

Memantine in Moderate to Severe Alzheimer's Disease: a Meta-Analysis of Randomised Clinical Trials

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Key Words

Memantine · Alzheimer's disease, moderate to severe ·
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Abstract

The efficacy of memantine in Alzheimer's disease (AD) has been investigated in multiple randomised, placebo-controlled phase III trials. Recently, the indication label for memantine in Europe was extended to cover patients with moderate to severe AD, i.e. Mini-Mental State Exam total scores below 20. The efficacy data for memantine in this patient subgroup has been summarised by a meta-analysis of 1,826 patients in six trials. Efficacy was assessed using measures of global status (Clinician's Interview-Based Impression of Change Plus Caregiver Input), cognition (Alzheimer's Disease Assessment Scale – Cognitive Subscale, or Severe Impairment Battery), function (Alzheimer's Disease Cooperative Study Activities of Daily Living 19- or 23-item scale), and behaviour (Neuropsychiatric Inventory). Results (without replacement of missing values) showed statistically significant effects for memantine (vs. placebo) in each domain. Memantine was well tolerated, and the overall incidence rates of adverse events were comparable to placebo. This meta-analysis supports memantine's clinically relevant efficacy in patients with moderate to severe AD.

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that usually starts with memory loss and other cognitive deficits. At the time of clinical diagnosis, most patients are already in the moderate to severe stages of AD. Although there is no specific consensus definition of moderate to severe AD [1], patients with Mini-Mental State Exam (MMSE) scores between 10 and 20 are usually considered as having moderate AD and in a recent paper [2] MMSE scores were shown to be a useful surrogate for the staging of dementia.

The moderate stage of AD is characterised by a rapid decline of cognitive function and the occurrence of neuropsychiatric (behavioural) symptoms. In the severe stages of disease, patients develop major cognitive, functional, and behavioural difficulties that eventually result in complete dependence on carer support. Therefore, improvements or stabilisation in cognitive performance, daily function and/or behavioural symptoms have the potential to raise and extend the independence levels of the person with AD and, through this, the quality of life for both patient and carer.

Memantine is a moderate-affinity, uncompetitive, voltage-dependent NMDA receptor antagonist with fast on-off kinetics [3]. Clinical studies have demonstrated that memantine can produce significant improvement

Table 1. Overview of the design of six phase III clinical studies of memantine in AD

Study No.	MMSE inclusion range (mean) ¹	Duration/design ²	Treated patients, n	Key efficacy parameters
MEM-MD-10	10–22 (17.3)	24 weeks	403 PBO: 202 MEM: 201	ADAS-Cog CIBIC-Plus ADCS-ADL ₂₃ NPI
MEM-MD-12	10–22 (16.9)	24 weeks in patients already receiving donepezil, rivastigmine, or galantamine	433 PBO: 216 MEM: 217	ADAS-Cog CIBIC-Plus ADCS-ADL ₂₃ NPI
LU-99679	11–23 (18.7)	24 weeks	470 PBO: 152 MEM: 318	ADAS-Cog CIBIC-Plus ADCS-ADL ₂₃ NPI
MEM-MD-01	5–14 (10.1)	24 weeks	350 PBO: 172 MEM: 178	SIB CIBIC-Plus ADCS-ADL ₁₉ NPI
MEM-MD-02	5–14 (10.0)	24 weeks in patients already receiving donepezil	403 PBO: 201 MEM: 203	SIB CIBIC-Plus ADCS-ADL ₁₉ NPI
MRZ-9605	3–14 (7.7)	28 weeks	252 PBO: 126 MEM: 126	SIB CIBIC-Plus ADCS-ADL ₁₉ NPI

PBO = Placebo; MEM = memantine.

¹ Evaluable for safety (EFS) population.

² All studies were double-blind and placebo-controlled.

over placebo in clinical global measures, as well as in specific tests of cognition, function, and behaviour [4–8].

