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Improvement in behavioural symptoms in patients with moderate to severe Alzheimer's disease by memantine: a pooled data analysis

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SUMMARY

Introduction Behavioural disturbances are a common and distressing aspect of Alzheimer's disease (AD). This pooled analysis evaluated the specific benefits of memantine on behavioural disturbances in patients with moderate to severe AD.
Methods Data were pooled from six 24/28-week, randomised, placebo-controlled, double-blind studies. Of the 2,311 patients included in these studies, 1,826 patients with moderate to severe AD (MMSE <20) were included in this analysis, corresponding to the extended indication for memantine in Europe. In this subgroup, 959 patients received memantine 20 mg/day and 867 received placebo. Behavioural symptoms were rated using the Neuropsychiatric Inventory (NPI) total and single-item scores at weeks 12 and 24/28.
Results At weeks 12 and 24/28, ITT analysis demonstrated that memantine treatment produced statistically significant benefits over placebo treatment in NPI total score ($p = 0.001$ and $p = 0.008$), and in NPI single items: delusions ($p = 0.007$ week 12, $p = 0.001$ week 24/28), hallucinations ($p = 0.037$ week 12), agitation/aggression ($p = 0.001$ week 12, $p = 0.001$ week 24/28), and irritability/lability ($p = 0.005$ week 24/28), LOCF population. Analysis of the patients without symptoms at baseline indicated reduced emergence of agitation/aggression ($p = 0.002$), delusions ($p = 0.047$), and disinhibition ($p = 0.011$), at week 12, and of agitation/aggression ($p = 0.002$), irritability/lability ($p = 0.004$), and night-time behaviour ($p = 0.050$) at week 24/28 in those receiving memantine. OC analyses yielded similar results.
Conclusions The data suggest that memantine is effective in treating and preventing the behavioural symptoms of moderate to severe AD. Specific persistent benefits were observed on the symptoms of delusions and agitation/aggression, which are known to be associated with rapid disease progression, increased caregiver burden, early institutionalisation, and increased costs of care. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — memantine; behaviour; Alzheimer's disease; pooled data; agitation; Neuropsychiatric Inventory

INTRODUCTION

Behavioural symptoms are a distressing aspect of Alzheimer's disease (AD) for both patient and caregiver. Behavioural symptoms such as aggression, agitation and psychosis are common in the moderate to severe stages of the disease (Mega *et al*., 1996; Devanand *et al*., 1997; Senanarong *et al*., 2004), and represent an aspect of disease burden that is physically, emotionally, and economically challenging (Murman *et al*., 2002). Furthermore, these symptoms correlate with accelerated disease progression (Lopez *et al*., 1991; Holtzer *et al*., 2003), and early transfer to institutional care (Yaffe *et al*., 2002), independent of concomitant psychotropic drug usage (Holtzer *et al*., 2003).

Memantine is an uncompetitive NMDA receptor antagonist with moderate affinity and rapid voltage-dependent kinetics (Parsons *et al*., 1999). It is the only treatment in clinical use for AD that targets the

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glutamatergic system, which is implicated in the pathophysiology of neurodegenerative diseases, including AD. Memantine is the only drug approved in Europe for the treatment of patients with moderate to severe AD.

Memantine has been shown to be effective on cognitive, functional and behavioural outcomes and the drug is well tolerated and safe (Winblad and Poritis, 1999; Reisberg *et al*., 2003; Tariot *et al*., 2004; Peskind *et al*., 2006). Specific analyses of behavioural symptoms of AD indicate that memantine has a beneficial effect on agitation/aggression (Gauthier *et al*., 2005; Cummings *et al*., 2006), and further studies support a beneficial effect of memantine on behaviour (Peskind *et al.*, 2006).

The aim of this *post hoc* analysis was to further investigate the effect of memantine treatment on the behavioural symptoms of AD in a pooled sample of patients. The analysis is based on pooled data from six 24/28-week studies; three in patients with mild to moderate AD and three in patients with moderate to severe AD. In this *post hoc* analysis, patients with moderate to severe AD (MMSE <20) were included, corresponding to the approved indication for memantine in Europe. Memantine is also available for moderate to severe AD in the US.

