Memantine for dementia (Review)

McShane R, Areosa Sastre A, Minakaran N

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[Intervention Review]

Memantine for dementia

Rupert McShane[1], Almudena Areosa Sastre[2], Neda Minakaran[3]

[1]Department of Psychiatry, University of Oxford, Oxford, UK. [2]Madrid, Spain. [3]Clinical Medical School, University of Oxford, Oxford, UK

Contact address: Rupert McShane, Department of Psychiatry, University of Oxford, John Radcliffe Hospital, Room 7611, Oxford, Oxfordshire, OX3 9DU, UK. rupert.mcshane@obmh.nhs.uk. Rupert.McShane@obmh.nhs.uk.

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ABSTRACT

Background

Memantine, a low affinity antagonist to glutamate NMDA receptors, may prevent excitatory neurotoxicity in dementia.

Objectives

To determine efficacy and safety of memantine for people with Alzheimer's disease (AD), vascular (VD) and mixed dementia.

Search strategy

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group was searched on 8 February 2006. This register contains references from all major healthcare databases and many ongoing trial databases and is updated regularly. In addition, the search engines Copernic and Google were used to identify unpublished trials through inspection of the websites of licensing bodies like the FDA , EMEA and NICE and of companies' websites (Lundbeck, Merz, Forest, Suntori etc) and clinical trials registries.

Selection criteria

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

Data collection and analysis

Data were pooled where possible. Intention-to-treat (ITT) and observed case (OC) analyses are reported.

Main results

1. Moderate to severe AD. Two out of three six month studies show a small beneficial effect of memantine. Pooled data indicate a beneficial effect at six months on cognition (2.97 points on the 100 point SIB, 95% CI 1.68 to 4.26, P < 0.00001), activities of daily living (1.27 points on the 54 point ADCS-ADLsev, 95% CI 0.44 to 2.09, P = 0.003) and behaviour (2.76 points on the 144 point NPI, 95% CI 0.88 to 4.63, P=0.004), supported by clinical impression of change (0.28 points on the 7 point CIBIC+, 95% CI 0.15 to 0.41, P < 0.0001).

2. Mild to moderate AD. Pooled data from three unpublished studies indicate a marginal benefical effect at six months on ITT cognition (0.99 points on the 70 point ADAS-Cog, 95% CI 0.21 to 1.78, P = 0.01) which was barely detectable clinically (0.13 CIBIC+ points, 95% CI 0.01 to 0.25, P = 0.03) but no effect on behaviour, activities of daily living or OC analysis of cognition.

3. Mild to moderate vascular dementia. Pooled data from two six month studies indicated a small beneficial effect of memantine on cognition (1.85 ADAS-Cog points, 95% CI 0.88 to 2.83, P = 0.0002), and behaviour (0.84 95% CI 0.06 to 0.91, P = 0.03) but this was not supported by clinical global measures.

4. Patients taking memantine were slightly less likely to develop agitation (134/1739, 7.7% versus 175/1873, 9.3% OR 0.78, 95% CI 0.61 to 0.99, P = 0.04). This effect was slightly larger, but still small, in moderate to severe AD (58/506 [12%] vs 88/499 [18%]; OR = 0.6, 95% CI 0.42 to 0.86, P = 0.005). There is no evidence either way about whether it has an effect on agitation which is already present.

5. Memantine is well tolerated.

Authors' conclusions

Memantine has a small beneficial effect at six months in moderate to severe AD. In patients with mild to moderate dementia, the small beneficial effect on cognition was not clinically detectable in those with vascular dementia and was detectable in those with AD. Memantine is well tolerated.

PLAIN LANGUAGE SUMMARY

Some evidence of efficacy of memantine for dementia

Memantine has a small beneficial, clinically detectable effect on cognitive function and functional decline measured at 6 months in patients with moderate to severe Alzheimer's Disease (AD). In patients with mild to moderate dementia, the small beneficial effect on cognition was not clinically detectable in those with vascular dementia and barely detectable in those with AD. It is well tolerated. Slightly fewer patients with moderate to severe AD taking memantine develop agitation, but there is no evidence either way about whether it has an effect on agitation which is already present.

BACKGROUND

Alzheimer's Disease is the commonest cause of dementia, and is found in at least 50% of autopsies of demented patients. The prevalence of the disease is approximately 1 to 2% at the age of 65, but doubles every 5 years to at least the age of 90. The disease is progressive. Memory impairment is the cardinal feature and is usually one of the first characteristics observed. As Alzheimer's disease progresses, memory and other cognitive deficits become increasingly evident and interfere with usual activities. Substantial progress has been made in understanding the basic neurobiology of this disease and new drugs have become available for symptomatic treatment. The focus of symptomatic treatment of Alzheimer's disease has been the enhancement of cholinergic transmission. However, there are other possible therapeutic approaches based on neurotransmitter substitution or modulation including serotoninergic, noradrenergic substances or neuropeptides, and those acting on excitatory amino acid receptors, such as for glutamic acid (Emre 2001).

Vascular dementia is the second most common cause of dementia in western societies. It affects 1 to 20% of people aged 65 years or older. The cognitive decline of vascular dementia is secondary to some form of vascular injury to the brain. It is a heterogeneous condition and clinical manifestations differ depending on the size and location of the cerebrovascular lesions. There is no therapy proven to reverse the neurological damage. At present, interventions focus on the prevention of the disease by better control of cardiovascular risk factors.

Mixed dementia, due to a combination of both Alzheimer type pathology and ischaemia, is being increasingly recognised. In autopsy studies mixed dementia has been reported as accounting for between 0% and 55% of cases of dementia. In addition to co-occurrence due simply to chance, Alzheimer's disease and vascular dementia may have aetiological or pathogenetic factors in common (Kalaria 1999). In comparison with sufferers from Alzheimer's disease, 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. There have been few studies relevant to the prevention and treatment of mixed dementia (Zeckry 2002).

L-glutamate is the main excitatory neurotransmitter in the central nervous system, implicated in neural transmission, learning, memory processes and neuronal plasticity (Sucher 1996). There is evidence that enhancement of the excitatory action of this amino acid plays a role in the pathogenesis of Alzheimer's disease and in the damage due to an ischaemic stroke (Cacabelos 1999). However, physiological glutamate activity is required for normal brain activity and so cannot be abolished completely (Kornhuber 1997). Low affinity N-methyl-D-aspartate (NMDA) type receptor antagonists, such as memantine, might prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate necessary for learning and memory.

Memantine was first synthesized at Eli Lilly as an agent to lower elevated blood sugar level, but was ineffective. In 1972, Merz applied for a German patent for memantine as a potential treatment for various neurological diseases, citing evidence for a beneficial effect on central nervous system activity. In 1975 and 1978, patents were granted in Germany and the USA respectively (Parsons 1999). Since then the drug has been tested in animal models of cognition and found to reverse deficits in learning and synaptic plasticity (Möbius 1999). It has been tested in several phase II and III clinical studies in the last fifteen years. These trials involved people with Alzheimer's, vascular, and mixed dementia at different stages.

Memantine (Ebixa® and Axura® (Europe) and Namenda® (USA)) was approved in February 2002 by the European Agency for the Evaluation of Medical Products (EMEA) (EMEA 2004) for the treatment of "moderately severe to severe Alzheimer's disease" and in 2003 by the USA Food and Drug Administration (FDA) (Anonymous 2003; Forest 2003) for the treatment of moderate to severe Alzheimer's disease. Memantine has not been approved for vascular dementia or earlier stages of Alzheimer disease in either jurisdiction Applications have been unsuccessfully filed with the FDA and EMEA for licenses for the treatment of mild to moderate Alzheimer's disease (Forest 2005b; Lundbeck 2005).

The UK National Institute for Clinical Excellence published consultation documents on the cost-effectiveness of drugs for Alzheimer's disease, including memantine in March 2005 and January 2006 (NICE 2005; NICE 2006). The consultation documents recommend that memantine should not be publicly funded for the treatment of moderately severe to severe AD, except as part of studies designed to generate data on long-term outcomes, disease progression, quality of life and costs. A final decision is expected in July 2006.

OBJECTIVES

The primary aim of the review was to assess the efficacy and safety of memantine for the treatment of dementia, as revealed in clinical trials involving people with Alzheimer's, vascular, or mixed dementia.

METHODS

Criteria for considering studies for this review

Types of studies

Studies were selected for this review if they fulfilled the following criteria:
1-Clinical trials in Alzheimer's disease, vascular dementia, mixed dementia, or unspecified dementia
2-Double-blind, parallel-group, placebo-controlled, with randomized and unconfounded treatment assignment to placebo or memantine
3-Sample selection criteria were specified
4-Outcome instruments were specified
5-Duration was specified

Types of participants

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

Types of interventions

Treatment with memantine at any dose and by any route of administration in an acceptable clinical trial.

Types of outcome measures

The primary outcomes of interest are:
1- Clinical Global Impression
2- Cognitive function
3- Functional performance
4- Behavioural disturbance
5- Effect on carers
6- Quality of Life
7- Incidence and severity of adverse effects
8- Institutionalization
9- Costs

Search methods for identification of studies

The trials were identified from an updated search of the trial-based Specialized Register of the Cochrane Dementia and Cognitive Improvement Group on 8 February 2006 using the terms: memantin*, D-145, DMAA, DRG-0267, ebixa, axura and namenda The Specialized Register at that time contained records from the following databases:

- CENTRAL: July 2005 (issue 3);
- MEDLINE: 1966 to 2005/08, week 2;

- EMBASE: 1980 to 2005/08, week 2;
- PsycINFO: 1887 to 2005/07;
- CINAHL: 1982 to 2004/07;
- SIGLE (Grey Literature in Europe): 1980 to 2004/06;
- ISTP (Index to Scientific and Technical Proceedings): to May 2000;
- INSIDE (BL database of Conference Proceedings and Journals): to June 2000;
- Aslib Index to Theses (UK and Ireland theses): 1970 to March 2003;
- Dissertation Abstract (USA): 1861 to March 2003;
- http://clinicalstudies.info.nih.gov/;
- National Research Register (issue 3/2005)
- ClinicalTrials.gov: last searched 1 January 2006;
- LILACS (Latin American and Caribbean Health Science Literature): last searched April 2003
- http://www.forestclinicaltrials.com/: last searched 1 September 2005
- ClinicalStudyResults.org: last searched 1 February 2006
- http://www.lillytrials.com/index.shtml: last searched 28 August 2005
- ISRCTN Register: last searched 1 September 2005
- IPFMA Clinical trials Register: www.ifpma.org/clinicaltrials.html: last searched September 2005

The search strategies used to identify relevant records in MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS can be found in the Group's module.

Press releases from Merz, Lundbeck and Forest Laboratories were searched (February 2006) and all releases pertaining to Memantine were examined. Enquiries were made of Forest Laboratories, Merz and Lundbeck (11/08/04) as to whether there are any further completed unpublished Phase 3 studies beyond these two. A further request in January 2006 to Lundbeck for copies of all conference posters was referred to Merz. None have yet been received (February 9th 2006)

The Forest and Lundbeck clinical trials registry was examined in February 2006 (Forest 2005a).

We used Copernic to search the Internet for the terms of the form ' memantine MD-01', ' memantine MD-02' etc on the basis that this appeared to be the numbering system of trials. We searched for Ebixa, Namenda and Axura as well.

Data collection and analysis

SELECTION OF STUDIES

Abstracts of the references retrieved by the search were read by one reviewer (AAS) who discarded those that were clearly not eligible for inclusion. One reviewer (AAS) studied the full text of the remaining references and selected studies for inclusion. This selection was checked by Jacqueline Birks and Rupert McShane (Coordinating Editors CDCIG). Any disparity in the final lists was resolved by discussion in order to arrive at the final list of included studies. Abstracts from an updated search of the Cochrane Specialist Register in October 2005 and February 2006 were reviewed for new RCTs by RM.

QUALITY ASSESSMENT

The reviewer assessed the methodological quality of each trial using the Cochrane Collaboration guidelines (Mulrow 1997). In Category A (adequate), the report describes allocation of treatment by: (i) some form of centralized randomized scheme, such as having to provide details of an enrolled participant to an office by phone to receive the treatment group allocation; (ii) some form of randomization scheme controlled by a pharmacy; (iii) numbered or coded containers, such as in a pharmaceutical trial in which capsules from identical-looking numbered bottles are administrated sequentially to enrolled participants; (iv) an on-site or coded computer system, given that the allocations were in a locked, unreadable file that could be accessed only after inputting the characteristics of an enrolled participant; or (v) if assignment envelopes were used, the report should at least specify that they were sequentially numbered, sealed, and opaque; (vi) other combinations of described elements of the process that provide assurance of adequate concealment. Category B (intermediate) is where the report describes allocation of treatment by: (i) use of a "list" or "table" to allocate assignments; (ii) use of "envelopes" or "sealed envelopes"; (iii) stating the study as "randomized" without further detail. Category C (inadequate) is where the report describes allocation of treatment by: (i) alternation; (ii) reference to case record numbers, dates of birth, day of week, or any other such approach; (iii) any allocation procedure that is entirely transparent before assignment, such as an open list of random numbers or assignments. Empirical research has shown that lack of adequate allocation concealment is associated with bias. Trials with unclear concealment measures have been shown liable to yield more pronounced estimates of treatment effects than trials that have taken adequate measures to conceal allocation schedules, but the effect is less pronounced than in inadequately concealed trials (Chalmers 1983; Schulz 1995). Trials were to be considered if they conformed to categories A or B, but those falling into category C were excluded. Other aspects of trial quality were not assessed by a scoring system although details were noted of blinding, appropriateness of methods and the number of patients lost to follow-up.

DATA COLLECTION

Data for the meta-analyses were based on reported summary statistics for each study. The summary statistics required for each trial and each outcome for continuous data were the mean change from baseline, the standard error of the mean change, and the number of patients for each treatment group at each assessment. Where changes from baseline were not reported, the mean, standard deviation and the number of patients for each treatment group at each time point were extracted.

For binary data the numbers in each treatment group and the numbers experiencing the outcome of interest were sought. For

the global impression of change, the endpoint itself is of clinical relevance as all patients are by definition at the same baseline score. The baseline assessment is defined as the latest available assessment prior to randomization, but no longer than two months prior.

For the intention-to-treat analyses data were sought for each outcome measure on every patient randomized, irrespective of compliance. Analyses of completers was restricted to data on every patient who completed the study on treatment.

DATA ANALYSIS

The outcomes measured in clinical trials of dementia and cognitive impairment often arise from ordinal rating scales. Where the rating scales used in the trials have a reasonably large number of categories (more than 10) the data were treated as continuous variables arising from a normal distribution.

Summary statistics (n, mean and standard deviation) were required for each rating scale at each assessment time for each treatment group in each trial for change from baseline. When change from baseline results are not reported, the required summary statistics were calculated from the baseline and assessment time treatment group means and standard deviations. In this case a zero correlation between the measurements at baseline and assessment time was assumed. This method overestimates the standard deviation of the change from baseline, but this conservative approach is considered to be preferable in a meta-analysis.

The meta-analyses sometimes required the combination of data from trials that did not use the same rating scale to assess an outcome. The measure of the treatment difference for any outcome is the weighted mean difference (WMD) when the pooled trials used the same rating scale or test, and the standardized mean difference (SMD) - the absolute mean difference divided by the standard deviation - when they used different rating scales or tests. The duration of the trials varied from 4 to 28 weeks. The range was considered too great to combine all trials into one meta-analysis. Separate analyses are therefore presented for various time periods. For binary outcomes, such as dead or alive, clinical improvement or no clinical improvement, the odds ratio was used to measure treatment effect.

Overall estimates of the treatment difference are presented. In all cases the overall estimate from a fixed effects model is presented and a test for heterogeneity, using a standard chi-square statistic, has been performed. If a test of heterogeneity was negative then a weighted estimate of the typical treatment effect across trials, the 'typical odds ratio' (i.e. the odds of an unfavourable outcome amongst treatment-allocated patients compared to the corresponding odds amongst controls) was calculated using Peto's log-rank test adapted for ordinal data.

Data from patients who were treated 'per protocol' were used in 'observed case' analyses when the latter were not available. Observed case data were substituted for last observation carried forward data in two published studies (9408/Orgogozo 2002; 9202/Wilcock 2002) where the latter were not available for some measures.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Twelve trials were identified that met inclusion criteria. They studied the efficacy and tolerability of various dosages of memantine in different types of dementia and at different stages of the disease (Ditzler 1991; Gortelmeyer 1992; 9408/Orgogozo 2002; Pantev 1993; MD-10/Peskind 2004; 9605/Reisberg 2003; MD-02/Tariot 2004; 9202/Wilcock 2002; 9403/Winblad 1999; MD-01; 99679(Lundbeck); MD-12). These trials were sponsored by Merz Pharma KGaA, Frankfurt, Germany (Ditzler 1991; Gortelmeyer 1992; 9408/Orgogozo 2002; Pantev 1993; 9605/Reisberg 2003; 9202/Wilcock 2002; 9403/Winblad 1999), and Forest Laboratories (MD-10/Peskind 2004; MD-02/Tariot 2004; MD-01; MD-12).

MD-01, MD-10/Peskind 2004, MD-12, 99679(Lundbeck) have yet to be published in peer reviewed journals. Reference to 99679(Lundbeck) in the Lundbeck clinical trial registry states 'publication process ongoing' (February 9th 2006). The study was completed before January 2004.

Three previously unidentified completed studies are referred to on the Lundbeck Clinical Trial Registry as 'publication process ongoing': 10116 (Lundbeck) is a double blind placebo controlled parallel group studies in Alzheimer's disease which evaluates efficacy, safety and tolerability and was started in January 2002; Studies 10113 and 10114 are double blind placebo controlled parallel group evaluations of safety and tolerabiliy in Alzheimer's disease. Although we were told that two of these have been reported as conference posters and that Merz would forward these, we had not received them by the time of submission of this review.

