15/202	25/201		11.39%	0.6[0.32,1.1]
Subtotal (95% CI)	**1101**	**1101**		**42.98%**	**0.99[0.75,1.3]**
Total events: 94 (Memantine), 94 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=9.6, df=4(P=0.05); I^2=58.34%					
Test for overall effect: Z=0.09(P=0.93)					
Total (95% CI)	**2375**	**2286**		**100%**	**0.94[0.79,1.13]**
Total events: 213 (Memantine), 218 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=16.35, df=13(P=0.23); I^2=20.48%					
Test for overall effect: Z=0.64(P=0.52)					
Test for subgroup differences: Chi^2=0.2, df=1 (P=0.65), I^2=0%					

Favours memantine — Favours placebo

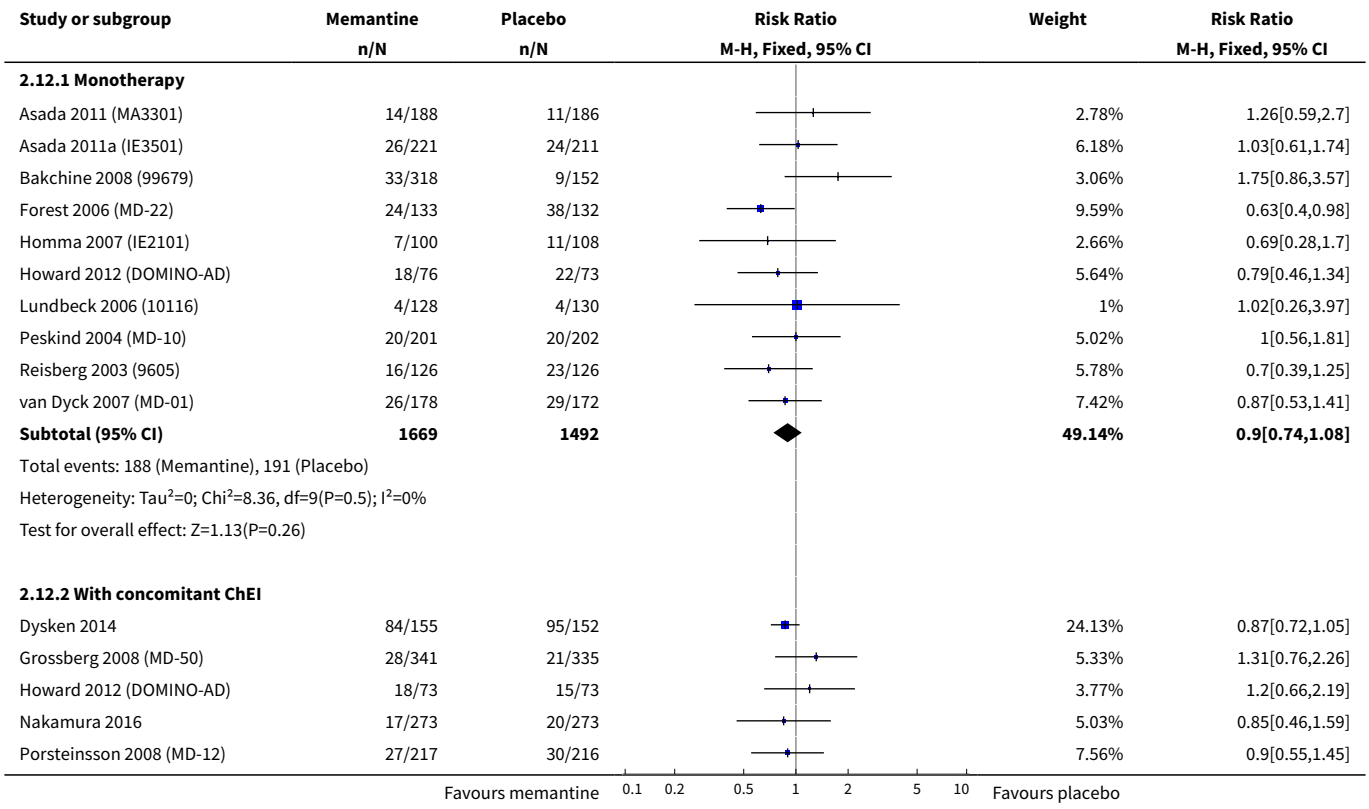
Analysis 2.11. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 11 Adverse events - by ChEI.

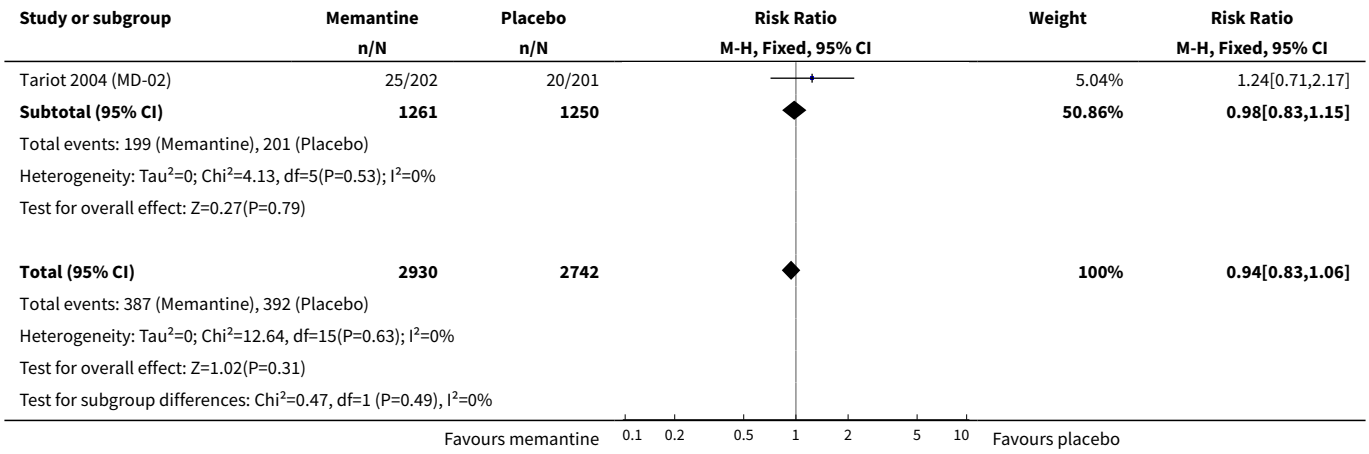
Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
2.11.1 Monotherapy					
Asada 2011a (IE3501)	180/221	167/211		14.68%	1.03[0.94,1.13]
Bakchine 2008 (99679) SG	0/169	0/77			Not estimable
Forest 2006 (MD-22)	124/133	129/132		11.13%	0.95[0.91,1.01]
Homma 2007 (IE2101)	72/100	78/108		6.45%	1[0.84,1.18]
Lundbeck 2006 (10116)	19/128	23/130		1.96%	0.84[0.48,1.46]
Peskind 2004 (MD-10) SG	0/130	0/143			Not estimable
Reisberg 2003 (9605)	106/126	109/126		9.37%	0.97[0.88,1.08]
van Dyck 2007 (MD-01)	131/178	125/172		10.93%	1.01[0.89,1.15]
Subtotal (95% CI)	**1185**	**1099**		**54.51%**	**0.99[0.94,1.04]**
Total events: 632 (Memantine), 631 (Placebo)					

Favours memantine — Favours placebo

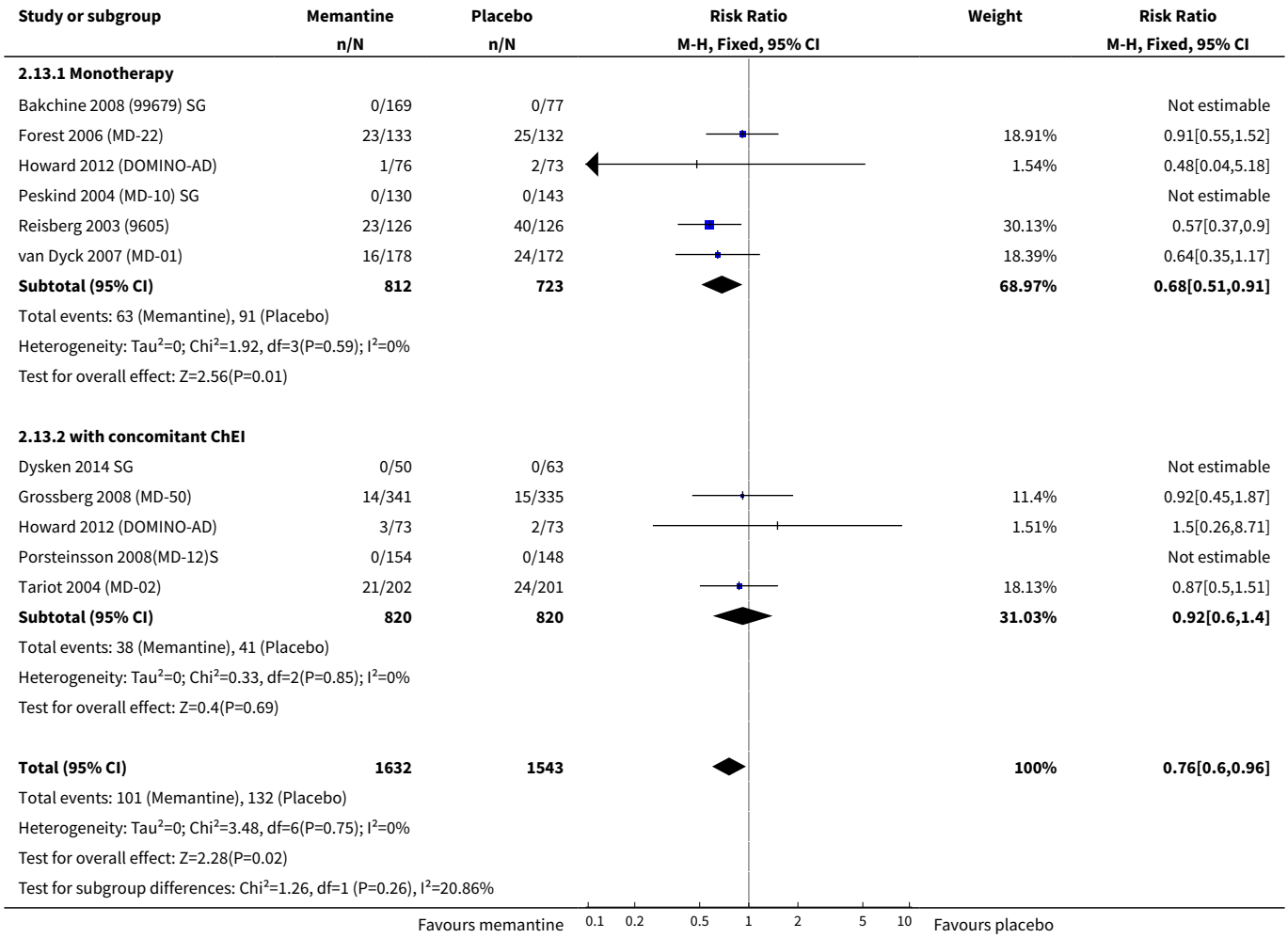


Analysis 2.12. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 12 Serious adverse events - by ChEI.

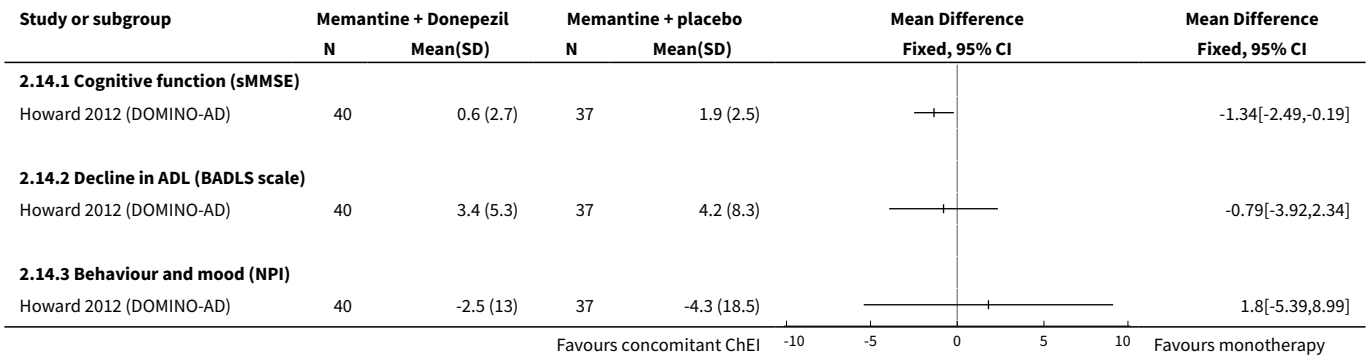




Analysis 2.13. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 13 Number suffering agitation as an adverse event - by ChEI.



Analysis 2.14. Comparison 2 Memantine 20 mg or equivalent vs placebo in patients taking versus not taking cholinesterase inhibitors with moderate to severe Alzheimer's disease 24- to 30-week data, Outcome 14 Memantine + donepezil vs memantine + placebo.



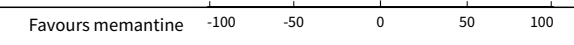
Comparison 3. Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation

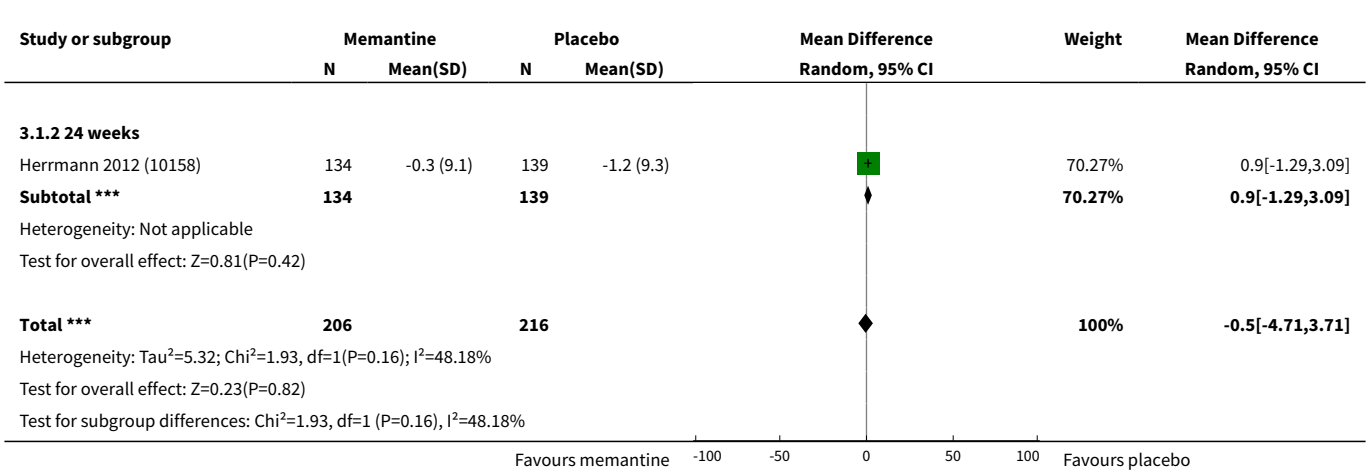
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cohen Mansfield Agitation Inventory (MD)	2	422	Mean Difference (IV, Random, 95% CI)	-0.50 [-4.71, 3.71]
1.1 12 weeks	1	149	Mean Difference (IV, Random, 95% CI)	-3.80 [-10.06, 2.46]
1.2 24 weeks	1	273	Mean Difference (IV, Random, 95% CI)	0.90 [-1.29, 3.09]
2 Cohen Mansfield Agitation Inventory (SMD)	2	306	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.12, 0.33]
2.1 12 weeks	1	33	Std. Mean Difference (IV, Random, 95% CI)	0.21 [-0.48, 0.89]
2.2 24 weeks	1	273	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.14, 0.33]
3 NPI agitation subscale	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
3.1 12 weeks	2	146	Mean Difference (IV, Random, 95% CI)	-0.39 [-1.90, 1.13]
3.2 24 weeks	1	324	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]
4 Number suffering agitation	3	556	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [1.04, 5.50]
4.1 12 weeks	2	187	Risk Ratio (M-H, Fixed, 95% CI)	5.0 [0.26, 97.00]
4.2 24 weeks	1	369	Risk Ratio (M-H, Fixed, 95% CI)	2.20 [0.92, 5.27]
5 Clinical Global	3	443	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.34, 0.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 12 weeks	2	168	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.59, 0.02]
5.2 24 weeks	1	275	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.20, 0.28]
6 Cognitive Function: SIB	3	486	Mean Difference (IV, Random, 95% CI)	-4.34 [-14.58, 5.89]
6.1 12 weeks	2	162	Mean Difference (IV, Random, 95% CI)	-10.00 [-16.15, -3.85]
6.2 24 weeks	1	324	Mean Difference (IV, Random, 95% CI)	0.48 [-1.61, 2.57]
7 Decline in ADL: ADCS-ADL19	3	458	Mean Difference (IV, Fixed, 95% CI)	1.48 [-0.19, 3.15]
7.1 12 weeks	2	182	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-4.18, 3.98]
7.2 24 weeks	1	276	Mean Difference (IV, Fixed, 95% CI)	1.80 [-0.03, 3.63]
8 Behaviour and Mood	3	470	Mean Difference (IV, Random, 95% CI)	-1.51 [-8.05, 5.03]
8.1 12 weeks	2	146	Mean Difference (IV, Random, 95% CI)	-3.76 [-14.09, 6.58]
8.2 24 weeks	1	324	Mean Difference (IV, Random, 95% CI)	1.23 [-2.19, 4.65]
9 All-cause discontinuation	3	555	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.79, 1.52]
9.1 12 weeks	2	186	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.78, 1.99]
9.2 24 weeks	1	369	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.63, 1.56]
10 Discontinuations due to adverse events	3	556	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.88, 2.21]
11 Number suffering at least one adverse event	3	556	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.95, 1.20]
12 Number suffering serious adverse events	3	556	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.85, 3.20]

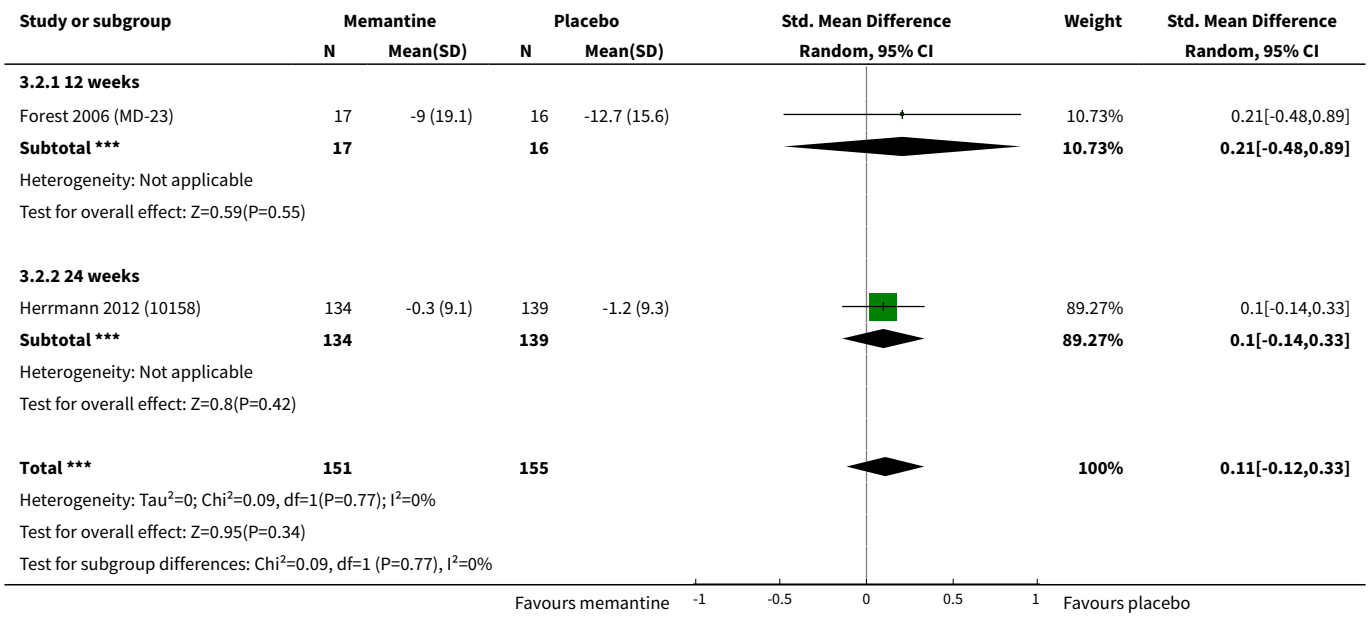
Analysis 3.1. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 1 Cohen Mansfield Agitation Inventory (MD).

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.1.1 12 weeks							
Fox 2012 (MAGD)	72	53.5 (19.2)	77	57.3 (19.8)		29.73%	-3.8[-10.06,2.46]
Subtotal ***	**72**		**77**			**29.73%**	**-3.8[-10.06,2.46]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.19(P=0.23)							

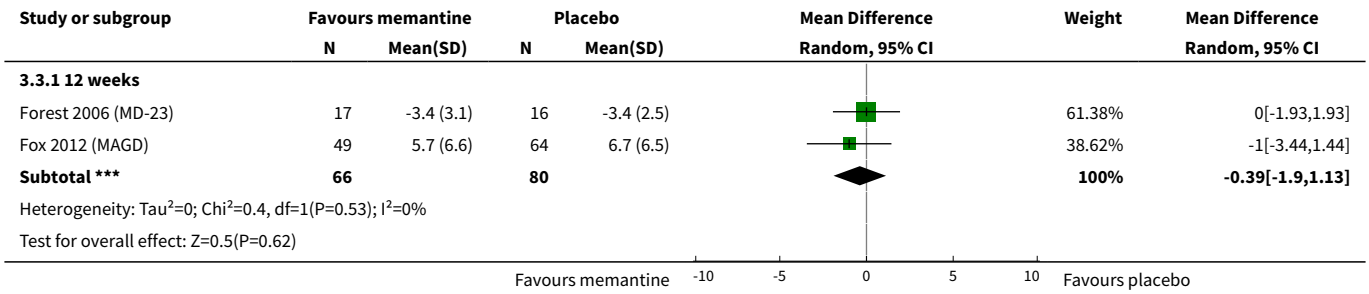




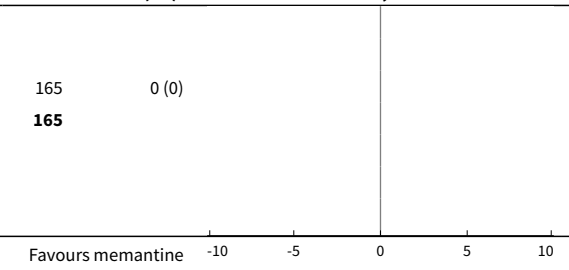
Analysis 3.2. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 2 Cohen Mansfield Agitation Inventory (SMD).



Analysis 3.3. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 3 NPI agitation subscale.

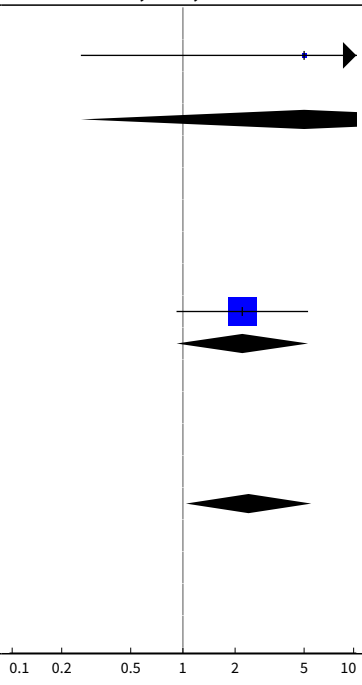


Study or subgroup	Favours memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
3.3.2 24 weeks							
Herrmann 2012 (10158)	159	0 (0)	165	0 (0)			Not estimable
Subtotal ***	**159**		**165**				**Not estimable**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



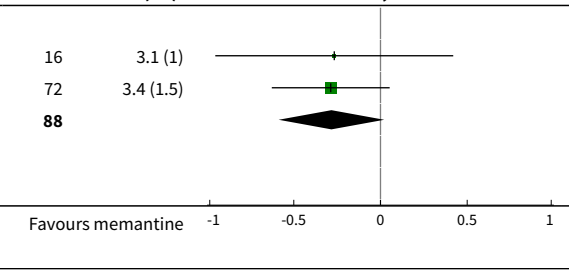
Analysis 3.4. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 4 Number suffering agitation.

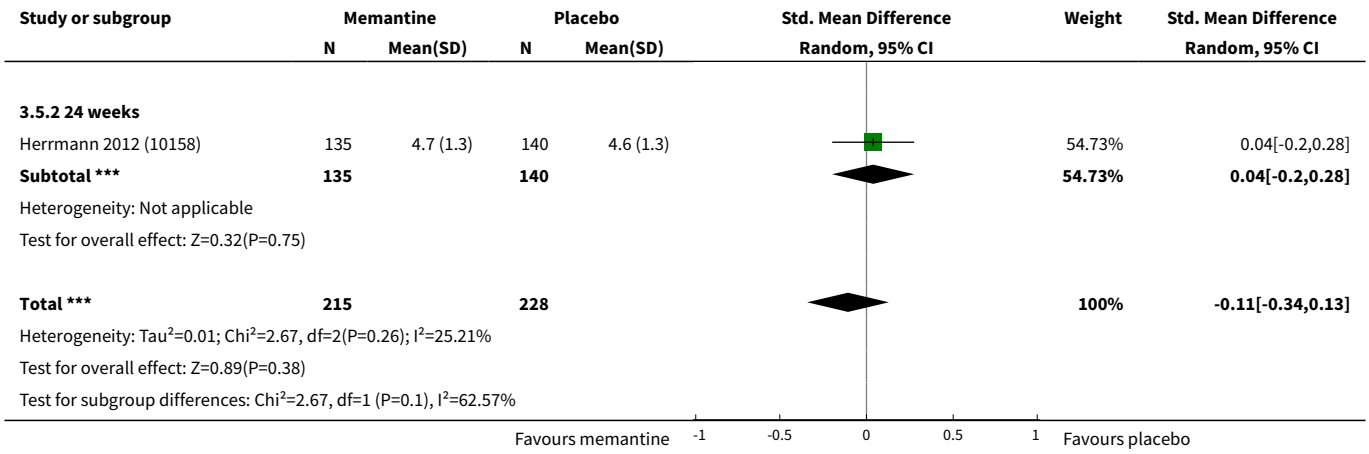
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.4.1 12 weeks					
Forest 2006 (MD-23)	2/17	0/17		6.75%	5[0.26,97]
Fox 2012 (MAGD)	0/74	0/79			Not estimable
Subtotal (95% CI)	**91**	**96**		**6.75%**	**5[0.26,97]**
Total events: 2 (Treatment), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.06(P=0.29)					
3.4.2 24 weeks					
Herrmann 2012 (10158)	15/182	7/187		93.25%	2.2[0.92,5.27]
Subtotal (95% CI)	**182**	**187**		**93.25%**	**2.2[0.92,5.27]**
Total events: 15 (Treatment), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.77(P=0.08)					
Total (95% CI)	**273**	**283**		**100%**	**2.39[1.04,5.5]**
Total events: 17 (Treatment), 7 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=2.05(P=0.04)					
Test for subgroup differences: Chi^2=0.27, df=1 (P=0.6), I^2=0%					



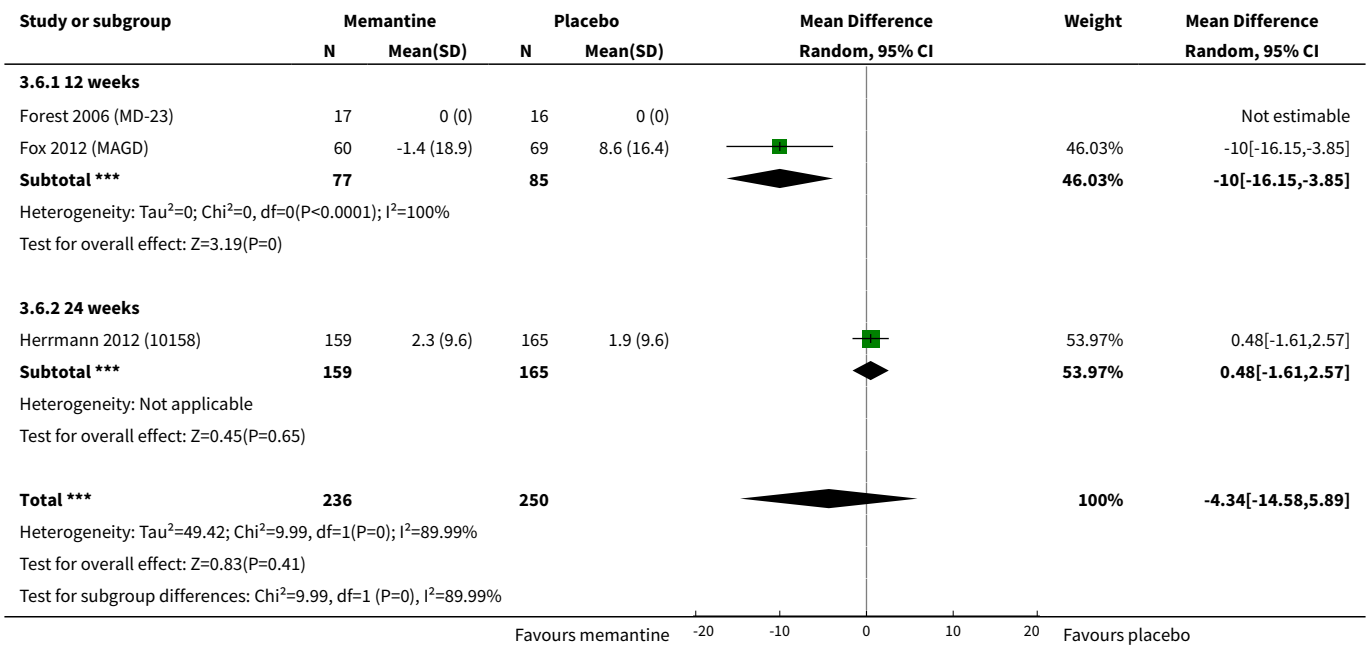
Analysis 3.5. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 5 Clinical Global.

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
3.5.1 12 weeks							
Forest 2006 (MD-23)	17	2.8 (1.2)	16	3.1 (1)		10.77%	-0.27[-0.95,0.42]
Fox 2012 (MAGD)	63	3 (1.4)	72	3.4 (1.5)		34.5%	-0.29[-0.63,0.05]
Subtotal ***	**80**		**88**			**45.27%**	**-0.28[-0.59,0.02]**
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.96); I^2=0%							
Test for overall effect: Z=1.82(P=0.07)							

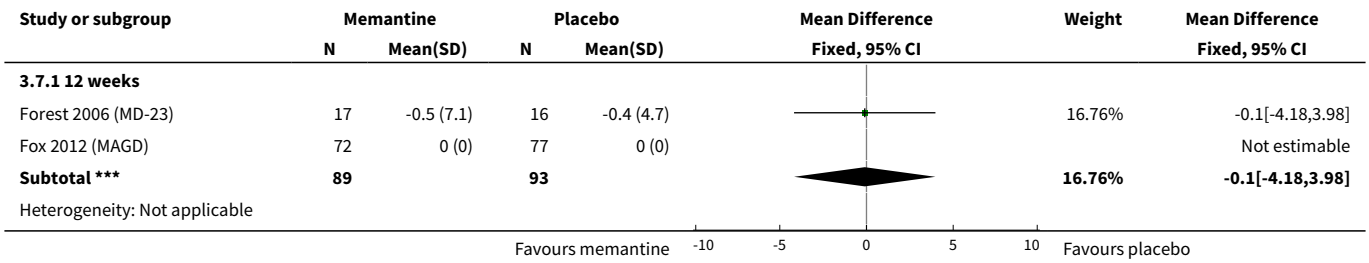


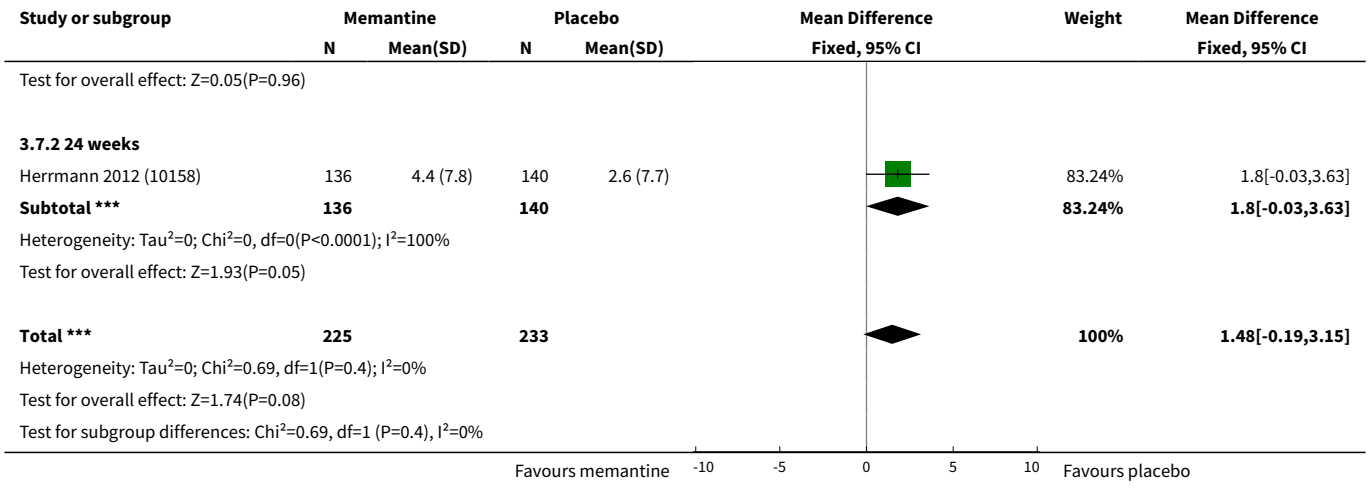


Analysis 3.6. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 6 Cognitive Function: SIB.

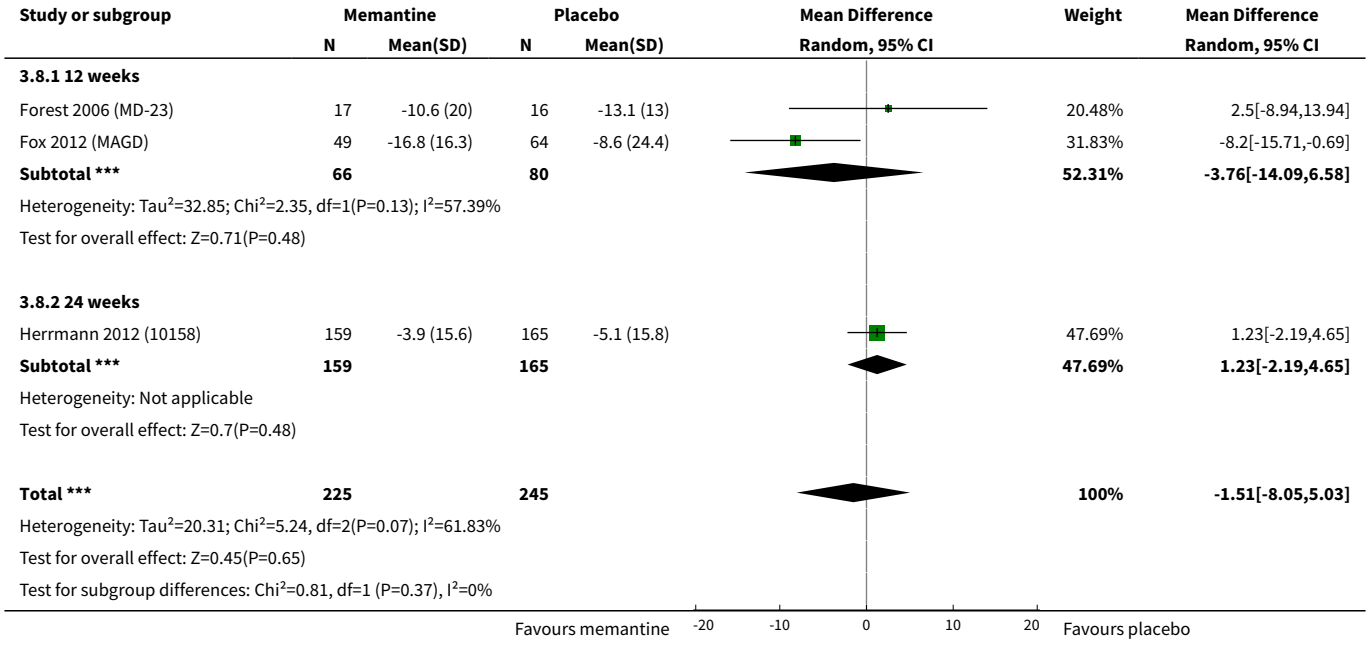


Analysis 3.7. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 7 Decline in ADL: ADCS-ADL19.

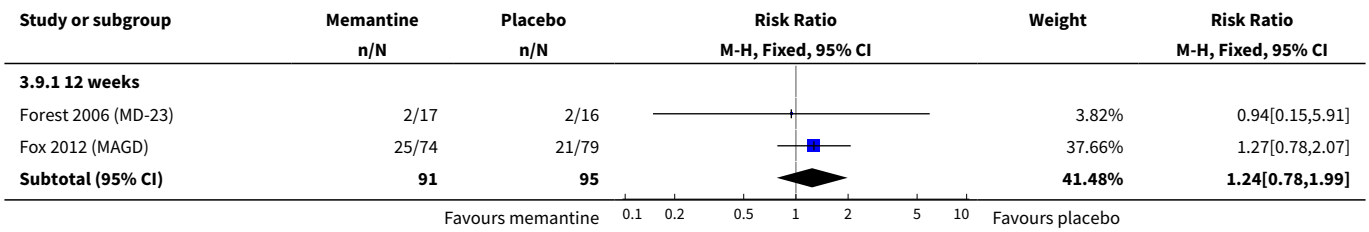


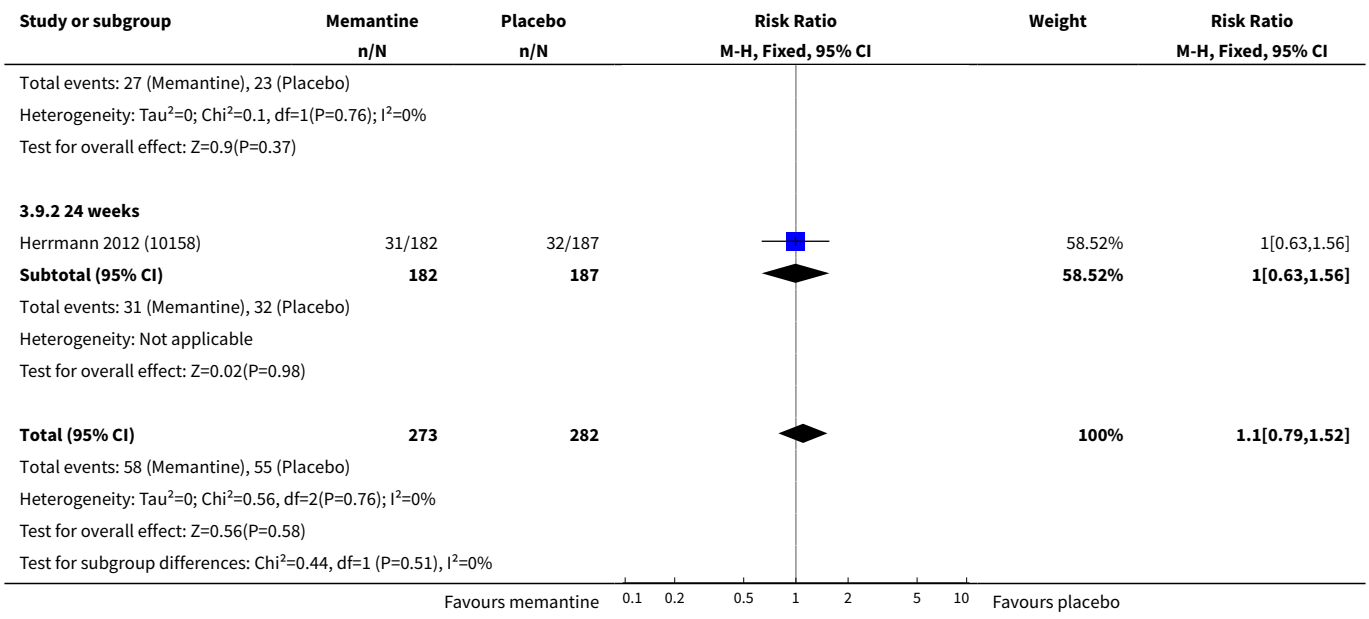


Analysis 3.8. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 8 Behaviour and Mood.

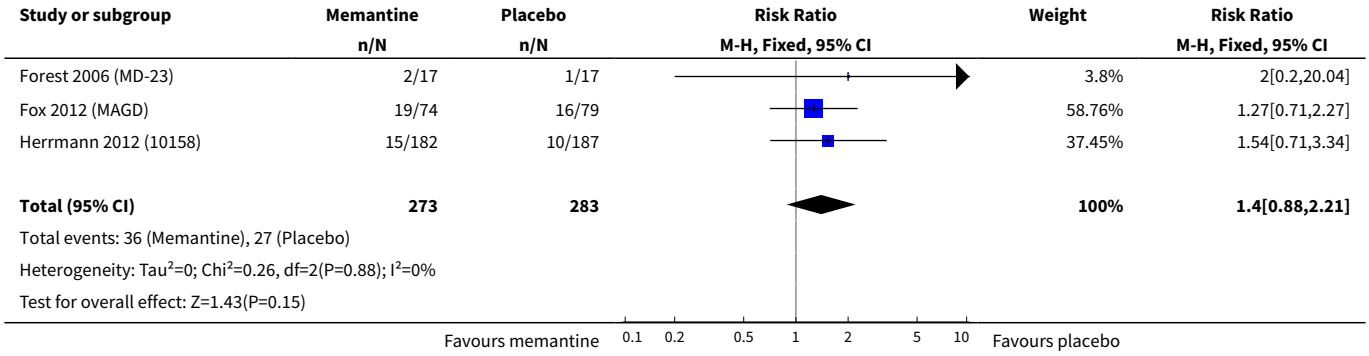


Analysis 3.9. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 9 All-cause discontinuation.

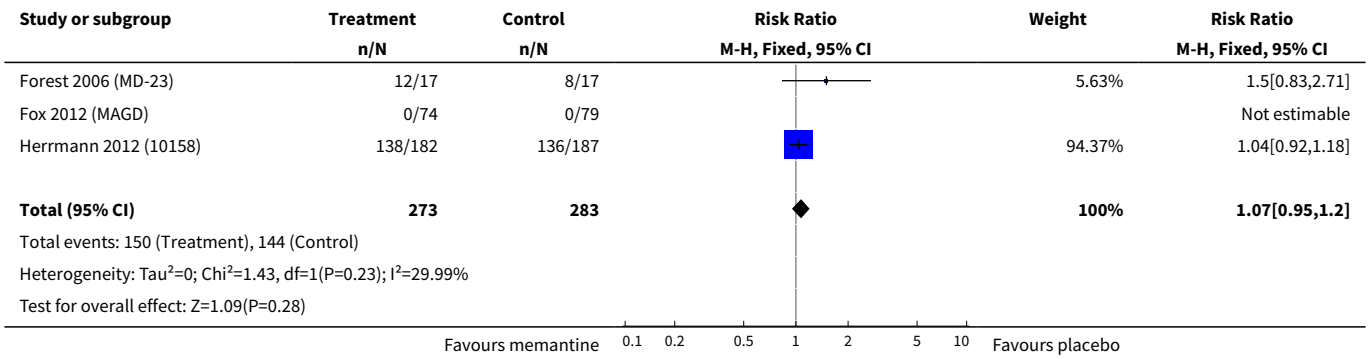




Analysis 3.10. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 10 Discontinuations due to adverse events.

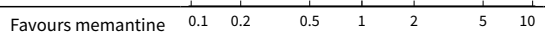


Analysis 3.11. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 11 Number suffering at least one adverse event.



Analysis 3.12. Comparison 3 Memantine 20 mg or equivalent vs placebo for moderate-to-severe AD with agitation, Outcome 12 Number suffering serious adverse events.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Forest 2006 (MD-23)	3/17	2/17		15.56%	1.5[0.29,7.87]
Fox 2012 (MAGD)	0/74	0/79			Not estimable
Herrmann 2012 (10158)	18/182	11/187		84.44%	1.68[0.82,3.46]
Total (95% CI)	**273**	**283**		**100%**	**1.65[0.85,3.2]**
Total events: 21 (Treatment), 13 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.9); I^2=0%					
Test for overall effect: Z=1.49(P=0.14)					

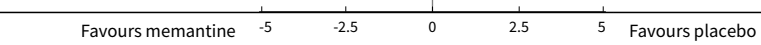


Comparison 4. Memantine 20 mg vs placebo for mild AD (MMSE 20-23) OC six-month studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical global: CIBIC+	4	621	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.30, 0.12]
2 Cognitive function: ADASCog	5		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
2.1 ADAS cog at 6 months	4	619	Mean Difference (IV, Fixed, 95% CI)	-0.21 [-1.38, 0.95]
2.2 MMSE at 12 months - final values	1	26	Mean Difference (IV, Fixed, 95% CI)	-1.15 [-3.47, 1.17]
3 Decline in ADL: ADCS-ADL23	4	621	Mean Difference (IV, Fixed, 95% CI)	0.07 [-1.66, 1.80]
4 Behaviour and mood: NPI	4	621	Mean Difference (IV, Fixed, 95% CI)	0.29 [-1.58, 2.16]

Analysis 4.1. Comparison 4 Memantine 20 mg vs placebo for mild AD (MMSE 20-23) OC six-month studies, Outcome 1 Clinical global: CIBIC+.

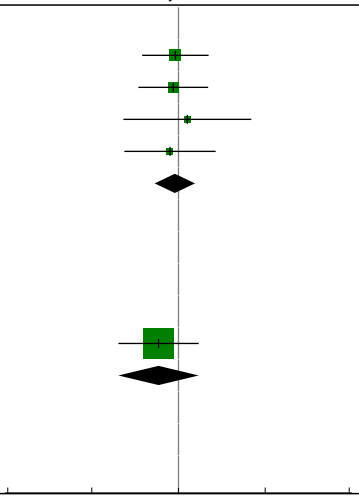
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bakchine 2008 (99679) SG	125	4 (1.3)	73	4 (1.2)		33.98%	0[-0.36,0.36]
Dysken 2014 SG	105	0 (0)	89	0 (0)			Not estimable
Peskind 2004 (MD-10) SG	58	3.9 (1)	50	4.1 (1.1)		29.13%	-0.2[-0.59,0.19]
Porsteinsson 2008(MD-12)S	57	4.1 (1)	64	4.2 (0.9)		36.89%	-0.09[-0.44,0.26]



Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Total ***	**345**		**276**			**100%**	**-0.09[-0.3,0.12]**
Heterogeneity: Tau²=0; Chi²=0.54, df=2(P=0.76); I²=0%							
Test for overall effect: Z=0.85(P=0.4)							

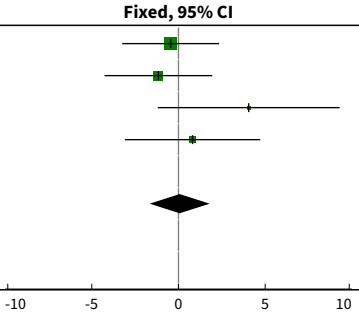
Analysis 4.2. Comparison 4 Memantine 20 mg vs placebo for mild AD (MMSE 20-23) OC six-month studies, Outcome 2 Cognitive function: ADASCog.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
4.2.1 ADAS cog at 6 months							
Bakchine 2008 (99679) SG	125	-2.8 (7.4)	72	-2.6 (6.1)		36.96%	-0.18[-2.1,1.74]
Dysken 2014 SG	105	0.5 (7.1)	89	0.8 (7.2)		33.5%	-0.3[-2.31,1.71]
Peskind 2004 (MD-10) SG	59	-1.4 (10.3)	48	-1.9 (9.1)		9.97%	0.51[-3.18,4.2]
Porsteinsson 2008(MD-12)S	57	-2 (7.7)	64	-1.5 (7)		19.57%	-0.49[-3.12,2.14]
Subtotal ***	**346**		**273**			**100%**	**-0.21[-1.38,0.95]**
Heterogeneity: Tau²=0; Chi²=0.2, df=3(P=0.98); I²=0%							
Test for overall effect: Z=0.36(P=0.72)							
4.2.2 MMSE at 12 months - final values							
Holland 2013	13	-27.1 (2.3)	13	-26 (3.6)		100%	-1.15[-3.47,1.17]
Subtotal ***	**13**		**13**			**100%**	**-1.15[-3.47,1.17]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.97(P=0.33)							
Test for subgroup differences: Chi²=0.5, df=1 (P=0.48), I²=0%							



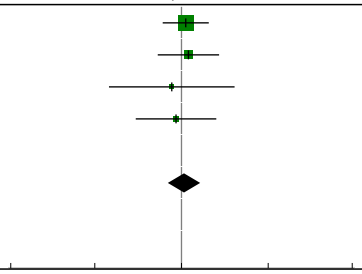
Analysis 4.3. Comparison 4 Memantine 20 mg vs placebo for mild AD (MMSE 20-23) OC six-month studies, Outcome 3 Decline in ADL: ADCS-ADL23.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bakchine 2008 (99679) SG	124	1.6 (10.3)	73	2 (9.3)		38.38%	-0.45[-3.25,2.35]
Dysken 2014 SG	105	1.9 (11)	89	3 (11)		31.06%	-1.16[-4.27,1.95]
Peskind 2004 (MD-10) SG	59	-0.7 (13)	50	-4.8 (14.7)		10.9%	4.05[-1.2,9.3]
Porsteinsson 2008(MD-12)S	57	-0.5 (12.2)	64	-1.3 (9.3)		19.66%	0.81[-3.1,4.72]
Total ***	**345**		**276**			**100%**	**0.07[-1.66,1.8]**
Heterogeneity: Tau²=0; Chi²=3.08, df=3(P=0.38); I²=2.73%							
Test for overall effect: Z=0.08(P=0.94)							



Analysis 4.4. Comparison 4 Memantine 20 mg vs placebo for mild AD (MMSE 20-23) OC six-month studies, Outcome 4 Behaviour and mood: NPI.

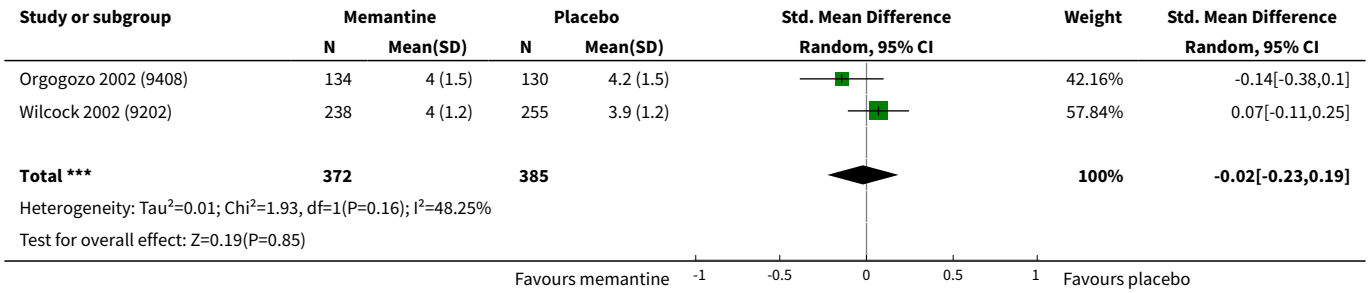
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bakchine 2008 (99679) SG	124	-2.6 (9.5)	73	-3.1 (9)		49.37%	0.49[-2.17,3.15]
Dysken 2014	105	-0.5 (12.5)	89	-1.3 (12.6)		27.84%	0.8[-2.74,4.34]
Peskind 2004 (MD-10) SG	59	-4.8 (21.5)	50	-3.6 (17)		6.64%	-1.12[-8.36,6.12]
Porsteinsson 2008(MD-12)S	57	-2.3 (13.3)	64	-1.7 (12.7)		16.15%	-0.63[-5.28,4.02]
Total ***	**345**		**276**			**100%**	**0.29[-1.58,2.16]**
Heterogeneity: Tau^2=0; Chi^2=0.4, df=3(P=0.94); I^2=0%							
Test for overall effect: Z=0.3(P=0.76)							



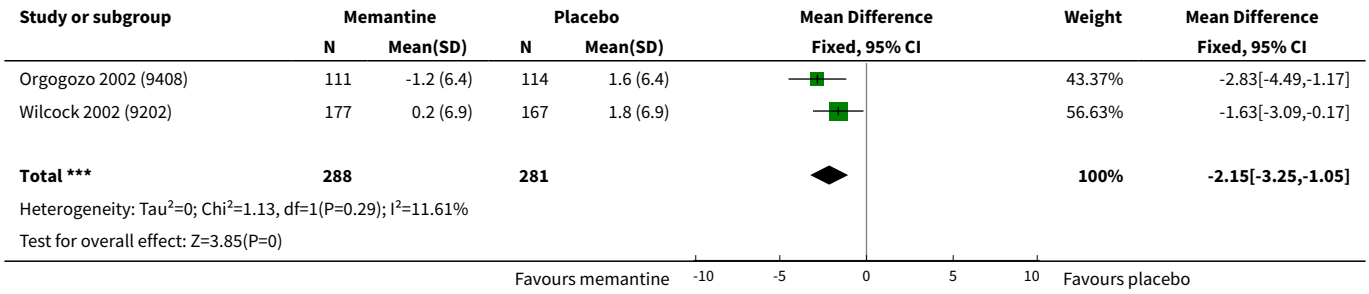
Comparison 5. Memantine 20 mg vs placebo for mild-to-moderate vascular dementia. Six-month studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global: CGI	2	757	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.23, 0.19]
2 Cognitive function: ADAS-Cog	2	569	Mean Difference (IV, Fixed, 95% CI)	-2.15 [-3.25, -1.05]
3 Decline in ADL: NOSGER self-care subscale	2	542	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.20, 0.13]
4 Behaviour: NOSGER disturbing behaviour subscale	2	541	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.37, -0.03]
5 Cognitive function: ADAS-Cog: post-hoc subgroup analysis	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 Mild-to-moderate (MMSE >14)	2	467	Mean Difference (IV, Fixed, 95% CI)	-1.64 [-2.83, -0.45]
5.2 Moderate (MMSE ≤ 14)	2	102	Mean Difference (IV, Fixed, 95% CI)	-4.51 [-7.21, -1.81]
6 All-cause discontinuation	2	900	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.83, 1.34]
7 Discontinuation due to adverse events	2	900	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.73, 1.64]
8 Number suffering at least one adverse event	2	900	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.11]
9 Number suffering agitation as an adverse event	2	900	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.33, 0.96]

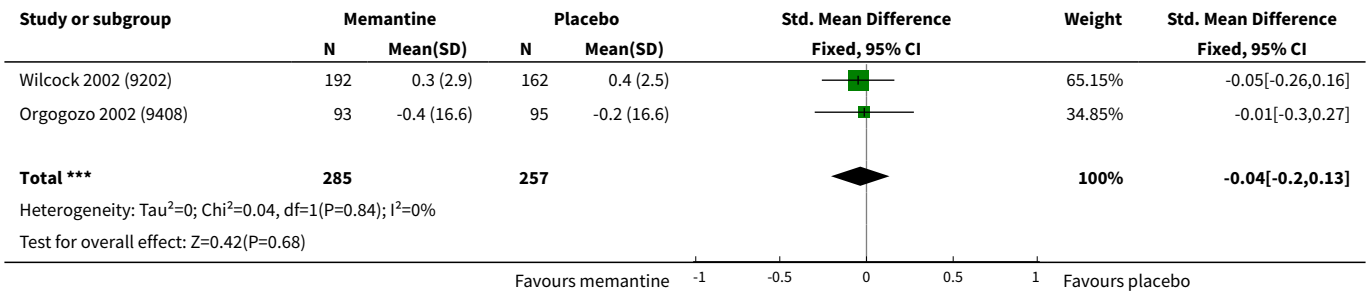
Analysis 5.1. Comparison 5 Memantine 20 mg vs placebo for mild-to-moderate vascular dementia. Six-month studies, Outcome 1 Clinical Global: CGI.



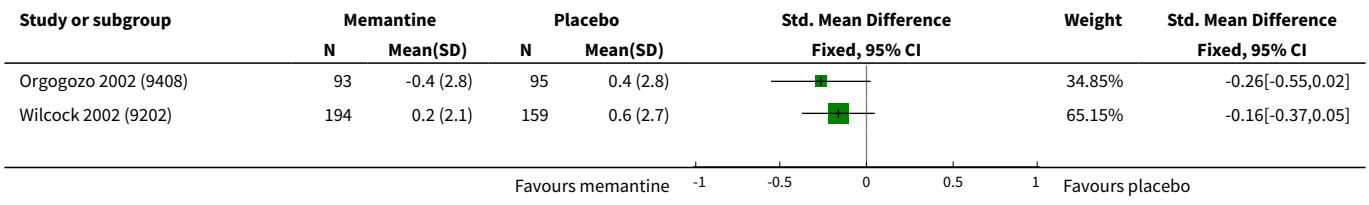
Analysis 5.2. Comparison 5 Memantine 20 mg vs placebo for mild-to-moderate vascular dementia. Six-month studies, Outcome 2 Cognitive function: ADAS-Cog.

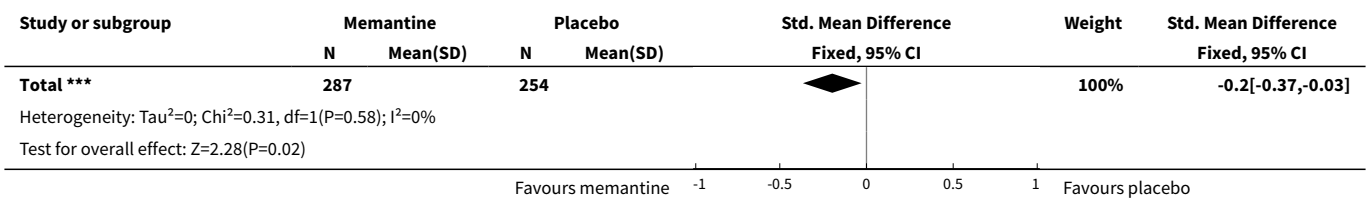


Analysis 5.3. Comparison 5 Memantine 20 mg vs placebo for mild-to-moderate vascular dementia. Six-month studies, Outcome 3 Decline in ADL: NOSGER self-care subscale.

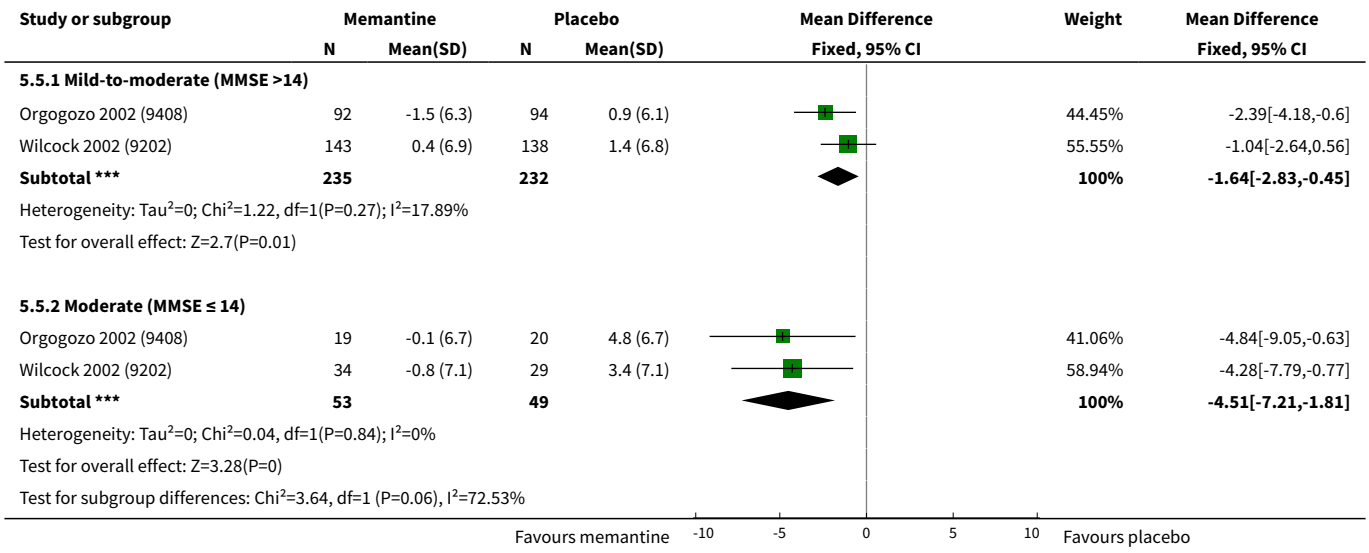


Analysis 5.4. Comparison 5 Memantine 20 mg vs placebo for mild-to-moderate vascular dementia. Six-month studies, Outcome 4 Behaviour: NOSGER disturbing behaviour subscale.

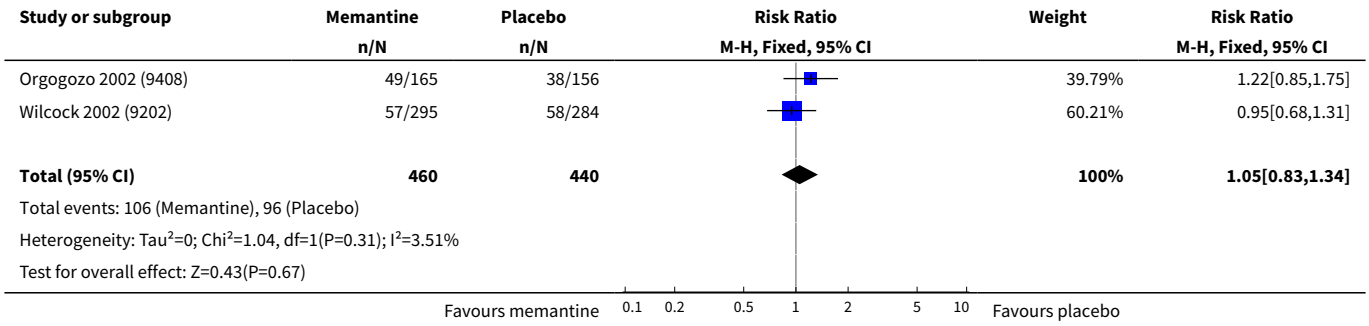




Analysis 5.5. Comparison 5 Memantine 20 mg vs placebo for mild-to-moderate vascular dementia. Six-month studies, Outcome 5 Cognitive function: ADAS-Cog: post-hoc subgroup analysis.



Analysis 5.6. Comparison 5 Memantine 20 mg vs placebo for mild-to-moderate vascular dementia. Six-month studies, Outcome 6 All-cause discontinuation.



Analysis 5.7. Comparison 5 Memantine 20 mg vs placebo for mild-to-moderate vascular dementia. Six-month studies, Outcome 7 Discontinuation due to adverse events.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Orgogozo 2002 (9408)	19/165	20/156		47.05%	0.9[0.5,1.62]
Wilcock 2002 (9202)	27/295	20/284		52.95%	1.3[0.75,2.26]
Total (95% CI)	**460**	**440**		**100%**	**1.09[0.73,1.64]**
Total events: 46 (Memantine), 40 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.8, df=1(P=0.37); I^2=0%					
Test for overall effect: Z=0.43(P=0.67)					

Analysis 5.8. Comparison 5 Memantine 20 mg vs placebo for mild-to-moderate vascular dementia. Six-month studies, Outcome 8 Number suffering at least one adverse event.

Study or subgroup	Memantine n/N	Placebol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Orgogozo 2002 (9408)	125/165	115/156		35.37%	1.03[0.9,1.17]
Wilcock 2002 (9202)	226/295	212/284		64.63%	1.03[0.94,1.13]
Total (95% CI)	**460**	**440**		**100%**	**1.03[0.95,1.11]**
Total events: 351 (Memantine), 327 (Placebol)					
Heterogeneity: Tau^2=0; Chi^2=0, df=1(P=0.99); I^2=0%					
Test for overall effect: Z=0.69(P=0.49)					

Analysis 5.9. Comparison 5 Memantine 20 mg vs placebo for mild-to-moderate vascular dementia. Six-month studies, Outcome 9 Number suffering agitation as an adverse event.

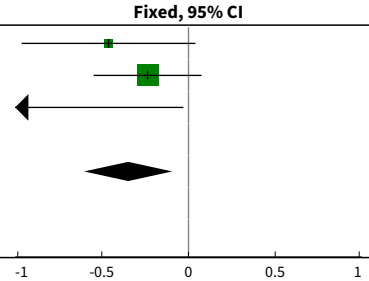
Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Orgogozo 2002 (9408)	9/165	11/156		32.55%	0.77[0.33,1.82]
Wilcock 2002 (9202)	11/295	23/284		67.45%	0.46[0.23,0.93]
Total (95% CI)	**460**	**440**		**100%**	**0.56[0.33,0.96]**
Total events: 20 (Memantine), 34 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=2.1(P=0.04)					

Comparison 6. Memantine vs placebo for Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). ITT-LOCF Data

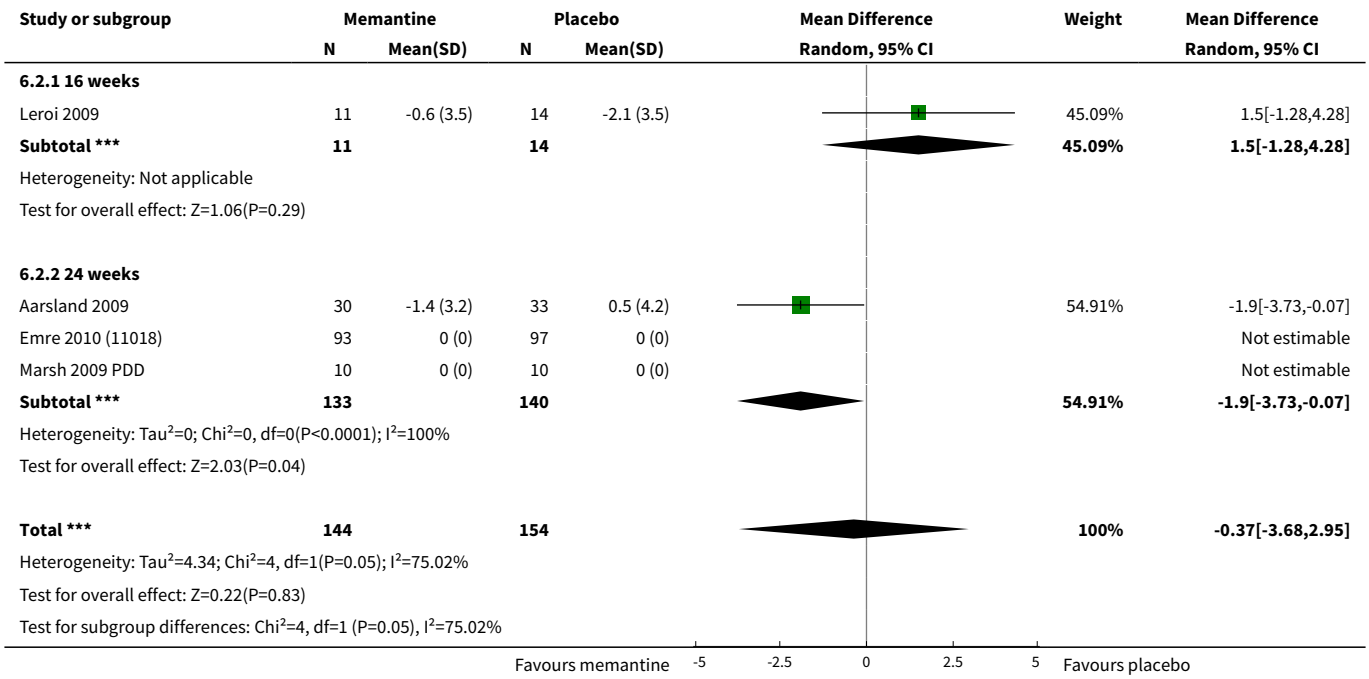
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global (24 weeks)	3	243	Std. Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.60, -0.09]
2 Cognitive Function	4	298	Mean Difference (IV, Random, 95% CI)	-0.37 [-3.68, 2.95]
2.1 16 weeks	1	25	Mean Difference (IV, Random, 95% CI)	1.5 [-1.28, 4.28]
2.2 24 weeks	3	273	Mean Difference (IV, Random, 95% CI)	-1.90 [-3.73, -0.07]
3 Decline in ADL (24 weeks)	3	243	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.65, 0.11]
4 Behaviour and Mood: NPI	4	267	Mean Difference (IV, Random, 95% CI)	-2.09 [-4.84, 0.66]
4.1 16 weeks	1	25	Mean Difference (IV, Random, 95% CI)	-2.60 [-15.60, 10.40]
4.2 24 weeks	3	242	Mean Difference (IV, Random, 95% CI)	-2.18 [-5.57, 1.21]
5 All-cause discontinuation	4	312	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.55, 1.28]
6 Discontinuation due to adverse events	4	315	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.54, 1.63]
7 Number suffering at least one adverse event	4	315	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.79, 1.28]

Analysis 6.1. Comparison 6 Memantine vs placebo for Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). ITT-LOCF Data, Outcome 1 Clinical Global (24 weeks).

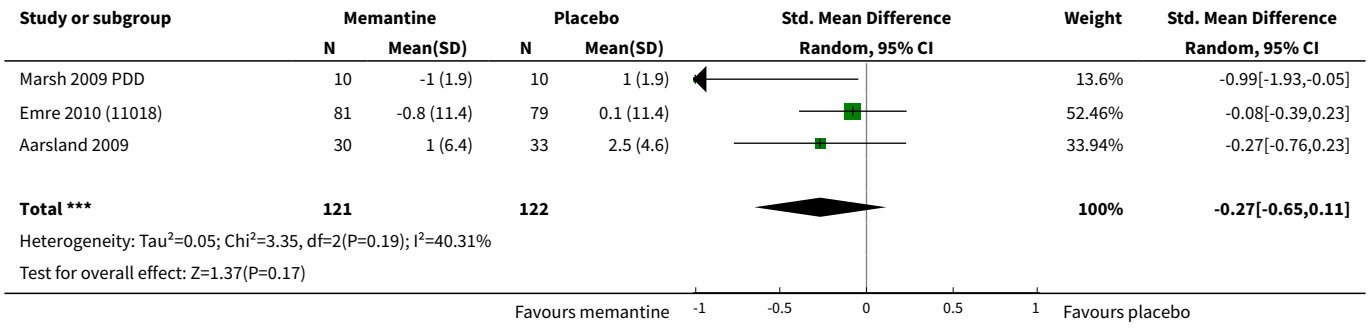
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Aarsland 2009	30	3.5 (1.5)	33	4.2 (1.5)		25.75%	-0.46[-0.96,0.04]
Emre 2010 (11018)	81	3.4 (1.3)	79	3.7 (1.3)		66.9%	-0.24[-0.55,0.07]
Marsh 2009 PDD	10	2.7 (1.3)	10	4.1 (1.4)		7.35%	-0.97[-1.91,-0.03]
Total ***	**121**		**122**			**100%**	**-0.35[-0.6,-0.09]**
Heterogeneity: Tau^2=0; Chi^2=2.37, df=2(P=0.31); I^2=15.49%							
Test for overall effect: Z=2.68(P=0.01)							



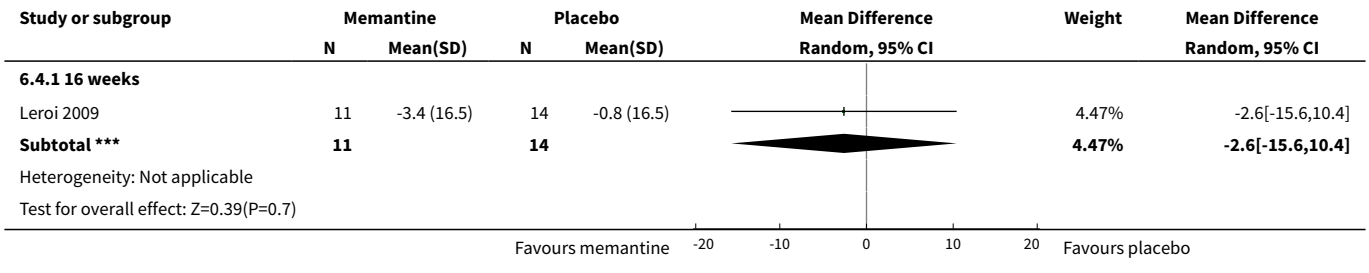
Analysis 6.2. Comparison 6 Memantine vs placebo for Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). ITT-LOCF Data, Outcome 2 Cognitive Function.

