

Memantine Therapy of Behavioral Symptoms in Community-Dwelling Patients with Moderate to Severe Alzheimer's Disease

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Key Words

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Abstract

Memantine is a moderate-affinity, uncompetitive antagonist of N-methyl-D-aspartate receptors, approved for the treatment of moderate to severe Alzheimer's disease (AD). Available data suggest that, in addition to its benefits on cognition, function, and global status, memantine treatment may also help alleviate behavioral symptoms. This article provides an overview of the prevalence, assessment, and treatment of behavioral disturbances in AD, and summarizes current knowledge regarding the effects of memantine on the behavior of community-dwelling patients. We searched EMBASE and PubMed (January 1992 to October 2008) for reports on memantine trials that involved outpatients with moderate to severe AD. All previously unpublished data were obtained from Forest Laboratories, Inc. Behavioral outcomes were assessed in three completed, double-blind, placebo-controlled trials. Overall, patients who received memantine performed better on behavioral measures than those treated with placebo. Post-hoc analyses suggest that memantine treatment was associated with

a reduced severity or emergence of specific symptoms, particularly agitation and aggression. Prospective, well-designed trials are warranted to evaluate the efficacy of memantine in patients with significant behavioral symptoms.

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Introduction

While memory loss and cognitive decline are often seen as the hallmark symptoms of Alzheimer's disease (AD), behavioral disturbances contribute significantly to the overall burden of the disease. Behavioral symptoms in AD can be classified as psychotic (delusions and hallucinations) or nonpsychotic (apathy, depression, agitation, aggression, anxiety, irritability, and aberrant motor behavior), all of which can cause significant distress for the patient and caregiver. In patients with AD, the severity of most behavioral disturbances is associated with the severity of dementia [1, 2]; in addition, the presence of psychosis (i.e. delusions and hallucinations) has been shown to be predictive of functional decline [3]. The presence of behavioral symptoms in general increases the likelihood of patient placement into long-term care facilities, which increases the costs of patient care [4–8].

Therefore, the attenuation of behavioral disturbances represents an important goal in the management of AD.

Behavioral problems in patients with AD are managed using both pharmacological [9, 10] and nonpharmacological [11–14] interventions. Recent studies suggest that drugs currently approved to treat cognitive symptoms in AD (cholinesterase inhibitors and memantine) may also have psychotropic effects [5, 15]. Memantine, an N-methyl-D-aspartate receptor antagonist approved for the treatment of patients with moderate to severe AD, is believed to improve glutamatergic neurotransmission and reduce the damaging effects caused by excessive glutamate stimulation [16]. In addition to benefits on cognition [17–19], memantine may play a role in preventing and alleviating behavioral symptoms associated with AD [20, 21].

This review summarizes the behavioral disturbances associated with AD and the effectiveness of memantine treatment on behavioral outcomes in clinical trials involving community-dwelling patients.

Behavioral Disturbances in AD: Prevalence and Characterization

The prevalence of behavioral symptoms in AD varies by study. Several estimates predict that approximately 90% of patients with AD will develop at least one behavioral symptom over the course of the disease [22–25], and more than 75% will develop two or more symptoms [22]. Available evidence suggests that the distribution and reporting of behavioral problems among patients with dementia are very complex, and that reported symptoms may depend on factors such as a patient's race [24] or characteristics of the caregiver [26]. In some patients with AD, behavioral disturbances emerge early in the disease, possibly before the diagnosis [27, 28]. In general, the symptoms become more severe as the disease progresses [2], with apathy, anxiety, depression, irritability, and agitation being the most frequent [29]. For a summary of behavioral symptom characteristics, associated neuropathology, and prevalence in AD, please refer to online supplementary table 1 (www.karger.com/doi/10.1159/000200013).

In an effort to group the behavioral disturbances observed in AD, the term 'behavioral and psychological symptoms of dementia' was created [8]. However, this category has been considered too broad for either diagnostic or regulatory purposes, and several organizations support the development of diagnostic criteria for more specific syndromes of AD [30, 31]. Provisional criteria

have been developed for psychosis of AD [32] and depression of AD [28], with the former receiving the most support and use [30, 31, 33, 34].

Treatment

Current strategies to manage behavioral problems in patients with AD include the use of pharmacological [10, 11, 35–41] and behavioral interventions [11–14, 42]. Commonly prescribed drugs include antidepressants, antipsychotics, anticonvulsants, and anxiolytics [42, 43]; however, these pharmacological agents are not specifically indicated for use in patients with AD. A summary of properties of agents used for the treatment of behavioral problems in AD can be found in supplementary table 2 (www.karger.com/doi/10.1159/000200013).