Memantine was registered in Europe in 2002 with the indication of moderately severe to severe AD and was first marketed in the USA in 2003. The indication of memantine in Europe has recently been extended to cover the moderate to severe AD patient population, i.e. patients with an MMSE total score of less than 20. The present meta-analysis was conducted during the European regulatory review process in order to investigate the clinical effects of memantine in this specific patient population.

Methods

Study Design

A post-hoc meta-analysis was performed on the results from six large-scale studies of memantine. The individual studies selected for analysis had to fulfil the following criteria: they had

to be phase III trials, to include patients with a diagnosis of AD, and to have a double-blind observation period of at least 24 weeks. The studies shared similar endpoints, and all six studies were placebo-controlled, randomised, double-blind, multicentre, parallel-group trials with a 6-month treatment period, including a 4-week titration phase (table 1). Memantine patients received a fixed dose of 20 mg/day during the maintenance phase, with four studies testing memantine treatment as monotherapy versus placebo, and two studies administering memantine or placebo to patients stabilised on acetylcholinesterase inhibitor treatment (table 1).

Patients entering the studies were outpatients with a diagnosis of probable AD, and were aged ≥ 50 years. Three of the studies included patients with mild to moderate AD, and three studies assessed patients with moderate to severe AD (table 1). Further details of individual study design and entrance criteria have been presented previously [4, 5, 9–11].

Efficacy Analysis

A meta-analysis of the efficacy parameters was conducted in the subgroup of patients with moderate to severe AD. Following

discussion with European regulators, this subgroup was defined as patients with an MMSE score at baseline/screening of <20.

Efficacy was analysed in the intent-to-treat population, defined as all patients with at least one post-baseline efficacy assessment. Missing observations were not replaced [observed-cases (OC) approach]. In addition, a sensitivity analysis using the last-observation-carried-forward (LOCF) approach was conducted. Summary statistics were calculated for each individual study at week 24/28. These summary statistics included the arithmetic mean change from baseline at week 24/28, the standard deviation of the mean change from baseline, and the number of patients in each treatment group for the domains cognition, function, and behaviour. For the global domain, the actual arithmetic mean values and corresponding standard deviation were used.

As the meta-analyses required the combination of different rating scales within the same domain across the selected trials [for cognition the Severe Impairment Battery (SIB) and Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog) had been used], the treatment effect for each outcome was presented by standardized mean differences (SMD), i.e. the absolute mean differences divided by the standard deviation (SD).

Overall estimates of the SMD and corresponding confidence intervals were based upon a fixed-effect model using RevMan 4.2 software. Statistical testing for heterogeneity was done by standard χ^2 statistic; p values of 0.10 or less were considered as a criterion for potential heterogeneity.

The following domains of efficacy were analysed (table 1):

Global status: Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus). This is a 7-point scale evaluating a patient's clinical change through patient interviews by an independent clinician including caregiver input (ratings range from 1 = very much improved to 7 = very much worse, with 4 = no change) [12, 13].

Cognition: ADAS-Cog or the SIB. ADAS-Cog is the standard instrument for assessing cognition in studies of patients with mild to moderate AD, and includes 11 subdomains with total scores ranging from 0 to 70, in which a decreasing score signifies an improvement [14]. The SIB is a 40-item scale with a range of total scores from 0 (worst result) to 100 (best result) [15, 16] and has become standard for assessing cognition in studies of patients with moderately severe to severe AD.

Function: Alzheimer's Disease Cooperative Study Activities of Daily Living 19- or 23-item scale (ADCS-ADL_{19/23}). This scale is based on interviews with carers or others close to the patient to assess how the patient copes with activities of daily living. The 19-item subset is used for patients with moderate to severe AD, and the 23-item subset is used for patients with mild to moderate AD [17, 18].

Behaviour: Neuropsychiatric Inventory (NPI). The instrument is based upon a carer interview and quantifies patient behaviour on 12 subscales (e.g., agitation/aggression, delusions, hallucinations) by multiplying severity by frequency ratings. The total score is obtained through summation of domain subscores, and decreasing scores indicate improvement [19].