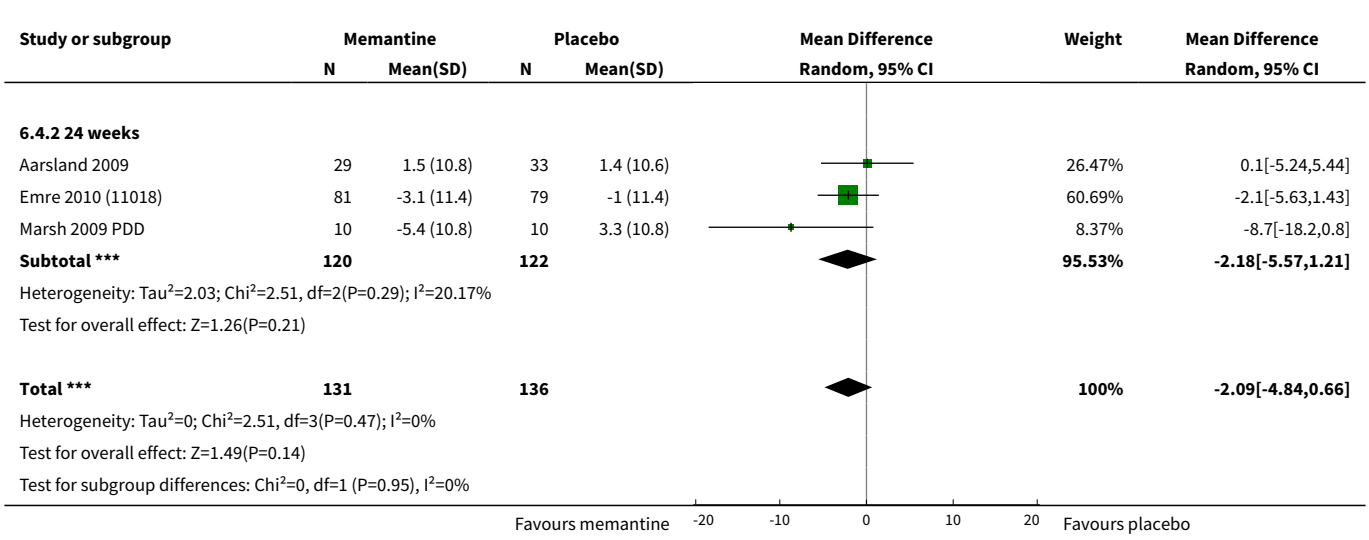


Analysis 6.3. Comparison 6 Memantine vs placebo for Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). ITT-LOCF Data, Outcome 3 Decline in ADL (24 weeks).

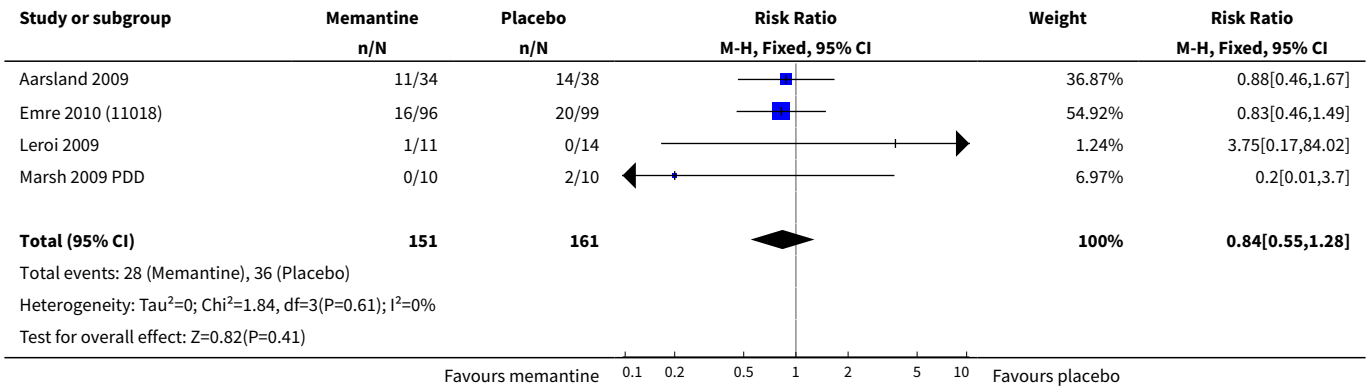


Analysis 6.4. Comparison 6 Memantine vs placebo for Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). ITT-LOCF Data, Outcome 4 Behaviour and Mood: NPI.

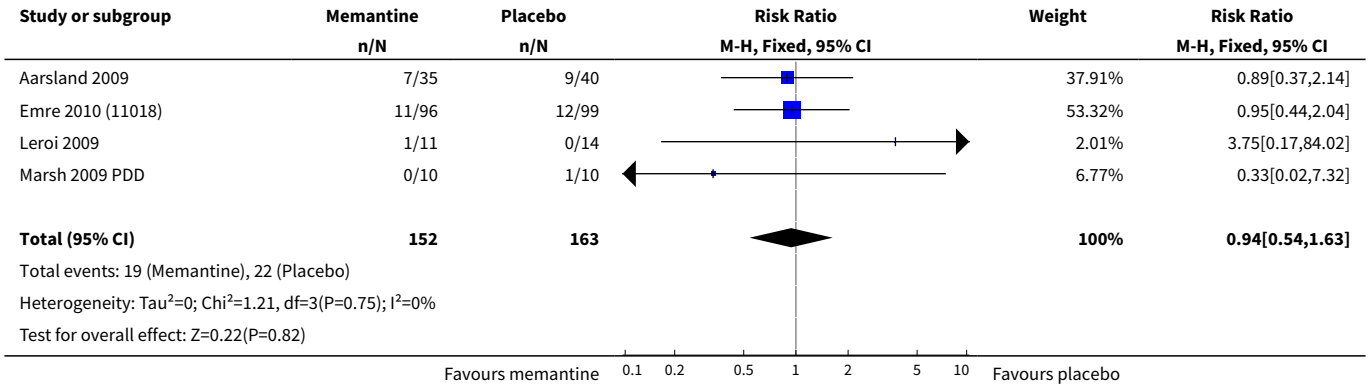




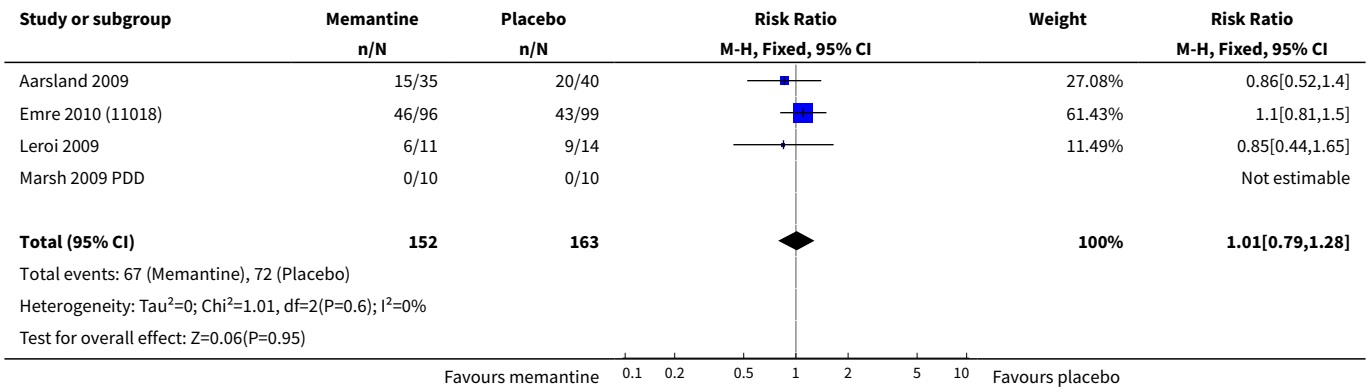
Analysis 6.5. Comparison 6 Memantine vs placebo for Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). ITT-LOCF Data, Outcome 5 All-cause discontinuation.



Analysis 6.6. Comparison 6 Memantine vs placebo for Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). ITT-LOCF Data, Outcome 6 Discontinuation due to adverse events.



Analysis 6.7. Comparison 6 Memantine vs placebo for Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB). ITT-LOCF Data, Outcome 7 Number suffering at least one adverse event.

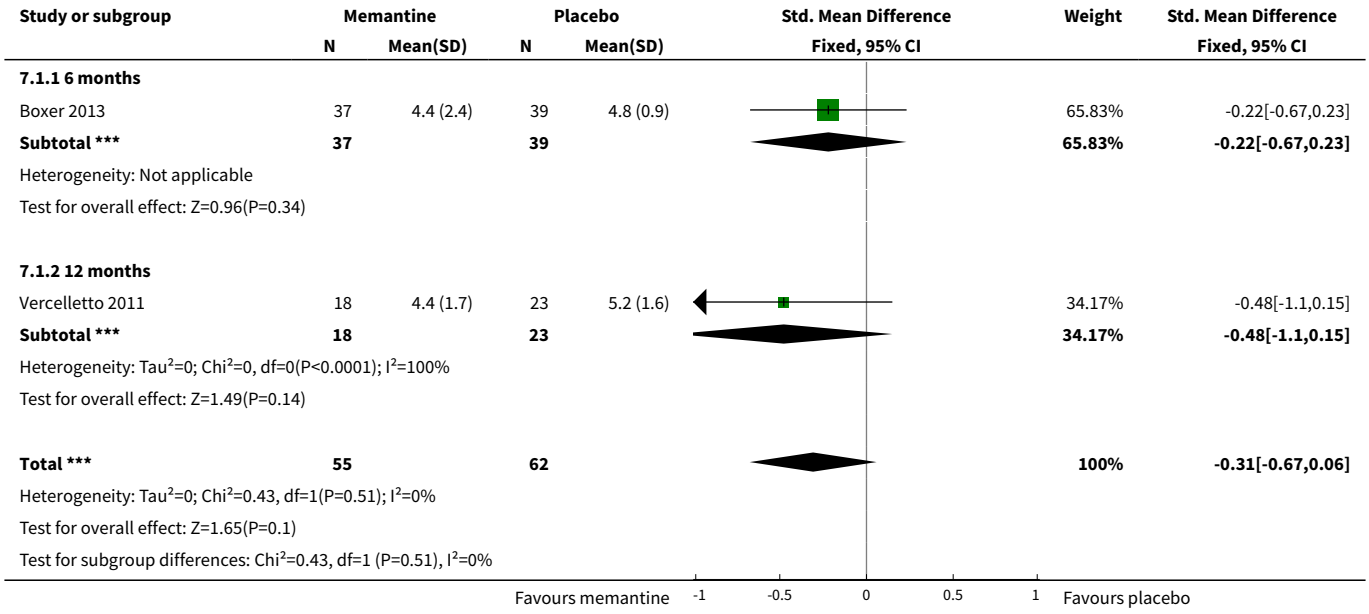


Comparison 7. Memantine vs placebo for frontotemporal dementia (FTD)

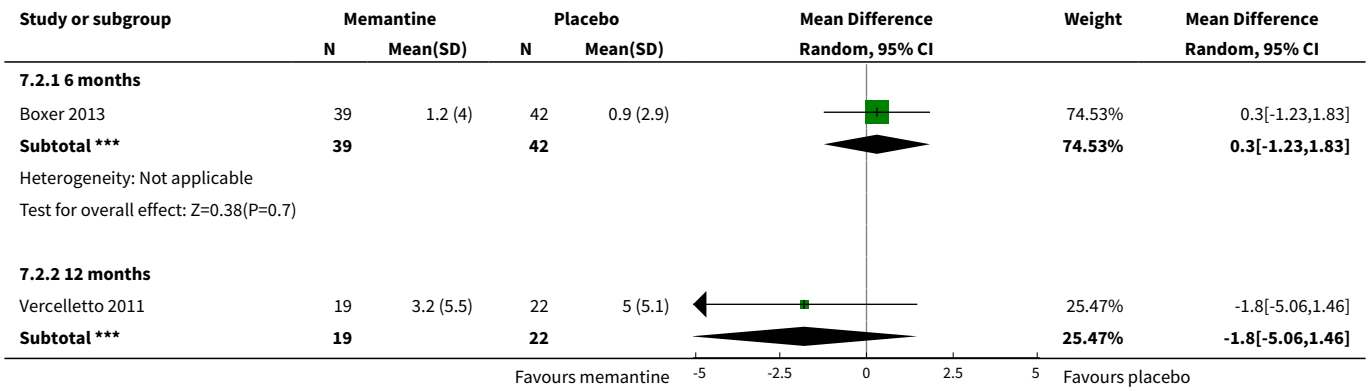
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global	2	117	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.67, 0.06]
1.1 6 months	1	76	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.67, 0.23]
1.2 12 months	1	41	Std. Mean Difference (IV, Fixed, 95% CI)	-0.48 [-1.10, 0.15]
2 Cognitive Function: MMSE	2	122	Mean Difference (IV, Random, 95% CI)	-0.23 [-2.03, 1.56]
2.1 6 months	1	81	Mean Difference (IV, Random, 95% CI)	0.30 [-1.23, 1.83]
2.2 12 months	1	41	Mean Difference (IV, Random, 95% CI)	-1.80 [-5.06, 1.46]
3 Behaviour and Mood: Neuropsychiatric Inventory (NPI) Total	2	115	Mean Difference (IV, Fixed, 95% CI)	-3.16 [-8.06, 1.74]
3.1 6 months	1	76	Mean Difference (IV, Fixed, 95% CI)	-2.20 [-8.01, 3.61]
3.2 12 months	1	39	Mean Difference (IV, Fixed, 95% CI)	-5.5 [-14.60, 3.60]
4 All-cause discontinuation	2	133	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.58, 4.06]
5 Discontinuation due to adverse events	2	133	Risk Ratio (M-H, Random, 95% CI)	1.25 [0.35, 4.44]

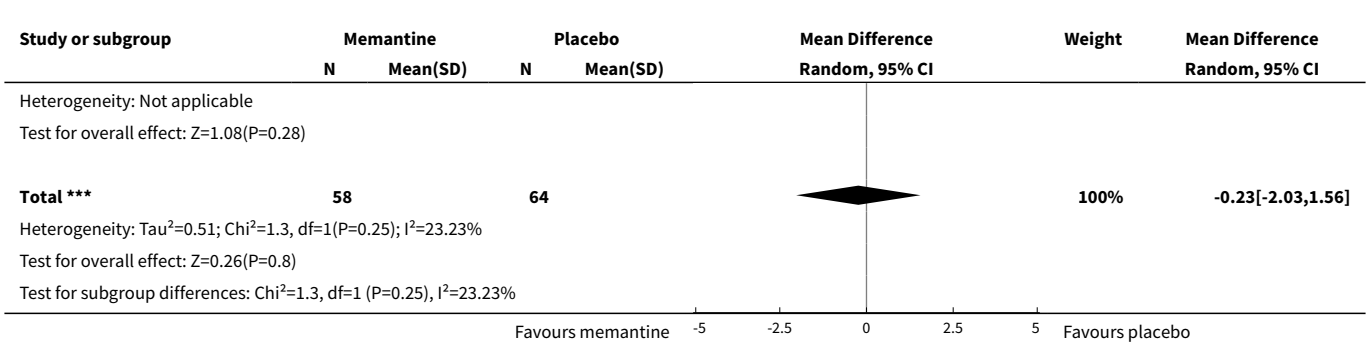
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6 Number suffering at least one adverse event	2	133	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.33]
7 Number suffering at serious adverse events	2	133	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.07, 2.94]
8 Number suffering agitation as an adverse event	2	133	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.01, 4.34]

Analysis 7.1. Comparison 7 Memantine vs placebo for frontotemporal dementia (FTD), Outcome 1 Clinical Global.

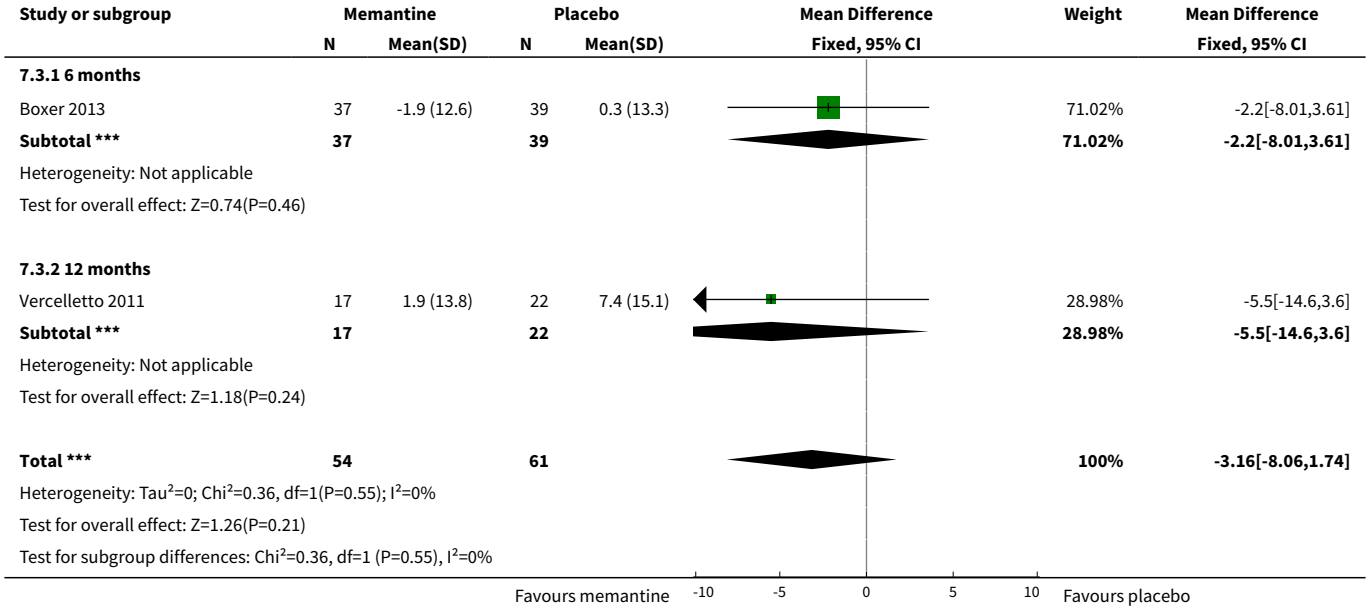


Analysis 7.2. Comparison 7 Memantine vs placebo for frontotemporal dementia (FTD), Outcome 2 Cognitive Function: MMSE.

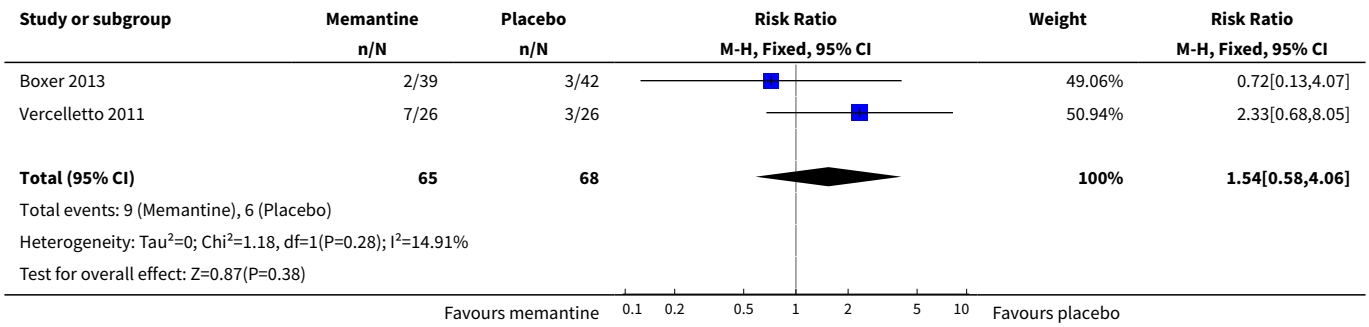




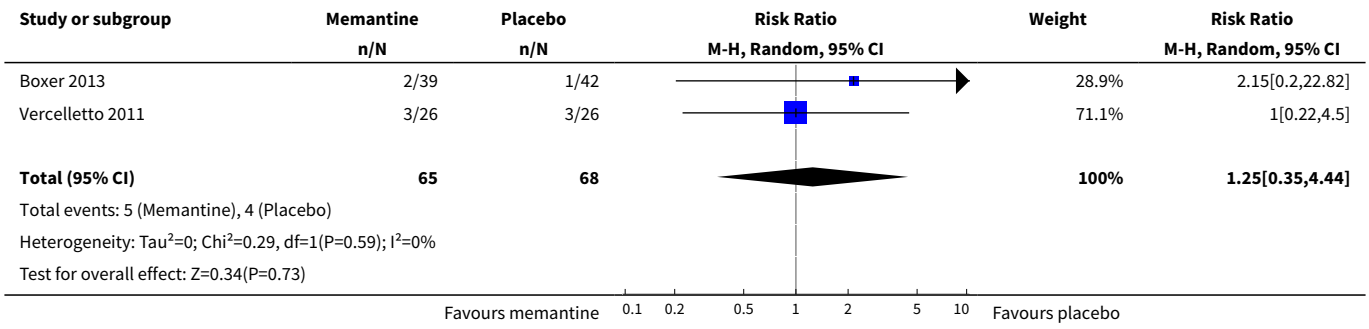
Analysis 7.3. Comparison 7 Memantine vs placebo for frontotemporal dementia (FTD), Outcome 3 Behaviour and Mood: Neuropsychiatric Inventory (NPI) Total.



Analysis 7.4. Comparison 7 Memantine vs placebo for frontotemporal dementia (FTD), Outcome 4 All-cause discontinuation.



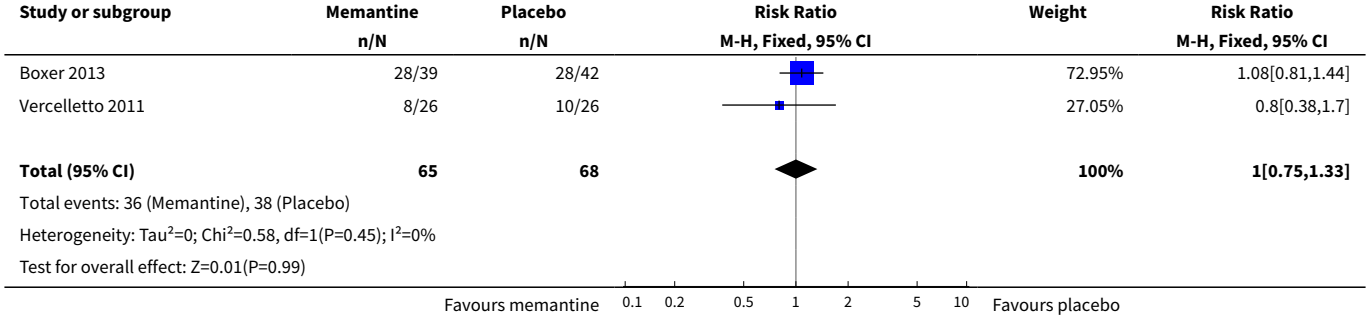
Analysis 7.5. Comparison 7 Memantine vs placebo for frontotemporal dementia (FTD), Outcome 5 Discontinuation due to adverse events.



Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Boxer 2013	2/39	1/42		28.9%	2.15[0.2,22.82]
Vercelletto 2011	3/26	3/26		71.1%	1[0.22,4.5]
Total (95% CI)	**65**	**68**		**100%**	**1.25[0.35,4.44]**
Total events: 5 (Memantine), 4 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.29, df=1(P=0.59); I^2=0%					
Test for overall effect: Z=0.34(P=0.73)					

Favours memantine 0.1 0.2 0.5 1 2 5 10 Favours placebo

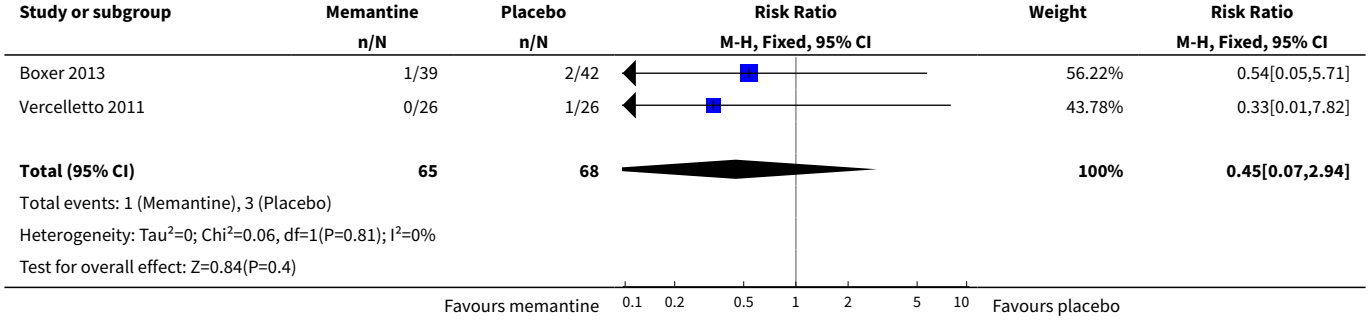
Analysis 7.6. Comparison 7 Memantine vs placebo for frontotemporal dementia (FTD), Outcome 6 Number suffering at least one adverse event.



Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Boxer 2013	28/39	28/42		72.95%	1.08[0.81,1.44]
Vercelletto 2011	8/26	10/26		27.05%	0.8[0.38,1.7]
Total (95% CI)	**65**	**68**		**100%**	**1[0.75,1.33]**
Total events: 36 (Memantine), 38 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.58, df=1(P=0.45); I^2=0%					
Test for overall effect: Z=0.01(P=0.99)					

Favours memantine 0.1 0.2 0.5 1 2 5 10 Favours placebo

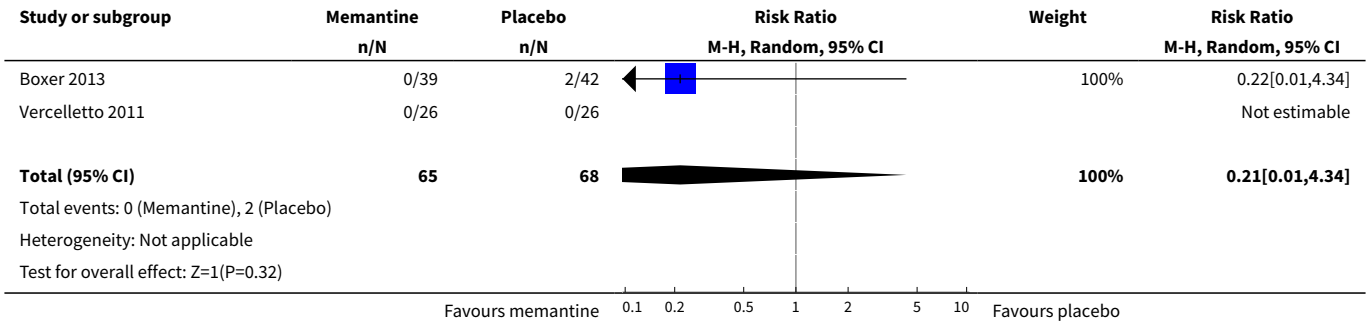
Analysis 7.7. Comparison 7 Memantine vs placebo for frontotemporal dementia (FTD), Outcome 7 Number suffering at serious adverse events.



Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Boxer 2013	1/39	2/42		56.22%	0.54[0.05,5.71]
Vercelletto 2011	0/26	1/26		43.78%	0.33[0.01,7.82]
Total (95% CI)	**65**	**68**		**100%**	**0.45[0.07,2.94]**
Total events: 1 (Memantine), 3 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%					
Test for overall effect: Z=0.84(P=0.4)					

Favours memantine 0.1 0.2 0.5 1 2 5 10 Favours placebo

Analysis 7.8. Comparison 7 Memantine vs placebo for frontotemporal dementia (FTD), Outcome 8 Number suffering agitation as an adverse event.



Comparison 8. SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global - by dementia type and severity	21	5098	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.21, -0.09]
1.1 Alzheimer's disease - mild	4	621	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.27, 0.12]
1.2 Alzheimer's disease - moderate to severe	14	3126	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.28, -0.13]
1.3 Alzheimer's disease with agitation	1	275	Std. Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.20, 0.28]
1.4 Vascular dementia - mild to moderate	2	757	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.15, 0.14]
1.5 Parkinson's disease dementia / DLB - mild to moderate	3	243	Std. Mean Difference (IV, Fixed, 95% CI)	-0.35 [-0.60, -0.09]
1.6 Fronto Temporal Dementia - mild	1	76	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.67, 0.23]
2 Cognitive Function - by dementia type and severity	20	5303	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.28, -0.17]
2.1 Alzheimer's disease - mild	4	619	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.19, 0.13]
2.2 Alzheimer's disease - moderate to severe	15	3647	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.34, -0.21]
2.3 Alzheimer's disease with agitation	1	324	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.17, 0.27]
2.4 Vascular dementia - mild-to-moderate	2	569	Std. Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.48, -0.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.5 PDD/DLB - mild to moderate	1	63	Std. Mean Difference (IV, Fixed, 95% CI)	-0.50 [-1.00, 0.00]
2.6 Fronto Temporal Dementia - mild	1	81	Std. Mean Difference (IV, Fixed, 95% CI)	0.09 [-0.35, 0.52]
3 Decline in ADL - by dementia type and severity	21	4887	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.16, -0.04]
3.1 Alzheimer's disease - mild	4	621	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.14, 0.18]
3.2 Alzheimer's Disease - moderate to severe	14	3124	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.24, -0.09]
3.3 Alzheimer's disease with agitation	1	276	Std. Mean Difference (IV, Fixed, 95% CI)	0.23 [-0.01, 0.47]
3.4 Vascular dementia - mild-to-moderate	2	542	Std. Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.20, 0.13]
3.5 PDD/DLB - mild to moderate	3	243	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.45, 0.06]
3.6 Fronto Temporal Dementia - mild	1	81	Std. Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Behaviour and mood - by dementia type and severity	23	5525	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.17, -0.06]
4.1 Alzheimer's Disease - mild	4	621	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.14, 0.18]
4.2 AD - moderate to severe	15	3721	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.21, -0.08]
4.3 Alzheimer's disease with agitation	1	324	Std. Mean Difference (IV, Fixed, 95% CI)	0.08 [-0.14, 0.30]
4.4 Vascular dementia - mild-to-moderate	2	541	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.37, -0.03]
4.5 PDD/DLB - mild to moderate	3	242	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.43, 0.07]
4.6 Fronto Temporal Dementia - mild	1	76	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.62, 0.28]
5 Number suffering agitation - by dementia type and severity	19	5933	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.71, 1.01]
5.1 Alzheimer's disease mild-to-moderate	5	1890	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.70, 1.58]
5.2 Alzheimer's disease moderate-to-severe	7	2505	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.58, 0.93]
5.3 AD with agitation (increased severity)	2	403	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [1.04, 5.50]

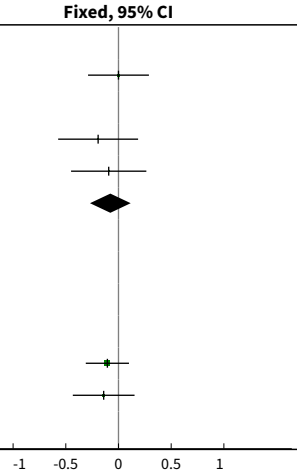
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.4 Vascular dementia mild-to-moderate	2	900	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.33, 0.96]
5.5 Fronto Temporal Dementia	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.34]
5.6 Mixed dementia mild-to-moderate	2	154	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.71, 3.31]
6 Number suffering agitation - by dementia type and ChEI	17	5392	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.69, 0.99]
6.1 Alzheimer's disease monotherapy	5	1624	Risk Ratio (M-H, Fixed, 95% CI)	0.66 [0.49, 0.89]
6.2 Alzheimer's disease with concomitant ChEI	6	2230	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.68, 1.22]
6.3 Alzheimer's disease with agitation with concomitant ChEI	2	403	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [1.04, 5.50]
6.4 Vascular dementia monotherapy implied	2	900	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.33, 0.96]
6.5 Fronto Temporal Dementia - monotherapy	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.34]
6.6 Mixed dementia - unclear ChEI	2	154	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.71, 3.31]
7 All-cause discontinuation (all durations) - by dementia type and severity	33	8116	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.90, 1.08]
7.1 Alzheimer's Disease - mild	5	722	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.08, 2.81]
7.2 Alzheimer's disease - moderate to severe	18	5200	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.83, 1.04]
7.3 Alzheimer's disease with agitation	3	555	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.79, 1.52]
7.4 Vascular dementia mild-to-moderate	2	900	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.83, 1.34]
7.5 PDD/DLB mild-to-moderate	4	312	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.55, 1.28]
7.6 Fronto Temporal Dementia mild	2	133	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.58, 4.06]
7.7 AIDS complex dementia	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.52, 1.94]
7.8 Mixed dementia mild-to-moderate	2	154	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.30, 2.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Discontinuation due to adverse events - by dementia type and severity	31	7968	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.90, 1.18]
8.1 Alzheimer's Disease - mild	5	722	Risk Ratio (M-H, Fixed, 95% CI)	2.12 [1.03, 4.39]
8.2 Alzheimer's Disease - moderate to severe	18	5202	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.11]
8.3 Alzheimer's disease with agitation	3	556	Risk Ratio (M-H, Fixed, 95% CI)	1.40 [0.88, 2.21]
8.4 Vascular dementia mild-to-moderate	2	900	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.73, 1.64]
8.5 Fronto Temporal Dementia	2	133	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [0.37, 4.48]
8.6 AIDS Complex dementia	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.37, 2.70]
8.7 PDD/DLB mild-to-moderate	4	315	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.54, 1.63]
9 Number suffering at least one adverse event - by dementia type and severity	30	8139	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [1.00, 1.06]
9.1 Alzheimer's disease mild-to-moderate	9	2624	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.08]
9.2 Alzheimer's disease moderate-to-severe	10	3596	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.97, 1.06]
9.3 Alzheimer's disease with agitation	2	403	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.95, 1.20]
9.4 Vascular dementia mild-to-moderate	2	900	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.95, 1.11]
9.5 Fronto Temporal Dementia	2	133	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.75, 1.33]
9.6 PDD/DLB mild-to-moderate	3	295	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.79, 1.28]
9.7 AIDS complex dementia	1	106	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.8 Mixed dementia mild-to-moderate	1	82	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.91, 2.12]
10 Number suffering at least one serious AE - by dementia type and severity	27	8138	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.02]
10.1 Alzheimer's disease mild-to-moderate	9	2798	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.79, 1.07]

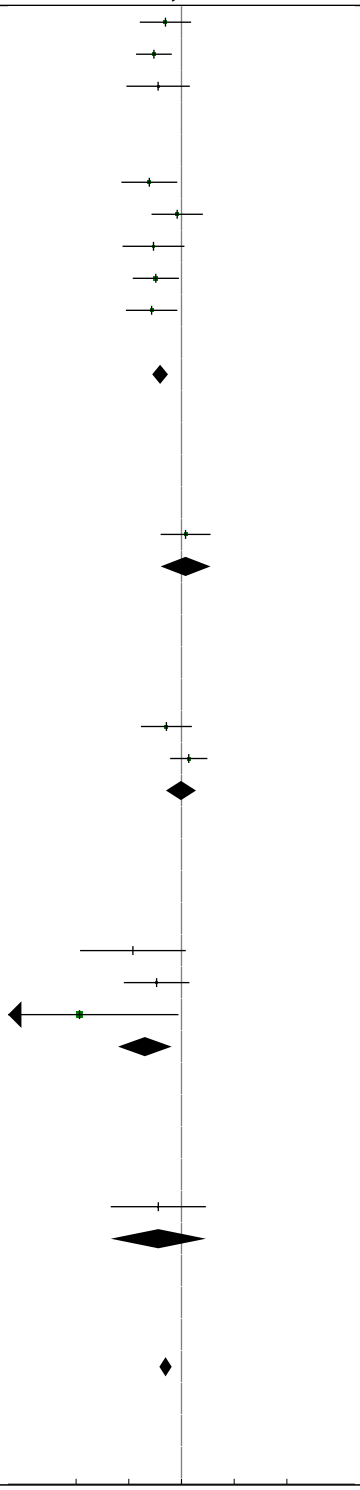
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2 Alzheimer's disease moderate-to-severe	10	3684	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.77, 1.08]
10.3 Alzheimer's disease with agitation	2	403	Risk Ratio (M-H, Fixed, 95% CI)	1.65 [0.85, 3.20]
10.4 Vascular dementia mild-to-moderate	2	900	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.62, 1.09]
10.5 Fronto Temporal Dementia	2	133	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.30, 1.66]
10.6 PDD/DLB mild-to-moderate	2	220	Risk Ratio (M-H, Fixed, 95% CI)	1.43 [0.69, 2.97]
11 Number suffering agitation as an adverse event - by dementia type	20	6008	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.71, 1.01]
11.1 Alzheimer's disease	12	4395	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.66, 0.99]
11.2 AD with agitation (increased severity)	2	403	Risk Ratio (M-H, Fixed, 95% CI)	2.39 [1.04, 5.50]
11.3 Vascular dementia	2	900	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.33, 0.96]
11.4 Parkinson's Disease Dementia / Dementia Lewy Bodies	1	75	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.5 Fronto Temporal Dementia	1	81	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.34]
11.6 Mixed dementia	2	154	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.71, 3.31]

Analysis 8.1. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 1 Clinical Global - by dementia type and severity.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.1.1 Alzheimer's disease - mild							
Bakchine 2008 (99679) SG	125	4 (1.3)	73	4 (1.2)		4.1%	0[-0.29,0.29]
Dysken 2014 SG	105	0 (0)	89	0 (0)			Not estimable
Peskind 2004 (MD-10) SG	58	3.9 (1)	50	4.1 (1.1)		2.37%	-0.19[-0.57,0.19]
Porsteinsson 2008(MD-12)S	57	4.1 (1)	64	4.2 (0.9)		2.68%	-0.09[-0.45,0.26]
Subtotal ***	**345**		**276**			**9.15%**	**-0.08[-0.27,0.12]**
Heterogeneity: Tau²=0; Chi²=0.64, df=2(P=0.73); I²=0%							
Test for overall effect: Z=0.78(P=0.43)							
8.1.2 Alzheimer's disease - moderate to severe							
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		8.13%	-0.11[-0.31,0.1]
Bakchine 2008 (99679) SG	145	4.2 (1.1)	65	4.4 (1.2)		3.98%	-0.14[-0.43,0.15]
Dysken 2014 SG	50	0 (0)	63	0 (0)			Not estimable

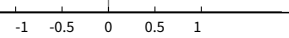


Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Forest 2006 (MD-22)	131	3.6 (1.4)	129	3.8 (1.3)		5.76%	-0.15[-0.4,0.09]
Grossberg 2008 (MD-50)	269	3.8 (1.1)	272	4.1 (1.2)		11.92%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	4.4 (1.6)	87	4.7 (1.3)		3.77%	-0.22[-0.52,0.08]
Howard 2012 (DOMINO-AD)	77	0 (0)	66	0 (0)			Not estimable
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Peskind 2004 (MD-10) SG	106	4.4 (1)	116	4.7 (1.1)		4.86%	-0.31[-0.57,-0.04]
Porsteinsson 2008(MD-12)S	135	4.5 (1)	125	4.5 (1)		5.77%	-0.04[-0.28,0.2]
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		3.97%	-0.27[-0.56,0.03]
Tariot 2004 (MD-02)	172	4.4 (1.1)	152	4.6 (1.1)		7.12%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	134	4.3 (1.1)	127	4.6 (1)		5.74%	-0.28[-0.53,-0.04]
Wang 2013	13	0 (0)	13	0 (0)			Not estimable
Subtotal ***	**1626**		**1500**			**61.01%**	**-0.2[-0.28,-0.13]**
Heterogeneity: Tau²=0; Chi²=4.7, df=9(P=0.86); I²=0%							
Test for overall effect: Z=5.32(P<0.0001)							
8.1.3 Alzheimer's disease with agitation							
Herrmann 2012 (10158)	135	4.7 (1.3)	140	4.6 (1.3)		6.11%	0.04[-0.2,0.28]
Subtotal ***	**135**		**140**			**6.11%**	**0.04[-0.2,0.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.32(P=0.75)							
8.1.4 Vascular dementia - mild to moderate							
Orgogozo 2002 (9408)	134	4 (1.5)	130	4.2 (1.5)		5.85%	-0.14[-0.38,0.1]
Wilcock 2002 (9202)	238	4 (1.2)	255	3.9 (1.2)		10.93%	0.07[-0.11,0.25]
Subtotal ***	**372**		**385**			**16.78%**	**-0[-0.15,0.14]**
Heterogeneity: Tau²=0; Chi²=1.93, df=1(P=0.16); I²=48.25%							
Test for overall effect: Z=0.07(P=0.95)							
8.1.5 Parkinson's disease dementia / DLB - mild to moderate							
Aarsland 2009	30	3.5 (1.5)	33	4.2 (1.5)		1.36%	-0.46[-0.96,0.04]
Emre 2010 (11018)	81	3.4 (1.3)	79	3.7 (1.3)		3.53%	-0.24[-0.55,0.07]
Marsh 2009 PDD	10	2.7 (1.3)	10	4.1 (1.4)		0.39%	-0.97[-1.91,-0.03]
Subtotal ***	**121**		**122**			**5.28%**	**-0.35[-0.6,-0.09]**
Heterogeneity: Tau²=0; Chi²=2.37, df=2(P=0.31); I²=15.49%							
Test for overall effect: Z=2.68(P=0.01)							
8.1.6 Fronto Temporal Dementia - mild							
Boxer 2013	37	4.4 (2.4)	39	4.8 (0.9)		1.68%	-0.22[-0.67,0.23]
Subtotal ***	**37**		**39**			**1.68%**	**-0.22[-0.67,0.23]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.96(P=0.34)							
Total ***	**2636**		**2462**			**100%**	**-0.15[-0.21,-0.09]**
Heterogeneity: Tau²=0; Chi²=20.93, df=19(P=0.34); I²=9.23%							
Test for overall effect: Z=5.08(P<0.0001)							
Test for subgroup differences: Chi²=11.3, df=1 (P=0.05), I²=55.74%							



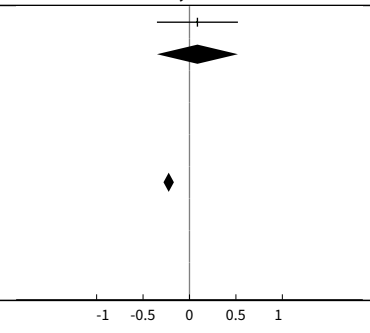
Analysis 8.2. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 2 Cognitive Function - by dementia type and severity.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.2.1 Alzheimer's disease - mild							
Bakchine 2008 (99679) SG	125	-2.8 (7.4)	72	-2.6 (6.1)		3.74%	-0.03[-0.32,0.26]
Dysken 2014 SG	105	0.5 (7.1)	89	0.8 (7.2)		3.94%	-0.04[-0.32,0.24]
Peskind 2004 (MD-10) SG	59	-1.4 (10.3)	48	-1.9 (9.1)		2.17%	0.05[-0.33,0.43]
Porsteinsson 2008(MD-12)S	57	-2 (7.7)	64	-1.5 (7)		2.47%	-0.07[-0.42,0.29]
Subtotal ***	**346**		**273**			**12.31%**	**-0.03[-0.19,0.13]**
Heterogeneity: Tau^2=0; Chi^2=0.22, df=3(P=0.97); I^2=0%							
Test for overall effect: Z=0.31(P=0.75)							
8.2.2 Alzheimer's disease - moderate to severe							
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		7.35%	-0.42[-0.63,-0.22]
Bakchine 2008 (99679) SG	146	-0.9 (6.4)	65	0.7 (6.4)		3.66%	-0.25[-0.54,0.05]
Dysken 2014 SG	50	3.1 (7.6)	63	6.6 (7.3)		2.22%	-0.48[-0.86,-0.1]
Forest 2006 (MD-22)	132	0 (0)	131	0 (0)			Not estimable
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		10.98%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		3.4%	-0.48[-0.78,-0.18]
Howard 2012 (DOMINO-AD)	77	1.2 (2.6)	66	2.4 (3.8)		2.86%	-0.36[-0.69,-0.03]
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Nakamura 2016	268	1.3 (8.2)	269	2.2 (8.1)		10.97%	-0.1[-0.27,0.07]
Peskind 2004 (MD-10) SG	101	0.8 (5.9)	114	2.2 (7)		4.36%	-0.22[-0.48,0.05]
Porsteinsson 2008(MD-12)S	133	0.9 (6)	123	2 (5.8)		5.21%	-0.19[-0.44,0.05]
Reisberg 2003 (9605)	96	4.5 (11.5)	83	10.2 (12.7)		3.54%	-0.47[-0.77,-0.17]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		6.5%	-0.37[-0.59,-0.15]
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		5.25%	-0.05[-0.29,0.2]
Wang 2013	11	0 (7.2)	11	5.6 (5.9)		0.41%	-0.82[-1.7,0.06]
Subtotal ***	**1886**		**1761**			**66.69%**	**-0.27[-0.34,-0.21]**
Heterogeneity: Tau^2=0; Chi^2=17.17, df=12(P=0.14); I^2=30.1%							
Test for overall effect: Z=7.83(P<0.0001)							
8.2.3 Alzheimer's disease with agitation							
Herrmann 2012 (10158)	159	2.3 (9.6)	165	1.9 (9.6)		6.62%	0.05[-0.17,0.27]
Subtotal ***	**159**		**165**			**6.62%**	**0.05[-0.17,0.27]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.45(P=0.65)							
8.2.4 Vascular dementia - mild-to-moderate							
Orgogozo 2002 (9408)	111	-1.2 (6.4)	114	1.6 (6.4)		4.49%	-0.44[-0.71,-0.18]
Wilcock 2002 (9202)	177	0.2 (6.9)	167	1.8 (6.9)		6.98%	-0.24[-0.45,-0.02]
Subtotal ***	**288**		**281**			**11.47%**	**-0.32[-0.48,-0.15]**
Heterogeneity: Tau^2=0; Chi^2=1.43, df=1(P=0.23); I^2=30.01%							
Test for overall effect: Z=3.75(P=0)							
8.2.5 PDD/DLB - mild to moderate							
Aarsland 2009	30	-1.4 (3.2)	33	0.5 (4.2)		1.24%	-0.5[-1,0]
Subtotal ***	**30**		**33**			**1.24%**	**-0.5[-1,0]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.95(P=0.05)							
8.2.6 Fronto Temporal Dementia - mild							



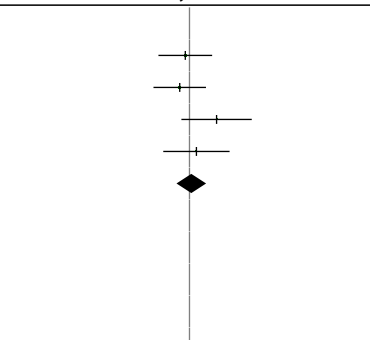
Favours memantine — Favours placebo

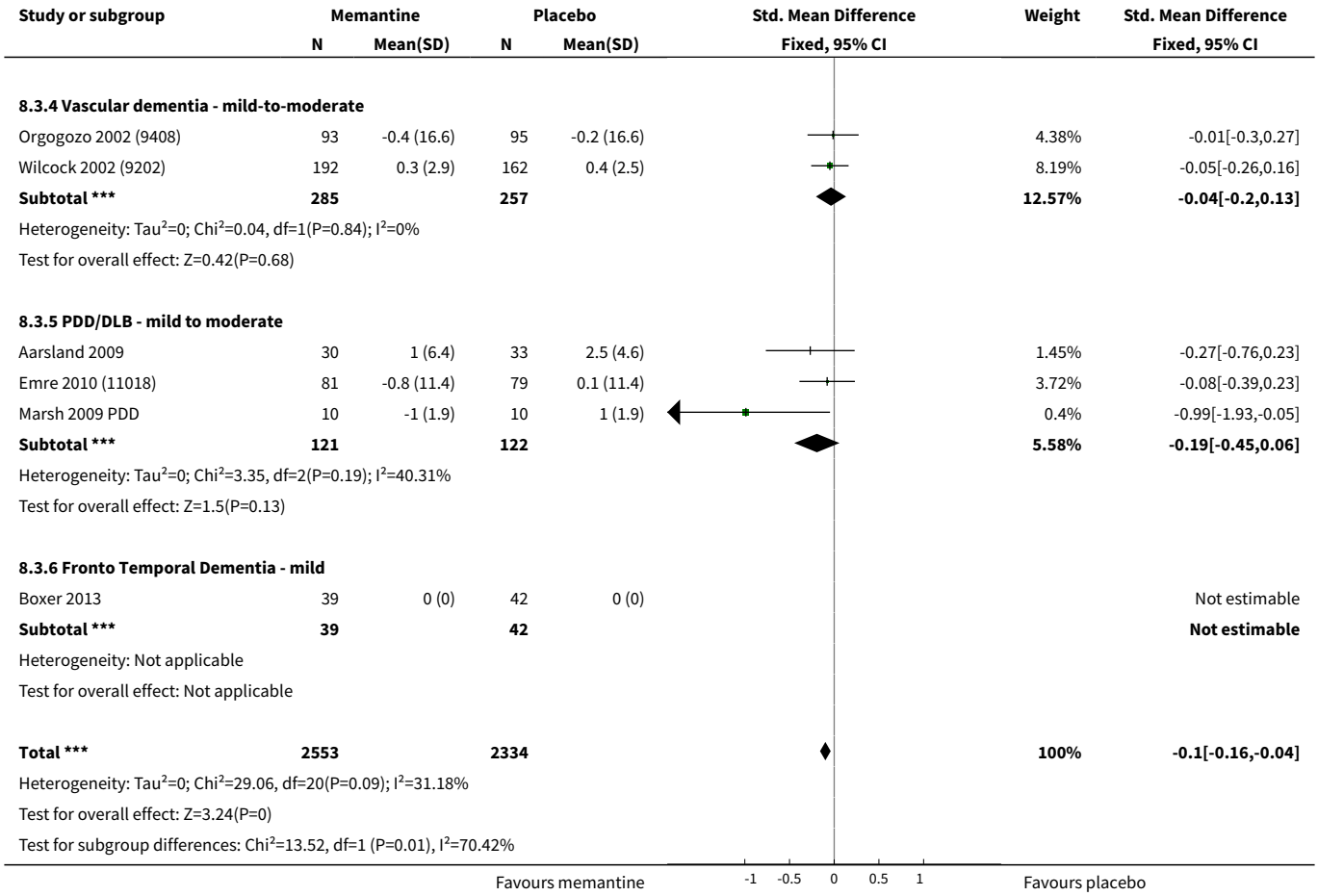
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Boxer 2013	39	1.2 (4)	42	0.9 (2.9)		1.65%	0.09[-0.35,0.52]
Subtotal ***	**39**		**42**			**1.65%**	**0.09[-0.35,0.52]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.38(P=0.7)							
Total ***	**2748**		**2555**			**100%**	**-0.22[-0.28,-0.17]**
Heterogeneity: Tau²=0; Chi²=37.18, df=21(P=0.02); I²=43.52%							
Test for overall effect: Z=7.83(P<0.0001)							
Test for subgroup differences: Chi²=18.36, df=1 (P=0), I²=72.77%							



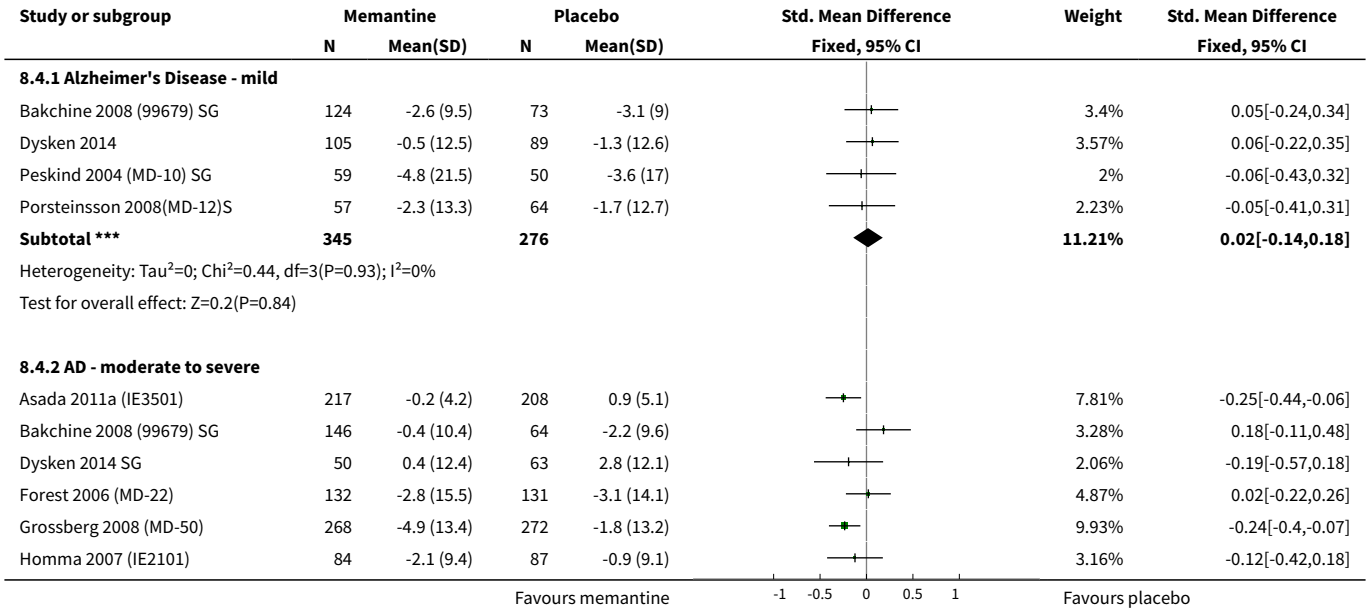
Analysis 8.3. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 3 Decline in ADL - by dementia type and severity.

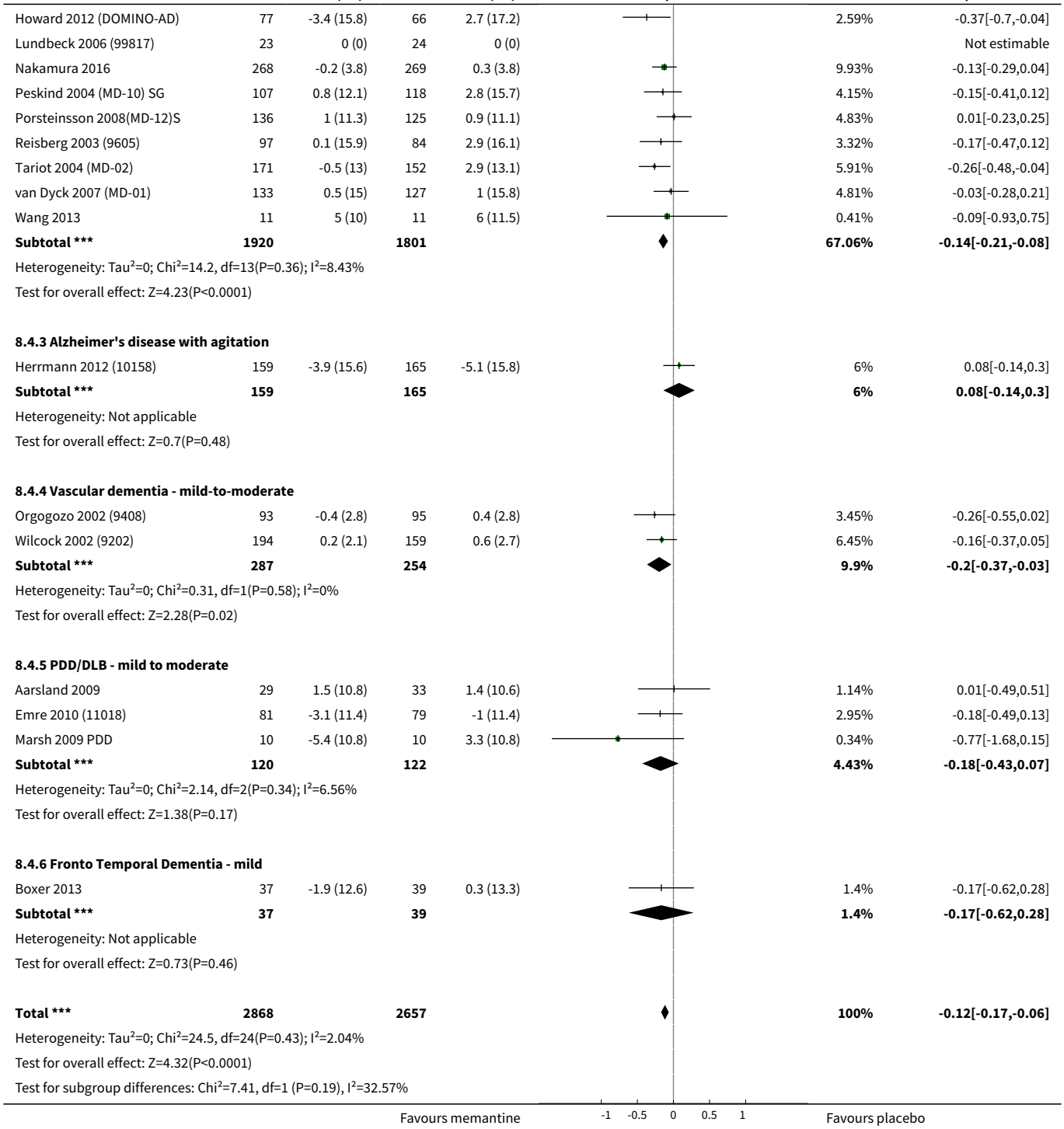
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
8.3.1 Alzheimer's disease - mild							
Bakchine 2008 (99679) SG	124	1.6 (10.3)	73	2 (9.3)		4.28%	-0.05[-0.33,0.24]
Dysken 2014 SG	105	1.9 (11)	89	3 (11)		4.48%	-0.11[-0.39,0.18]
Peskind 2004 (MD-10) SG	59	-0.7 (13)	50	-4.8 (14.7)		2.49%	0.29[-0.09,0.67]
Porsteinsson 2008(MD-12)S	57	-0.5 (12.2)	64	-1.3 (9.3)		2.81%	0.07[-0.28,0.43]
Subtotal ***	**345**		**276**			**14.07%**	**0.02[-0.14,0.18]**
Heterogeneity: Tau²=0; Chi²=3.01, df=3(P=0.39); I²=0.46%							
Test for overall effect: Z=0.24(P=0.81)							
8.3.2 Alzheimer's Disease - moderate to severe							
Asada 2011a (IE3501)	193	0 (0)	175	0 (0)			Not estimable
Bakchine 2008 (99679) SG	146	2.6 (8.2)	64	2.8 (7.4)		4.15%	-0.03[-0.32,0.27]
Dysken 2014 SG	50	3.6 (11.2)	63	6.7 (10.9)		2.57%	-0.27[-0.65,0.1]
Forest 2006 (MD-22)	130	1.9 (6)	129	3.3 (7.4)		6%	-0.21[-0.45,0.04]
Grossberg 2008 (MD-50)	268	0.3 (8.1)	272	1.1 (7.8)		12.56%	-0.1[-0.27,0.07]
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		3.98%	-0.1[-0.4,0.2]
Howard 2012 (DOMINO-AD)	77	3.8 (6.9)	66	5 (7.1)		3.3%	-0.17[-0.5,0.16]
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Peskind 2004 (MD-10) SG	107	4 (8.8)	118	5.3 (7)		5.21%	-0.17[-0.43,0.09]
Porsteinsson 2008(MD-12)S	136	3.6 (7)	125	3.9 (8)		6.07%	-0.03[-0.27,0.21]
Reisberg 2003 (9605)	97	2.5 (6.3)	84	5.9 (6.8)		4.06%	-0.52[-0.82,-0.22]
Tariot 2004 (MD-02)	172	1.7 (6.7)	152	3.3 (6.8)		7.47%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	133	1.3 (6.9)	127	2.3 (6.8)		6.04%	-0.15[-0.39,0.1]
Wang 2013	11	0 (0)	11	0 (0)			Not estimable
Subtotal ***	**1627**		**1497**			**61.4%**	**-0.16[-0.24,-0.09]**
Heterogeneity: Tau²=0; Chi²=9.14, df=10(P=0.52); I²=0%							
Test for overall effect: Z=4.23(P<0.0001)							
8.3.3 Alzheimer's disease with agitation							
Herrmann 2012 (10158)	136	4.4 (7.8)	140	2.6 (7.7)		6.39%	0.23[-0.01,0.47]
Subtotal ***	**136**		**140**			**6.39%**	**0.23[-0.01,0.47]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.92(P=0.06)							





Analysis 8.4. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 4 Behaviour and mood - by dementia type and severity.

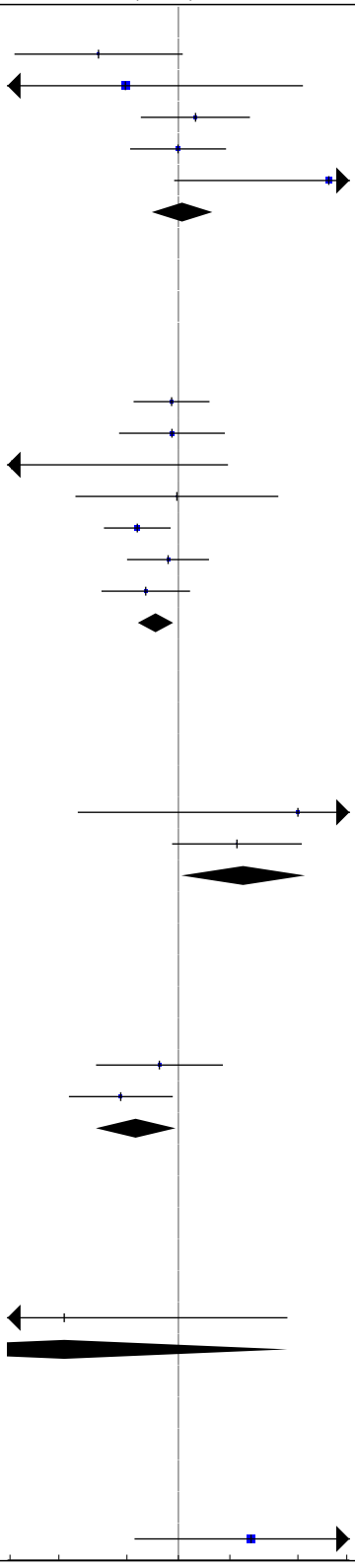


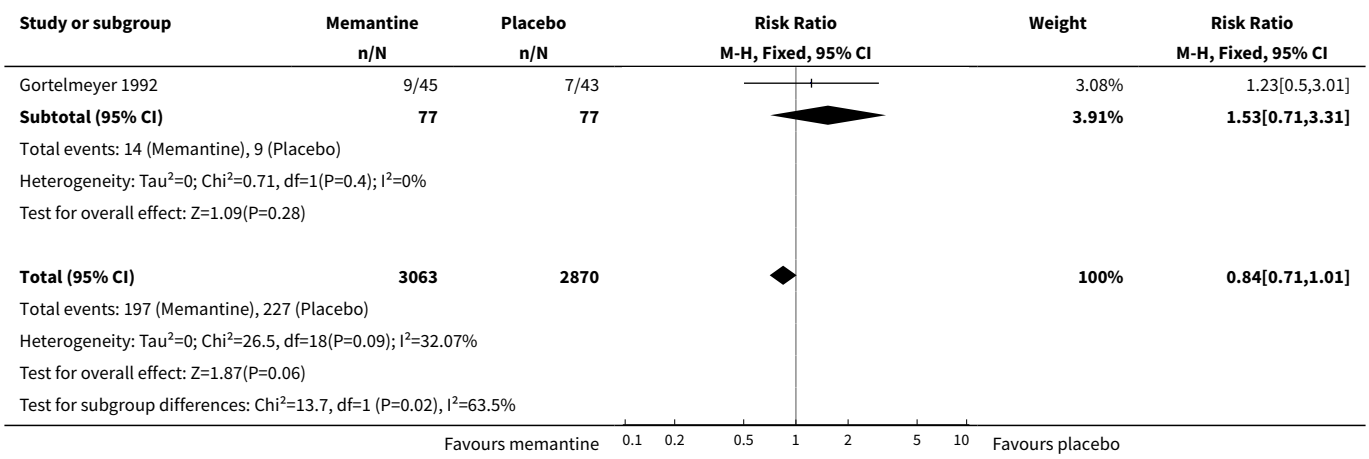


Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Howard 2012 (DOMINO-AD)	77	-3.4 (15.8)	66	2.7 (17.2)		2.59%	-0.37[-0.7,-0.04]
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Nakamura 2016	268	-0.2 (3.8)	269	0.3 (3.8)		9.93%	-0.13[-0.29,0.04]
Peskind 2004 (MD-10) SG	107	0.8 (12.1)	118	2.8 (15.7)		4.15%	-0.15[-0.41,0.12]
Porsteinsson 2008(MD-12)S	136	1 (11.3)	125	0.9 (11.1)		4.83%	0.01[-0.23,0.25]
Reisberg 2003 (9605)	97	0.1 (15.9)	84	2.9 (16.1)		3.32%	-0.17[-0.47,0.12]
Tariot 2004 (MD-02)	171	-0.5 (13)	152	2.9 (13.1)		5.91%	-0.26[-0.48,-0.04]
van Dyck 2007 (MD-01)	133	0.5 (15)	127	1 (15.8)		4.81%	-0.03[-0.28,0.21]
Wang 2013	11	5 (10)	11	6 (11.5)		0.41%	-0.09[-0.93,0.75]
Subtotal ***	**1920**		**1801**			**67.06%**	**-0.14[-0.21,-0.08]**
Heterogeneity: Tau²=0; Chi²=14.2, df=13(P=0.36); I²=8.43%							
Test for overall effect: Z=4.23(P<0.0001)							
8.4.3 Alzheimer's disease with agitation							
Herrmann 2012 (10158)	159	-3.9 (15.6)	165	-5.1 (15.8)		6%	0.08[-0.14,0.3]
Subtotal ***	**159**		**165**			**6%**	**0.08[-0.14,0.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.7(P=0.48)							
8.4.4 Vascular dementia - mild-to-moderate							
Orgogozo 2002 (9408)	93	-0.4 (2.8)	95	0.4 (2.8)		3.45%	-0.26[-0.55,0.02]
Wilcock 2002 (9202)	194	0.2 (2.1)	159	0.6 (2.7)		6.45%	-0.16[-0.37,0.05]
Subtotal ***	**287**		**254**			**9.9%**	**-0.2[-0.37,-0.03]**
Heterogeneity: Tau²=0; Chi²=0.31, df=1(P=0.58); I²=0%							
Test for overall effect: Z=2.28(P=0.02)							
8.4.5 PDD/DLB - mild to moderate							
Aarsland 2009	29	1.5 (10.8)	33	1.4 (10.6)		1.14%	0.01[-0.49,0.51]
Emre 2010 (11018)	81	-3.1 (11.4)	79	-1 (11.4)		2.95%	-0.18[-0.49,0.13]
Marsh 2009 PDD	10	-5.4 (10.8)	10	3.3 (10.8)		0.34%	-0.77[-1.68,0.15]
Subtotal ***	**120**		**122**			**4.43%**	**-0.18[-0.43,0.07]**
Heterogeneity: Tau²=0; Chi²=2.14, df=2(P=0.34); I²=6.56%							
Test for overall effect: Z=1.38(P=0.17)							
8.4.6 Fronto Temporal Dementia - mild							
Boxer 2013	37	-1.9 (12.6)	39	0.3 (13.3)		1.4%	-0.17[-0.62,0.28]
Subtotal ***	**37**		**39**			**1.4%**	**-0.17[-0.62,0.28]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.73(P=0.46)							
Total ***	**2868**		**2657**			**100%**	**-0.12[-0.17,-0.06]**
Heterogeneity: Tau²=0; Chi²=24.5, df=24(P=0.43); I²=2.04%							
Test for overall effect: Z=4.32(P<0.0001)							
Test for subgroup differences: Chi²=7.41, df=1 (P=0.19), I²=32.57%							

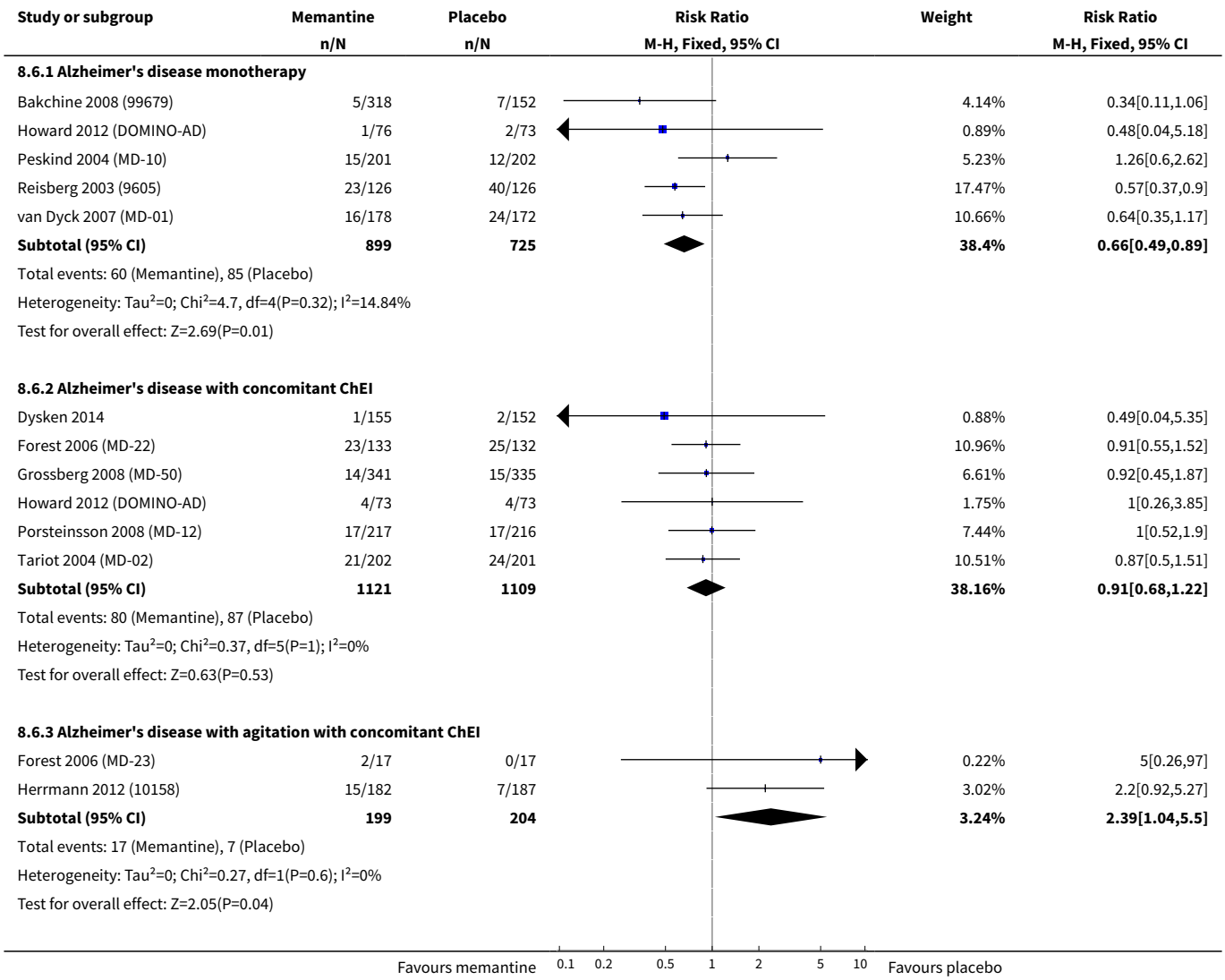
Analysis 8.5. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 5 Number suffering agitation - by dementia type and severity.

