Notice of Correction 6/20/2011: The acknowledgment "Dr. Wilcock was partly supported by the NIHR Oxford Biomedical Research Centre" has been added to page 341.

Memantine for Agitation/Aggression and Psychosis in Moderately Severe to Severe Alzheimer's Disease: A Pooled Analysis of 3 Studies

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Objective: Long-standing evidence indicates that Alzheimer's disease patients with behavioral symptoms have a worse prognosis and a more rapid disease progression. The current retrospective analysis evaluated the efficacy and safety of memantine in a subpopulation of patients with Alzheimer's disease exhibiting behavioral symptoms of agitation/aggression or psychosis at baseline.

Method: A pooled analysis was conducted in people with agitation/aggression or psychosis from 3 large 6-month, randomized studies in moderately severe to severe Alzheimer's disease. The effect of memantine and placebo on these specific symptoms was evaluated using the Neuropsychiatric Inventory (NPI) subitem cluster of agitation and psychosis. Outcomes on global, cognitive, and functional measures were also analyzed.

Results: Sixty percent of the total patient group had baseline symptoms of agitation/aggression, delusions, or hallucinations on the NPI. At both 12 and 24/28 weeks, there was a significant treatment advantage for memantine over placebo for the proportion of patients showing improvement on the defined neuropsychiatric symptom cluster (55.6% vs. 44.4% at week 12, $p = .008$; 58.0% vs. 44.8% at week 24/28, $p = .002$) and specifically for the treatment of agitation/aggression (55.3% vs. 43.1% at week 12, $p = .011$; 61.0% vs. 45.0% at week 24/28, $p < .001$). Placebo-treated patients in this population demonstrated an accelerated disease progression for global (Clinician's Interview-Based Impression of Change Plus Caregiver Input), cognitive (Severe Impairment Battery), and functional (Alzheimer Disease Cooperative Study Activities of Daily Living Inventory 19-item scale) outcomes, but memantine conferred statistically significant benefit for all measures. Tolerability in this population remained good, and fewer memantine-treated patients than placebo-treated patients withdrew due to adverse events.

Conclusions: This post hoc analysis provides important evidence from placebo-controlled trials that memantine may be a safe and effective treatment in Alzheimer's disease patients with agitation/aggression or psychosis, who are otherwise prone to rapid progression. Memantine treatment provided benefits in cognitive, functional, and global outcomes in these patients and for their agitation/aggression.

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See also Commentary on page 339.

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Worldwide, 24.3 million people suffer from dementia,[1] and the majority of these people have Alzheimer's disease (AD). AD is a devastating illness that results in a progressive decline in cognitive ability and functional capacity. Symptoms of agitation/aggression and psychosis are common, with more than 90% of people with dementia developing 1 or more of these problems at some point during their illness.[2,3] Of these symptoms, agitation and aggression are the most frequent and the most persistent.[4] Behavioral and psychotic symptoms are associated with rapid disease progression, and symptoms of agitation and psychosis have been repeatedly highlighted as major determinants of institutionalization and increased direct costs of care.[5–15] Furthermore, these distressing symptoms increase caregiver burden and give rise to clinically significant depression.[9,16–18] Thus, these patients and their caregivers are particularly vulnerable to a range of significant adverse outcomes.

Neuroleptic drugs are widely used off-license as the first-line pharmacologic treatment for neuropsychiatric

Reprinted with correction to page 341.

symptoms in people with dementia, with one study showing that 58% of nursing home residents with dementia were receiving antipsychotics.[19] While there is a clear indication of benefit of atypical neuroleptics (risperidone, olanzapine, quetiapine, aripiprazole) in the treatment of aggression (20% advantage over placebo in responder rates) from a substantial evidence base of 18 randomized, placebo-controlled, clinical trials with durations between 6 and 12 weeks, improvements in psychotic symptoms are more marginal, the impact on nonaggressive agitation has not been adequately clarified, and the magnitude of change has not been sufficient to be clinically meaningful.[20–22] In addition, longer term efficacy has not been established with neuroleptic withdrawal studies, and the small number of trials lasting longer than 3 months have failed to identify any significant advantage for neuroleptic treatment compared with placebo.[22–25]

Moderate benefits in the treatment of aggression can be useful and are probably more substantial for people with more severe symptoms. However, there have been increasing concerns regarding the safety of these drugs for people with dementia. Recent evidence has highlighted a number of potential risks associated with neuroleptic treatments, in addition to established side effects such as parkinsonism and sedation.[21] These include stroke and other adverse cerebrovascular events, increased mortality, edema, increased upper respiratory tract infections, and falls, leading to a series of warnings regarding these compounds in people with dementia by, for example, the Food and Drug Administration in the United States and the Committee for the Safety of Medicines in the United Kingdom.[20,21,26–30]

Furthermore, several clinical and pathologic studies indicate that neuroleptics may accelerate cognitive decline and disease pathology.[21,31,32] A recent randomized, double-blind, placebo-controlled study[22] of 3 atypical antipsychotic drugs (olanzapine, quetiapine, and risperidone) in the management of outpatients with AD and psychosis, aggression, or agitation demonstrated that, over a 9-month follow-up period, while patients receiving antipsychotic treatment were less likely to discontinue therapy due to lack of efficacy, they were more likely to discontinue due to intolerability/adverse events. The advantages of atypical antipsychotic treatment related to efficacy were, therefore, offset by the adverse effects of these drugs.[22] These disappointing findings highlight the continued need for alternative treatments.

