A Responder Analysis of Memantine Treatment in Patients With Alzheimer Disease Maintained on Donepezil

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Objective: *The objective of this study was to examine the clinical utility of memantine for moderate-to-severe Alzheimer disease (AD) using responder analyses.* **Method:** *Data from a previously published 24-week, randomized, double-blind, placebo-controlled trial of 10 mg memantine twice a day in patients with moderate-to-severe AD (N=404) on stable donepezil therapy were evaluated using three sets of responder criteria. Response rates were calculated and analyzed for the intention-to-treat population using a generalized estimating equations model. The following outcomes were examined separately and in combination: the Alzheimer's Disease Cooperative Study–Activities of Daily Living 19-Item Inventory (ADCS-ADL$_{19}$), Severe Impairment Battery (SIB), Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), and Neuropsychiatric Inventory (NPI).* **Results:** *When treatment response required cognitive improvement relative to baseline, memantine yielded higher response rates than placebo. When treatment response was defined as stabilization of individual outcomes, memantine resulted in significantly higher response rates than placebo for all outcomes, with number needed to treat (NNT) ranging from 8–10. More conservative definitions of response that required simultaneous stabilization on multiple outcome measures again favored memantine treatment for six of 10 combinatorial definitions.* **Conclusions:** *These responder analyses may assist clinicians in evaluating the impact of memantine in a relevant clinical scenario, i.e., in patients with AD previously stabilized on a cholinesterase inhibitor. The current results indicate that in this setting, memantine produces both improvement and stabilization of symptoms, across multiple outcomes, and thus provides a clinically important treatment benefit for patients with moderate-to-severe AD.* (Am J Geriatr Psychiatry 2006; 14:428–437)

Key Words: Memantine, NMDA receptor antagonist, Alzheimer disease

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Treatments for Alzheimer disease (AD) and other dementias seeking marketing approval in the United States are required to demonstrate efficacy through the use of a cognitive outcome measure in conjunction with a global assessment.[1] Clinical trials of AD therapies typically report treatment effects for these outcome measures by comparing mean change scores between active and placebo groups. Yet clinicians must make treatment decisions for individual patients, which are complicated by variation in response among patients. Responder analyses have been developed to characterize patients who "respond" to treatment compared with their own baseline performance using predefined criteria on specific outcome measures.[2] Responder analyses therefore allow determination of the actual proportion of patients who benefit from the treatment.

Previous AD therapeutic trials have commonly defined response as improvement in cognitive abilities relative to baseline. For trials of cholinesterase inhibitors in patients with AD of mild-to-moderate severity, package inserts have routinely shown the magnitude of response by determining the number of patients who experience at least a four-point or seven-point improvement on the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-cog) over six months.[2–4] These outcomes have been compared with reversing the disease process by approximately 6 months or 1 year, respectively.[5] With increasing perspective on the impact of AD therapies, many experts have begun to examine alternative definitions of treatment success. Particular attention has been focused on criteria that emphasize noncognitive domains such as activities of daily living and behavior disturbance.[2] Although cognition remains a key feature of any dementing illness, declines in functional abilities and emergence of behavioral symptoms in AD are often more distressing to caregivers[6] and more likely to lead to institutionalization.[7]

Furthermore, in the setting of an otherwise relentless progressive disorder, a postponing of decline in any of these domains represents a significant achievement. Treatment response may thus include not only improvement from baseline, but also long-term stabilization. Caregivers often report that they can maintain an acceptable quality of life as long as the patient does not deteriorate further.[2] Therefore, in a therapeutic AD trial, the preservation of baseline levels of cognition, activities of daily living, and behavior may constitute an important treatment response.

