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# Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies

S. Gauthier[1]*, Y. Wirth[2] and H. J. Möbius[2]

[1]*MCSA Alzheimer's Disease Research Unit, McGill Centre for Studies in Aging, Quebec, Canada*
[2]*Merz Pharmaceuticals GmbH, Frankfurt, Germany*

## SUMMARY

**Introduction** Behavioural symptoms are common in moderate to severe Alzheimer's disease (AD). We have analysed the databases of two randomised studies with regard to the effects of memantine treatment on behavioural symptoms, measured using the 12-item version of the Neuropsychiatric Inventory (NPI).

**Subjects** The monotherapy study (memantine only) reported by Reisberg *et al*. (2003) involved 252 patients with baseline MMSE total score of between 3 and 14, whereas the combination study (memantine and donepezil) reported by Tariot *et al*. (2004) comprised 404 patients with MMSE scores of between 5 and 14. In both studies, patients received 10 mg memantine b.i.d. or matching placebo, and lived in the community.

**Methods** For both studies NPI total and individual domains scores were analysed in the ITT population. For the monotherapy study a dichotomised analysis was performed separately for patients who had behavioural symptoms at baseline and for those without pre-existing symptoms. Furthermore, a factor analysis was used to identify any behavioural clusters within the patient population.

**Results** In both studies, the change in NPI total scores at endpoint was consistently in favour of memantine treatment, reaching statistical significance in the combination study ($p = 0.002$). Memantine treatment showed a significant beneficial effect in comparison to placebo treatment in the NPI agitation/aggression domain in both studies ($p = 0.008$; $p = 0.001$).

The dichotomised analysis of the monotherapy study showed that there was significantly less agitation/aggression emerging in the memantine-treated group compared to placebo ($p = 0.003$). Factor analysis showed that hyperactivity accounted for 27% of the data variance.

**Conclusions** Memantine has a beneficial effect on the behavioural symptoms of patients with moderate to severe AD, with the most pronounced effect on agitation/aggression. 

KEY WORDS — memantine; behaviour; Alzheimer's disease

## INTRODUCTION

The symptomatology of AD changes over the course of the disease. Cognitive symptoms, most specifically a progressive loss of short-term memory, predominate in the milder stages of AD, while the clinical features of more advanced AD are marked by behavioural disturbances and increasing functional deficiencies. The non-cognitive behavioural manifestations of the disease, such as mood disorders, anxiety, psychotic features, and agitation/aggression are often as great a burden as the cognitive decline for the patients and their families or caregivers. Psychotic symptoms and agitation/aggression can increase the caregiver burden enormously and often become the determining factors for nursing home placement (Ferris *et al*., 1987).

After its approval in Europe memantine was also registered by the FDA for the treatment of moderate to severe AD and is the only drug worldwide approved for this indication. Memantine is a specific, moderate affinity, uncompetitive *N*-methyl-D-aspartate (NMDA) receptor antagonist, with strong voltage

*Correspondence to: S. Gauthier, MCSA Alzheimer's Disease Research Unit, McGill Centre for Studies in Aging, Quebec, Canada. Tel: +1-514 766 2010. Fax: 1 514 888 4050.
E-mail: serge.gauthier@mcgill.ca

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dependency and rapid blocking/unblocking kinetics. These features allow memantine to block the sustained activation of NMDA receptors by elevated concentrations of glutamate under pathological conditions, but rapidly leave the NMDA channel upon transient physiological activation by millimolar concentrations of synaptic glutamate (Parsons *et al*., 1993). These properties are thought to be the basis for the excellent tolerability of memantine in clinical use. Memantine has no direct effects on cholinergic neurotransmission and is the only compound in clinical use for AD that targets the glutamatergic system.

Memantine has shown efficacy in two studies in the moderate to severe AD patient population (Reisberg *et al*., 2003; Tariot *et al*., 2004). In these studies, the effects of memantine on behaviour were assessed using the Neuropsychiatric Inventory (NPI). The present paper is based on the study databases, including a number of subanalyses.

## METHODS

### *Patients and study design*

Effects of memantine on behaviour were analysed in databases of two clinical trials. A 28-week study in 252 moderate to severe AD patients, who received memantine (20 mg/day) or placebo (Reisberg *et al*., 2003) and a 24-week study, where 404 patients with moderate to severe AD who have been under donepezil treatment for at least 6 months and on stable donepezil doses (5 or 10 mg/day) for at least 3 months and throughout the trial, received memantine (20 mg/day) or placebo. Both studies were randomised, double-blind, placebo-controlled clinical investigations, and detailed descriptions of methods and patient eligibility have been published previously (Reisberg *et al*., 2003; Tariot *et al*., 2004).