A clinical dilemma has resulted: neuropsychiatric symptoms can be extremely distressing for people with dementia and their caregivers, can precipitate nursing home placement,[11] and can put people at serious risk of injury, but neuroleptic treatments increase the likelihood of serious detrimental outcomes. There is an urgent need for pharmacologic therapies that are safe and offer long-term efficacy in the management of behavioral symptoms in these individuals. Although there is some indication of possible benefit in the treatment of agitation with anticonvulsants such as carbamazepine or sodium valproate, and antidepressants such as trazodone, the literature is inconsistent, the evidence is inconclusive, and some of these treatments are associated with considerable side effects.[33–35]

Cholinesterase inhibitors may offer another alternative, although there are limited studies focusing on people with significant neuropsychiatric symptoms, and the main benefits appear to be related to mood disturbance rather than agitation and aggression.[36] Three studies[37–39] have prospectively evaluated the potential neuropsychiatric benefits of donepezil in AD patients with symptomatic disturbance at baseline. Tariot and colleagues[37] studied 208 nursing home patients over 24 weeks with the nursing home version of the Neuropsychiatric Inventory (NPI-NH) and showed no significant differences versus placebo for any assessment visit, although a secondary responder analysis highlighted a possible advantage for the agitation/aggression subitem. Holmes and colleagues[38] studied 134 mild to moderate AD patients with marked neuropsychiatric symptoms at baseline (NPI total score > 11 points), using a randomized withdrawal design. After 12 weeks of open-label treatment with donepezil, patients were randomly assigned to either continue treatment with donepezil or switch to placebo for up to 12 further weeks. Maintaining treatment with donepezil offered statistically significant advantage over placebo overall (NPI total score), but effects on the individual symptoms (i.e., on agitation/aggression and the psychotic subitems) were not presented for the randomized phase of the trial.[38] Finally, a recent article[39] has reported the findings of the CALM-AD trial, which evaluated 272 AD patients with clinically significant agitation. After 12 weeks of treatment, there was no statistical difference on the Cohen-Mansfield Agitation Inventory and NPI scale (primary and secondary outcomes) between patients randomly assigned to donepezil and those given placebo.

Behavioral disturbances in general, and agitation in particular, become more evident as dementia severity increases.[17,40] In addition to finding effective and safe alternatives for treatment, it is important to prevent these symptoms from emerging and thus the potential pattern of accelerated decline of AD from becoming established.

The efficacy and tolerability of memantine, an *N*-methyl-D-aspartate antagonist, for the treatment of patients with moderately severe to severe AD have been established in a number of placebo-controlled studies, with significant benefits in global, cognitive, functional, and behavioral domains, compared with placebo.[41–43] Emerging evidence indicates that memantine may also be helpful in treating neuropsychiatric symptoms of agitation/aggression and psychosis.[44–46] The current article details work presented to the National Institute for Health and

Reprinted with correction to page 341.

Clinical Excellence (NICE), describing the impact of memantine in a group of patients for whom clinicians had witnessed particular symptom benefit. The work was reported to NICE as part of their review of antidementia drugs in the United Kingdom. A post hoc, pooled, subanalysis of three 6-month, randomized, placebo-controlled studies of memantine in people with moderately severe to severe AD is described, focusing on patients with agitation/aggression and/or psychosis at baseline.

METHOD

Design of the Original Studies

The present analysis is based upon the results of three 6-month, randomized, placebo-controlled studies.[41,42,47] All of the trials were multicenter, double-blind, parallel-group, and of 24 or 28 weeks' duration. Memantine was up-titrated to a fixed dose of 20 mg daily (10 mg b.i.d.) over 3 weeks in 5-mg increments. In one study,[42] memantine or placebo was added to existing stabilized treatment with donepezil. The other trials did not include people taking cholinesterase inhibitors. The entry criteria for the 3 trials included the presence of moderately severe to severe AD (Mini-Mental State Examination [MMSE] score between 14 and 3, or 14 and 5). The main efficacy parameters common to all studies included the Severe Impairment Battery (SIB) as a measure of cognition, the Alzheimer Disease Cooperative Study Activities of Daily Living Inventory 19-item scale (ADCS-ADL_{19}) as a functional outcome, the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) as a measure of global function, and the Neuropsychiatric Inventory (NPI) as a measure of behavioral disturbance. Postbaseline NPI assessments were conducted at week 12 and at study endpoint (week 24/28) only.

Current Analyses

The primary aim of the current report is to present the effects of memantine in the treatment of patients with AD demonstrating symptoms of agitation/aggression and/or psychosis. Data from the 3 original trials were pooled and integrated. Patients were included in the behaviorally disturbed population (BDP) if they scored > 0 on any of the 3 NPI symptoms (agitation/aggression, delusions, hallucinations) at baseline, i.e., they had demonstrated evidence of at least 1 of these symptoms within 4 weeks of the assessment. Of the 983 patients comprising the total pooled population, 593 (60%) had agitation/aggression or psychosis at baseline (287 placebo, 306 memantine) and were defined as BDP patients for analysis. The effect of memantine and placebo on these specific symptoms was evaluated using the NPI subitem cluster of agitation and psychosis (i.e., the combined score on the 3 items of agitation/aggression, delusions, and hallucinations). This cluster has previously been used to evaluate the effectiveness of an antipsychotic in AD patients.[48]

Statistical Methods

Statistical analyses for efficacy were conducted on the full analysis set for BDP patients, comprising all randomized patients receiving treatment and 1 valid postbaseline efficacy evaluation. Analyses were conducted using both last-observation-carried-forward (LOCF) and observed case (OC) methods. The analyses considered change from baseline and compared performance in the memantine- and placebo-treated groups, with analysis of variance when analyzing NPI cluster and single-item scores, and with analysis of covariance models when analyzing SIB, ADCS-ADL_{19}, and CIBIC-Plus total scores. In addition, categorical data (e.g., the proportion of patients who improved within a treatment group) were compared between treatment groups using a χ^2 test. Presentation and statistical analysis of tolerability data have been performed on the all patients treated set, comprising all individuals randomly assigned to study treatment and receiving at least 1 dose.