Some responder criteria have begun to incorporate combined effects across multiple scales. The European Medicine Evaluation Agency (EMEA), in issuing new guidelines for trials of symptomatic treatments in AD, introduced a definition of responders corresponding to a prespecified degree of improvement in cognition and stabilization in both functional and global abilities.[8] One U.S. treatment study with memantine used a somewhat different criterion, prespecifying treatment responders as patients who showed no deterioration in global abilities and no deterioration in *either* functional or cognitive abilities.[9]

Memantine was approved in the United States in 2003 for the treatment of moderate-to-severe AD,[10] having already been available in the European Union since 2002. It represents the first of a new class of therapeutic compounds with a mechanism of action distinct from cholinesterase inhibitors. Excessive stimulation of *N*-methyl-D-aspartate (NMDA) receptors, which are normally involved in learning and memory, is thought to contribute to the cognitive impairment and neuronal death seen in AD.[11] Memantine, an NMDA receptor antagonist with moderate affinity, fast on/off kinetics, and strong voltage dependence, is believed to modulate NMDA receptors without interfering with normal receptor function.[12] Several clinical trials have demonstrated the superiority of memantine over placebo for the treatment of AD.[9,13–15] A 12-week, double-blind, placebo-controlled trial of 166 institutionalized patients with severe dementia showed global improvements and reduction of care dependence with memantine treatment.[15] A 28-week trial of 252 patients with moderate-to-severe AD showed benefit of memantine over placebo on cognitive, functional, and global outcomes.[9] A subsequent 24–week trial of 350 patients with moderate–to–severe AD (Study MEM–MD–01) showed an advantage of memantine over placebo on cognitive and global outcomes at intermediate time points, but did not achieve statistical significance at endpoint (summary available at www.forestclinicaltrials.com). The most recently published trial by Tariot et al. (and the basis for this article)

demonstrated efficacy of memantine in patients taking stable doses of the cholinesterase inhibitor, donepezil.[14] In this 24-week trial involving 404 patients with moderate-to-severe AD, memantine exhibited significant benefit over placebo on all outcome measures.[14]

In this report, response rates were assessed using data from the Tariot et al. study[14] with the goal of assisting clinicians in evaluating the potential impact of memantine treatment in a common clinical setting, i.e., in individual patients with AD previously stabilized on a cholinesterase inhibitor. Response rates for cognitive, functional, global, and behavioral outcomes were measured individually and in combination. Although not specified a priori in the protocol, three different "responder" criteria were used in these post hoc analyses: 1) clinically significant cognitive improvement from baseline (as defined by selected improvements on the cognitive outcome measure); 2) stabilization (improvement or lack of deterioration) in each or any of the four major outcome measures used in the study; and 3) combined stabilization across multiple outcome measures.

METHODS

Summary of the Trial Design

These responder analyses were performed using data from the previously reported 24-week, multicenter, placebo-controlled, double-blind trial of memantine (20 mg/day) in patients on stable donepezil treatment.[14] Among the major inclusion criteria were a diagnosis of probable AD (N = 404) based on NINCDS-ADRDA criteria,[16] a Mini-Mental State Examination (MMSE)[17] score of 5–14, a baseline age of ≥50 years, and written informed consent provided by the caregiver and patient or legal representative. The study was a prospective, fixed-dose trial with a one- to two-week single-blind placebo lead-in to assess compliance. Patients were then randomized to receive double-blind treatment with placebo or memantine for 24 weeks. Memantine administration was titrated in 5-mg weekly increments from a starting dose of 5 mg/day to 20 mg/day (10 mg twice a day) by week 4.

Outcome Measures Used to Evaluate Response

Response rates for the memantine and placebo groups were determined for the following four outcome measures: the Severe Impairment Battery (SIB),[18] the 19-item Alzheimer's Disease Cooperative Study–Activities of Daily Living inventory (ADCS-ADL_{19}),[19] the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus),[20] and the Neuropsychiatric Inventory (NPI).[21] The SIB is a validated, reliable, and sensitive test to measure cognitive change in patients with more severe AD.[18] It assesses memory, orientation, language, attention, visuospatial ability, and construction. Scores range from 0–100, with higher scores signifying greater cognitive ability. The ADCS-ADL_{19} is a 19-item inventory measuring the level of independence in performing activities of daily living, designed and validated for later stages of dementia.[19] Scores (0–54, with higher scores indicating better daily functioning) on this measure are based on the caregiver's assessment of the patient's ADL performance. The CIBIC-Plus is a seven-point global change rating based on structured interviews with both patient and caregiver.[20] Change from baseline is rated on a scale from one (marked improvement) to seven (marked worsening). The NPI assesses the frequency and severity of 12 behavioral symptoms based on a caregiver interview.[21] NPI scores range between zero and 144, with higher scores reflecting greater behavioral dysfunction.