Safety Analysis

Safety data were analysed in the evaluable-for-safety population, defined as all randomised patients receiving at least one dose of study medication. Meta-analyses were conducted for the subgroups of patients with MMSE total scores <20 for the following

Table 2. Baseline patient demographics and characteristics (MMSE <20, intent-to-treat population)

Characteristic	Memantine (n = 959)	Placebo (n = 867)
Age, years	76.2 ± 8.1	76.2 ± 8.3
Female	644 (67%)	550 (63%)
Caucasian	865 (90%)	788 (91%)
Height, cm	163 ± 10.4	163 ± 10.5
Weight, kg	67.0 ± 13.9	67.9 ± 14.2
MMSE score	12.3 ± 4.2	12.2 ± 4.1

Mean ± SD are given except for the characteristics 'female' and 'Caucasian'.

binary outcomes: premature discontinuation (drop-out) for any reason, and drop-out due to adverse events (AEs). Odds ratios (OR) were calculated for these outcomes using a fixed-effect model.

In addition, the safety section of this paper presents data from the memantine safety and tolerability database on which the revised European memantine SPC is based. This database includes a larger population than that of the present meta-analysis and combines safety data from phase III studies of memantine in patients with mild to severe dementia (including both AD and vascular dementia), as well as a review of post-marketing experience. Incidences of treatment-emergent adverse events were calculated for the evaluable-for-safety population of this larger safety data base.

Results

Study Population

In total, 1,826 patients (959 on memantine; 867 on placebo) were part of the moderate to severe AD subgroup (MMSE <20). The mean patient age was 76 years, and there were no clinically relevant differences between treatment groups in terms of baseline demographic characteristics (table 2).

Efficacy

In the following, results of the observed cases analysis are presented. There was a statistically significant effect in favour of memantine treatment in all four key efficacy domains – global status, cognition, function, and behaviour.

Overall standardised effect sizes versus placebo were: 0.22 (p < 0.001) for the global domain; 0.26 (p < 0.001) for the cognitive domain, 0.18 (p < 0.001) for the functional domain, and 0.12 (p = 0.03) for the behavioural domain. Efficacy results for each study as well as the combined

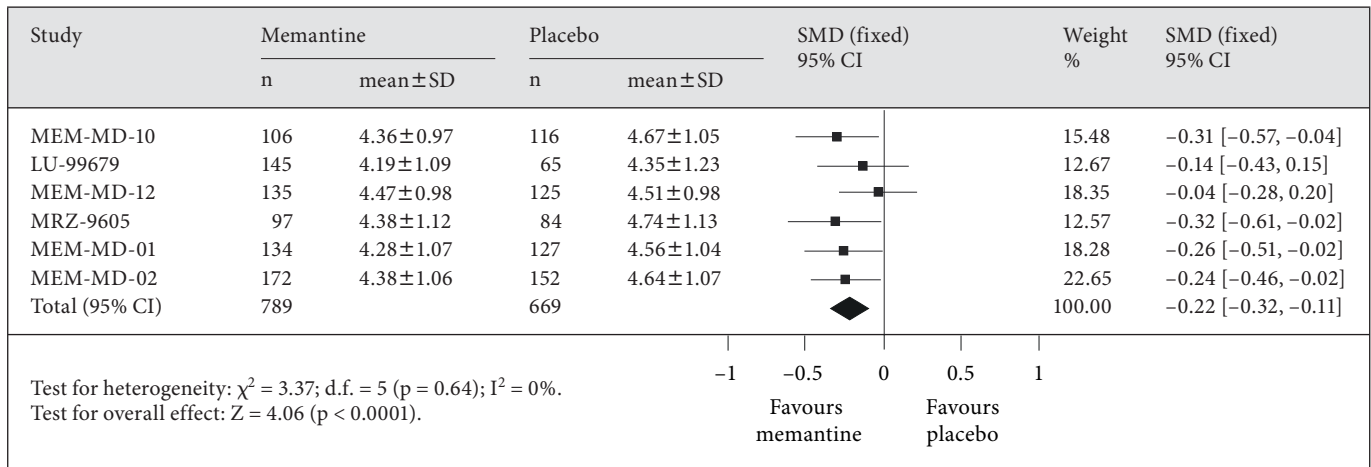


Fig. 1. Efficacy: global domain. Mean values larger than 4 indicate worsening.