The total sample size of 593 patients for the BDP was considered adequate for detecting clinically meaningful differences. Using a significance level of 5%, the power for detecting standardized effect sizes as small as 0.27 is above 90%.

Due to the post hoc nature of the analyses presented in the article, with no hypotheses being prespecified, no attempts to adjust for multiplicity were made, and all hypotheses were tested at the 5% level of significance. This should be taken into consideration in the interpretation of results, particularly for p values approaching the 5% level. However, the majority of the p values presented fall well below 5%.

RESULTS

Apart from baseline total NPI score, the BDP patient group resembled the total pooled trial population in terms of demographics, disease severity, and baseline evaluations (Table 1). This similarity included the mean baseline MMSE score, which was comparable between the BDP group (9.2) and the total population (9.5), for memantine-treated patients. Furthermore, all other baseline values were also similar between the memantine- and placebo-treated patient groups (Table 1).

Within the BDP patient group at baseline, 454 patients (76.6%) had symptoms of agitation/aggression, 336 (56.7%) had symptoms of delusions, and 172 (29.0%) had symptoms of hallucinations.

The Effect of Memantine Treatment on the Symptoms of Agitation/Aggression and Psychosis

There was a significant advantage for the memantine group compared with those receiving placebo on the NPI

Reprinted with correction to page 341.

Table 1. Baseline Characteristics of the Behaviorally Disturbed Population and Total Pooled Population

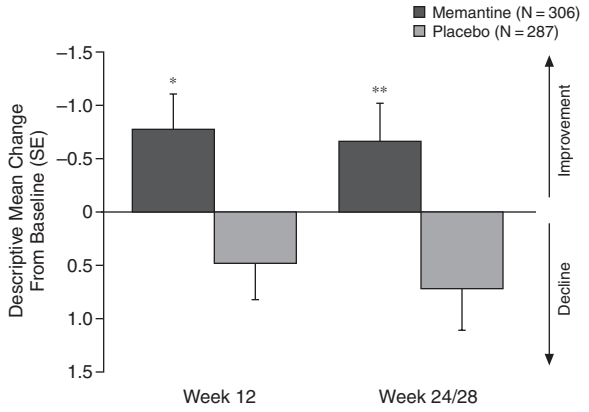
Characteristic	Behaviorally Disturbed Population		Total Pooled Population	
	Memantine (N = 306)	Placebo (N = 287)	Memantine (N = 495)	Placebo (N = 488)
Age, mean (SD), y	76.9 (8.4)	76.7 (7.9)	76.5 (8.4)	76.6 (8.2)
Sex, female, N (%)	211 (69.0)	189 (65.9)	339 (68.5)	328 (67.2)
Race, white, N (%)	264 (86.3)	248 (86.4)	429 (86.7)	433 (88.7)
MMSE score, mean (SD)	9.2 (3.3)	9.6 (3.1)	9.5 (3.3)	9.8 (3.2)
SIB score, mean (SD)	72.4 (19.4)	74.2 (19.2)	74.6 (18.5)	75.4 (18.5)
ADCS-ADL$_{19}$ score, mean (SD)	30.2 (10.5)	31.2 (10.7)	32.6 (10.7)	33.1 (10.8)
NPI total score, mean (SD)	24.2 (15.8)	22.9 (15.7)	17.9 (15.5)	16.5 (15.0)

Abbreviations: ADCS-ADL$_{19}$ = Alzheimer Disease Cooperative Study Activities of Daily Living Inventory 19-item scale, MMSE = Mini-Mental State Examination, NPI = Neuropsychiatric Inventory, SIB = Severe Impairment Battery.

cluster (agitation/aggression, delusions, and hallucinations) score at both week 12 (–0.8 points vs. 0.5 points; p = .0014) and week 24/28 (–0.7 points vs. 0.7 points; p = .0004) (Figure 1). Further, a significantly higher proportion of the memantine-treated patients showed improvement on this symptom cluster, compared with placebo, at week 12 (55.6% vs. 44.4%; p = .008) and week 24/28 (58.0% vs. 44.8%; p = .002) (Table 2).

In a secondary analysis of the 3 individual NPI items, a significantly greater proportion of patients receiving memantine treatment experienced improvement in agitation/aggression, compared with placebo, at week 12 (55.3% vs. 43.1%; p = .011) and week 24/28 (61.0% vs. 45.0%; p < .001) (Table 2). The proportions of responders in the single items delusions and hallucinations were numerically higher for patients receiving memantine, but the difference from placebo did not reach statistical significance.

Figure 1. Behaviorally Disturbed Population Performance on the NPI Subitem Cluster (agitation/aggression, delusions, hallucinations)



*p < .01.
**p < .001.
Abbreviation: NPI = Neuropsychiatric Inventory.

