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Psychiatric symptoms and caregiver distress in patients with moderate to severe Alzheimer's disease treated with memantine

Martínez Rivera Marta[1*], Menéndez-González Manuel[2], Calatayud María Teresa[3]

1 Geriatrics, Hospital Álvarez-Buylla, Mieres, Spain
2 Neurology, Hospital Álvarez-Buylla, Mieres, Spain. Departamento de Morfología y Biología Celular, Universidad de Oviedo, Spain
3 Neurology, Hospital Universitario Central de Asturias, Oviedo, Spain

Corresponding author:

* **Address:** Marta Martínez Rivera, Geriatría, Hospital Álvarez-Buylla, Spain Tel: +34 985 458 500

Fax: +34 985 458 509

E-mail: martamrivera@fneurociencias.org

Abstract

Objective: This post-marketing study aimed to assess the efficacy of memantine on the psychiatric and behavioural symptoms of Alzheimer's disease (AD), and associated caregiver distress.

Methods: Patients with moderate to severe AD who were initiating treatment with memantine 20 mg/day, were enrolled in this 4-month post-marketing study. Study visits/assessments took place at the point of treatment initiation (pre-treatment/baseline), and after ~4 months of memantine treatment (post-treatment/endpoint). Main outcome measures were change from baseline to endpoint in individual domains of the Neuropsychiatric Inventory-questionnaire (NPI-Q), and the NPI caregiver distress scale (NPI-D). Both these analyses were based upon caregiver interview. During the study period, the concomitant use of other medications for psychiatric symptoms was also assessed.

Results: At endpoint, the most marked improvements from baseline for patients and caregivers were observed in the NPI domains of delusions (NPI-Q, p=0.037; NPI-D, p=0.028), agitation/aggression (NPI-Q, p=0.041), and apathy/indifference (NPI-D, p=0.042). There was also significant worsening in the domains of irritability/lability (NPI-Q, p=0.041) and night-time behavioural disturbances (NPI-D, p=0.039). Significantly fewer patients were receiving neuroleptic medications at endpoint (25 patients) than at baseline (40 patients; p=0.037).

Conclusions: This open label study suggests that Memantine treatment can improve specific psychiatric and behavioural symptoms in patients with moderate to severe AD, producing a parallel reduction in caregiver distress. The observed negative effect on certain symptoms, e.g., patient irritability/lability, may be related to improvement in other areas, e.g., apathy. Memantine also reduces the need for neuroleptic medications.

Key words: Alzheimer's disease (AD), memantine, caregiver, psychiatric symptoms, behaviour, post-marketing study

Introduction

Alzheimer's disease (AD) is a neurodegenerative condition, which initially damages the medial structures of temporal lobes, resulting in a memory deficit. With time, the memory deficit increases, and brain damage extends throughout the temporal lobes, the frontal lobes and associated cortices, and finally results in an aphasic-apraxic-agnosic syndrome. In addition, psychiatric and behavioural symptoms are characteristic of AD, and are present in almost all patients. Overall, 92% of AD patients experience at least one psychiatric or behavioural symptom, 81% have two or more symptoms, and 51% have four or more symptoms (Finkel, 2003). Psychiatric and behavioural symptoms have an impact on caregiver distress that appears to be greater than that of cognitive and functional impairment

(Craig *et al*., 2005; Artaso *et al*., 2001; Ferris *et al*., 1987; Borrie *et al*., 2006; Kaufer *et al*., 1998). In particular, delusions (Riello *et al*., 2002), sleep disorders (McCurry *et al*., 1999), and agitation/aggression (Borrie *et al*., 2006) have been reported as the most distressing symptoms for the caregiver. Furthermore, there is evidence that caregiver distress may, in turn, influence patient mood and behaviour (Riello *et al*., 2002). In clinical practice, it would be desirable to employ a systematic approach for the management of these symptoms (Robinson *et al*., 2001; Hosaka and Sugiyama, 1999), as it is clear that their effects are wide-ranging, impacting not only on patients, but also their caregivers/family members.