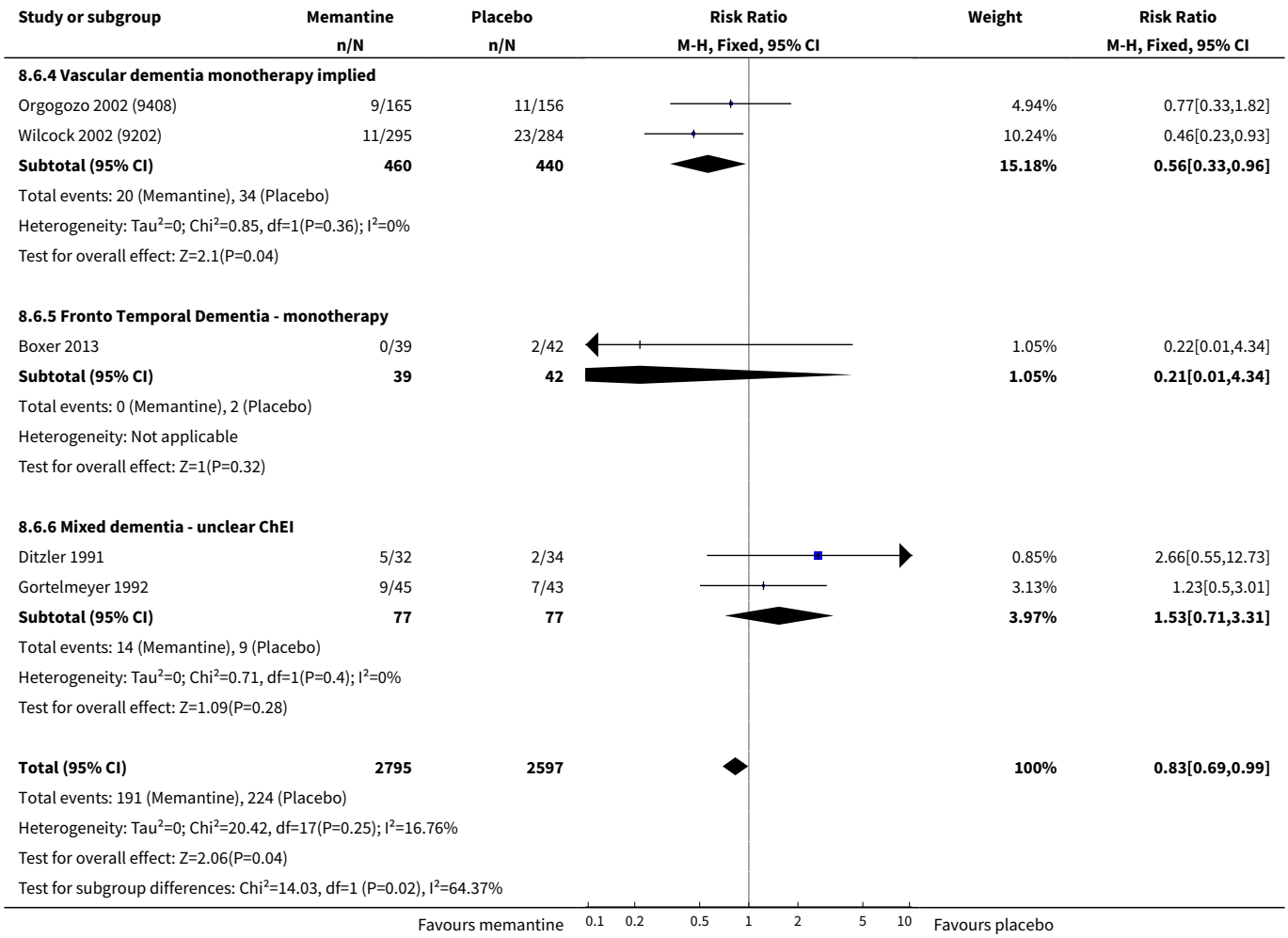
Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.5.1 Alzheimer's disease mild-to-moderate					
Bakchine 2008 (99679)	5/318	7/152		4.07%	0.34[0.11,1.06]
Dysken 2014	1/155	2/152		0.87%	0.49[0.04,5.35]
Peskind 2004 (MD-10)	15/201	12/202		5.15%	1.26[0.6,2.62]
Porsteinsson 2008 (MD-12)	17/217	17/216		7.33%	1[0.52,1.9]
Wilkinson 2012 (10112)	7/133	1/144		0.41%	7.58[0.94,60.79]
Subtotal (95% CI)	**1024**	**866**		**17.84%**	**1.05[0.7,1.58]**
Total events: 45 (Memantine), 39 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=7.89, df=4(P=0.1); I^2=49.33%					
Test for overall effect: Z=0.23(P=0.82)					
8.5.2 Alzheimer's disease moderate-to-severe					
Forest 2006 (MD-22)	23/133	25/132		10.8%	0.91[0.55,1.52]
Grossberg 2008 (MD-50)	14/341	15/335		6.51%	0.92[0.45,1.87]
Hofbauer 2009 (MD-71)	0/135	4/129		1.98%	0.11[0.01,1.95]
Howard 2012 (DOMINO-AD)	4/149	4/146		1.74%	0.98[0.25,3.84]
Reisberg 2003 (9605)	23/126	40/126		17.21%	0.57[0.37,0.9]
Tariot 2004 (MD-02)	21/202	24/201		10.35%	0.87[0.5,1.51]
van Dyck 2007 (MD-01)	16/178	24/172		10.5%	0.64[0.35,1.17]
Subtotal (95% CI)	**1264**	**1241**		**59.08%**	**0.73[0.58,0.93]**
Total events: 101 (Memantine), 136 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=4.62, df=6(P=0.59); I^2=0%					
Test for overall effect: Z=2.54(P=0.01)					
8.5.3 AD with agitation (increased severity)					
Forest 2006 (MD-23)	2/17	0/17		0.22%	5[0.26,97]
Herrmann 2012 (10158)	15/182	7/187		2.97%	2.2[0.92,5.27]
Subtotal (95% CI)	**199**	**204**		**3.19%**	**2.39[1.04,5.5]**
Total events: 17 (Memantine), 7 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.27, df=1(P=0.6); I^2=0%					
Test for overall effect: Z=2.05(P=0.04)					
8.5.4 Vascular dementia mild-to-moderate					
Orgogozo 2002 (9408)	9/165	11/156		4.86%	0.77[0.33,1.82]
Wilcock 2002 (9202)	11/295	23/284		10.08%	0.46[0.23,0.93]
Subtotal (95% CI)	**460**	**440**		**14.95%**	**0.56[0.33,0.96]**
Total events: 20 (Memantine), 34 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.85, df=1(P=0.36); I^2=0%					
Test for overall effect: Z=2.1(P=0.04)					
8.5.5 Fronto Temporal Dementia					
Boxer 2013	0/39	2/42		1.04%	0.22[0.01,4.34]
Subtotal (95% CI)	**39**	**42**		**1.04%**	**0.21[0.01,4.34]**
Total events: 0 (Memantine), 2 (Placebo)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1(P=0.32)					
8.5.6 Mixed dementia mild-to-moderate					
Ditzler 1991	5/32	2/34		0.83%	2.66[0.55,12.73]



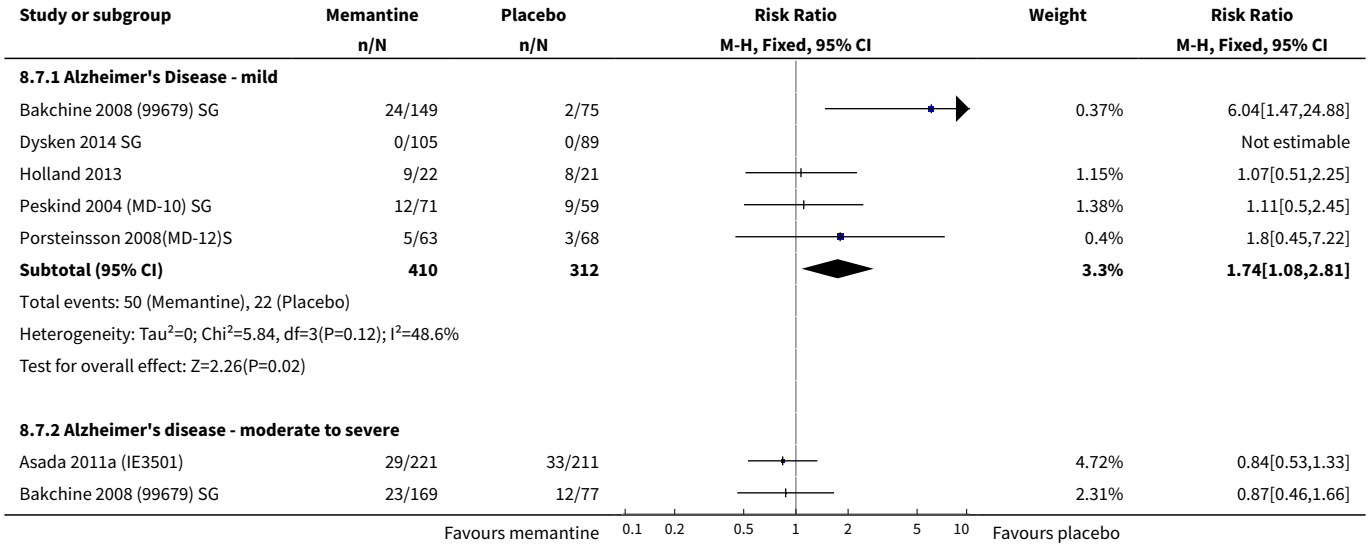


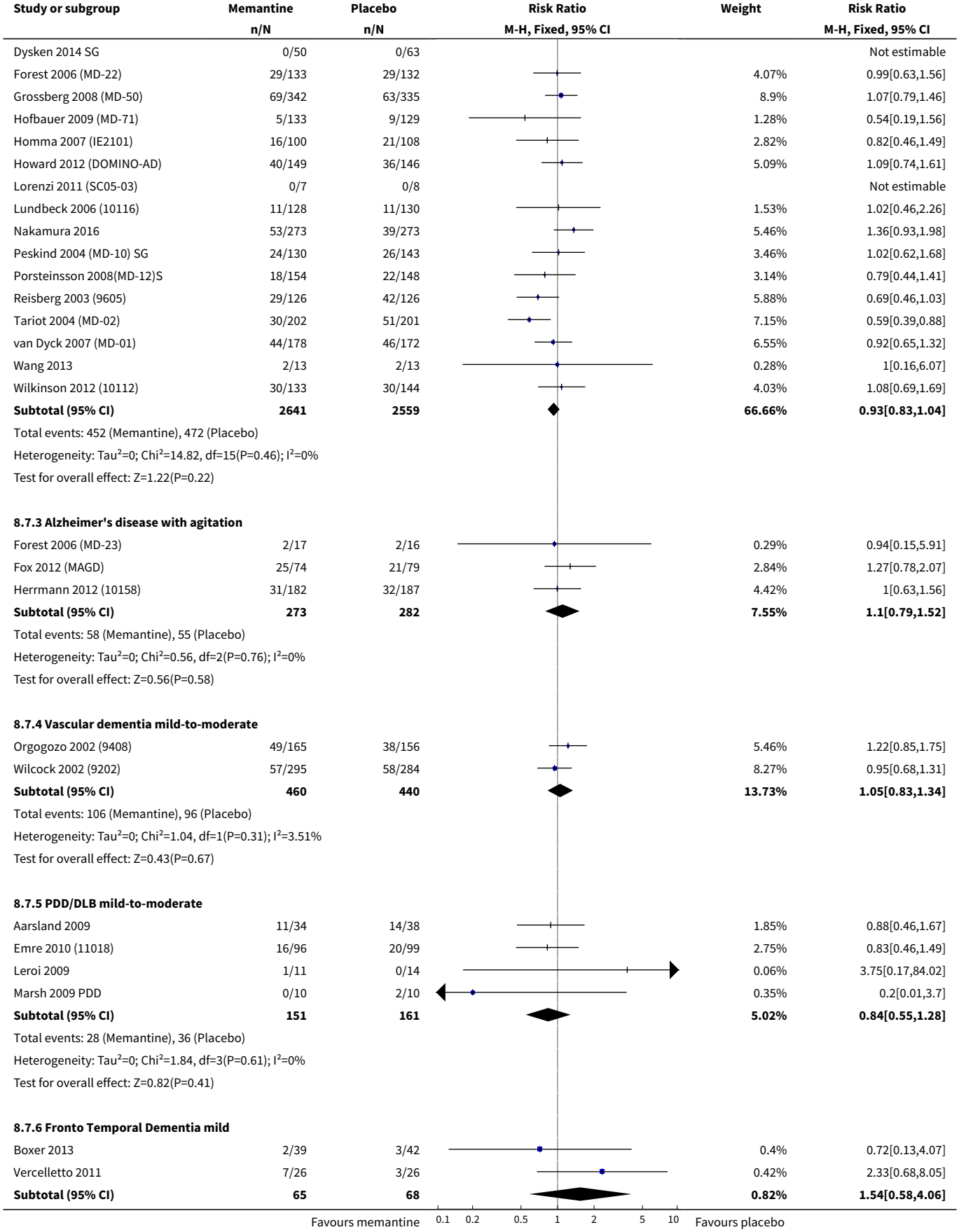
Analysis 8.6. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 6 Number suffering agitation - by dementia type and ChEI.

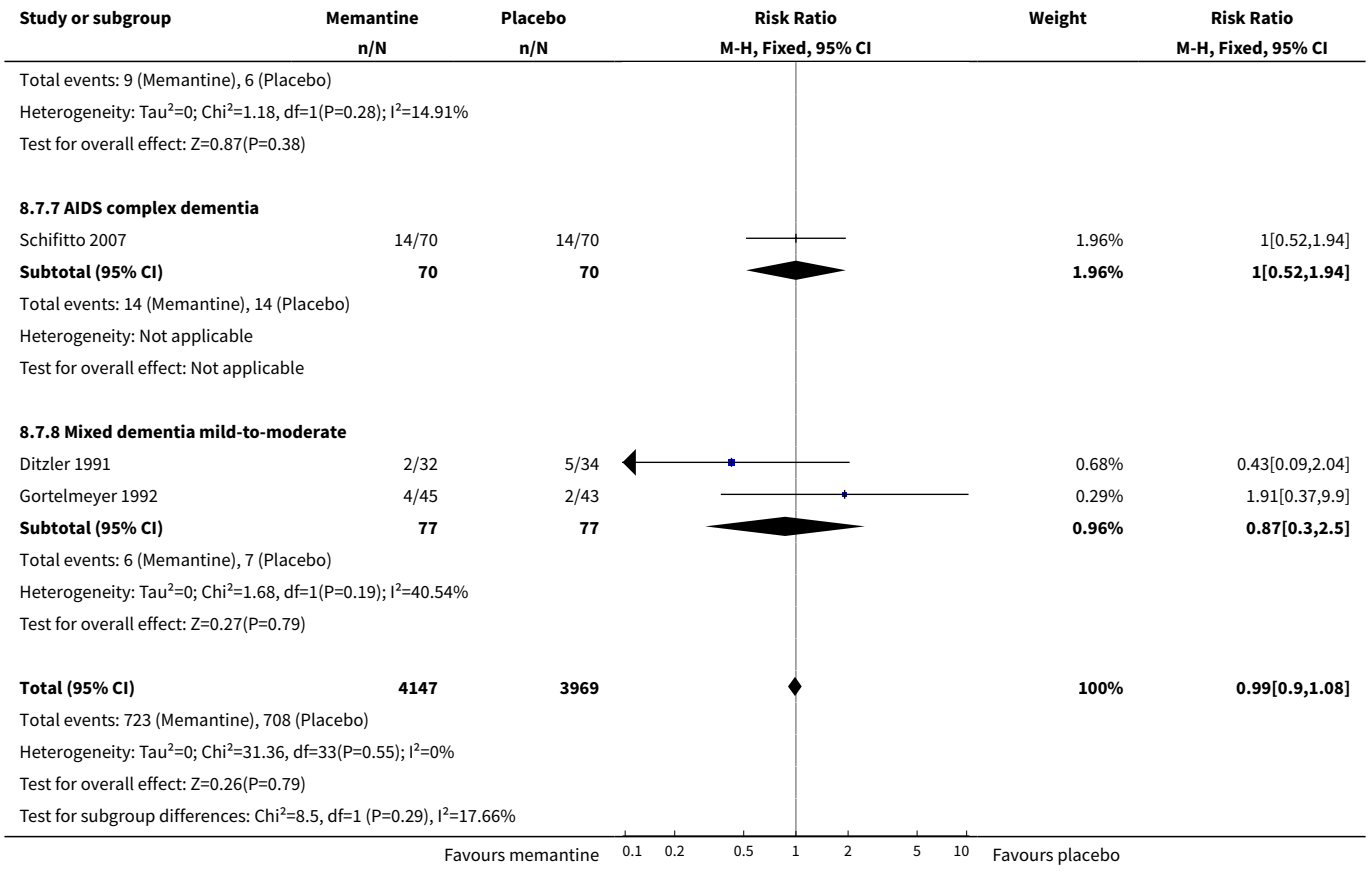




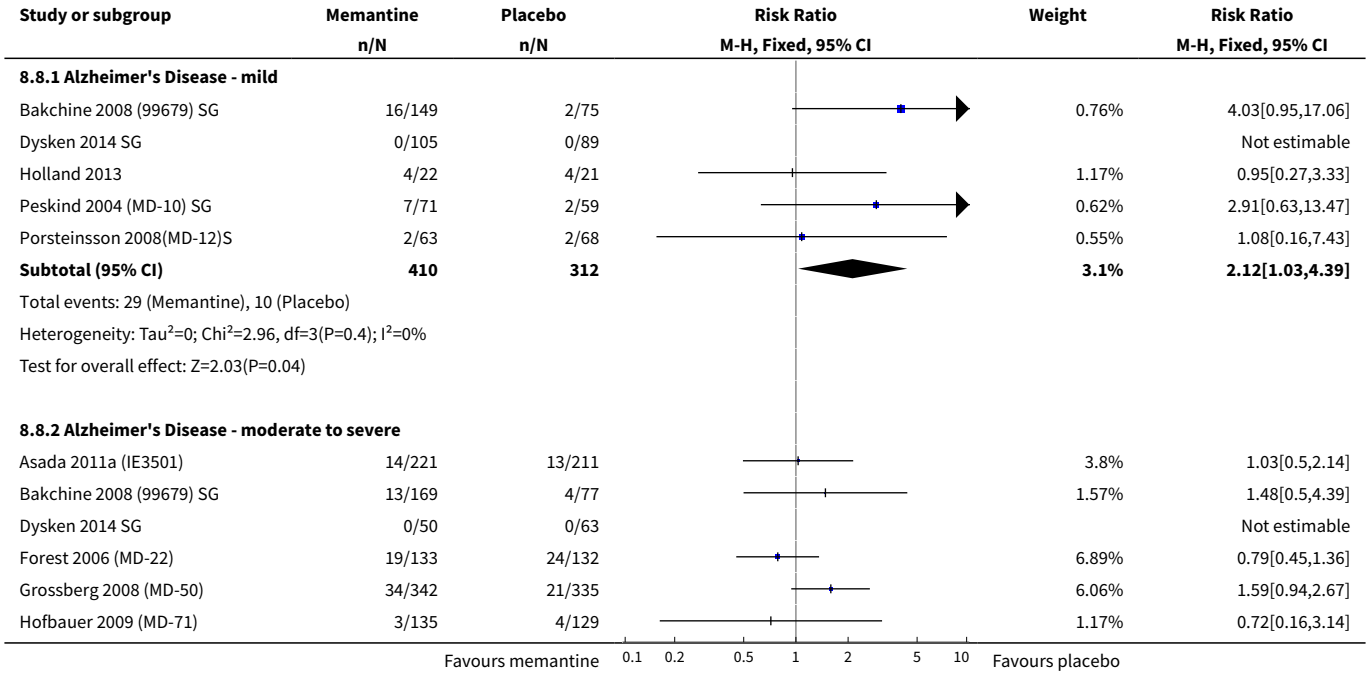
Analysis 8.7. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 7 All-cause discontinuation (all durations) - by dementia type and severity.

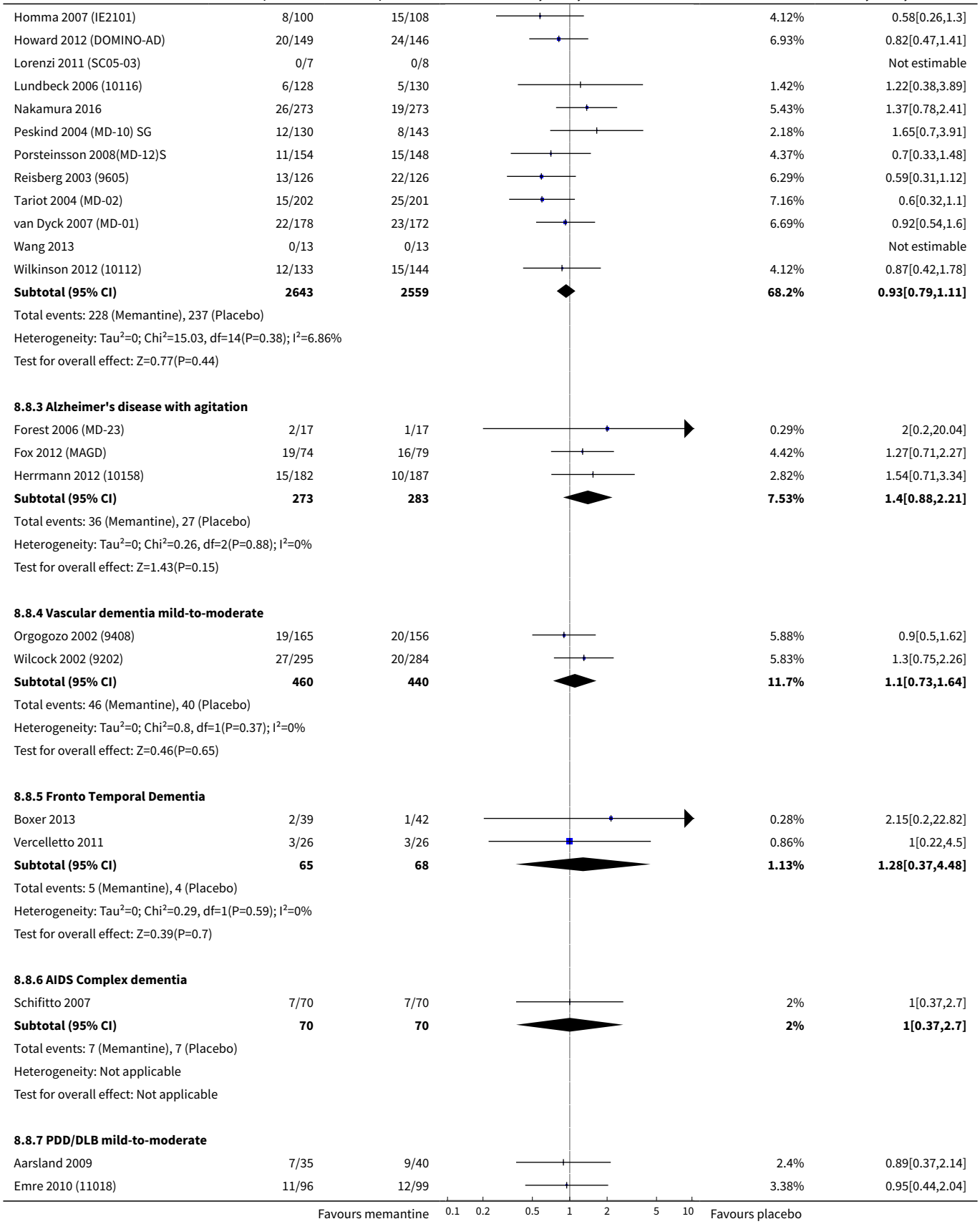


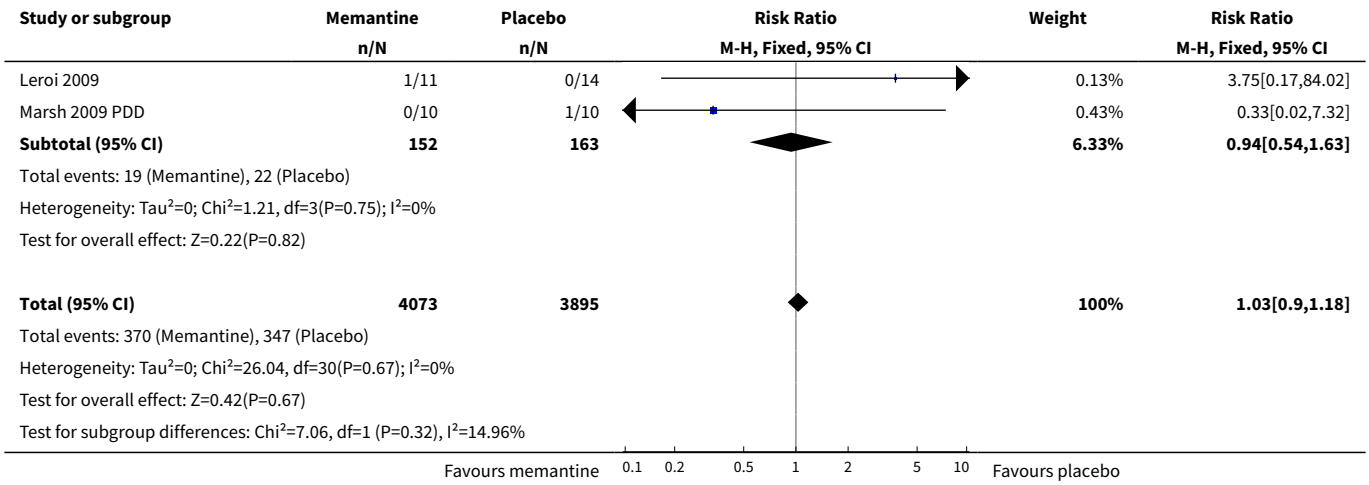




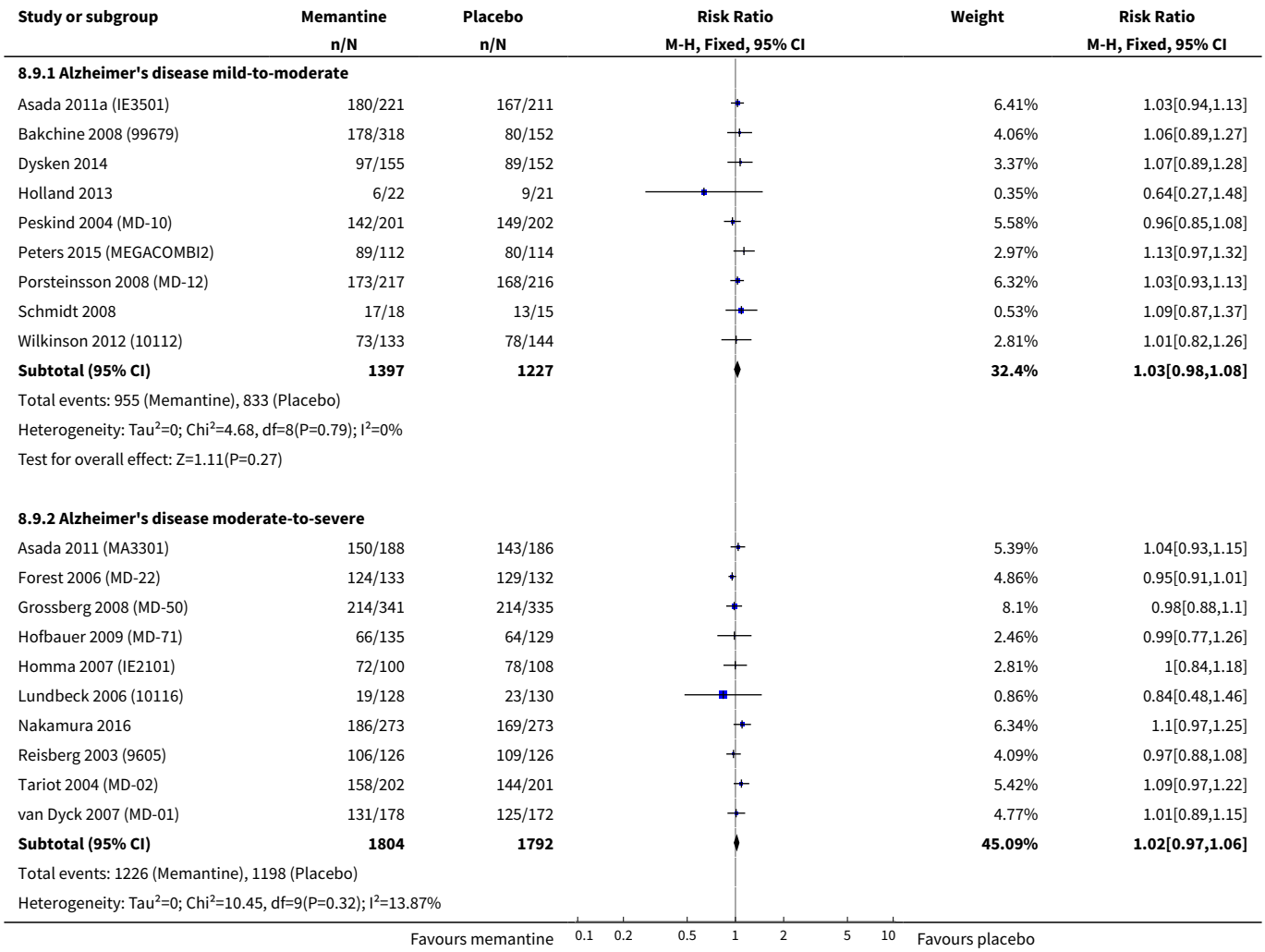
Analysis 8.8. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 8 Discontinuation due to adverse events - by dementia type and severity.

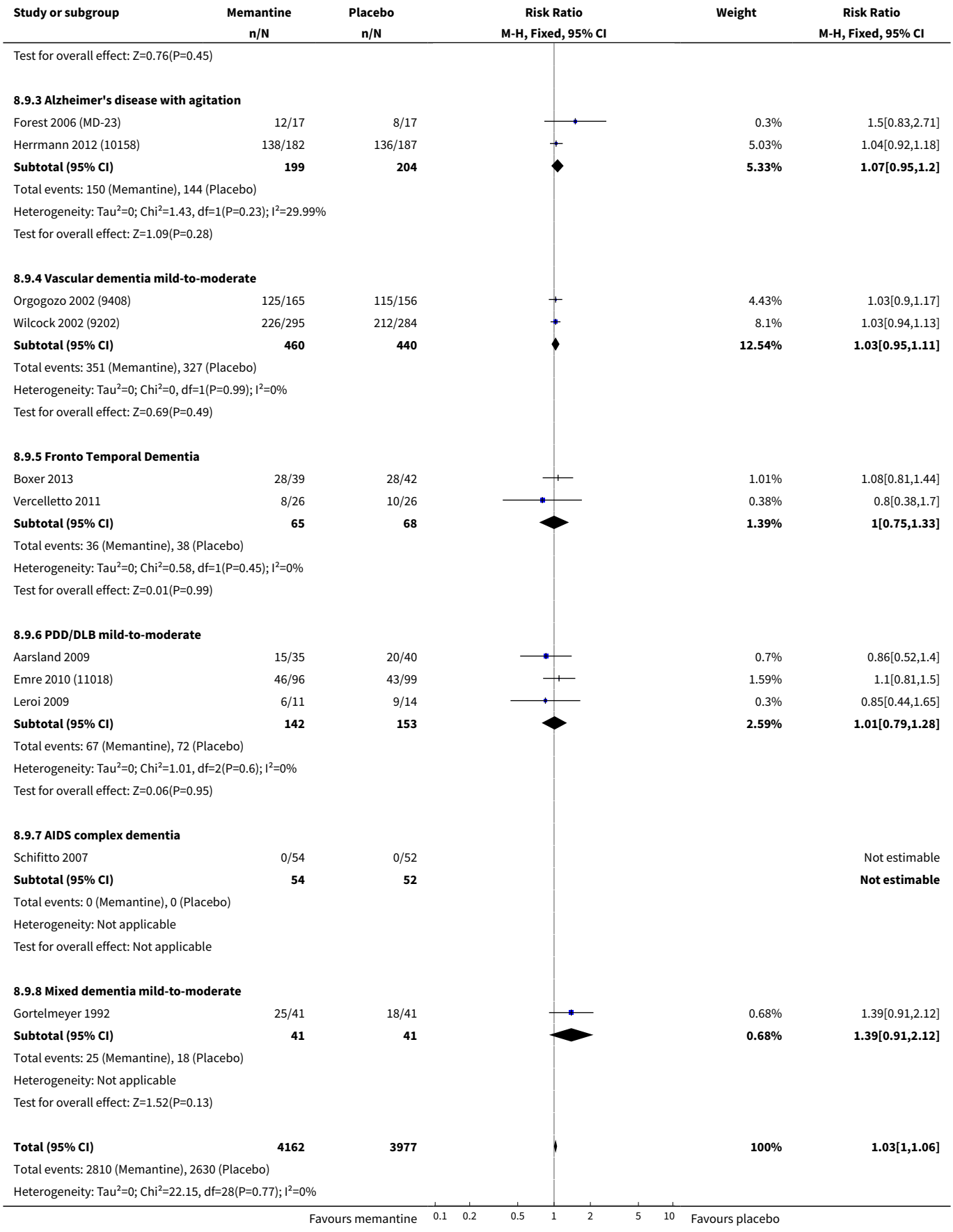






Analysis 8.9. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 9 Number suffering at least one adverse event - by dementia type and severity.





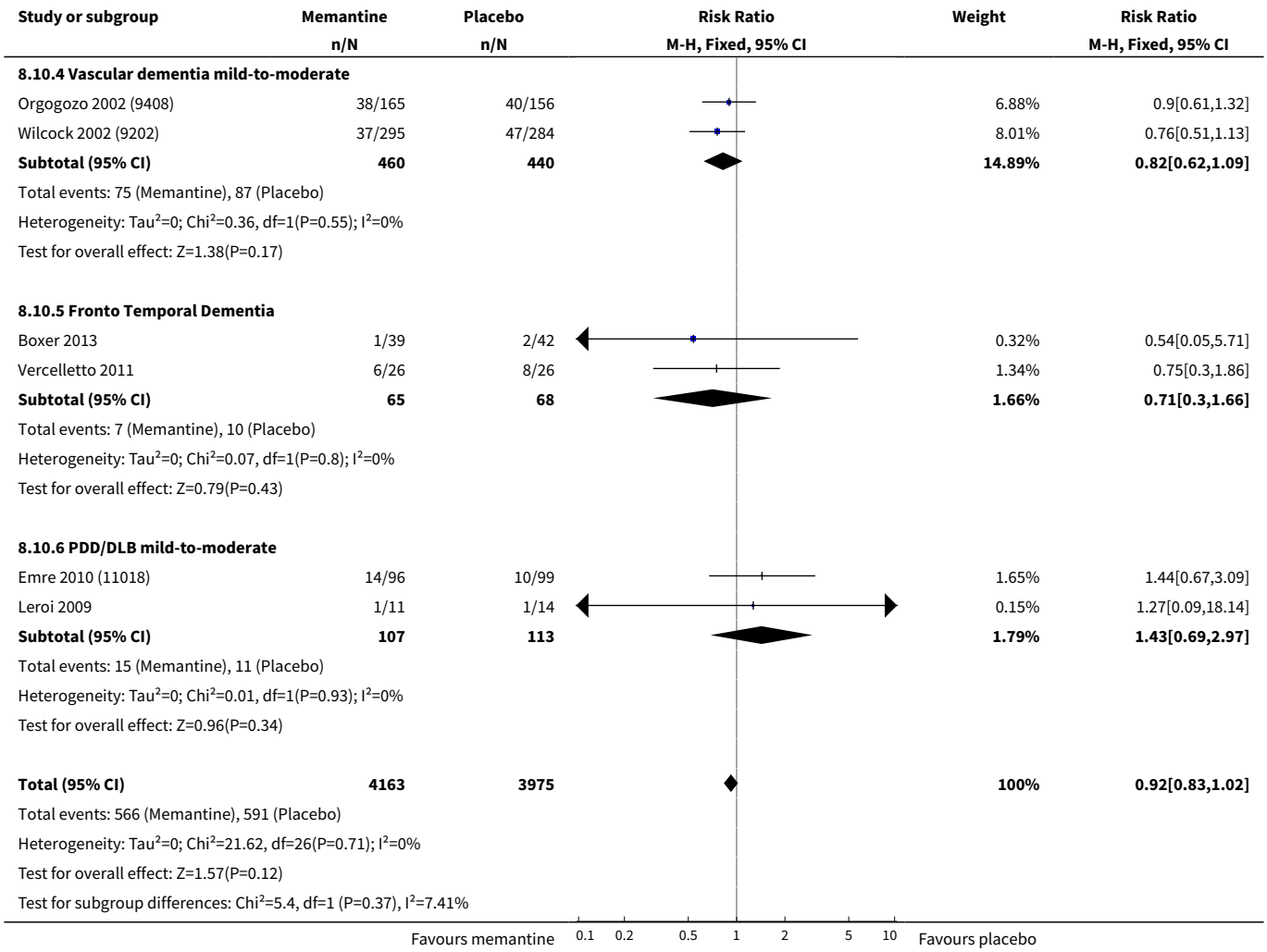
Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=1.8(P=0.07)					
Test for subgroup differences: Chi²=2.66, df=1 (P=0.85), I²=0%					

Favours memantine 0.1 0.2 0.5 1 2 5 10 Favours placebo

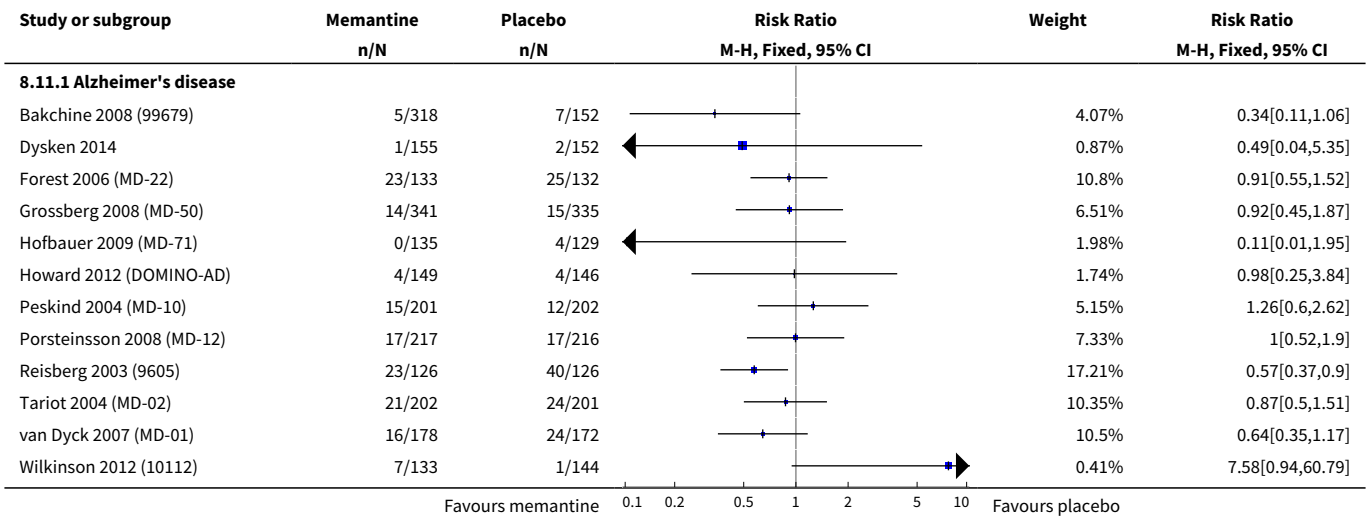
Analysis 8.10. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 10 Number suffering at least one serious AE - by dementia type and severity.

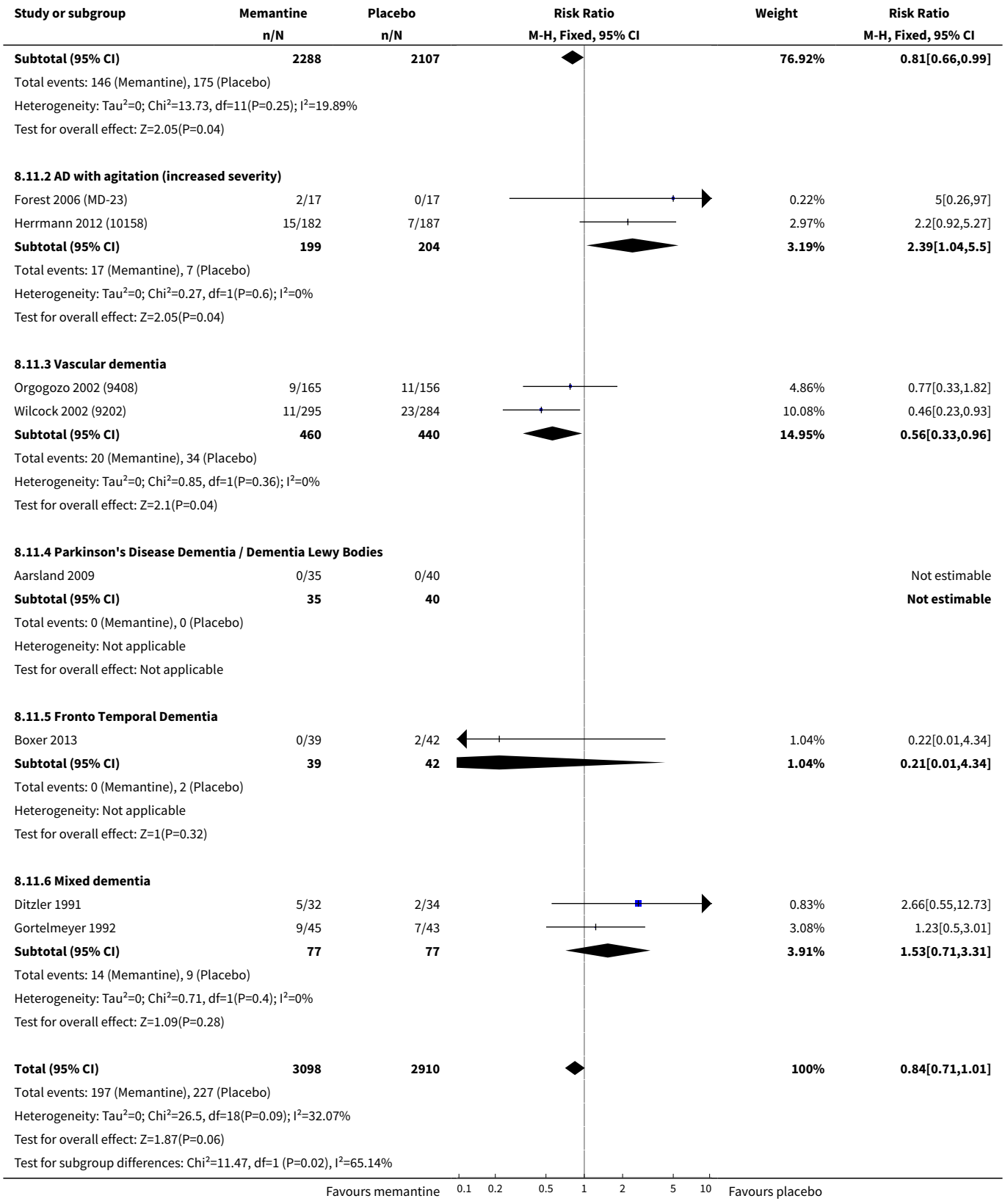
Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
8.10.1 Alzheimer's disease mild-to-moderate					
Asada 2011 (MA3301)	14/188	11/186		1.85%	1.26[0.59,2.7]
Bakchine 2008 (99679)	33/318	9/152		2.04%	1.75[0.86,3.57]
Dysken 2014	84/155	95/152		16.05%	0.87[0.72,1.05]
Forest 2006 (MD-22)	24/133	38/132		6.38%	0.63[0.4,0.98]
Holland 2013	2/22	3/21		0.51%	0.64[0.12,3.44]
Peskind 2004 (MD-10)	20/201	20/202		3.34%	1[0.56,1.81]
Peters 2015 (MEGACOMBI2)	15/112	15/114		2.49%	1.02[0.52,1.98]
Porsteinsson 2008 (MD-12)	27/217	30/216		5.03%	0.9[0.55,1.45]
Wilkinson 2012 (10112)	17/133	20/144		3.21%	0.92[0.5,1.68]
Subtotal (95% CI)	**1479**	**1319**		**40.9%**	**0.92[0.79,1.07]**
Total events: 236 (Memantine), 241 (Placebo)					
Heterogeneity: Tau²=0; Chi²=7.29, df=8(P=0.51); I²=0%					
Test for overall effect: Z=1.12(P=0.26)					
8.10.2 Alzheimer's disease moderate-to-severe					
Asada 2011a (IE3501)	26/221	24/211		4.11%	1.03[0.61,1.74]
Grossberg 2008 (MD-50)	28/341	21/335		3.54%	1.31[0.76,2.26]
Hofbauer 2009 (MD-71)	4/135	13/129		2.22%	0.29[0.1,0.88]
Homma 2007 (IE2101)	7/100	11/108		1.77%	0.69[0.28,1.7]
Howard 2012 (DOMINO-AD)	59/149	64/146		10.82%	0.9[0.69,1.18]
Lundbeck 2006 (10116)	4/128	4/130		0.66%	1.02[0.26,3.97]
Nakamura 2016	17/273	20/273		3.35%	0.85[0.46,1.59]
Reisberg 2003 (9605)	16/126	23/126		3.85%	0.7[0.39,1.25]
Tariot 2004 (MD-02)	25/202	20/201		3.35%	1.24[0.71,2.17]
van Dyck 2007 (MD-01)	26/178	29/172		4.93%	0.87[0.53,1.41]
Subtotal (95% CI)	**1853**	**1831**		**38.61%**	**0.91[0.77,1.08]**
Total events: 212 (Memantine), 229 (Placebo)					
Heterogeneity: Tau²=0; Chi²=8.54, df=9(P=0.48); I²=0%					
Test for overall effect: Z=1.09(P=0.28)					
8.10.3 Alzheimer's disease with agitation					
Forest 2006 (MD-23)	3/17	2/17		0.33%	1.5[0.29,7.87]
Herrmann 2012 (10158)	18/182	11/187		1.82%	1.68[0.82,3.46]
Subtotal (95% CI)	**199**	**204**		**2.15%**	**1.65[0.85,3.2]**
Total events: 21 (Memantine), 13 (Placebo)					
Heterogeneity: Tau²=0; Chi²=0.02, df=1(P=0.9); I²=0%					
Test for overall effect: Z=1.49(P=0.14)					

Favours memantine 0.1 0.2 0.5 1 2 5 10 Favours placebo



Analysis 8.11. Comparison 8 SUMMARY: memantine 20 mg/day or equivalent vs placebo at six to seven months, by dementia type and by severity, Outcome 11 Number suffering agitation as an adverse event - by dementia type.



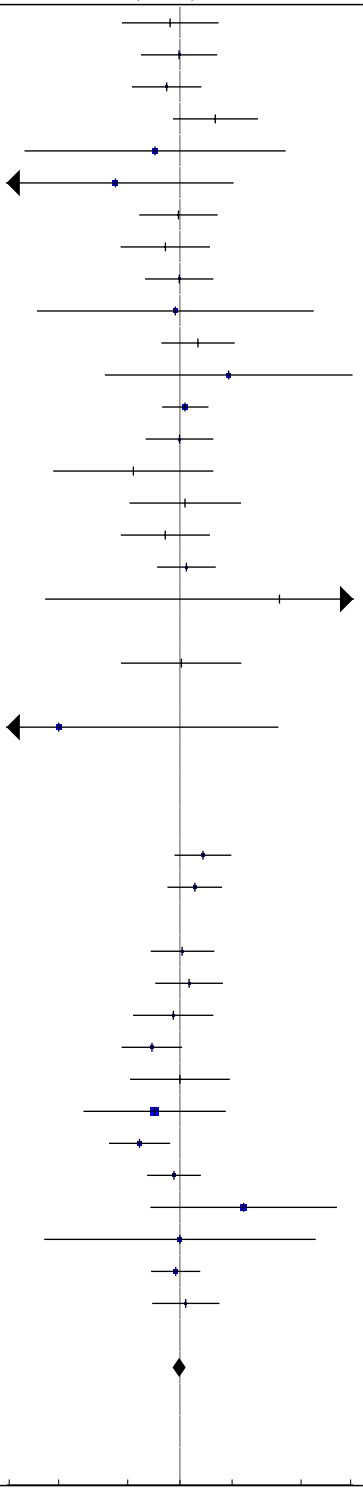


Comparison 9. Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause discontinuation	41	8998	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.91, 1.08]
2 Discontinuation due to adverse events	41	9004	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.92, 1.21]
3 Number suffering at least one adverse event	41	8960	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [1.00, 1.06]
4 Number suffering serious adverse events	41	8960	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.83, 1.02]
5 Number suffering agitation as an adverse event	22	6814	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.71, 1.01]
6 Number suffering insomnia as an adverse event	19	5354	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.73, 1.20]
7 Number suffering confusion as an adverse event	13	4509	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.91, 1.65]
8 Number suffering depression as an adverse event	10	3052	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.70, 1.60]
9 Number suffering headache as an adverse event	16	4889	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.00, 1.66]
10 Number suffering hypertension as an adverse event	8	3175	Risk Ratio (M-H, Fixed, 95% CI)	1.76 [1.14, 2.70]
11 Number suffering dizziness as an adverse event	19	6395	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [1.28, 1.98]
12 Number suffering falls as an adverse event	20	6743	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.13]
13 Number suffering accidental injury as an adverse event	10	3813	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.62, 1.05]
14 Number suffering urinary incontinence as an adverse event	8	2724	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.73, 1.72]
15 Number suffering diarrhoea as an adverse event	18	6186	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.66, 1.02]
16 Number suffering influenza like symptoms as an adverse event	7	2836	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.87, 1.70]

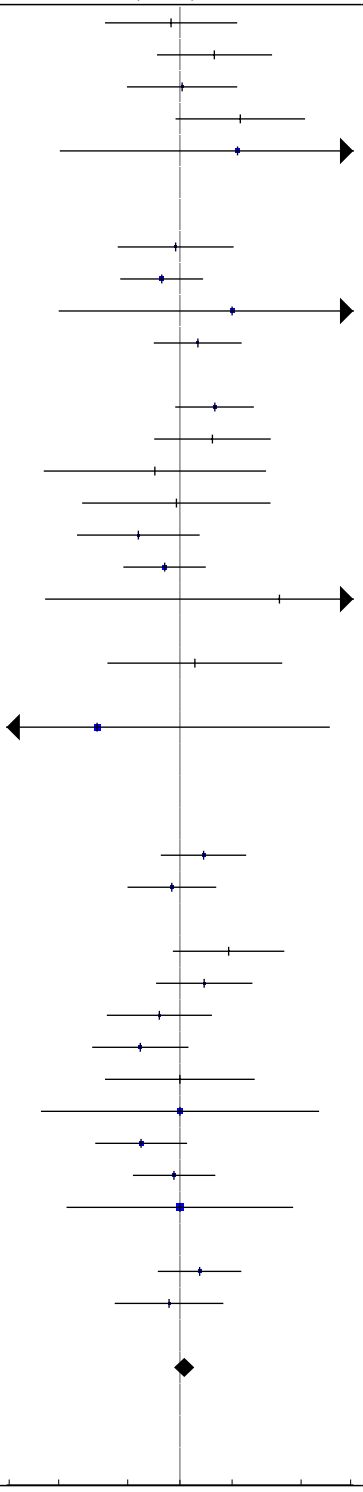
Analysis 9.1. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 1 All-cause discontinuation.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aarsland 2009	11/34	14/38		1.66%	0.88[0.46,1.67]
Asada 2011 (MA3301)	26/188	26/186		3.27%	0.99[0.6,1.64]
Asada 2011a (IE3501)	29/221	33/211		4.23%	0.84[0.53,1.33]
Bakchine 2008 (99679)	47/318	14/152		2.37%	1.6[0.91,2.82]
Boxer 2013	2/39	3/42		0.36%	0.72[0.13,4.07]
Ditzler 1991	2/32	5/34		0.61%	0.43[0.09,2.04]
Dysken 2014	24/155	24/152		3.03%	0.98[0.58,1.65]
Emre 2010 (11018)	16/96	20/99		2.47%	0.83[0.46,1.49]
Forest 2006 (MD-22)	29/133	29/132		3.64%	0.99[0.63,1.56]
Forest 2006 (MD-23)	2/17	2/16		0.26%	0.94[0.15,5.91]
Fox 2012 (MAGD)	25/74	21/79		2.54%	1.27[0.78,2.07]
Gortelmeyer 1992	4/45	2/43		0.26%	1.91[0.37,9.9]
Grossberg 2008 (MD-50)	69/342	63/335		7.97%	1.07[0.79,1.46]
Herrmann 2012 (10158)	31/182	32/187		3.95%	1[0.63,1.56]
Hofbauer 2009 (MD-71)	5/133	9/129		1.14%	0.54[0.19,1.56]
Holland 2013	9/22	8/21		1.02%	1.07[0.51,2.25]
Homma 2007 (IE2101)	16/100	21/108		2.53%	0.82[0.46,1.49]
Howard 2012 (DOMINO-AD)	40/149	36/146		4.55%	1.09[0.74,1.61]
Leroi 2009	1/11	0/14		0.06%	3.75[0.17,84.02]
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Lundbeck 2006 (10116)	11/128	11/130		1.37%	1.02[0.46,2.26]
Lundbeck 2006 (99817)	0/23	0/24			Not estimable
Marsh 2009 PDD	0/10	2/10		0.31%	0.2[0.01,3.7]
Merz 2003 (MRZ-9104)	0/27	0/29			Not estimable
Merz 2003 (MRZ-9105)	0/15	0/12			Not estimable
Merz 2003 (MRZ-9206)	0/28	0/28			Not estimable
Nakamura 2016	53/273	39/273		4.88%	1.36[0.93,1.98]
Orgogozo 2002 (9408)	49/165	38/156		4.89%	1.22[0.85,1.75]
Pantev 1993	0/30	0/30			Not estimable
Peskind 2004 (MD-10)	36/201	35/202		4.37%	1.03[0.68,1.58]
Peters 2015 (MEGACOMBI2)	30/112	27/114		3.35%	1.13[0.72,1.77]
Porsteinsson 2008 (MD-12)	23/217	25/216		3.14%	0.92[0.54,1.56]
Reisberg 2003 (9605)	29/126	42/126		5.26%	0.69[0.46,1.03]
Schifitto 2007	14/70	14/70		1.75%	1[0.52,1.94]
Schmidt 2008	5/18	7/18		0.88%	0.71[0.28,1.84]
Tariot 2004 (MD-02)	30/202	51/201		6.4%	0.59[0.39,0.88]
van Dyck 2007 (MD-01)	44/178	46/172		5.86%	0.92[0.65,1.32]
Vercelletto 2011	7/26	3/26		0.38%	2.33[0.68,8.05]
Wang 2013	2/13	2/13		0.25%	1[0.16,6.07]
Wilcock 2002 (9202)	57/295	58/284		7.4%	0.95[0.68,1.31]
Wilkinson 2012 (10112)	30/133	30/144		3.61%	1.08[0.69,1.69]
Total (95% CI)	**4588**	**4410**		**100%**	**0.99[0.91,1.08]**
Total events: 808 (Memantine), 792 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=27.29, df=34(P=0.79); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					



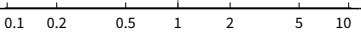
Analysis 9.2. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 2 Discontinuation due to adverse events.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aarsland 2009	7/35	9/40		2.24%	0.89[0.37,2.14]
Asada 2011 (MA3301)	16/188	10/186		2.68%	1.58[0.74,3.4]
Asada 2011a (IE3501)	14/221	13/211		3.54%	1.03[0.5,2.14]
Bakchine 2008 (99679)	28/318	6/152		2.16%	2.23[0.94,5.27]
Boxer 2013	2/39	1/42		0.26%	2.15[0.2,22.82]
Ditzler 1991	0/32	0/34			Not estimable
Dysken 2014	0/155	0/152			Not estimable
Emre 2010 (11018)	11/96	12/99		3.14%	0.95[0.44,2.04]
Forest 2006 (MD-22)	19/133	24/132		6.41%	0.79[0.45,1.36]
Forest 2006 (MD-23)	2/17	1/17		0.27%	2[0.2,20.04]
Fox 2012 (MAGD)	19/74	16/79		4.12%	1.27[0.71,2.27]
Gortelmeyer 1992	0/45	0/43			Not estimable
Grossberg 2008 (MD-50)	34/342	21/335		5.65%	1.59[0.94,2.67]
Herrmann 2012 (10158)	15/182	10/187		2.63%	1.54[0.71,3.34]
Hofbauer 2009 (MD-71)	3/135	4/129		1.09%	0.72[0.16,3.14]
Holland 2013	4/22	4/21		1.09%	0.95[0.27,3.33]
Homma 2007 (IE2101)	8/100	15/108		3.84%	0.58[0.26,1.3]
Howard 2012 (DOMINO-AD)	20/149	24/146		6.45%	0.82[0.47,1.41]
Leroi 2009	1/11	0/14		0.12%	3.75[0.17,84.02]
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Lundbeck 2006 (10116)	6/128	5/130		1.32%	1.22[0.38,3.89]
Lundbeck 2006 (99817)	0/23	0/24			Not estimable
Marsh 2009 PDD	0/10	1/10		0.4%	0.33[0.02,7.32]
Merz 2003 (MRZ-9104)	0/27	0/29			Not estimable
Merz 2003 (MRZ-9105)	0/15	0/12			Not estimable
Merz 2003 (MRZ-9206)	0/28	0/28			Not estimable
Nakamura 2016	26/273	19/273		5.06%	1.37[0.78,2.41]
Orgogozo 2002 (9408)	19/165	20/156		5.47%	0.9[0.5,1.62]
Pantev 1993	0/30	0/30			Not estimable
Peskind 2004 (MD-10)	19/201	10/202		2.65%	1.91[0.91,4]
Peters 2015 (MEGACOMBI2)	19/112	14/114		3.69%	1.38[0.73,2.62]
Porsteinsson 2008 (MD-12)	13/217	17/216		4.53%	0.76[0.38,1.53]
Reisberg 2003 (9605)	13/126	22/126		5.85%	0.59[0.31,1.12]
Schifitto 2007	7/70	7/70		1.86%	1[0.37,2.7]
Schmidt 2008	2/18	2/18		0.53%	1[0.16,6.35]
Tariot 2004 (MD-02)	15/202	25/201		6.67%	0.6[0.32,1.1]
van Dyck 2007 (MD-01)	22/178	23/172		6.23%	0.92[0.54,1.6]
Vercelletto 2011	3/26	3/26		0.8%	1[0.22,4.5]
Wang 2013	0/13	0/13			Not estimable
Wilcock 2002 (9202)	27/295	20/284		5.42%	1.3[0.75,2.26]
Wilkinson 2012 (10112)	12/133	15/144		3.83%	0.87[0.42,1.78]
Total (95% CI)	**4591**	**4413**		**100%**	**1.06[0.92,1.21]**
Total events: 406 (Memantine), 373 (Placebo)					
Heterogeneity: $Tau^2=0$; $Chi^2=26.76$, df=30(P=0.64); $I^2=0\%$					
Test for overall effect: Z=0.81(P=0.42)					



Analysis 9.3. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 3 Number suffering at least one adverse event.

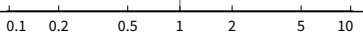
Study or subgroup	Memantine n/N	Placebol n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aarsland 2009	15/35	20/40		0.71%	0.86[0.52,1.4]
Asada 2011 (MA3301)	150/188	143/186		5.48%	1.04[0.93,1.15]
Asada 2011a (IE3501)	180/221	167/211		6.51%	1.03[0.94,1.13]
Bakchine 2008 (99679)	178/318	80/152		4.12%	1.06[0.89,1.27]
Boxer 2013	28/39	28/42		1.03%	1.08[0.81,1.44]
Ditzler 1991	0/32	0/34			Not estimable
Dysken 2014	97/155	89/152		3.42%	1.07[0.89,1.28]
Emre 2010 (11018)	46/96	43/99		1.61%	1.1[0.81,1.5]
Forest 2006 (MD-22)	124/133	129/132		4.93%	0.95[0.91,1.01]
Forest 2006 (MD-23)	12/17	8/17		0.3%	1.5[0.83,2.71]
Fox 2012 (MAGD)	0/74	0/79			Not estimable
Gortelmeyer 1992	25/41	18/41		0.69%	1.39[0.91,2.12]
Grossberg 2008 (MD-50)	214/341	214/335		8.22%	0.98[0.88,1.1]
Herrmann 2012 (10158)	138/182	136/187		5.11%	1.04[0.92,1.18]
Hofbauer 2009 (MD-71)	66/135	64/129		2.49%	0.99[0.77,1.26]
Holland 2013	6/22	9/21		0.35%	0.64[0.27,1.48]
Homma 2007 (IE2101)	72/100	78/108		2.86%	1[0.84,1.18]
Howard 2012 (DOMINO-AD)	0/149	0/146			Not estimable
Leroi 2009	6/11	9/14		0.3%	0.85[0.44,1.65]
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Lundbeck 2006 (10116)	19/128	23/130		0.87%	0.84[0.48,1.46]
Lundbeck 2006 (99817)	0/23	0/24			Not estimable
Marsh 2009 PDD	0/10	0/10			Not estimable
Merz 2003 (MRZ-9104)	0/27	0/29			Not estimable
Merz 2003 (MRZ-9105)	0/15	0/12			Not estimable
Merz 2003 (MRZ-9206)	0/28	0/28			Not estimable
Nakamura 2016	186/273	169/273		6.44%	1.1[0.97,1.25]
Orgogozo 2002 (9408)	125/165	115/156		4.5%	1.03[0.9,1.17]
Pantev 1993	0/30	0/30			Not estimable
Peskind 2004 (MD-10)	142/201	149/202		5.66%	0.96[0.85,1.08]
Peters 2015 (MEGACOMBI2)	89/112	80/114		3.02%	1.13[0.97,1.32]
Porsteinsson 2008 (MD-12)	173/217	168/216		6.41%	1.03[0.93,1.13]
Reisberg 2003 (9605)	106/126	109/126		4.15%	0.97[0.88,1.08]
Schifitto 2007	0/54	0/52			Not estimable
Schmidt 2008	17/18	13/15		0.54%	1.09[0.87,1.37]
Tariot 2004 (MD-02)	158/202	144/201		5.5%	1.09[0.97,1.22]
van Dyck 2007 (MD-01)	131/178	125/172		4.84%	1.01[0.89,1.15]
Vercelletto 2011	8/26	10/26		0.38%	0.8[0.38,1.7]
Wang 2013	0/13	0/13			Not estimable
Wilcock 2002 (9202)	226/295	212/284		8.23%	1.03[0.94,1.13]
Wilkinson 2012 (10112)	46/133	36/144		1.32%	1.38[0.96,2]
Total (95% CI)	**4570**	**4390**		**100%**	**1.03[1,1.06]**
Total events: 2783 (Memantine), 2588 (Placebol)					
Heterogeneity: Tau^2=0; Chi^2=25.58, df=28(P=0.6); I^2=0%					
Test for overall effect: Z=2.12(P=0.03)					



Favours memantine — Favours placebo

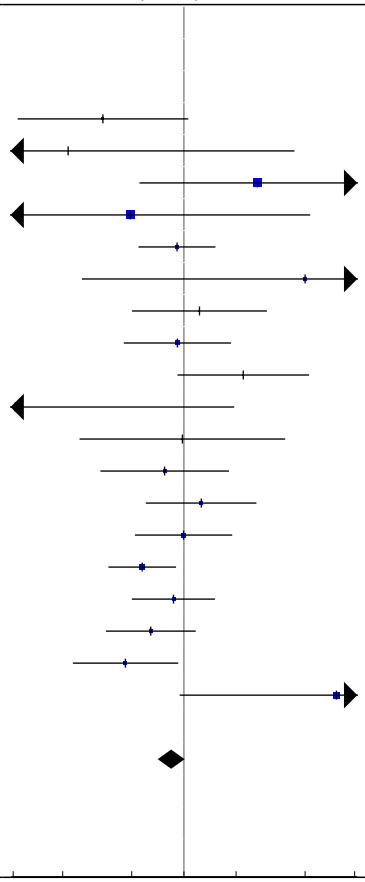
Analysis 9.4. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 4 Number suffering serious adverse events.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aarsland 2009	0/35	0/40			Not estimable
Asada 2011 (MA3301)	14/188	11/186		1.85%	1.26[0.59,2.7]
Asada 2011a (IE3501)	26/221	24/211		4.11%	1.03[0.61,1.74]
Bakchine 2008 (99679)	33/318	9/152		2.04%	1.75[0.86,3.57]
Boxer 2013	1/39	2/42		0.32%	0.54[0.05,5.71]
Ditzler 1991	0/32	0/34			Not estimable
Dysken 2014	84/155	95/152		16.05%	0.87[0.72,1.05]
Emre 2010 (11018)	14/96	10/99		1.65%	1.44[0.67,3.09]
Forest 2006 (MD-22)	24/133	38/132		6.38%	0.63[0.4,0.98]
Forest 2006 (MD-23)	3/17	2/17		0.33%	1.5[0.29,7.87]
Fox 2012 (MAGD)	0/74	0/79			Not estimable
Gortelmeyer 1992	0/41	0/41			Not estimable
Grossberg 2008 (MD-50)	28/341	21/335		3.54%	1.31[0.76,2.26]
Herrmann 2012 (10158)	18/182	11/187		1.82%	1.68[0.82,3.46]
Hofbauer 2009 (MD-71)	4/135	13/129		2.22%	0.29[0.1,0.88]
Holland 2013	2/22	3/21		0.51%	0.64[0.12,3.44]
Homma 2007 (IE2101)	7/100	11/108		1.77%	0.69[0.28,1.7]
Howard 2012 (DOMINO-AD)	59/149	64/146		10.82%	0.9[0.69,1.18]
Leroi 2009	1/11	1/14		0.15%	1.27[0.09,18.14]
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Lundbeck 2006 (10116)	4/128	4/130		0.66%	1.02[0.26,3.97]
Lundbeck 2006 (99817)	0/23	0/24			Not estimable
Marsh 2009 PDD	0/10	0/10			Not estimable
Merz 2003 (MRZ-9104)	0/27	0/29			Not estimable
Merz 2003 (MRZ-9105)	0/15	0/12			Not estimable
Merz 2003 (MRZ-9206)	0/28	0/28			Not estimable
Nakamura 2016	17/273	20/273		3.35%	0.85[0.46,1.59]
Orgogozo 2002 (9408)	38/165	40/156		6.88%	0.9[0.61,1.32]
Pantev 1993	0/30	0/30			Not estimable
Peskind 2004 (MD-10)	20/201	20/202		3.34%	1[0.56,1.81]
Peters 2015 (MEGACOMBI2)	15/112	15/114		2.49%	1.02[0.52,1.98]
Porsteinsson 2008 (MD-12)	27/217	30/216		5.03%	0.9[0.55,1.45]
Reisberg 2003 (9605)	16/126	23/126		3.85%	0.7[0.39,1.25]
Schifitto 2007	0/54	0/52			Not estimable
Schmidt 2008	0/18	0/15			Not estimable
Tariot 2004 (MD-02)	25/202	20/201		3.35%	1.24[0.71,2.17]
van Dyck 2007 (MD-01)	26/178	29/172		4.93%	0.87[0.53,1.41]
Vercelletto 2011	6/26	8/26		1.34%	0.75[0.3,1.86]
Wang 2013	0/13	0/13			Not estimable
Wilcock 2002 (9202)	37/295	47/284		8.01%	0.76[0.51,1.13]
Wilkinson 2012 (10112)	17/133	20/144		3.21%	0.92[0.5,1.68]
Total (95% CI)	**4570**	**4390**		**100%**	**0.92[0.83,1.02]**
Total events: 566 (Treatment), 591 (Control)					
Heterogeneity: Tau^2=0; Chi^2=21.62, df=26(P=0.71); I^2=0%					
Test for overall effect: Z=1.57(P=0.12)					



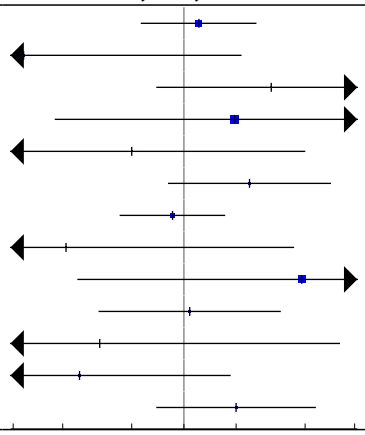
Analysis 9.5. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 5 Number suffering agitation as an adverse event.