MRZ-9105 was a 12 week study in Portugal of 27 patients with 'mild to moderate severe stages of primary dementia'. MRZ-9104 was a 13 week study in France of 56 patients with AD of severity that we were unable to establish. MRZ-9206 was a 14 week study in Sweden of 56 patients with 'moderately severe VD'. We have not been able to identify the results or any associated publications or announcements belonging to these three studies.

METHODS

All included trials were of parallel-group design. There were nine phase III studies that lasted between 12 and 28 weeks (9408/Orgogozo 2002; 9605/Reisberg 2003; 9202/Wilcock 2002; 9403/Winblad 1999; MD-02/Tariot 2004; MD-10/Peskind 2004; MD-01; MD-12; 99679(Lundbeck)). The other three included studies were phase II trials that lasted four or six weeks (Ditzler 1991; Gortelmeyer 1992; Pantev 1993).

PARTICIPANTS

The number of participants ranged from 60 to 579.

The diagnosis of dementia was established using the last versions of the Diagnostic and Statistical Manual of Mental Disor-

ders (DSM III-R; DSM IV) (Gortelmeyer 1992; 9408/Orgogozo 2002; Pantev 1993; 9605/Reisberg 2003; 9403/Winblad 1999). Two studies involved only people with vascular dementia defined by the National Institute of Neurological Disorders and Stroke and the Association International pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) (9408/Orgogozo 2002; 9202/Wilcock 2002). Six studies were restricted to people with Alzheimer's disease diagnosed according to the criteria of the National Institute of Neurologic, Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA: McKhann 1984) (MD-10/Peskind 2004; MD-12; 99679(Lundbeck); 9605/Reisberg 2003; MD-02/Tariot 2004; MD-01). Three studies included both types of dementia in various proportions (Ditzler 1991; Gortelmeyer 1992; 9403/Winblad 1999). In these studies, the Hachinski score was used to differentiate between Alzheimer's disease and vascular dementia (Ditzler 1991; Gortelmeyer 1992; 9403/Winblad 1999). In one trial there is no record of an attempt to distinguish different types of dementia (Pantev 1993).

Seven studies included participants with mild to moderate impairment as defined by scores on the Mini Mental State Examination (MMSE) of Folstein 1975 (9408/Orgogozo 2002; MD-10/Peskind 2004; 99679(Lundbeck); MD-12; 9202/Wilcock 2002)

INTERVENTIONS

The trials studied different dosages of memantine with placebo. The doses used ranged from 10 to 30 mg/day. Most of the trials started with low doses progressively increasing to 20 mg/day to target levels. MD-02/Tariot 2004 and MD-12 compared the efficacy and safety of memantine in patients receiving stable treatment with donepezil.

OUTCOME MEASURES

The following range of outcome measures was used in the trials. Additional Table 2 summarises their use in the included studies.

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 participants 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) (Guy 1976) is a global rating of all domains of a patient's current condition in comparison with baseline. 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 Ditzler 1991.

*Clinical Global Impression (CGI). This seven point rating of severity of illness was used in Gortelmeyer 1992 to assess whether patients improved, remained unchanged or worsened.

* The Sandoz Clinical Assessment Geriatric Scale (SCAG) (Shader 1974) is a physician rating. 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 Pantev 1993.

2- Cognitive Tests:

* The cognitive part of the Alzheimer's Disease Assessment Scale (ADAS-Cog) (Rosen 1984) 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

or the Sandoz Clinical Assessment Geriatric Scale (SCAG) (Ditzler 1991; Gortelmeyer 1992). The participants in Pantev 1993 were equally divided between mild, moderate and severe disease as assessed by the SCAG. Three studies enrolled severely impaired patients according to the MMSE and the Global Deterioration Scale (GDS) (9605/Reisberg 2003; 9403/Winblad 1999) or MMSE score alone (MD-02/Tariot 2004).

The details of the participants at baseline are reported in Table 1. 9408/Orgogozo 2002 and MD-02/Tariot 2004 described the characteristics of the participants more comprehensively than the other studies. Most of the studies specified race, duration of the diagnosis or the number of dependent patients at baseline, but only three trials reported concomitant diseases (Ditzler 1991; Pantev 1993; MD-02/Tariot 2004). One study reported previous use of drugs for dementia by the participants but without specifying types (9403/Winblad 1999). Two studies (MD-02/Tariot 2004; MD-12) enrolled only patients with a diagnosis of AD and ongoing cholinesterase inhibitors therapy with donepezil for more than 6 months before entrance into the study and at a stable dose (5 to 10 mg/dl) for at least 3 months. The exclusion criteria are not specified in one study which has only been reported as a poster at conferences (MD-10/Peskind 2004)

(0 to 8), word recall (0 to 10) and word recognition (0 to 12). 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) (Schmitt 1997) evaluates cognitive performance in advanced Alzheimer's Disease. 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) (Galasko 1997) was specifically designed to assess functional capacity over a broad range of severity in patients with Alzheimer's disease. The 19 item ADCS-ADLsev19 has 54 points. The 23 item ADCS-ADL23 has 78 points.

* 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) (Van der Kam 1989) is a 45 item observer-rated scale for the assessment of functional and behavioural disturbances of geriatric patients, performed by nursing staff. 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) (Spiegel 1991) contains 30 items of behaviour, each rated in a 5-point scale according to frequency of occurrence. Item scores are summarized into 6 dimension scores (memory, instrumental activities of daily life, self-care activities of daily living, mood, social behaviour, and disturbance behaviour).

4- Mood and Behavioural measures:

* Neuropsychiatric Inventory (NPI) (Cummings 1994) assesses the frequency and the severity of behavioral and neuropsychiatric symptoms in patients with dementia based on an interview with the caregiver. There are 12 items with a total score ranging from 0 to 144.

* Nurses Observation Scale for Inpatient Evaluation (NOSIE) (Honigfeld 1974) assesses behaviour of psychiatric patients. 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) (Shader 1974) is a physician rating scale. 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.

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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) (Gottfries 1982) is a 26 item, physician assessed observer scale based on caregiver's information and an interview with the patient. 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) (Wimo 1988) 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 1 month) and follow-up questionnaire (assessing specific events that occurred during the past 3 months). 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 and severity of reported adverse effects.

Risk of bias in included studies

9202/Wilcock 2002, 9403/Winblad 1999 and 9408/ Orgogozo 2000 studies reported that they were conducted to GCP standard. Since 9605/Reisberg 2003, MD-02/Tariot 2004, MD-01 and MD-10/Peskind 2004, 99679(Lundbeck) and MD-12 have been submitted for licensing approval it is highly likely that they too were conducted to GCP standard. All the studies are described as double-blind and randomized, but only three described the method of concealment of allocation (Gortelmeyer 1992; 9605/Reisberg 2003; MD-02/Tariot 2004). 9605/Reisberg 2003

and 9408/ Orgogozo 2000 reported the use a Ran Code program for this purpose and MD-02/Tariot 2004 used a randomization list generated by the Department of Biostatistics at Forest Laboratories.

Effects of interventions

Presentation of the results is divided according to the aetiology and severity of the dementia of the trial participants and duration of studies (sections 1 to 5). In sections 6 and 7 the results of pooled analyses are presented.

1- Effect of memantine (20 mg/day) on patients with moderate to severe Alzheimer disease at 24 to 28 weeks:

Three trials were identified in which compared the effect of six months of memantine and placebo in patients with moderate to severe Alzheimer's disease. This is the group for which memantine is licensed. 9605/Reisberg 2003 and MD-01 studied patients with an MMSE of 3-14 and 5-14 respectively. MD-02/Tariot 2004 studied patients with an MMSE of 5-14 who were also receiving stable treatment with donepezil. The same main outcome measures were used in all three studies.

* Global Impression: After six months there was a significant difference in the clinical impression of change, as measured by the 7 point CIBIC-Plus (ITT- LOCF), in favour of memantine (0.28 CIBIC+points, 95% Confidence Interval (CI) 0.15 to 0.41, P < 0.0001).

* Cognition: There was a significant difference in cognitive function, as measured by the 100 point SIB (ITT-LOCF), in favour of memantine (2.97 SIB points, 95% CI 1.68 to 4.26, P < 0.00001). There was substantial inconsistency between the three studies (I^2 = 74%). MD-01 found no statistically significant effect. The smallest study, 9605/Reisberg 2003, found the largest effect.

* Activities of daily living: There was a significant difference in ability to perform activities of daily living, as assessed using the 54 point ADCS-ADLsev19 scale (ITT-LOCF), in favour of memantine (1.27 ADCS-ADLsev points, 95% CI 0.44 to 2.09, P = 0.003).

* Mood and behaviour: Patients taking memantine had significantly less worsening of mood and behaviour, as assessed on the 144 point NPI (ITT-LOCF), by six months (2.76 NPI points, 95% CI 0.88 to 4.63, P=0.004). Agitation occurred less commonly as an adverse event in those taking memantine (58/506 [12%] compared to those taking placebo (88/499 [18%]; Peto odds ratio (OR) = 0.6, 95% CI 0.42 to 0.86, P = 0.005). No evidence was presented to suggest that mood and behaviour problems which were apparent at the time of study entry were more likely to resolve in those taking memantine.

*Dropouts: The drop-out rate was significantly lower in the group of patients receiving memantine (103/507, 20.3% versus 139/499, 27.9% OR 0.66, 95% CI 0.49 to 0.88, P = 0.005).

* Adverse events: Memantine was well tolerated. There was no significant difference in the number of patients suffering at least one adverse event. Agitation occurred less commonly as an adverse event in all three studies in those taking memantine (58/506 [12%]) compared to those taking placebo (88/499 [18%]; OR = 0.6, 95% CI 0.42 to 0.86, P = 0.005). There were no other consistent differences in adverse events and no significant differences between memantine and placebo.

* Resource utilisation and cost effectiveness: Resource utilisation data and a cost analysis are available only for the 9605/Reisberg 2003 study (Wimo 2003). Based on data from the third and sixth month of the study, caregivers of patients taking memantine spent fewer hours/month in caregiving tasks and supervision. The unadjusted difference of 42 hours in the treated per protocol population did not reach significance (95% CI 113 to -29, P = 0.2). However, the difference was statistically significant (52 hours, 95%CI 95 to 7, P = 0.02) following adjustment for baseline caregiver time, residential status, caregiver gender, patient gender and caregiver-patient relationship, and in the LOCF-ITT population (46 hours 95%CI 10 to 81, P = 0.01). Of patients living in the community at the start of the study, 5/66 patients taking placebo and 1/84 patients taking memantine were admitted to an institution. The statistical significance of this depends on the test used. Overall costs to carers (in 1999 $US) were lower in the memantine, compared with the placebo group (824$US, 95% CI 906 to 742, P < 0.00001). Direct medical costs for the patient were greater in the memantine group (164 $US, 95% CI 161 to 169, P < 0.00001). Total societal costs were $1090 per month less in the group taking memantine (95%CI 1955 to 225, P = 0.01).

2-Effect of memantine (20 mg/day) on patients with mild to moderate Alzheimer disease at 24 weeks:

Three trials were identified that studied the effect of memantine on patients with mild to moderate Alzheimer's disease (MD-10/Peskind 2004; 99679(Lundbeck); MD-12).

*Global Impression: There was a significant difference in the clinical impression of change measured by the CIBIC-Plus (ITT) after 24 weeks (0.13 points, 95% CI 0.01 to 0.25, P = 0.03)

* Cognition: In the intention-to-treat analysis there was a significant difference in favour of memantine on the 70 point ADAS-Cog (0.99 ADAS-Cog points, 95% CI 0.21 to 1.78, P = 0.01). Conference presentation of observed case data from MD-10/Peskind 2004 showed no significant difference: 1.10 ADAS-Cog points, 95% CI 2.52 to -0.32. Observed case data were not available for the other two trials.

* Function: There was no significant difference in ADCS-ADL23 scores at 24 weeks (0.20 ADCS-ADL23 points, 95% CI -0.87 to 21.27, P = 0.72)

* Mood and Behaviour: There was no significant difference in NPI scores at 24 weeks (-0.25 NPI points, 95% CI -1.48 to 0.98, P = 0.69)

*Dropouts: There was no significant difference in drop-out rate (106/736, 14.4% versus 74/570, 13.0% OR 1.16, 95% CI 0.83 to 1.60, P = 0.38).

*Adverse events: There was no significant difference in the number of patients experiencing at least one adverse event (493/736, 67.0% versus 397/570, 69.6% OR 1.04, 95% CI 0.81 to 1.33, P = 0.76). In contrast to the finding in moderate-to-severe AD, there was no difference in the number of patients experiencing agitation as an adverse event (37/736, 5.0% versus 36/570, 6.3% OR 0.91, 95% CI 0.57 to 1.46, P = 0.70). Data from other individual adverse events are not available for all three trials. Significantly more people on memantine suffered somnolence by the end of the treatment (OR: 7.49, 95% CI 1.68 to 33.38, P = 0.008) in MD-10/Peskind 2004.

3-Effect of memantine (20 mg/day) on patients with mild to moderate vascular dementia at 28 weeks:

Two trials studied the effect of memantine on patients with mild to moderate vascular dementia (9408/Orgogozo 2002; 9202/Wilcock 2002).

* Global Impression: There was no difference in the clinical global for memantine (20 mg/day) compared with placebo at 28 weeks (WMD 0.03, 95% CI -0.13 to 0.19, P = 0.72)

* Cognition: Both studies provided ADAS-Cog data (9408/Orgogozo 2002 (ITT-LOCF), 9202/Wilcock 2002 (OC)). The change from baseline at the 28 weeks analysis gave statistically significant results in favour of memantine for 20 mg/day (1.85 ADASCog points, 95% CI 0.88 to 2.83, P = 0.0002).

* Activities of daily living: On the NOSGER self care subscale there was no difference between memantine and placebo groups (0.12, 95% CI -0.43 to 0.67, P = 0.66).

* Combination scales: Both studies reported data for memantine 20 mg/day using the GBS change from baseline at 28 weeks and found no statistically significant differences from placebo (WMD -1.81, 95% CI -4.21 to 0.58, P = 0.14) There were no differences in the NOSGER (complete scale) at 28 weeks in the same studies (WMD -0.92, 95% CI -2.90 to 1.05, P = 0.4).

* Behaviour: There was significantly less agitation in the memantine group compared with placebo (20/460 [4.3%] versus 34/440 [7.7%], OR 0.54, 95%CI 0.31 to 0.96, P = 0.04) . On the NOSGER disturbing behaviour subscale, there was less disturbed behaviour in the memantine group (0.48 points 95%CI 0.06 to 0.91, P = 0.03)

* The drop-out rates and the numbers of people with any adverse event, dizziness or confusion were similar in treatment and placebo groups.

4-Effect of memantine (10 mg/day) in patients with severe vascular dementia, Alzheimer's disease and mixed dementia at 12 weeks:

9403/Winblad 1999 explored the effect of memantine (10 mg/day) in patients in long stay facilities with severe Alzheimer's disease, vascular dementia or mixed dementia at 12 weeks.

* Global Impression: There was a large benefit in favour of memantine (10 mg/day) compared with placebo at 12 weeks, for the numbers improved on the CGI (60/82 [73%] compared with 38/84 [45%]: OR 3.30, 95% CI 1.72 to 6.33, P = 0.0003)

* Function: 9403/Winblad 1999 provided data on the change from baseline at 12 weeks using the BGP care dependence subscore. Using the Wilcoxon Stratified test, the authors found a significant difference in favour of memantine. Using odds ratios there was no statistically significant difference between memantine 10 mg/day and placebo.

5- Effect of memantine (20 or 30 mg/day) in patients with mild to moderate vascular dementia, Alzheimer's disease or mixed dementia at 4 to 6 weeks:

* Global Impression: There was a benefit in favour of memantine (20 to 30 mg/day) compared with placebo at 4 to 6 weeks, as measured by various scales (SMD 0.76, 95% CI 1.04 to 0.48, P < 0.0001) (Ditzler 1991; Gortelmeyer 1992; Pantev 1993).

* Cognition: One study measured cognition using the SKT (Ditzler 1991). The change from baseline at 6 weeks for 30 mg/day gave statistically significant results in favour of memantine (3.04 SKT points, 95% CI 5.68 to 0.40, P = 0.02).

* Activities of daily living: One study provided data using a non-validated scale for measuring five simple instrumental tasks under the guidance of an investigator (Ditzler 1991). When pooled with the results from Pantev 1993 (BGP, need of help subscore), the OC analysis gave statistically significant results in favour of memantine for 30 mg/day in 6 weeks (SMD 1.34, 95% CI 1.73 to 0.94, P < 0.00001). However, there are discrepancies in the presentation of the results in different tables of the report of Pantev 1993.

* Mood and behaviour: One trial provided data using the NOSIE for memantine 30 mg/day at 6 weeks (Pantev 1993). The SCAG totals from Gortelmeyer 1992 and Ditzler 1991 were pooled with this on the grounds that many of the items from the SCAG are neuropsychiatric symptoms. Memantine had a significant beneficial effect (SMD 1.16, 95%CI 1.46 to 0.86, P < 0.0001).

* Adverse effects: Memantine seemed to be well tolerated in these studies (Ditzler 1991; Gortelmeyer 1992; Pantev 1993). There were no significant differences between memantine and placebo in the total number of adverse events. In one study the incidence of restlessness by the end of the treatment at 6 weeks was statistically significantly lower in the placebo group than in the group taking memantine 30 mg/day (Ditzler 1991) (15/30 compared with 2/29: OR 13.50, 95% CI 2.71 to 67.19, P = 0.001).