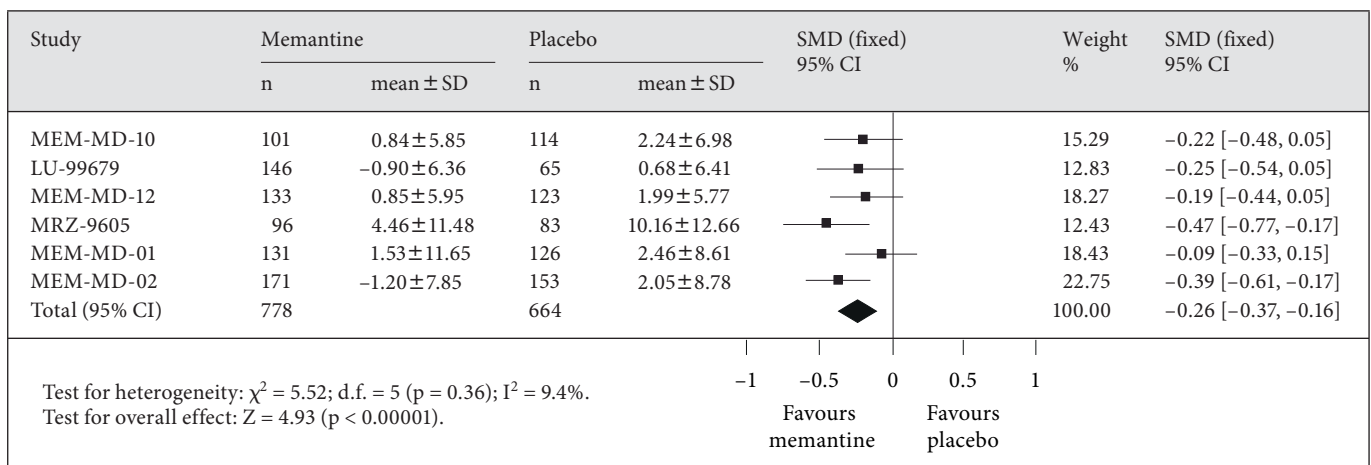


Fig. 2. Efficacy: cognitive domain. Positive mean values indicate worsening for the ADAS-Cog and for the SIB.

meta-analyses are shown in figures 1–4. The LOCF analysis resulted in similar overall effect sizes.

There was no sign of heterogeneity in all OC and LOCF analyses, except for the behavioural domain (in the LOCF analysis only).

Safety and Tolerability

More memantine-treated patients than placebo-treated patients completed the studies (82 vs. 77%). The overall rates of premature discontinuation for any reason (fig. 5) were 18% for the memantine patients and 23% for placebo, which resulted in an odds ratio of 0.73 for memantine. For discontinuations due to AEs (fig. 6), inci-

dences for memantine and placebo patients were very similar (odds ratio 0.80).

The larger safety population analysed for the revised European label included 3,379 patients (1,784 memantine; 1,595 placebo) with mild to severe dementia (AD and vascular dementia). Patients had a mean exposure to memantine of 154 days. The overall incidence of treatment-emergent adverse events with memantine did not differ from that of placebo (~70% in each group), and most AEs were mild to moderate in severity. The most frequently occurring AEs, with a higher incidence in the memantine group than in the placebo group, were dizziness (6.3 vs. 5.6% for memantine and placebo, respec-