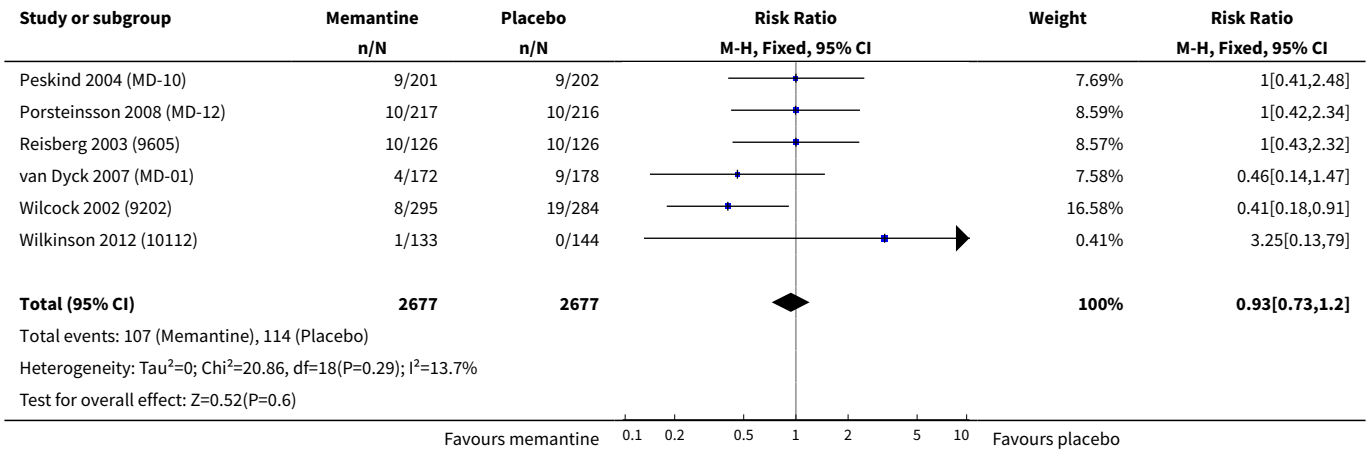
Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Aarsland 2009	0/35	0/40			Not estimable
Asada 2011 (MA3301)	0/188	0/186			Not estimable
Asada 2011a (IE3501)	0/221	0/211			Not estimable
Bakchine 2008 (99679)	5/318	7/152		4.07%	0.34[0.11,1.06]
Boxer 2013	0/39	2/42		1.04%	0.22[0.01,4.34]
Ditzler 1991	5/32	2/34		0.83%	2.66[0.55,12.73]
Dysken 2014	1/155	2/152		0.87%	0.49[0.04,5.35]
Forest 2006 (MD-22)	23/133	25/132		10.8%	0.91[0.55,1.52]
Forest 2006 (MD-23)	2/17	0/17		0.22%	5[0.26,97]
Gortelmeyer 1992	9/45	7/43		3.08%	1.23[0.5,3.01]
Grossberg 2008 (MD-50)	14/341	15/335		6.51%	0.92[0.45,1.87]
Herrmann 2012 (10158)	15/182	7/187		2.97%	2.2[0.92,5.27]
Hofbauer 2009 (MD-71)	0/135	4/129		1.98%	0.11[0.01,1.95]
Howard 2012 (DOMINO-AD)	4/149	4/146		1.74%	0.98[0.25,3.84]
Orgogozo 2002 (9408)	9/165	11/156		4.86%	0.77[0.33,1.82]
Peskind 2004 (MD-10)	15/201	12/202		5.15%	1.26[0.6,2.62]
Porsteinsson 2008 (MD-12)	17/217	17/216		7.33%	1[0.52,1.9]
Reisberg 2003 (9605)	23/126	40/126		17.21%	0.57[0.37,0.9]
Tariot 2004 (MD-02)	21/202	24/201		10.35%	0.87[0.5,1.51]
van Dyck 2007 (MD-01)	16/178	24/172		10.5%	0.64[0.35,1.17]
Wilcock 2002 (9202)	11/295	23/284		10.08%	0.46[0.23,0.93]
Wilkinson 2012 (10112)	7/133	1/144		0.41%	7.58[0.94,60.79]
Total (95% CI)	**3507**	**3307**		**100%**	**0.84[0.71,1.01]**
Total events: 197 (Memantine), 227 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=26.5, df=18(P=0.09); I^2=32.07%					
Test for overall effect: Z=1.87(P=0.06)					



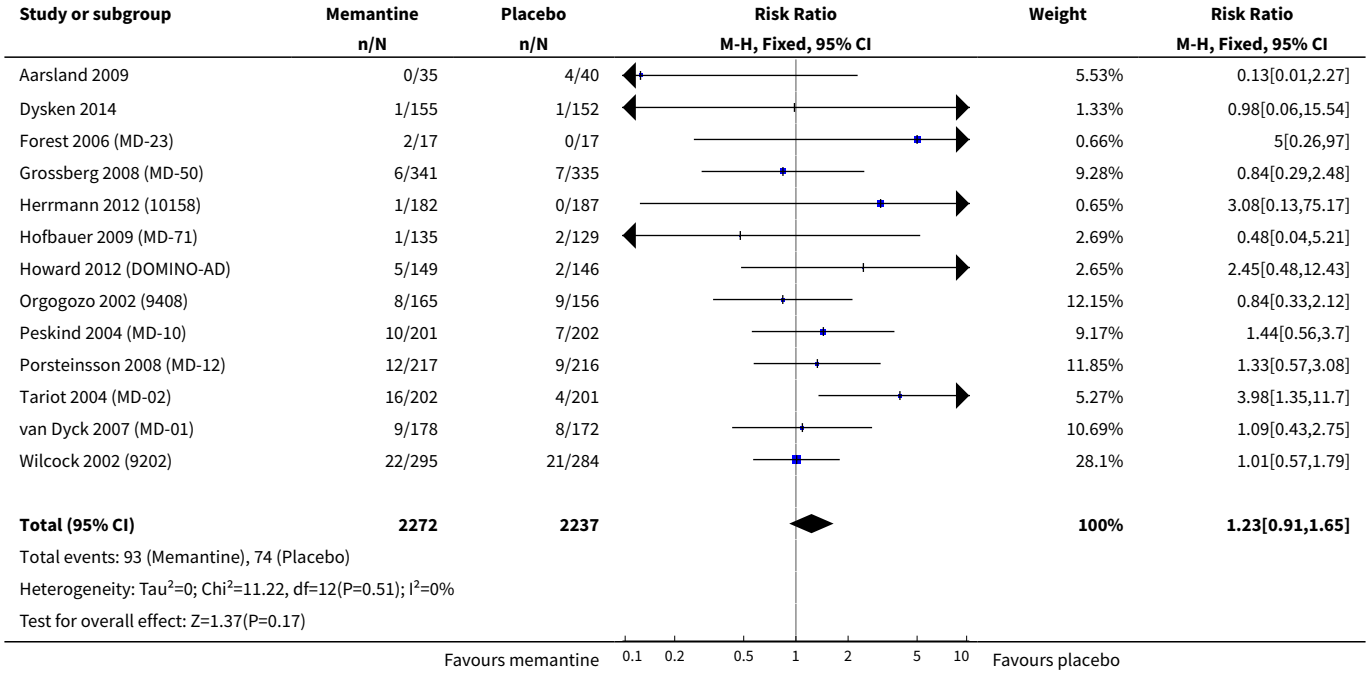
Analysis 9.6. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 6 Number suffering insomnia as an adverse event.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asada 2011a (IE3501)	14/221	11/211		9.64%	1.22[0.56,2.62]
Boxer 2013	0/39	4/42		3.72%	0.12[0.01,2.15]
Ditzler 1991	6/32	2/34		1.66%	3.19[0.69,14.66]
Dysken 2014	2/155	1/152		0.86%	1.96[0.18,21.4]
Forest 2006 (MD-23)	1/17	2/17		1.71%	0.5[0.05,5.01]
Gortelmeyer 1992	10/45	4/43		3.5%	2.39[0.81,7.05]
Grossberg 2008 (MD-50)	14/341	16/335		13.83%	0.86[0.43,1.73]
Hofbauer 2009 (MD-71)	0/129	2/135		2.09%	0.21[0.01,4.32]
Holland 2013	2/22	0/21		0.44%	4.78[0.24,94.12]
Homma 2007 (IE2101)	5/100	5/108		4.12%	1.08[0.32,3.62]
Howard 2012 (DOMINO-AD)	0/149	1/146		1.3%	0.33[0.01,7.95]
Marsh 2009 PDD	1/10	4/10		3.43%	0.25[0.03,1.86]
Nakamura 2016	10/273	5/273		4.28%	2[0.69,5.77]

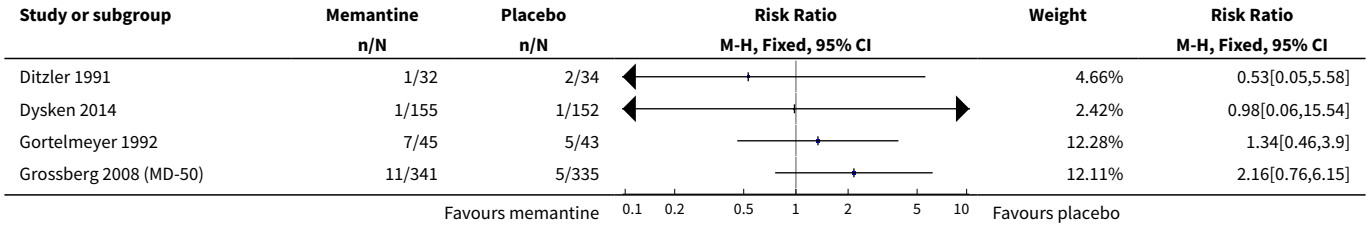


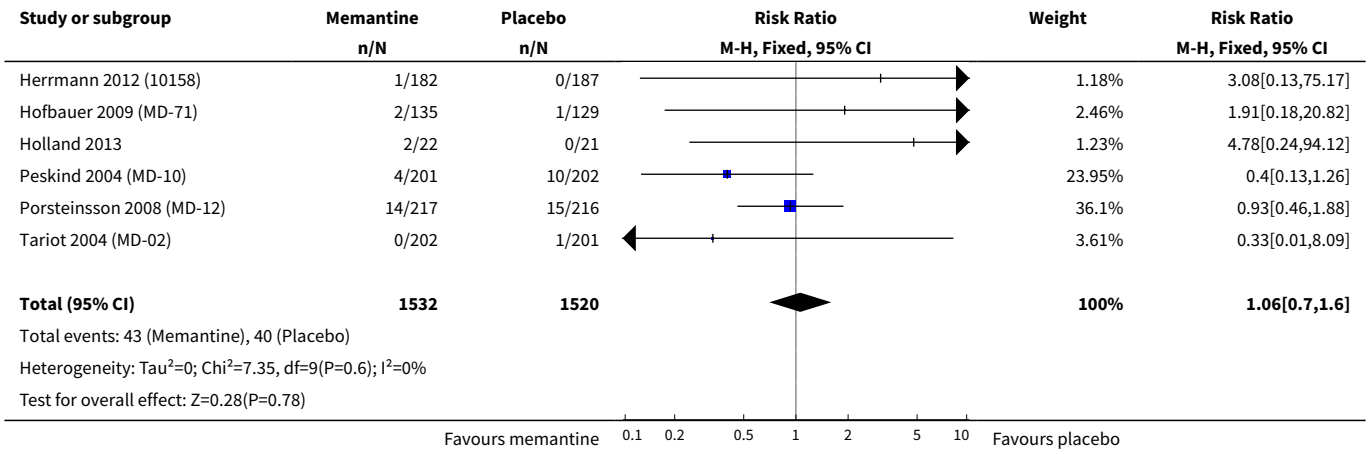


Analysis 9.7. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 7 Number suffering confusion as an adverse event.

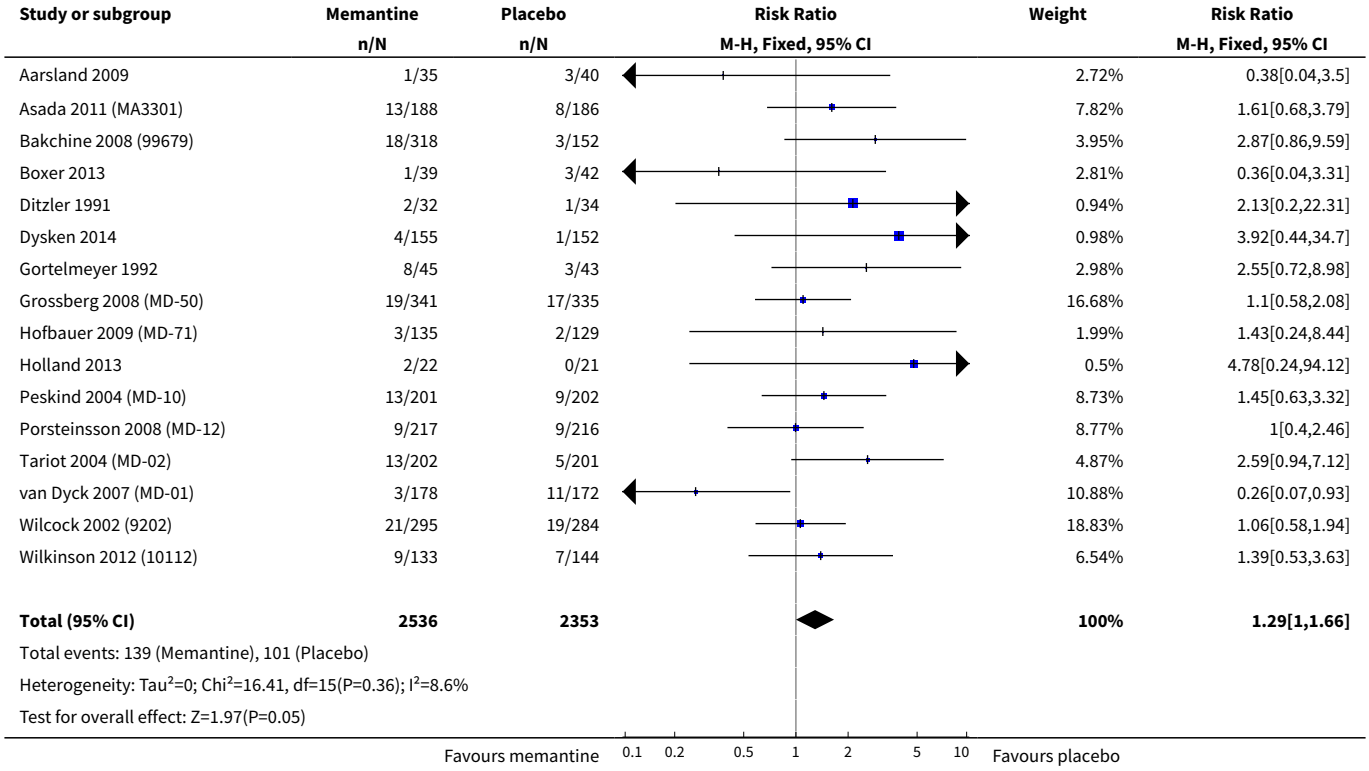


Analysis 9.8. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 8 Number suffering depression as an adverse event.

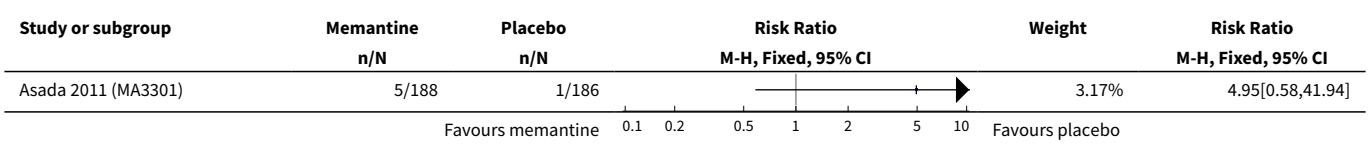


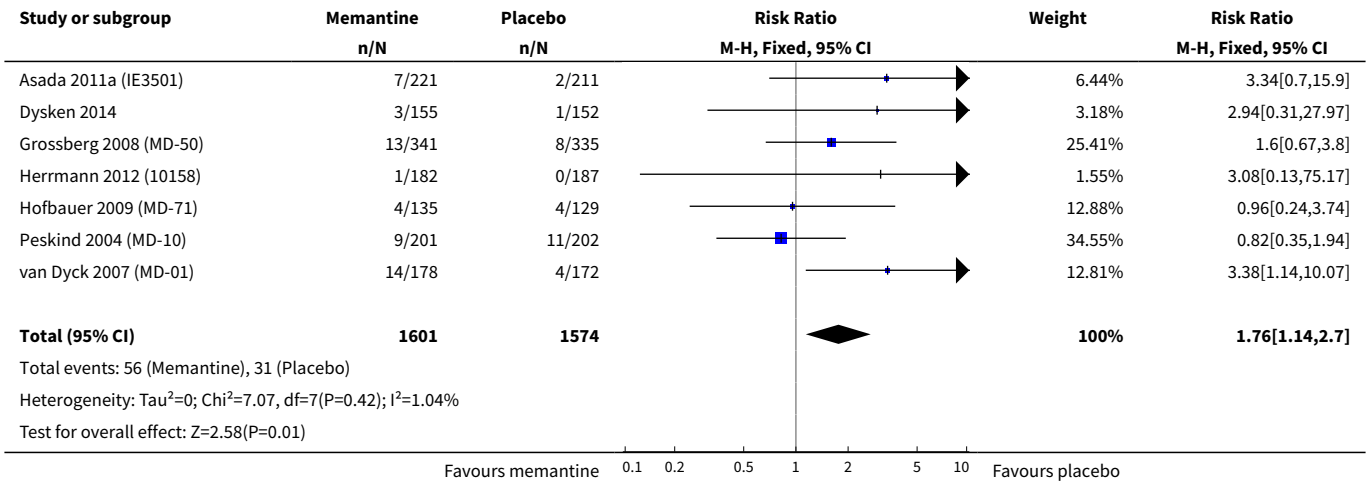


Analysis 9.9. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 9 Number suffering headache as an adverse event.

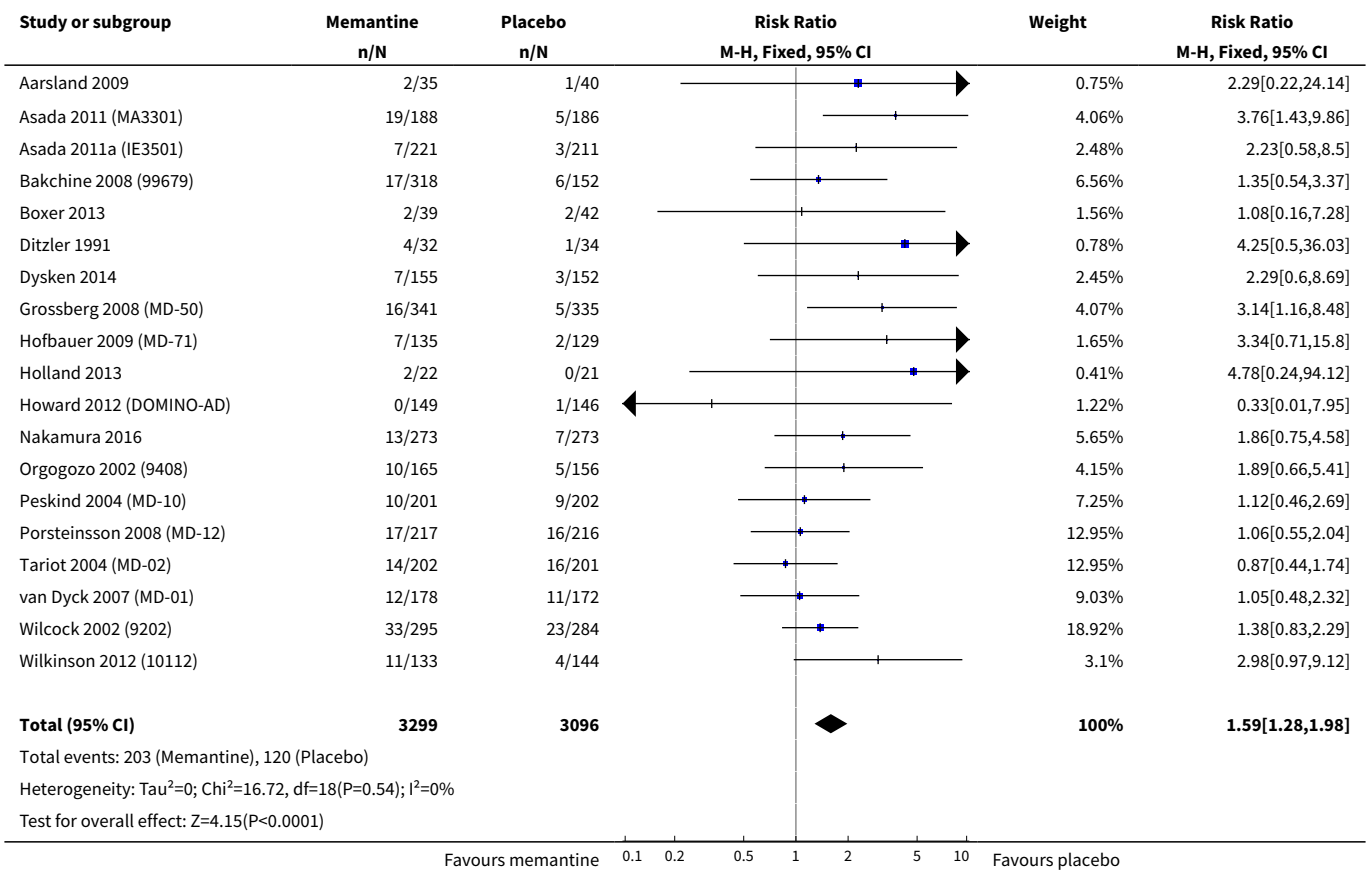


Analysis 9.10. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 10 Number suffering hypertension as an adverse event.



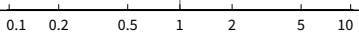


Analysis 9.11. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 11 Number suffering dizziness as an adverse event.



Analysis 9.12. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 12 Number suffering falls as an adverse event.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asada 2011 (MA3301)	15/188	14/186		4.72%	1.06[0.53,2.13]
Asada 2011a (IE3501)	25/221	25/211		8.57%	0.95[0.57,1.61]
Boxer 2013	5/39	2/42		0.65%	2.69[0.55,13.08]
Dysken 2014	28/155	31/152		10.49%	0.89[0.56,1.4]
Emre 2010 (11018)	8/96	8/99		2.64%	1.03[0.4,2.64]
Forest 2006 (MD-22)	46/133	47/132		15.81%	0.97[0.7,1.35]
Forest 2006 (MD-23)	2/17	1/17		0.34%	2[0.2,20.04]
Grossberg 2008 (MD-50)	19/341	26/335		8.79%	0.72[0.41,1.27]
Herrmann 2012 (10158)	19/182	8/187		2.65%	2.44[1.1,5.43]
Hofbauer 2009 (MD-71)	4/135	4/129		1.37%	0.96[0.24,3.74]
Homma 2007 (IE2101)	6/100	8/108		2.58%	0.81[0.29,2.25]
Howard 2012 (DOMINO-AD)	10/149	12/146		4.06%	0.82[0.36,1.83]
Nakamura 2016	8/273	11/273		3.69%	0.73[0.3,1.78]
Peskind 2004 (MD-10)	15/201	15/202		5.02%	1[0.5,2]
Porsteinsson 2008 (MD-12)	22/217	15/216		5.04%	1.46[0.78,2.74]
Reisberg 2003 (9605)	9/126	9/126		3.02%	1[0.41,2.44]
Tariot 2004 (MD-02)	15/202	14/201		4.7%	1.07[0.53,2.15]
van Dyck 2007 (MD-01)	10/178	17/172		5.8%	0.57[0.27,1.21]
Wilcock 2002 (9202)	18/295	21/284		7.17%	0.83[0.45,1.52]
Wilkinson 2012 (10112)	8/133	9/144		2.9%	0.96[0.38,2.42]
Total (95% CI)	**3381**	**3362**		**100%**	**0.98[0.84,1.13]**
Total events: 292 (Memantine), 297 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=13, df=19(P=0.84); I^2=0%					
Test for overall effect: Z=0.32(P=0.75)					



Favours memantine — Favours placebo

Analysis 9.13. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 13 Number suffering accidental injury as an adverse event.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bakchine 2008 (99679)	16/318	8/152		9.22%	0.96[0.42,2.18]
Dysken 2014	1/155	1/152		0.86%	0.98[0.06,15.54]
Howard 2012 (DOMINO-AD)	0/149	1/146		1.29%	0.33[0.01,7.95]
Orgogozo 2002 (9408)	5/165	6/156		5.26%	0.79[0.25,2.53]
Peskind 2004 (MD-10)	12/201	11/202		9.35%	1.1[0.5,2.43]
Porsteinsson 2008 (MD-12)	20/217	16/216		13.66%	1.24[0.66,2.34]
Reisberg 2003 (9605)	10/126	11/126		9.37%	0.91[0.4,2.06]
Tariot 2004 (MD-02)	10/202	16/201		13.67%	0.62[0.29,1.34]
van Dyck 2007 (MD-01)	10/178	13/172		11.27%	0.74[0.33,1.65]
Wilcock 2002 (9202)	17/295	30/284		26.05%	0.55[0.31,0.97]
Total (95% CI)	**2006**	**1807**		**100%**	**0.81[0.62,1.05]**
Total events: 101 (Memantine), 113 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.24, df=9(P=0.81); I^2=0%					
Test for overall effect: Z=1.58(P=0.12)					

Favours memantine — Favours placebo

Analysis 9.14. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 14 Number suffering urinary incontinence as an adverse event.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dysken 2014	1/155	0/152		1.36%	2.94[0.12,71.67]
Homma 2007 (IE2101)	1/100	3/108		7.76%	0.36[0.04,3.4]
Howard 2012 (DOMINO-AD)	2/149	2/146		5.43%	0.98[0.14,6.86]
Peskind 2004 (MD-10)	0/201	1/202		4.02%	0.33[0.01,8.17]
Reisberg 2003 (9605)	14/126	14/126		37.64%	1[0.5,2.01]
Tariot 2004 (MD-02)	11/202	6/201		16.17%	1.82[0.69,4.84]
Wilcock 2002 (9202)	11/284	9/295		23.74%	1.27[0.53,3.02]
Wilkinson 2012 (10112)	0/133	1/144		3.87%	0.36[0.01,8.78]
Total (95% CI)	**1350**	**1374**		**100%**	**1.12[0.73,1.72]**
Total events: 40 (Memantine), 36 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=3.52, df=7(P=0.83); I^2=0%					
Test for overall effect: Z=0.52(P=0.6)					

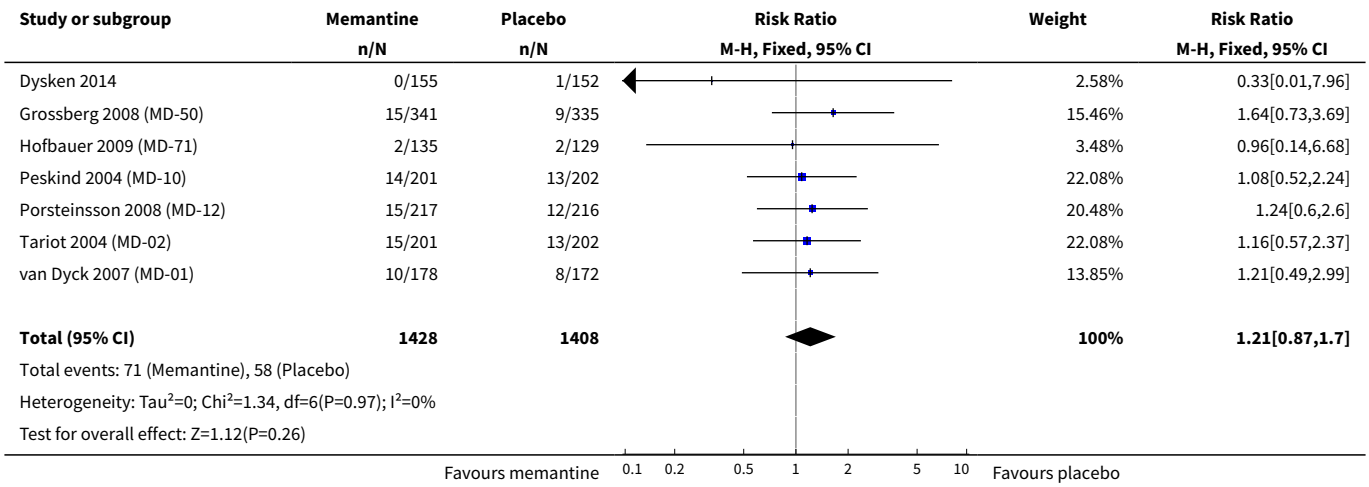
Favours memantine — Favours placebo

Analysis 9.15. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 15 Number suffering diarrhoea as an adverse event.

Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Asada 2011 (MA3301)	9/188	13/186		7.48%	0.68[0.3,1.56]
Asada 2011a (IE3501)	10/221	13/211		7.62%	0.73[0.33,1.64]
Dysken 2014	4/155	5/152		2.89%	0.78[0.21,2.87]
Forest 2006 (MD-22)	19/133	20/132		11.5%	0.94[0.53,1.68]
Forest 2006 (MD-23)	2/17	1/17		0.57%	2[0.2,20.04]
Gortelmeyer 1992	2/45	10/43		5.86%	0.19[0.04,0.82]
Grossberg 2008 (MD-50)	17/341	13/335		7.51%	1.28[0.63,2.6]
Hofbauer 2009 (MD-71)	2/135	5/129		2.93%	0.38[0.08,1.94]
Homma 2007 (IE2101)	3/100	2/108		1.1%	1.62[0.28,9.5]
Howard 2012 (DOMINO-AD)	2/149	6/146		3.47%	0.33[0.07,1.59]
Nakamura 2016	8/273	10/273		5.73%	0.8[0.32,2]
Peskind 2004 (MD-10)	9/201	5/202		2.86%	1.81[0.62,5.3]
Porsteinsson 2008 (MD-12)	12/217	14/216		8.04%	0.85[0.4,1.8]
Reisberg 2003 (9605)	12/126	10/126		5.73%	1.2[0.54,2.68]
Tariot 2004 (MD-02)	9/202	17/201		9.76%	0.53[0.24,1.15]
van Dyck 2007 (MD-01)	8/172	10/178		5.63%	0.83[0.33,2.05]
Wilcock 2002 (9202)	12/295	10/284		5.84%	1.16[0.51,2.63]
Wilkinson 2012 (10112)	4/133	10/144		5.5%	0.43[0.14,1.35]
Total (95% CI)	**3103**	**3083**		**100%**	**0.82[0.66,1.02]**
Total events: 144 (Memantine), 174 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=15.21, df=17(P=0.58); I^2=0%					
Test for overall effect: Z=1.8(P=0.07)					

Favours memantine — Favours placebo

Analysis 9.16. Comparison 9 Adverse reactions: memantine vs placebo for mild to severe dementia. All diagnoses, all durations, Outcome 16 Number suffering influenza like symptoms as an adverse event.



Comparison 10. APPENDIX 3: Comparison of LOCF and OC analyses: memantine 20 mg or equivalent versus placebo for Alzheimer's disease. 24-to 30-week data

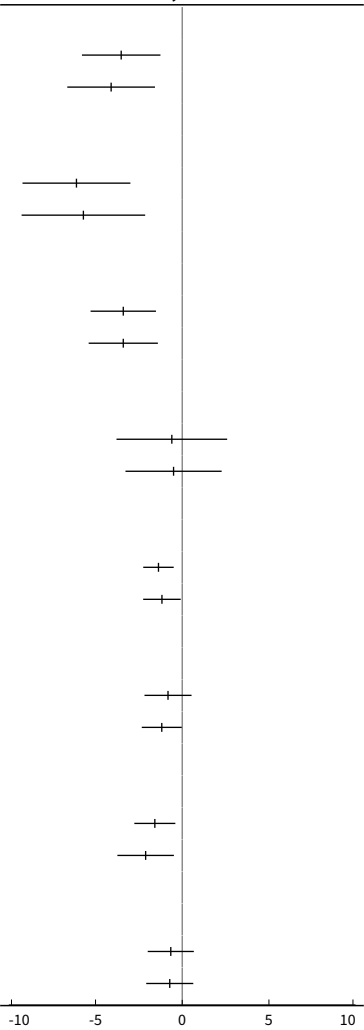
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Cognitive function	11		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.1 1) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.2 2) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.3 3) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.4 4) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.5 PP then Retrieved dropout	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 PP then retrieved dropout - AChEI only	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.7 PP then Retrieved dropout - no AChEI	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.8 5) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.9 6) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.10 7) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.11 OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.12 OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.13 Per protocol then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Decline in ADL: ADCS-ADL19/23	10		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
2.1 1) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.2 2) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.3 3) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.4 4) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 5) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.6 6) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.7 7) OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.8 PP then Retrieved Dropout	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.9 PP then Retrieved Dropout - AChEI only	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.10 PP then Retrieved dropout - no AChEI	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.11 OC then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.12 Per protocol then LOCF	1		Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Cognitive Function: SIB/ADASCog/ MMSE	17		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.1 OC	12	2901	Std. Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.33, -0.19]
3.2 LOCF	8	3066	Std. Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.33, -0.18]
3.3 Missing at random assumption	2	203	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.47, 0.08]
3.4 Per protocol	1	143	Std. Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.69, -0.03]
3.5 Retrieved dropout	1	246	Std. Mean Difference (IV, Fixed, 95% CI)	-0.39 [-0.64, -0.14]
4 Decline in Activities of Daily Living	14		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 OC only	10	2874	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.19, -0.03]

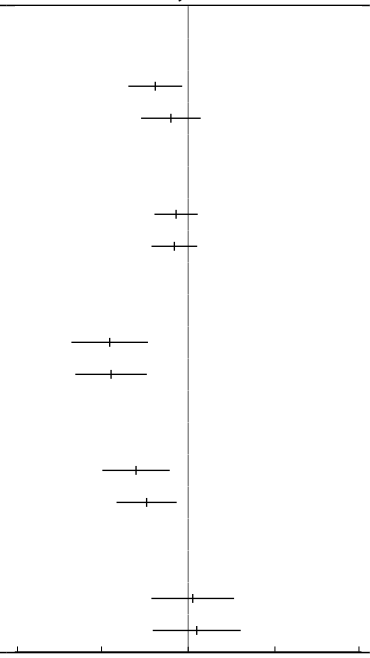
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4.2 LOCF	6	2107	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.21, -0.04]
4.3 Missing at random assumption	2	203	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.29, 0.26]
4.4 Per protocol	1	143	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.50, 0.16]
4.5 Retrieved dropout	1	246	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.47, 0.03]

Analysis 10.1. Comparison 10 APPENDIX 3: Comparison of LOCF and OC analyses: memantine 20 mg or equivalent versus placebo for Alzheimer's disease. 24-to 30-week data, Outcome 1 Cognitive function.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
10.1.1 1) OC then LOCF						
Homma 2007 (IE2101)	100	-0.1 (6.5)	107	3.4 (9.8)		-3.52[-5.78,-1.26]
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		-4.1[-6.63,-1.57]
10.1.2 2) OC then LOCF						
Reisberg 2003 (9605)	124	4 (11.3)	123	10.1 (13.5)		-6.1[-9.21,-2.99]
Reisberg 2003 (9605)	96	4.5 (11.5)	83	10.2 (12.7)		-5.7[-9.26,-2.14]
10.1.3 3) OC then LOCF						
Tariot 2004 (MD-02)	198	-0.9 (9.4)	196	2.5 (9.7)		-3.4[-5.29,-1.51]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		-3.4[-5.4,-1.4]
10.1.4 4) OC then LOCF						
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		-0.6[-3.79,2.59]
van Dyck 2007 (MD-01)	170	2 (13)	165	2.5 (12.9)		-0.5[-3.27,2.27]
10.1.5 PP then Retrieved dropout						
Howard 2012 (DOMINO-AD)	123	1.9 (3.3)	123	3.3 (3.7)		-1.37[-2.25,-0.49]
Howard 2012 (DOMINO-AD)	77	1.2 (2.6)	66	2.4 (3.8)		-1.17[-2.25,-0.09]
10.1.6 PP then retrieved dropout - AChEI only						
Howard 2012 (DOMINO-AD)	40	0.6 (2.7)	41	1.4 (3.5)		-0.82[-2.18,0.54]
Howard 2012 (DOMINO-AD)	63	0.8 (3.1)	63	1.9 (3.5)		-1.18[-2.33,-0.03]
10.1.7 PP then Retrieved dropout - no AChEI						
Howard 2012 (DOMINO-AD)	60	3.1 (3.2)	60	4.6 (3.4)		-1.58[-2.76,-0.4]
Howard 2012 (DOMINO-AD)	37	1.9 (2.5)	25	4 (3.6)		-2.11[-3.74,-0.48]
10.1.8 5) OC then LOCF						
Bakchine 2008 (99679)	311	-1.7 (7.2)	151	-1 (6.6)		-0.66[-1.99,0.67]
Bakchine 2008 (99679)	271	-1.8 (6.9)	137	-1 (6.4)		-0.72[-2.08,0.64]

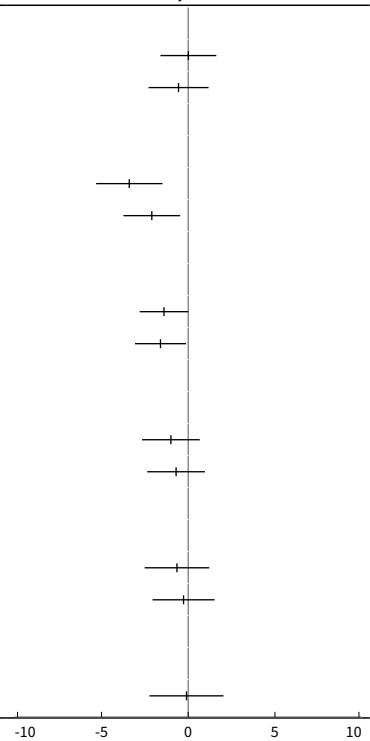


Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
10.1.9 6) OC then LOCF						
Peskind 2004 (MD-10)	195	-0.8 (7.8)	198	1.1 (7.9)		-1.9[-3.45,-0.35]
Peskind 2004 (MD-10)	160	0 (7.8)	162	1 (7.9)		-1[-2.72,0.72]
10.1.10 7) OC then LOCF						
Porsteinsson 2008 (MD-12)	212	0.1 (6.6)	212	0.8 (6.6)		-0.7[-1.95,0.55]
Porsteinsson 2008 (MD-12)	190	0 (6.6)	187	0.8 (6.4)		-0.8[-2.12,0.52]
10.1.11 OC then LOCF						
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		-4.53[-6.74,-2.32]
Asada 2011a (IE3501)	218	0.4 (9.9)	206	4.9 (11.7)		-4.45[-6.51,-2.39]
10.1.12 OC then LOCF						
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		-3.01[-4.95,-1.07]
Grossberg 2008 (MD-50)	332	-2.7 (11.2)	327	-0.3 (11.5)		-2.4[-4.13,-0.67]
10.1.13 Per protocol then LOCF						
Peters 2015 (MEGACOMBI2)	94	2 (8.4)	96	1.8 (8.3)		0.26[-2.12,2.64]
Peters 2015 (MEGACOMBI2)	84	2.5 (8.3)	86	2 (8.5)		0.49[-2.05,3.03]

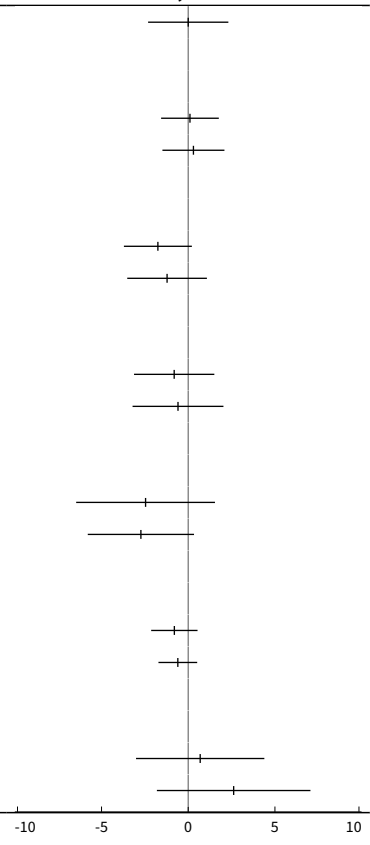


Analysis 10.2. Comparison 10 APPENDIX 3: Comparison of LOCF and OC analyses: memantine 20 mg or equivalent versus placebo for Alzheimer's disease. 24-to 30-week data, Outcome 2 Decline in ADL: ADCS-ADL19/23.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
10.2.1 1) OC then LOCF						
Homma 2007 (IE2101)	100	1.7 (6.2)	107	1.6 (5.6)		0.01[-1.6,1.62]
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		-0.56[-2.29,1.17]
10.2.2 2) OC then LOCF						
Reisberg 2003 (9605)	97	2.5 (6.3)	84	5.9 (6.8)		-3.4[-5.31,-1.49]
Reisberg 2003 (9605)	124	3.1 (6.8)	123	5.2 (6.3)		-2.1[-3.74,-0.46]
10.2.3 3) OC then LOCF						
Tariot 2004 (MD-02)	198	2 (7)	197	3.4 (7.2)		-1.4[-2.8,0]
Tariot 2004 (MD-02)	172	1.7 (6.7)	152	3.3 (6.8)		-1.6[-3.07,-0.13]
10.2.4 4) OC then LOCF						
van Dyck 2007 (MD-01)	133	1.3 (6.9)	127	2.3 (6.8)		-1[-2.66,0.66]
van Dyck 2007 (MD-01)	171	2 (7.9)	165	2.7 (7.7)		-0.7[-2.36,0.96]
10.2.5 5) OC then LOCF						
Bakchine 2008 (99679)	304	2.1 (9.9)	146	2.8 (9.2)		-0.65[-2.51,1.21]
Bakchine 2008 (99679)	270	2.1 (9.2)	137	2.4 (8.4)		-0.27[-2.06,1.52]
10.2.6 6) OC then LOCF						
Peskind 2004 (MD-10)	196	2.9 (10.8)	198	3 (10.8)		-0.1[-2.23,2.03]

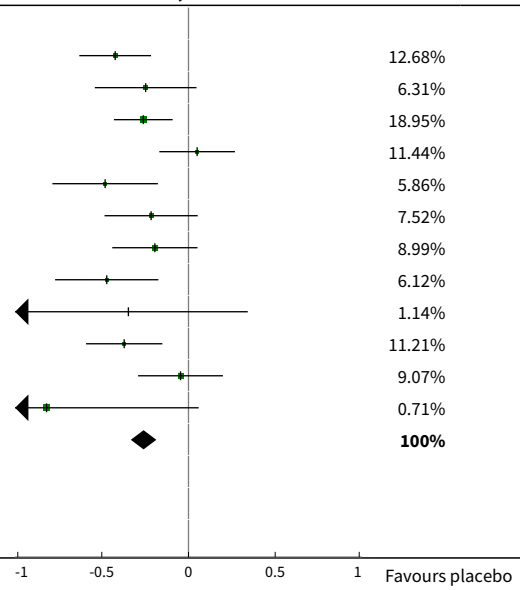


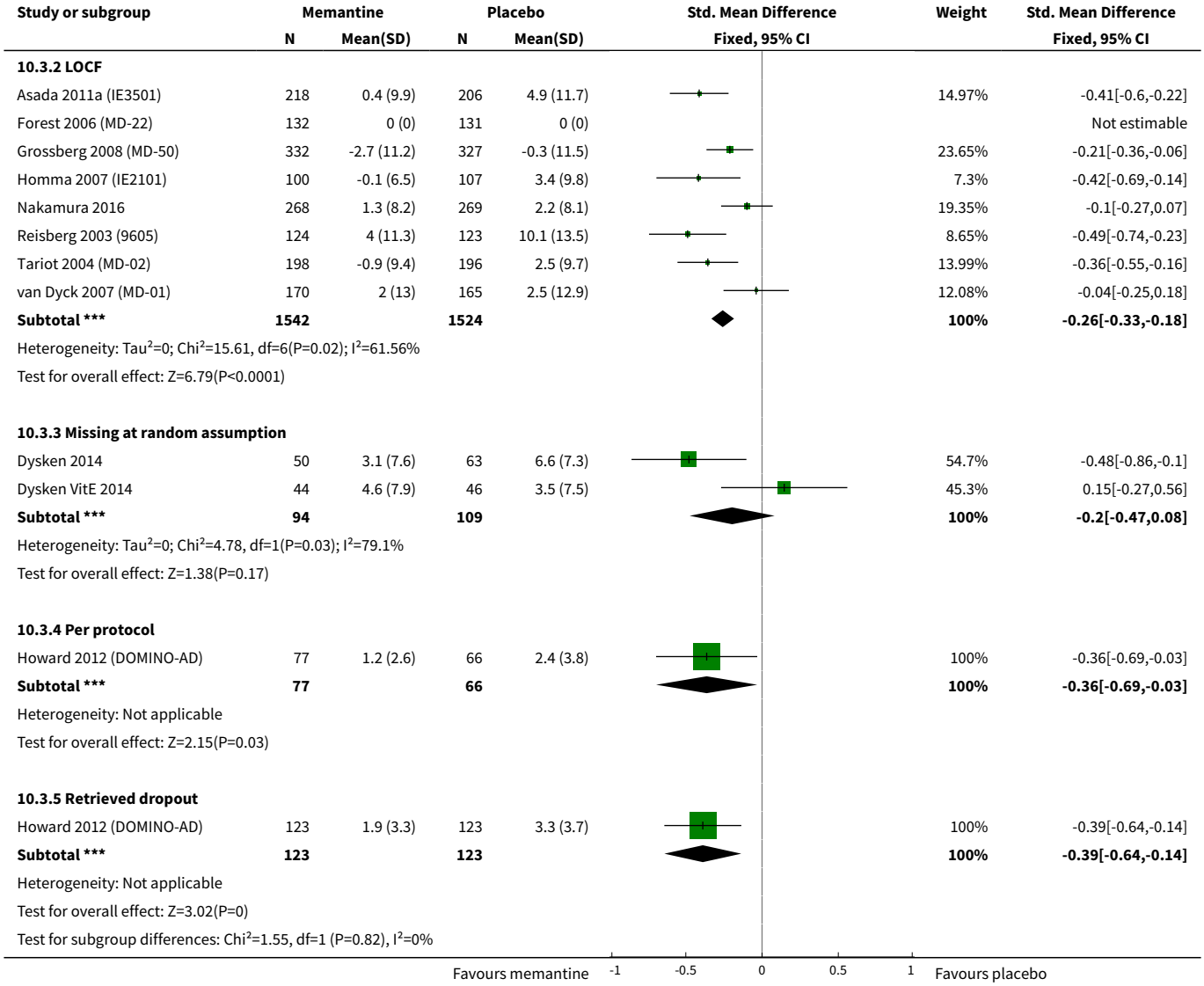
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Mean Difference Fixed, 95% CI	Mean Difference Fixed, 95% CI
Peskind 2004 (MD-10)	166	2.3 (10.7)	168	2.3 (10.9)		0[-2.31,2.31]
10.2.7 7) OC then LOCF						
Porsteinsson 2008 (MD-12)	214	3 (8.8)	213	2.9 (8.8)		0.1[-1.56,1.76]
Porsteinsson 2008 (MD-12)	193	2.4 (9)	189	2.1 (8.8)		0.3[-1.49,2.09]
10.2.8 PP then Retrieved Dropout						
Howard 2012 (DOMINO-AD)	123	5.6 (7.4)	123	7.3 (8.3)		-1.75[-3.71,0.21]
Howard 2012 (DOMINO-AD)	77	3.8 (6.9)	66	5 (7.1)		-1.22[-3.52,1.08]
10.2.9 PP then Retrieved Dropout - AChEI only						
Howard 2012 (DOMINO-AD)	63	4.2 (6)	63	5 (7.2)		-0.81[-3.13,1.51]
Howard 2012 (DOMINO-AD)	40	3.4 (5.3)	41	4 (6.7)		-0.59[-3.21,2.03]
10.2.10 PP then Retrieved dropout - no AChEI						
Howard 2012 (DOMINO-AD)	37	4.2 (8.4)	25	6.7 (7.6)		-2.46[-6.46,1.54]
Howard 2012 (DOMINO-AD)	60	7 (8.4)	60	9.7 (8.7)		-2.73[-5.79,0.33]
10.2.11 OC then LOCF						
Grossberg 2008 (MD-50)	268	0.3 (8.1)	272	1.1 (7.8)		-0.8[-2.14,0.54]
Grossberg 2008 (MD-50)	331	0.7 (6.9)	328	1.3 (7.7)		-0.6[-1.72,0.52]
10.2.12 Per protocol then LOCF						
Peters 2015 (MEGACOMBI2)	94	6.9 (12.9)	96	6.2 (13.1)		0.69[-3.01,4.39]
Peters 2015 (MEGACOMBI2)	66	8.5 (13.2)	70	5.9 (13.1)		2.62[-1.81,7.05]



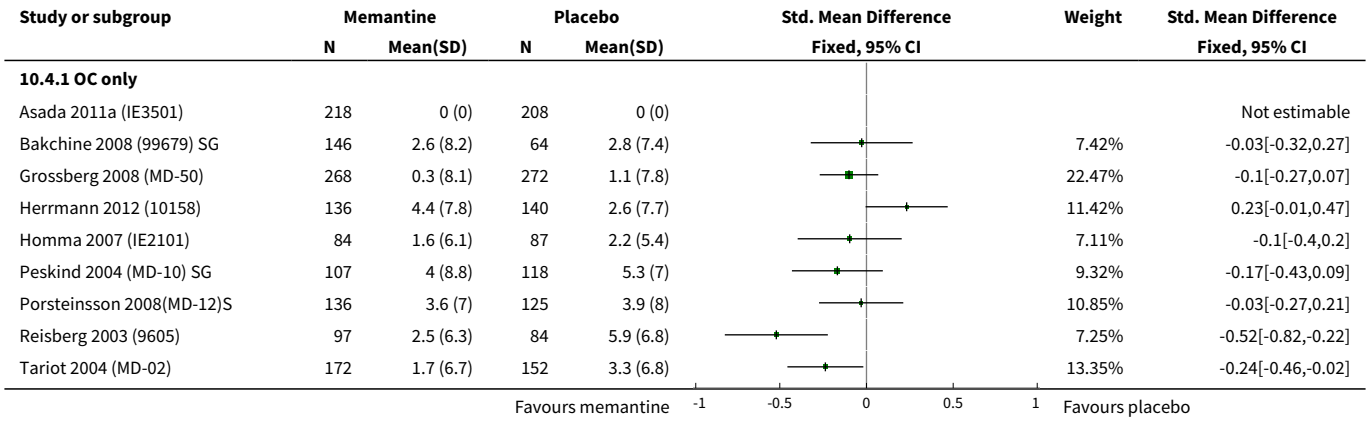
Analysis 10.3. Comparison 10 APPENDIX 3: Comparison of LOCF and OC analyses: memantine 20 mg or equivalent versus placebo for Alzheimer's disease. 24-to 30-week data, Outcome 3 Cognitive Function: SIB/ADASCog/MMSE.

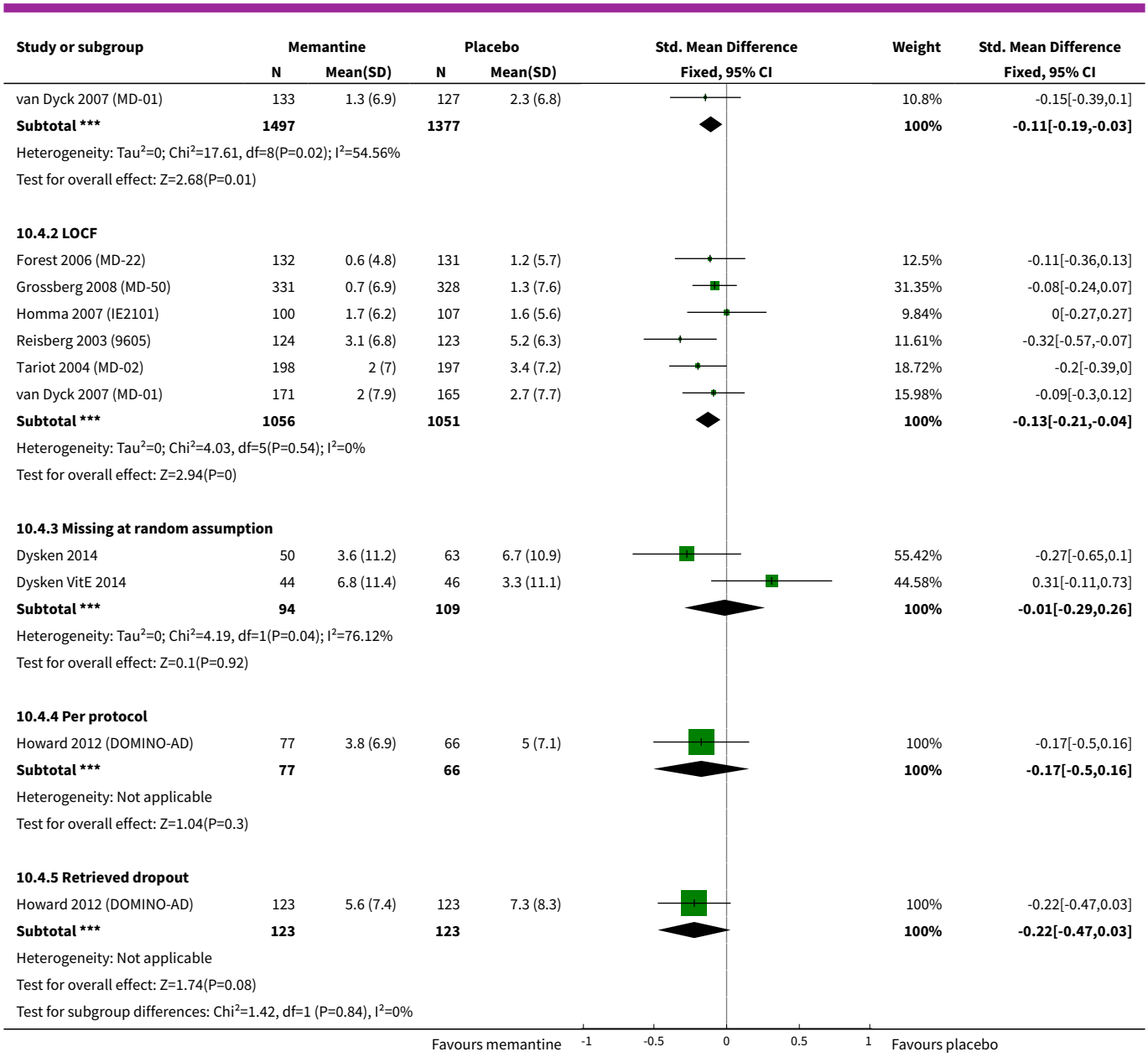
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
10.3.1 OC							
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		12.68%	-0.42[-0.63,-0.22]
Bakchine 2008 (99679) SG	146	-0.9 (6.4)	65	0.7 (6.4)		6.31%	-0.25[-0.54,0.05]
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		18.95%	-0.26[-0.43,-0.09]
Herrmann 2012 (10158)	159	2.3 (9.6)	165	1.9 (9.6)		11.44%	0.05[-0.17,0.27]
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		5.86%	-0.48[-0.78,-0.18]
Peskind 2004 (MD-10) SG	101	0.8 (5.9)	114	2.2 (7)		7.52%	-0.22[-0.48,0.05]
Porsteinsson 2008(MD-12)S	133	0.9 (6)	123	2 (5.8)		8.99%	-0.19[-0.44,0.05]
Reisberg 2003 (9605)	96	4.5 (11.5)	83	10.2 (12.7)		6.12%	-0.47[-0.77,-0.17]
Schmidt 2008	16	-2.2 (7.4)	17	0.4 (7.2)		1.14%	-0.35[-1.04,0.34]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		11.21%	-0.37[-0.59,-0.15]
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		9.07%	-0.05[-0.29,0.2]
Wang 2013	11	0 (7.2)	11	5.6 (5.9)		0.71%	-0.82[-1.7,0.06]
Subtotal ***	**1511**		**1390**			**100%**	**-0.26[-0.33,-0.19]**
Heterogeneity: Tau²=0; Chi²=20.03, df=11(P=0.04); I²=45.07%							
Test for overall effect: Z=6.89(P<0.0001)							





Analysis 10.4. Comparison 10 APPENDIX 3: Comparison of LOCF and OC analyses: memantine 20 mg or equivalent versus placebo for Alzheimer's disease. 24-to 30-week data, Outcome 4 Decline in Activities of Daily Living.





Comparison 11. APPENDIX 4: memantine vs placebo for mild to severe Alzheimer's disease. OC. 12-52 weeks

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical Global	24	5575	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.26, -0.14]
2 Cognitive Function	24	5670	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.24, -0.13]
3 Decline in ADL	24	5716	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.17, -0.04]

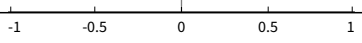
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
4 Behaviour and Mood	24	5718	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.19, -0.07]
5 Clinical Global - sensitivity analysis for high RoB	17	4552	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.26, -0.13]
6 Cognitive Function - sensitivity analysis for high risk of bias	19	5354	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.23, -0.12]
7 Decline in ADL - sensitivity analysis on high RoB	17	4837	Std. Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.15, -0.02]
8 Behaviour and Mood - sensitivity analysis on high RoB	17	5240	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.18, -0.06]

Analysis 11.1. Comparison 11 APPENDIX 4: memantine vs placebo for mild to severe Alzheimer's disease. OC. 12-52 weeks, Outcome 1 Clinical Global.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Asada 2011 (MA3301)	187	4.3 (1)	180	4.5 (1)		9.39%	-0.25[-0.45,-0.04]
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		9.44%	-0.11[-0.31,0.1]
Bakchine 2008 (99679)	270	4.1 (1.2)	138	4.2 (1.2)		9.42%	-0.05[-0.25,0.16]
Dysken 2014	140	0 (0)	137	0 (0)			Not estimable
Forest 2006 (MD-22)	131	3.6 (1.4)	129	3.8 (1.3)		6.68%	-0.15[-0.4,0.09]
Grossberg 2008 (MD-50)	269	3.8 (1.1)	272	4.1 (1.2)		13.83%	-0.26[-0.43,-0.09]
Hofbauer 2009 (MD-71)	133	-1.3 (5.9)	124	0 (5.9)		6.58%	-0.22[-0.47,0.03]
Holland 2013	13	0 (0)	13	0 (0)			Not estimable
Homma 2007 (IE2101)	84	4.4 (1.6)	87	4.7 (1.3)		4.38%	-0.22[-0.52,0.08]
Howard 2012 (DOMINO-AD)	77	0 (0)	58	0 (0)			Not estimable
Lundbeck 2006 (10116)	61	0 (0)	65	0 (0)			Not estimable
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Merz 2003 (MRZ-9104)	27	0 (0)	29	0 (0)			Not estimable
Nakamura 2016	268	0 (0)	269	0 (0)			Not estimable
Peskind 2004 (MD-10)	164	4.2 (1)	166	4.5 (1.1)		8.42%	-0.29[-0.5,-0.07]
Peters 2015 (MEGACOMBI2)	84	0 (0)	86	0 (0)			Not estimable
Porsteinsson 2008 (MD-12)	192	4.4 (1)	189	4.4 (1)		9.82%	-0.04[-0.24,0.16]
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		4.6%	-0.27[-0.56,0.03]
Schmidt 2008	15	0.3 (0.6)	12	0.5 (0.8)		0.68%	-0.28[-1.04,0.48]
Tariot 2004 (MD-02)	172	4.4 (1.1)	152	4.6 (1.1)		8.26%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	134	4.3 (1.1)	127	4.6 (1)		6.66%	-0.28[-0.53,-0.04]
Wang 2013	11	0 (0)	11	0 (0)			Not estimable
Wilkinson 2012 (10112)	110	0 (0)	118	0 (0)			Not estimable
Winblad 1999 (9403) AD	39	3.1 (0.6)	37	3.5 (0.6)		1.86%	-0.64[-1.11,-0.18]
Total ***	**2891**		**2684**			**100%**	**-0.2[-0.26,-0.14]**

Heterogeneity: Tau²=0; Chi²=11.21, df=13(P=0.59); I²=0%

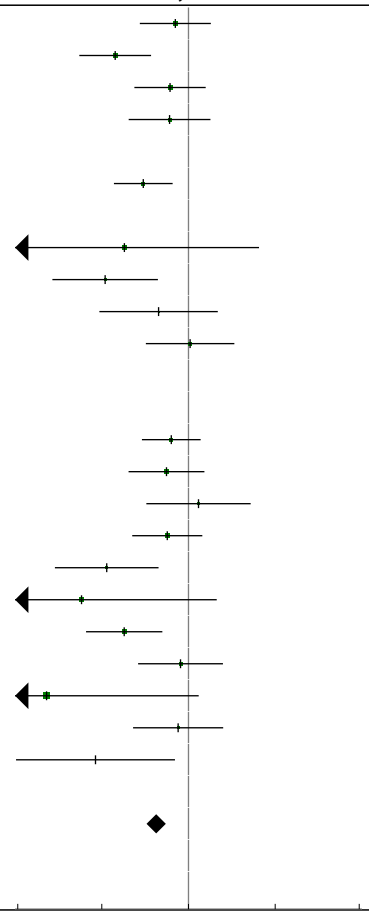
Test for overall effect: Z=6.27(P<0.0001)



Favours memantine — Favours placebo

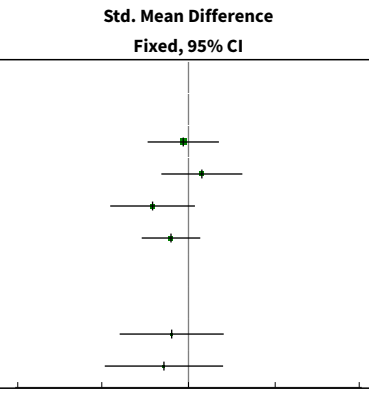
Analysis 11.2. Comparison 11 APPENDIX 4: memantine vs placebo for mild to severe Alzheimer's disease. OC. 12-52 weeks, Outcome 2 Cognitive Function.

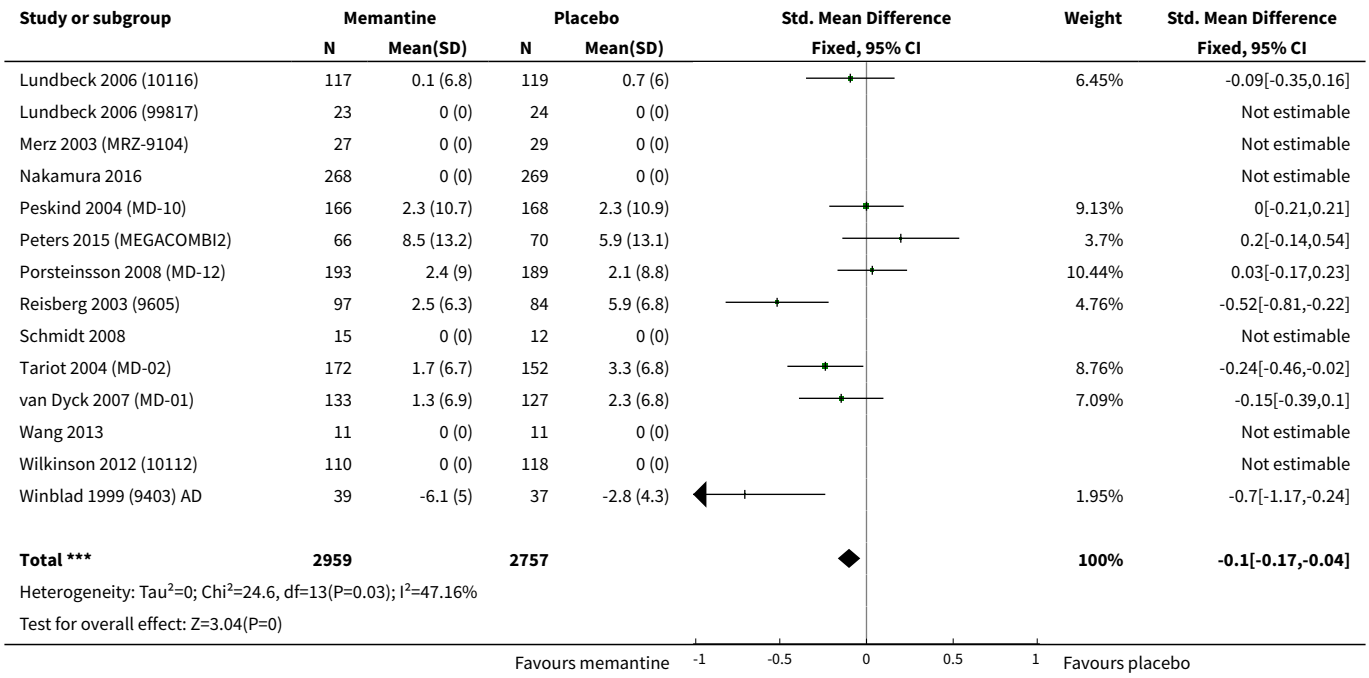
Study or subgroup	Memantine		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Asada 2011 (MA3301)	187	1.5 (4.7)	180	1.8 (4.6)		7.39%	-0.08[-0.28,0.13]
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		7.24%	-0.42[-0.63,-0.22]
Bakchine 2008 (99679)	271	-1.8 (6.9)	137	-1 (6.4)		7.33%	-0.11[-0.31,0.1]
Dysken 2014	140	3.3 (8.5)	137	4.3 (8.7)		5.58%	-0.11[-0.34,0.13]
Forest 2006 (MD-22)	132	0 (0)	131	0 (0)			Not estimable
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		10.82%	-0.26[-0.43,-0.09]
Hofbauer 2009 (MD-71)	133	0 (0)	124	0 (0)			Not estimable
Holland 2013	13	-27.1 (2.3)	13	-26 (3.6)		0.51%	-0.37[-1.15,0.41]
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		3.35%	-0.48[-0.78,-0.18]
Howard 2012 (DOMINO-AD)	77	3.5 (3.6)	58	4.1 (3.7)		2.66%	-0.17[-0.51,0.17]
Lundbeck 2006 (10116)	117	1.5 (10.3)	119	1.4 (11)		4.76%	0.01[-0.25,0.26]
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Merz 2003 (MRZ-9104)	27	0 (0)	29	0 (0)			Not estimable
Nakamura 2016	268	1.3 (8.2)	269	2.2 (8.1)		10.82%	-0.1[-0.27,0.07]
Peskind 2004 (MD-10)	160	0 (7.8)	162	1 (7.9)		6.48%	-0.13[-0.35,0.09]
Peters 2015 (MEGACOMBI2)	84	2.5 (8.3)	86	2 (8.5)		3.43%	0.06[-0.24,0.36]
Porsteinsson 2008 (MD-12)	190	0 (6.6)	187	0.8 (6.4)		7.59%	-0.12[-0.32,0.08]
Reisberg 2003 (9605)	96	4.5 (11.5)	82	10.2 (12.7)		3.47%	-0.47[-0.77,-0.17]
Schmidt 2008	15	1 (8.1)	12	8.2 (14.4)		0.51%	-0.62[-1.4,0.16]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		6.4%	-0.37[-0.59,-0.15]
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		5.18%	-0.05[-0.29,0.2]
Wang 2013	11	0 (7.2)	11	5.6 (5.9)		0.4%	-0.82[-1.7,0.06]
Wilkinson 2012 (10112)	110	0.4 (5.1)	118	0.7 (5.2)		4.59%	-0.06[-0.32,0.2]
Winblad 1999 (9403) AD	39	-2.1 (1.9)	37	-1.1 (1.8)		1.48%	-0.54[-0.99,-0.08]
Total ***	**2942**		**2728**			**100%**	**-0.19[-0.24,-0.13]**
Heterogeneity: Tau^2=0; Chi^2=31.94, df=19(P=0.03); I^2=40.52%							
Test for overall effect: Z=6.56(P<0.0001)							



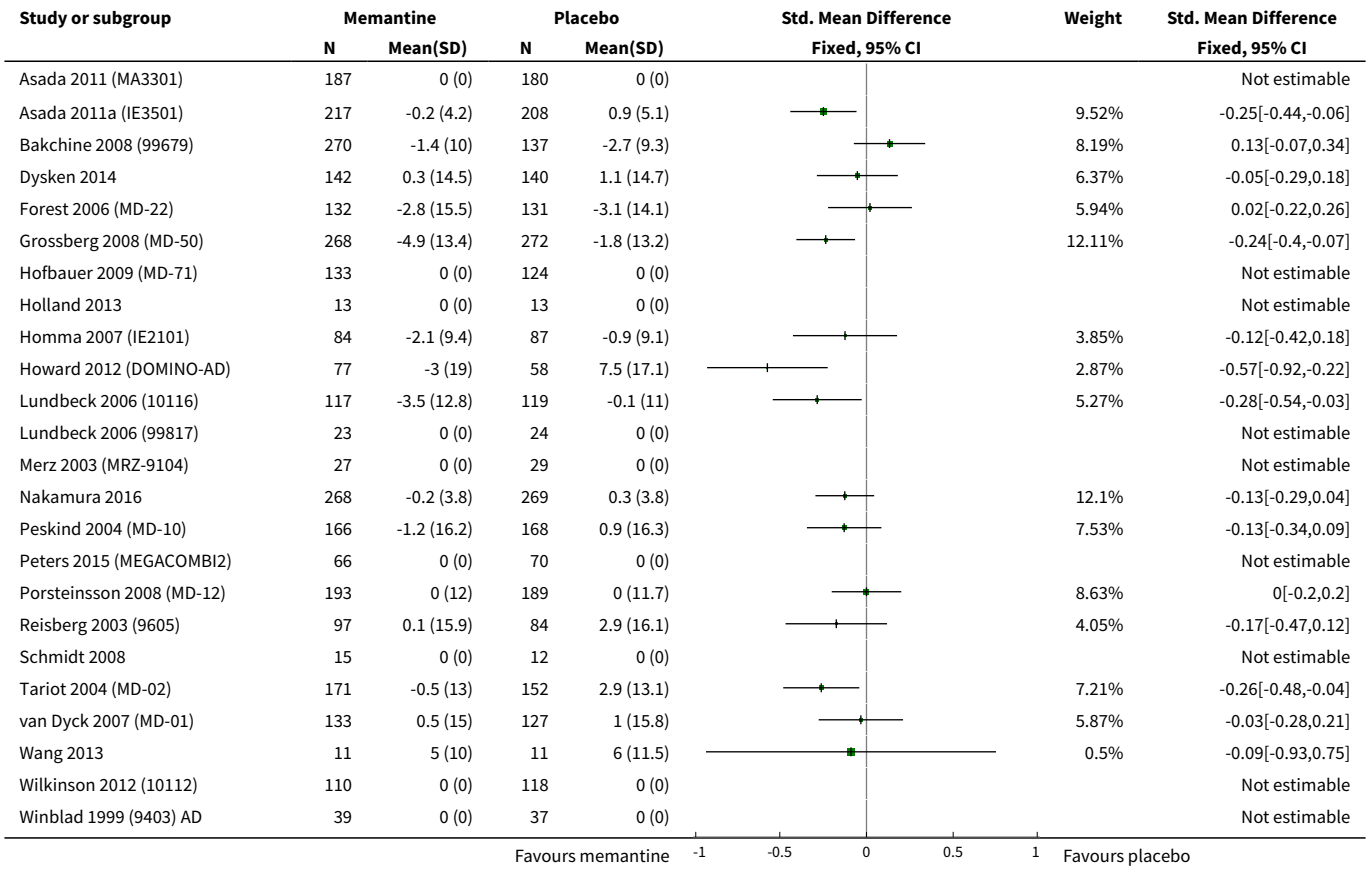
Analysis 11.3. Comparison 11 APPENDIX 4: memantine vs placebo for mild to severe Alzheimer's disease. OC. 12-52 weeks, Outcome 3 Decline in ADL.

Study or subgroup	Memantine		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Asada 2011 (MA3301)	187	0 (0)	180	0 (0)			Not estimable
Asada 2011a (IE3501)	218	0 (0)	208	0 (0)			Not estimable
Bakchine 2008 (99679)	270	2.1 (9.2)	137	2.4 (8.4)		9.94%	-0.03[-0.24,0.18]
Dysken 2014	142	-7 (14.4)	140	-8.1 (14.6)		7.71%	0.08[-0.16,0.31]
Forest 2006 (MD-22)	130	1.9 (6)	129	3.3 (7.4)		7.04%	-0.21[-0.45,0.04]
Grossberg 2008 (MD-50)	268	0.3 (8.1)	272	1.1 (7.8)		14.75%	-0.1[-0.27,0.07]
Hofbauer 2009 (MD-71)	133	0 (0)	124	0 (0)			Not estimable
Holland 2013	13	0 (0)	13	0 (0)			Not estimable
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		4.67%	-0.1[-0.4,0.2]
Howard 2012 (DOMINO-AD)	77	8.1 (6.8)	58	9.1 (8.3)		3.61%	-0.14[-0.48,0.2]

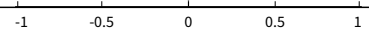




Analysis 11.4. Comparison 11 APPENDIX 4: memantine vs placebo for mild to severe Alzheimer's disease. OC. 12-52 weeks, Outcome 4 Behaviour and Mood.