METHODS

Study design

Data were pooled from six multicentre, randomised, placebo-controlled, parallel-group, double-blind studies of memantine 20 mg/day. Details of five of these studies have been published previously (Reisberg *et al*., 2003; Tariot *et al*., 2004; Peskind *et al*., 2006; Bakchine and Loft, 2007; van Dyck *et al*., 2007), and designs of all six studies are summarised in Table 1. This dataset was originally created for the regulatory submission to the European Authorities, which resulted in the expansion of memantine's indication to include moderate AD.

Study subjects were outpatients with mild to moderate AD (three studies) or moderate to severe AD (three studies), who were aged $\geq$50 years at baseline. All studies were 24 weeks in duration, except for the study published by Reisberg and colleagues in which the treatment duration was 28 weeks. Dosing of memantine was initiated at 5 mg/day and titrated up in weekly steps of 5 mg/day to 20 mg/day in all studies. The dosing regimen was b.i.d., except in one study where memantine was administered once-daily (MEM-MD-12; Porsteinsson *et al.*, in press). In studies MEM-MD-12 and MEM-MD-02, memantine or placebo treatment was added to existing stable treatment with an acetylcholinesterase inhibitor, AChEI (Tariot *et al*., 2004; Porsteinsson *et al.*, in press). Patients on concomitant AChEI treatment had to be treated for at least 6 months before starting the study, and to be on stable dosing for at least 3 months prior to, and throughout, the study. Concomitant psychotropic medications were allowed in all studies, except study MRZ-9605 (Reisberg *et al*., 2003; Tariot *et al*., 2004; Peskind *et al*., 2006; Porsteinsson *et al*., in press; H. Lundbeck A/S, Data on file). Randomisation was preserved, and patients were equally assigned with the exception of Study 99679 in which the randomisation scheme used a 2:1 ratio to allocate more patients to memantine than placebo.

Behavioural outcome measure – Neuropsychiatric Inventory

The Neuropsychiatric Inventory (NPI) is a 12-item scale that assesses a range of different behavioural

Table 1. Summary of six memantine (20 mg/day) studies in patients with Alzheimer's disease

Study/setting	MMSE inclusion range (mean)	Duration/design*	Number of patients included
Studies in mild to moderate AD			
MEM-MD-10 Peskind *et al*. (2006) US	10–22 (17.3)	24 weeks	403
MEM-MD-12 Porsteinsson *et al*. (in press) US	10–22 (16.9)	24 weeks, in patients on stable dose of donepezil, rivastigmine, or galantamine	433
99679 Bakchine and Loft 2007 Europe	11–23 (18.7)	24 weeks	470
Studies in moderate to severe AD			
MRZ-9605 Reisberg *et al*. (2003) US	3–14 (7.9)	28 weeks	252
MEM-MD-01 van Dyck *et al*. (2007) US	5–14 (10.1)	24 weeks	350
MEM-MD-02 Tariot *et al*. (2004) US	5–14 (10.0)	24 weeks, in patients on stable dose of donepezil	403

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

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symptoms (Cummings *et al*., 1994; Cummings, 1997). The NPI has demonstrated reliability, sensitivity and validity for assessing behavioural change in patients with AD. The assessment is based on caregiver interviews relating to 12 behavioural items, and the NPI total score (0–144) is the sum of these single items. A decreasing total score indicates an improvement in psychopathology.

The NPI was used as a measure of behavioural symptoms in all six memantine studies analysed here, which allowed pooling of the data. The NPI assessments were done at baseline and at week 12 and week 24/28.

In addition, the impact of treatment relative to the presence or absence of symptoms (NPI single items) at baseline was also assessed. For the purposes of this evaluation, the following definitions were employed:

- symptom improvement: lower NPI single-item score at study endpoint than at baseline, and therefore only assessed in patients who displayed the symptom at baseline (NPI single-item score >0).
- symptom emergence: appearance of a new symptom (NPI single-item post-baseline score >0), and therefore only assessed in patients who did not have this symptom at baseline (NPI single-item baseline score $= 0$).