6- Pooled analyses: Effect of memantine in mild to severe Alzheimer's disease and vascular dementia at 24 to 28 weeks:

The results of eight, six-month trials were pooled (9605/Reisberg 2003; MD-02/Tariot 2004;MD-01; 9202/Wilcock 2002; 9408/Orgogozo 2002; MD-10/Peskind 2004; MD-12; 99679(Lundbeck)). There was a significant benefit of memantine at six months on all four main outcome measures.

* Global Impression: There was a significant benefit of memantine apparent on 7-point clinical global measures of change (WMD 0.15, 95% CI 0.07 to 0.23, P = 0.0001).

* Cognition: There was a significant benefit of memantine on cognitive function (SMD 0.24, 95% CI 0.17 to 0.30, P < 0.00001).

*Function: There was a significant benefit of memantine on pa-

tients' ability to perform activities of daily living (SMD 0.08, 95% CI 0.01 to 0.15, P = 0.03).
* Mood and behaviour: There was a significant benefit of memantine on patient's mood and behaviour as assessed by the NPI or the 'disturbed behaviour' subscale of the NOSGER (SMD 0.11, 95% CI 0.04 to 0.19, P = 0.003).
* Drop-outs: There was no significant difference in the dropout rate (315/1703, 18.5% versus 309/1509, 20.5% OR 0.91, 95% CI 0.76 to 1.09, P = 0.32)
* Adverse effects: There was no significant difference in the number of patients experiencing at least one adverse event (1239/1702, 72.8% versus 1103/1509, 73.1% OR 1.09, 95% CI 0.93 to 1.27, P = 0.31). Overall, a significantly lower number of patients taking memantine experienced agitation as an adverse event (134/1739, 7.7% versus 175/1873, 9.3% OR 0.78, 95% CI 0.61 to 0.99, P = 0.04). Data from other individual adverse events are not available for all trials.
Within the eight studies, one reported significantly more somnolence (OR 7.49, 95% CI 1.68 to 33.38) (MD-10/Peskind 2004), one reported more constipation (OR 2.57, 95% CI 1.29 to 5.12, P = 0.007) (9202/Wilcock 2002), and one reported more hypertension (OR 3.59, 95%CI 1.16 to 11.12, P = 0.03) (MD-01) in patients on memantine.

7- Pooled analyses - (10 to 30 mg/day) in patients with mild to moderate vascular dementia, Alzheimer's disease or mixed dementia at 4 to 12 weeks:

The only type of outcome measure that was available in all four shorter trials (9403/Winblad 1999; Ditzler 1991; Gortelmeyer 1992; Pantev 1993) was for clinical global.
* Global Impression: There was a significant benefit of memantine (SMD 0.62, 95% CI 0.41 to 0.82, P < 0.00001).

DISCUSSION

The pooled results of three trials in patients with moderate to severe AD (9605/Reisberg 2003; MD-02/Tariot 2004; MD-01) suggest that taking 20 mg memantine daily has a positive effect on cognition, mood, behaviour and the ability to perform activities of daily living. These results are supported by a positive effect in the clinical impression of change which suggests that the effect is clinically detectable. The effect sizes were of 0.3 CIBIC+ points, 3.0 SIB points, 2.8 NPI points, and 1.3 ADCS-ADLsev points. There was substantial heterogeneity between studies in the effect on cognitive function. This was driven by the different effect sizes of the MD-01 and 9605/Reisberg 2003 studies. The moderate heterogeneity found in the effect on behaviour and mood was due to the different results of MD-01 compared to the other two studies. The heterogeneity did not seem to have arisen because the results of MD-02/Tariot 2004 were very different from the other two. This is important because it suggests that co-treatment with donepezil does not influence the effect of memantine. It is not clear why the results of MD-01 were different to those of the other two studies. Baseline cognitive function was broadly comparable in the three studies.

The results in patients with mild to moderate vascular dementia suggest a beneficial effect of 20 mg/day of memantine on cognitive function measured at 28 weeks (1.9 ADAS-Cog points). However, these results are not supported by an effect on the clinical impression of change. This suggests that, in patients with mild to moderate vascular dementia, the effect on cognitive function is not translated into clinically detectable changes. Although there was significant heterogeneity in the results of 9408/Orgogozo 2002 and 9202/Wilcock 2002, which remains to be adequately explained, the 9408/Orgogozo 2002 study was not greatly different in result from the studies in AD.

The results of trials in patients with mild to moderate AD (MD-10/Peskind 2004; MD-12; 99679(Lundbeck)) suggest a beneficial effect of 20 mg/day of memantine on cognitive function measured at 24 weeks (1.0 ADAS-Cog point), supported by a small positive effect in the clinical impression of change (0.1 CIBIC+ point). Observed case data from one study (MD-10/Peskind 2004) did not support the benefit on cognitive function seen on LOCF data. Observed case data on cognitive function have not been published for any study of mild to moderate AD.

The shorter, smaller studies suggest that there is a possible early benefit of the treatment. The standardised effect sizes on clinical global (SMD 0.6) and mood and behaviour (SMD 1.2) are larger than for the longer studies. However, there are many reasons to be wary of drawing such an inference. First, insufficient information is available from phase III studies to be able to examine any early beneficial effect. The graphs in 9605/Reisberg 2003 and MD-02/Tariot 2004 do not suggest any waning of effect after 12 weeks, which would argue against using the drug as a short term treatment. Second, trials conducted early in the development of a drug are typically more positive than later ones and shorter trials are typically more positive than longer ones. Thirdly, data from three short studies (MRZ-9104; MRZ-9105; MRZ-9206) were not available.

The adverse effects profile and tolerability are good and drop-out rates were generally low and similar in treatment and placebo groups.

Agitation

A consistent effect throughout the studies of moderate-to-severe dementia was a small reduction in the incidence of agitation. This is a common problem in late dementia for which improved treatments and prevention strategies are necessary. The finding is therefore potentially important. However, the effect size is small: 17 patients would need to be treated for six months to prevent one occurrence of agitation. It was not a pre-specified hypothesis and therefore needs to be treated cautiously.

Importantly, there was no available evidence addressing the question as to whether prevalent agitation can be usefully treated with memantine. MD-23 is listed as an ongoing trial on the Forest Clinical Trials Registry as a study of agitated, non-institutionalised patients with moderate to severe AD which started recruitment in October 2004. A recent Appraisal Consultation Document by NICE makes the following comment on the basis of data submitted in confidence by Lundbeck about "analyses ...undertaken for patients who were defined as 'behaviourally disturbed': For the analyses containing all three RCTs, less deterioration in cognitive function for patients receiving memantine as measured by the SIB (mean change from baseline for memantine [± donepezil] + versus placebo [± donepezil] -1.59 and -6.69, respectively, $p < 0.001$), ADCS-ADL (mean changes from baseline: -2.87 and -4.76, $p = 0.001$), NPI-cluster (mean changes from baseline: -0.65 and 0.74, $p < 0.001$) and CIBIC-plus (mean changes from baseline: 4.54 and 4.88, $p < 0.001$) was observed." The difference in change in clinical global in this subgroup (0.34 CIBIC+ points) is similar to that in the overall group. It is not possible to comment on how far the CIBIC+ change in the overall group is driven by the more disturbed subgroup. The difference in change in behaviour (1.39 NPI-cluster points) cannot be compared since data on this 'NPI-cluster' score is not available in the published studies.

Limitations

A limitation of this analysis is the small number of studies of each different severity and subtype of dementia which have been conducted. This reduces the statistical power to identify heterogeneity. Although the reporting of the studies is generally adequate, there are some details which are not addressed. For example, participants studied are not well characterized in terms of comorbidity or in the level of control of vascular risk factors, facts that could have influenced the results (Teresi 1997). The duration of the recent phase III studies is sufficient for licensing purposes. It would have been appropriate to include measures of executive function, as these are particularly impaired in vascular dementia and are not adequately dealt with by the ADAS-Cog (Roman 1999). No 6 month studies have been conducted in nursing home populations. MEM-MD22 is listed as an ongoing trial on the Forest Clinical Trials Registry as a study of nursing home patients with moderate to severe AD which started recrtuiment in October 2004.

A source of bias in the analysis of these studies is likely to lead to an under-estimation of the effect size. Since patients taking placebo tended to drop out earlier than those taking memantine, the practice of carrying forward the last observation will tend to reduce the difference between placebo and memantine.

The indications for treatment of severe dementia raise ethical issues. The benefits of slowing Alzheimer's disease progression in the later stages can be controversial (Post 1997). It is possible that the drug only extends the total time of deterioration without reducing the personal or social burden of the disease (Dresser 2000). The major phase III studies were too short and small to be expected to show any effect of memantine on life expectancy. In future studies it will also be important to assess patients at shorter intervals than 6 months, to include measures of patient quality of life, caregiver burden and costs, and to assess effect on mortality over a longer period than 6 months.

It has been suggested that memantine may exert a neuroprotective effect in early stages of dementia (Cacabelos 1999). There is no evidence for this from these clinical studies but an open label volumetric MRI study (MEM-MD15) started recruiting in June 2005.

Publication bias

The results of MD-01, which showed no effect of memantine, were posted on its clinical trials registry by Forest Laboratories on 2nd May 2005, more than 2 years after completion (23rd April 2003). They were not included in Lundbeck's June 2004 submission concerning moderate to severe AD to the UK National Clinical Institute for Excellence. Data from three short studies (MRZ-9104; MRZ-9105; MRZ-9206) were not available. It is possible that 10116 (Lundbeck) is a further unpublished, unannounced trial with important efficacy data.

Cost-effectiveness

An important question is whether the effect size is great enough to merit its purchase by health authorities, not least because the overall effect sizes are small. However, it is possible that small benefits at the moderate and severe stages have a greater impact on measures of quality of life and on cost-effectiveness than early in the course of dementia. Only one published analysis of costs incurred during an RCT has been conducted. This suggested a trade-off between costs which are borne by the caregiver (lower on memantine) and the direct medical costs (i.e. the drug) borne by the patient. These results should be treated with caution because they are only available in one trial and need to be confirmed.

The January 2006 NICE Appraisal Consultation Document gives an estimate of cost per QALY gained for patients with moderate to severe AD as approximately £35,000. However, it would appear from this Consultation Document that insufficiently detailed material was submitted by Lundbeck to allow the committee to evaluate various assumptions and definitions. The submission was, in part, based on presentation of data from selected studies which greatly increased the liklihood of bias. On the other hand, the data presented above, which were available to NICE, do not support the committee's conclusion that "the evidence for the clinical effectiveness of memantine was currently insufficient". The weight given in the NICE evaluation to an analysis based on MMSE changes may be inappropriate at lower MMSE levels.

AUTHORS' CONCLUSIONS

Implications for practice

Memantine 20 mg/day caused a clinically noticeable reduction in deterioration over 28 weeks compared with placebo in patients with moderate to severe Alzheimer's disease. This was supported by less functional and cognitive deterioration. Patients taking memantine were less likely to become agitated. Patients with mild to moderate dementia receiving memantine 20 mg/day had less cognitive deterioration at 28 weeks but the effects were not clinically discernible in those with vascular dementia. They were discernible in those with Alzheimer's disease. The drug is well tolerated in general and the incidence of adverse effects is low. The published data would only therefore justify the prescription of memantine for patients with moderate to severe AD, typically defined as those with an MMSE less than 15.

Implications for research

Studies assessing the neuroprotection hypothesis need to be longer than 6 months. Whether prescriptions of memantine for moderate-to-severe AD are publicly funded should depend on the results from longer studies of the effect of memantine on quality and duration of life, and how it performs in trials in more typical populations than are usual in licensing studies. Since the drug seems to be effective for moderate-to-severe AD, and is the only licensed drug available for this indication, robust data on the cost and effectiveness of other options for moderate-to-severe dementia are needed to inform the funding decision. Pragmatic studies should include comparisons of memantine with care-as-usual, since this is what would be available to most people if memantine is not publicly funded.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

10116 (Lundbeck)

Methods	Randomised double-blind parallel-group placebo controlled
Participants	
Interventions	
Outcomes	'Efficacy, safety and tolerability'
Notes	Started in 2002 Further details not available Lundbeck Trial Registry

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

9202/Wilcock 2002

Methods	Randomized double-blind parallel-group placebo-controlled Duration: 28 weeks
Participants	Country: UK No of Centres: 57 Diagnosis: vascular dementia according to the NICDS-AIREN criteria. Inclusion: MMSE: 10-22. 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+-6,9; Placebo: 77,6+-7. Sex (female%): Memantine: 48%; Placebo: 49%
Interventions	Route: Oral Treatment: Memantine: 20 mg /day Control: Placebo

9202/Wilcock 2002 (*Continued*)

Outcomes	Primary end points: ADAS-cog, CGI-C Secondary outcomes: NOSGER
Notes	ITT Population: 548 (95%). PP Population: 368 (64%)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

9403/Winblad 1999

Methods	Randomized double-blind parallel-group placebo-controlled Duaration: 12 weeks
Participants	Country: Latvia No of centres: 7 Diagnosis: DSM-III-R for the diagnosis of dementia and used the Hachinski ischaemia score (HIS) modified by Rosen to separate subgroups with AD and VD. Exclusion: drugs affecting central nervous system, chronic or terminal diseases, progressive heart failure, severe renal impairment, impaired thyroid function, severe cardiac arrhythmia, unstable diabetes mellitus, chronic liver disease, low vitamin B12, abnormal blood chemistry, alcoholism, drug abuse, major depression, epilepsy, Parkinson's disease. Use of neuroleptics, tricyclic antidepressants, hypnotics, nootropics, drugs stimulating cerebral circulation, MAO inhibitors. Total No: 166 Age: females: 73,9+-5,6; males: 68,4+-5,6 Sex (female %): Memantine: 59,8%; placebo: 56%.
Interventions	Route: Oral Treatment: memantine 10 mg/ day. Treatment started at 5 mg/day and increased in one week to 10 mg/day Control: Placebo: o.i.d.
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 describing spontaneous reports.

9403/Winblad 1999 (*Continued*)

Notes	ITT Population: 166 (98%) PP Population: 151 (90%)

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

9408/Orgogozo 2002

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. Inclusion: MMSE: 12-20 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 No of patients: 321 Age: Placebo: 76,1+-8,68; Memantine: 76,6+-6,6 Sex (%females): Memantine: 52,5%; Placebo: 43%.
Interventions	Route: Oral Treatment: memantine 20 mg/day Treatment started at 5 mg/day and increased in three weeks to 20 mg/day Control: Placebo o.i.d.
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) Safe and tolerability
Notes	ITT population: 288 (90%) PP Population: 188 (59%)

9408/Orgogozo 2002 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

9605/Reisberg 2003

Methods	Randomized double-blind parallel-group placebo-controlled Duration: 28 weeks
Participants	Country: USA No of centres: 32 Diagnosis: Alzheimer's disease by DSM-IV and NINCDS-ADRDA Inclusion: MMSE:3-14; GDS:6; FAST: 6 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+-8,07. Sex (females%): Memantine: 72,2; Placebo: 65,5. Baseline SIB-67
Interventions	Route: oral Treatment: memantine 20 mg /day Control: Placebo
Outcomes	Primary end points: NYU CIBIC-plus; Modified; Modified ADCS-ADL Inventory Secondary outcomes: Severe Impairment Battery (SIB); FAST, NPI
Notes	ITT Population: 236 (94%). PP Population: 181 (72%)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

99679(Lundbeck)

Methods	Randomized, double-blind, parallel-group, placebo-controlled Duration: 26 weeks
Participants	Mild to moderate AD 65 European sites
Interventions	20 mg monotherapy
Outcomes	Primary end points: CIBIC+, ADAS-Cog; Secondary: ADCS-ADL23, NPI
Notes	ITT population: 461/470 2:1 memantine to placebo allocation

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Ditzler 1991

Methods	Randomized double-blind parallel-group placebo-controlled 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%
Interventions	Route: Oral Treatment: memantine: 30 mg. Treatment commenced at 10 mg/day and in 2 weeks increased to 30 mg/day
Outcomes	Physician's global impression„ SCAG, The Syndrom- Kurtztest, ADL test
Notes	

Ditzler 1991 (*Continued*)

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Gortelmeyer 1992

Methods	Randomized double-blind parallel-group placebo-Controlled Duration: 6 weeks
Participants	Country: Germany No. of centres: 2 Diagnosis: dementia defined by DSM-III. 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%
Interventions	Route: Oral Treatment: memantine 20 mg/ day. Treatment commenced at 10 mg/day and after 3 days was increased to 20 mg/day. Control: Placebo 1 tablet the first 3 days and after 2 tablets/day
Outcomes	SCAG, CGI, GBS, ADL behaviour investigation, Tapping test, trace test
Notes	No. not included in the analysis: 83

Risk of bias		
Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

MD-01

Methods	Randomized double-blind parallel-group placebo-controlled Duration: 24 weeks
Participants	Country: US 350 patients moderate to severe AD. Diagnosis: Alzheimer´ s disease by NlNCDS-ADRDA; Inclusion: MMSE: 5-14. Age at least 50. Age: placebo: 78 +-7.6, memantine:78 +-8.2 Sex (%females): placebo: 70.3%, memantine: 72.5%. Baseline SIB: ~76
Interventions	Route: oral Treatment: 20 mg memantine daily Control: placebo
Outcomes	Primary end points: SIB, ADCS-ADL19. Secondary outcomes: CIBIC-Plus, NPI, BGP, FAST
Notes	ITT Population: 336 (96%) PP Population: 260 (74%)

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

MD-02/Tariot 2004

Methods	Randomized double-blind parallel-group placebo-controlled. Duration: 24 weeks
Participants	Country: USA No of centers: 37 Diagnosis: Alzheimer´ s disease by NlNCDS-ADRDA; 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 defeciency; active pulmonary, gastrointestina, renal, hepatic, endocrine, or cardiovascular disease; other psychiatric or central nervous system disorders other than AD, HIS more than 4. Baseline SIB ~79