Memantine, an uncompetitive *N*-methyl-D-aspartate (NMDA) glutamatergic receptor antagonist, has been approved for the treatment of moderate to severe AD in more than 70 countries worldwide. The efficacy of memantine on global performance, cognition, and function, as well as its good tolerability, have been demonstrated in clinical studies of patients with AD (Reisberg *et al*., 2003; van Dyck *et al*., 2007; Tariot *et al*., 2004; Robinson and Keating, 2006; Bakchine and Loft, 2008; Peskind *et al*., 2006; Winblad *et al*., 2007). However, memantine has also shown efficacy in the treatment of the psychiatric and behavioural aspects of AD (Gauthier *et al*., 2007).

The Neuropsychiatric Inventory (NPI) (Cummings, 1997; Cummings *et al*., 1994; Vilalta-Franch *et al*., 1999) is a useful instrument to assess the response of neuropsychiatric symptoms to treatment strategies in dementia. This post-marketing study was designed to evaluate the effect of memantine on each NPI symptomatic domain, and on consequent caregiver distress. The study also aimed to assess the use of other drugs for the treatment of psychiatric symptoms (neuroleptics, antidepressants, and benzodiazepines) in patients receiving memantine treatment.

Methods

Patients

Patients were enrolled at three study centres in Spain from September 2006 to March 2007, and were entered into the study at the time of treatment initiation with memantine. Patients and their caregivers provided informed consent for entry into the study.

Inclusion criteria were: diagnosis of probable AD according to NINDS-ADRDA criteria; MMSE 5–20 or GDS stages 5–6, inclusive (i.e., moderate to severe disease); recent (within 12 months) MRI or CT scan consistent with a diagnosis of AD; age ≥60 years; intention of treatment initiation with memantine; residence in the community; collaboration of the patient's main caregiver. In all cases, the diagnosis of AD was made clinically through neuropsychological assessment, and exclusion of other possible causes in accordance with the recommendations of the American Academy of Neurology Quality Standards Subcommittee (Knopman *et al*., 2001).

Exclusion criteria were: clinically significant vitamin B_{12} or folate deficiency; active pulmonary, gastrointestinal, renal, hepatic, endocrine or cardiovascular disease or other psychiatric or central nervous system disorders; treatment with unstable doses of antidepressants, antipsychotics or benzodiazepines in the 2 months prior to study enrolment. However, patients on stable doses of these medications prior to the study were included, with any medication changes permitted and recorded during the study.

Treatment

Treatment with 20 mg/day memantine (tablets/solution) was prescribed to all patients in the study, including a 3-week dose-titration schedule in accordance with the standard recommendations of the memantine Summary of Product Characteristics. Investigators were allowed to modify this schedule on a per-patient basis for tolerability reasons.

Outcome measures

The main outcome measures of the study were change from baseline in two validated variants of the NPI (Cummings *et al*., 1994; Cummings, 1997; Vilalta-Franch *et al*., 1999): the NPI-questionnaire, NPI-Q (Boada *et al*., 2002; Kaufer *et al*., 2000), to assess patients' psychiatric and behavioural symptoms, and the NPI caregiver distress scale, NPI-D (Kaufer *et al*., 1998), to assess the impact of psychiatric and behavioural symptoms on caregiver distress. These NPI assessments are standardised caregiver interviews that examine 12 individual behavioural domains: delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, euphoria/elation, apathy/indifference, disinhibition, irritability/lability, aberrant motor behaviour, night-time behavioural disturbances, and appetite/eating changes. Each domain of the NPI-Q is rated for frequency (1–4) and severity (1–3), and the overall score for a domain is the product of frequency and severity (Boada *et al*., 2002). On the NPI-D, each domain is rated for level of caregiver distress (0–5) (Kaufer *et al*., 1998). The NPI total scores are the sum of the individual domain scores, with higher scores indicating more serious behavioural symptoms (NPI-Q) or greater caregiver distress (NPI-D). No cutting-point or reference values exist for this scale.