Statistical methods

Post hoc efficacy analyses were conducted on the full analysis set (FAS), which included the intent-to-treat (ITT) populations of each individual study (patients who received at least one dose of memantine and had at least one post-baseline efficacy assessment on the primary efficacy scales). In order to reflect the population for which memantine is an approved treatment in Europe and the US, patients with an MMSE score ≥ 20 were excluded. Analyses based on the NPI total score were performed on change from baseline using analysis of covariance (ANCOVA) adjusted for centre and baseline.

Because NPI single-item scores can attain only a limited number of values with no intermediate values, normal distribution of the data cannot always be assumed. Therefore, analyses of the single-item scores were performed using the nonparametric Kruskall–Wallis test for mean change from baseline. Proportions of patients with 'symptom improvement' and 'symptom emergence' were compared using a χ^2 test, and were restricted to the subgroups of patients indicated above in the definitions of these two criteria.

All analyses presented in this paper were *post hoc* analyses without a pre-specified primary analysis and no adjustment for multiplicity was performed.

The data presented came from H. Lundbeck A/S. The authors had free and open access to the data, and were free to request/perform analyses as they saw fit for the purpose of this communication.

RESULTS

Patient demographics and baseline characteristics

The pooled study population included a total of 2,311 patients (1,242 patients treated with memantine and 1,069 patients treated with placebo). Of these, 1,826 patients had baseline MMSE scores <20 (959 treated with memantine and 867 treated with placebo), and 1,788 patients (938 treated with memantine and 850 treated with placebo) were included in the FAS for these analyses.

The mean baseline severity of disease (MMSE score) for each study is shown in Table 1. Within each study, the two treatment groups were well matched in terms of baseline parameters.

The baseline demographics and clinical characteristics of the study population, i.e., those patients with MMSE <20 at baseline, are shown in Table 2. Within the study population, the two treatment groups were well matched in terms of baseline parameters.

In this population of patients with moderate to severe AD (MMSE <20), the most frequent behavioural symptoms at baseline were agitation/aggression, depression, anxiety, apathy/indifference, irritability/lability, and aberrant motor behaviour—each present in $>30\%$ of patients in memantine and placebo groups (Table 2).

NPI scores

NPI total scores. Memantine-treated patients showed statistically significantly better NPI total scores than placebo-treated patients at week 12 and week 24/28 (FAS: $p = 0.001$, LOCF; $p = 0.008$, LOCF) (Figure 1).

NPI single-item scores. Memantine-treated patients showed statistically significantly superior treatment effects compared with placebo-treated patients in NPI single items at week 12 (delusions, $p = 0.007$; hallucinations, $p = 0.037$; and agitation/aggression, $p = 0.001$) (Figure 2), and at week 24/28 (delusions, $p = 0.001$; agitation/aggression, $p = 0.001$; and irritability/lability, $p = 0.005$ (Figure 3). The OC findings were comparable to the LOCF analyses.

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Table 2. Baseline demographics and clinical characteristics of the study population (MMSE <20)