MD-02/Tariot 2004 (*Continued*)

Interventions	Route: oral Treatment: Memantine 20 mg/day and donepezil 5 or 10 mg/day. Control: Placebo and donepezil 5-10 mg/day.
Outcomes	Primary end points: SIB, ADCS-ADL19. Secondary outcomes: CIBIC-Plus, NPI, BGP.
Notes	- ITT Population: 395 (98%) - PP Population: 322 (80%)

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Yes	A - Adequate

MD-10/Peskind 2004

Methods	Randomized double-blind parallel-group placebo-controlled Durantion: 24 weeks
Participants	Country: USA No. of Centres: not stated Diagnosis: Alzheimer's disease by NINCDS-ADRDA Inclusion: MMSE: 10-22 Exclusion: not stated Total No of patients: 403 Age: placebo: 77 +-8,2, mamantine:78 +-7,3 Sex (%females): placebo: 57,4%, memantine: 60,2%
Interventions	Route: oral Treatment: memantine 20 mg/day (10 mg b.i.d. titrated over a 4-week period) Control: placebo
Outcomes	Primary end points: ADAS-Cog, CIBIC-plus Secondary outcomes: ADCS-ADL, NPI, Safety
Notes	- ITT Population: 394 (98%) - PP Population: 332 (82%)

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

MD-12

Methods	Randomized double-blind parallel-group placebo-controlled Duration: 24 weeks
Participants	Country: US 432 participants mild to moderate AD on ChEI
Interventions	Route: oral Treatment: memantine 20 mg/day (10 mg b.i.d. titrated over a 4-week period). On stable dose of ChEI. Control: placebo plus continued ChEI
Outcomes	ADAS-Cog; Secondary: ADCS-ADL23, NPI
Notes	ITT population: 427/433

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

MRZ-9104

Methods	Randomized double-blind parallel-group placebo-controlled
Participants	Country: France 56 participants AD of unknown severity
Interventions	13 weeks 20 mg memantine monotherapy
Outcomes	
Notes	No results available

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

MRZ-9105

Methods	Randomized double-blind parallel-group placebo-controlled
Participants	Country: Portugal 27 participants Mild to moderate severe stages of primary dementia
Interventions	12 weeks monotherapy 20 mg memantine
Outcomes	
Notes	No results available

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

MRZ-9206

Methods	Randomized double-blind parallel-group placebo-controlled
Participants	56 participants Moderately severe VD
Interventions	Monotherapy 20 mg memantine 14 weeks
Outcomes	
Notes	No results available

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	D - Not used

Pantev 1993

Methods	Randomized double-blind parallel-group placebo-controlled 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 participants: 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
Notes	No. not included in the analysis: 59?

Risk of bias

Item	**Authors' judgement**	**Description**
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ambrozi 1988	Included patients suffering from any severe chronic disease of the Central Nervous System
Fleischhacker 1986	Single-blind trial
Gavrilova 1995	Open clinical trial
Jones 2005	Not placebo controlled
Riepe 2005	Open label study

(*Continued*)

Scharre 2005	Not AD but frontotemporal dementia

Characteristics of ongoing studies *[ordered by study ID]*

95722/Ashford

Trial name or title	A Randomized, Placebo-Controlled, 52-Week Clinical Trial in patients with AD
Methods	
Participants	-N=20 -country: USA
Interventions	memantine versus placebos
Outcomes	-MRS measures of brain -NAA and MRI measures of hippocampal volume -ADAS-Cog and caregiver and clinician ratings
Starting date	-recruiting at 110106 -Study start:May 2005; Expected completion:June 2007
Contact information	-aimee.stepp@stanford.edu -ClinicalTrials.gov Identifier: NCT00255086
Notes	blinding unclear

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 5. ChEi as usual, plus memantine
Outcomes	what evidence is there that altering therapy, after initial treatment starts to fail, will benefit the patient?
Starting date	unknown

Bullock 2005 (*Continued*)

Contact information	ISRCTN55568578
Notes	

CSP#546

Trial name or title	randomised placebo controlled double-blind trial in patients with mild to moderate AD taking donopezil
Methods	
Participants	-N=840 -
Interventions	1. alpha-tocopherol plus memantine placebo 2. memantine (Namenda) plus alpha-tocopherol placebo 3.alpha-tocopherol plus memantine 4.alpha-tocopherol placebo plus memantine placebo
Outcomes	-ADCS -ADL -ADAS-cog -MMSE//NPI
Starting date	Jan 2006: not yet open for recruitment
Contact information	ClinicalTrials.gov Identifier: NCT00235716
Notes	

MD-22

Trial name or title	A randomised, double-blind, placebo-controlled evaluation of the effectiveness and safety of memantine in nursing home residents with moderate to severe AD
Methods	
Participants	-three months trial -USA
Interventions	memantine versus placebo
Outcomes	
Starting date	5 October 2004
Contact information	www.forestclinicaltrials.com
Notes	recruitment finished in March 2005

MD-23

Trial name or title	A randomised, double-blind, placebo-controlled evaluation of the effectiveness and safety of memantine in non-institutionalised agitated patients with moderate to severe AD
Methods	
Participants	USA
Interventions	
Outcomes	
Starting date	27 October 2004
Contact information	www.forestclinicaltrials.com
Notes	

MD-51

Trial name or title	Open-Label Evaluation of the Safety of Memantine in Patients with Moderate-to-Severe Dementia of the Alzheimer's Type
Methods	
Participants	
Interventions	
Outcomes	safety and tolerability of memantine in outpatients
Starting date	Recruitment: Open (at August 2005)
Contact information	http://www.forestclinicaltrials.com/CTR/CTRController/CTROngoingListStudies
Notes	

MEM-MD-50

Trial name or title	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
Methods	
Participants	
Interventions	
Outcomes	safety

MEM-MD-50 (*Continued*)

Starting date	Start Date: 19-MAY-2005 //recruiting.
Contact information	http://www.forestclinicaltrials.com/CTR/CTRController/CTROngoingListStudies
Notes	

Reisberg 2005

Trial name or title	randomized, controlled, single blind trial
Methods	
Participants	-N=20 -Moderate to severe AD -USA
Interventions	comprehensive individualized management approach and memantine versus ???
Outcomes	Clinician Interview-Based Assessment of Change Plus Caregiver Input (CIBIC-Plus)//Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory modified for severe dementia (ADCS-ADLsev)//Severe Impairment Battery//Mini-Mental State Examination (MMSE)//Functional Assessment Staging//Global Deterioration Scale//Behavioral Pathology in Alzheimer's Disease-Frequency Weighted//Memory and Behavior Problems Checklist
Starting date	-Begin date: August 2005 -Enddate: April 2006
Contact information	ClinicalTrials.gov Identifier: NCT00120874
Notes	DH: Difficult to make out from info available if it is memantine which is on trial or the management approach. On balance it is probably the latter and if so this trial does NOT belong here

SUN Y7017

Trial name or title	memantine versus placebo for severe to moderately severe AD
Methods	
Participants	Japan
Interventions	
Outcomes	
Starting date	
Contact information	http://www.dsup.co.jp/eg/research/index.html

SUN Y7017 (*Continued*)

Notes	Daiichi Suntori Pharma

SUN Y7017m

Trial name or title	memantine versus placebo for mild to moderate AD
Methods	
Participants	Japan
Interventions	
Outcomes	
Starting date	
Contact information	http://www.dsup.co.jp/eg/research/index.html
Notes	Daiichi Suntori Pharma

Vasavan Nair 2004

Trial name or title	randomized controlled trial of memantine versus placebo for moderate to severe AD
Methods	
Participants	-N= ? -Country: Canada -CHIs allowed
Interventions	memantine versus placebo
Outcomes	behavioural aspects of moderate to advanced Alzheimer Disease, such as moodiness, irritability, indifference or apathy, pacing or wandering, changing eating habits or types of food preferred
Starting date	-duration 6 months
Contact information	chantal.archer@douglas.mcgill.ca
Notes	Is Gauthier involved in this trial?

DATA AND ANALYSES

Comparison 1. Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data.

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global: CIBIC+ (24-28 weeks)	3	964	Mean Difference (IV, Fixed, 95% CI)	0.28 [0.15, 0.41]
2 Cognitive function: SIB (change from baseline at 24-28 weeks)	3	976	Mean Difference (IV, Fixed, 95% CI)	2.97 [1.68, 4.26]
3 Activities of daily living: ADCS-ADLsev19 (change from baseline at 24-28 weeks)	3	978	Mean Difference (IV, Fixed, 95% CI)	1.27 [0.44, 2.09]
4 Behaviour and mood: NPI total (change from baseline at 24-28 weeks)	3	936	Mean Difference (IV, Fixed, 95% CI)	2.76 [0.88, 4.63]
5 Number of dropouts	3	1006	Odds Ratio (M-H, Fixed, 95% CI)	0.66 [0.49, 0.88]
6 Number suffering at least one adverse event	3	1005	Odds Ratio (M-H, Fixed, 95% CI)	1.13 [0.84, 1.52]
7 Number suffering agitation as an adverse event	3	1005	Odds Ratio (M-H, Fixed, 95% CI)	0.60 [0.42, 0.86]

Comparison 2. Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical global: CIBIC+ (at 24 weeks)	3	1281	Mean Difference (IV, Fixed, 95% CI)	0.13 [0.01, 0.25]
2 Cognitive function: ADAS-Cog (change from baseline at 24 weeks)	3	1279	Mean Difference (IV, Fixed, 95% CI)	0.99 [0.21, 1.78]
3 Activities of daily living: ADCS-ADL23 (change from baseline at 24 weeks)	3	1271	Mean Difference (IV, Fixed, 95% CI)	0.20 [-0.87, 1.27]
4 Mood and behaviour: NPI total (change from baseline at 24 weeks)	3	1252	Mean Difference (IV, Fixed, 95% CI)	-0.25 [-1.48, 0.98]
5 Number of dropouts	3	1306	Odds Ratio (M-H, Fixed, 95% CI)	1.16 [0.83, 1.60]
6 Number suffering agitation as an adverse event	3	1306	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.57, 1.46]
7 Number suffering fall as an adverse event	2	836	Odds Ratio (M-H, Fixed, 95% CI)	0.83 [0.41, 1.67]

8 Number suffering somnolence as an adverse event	1	403	Odds Ratio (M-H, Fixed, 95% CI)	7.49 [1.68, 33.38]
9 Number suffering confusion as an adverse event	2	836	Odds Ratio (M-H, Fixed, 95% CI)	1.40 [0.72, 2.70]
10 Number suffering at least one adverse event	3	1306	Odds Ratio (M-H, Fixed, 95% CI)	1.04 [0.81, 1.33]
11 Number suffering depression as an adverse event	2	836	Odds Ratio (M-H, Fixed, 95% CI)	0.71 [0.38, 1.32]

Comparison 3. Memantine vs placebo for mild-to-moderate vascular dementia. 6 month studies. LOCF or OC data

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global: CGI (at 28 weeks) ITT-LOCF or OC	2	775	Mean Difference (IV, Fixed, 95% CI)	0.03 [-0.13, 0.19]
2 Cognitive function ADAS-Cog (change from baseline at 28 weeks) ITT-LOCF	2	815	Mean Difference (IV, Fixed, 95% CI)	1.85 [0.88, 2.83]
3 Activities of daily living : NOSGER self care subscale (change from baseline at 28 weeks) OC	2	542	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.43, 0.67]
4 Behaviour: NOSGER disturbing behaviour subscale (change from baseline at 28 weeks) OC	2	541	Mean Difference (IV, Fixed, 95% CI)	0.48 [0.06, 0.91]

Comparison 4. Memantine vs placebo for severe Alzheimer disease, vascular and mixed dementia (12 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Activities of daily living (change from baseline at 12 weeks)	1	166	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-5.65, 1.65]
1.1 Dose 10 mg/day, BGP subscore care dependence (change from baseline at 12 weeks)	1	166	Mean Difference (IV, Fixed, 95% CI)	-2.0 [-5.65, 1.65]
2 CGIC (numbers improved at 12 weeks)	1	166	Odds Ratio (M-H, Fixed, 95% CI)	3.30 [1.72, 6.33]
2.1 Dose 10mg/day	1	166	Odds Ratio (M-H, Fixed, 95% CI)	3.30 [1.72, 6.33]
3 Number of drop-outs	1	166	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.25, 4.25]
4 Number suffering at least one adverse event	1	166	Odds Ratio (M-H, Fixed, 95% CI)	1.03 [0.49, 2.16]

Comparison 5. Memantine vs placebo for dementia (cause not specified) (4-6 weeks)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Global	3	213	Std. Mean Difference (IV, Fixed, 95% CI)	-0.76 [-1.04, -0.48]
1.1 Dose 30mg/day, Physicians global impression (6 weeks)	1	66	Std. Mean Difference (IV, Fixed, 95% CI)	-0.82 [-1.33, -0.32]
1.2 Dose 30mg/day, SCAG Clinical global impression of disturbances (4 weeks)	1	59	Std. Mean Difference (IV, Fixed, 95% CI)	-1.04 [-1.58, -0.49]
1.3 Dose 20mg/day, CGI (6 weeks)	1	88	Std. Mean Difference (IV, Fixed, 95% CI)	-0.55 [-0.98, -0.13]
2 Cognition	1	59	Mean Difference (IV, Fixed, 95% CI)	-3.04 [-5.68, -0.40]
2.1 Dose 30mg/day, SKT (change from baseline at 6 weeks)	1	59	Mean Difference (IV, Fixed, 95% CI)	-3.04 [-5.68, -0.40]
3 Activities of daily living	2	126	Std. Mean Difference (IV, Fixed, 95% CI)	-1.34 [-1.73, -0.94]
3.1 Dose 30mg/day, BGP care dependence subsscale (change from baseline at 6 weeks)	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	-2.05 [-2.68, -1.42]
3.2 Dose 30mg/day, ADL-test total time (6 weeks)	1	66	Std. Mean Difference (IV, Fixed, 95% CI)	-0.88 [-1.39, -0.37]
4 Mood and behaviour	3	208	Std. Mean Difference (IV, Fixed, 95% CI)	-1.16 [-1.46, -0.86]
4.1 Dose 30mg/day, NOSIE (change from baseline at 4 weeks)	1	60	Std. Mean Difference (IV, Fixed, 95% CI)	-2.02 [-2.65, -1.39]
4.2 Dose 30mg/day, SCAG total (change from baseline at 6 weeks)	2	148	Std. Mean Difference (IV, Fixed, 95% CI)	-0.91 [-1.25, -0.57]
5 Number of dropouts	2	154	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.27, 2.67]
6 Number suffering at least one adverse event	1	82	Odds Ratio (M-H, Fixed, 95% CI)	2.00 [0.83, 4.81]
7 Number suffering agitation as an adverse event	1	59	Odds Ratio (M-H, Fixed, 95% CI)	2.7 [0.48, 15.19]
8 Number suffering restlessness as an adverse event	1	59	Odds Ratio (M-H, Fixed, 95% CI)	13.5 [2.71, 67.18]

Comparison 6. Memantine vs placebo for mild to severe dementia. All published, 6 month studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global: CIBIC+ or CGI-C	8	3020	Stand. Tx effect (Fixed, 95% CI)	0.15 [0.07, 0.23]
2 Cognitive function: standardised	8	3070	Stand. Tx effect (Fixed, 95% CI)	0.24 [0.17, 0.30]

3 Activities of daily living: standardised	8	2791	Stand. Tx effect (Fixed, 95% CI)	0.08 [0.01, 0.15]
4 Behaviour and mood: standardised	8	2729	Stand. tx effect (Fixed, 95% CI)	0.11 [0.04, 0.19]
5 Number of dropouts	8	3212	Odds Ratio (M-H, Fixed, 95% CI)	0.91 [0.76, 1.09]
6 Number suffering at least one adverse event	8	3211	Odds Ratio (M-H, Fixed, 95% CI)	1.09 [0.93, 1.27]
7 Number suffering agitation as an adverse event	8	3612	Odds Ratio (M-H, Fixed, 95% CI)	0.78 [0.61, 0.99]
8 Number suffering confusion as an adverse event	6	2489	Odds Ratio (M-H, Fixed, 95% CI)	1.31 [0.93, 1.87]
9 Number suffering hypertension	1	350	Odds Ratio (M-H, Fixed, 95% CI)	3.59 [1.16, 11.12]
10 Number suffering dizziness as an adverse event	6	2489	Odds Ratio (M-H, Fixed, 95% CI)	1.18 [0.86, 1.60]
11 Number suffering headache as an adverse event	4	1765	Odds Ratio (M-H, Fixed, 95% CI)	1.02 [0.67, 1.56]
12 Number suffering fall as an adverse event	6	2420	Odds Ratio (M-H, Fixed, 95% CI)	0.96 [0.71, 1.30]
13 Number suffering insomnia as an adverse event	4	1614	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.59, 1.43]
14 Number suffering accidental injury as an adverse event	6	2308	Odds Ratio (M-H, Fixed, 95% CI)	0.70 [0.50, 0.98]
15 Number suffering urinary incontinence as an adverse event	3	1234	Odds Ratio (M-H, Fixed, 95% CI)	1.12 [0.67, 1.85]
16 Number suffering from diarrhoea as an adverse event	4	1584	Odds Ratio (M-H, Fixed, 95% CI)	0.86 [0.56, 1.33]
17 Number suffering from influenza like symptoms as an adverse event	4	1589	Odds Ratio (M-H, Fixed, 95% CI)	1.08 [0.72, 1.63]

Comparison 7. Memantine vs placebo for mild to severe dementia. All 4-12 week studies

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Clinical Global: standardised	4	377	Stand. Tx effect (Fixed, 95% CI)	0.62 [0.41, 0.82]
2 Cognitive function: standardised	1	59	Stand. Tx effect (Fixed, 95% CI)	0.59 [0.11, 1.07]
3 Activities of daily living: standardised	3	292	Stand. Tx effect (Fixed, 95% CI)	0.73 [0.50, 0.96]
4 Mood and behaviour: standardised	3	208	Stand. Tx effect (Fixed, 95% CI)	1.27 [0.99, 1.54]
5 Number of drop-outs	3	320	Odds Ratio (M-H, Fixed, 95% CI)	0.92 [0.38, 2.23]
6 Number suffering at least one adverse event	2	248	Odds Ratio (M-H, Fixed, 95% CI)	1.36 [0.77, 2.38]
7 Number suffering agitation as an adverse event	1	59	Odds Ratio (M-H, Fixed, 95% CI)	2.7 [0.48, 15.19]

Analysis 1.1. Comparison 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data., Outcome 1 Clinical Global: CIBIC+ (24-28 weeks).