Patients and their caregivers attended two visits – a pre-treatment visit at the point of inclusion into the study (baseline), and a post-treatment visit after 4 (±1) months of memantine treatment (endpoint). The NPI-Q and NPI-D total and individual domain scores were assessed at both visits.
The initiation, withdrawal, and dose increase/decrease of neuroleptics, antidepressants, and benzodiazepines were also examined as an exploratory study endpoint during the memantine treatment period. Other changes in medication were also recorded.

Statistical analysis

Statistical analyses were performed using SPSS v14.0. Parametric tests were used since the sample follows a normal distribution. A Student (paired) t-test analysis was used to compare differences between the treatment means at baseline and endpoint for each NPI-Q and NPI-D domain. The null-hypothesis of equal means (baseline vs endpoint) was tested on a level of significance of 0.05 (two-sided). Two-sided 95% confidence intervals were also used to describe the effects.

Differences between the number of patients receiving concomitant medications at endpoint and at baseline were analysed using a Chi-square test. Sample-size determination: $N = [(Za + Z\beta)^2 \cdot DEd^2] / dif^2 = 130$

Results

Patients

In total, 150 patients were enrolled in the study – 67 men and 83 women. The age range was 67–91 years, with a mean age of 78.46 years (SD: 8.05) and, at baseline, the median MMSE score was 16, and the median GDS score was 5. No patients required permanent treatment withdrawal during the study period. Treatment was temporarily withdrawn due to hospital admission in two patients, but the initial treatment schedule was resumed after discharge. At endpoint, 82% of patients were receiving full doses of memantine (20 mg/day), and the mean dose was 17.20 mg/day (SD: 4.34).

Regarding concomitant medications at baseline, 40 patients were taking neuroleptics, 36 patients were taking antidepressants, 38 patients were taking benzodiazepines, and 56 patients were taking acetylcholinesterase inhibitors.

Effect of treatment on patients

The mean change from baseline in NPI-Q total score was -0.85 (SD: 0.598; p=0.141). From baseline to endpoint, statistically significant benefits (i.e., score reductions) were observed in the NPI-Q domains of delusions (p=0.037), and agitation/aggression (p=0.041), with a marked (but non-significant) decrease in apathy/indifference (**Table 1**). A statistically significant worsening (i.e., score increase) was observed in the irritability/lability domain (p=0.041). No statistically significant differences were observed for other domains.

Repercussion on caregiver distress

The mean change from baseline in NPI-D total score was -0.85 (SD: 0.618; p = 0.215). Statistically significant benefits (i.e., score reductions) were observed in the NPI domains of delusions (p = 0.028) and apathy/indifference (p=0.042), with a marked (but non-significant) decrease in mean agitation/aggression score (**Table 2**). A statistically significant worsening (i.e., score in-

TABLE 1. Mean (SD) change from baseline in NPI-Q scores.

NPI item	Change from pre-treatment to post-treatment (n=150)		
	Mean	SD	p-value*
Delusions	-1.52	0.571	0.037
Hallucinations	0.61	1.342	0.224
Agitation/aggression	-1.80	0.881	0.041
Depression/dysphoria	-0.42	1.917	0.423
Anxiety	0.31	2.344	0.152
Euphoria/elation	0.26	1.726	0.532
Apathy/indifference	-2.10	1.011	0.237
Disinhibition	-0.68	1.075	0.223
Irritability/lability	1.32	0.593	0.041
Aberrant motor behaviour	0.04	1.276	0.281
Night-time behavioural disturbances	0.40	1.277	0.114
Appetite/eating changes	-0.01	1.880	0.438

* Student t-test for comparison of baseline vs endpoint; significant (p<0.05) differences are shown in italics
NPI=Neuropsychiatric Inventory

TABLE 2. Mean (SD) change from baseline in NPI-D scores.