Characteristic	Study population (MMSE <20)		
	Placebo ($n = 867$)	Memantine ($n = 959$)	Total ($n = 1,826$)
Gender female, *n* (%)	550 (63.4)	644 (67.2)	1,194 (65.4)
Age, mean (SD), years	76.2 (8.3)	76.2 (8.1)	76.2 (8.2)
Caucasian race, *n* (%)	788 (90.9)	865 (90.2)	1,653 (90.5)
ADAS-Cog, mean (SD)	30.3 (9.7) (n = 367)	31.6 (10.2) (n = 450)	31.0 (10.0) (n = 817)
CIBIC severity, mean (SD)	4.3 (0.8) (n = 741)	4.4 (0.8) (n = 833)	4.4 (0.8) (n = 1,574)
SIB score, mean (SD)	75.4 (18.5) (n = 499)	74.3 (18.8) (n = 505)	74.8 (18.7) (n = 1,004)
ADCS-ADL$_{23}$, mean (SD)	52.7 (13.2) (n = 368)	51.3 (14.7) (n = 453)	51.9 (14.1) (n = 821)
ADCS-ADL$_{19}$, mean (SD)	33.1 (10.7) (n = 499)	32.5 (10.8) (n = 506)	32.8 (10.7) (n = 1,005)
MMSE score, mean (SD)	12.2 (4.1)	12.3 (4.2)	12.2 (4.2)
NPI total, mean (SD)	15.4 (14.6)	15.9 (14.7)	15.6 (14.6)
NPI single items score for those patients who were symptomatic for the item			
Delusions (PBO $n = 244$; MEM $n = 290$)	3.83 (2.75)	3.91 (2.90)	3.88 (2.83)
Hallucinations (PBO $n = 116$; MEM $n = 138$)	3.34 (2.39)	3.36 (2.73)	3.35 (2.57)
Agitation/aggression (PBO $n = 369$; MEM $n = 397$)	3.51 (2.69)	3.36 (2.45)	3.43 (2.57)
Depression (PBO $n = 382$; MEM $n = 419$)	2.67 (2.17)	3.01 (2.31)	2.85 (2.25)
Anxiety (PBO $n = 331$; MEM $n = 383$)	3.65 (2.60)	3.77 (2.67)	3.71 (2.64)
Elation/euphoria (PBO $n = 65$; MEM $n = 83$)	2.68 (2.08)	3.63 (2.37)	3.21 (2.29)
Apathy/indifference (PBO $n = 476$; MEM $n = 546$)	5.30 (2.95)	5.59 (2.98)	5.45 (2.97)
Disinhibition (PBO $n = 174$; MEM $n = 191$)	2.84 (2.39)	3.57 (2.92)	3.22 (2.70)
Irritability/lability (PBO n = 296; MEM n = 343)	3.75 (2.82)	3.72 (2.82)	3.73 (2.82)
Aberrant motor behaviour (PBO $n = 362$; MEM $n = 366$)	5.00 (3.03)	4.94 (2.96)	4.97 (2.99)
Night-time behaviour (PBO $n = 190$; MEM $n = 229$)	5.11 (3.10)	4.62 (3.13)	4.84 (3.12)
Appetite/eating change (PBO $n = 255$; MEM $n = 280$)	5.47 (2.93)	5.12 (2.92)	5.29 (2.93)
Receiving concomitant medications, *n* (%)			
Antidepressants	13 (1.5)	32 (3.3)	45 (2.5)
Antipsychotics	2 (0.2)	10 (1.0)	12 (0.7)
Anxiolytics/hypnotics	1 (0.1)	11 (1.1)	12 (0.7)

PBO = Placebo; MEM = memantine.

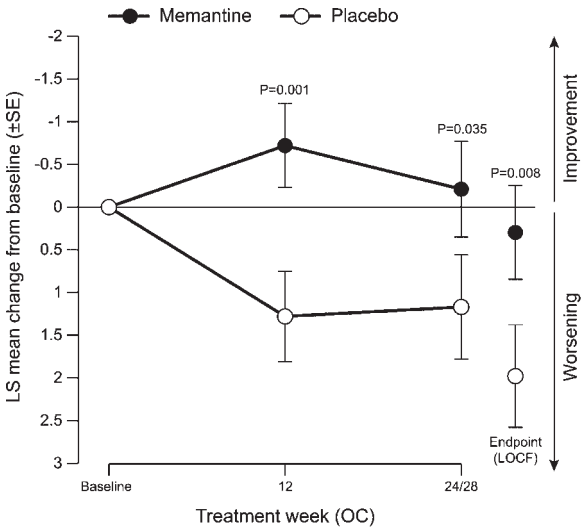

Figure 1. Neuropsychiatric inventory (NPI) – total score (FAS, OC/LOCF).

Analysis of symptom improvement

In the subset of patients who were symptomatic for the NPI items at baseline, a higher proportion of memantine-treated patients experienced improvement than those receiving placebo for 8 out of 12 individual items. No item was statistically significantly worse on memantine than on placebo. Statistically significantly more memantine-treated patients than placebo-treated patients showed symptom improvement at week 24/28 in the items of delusions ($p = 0.045$), agitation/aggression ($p = 0.028$), and disinhibition ($p = 0.048$) (Figure 4). In the OC analysis, the items of agitation/aggression, and disinhibition were significantly in favour of memantine treatment. Furthermore, at week 12, 68% of patients treated with memantine, versus 49% of patients treated with placebo, showed improvement in the NPI item hallucinations ($p = 0.003$, LOCF).