Statistical Analyses

All analyses were performed on the modified intention-to-treat (ITT) population, which included all randomized patients who received at least one dose of double-blind study medication and completed at least one postbaseline SIB or ADCS-ADL_{19} assessment. A generalized estimating equations (GEE) approach, an adaptation of generalized linear modeling, was used.[22] The GEE method takes into account correlation between repeated observations on individual subjects that occurs when subjects are evaluated with the same outcome measures over time. For these analyses, an unstructured covariance matrix

was used to model the correlation over time. Individual patient responses were determined for each outcome measure by comparing scores at 24 weeks of treatment to baseline. Response was defined using three different criteria: 1) varying degrees of improvement on the SIB, 2) stabilization on each of the four individual outcome measures, and 3) stabilization on combined (paired or triple) outcome measures. The proportion of responders in each treatment arm was determined according to each criterion. For individual outcome measures, the GEE model used treatment group, visit, and treatment-by-visit as factors and baseline value as covariate. For combinations of measures or an individual measure within a group of measures, the GEE model used treatment group, visit, and treatment-by-visit as factors. Study site was not a significant covariate for any outcome. The difference in the proportion of responders between groups, termed "absolute risk reduction,"[23] was analyzed for significance using a Wald chi-squared test at the $\alpha = 0.05$ level of significance with no adjustments for multiple comparisons. SAS version 6.12 (SAS Institute, Cary, NC) was used for all analyses.

Finally, we calculated an additional measure of treatment effect, the "number needed to treat" (NNT), which is considered useful in rendering research trial data meaningful for clinical decision-making.[24] In this case, the NNT is the number of patients who need to be treated with memantine and placebo for one additional patient to respond to memantine according to a specified criterion.

RESULTS

Patient Characteristics

Treatment groups were well-matched at baseline (Table 1). Patients in the memantine group weighed slightly but significantly more at baseline. Adding this variable post hoc to the analyses did not affect outcomes.[14] No other statistically significant differences were observed at baseline or throughout the trial period.

Effect of Memantine on Improvement of Cognitive Performance

As reported previously for the Tariot et al. study, in patients maintained on a stable dose of donepezil, memantine treatment was associated with a significant advantage over placebo in cognitive performance as measured by the SIB.[14] When treatment "response" was considered to require cognitive *improvement* relative to baseline, memantine treatment was found to yield higher response rates than placebo for several selected SIB increments (Table 2). The calculated absolute risk reduction between memantine and placebo ranged from 5.0–11.6 percentage points in favor of memantine and was significant for the broadest increment (>zero-point improvement) and the ≥8-point improvement increment. NNT ranged from 9–20, consistent with the absolute

TABLE 1. Baseline Patient Characteristics[a]

Characteristics	Placebo (N = 201)	Memantine (N = 202)
Age, mean (SD), years	75.5 (8.73)	75.5 (8.45)
Female, percent	67	63
Weight, mean (SD), kg	66.4 (14.12)	70.7[b] (14.31)
Donepezil dose, mean (SD), mg	9.49 (1.88)	9.25 (1.79)
Donepezil treatment duration, mean (SD), weeks	129 (70.3)	126 (64.9)
MMSE score, mean (SD)	10.2 (2.98)	9.9 (3.13)
SIB score, LS mean (SE) [range][c]	80.0 (1.13) [20–100]	78.0 (1.11) [23–98]
ADCS-ADL$_{19}$ score, LS mean (SE) [range][c]	35.8 (0.74) [9–54]	35.5 (0.73) [4–54]
NPI score, LS mean (SE) [range][c]	13.4 (1.08) [0–60]	13.4 (1.07) [0–67]