Review: Memantine for dementia

Comparison: 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data.

Outcome: 1 Clinical Global: CIBIC+ (24-28 weeks)

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
9605/Reisberg 2003	118	-4.5 (1.12)	118	-4.8 (1.09)		22.4 %	0.30 [0.02, 0.58]
MD-02/Tariot 2004	198	-4.41 (1.04)	196	-4.66 (1.05)		41.8 %	0.25 [0.04, 0.46]
MD-01	171	-4.3 (1.05)	163	-4.6 (1.03)		35.8 %	0.30 [0.08, 0.52]
Total (95% CI)	**487**		**477**			**100.0 %**	**0.28 [0.15, 0.41]**

Heterogeneity: Chi^2 = 0.13, df = 2 (P = 0.94); I^2 =0.0%

Test for overall effect: Z = 4.10 (P = 0.000042)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data., Outcome 2 Cognitive function: SIB (change from baseline at 24-28 weeks).

Review: Memantine for dementia

Comparison: 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data.

Outcome: 2 Cognitive function: SIB (change from baseline at 24-28 weeks)

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
9605/Reisberg 2003	124	-4 (11.34)	123	-10.1 (13.5)		17.2 %	6.10 [2.99, 9.21]
MD-02/Tariot 2004	198	0.9 (9.42)	196	-2.5 (9.66)		46.9 %	3.40 [1.52, 5.28]
MD-01	170	-1.7 (11.34)	165	-2.6 (8.61)		35.9 %	0.90 [-1.25, 3.05]
Total (95% CI)	**492**		**484**			**100.0 %**	**2.97 [1.68, 4.26]**

Heterogeneity: Chi^2 = 7.64, df = 2 (P = 0.02); I^2 =74%

Test for overall effect: Z = 4.51 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 1.3. Comparison 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data., Outcome 3 Activities of daily living: ADCS-ADLsev19 (change from baseline at 24-28 weeks).

Review: Memantine for dementia

Comparison: 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data.

Outcome: 3 Activities of daily living: ADCS-ADLsev19 (change from baseline at 24-28 weeks)

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
9605/Reisberg 2003	124	-3.1 (6.79)	123	-5.2 (6.33)		25.6 %	2.10 [0.46, 3.74]
MD-02/Tariot 2004	198	-2 (7.04)	197	-3.4 (7.16)		35.0 %	1.40 [0.00, 2.80]
MD-01	171	-1.5 (6.8)	165	-2.1 (5.52)		39.3 %	0.60 [-0.72, 1.92]
Total (95% CI)	**493**		**485**			**100.0 %**	**1.27 [0.44, 2.09]**

Heterogeneity: Chi^2 = 2.01, df = 2 (P = 0.37); I^2 =0%

Test for overall effect: Z = 2.99 (P = 0.0028)

Test for subgroup differences: Not applicable

Analysis 1.4. Comparison 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data., Outcome 4 Behaviour and mood: NPI total (change from baseline at 24-28 weeks).

Review: Memantine for dementia

Comparison: 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data.

Outcome: 4 Behaviour and mood: NPI total (change from baseline at 24-28 weeks)

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
9605/Reisberg 2003	120	-0.5 (15.76)	119	-3.8 (16.06)		21.6 %	3.30 [-0.73, 7.33]
MD-02/Tariot 2004	193	0.1 (13.61)	189	-3.7 (13.61)		47.2 %	3.80 [1.07, 6.53]
MD-01	161	1 (15.86)	154	0.2 (14.52)		31.2 %	0.80 [-2.56, 4.16]
Total (95% CI)	**474**		**462**			**100.0 %**	**2.76 [0.88, 4.63]**

Heterogeneity: Chi^2 = 1.94, df = 2 (P = 0.38); I^2 =0.0%

Test for overall effect: Z = 2.88 (P = 0.0040)

Test for subgroup differences: Not applicable

Analysis 1.5. Comparison 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data., Outcome 5 Number of dropouts.

Review: Memantine for dementia

Comparison: 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data.

Outcome: 5 Number of dropouts

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9605/Reisberg 2003	29/126	42/126		29.1 %	0.60 [0.34, 1.04]
MD-02/Tariot 2004	30/203	51/201		39.3 %	0.51 [0.31, 0.84]
MD-01	44/178	46/172		31.7 %	0.90 [0.56, 1.45]
Total (95% CI)	**507**	**499**		**100.0 %**	**0.66 [0.49, 0.88]**

Total events: 103 (Treatment), 139 (Control)

Heterogeneity: $Chi^2 = 2.74$, df = 2 (P = 0.25); $I^2 = 27\%$

Test for overall effect: Z = 2.80 (P = 0.0052)

Analysis 1.6. Comparison 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data., Outcome 6 Number suffering at least one adverse event.

Review: Memantine for dementia

Comparison: 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data.

Outcome: 6 Number suffering at least one adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9605/Reisberg 2003	106/126	109/126		21.0 %	0.83 [0.41, 1.66]
MD-02/Tariot 2004	158/202	145/201		38.4 %	1.39 [0.88, 2.19]
MD-01	131/178	125/172		40.7 %	1.05 [0.65, 1.68]
Total (95% CI)	**506**	**499**		**100.0 %**	**1.13 [0.84, 1.52]**

Total events: 395 (Treatment), 379 (Control)

Heterogeneity: $Chi^2 = 1.64$, df = 2 (P = 0.44); $I^2 = 0.0\%$

Test for overall effect: Z = 0.82 (P = 0.41)

Analysis 1.7. Comparison 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data., Outcome 7 Number suffering agitation as an adverse event.

Review: Memantine for dementia

Comparison: 1 Memantine vs placebo for moderate-to-severe Alzheimer's disease. 6 month studies. ITT-LOCF data.

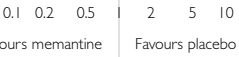
Outcome: 7 Number suffering agitation as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9605/Reisberg 2003	23/126	40/126		42.6 %	0.48 [0.27, 0.86]
MD-01	16/178	24/172		29.0 %	0.61 [0.31, 1.19]
MD-02/Tariot 2004	19/202	24/201		28.4 %	0.77 [0.41, 1.45]
Total (95% CI)	**506**	**499**		**100.0 %**	**0.60 [0.42, 0.86]**

Total events: 58 (Treatment), 88 (Control)

Heterogeneity: Chi^2 = 1.12, df = 2 (P = 0.57); I^2 =0.0%

Test for overall effect: Z = 2.78 (P = 0.0055)



Analysis 2.1. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 1 Clinical global: CIBIC+ (at 24 weeks).

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

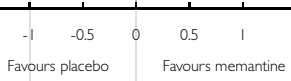
Outcome: 1 Clinical global: CIBIC+ (at 24 weeks)

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
99679(Lundbeck)	310	-4.18 (1.22)	151	-4.23 (1.26)		24.6 %	0.05 [-0.19, 0.29]
MD-10/Peskind 2004	196	-4.2 (0.98)	197	-4.5 (1.12)		33.5 %	0.30 [0.09, 0.51]
MD-12	214	-4.38 (1)	213	-4.42 (0.96)		41.9 %	0.04 [-0.15, 0.23]
Total (95% CI)	**720**		**561**			**100.0 %**	**0.13 [0.01, 0.25]**

Heterogeneity: Chi^2 = 3.88, df = 2 (P = 0.14); I^2 =48%

Test for overall effect: Z = 2.11 (P = 0.035)

Test for subgroup differences: Not applicable



Analysis 2.2. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 2 Cognitive function: ADAS-Cog (change from baseline at 24 weeks).

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

Outcome: 2 Cognitive function: ADAS-Cog (change from baseline at 24 weeks)

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
99679(Lundbeck)	311	1.69 (7.23)	151	1.03 (6.64)		34.8 %	0.66 [-0.67, 1.99]
MD-10/Peskind 2004	195	0.8 (7.81)	198	-1.1 (7.87)		25.6 %	1.90 [0.35, 3.45]
MD-12	212	-0.1 (6.55)	212	-0.8 (6.55)		39.6 %	0.70 [-0.55, 1.95]
Total (95% CI)	**718**		**561**			**100.0 %**	**0.99 [0.21, 1.78]**

Heterogeneity: Chi^2 = 1.77, df = 2 (P = 0.41); I^2 =0.0%

Test for overall effect: Z = 2.48 (P = 0.013)

Test for subgroup differences: Not applicable

Analysis 2.3. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 3 Activities of daily living: ADCS-ADL23 (change from baseline at 24 weeks).

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

Outcome: 3 Activities of daily living: ADCS-ADL23 (change from baseline at 24 weeks)

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
99679(Lundbeck)	304	-2.14 (9.94)	146	-2.79 (9.18)		33.2 %	0.65 [-1.21, 2.51]
MD-10/Peskind 2004	196	-2.9 (10.78)	198	-3 (10.83)		25.3 %	0.10 [-2.03, 2.23]
MD-12	214	-3 (8.78)	213	-2.9 (8.76)		41.6 %	-0.10 [-1.76, 1.56]
Total (95% CI)	**714**		**557**			**100.0 %**	**0.20 [-0.87, 1.27]**

Heterogeneity: Chi^2 = 0.36, df = 2 (P = 0.84); I^2 =0.0%

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Not applicable

Analysis 2.4. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 4 Mood and behaviour: NPI total (change from baseline at 24 weeks).

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

Outcome: 4 Mood and behaviour: NPI total (change from baseline at 24 weeks)

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
99679(Lundbeck)	304	0.85 (1.81)	146	1.95 (9.91)		57.8 %	-1.10 [-2.72, 0.52]
MD-10/Peskind 2004	191	1.4 (16.58)	190	-2.1 (16.81)		13.5 %	3.50 [0.15, 6.85]
MD-12	212	-0.7 (12.08)	209	-0.4 (12)		28.7 %	-0.30 [-2.60, 2.00]
Total (95% CI)	**707**		**545**			**100.0 %**	**-0.25 [-1.48, 0.98]**

Heterogeneity: Chi² = 5.86, df = 2 (P = 0.05); I² =66%

Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable

Analysis 2.5. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 5 Number of dropouts.

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

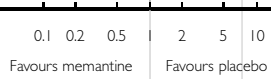
Outcome: 5 Number of dropouts

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
99679(Lundbeck)	47/318	14/152		24.0 %	1.71 [0.91, 3.21]
MD-10/Peskind 2004	36/201	35/202		42.6 %	1.04 [0.62, 1.74]
MD-12	23/217	25/216		33.3 %	0.91 [0.50, 1.65]
Total (95% CI)	**736**	**570**		**100.0 %**	**1.16 [0.83, 1.60]**

Total events: 106 (Treatment), 74 (Control)

Heterogeneity: Chi² = 2.27, df = 2 (P = 0.32); I² =12%

Test for overall effect: Z = 0.87 (P = 0.38)



Analysis 2.6. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 6 Number suffering agitation as an adverse event.

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

Outcome: 6 Number suffering agitation as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
99679(Lundbeck)	5/318	7/152		25.8 %	0.33 [0.10, 1.06]
MD-10/Peskind 2004	15/201	12/202		30.7 %	1.28 [0.58, 2.80]
MD-12	17/217	17/216		43.5 %	1.00 [0.49, 2.00]
Total (95% CI)	**736**	**570**		**100.0 %**	**0.91 [0.57, 1.46]**

Total events: 37 (Treatment), 36 (Control)

Heterogeneity: Chi^2 = 3.68, df = 2 (P = 0.16); I^2 =46%

Test for overall effect: Z = 0.39 (P = 0.70)

Analysis 2.7. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 7 Number suffering fall as an adverse event.

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

Outcome: 7 Number suffering fall as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
MD-10/Peskind 2004	15/201	15/202		79.8 %	1.01 [0.48, 2.12]
MD-12	0/217	3/216		20.2 %	0.14 [0.01, 2.73]
Total (95% CI)	**418**	**418**		**100.0 %**	**0.83 [0.41, 1.67]**

Total events: 15 (Treatment), 18 (Control)

Heterogeneity: Chi^2 = 1.63, df = 1 (P = 0.20); I^2 =39%

Test for overall effect: Z = 0.52 (P = 0.60)

Analysis 2.8. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 8 Number suffering somnolence as an adverse event.

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

Outcome: 8 Number suffering somnolence as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
MD-10/Peskind 2004	14/201	2/202		100.0 %	7.49 [1.68, 33.38]
Total (95% CI)	**201**	**202**		**100.0 %**	**7.49 [1.68, 33.38]**
Total events: 14 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.64 (P = 0.0083)					

Analysis 2.9. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 9 Number suffering confusion as an adverse event.

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

Outcome: 9 Number suffering confusion as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
MD-10/Peskind 2004	10/201	7/202		43.8 %	1.46 [0.54, 3.91]
MD-12	12/217	9/216		56.2 %	1.35 [0.56, 3.26]
Total (95% CI)	**418**	**418**		**100.0 %**	**1.40 [0.72, 2.70]**
Total events: 22 (Treatment), 16 (Control)					
Heterogeneity: Chi^2 = 0.01, df = 1 (P = 0.91); I^2 =0.0%					
Test for overall effect: Z = 0.99 (P = 0.32)					

Analysis 2.10. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 10 Number suffering at least one adverse event.

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

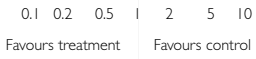
Outcome: 10 Number suffering at least one adverse event

Study or subgroup	Memantine n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
99679(Lundbeck)	178/318	80/152		38.0 %	1.14 [0.78, 1.69]
MD-10/Peskind 2004	142/201	149/202		34.8 %	0.86 [0.55, 1.32]
MD-12	173/217	168/216		27.2 %	1.12 [0.71, 1.78]
Total (95% CI)	**736**	**570**		**100.0 %**	**1.04 [0.81, 1.33]**

Total events: 493 (Memantine), 397 (Placebo)

Heterogeneity: Chi^2 = 1.10, df = 2 (P = 0.58); I^2 =0.0%

Test for overall effect: Z = 0.30 (P = 0.76)



Analysis 2.11. Comparison 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data, Outcome 11 Number suffering depression as an adverse event.

Review: Memantine for dementia

Comparison: 2 Memantine vs placebo for mild-to-moderate Alzheimer's disease. Published, 6 month studies. ITT-LOCF data

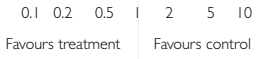
Outcome: 11 Number suffering depression as an adverse event

Study or subgroup	Memantine n/N	Placebo n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
MD-10/Peskind 2004	4/201	10/202		41.0 %	0.39 [0.12, 1.26]
MD-12	14/217	15/216		59.0 %	0.92 [0.43, 1.96]
Total (95% CI)	**418**	**418**		**100.0 %**	**0.71 [0.38, 1.32]**

Total events: 18 (Memantine), 25 (Placebo)

Heterogeneity: Chi^2 = 1.47, df = 1 (P = 0.23); I^2 =32%

Test for overall effect: Z = 1.10 (P = 0.27)



Analysis 3.1. Comparison 3 Memantine vs placebo for mild-to-moderate vascular dementia. 6 month studies. LOCF or OC data, Outcome 1 Clinical Global: CGI (at 28 weeks) ITT-LOCF or OC.

Review: Memantine for dementia

Comparison: 3 Memantine vs placebo for mild-to-moderate vascular dementia. 6 month studies. LOCF or OC data

Outcome: 1 Clinical Global: CGI (at 28 weeks) ITT-LOCF or OC

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
9202/Wilcock 2002	277	-4.07 (1.06)	270	-4.04 (1.06)		81.5 %	-0.03 [-0.21, 0.15]
9408/Orgogozo 2002	114	-3.82 (1.39)	114	-4.11 (1.48)		18.5 %	0.29 [-0.08, 0.66]
Total (95% CI)	**391**		**384**			**100.0 %**	**0.03 [-0.13, 0.19]**

Heterogeneity: Chi² = 2.31, df = 1 (P = 0.13); I² =57%

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Not applicable

Analysis 3.2. Comparison 3 Memantine vs placebo for mild-to-moderate vascular dementia. 6 month studies. LOCF or OC data, Outcome 2 Cognitive function ADAS-Cog (change from baseline at 28 weeks) ITT-LOCF.

Review: Memantine for dementia

Comparison: 3 Memantine vs placebo for mild-to-moderate vascular dementia. 6 month studies. LOCF or OC data

Outcome: 2 Cognitive function ADAS-Cog (change from baseline at 28 weeks) ITT-LOCF

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
9202/Wilcock 2002	266	-0.53 (7.02)	261	-2.28 (7.77)		59.2 %	1.75 [0.48, 3.02]
9408/Orgogozo 2002	147	0.4 (6.6)	141	-1.6 (6.6)		40.8 %	2.00 [0.48, 3.52]
Total (95% CI)	**413**		**402**			**100.0 %**	**1.85 [0.88, 2.83]**

Heterogeneity: Chi² = 0.06, df = 1 (P = 0.80); I² =0.0%

Test for overall effect: Z = 3.73 (P = 0.00019)

Test for subgroup differences: Not applicable

Analysis 3.3. Comparison 3 Memantine vs placebo for mild-to-moderate vascular dementia. 6 month studies. LOCF or OC data, Outcome 3 Activities of daily living : NOSGER self care subscale (change from baseline at 28 weeks) OC.