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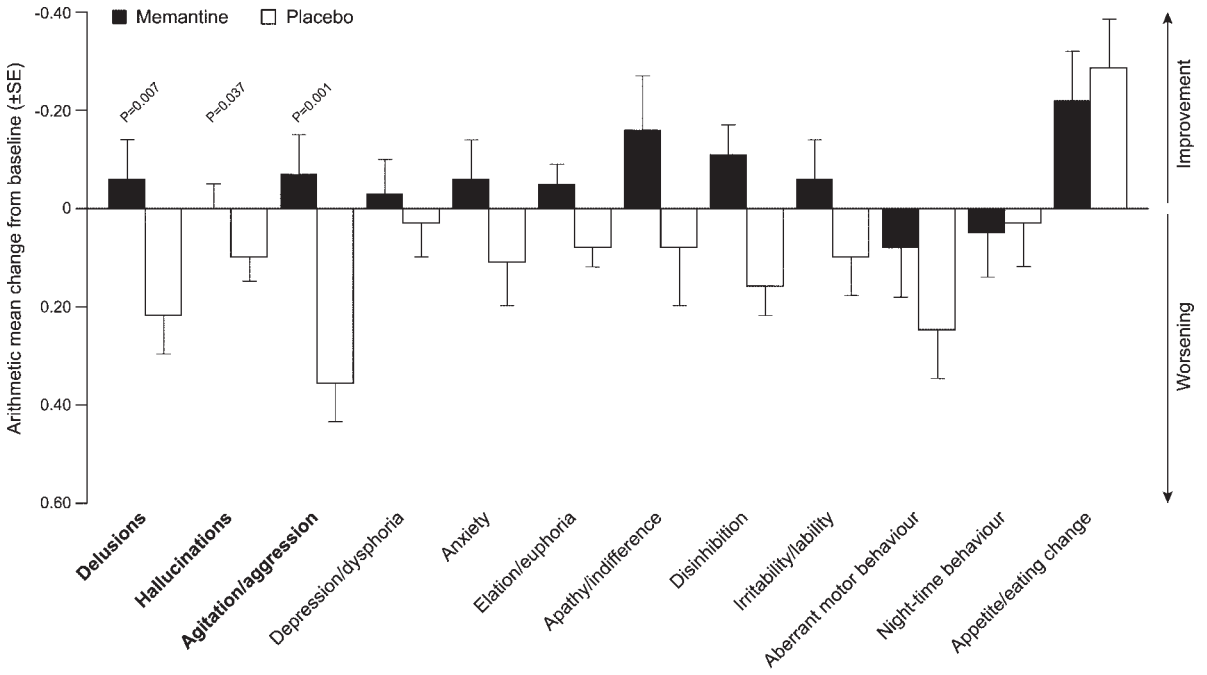

Figure 2. NPI single items at week 12 (FAS, LOCF).