### *Behavioural outcome measure*

*Neuropsychiatric inventory (NPI)—12-item version*
The NPI was developed to assess behavioural disturbances occurring in dementia patients (Cummings *et al*., 1994). In both studies analysed here, the NPI was employed as a measure of behavioural status in AD.

The modified NPI consists of 12 domains/subscales that are designed to rate specific behavioural characteristics (delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, night-time behaviour, and appetite/eating change) (Cummings, 1997).

Data are obtained through an interview with the patient's carer. For each domain, the frequency and severity of each behaviour type is rated, and the domain score is calculated by multiplying severity by frequency. Severity is rated from 'mild' (1) to 'severe' (3), and frequency from 'occasionally' (1) to 'very frequently' (4). If the symptom is absent, the domain scores equals to zero (0).

The NPI total score is the sum of the individual domain scores and ranges from 0-144 with higher scores indicating more severe psychopathology.

Patients were assessed for change from baseline to Week 28 (endpoint) in the monotherapy study, and from baseline to Week 24 (endpoint) in the combination study.

### *Post hoc statistical analyses*

*NPI analysis (Monotherapy and Combination study).* NPI data were analysed using statistical software SAS version 8.2. All statistical tests were two-sided, and $p$-values $\leq 0.05$ were considered statistically significant. No adjustment was made for multiple testing.

*Categorical analysis (monotherapy study).* Two categorical analyses were carried out to assess the impact of treatment relative to the presence or absence of symptoms at baseline. Symptom prevalence at baseline was calculated by dividing the number of patients with the symptom by the total number of patients available for that assessment. The two categories were:

- Symptom improvement i.e. lower NPI item score at study endpoint than at baseline—included only patients who exhibited the symptom at baseline (NPI item score $> 0$)
- Symptom emergence i.e. appearance of a new symptom (NPI item score $> 0$) at some point post-baseline—included only patients who did not have the symptom at baseline (NPI item score $= 0$)

Treatment differences between groups were assessed using the Cochran-Mantel-Haenszel Test Row Means Score with Modridit scoring.

*Factor analysis (monotherapy study).* The baseline scores of the 12 individual NPI items were submitted to a factor analysis with the aim of detecting behavioural subsyndromes in concordance with literature (Aalten *et al*., 2003).

The individual NPI items were submitted to a principal component analysis using an orthogonal rotational procedure (Varimax). Initial factors were selected on the basis of eigenvalues greater than 1. Factor loadings $\geq 0.45$ were included, and three factors were selected.

### *Safety*

The main results of the safety and tolerability analyses in these studies have been published previously (Reisberg *et al*., 2003; Tariot *et al*., 2004). In summary, patients underwent neurological and physical examinations, and were assessed using vital signs, ECG, and laboratory tests. The occurrence of adverse events and discontinuations were also recorded.

## RESULTS

### *Baseline characteristics*

The study populations comprised 252 randomised patients in the monotherapy study, and 404 randomised patients in the combination study.

In both studies, baseline characteristics were similar between the two treatment groups (Table 1).

### *NPI scores*

*NPI-total scores.* The change from baseline in NPI total score showed a statistically significant advantage for memantine-treated patients over placebo-treated patients in the combination study at Week 24 ($p = 0.002$) (Tariot *et al*., 2004). This was consistent with the numerical advantage seen for memantine-treated patients in the monotherapy study (Reisberg *et al*., 2003).

*NPI domain scores.* Nine out of 12 domain scores favoured memantine treatment over placebo in the monotherapy study and 10 out of 12 in the combination study. In both studies, analysis of the individual NPI domains from baseline to endpoint revealed a statistically significant benefit for memantine-treated patients in the domain of agitation/aggression ($p = 0.008$ monotherapy study; $p = 0.001$ combination study).

In addition, memantine produced a statistically significant improvement in the domains of delusions ($p = 0.04$ monotherapy study), irritability/lability ($p = 0.005$ combination study), appetite/eating change ($p = 0.045$ combination study), and a trend towards improvement in the depression/dysphoria domain ($p = 0.07$ monotherapy study) (Figure 1).

### *Categorical analysis*

At baseline, the prevalence of each behavioural subtype (NPI domain) was similar between the memantine- and placebo-treated groups (Figure 2) with the notable exception in the monotherapy trial that the memantine group had a significantly higher prevalence of delusions at baseline ($p = 0.015$, Fisher's exact two-sided) and appetite/eating change ($p = 0.003$, Fisher's exact two-sided), when compared with the placebo group.