[a]Patients from the Tariot et al. study,[14] with moderate-to-severe Alzheimer disease maintained on stable donepezil.
[b]Two-way analysis of variance additive model (treatment, center) $F = 8.65$; $df = 1, 365$; $p = 0.003$ versus placebo.
[c]N = 197 (placebo) and N = 198 (memantine) representing the intention-to-treat (ITT) population.
SD: Standard deviation; MMSE: Mini-Mental State Examination; SIB: Severe Impairment Battery; ADCS-ADL$_{19}$: Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (19 items); NPI: Neuropsychiatric Inventory.

TABLE 2. SIB Response Rates for Selected Degrees of Cognitive Improvement

SIB Improvement	Response Rate (%)		Absolute Risk Reduction (%)	95% CI	NNT (95% CI)	p Value
	Memantine	Placebo				
>0 points	57.3 (N = 98/171)	45.8 (N = 70/153)	11.6	0.7–22.4	9 (4–137)	0.0372
≥4 points	34.5 (N = 59/171)	26.8 (N = 41/153)	7.7	−2.3–17.7	13 (6–NS)	0.1264
≥8 points	16.4 (N = 28/171)	7.8 (N = 12/153)	8.5	1.5–15.5	12 (6–65)	0.0214
≥12 points	7.6 (N = 13/171)	2.6 (N = 4/153)	5.0	0.3–9.7	20 (10–358)	0.0719

Notes: A generalized estimating equations model was used as explained in the text. Response rate is the percentage of patients with specified SIB improvement after 24 weeks of treatment, and the absolute risk reduction is the arithmetic difference between response rates for memantine and placebo. p values for the comparison between the memantine and placebo groups were calculated using a Wald chi-squared test ($df = 1$).

SIB: Severe Impairment Battery; NNT: number needed to treat; CI: confidence interval; NS: nonsignificant.

risk reduction. Measurement of cognitive improvement on the SIB (particularly at larger improvement increments) may have been restricted by ceiling effects given that 45.4% of the sample had scores >80 and 18.2% >90 at baseline.

Effect of Memantine on Stabilization of Individual Outcome Measures

In the previously published report, significant benefit of memantine over placebo was observed for the ADCS-ADL$_{19}$, CIBIC-Plus, and NPI in addition to the SIB.[14] When treatment response was defined as *stabilization* of individual outcome measures, memantine treatment resulted in significantly higher stabilization rates than placebo for all four outcome measures (Table 3). The calculated absolute risk reduction between memantine and placebo ranged from 10.4–12.8 percentage points in favor of memantine, with NNT ranging from eight for the NPI to 10 for the ADCS-ADL.$_{19}$ When response was based on stabilization of any one of three or four single outcome measures, overall response rates increased (83.6%–90.6% for memantine; 73.7%–81.6% for placebo), the risk reductions remained statistically sig-

TABLE 3. Response Rates for Stabilization on Individual Outcome Measures

Response Measure	Response Rate (%)		Absolute Risk Reduction (%)	95% CI	NNT (95% CI)	p Value
	Memantine	Placebo				
SIB	62.6 (N = 107/171)	51.6 (N = 79/153)	10.9	0.2–21.7	9 (5–499)	0.0443
ADCS-ADL$_{19}$	45.9 (N = 79/172)	35.5 (N = 54/152)	10.4	−0.2–21.2	10 (5–NS)	0.0318
CIBIC-Plus	55.2 (N = 95/172)	44.1 (N = 67/152)	11.2	0.3–22.0	9 (5–320)	0.0223
NPI	60.8 (N = 104/171)	48.0 (N = 73/152)	12.8	2.0–23.6	8 (4–50)	0.0129
SIB or ADCS-ADL$_{19}$ or CIBIC-Plus	83.6 (N = 143/171)	73.7 (N = 112/152)	9.9	1.0–18.9	10 (5–99)	0.0137
SIB or ADCS-ADL$_{19}$ or CIBIC-Plus or NPI	90.6 (N = 154/170)	81.6 (N = 124/152)	9.0	1.4–16.6	11 (6–69)	0.0175