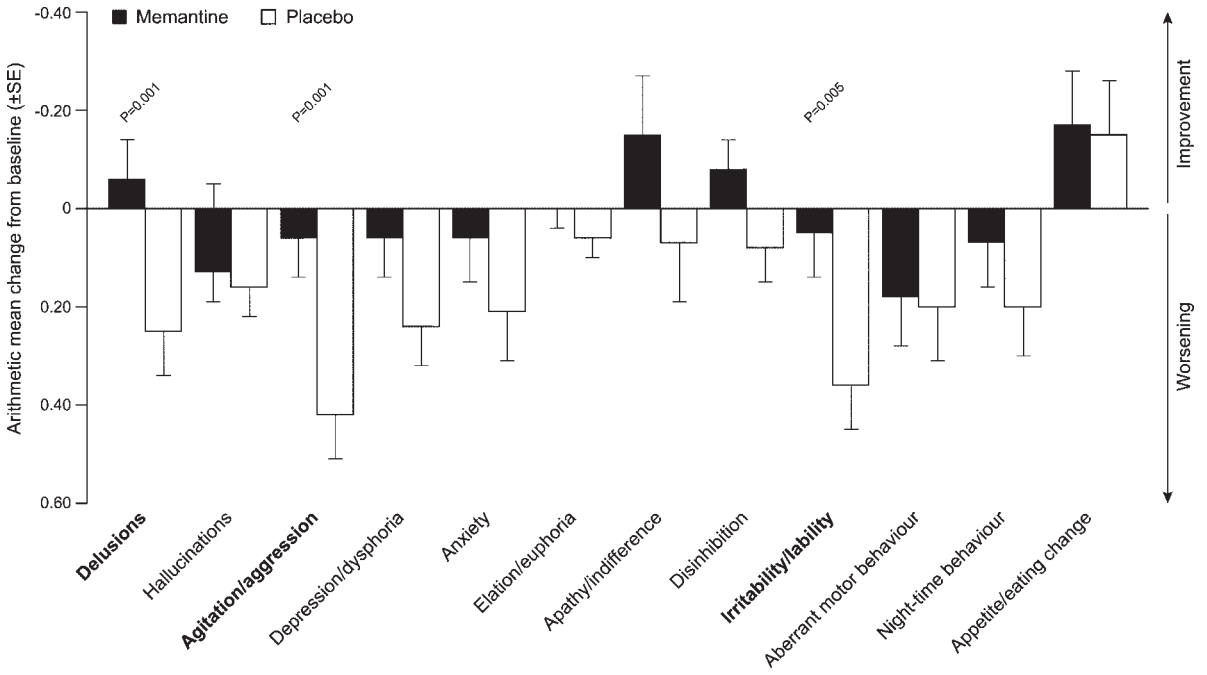

Figure 3. NPI single items at week 24/28 (FAS, LOCF).

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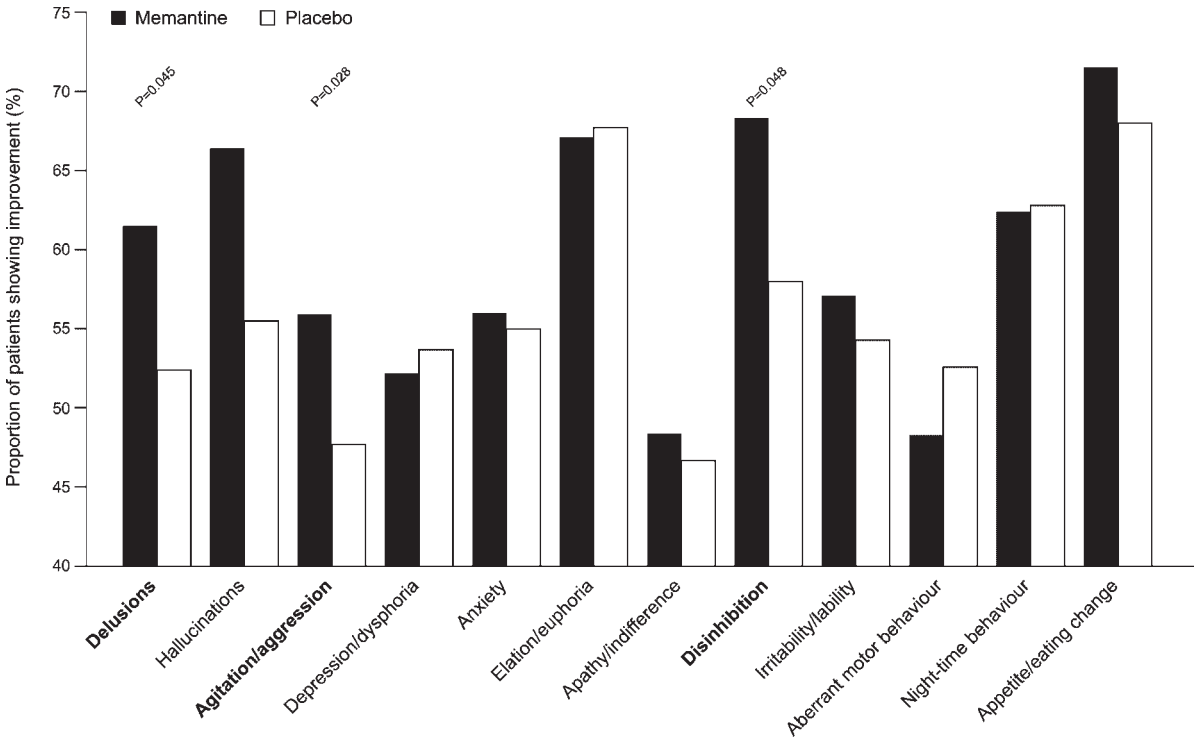