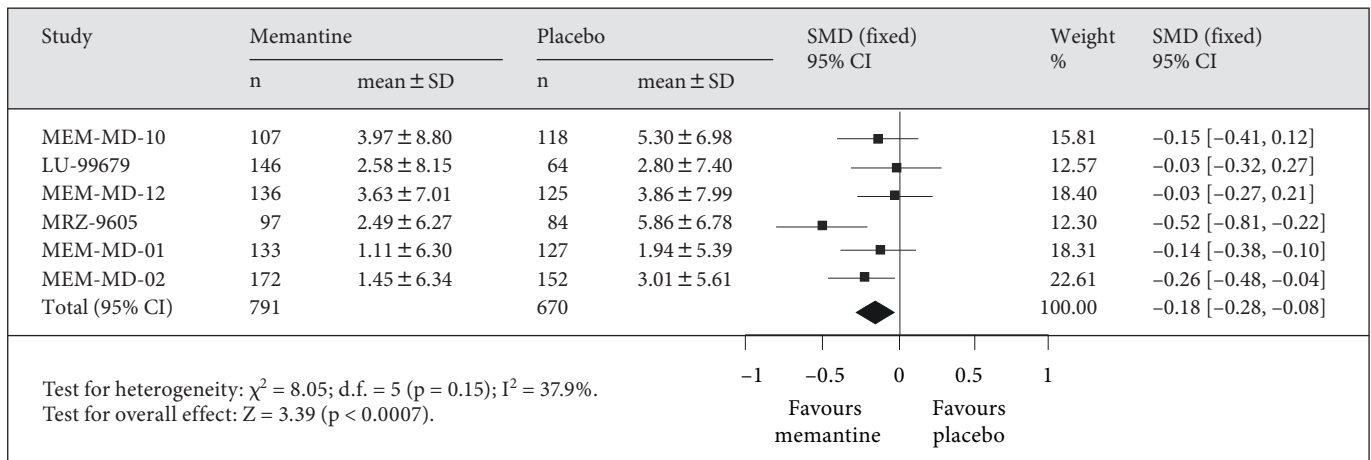


Fig. 3. Efficacy: functional domain. Positive mean values indicate worsening.

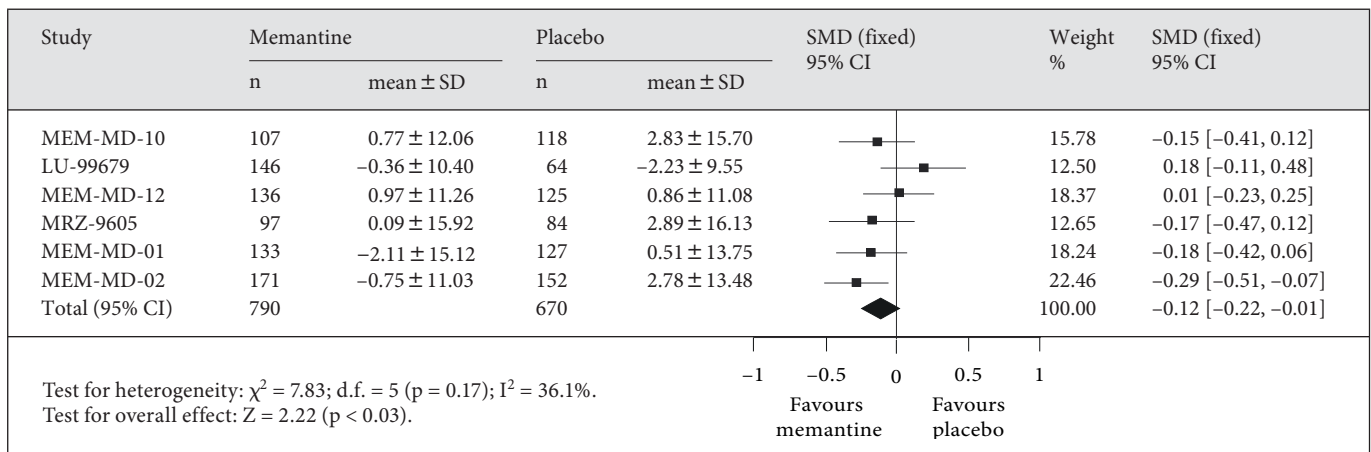


Fig. 4. Efficacy: behavioural domain. Positive mean values indicate worsening.

tively), headache (5.2 vs. 3.9%), constipation (4.6 vs. 2.6%) and somnolence (3.4 vs. 2.2%). The incidence of serious AEs was slightly lower in the memantine group, as compared with the placebo group (12.7 vs. 13.8%), and the majority of serious AEs were considered to be unrelated to the study medication.