Notes: A generalized estimating equations model was used as explained in the text. Response rate is the percentage of patients with stabilization of symptoms after 24 weeks of treatment, and the absolute risk reduction is the arithmetic difference between response rates for memantine and placebo. p values for the comparison between the memantine and placebo groups were calculated using a Wald chi-squared test ($df = 1$).

SIB: Severe Impairment Battery; ADCS-ADL$_{19}$: Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (19 item); CIBIC-Plus: Clinician's Interview Based Impression of Change Plus Caregiver Input; NPI: Neuropsychiatric Inventory; NNT: number needed to treat; CI: confidence interval; NS: nonsignificant.

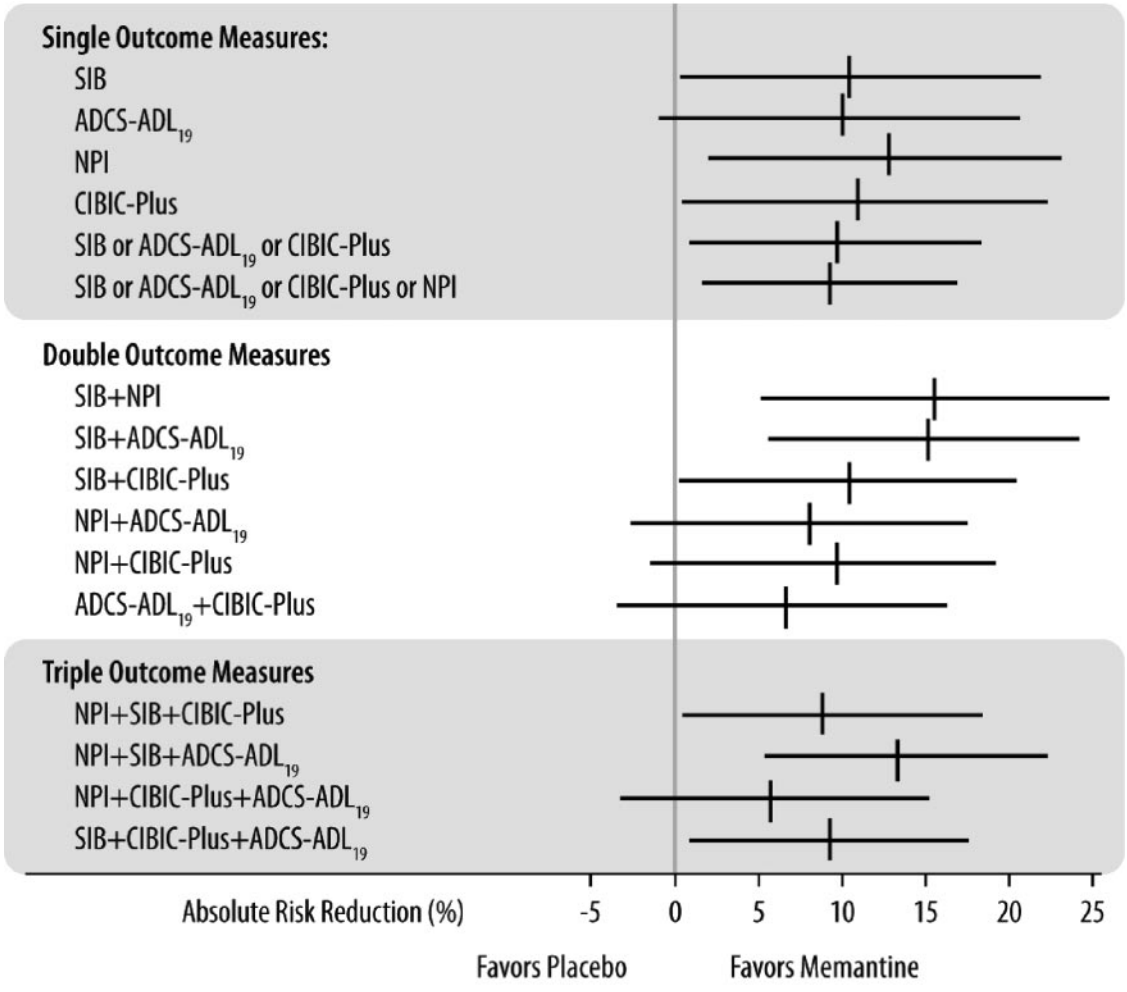
nificant in favor of memantine (Table 3), and the NNT ranged from 10–11. The 95% confidence intervals (CIs) for all of the risk reductions favored memantine treatment (Figure 1).