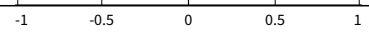


Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Total ***	**2959**		**2759**		◆	**100%**	**-0.13[-0.19,-0.07]**
Heterogeneity: Tau^2=0; Chi^2=22.4, df=14(P=0.07); I^2=37.5%							
Test for overall effect: Z=4.41(P<0.0001)							



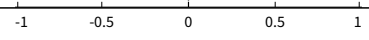
Analysis 11.5. Comparison 11 APPENDIX 4: memantine vs placebo for mild to severe Alzheimer's disease. OC. 12-52 weeks, Outcome 5 Clinical Global - sensitivity analysis for high RoB.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Asada 2011 (MA3301)	187	4.3 (1)	180	4.5 (1)		9.63%	-0.25[-0.45,-0.04]
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		9.68%	-0.11[-0.31,0.1]
Bakchine 2008 (99679)	270	4.1 (1.2)	138	4.2 (1.2)		9.66%	-0.05[-0.25,0.16]
Dysken 2014	140	0 (0)	137	0 (0)			Not estimable
Forest 2006 (MD-22)	131	3.6 (1.4)	129	3.8 (1.3)		6.86%	-0.15[-0.4,0.09]
Grossberg 2008 (MD-50)	269	3.8 (1.1)	272	4.1 (1.2)		14.19%	-0.26[-0.43,-0.09]
Hofbauer 2009 (MD-71)	133	-1.3 (5.9)	124	0 (5.9)		6.75%	-0.22[-0.47,0.03]
Holland 2013	13	0 (0)	13	0 (0)			Not estimable
Homma 2007 (IE2101)	84	4.4 (1.6)	87	4.7 (1.3)		4.49%	-0.22[-0.52,0.08]
Lundbeck 2006 (10116)	61	0 (0)	65	0 (0)			Not estimable
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Peskind 2004 (MD-10)	164	4.2 (1)	166	4.5 (1.1)		8.64%	-0.29[-0.5,-0.07]
Porsteinsson 2008 (MD-12)	192	4.4 (1)	189	4.4 (1)		10.08%	-0.04[-0.24,0.16]
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		4.72%	-0.27[-0.56,0.03]
Tariot 2004 (MD-02)	172	4.4 (1.1)	152	4.6 (1.1)		8.47%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	134	4.3 (1.1)	127	4.6 (1)		6.83%	-0.28[-0.53,-0.04]
Wilkinson 2012 (10112)	110	0 (0)	118	0 (0)			Not estimable
Total ***	**2370**		**2182**		◆	**100%**	**-0.19[-0.26,-0.13]**
Heterogeneity: Tau^2=0; Chi^2=7.57, df=11(P=0.75); I^2=0%							
Test for overall effect: Z=5.92(P<0.0001)							

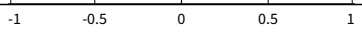


Analysis 11.6. Comparison 11 APPENDIX 4: memantine vs placebo for mild to severe Alzheimer's disease. OC. 12-52 weeks, Outcome 6 Cognitive Function - sensitivity analysis for high risk of bias.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Asada 2011 (MA3301)	187	1.5 (4.7)	180	1.8 (4.6)		7.79%	-0.08[-0.28,0.13]
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		7.63%	-0.42[-0.63,-0.22]
Bakchine 2008 (99679)	271	-1.8 (6.9)	137	-1 (6.4)		7.72%	-0.11[-0.31,0.1]
Dysken 2014	140	3.3 (8.5)	137	4.3 (8.7)		5.87%	-0.11[-0.34,0.13]
Forest 2006 (MD-22)	132	0 (0)	131	0 (0)			Not estimable
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		11.39%	-0.26[-0.43,-0.09]
Hofbauer 2009 (MD-71)	133	0 (0)	124	0 (0)			Not estimable
Holland 2013	13	-27.1 (2.3)	13	-26 (3.6)		0.54%	-0.37[-1.15,0.41]



Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		3.53%	-0.48[-0.78,-0.18]
Lundbeck 2006 (10116)	117	1.5 (10.3)	119	1.4 (11)		5.01%	0.01[-0.25,0.26]
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Nakamura 2016	268	1.3 (8.2)	269	2.2 (8.1)		11.39%	-0.1[-0.27,0.07]
Peskind 2004 (MD-10)	160	0 (7.8)	162	1 (7.9)		6.83%	-0.13[-0.35,0.09]
Peters 2015 (MEGACOMBI2)	84	2.5 (8.3)	86	2 (8.5)		3.61%	0.06[-0.24,0.36]
Porsteinsson 2008 (MD-12)	190	0 (6.6)	187	0.8 (6.4)		7.99%	-0.12[-0.32,0.08]
Reisberg 2003 (9605)	96	4.5 (11.5)	82	10.2 (12.7)		3.65%	-0.47[-0.77,-0.17]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		6.74%	-0.37[-0.59,-0.15]
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		5.46%	-0.05[-0.29,0.2]
Wilkinson 2012 (10112)	110	0.4 (5.1)	118	0.7 (5.2)		4.84%	-0.06[-0.32,0.2]
Total * **	**2773**		**2581**			**100%**	**-0.18[-0.23,-0.12]**
Heterogeneity: Tau^2=0; Chi^2=26.41, df=15(P=0.03); I^2=43.2%							
Test for overall effect: Z=6.05(P<0.0001)							

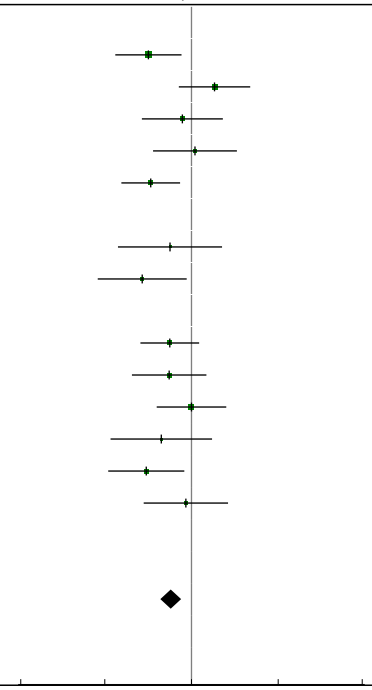


Analysis 11.7. Comparison 11 APPENDIX 4: memantine vs placebo for mild to severe Alzheimer's disease. OC. 12-52 weeks, Outcome 7 Decline in ADL - sensitivity analysis on high RoB.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Asada 2011 (MA3301)	187	0 (0)	180	0 (0)			Not estimable
Asada 2011a (IE3501)	218	0 (0)	208	0 (0)			Not estimable
Bakchine 2008 (99679)	270	2.1 (9.2)	137	2.4 (8.4)		10.53%	-0.03[-0.24,0.18]
Dysken 2014	142	-7 (14.4)	140	-8.1 (14.6)		8.16%	0.08[-0.16,0.31]
Forest 2006 (MD-22)	130	1.9 (6)	129	3.3 (7.4)		7.46%	-0.21[-0.45,0.04]
Grossberg 2008 (MD-50)	268	0.3 (8.1)	272	1.1 (7.8)		15.62%	-0.1[-0.27,0.07]
Hofbauer 2009 (MD-71)	133	0 (0)	124	0 (0)			Not estimable
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		4.94%	-0.1[-0.4,0.2]
Lundbeck 2006 (10116)	117	0.1 (6.8)	119	0.7 (6)		6.83%	-0.09[-0.35,0.16]
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Peskind 2004 (MD-10)	166	2.3 (10.7)	168	2.3 (10.9)		9.67%	0[-0.21,0.21]
Peters 2015 (MEGACOMBI2)	66	8.5 (13.2)	70	5.9 (13.1)		3.91%	0.2[-0.14,0.54]
Porsteinsson 2008 (MD-12)	193	2.4 (9)	189	2.1 (8.8)		11.06%	0.03[-0.17,0.23]
Reisberg 2003 (9605)	97	2.5 (6.3)	84	5.9 (6.8)		5.04%	-0.52[-0.81,-0.22]
Tariot 2004 (MD-02)	172	1.7 (6.7)	152	3.3 (6.8)		9.28%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	133	1.3 (6.9)	127	2.3 (6.8)		7.5%	-0.15[-0.39,0.1]
Wilkinson 2012 (10112)	110	0 (0)	118	0 (0)			Not estimable
Total * **	**2509**		**2328**			**100%**	**-0.09[-0.15,-0.02]**
Heterogeneity: Tau^2=0; Chi^2=17.94, df=11(P=0.08); I^2=38.67%							
Test for overall effect: Z=2.55(P=0.01)							

Analysis 11.8. Comparison 11 APPENDIX 4: memantine vs placebo for mild to severe Alzheimer's disease. OC. 12-52 weeks, Outcome 8 Behaviour and Mood - sensitivity analysis on high RoB.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Asada 2011 (MA3301)	187	0 (0)	180	0 (0)			Not estimable
Asada 2011a (IE3501)	217	-0.2 (4.2)	208	0.9 (5.1)		9.85%	-0.25[-0.44,-0.06]
Bakchine 2008 (99679)	270	-1.4 (10)	137	-2.7 (9.3)		8.48%	0.13[-0.07,0.34]
Dysken 2014	142	0.3 (14.5)	140	1.1 (14.7)		6.59%	-0.05[-0.29,0.18]
Forest 2006 (MD-22)	132	-2.8 (15.5)	131	-3.1 (14.1)		6.15%	0.02[-0.22,0.26]
Grossberg 2008 (MD-50)	268	-4.9 (13.4)	272	-1.8 (13.2)		12.53%	-0.24[-0.4,-0.07]
Hofbauer 2009 (MD-71)	133	0 (0)	124	0 (0)			Not estimable
Homma 2007 (IE2101)	84	-2.1 (9.4)	87	-0.9 (9.1)		3.99%	-0.12[-0.42,0.18]
Lundbeck 2006 (10116)	117	-3.5 (12.8)	119	-0.1 (11)		5.46%	-0.28[-0.54,-0.03]
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Nakamura 2016	268	-0.2 (3.8)	269	0.3 (3.8)		12.52%	-0.13[-0.29,0.04]
Peskind 2004 (MD-10)	166	-1.2 (16.2)	168	0.9 (16.3)		7.79%	-0.13[-0.34,0.09]
Porsteinsson 2008 (MD-12)	193	0 (12)	189	0 (11.7)		8.93%	0[-0.2,0.2]
Reisberg 2003 (9605)	97	0.1 (15.9)	84	2.9 (16.1)		4.19%	-0.17[-0.47,0.12]
Tariot 2004 (MD-02)	171	-0.5 (13)	152	2.9 (13.1)		7.46%	-0.26[-0.48,-0.04]
van Dyck 2007 (MD-01)	133	0.5 (15)	127	1 (15.8)		6.07%	-0.03[-0.28,0.21]
Wilkinson 2012 (10112)	110	0 (0)	118	0 (0)			Not estimable
Total ***	**2711**		**2529**			**100%**	**-0.12[-0.18,-0.06]**
Heterogeneity: Tau^2=0; Chi^2=16.09, df=12(P=0.19); I^2=25.43%							
Test for overall effect: Z=3.92(P<0.0001)							



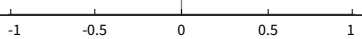
Comparison 12. APPENDIX 4: subgroup analysis by duration: memantine 20 mg or equivalent vs placebo for mild-to-severe Alzheimer's disease. OC. 12-52 weeks

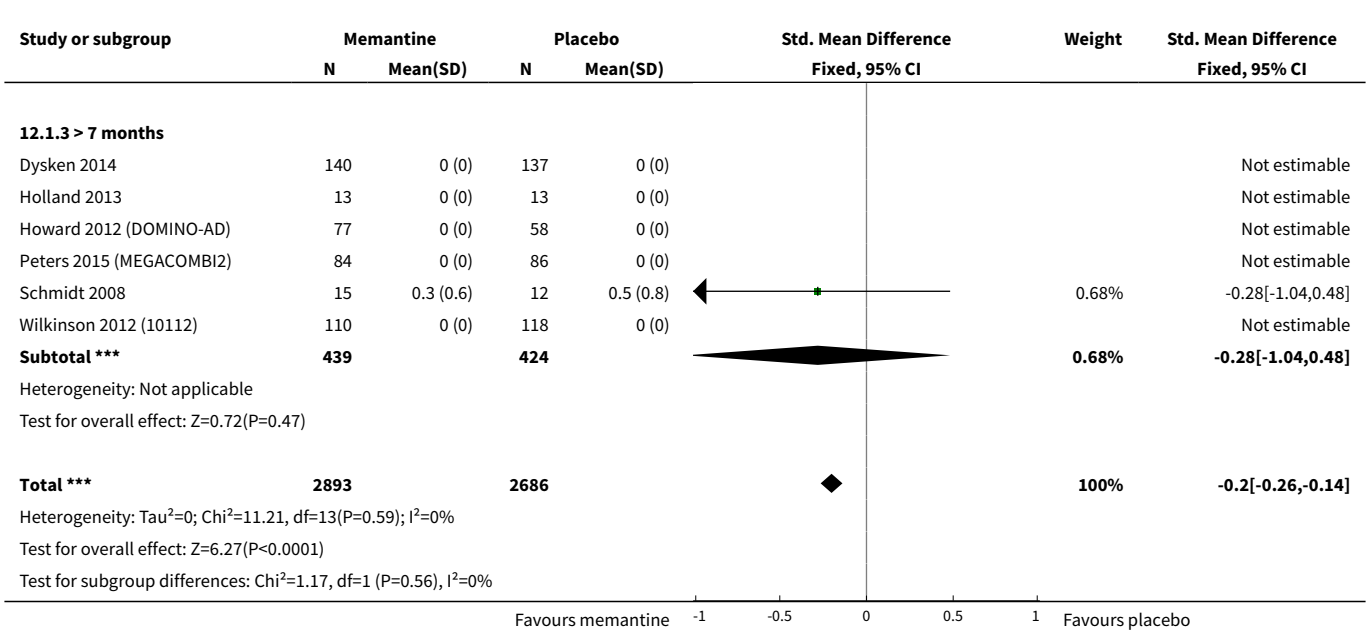
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global - CIBIC Plus, CGI-I, or ADCS-CGIC	24	5579	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.26, -0.14]
1.1 < 6 months	4	515	Std. Mean Difference (IV, Fixed, 95% CI)	-0.31 [-0.53, -0.10]
1.2 6-7 months	14	4201	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.26, -0.12]
1.3 > 7 months	6	863	Std. Mean Difference (IV, Fixed, 95% CI)	-0.28 [-1.04, 0.48]
2 Cognitive Function	24	5670	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.24, -0.13]
2.1 < 6 months	4	625	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.34, 0.10]
2.2 6-7 months	14	4182	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.28, -0.15]
2.3 > 7 months	6	863	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.23, 0.04]
3 Decline in ADL - BGP, AD-CS-ADL 19 or 23	24	5716	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.17, -0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 < 6 months	4	625	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.46, -0.01]
3.2 6-7 months	14	4257	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.19, -0.04]
3.3 >7 months	6	834	Std. Mean Difference (IV, Fixed, 95% CI)	0.05 [-0.11, 0.22]
4 Behaviour and Mood (Standardised NPI or NPI-NH Total)	23	5582	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.19, -0.07]
4.1 < 6 months	4	625	Std. Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.54, -0.03]
4.2 6-7 months	14	4259	Std. Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.18, -0.05]
4.3 > 7 months	5	698	Std. Mean Difference (IV, Fixed, 95% CI)	-0.21 [-0.41, -0.02]

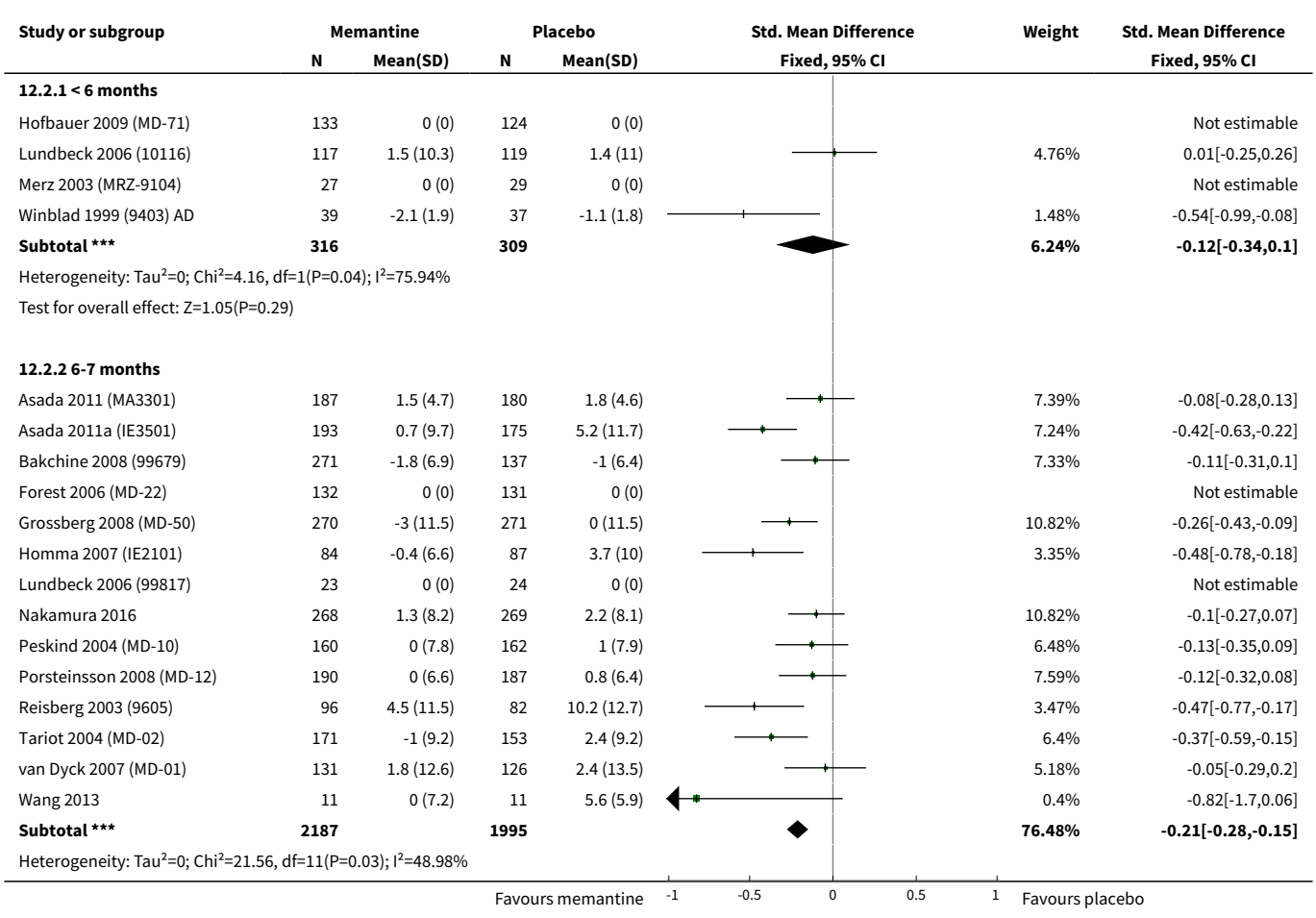
Analysis 12.1. Comparison 12 APPENDIX 4: subgroup analysis by duration: memantine 20 mg or equivalent vs placebo for mild-to-severe Alzheimer's disease. OC. 12-52 weeks, Outcome 1 Clinical Global - CIBIC Plus, CGI-I, or ADCS-CGIC.

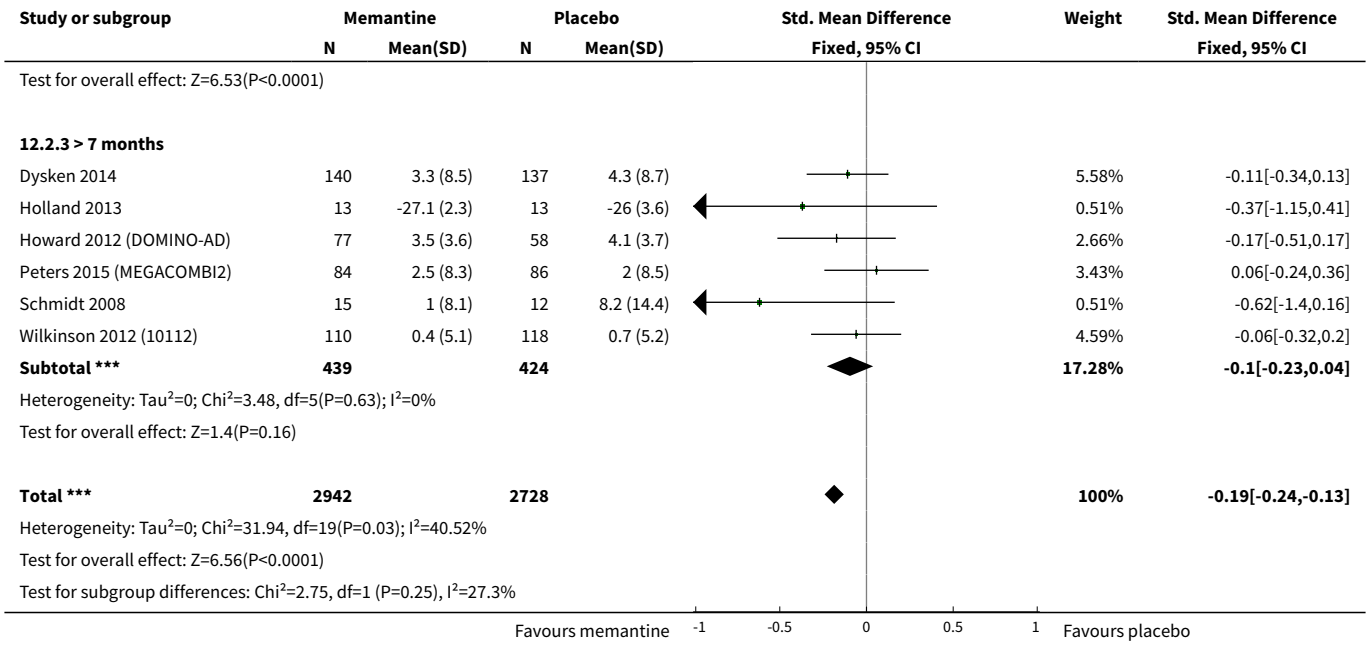
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
12.1.1 < 6 months							
Hofbauer 2009 (MD-71)	133	-1.3 (5.9)	124	0 (5.9)		6.58%	-0.22[-0.47,0.03]
Lundbeck 2006 (10116)	61	0 (0)	65	0 (0)			Not estimable
Merz 2003 (MRZ-9104)	27	0 (0)	29	0 (0)			Not estimable
Winblad 1999 (9403) AD	39	3.1 (0.6)	37	3.5 (0.6)		1.86%	-0.64[-1.11,-0.18]
Subtotal ***	**260**		**255**			**8.43%**	**-0.31[-0.53,-0.1]**
Heterogeneity: Tau^2=0; Chi^2=2.52, df=1(P=0.11); I^2=60.3%							
Test for overall effect: Z=2.83(P=0)							
12.1.2 6-7 months							
Asada 2011 (MA3301)	187	4.3 (1)	180	4.5 (1)		9.39%	-0.25[-0.45,-0.04]
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		9.44%	-0.11[-0.31,0.1]
Bakchine 2008 (99679)	270	4.1 (1.2)	138	4.2 (1.2)		9.42%	-0.05[-0.25,0.16]
Forest 2006 (MD-22)	131	3.6 (1.4)	129	3.8 (1.3)		6.68%	-0.15[-0.4,0.09]
Grossberg 2008 (MD-50)	269	3.8 (1.1)	272	4.1 (1.2)		13.83%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	4.4 (1.6)	87	4.7 (1.3)		4.38%	-0.22[-0.52,0.08]
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Nakamura 2016	268	0 (0)	269	0 (0)			Not estimable
Peskind 2004 (MD-10)	164	4.2 (1)	166	4.5 (1.1)		8.42%	-0.29[-0.5,-0.07]
Porsteinsson 2008 (MD-12)	192	4.4 (1)	189	4.4 (1)		9.82%	-0.04[-0.24,0.16]
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		4.6%	-0.27[-0.56,0.03]
Tariot 2004 (MD-02)	172	4.4 (1.1)	152	4.6 (1.1)		8.26%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	134	4.3 (1.1)	127	4.6 (1)		6.66%	-0.28[-0.53,-0.04]
Wang 2013	13	0 (0)	13	0 (0)			Not estimable
Subtotal ***	**2194**		**2007**			**90.89%**	**-0.19[-0.26,-0.12]**
Heterogeneity: Tau^2=0; Chi^2=7.52, df=10(P=0.68); I^2=0%							
Test for overall effect: Z=5.66(P<0.0001)							





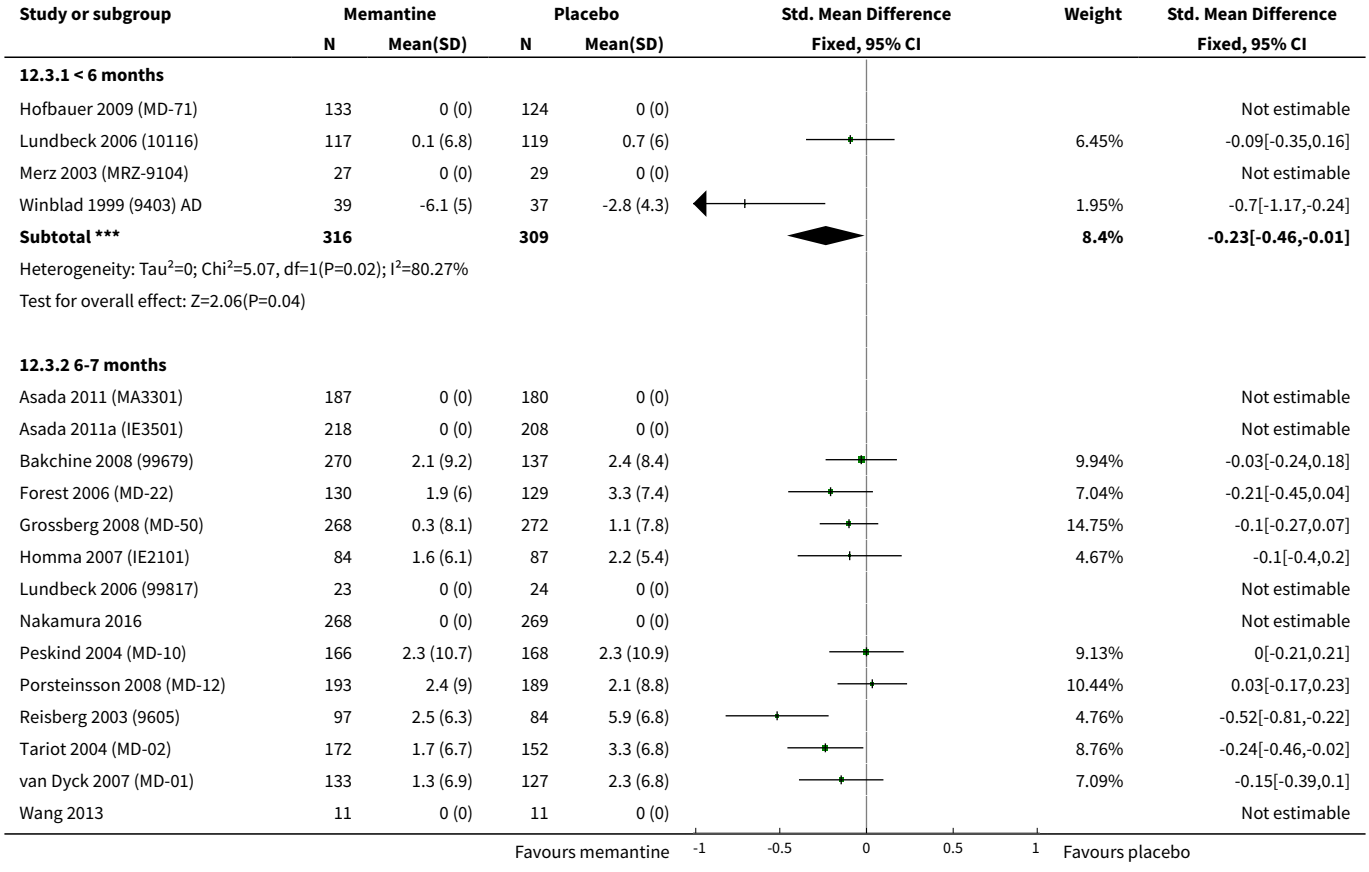
Analysis 12.2. Comparison 12 APPENDIX 4: subgroup analysis by duration: memantine 20 mg or equivalent vs placebo for mild-to-severe Alzheimer's disease. OC. 12-52 weeks, Outcome 2 Cognitive Function.



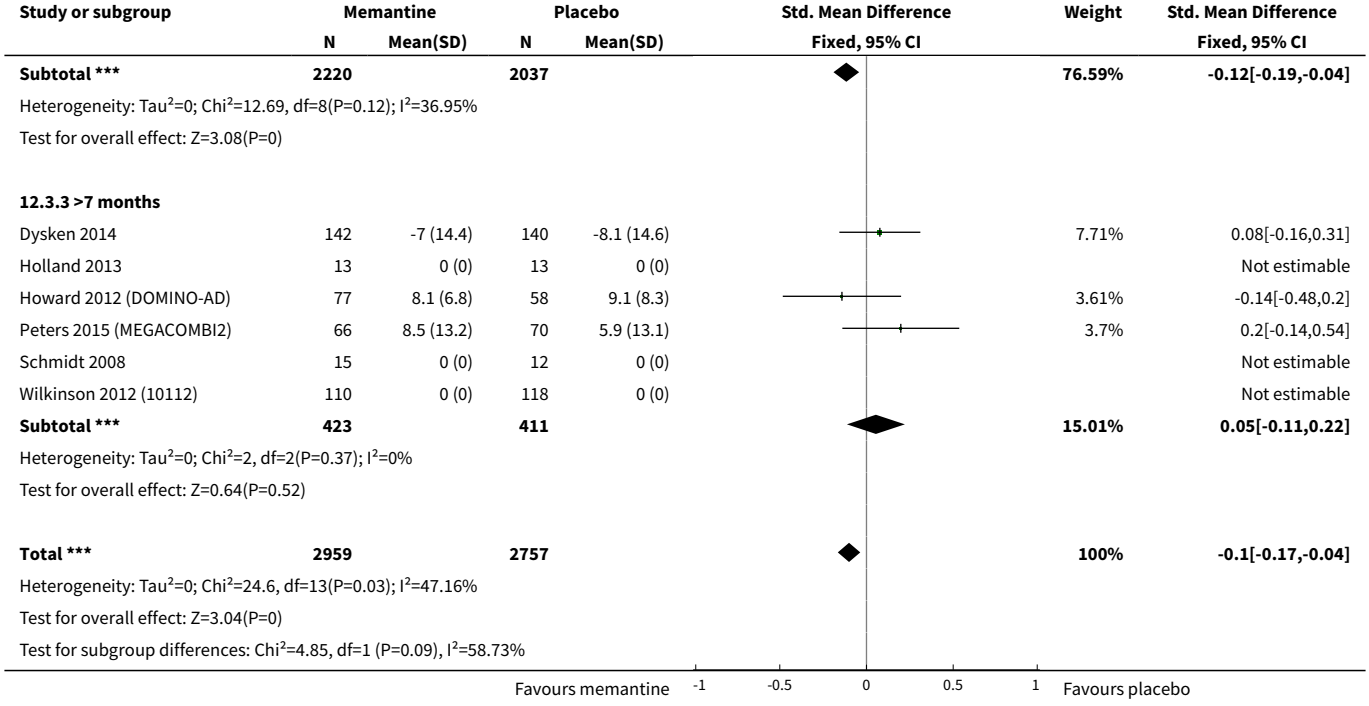


Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Test for overall effect: Z=6.53(P<0.0001)							
12.2.3 > 7 months							
Dysken 2014	140	3.3 (8.5)	137	4.3 (8.7)		5.58%	-0.11[-0.34,0.13]
Holland 2013	13	-27.1 (2.3)	13	-26 (3.6)		0.51%	-0.37[-1.15,0.41]
Howard 2012 (DOMINO-AD)	77	3.5 (3.6)	58	4.1 (3.7)		2.66%	-0.17[-0.51,0.17]
Peters 2015 (MEGACOMBI2)	84	2.5 (8.3)	86	2 (8.5)		3.43%	0.06[-0.24,0.36]
Schmidt 2008	15	1 (8.1)	12	8.2 (14.4)		0.51%	-0.62[-1.4,0.16]
Wilkinson 2012 (10112)	110	0.4 (5.1)	118	0.7 (5.2)		4.59%	-0.06[-0.32,0.2]
Subtotal ***	**439**		**424**			**17.28%**	**-0.1[-0.23,0.04]**
Heterogeneity: Tau²=0; Chi²=3.48, df=5(P=0.63); I²=0%							
Test for overall effect: Z=1.4(P=0.16)							
Total ***	**2942**		**2728**			**100%**	**-0.19[-0.24,-0.13]**
Heterogeneity: Tau²=0; Chi²=31.94, df=19(P=0.03); I²=40.52%							
Test for overall effect: Z=6.56(P<0.0001)							
Test for subgroup differences: Chi²=2.75, df=1 (P=0.25), I²=27.3%							

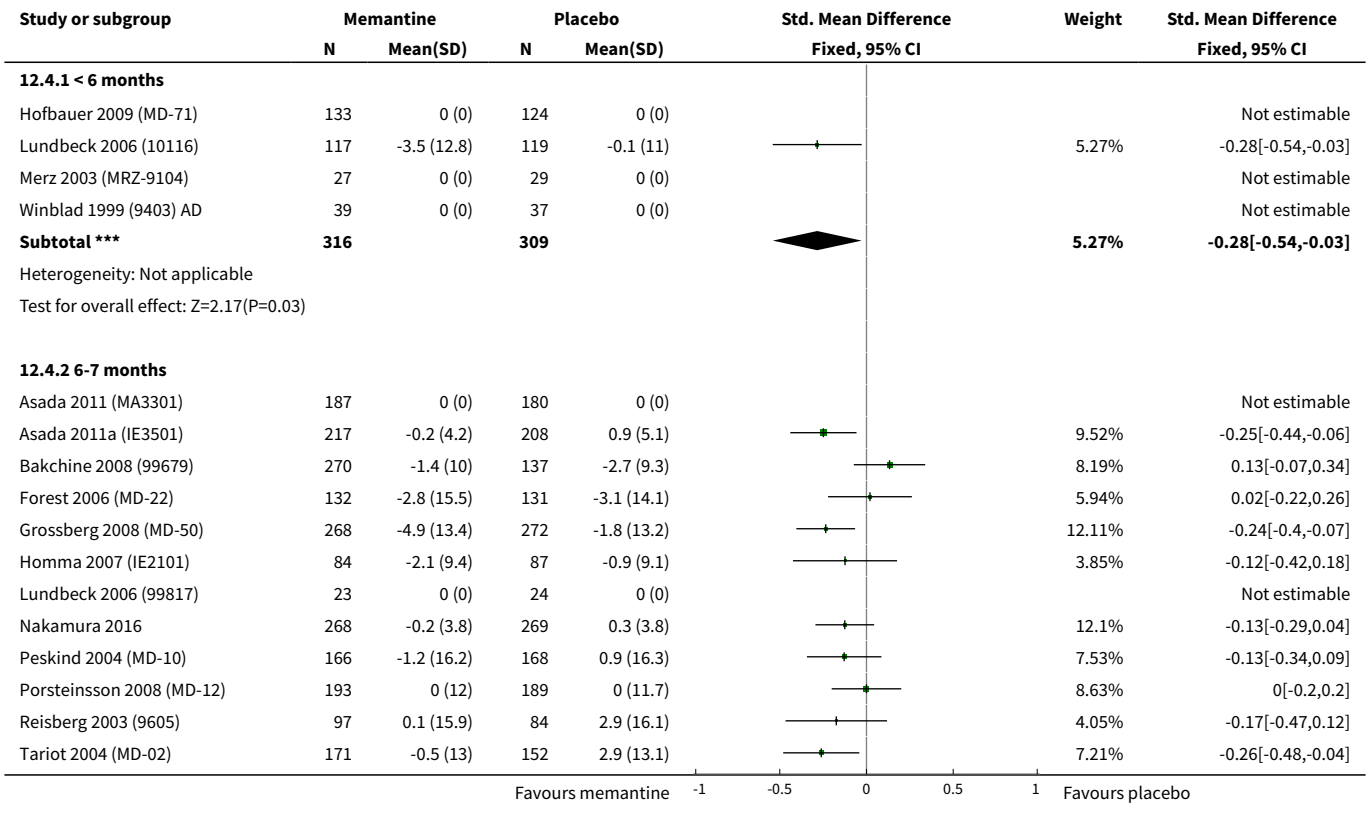
Analysis 12.3. Comparison 12 APPENDIX 4: subgroup analysis by duration: memantine 20 mg or equivalent vs placebo for mild-to-severe Alzheimer's disease. OC. 12-52 weeks, Outcome 3 Decline in ADL - BGP, ADCS-ADL 19 or 23.

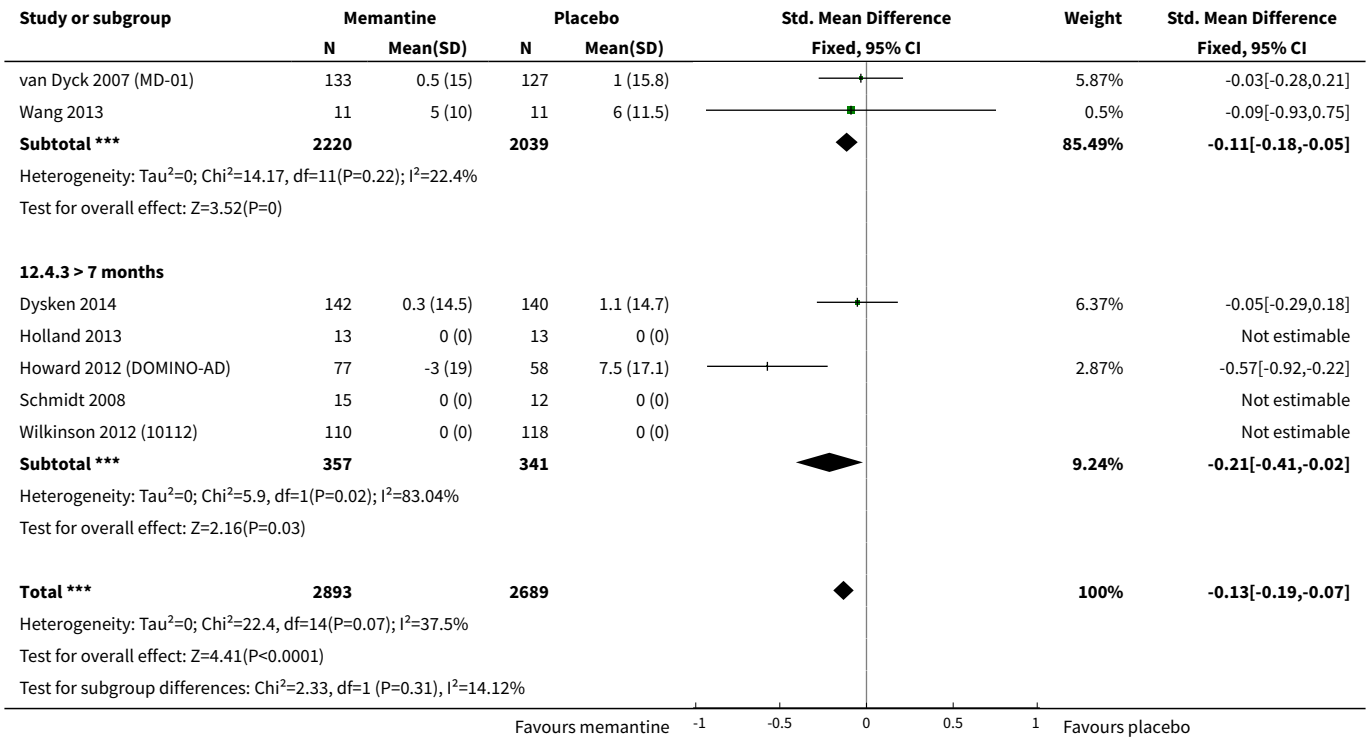


Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
12.3.1 < 6 months							
Hofbauer 2009 (MD-71)	133	0 (0)	124	0 (0)			Not estimable
Lundbeck 2006 (10116)	117	0.1 (6.8)	119	0.7 (6)		6.45%	-0.09[-0.35,0.16]
Merz 2003 (MRZ-9104)	27	0 (0)	29	0 (0)			Not estimable
Winblad 1999 (9403) AD	39	-6.1 (5)	37	-2.8 (4.3)		1.95%	-0.7[-1.17,-0.24]
Subtotal ***	**316**		**309**			**8.4%**	**-0.23[-0.46,-0.01]**
Heterogeneity: Tau²=0; Chi²=5.07, df=1(P=0.02); I²=80.27%							
Test for overall effect: Z=2.06(P=0.04)							
12.3.2 6-7 months							
Asada 2011 (MA3301)	187	0 (0)	180	0 (0)			Not estimable
Asada 2011a (IE3501)	218	0 (0)	208	0 (0)			Not estimable
Bakchine 2008 (99679)	270	2.1 (9.2)	137	2.4 (8.4)		9.94%	-0.03[-0.24,0.18]
Forest 2006 (MD-22)	130	1.9 (6)	129	3.3 (7.4)		7.04%	-0.21[-0.45,0.04]
Grossberg 2008 (MD-50)	268	0.3 (8.1)	272	1.1 (7.8)		14.75%	-0.1[-0.27,0.07]
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		4.67%	-0.1[-0.4,0.2]
Lundbeck 2006 (99817)	23	0 (0)	24	0 (0)			Not estimable
Nakamura 2016	268	0 (0)	269	0 (0)			Not estimable
Peskind 2004 (MD-10)	166	2.3 (10.7)	168	2.3 (10.9)		9.13%	0[-0.21,0.21]
Porsteinsson 2008 (MD-12)	193	2.4 (9)	189	2.1 (8.8)		10.44%	0.03[-0.17,0.23]
Reisberg 2003 (9605)	97	2.5 (6.3)	84	5.9 (6.8)		4.76%	-0.52[-0.81,-0.22]
Tariot 2004 (MD-02)	172	1.7 (6.7)	152	3.3 (6.8)		8.76%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	133	1.3 (6.9)	127	2.3 (6.8)		7.09%	-0.15[-0.39,0.1]
Wang 2013	11	0 (0)	11	0 (0)			Not estimable



Analysis 12.4. Comparison 12 APPENDIX 4: subgroup analysis by duration: memantine 20 mg or equivalent vs placebo for mild-to-severe Alzheimer's disease. OC. 12-52 weeks, Outcome 4 Behaviour and Mood (Standardised NPI or NPI-NH Total).



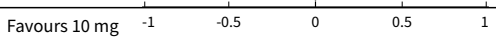


Comparison 13. APPENDIX 4: memantine 10 mg versus 20 mg memantine for Alzheimer's disease (12-24 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global; 10mg versus 20mg	2	545	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.12, 0.22]
2 Cognitive function; 10mg vs 20 mg	2	545	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.48, 0.68]
3 Decline in ADL; 10mg versus 20mg	2	546	Mean Difference (IV, Random, 95% CI)	-0.15 [-1.86, 1.56]
4 Behaviour and mood; 10mg versus 20mg	2	547	Mean Difference (IV, Random, 95% CI)	1.70 [-1.06, 4.46]
5 Clinical Global	3	623	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.50, -0.02]
6 Cognitive function	3	623	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.45, -0.06]
7 Decline in activities of daily living	3	623	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.92, 0.16]
8 Behaviour and mood	3	626	Mean Difference (IV, Random, 95% CI)	-0.55 [-3.25, 2.15]

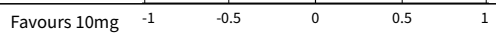
Analysis 13.1. Comparison 13 APPENDIX 4: memantine 10 mg versus 20 mg memantine for Alzheimer's disease (12-24 weeks), Outcome 1 Clinical Global; 10mg versus 20mg.

Study or subgroup	Memantine 10 mg N	Memantine 10 mg Mean(SD)	Memantine 20 mg N	Memantine 20 mg Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Homma 2007 (IE2101)	92	4.6 (1.5)	83	4.4 (1.6)		32.03%	0.12[-0.18,0.42]
Asada 2011 (MA3301)	190	4.3 (1.1)	180	4.3 (1)		67.97%	0.02[-0.18,0.22]
Total ***	**282**		**263**			**100%**	**0.05[-0.12,0.22]**
Heterogeneity: Tau^2=0; Chi^2=0.31, df=1(P=0.58); I^2=0%							
Test for overall effect: Z=0.6(P=0.55)							



Analysis 13.2. Comparison 13 APPENDIX 4: memantine 10 mg versus 20 mg memantine for Alzheimer's disease (12-24 weeks), Outcome 2 Cognitive function; 10mg vs 20 mg.

Study or subgroup	Memantine 10 mg N	Memantine 10 mg Mean(SD)	Memantine 20 mg N	Memantine 20 mg Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Asada 2011 (MA3301)	190	0.6 (4.5)	180	1.4 (4.5)		51.8%	-0.19[-0.39,0.02]
Homma 2007 (IE2101)	92	2.9 (9.1)	83	-0.4 (6.6)		48.2%	0.4[0.1,0.7]
Total ***	**282**		**263**			**100%**	**0.1[-0.48,0.68]**
Heterogeneity: Tau^2=0.16; Chi^2=10.13, df=1(P=0); I^2=90.13%							
Test for overall effect: Z=0.33(P=0.74)							

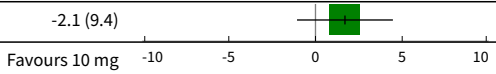


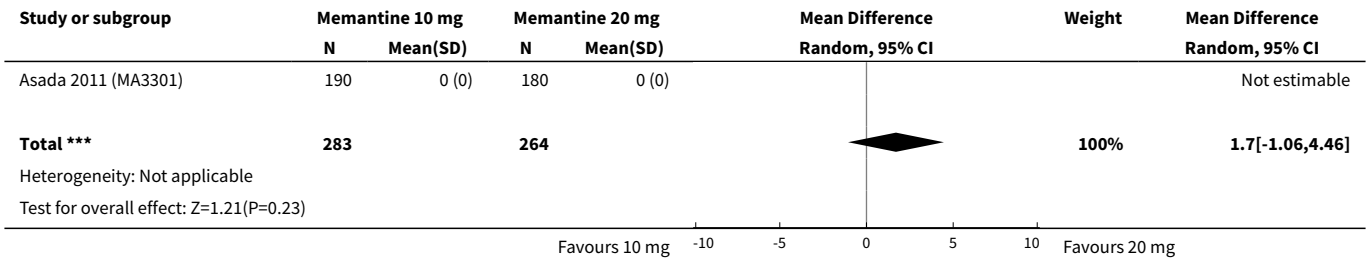
Analysis 13.3. Comparison 13 APPENDIX 4: memantine 10 mg versus 20 mg memantine for Alzheimer's disease (12-24 weeks), Outcome 3 Decline in ADL; 10mg versus 20mg.

Study or subgroup	Memantine 10 mg N	Memantine 10 mg Mean(SD)	Memantine 20 mg N	Memantine 20 mg Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Homma 2007 (IE2101)	93	1.5 (5.3)	83	1.6 (6.1)		100%	-0.15[-1.86,1.56]
Asada 2011 (MA3301)	190	0 (0)	180	0 (0)			Not estimable
Total ***	**283**		**263**			**100%**	**-0.15[-1.86,1.56]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.17(P=0.86)							

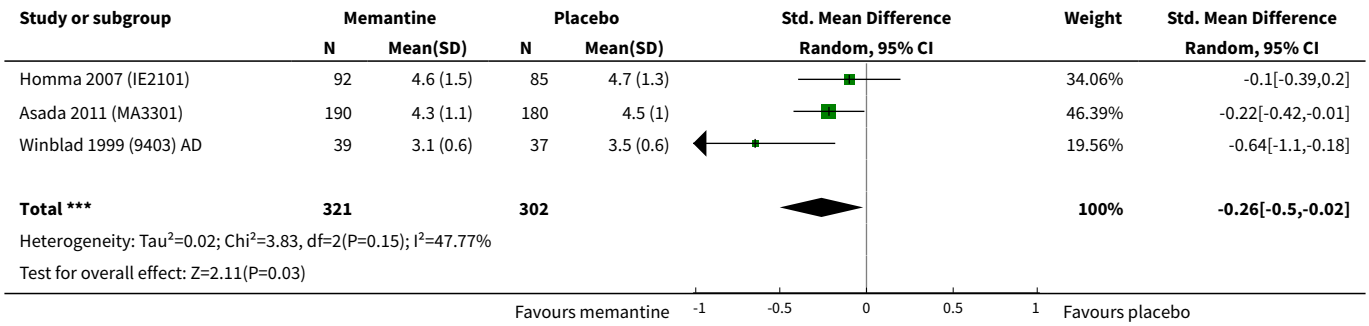
Analysis 13.4. Comparison 13 APPENDIX 4: memantine 10 mg versus 20 mg memantine for Alzheimer's disease (12-24 weeks), Outcome 4 Behaviour and mood; 10mg versus 20mg.

Study or subgroup	Memantine 10 mg N	Memantine 10 mg Mean(SD)	Memantine 20 mg N	Memantine 20 mg Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Homma 2007 (IE2101)	93	-0.4 (9.4)	84	-2.1 (9.4)		100%	1.7[-1.06,4.46]

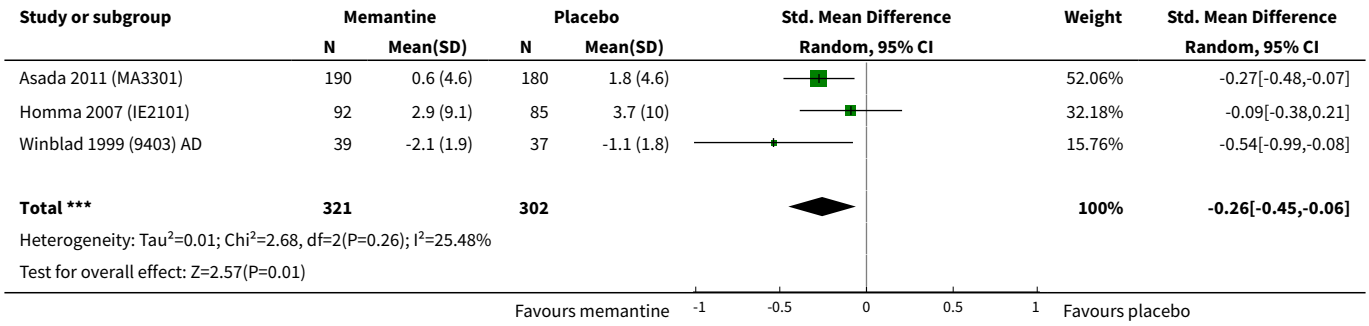




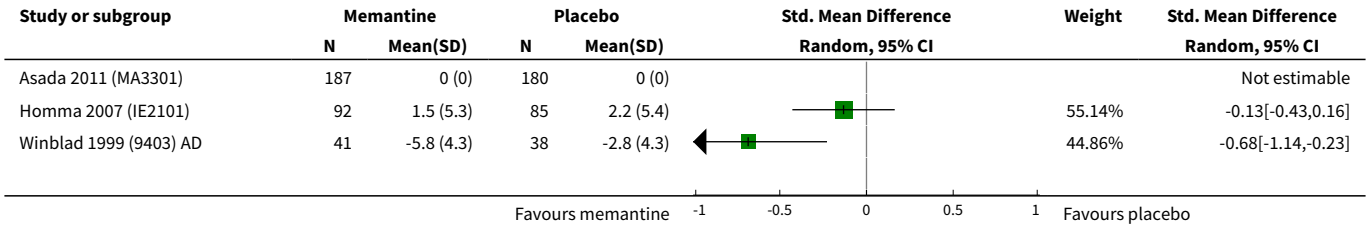
Analysis 13.5. Comparison 13 APPENDIX 4: memantine 10 mg versus 20 mg memantine for Alzheimer's disease (12-24 weeks), Outcome 5 Clinical Global.

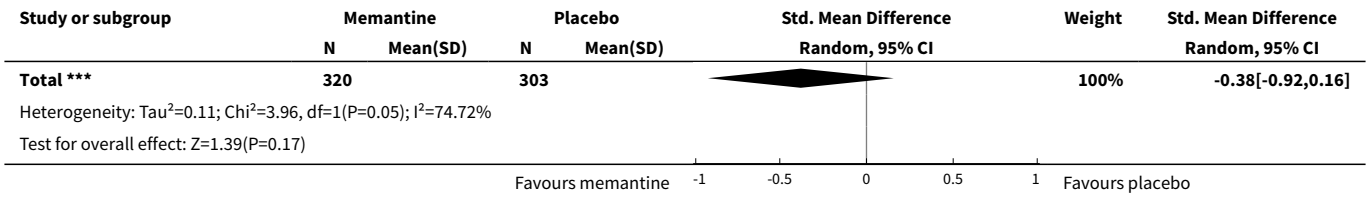


Analysis 13.6. Comparison 13 APPENDIX 4: memantine 10 mg versus 20 mg memantine for Alzheimer's disease (12-24 weeks), Outcome 6 Cognitive function.

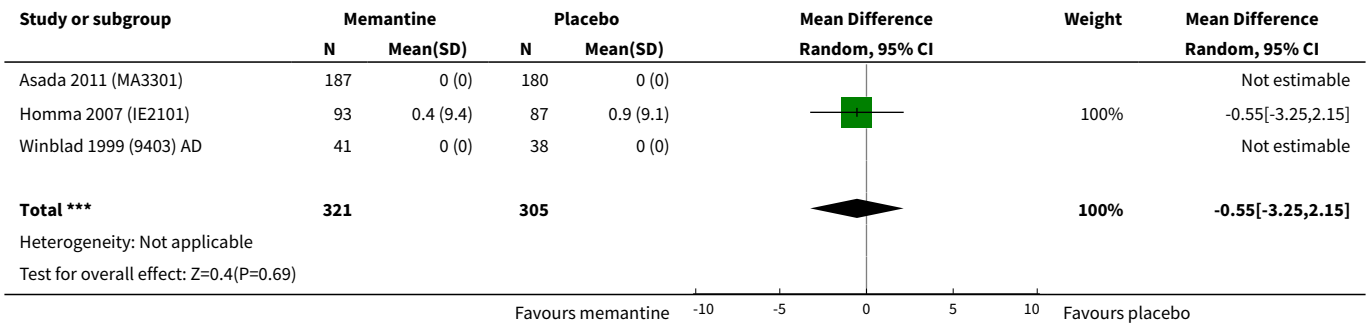


Analysis 13.7. Comparison 13 APPENDIX 4: memantine 10 mg versus 20 mg memantine for Alzheimer's disease (12-24 weeks), Outcome 7 Decline in activities of daily living.





Analysis 13.8. Comparison 13 APPENDIX 4: memantine 10 mg versus 20 mg memantine for Alzheimer's disease (12-24 weeks), Outcome 8 Behaviour and mood.



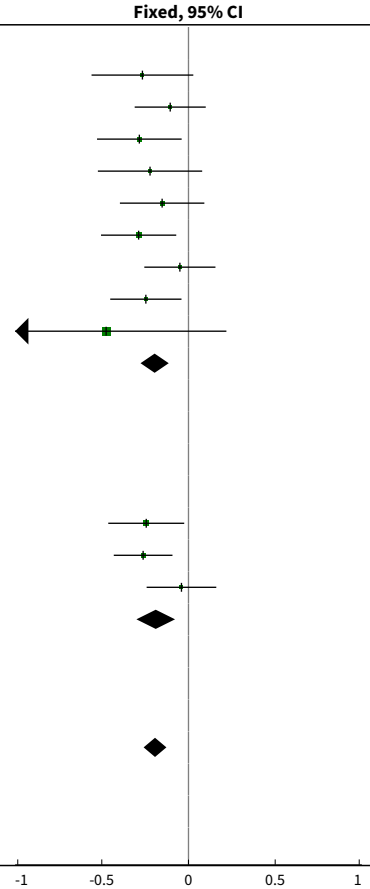
Comparison 14. APPENDIX 4: subgroup analysis by presence/absence of ChEI; 20 mg; six to seven months

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global: subgroup analysis by +/- ChEI	12	3624	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.26, -0.13]
1.1 Monotherapy (studies ordered by decreasing mean severity)	9	2378	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.28, -0.11]
1.2 With concomitant ChEI (studies ordered by decreasing mean severity)	3	1246	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.30, -0.08]
2 Cognitive Function subgroup analysis by +/- ChEI	16	4501	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.28, -0.16]
2.1 Monotherapy (studies ordered by decreasing mean severity)	10	2189	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.32, -0.15]
2.2 With concomitant ChEI (studies ordered by decreasing mean severity)	7	2312	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.28, -0.12]
3 Decline in ADL subgroup analysis by +/- ChEI	12	3432	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.19, -0.05]
3.1 Monotherapy (studies ordered by decreasing mean severity)	7	1674	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.24, -0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.2 With concomitant ChEI (studies ordered by decreasing mean severity)	6	1758	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.19, -0.01]
4 Behaviour and Mood: subgroup analysis by +/- ChEI	14	4270	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.18, -0.06]
4.1 Monotherapy (studies ordered by decreasing mean severity)	9	2125	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.17, 0.00]
4.2 With concomitant ChEI (studies ordered by decreasing mean severity)	6	2145	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.24, -0.07]

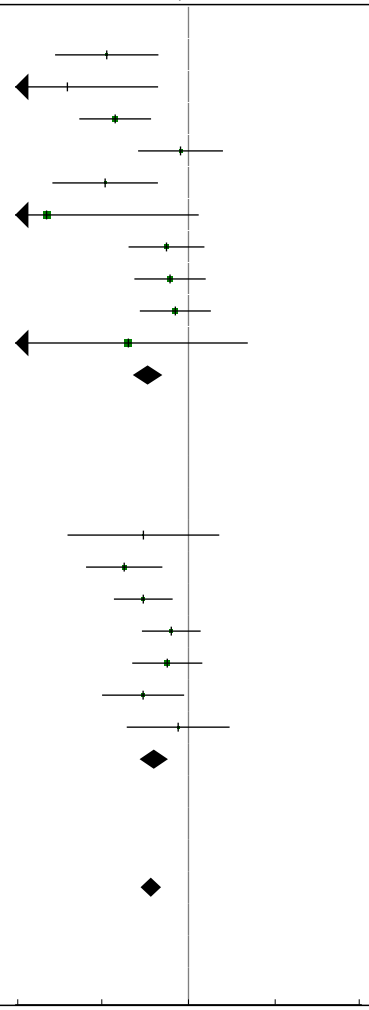
Analysis 14.1. Comparison 14 APPENDIX 4: subgroup analysis by presence/absence of ChEI; 20 mg; six to seven months, Outcome 1 Clinical Global: subgroup analysis by +/- ChEI.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
14.1.1 Monotherapy (studies ordered by decreasing mean severity)							
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		5.02%	-0.27[-0.56,0.03]
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		10.29%	-0.11[-0.31,0.1]
van Dyck 2007 (MD-01)	134	4.3 (1.1)	127	4.6 (1)		7.26%	-0.28[-0.53,-0.04]
Homma 2007 (IE2101)	84	4.4 (1.6)	87	4.7 (1.3)		4.78%	-0.22[-0.52,0.08]
Forest 2006 (MD-22)	131	3.6 (1.4)	129	3.8 (1.3)		7.29%	-0.15[-0.4,0.09]
Peskind 2004 (MD-10)	164	4.2 (1)	166	4.5 (1.1)		9.18%	-0.29[-0.5,-0.07]
Bakchine 2008 (99679)	270	4.1 (1.2)	138	4.2 (1.2)		10.27%	-0.05[-0.25,0.16]
Asada 2011 (MA3301)	187	4.3 (1)	180	4.5 (1)		10.24%	-0.25[-0.45,-0.04]
Schmidt 2008	16	-0.1 (0.4)	17	0.2 (0.8)		0.9%	-0.47[-1.17,0.22]
Subtotal * **	**1273**		**1105**			**65.21%**	**-0.2[-0.28,-0.11]**
Heterogeneity: Tau^2=0; Chi^2=5.1, df=8(P=0.75); I^2=0%							
Test for overall effect: Z=4.7(P<0.0001)							
14.1.2 With concomitant ChEI (studies ordered by decreasing mean severity)							
Tariot 2004 (MD-02)	172	4.4 (1.1)	152	4.6 (1.1)		9.01%	-0.24[-0.46,-0.02]
Grossberg 2008 (MD-50)	269	3.8 (1.1)	272	4.1 (1.2)		15.08%	-0.26[-0.43,-0.09]
Porsteinsson 2008 (MD-12)	192	4.4 (1)	189	4.4 (1)		10.71%	-0.04[-0.24,0.16]
Subtotal * **	**633**		**613**			**34.79%**	**-0.19[-0.3,-0.08]**
Heterogeneity: Tau^2=0; Chi^2=3.05, df=2(P=0.22); I^2=34.34%							
Test for overall effect: Z=3.32(P=0)							
Total * **	**1906**		**1718**			**100%**	**-0.19[-0.26,-0.13]**
Heterogeneity: Tau^2=0; Chi^2=8.16, df=11(P=0.7); I^2=0%							
Test for overall effect: Z=5.76(P<0.0001)							
Test for subgroup differences: Chi^2=0.01, df=1 (P=0.93), I^2=0%							



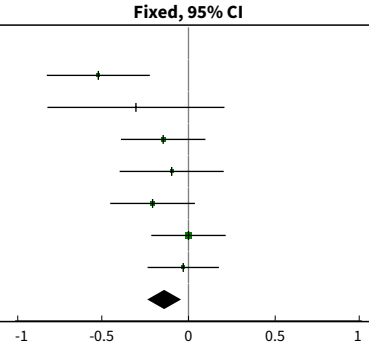
Analysis 14.2. Comparison 14 APPENDIX 4: subgroup analysis by presence/absence of ChEI; 20 mg; six to seven months, Outcome 2 Cognitive Function subgroup analysis by +/- ChEI.

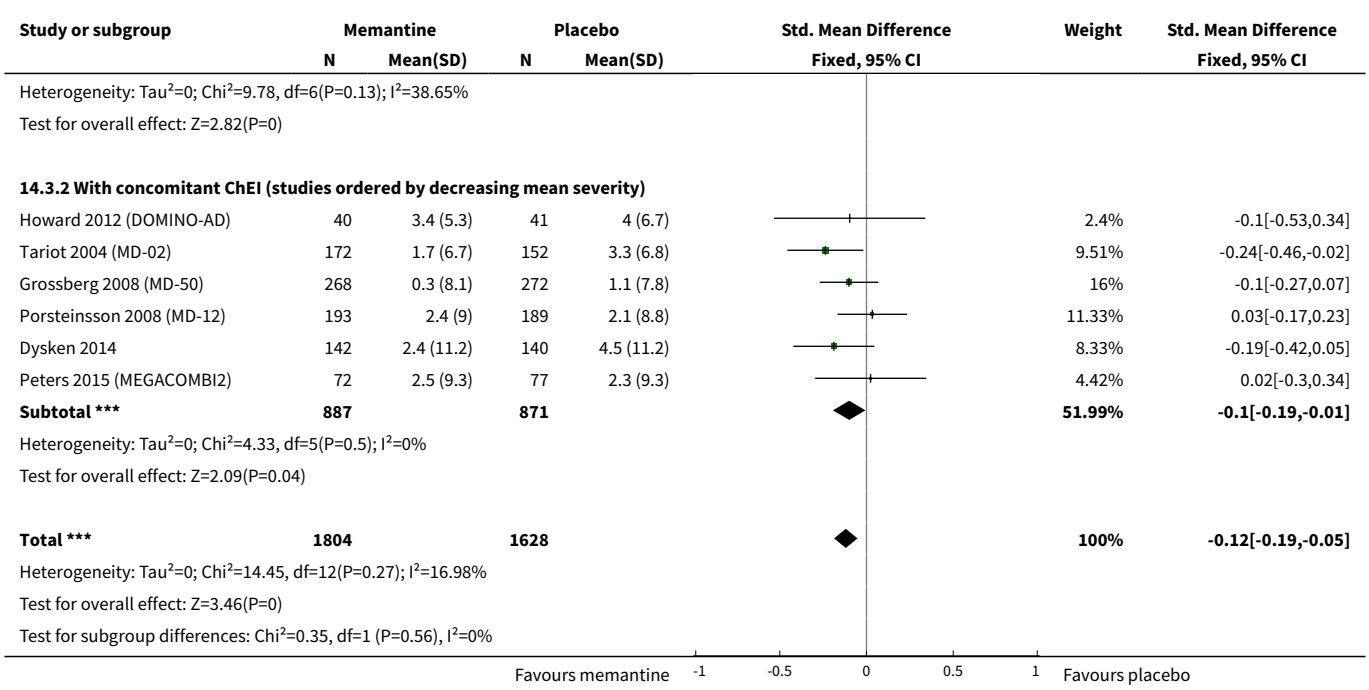
Study or subgroup	Favours memantine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
14.2.1 Monotherapy (studies ordered by decreasing mean severity)							
Reisberg 2003 (9605)	96	4.5 (11.5)	83	10.2 (12.7)		3.93%	-0.47[-0.77,-0.17]
Howard 2012 (DOMINO-AD)	37	1.9 (2.5)	25	4 (3.6)		1.27%	-0.7[-1.22,-0.18]
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		8.14%	-0.42[-0.63,-0.22]
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		5.82%	-0.05[-0.29,0.2]
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		3.76%	-0.48[-0.78,-0.18]
Wang 2013	11	0 (7.2)	11	5.6 (5.9)		0.45%	-0.82[-1.7,0.06]
Peskind 2004 (MD-10)	160	0 (7.8)	162	1 (7.9)		7.28%	-0.13[-0.35,0.09]
Bakchine 2008 (99679)	271	-1.8 (6.9)	137	-1 (6.4)		8.24%	-0.11[-0.31,0.1]
Asada 2011 (MA3301)	187	1.5 (4.7)	180	1.8 (4.6)		8.31%	-0.08[-0.28,0.13]
Schmidt 2008	16	-2.2 (7.4)	17	0.4 (7.2)		0.73%	-0.35[-1.04,0.34]
Subtotal ***	**1186**		**1003**			**47.95%**	**-0.24[-0.32,-0.15]**
Heterogeneity: Tau^2=0; Chi^2=19.96, df=9(P=0.02); I^2=54.91%							
Test for overall effect: Z=5.43(P<0.0001)							
14.2.2 With concomitant ChEI (studies ordered by decreasing mean severity)							
Howard 2012 (DOMINO-AD)	40	0.6 (2.7)	41	1.4 (3.5)		1.82%	-0.26[-0.7,0.18]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		7.2%	-0.37[-0.59,-0.15]
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		12.16%	-0.26[-0.43,-0.09]
Nakamura 2016	268	1.3 (8.2)	269	2.2 (8.1)		12.16%	-0.1[-0.27,0.07]
Porsteinsson 2008 (MD-12)	190	0 (6.6)	187	0.8 (6.4)		8.53%	-0.12[-0.32,0.08]
Dysken 2014	140	1.1 (7.3)	137	3 (7.4)		6.22%	-0.26[-0.5,-0.03]
Peters 2015 (MEGACOMBI2)	90	-0.3 (6.8)	85	0.1 (6.6)		3.96%	-0.06[-0.36,0.24]
Subtotal ***	**1169**		**1143**			**52.05%**	**-0.2[-0.28,-0.12]**
Heterogeneity: Tau^2=0; Chi^2=5.93, df=6(P=0.43); I^2=0%							
Test for overall effect: Z=4.8(P<0.0001)							
Total ***	**2355**		**2146**			**100%**	**-0.22[-0.28,-0.16]**
Heterogeneity: Tau^2=0; Chi^2=26.24, df=16(P=0.05); I^2=39.03%							
Test for overall effect: Z=7.22(P<0.0001)							
Test for subgroup differences: Chi^2=0.35, df=1 (P=0.55), I^2=0%							



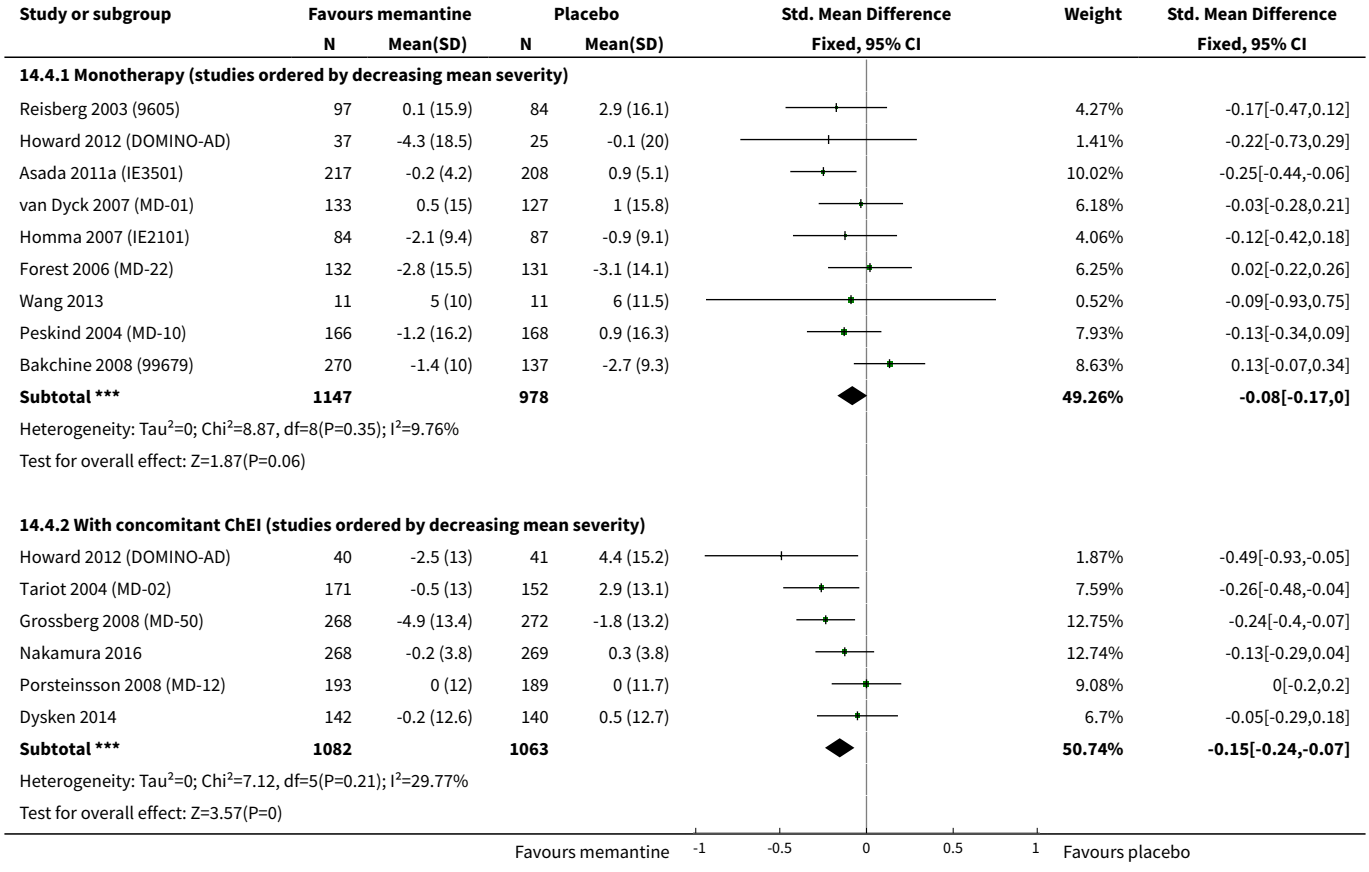
Analysis 14.3. Comparison 14 APPENDIX 4: subgroup analysis by presence/absence of ChEI; 20 mg; six to seven months, Outcome 3 Decline in ADL subgroup analysis by +/- ChEI.