Impact of Memantine Treatment on Other Key AD Outcomes in People With Agitation/Aggression or Psychosis

The benefits of memantine on other key AD outcomes in the patients with agitation/aggression or psychosis are presented in Figure 2. Statistically significant benefits over placebo (OC and LOCF analyses) were seen with memantine on the SIB and ADCS-ADL$_{19}$ scales at all postbaseline visits. On the CIBIC-Plus assessment, statistically significant benefits over placebo (OC and LOCF analyses) were seen with memantine at week 12 and week 24/28. For comparison, in the total pooled trial population, the least squares (LS) mean changes from baseline scores at endpoint were –2.0 versus –5.1 (p < .001) on the SIB and –2.9 versus –4.2 (p = .002) on the ADCS-ADL$_{19}$, and the LS mean scores were 4.46 versus 4.70 (p < .001) on the CIBIC-Plus for memantine versus placebo treatment, respectively.

In the BDP group, memantine-treated patients, compared with placebo-treated patients, were significantly more likely to be improved or stabilized relative to baseline values of SIB, CIBIC-Plus, and ADCS-ADL at the study endpoint (week 24/28, LOCF) (Table 3).

Safety and Tolerability in Patients With Agitation/Aggression or Psychosis

Memantine-treated patients from the BDP had significantly fewer withdrawals relative to placebo (22.9% vs. 32.3%; p < .01), fewer withdrawals due to adverse events (10.3% vs. 17.3%; p < .05), and overall comparable rates of treatment-emergent adverse events (82.6% vs. 79.9%) (Table 4). The difference in withdrawals due to adverse events between treatment groups was largely driven by a 3-fold higher level of withdrawals due to symptoms of agitation or psychosis (2.6% vs. 7.5%; p < .01) in placebo-treated patients.

Evidence of More Rapid Disease Progression in Behaviorally Disturbed Patients

Placebo-treated BDP patients demonstrated considerably greater decline in the 6-month studies, compared with placebo-treated patients without these symptoms at baseline (87% more decline on SIB and 48% more decline on ADCS-ADL$_{19}$ [both LS mean change from

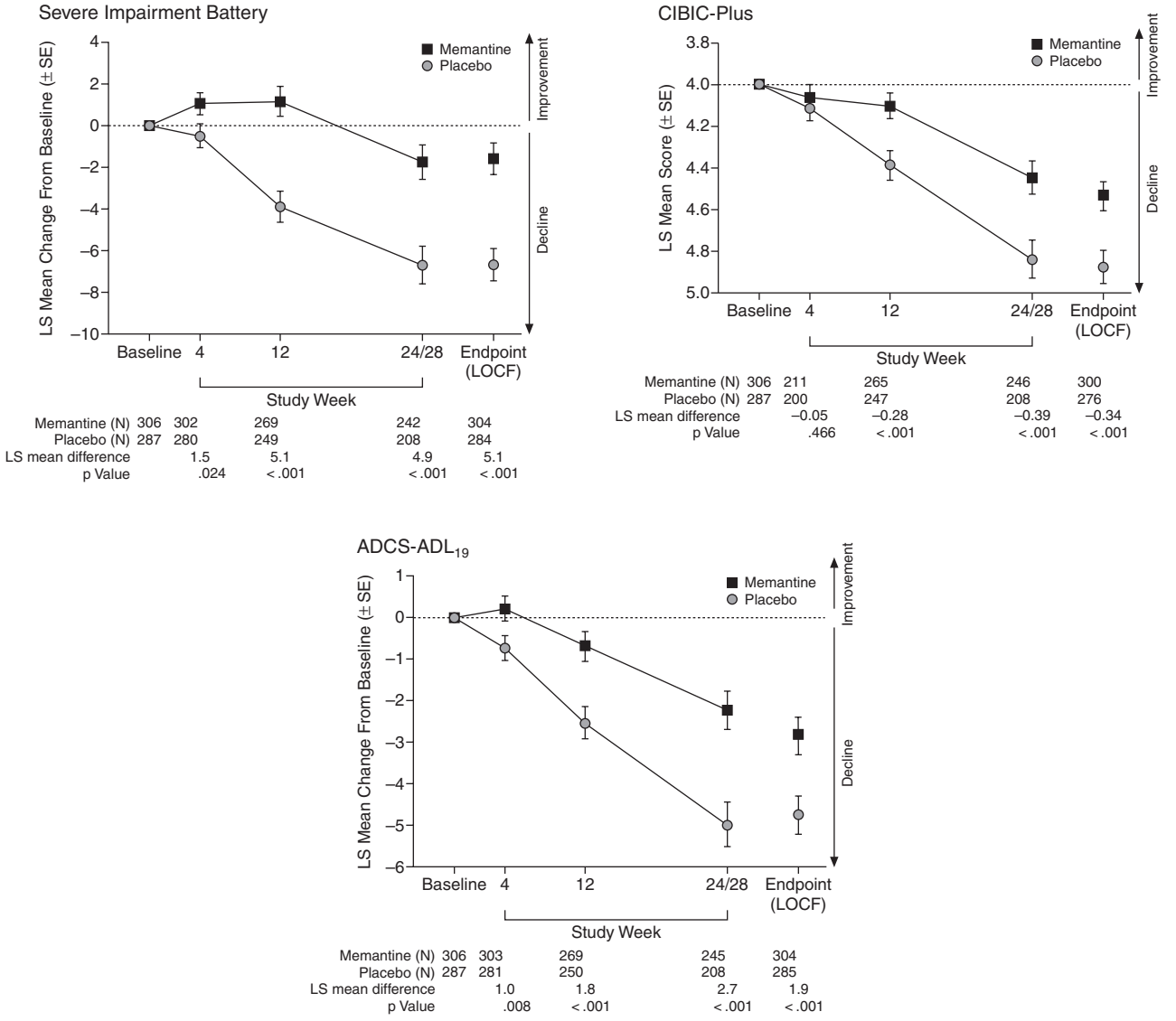
Reprinted with correction to page 341.