Review: Memantine for dementia

Comparison: 3 Memantine vs placebo for mild-to-moderate vascular dementia. 6 month studies. LOCF or OC data

Outcome: 3 Activities of daily living : NOSGER self care subscale (change from baseline at 28 weeks) OC

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
9202/Wilcock 2002	192	-0.27 (2.87)	162	-0.4 (2.45)		97.5 %	0.13 [-0.42, 0.68]
9408/Orgogozo 2002	93	-0.4 (12.1)	95	-0.19 (12.1)		2.5 %	-0.21 [-3.67, 3.25]
Total (95% CI)	**285**		**257**			**100.0 %**	**0.12 [-0.43, 0.67]**

Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² =0.0%

Test for overall effect: Z = 0.44 (P = 0.66)

Test for subgroup differences: Not applicable

Analysis 3.4. Comparison 3 Memantine vs placebo for mild-to-moderate vascular dementia. 6 month studies. LOCF or OC data, Outcome 4 Behaviour: NOSGER disturbing behaviour subscale (change from baseline at 28 weeks) OC.

Review: Memantine for dementia

Comparison: 3 Memantine vs placebo for mild-to-moderate vascular dementia. 6 month studies. LOCF or OC data

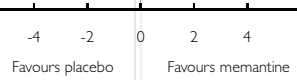
Outcome: 4 Behaviour: NOSGER disturbing behaviour subscale (change from baseline at 28 weeks) OC

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
9202/Wilcock 2002	194	-0.19 (2.05)	159	-0.57 (2.65)		71.7 %	0.38 [-0.12, 0.88]
9408/Orgogozo 2002	93	0.36 (2.8)	95	-0.38 (2.8)		28.3 %	0.74 [-0.06, 1.54]
Total (95% CI)	**287**		**254**			**100.0 %**	**0.48 [0.06, 0.91]**

Heterogeneity: Chi² = 0.56, df = 1 (P = 0.46); I² =0.0%

Test for overall effect: Z = 2.22 (P = 0.027)

Test for subgroup differences: Not applicable

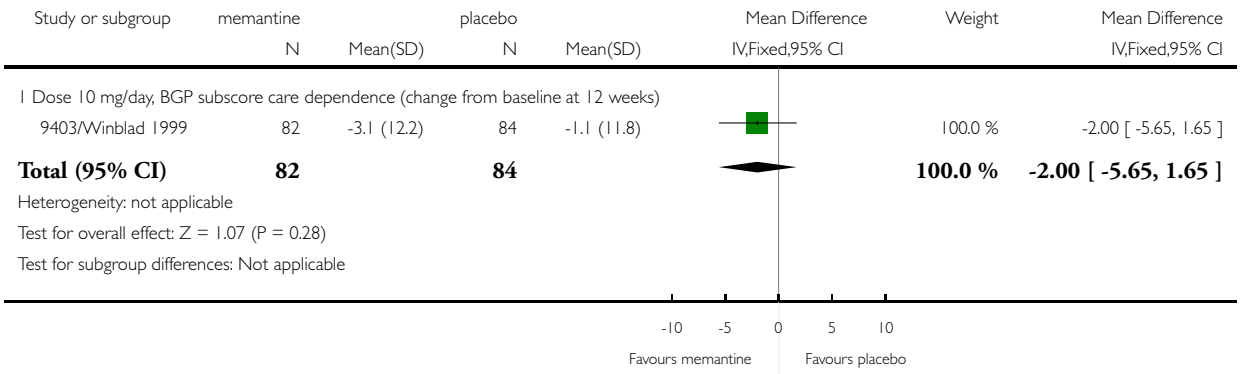


Analysis 4.1. Comparison 4 Memantine vs placebo for severe Alzheimer disease, vascular and mixed dementia (12 weeks), Outcome 1 Activities of daily living (change from baseline at 12 weeks).

Review: Memantine for dementia

Comparison: 4 Memantine vs placebo for severe Alzheimer disease, vascular and mixed dementia (12 weeks)

Outcome: 1 Activities of daily living (change from baseline at 12 weeks)

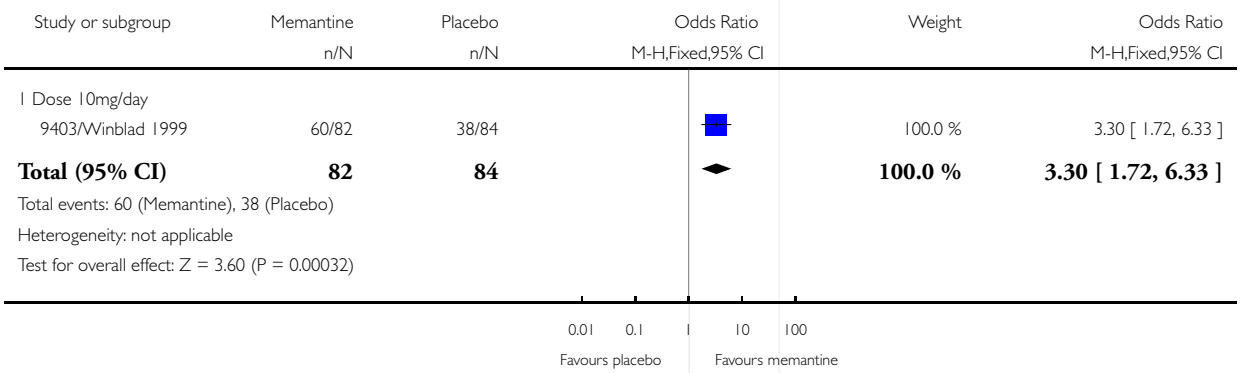


Analysis 4.2. Comparison 4 Memantine vs placebo for severe Alzheimer disease, vascular and mixed dementia (12 weeks), Outcome 2 CGIC (numbers improved at 12 weeks).

Review: Memantine for dementia

Comparison: 4 Memantine vs placebo for severe Alzheimer disease, vascular and mixed dementia (12 weeks)

Outcome: 2 CGIC (numbers improved at 12 weeks)



Analysis 4.3. Comparison 4 Memantine vs placebo for severe Alzheimer disease, vascular and mixed dementia (12 weeks), Outcome 3 Number of drop-outs.

Review: Memantine for dementia

Comparison: 4 Memantine vs placebo for severe Alzheimer disease, vascular and mixed dementia (12 weeks)

Outcome: 3 Number of drop-outs

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9403/Winblad 1999	4/82	4/84		100.0 %	1.03 [0.25, 4.25]
Total (95% CI)	**82**	**84**		**100.0 %**	**1.03 [0.25, 4.25]**
Total events: 4 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.03 (P = 0.97)					

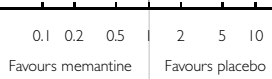
Analysis 4.4. Comparison 4 Memantine vs placebo for severe Alzheimer disease, vascular and mixed dementia (12 weeks), Outcome 4 Number suffering at least one adverse event.

Review: Memantine for dementia

Comparison: 4 Memantine vs placebo for severe Alzheimer disease, vascular and mixed dementia (12 weeks)

Outcome: 4 Number suffering at least one adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9403/Winblad 1999	18/82	18/84		100.0 %	1.03 [0.49, 2.16]
Total (95% CI)	**82**	**84**		**100.0 %**	**1.03 [0.49, 2.16]**
Total events: 18 (Treatment), 18 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.93)					



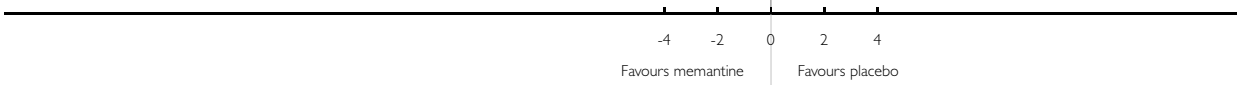
Analysis 5.1. Comparison 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks), Outcome 1 Global.

Review: Memantine for dementia

Comparison: 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks)

Outcome: 1 Global

Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Dose 30mg/day, Physicians global impression (6 weeks)							
Ditzler 1991	32	1.78 (0.87)	34	2.5 (0.86)		30.8 %	-0.82 [-1.33, -0.32]
Subtotal (95% CI)	**32**		**34**			**30.8 %**	**-0.82 [-1.33, -0.32]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.20 (P = 0.0014)							
2 Dose 30mg/day, SCAG Clinical global impression of disturbances (4 weeks)							
Pantev 1993	30	5.4 (0.81)	29	6.21 (0.73)		26.2 %	-1.04 [-1.58, -0.49]
Subtotal (95% CI)	**30**		**29**			**26.2 %**	**-1.04 [-1.58, -0.49]**
Heterogeneity: not applicable							
Test for overall effect: Z = 3.72 (P = 0.00020)							
3 Dose 20mg/day, CGI (6 weeks)							
Gortelmeyer 1992	45	1.56 (0.66)	43	1.93 (0.67)		43.0 %	-0.55 [-0.98, -0.13]
Subtotal (95% CI)	**45**		**43**			**43.0 %**	**-0.55 [-0.98, -0.13]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.54 (P = 0.011)							
Total (95% CI)	**107**		**106**			**100.0 %**	**-0.76 [-1.04, -0.48]**
Heterogeneity: Chi^2 = 1.96, df = 2 (P = 0.38); I^2 =0.0%							
Test for overall effect: Z = 5.34 (P < 0.00001)							
Test for subgroup differences: Chi^2 = 1.96, df = 2 (P = 0.38), I^2 =0.0%							

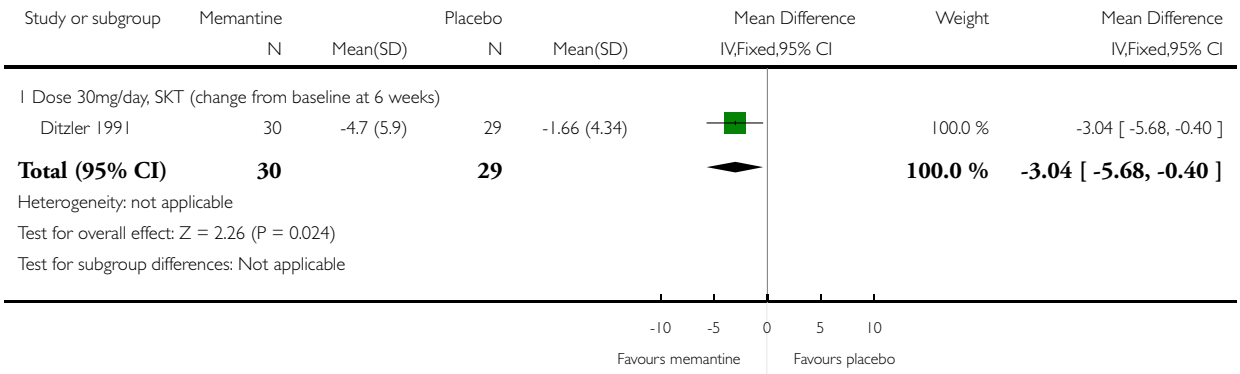


Analysis 5.2. Comparison 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks), Outcome 2 Cognition.

Review: Memantine for dementia

Comparison: 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks)

Outcome: 2 Cognition

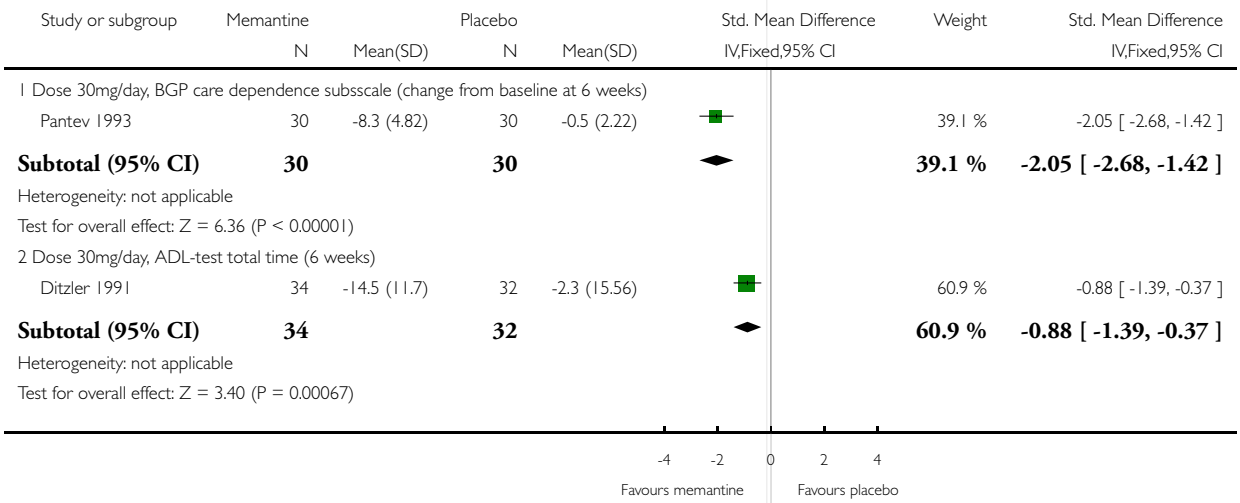


Analysis 5.3. Comparison 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks), Outcome 3 Activities of daily living.

Review: Memantine for dementia

Comparison: 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks)

Outcome: 3 Activities of daily living



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Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
Total (95% CI)	**64**		**62**			**100.0 %**	**-1.34 [-1.73, -0.94]**
Heterogeneity: Chi² = 8.03, df = 1 (P = 0.005); I² =88%							
Test for overall effect: Z = 6.63 (P < 0.00001)							
Test for subgroup differences: Chi² = 8.03, df = 1 (P = 0.00), I² =88%							

Analysis 5.4. Comparison 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks), Outcome 4 Mood and behaviour.

Review: Memantine for dementia

Comparison: 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks)

Outcome: 4 Mood and behaviour

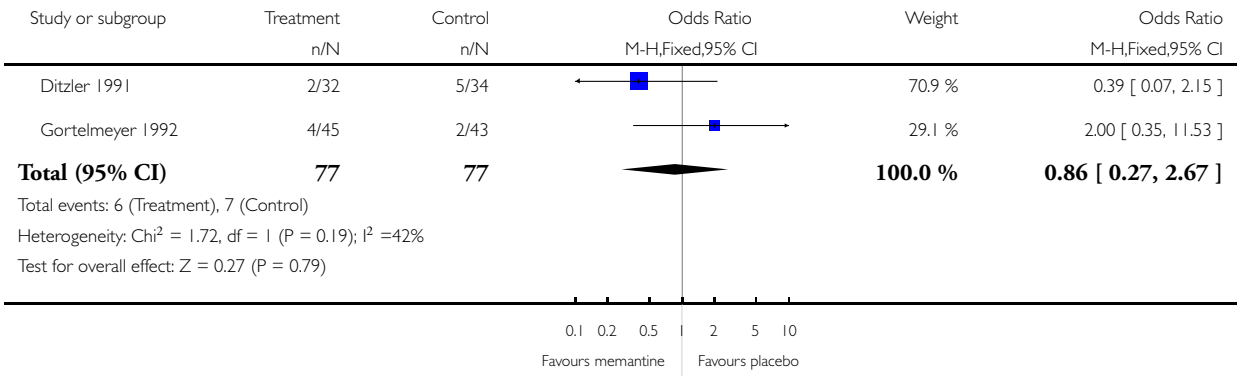
Study or subgroup	Memantine N	Mean(SD)	Placebo N	Mean(SD)	Std. Mean Difference IV,Fixed,95% CI	Weight	Std. Mean Difference IV,Fixed,95% CI
1 Dose 30mg/day, NOSIE (change from baseline at 4 weeks)							
Pantev 1993	30	-22.7 (14.08)	30	-0.6 (5.93)		22.7 %	-2.02 [-2.65, -1.39]
Subtotal (95% CI)	**30**		**30**			**22.7 %**	**-2.02 [-2.65, -1.39]**
Heterogeneity: not applicable							
Test for overall effect: Z = 6.29 (P < 0.00001)							
2 Dose 30mg/day, SCAG total (change from baseline at 6 weeks)							
Ditzler 1991	32	-18 (11.3)	34	-4 (11.7)		32.3 %	-1.20 [-1.73, -0.68]
Gortelmeyer 1992	41	-18.1 (16)	41	-6.4 (17)		45.0 %	-0.70 [-1.15, -0.26]
Subtotal (95% CI)	**73**		**75**			**77.3 %**	**-0.91 [-1.25, -0.57]**
Heterogeneity: Chi² = 2.01, df = 1 (P = 0.16); I² =50%							
Test for overall effect: Z = 5.24 (P < 0.00001)							
Total (95% CI)	**103**		**105**			**100.0 %**	**-1.16 [-1.46, -0.86]**
Heterogeneity: Chi² = 11.23, df = 2 (P = 0.004); I² =82%							
Test for overall effect: Z = 7.60 (P < 0.00001)							
Test for subgroup differences: Chi² = 9.21, df = 1 (P = 0.00), I² =89%							

Analysis 5.5. Comparison 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks), Outcome 5 Number of dropouts.