Data from the monotherapy study showed a significant emergence of agitation/aggression in the placebo group, which was much less pronounced in the memantine group ($p = 0.008$) (Figure 3). Consistent with this finding, categorical analysis of symptom improvement from baseline revealed that memantine-treated patients showed improvement in the agitation/aggression domain, when compared to the placebo group (Figure 4).

### *Factor analysis*

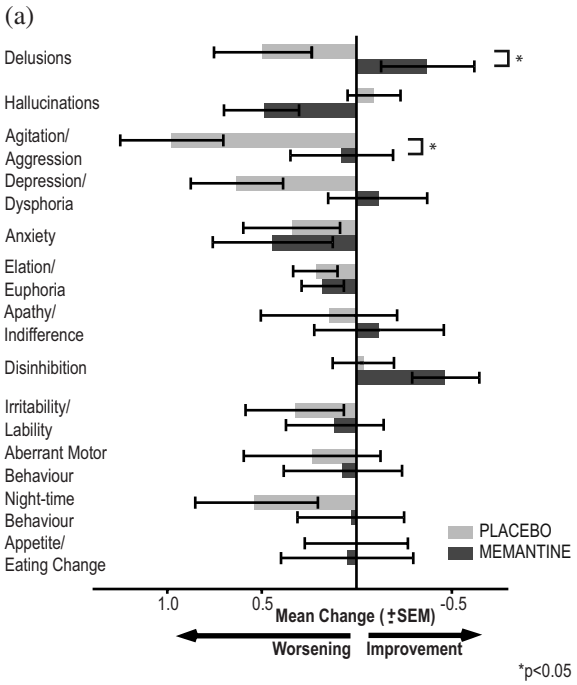
A factor analysis has been conducted in order to investigate whether patents included in this study reflect a representative group of AD patients with respect to their behavioural disturbances.

Principal component analysis of the NPI data reduced the 12 NPI domain variables to three factors (factors were selected on the basis of preexisting

Table 1. Baseline demographics and characteristics (all randomised patients)

| Characteristic | Monotherapy study | | Combination study | |
|---|---|---|---|---|
| | Memantine ($n = 126$) | Placebo ($n = 126$) | Memantine* ($n = 202$) | Placebo ($n = 201$) |
| Age, years ($\pm$SD) | 75.9 ($\pm$8.40) | 76.3 ($\pm$7.76) | 75.5 ($\pm$8.45) | 75.5 ($\pm$8.73) |
| No. female (%) | 91 (72) | 79 (63) | 128 (63) | 134 (67) |
| No. Caucasian (%) | 112 (89) | 115 (91) | 182 (90) | 186 (93) |
| MMSE score, mean ($\pm$SD) | 7.7 ($\pm$3.72) | 8.1 ($\pm$3.57) | 9.9 ($\pm$3.13) | 10.2 ($\pm$2.98) |
| NPI total score, mean ($\pm$SD) | 21.4 ($\pm$15.83) | 19.5 ($\pm$15.55) | 13.7 ($\pm$14.05) | 13.9 ($\pm$12.78) |

*One patient withdrew before receiving study medication.



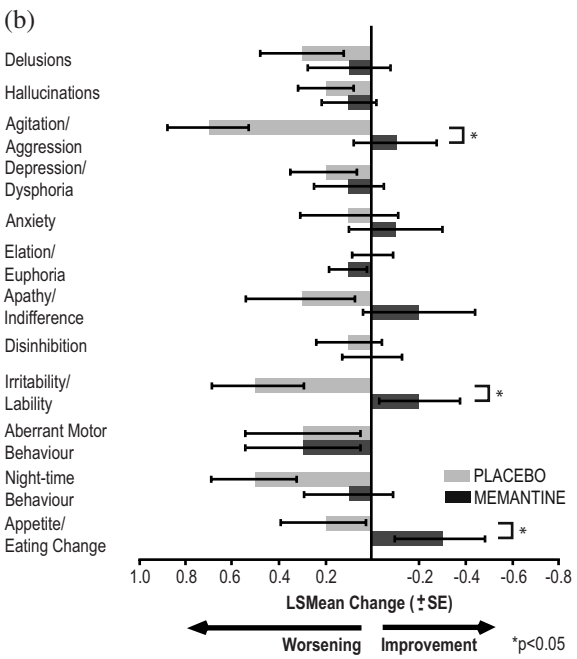




Figure 1. Mean change from baseline in NPI-domain scores (ITT, LOCF) (a) Monotherapy study; (b) Combination study