Figure 4. Improvements in single NPI items in subgroup of patients with baseline symptoms (week 24/28; LOCF).

Analysis of symptom emergence

In the subset of patients who were asymptomatic for the individual NPI items at baseline, statistically significantly more memantine-treated patients than placebo-treated patients remained asymptomatic at week 12 in the items agitation/aggression (86% *vs* 79%; $p = 0.002$, LOCF), delusions (90% *vs* 87%; $p = 0.047$, LOCF), and disinhibition (92% *vs* 88%; $p = 0.011$, LOCF). At week 24/28, statistically significantly more memantine-treated patients than placebo-treated patients remained asymptomatic in the items agitation/aggression ($p = 0.002$), irritability/lability ($p = 0.004$), and night-time behaviour ($p = 0.050$) (Figure 5). The results of the OC analysis produced similar findings.

DISCUSSION

This was a *post hoc* analysis of data pooled from six placebo-controlled studies of memantine. The studies included patients with AD, ranging from mild to severe severity, and a group of patients with moderate to severe AD (MMSE below 20) was selected for analysis. The focus of this analysis was an evaluation of the specific effects of memantine on behavioural disturbances, although the patient group chosen was not specifically selected for having behavioural disturbances.

Memantine-treated patients with moderate to severe AD showed statistically significant benefits compared with placebo-treated patients, on the NPI total score, indicative of a benefit of memantine on behavioural symptoms. Significant effects were seen as early as week 12. This observation was reinforced by specific analysis of NPI single items, which showed statistically significant differences in favour of memantine for the individual symptoms delusions, hallucinations, agitation/aggression and irritability/lability. For patients with behavioural symptoms at baseline, memantine was especially effective in improving present symptoms of delusions, agitation/aggression, and disinhibition, during the 6 months of treatment.

Optimising the management of patients with AD involves reducing the emergence of new symptoms as well as controlling existing behavioural changes. In

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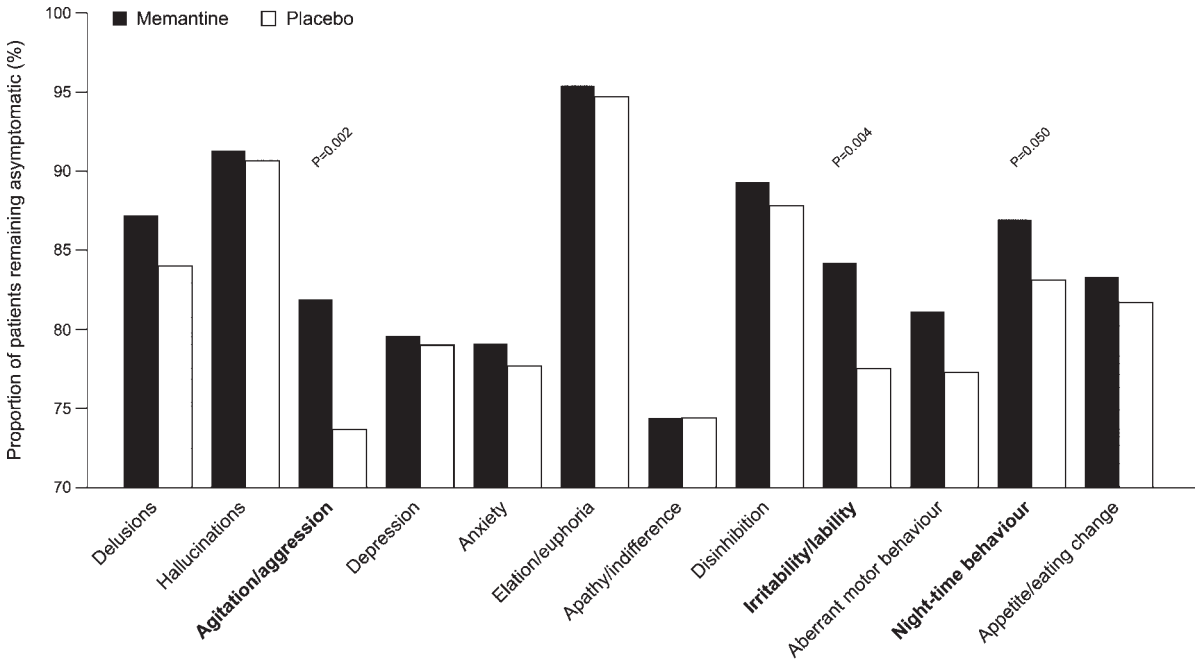