Table 2. Proportion of Symptomatic Patients Showing Treatment Benefit on NPI Subitem Cluster and the Individual Subitems of Agitation/Aggression, Delusions, and Hallucinations at Weeks 12 and 24/28 (LOCF)[a]

	Week 12				Week 24/28			
NPI Item	Memantine, N/N (%)	Placebo, N/N (%)	Difference (%)	p Value	Memantine, N/N (%)	Placebo, N/N (%)	Difference (%)	p Value
3-item cluster	158/284 (55.6)	119/268 (44.4)	11.2	.008	167/288 (58.0)	121/270 (44.8)	13.2	.002
Agitation/aggression	119/215 (55.3)	90/209 (43.1)	12.2	.011	133/218 (61.0)	95/211 (45.0)	16.0	< .001
Delusions	89/160 (55.6)	75/145 (51.7)	3.9	.495	97/163 (59.5)	74/147 (50.3)	9.2	.105
Hallucinations	49/79 (62.0)	39/81 (48.1)	13.9	.078	50/81 (61.7)	44/81 (54.3)	7.4	.340

[a]In each case (NPI cluster results and individual subitems), results are presented for patients displaying baseline symptoms (NPI score > 0) and with a subsequent NPI assessment at either week 12 or week 24/28.
Abbreviations: LOCF = last observation carried forward, NPI = Neuropsychiatric Inventory.

Figure 2. Severe Impairment Battery, CIBIC-Plus, and ADCS-ADL$_{19}$ Scores by Visit (OC) and at Endpoint (LOCF) in the Behaviorally Disturbed Population



Abbreviations: ADCS-ADL$_{19}$ = Alzheimer Disease Cooperative Study Activities of Daily Living Inventory 19-item scale, CIBIC-Plus = Clinician's Interview-Based Impression of Change Plus Caregiver Input, LOCF = last observation carried forward, LS = least squares, OC = observed cases.

Reprinted with correction to page 341.

Table 3. Proportion of Behaviorally Disturbed Patients Demonstrating Improvement or Stabilization Relative to Baseline at Endpoint (LOCF) on Cognitive, Global, and Functional Outcomes

Scale (total score)	Memantine, N/N (%)	Placebo, N/N (%)	Difference (%)	p Value
SIB	165/304 (54.3)	101/284 (35.6)	18.7	< .001
CIBIC-Plus	166/300 (55.3)	116/276 (42.0)	13.3	.001
ADCS-ADL$_{19}$	130/304 (42.8)	85/285 (29.8)	12.9[a]	.001

[a]Difference due to rounding errors.
Abbreviations: ADCS-ADL$_{19}$ = Alzheimer Disease Cooperative Study Activities of Daily Living Inventory 19-item scale, CIBIC-Plus = Clinician's Interview-Based Impression of Change Plus Caregiver Input, LOCF = last observation carried forward, SIB = Severe Impairment Battery.

Table 4. Behaviorally Disturbed Patient Withdrawals and Treatment-Emergent Adverse Events (all patients treated set), N (%)

	Memantine (N = 310)	Placebo (N = 294)
Reason for withdrawal		
Any reason	71 (22.9)	95 (32.3)
Adverse event	32 (10.3)	51 (17.3)
Adverse events of agitation or psychosis	8 (2.6)	22 (7.5)
Withdrawal of consent	23 (7.4)	27 (9.2)
Protocol violation	6 (1.9)	9 (3.1)
Lack of efficacy	2 (0.6)	3 (1.0)
Lost to follow-up	2 (0.6)	0 (0.0)
Administrative or other reasons	6 (1.9)	5 (1.7)
Incidence of treatment-emergent adverse events reported by ≥ 5% in either group		
One or more adverse events	256 (82.6)	235 (79.9)
Agitation	56 (18.1)	68 (23.1)
Urinary tract infection	30 (9.7)	28 (9.5)
Fall	27 (8.7)	31 (10.5)
Diarrhea	24 (7.7)	20 (6.8)
Inflicted injury	23 (7.4)	32 (10.9)
Urinary incontinence	22 (7.1)	22 (7.5)
Hallucination	21 (6.8)	13 (4.4)
Insomnia	20 (6.5)	25 (8.5)
Confusion	18 (5.8)	15 (5.1)
Dizziness	18 (5.8)	16 (5.4)
Vomiting	18 (5.8)	10 (3.4)
Anorexia	17 (5.5)	11 (3.7)
Constipation	17 (5.5)	18 (6.1)
Headache	17 (5.5)	15 (5.1)
Hypertension	17 (5.5)	7 (2.4)
Influenza-like symptoms	17 (5.5)	19 (6.5)
Somnolence	16 (5.2)	11 (3.7)
Depression	14 (4.5)	15 (5.1)
Fecal incontinence	13 (4.2)	18 (6.1)
Incidence of other relevant treatment-emergent adverse events		
Peripheral edema	15 (4.8)	12 (4.1)
Upper respiratory tract infection	15 (4.8)	14 (4.8)
Cerebrovascular disorder	1 (0.3)	4 (1.4)

baseline] and 66% more decline on CIBIC-Plus [LS mean score]).