NPI item	Change from pre-treatment to post-treatment (n=150)		
	Mean	SD	p-value*
Delusions	-1.46	0.697	0.028
Hallucinations	0.22	1.556	0.262
Agitation/aggression	-1.78	1.003	0.217
Depression/dysphoria	0.06	2.043	0.361
Anxiety	0.80	2.410	0.272
Euphoria/elation	0.02	1.727	0.166
Apathy/indifference	-1.84	0.599	0.042
Disinhibition	-0.52	2.069	0.324
Irritability/lability	0.78	0.209	0.452
Aberrant motor behaviour	0.24	2.479	0.323
Night-time behavioural disturbances	0.82	0.280	0.039
Appetite/eating changes	-0.17	1.166	0.142

* Student t-test for comparison of baseline vs endpoint; significant (p<0.05) differences are shown in italics
NPI=Neuropsychiatric Inventory

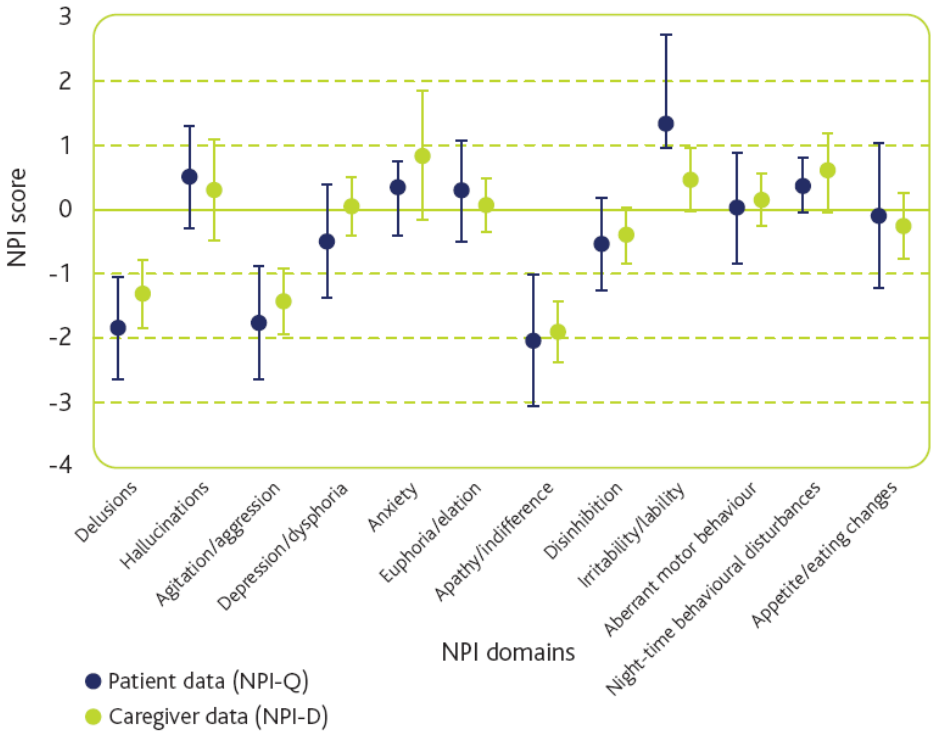

FIGURE 1. Change in the NPI domain scores of patients and caregivers (baseline vs endpoint, mean and 95% CI). Patients' and caregivers' paired data. Note that NPI-Q and NPI-D are different scales.

crease) was observed in the domain of night-time behavioural disturbances (p = 0.039). No significant differences were obtained in the other domains.

Concomitant treatments

The comparison between the number of patients receiving concomitant drug classes at baseline and endpoint is shown in **Table 3**. Of the 40 patients receiving neuroleptic treatment at baseline, treatment was withdrawn in 17 patients at endpoint, the dose was reduced in five patients and increased in one patient, and two patients not receiving neuroleptics at baseline had initiated neuroleptic treatment during the study. Significant differences were observed in the number of patients who received neuroleptics at the study endpoint vs baseline (Table 3).

TABLE 3. Concomitant use of drugs at the start and end of the study period.

Drug class	No. of memantine patients taking concomitant drug (n=150)				p-value*
	Baseline	Discontinued	Initiated	Endpoint	
Neuroleptics	40	17a	2d	25	0.037
Antidepressants	36	12b	0	24	0.107
Benzodiazepines	38	12c	2	28	0.203
Acetylcholinesterase inhibitors	56	9	5	52	0.244

* Chi-square test for comparison of baseline vs endpoint; significant ($p<0.05$) differences are shown in italics
There were also dose reductions in a5 patients, b1 patient, c2 patients; and a dose increase in d1 patient.