The potential benefits of adjunct pharmacotherapy should be weighed against the risks of polypharmacy, the higher cost of treatment, and the increased possibility of noncompliance. A recent study of patients with dementia in nursing homes and acute geriatric wards indicated that 87% of patients in the study were taking at least one psychotropic medication, and 11% were taking four or more; the mean number of drugs used by patients with dementia was 8.4 [23]. Recent concerns, particularly those regarding a potentially increased risk of stroke and all-cause mortality associated with both conventional [44, 45] and atypical [46–48] antipsychotic use in elderly patients with dementia, have led to a re-evaluation of antipsychotic use in patients with less severe behavioral problems. The authors of the recently completed Clinical Antipsychotic Trials of Intervention Effectiveness Project in patients with AD (CATIE-AD) [46] concluded that the potential efficacy of atypical antipsychotic drugs for the treatment of psychosis, aggression, or agitation in patients with AD is offset by an increased possibility of adverse effects.

Current treatment guidelines suggest taking a stepwise approach to alleviating behavioral symptoms, beginning with nonpharmacological methods and adding atypical antipsychotic medications only in instances of severe behavioral problems [49]. Consequently, medications traditionally used to treat cognitive deficits in AD are now being investigated for efficacy in treating the behavioral symptoms of the disease. Since memantine is approved for patients in moderate to severe stages of AD [17, 18, 50], and since such patients are very likely to experience behavioral problems, the behavioral benefits of memantine may be of considerable interest.

Methods

To summarize the effects of memantine treatment on behavioral symptoms in AD, we conducted a search of all papers published between January 1992 and October 2008, according to EMBASE/Medline databases. The search was performed using the terms 'memantine AND (moderate OR severe) AND Alzheimer', with search limitations of articles in English, clinical trials, meta-analyses, and randomized controlled trials (PubMed and EMBASE) and Cochrane reviews (EMBASE). Studies with patients residing in nursing homes or assisted living facilities were excluded, since these patients may have significantly different baseline characteristics (severity of dementia, behavioral symptoms, concomitant medications, level of independence, etc.). To determine the quality of reporting in these studies, we compared them with the 2001 Consolidated Standards of Reporting Trials (CONSORT) Statement [51, 52]. Behavioral data were extracted from primary study reports, as well as from post-hoc, pooled, and meta-analyses; any unpublished supplemental information was provided by Forest Laboratories, Inc. For the purpose of this review, Cohen's *d* effect sizes were calculated by Forest Research Institute, using the pre-specified intent to treat (ITT) population, mean values of change from baseline to endpoint, pooled standard deviations, and the last observation carried forward (LOCF) approach.

Memantine: Efficacy in Treating Behavioral Symptoms

From January 1992 to October 2008, a total of three double-blind, placebo-controlled memantine studies conducted in community-dwelling patients with moderate to severe AD were registered with EMBASE and PubMed [17, 18, 53]. The study reports for all three trials conformed with a majority of the 22 recommendations outlined in the 2001 CONSORT Statement (table 1) [51, 52].

In the three memantine trials [17, 18, 53], two scales were used to measure behavioral symptom changes: the Neuropsychiatric Inventory (NPI) and the Behavioral Rating Scale for Geriatric Patients (BGP). The NPI is a validated outcome measure designed to assess behavioral symptoms in patients with AD and other dementias [54, 55]. It covers 12 behavioral domains: agitation, irritability, anxiety, dysphoria, hallucinations, delusions, apathy, euphoria, disinhibition, aberrant motor behavior, nighttime disturbances, and appetite and eating abnormalities. The frequency and severity of each symptom are recorded, with each domain contributing a maximum of 12 points (higher score reflects greater impairment), for a maximum total score of 144. The NPI was used in all three memantine trials involving community-dwelling patients with moderate to severe AD [17, 18, 53].

The BGP [56, 57], widely used in European clinical trials (including a memantine trial involving institutionalized patients with dementia [50]), was also an assessment tool in two of the three US-based memantine trials in outpatients with moderate to severe AD [18, 53]. This scale is a Dutch translation and adaptation of the Stockton Geriatric Rating Scale, which has subsequently been re-translated into English and other languages. The BGP-Care Dependency subscale assesses cognitive and functional characteristics associated with increased need for care. The maximum score on this subscale is 46; a higher score indicates greater impairment.