Effect of Memantine on Stabilization of Combined Outcome Measures

To explore more conservative definitions of efficacy that include multiple domains affected in AD, response rates and absolute risk reductions were determined for every possible paired and triple combination of outcome measures. Similar to the results obtained for individual measures, the risk reductions for all combinations favored memantine over placebo (Table 4). The responder definition with the greatest risk reduction used the SIB and NPI together, with 41.8% of memantine patients responding compared with 26.3% in the placebo group (Table 4) and an NNT of six. For triple combinations, the largest risk reduction was for responders who showed improvement or stabilization on the NPI, SIB, and the ADCS-ADL$_{19}$, with a 13.8% risk reduction in favor of memantine and an NNT of seven.

There were 10 possible double and triple re-

FIGURE 1. Absolute Risk Reductions and 95% Confidence Intervals for All Individual and Combinations of Measures



Notes: Horizontal lines indicate 95% confidence intervals; vertical lines indicate absolute risk reductions.

SIB: Severe Impairment Battery; ADCS-ADL$_{19}$: Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (19 items); CIBIC-Plus: Clinician's Interview Based Impression of Change Plus Caregiver Input; NPI: Neuropsychiatric Inventory.

TABLE 4. Response Rates for Stabilization on Combined Outcome Measures

Response Measures	Response Rate (%)		Absolute Risk Reduction (%)	95% CI	NNT (95% CI)	p Value
	Memantine	Placebo				
Paired combinations of measures						
SIB + NPI	41.8 (N = 71/170)	26.3 (N = 40/152)	15.4	5.3–25.6	6 (4–19)	0.0031
SIB + ADCS-ADL$_{19}$	35.7 (N = 61/171)	20.4 (N = 31/152)	15.3	5.7–24.9	7 (4–18)	0.0017
SIB + CIBIC-Plus	38.6 (N = 66/171)	28.3 (N = 43/152)	10.3	0.1–20.5	10 (5–1193)	0.0548
NPI + ADCS-ADL$_{19}$	32.7 (N = 56/171)	25.0 (N = 38/152)	7.7	−2.1–17.6	13 (6–NS)	0.0998
NPI + CIBIC-Plus	38.0 (N = 65/171)	28.3 (N = 43/152)	9.7	−0.5–19.9	10 (5–NS)	0.0420
CIBIC-Plus + ADCS-ADL$_{19}$	30.8 (N = 53/172)	24.3 (N = 37/152)	6.5	−3.2–16.2	15 (6–NS)	0.1430
Triple combinations of measures						
NPI + SIB + CIBIC-Plus	27.1 (N = 46/170)	17.8 (N = 27/152)	9.3	0.3–18.3	11 (5–375)	0.0393
NPI + SIB + ADCS-ADL$_{19}$	27.6 (N = 47/170)	13.8 (N = 21/152)	13.8	5.2–22.5	7 (4–19)	0.0024
NPI + CIBIC-Plus + ADCS-ADL$_{19}$	25.7 (N = 44/171)	19.7 (N = 30/152)	6.0	−3.1–15.1	17 (7–NS)	0.1353
SIB + CIBIC-Plus + ADCS-ADL$_{19}$	24.6 (N = 42/171)	15.1 (N = 23/152)	9.4	0.8–18.0	11 (6–122)	0.0254