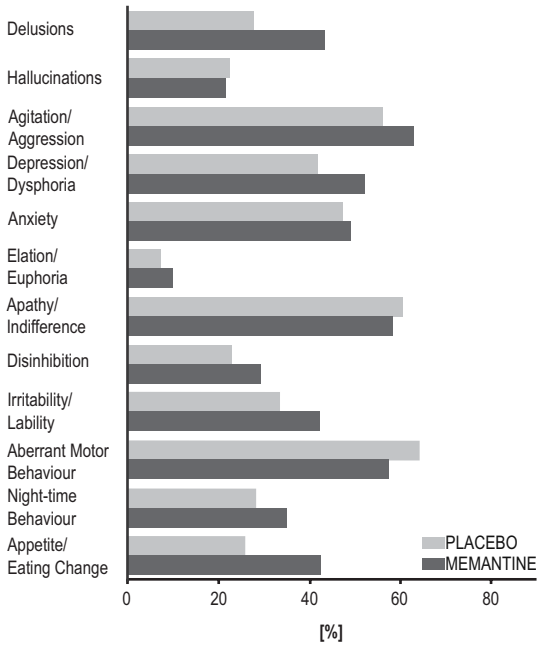



Figure 2. Prevalence of behavioural symptoms at baseline (monotherapy study)

factorial solutions), thereby suggesting three behavioural subsyndromes—hyperactivity, psychosis and mood apathy. Factor 1 (hyperactivity) accounted for 26.8% of the data variance, with high loadings in domains including agitation/aggression, depression/

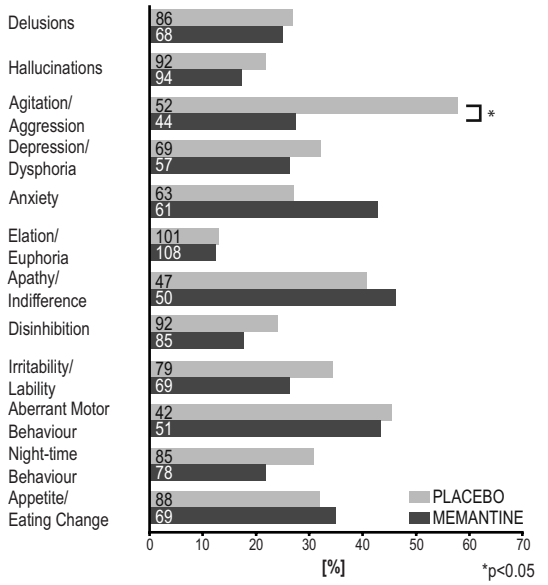



Figure 3. Emergence of behavioural symptoms from baseline (monotherapy study)

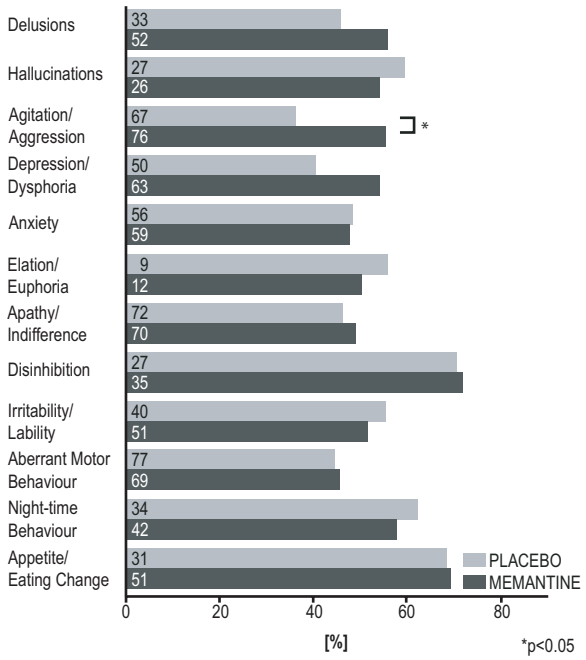



Figure 4. Improvement of behavioural symptoms from baseline (monotherapy study)

dysphoria, anxiety, and irritability/lability, apathy/indifference and appetite/eating change. Factor 2 (psychosis) represented 11.8% of the data variance and included high loadings in the domains of delusions and hallucinations. Factor 3 (mood/apathy) represented 10.4% of the data variance and included high loadings in elation/euphoria, disinhibition, and apathy/indifference.

### *Safety and tolerability*

As previously reported, most adverse events were mild to moderate in severity. In the monotherapy study, considering the most frequently reported adverse events (Table 2), memantine-treated patients experienced significantly fewer episodes of agitation than those receiving placebo ($p = 0.02$, chi-square test) (Reisberg *et al*., 2003).