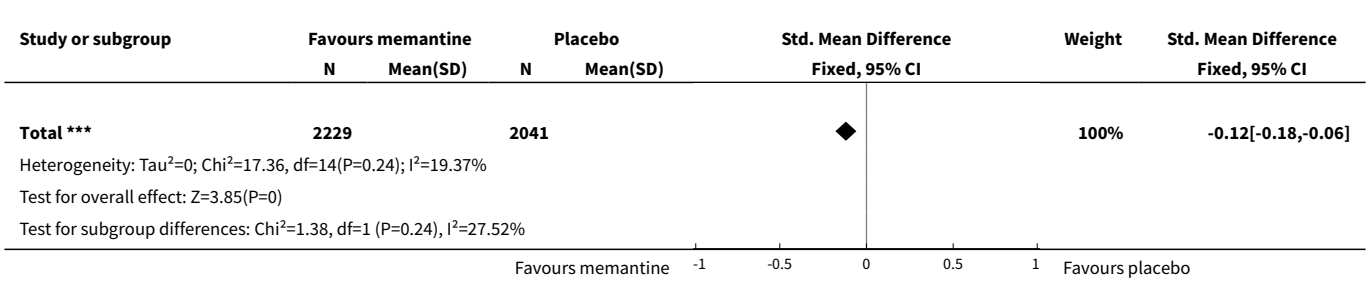
Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
14.3.1 Monotherapy (studies ordered by decreasing mean severity)							
Reisberg 2003 (9605)	97	2.5 (6.3)	84	5.9 (6.8)		5.17%	-0.52[-0.82,-0.22]
Howard 2012 (DOMINO-AD)	37	4.2 (8.3)	25	6.7 (7.6)		1.75%	-0.3[-0.81,0.21]
van Dyck 2007 (MD-01)	133	1.3 (6.9)	127	2.3 (6.8)		7.69%	-0.15[-0.39,0.1]
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		5.07%	-0.1[-0.4,0.2]
Forest 2006 (MD-22)	130	1.9 (6)	129	3.3 (7.4)		7.64%	-0.21[-0.45,0.04]
Peskind 2004 (MD-10)	166	2.3 (10.7)	168	2.3 (10.9)		9.91%	0[-0.21,0.21]
Bakchine 2008 (99679)	270	2.1 (9.2)	137	2.4 (8.4)		10.79%	-0.03[-0.24,0.18]
Subtotal ***	**917**		**757**			**48.01%**	**-0.14[-0.24,-0.04]**





Analysis 14.4. Comparison 14 APPENDIX 4: subgroup analysis by presence/absence of ChEI; 20 mg; six to seven months, Outcome 4 Behaviour and Mood: subgroup analysis by +/- ChEI.





Comparison 15. APPENDIX 4: subgroup analysis by severity/stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Clinical Global	12	3624	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.26, -0.13]
2 Cognitive Function	16	4500	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.27, -0.16]
3 Decline in ADL	12	3432	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.19, -0.05]
4 Behaviour and Mood	14	4270	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.18, -0.06]
5 Clinical Global	12	3624	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.26, -0.13]
5.1 mild to moderate	5	1519	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.26, -0.06]
5.2 moderate to severe	7	2105	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.30, -0.13]
6 Cognitive Function	16	4500	Std. Mean Difference (IV, Fixed, 95% CI)	-0.22 [-0.27, -0.16]
6.1 mild to moderate	7	1959	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.22, -0.04]
6.2 moderate to severe	9	2541	Std. Mean Difference (IV, Fixed, 95% CI)	-0.28 [-0.36, -0.20]
7 Decline in ADL	12	3432	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.19, -0.05]
7.1 mild to moderate	5	1554	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.13, 0.07]
7.2 moderate to severe	7	1878	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.28, -0.10]

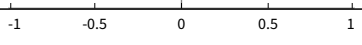
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Behaviour and Mood	14	4270	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.18, -0.06]
8.1 mild to moderate	4	1405	Std. Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.11, 0.10]
8.2 moderate to severe	10	2865	Std. Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.25, -0.10]
9 All-cause discontinuation, by type of disease and severity	23	6571	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.88, 1.09]
9.1 Alzheimer's disease mild-to-moderate	9	2305	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.90, 1.31]
9.2 Alzheimer's disease moderate-to-severe	14	4266	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.83, 1.06]
10 Discontinuation due to adverse events, by disease type and severity	20	6227	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.88, 1.20]
10.1 Alzheimer's disease mild-to-moderate	7	1985	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [1.04, 1.91]
10.2 Alzheimer's disease moderate-to-severe	13	4242	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.10]

Analysis 15.1. Comparison 15 APPENDIX 4: subgroup analysis by severity/stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 1 Clinical Global.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Asada 2011 (MA3301)	187	4.3 (1)	180	4.5 (1)		10.24%	-0.25[-0.45,-0.04]
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		10.29%	-0.11[-0.31,0.1]
Bakchine 2008 (99679)	270	4.1 (1.2)	138	4.2 (1.2)		10.27%	-0.05[-0.25,0.16]
Forest 2006 (MD-22)	131	3.6 (1.4)	129	3.8 (1.3)		7.29%	-0.15[-0.4,0.09]
Grossberg 2008 (MD-50)	269	3.8 (1.1)	272	4.1 (1.2)		15.08%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	4.4 (1.6)	87	4.7 (1.3)		4.78%	-0.22[-0.52,0.08]
Peskind 2004 (MD-10)	164	4.2 (1)	166	4.5 (1.1)		9.18%	-0.29[-0.5,-0.07]
Porsteinsson 2008 (MD-12)	192	4.4 (1)	189	4.4 (1)		10.71%	-0.04[-0.24,0.16]
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		5.02%	-0.27[-0.56,0.03]
Schmidt 2008	16	-0.1 (0.4)	17	0.2 (0.8)		0.9%	-0.47[-1.17,0.22]
Tariot 2004 (MD-02)	172	4.4 (1.1)	152	4.6 (1.1)		9.01%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	134	4.3 (1.1)	127	4.6 (1)		7.26%	-0.28[-0.53,-0.04]
Total * **	**1906**		**1718**			**100%**	**-0.19[-0.26,-0.13]**

Heterogeneity: Tau²=0; Chi²=8.16, df=11(P=0.7); I²=0%

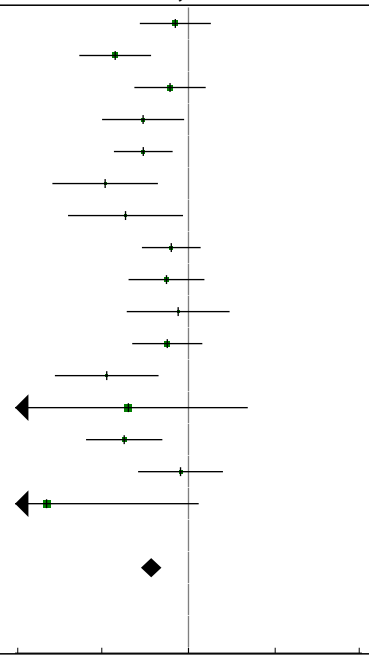
Test for overall effect: Z=5.76(P<0.0001)



Favours memantine — Favours placebo

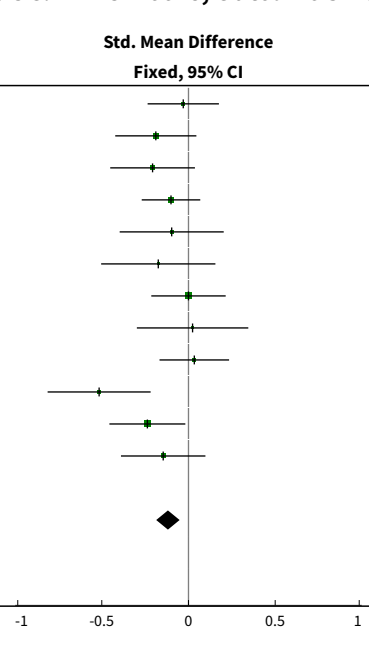
Analysis 15.2. Comparison 15 APPENDIX 4: subgroup analysis by severity/stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 2 Cognitive Function.

Study or subgroup	Memantine		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Asada 2011 (MA3301)	187	1.5 (4.7)	180	1.8 (4.6)		8.31%	-0.08[-0.28,0.13]
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		8.14%	-0.42[-0.63,-0.22]
Bakchine 2008 (99679)	271	-1.8 (6.9)	137	-1 (6.4)		8.24%	-0.11[-0.31,0.1]
Dysken 2014	140	1.1 (7.3)	137	3 (7.4)		6.22%	-0.26[-0.5,-0.03]
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		12.15%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		3.76%	-0.48[-0.78,-0.18]
Howard 2012 (DOMINO-AD)	77	1.2 (2.6)	66	2.4 (3.8)		3.17%	-0.36[-0.69,-0.03]
Nakamura 2016	268	1.3 (8.2)	269	2.2 (8.1)		12.15%	-0.1[-0.27,0.07]
Peskind 2004 (MD-10)	160	0 (7.8)	162	1 (7.9)		7.28%	-0.13[-0.35,0.09]
Peters 2015 (MEGACOMBI2)	90	-0.3 (6.8)	85	0.1 (6.6)		3.96%	-0.06[-0.36,0.24]
Porsteinsson 2008 (MD-12)	190	0 (6.6)	187	0.8 (6.4)		8.53%	-0.12[-0.32,0.08]
Reisberg 2003 (9605)	96	4.5 (11.5)	82	10.2 (12.7)		3.9%	-0.47[-0.77,-0.17]
Schmidt 2008	16	-2.2 (7.4)	17	0.4 (7.2)		0.73%	-0.35[-1.04,0.34]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		7.19%	-0.37[-0.59,-0.15]
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		5.82%	-0.05[-0.29,0.2]
Wang 2013	11	0 (7.2)	11	5.6 (5.9)		0.45%	-0.82[-1.7,0.06]
Total ***	**2355**		**2145**			**100%**	**-0.22[-0.27,-0.16]**
Heterogeneity: Tau²=0; Chi²=23.68, df=15(P=0.07); I²=36.65%							
Test for overall effect: Z=7.14(P<0.0001)							



Analysis 15.3. Comparison 15 APPENDIX 4: subgroup analysis by severity/stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 3 Decline in ADL.

Study or subgroup	Memantine		Placebo		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Fixed, 95% CI		Fixed, 95% CI
Bakchine 2008 (99679)	270	2.1 (9.2)	137	2.4 (8.4)		10.78%	-0.03[-0.24,0.18]
Dysken 2014	142	2.4 (11.2)	140	4.5 (11.2)		8.33%	-0.19[-0.42,0.05]
Forest 2006 (MD-22)	130	1.9 (6)	129	3.3 (7.4)		7.64%	-0.21[-0.45,0.04]
Grossberg 2008 (MD-50)	268	0.3 (8.1)	272	1.1 (7.8)		15.99%	-0.1[-0.27,0.07]
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		5.06%	-0.1[-0.4,0.2]
Howard 2012 (DOMINO-AD)	77	3.8 (6.9)	66	5 (7.1)		4.2%	-0.17[-0.5,0.16]
Peskind 2004 (MD-10)	166	2.3 (10.7)	168	2.3 (10.9)		9.9%	0[-0.21,0.21]
Peters 2015 (MEGACOMBI2)	72	2.5 (9.3)	77	2.3 (9.3)		4.41%	0.02[-0.3,0.34]
Porsteinsson 2008 (MD-12)	193	2.4 (9)	189	2.1 (8.8)		11.33%	0.03[-0.17,0.23]
Reisberg 2003 (9605)	97	2.5 (6.3)	84	5.9 (6.8)		5.17%	-0.52[-0.81,-0.22]
Tariot 2004 (MD-02)	172	1.7 (6.7)	152	3.3 (6.8)		9.5%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	133	1.3 (6.9)	127	2.3 (6.8)		7.69%	-0.15[-0.39,0.1]
Total ***	**1804**		**1628**			**100%**	**-0.12[-0.19,-0.05]**
Heterogeneity: Tau²=0; Chi²=13.9, df=11(P=0.24); I²=20.84%							
Test for overall effect: Z=3.44(P=0)							



Analysis 15.4. Comparison 15 APPENDIX 4: subgroup analysis by severity/stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 4 Behaviour and Mood.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Asada 2011a (IE3501)	217	-0.2 (4.2)	208	0.9 (5.1)		10.02%	-0.25[-0.44,-0.06]
Bakchine 2008 (99679)	270	-1.4 (10)	137	-2.7 (9.3)		8.62%	0.13[-0.07,0.34]
Dysken 2014	142	-0.2 (12.6)	140	0.5 (12.7)		6.7%	-0.05[-0.29,0.18]
Forest 2006 (MD-22)	132	-2.8 (15.5)	131	-3.1 (14.1)		6.25%	0.02[-0.22,0.26]
Grossberg 2008 (MD-50)	268	-4.9 (13.4)	272	-1.8 (13.2)		12.75%	-0.24[-0.4,-0.07]
Homma 2007 (IE2101)	84	-2.1 (9.4)	87	-0.9 (9.1)		4.06%	-0.12[-0.42,0.18]
Howard 2012 (DOMINO-AD)	77	-3.4 (15.8)	66	2.7 (17.2)		3.32%	-0.37[-0.7,-0.04]
Nakamura 2016	268	-0.2 (3.8)	269	0.3 (3.8)		12.74%	-0.13[-0.29,0.04]
Peskind 2004 (MD-10)	166	-1.2 (16.2)	168	0.9 (16.3)		7.92%	-0.13[-0.34,0.09]
Porsteinsson 2008 (MD-12)	193	0 (12)	189	0 (11.7)		9.08%	0[-0.2,0.2]
Reisberg 2003 (9605)	97	0.1 (15.9)	84	2.9 (16.1)		4.26%	-0.17[-0.47,0.12]
Tariot 2004 (MD-02)	171	-0.5 (13)	152	2.9 (13.1)		7.59%	-0.26[-0.48,-0.04]
van Dyck 2007 (MD-01)	133	0.5 (15)	127	1 (15.8)		6.18%	-0.03[-0.28,0.21]
Wang 2013	11	5 (10)	11	6 (11.5)		0.52%	-0.09[-0.93,0.75]
Total * **	**2229**		**2041**			**100%**	**-0.12[-0.18,-0.06]**
Heterogeneity: Tau^2=0; Chi^2=16.72, df=13(P=0.21); I^2=22.24%							
Test for overall effect: Z=3.85(P=0)							

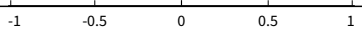
Favours memantine — Favours placebo

Analysis 15.5. Comparison 15 APPENDIX 4: subgroup analysis by severity/stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 5 Clinical Global.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
15.5.1 mild to moderate							
Asada 2011 (MA3301)	187	4.3 (1)	180	4.5 (1)		10.24%	-0.25[-0.45,-0.04]
Bakchine 2008 (99679)	270	4.1 (1.2)	138	4.2 (1.2)		10.27%	-0.05[-0.25,0.16]
Peskind 2004 (MD-10)	164	4.2 (1)	166	4.5 (1.1)		9.18%	-0.29[-0.5,-0.07]
Porsteinsson 2008 (MD-12)	192	4.4 (1)	189	4.4 (1)		10.71%	-0.04[-0.24,0.16]
Schmidt 2008	16	-0.1 (0.4)	17	0.2 (0.8)		0.9%	-0.47[-1.17,0.22]
Subtotal * **	**829**		**690**			**41.29%**	**-0.16[-0.26,-0.06]**
Heterogeneity: Tau^2=0; Chi^2=5.26, df=4(P=0.26); I^2=23.97%							
Test for overall effect: Z=3.03(P=0)							
15.5.2 moderate to severe							
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		10.29%	-0.11[-0.31,0.1]
Forest 2006 (MD-22)	131	3.6 (1.4)	129	3.8 (1.3)		7.29%	-0.15[-0.4,0.09]
Grossberg 2008 (MD-50)	269	3.8 (1.1)	272	4.1 (1.2)		15.08%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	4.4 (1.6)	87	4.7 (1.3)		4.78%	-0.22[-0.52,0.08]
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		5.02%	-0.27[-0.56,0.03]
Tariot 2004 (MD-02)	172	4.4 (1.1)	152	4.6 (1.1)		9.01%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	134	4.3 (1.1)	127	4.6 (1)		7.26%	-0.28[-0.53,-0.04]
Subtotal * **	**1077**		**1028**			**58.71%**	**-0.22[-0.3,-0.13]**
Heterogeneity: Tau^2=0; Chi^2=2.13, df=6(P=0.91); I^2=0%							
Test for overall effect: Z=4.97(P<0.0001)							

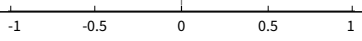
Favours memantine — Favours placebo

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Total ***	**1906**		**1718**			**100%**	**-0.19[-0.26,-0.13]**
Heterogeneity: Tau^2=0; Chi^2=8.16, df=11(P=0.7); I^2=0%							
Test for overall effect: Z=5.76(P<0.0001)							
Test for subgroup differences: Chi^2=0.77, df=1 (P=0.38), I^2=0%							



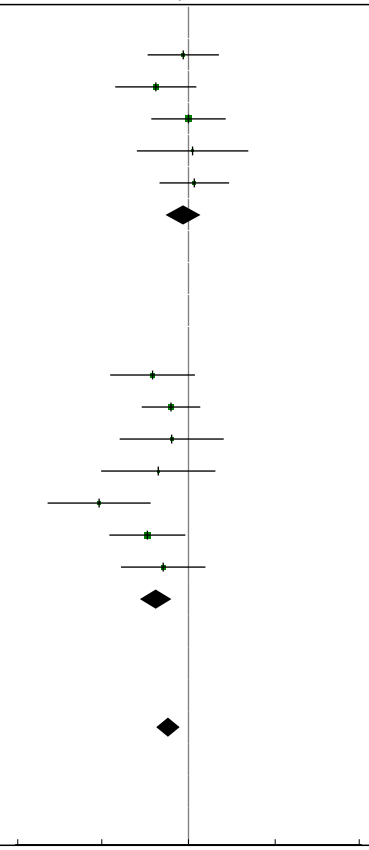
Analysis 15.6. Comparison 15 APPENDIX 4: subgroup analysis by severity/stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 6 Cognitive Function.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
15.6.1 mild to moderate							
Asada 2011 (MA3301)	187	1.5 (4.7)	180	1.8 (4.6)		8.31%	-0.08[-0.28,0.13]
Bakchine 2008 (99679)	271	-1.8 (6.9)	137	-1 (6.4)		8.24%	-0.11[-0.31,0.1]
Dysken 2014	140	1.1 (7.3)	137	3 (7.4)		6.22%	-0.26[-0.5,-0.03]
Peskind 2004 (MD-10)	160	0 (7.8)	162	1 (7.9)		7.28%	-0.13[-0.35,0.09]
Peters 2015 (MEGACOMBI2)	90	-0.3 (6.8)	85	0.1 (6.6)		3.96%	-0.06[-0.36,0.24]
Porsteinsson 2008 (MD-12)	190	0 (6.6)	187	0.8 (6.4)		8.53%	-0.12[-0.32,0.08]
Schmidt 2008	16	-2.2 (7.4)	17	0.4 (7.2)		0.73%	-0.35[-1.04,0.34]
Subtotal ***	**1054**		**905**			**43.27%**	**-0.13[-0.22,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=2.11, df=6(P=0.91); I^2=0%							
Test for overall effect: Z=2.82(P=0)							
15.6.2 moderate to severe							
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		8.14%	-0.42[-0.63,-0.22]
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		12.15%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		3.76%	-0.48[-0.78,-0.18]
Howard 2012 (DOMINO-AD)	77	1.2 (2.6)	66	2.4 (3.8)		3.17%	-0.36[-0.69,-0.03]
Nakamura 2016	268	1.3 (8.2)	269	2.2 (8.1)		12.15%	-0.1[-0.27,0.07]
Reisberg 2003 (9605)	96	4.5 (11.5)	82	10.2 (12.7)		3.9%	-0.47[-0.77,-0.17]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		7.19%	-0.37[-0.59,-0.15]
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		5.82%	-0.05[-0.29,0.2]
Wang 2013	11	0 (7.2)	11	5.6 (5.9)		0.45%	-0.82[-1.7,0.06]
Subtotal ***	**1301**		**1240**			**56.73%**	**-0.28[-0.36,-0.2]**
Heterogeneity: Tau^2=0; Chi^2=15.37, df=8(P=0.05); I^2=47.95%							
Test for overall effect: Z=7.02(P<0.0001)							
Total ***	**2355**		**2145**			**100%**	**-0.22[-0.27,-0.16]**
Heterogeneity: Tau^2=0; Chi^2=23.68, df=15(P=0.07); I^2=36.65%							
Test for overall effect: Z=7.14(P<0.0001)							
Test for subgroup differences: Chi^2=6.2, df=1 (P=0.01), I^2=83.86%							



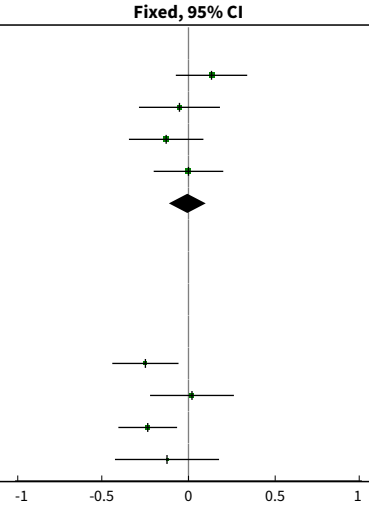
Analysis 15.7. Comparison 15 APPENDIX 4: subgroup analysis by severity/stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 7 Decline in ADL.

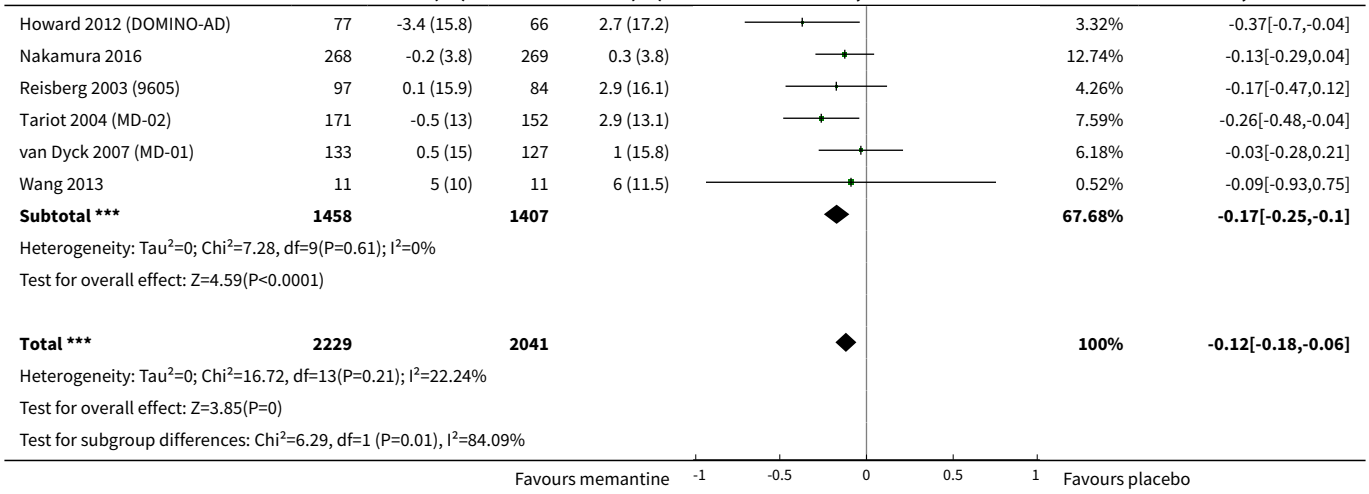
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
15.7.1 mild to moderate							
Bakchine 2008 (99679)	270	2.1 (9.2)	137	2.4 (8.4)		10.78%	-0.03[-0.24,0.18]
Dysken 2014	142	2.4 (11.2)	140	4.5 (11.2)		8.33%	-0.19[-0.42,0.05]
Peskind 2004 (MD-10)	166	2.3 (10.7)	168	2.3 (10.9)		9.9%	0[-0.21,0.21]
Peters 2015 (MEGACOMBI2)	72	2.5 (9.3)	77	2.3 (9.3)		4.41%	0.02[-0.3,0.34]
Porsteinsson 2008 (MD-12)	193	2.4 (9)	189	2.1 (8.8)		11.33%	0.03[-0.17,0.23]
Subtotal ***	**843**		**711**			**44.75%**	**-0.03[-0.13,0.07]**
Heterogeneity: Tau^2=0; Chi^2=2.33, df=4(P=0.68); I^2=0%							
Test for overall effect: Z=0.61(P=0.54)							
15.7.2 moderate to severe							
Forest 2006 (MD-22)	130	1.9 (6)	129	3.3 (7.4)		7.64%	-0.21[-0.45,0.04]
Grossberg 2008 (MD-50)	268	0.3 (8.1)	272	1.1 (7.8)		15.99%	-0.1[-0.27,0.07]
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		5.06%	-0.1[-0.4,0.2]
Howard 2012 (DOMINO-AD)	77	3.8 (6.9)	66	5 (7.1)		4.2%	-0.17[-0.5,0.16]
Reisberg 2003 (9605)	97	2.5 (6.3)	84	5.9 (6.8)		5.17%	-0.52[-0.81,-0.22]
Tariot 2004 (MD-02)	172	1.7 (6.7)	152	3.3 (6.8)		9.5%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	133	1.3 (6.9)	127	2.3 (6.8)		7.69%	-0.15[-0.39,0.1]
Subtotal ***	**961**		**917**			**55.25%**	**-0.19[-0.28,-0.1]**
Heterogeneity: Tau^2=0; Chi^2=6.38, df=6(P=0.38); I^2=6%							
Test for overall effect: Z=4.08(P<0.0001)							
Total ***	**1804**		**1628**			**100%**	**-0.12[-0.19,-0.05]**
Heterogeneity: Tau^2=0; Chi^2=13.9, df=11(P=0.24); I^2=20.84%							
Test for overall effect: Z=3.44(P=0)							
Test for subgroup differences: Chi^2=5.18, df=1 (P=0.02), I^2=80.71%							



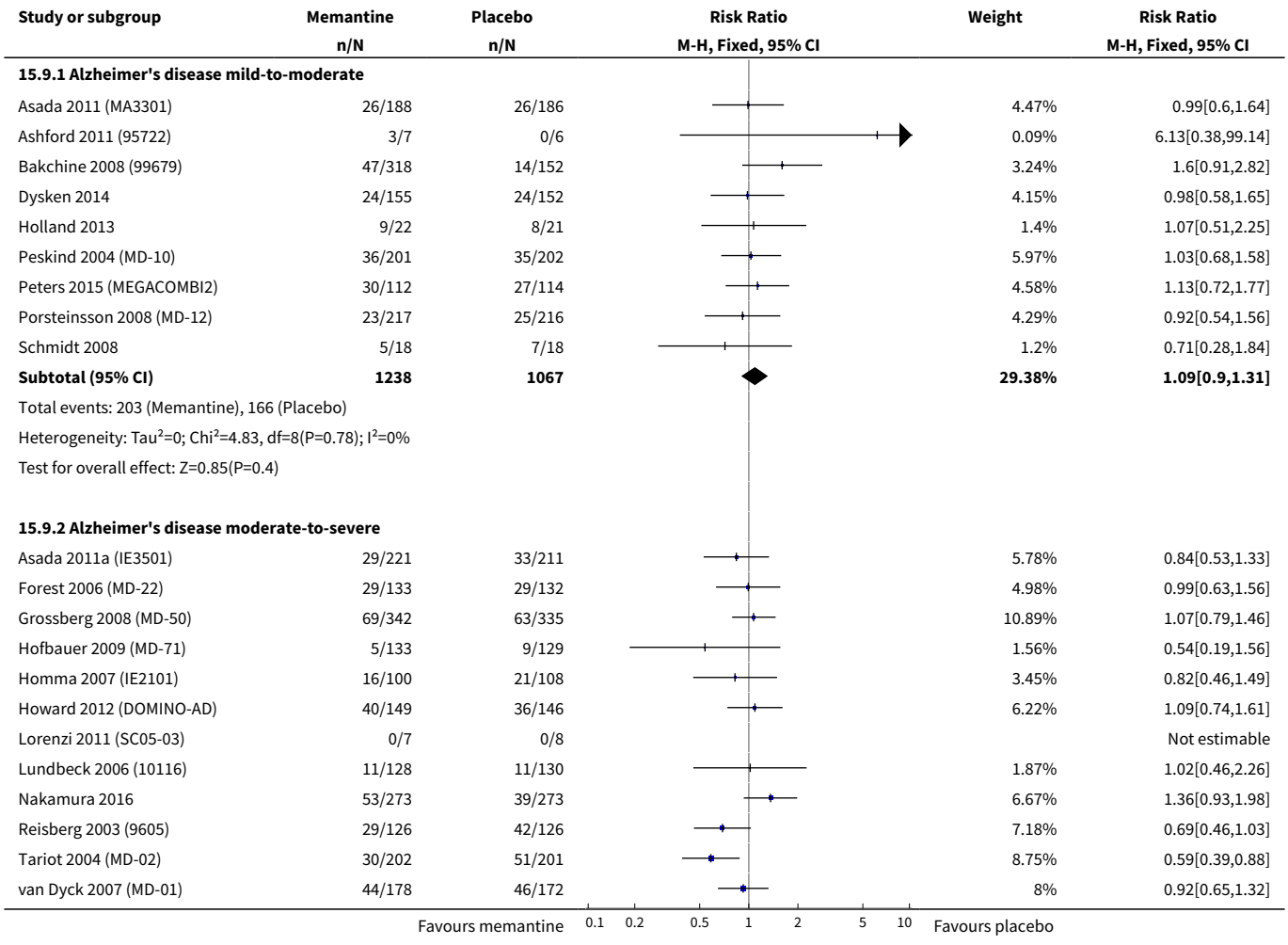
Analysis 15.8. Comparison 15 APPENDIX 4: subgroup analysis by severity/stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 8 Behaviour and Mood.

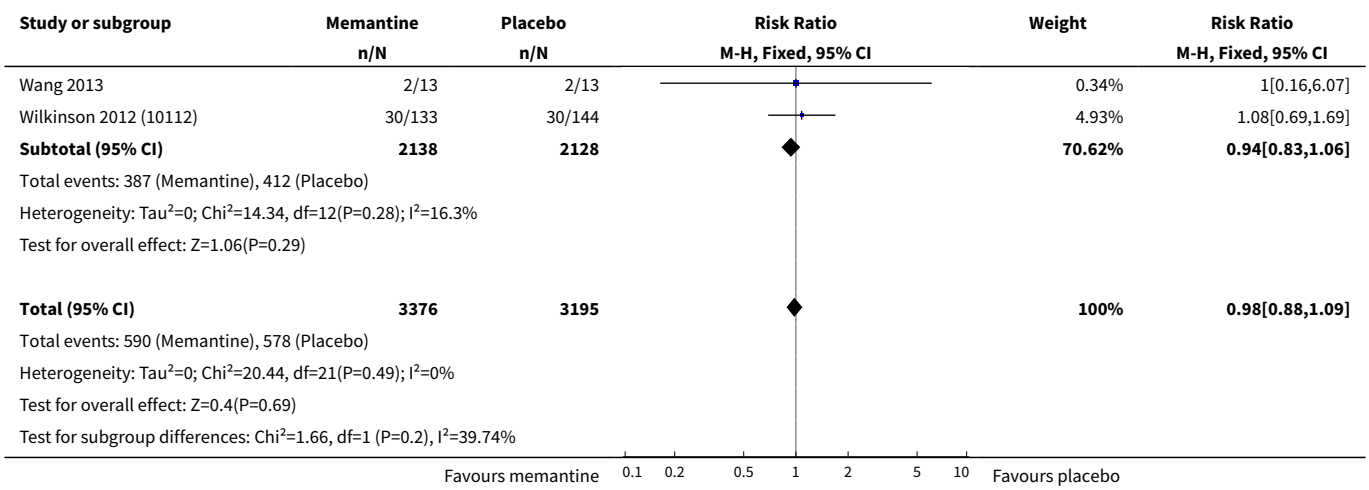
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
15.8.1 mild to moderate							
Bakchine 2008 (99679)	270	-1.4 (10)	137	-2.7 (9.3)		8.62%	0.13[-0.07,0.34]
Dysken 2014	142	-0.2 (12.6)	140	0.5 (12.7)		6.7%	-0.05[-0.29,0.18]
Peskind 2004 (MD-10)	166	-1.2 (16.2)	168	0.9 (16.3)		7.92%	-0.13[-0.34,0.09]
Porsteinsson 2008 (MD-12)	193	0 (12)	189	0 (11.7)		9.08%	0[-0.2,0.2]
Subtotal ***	**771**		**634**			**32.32%**	**-0.01[-0.11,0.1]**
Heterogeneity: Tau^2=0; Chi^2=3.16, df=3(P=0.37); I^2=4.93%							
Test for overall effect: Z=0.13(P=0.9)							
15.8.2 moderate to severe							
Asada 2011a (IE3501)	217	-0.2 (4.2)	208	0.9 (5.1)		10.02%	-0.25[-0.44,-0.06]
Forest 2006 (MD-22)	132	-2.8 (15.5)	131	-3.1 (14.1)		6.25%	0.02[-0.22,0.26]
Grossberg 2008 (MD-50)	268	-4.9 (13.4)	272	-1.8 (13.2)		12.75%	-0.24[-0.4,-0.07]
Homma 2007 (IE2101)	84	-2.1 (9.4)	87	-0.9 (9.1)		4.06%	-0.12[-0.42,0.18]



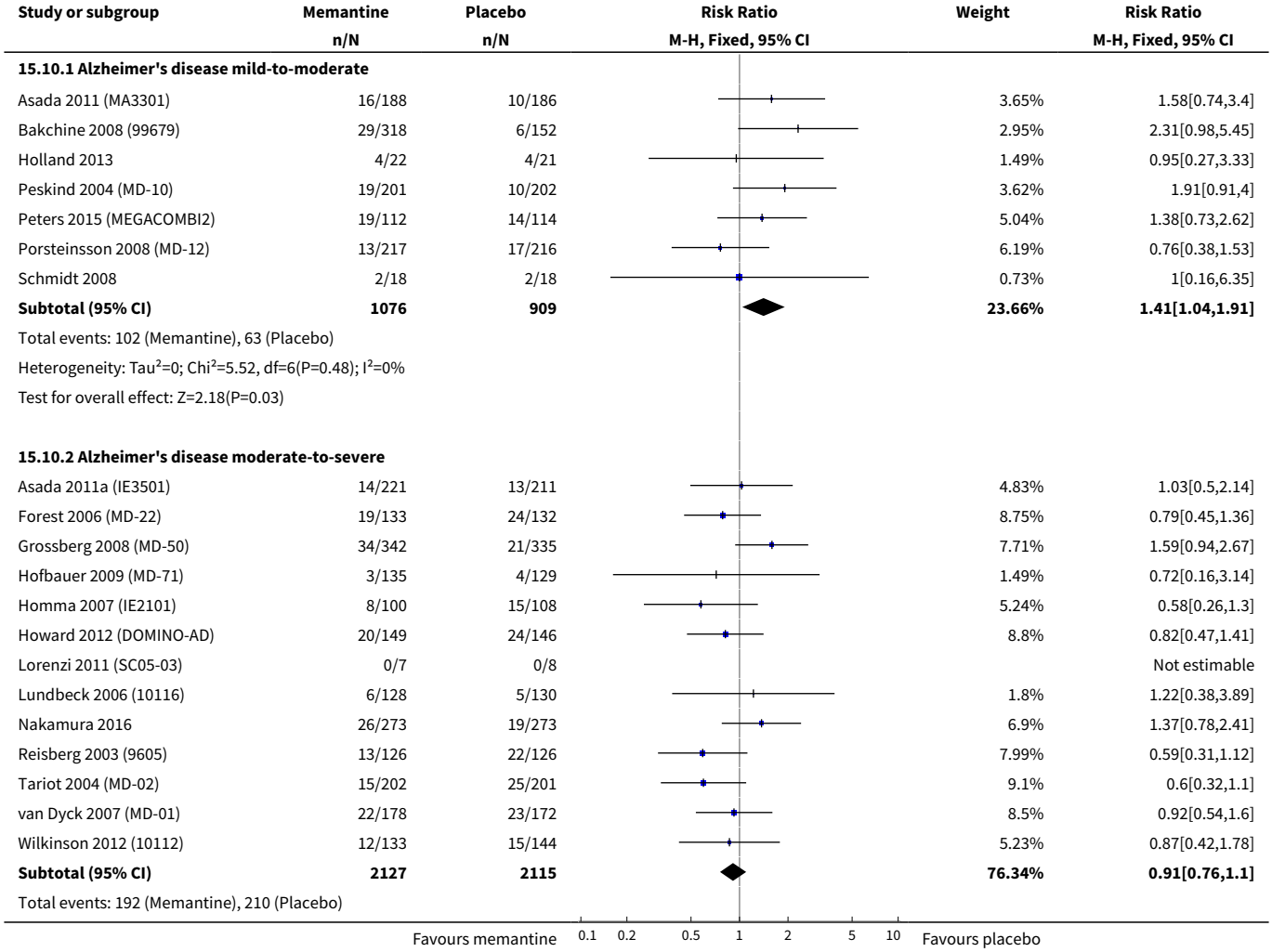


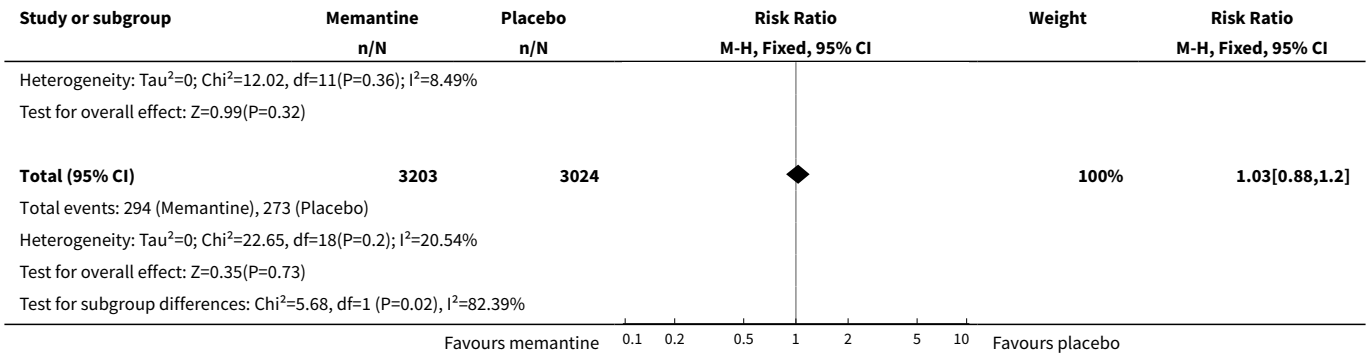
Analysis 15.9. Comparison 15 APPENDIX 4: subgroup analysis by severity/stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 9 All-cause discontinuation, by type of disease and severity.





Analysis 15.10. Comparison 15 APPENDIX 4: subgroup analysis by severity/ stage of AD: memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 10 Discontinuation due to adverse events, by disease type and severity.





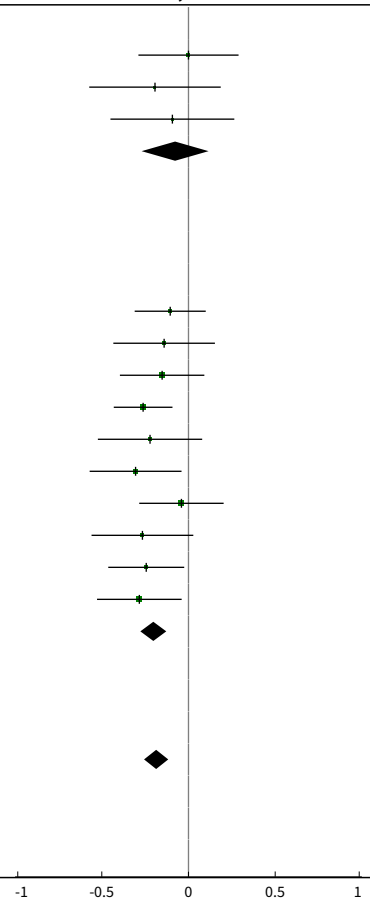
Comparison 16. APPENDIX 4: subgroup analysis by severity/stage of AD: mild versus moderate/severe memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global - mild vs moderate/severe	10	3224	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.26, -0.12]
1.1 mild	3	427	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.27, 0.12]
1.2 moderate to severe	10	2797	Std. Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.28, -0.13]
2 Cognitive Function - mild vs moderate/severe	13	3955	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.30, -0.17]
2.1 mild	4	619	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.19, 0.13]
2.2 moderate to severe	13	3336	Std. Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.34, -0.21]
3 Decline in ADL - mild vs moderate/severe	11	3308	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.20, -0.06]
3.1 mild	4	621	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.14, 0.18]
3.2 moderate to severe	11	2687	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.24, -0.09]
4 Behaviour and Mood - mild vs moderate/severe	14	4295	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.18, -0.06]
4.1 mild	4	621	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.14, 0.18]
4.2 moderate to severe	14	3674	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.21, -0.08]

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5 All-cause discontinuation - mild vs moderate/severe	19	5922	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.87, 1.08]
5.1 mild	5	722	Risk Ratio (M-H, Fixed, 95% CI)	1.74 [1.08, 2.81]
5.2 moderate to severe	18	5200	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.83, 1.04]
6 Discontinuations due to adverse events - mild vs moderate/severe	20	6150	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.86, 1.18]
6.1 Mild	6	948	Risk Ratio (M-H, Fixed, 95% CI)	1.71 [1.06, 2.76]
6.2 Moderate to severe	18	5202	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.11]

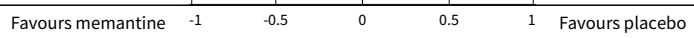
Analysis 16.1. Comparison 16 APPENDIX 4: subgroup analysis by severity/stage of AD: mild versus moderate/severe memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 1 Clinical Global - mild vs moderate/severe.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
16.1.1 mild							
Bakchine 2008 (99679) SG	125	4 (1.3)	73	4 (1.2)		5.84%	0[-0.29,0.29]
Peskind 2004 (MD-10) SG	58	3.9 (1)	50	4.1 (1.1)		3.38%	-0.19[-0.57,0.19]
Porsteinsson 2008(MD-12)S	57	4.1 (1)	64	4.2 (0.9)		3.81%	-0.09[-0.45,0.26]
Subtotal ***	**240**		**187**			**13.04%**	**-0.08[-0.27,0.12]**
Heterogeneity: Tau^2=0; Chi^2=0.64, df=2(P=0.73); I^2=0%							
Test for overall effect: Z=0.78(P=0.43)							
16.1.2 moderate to severe							
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		11.59%	-0.11[-0.31,0.1]
Bakchine 2008 (99679) SG	145	4.2 (1.1)	65	4.4 (1.2)		5.67%	-0.14[-0.43,0.15]
Forest 2006 (MD-22)	131	3.6 (1.4)	129	3.8 (1.3)		8.21%	-0.15[-0.4,0.09]
Grossberg 2008 (MD-50)	269	3.8 (1.1)	272	4.1 (1.2)		16.98%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	4.4 (1.6)	87	4.7 (1.3)		5.38%	-0.22[-0.52,0.08]
Peskind 2004 (MD-10) SG	106	4.4 (1)	116	4.7 (1.1)		6.93%	-0.31[-0.57,-0.04]
Porsteinsson 2008(MD-12)S	135	4.5 (1)	125	4.5 (1)		8.22%	-0.04[-0.28,0.2]
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		5.65%	-0.27[-0.56,0.03]
Tariot 2004 (MD-02)	172	4.4 (1.1)	152	4.6 (1.1)		10.15%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	134	4.3 (1.1)	127	4.6 (1)		8.18%	-0.28[-0.53,-0.04]
Subtotal ***	**1463**		**1334**			**86.96%**	**-0.2[-0.28,-0.13]**
Heterogeneity: Tau^2=0; Chi^2=4.7, df=9(P=0.86); I^2=0%							
Test for overall effect: Z=5.32(P<0.0001)							
Total ***	**1703**		**1521**			**100%**	**-0.19[-0.26,-0.12]**
Heterogeneity: Tau^2=0; Chi^2=6.75, df=12(P=0.87); I^2=0%							
Test for overall effect: Z=5.24(P<0.0001)							
Test for subgroup differences: Chi^2=1.41, df=1 (P=0.23), I^2=29.15%							



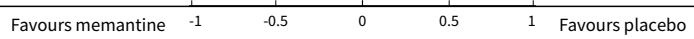
Analysis 16.2. Comparison 16 APPENDIX 4: subgroup analysis by severity/stage of AD: mild versus moderate/severe memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 2 Cognitive Function - mild vs moderate/severe.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
16.2.1 mild							
Bakchine 2008 (99679) SG	125	-2.8 (7.4)	72	-2.6 (6.1)		4.73%	-0.03[-0.32,0.26]
Dysken 2014 SG	105	0.5 (7.1)	89	0.8 (7.2)		4.99%	-0.04[-0.32,0.24]
Peskind 2004 (MD-10) SG	59	-1.4 (10.3)	48	-1.9 (9.1)		2.74%	0.05[-0.33,0.43]
Porsteinsson 2008(MD-12)S	57	-2 (7.7)	64	-1.5 (7)		3.12%	-0.07[-0.42,0.29]
Subtotal ***	**346**		**273**			**15.59%**	**-0.03[-0.19,0.13]**
Heterogeneity: Tau²=0; Chi²=0.22, df=3(P=0.97); I²=0%							
Test for overall effect: Z=0.31(P=0.75)							
16.2.2 moderate to severe							
Asada 2011a (IE3501)	193	0.7 (9.7)	175	5.2 (11.7)		9.3%	-0.42[-0.63,-0.22]
Bakchine 2008 (99679) SG	146	-0.9 (6.4)	65	0.7 (6.4)		4.63%	-0.25[-0.54,0.05]
Dysken 2014 SG	50	3.1 (7.6)	63	6.6 (7.3)		2.81%	-0.48[-0.86,-0.1]
Grossberg 2008 (MD-50)	270	-3 (11.5)	271	0 (11.5)		13.9%	-0.26[-0.43,-0.09]
Homma 2007 (IE2101)	84	-0.4 (6.6)	87	3.7 (10)		4.3%	-0.48[-0.78,-0.18]
Howard 2012 (DOMINO-AD)	77	1.2 (2.6)	66	2.4 (3.8)		3.62%	-0.36[-0.69,-0.03]
Nakamura 2016	268	1.3 (8.2)	269	2.2 (8.1)		13.89%	-0.1[-0.27,0.07]
Peskind 2004 (MD-10) SG	101	0.8 (5.9)	114	2.2 (7)		5.52%	-0.22[-0.48,0.05]
Porsteinsson 2008(MD-12)S	133	0.9 (6)	123	2 (5.8)		6.59%	-0.19[-0.44,0.05]
Reisberg 2003 (9605)	96	4.5 (11.5)	82	10.2 (12.7)		4.46%	-0.47[-0.77,-0.17]
Tariot 2004 (MD-02)	171	-1 (9.2)	153	2.4 (9.2)		8.23%	-0.37[-0.59,-0.15]
van Dyck 2007 (MD-01)	131	1.8 (12.6)	126	2.4 (13.5)		6.65%	-0.05[-0.29,0.2]
Wang 2013	11	0 (7.2)	11	5.6 (5.9)		0.52%	-0.82[-1.7,0.06]
Subtotal ***	**1731**		**1605**			**84.41%**	**-0.27[-0.34,-0.21]**
Heterogeneity: Tau²=0; Chi²=17.16, df=12(P=0.14); I²=30.06%							
Test for overall effect: Z=7.83(P<0.0001)							
Total ***	**2077**		**1878**			**100%**	**-0.24[-0.3,-0.17]**
Heterogeneity: Tau²=0; Chi²=25.24, df=16(P=0.07); I²=36.6%							
Test for overall effect: Z=7.31(P<0.0001)							
Test for subgroup differences: Chi²=7.86, df=1 (P=0.01), I²=87.27%							

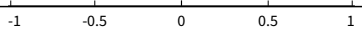


Analysis 16.3. Comparison 16 APPENDIX 4: subgroup analysis by severity/stage of AD: mild versus moderate/severe memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 3 Decline in ADL - mild vs moderate/severe.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
16.3.1 mild							
Bakchine 2008 (99679) SG	124	1.6 (10.3)	73	2 (9.3)		5.67%	-0.05[-0.33,0.24]
Dysken 2014 SG	105	1.9 (11)	89	3 (11)		5.94%	-0.11[-0.39,0.18]
Peskind 2004 (MD-10) SG	59	-0.7 (13)	50	-4.8 (14.7)		3.31%	0.29[-0.09,0.67]
Porsteinsson 2008(MD-12)S	57	-0.5 (12.2)	64	-1.3 (9.3)		3.72%	0.07[-0.28,0.43]
Subtotal ***	**345**		**276**			**18.64%**	**0.02[-0.14,0.18]**
Heterogeneity: Tau²=0; Chi²=3.01, df=3(P=0.39); I²=0.46%							

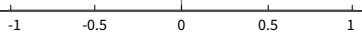


Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Test for overall effect: Z=0.24(P=0.81)							
16.3.2 moderate to severe							
Bakchine 2008 (99679) SG	146	2.6 (8.2)	64	2.8 (7.4)		5.49%	-0.03[-0.32,0.27]
Dysken 2014 SG	50	3.6 (11.2)	63	6.7 (10.9)		3.41%	-0.27[-0.65,0.1]
Forest 2006 (MD-22)	130	1.9 (6)	129	3.3 (7.4)		7.95%	-0.21[-0.45,0.04]
Grossberg 2008 (MD-50)	268	0.3 (8.1)	272	1.1 (7.8)		16.65%	-0.1[-0.27,0.07]
Homma 2007 (IE2101)	84	1.6 (6.1)	87	2.2 (5.4)		5.27%	-0.1[-0.4,0.2]
Howard 2012 (DOMINO-AD)	77	3.8 (6.9)	66	5 (7.1)		4.37%	-0.17[-0.5,0.16]
Peskind 2004 (MD-10) SG	107	4 (8.8)	118	5.3 (7)		6.9%	-0.17[-0.43,0.09]
Porsteinsson 2008(MD-12)S	136	3.6 (7)	125	3.9 (8)		8.04%	-0.03[-0.27,0.21]
Reisberg 2003 (9605)	97	2.5 (6.3)	84	5.9 (6.8)		5.38%	-0.52[-0.81,-0.22]
Tariot 2004 (MD-02)	172	1.7 (6.7)	152	3.3 (6.8)		9.89%	-0.24[-0.46,-0.02]
van Dyck 2007 (MD-01)	133	1.3 (6.9)	127	2.3 (6.8)		8%	-0.15[-0.39,0.1]
Subtotal ***	**1400**		**1287**			**81.36%**	**-0.16[-0.24,-0.09]**
Heterogeneity: Tau^2=0; Chi^2=9, df=10(P=0.53); I^2=0%							
Test for overall effect: Z=4.22(P<0.0001)							
Total ***	**1745**		**1563**			**100%**	**-0.13[-0.2,-0.06]**
Heterogeneity: Tau^2=0; Chi^2=16.16, df=14(P=0.3); I^2=13.36%							
Test for overall effect: Z=3.7(P=0)							
Test for subgroup differences: Chi^2=4.15, df=1 (P=0.04), I^2=75.89%							

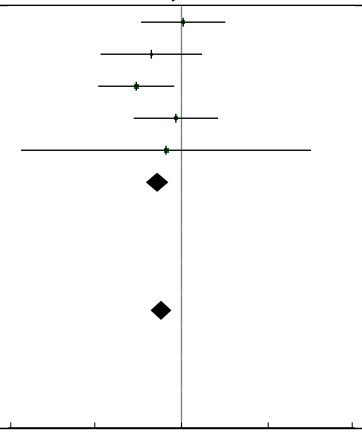


Analysis 16.4. Comparison 16 APPENDIX 4: subgroup analysis by severity/stage of AD: mild versus moderate/severe memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 4 Behaviour and Mood - mild vs moderate/severe.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
16.4.1 mild							
Bakchine 2008 (99679) SG	124	-2.6 (9.5)	73	-3.1 (9)		4.35%	0.05[-0.24,0.34]
Dysken 2014 SG	105	-0.5 (12.5)	89	-1.3 (12.6)		4.56%	0.06[-0.22,0.35]
Peskind 2004 (MD-10) SG	59	-4.8 (21.5)	50	-3.6 (17)		2.56%	-0.06[-0.43,0.32]
Porsteinsson 2008(MD-12)S	57	-2.3 (13.3)	64	-1.7 (12.7)		2.85%	-0.05[-0.41,0.31]
Subtotal ***	**345**		**276**			**14.32%**	**0.02[-0.14,0.18]**
Heterogeneity: Tau^2=0; Chi^2=0.44, df=3(P=0.93); I^2=0%							
Test for overall effect: Z=0.2(P=0.84)							
16.4.2 moderate to severe							
Asada 2011a (IE3501)	217	-0.2 (4.2)	208	0.9 (5.1)		9.98%	-0.25[-0.44,-0.06]
Bakchine 2008 (99679) SG	146	-0.4 (10.4)	64	-2.2 (9.6)		4.2%	0.18[-0.11,0.48]
Dysken 2014 SG	50	0.4 (12.4)	63	2.8 (12.1)		2.63%	-0.19[-0.57,0.18]
Forest 2006 (MD-22)	132	-2.8 (15.5)	131	-3.1 (14.1)		6.22%	0.02[-0.22,0.26]
Grossberg 2008 (MD-50)	268	-4.9 (13.4)	272	-1.8 (13.2)		12.69%	-0.24[-0.4,-0.07]
Homma 2007 (IE2101)	84	-2.1 (9.4)	87	-0.9 (9.1)		4.04%	-0.12[-0.42,0.18]
Howard 2012 (DOMINO-AD)	77	-3.4 (15.8)	66	2.7 (17.2)		3.31%	-0.37[-0.7,-0.04]
Nakamura 2016	268	-0.2 (3.8)	269	0.3 (3.8)		12.68%	-0.13[-0.29,0.04]
Peskind 2004 (MD-10) SG	107	0.8 (12.1)	118	2.8 (15.7)		5.3%	-0.15[-0.41,0.12]

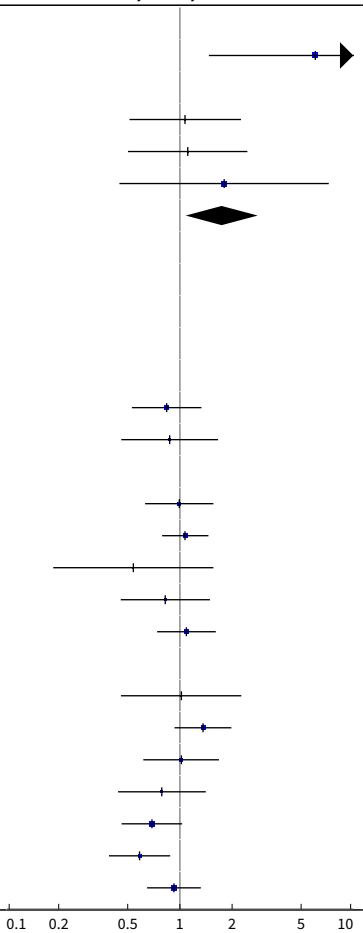


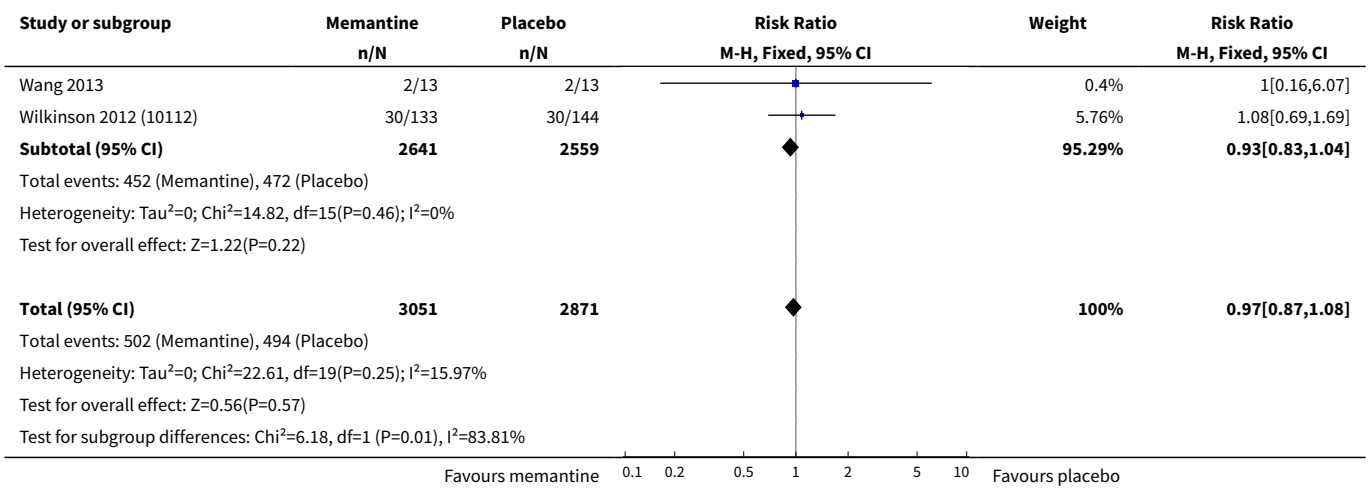
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Porsteinsson 2008(MD-12)S	136	1 (11.3)	125	0.9 (11.1)		6.17%	0.01[-0.23,0.25]
Reisberg 2003 (9605)	97	0.1 (15.9)	84	2.9 (16.1)		4.25%	-0.17[-0.47,0.12]
Tariot 2004 (MD-02)	171	-0.5 (13)	152	2.9 (13.1)		7.55%	-0.26[-0.48,-0.04]
van Dyck 2007 (MD-01)	133	0.5 (15)	127	1 (15.8)		6.15%	-0.03[-0.28,0.21]
Wang 2013	11	5 (10)	11	6 (11.5)		0.52%	-0.09[-0.93,0.75]
Subtotal * **	**1897**		**1777**			**85.68%**	**-0.14[-0.21,-0.08]**
Heterogeneity: Tau^2=0; Chi^2=14.2, df=13(P=0.36); I^2=8.43%							
Test for overall effect: Z=4.23(P<0.0001)							
Total * **	**2242**		**2053**			**100%**	**-0.12[-0.18,-0.06]**
Heterogeneity: Tau^2=0; Chi^2=17.83, df=17(P=0.4); I^2=4.68%							
Test for overall effect: Z=3.84(P=0)							
Test for subgroup differences: Chi^2=3.2, df=1 (P=0.07), I^2=68.74%							



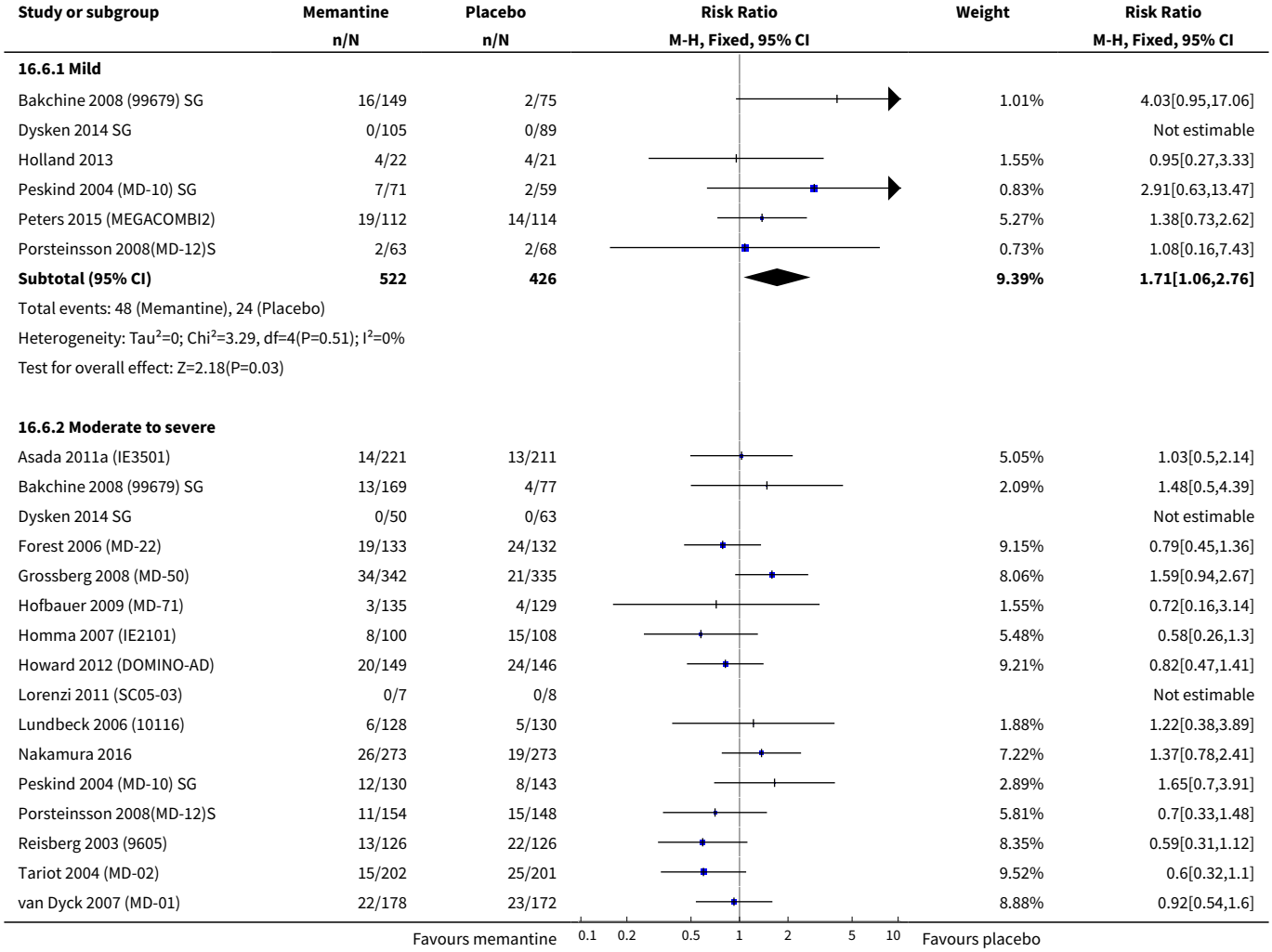
Analysis 16.5. Comparison 16 APPENDIX 4: subgroup analysis by severity/stage of AD: mild versus moderate/severe memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 5 All-cause discontinuation - mild vs moderate/severe.

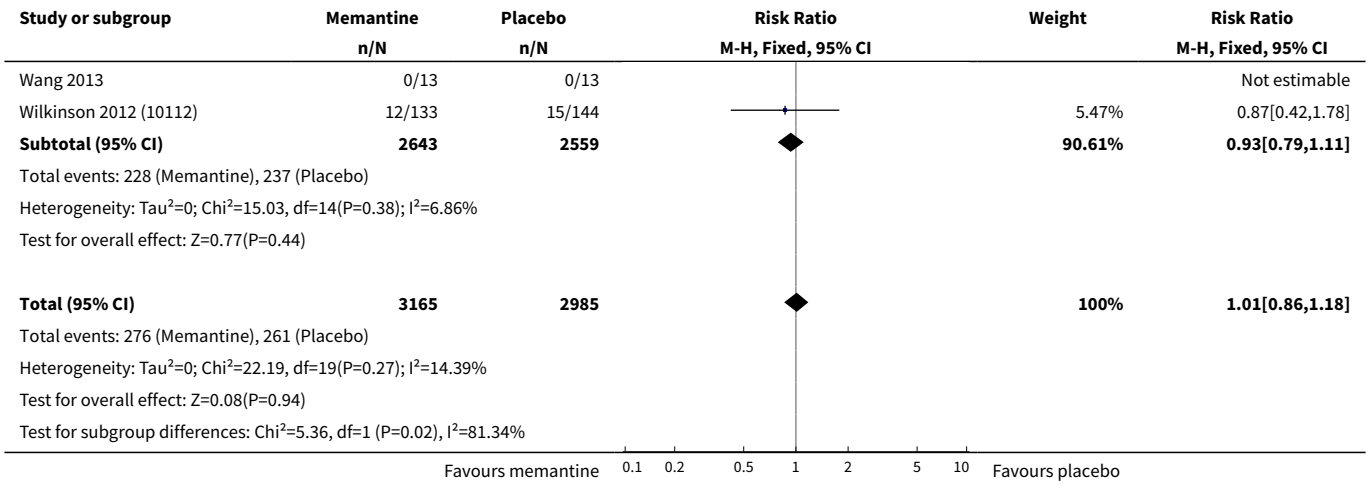
Study or subgroup	Memantine n/N	Placebo n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
16.5.1 mild					
Bakchine 2008 (99679) SG	24/149	2/75		0.53%	6.04[1.47,24.88]
Dysken 2014 SG	0/105	0/89			Not estimable
Holland 2013	9/22	8/21		1.64%	1.07[0.51,2.25]
Peskind 2004 (MD-10) SG	12/71	9/59		1.97%	1.11[0.5,2.45]
Porsteinsson 2008(MD-12)S	5/63	3/68		0.58%	1.8[0.45,7.22]
Subtotal (95% CI)	**410**	**312**		**4.71%**	**1.74[1.08,2.81]**
Total events: 50 (Memantine), 22 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=5.84, df=3(P=0.12); I^2=48.6%					
Test for overall effect: Z=2.26(P=0.02)					
16.5.2 moderate to severe					
Asada 2011a (IE3501)	29/221	33/211		6.75%	0.84[0.53,1.33]
Bakchine 2008 (99679) SG	23/169	12/77		3.3%	0.87[0.46,1.66]
Dysken 2014 SG	0/50	0/63			Not estimable
Forest 2006 (MD-22)	29/133	29/132		5.82%	0.99[0.63,1.56]
Grossberg 2008 (MD-50)	69/342	63/335		12.73%	1.07[0.79,1.46]
Hofbauer 2009 (MD-71)	5/133	9/129		1.83%	0.54[0.19,1.56]
Homma 2007 (IE2101)	16/100	21/108		4.04%	0.82[0.46,1.49]
Howard 2012 (DOMINO-AD)	40/149	36/146		7.27%	1.09[0.74,1.61]
Lorenzi 2011 (SC05-03)	0/7	0/8			Not estimable
Lundbeck 2006 (10116)	11/128	11/130		2.18%	1.02[0.46,2.26]
Nakamura 2016	53/273	39/273		7.8%	1.36[0.93,1.98]
Peskind 2004 (MD-10) SG	24/130	26/143		4.95%	1.02[0.62,1.68]
Porsteinsson 2008(MD-12)S	18/154	22/148		4.49%	0.79[0.44,1.41]
Reisberg 2003 (9605)	29/126	42/126		8.4%	0.69[0.46,1.03]
Tariot 2004 (MD-02)	30/202	51/201		10.22%	0.59[0.39,0.88]
van Dyck 2007 (MD-01)	44/178	46/172		9.36%	0.92[0.65,1.32]





Analysis 16.6. Comparison 16 APPENDIX 4: subgroup analysis by severity/stage of AD: mild versus moderate/severe memantine 20 mg or equivalent vs placebo. OC. 24-28 weeks, Outcome 6 Discontinuations due to adverse events - mild vs moderate/severe.