Review: Memantine for dementia

Comparison: 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks)

Outcome: 5 Number of dropouts

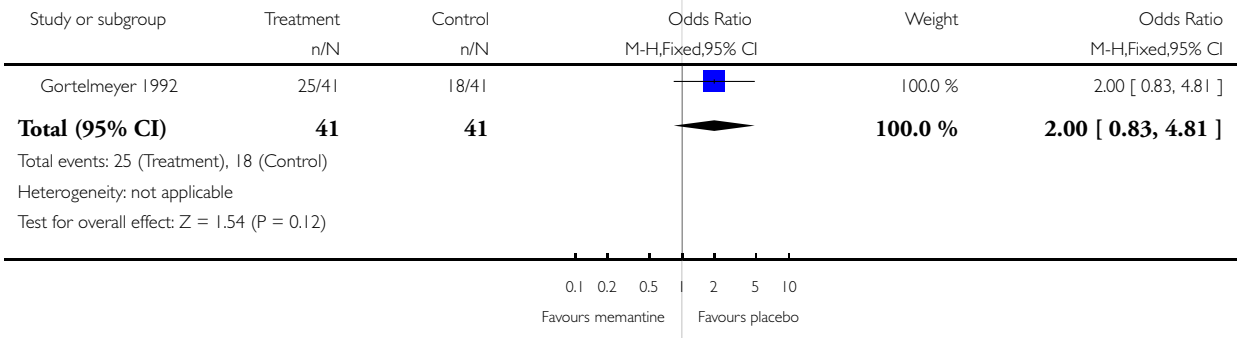


Analysis 5.6. Comparison 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks), Outcome 6 Number suffering at least one adverse event.

Review: Memantine for dementia

Comparison: 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks)

Outcome: 6 Number suffering at least one adverse event



Analysis 5.7. Comparison 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks), Outcome 7 Number suffering agitation as an adverse event.

Review: Memantine for dementia

Comparison: 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks)

Outcome: 7 Number suffering agitation as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Ditzler 1991	5/30	2/29		100.0 %	2.70 [0.48, 15.19]
Total (95% CI)	**30**	**29**		**100.0 %**	**2.70 [0.48, 15.19]**
Total events: 5 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.13 (P = 0.26)					

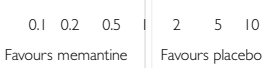
Analysis 5.8. Comparison 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks), Outcome 8 Number suffering restlessness as an adverse event.

Review: Memantine for dementia

Comparison: 5 Memantine vs placebo for dementia (cause not specified) (4-6 weeks)

Outcome: 8 Number suffering restlessness as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
Ditzler 1991	15/30	2/29		100.0 %	13.50 [2.71, 67.18]
Total (95% CI)	**30**	**29**		**100.0 %**	**13.50 [2.71, 67.18]**
Total events: 15 (Treatment), 2 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.18 (P = 0.0015)					



Analysis 6.1. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 1 Clinical Global: CIBIC+ or CGI-C.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

Outcome: 1 Clinical Global: CIBIC+ or CGI-C

Study or subgroup	Treatment N	Control N	Stand. Tx effect (SE)	Stand. Tx effect IV,Fixed,95% CI	Weight	Stand. Tx effect IV,Fixed,95% CI
9605/Reisberg 2003	118	118	0.3 (0.1439)		7.3 %	0.30 [0.02, 0.58]
MD-02/Tariot 2004	198	196	0.25 (0.1053)		13.7 %	0.25 [0.04, 0.46]
MD-01	171	163	0.3 (0.1131)		11.8 %	0.30 [0.08, 0.52]
9202/Wilcock 2002	277	270	-0.03 (0.0907)		18.4 %	-0.03 [-0.21, 0.15]
9408/Orgogozo 2002	114	114	0.29 (0.1902)		4.2 %	0.29 [-0.08, 0.66]
MD-10/Peskind 2004	196	197	0.287 (0.1061)		13.5 %	0.29 [0.08, 0.49]
MD-12	214	213	0.0409 (0.0969)		16.1 %	0.04 [-0.15, 0.23]
99679(Lundbeck)	310	151	0.0406 (0.1005)		15.0 %	0.04 [-0.16, 0.24]
Total (95% CI)					**100.0 %**	**0.15 [0.07, 0.23]**

Heterogeneity: Chi² = 12.35, df = 7 (P = 0.09); I² =43%

Test for overall effect: Z = 3.84 (P = 0.00012)

Test for subgroup differences: Not applicable

Analysis 6.2. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 2 Cognitive function: standardised.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

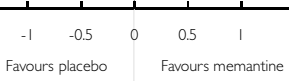
Outcome: 2 Cognitive function: standardised

Study or subgroup	Treatment N	Control N	Stand. Tx effect (SE)	Stand. Tx effect IV,Fixed,95% CI	Weight	Stand. Tx effect IV,Fixed,95% CI
9605/Reisberg 2003	124	123	0.4904 (0.1273)		6.9 %	0.49 [0.24, 0.74]
MD-02/Tariot 2004	198	196	0.36 (0.0975)		11.7 %	0.36 [0.17, 0.55]
MD-01	170	165	0.0893 (0.109)		9.4 %	0.09 [-0.12, 0.30]
9202/Wilcock 2002	266	261	0.2367 (0.0873)		14.6 %	0.24 [0.07, 0.41]
9408/Orgogozo 2002	147	141	0.3 (0.07)		22.7 %	0.30 [0.16, 0.44]
MD-10/Peskind 2004	195	198	0.2426 (0.1009)		10.9 %	0.24 [0.04, 0.44]
MD-12	212	212	0.107 (0.0972)		11.8 %	0.11 [-0.08, 0.30]
99679(Lundbeck)	311	151	0.0938 (0.0964)		12.0 %	0.09 [-0.10, 0.28]
Total (95% CI)					**100.0 %**	**0.24 [0.17, 0.30]**

Heterogeneity: Chi^2 = 12.20, df = 7 (P = 0.09); I^2 =43%

Test for overall effect: Z = 7.11 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 6.3. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 3 Activities of daily living: standardised.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

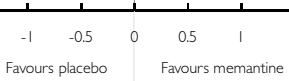
Outcome: 3 Activities of daily living: standardised

Study or subgroup	Treatment N	Control N	Stand. Tx effect (SE)	Stand. Tx effect IV,Fixed,95% CI	Weight	Stand. Tx effect IV,Fixed,95% CI
9605/Reisberg 2003	124	123	0.3205 (0.1273)		8.4 %	0.32 [0.07, 0.57]
MD-02/Tariot 2004	198	197	0.1974 (0.1006)		13.4 %	0.20 [0.00, 0.39]
MD-01	171	165	0.0968 (0.1089)		11.5 %	0.10 [-0.12, 0.31]
9202/Wilcock 2002	192	162	0.0481 (0.0871)		17.9 %	0.05 [-0.12, 0.22]
9408/Orgogozo 2002	93	95	-0.02 (0.1425)		6.7 %	-0.02 [-0.30, 0.26]
MD-10/Peskind 2004	196	198	0.0093 (0.1008)		13.4 %	0.01 [-0.19, 0.21]
MD-12	214	213	-0.0114 (0.0969)		14.5 %	-0.01 [-0.20, 0.18]
99679(Lundbeck)	304	146	0.0671 (0.098)		14.2 %	0.07 [-0.12, 0.26]
Total (95% CI)					**100.0 %**	**0.08 [0.01, 0.15]**

Heterogeneity: Chi^2 = 6.98, df = 7 (P = 0.43); I^2 =0.0%

Test for overall effect: Z = 2.19 (P = 0.028)

Test for subgroup differences: Not applicable



Analysis 6.4. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 4 Behaviour and mood: standardised.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

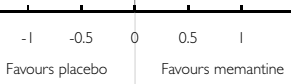
Outcome: 4 Behaviour and mood: standardised

Study or subgroup	Treatment N	Control N	Stand. tx effect (SE)	Stand. tx effect IV,Fixed,95% CI	Weight	Stand. tx effect IV,Fixed,95% CI
9605/Reisberg 2003	120	119	0.2078 (0.1297)		8.8 %	0.21 [-0.05, 0.46]
MD-02/Tariot 2004	193	189	0.28 (0.1023)		14.1 %	0.28 [0.08, 0.48]
MD-01	161	154	0.0526 (0.1127)		11.6 %	0.05 [-0.17, 0.27]
9202/Wilcock 2002	194	159	0.1607 (0.105)		13.4 %	0.16 [-0.05, 0.37]
9408/Orgogozo 2002	93	95	0.26 (0.1425)		7.3 %	0.26 [-0.02, 0.54]
MD-10/Peskind 2004	191	190	0.21 (0.1025)		14.0 %	0.21 [0.01, 0.41]
MD-12	212	209	-0.0249 (0.0976)		15.5 %	-0.02 [-0.22, 0.17]
99679(Lundbeck)	304	146	-0.1046 (0.0978)		15.4 %	-0.10 [-0.30, 0.09]
Total (95% CI)					**100.0 %**	**0.11 [0.04, 0.19]**

Heterogeneity: Chi² = 12.60, df = 7 (P = 0.08); I² =44%

Test for overall effect: Z = 2.96 (P = 0.0031)

Test for subgroup differences: Not applicable



Analysis 6.5. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 5 Number of dropouts.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

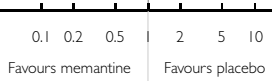
Outcome: 5 Number of dropouts

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9605/Reisberg 2003	29/126	42/126		12.8 %	0.60 [0.34, 1.04]
MD-02/Tariot 2004	30/203	51/201		17.2 %	0.51 [0.31, 0.84]
MD-01	44/178	46/172		13.9 %	0.90 [0.56, 1.45]
9202/Wilcock 2002	57/295	58/284		18.8 %	0.93 [0.62, 1.40]
9408/Orgogozo 2002	49/165	38/156		10.8 %	1.31 [0.80, 2.15]
MD-10/Peskind 2004	36/201	35/202		11.3 %	1.04 [0.62, 1.74]
MD-12	23/217	25/216		8.8 %	0.91 [0.50, 1.65]
99679(Lundbeck)	47/318	14/152		6.4 %	1.71 [0.91, 3.21]
Total (95% CI)	**1703**	**1509**		**100.0 %**	**0.91 [0.76, 1.09]**

Total events: 315 (Treatment), 309 (Control)

Heterogeneity: Chi^2 = 13.53, df = 7 (P = 0.06); I^2 =48%

Test for overall effect: Z = 1.00 (P = 0.32)



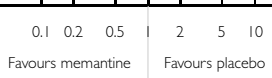
Analysis 6.6. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 6 Number suffering at least one adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

Outcome: 6 Number suffering at least one adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9605/Reisberg 2003	106/126	109/126		6.0 %	0.83 [0.41, 1.66]
MD-02/Tariot 2004	158/202	145/201		11.0 %	1.39 [0.88, 2.19]
MD-01	131/178	125/172		11.7 %	1.05 [0.65, 1.68]
9202/Wilcock 2002	226/295	212/284		17.6 %	1.11 [0.76, 1.63]
9408/Orgogozo 2002	125/165	115/156		10.0 %	1.11 [0.67, 1.84]
99679(Lundbeck)	178/318	80/152		16.6 %	1.14 [0.78, 1.69]
MD-10/Peskind 2004	142/201	149/202		15.2 %	0.86 [0.55, 1.32]
MD-12	173/217	168/216		11.9 %	1.12 [0.71, 1.78]
Total (95% CI)	**1702**	**1509**		**100.0 %**	**1.09 [0.93, 1.27]**
Total events: 1239 (Treatment), 1103 (Control)					
Heterogeneity: Chi^2 = 2.97, df = 7 (P = 0.89); I^2 =0.0%					
Test for overall effect: Z = 1.01 (P = 0.31)					



Analysis 6.7. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 7 Number suffering agitation as an adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

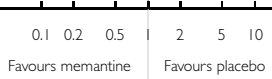
Outcome: 7 Number suffering agitation as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9605/Reisberg 2003	23/126	40/126		21.1 %	0.48 [0.27, 0.86]
MD-02/Tariot 2004	19/202	24/201		14.1 %	0.77 [0.41, 1.45]
MD-01	16/178	24/172		14.3 %	0.61 [0.31, 1.19]
MD-10/Peskind 2004	15/201	12/202		7.1 %	1.28 [0.58, 2.80]
99679(Lundbeck)	24/355	24/516		11.8 %	1.49 [0.83, 2.66]
9202/Wilcock 2002	11/295	23/284		14.6 %	0.44 [0.21, 0.92]
9408/Orgogozo 2002	9/165	11/156		6.9 %	0.76 [0.31, 1.89]
MD-12	17/217	17/216		10.1 %	1.00 [0.49, 2.00]
Total (95% CI)	**1739**	**1873**		**100.0 %**	**0.78 [0.61, 0.99]**

Total events: 134 (Treatment), 175 (Control)

Heterogeneity: Chi^2 = 12.15, df = 7 (P = 0.10); I^2 =42%

Test for overall effect: Z = 2.05 (P = 0.040)



Analysis 6.8. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 8 Number suffering confusion as an adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

Outcome: 8 Number suffering confusion as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9202/Wilcock 2002	22/295	21/284		35.9 %	1.01 [0.54, 1.88]
9408/Orgogozo 2002	8/165	9/156		16.0 %	0.83 [0.31, 2.21]
MD-01	9/178	8/172		14.0 %	1.09 [0.41, 2.90]
MD-02/Tariot 2004	16/202	4/201		6.7 %	4.24 [1.39, 12.90]
MD-10/Peskind 2004	10/201	7/202		12.0 %	1.46 [0.54, 3.91]
MD-12	12/217	9/216		15.4 %	1.35 [0.56, 3.26]
Total (95% CI)	**1258**	**1231**		**100.0 %**	**1.31 [0.93, 1.87]**
Total events: 77 (Treatment), 58 (Control)					
Heterogeneity: Chi^2 = 5.96, df = 5 (P = 0.31); I^2 =16%					
Test for overall effect: Z = 1.53 (P = 0.13)					

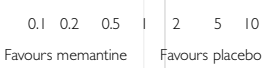
Analysis 6.9. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 9 Number suffering hypertension.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

Outcome: 9 Number suffering hypertension

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
MD-01	14/178	4/172		100.0 %	3.59 [1.16, 11.12]
Total (95% CI)	**178**	**172**		**100.0 %**	**3.59 [1.16, 11.12]**
Total events: 14 (Treatment), 4 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.21 (P = 0.027)					



Analysis 6.10. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 10 Number suffering dizziness as an adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

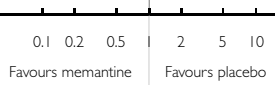
Outcome: 10 Number suffering dizziness as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
MD-02/Tariot 2004	14/202	16/201		20.1 %	0.86 [0.41, 1.81]
MD-01	12/178	11/172		14.0 %	1.06 [0.45, 2.47]
9202/Wilcock 2002	33/295	23/284		28.0 %	1.43 [0.82, 2.50]
9408/Orgogozo 2002	10/165	5/156		6.5 %	1.95 [0.65, 5.83]
MD-10/Peskind 2004	10/201	9/202		11.5 %	1.12 [0.45, 2.82]
MD-12	16/217	16/216		20.0 %	1.00 [0.48, 2.04]
Total (95% CI)	**1258**	**1231**		**100.0 %**	**1.18 [0.86, 1.60]**

Total events: 95 (Treatment), 80 (Control)

Heterogeneity: $Chi^2 = 2.23$, df = 5 (P = 0.82); $I^2 = 0.0\%$

Test for overall effect: Z = 1.02 (P = 0.31)



Analysis 6.11. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 11 Number suffering headache as an adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

Outcome: 11 Number suffering headache as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9202/Wilcock 2002	21/295	19/284		42.5 %	1.07 [0.56, 2.03]
MD-01	3/178	11/172		26.0 %	0.25 [0.07, 0.92]
MD-02/Tariot 2004	13/202	5/201		11.1 %	2.70 [0.94, 7.71]
MD-12	9/217	9/216		20.4 %	1.00 [0.39, 2.56]
Total (95% CI)	**892**	**873**		**100.0 %**	**1.02 [0.67, 1.56]**

Total events: 46 (Treatment), 44 (Control)

Heterogeneity: $Chi^2 = 7.82$, df = 3 (P = 0.05); $I^2 = 62\%$

Test for overall effect: Z = 0.10 (P = 0.92)

Analysis 6.12. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 12 Number suffering fall as an adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

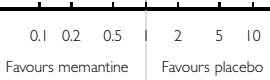
Outcome: 12 Number suffering fall as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9202/Wilcock 2002	18/295	21/284		23.6 %	0.81 [0.42, 1.56]
9605/Reisberg 2003	9/126	9/126		9.8 %	1.00 [0.38, 2.61]
MD-01	10/178	17/172		19.2 %	0.54 [0.24, 1.22]
MD-02/Tariot 2004	15/202	14/201		15.3 %	1.07 [0.50, 2.28]
MD-10/Peskind 2004	15/201	15/202		16.3 %	1.01 [0.48, 2.12]
MD-12	22/217	15/216		15.9 %	1.51 [0.76, 3.00]
Total (95% CI)	**1219**	**1201**		**100.0 %**	**0.96 [0.71, 1.30]**

Total events: 89 (Treatment), 91 (Control)

Heterogeneity: Chi^2 = 3.94, df = 5 (P = 0.56); I^2 =0.0%

Test for overall effect: Z = 0.25 (P = 0.80)



Analysis 6.13. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 13 Number suffering insomnia as an adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

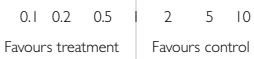
Outcome: 13 Number suffering insomnia as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9202/Wilcock 2002	8/295	19/284		45.8 %	0.39 [0.17, 0.90]
9605/Reisberg 2003	13/126	10/126		21.8 %	1.33 [0.56, 3.17]
MD-01	9/172	4/178		9.1 %	2.40 [0.73, 7.95]
MD-12	10/217	10/216		23.3 %	1.00 [0.41, 2.44]
Total (95% CI)	**810**	**804**		**100.0 %**	**0.92 [0.59, 1.43]**