Individual Trials: Total NPI Score

Three trials met the inclusion criteria: MRZ-90001-9605, authored by Reisberg et al. [17], MEM-MD-01 by van Dyck et al. [53], and MEM-MD-02 by Tariot et al. [18]. The trial by Reisberg et al. [17] used only the NPI as a behavior assessment tool, and the trials by van Dyck et al. [53] and Tariot et al. [18] utilized both the NPI and BGP [18, 53]. The basic properties of these studies, including a summary of behavioral outcomes and effect sizes, are presented in table 2.

The trials by Reisberg et al. [17] and van Dyck et al. [53] found no statistically significant differences between memantine and placebo groups at study endpoint on the NPI total score, although the mean NPI score of the memantine-treated group in the Reisberg et al. [17] study remained stable over the course of the trial, while the placebo-treated group showed a slight clinical decline. In the study by Tariot et al. [18], patients treated with memantine and donepezil significantly outperformed patients treated with placebo and donepezil on the total NPI score at both week 12 and study endpoint [18, 58].

Individual NPI Items

A post-hoc analysis of individual NPI items revealed a significant advantage for memantine therapy over placebo at study endpoint on the item of agitation/aggression in the studies by Reisberg et al. [17] and Tariot et al. [18, 58, 59]; in the trial by van Dyck et al. [53], the benefit was significant at week 12 (last observation carried forward analysis), but not at endpoint. In addition, memantine therapy in the study by Tariot et al. [18] was found to provide a significant advantage at study endpoint on the items of irritability/lability and appetite/eating change, and on the item of delusions in the trial by Reisberg et al. [17, 58, 59] (table 2). Placebo-treated patients did not show significant advantages over memantine-treated patients on any item in any of the 3 studies.

Table 1. CONSORT [51, 52] evaluation of memantine trials involving outpatients with moderate to severe AD

Item	Topic	Descriptor	Report	Reisberg et al. [17]	Tariot et al. [18]	van Dyck et al. [53]
Title and abstract						
1	Allocation to treatment	Allocation of participants to interventions (e.g. 'randomized').	Y	Y	Y	Y
Introduction						
2	Background	Scientific background and explanation of rationale.	Y	Y	Y	Y
Methods						
3	Participants	Eligibility criteria; settings and locations where the data were collected.	Y	Y	Y	Y
4	Interventions	Precise details of the interventions intended for each group and how and when they were actually administered.	Y (imprecise)	Y	Y	Y (imprecise)
5	Objectives	Specific objectives and hypotheses.	N	Y	Y	N
6	Outcomes	Clearly defined primary and secondary outcome measures.	Y	Y	Y	Y
7	Sample size	How sample size was determined.	N	Y	Y	Y
8	Randomization – sequence generation	Detailed method used to generate the random allocation sequence.	Y	Y	Y	N
9	Randomization – allocation concealment	Method used to implement the random allocation sequence.	N	Y (imprecise)	N	N
10	Randomization – implementation	Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.	N	Y	N	N
11	Blinding (masking)	Blinding of participants, those administering the interventions, and those assessing the outcomes: if done, how the success of blinding was evaluated.	Y (no success data)	Y	Y	Y (sparse detail)
12	Statistical methods	Statistical methods used to compare groups for primary outcome(s); methods for additional analyses, such as subgroup analyses and adjusted analyses.	Y	Y	Y	Y
Results						
13	Participant flow	Flow of participants through each stage (a diagram is strongly recommended).	Y (no diagram)	Y	Y	Y
14	Recruitment	Dates defining the periods of recruitment and follow-up.	Y (screening only)	Y (imprecise)	Y	Y (imprecise)
15	Baseline data	Baseline demographic and clinical characteristics of each group.	Y	Y	Y	Y
16	Numbers analyzed	Number of participants in each group included in each analysis and whether the analysis was by 'intention to treat'. If feasible, state the results in absolute numbers.	Y	Y	Y	Y
17	Outcomes and estimation	For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision (e.g. 95% CI).	Y (no effect sizes or 95% CI data)	Y (no effect sizes or 95% CI data)	Y	Y (no effect sizes or 95% CI data)
18	Ancillary analyses	Address multiplicity by reporting any other analyses performed, including subgroup analyses and adjusted analyses, indicating those prespecified and those exploratory.	Y (imprecise)	Y	Y	Y
19	Adverse events	All important adverse events or side effects in each intervention group.	Y	Y	Y	Y
Discussion						
20	Interpretation	Interpretation of the results, taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	Y	Y	Y	Y
21	Generalizability	Generalizability (external validity) of the trial findings.	Y	Y	Y	Y
22	Overall evidence	General interpretation of the results in the context of current evidence.	Y	Y	Y	Y
Y indicates full compliance with a particular CONSORT recommendation; Y with parentheses indicates partial compliance; N indicates a lack of compliance.						