Comparison 17. APPENDIX 4: subgroup analysis by severity/stage of AD: severe versus moderate

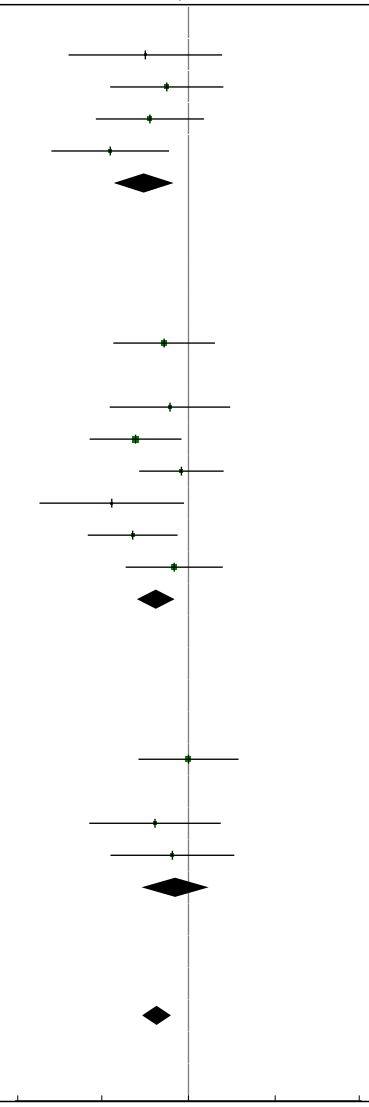
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global: post-hoc within-trial subgroup analyses	8	2597	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.27, -0.10]
1.1 severe (MMSE mean <10)	4	523	Std. Mean Difference (IV, Fixed, 95% CI)	-0.26 [-0.43, -0.09]
1.2 moderate (subgroup MMSE 10 to <20)	8	1453	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.30, -0.08]
1.3 mild (subgroup MMSE ≥20)	4	621	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.27, 0.12]
2 Cognitive Function: post-hoc within-trial subgroup analyses	8	2598	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.34, -0.14]
2.1 severe (MMSE <10)	4	531	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.67, -0.11]
2.2 moderate (subgroup MMSE 10 to <20)	8	1448	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.37, -0.16]
2.3 mild (subgroup MMSE ≥20)	4	619	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.19, 0.13]
3 Decline in ADL: post-hoc within-trial subgroup analyses	8	2615	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.18, -0.02]
3.1 severe (MMSE mean <10)	4	531	Std. Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.35, -0.01]
3.2 moderate (subgroup MMSE 10 to <20)	8	1463	Std. Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.23, -0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.3 mild (subgroup MMSE ≥20)	4	621	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.14, 0.18]
4 Clinical Global: by severity of disease	10	3224	Std. Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.26, -0.12]
4.1 severe (MMSE mean <10)	2	548	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.33, 0.01]
4.2 moderate/severe (MMSE mean 10-12)	5	1557	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.34, -0.14]
4.3 moderate (post hoc within-trial subgroup)	3	692	Std. Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.31, -0.00]
4.4 mild (post hoc within-trial subgroup MMSE ≥20)	3	427	Std. Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.27, 0.12]
5 Cognitive Function: by severity of disease	14	4131	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.29, -0.17]
5.1 severe (MMSE mean <10)	3	690	Std. Mean Difference (IV, Fixed, 95% CI)	-0.42 [-0.57, -0.27]
5.2 moderate/severe (MMSE mean 10-12)	6	1852	Std. Mean Difference (IV, Fixed, 95% CI)	-0.23 [-0.32, -0.14]
5.3 moderate (post hoc within-trial subgroup)	4	795	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.40, -0.11]
5.4 mild (post hoc within-trial subgroup and mean MMSE ≥20)	5	794	Std. Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.17, 0.11]
6 Decline in ADL: by severity of disease	12	3457	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.19, -0.06]
6.1 severe (MMSE mean <10)	2	324	Std. Mean Difference (IV, Fixed, 95% CI)	-0.36 [-0.59, -0.14]
6.2 moderate/severe (MMSE mean 10-12)	5	1554	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.25, -0.05]
6.3 moderate (post hoc within-trial subgroup)	4	809	Std. Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.25, 0.04]
6.4 mild (post hoc within-trial subgroup and mean MMSE ≥20)	5	770	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.12, 0.16]
7 Behaviour and Mood: by severity of disease	14	4295	Std. Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.18, -0.06]
7.1 severe (MMSE mean <10)	3	749	Std. Mean Difference (IV, Fixed, 95% CI)	-0.25 [-0.40, -0.11]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.2 moderate/severe (MMSE mean 10-12)	7	2116	Std. Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.23, -0.06]
7.3 moderate (post hoc within-trial subgroup)	4	809	Std. Mean Difference (IV, Fixed, 95% CI)	-0.02 [-0.17, 0.12]
7.4 mild (post hoc within-trial subgroup MMSE ≥20)	4	621	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.14, 0.18]

Analysis 17.1. Comparison 17 APPENDIX 4: subgroup analysis by severity/stage of AD: severe versus moderate, Outcome 1 Clinical Global: post-hoc within-trial subgroup analyses.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
17.1.1 severe (MMSE mean <10)							
Homma 2007 (IE2101)	40	4.2 (1.6)	39	4.6 (1.2)		3.52%	-0.25[-0.69,0.19]
Reisberg 2003 (9605)	75	4.8 (1.2)	70	4.9 (1.2)		6.5%	-0.13[-0.45,0.2]
Tariot 2004 (MD-02)	89	4.7 (1)	72	4.9 (1)		7.11%	-0.22[-0.53,0.09]
van Dyck 2007 (MD-01)	75	4.4 (1)	63	4.9 (1)		6%	-0.45[-0.79,-0.11]
Subtotal ***	**279**		**244**			**23.13%**	**-0.26[-0.43,-0.09]**
Heterogeneity: Tau²=0; Chi²=1.94, df=3(P=0.59); I²=0%							
Test for overall effect: Z=2.93(P=0)							
17.1.2 moderate (subgroup MMSE 10 to <20)							
Bakchine 2008 (99679) SG	145	4.2 (1.1)	65	4.4 (1.2)		8.05%	-0.14[-0.43,0.15]
Dysken 2014 SG	50	0 (0)	63	0 (0)			Not estimable
Homma 2007 (IE2101)	60	4.5 (1.5)	68	4.6 (1.3)		5.72%	-0.11[-0.45,0.24]
Peskind 2004 (MD-10) SG	106	4.4 (1)	116	4.7 (1.1)		9.84%	-0.31[-0.57,-0.04]
Porsteinsson 2008(MD-12)S	135	4.5 (1)	125	4.5 (1)		11.67%	-0.04[-0.28,0.2]
Reisberg 2003 (9605)	43	4.2 (1.2)	48	4.7 (1.1)		3.98%	-0.44[-0.86,-0.03]
Tariot 2004 (MD-02)	109	4.2 (1)	124	4.5 (1)		10.3%	-0.32[-0.58,-0.06]
van Dyck 2007 (MD-01)	96	4.1 (1.1)	100	4.2 (1.1)		8.8%	-0.08[-0.36,0.2]
Subtotal ***	**744**		**709**			**58.36%**	**-0.19[-0.3,-0.08]**
Heterogeneity: Tau²=0; Chi²=5.47, df=6(P=0.48); I²=0%							
Test for overall effect: Z=3.4(P=0)							
17.1.3 mild (subgroup MMSE ≥20)							
Bakchine 2008 (99679) SG	125	4 (1.3)	73	4 (1.2)		8.29%	0[-0.29,0.29]
Dysken 2014 SG	105	0 (0)	89	0 (0)			Not estimable
Peskind 2004 (MD-10) SG	58	3.9 (1)	50	4.1 (1.1)		4.81%	-0.19[-0.57,0.19]
Porsteinsson 2008(MD-12)S	57	4.1 (1)	64	4.2 (0.9)		5.42%	-0.09[-0.45,0.26]
Subtotal ***	**345**		**276**			**18.51%**	**-0.08[-0.27,0.12]**
Heterogeneity: Tau²=0; Chi²=0.64, df=2(P=0.73); I²=0%							
Test for overall effect: Z=0.78(P=0.43)							
Total ***	**1368**		**1229**			**100%**	**-0.18[-0.27,-0.1]**
Heterogeneity: Tau²=0; Chi²=9.94, df=13(P=0.7); I²=0%							
Test for overall effect: Z=4.35(P<0.0001)							



Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Test for subgroup differences: Chi²=1.89, df=1 (P=0.39), I²=0%							

Favours memantine -1 -0.5 0 0.5 1 Favours placebo

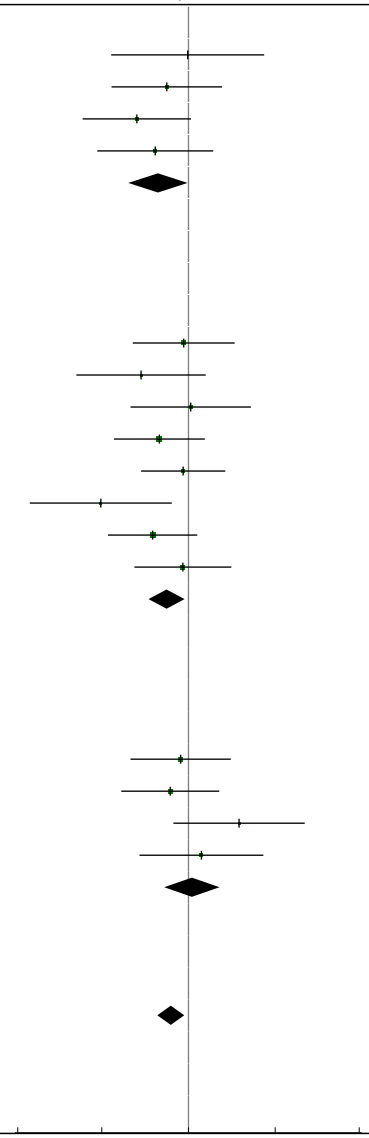
Analysis 17.2. Comparison 17 APPENDIX 4: subgroup analysis by severity/stage of AD: severe versus moderate, Outcome 2 Cognitive Function: post-hoc within-trial subgroup analyses.

Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
17.2.1 severe (MMSE <10)							
Homma 2007 (IE2101)	40	0.8 (6.5)	39	5.1 (12.6)		3.81%	-0.42[-0.87,0.02]
Reisberg 2003 (9605)	79	5.9 (15.1)	73	11.9 (14.1)		6.17%	-0.41[-0.73,-0.08]
Tariot 2004 (MD-02)	89	0.3 (9.1)	72	6.5 (8.7)		6.21%	-0.7[-1.02,-0.38]
van Dyck 2007 (MD-01)	75	5.2 (11)	64	5.6 (11.6)		5.87%	-0.03[-0.37,0.3]
Subtotal ***	**283**		**248**			**22.05%**	**-0.39[-0.67,-0.11]**
Heterogeneity: Tau²=0.05; Chi²=7.91, df=3(P=0.05); I²=62.1%							
Test for overall effect: Z=2.68(P=0.01)							
17.2.2 moderate (subgroup MMSE 10 to <20)							
Bakchine 2008 (99679) SG	146	-0.9 (6.4)	65	0.7 (6.4)		6.95%	-0.25[-0.54,0.05]
Dysken 2014 SG	50	3.1 (7.6)	63	6.6 (7.3)		4.94%	-0.48[-0.86,-0.1]
Homma 2007 (IE2101)	60	-0.7 (6.6)	68	2.5 (7.7)		5.46%	-0.44[-0.79,-0.09]
Peskind 2004 (MD-10) SG	101	0.8 (5.9)	114	2.2 (7)		7.73%	-0.22[-0.48,0.05]
Porsteinsson 2008(MD-12)S	133	0.9 (6)	123	2 (5.8)		8.54%	-0.19[-0.44,0.05]
Reisberg 2003 (9605)	45	-1.6 (15.2)	50	5.8 (14.1)		4.36%	-0.5[-0.91,-0.09]
Tariot 2004 (MD-02)	109	-1.9 (8.7)	124	0 (8.7)		8.09%	-0.23[-0.48,0.03]
van Dyck 2007 (MD-01)	96	-1.2 (10.7)	101	0.6 (10.6)		7.36%	-0.17[-0.45,0.11]
Subtotal ***	**740**		**708**			**53.43%**	**-0.27[-0.37,-0.16]**
Heterogeneity: Tau²=0; Chi²=4.45, df=7(P=0.73); I²=0%							
Test for overall effect: Z=5.03(P<0.0001)							
17.2.3 mild (subgroup MMSE ≥20)							
Bakchine 2008 (99679) SG	125	-2.8 (7.4)	72	-2.6 (6.1)		7.05%	-0.03[-0.32,0.26]
Dysken 2014 SG	105	0.5 (7.1)	89	0.8 (7.2)		7.28%	-0.04[-0.32,0.24]
Peskind 2004 (MD-10) SG	59	-1.4 (10.3)	48	-1.9 (9.1)		4.85%	0.05[-0.33,0.43]
Porsteinsson 2008(MD-12)S	57	-2 (7.7)	64	-1.5 (7)		5.34%	-0.07[-0.42,0.29]
Subtotal ***	**346**		**273**			**24.52%**	**-0.03[-0.19,0.13]**
Heterogeneity: Tau²=0; Chi²=0.22, df=3(P=0.97); I²=0%							
Test for overall effect: Z=0.31(P=0.75)							
Total ***	**1369**		**1229**			**100%**	**-0.24[-0.34,-0.14]**
Heterogeneity: Tau²=0.01; Chi²=22.8, df=15(P=0.09); I²=34.2%							
Test for overall effect: Z=4.86(P<0.0001)							
Test for subgroup differences: Chi²=7.87, df=1 (P=0.02), I²=74.59%							

Favours memantine -1 -0.5 0 0.5 1 Favours placebo

Analysis 17.3. Comparison 17 APPENDIX 4: subgroup analysis by severity/stage of AD: severe versus moderate, Outcome 3 Decline in ADL: post-hoc within-trial subgroup analyses.

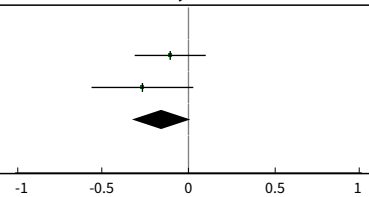
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
17.3.1 severe (MMSE mean <10)							
Homma 2007 (IE2101)	40	1.2 (7.2)	39	1.2 (5.9)		3.1%	-0[-0.45,0.44]
Reisberg 2003 (9605)	79	5.4 (7.3)	73	6.3 (7)		5.94%	-0.13[-0.44,0.19]
Tariot 2004 (MD-02)	89	2.9 (6.2)	72	4.8 (6.3)		6.18%	-0.3[-0.61,0.01]
van Dyck 2007 (MD-01)	75	2.2 (6.5)	64	3.4 (6.5)		5.39%	-0.19[-0.53,0.14]
Subtotal ***	**283**		**248**			**20.61%**	**-0.18[-0.35,-0.01]**
Heterogeneity: Tau^2=0; Chi^2=1.27, df=3(P=0.74); I^2=0%							
Test for overall effect: Z=2.02(P=0.04)							
17.3.2 moderate (subgroup MMSE 10 to <20)							
Bakchine 2008 (99679) SG	146	2.6 (8.2)	64	2.8 (7.4)		6.98%	-0.03[-0.32,0.27]
Dysken 2014 SG	50	3.6 (11.2)	63	6.7 (10.9)		4.33%	-0.27[-0.65,0.1]
Homma 2007 (IE2101)	60	2 (5.5)	68	1.9 (5.5)		5%	0.01[-0.33,0.36]
Peskind 2004 (MD-10) SG	107	4 (8.8)	118	5.3 (7)		8.77%	-0.17[-0.43,0.09]
Porsteinsson 2008(MD-12)S	136	3.6 (7)	125	3.9 (8)		10.22%	-0.03[-0.27,0.21]
Reisberg 2003 (9605)	45	0.8 (7.1)	50	4.3 (6.7)		3.6%	-0.51[-0.91,-0.1]
Tariot 2004 (MD-02)	109	1.1 (6.3)	125	2.4 (6.3)		9.09%	-0.21[-0.46,0.05]
van Dyck 2007 (MD-01)	96	0.6 (6.5)	101	0.8 (6.4)		7.72%	-0.03[-0.31,0.25]
Subtotal ***	**749**		**714**			**55.71%**	**-0.13[-0.23,-0.02]**
Heterogeneity: Tau^2=0; Chi^2=6.45, df=7(P=0.49); I^2=0%							
Test for overall effect: Z=2.38(P=0.02)							
17.3.3 mild (subgroup MMSE ≥20)							
Bakchine 2008 (99679) SG	124	1.6 (10.3)	73	2 (9.3)		7.21%	-0.05[-0.33,0.24]
Dysken 2014 SG	105	1.9 (11)	89	3 (11)		7.55%	-0.11[-0.39,0.18]
Peskind 2004 (MD-10) SG	59	-0.7 (13)	50	-4.8 (14.7)		4.2%	0.29[-0.09,0.67]
Porsteinsson 2008(MD-12)S	57	-0.5 (12.2)	64	-1.3 (9.3)		4.73%	0.07[-0.28,0.43]
Subtotal ***	**345**		**276**			**23.68%**	**0.02[-0.14,0.18]**
Heterogeneity: Tau^2=0; Chi^2=3.01, df=3(P=0.39); I^2=0.46%							
Test for overall effect: Z=0.24(P=0.81)							
Total ***	**1377**		**1238**			**100%**	**-0.1[-0.18,-0.02]**
Heterogeneity: Tau^2=0; Chi^2=13.89, df=15(P=0.53); I^2=0%							
Test for overall effect: Z=2.58(P=0.01)							
Test for subgroup differences: Chi^2=3.16, df=1 (P=0.21), I^2=36.74%							



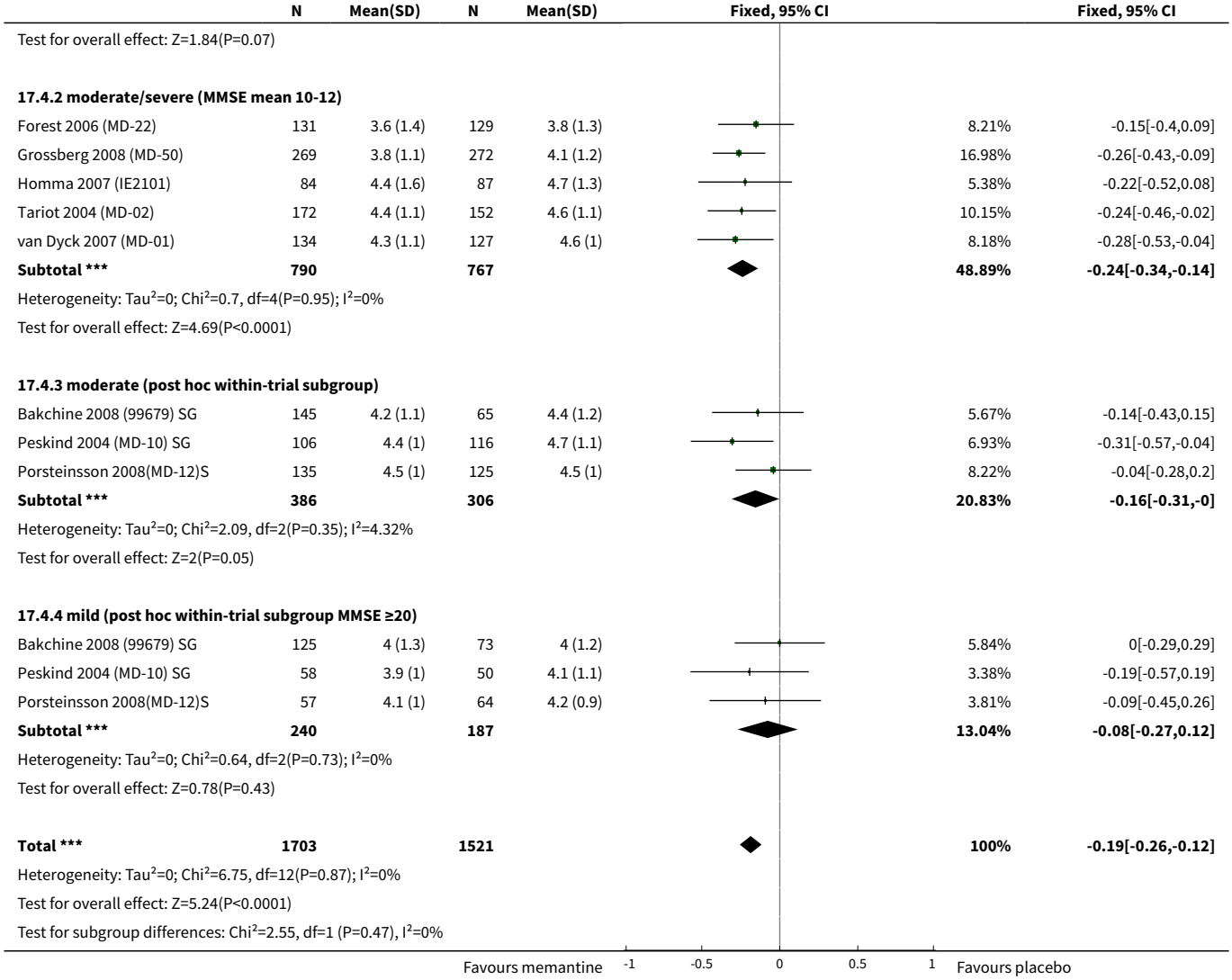
Favours memantine — Favours placebo

Analysis 17.4. Comparison 17 APPENDIX 4: subgroup analysis by severity/stage of AD: severe versus moderate, Outcome 4 Clinical Global: by severity of disease.

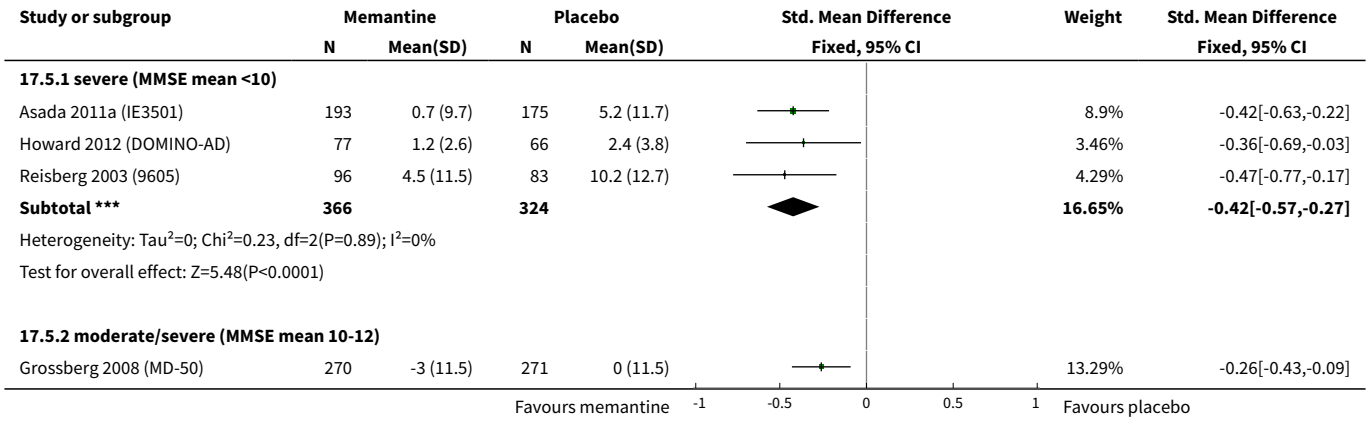
Study or subgroup	Memantine N	Memantine Mean(SD)	Placebo N	Placebo Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
17.4.1 severe (MMSE mean <10)							
Asada 2011a (IE3501)	190	4.5 (1.1)	177	4.6 (1)		11.59%	-0.11[-0.31,0.1]
Reisberg 2003 (9605)	97	4.4 (1.1)	84	4.7 (1.1)		5.65%	-0.27[-0.56,0.03]
Subtotal ***	**287**		**261**			**17.24%**	**-0.16[-0.33,0.01]**
Heterogeneity: Tau^2=0; Chi^2=0.77, df=1(P=0.38); I^2=0%							

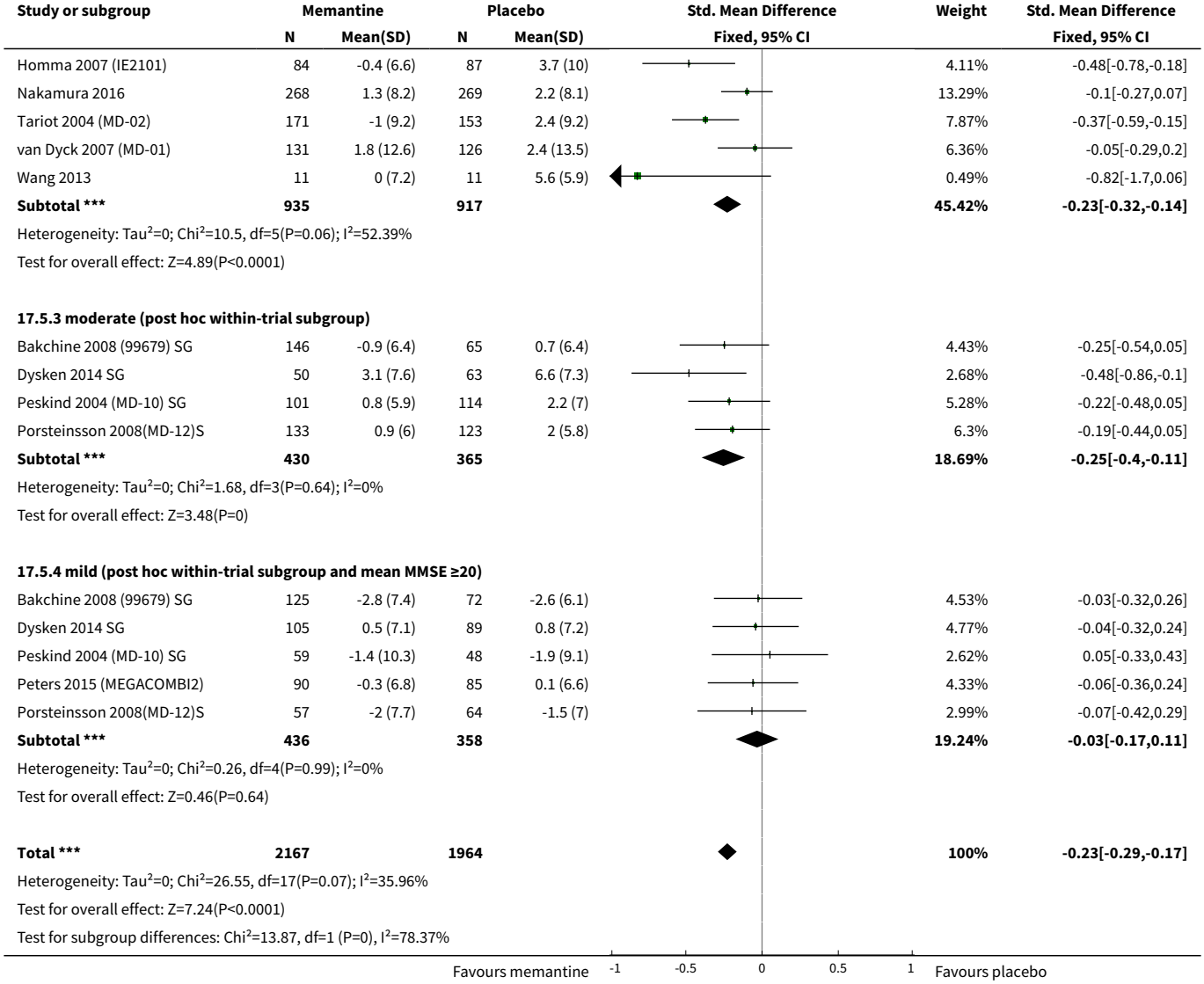


Favours memantine — Favours placebo

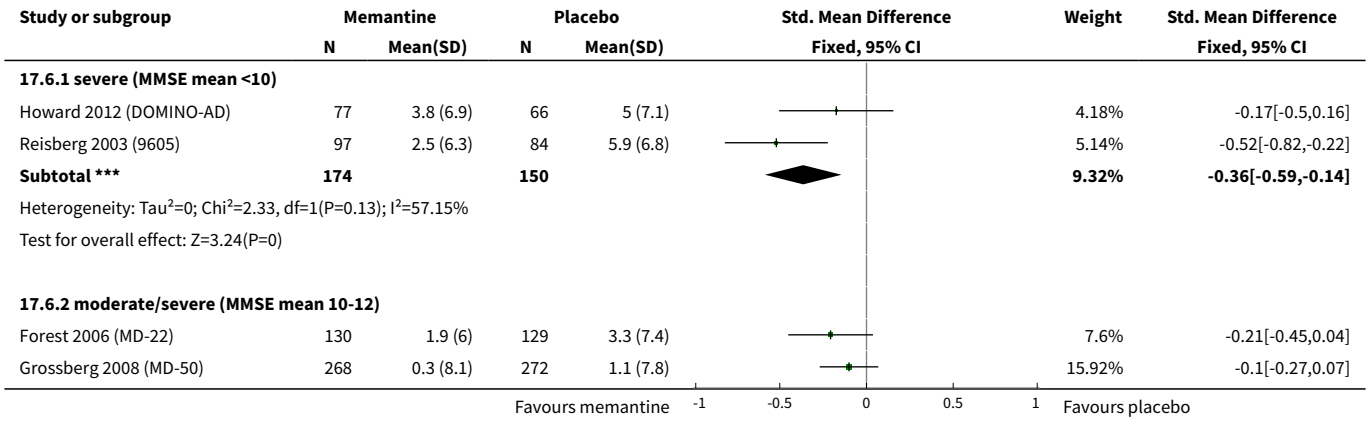


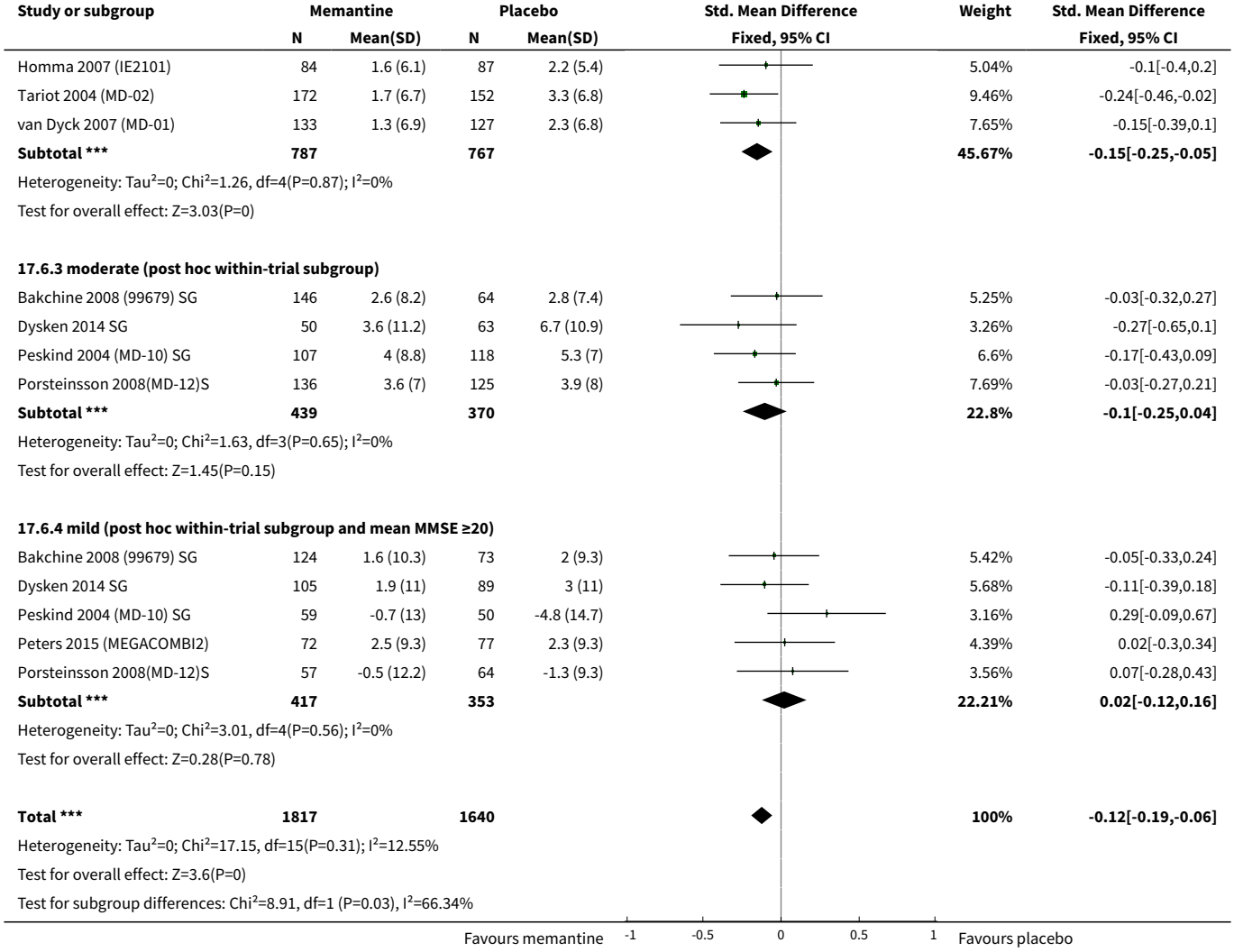
Analysis 17.5. Comparison 17 APPENDIX 4: subgroup analysis by severity/stage of AD: severe versus moderate, Outcome 5 Cognitive Function: by severity of disease.



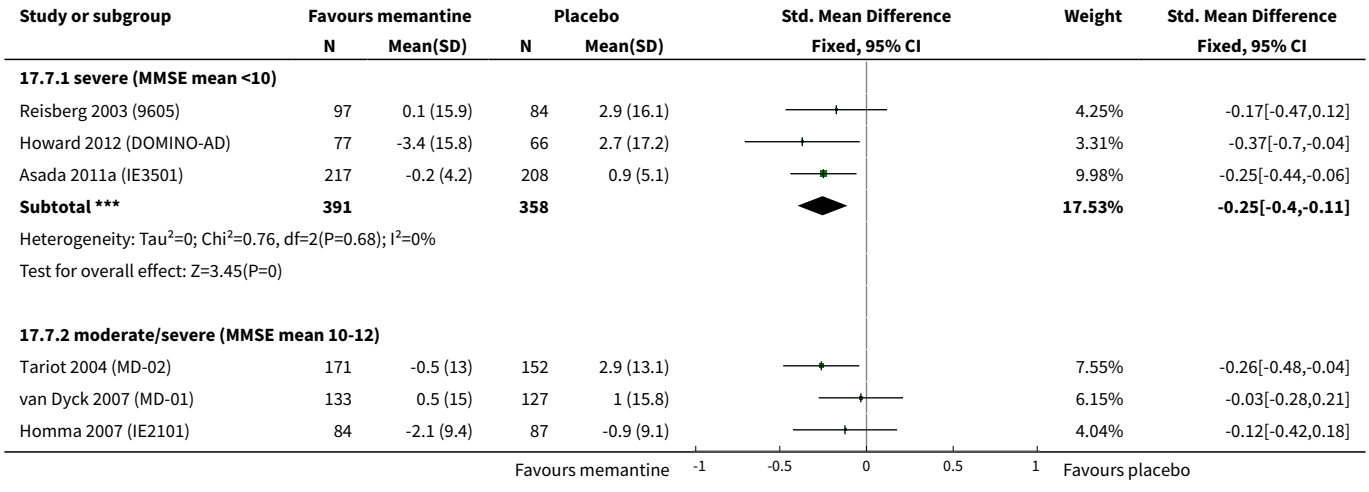


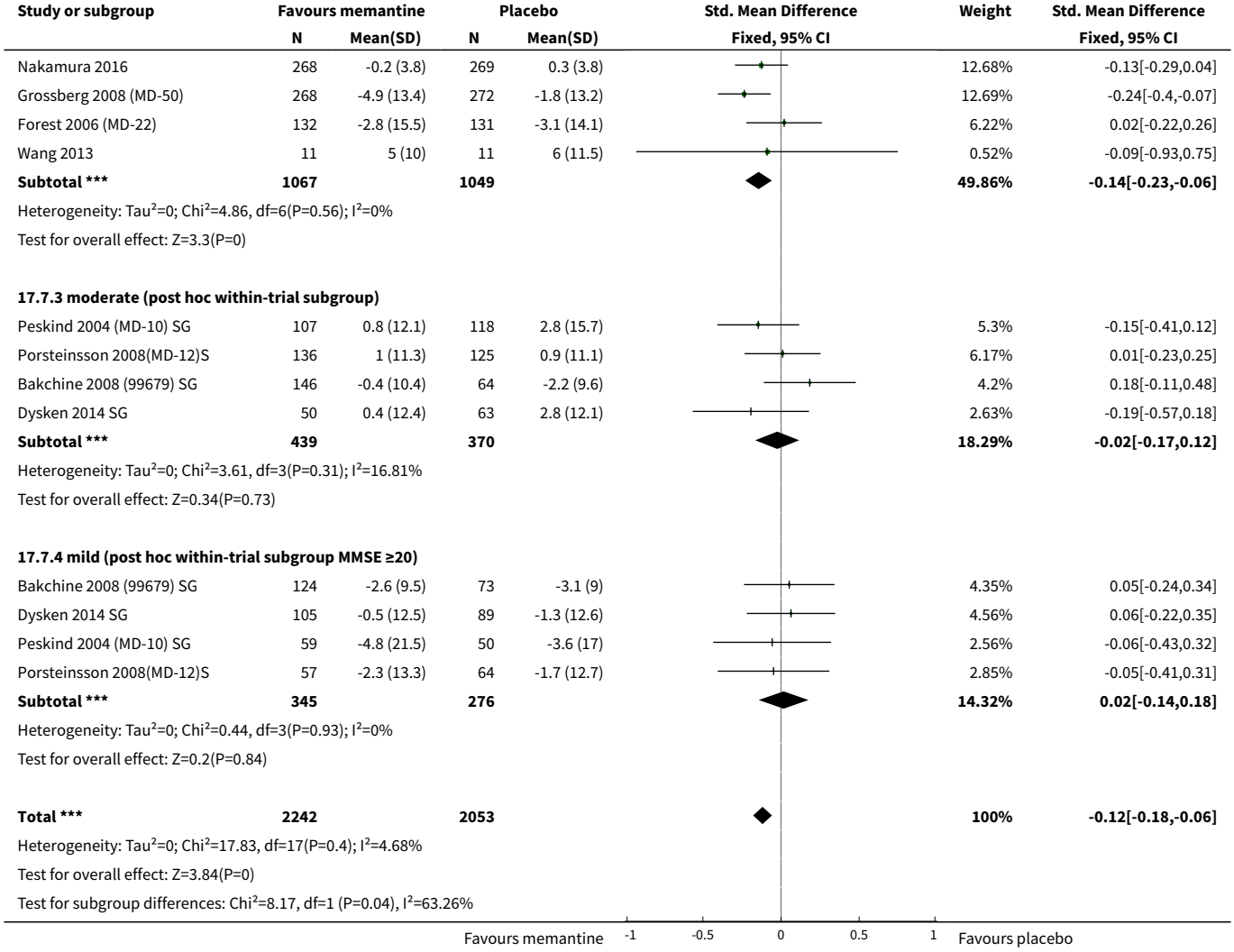
Analysis 17.6. Comparison 17 APPENDIX 4: subgroup analysis by severity/stage of AD: severe versus moderate, Outcome 6 Decline in ADL: by severity of disease.





Analysis 17.7. Comparison 17 APPENDIX 4: subgroup analysis by severity/stage of AD: severe versus moderate, Outcome 7 Behaviour and Mood: by severity of disease.





ADDITIONAL TABLES

Table 1. Efficacy outcome measures in Alzheimer's disease (AD) and vascular dementia trials

Study	Clinical Global	Cognitive function	Decline in ADL	Behaviour and mood	
	CIBIC-Plus	GCP-Cog	ADCS-ADL23	BEHAVE-AD	Other
Alzheimers' disease studies				X	
Asada 2011 (MA3301)	X	X			Japanese versions. DAD, Caregiver-rated Crichton Scale, MMSE, CDR
Asada 2011a (IE3501)	X	X		X	Japanese versions
Ashford 2011 (95722)		X			MMSE
Bakchine 2008 (99679)	X	X	X	X	
Dysken 2014		X	X	X	MMSE, Caregiver activity survey
Forest 2006 (MD-22)	X			X	NPI nursing home version; CMAI
Forest 2006 (MD-23)	X		X	X	CMAI, NPI-Agitation
Fox 2012 (MAGD)	X	X		X	CMAI, MMSE, QOL-AD, incidence of agitation
Herrmann 2012 (10158)	X	X	X	X	CMAI
Grossberg 2008 (MD-50)	X	X	X	X	
Hofbauer 2009 (MD-71)					FLCI, ASHA FACS (caregiver assessment)
Holland 2013		X			DriveABLE On-Road Test, MMSE
Homma 2007 (IE2101)	X	X	X	X	Japanese versions.MMSE, FAST, BEHAVE-AD. ADL scale not stated
Howard 2012 (DOMINO-AD)			X	X	EQ-5D, GHQ-12

Table 1. Efficacy outcome measures in Alzheimer's disease (AD) and vascular dementia trials *(Continued)*

Lorenzi 2011 (SC05-03)			X				Final values only, no change scores
Lundbeck 2006 (10116)			X	X	X		MMSE
Nakamura 2016			X			X	Japanese versions; Crichton scale
Peskind 2004 (MD-10)	X	X		X	X		
Peters 2015 (MEGACOMBI2)		X		X	X		CDR sum of boxes
Porsteinsson 2008 (MD-12)	X	X		X	X		
Reisberg 2003 (9605)	X		X	X	X		FAST; ADL modified for severe dementia
Schmidt 2008		X	X	X	X		MMSE; ADL scale not stated
Tariot 2004 (MD-02)	X		X	X	X		
van Dyck 2007 (MD-01)	X		X	X	X		FAST
Wang 2013			X		X		MMSE, ADAS-Cog
Wilkinson 2012 (10112)			X		X		Change in total brain volume, Agitation
Vascular Dementia or dementia syndrome							
Ditzler 1991	X (PGI scale)			X			Physician's Global Impression, Syndrom Kurztest, SCAG; ADL scale not stated
Gortelmeyer 1992		X		X			GBS, Tapping test, Trace test, SCAG; modified ADL
Orgogozo 2002 (9408)	X		X	X (NOSGER)		X (NOSGER)	CGIC, GBS, MMSE, NOSGER subscales for self-care ADL and disturbing behaviour
Pantev 1993					X		Global assessment of clinical efficacy, NOSIE-Index, SCAG
Wilcock 2002 (9202)		X	X	X (NOSGER)		X (NOSGER)	NOSGER subscales for self-care ADL and disturbing behaviour
Winblad 1999 (9403)		X	X (BGP		X		D-scale, AD subgroup also reported

Table 1. Efficacy outcome measures in Alzheimer's disease (AD) and vascular dementia trials *(Continued)*

				cog- ni- tive sub- scale)			

Table 2. Baseline characteristics of participants in the included studies - Alzheimer's disease (AD)

Study	Number randomised	Diagnosis	Severity of disease	Mean age	Mean MMSE	% female	duration (weeks)
MODERATE-TO-SEVERE AD							
Asada 2011a (IE3501)	432	AD	moderately severe-to-severe	not stated	˜9.9	not stated	24
Forest 2006 (MD-22)	165	AD Nursing home	moderate-to-severe	85.3	˜11.3	85	24
Forest 2006 (MD-23)	34	AD agitation	moderate-to-severe	79.6	3-18	80	12
Fox 2012 (MAGD)	153	AD agitation	moderate-to-severe MMSE < 20	84.1	7.5	72	12
Herrmann 2012 (10158)	369	AD agitation	moderate-to-severe	˜74.9	11.9	˜58.3	24
Grossberg 2008 (MD-50)	677	AD	moderate-to-severe	76.5	10.8	72	24
Hofbauer 2009 (MD-71)	265	AD	moderate	˜74.9	10-19	58	12
Homma 2007 (IE2101)	207	AD	moderate-to-severe MMSE 5-14	73.4	˜10.3	72	24
Howard 2012 (DOMINO-AD)	295	AD	moderate-to-severe (52% severe 5 to 9)	77.1	9.1	65	52
Lorenzi 2011 (SC05-03)	15	AD	moderate-to-severe	76.5	˜14.5	87	26
Lundbeck 2006 (10116)	250	AD	MMSE 5-18	72.3	11.8	60	16
Nakamura 2016	546	AD	moderate-to-severe	˜78.5	˜10.8	˜72.8	24

Table 2. Baseline characteristics of participants in the included studies - Alzheimer's disease (AD) *(Continued)*

Reisberg 2003 (9605)	252	AD	moderately severe-to-severe	76.1	7.9	67	28
Tariot 2004 (MD-02)	404	AD	moderate-to-severe	75.5	9.9	64.8	24
van Dyck 2007 (MD-01)	350	AD	moderate-to-severe	78.2	˜10.1	71.4	24
Winblad 1999 (9403) AD	79	AD	severe	˜74.2	6.7	˜67	12
MILD-TO-MODERATE AD							
Asada 2011 (MA3301)	367	AD	mild-to-moderate MMSE 10-23	not stated	10-23	not stated	24
Ashford 2011 (95722)	13	AD	mild- to-moderate	76	˜21	38	52
Bakchine 2008 (99679)	470	AD	mild-to-moderate 11-23	74	˜18.7	65	26
Dysken 2014	307 and 306 (vit E)	AD	mild-to-moderate	˜79.1	20.8	˜3 (97% male)	5 years
Holland 2013	26	AD	mild	79.3	˜27.9	35	52
Peters 2015 (MEGACOM-BI2)	226	AD	mild-to-moderate	˜72.4	˜22.2	˜63.7	52
Peskind 2004 (MD-10)	403	AD	mild-to-moderate	77.5	17.1	58.8	24
Porsteinsson 2008 (MD-12)	432	AD	mild-to-moderate	˜75.5	˜16.8	˜52	24
Schmidt 2008	37	AD	mild-to-moderate	76.2	19.0	64	52
Wang 2015	22	AD	mild-to-moderate	˜65	˜12.1	64	22
Wilkinson 2012 (10112)	277	AD	moderate	74	16.8	57	52

Table 3. Summary of findings: moderate-to-severe Alzheimer's disease (AD), six to seven months, memantine with concomitant cholinesterase inhibitors (ChEIs)

Memantine 20 mg or equivalent compared to placebo, with concomitant ChEI, for moderate-to-severe AD. 24-30 week data. OC

Population: Alzheimer's disease, moderate-to-severe
Intervention: memantine 20 mg or equivalent, with concomitant ChEI
Comparison: placebo, with concomitant ChEI

Continuous outcomes	Score with placebo (median)	Mean improvement in change score between memantine and placebo	SMD (95% CI) meta-analysis findings	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Clinical Global (CIBIC+) 7-point Likert scale	The median CIBIC+ score was 4.5 [3] (i.e. deterioration with time)	MD: 0.21 (0.06 to 0.36)	-0.21 (-0.32 to -0.09)	1125 (3 RCTs)	⊕⊕⊕⊖ MODERATE [1]	Analysed as mean difference. Random effects (Analysis 2.8) [SMD as a negative outcome (Analysis 2.1)]
Cognitive Function (SIB) 100-point scale	Mean SIB score at baseline: 77.6. Mean change from baseline (positive scale): -1.2 [4] (i.e. slight deterioration with time)	MD: 2.48 (1.45 to 3.41)	-0.24 (-0.33 to -0.14)	1852 (6 RCTs)	⊕⊕⊕⊕ HIGH	SMD as a negative outcome (Analysis 2.2) Converted to SIB scale (and scale direction inverted); median SD(pooled) = 10.34.
Performance on ADL: (ADCS-ADL19) 54-point scale	Mean ADCS-ADL19 score at baseline: 34.3. Mean change from baseline (positive scale): -2.2 [5] (i.e. deterioration over time)	MD: 0.95 (0.22 to 1.76)	-0.13 (-0.24 to -0.03)	1319 (5 RCTs)	⊕⊕⊕⊕ HIGH	SMD for decline in ADL as a negative outcome (Analysis 2.3) Converted to ADCS-ADL19 scale (and scale direction inverted); median SD(pooled) = 7.33.
Behaviour and Mood (NPI) 144-point scale	Median baseline NPI score was 16.5. Median change from baseline (negative scale): 2.80 [6] (i.e. deterioration with time)	MD: 2.20 (1.10 to 3.29)	-0.18 (-0.27 to -0.09)	1855 (6 RCTs)	⊕⊕⊕⊕ HIGH	SMD as a negative outcome (Analysis 2.4) Converted to NPI scale; median SD(pooled) = 12.20

Binary outcomes	Anticipated absolute effects		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo (median)	Risk with memantine				
All-cause discontinuation	168 per 1000	156 per 1000 (139 to 175)	RR 0.93 (0.83 to 1.04)	5087 (17 RCTs) 924 events	⊕⊕⊕⊕ HIGH	RR for all moderate-to-severe AD studies (apart from those with agitation) (Analysis 16.5).

Table 3. Summary of findings: moderate-to-severe Alzheimer's disease (AD), six to seven months, memantine with concomitant cholinesterase inhibitors (ChEIs) *(Continued)*

	Difference: 12 fewer people per 1000 discontinued treatment for any cause (95% CI 29 fewer to 7 more)					Median control group risk for 6 studies in 2089 people with moderate-to-severe AD without agitation, receiving ChEIs (Analysis 2.9)
Number suffering at least one adverse event	639 per 1000 Difference: 19 more people per 1000 suffered adverse events (95% CI 0 to 38 more)	658 per 1000 (639 to 677)	RR 1.03 (1.00 to 1.06)	8033 (29 RCTs) 5371 events	⊕⊕⊕⊕ HIGH	RR from all studies (Analysis 9.3). Median control group risk for moderate-to-severe AD studies in people receiving ChEIs (Analysis 2.11)
Number suffering at least one serious adverse event	114 per 1000 Difference: 10 fewer people per 1000 suffered serious adverse events (95% CI 21 fewer to 2 more)	104 per 1000 (93 to 116)	RR 0.91 (0.82 to 1.02)	6482 (19 RCTs) 918 events	⊕⊕⊕⊕ HIGH	RR and median control risk from all AD studies (except those with agitation) (from Analysis 8.10)
Number suffering agitation as an adverse event	45 per 1000 Difference: 4 fewer people per 1000 suffered agitation as an adverse event (95% CI 18 fewer to 18 more)	41 per 1000 (27 to 63)	RR 0.92 (0.60 to 1.40)	1225 (5 RCTs) 3 79 events	⊕⊕⊖⊖ LOW [2]	RR and median control group risk for studies in people with moderate-to-severe AD without agitation, receiving ChEIs (Analysis 2.13)

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). We adopt the convention that a negative mean difference always means an improvement (i.e. favouring memantine)

CI: confidence interval; **MD:** mean difference; **RR:** Risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Some inconsistency or variation in the point estimates (downgraded once for inconsistency)
[2] 79 events; imprecision around relative effect (CI crossing 1.25 and 0.75)(downgraded twice)
[3] Median control group values for 3 studies reporting CIBIC+ (Grossberg 2008 (MD-50); Porsteinsson 2008(MD-12)S; Tariot 2004 (MD-02))
[4] Mean control group baseline scores and mean control group change from baseline for 2 studies reporting SIB (Grossberg 2008 (MD-50); Tariot 2004 (MD-02))
[5] Mean control group baseline scores and mean control group change from baseline for the 2 studies reporting ADCS-ADL19 (Grossberg 2008 (MD-50); Tariot 2004 (MD-02))
[6] Median control group baseline scores and median control group change from baseline for the 5 studies reporting NPI (Dysken 2014 SG; Grossberg 2008 (MD-50); Howard 2012 (DOMINO-AD); Porsteinsson 2008(MD-12)S; Tariot 2004 (MD-02))

Table 4. Summary of findings: moderate-to-severe Alzheimer's disease (AD), six to seven months, monotherapy

Memantine 20 mg or equivalent compared to placebo, monotherapy, for moderate-to-severe AD. 24-to 30-week data observed case (OC)

Population: Alzheimer's disease, moderate-to-severe
Intervention: memantine 20 mg or equivalent, as monotherapy
Comparison: placebo

Outcomes	Score with placebo (median)	Mean improvement in change score between memantine and placebo	SMD (95% CI) meta-analysis findings	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Clinical Global (CIBIC+) 7-point Likert scale	The median CIBIC+ score was 4.64 [3] (i.e. deterioration with time)	MD: 0.22 (0.11 to 0.33)	-0.20 (-0.30 to -0.10)	1672 (7 RCTs)	⊕⊕⊕⊕ HIGH	SMD as a negative outcome (Analysis 2.1). Converted to CIBIC+ scale; median SD(pooled) = 1.09.
Cognitive Function (SIB) 100-point scale	Median SIB score at baseline: 68.3. Median change from baseline (positive scale): -5.6 [4] (i.e. deterioration with time)	MD: 3.97 (2.77 to 5.18)	-0.33 (-0.43 to -0.23)	1485 (8 RCTs)	⊕⊕⊕⊕ HIGH [1]	SMD as a negative outcome (Analysis 2.2) Converted to SIB scale (and scale direction inverted); median SD(pooled) = 12.04.
Performance on ADL (ADCS-ADL19) 54-point scale	Mean ADCS-ADL19 score at baseline: 30.5. Mean change from baseline (positive scale): -4.1[5] (i.e. deterioration with time)	MD: 1.33 (0.20 to 2.00)	-0.20 (-0.30 to -0.09)	1368 (7 RCTs)	⊕⊕⊕⊕ HIGH	SMD for decline in ADL as a negative outcome (Analysis 2.3) Converted to ADCS-ADL19 scale (and scale direction inverted); median SD(pooled) = 6.67.
Behaviour and Mood (NPI) 144-point scale	Median baseline NPI score was 18.5. Median change from baseline (negative scale): 1.95 [6] (i.e. slight deterioration with time)	MD: 1.57 (0.16 to 2.98)	-0.10 (-0.19 to -0.01)	1819 (9 RCTs)	⊕⊕⊕⊕ HIGH	SMD as a negative outcome (Analysis 2.4) Converted to NPI scale; median SD(pooled) = 15.70.

Binary outcomes	Anticipated absolute effects		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo (median)	Risk with memantine				
All-cause discontinuation	188 per 1000	175 per 1000 (156 to 196)	RR 0.93 (0.83 to 1.04)	5087 (17 RCTs) 924 events	⊕⊕⊕⊕ HIGH	RR for all studies in people with moderate-to-severe AD (apart from those with agitation) (Analysis 16.5).

Table 4. Summary of findings: moderate-to-severe Alzheimer's disease (AD), six to seven months, monotherapy *(Continued)*

	Difference: 13 fewer people per 1000 discontinued treatment for any cause (95% CI 32 fewer to 8 more)					Median control group risk for 10 studies in 2459 people with moderate-to-severe AD without agitation, receiving monotherapy (Analysis 2.9)
Number suffering at least one adverse event	760 per 1000	783 per 1000 (760 to 806)	RR 1.03 (1.00 to 1.06)	8033 (29 RCTs) 5371 events	⊕⊕⊕⊕ HIGH	RR from all studies (Analysis 9.3).Median control group risk for moderate-to-severe AD studies in people receiving monotherapy (Analysis 2.11)
	Difference: 23 more people per 1000 suffered adverse events (95% CI 0 to 46 more)					
Number suffering at least one serious adverse event	114 per 1000	104 per 1000 (93 to 116)	RR 0.91 (0.82 to 1.02)	6482 (19 RCTs) 918 events	⊕⊕⊕⊕ HIGH	RR and median control risk from all AD studies (except those with agitation) (from Analysis 8.10)
	Difference: 10 fewer people per 1000 suffered serious adverse events (95% CI 21 fewer to 2 more)					
Number suffering agitation as an adverse event	164 per 1000	112 per 1000 (84 to 149)	RR 0.68 (0.51 to 0.91)	1016 (4 RCTs) 154 events	⊕⊕⊕⊖ MODERATE [2]	RR and median control group risk for studies in people with moderate-to-severe AD without agitation, receiving monotherapy (Analysis 2.13)
	Difference: 52 fewer people per 1000 suffered agitation as an adverse event (95% CI 80 to 15 fewer)					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** Risk ratio; **OR:** Odds ratio;

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Some inconsistency in point estimates, but insufficient to downgrade
[2] Some imprecision (193 events and borderline for CI crossing 1; CI crossed 0.75) and some inconsistency in point estimates - downgrade once overall
[3] Median control group values for 4 studies reporting CIBIC+ (Bakchine 2008 (99679) SG; Peskind 2004 (MD-10) SG; Reisberg 2003 (9605); van Dyck 2007 (MD-01))
[4] Median control group baseline scores and mean control group change from baseline for 3 studies reporting SIB (Reisberg 2003 (9605); van Dyck 2007 (MD-01); Wang 2013)
[5] Mean control group baseline scores and mean control group change from baseline for the 2 studies reporting ADCS-ADL19 (Reisberg 2003 (9605); van Dyck 2007 (MD-01))
[6] Median control group baseline scores and median control group change from baseline for the 4 studies reporting NPI (Howard 2012 (DOMINO-AD); Reisberg 2003 (9605); van Dyck 2007 (MD-01); Wang 2013)

Table 5. Summary of findings: moderate-to-severe Alzheimer's disease (AD), selected for agitation

Memantine 20 mg or equivalent compared to placebo, for moderate-to-severe AD, selected for agitation

Population: Alzheimer's disease, moderate-to-severe, selected for agitation
Intervention: memantine 20 mg or equivalent
Comparison: placebo

Outcomes	Score with placebo (median)	Mean improvement in change score between memantine and placebo	SMD (95% CI) meta-analysis findings	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Clinical Global (CIBIC+) 7-point Likert scale	The CIBIC+ score from one study was 4.63 [5] (i.e. deterioration with time)	MD: 0.14 (-0.17 to 0.44) (random effects) 24 week study only: MD: -0.05 (-0.35 to 0.25) (Herrmann 2012 (10158))	-0.11 (-0.34 to 0.13) (random effects)	443 (3 RCTs) 24 week study: 275 participants	⊕⊕⊖⊖ LOW[1]	SMD as a negative outcome (Analysis 3.5). Heterogeneity between 12 weeks (2 studies) and 24 weeks. Converted to CIBIC+ scale; SD(pooled) = 1.29 (Herrmann 2012 (10158)).
Cognitive Function (SIB) 100-point scale	Mean SIB score at baseline: 68.1. Median change from baseline (positive scale): -5.23 [6] (i.e. deterioration with time)	MD: 4.34 (-5.89 to 14.58) (random effects) 24 week study only: MD: -0.48 (-2.57 to 1.61) (Herrmann 2012 (10158))	-0.24 (-0.84 to 0.36) (random effects)	453 (2 RCTs)	⊕⊖⊖⊖ VERY LOW[2]	Analysed as mean difference (Analysis 3.6). [SMD as a negative outcome]
Performance on ADL (ADCS-ADL19) 54-point scale	Mean ADCS-ADL19 score at baseline: 32.5. Mean change from baseline (positive scale): -1.08[7] (i.e. slight deterioration with time)	MD: -1.48 (-3.15 to 0.19)	0.21 (-0.02 to 0.43)	309 (2 RCTs)	⊕⊕⊖⊖ LOW[3]	Analysed as mean difference (Analysis 3.7) [SMD for decline in ADL as a negative outcome]
Behaviour and Mood (NPI) 144-point scale	Median baseline NPI score was 33.3. Median change from baseline (negative scale): -8.6 [8] (i.e. improvement with time)	MD: 1.51 (-5.03 to 8.05) (random effects)	-0.07 (-0.41 to 0.27) (random effects)	470 (3 RCTs)	⊕⊖⊖⊖ VERY LOW[4]	Analysed as mean difference (random effects) (Analysis 3.8) [SMD as a negative outcome]
Agitation (Cohen Mansfield Agitation Inventory)	Mean baseline CMAI score was 57.7 Mean change from baseline (negative score) was	MD: 0.50 (-3.71 to 4.71) (random effects)	0.11 (-0.12 to 0.33) 2 studies in 306 participants	455 (3 RCTs)	⊕⊕⊕⊖ MODERATE[10]	MD and SMD as negative outcomes (Analysis 3.1; Analysis 3.2).

Table 5. Summary of findings: moderate-to-severe Alzheimer's disease (AD), selected for agitation *(Continued)*

range 29 - 203 points	-6.1[9] (i.e. improvement with time)	2 studies in 422 participants				One study reported final scores (Fox 2012 (MAGD)), so not included in SMD. One study reported CMAI-C (Forest 2006 (MD-23)), so not included in MD meta-analysis

Binary outcomes	Anticipated absolute effects		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo (median)	Risk with memantine				
All-cause discontinuation	171 per 1000	188 per 1000 (135 to 260)	RR 1.10 (0.79 to 1.52)	555 (3 RCTs) 113 events	⊕⊕⊕⊖ MODERATE[11]	RR for all 3 studies in people with moderate-to-severe AD selected for agitation (Analysis 3.9). Median control group risk for 3 studies in 555 people with moderate-to-severe AD selected for agitation (Analysis 3.9)
	Difference: 17 more people per 1000 discontinued treatment for any cause (95% CI 36 fewer to 89 more)					
Number suffering at least one adverse event	600 per 1000	618 per 1000 (600 to 636)	RR 1.03 (1.00 to 1.06)	8033 (29 RCTs) 5371 events	⊕⊕⊕⊕ HIGH	RR from all studies (Analysis 9.3).Mean control group risk for 2 moderate-to-severe AD studies in people selected for agitation (Analysis 3.11)
	Difference: 18 more people per 1000 suffered adverse events (95% CI 0 to 36 more)					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** Risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Inconsistency in point estimates between 24 week and 12 week studies (downgrade once); imprecision (crossed null and SMD 0.30) (downgrade once)
[2] Inconsistency between 24 week and 12 week studies (I^2 =90%) (downgrade twice); imprecision (very wide CI crossing SMD +0.30 and -0.30 (downgrade twice)
[3] Imprecision (crossed null and SMD 0.40) (downgrade once); some inconsistency in point estimates and risk of bias from baseline differences (downgrade once across the two domains)
[4] Inconsistency (I^2 = 62%, P = 0.07) (downgrade once); risk of bias (due to baseline differences) (downgrade once); imprecision (wide CI: SMD crossing -0.2 and 0.4) (downgrade twice)
[5] Control group value for 1 study reporting CIBIC+ (Herrmann 2012 (10158))

[6] Mean control group baseline scores and mean control group change from baseline for 2 studies reporting SIB (Fox 2012 (MAGD); Herrmann 2012 (10158))
[7] Mean control group baseline scores and mean control group change from baseline for the 2 studies reporting ADCS-ADL19 (Forest 2006 (MD-23); Herrmann 2012 (10158))
[8] Median control group baseline scores and median control group change from baseline for the 3 studies reporting NPI (Forest 2006 (MD-23); Fox 2012 (MAGD); Herrmann 2012 (10158))
[9] Mean control group baseline scores and mean control group change from baseline for the 2 studies reporting CMAI (Fox 2012 (MAGD); Herrmann 2012 (10158))
[10] Some inconsistency for two studies reporting CMAI and some imprecision (SMD crossing 0.3 and null) (downgrade once overall)
[11] Imprecision (113 events) (downgrade once)

Table 6. Summary of findings: mild Alzheimer's disease (AD) (MMSE 20 to 23) observed case (OC) - six-month studies

Memantine 20 mg compared to placebo for mild AD (MMSE 20-23) observed case (OC) - six-month studies for dementia						
Population: mild Alzheimer's disease **Intervention**: memantine 20 mg **Comparison:** placebo						
Continuous outcomes	**Score with placebo (median)**	**Mean improvement in change score between memantine and placebo**	**SMD (95% CI) meta-analysis findings**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Clinical Global (CIBIC+) 7-point Likert scale	Median CIBIC+ score was 4.1 [5] (i.e. no change with time)	MD: 0.09 (-0.12 to 0.30)	-0.08 (-0.27 to 0.12)	427 (3 RCTs)	⊕⊕⊖⊖ LOW [1]	Analysed as mean difference (Analysis 4.1). [SMD as a negative outcome (Analysis 16.1)]
Cognitive function (ADAS-Cog) 70-point scale	Baseline ADAS-Cog scores not reported. Median change from baseline in ADAS-Cog score (negative scale): -1.7 [6] (i.e. improvement with time)	MD: 0.21 (-0.95 to 1.38)	-0.03 (-0.19 to 0.13)	619 (4 RCTs)	⊕⊕⊕⊖ MODERATE [2]	Analysed as mean difference (Analysis 4.2). [SMD as a negative outcome (Analysis 16.2).]
Performance on ADL (ADCS-ADL23) 78-point scale	Baseline ADL scores not reported. Median change from baseline in ADCS-ADL23 (positive scale) was -0.34 [7] (i.e. no change with time)	MD: -0.07 (-1.80 to 1.66)	0.02 (-0.14 to 0.18)	621 (4 RCTs)	⊕⊕⊕⊖ MODERATE [3]	Analysed as mean difference for decline in ADL (Analysis 4.3). [SMD as a negative outcome (Analysis 16.3)] Direction of scale reversed for ADL outcome.
Behaviour and mood: (NPI) 144-point scale	Baseline NPI scores not reported.	MD: -0.29 (-2.16 to 1.58)	0.02 (-0.14 to 0.18)	621 (4 RCTs)	⊕⊕⊕⊖ MODERATE [2]	Analysed as mean difference. [SMD as a negative outcome (Analysis 16.4)].

Table 6. Summary of findings: mild Alzheimer's disease (AD) (MMSE 20 to 23) observed case (OC) - six-month studies *(Continued)*

	Median change from baseline in NPI was -2.4 (i.e. slight improvement with time) [8]					
Binary outcomes	**Anticipated absolute effects**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo (median)	**Risk with memantine**				
All-cause discontinuation	100 per 1000	174 per 1000 (108 to 281)	RR 1.74 (1.08 to 2.81)	528 (4 RCTs) 72 events	⊕⊖⊖⊖ VERY LOW [4]	RR and median control group risk for mild AD studies (Analysis 16.5)
	Difference: 74 more people per 1000 discontinued treatment for any cause (95% CI 8 to 181 more)					
Number suffering at least one adverse event	429 per 1000	442 per 1000 (429 to 455)	RR 1.03 (1.00 to 1.06)	8033 (29 RCTs) 5371 events	⊕⊕⊕⊕ HIGH	RR from all studies (Analysis 9.3).Control group risk taken from Holland 2013 study
	Difference: 13 more people per 1000 suffered adverse events (95% CI 0 to 26 more)					
Number suffering at least one serious adverse event	114 per 1000	104 per 1000 (93 to 116)	RR 0.91 (0.82 to 1.02)	6482 (19 RCTs) 918 events	⊕⊕⊕⊕ HIGH	RR and median control risk from all AD studies (except those with agitation) (from Analysis 8.10)
	Difference: 10 fewer people per 1000 suffered serious adverse events (95% CI 21 fewer to 2 more)					
Number suffering agitation as an adverse event	Outcome not reported by any study			0 RCTs		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** Risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] All studies are post-hoc subgroups (downgrade once on risk of bias); imprecision - 427 patients and SMD estimate crosses null and is consistent with appreciable benefit and no benefit (downgrade once)
[2] All studies are post-hoc subgroups (downgrade once on risk of bias)

[3] All studies are post-hoc subgroups (downgrade once on risk of bias) and some inconsistency in the point estimates (but not sufficient to downgrade)
[4] Majority of the information from post-hoc subgroups (downgrade once on risk of bias); imprecision: 72 events, and CI crossed 1.25 (downgrade once); inconsistency (I^2 = 49%) downgrade once
[5] Median control group values for 3 studies reporting CIBIC+ (Bakchine 2008 (99679) SG; Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S)
[6] Median control group change from baseline for 4 studies reporting ADAS-Cog (Bakchine 2008 (99679) SG; Dysken 2014 SG; Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S)
[7] Median control group change from baseline for the 4 studies reporting ADCS-ADL23 (Bakchine 2008 (99679) SG; Dysken 2014 SG; Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S)
[8] Median control group change from baseline for the 4 studies reporting NPI (Bakchine 2008 (99679) SG; Dysken 2014 SG; Peskind 2004 (MD-10) SG; Porsteinsson 2008(MD-12)S)

Table 7. Summary of findings: Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB)

Memantine compared to placebo for Parkinson's disease dementia (PDD) and Dementia with Lewy Bodies (DLB)

Population: Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB)
Intervention: memantine
Comparison: placebo

Continuous outcomes	Score with placebo (median)	Mean improvement in change score between memantine and placebo	SMD (95% CI) meta-analysis findings	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Clinical Global (CIBIC+) 7-point Likert scale	CIBIC+ score from 1 study was 4.1 (i.e. no change)	MD: 0.49 (0.13 to 0.83)	-0.35 (-0.60 to -0.09)	243 (3 RCTs)	⊕⊕⊖⊖ LOW [1]	SMD as a negative outcome (Analysis 6.1) Back transformed to CIBIC+ scale using SD(pooled) = 1.39 (from 1 study (Marsh 2009 PDD)).
Cognitive Function: (MMSE) 30-point scale	MMSE score: 20.0 (at 24 weeks). Change from baseline (positive scale): -0.5 (i.e. slight deterioration with time) (one study)	MD: 1.9 (0.07 to 3.73)	-0.50(-1.00 to 0.00)	63 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2]	One study at 24 weeks and one at 16 weeks only for this outcome; highly heterogeneous. So 24 week study reported only (Aarsland 2009). MMSE scale direction was reversed (Analysis 6.2)
Performance on ADL (ADCS-ADL23) 78-point scale	ADCS-ADL23 score at baseline: 48 Change from baseline (positive scale): -0.1 (i.e. no change with time) (one study)	MD: 3.07 (-1.25 to 7.4)	-0.27 (-0.67 to 0.07)	243 (3 RCTs)	⊕⊖⊖⊖ VERY LOW [3]	SMD decline in ADL as a negative outcome (Analysis 6.3). Random effects. Back transformed to ADCS-ADL23 scale, using results from one study (Emre 2010

Table 7. Summary of findings: Parkinson's disease dementia (PDD) and dementia with Lewy bodies (DLB) *(Continued)*

		(11018)). SD(pooled) = 11.38.				
Behaviour and Mood (NPI) 144-point scale	Median NPI score at baseline: 13.0 Median change from baseline (negative scale): 1.4 (i.e. slight deterioration with time)	MD: 2.18 (-1.21 to 5.57)	-0.18 (-0.43 to 0.07)	242 (3 RCTs)	⊕⊕⊖⊖ LOW [4]	Random effects. Analysed as mean difference (Analysis 6.4). [SMD as a negative outcome (Analysis 8.4)]
Binary outcomes	**Anticipated absolute effects**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo (median)	**Risk with memantine**				
All-cause discontinuation	201 per 1000	169 per 1000 (111 to 257)	RR 0.84 (0.55 to 1.28)	312 (4 RCTs) 64 events	⊕⊕⊖⊖ LOW [5]	RR and control group risk from PDD or DLB studies (Analysis 6.5)
	Difference: 32 fewer people per 1000 discontinued treatment for any cause (95% CI 90 fewer to 56 more)					
Number suffering at least one adverse event	500 per 1000	515 per 1000 (500 to 530)	RR 1.03 (1.00 to 1.06)	8033 (29 RCTs) 5371 events	⊕⊕⊕⊕ HIGH	RR from all studies (Analysis 9.3). Median control group risk for PDD or DLB studies (Analysis 6.7).
	Difference: 15 more people per 1000 suffered adverse events (95% CI 0 to 30 more)					
Number suffering at least one serious adverse event	86 per 1000	123 per 1000 (59 to 255)	RR 1.43 (0.69 to 2.97)	220 (2 RCTs) 26 events	⊕⊕⊖⊖ LOW [5]	RR and control group risk from PDD or DLB studies (Analysis 8.10)
	Difference: 37 more people per 1000 suffered serious adverse events (95% CI 27 fewer to 169 more)					
Number suffering agitation as an adverse event	Outcome not reported for either study			0 RCTs		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** Risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Majority of the information at high risk of bias and number of patients estimated (downgrade once); imprecision - 243 patients (below optimal information size) (downgrade once)
[2] Reporting bias (2 larger studies did not report outcome) and high risk of bias for remaining study (downgrade once), inconsistency with 16 weeks study high (I^2 = 75%) (downgrade once), imprecision (only 63 patients, wide CI) (downgrade once)
[3] Majority of information at high risk of bias (downgrade once), inconsistency in point estimates (I^2 = 40%) (downgrade once) and imprecision (243 participants and CI crossed null and consistent with both benefit and no difference) (downgrade once)
[4] Majority of information at high risk of bias (downgrade once), some inconsistency in point estimates (I^2 = 20%) (not downgraded) and imprecision (243 patients; CI crossed null and included benefit and no difference) (downgrade once)
[5] Imprecision: CI crossed both 1.25 and 0.75, and CI fairly wide around absolute effect (downgrade twice)

Table 8. Summary of findings: frontotemporal dementia (FTD)

Memantine compared to placebo for Frontotemporal dementia (FTD)						
Population: frontotemporal dementia **Intervention**: memantine **Comparison:** placebo						
Continuous outcomes	**Score with placebo (median)**	**Mean improvement in change score between memantine and placebo**	**SMD (95% CI) meta-analysis findings**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Clinical Global (CGIC) 7-point Likert scale	CGIC score from 1 study was 4.8 (i.e. deterioration with time)	MD: 0.56 (-0.11 to 1.21)	-0.31 (-0.67 to 0.06)	117 (2 RCTs)	⊕⊕⊖⊖ LOW [1]	SMD as a negative outcome (Analysis 7.1) Back transformed to CGIC scale using SD (pooled) = 1.80 (from 1 study (Boxer 2013).
Cognitive Function: (MMSE) 30-point scale	MMSE score: 25.1 (at 26 weeks). Change from baseline (positive scale): -0.9 (i.e. deterioration with time) (one study)	MD -0.30 (-1.83 to 1.23)	0.09 (-0.35 to 0.52)	81 (1 RCT)	⊕⊖⊖⊖ VERY LOW [2]	One study at 6 months and one at 12 months for this outcome; some heterogeneity so 6-month study reported only (Boxer 2013) (Analysis 7.2). MMSE scale direction was reversed. [SMD as a negative outcome (Analysis 8.2)]
Performance on ADL % DAD score = yes at 12 months	Baseline score: 58.3%. Change from baseline (positive scale): -19.5% (i.e. deterioration) (one study)	MD: 12.10% (-1.40 to 25.60)	-	39 (1 RCT)	⊕⊖⊖⊖ VERY LOW [3]	Decline in ADL not reported in either study. Percentage with DAD score = yes reported in Vercelletto 2011 at 12 months.
Behaviour and Mood (NPI)	NPI score at baseline: 21.5. Change from baseline (negative scale): 0.3 (i.e. no difference) (one study)	MD: 3.16 (-3.61 to 8.01)	-0.17 (-0.62 to 0.28)	115 (2 RCTs)	⊕⊕⊖⊖ LOW [4]	Analysed as mean difference (Analysis 7.3). Baseline score and change from base-

Table 8. Summary of findings: frontotemporal dementia (FTD) *(Continued)*

144-point scale						line for 26-week study (Boxer 2013). [SMD as a negative outcome (Analysis 8.4)]
Binary outcomes	**Anticipated absolute effects**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo (median)	**Risk with memantine**				
All-cause discontinuation	71 per 1000	109 per 1000 (38 to 288)	RR 1.54 (0.54 to 4.06)	133 (2 RCTs) 15 events	⊕⊕⊖⊖ LOW [5]	RR from FTD studies; control group risk from 26 week study (Analysis 7.4)
	Difference: 38 more people per 1000 discontinued treatment for any cause (95% CI 33 fewer to 217 more)					
Number suffering at least one adverse event	667 per 1000	687 per 1000 (667 to 707)	RR 1.03 (1.00 to 1.06)	8033 (29 RCTs) 5371 events	⊕⊕⊕⊕ HIGH	RR from all studies (Analysis 9.3).Control group risk for 26-week FTD study
	Difference: 20 more people per 1000 suffered adverse events (95% CI 0 to 40 more)					
Number suffering at least one severe adverse event	48 per 1000	34 per 1000 (14 to 80)	RR 0.71 (0.30 to 1.66)	133 (2 RCTs) 17 events	⊕⊕⊖⊖ LOW [5]	RR and control group risk from FTD study at 26 weeks (Analysis 8.10)
	Difference: 14 fewer people per 1000 suffered adverse events (95% CI 34 fewer to 32 more)					
Number suffering agitation as an adverse event	48 per 1000	10 per 1000 (0.5 to 208)	RR 0.21 (0.01 to 4.34)	81 (1 RCT)	⊕⊖⊖⊖ VERY LOW [6]	RR and control group risk from FTD study at 26 weeks (Analysis 7.8)
	Difference: 38 fewer people per 1000 suffered adverse events (95% CI 48 fewer to 160 more)					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD:** mean difference; **RR:** Risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

[1] Majority of the information at high risk of bias (downgrade once); imprecision - 117 patients (below optimal information size) (downgrade once)

[2] Inconsistency in point estimates (I^2 = 23%) (downgrade once) and Imprecision (122 patients and wide confidence interval) (downgrade twice)
[3] Imprecision (39 participants and CI crossed null and consistent with both benefit and no difference) (downgrade twice); indirect outcome (percentage DAD score at 12 months) and borderline high risk of bias (differential missing data) (downgrade once)
[4] Some inconsistency in point estimates and Imprecision (122 patients and wide confidence interval) (downgrade twice overall)
[5] Inconsistency in point estimates (downgrade once); Imprecision: 15 events and CI crossed both 1.25 and 0.75 (downgrade twice)
[6] Imprecision: 17 events and wide CI (downgrade twice)
[7] Imprecision: 2 events and very wide CI (downgrade twice): high risk of bias - number discontinuing treatment greater than number of events (downgrade twice)

Table 9. Subgroup analysis: concomitant ChEI therapy versus monotherapy; six to seven month studies in moderate-to-severe Alzheimer's disease (AD)

	Number of Studies			Number of Participants			Standardised Effect Estimate			Heterogeneity (I^2)			Test for subgroup differences
Domain	**All**	**with ChEI**	**no ChEI**	**All**	**with ChEI**	**no ChEI**	**All**	**with ChEI**	**no ChEI**	**All**	**with ChEI**	**no ChEI**	
Clinical Global (Analysis 2.1)	10	3	7	2797	1125	1672	-0.20 (-0.28 to -0.13)	-0.21 (-0.32 to -0.09)	-0.20 (-0.30 to -0.10)	0%	13%	0%	I^2 = 0%, P = 0.99
Cognitive Function (Analysis 2.2)	14	6	8	3337	1852	1485	-0.28 (-0.35 to -0.21)	-0.24 (-0.33 to -0.14)	-0.33 (-0.43 to -0.23)	33%	13%	41%	I^2 = 44%, P = 0.18
Decline in Activities of Daily Living (Analysis 2.3)	12	5	7	2687	1319	1368	-0.17 (-0.24 to -0.09)	-0.13 (-0.24 to -0.03)	-0.20 (-0.30 to -0.09)	0%	0%	10%	I^2 = 0%, P = 0.43
Behaviour and Mood (Analysis 2.4)	15	6	9	3674	1855	1819	-0.14 (-0.21 to -0.08)	-0.18 (-0.27 to -0.09)	-0.10 (-0.19 to -0.01)	6%	10%	0%	I^2 = 35%, P = 0.21
All-cause discontinuation (Analysis 2.9)	15	6	10	4548	2089	2459	RR 0.93 (0.82 to 1.05)	RR 0.94 (0.78 to 1.13)	RR 0.92 (0.78 to 1.08)	9%	61%	0%	I^2 = 0%, P = 0.83
Adverse events (Analysis 2.11)	9	3	6	3390	1625	1765	RR 1.02 (0.98 to 1.06)	RR 1.05 (0.98 to 1.12)	RR 0.99 (0.94 to 1.04)	23%	13%	0%	I^2 = 46%, P = 0.17
Agitation as an adverse event (Analysis 2.13)	10	5	6	3854	1965	1889	RR 0.79 (0.64 to 0.97)	RR 0.93 (0.65 to 1.31)	RR 0.72 (0.55 to 0.93)	0%	0%	15%	I^2 = 25.1%, P = 0.25

Six studies were conducted on patients with moderate-to-severe disease receiving ChEI therapy, these were:
Dysken 2014: patients were on ongoing ChEI therapy with any ChEI (donepezil, rivastigmine or galantamine), as maintenance dosage for at least 4 weeks
Grossberg 2008 (MD-50): patients were on ongoing ChEI therapy with a stable dose of any ChEI for 3 months or longer, patients must remain on the same dose throughout the study.
Howard 2012 (DOMINO-AD): patients were on ongoing ChEI therapy with donepezil for at least 3 months and had received a dose of 10 mg for at least the previous 6 weeks. Patients were randomised to continue or discontinue donepezil. The patient's prescribing clinician was considering a change in drug treatment.