Total events: 40 (Treatment), 43 (Control)

Heterogeneity: $Chi^2 = 7.22$, df = 3 (P = 0.07); $I^2 = 58\%$

Test for overall effect: Z = 0.38 (P = 0.71)



Analysis 6.14. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 14 Number suffering accidental injury as an adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

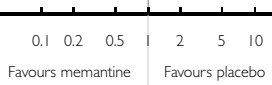
Outcome: 14 Number suffering accidental injury as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9202/Wilcock 2002	17/295	30/284		34.7 %	0.52 [0.28, 0.96]
9408/Orgogozo 2002	5/165	6/156		7.2 %	0.78 [0.23, 2.61]
9605/Reisberg 2003	10/126	11/126		12.2 %	0.90 [0.37, 2.20]
MD-01	10/178	13/172		15.0 %	0.73 [0.31, 1.71]
MD-02/Tariot 2004	10/202	16/201		18.4 %	0.60 [0.27, 1.36]
MD-10/Peskind 2004	12/201	11/202		12.4 %	1.10 [0.47, 2.56]
Total (95% CI)	**1167**	**1141**		**100.0 %**	**0.70 [0.50, 0.98]**

Total events: 64 (Treatment), 87 (Control)

Heterogeneity: $Chi^2 = 2.50$, df = 5 (P = 0.78); $I^2 = 0.0\%$

Test for overall effect: Z = 2.06 (P = 0.039)



Analysis 6.15. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 15 Number suffering urinary incontinence as an adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

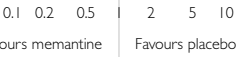
Outcome: 15 Number suffering urinary incontinence as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9202/Wilcock 2002	9/284	11/295		36.6 %	0.84 [0.34, 2.07]
9605/Reisberg 2003	14/126	14/126		43.5 %	1.00 [0.46, 2.19]
MD-02/Tariot 2004	11/202	6/201		19.9 %	1.87 [0.68, 5.16]
Total (95% CI)	**612**	**622**		**100.0 %**	**1.12 [0.67, 1.85]**

Total events: 34 (Treatment), 31 (Control)

Heterogeneity: Chi² = 1.44, df = 2 (P = 0.49); I² =0.0%

Test for overall effect: Z = 0.43 (P = 0.67)



Analysis 6.16. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 16 Number suffering from diarrhoea as an adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

Outcome: 16 Number suffering from diarrhoea as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
9202/Wilcock 2002	12/295	10/284		22.0 %	1.16 [0.49, 2.73]
9605/Reisberg 2003	12/126	10/126		20.3 %	1.22 [0.51, 2.94]
MD-01	8/172	10/178		21.1 %	0.82 [0.32, 2.13]
MD-02/Tariot 2004	9/202	17/201		36.6 %	0.50 [0.22, 1.16]
Total (95% CI)	**795**	**789**		**100.0 %**	**0.86 [0.56, 1.33]**

Total events: 41 (Treatment), 47 (Control)

Heterogeneity: Chi² = 2.67, df = 3 (P = 0.45); I² =0.0%

Test for overall effect: Z = 0.68 (P = 0.50)

Analysis 6.17. Comparison 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies, Outcome 17 Number suffering from influenza like symptoms as an adverse event.

Review: Memantine for dementia

Comparison: 6 Memantine vs placebo for mild to severe dementia. All published, 6 month studies

Outcome: 17 Number suffering from influenza like symptoms as an adverse event

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H,Fixed,95% CI	Weight	Odds Ratio M-H,Fixed,95% CI
MD-01	10/178	8/172		17.1 %	1.22 [0.47, 3.17]
MD-02/Tariot 2004	13/201	15/202		31.1 %	0.86 [0.40, 1.86]
MD-10/Peskind 2004	14/201	13/202		26.8 %	1.09 [0.50, 2.38]
MD-12	15/217	12/216		24.9 %	1.26 [0.58, 2.76]
Total (95% CI)	**797**	**792**		**100.0 %**	**1.08 [0.72, 1.63]**

Total events: 52 (Treatment), 48 (Control)

Heterogeneity: Chi² = 0.54, df = 3 (P = 0.91); I² =0.0%

Test for overall effect: Z = 0.39 (P = 0.70)

Analysis 7.1. Comparison 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies, Outcome 1 Clinical Global: standardised.

Review: Memantine for dementia

Comparison: 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies

Outcome: 1 Clinical Global: standardised

Study or subgroup	Memantine N	Placebo N	Stand. Tx effect (SE)	Stand. Tx effect IV,Fixed,95% CI	Weight	Stand. Tx effect IV,Fixed,95% CI
9403/Winblad 1999	82	84	0.3994 (0.1552)		43.8 %	0.40 [0.10, 0.70]
Ditzler 1991	32	32	0.839 (0.2463)		17.4 %	0.84 [0.36, 1.32]
Gortelmeyer 1992	45	43	0.5597 (0.2133)		23.2 %	0.56 [0.14, 0.98]
Pantev 1993	30	29	1.0587 (0.2604)		15.6 %	1.06 [0.55, 1.57]
Total (95% CI)					**100.0 %**	**0.62 [0.41, 0.82]**

Heterogeneity: Chi² = 5.73, df = 3 (P = 0.13); I² =48%

Test for overall effect: Z = 5.99 (P < 0.00001)

Test for subgroup differences: Not applicable

Analysis 7.2. Comparison 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies, Outcome 2 Cognitive function: standardised.

Review: Memantine for dementia

Comparison: 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies

Outcome: 2 Cognitive function: standardised

Study or subgroup	Memantine N	Placebo N	Stand. Tx effect (SE)	Stand. Tx effect IV,Fixed,95% CI	Weight	Stand. Tx effect IV,Fixed,95% CI
Ditzler 1991	30	29	0.5906 (0.2463)		100.0 %	0.59 [0.11, 1.07]
Total (95% CI)					**100.0 %**	**0.59 [0.11, 1.07]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.40 (P = 0.016)

Test for subgroup differences: Not applicable

Analysis 7.3. Comparison 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies, Outcome 3 Activities of daily living: standardised.

Review: Memantine for dementia

Comparison: 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies

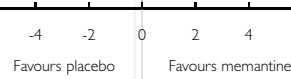
Outcome: 3 Activities of daily living: standardised

Study or subgroup	Memantine N	Placebo N	Stand. Tx effect (SE)	Stand. Tx effect IV,Fixed,95% CI	Weight	Stand. Tx effect IV,Fixed,95% CI
9403/Winblad 1999	82	84	0.1672 (0.1552)		56.9 %	0.17 [-0.14, 0.47]
Ditzler 1991	34	32	0.897 (0.2463)		22.6 %	0.90 [0.41, 1.38]
Pantev 1993	30	30	2.0965 (0.2582)		20.5 %	2.10 [1.59, 2.60]
Total (95% CI)					**100.0 %**	**0.73 [0.50, 0.96]**

Heterogeneity: Chi^2 = 41.62, df = 2 (P<0.00001); I^2 =95%

Test for overall effect: Z = 6.22 (P < 0.00001)

Test for subgroup differences: Not applicable



Analysis 7.4. Comparison 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies, Outcome 4 Mood and behaviour: standardised.

Review: Memantine for dementia

Comparison: 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies

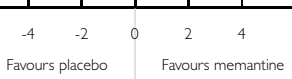
Outcome: 4 Mood and behaviour: standardised

Study or subgroup	Memantine N	Placebo N	Stand. Tx effect (SE)	Stand. Tx effect IV,Fixed,95% CI	Weight	Stand. Tx effect IV,Fixed,95% CI
Ditzler 1991	32	34	1.2269 (0.2463)		31.7 %	1.23 [0.74, 1.71]
Gortelmeyer 1992	41	41	0.7132 (0.2209)		39.4 %	0.71 [0.28, 1.15]
Pantev 1993	30	30	2.0633 (0.2582)		28.9 %	2.06 [1.56, 2.57]
Total (95% CI)					**100.0 %**	**1.27 [0.99, 1.54]**

Heterogeneity: Chi^2 = 15.82, df = 2 (P = 0.00037); I^2 =87%

Test for overall effect: Z = 9.13 (P < 0.00001)

Test for subgroup differences: Not applicable

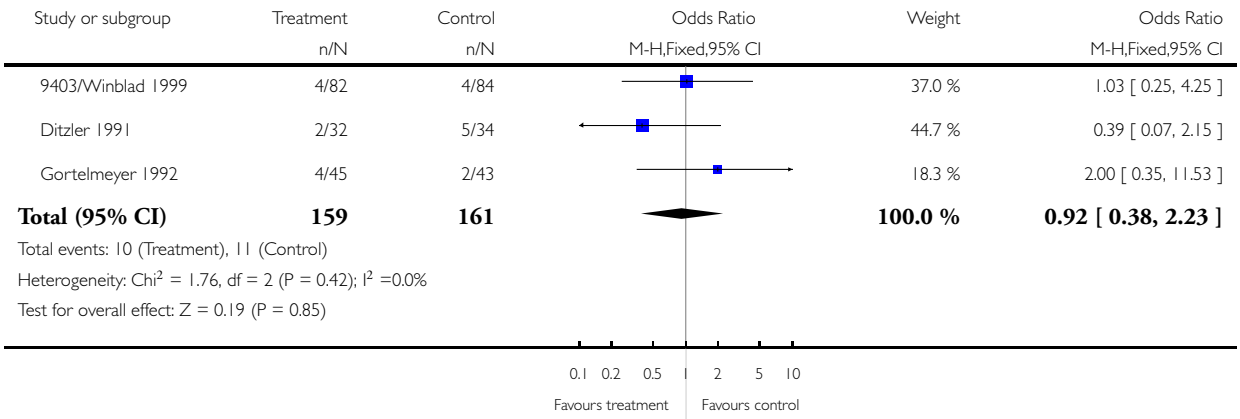


Analysis 7.5. Comparison 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies, Outcome 5 Number of drop-outs.

Review: Memantine for dementia

Comparison: 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies

Outcome: 5 Number of drop-outs

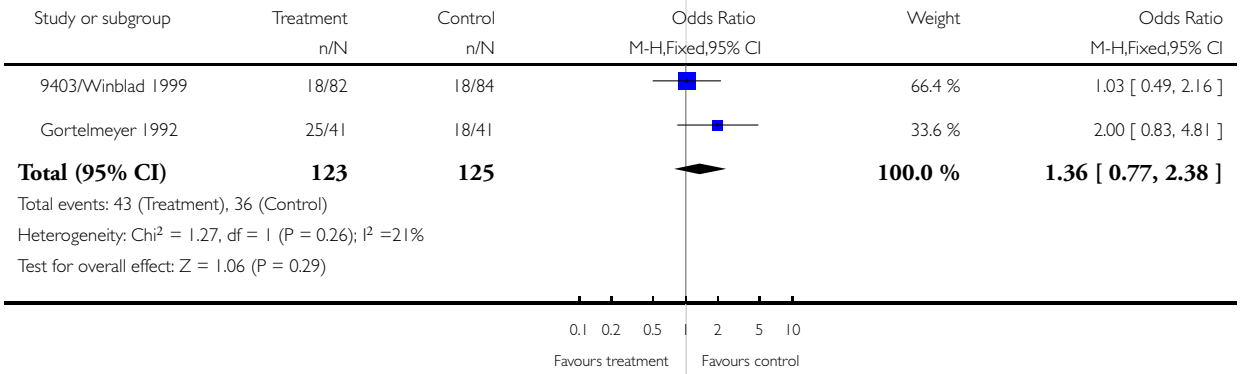


Analysis 7.6. Comparison 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies, Outcome 6 Number suffering at least one adverse event.

Review: Memantine for dementia

Comparison: 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies

Outcome: 6 Number suffering at least one adverse event

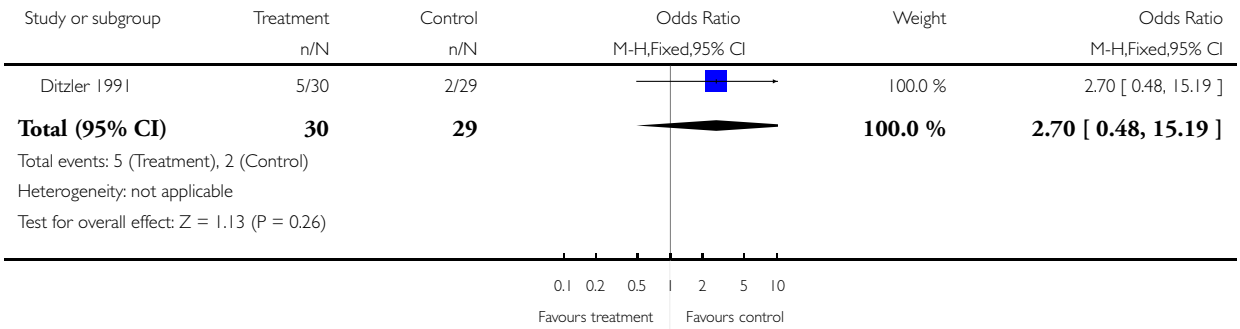


Analysis 7.7. Comparison 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies, Outcome 7 Number suffering agitation as an adverse event.

Review: Memantine for dementia

Comparison: 7 Memantine vs placebo for mild to severe dementia. All 4-12 week studies

Outcome: 7 Number suffering agitation as an adverse event



ADDITIONAL TABLES

Table 1. Baseline characteristics of participants in the included studies

Study	Number randomized	Diagnosis	Severity of disease	Mean age (s.e.)	Mean MMSE (s.e.)	Mean SCAG (s.e.)	Mean ADAS-Cog (s.e.)	% female	duration (weeks)
Ditzler 1991	66	AD (6%), VD (79%), MD (15%)	mild to moderate	72.2		63.3		65	6
Gortelmeyer 1992	88	AD (9%), VD (76%), MD (15%)	mild to moderate	71.5	24.1	64.2		68	6
9408/ Orgogozo 2002	321	VD	mild to moderate	76.4 (6.7)	16.9 (2.5)		21.0 (9.1)	47	28
Pantev 1993	60	all dementias	mild to moderately severe	72.4 (5.7)		85.3 (3.8)		75	4
9605/Reisberg 2003	252	AD	moderately severe to severe	76.1(8.07)	7,9 (3,64)			67	28

Table 1. Baseline characteristics of participants in the included studies (*Continued*)

9202/ Wilcock 2002	579	VD	mild to moderate	77	17.6 (3.25)			48	28
Winblad 1999	167	AD (48%) , VD + MD (52%)	severe	71.6 (5.6)	6.3 (2.7)			58	12
MD-02/ Tariot 2004	404	AD	moderate to severe	75.5	9,9 (3,13)			64,8	24
MD-10/ Peskind 2004	403	AD	mild to moderate	77.5 (7.8)	17.1 (3.6)		27.3 (10.6)	58.8	24
MD-01	350	AD	moderate to severe	78.2 (7.9)				71.4	24
MD-12	432	AD	mild to moderate						24
99679	470	AD	mild to moderate						26
MRZ-9104	56	AD							13
MRZ-9105	27	primary dementia	mild to severe						12
MRZ-9206	56	VD	moderate to severe	77.5 (7.8)	M: 17.2 (3.4) , P: 17.4 (3.7)		M: 27.3 (9.7) P: 27.2 (11)	58.8	14

Table 2. Outcome measures

Study	ADAS-Cog	SIB	ADCS-ADL	ADL	BGP	CIBIC-Plus	CGIC	NPI	Other
9202/ Wilcock 2002	X						X		NOSGER

Table 2. Outcome measures (*Continued*)

9408/ Orgogozo 2000	X					X	X		GBS, MMSE, NOSGER
9403/ Winblad 1999					X		X		
9605/Reisberg 2003		X	X			X		X	FAST, SIB
Ditzler 1991				X					Physician's Global Impression, Syndrom Kurztest, SCAG
Gortelmeyer 1992				X					CGI, GBS, Tapping test, Trace test, SCAG
99679 (Lundbeck)									
MD-01		X	X		X	X		X	FAST, SIB
MD-02/ Tariot 2004		X	X		X	X		X	SIB
MD-10/ Peskind 2004	X		X			X		X	
MD-12									
MRZ-9104									
MRZ-9105									
MRZ-9206									
Pantev 1993					X				Global assessment of clinical efficacy, NOSIE-Index, Physician's global rating of tolerability, SCAG

WHAT'S NEW

Last assessed as up-to-date: 21 February 2006.

Date	Event	Description
4 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2001

Review first published: Issue 1, 2003

Date	Event	Description
22 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

-AAS: drafting of earlier review versions, search for trials, obtaining copies of trial reports, selection of trials for inclusion/exclusion; extraction of data, entry of data, interpretation of data analysis

-RM: drafting of review version, identification of trials, obtaining copies of trial reports, extraction of data, entry of data, data analysis, interpretation

-NM: search for trials, extracted data, data entry, data analysis

-Jacqueline Birks assisted in the selection of trials for inclusion and exclusion and checked the analyses

-Dymphna Hermans : performed the searches

-Contact editor: Lon Schneider

-Consumer editor: Corinne Cavender

The first version of this review was peer reviewed anonymously

The April 05 update of this review was peer reviewed

DECLARATIONS OF INTEREST

There is no known conflict of interest. RM 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.

SOURCES OF SUPPORT

Internal sources

- Cochrane Dementia & Cognitive Improvement Group, UK.

External sources

- Alzheimer's Society, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Activities of Daily Living; Alzheimer Disease [drug therapy]; Cognition Disorders [drug therapy]; Dementia [*drug therapy]; Dementia, Vascular [drug therapy]; Excitatory Amino Acid Antagonists [*therapeutic use]; Memantine [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Aged; Aged, 80 and over; Humans