Figure 5. Prevention of symptom emergence (NPI single items), in subgroup of patients without baseline symptoms (week 24/28; LOCF).

this pooled analysis, memantine prevented the emergence of several behavioural symptoms (agitation/aggression, irritability/lability, night-time behaviour) in patients who were asymptomatic at baseline.

In the analyses presented here, memantine consistently produced favourable effects in the item agitation/aggression. This symptom is a distressing behavioural disturbance in AD patients as well as being the most frequent behavioural symptom (Haupt *et al*., 2000), and it has been cited by caregivers as the most problematic AD symptom (Alzheimer Europe, 2006). These difficulties not only confer emotional strain on patients and caregivers, but symptoms such as night-time disturbances, can present a considerable physical challenge. As the AD progresses, these symptoms may prompt patient transfer to institutional care (Yaffe *et al*., 2002) thus increasing the socio-economic burden of the disease.

Behavioural symptoms are key targets in the treatment of AD. Antipsychotic drugs have been widely used off-licence in people with dementia as pharmacological treatment for neuropsychiatric symptoms. However, there are concerns due to increased mortality risk in elderly patients receiving typical and atypical psychotics (Schneider *et al*., 2005; Wang *et al*., 2005). Indeed, warnings have been issued against the use of atypical antipsychotics in dementia (MHRA, 2004; FDA, 2005) due to associations with cognitive decline, extrapyramidal symptoms, lowered blood pressure, sedation and the raised mortality risk, indicating a need for alternative treatment options. Recent studies have shown no drug–placebo difference between antipsychotics and placebo as well as a substantial number of side effects compared to placebo (Schneider *et al*., 2006). These studies emphasise the importance of finding alternatives to treat agitation in AD; the current data indicate that memantine reduces the emergence of new behavioural disturbances and decreases agitation; they suggest that memantine may allow the clinician employing memantine to avoid the use of antipsychotics in some patients.

The mechanism by which memantine produces improvement in behavioural symptoms in AD patients is not clear. Agitation and psychosis in AD appear to be associated with a greater density of neurofibrillary tangles, rather than amyloid plaque pathology (Farber *et al*., 2000; Tekin *et al*., 2001). Although speculative at this stage, there is evidence to show that memantine may have an effect on tau pathology (Li *et al*., 2004; Amadoro *et al*., 2006), and studies have shown that memantine inhibits abnormal phosphorylation of tau

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(Li *et al*., 2004; Chohan *et al*., 2006; Gunnarsson *et al*., 2006). However, it remains to be shown whether these tau-related effects of memantine account for the beneficial clinical effect on agitation and psychosis in behaviourally disturbed patients.

Patients participating in this study were not selected for the presence or severity of behavioural disturbances and the analysis of these symptoms is *post hoc*. Caution is warranted in interpreting the findings. This analysis supports the efficacy of memantine both in treating and preventing the emergence of behavioural symptoms in patients with moderate to severe AD. This benefit is most pronounced for the symptoms agitation/aggression, which are associated with rapid disease progression, increased caregiver burden, early institutionalisation, and increased costs of care.

CONFLICT OF INTEREST

None.

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