Table 2. Summary of double-blind, placebo-controlled memantine trials involving outpatients with moderate to severe AD

Study ^a	Trial design	Psychoactive drug use	Behavioral outcome measure	Treatment groups	Score at baseline ^b	Mean score change from baseline at endpoint ^b	Effect size (95% CI) ^c	Significant individual domains
Reisberg et al. [17]	28 weeks 20 mg/day n = 252 monotherapy	no antipsychotics, anxiolytics, or neuroleptics permitted	NPI	Pbo Mem	19.5 21.4	3.6 0.4	−0.21 (−0.45, 0.04)	delusions* [59] agitation/aggression** [59]
Tariot et al. [18]	24 weeks 20 mg/day n = 404 combination therapy	– antidepressants: Pbo/Don, 36%; Mem/Don, 36% – anxiolytics or neuroleptics: Pbo/Don, 26%; Mem/Don, 22%	NPI**	Pbo/Don	13.6	3.60	−0.30 (−0.51, −0.10)	agitation/aggression** [58, 59] irritability/lability** [58, 59] appetite/eating change * [58, 59]
				Mem/Don	13.4	−0.24		
			BGP***	Pbo/Don	13.4 ^c	3.1 ^c	−0.34 (−0.55, −0.13)	
				Mem/Don	13.0 ^c	1.0 ^c		
van Dyck et al. [53]	24 weeks 20 mg/day n = 350 monotherapy	– antidepressants: Pbo, 29%; Mem, 32% – anxiolytics or neuroleptics: Pbo, 31%; Mem, 30%	NPI	Pbo	17.5	−0.2 ^c	−0.05 (−0.27, 0.17)	none ^c none ^c
				Mem	20.3	−1.0 ^c		
			BGP	Pbo	16.7	1.4 ^c	−0.14 (−0.37, 0.09)	
				Mem	17.3	0.6 ^c		

Don = Donepezil group; Mem = memantine group; Pbo = placebo group.

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

^a No study included patients with severe behavioral problems.

^b All efficacy values are according to the LOCF approach.

^c New data, obtained/calculated for this report.

A post-hoc analysis that focused solely on the Tariot et al. [18] study reported that in patients who were asymptomatic at baseline for each individual symptom of agitation/aggression, irritability/lability, and nighttime behavioral disturbances, a significantly lower proportion of memantine-treated patients demonstrated an emergence of these symptoms compared to patients treated with placebo [58]. No NPI symptoms emerged in a significantly higher proportion of memantine-treated patients [58]. In addition, memantine-treated patients who demonstrated agitation at baseline experienced a significant mean improvement at endpoint on this NPI item, compared to their placebo-treated counterparts [58]. It should be noted, however, that the trial was not designed to examine differences in individual NPI items, and that baseline matching of the two groups was not performed according to individual NPI item scores.

Pooled Analyses and Meta-Analyses: Total NPI Score

Two approaches have been employed in combining trial data for the purpose of meta-analysis in memantine

studies in moderate to severe AD. In the first approach, used by McShane et al. [19] and Doody et al. [60], the dataset was created by compiling data from all three 6-month, placebo-controlled trials of memantine in moderate to severe AD that used the NPI [17, 18, 53]. The study group was then analyzed for the effects of memantine treatment on overall behavioral symptomatology (i.e. the mean change from baseline of the total NPI score). Both studies used the same statistical tools, and both found an overall significant (and homogeneous) advantage of memantine over placebo.

In the second approach, utilized in a meta-analysis by Winblad et al. [61], the data from memantine trials in moderate to severe AD [17, 18, 53] were combined with those of patients from the three memantine trials in mild to moderate AD [62–64] who were in the moderate stage of the disease (baseline MMSE score of 19 or below). The second approach also demonstrated a significant benefit of memantine over placebo on the total NPI score [61].

Pooled Analyses and Meta-Analyses: Individual NPI Items and Item Clusters

The two approaches outlined above were also used in meta-analyses that focused on the efficacy of memantine on individual behavioral symptoms in patients with moderate to severe AD. An analysis by Cummings and Olin [65] examined the data from all participants in the trials by Reisberg et al. [17], van Dyck et al. [53], and Tariot et al. [18], and found that three NPI domains demonstrated homogeneous, statistically significant treatment differences in favor of memantine: delusions, agitation/aggression, and irritability/lability. The other individual-item meta-analysis by Gauthier et al. [20] utilized the data of all the participants from the trials of Reisberg et al. [17], van Dyck et al. [53], and Tariot et al. [18], together with those of patients from the three memantine trials in mild to moderate AD [62–64] who were in the moderate stage of the disease (baseline MMSE score of 19 or below). This study also found that the memantine-treated patients demonstrated a significantly lower mean score change from baseline at endpoint (i.e. better performance) than the placebo-treated patients on the NPI items of delusions, agitation/aggression, and irritability/lability, as well as on a fourth item, hallucinations [20]. Memantine treatment also significantly reduced the emergence of agitation/aggression, irritability/lability, and nighttime behavior [20], according to this analysis.