Discussion

This meta-analysis comprised results of six individual phase III studies of memantine, using a subgroup of patients with moderate to severe AD. Memantine treatment

resulted in a statistically significant benefit in four efficacy domains: the cognitive, functional, global, and behavioural endpoint. These data were the basis for the extension of the memantine indication to comprise moderate and severe AD in Europe.

The six studies in this meta-analysis had a similar design, and all were phase III, placebo-controlled, double-blind, and parallel-group trials, with a double-blind treatment period of 6 months. Patients in the studies were randomly assigned to either placebo or active treatment and in the selected subgroup of patients with MMSE total scores below 20, treatment arms were equally balanced with regard to age, gender, etc., although the ran-

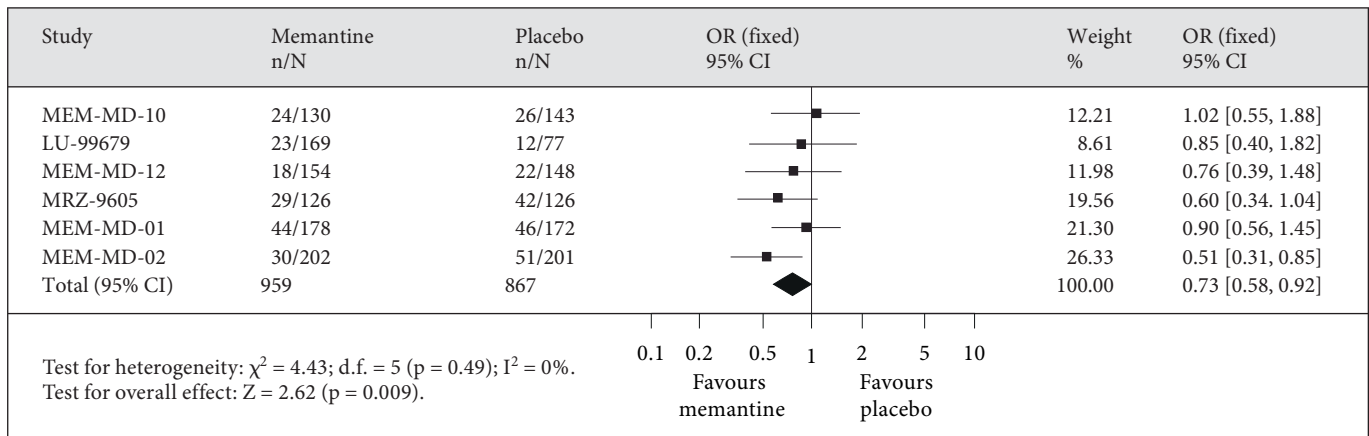


Fig. 5. Overall rates of premature discontinuation for any reason. Favouring memantine indicates lower rates of discontinuation in the memantine treatment arms than for placebo.