Reduced Emergence of Behavioral Disturbance With Memantine

Of those patients who were asymptomatic at baseline (i.e., did not have agitation/aggression or psychosis), significantly fewer memantine-treated patients went on to develop these key symptoms at 12 weeks (20.3% of memantine-treated patients compared with 31.9% of placebo-treated patients [p = .010]) and 24/28 weeks (24.2% of memantine-treated patients compared with 37.0% of placebo-treated patients [p = .007]), compared with placebo. Thus, in addition to the 60% of patients from the total pooled population who already displayed these symptoms at baseline, a further 37% of the remaining placebo-treated patients had also developed these symptoms at the 6-month timepoint, compared with only 24% for memantine.

The preventive benefit of memantine was also evident in the proportion of patients not included in the BDP (i.e., without baseline symptoms) in whom an adverse event of agitation was reported (12.2% vs. 6.1% for placebo and memantine, respectively, p < .05).

DISCUSSION

The current pooled analysis demonstrates that memantine treatment confers significantly greater overall benefit (cognition, activities of daily living, global function) than placebo in the treatment of patients with agitation/aggression and/or psychosis in the context of AD. These symptoms are known to be associated with rapid disease progression, increased caregiver burden, and early institutionalization and can add to the risk of injury to the patient or others. Thus, the findings from this analysis suggest that memantine confers benefit in these vulnerable patients.

In addition to the benefits demonstrated for cognition, function, and global outcome, positive effects were also shown on some behavioral measures for these patients. In this sample of 593 patients with moderately severe to severe AD and agitation/aggression or psychosis, a significantly greater proportion of memantine-treated patients than placebo-treated patients experienced improvement of agitation/aggression at both weeks 12 and 24/28. For psychosis, there was numerical superiority in favor of memantine treatment, but the treatment advantage did not reach statistical significance in this analysis. This finding may reflect some loss of power attributable to the lower number of patients evaluable with psychotic symptoms relative to those with agitation/aggression symptoms. Indeed, in a recently conducted pooled analysis involving larger patient numbers from 6 memantine studies over 24/28 weeks (involving patients with moderate to severe AD, MMSE < 20, and including patients from 3 further trials in mild to moderate AD), statistically significantly more memantine- than

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placebo-treated patients, who were symptomatic at baseline, showed improvement on hallucinations at week 12 ($p < .01$) and delusions at week 24/28 ($p < .05$).[45]

As others have demonstrated,[5–8] the data from these analyses confirm that, left untreated, patients with AD and symptoms of agitation/aggression and/or psychosis are indeed prone to a more rapid disease progression. This effect is not accounted for by their baseline severity of disease, since the BDP patients are no more demented than the total patient population under study (see Table 1). Furthermore, the accelerated disease progression is seen for those with only mild agitation/aggression, delusions, or hallucinations at baseline.

The reason why AD patients with symptoms of agitation and/or psychosis should decline most rapidly remains unknown. However, there is growing speculation and converging evidence from neuropsychometric, neuroimaging, and postmortem investigations that frontal lobe dysfunction and/or disruption to frontal-subcortical circuitry is particularly evident in these individuals.[49–52]

Although the current study is a pooled retrospective analysis, it focuses specifically on people with agitation/aggression or psychosis participating in randomized controlled trials with memantine, and therefore provides novel data regarding the treatment of these symptoms in these patients with AD. The entry threshold for inclusion in the analysis was low, requiring only the presence of 1 of 3 specific neuropsychiatric symptoms and not specifying a severity threshold.

Psychological interventions for neuropsychiatric symptoms can be effective (for a review, see Spira and Edelstein[53]), but the identification of a safe and effective pharmacologic therapy for these symptoms is also an urgent clinical priority. The current data suggest that memantine could offer a viable alternative for the treatment of mild to moderate aggression and agitation. The degree of treatment benefit at 12 weeks (response rate 13% higher than that seen with placebo) is comparable to responder rates reported for neuroleptics.[22,54,55] For example, a recent study in a similar patient population reported response rates of 5% to 11% at 12 weeks for 3 atypical antipsychotics.[22] However, the current analysis of memantine also indicated sustained efficacy at 24/28 weeks, and there were benefits rather than detriments in cognition and function. Furthermore, the adverse event profile was similar to that of placebo treatment, with no evidence of events frequently seen under atypical antipsychotic treatment (e.g., peripheral edema, upper respiratory tract infection, cerebrovascular disorder).

Further randomized, controlled trials focusing specifically upon people with agitation/aggression and psychosis are needed (including patients with very severe symptoms). Nevertheless, these findings contribute to our knowledge and suggest that memantine may have advantages over some other pharmacologic therapies for the vulnerable patient group who experience agitation/aggression and/or psychosis in the context of AD. The mechanisms for the actions of memantine upon agitation and, potentially, psychotic symptoms are not fully understood, and the increasing speculation of an effect of memantine on tau pathology requires further elucidation.[56–58]