An additional report by Wilcock et al. [21], which combined the data from the three memantine trials in moderate to severe AD [17, 18, 53], looked at all the patients from those trials who experienced agitation/aggression or psychosis at baseline (i.e. had a score >0 on at least one of the following NPI items: agitation/aggression, delusions, and hallucinations). The study found that, at endpoint and at week 12, memantine-treated patients with baseline symptoms of either agitation/aggression or psychosis demonstrated a significant improvement on that symptom cluster compared to their placebo-treated counterparts, both in terms of the mean score change from baseline and in terms of the proportion of patients who demonstrated a clinical improvement [21].

Discussion

Collectively, these findings suggest that 6 months of memantine treatment significantly reduce behavioral disturbances in outpatients with moderate to severe AD. This conclusion is further strengthened by the results of a recently completed 24-week, double-blind, placebo-

controlled trial of an extended-release memantine formulation (28 mg/day, once daily), involving 676 community-dwelling patients with moderate to severe AD who were receiving concurrent, stable treatment with a cholinesterase inhibitor [66]. The group treated with memantine demonstrated a mean (SD) baseline to endpoint improvement of 4.3 (14.6) points on the total NPI, which was significantly greater than an improvement of 1.6 (12.7) points observed in the placebo group (LOCF; $p = 0.005$) [66]. These results were presented at the 2008 International Conference on Alzheimer's Disease (ICAD), and at the time of this review have not been published in a peer-review journal.

The consistent effect of memantine on symptoms of agitation/aggression may be of particular significance in the treatment of AD. According to multiple reports, aggressive behavior and agitation occur in approximately 30% of all patients with dementia [29, 67] and are correlated with an increased risk of nursing home placement [68]. Such symptoms are traditionally treated with antipsychotic medications; however, recent guidelines advise against using antipsychotics in elderly patients, due to an increased likelihood of serious cerebrovascular events [46, 48]. Therefore, the consistently reported alleviation of agitation and aggression in memantine-treated outpatients with moderate to severe AD merits further investigation, particularly if delay of institutionalization is a possible outcome. It should be noted that a recent trial of this nature, specifically designed to assess treatment benefits of the cholinesterase inhibitor donepezil in patients with moderate to severe AD who experienced clinical agitation, failed to show a significant advantage of donepezil treatment over placebo [69].

Limitations

With the exception of studies conducted in institutionalized patients (e.g. a trial of memantine involving nursing home residents with dementia [50]), most AD trials exclude patients with significant behavioral disturbances at screening. Although some patients subsequently develop behavioral symptoms during the trial, the participants typically do not express the range of disturbances generally seen in AD. This is particularly the case for trials involving patients with moderate to severe AD, as baseline NPI scores in these studies are relatively low compared to what is typically seen in such patients. Therefore, the information obtained in these studies cannot be readily extended to patients in naturalistic settings, since such patients are likely to experience severe behavioral symptoms. In addition, the trials were not de-

signed to detect differences between groups on individual NPI items.

Although all trial groups were generally balanced in terms of psychotropic use, it cannot be ruled out that concomitant medications may have acted as a confounding factor in analyzing behavioral symptomatology. To properly assess the effectiveness of memantine in alleviating and preventing behavioral disturbances, clinical trials involving patients who meet specific behavioral criteria and concomitant medication restrictions are warranted.

Conclusion

Considering the prevalence, high cost, and negative impact of behavioral problems in AD, coupled with the risks associated with polypharmacy, it is important to consider whether the currently prescribed AD treatments can provide behavioral benefits. Current data provide evidence that memantine, in addition to its effects on cognition and daily functioning, may be efficacious in alleviating or preventing behavioral symptoms in patients with moderate to severe AD who are still living in the

community. The consistent effect of memantine treatment on agitation/aggression and irritability/lability across multiple trials and in meta-analyses is notable. Prospective, randomized, placebo-controlled trials in outpatient settings using behavior as the primary outcome are warranted, so that we may better understand the clinical impact of these drugs.

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