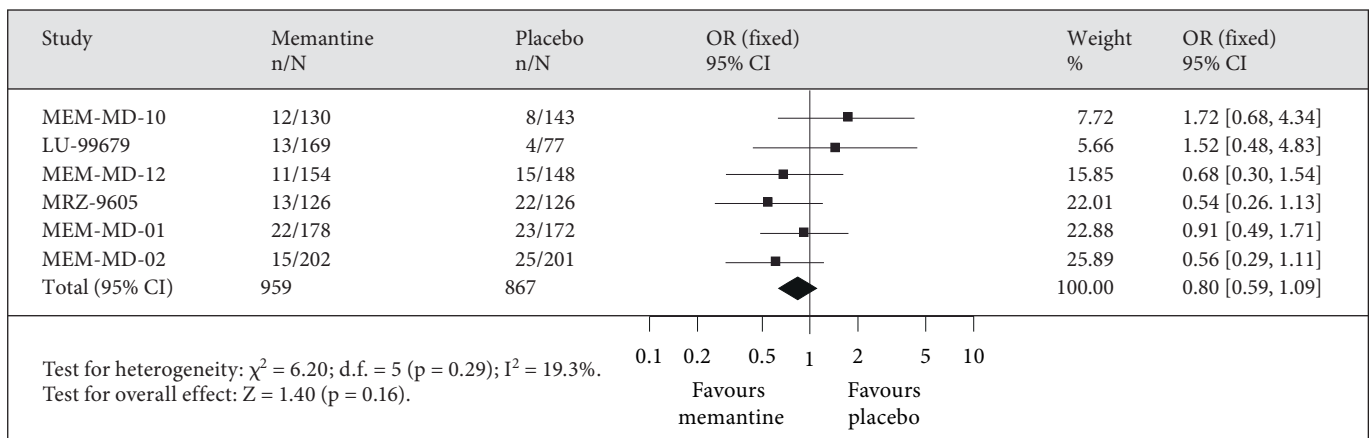


Fig. 6. Discontinuations due to AEs. Favouring memantine indicates lower rates of discontinuation in the memantine treatment arms than for placebo.

domisation did not extend to this post-hoc selected subgroup.

The standardised effect size of memantine on the cognitive domain in the present analysis (0.26, OC) was comparable to the 0.2–0.4 range seen for other anti-dementia treatments [20–22]. The effect size of memantine on the global domain (0.22), as assessed by the CIBIC-Plus instrument (by itself a measure of clinical relevance), supported the clinical importance of this cognitive benefit.

The meta-analysis also highlighted a significant improvement in function (i.e. activities of daily living) with memantine versus placebo. While this overall result was significant and individual study results were homoge-

neous, there was a slightly higher effect size for the studies that included severe AD patients than for those in mild to moderate AD. This may be because the ADCS-ADL₁₉ scale (assessing mainly basic functions) is more sensitive to change than the 23-item version used in the mild to moderate AD studies.

In terms of behaviour, memantine significantly improved the NPI total score, although interpretation of this result is limited by the heterogeneity of the results (not in the OC but in the LOCF analysis). From a clinical point of view, the NPI total score is not necessarily the only useful parameter for the assessment of behavioural effect as it combines a set of 12 different symp-

toms and changes in the various domains do not always follow the same direction. For this reason, analyses of individual domain (or symptom) scores and clusters of individual symptoms receive more and more attention [23, 24]. Pooled analyses of memantine studies have examined NPI symptoms individually and provide additional information on behavioural effects. In these single-domain analyses, memantine treatment demonstrated consistent benefit across several behavioural domains, and most notably induced a significant reduction versus placebo in the symptoms of agitation and/or aggression [6, 8].

Furthermore, the odds ratios for all premature discontinuations as well as for discontinuations due to AEs slightly favoured memantine treatment over placebo, suggesting excellent tolerability of memantine.

So far, there are two published meta-analyses of memantine trials. One is a poster by Doody et al. [25] that comprised the entire population of this set of six trials and had similar results overall (with slightly smaller effect sizes than those in the present analysis). Our analysis specifically targeted the population that was the basis for

the European label of moderate to severe AD and the results were in line with those of Doody et al. [25].

The second is the *Cochrane Review* [26] that, in addition, included vascular dementia trials, as well as older trials of shorter duration. In this review, two separate meta-analyses were conducted for the three trials in moderate to severe and for those in mild to moderate AD. The authors conclude that in mild to moderate AD the cognitive benefit was still 'clinically discernible' (as reflected in the global ratings of change) but less pronounced than in the moderate to severe studies.

In summary, the results of this meta-analysis present additional support for the clinically meaningful benefit of memantine for patients with moderate to severe AD. These effects may translate into a worthwhile influence on quality of life for both patients and carers.

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