Notes: A generalized estimating equations model was used as explained in the text. Response rate is the percentage of patients with stabilization of symptoms after 24 weeks of treatment, and the absolute risk reduction is the arithmetic difference between response rates for memantine and placebo. p values for the comparison between the memantine and placebo groups were calculated using a Wald chi-squared test ($df = 1$).

SIB: Severe Impairment Battery; ADCS-ADL$_{19}$: Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (19 item); CIBIC-Plus: Clinician's Interview Based Impression of Change Plus Caregiver Input; NPI: Neuropsychiatric Inventory; NNT: number needed to treat; CI: confidence interval; NS: nonsignificant.

sponder definitions. Statistical analysis showed that a significantly greater proportion of memantine patients than placebo patients responded for six of these combinations (Table 4). The 95% CIs associated with the absolute risk reductions for all combinations of measures favored memantine treatment (Figure 1).

DISCUSSION

The efficacy of memantine, as assessed by treatment differences in mean change scores, has been previously demonstrated in the present sample of patients concurrently taking donepezil,[14] as well as in other trials.[9,13,15] To assist the clinician in assessing expectations for memantine treatment in individual patients, the present post hoc investigation examined data from this previous trial[14] in terms of treatment response rates according to three different sets of criteria.

When treatment "response" required cognitive improvement relative to baseline, memantine/donepezil cotreatment yielded higher response rates than placebo/donepezil treatment for several SIB increments ranging from zero to 12 points. In previous trials of cholinesterase inhibitors in mild-to-moderate patients, a common definition of response has involved an improvement of ≥4 ADAS-cog points over six months,[2–4] which has been likened to reversing the disease process by approximately six months.[5] In comparison to the ADAS-cog, average 6-month rates of decline for the SIB are not well established and have ranged widely in previous studies of patients with moderate-to-severe AD. These include a 14.5-point deterioration in an observational study of untreated patients,[18] 3.6-point[25] and 10.1-point[9] drops in placebo groups of treatment

studies, and a 2.4-point worsening in the placebo group of the present treatment study.[14] Clearly, additional longitudinal experience with the SIB is necessary to interpret the extent of "symptom reversal" for various SIB improvements (Table 2). Moreover, these rates of cognitive improvement may only apply to patients already stabilized on a cholinesterase inhibitor, because a trial of memantine monotherapy involved greater overall deterioration in the SIB in both active and placebo groups.[9]

These cognitive improvements for memantine in moderate-to-severe AD are not unlike those for cholinesterase inhibitors in mild-to-moderate AD. Responder analyses of trial data for cholinesterase inhibitor treatment indicate that 12%–20% of patients taking a cholinesterase inhibitor may show marked improvement in cognitive performance as defined by a ≥7-point change on the ADAS-cog, compared with 2%–6% of patients taking placebo.[3,26] When the response criterion is relaxed to a ≥4-point improvement on the ADAS-cog, a greater percentage of patients in both groups (25%–50% cholinesterase inhibitor versus 15%–25% placebo) are characterized as responders, although cholinesterase inhibitor treatment remains superior to placebo.[3,26] Thus, although the reported mean score difference between cholinesterase inhibitor and placebo groups on the 70-point ADAS-cog scale is only approximately 2.5–3.5 points over a six-month period, responder analyses reveal important benefits for individual patients.

When treatment response was alternatively defined as stabilization of individual outcome measures, memantine treatment resulted in significantly increased response rates over placebo for every individual outcome measure (Table 3). Thus, improvement or stabilization of symptoms in individual cognitive, functional, global, and behavioral domains was seen for 45.9%–62.6% of memantine patients compared with 35.5%–51.6% of placebo patients. When the response criterion was relaxed to encompass response in any of three or four domains, the number of responders rose for both groups (83.6%–90.6% memantine versus 73.7%–81.6% placebo), with memantine treatment remaining significantly superior to placebo. These results indicate that patients already taking donepezil benefit significantly from the addition of memantine treatment across multiple symptom domains.