CONCLUSIONS

In summary, we report here evidence suggesting that memantine is effective in treating AD patients with symptoms of agitation/aggression and psychosis, who are otherwise prone to rapid decline. Benefits were also seen in behavior (agitation/aggression), as well as cognition, global function, and activities of daily living. Memantine was effective at preventing the accelerated deterioration observed in agitated/psychotic AD patients and was associated with a favorable tolerability profile relative to placebo. Although post hoc, these results suggest that memantine may have significant utility in the overall management of these patients and could provide specific benefit for mild to moderate agitation/aggression and potentially psychosis in AD, although further definitive clinical trial evidence is needed.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), donepezil (Aricept), memantine (Namenda), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

REFERENCES

1. Ferri CP, Prince M, Brayne C, et al. Global prevalence of dementia: a Delphi consensus study. Lancet 2005;366:2112–2117
2. Ballard C, Gray A, Ayre G. Psychotic symptoms, aggression and restlessness in dementia. Rev Neurol (Paris) 1999;155(suppl 4):S44–S52
3. Levy ML, Cummings JL, Fairbanks LA, et al. Longitudinal assessment of symptoms of depression, agitation, and psychosis in 181 patients with Alzheimer's disease. Am J Psychiatry 1996;153(11):1438–1443
4. Haupt M, Kurz A, Jänner M. A 2-year follow-up of behavioural and psychological symptoms in Alzheimer's disease. Dement Geriatr Cogn Disord 2000;11:147–152
5. Stern Y, Mayeux R, Sano M, et al. Predictors of disease course in patients with probable Alzheimer's disease. Neurology 1987;37:1649–1653
6. Lopez OL, Becker JT, Brenner RP, et al. Alzheimer's disease with delusions and hallucinations: neuropsychological and electroencephalographic correlates. Neurology 1991;41:906–912
7. Drevets WC, Rubin EH. Psychotic symptoms and the longitudinal course of senile dementia of the Alzheimer type. Biol Psychiatry 1989;25:39–48
8. Jeste DV, Wragg RE, Salmon DP, et al. Cognitive deficits of patients with Alzheimer's disease with and without delusions. Am J Psychiatry 1992;149:184–189
9. Rabins PV, Mace NL, Lucas MJ. The impact of dementia on the family. JAMA 1982;248:333–335
10. Ferris SH, Steinberg G, Shulman E, et al. Institutionalization of Alzheimer's disease patients: reducing precipitating factors through family counseling. Home Health Care Serv Q 1987;8:23–51
11. Steele C, Rovner B, Chase GA, et al. Psychiatric symptoms and nursing home placement of patients with Alzheimer's disease. Am J Psychiatry 1990;147:1049–1051
12. Stern Y, Tang M-X, Albert MS, et al. Predicting time to nursing home care and death in individuals with Alzheimer disease. JAMA 1997;277:806–812
13. Knopman DS, Berg JD, Thomas R, et al. Nursing home placement is

Reprinted with correction to page 341.