Results from the combination study showed that no adverse events occurred in more than 10% of patients in the memantine group. Agitation occurred in 24 patients receiving placebo (11.9%), and in 19 patients receiving memantine (9.4%).

In the monotherapy study, 22 placebo-treated patients (17%) discontinued therapy due to adverse events, compared to 13 patients (10%) receiving memantine. Agitation was cited as the most common reason for discontinuation (7% placebo patients, 5% memantine patients).

Table 2. Most frequently reported adverse events (monotherapy study)[#]

| Adverse event | No. patients (%) | |
|---|---|---|
| | Memantine ($n = 126$) | Placebo ($n = 126$) |
| Any adverse event | 106 (84) | 109 (87) |
| Agitation | 23 (18)* | 40 (32) |
| Urinary incontinence | 14 (11) | 14 (11) |
| Urinary tract infection | 7 (6) | 17 (13) |
| Insomnia | 13 (10) | 10 (8) |
| Diarrhoea | 12 (10) | 10 (8) |

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[#]Adverse events occurring in at least 10% of the patients in either treatment group.
*$p = 0.02$ *vs* placebo (chi-square test), all other adverse events showed no significant difference between groups.

In the combination study, 15 patients (7%) discontinued treatment due to adverse events, compared to 25 patients (12%) from the placebo group. Agitation as reason for study discontinuation was given in three patients (1.5%) of the placebo-treated patients compared to two patients (1%) of the memantine treated patients.

## DISCUSSION

Neuropsychiatric symptoms associated with dementia are being increasingly recognised as a major component of the burden for families and patients with AD. Agitation/aggression in particular has been associated with frontal lobe dysfunction in AD and has a marked impact on caregivers (Senararong *et al*., 2004). The analyses presented here demonstrate the benefits of memantine treatment on various neuropsychiatric symptoms associated with dementia with pronounced effects on agitation/aggression. Atypical neuroleptics have been shown to be useful in the management of some aspects of neuropsychiatric symptoms associated with dementia, including agitation/aggression. However, the safety of these drugs is under review (Profenno and Tariot, 2004). Cholinesterase inhibitors have been shown to have some effects on neuropsychiatric symptoms associated with dementia (Wynn and Cummings, 2004). In a double-blind study comparing donepezil to placebo in 'moderate to severe' AD (baseline MMSE 5-18, mean of 12; baseline mean NPI 12-item total 19) (Feldman *et al*., 2001), there was improvement in NPI total score and of the three domains of apathy/indifference, anxiety and depression/dysphoria, although there was no significant dif-

KEY POINTS

- Memantine has demonstrated benefits on behavioural symptoms in Alzheimer's disease
- Improvement on agitation appears to be the main behavioural effect of memantine in studies conducted up to now

ference for rates of symptom emergence (Gauthier *et al*., 2002). A sub-analysis of a pivotal double-blind study comparing galantamine to placebo in mild to moderate AD (MMSE 10–22, mean of 18; Mean NPI 10-item total 12) showed a significant reduction in the emergence of aberrant motor behaviour, apathy and disinhibition (Cummings *et al*., 2004a). In contrast to cholinesterase inhibitors, the effect of memantine on neuropsychiatric symptoms associated with dementia was especially pronounced in the domain agitation/aggression (Cummings *et al*., 2004b).

Aalten *et al*. (2003) showed in a factor analysis that dementia is associated with specific behavioural subsyndromes. The subsyndromes identified in this paper are comparable with the behavioural subsyndromes described by Aalten *et al*. (2003). This shows that the patients included in the monotherapy study are representative for AD patients in general with respect to their behavioural disturbances.

The effects of memantine on agitation/aggression was observed either as a reduction if present at onset of treatment or as a delay in emergence in asymptomatic patients. This anti-agitation/aggression effect of memantine appears to be unique as compared to other class of drugs used for the management of neuropsychiatric symptoms associated with dementia, and the excellent safety profile of memantine could justify an increasing use of this agent, as monotherapy or even in combination with cholinesterase inhibitors.

In addition, the use of memantine may allow a reduction in concomitant medications, including neuroleptics. Since agitation/aggression is one of the major factors determining institutionalisation (Ferris *et al*., 1987), the benefit of memantine on this symptom might translate into a reduction of resource utilisation and health costs. A significant reduction in caregiver time and costs as well as societal costs was shown in the pharmacoeconomic evaluation of the monotherapy study (Wimo *et al*., 2003). This study also showed that time to institutionalisation and institutionalisation at endpoint was favourable for patients under memantine treatment in comparison to placebo treatment.

Further studies are required to confirm the anti-agitation/aggression actions of memantine and explain this action.

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