Nakamura 2016: patients had been on donepezil for at least four weeks when recruited and then had 12 weeks single blind observation period on donepezil. Only those stable continued to the double blind period.
Porsteinsson 2008 (MD-12): patients were on ongoing ChEI therapy with any ChEI for 6 months or longer, and a stable dosing regimen for 3 months or longer (donepezil 5-10 mg/day; rivastigmine 6, 9 or 12 mg/day; galantamine 16 or 24 mg/day)
Tariot 2004 (MD-02): patients were on ongoing ChEI therapy with donepezil for more than 6 months before entry into the trial and at a stable dose (5-10mg/day) for at least 3 months.

Table 10. Comparison of analyses in people with moderate-to-severe AD, selected versus not selected for agitation at six to seven months

	Patients not selected for agitation (with moderate-to-severe AD)			Patients selected for agitation		
	With / without ChEI (24-28 weeks)	**No ChEI (24-28 weeks)**	**With ChEI (24-28 weeks)**	**With / without ChEI, mainly with (12 & 24 weeks)**	**With ChEI (24 weeks)**	**With / without ChEI - majority without (12 weeks)**
Clinical global (SMD)	-0.20 (-0.28 to -0.13) n = 10 studies; 2797 patients I^2 = 0%, P = 0.86	-0.20 (-0.30 to -0.10) n = 7; 1672 patients I^2 = 0%, P = 0.88	-0.21 (-0.32 to -0.09) n = 3; 1125 patients I^2 = 13%, P = 0.32	-0.11 (-0.34 to 0.13) n = 3; 443 patients I^2 = 25%, P = 0.26	0.04 (-0.20 to 0.28) n = 1; 324 patients	-0.28 (-0.59 to 0.02) n = 2; 168 patients I^2 = 0%, P = 0.96
Cognitive function (SMD)	-0.28 (-0.35 to -0.21) n = 13; 3337 patients I^2 = 30%, P = 0.14	-0.33 (-0.43 to -0.23) n = 8; 1485 patients I^2 = 41%, P = 0.11	-0.24 (-0.33 to -0.14) n = 6; 1852 patients I^2 = 13%, P = 0.33	Not pooled I^2 = 90%, P = 0.002	0.05 (-0.17 to 0.27) n = 1, 324 patients	-0.56 (-0.92 to -0.21) n = 1; 129 patients (with ~20% ChEI)
Decline in ADL (SMD)	-0.17 (-0.24 to -0.09) n = 11; 2687 patients I^2 = 0%, P = 0.582	-0.20 (-0.30 to -0.09) n = 7; 1368 patients I^2 = 10%, P = 0.36	-0.13 (-0.24 to -0.03) n = 5; 1319 patients I^2 = 0%, P = 0.69	0.21 (-0.02 to 0.43) n = 2; 309 patients I^2 = 0%, P = 0.40	0.23 (-0.01 to 0.47) n = 1; 276 patients	-0.02 (-0.70 to 0.67) n = 1; 33 patients (with ChEI)
Behaviour and mood (SMD)	-0.14 (-0.21 to -0.08) n = 14; 3674 patients I^2 =6%, P = 0.39	-0.10 (-0.19 to -0.01) n = 9; 1819 patients I^2 = 0%, P = 0.46	-0.18 (-0.27 to -0.09) n = 6; 1855 patients I^2 = 10%, P = 0.35	-0.07 (-0.41 to 0.27) n = 3; 470 patients I^2 = 62%, P = 0.07	0.08 (-0.14 to 0.30) n = 1; 324 patients	-0.20 (-0.69 to 0.29) n = 2; 146 patients I^2 = 43%, P = 0.19
CMAI (SMD)			-0.21 (-0.45 to 0.04) n = 1; 261 patients	0.11 (-0.12 to 0.33) n = 2; 306 patients I^2 = 0%, P = 0.77	0.10 (-0.14 to 0.33) n = 1; 273 patients	CMAI (final values): SMD: -0.19 (-0.52 to 0.13) n = 1; 149 patients CMAI (community): SMD: 0.21 (-0.48 to 0.89) n = 1; 33 patients
Proportion	0.76 (0.601 to 0.96)	0.68 (0.51, 0.91)	0.92 (0.54 to 1.31)	RR 2.39 (1.04 to 5.50)	2.20 (0.92 to 5.27)	5.00 (0.26 to 97.00)

Table 10. Comparison of analyses in people with moderate-to-severe AD, selected versus not selected for agitation at six to seven months *(Continued)*

with agitation (RR)	6 studies; 2 241 patients I^2 = 0%, P = 0.67	4 studies; 1016 patients I^2 = 0%, P = 0.59	3 studies; 1225 patients I^2 = 0% and 0.85	2 studies; 403 patients I^2 = 0%, P = 0.60	1 study; 369 patients	1 study; 34 patients (with ChEI)

Table 11. Adverse events

Adverse event	Number of studies (participants)	RR (95% CI)	Heterogeneity (I^2)	GRADE rating
Insomnia (Analysis 9.6)	19 (5354), 221 events	0.93 (0.73 to 1.20)	I^2 = 14%, P = 0.29	LOW (downgraded on imprecision and reporting bias < 70% patients had AE data)
Confusion (Analysis 9.7)	13 (4509), 167 events	1.23 (0.91 to 1.65)	I^2 = 0%, P = 0.51	LOW (downgraded on imprecision and reporting bias < 70% patients had AE data)
Depression (Analysis 9.8)	10 (3052), 83 events	1.06 (0.70 to 1.60)	I^2 = 0%, P = 0.60	VERY LOW (downgraded on imprecision (twice), inconsistency in point estimates (once) and reporting bias <40% patients had AE data (twice))
Headache (Analysis 9.9)	16 (4889), 240 events	1.29 (1.00 to 1.66)	I^2 = 9%,P = 0.36	LOW (downgraded on imprecision (once) and reporting bias <70% patients had AE data)
Hypertension (Analysis 9.10)	8 (3175), 87 events	1.76 (1.14 to 2.70)	I^2 = 1%, P = 0.42	VERY LOW (downgraded on imprecision (twice), inconsistency in point estimates (once) and reporting bias <40% patients had AE data (twice))
Dizziness (Analysis 9.11)	19 (6395), 323 events	1.59 (1.28 to 1.98)	I^2 = 0%, P = 0.49	MODERATE (downgraded on inconsistency in point estimates)
Falls (Analysis 9.12)	20 (6743), 589 events	0.98 (0.84 to 1.13)	I^2 = 0%, P = 0.84	HIGH
Accidental injury (Analysis 9.13)	10 (3813), 214 events	0.81 (0.62 to 1.05)	I^2 = 0%, P = 0.81	VERY LOW (downgraded on imprecision (once) and twice on reporting bias (< 50% patients and 1 in 4 studies)
Urinary incontinence (Analysis 9.14)	8 (2724), 76 events	1.12 (0.73 to 1.72)	I^2 = 0%, P = 0.83	VERY LOW (downgraded on imprecision (twice), inconsistency in point estimates (once) and reporting bias <4 0% patients had AE data (twice))
Diarrhoea (Analysis 9.15)	18 (6186), 318 events	0.82 (0.66 to 1.02)	I^2 = 0%, P = 0.58	LOW (downgraded on imprecision (once), some inconsistency in point estimates and reporting bias <70% patients had AE data (once further))
Influenza-like symptoms (Analysis 9.16)	7 (2836), 129 events	1.21 (0.87 to 1.70)	I^2 = 0%, P = 0.97	VERY LOW (downgraded on imprecision (once), and reporting bias < 40% patients and 1/6 studies had AE data (twice))

APPENDICES

Appendix 1. Search: September 2011, February 2016, March 2017 and March 2018

Source	Search strategy	Hits retrieved
1. ALOIS (www.medicine.ox.ac.uk/alois) [Date of most recent search: 25 March 2018]	Advanced searched: memantine, D-145, DMAA, DRG-0267, ebixa, abixa, axura, akatinol, memox and namenda	All dates to Mar 2017: 266 Mar 2018: 0
2. MEDLINE In-process and other non-indexed citations and MEDLINE 1945-24 March 2018 (Ovid SP) [Date of most recent search: 25 March 2018]	1. exp Dementia/ 2. Delirium/ 3. Wernicke Encephalopathy/ 4. Delirium, Dementia, Amnestic, Cognitive Disorders/ 5. dement*.mp. 6. alzheimer*.mp. 7. (lewy* adj2 bod*).mp. 8. deliri*.mp. 9. (chronic adj2 cerebrovascular).mp. 10. ("organic brain disease" or "organic brain syndrome").mp. 11. ("normal pressure hydrocephalus" and "shunt*").mp. 12. "benign senescent forgetfulness".mp. 13. (cerebr* adj2 deteriorat*).mp. 14. (cerebral* adj2 insufficient*).mp. 15. (pick* adj2 disease).mp. 16. (creutzfeldt or jcd or cjd).mp. 17. huntington*.mp. 18. binswanger*.mp. 19. korsako*.mp. 20. or/1-19 21. exp *Memantine/ 22. memantin*.mp. 23. (axura* or akatinol*).mp. 24. namenda*.mp. 25. (ebixa* or abixa*).mp. 26. memox*.mp.	Sept 2011: 157 Feb 2016: 168 Mar 2017: 97 Mar 2018: 89

(Continued)

	27. or/21-26	
	28. 20 and 27	
	29. randomized controlled trial.pt.	
	30. controlled clinical trial.pt.	
	31. random*.ab.	
	32. placebo.ab.	
	33. drug therapy.fs.	
	34. trial.ab.	
	35. groups.ab.	
	36. or/29-35	
	37. (animals not (humans and animals)).sh.	
	38. 36 not 37	
	39. 28 and 38	
3. EMBASE 1980-2018 March 24 (Ovid SP) [Date of most recent search: 25 March 2018]	1. exp dementia/ 2. Lewy body/ 3. delirium/ 4. Wernicke encephalopathy/ 5. cognitive defect/ 6. dement*.mp. 7. alzheimer*.mp. 8. (lewy* adj2 bod*).mp. 9. deliri*.mp. 10. (chronic adj2 cerebrovascular).mp. 11. ("organic brain disease" or "organic brain syndrome").mp. 12. "supranuclear palsy".mp. 13. ("normal pressure hydrocephalus" and "shunt*").mp. 14. "benign senescent forgetfulness".mp. 15. (cerebr* adj2 deteriorat*).mp. 16. (cerebral* adj2 insufficient*).mp. 17. (pick* adj2 disease).mp. 18. (creutzfeldt or jcd or cjd).mp. 19. huntington*.mp. 20. binswanger*.mp.	Sept: 2011: 249 Feb 2016: 261 Mar 2017: 151 Mar 2018: 142

(Continued)

	21. korsako*.mp.	
	22. CADASIL.mp.	
	23. or/1-22	
	24. exp *memantine/	
	25. memantin*.mp.	
	26. (axura* or akatinol*).mp.	
	27. namenda*.mp.	
	28. (ebixa* or abixa*).mp.	
	29. memox*.mp.	
	30. or/24-29	
	31. 23 and 30	
	32. randomized controlled trial/	
	33. exp controlled clinical trial/	
	34. random*.ab.	
	35. placebo.ab.	
	36. trial.ab.	
	37. groups.ab.	
	38. or/32-37	
	39. 31 and 38	
4. PSYCINFO 1806-March week 3 2018 (Ovid SP) [Date of most recent search: 25 March 2018]	1. exp Dementia/ 2. exp Delirium/ 3. exp Huntingtons Disease/ 4. exp Kluver Bucy Syndrome/ 5. exp Wernickes Syndrome/ 6. exp Cognitive Impairment/ 7. dement*.mp. 8. alzheimer*.mp. 9. (lewy* adj2 bod*).mp. 10. deliri*.mp. 11. (chronic adj2 cerebrovascular).mp. 12. ("organic brain disease" or "organic brain syndrome").mp. 13. "supranuclear palsy".mp. 14. ("normal pressure hydrocephalus" and "shunt*").mp. 15. "benign senescent forgetfulness".mp.	Sept 2011: 47 Feb 2016: 38 Mar 2017: 12 Mar 2018: 16

(Continued)

16. (cerebr* adj2 deteriorat*).mp.
17. (cerebral* adj2 insufficient*).mp.
18. (pick* adj2 disease).mp.
19. (creutzfeldt or jcd or cjd).mp.
20. huntington*.mp.
21. binswanger*.mp.
22. korsako*.mp.
23. ("parkinson* disease dementia" or PDD or "parkinson* dementia").mp.
24. or/1-23
25. memantin*.mp.
26. (axura* or akatinol*).mp.
27. namenda*.mp.
28. (ebixa* or abixa*).mp.
29. memox*.mp.
30. or/25-29
31. 30 and 24
32. random*.ab.
33. placebo.ab.
34. trial.ab.
35. groups.ab.
36. exp Clinical Trials/
37. or/32-36
38. 31 and 37

5. CINAHL (EBSCOhost)	S1 (MH "Dementia+")	Sept 2011: 22
[Date of most recent search: 25 March 2018]	S2 (MH "Delirium") or (MH "Delirium, Dementia, Amnestic, Cognitive Disorders")	Feb 2016: 39
	S3 (MH "Wernicke's Encephalopathy")	Mar 2017: 9
	S4 TX dement*	Mar 2018: 9
	S5 TX alzheimer*	
	S6 TX lewy* N2 bod*	
	S7 TX deliri*	
	S8 TX chronic N2 cerebrovascular	
	S9 TX "organic brain disease" or "organic brain syndrome"	
	S10 TX "normal pressure hydrocephalus" and "shunt*"	

(Continued)

	S11 TX "benign senescent forgetfulness" S12 TX cerebr* N2 deteriorat* S13 TX cerebral* N2 insufficient* S14 TX pick* N2 disease S15 TX creutzfeldt or jcd or cjd S16 TX huntington* S17 TX binswanger* S18 TX korsako* S19 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 S20 TX memantin* S21 TX (axura* or akatinol*) S22 TX namenda* S23 TX (ebixa* or abixa*) S24 TX memox* S25 S20 or S21 or S22 or S23 or S24 S26 S19 AND S25	
6. ISI Web of Science – all databases [includes: Web of Science (1945-present); BIOSIS Previews (1926-present); MEDLINE (1950-present); Journal Citation Reports] [Date of most recent search: 25 March 2018]	#1 Topic=(memantine OR axura OR akatinol OR namenda OR ebixa OR abixa OR memox) *Timespan=All Years* *Search language=English Lemmatization=On* #2 Topic=(dement* OR VCI OR "vascular congitive impairment*" OR VaD OR alzheimer* OR AD) *Timespan=All Years* *Search language=English Lemmatization=On* #3 #2 AND #1 *Timespan=All Years* *Search language=English Lemmatization=On* #4 Topic=(randomly OR trial OR placebo OR "double-blind*" OR RCT OR randomized OR randomised) #5 #3 AND #4	Sept 2011: 177 Feb 2016: 155 Mar 2017: 76 Mar 2018: 177

(Continued)

7. LILACS (BIREME) [Date of most recent search: 25 March 2018]	memantine OR axura OR akatinol OR namenda OR ebixa OR abixa OR memox [Words]	Sept 2011: 13 Feb 2016: 2 Mar 2017: 0 Mar 2018: 0
8. CENTRAL (*The Cochrane Library*) (Issue 3 of 12, 2018) [Date of most recent search: 25 March 2018]	#1 MeSH descriptor Memantine explode all trees #2 memantin* #3 axura* #4 akatinol* #5 namenda* #6 ebixa* #7 abixa* #8 memox* #9 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8)	Sept 2011: 275 Feb 2016: 24 Mar 2017: 80 Mar 2018: 65
9. Clinicaltrials.gov (www.clinicaltrials.gov) [Date of most recent search: 25 March 2018]	Interventional Studies | memantine OR axura OR akatinol OR namenda OR ebixa OR abixa OR memox	Sept 2011: 117 Feb 2016: 14 Mar 2017: 2 Mar 2018: 0
10. ICTRP Search Portal (http://apps.who.int/trialsearch) [includes: Australian New Zealand Clinical Trials Registry; ClinicalTrilas.gov; ISRCTN; Chinese Clinical Trial Registry; Clinical Trials Registry – India; Clinical Research Information Service – Republic of Korea; German Clinical Trials Register; Iranian Registry of Clinical Trials; Japan Primary Registries Network; Pan African Clinical Trial Registry; Sri Lanka Clinical Trials Registry; The Netherlands National Trial Register] [Date of most recent search: 25 March 2018]	Keyword search: memantine OR axura OR akatinol OR namenda OR ebixa OR abixa OR memox	Sept 2011: 173 Feb 2016: 12 Mar 2017: 17 Mar 2018: 0
Total before de-duplication		Sept 2011: 1336 Feb 2016: 717

(Continued)

	Mar 2017: 710 Mar 2018: 498 TOTAL: 3261 (266 from ALOIS; 2995 from other sources)
Total after de-duplication	Sept 2011: 976 Feb 2016: 502 Mar 2017: 13 Mar 2018: 14 TOTAL: 1505
Total after first assessment (removal of obviously not relevant)	304

Appendix 2. Outcome measures (brief description)

The following range of outcome measures was used in the trials. Table 1 summarises their use in the included studies for AD.

1. Global rating scales

- Clinician's Interview-Based Impression of Change scale (CIBIC-Plus) provides a global rating of function in four areas, general, cognitive, behaviour and activities of daily living. All patients are scored as 4 at baseline and subsequent assessments on a scale of 1 to 7 are relative to baseline, with 1 showing marked improvement and 7 marked worsening. Information is obtained from the caregiver and the patient. There are different versions: the Alzheimer's Disease Cooperative Study format (Schneider 1997) and the New York version (Reisberg 1997).
- The Clinical Global Impression of Change (CGIC) is a global rating of all domains of a patient's current condition in comparison with baseline (Guy 1976). It is a seven-point scale, from 1 (very much improved) to 7 (very much worse), 4 indicating no change. The assessment is conducted by the same clinician at both time points with input from relatives or carers.
- Physician's global impression. This unvalidated four-point rating of the dementia syndrome and patient's general health status was used in the Ditzler 1991 study.
- Clinical Global Impression (CGI). This seven-point rating of severity of illness was used in the Gortelmeyer 1992 study to assess whether patients improved, remained unchanged or worsened.
- The Sandoz Clinical Assessment Geriatric Scale (SCAG) is a physician rating (Shader 1974). It consists of 18 items and an overall impression (item 19), all rated on a seven-point format. There are five sub-scores: cognitive disturbances, disturbances in social behaviour, lack of drive, affective disturbances, somatic disturbances. Item 19 was used in the Pantev 1993 study.

2. Cognitive Tests

- The cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-Cog) comprises 11 individual tests, spoken language ability (0 to 5), comprehension of spoken language (0 to 5), recall of test instructions (0 to 5), word finding difficulty (0 to 5), following commands (0 to 5), naming object (0 to 5), construction drawing (0 to 5), ideational praxis (0 to 5), orientation (0 to 8), word recall (0 to 10) and word recognition (0 to 12) (Rosen 1984). The total score ranges from 0 to 70, the high score indicating greater impairment.
- Syndrom-Kurztest determines patient attention and memory disturbances (Kim 1993).
- Severe Impairment Battery (SIB) evaluates cognitive performance in advanced Alzheimer's Disease (Schmitt 1997). It is a 51-item scale which assesses social interaction, memory, language, visuospatial ability, attention, praxis and construction. The scores range from 0 (greatest impairment) to 100.

3. Activities of Daily Living

- Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL) was specifically designed to assess functional capacity over a broad range of severity in patients with Alzheimer's disease (Galasko 1997). The 19-item ADCS-ADLsev19 (ADCS-ADL19) has 54 points. The 23-item ADCS-ADL23 has 78 points. High score indicates greater functional capacity.

- Activities of daily living test. This scale evaluates patients' abilities to cope with five instrumental task under the guidance of a psychologist.
- Behavioural Rating Scale for Geriatric Patients (BGP) is a 45-item observer-rated scale for the assessment of functional and behavioural disturbances of geriatric patients, performed by nursing staff (Van der Kam 1989). The BGP contains several subscales: care dependence, aggressiveness, physical, mental, disability and depressiveness, and inactivity. The "care dependence" scale consists of 23 items, measures activities of daily living and has the highest reliability and validity. High score indicates lower functional capacity.
- Bristol Activities of Daily Living (BADL) is a caregiver rated scale. Scores range from 0 to 60, with higher scores indicating greater impairment (i.e. a negative outcome).
- Nurse's Observational Scale for Geriatric Patients (NOSGER) contains 30 items of behaviour, each rated in a five-point scale according to frequency of occurrence (Spiegel 1991). Item scores are summarised into six dimension scores (memory, instrumental activities of daily life, self-care activities of daily living, mood, social behaviour, and disturbance behaviour).
- Disability Assessement Daily (DAD) (Gélinas 1994) contains 40 items, 17 related to self-care and 23 items related to instrumental activities of daily living. Scores range from 0% to100%, with higher scores indicating greater impairment.

4. Mood and Behavioural measures

- Neuropsychiatric Inventory (NPI) assesses the frequency and the severity of behavioral and neuropsychiatric symptoms in patients with dementia based on an interview with the caregiver (Cummings 1994). There are 12 items with a total score ranging from 0 to 144. Higher scores indicate greater neuropsychiatric impairment.
- Cohen Mansfiedl Agitation Inventory (CMAI) assesses the frequency of behaviour on a seven-point scale (1: never; 2: less than once a week; 3: once or twice a week; 4: a few times a week; 5: once or twice a day; 6: a few times a day; 7: a few times an hour). There are 29 items (Cohen Mansfield 1989).
- Nurses Observation Scale for Inpatient Evaluation (NOSIE) assesses behaviour of psychiatric patients (Honigfeld 1974). It comprises 30 items of behaviour and the frequency of their occurrence. NOSIE subscale scores are for social competence, social interest, personal neatness, irritability, manifest psychosis, retardation, depression. Increasing values of the NOSIE index are indicative of improvement.
- Sandoz Clinical Assessment Geriatric Scale (SCAG) is a physician rating scale (Shader 1974). It consists of 18 items and an overall impression (item 19), all rated on a seven-point format. There are also five sub-scores: cognitive disturbances, disturbances in social behaviour, lack of drive, affective disturbances, somatic disturbances.
- Behavioural Rating Scale for Geriatric Patients (BGP) is a 45-item observer-rated scale for the assessment of functional and behavioural disturbances of geriatric patients, performed by nursing staff (Van der Kam 1989). The BGP contains several sub scales: care dependence, aggressiveness, physical, mental, disability and depressiveness, and inactivity. The "care dependence" scale consists of 23 items, measures activities of daily living and has the highest reliability and validity
- Nurse's Observational Scale for Geriatric Patients (NOSGER) contains 30 items of behaviour, each rated in a five-point scale according to frequency of occurrence (Spiegel 1991). Item scores are summarised into six dimension scores (memory, instrumental activities of daily life, self-care activities of daily living, mood, social behaviour, and disturbance behaviour).
- The BEHAVE-AD scale has 25 items, is based on caregiver interview and is more specific for psychotic disorders in people with dementia. There are seven subscales: paranoid and delusional ideation, hallucinations, disturbances of daily activities, aggression, sleep disturbances and circadian rhythm disorder, affective disorder, and anxiety or phobias. Higher scores indicate greater neuropsychiatric impairment.

5. Combination Scales

Several scales used in earlier studies combine elements that are now more commonly assessed using separate instruments. Such scales have been used as a different method from 'overall clinical impression' for the systematic global assessment of dementia. These combination scales typically have several subscales, the results of which are sometimes presented separately and can be included in meta-analyses.

- Gottfries-Brane-Steen Scale (GBS) is a 26-item, physician-assessed observer scale based on caregiver's information and an interview with the patient (Gottfries 1982). It comprises three subscales: motor performance, intellectual and emotional capacity, and a group of six symptoms commonly observed in dementia.
- Other combination scales used in studies of memantine are the SCAG, NOSIE, NOSGER and BGP which are detailed above.

6. Cost of resource utilisation

- Resource Utilization in Dementia questionnaire (RUD) is a structured interview of the patient's caregiver consisting of a baseline questionnaire (assessing basic patient demographic data and specific events that occurred during the past one month) and follow-up questionnaire (assessing specific events that occurred during the past three months) (Wimo 1988). The specific events included time spent caring for the patient, changes in the caregiver's work status, healthcare resource utilisation by the caregiver, healthcare resource utilisation by the patient and the patient's residential status.

7. Safety and tolerability were assessed by the frequency of reported adverse effects

Appendix 3. Last Observation carried forward (LOCF) versus observed case (OC) assumptions for missing data

Two sets of analyses were compared, one using results based on an OC assumption, and the other with a LOCF assumption. One study reported raw data for both a per protocol analysis and a retrieved dropout analysis (Howard 2012 (DOMINO-AD)). One reported a per protocol analysis at 52 weeks and LOCF at the end of the study (assumed to be 52 weeks) (Peters 2015 (MEGACOMBI2)).

Firstly, within-trial comparisons are reported in Analysis 10.1 and Analysis 10.2 for the outcomes cognitive function and decline in ADL. There is generally little difference between the results for OC and LOCF, with the possible exceptions of two studies for the decline in activities of daily living (ADL) (Peters 2015 (MEGACOMBI2); Reisberg 2003 (9605)).

Secondly, we conducted meta-analyses of studies in patients with moderate-to-severe dementia for the above outcomes, comparing analyses restricted to OC and LOCF data (Analysis 10.3; Analysis 10.4). Again, there appeared to be little difference between the results of two analyses, although there was heterogeneity within each analysis. We decided to report OC analyses in the main part of the review wherever possible: if studies did not report OC data, we used the data reported by the authors. The degree of missing data was assessed and is reported in the 'Risk of bias' section of the Characteristics of included studies table.

Appendix 4. Sensitivity and subgroup analyses to investigate heterogeneity in efficacy outcomes

Initially, we included data from all 24 trials in AD in the same forest plots (Analysis 11.1; Analysis 11.2; Analysis 11.3; Analysis 11.4) using the OC approach to missing data, wherever possible. Two studies had no results for any efficacy outcome (Lundbeck 2006 (99817); Merz 2003 (MRZ-9104). For most outcomes, there was too much heterogeneity to make overall statements of effect - this is seen in the variation of point estimates in the forest plots and in the statistics: for the cognitive function outcome (20/24 studies), I^2 was 41% and P = 0.03. For the decline in ADL (14/24), I^2 was 47% and the P value was 0.03. For the behaviour and mood outcome (15/24), I^2 was 38% and the P value was 0.07. However, for the clinical global rating (14/24 studies), I^2 was 0% and the P value for heterogeneity was 0.59. Therefore, we investigated the heterogeneity for these outcomes in sensitivity and subgroup analyses, which cover risk of bias, severity of AD and the presence or absence of concomitant ChEIs.

A4.1. Sensitivity analysis on the basis of high risk of bias

The effect of high risk of bias was investigated in sensitivity analyses (Analysis 11.5; Analysis 11.6; Analysis 11.7; Analysis 11.8). Exclusion of the trials at high risk of bias for one or more domains (see section Risk of bias in included studies) generally made little difference to the heterogeneity: for the cognitive function outcome (n = 16), I^2 for the sensitivity analysis was 43% and the P value was 0.03 (Analysis 11.6). For the decline in ADL (n = 12), I^2 was 39% and the P-value was 0.08 (Analysis 11.7). For the behaviour and mood outcome (n = 13), I^2 was 25% and the P value was 0.19 (Analysis 11.8), which was some improvement. We decided to continue using all the data because heterogeneity must have been attributable to factors other than high risk of bias.

A4.2. Effect of trial duration

Trial duration for the AD studies varied from 12 weeks to five years, with most studies examining the effects at six months. We investigated the effect of duration on the effectiveness of memantine, combining all studies regardless of duration, severity of dementia or presence of concomitant ChEIs. For the longest duration study we used 12-month interim data for comparability with the duration of the other longer-term studies (Dysken 2014).

Subgroup analyses by duration (fixed effect) (Analysis 12.1; Analysis 12.2; Analysis 12.3; Analysis 12.4) did not appear to explain the observed heterogeneity for any of the outcomes. The test for subgroup differences was I^2 = 0% for clinical global rating; 27.3% (P = 0.25) for cognitive function; 58.7% (P = 0.09) for decline in ADL and 4.1% (P = 0.31) for behaviour and mood. In all of these subgroup analyses except for global rating, some underlying heterogeneity still remained in the point estimates for the six- to seven-month subgroups (i.e. duration did not explain the heterogeneity).

The short-term studies (shorter than six months) were more likely to be conducted for hypothesis-generating purposes, so we focused on the studies with a duration of six months or more. This excluded from the analysis four short-term studies in 658 participants (Hofbauer 2009 (MD-71); Lundbeck 2006 (10116); Merz 2003 (MRZ-9104); Winblad 1999 (9403) AD). Data were available at six months pre-specified interim time points for four of the longer studies and therefore we used only six- to seven-month data and investigated other sources of heterogeneity (Dysken 2014; Howard 2012 (DOMINO-AD); Peters 2015 (MEGACOMBI2); Schmidt 2008). Three studies with a duration of more than seven months reported results for cognitive function at one year only and were not included in the efficacy analyses (but were analysed for the safety data) (Ashford 2011 (95722); Holland 2013; Wilkinson 2012 (10112)).

A4.3. Effect of dose

Three studies reported results for a dose of memantine (10 mg/day) that was lower than the licensing dose of 20 mg/day (Asada 2011 (MA3301); Homma 2007 (IE2101); Winblad 1999 (9403) AD); the first two of these studies also included a 20 mg/day memantine arm. The studies varied in severity of disease: the Asada 2011 (MA3301) study recruited participants with mild-to-moderate AD, the Homma 2007 (IE2101) study had moderate-to-severe AD participants and the Winblad 1999 (9403) AD study, reporting at 12 weeks, had participants with severe dementia and was an AD subgroup of the study. Head-to-head comparisons of 10 mg/day with 20 mg/day are shown in Analysis 13.1; Analysis 13.2; Analysis 13.3; Analysis 13.4, giving high heterogeneity (I^2 = 90%) for the cognitive function outcome. The comparisons of 10 mg/day memantine versus placebo gave some heterogeneity for the outcomes of clinical global rating (I^2 = 48%); cognitive function

(25%) and decline in ADL (75%) (Analysis 13.5; Analysis 13.6; Analysis 13.7; Analysis 13.8). Therefore, we omitted the 10 mg/day data from the rest of the analyses, and the licensed dose (20 mg/day) was used.

Following these dose and duration restrictions, there were 17 studies in 5813 participants in the efficacy analyses. Two further subgroup analyses were conducted, one examining the effect of concomitant ChEIs and the other investigating the effect of severity of disease.

A4.4. Effect of concomitant cholinesterase inhibitor (ChEI)

We explored subgroup analyses by the presence or absence of ChEIs, across all AD severities (except those in patients selected for agitation). These analyses are shown in Analysis 14.1; Analysis 14.2; Analysis 14.3; Analysis 14.4; within the ChEI subgroups, studies are ordered by decreasing severity.

The between-trial subgroup analyses (fixed effect, unless otherwise stated) showed the following results.

- Clinical global rating (Analysis 14.1): there was no significant difference between subgroups (monotherapy and concomitant ChEI) - test for subgroup differences: I^2 = 0%, P = 0.93
  - Monotherapy pooled estimate: 9 studies in 2378 participants: SMD -0.20 (95% CI -0.28 to -0.11)
  - Concomitant ChEIs pooled estimate: 3 studies in 1246 participants: SMD -0.19 (95% CI -0.30 to -0.08)
  - There was some heterogeneity in the ChEI subgroup (I^2 = 34%, P = 0.22), but none in the monotherapy group (I^2 = 0%, P = 0.75).
  - The overall heterogeneity (across both subgroups) was I^2 = 0%, P = 0.70
  - Overall estimate: 12 studies in 3624 participants: SMD -0.19 (95% CI -0.26 to -0.13)
- Cognitive function (Analysis 14.2): the test for subgroup differences was not significant (I^2 = 0%, P = 0.55)
  - Monotherapy pooled estimate: 10 studies in 2189 participants; SMD -0.24 (95% CI -0.32 to -0.15)
  - Concomitant ChEIs pooled estimate: 7 studies in 2312 participants: SMD -0.20 (95% CI -0.28 to -0.12)
  - There was heterogeneity in the monotherapy group (I^2 = 55%, P = 0.02), but none in the concomitant ChEI group (I^2 = 0%, P = 0.43).
  - The overall heterogeneity (across both subgroups) was I^2 = 39%, P = 0.05
  - Overall estimate: 16 studies (17 comparisons) in 4501 participants; SMD -0.22 (95% CI -0.28 to -0.16)
- Decline in ADL (Analysis 14.3): the test for subgroup differences was not significant (I^2 = 0%, P = 0.56)
  - Monotherapy pooled estimate: 7 studies in 1674 participants: SMD -0.14 (95% CI -0.24 to -0.04)
  - Concomitant ChEIs pooled estimate: 6 studies in 1758 participants: SMD -0.10 (95% CI -0.19 to -0.01)
  - There was no heterogeneity in the ChEI subgroup (I^2 = 0%,P = 0.50), and some heterogeneity in the monotherapy group (I^2 = 39%, P = 0.13).
  - The overall heterogeneity (across both subgroups) was I^2 = 17%, P = 0.27
  - Overall estimate: 12 studies in 3432 participants; SMD -0.12 (95% CI -0.19 to -0.05)
- Behaviour and mood (Analysis 14.4): the test for subgroup differences showed a small, non-significant difference (I^2 = 27.5%, P = 0.24)
  - Monotherapy pooled estimate: 9 studies in 2125 participants: SMD -0.08 (95% CI -0.17 to 0.00)
  - Concomitant ChEIs pooled estimate: 6 studies in 2145 participants: SMD -0.15 (95% CI -0.24 to -0.07)
  - There was some heterogeneity in the ChEI subgroup (I^2 = 30%, P = 0.21), but very little in the monotherapy group (I^2 = 10%, P = 0.35)
  - The overall heterogeneity (across both subgroups) was I^2 = 19%, P = 0.24
  - Overall estimate: 14 studies in 4270 participants; SMD -0.12 (95% CI -0.18 to -0.06)

Overall, the presence or absence of ChEIs does not appear to explain the heterogeneity. The ordering by severity suggests this may be an important factor.

A4.5. Effect of severity or stage of AD

Seventeen studies in 5811 randomised patients had six- to seven-month follow-up data, but not all studies reported each of the outcomes. Twelve studies reported data for the clinical global rating, 16 cognitive function, 12 decline in ADL and 14 behaviour–mood.

There was variation in the point estimates (but non-significant heterogeneity statistics) for the following outcomes: cognitive function (I^2 = 37%, P = 0.07) (Analysis 15.2); decline in ADL (I^2 = 21%, P = 0.24) (Analysis 15.3) and behaviour–mood (I^2 = 22%, P = 0.21) (Analysis 15.4), but little variation for clinical global rating (I^2 = 0%, P = 0.70) (Analysis 15.1).

A4.5.1. Subgroup analyses by severity of dementia: mild-to-moderate versus moderate-to-severe disease

We conducted subgroup analyses by severity of dementia, separating studies initially into mild-to-moderate and moderate-to-severe dementia subgroups, which were the populations defined in the trials.

The test for subgroup differences was highly significant across the subgroups mild-to-moderate and moderate-to-severe AD, for cognitive function, decline in ADL and behaviour and mood outcomes. However, there was no significant effect of AD severity on the clinical global rating outcome. There was some heterogeneity within the moderate-to-severe set of studies for cognitive function.

1. Clinical global rating: (Analysis 15.5)

- Mild to moderate AD: 5 studies, 1519 patients; SMD -0.16 (95% CI -0.26 to -0.06), with some heterogeneity in the point estimates (I^2 = 24%, P = 0.26)
- Moderate to severe AD: 7 studies, 2105 patients; SMD -0.22 (95% CI -0.30 to -0.13)
- Test for subgroup differences: I^2 = 0%, P = 0.38

2. Cognitive function (Analysis 15.6)

- Mild to moderate AD: 7 studies, 1959 patients; SMD -0.13 (95% CI -0.22 to -0.04)
- Moderate to severe AD: 9 studies, 2541 patients; SMD -0.28 (95% CI -0.36 to -0.20), with some heterogeneity (I^2 = 48%, P = 0.05 and variability in the point estimates)
- Test for subgroup differences: I^2 = 83.9%; P = 0.01

3. Decline in ADL (Analysis 15.7)

- Mild to moderate AD: 5 studies, 1554 patients; SMD -0.03 (95% CI -0.13 to 0.07)
- Moderate to severe AD: 7 studies, 1878 patients; SMD -0.19 (95% CI -0.28 to -0.10)
- Test for subgroup differences: I^2 = 80.7%, P = 0.02

4. Behaviour and mood (Analysis 15.8)

- Mild to moderate AD: 4 studies, 1405 patients; SMD -0.01 (95% CI -0.11 to 0.10)
- Moderate to severe AD: 10 studies, 2865 patients; SMD -0.17 (95% CI -0.25 to -0.10)
- Test for subgroup differences: I^2 = 84.1%; P = 0.01

There are two limitations to these subgroup analyses: they contain overlapping definitions of severity because patients with moderate dementia could be included in either moderate-to-severe or mild-to-moderate subgroups. In addition, the management of AD and the licensing of treatments for AD are based around the categories of mild AD and moderate-to-severe AD.

A4.5.2. Effect of severity or stage of AD: mild versus moderate-to-severe

We conducted further pre-specified subgroup analyses, comparing mild versus moderate-to-severe dementia subgroups, using within-trial post-hoc subgroup data (mild and moderate) from four studies (Bakchine 2008 (99679); Dysken 2014; Peskind 2004 (MD-10); Porsteinsson 2008 (MD-12)), together with data from trials in moderate-to-severe populations. As described in the Methods section, we calculated the within-trial subgroup OC data for people with mild AD for three studies (Bakchine 2008 (99679); Peskind 2004 (MD-10); Porsteinsson 2008 (MD-12)); results were for participants with MMSE scores of 20 or more. The Dysken 2014 authors provided data at six months divided into mild and moderate severities.

We combined the subgroup data for the moderate severity population with results for studies in people with moderate-to-severe AD; the mild subpopulation was reported as a separate subgroup. Studies in people with mild-to-moderate AD that did not give separate results for mild and moderate subgroups were left out of the analyses (Asada 2011 (MA3301); Peters 2015 (MEGACOMBI2); Schmidt 2008). These analyses therefore comprised results for 15 studies, of which four had results for both mild and moderate subgroups, giving 19 'trials'. We also conducted further analyses adding the Peters 2015 (MEGACOMBI2) study interim results at six months, because the mean MMSE score for the population was 21.7 (SD 3.2) (combination group) and 22.6 (SD 3.1) (ChEI alone) and so about 80% or 88% respectively participants had mild AD. The results for meta-analyses that included Peters 2015 (MEGACOMBI2) are given in brackets for the two outcomes (cognitive function and decline in ADL).

The summary statistics for the comparison of memantine and placebo in people with mild disease showed smaller effects than in people with moderate-to-severe disease. The test for subgroup differences (fixed effects) showed a significant difference for cognitive function, decline in ADL and the behaviour and mood outcomes. There was a small difference for the clinical global rating. There may have been a small amount of residual heterogeneity in the moderate-to-severe sets of studies for cognitive function and behaviour and mood.

1. Clinical global rating: (Analysis 16.1)

- Mild AD: 3 studies, 427 patients; SMD -0.08 (95% CI -0.27 to 0.12)
- Moderate to severe AD: 10 studies, 2797 patients; SMD -0.20 (95% CI -0.28 to -0.13)
- Test for subgroup differences: I^2 = 29.2%, P = 0.23

2. Cognitive function (Analysis 16.2)

- Mild AD: 4 studies, 619 patients; SMD -0.03 (95% CI -0.19 to 0.13) (with Peters 2015 (MEGACOMBI2): 5 studies, 794 patients, SMD -0.03 (-0.17 to 0.11)

- Moderate to severe AD: 13 studies, 3336 patients; SMD -0.27 (95% CI -0.34 to -0.21), some heterogeneity in the point estimates (I^2 = 30%, P = 0.14)
- Test for subgroup differences: I^2 = 87.3%; P = 0.005 (with Peters 2015 (MEGACOMBI2): I^2 = 89.0%, P = 0.003)

3. Decline in ADL (Analysis 16.3)

- Mild AD: 4 studies, 621 patients; SMD 0.02 (95% CI -0.14 to 0.18) (with Peters 2015 (MEGACOMBI2): 5 studies, 770 patients, SMD 0.02 (-0.12 to 0.16)
- Moderate to severe AD: 11 studies, 2687 patients; SMD -0.16 (95% CI -0.24 to -0.09)
- Test for subgroup differences: I^2 = 75.9%, P = 0.04 (with Peters 2015 (MEGACOMBI2): I^2 = 79.9%, P = 0.03)

4. Behaviour and mood (Analysis 16.4)

- Mild AD: 4 studies, 621 patients; SMD 0.02 (95% CI -0.14 to 0.18)
- Moderate to severe AD: 14 studies, 3674 patients; SMD -0.14 (95% CI -0.21 to -0.08), slight heterogeneity in the point estimates (but I^2 = 8%, P = 0.36)
- Test for subgroup differences: I^2 = 68.7%; P = 0.07

Limitations for this subgroup analysis are the use of post-hoc subgroups and the necessity of excluding from the analysis three studies in 468 participants with mild-to-moderate AD (Asada 2011 (MA3301); Peters 2015 (MEGACOMBI2); Schmidt 2008).

A4.5.2.1. Sensitivity analysis for the inclusion of post-hoc subgroups

Calculations of separate results for mild and moderate AD sub-populations involved post-hoc splitting and may give high risk of bias. We conducted sensitivity analyses for the moderate-to-severe AD population to investigate the effect of not including within-trial subgroup data for moderate dementia from the mild-to-moderate trials, comparing results from the two sets of analyses:

1. Clinical global rating

- Full analysis for 10 studies contributing data: SMD -0.20 (95% CI -0.28 to -0.13) (Analysis 16.1.2)
- Sensitivity analysis in 7 studies: SMD -0.22 (95% CI -0.30 to -0.13) (Analysis 15.5.2)

2. Cognitive function

- Full analysis in 13 studies: SMD -0.27 (95% CI -0.34 to -0.21); some heterogeneity I^2 = 30% (P = 0.14) (Analysis 16.2.2)
- Sensitivity analysis in 9 studies: SMD -0.28 (95% CI -0.36 to -0.20); heterogeneity I^2 = 48% (P = 0.05) (Analysis 15.6.2)

3. Decline in ADL

- Full analysis in 11 studies: SMD -0.16 (95% CI -0.24 to -0.09) (Analysis 16.3.2)
- Sensitivity analysis in 7 studies: -0.19 (95% CI -0.28 to -0.10) (Analysis 15.7.2)

4. Behaviour and mood

- Full analysis in 14 studies: SMD -0.14 (95% CI -0.21 to -0.08) (Analysis 16.4.2)
- Sensitivity analysis in 10 studies: SMD -0.17 (95% CI -0.25 to -0.10) (Analysis 15.8.2)

There is little difference between the full and sensitivity analyses, although the sensitivity analyses consistently gave slightly larger effects, and we decided to continue with the full analyses.

4.5.2.2. Change from baseline by severity

We also calculated the median and range for the standardised mean change from baseline for the placebo groups for each severity subgroup by dividing the change from baseline by the SD (pooled) for each study and taking the median across studies.

The following are the median (range) of the standardised mean change from baseline for all studies.

1. Clinical global rating

- Moderate to severe: 4.3 (range 2.9 to 4.6)
- Mild: 4.0 (range 3.1 to 4.3)

2. Cognitive function

- Moderate to severe: 0.35 (range 0 to 0.89)

- Mild: -0.20 (range -0.38 to 0.11) (with Peters 2015 (MEGACOMBI2) at six months: -0.20 (range -0.38 to 0.11))

3. Decline in ADL

- Moderate to severe: 0.49 (range 0.14 to 0.90)
- Mild: 0.04 (range -0.35 to 0.27) (with Peters 2015 (MEGACOMBI2) at six months: 0.20 (range -0.35 to 0.27))

4. Behaviour and mood

- Moderate to severe: 0.12 (range -0.22 to 0.56)
- Mild: -0.16 (range -0.33 to -0.10)

A4.5.3. Effect of severity or stage of AD: severe versus moderate AD

A4.5.3.1. Post-hoc within-trial subgroup analyses

We conducted a further post-hoc subgroup analysis, investigating whether there were different effects in severe versus moderate AD. One report (IQWIG 2009) gave post-hoc, within-trial, LOCF results for severe (MMSE < 10) and moderate subgroups in four studies in people with moderate-to-severe AD (Homma 2007 (IE2101); Reisberg 2003 (9605); Tariot 2004 (MD-02); van Dyck 2007 (MD-01)); the minimum MMSE scores were respectively 5, 3, 5 and 5. We combined the results for the moderate subgroups of these trials with those for the moderate post-hoc subgroups described in section A4.5.2; the mild post-hoc subgroups were also added to the results summary in order to study trends. This was done for clinical global rating, cognitive function and decline in ADL outcomes (Analysis 17.1; Analysis 17.2; Analysis 17.3); the IQWIG 2009 report did not give subgroup results for the behaviour and mood outcome.

The summary statistics for the severe and moderate AD groups and the statistics for the test for subgroup differences, in the absence of the mild subgroup, are given below for the two subgroups (moderate and severe).

We also calculated the median and range of the standardised mean change from baseline separately for the placebo groups, by dividing the change from baseline by the SD(pooled) for each study and taking the median across studies.

1. Clinical global rating (Analysis 17.1)

- Severe AD: 4 studies, 531 patients; SMD -0.26 (95% CI -0.43 to -0.09)
- Moderate AD: 8 studies, 1453 patients; SMD -0.19 (-0.30 to -0.08)
- Test for subgroup differences between severe and moderate AD subgroups: I^2 = 0%, P = 0.64
- c.f. mild AD: 4 studies 621 patients; SMD -0.08 (-0.27 to 0.12)

The median (range) standardised means for the placebo group were:

- severe = 4.4 (3.2 to 4.8); moderate = 4.1 (3.3 to 4.6) and mild = 4.0 (3.1 to 4.3).

2. Cognitive function (Analysis 17.2)

- Severe AD: 4 studies, 531 patients; SMD (random effects) -0.39 (95% CI -0.67 to -0.11), with significant heterogeneity I^2 = 82%, P = 0.05)
- Moderate AD: 8 studies, 1448 patients; SMD (random effects) -0.27 (95% CI -0.37 to -0.16)
- Test for subgroup differences between severe and moderate AD subgroups: I^2 = 30.6%, P = 0.23
- c.f. mild AD: 4 studies, 619 patients; SMD (random effects) -0.03 (95% CI -0.19 to 0.13)

The median (range) of the standardised mean changes from baseline for the placebo group were:

- severe = 0.62 (0.50 to 0.81); moderate = 0.34 (0.00 to 0.89) and mild = -0.20 (-0.38 to 0.11).

Additionally, one study with MMSE scores from 1 to 14 reported a post-hoc subgroup of participants with scores MMSE 5-14 and we calculated results for the subgroup with scores less than 5 (Nakamura 2016). The results were: scores 1-4: SMD 0.26 (-0.12 to 0.64) (50 participants) and scores 5-14: SMD -0.20 (-0.38 to -0.01).

3. Decline in ADL (Analysis 17.3)

- Severe AD: 4 studies, 531 patients; SMD -0.18 (95% CI -0.35 to -0.01)
- Moderate AD: 8 studies, 1463 patients; SMD -0.13 (95% CI -0.23 to -0.02), with some heterogeneity in point estimates (I^2 = 0%, P = 0.49)
- Test for subgroup differences between severe and moderate AD subgroups: I^2 = 0%, P = 0.63
- c.f. mild AD: 4 studies, 621 patients; SMD 0.02 (95% CI -0.14 to 0.18)

The median (range) of the standardised mean changes from baseline for the placebo group were:

- severe = 0.65 (0.18 to 0.88); moderate = 0.45 (0.13 to 0.67) and mild = 0.04 (-0.35 to 0.27).

A4.5.3.2. Post-hoc between-trial subgroup analyses

We conducted a second post-hoc analysis. We separated 13 AD studies according to their mean MMSE scores into severe (mean less than 10), moderate-to-severe (mean 10-12) and moderate (the post-hoc subgroups). The mild post-hoc subgroups were also added. We had no mean MMSE scores for the moderate post-hoc subgroups, but estimated these to be higher than 12 because the mild-to-moderate mean scores for the original studies were at least 16.9 and the proportion with moderate severity was about 70%. Therefore we treated the post-hoc moderate severity data as a separate subgroup. The limitation of this analysis is that the subgrouping is based on aggregate values (mean scores for the study) and there may be ecological fallacy problems. One study separated post-hoc their results for very severe (1-4) and moderate-to-severe disease (5-14).

We conducted these analyses to investigate trends, especially for the behaviour and mood outcome, which was not reported for the first analysis (Analysis 17.4; Analysis 17.5; Analysis 17.6; Analysis 17.7). We found general trends for increased efficacy with increasing AD severity for memantine versus placebo for all outcomes, although this was less pronounced for the clinical global rating outcome.

1. Clinical global rating (Analysis 17.4)

- Severe AD (study mean MMSE < 10): 2 studies, 548 patients; SMD -0.16 (95% CI -0.33 to 0.01)
- Moderate-severe AD (study mean 10-12): 5 studies, 1557 patients: SMD -0.24 (95% CI -0.34 to -0.14)
- Moderate AD (post-hoc) subgroups: 3 studies, 692 patients: SMD -0.16 (95% CI -0.32 to 0.00)
- Mild AD (post-hoc subgroups): 3 studies, 27 patients: SMD -0.08 (-0.27 to 0.12)
- Test for subgroup differences across all subgroups (including mild): I^2 = 0%, P = 0.47
- Test for subgroup differences between severe and moderate (post-hoc) subgroups: I^2 = 0%, P = 0.99

The median (range) of the standardised means for the placebo group were:

- severe (mean < 10) = 4.3 (range 4.2 to 4.4); moderate-severe (mean 10-12) = 3.6 (range 2.9 to 4.4);
- moderate (post-hoc) = 4.6 (range 3.8 to 4.6) and mild (post hoc) = 4.0 (range 3.1 to 4.3).

2. Cognitive function (Analysis 17.5)

- Severe AD (study mean MMSE < 10): 3 studies, 690 patients; SMD -0.42 (95% CI -0.57 to -0.27)
- Moderate-severe AD (study mean 10-12): 6 studies, 1852 patients; SMD -0.23 (95% CI -0.32 to -0.14), with some heterogeneity (I^2 = 52%, P = 0.06)
- Moderate AD (post-hoc) subgroups: 4 studies, 795 patients; SMD -0.25 (95% CI -0.40 to -0.11)
- Mild AD (post-hoc) subgroups and study MMSE mean ≥ 20: 5 studies, 794 patients; SMD -0.03 (95% CI -0.17 to 0.11)
- Test for subgroup differences across all subgroups (including mild): I^2 = 78.4%, P = 0.003
- Test for subgroup differences between severe and moderate (post-hoc) subgroups: I^2 = 60.7% and P = 0.11

The median (range) of the standardised mean changes from baseline for the placebo group were:

- Severe = 0.74 (range 0.48 to 0.85); moderate-severe (study mean 10-12) = 0.26 (range 0.00 to 0.85)
- Moderate (post-hoc) = 0.34 (range 0.11 to 0.89) and mild (post-hoc and MMSE study mean ≥ 20) = -0.20 (range -0.38 to 0.11)

3. Decline in ADL (Analysis 17.6)

- Severe AD (study mean MMSE < 10): 2 studies, 324 patients; SMD (random effects) -0.35 (95% CI -0.69 to -0.02); some heterogeneity (I^2 = 57%, P = 0.13)
- Moderate-severe AD (study mean 10-12): 5 studies, 1554 patients; SMD (random effects) -0.15 (95% CI -0.25 to -0.05)
- Moderate AD (post-hoc) subgroups: 4 studies, 809 patients; SMD (random effects) -0.10 (95% CI -0.25 to 0.04)
- Mild AD (post hoc and MMSE study mean ≥ 20) subgroups: 5 studies, 770 patients; SMD (random effects) 0.02 (95% CI -0.12 to 0.16)
- Test for subgroup differences across all subgroups (including mild): I^2 = 42.9%, P = 0.15 (random effects)
- Test for subgroup differences between severe and moderate (post-hoc) subgroups: I^2 = 44.1% and P = 0.18 (random effects)

The median (range) of the standardised mean changes from baseline for the placebo group were:

- Severe = 0.81 (range 0.72 to 0.91); moderate-severe (study mean 10-12) = 0.38 (range 0.14 to 0.49);
- Moderate (post-hoc) = 0.56 (range 0.35 to 0.67) and mild = 0.20 (range -0.35 to 0.27)

4. Behaviour and mood (Analysis 17.7)

- Severe AD (study mean MMSE < 10): 3 studies, 749 patients) SMD -0.25 (95% CI -0.40 to -0.11)
- Moderate-severe AD (mean 10-12): 6 studies, 1579 patients; SMD -0.15 (95% CI -0.25 to -0.05)
- Moderate AD (post-hoc) subgroups: 4 studies, 809 patients; SMD -0.02 (95% CI -0.17 to 0.12), with some heterogeneity (I^2 = 17%, P = 0.31)
- Mild AD (post-hoc) subgroups: 4 studies, 621 patients; SMD -0.02 (95% CI -0.14 to 0.18)
- Test for subgroup differences across all subgroups (including mild): I^2 = 63.5%, P = 0.04
- Test for subgroup differences between severe and moderate (post-hoc) subgroups: I^2 = 79.8% and P = 0.03

The median (range) of the standardised mean changes from baseline for the placebo group were:

- severe = 0.18 (range 0.16 to 0.20); moderate-severe (study mean 10-12) = -0.07 (range -0.21 to 0.56);
- moderate (post-hoc) = 0.14 (range -0.22 to 0.23) and mild = -0.16 (range -0.33 to -0.10).

These are exploratory post-hoc analyses on the basis of mean study values, so there may be aggregate effects (ecological fallacy). They give an indication that memantine may be more effective in patients with severe dementia for the outcomes of cognitive function, decline in ADL and behaviour and mood. For the latter outcome, memantine may not be very effective in people with either moderate or mild dementia, but this is very uncertain.

Appendix 5. Conclusions from subgroup analyses

After reducing the dataset to studies with the licensed dose (20 mg/day) and a duration of follow-up (six to seven months), we conducted subgroup analyses investigating the presence or absence of concomitant ChEI and two main approaches to severity of disease (mild–to–moderate versus moderate–to–severe, and mild versus moderate–to–severe) in 17 studies in 5813 randomised participants.

There is not much effect of concomitant ChEI as an effect modifier, but there are large differences in the test for subgroup differences related to severity. The exception to this may be for the behaviour and mood outcome, which also shows a small non-significant difference for the effect of concomitant ChEI.

We investigated effect modification further by conducting meta-regressions in STATA (StataCorp version 13). For the cognitive function outcome the following results were found:

- for the potential effect modifier of concomitant ChEI (versus monotherapy), the meta-regression coefficient was 0.60 (95% CI -1.06 to 2.26) and the proportion of between-study variance explained (adjusted R^2) was negative, suggesting a poor fit;
- for the potential effect modifier of severity (mild-to-moderate versus moderate-to-severe), the meta-regression coefficient was -1.61 (95% CI -2.94 to -0.27) and the proportion of between-study variance explained was 48.3%;
- Inclusion of both variables gave coefficients of -1.70 (95% CI -3.06 to -0.34) for severity and 0.66 (95% CI -0.70 to 2.02) for ChEI, with an adjusted R^2 of 42.0% and an overall model significance of 0.046.

The meta-regression for behaviour and mood gave negative adjusted R^2 values and suggested one study may have been an outlier (Nakamura 2016). In its absence, the meta-regressions that included both severity and ChEI gave coefficients.

- Behaviour and mood: -2.21 (95% CI -3.89 to -0.52) for severity and -1.81 (95% CI -3.49 to -0.13) for ChEI, with an adjusted R^2 of 100% and an overall model significance of 0.02.
- Cognitive function: -1.94 (95% CI -3.29 to -0.60) for severity and 0.37 (95% CI -0.98 to 1.72) for ChEI, with an adjusted R^2 of 59.1% and an overall model significance of 0.025 for cognitive function.

These meta-regressions are underpowered, but give an indication that much of the variance may be explained by the severity factor. We note that the coefficient for severity is negative, which means that there may be a bigger effect in the more severe populations.

All these findings suggest that it is more important to stratify the studies by severity first and then investigate the effect of ChEI to address our second objective.

On the basis of the evidence from these subgroup analyses, we decided to report, in the main text, the results separately for mild and moderate-to-severe AD, but not to report the results for patients with mild-to-moderate AD, because this is not a licensed indication. Thus, the main analyses reported in the text for AD are:

- moderate-to-severe AD; six to seven months duration;
- mild AD; six to seven months months duration.

We note that the medians of the standardised change from baseline for the placebo group varied between the mild, moderate and severe AD subgroups. In the moderate and severe disease subgroups, the cognitive function, decline in ADL, behaviour and mood, and, to a lesser extent, global scores, all tended to worsen over six months. By comparison, for the mild severity subgroup, the scores for the outcomes cognitive function, and behaviour and mood tended to improve with time.

Appendix 6. Subgroup analysis by concomitant cholinesterase inhibitor in people with moderate to severe AD

We conducted subgroup analyses to investigate any differences in the effect of memantine versus placebo as monotherapy or with concomitant ChEI in the moderate-to-severe AD population. Analysis 2.1; Analysis 2.2; Analysis 2.3 and Analysis 2.4 are between-trial subgroup analyses and Analysis 2.5; Analysis 2.6 and Analysis 2.7 show the within-trial, per protocol (PP) analyses for cognitive function (MMSE), decline in ADL (BADL) and neuropsychiatric inventory (NPI) outcomes (Howard 2012 (DOMINO-AD)).

6.1 Within-trial subgroup analyses

The Howard 2012 (DOMINO-AD) within-trial subgroup comparisons suffered from large and differential levels of missing data for the per protocol analysis and were probably underpowered, but have the benefit of being in the same population (participants on donepezil being considered for a change of medication). This population may, however, be unrepresentative. This evidence is too uncertain to draw conclusions. The randomised comparison of memantine plus donepezil versus memantine plus placebo (Analysis 2.14) had fewer missing data and suggested there may be a larger effect for the combination compared with monotherapy for cognitive function.

6.2. Between-trials subgroup analyses

Seven studies were in people who did not receive concomitant ChEIs (monotherapy) (Asada 2011a (IE3501); Bakchine 2008 (99679) SG; Forest 2006 (MD-22); Homma 2007 (IE2101); Peskind 2004 (MD-10) SG; Reisberg 2003 (9605); van Dyck 2007 (MD-01)). Five studies were in participants receiving ChEIs (Dysken 2014 SG; Grossberg 2008 (MD-50); Nakamura 2016; Porsteinsson 2008(MD-12)S; Tariot 2004 (MD-02)) and one study randomised participants to continuation or discontinuation of ChEIs (Howard 2012 (DOMINO-AD)). Not all the studies reported all the outcomes. We also report the median SMD change from baseline for the placebo groups for each subgroup.

The between-trial subgroup analyses (fixed effects) showed the following results:

1. Clinical global rating (Analysis 2.1): there was no significant difference between subgroups (monotherapy and concomitant ChEI) - test for subgroup differences: I^2 = 0%, P = 0.99

- Monotherapy pooled estimate: 7 studies in 1672 participants: SMD -0.20 (95% CI -0.30 to -0.10)
- Concomitant ChEIs pooled estimate: 3 studies in 1125 participants: SMD -0.21 (95% CI -0.32 to -0.09)
- There was slight heterogeneity in the ChEI subgroup (I^2 = 13%, P = 0.32), but none in the monotherapy group (I^2 = 0%, P = 0.88).
- The overall heterogeneity (across both subgroups) was I^2 = 0%, P = 0.86
- Overall estimate: 10 studies in 2797 participants: SMD -0.20 (95% CI -0.28 to -0.13
- Median (range) for standardised mean for the placebo group:
  - Monotherapy: 4.2 (range 2.9 to 4.6)
  - Combination therapy: 4.4 (range 3.6 to 4.6)

2. Cognitive function (Analysis 2.2): the test for subgroup differences showed a non-significant difference (I^2 = 44.2%, P = 0.18)

- Monotherapy pooled estimate: 8 studies in 1485 participants; SMD -0.33 (95% CI -0.43 to -0.23);
- Concomitant ChEIs pooled estimate: 6 studies in 1852 participants: SMD -0.24 (95% CI -0.33 to -0.14)
- There was some heterogeneity in the monotherapy group (I^2 = 41%, P = 0.11), and slight heterogeneity in the concomitant ChEI group (I^2 = 13%, P = 0.33).
- The overall heterogeneity (across both subgroups) was I^2 = 33%, P = 0.11
- Overall estimate: 13 studies (14 comparisons) in 3337 participants; SMD -0.28 (95% CI -0.35 to -0.21)
- Median (range) for the standardised mean change from baseline for the placebo group:
  - monotherapy: 0.48 (range 0.18 to 1.34);
  - combination therapy: 0.30 (range 0 to 0.89).

3. Decline in ADL (Analysis 2.3): the test for subgroup differences was not significant (I^2 = 0%, P = 0.43)

- Monotherapy pooled estimate: 7 studies in 1368 participants: SMD -0.20 (95% CI -0.30 to -0.09);
- Concomitant ChEIs pooled estimate: 5 studies in 1319 participants: SMD -0.13 (95% CI -0.24 to -0.03).
- There was no heterogeneity in the ChEI subgroup (I^2 = 0%, P = 0.69), and a little heterogeneity in the monotherapy group (I^2 = 10%, P = 0.36).
- The overall heterogeneity (across both subgroups) was I^2 = 0%, P = 0.58.
- Overall estimate: 11 studies (12 comparisons) in 2687 participants; SMD -0.17 (95% CI -0.24 to -0.09)
- Median (range) for the standardised mean change from baseline for the placebo group:
  - monotherapy: 0.49 (range 0.34 to 0.91);
  - combination therapy: 0.51 (range 0.14 to 0.67).

4. Behaviour and mood (Analysis 2.4): the test for subgroup differences showed a non-significant difference (I^2 = 35.2%, P = 0.21)

- Monotherapy pooled estimate: 9 studies in 1819 participants: SMD -0.10 (95% CI -0.19 to -0.01)
- Concomitant ChEIs pooled estimate: 6 studies in 1855 participants: SMD -0.18 (95% CI -0.27 to -0.09).
- There was slight heterogeneity in the ChEI subgroup (I^2 = 10%, P = 0.35), but none in the monotherapy group (I^2 = 0%, P = 0.46).
- The overall heterogeneity (across both subgroups) was I^2 = 6%, P = 0.39.
- Overall estimate: 14 studies (15 comparisons) in 3674 participants; SMD -0.14 (95% CI -0.21 to -0.08)
- Median (range) for the standardised mean change from baseline for the placebo group:
  - monotherapy: 0.07 (range -0.22 to 0.56);
  - combination therapy: 0.15 (range -0.13 to 0.31).

WHAT'S NEW

Date	Event	Description
19 March 2019	New citation required and conclusions have changed	Thirty-two new studies added and the content extensively revised. Conclusions changed. New joint lead author brought in.
25 March 2018	New search has been performed	A top-up search was performed on 25 March 2018.

HISTORY

Protocol first published: Issue 3, 2001
Review first published: Issue 1, 2003

Date	Event	Description
31 March 2017	New search has been performed	A top-up search was run for this review on 31 March 2017. New studies were added. Conclusions changed
1 February 2016	New search has been performed	A top-up search was run for this review on 1 February 2016
9 May 2010	New search has been performed	The last published update in 2006 included 12 trials. This update is a complete revision and includes 35 trials. The final search confirmed that the review included all available material on 6th May 2011.
15 July 2009	New search has been performed	Completion updated text. Updated search confirms no further includable studies
21 July 2008	New search has been performed	February 2008 search: retrieved a number of studies for consideration by the authors.
26 February 2006	New citation required and conclusions have changed	The main difference from the previous iteration of this review has been the replacement of imputed data for the trial MD-01 with the actual data. A new section focussing on the effect of memantine on agitation has been added. The numbering scheme for trials has been updated, usually in line with the designation used by sponsoring companies. Information on trials in progress has been updated. The order of authorship has been revised in the light of recent contributions of the authors. Neda Minakaran has joined the writing team.

CONTRIBUTIONS OF AUTHORS

Earlier versions

Neda Minakaran contributed search for trials, extracted data, data entry, data analysis to the previous version

Almudena Areosa Sartre contributed to all except the last version of this review through drafting, trial searching, obtaining copies of trial reports, selection of trials for inclusion–exclusion; extraction of data, entry of data, interpretation of data analysis

Jacqueline Birks assisted in the selection of trials for inclusion and exclusion and checked the analyses of early versions.

Dymphna Hermans performed previous searches.

Lon Schneider was the Contact Editor for previous versions

This update

MW, RMcS: complete revision of text, replicating data extraction, analysis, interpretation, drafting.

ER: Data extraction, analysis, drafting.

Lon Schneider, Karen Dagerman, and Julian Higgins contributed the analysis of data from mild AD patients.

DECLARATIONS OF INTEREST

Rupert McShane - won a randomly selected prize worth less than £500 for attending two consecutive early morning sessions sponsored by Merz and Lundbeck at the Stockholm 2005 IPA meeting. He was a local investigator for two investigator initiated studies of memantine which were funded by Lundbeck (a study of short-term treatment of memantine for agitation Fox 2012 (MAGD), and a six-month study assessing maintenance of antipsychotic versus switch to memantine (Ballard 2015 (MAIN-AD)); and for one MRC funded trial (Howard 2012 (DOMINO-AD)).

Maggi Westby - received remuneration for her role in writing this review.

Emmert Roberts - none known
Neda Minakaran - none known
Lon Schneider - none known
Lucy E Farrimond - none known
Nicola Maayan - none known
Jennifer Ware - none known
Jean Debarros - none known

SOURCES OF SUPPORT

Internal sources

- Cochrane Dementia & Cognitive Improvement Group, UK.

External sources

- Alzheimer's Society, UK.
- NIHR, UK.

This review update was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to the Cochrane Dementia and Cognitive Improvement group. The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, National Health Service or the Department of Health

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The analysis of memantine in mild Alzheimer's disease (AD), and assessment of dual versus monotherapy were not included in the protocol. The possibility of trials in non-AD or vascular dementia was omitted from the protocol, but in this update of the review each diagnosis is considered separately.

INDEX TERMS

Medical Subject Headings (MeSH)

Activities of Daily Living; Akathisia, Drug-Induced [etiology]; Alzheimer Disease [drug therapy]; Cognition Disorders [drug therapy]; Dementia [*drug therapy]; Dementia, Vascular [drug therapy]; Excitatory Amino Acid Antagonists [adverse effects] [*therapeutic use]; Memantine [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Withholding Treatment

MeSH check words

Aged; Aged, 80 and over; Humans