related to dementia progression: experience from a clinical trial. Neurology 1999;52:714–718
14. Yaffe K, Fox P, Newcomer R, et al. Patient and caregiver characteristics and nursing home placement in patients with dementia. JAMA 2002;287: 2090–2097
15. Murman DL, Chen Q, Powell MC, et al. The incremental direct costs associated with behavioral symptoms in AD. Neurology 2002;59:1721–1729
16. Hébert R, Dubois MF, Wolfson C, et al. Factors associated with long-term institutionalization of older people with dementia: data from the Canadian Study of Health and Aging. J Gerontol A Biol Sci Med Sci 2001 Nov;56:M693–M699
17. Senanarong V, Cummings JL, Fairbanks L, et al. Agitation in Alzheimer's disease is a manifestation of frontal lobe dysfunction. Dement Geriatr Cogn Disord 2004;17:14–20
18. Ballard CG, Eastwood C, Gahir M, et al. A follow up study of depression in the carers of dementia sufferers. BMJ 1996 Apr;312:947
19. Margallo-Lana M, Swann A, O'Brien J, et al. Prevalence and pharmacological management of behavioural and psychological symptoms amongst dementia sufferers living in care environments. Int J Geriatr Psychiatry 2001;16(1):39–44
20. Ballard C, Howard R. Neuroleptic drugs in dementia: benefits and harm. Nat Rev Neurosci 2006;7(6):492–500
21. Schneider LS, Dagerman K, Insel PS. Efficacy and adverse effects of atypical antipsychotics for dementia: meta-analysis of randomized, placebo-controlled trials. Am J Geriatr Psychiatry 2006;14:191–210
22. Schneider LS, Tariot PN, Dagerman KS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. N Engl J Med 2006;355:1525–1538
23. Bridges-Parlet S, Knopman D, Steffes S. Withdrawal of neuroleptic medications from institutionalized dementia patients, results of a double-blind, baseline-treatment-controlled pilot study. J Geriatr Psychiatry Neurol 1997;10:119–126
24. Cohen-Mansfield J, Lipson S, Werner P, et al. Withdrawal of haloperidol, thioridazine, and lorazepam in the nursing home: a controlled, double-blind study. Arch Intern Med 1999;159:1733–1740
25. Ballard CG, Thomas A, Fossey J, et al. A 3-month, randomized, placebo-controlled, neuroleptic discontinuation study in 100 people with dementia: the Neuropsychiatric Inventory median cutoff is a predictor of clinical outcome. J Clin Psychiatry 2004;65:114–119
26. Medicines and Healthcare Products Regulatory Agency Annual Report 2004. Available at: www.mhra.gov.uk. Accessibility verified January 18, 2008
27. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. JAMA 2005;294:1934–1943
28. Ballard C, Waite J. The effectiveness of atypical antipsychotics for the treatment of aggression and psychosis in Alzheimer's disease. Cochrane Database Syst Rev 2006;1:CD003476
29. Daal JO, van Lieshout JJ. Falls and medications in the elderly. Neth J Med 2005;63(3):91–96
30. FDA Public Health Advisory (11 April 2005). Deaths With Antipsychotics in Elderly Patients With Behavioral Disturbances. Available at: www.fda.gov/cder/drug/advisory/antipsychotics.htm. Accessibility verified January 18, 2008
31. Ballard C, Margallo-Lana M, Juszczak E, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised, double blind, placebo controlled trial. BMJ 2005;330:874–878
32. Ballard CG, Perry RH, McKeith IG, et al. Neuroleptics are associated with more severe tangle pathology in dementia with Lewy bodies. Int J Geriatr Psychiatry 2005;20:872–875
33. Tariot PN, Erb R, Podgorski CA, et al. Efficacy and tolerability of carbamazepine for agitation and aggression in dementia. Am J Psychiatry 1998;155:54–61
34. Lonergan ET, Cameron M, Luxenberg J. Valproic acid for agitation in dementia. Cochrane Database Syst Rev 2004;(2):CD003945
35. Sultzer DL, Gray KF, Gunay I, et al. A double-blind comparison of trazodone and haloperidol for treatment of agitation in patients with dementia. Am J Geriatr Psychiatry 1997;5:60–69
36. Gauthier S, Feldman H, Hecker J, et al. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. Int Psychogeriatr 2002;14:389–404
37. Tariot PN, Cummings JL, Katz IR, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. J Am Geriatr Soc 2001;49(12):1590–1599
38. Holmes C, Wilkinson D, Dean C, et al. The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. Neurology 2004;63(2):214–219
39. Howard RJ, Juszczak E, Ballard CG, et al. Donepezil for the treatment of agitation in Alzheimer's disease. N Engl J Med 2007;357(14): 1382–1392
40. Mega MS, Cummings JL, Fiorello T, et al. The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996;46:130–135
41. Reisberg B, Doody R, Stöffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333–1341
42. Tariot PN, Farlow MR, Grossberg GT, et al. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. JAMA 2004;291:317–324
43. Winblad B, Poritis N. Memantine in severe dementia: results of the M-Best study (benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999;14:135–146
44. Gauthier S, Wirth Y, Möbius HJ. Effects of memantine on behavioural symptoms in Alzheimer's disease patients: an analysis of the Neuropsychiatric Inventory (NPI) data of two randomised, controlled studies. Int J Geriatr Psychiatry 2005;20:459–464
45. Gauthier S, Cooper J, Loft H. Memantine improves behavioral symptoms in patients with moderate to severe Alzheimer's disease [poster]. Presented at the 10th International Conference on Alzheimer's Disease and Related Disorders (ICAD); July 15–20, 2006; Madrid, Spain
46. Cummings JL, Schneider E, Tariot PN, et al. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. Neurology 2006;67:57–63
47. van Dyck CH, Tariot PN, Meyers B, et al. A 24-week randomized controlled trial of memantine in patients with moderate-to-severe Alzheimer disease. Alzheimer Dis Assoc Disord 2007;21:136–143
48. Street JS, Clark WS, Gannon KS, et al. Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a double-blind, randomized, placebo-controlled trial. The HGEU Study Group. Arch Gen Psychiatry 2000;57(10): 968–976
49. Sultzer DL, Mahler ME, Mandelkern MA, et al. The relationship between psychiatric symptoms and regional cortical metabolism in Alzheimer's disease. J Neuropsychiatry Clin Neurosci 1995;7:476–484
50. Chen ST, Sultzer DL, Hinkin CH, et al. Executive dysfunction in Alzheimer's disease: association with neuropsychiatric symptoms and functional impairment. J Neuropsychiatry Clin Neurosci 1998; 10:426–432
51. Hirono N, Mega MS, Dinov ID, et al. Left frontotemporal hypoperfusion is associated with aggression in patients with dementia. Arch Neurol 2000;57:861–866
52. Tekin S, Mega MS, Masterman DM, et al. Orbitofrontal and anterior cingulate cortex neurofibrillary tangle burden is associated with agitation in Alzheimer disease. Ann Neurol 2001;49:355–361
53. Spira AP, Edelstein BA. Behavioral interventions for agitation in older adults with dementia: an evaluative review. Int Psychogeriatr 2006; 18(2):195–225
54. Schneider LS, Pollock VE, Lyness SA. A metaanalysis of controlled trials of neuroleptic treatment in dementia. J Am Geriatr Soc 1990;38 (5):553–563
55. De Deyn PP, Rabheru K, Rasmussen A, et al. A randomized trial of risperidone, placebo, and haloperidol for behavioral symptoms of dementia. Neurology 1999;53(5):946–955
56. Li L, Sengupta A, Haque N, et al. Memantine inhibits and reverses Alzheimer type abnormal hyperphosporylation of tau and associated neurodegeneration. FEBS Lett 2004;566:261–269
57. Amadoro G, Ciotti MT, Costanzi M, et al. NMDA receptor mediates tau-induced neurotoxicity by calpain and ERK/MAPK activation. PNAS 2006;103:2892–2897
58. Degerman Gunnarsson M, Kilander L, Basun H, et al. Reduction of phosphorylated tau during memantine treatment of Alzheimer's disease. Dement Geriatr Cogn Disord 2007;24(4):247–252

Reprinted with correction to page 341.