There were no significant differences between baseline and endpoint in the number of patients receiving antidepressants, benzodiazepines, or acetylcholinesterase inhibitors (Table 3).

Discussion

Memantine, both as monotherapy and as combination therapy with donepezil, has shown global efficacy in the management of psychiatric and behavioural symptoms in moderate to severe AD, as confirmed by a meta-analysis of six clinical studies (Winblad *et al*., 2007). *Post hoc* and pooled analyses have also demonstrated the benefits of memantine on specific behavioural items (Gauthier *et al*., 2005; Gauthier *et al*., 2007; Wilcock *et al*., 2008). However, no previous study has been prospectively designed to investigate the effect of memantine on individual NPI domains/symptoms, or assess how such benefits may impact upon caregiver distress. In the current post-marketing investigation, memantine produced an important improvement for patients in the NPI domains of delusions, agitation/aggression, and apathy/indifference, while a worsening was observed in irritability/lability. No relevant changes were observed for other symptomatic domains.

Regarding the improvement in the agitation/aggression domain a notable correlation was observed between our data and those from a *post hoc* analysis of data from two memantine clinical studies (Reisberg *et al*., 2003; Tariot *et al*., 2004), which also assessed the individual NPI domains in patients with moderate to severe AD (Gauthier *et al*., 2005). However, in contrast, results from the *post hoc* analysis and other studies observed benefits of memantine on irritability/lability symptoms (Olin and Cummings, 2006; Tariot *et al*., 2006; Cummings and Olin, 2006; Gauthier *et al*., 2005), while a worsening of symptoms was seen here. This symptomatic worsening may be linked to the marked reduction in apathy/indifference produced by memantine, which could potentially impact on patient irritability.

As expected, the NPI items for which a treatment-related benefit had repercussions on caregivers occurred in similar domains to those obtained for patient symptoms, with caregivers experiencing less distress due to patient delusions, agitation/aggression, and apathy/indifference. A correlation between patient agitation/aggression and caregiver distress has been demonstrated in previous studies (Craig *et al*., 2005; Borrie *et al*., 2006). A positive effect on these symptoms has also been observed with anticholinergic drug treatment (Cummings *et al*., 2004; Holmes *et al*., 2004; Cummings *et al*., 2006; Aupperle *et al*., 2004), although the therapeutic effect on aggression/agitation was not as pronounced. The exception to the patient–caregiver correlations in this study was night-time behavioural disturbances. For this symptomatic domain, the results indicated that memantine was associated with a significant negative effect on caregivers – a non-significant worsening of patients was observed in this domain.

Memantine was also associated with a worsening of patient irritability/lability, but although this did cause a numerical worsening in caregiver score, the impact was not found to be statistically significant. Thus, the effects of memantine show parallel trends in patients and caregivers, although these trends do not always reach statistical significance in both groups.

The psychiatric and behavioural symptoms of AD result in a substantial increase in the indirect costs of the disease (Butman *et al*., 2004) and, of all symptoms, agitation/aggression is the most frequent determinant of patient institutionalisation (Ferris *et al*., 1987). Therefore, by relieving these symptoms, memantine treatment could be expected to help reduce resource consumption and health costs. Furthermore, it is important to note that, as previously shown (Shua-Haim *et al*., 2006), treatment with memantine in this study reduces the need for neuroleptic drug consumption, and therefore any associated adverse effects, and direct and indirect costs. Overall, these benefits are consistent with results from an earlier pharmacoeconomic study, in which memantine monotherapy was associated with significant reductions in caregiver time and direct costs, as well as in social costs and time to institutionalisation (Wimo *et al*., 2003).

Conclusions

In this open-label study memantine treatment significantly improved psychiatric and behavioural symptoms related to delusions and agitation/aggression, and worsened irritability/lability, in patients with moderate to severe AD. In addition, memantine reduced the caregiver distress associated with patient delusions and apathy/indifference. However, it also negatively affected caregiver distress linked to patients' night-time behavioural disturbances. In addition, study indicates that memantine reduces the need for neuroleptic drug treatment related to baseline.

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