When treatment response was defined more stringently as stabilization of combinations of outcome measures, memantine treatment remained superior to placebo. Every possible combination of two or three measures was evaluated, and the absolute risk reductions for all 10 such combinations were similar and favored memantine, with six combinations reaching statistical significance. Responder definitions that included the SIB tended to result in the largest differences between memantine and placebo, particularly when the SIB was coupled with the ADCS-ADL$_{19}$ and NPI, in both the paired and triple combinations. Stabilization of the triple outcome measure SIB + CIBIC-Plus + ADCS-ADL$_{19}$ corresponds most closely to the responder definition introduced by the EMEA guidelines for trials of symptomatic treatments in AD involving combined cognitive, functional, and global abilities.[8] Applied to the present sample, this criterion yielded response rates of 24.6% for memantine and 15.1% for placebo (Table 4). Although the present responder analyses are limited to data from a single trial, the results reported here are consistent with those from an earlier 28-week trial of memantine monotherapy in patients with moderate-to-severe AD.[9,27] That study prespecified a somewhat less stringent responder criterion than the combination criteria analyzed here, requiring stabilization in CIBIC-Plus as well as *either* ADCS-ADL$_{19}$ or SIB with resultant response rates of 29% for memantine and 10% for placebo.

The NNT analyses of the present study are comparable with those of Livingston and Katona[27] for the 28-week memantine monotherapy trial.[9] Those authors also calculated NNT for stabilization of combinations of outcome measures, with values ranging from 6–11, similar to the present study (6–17). Two specific combination response criteria were identical to those used in the present study: 1) stabilization in CIBIC-Plus and SIB and ADCS-ADL$_{19}$: NNT = 18 (95% CI: nonsignificant), compared with 11 (95% CI: 6–122) in the present study; 2) stabilization in CIBIC-Plus and SIB: NNT = 7 (95% CI: 5–15), compared with 10 (95% CI: 5–1193) in the present study. Overall, these results suggest that patients with AD can experience a broader clinical response than previously appreciated when memantine is used alone or in combination with donepezil treatment, namely a simultaneous benefit in multiple outcomes.

The definition of a treatment responder should

depend in part on the mechanism of the particular therapy and the goals that can therefore reasonably be attained. "Symptomatic" treatments for AD may achieve short-term benefit in outcome measures, whereas putative "disease-modifying" agents may be directed at slowing neurodegeneration and disease progression. A disease-modifying therapy could accomplish valuable long-term stabilization without any short-term improvement, and so a definition of response that required short-term improvement would fail to capture that important benefit. Although not all details of its mechanism are understood, memantine is thought to block pathologic activation of NMDA receptors without interfering with normal receptor function.[12] On the basis of this action, both neuroprotective and symptomatic effects of memantine have been hypothesized that are relevant for AD.[12] Thus, it seems reasonable for responder analyses of memantine to consider both improvement and stabilization as potential benefits.

Perhaps the most significant limitation of this analysis is the absence of a statistical correction for the large number of responder criteria examined. Like with other post hoc responder analyses,[27] all between-group comparisons were made at the $\alpha = 0.05$ level of significance with no adjustments for multiple comparisons. Thus, the probability of a type I error—i.e., the risk that at least one measure of clinical response has been detected that actually occurred by chance—is substantially greater than 5%. However, this is a post hoc analysis of a study in which the significant effects on individual outcome measures are already established.[14] It estimates response rates on multiple outcomes using three different "responder" criteria, each of which has multiple subcriteria. As such, it intentionally casts a broad net in looking for potential signals of response across a vast array of criteria. Furthermore, the various responder criteria used are highly interrelated, because they are constructed either of multiple cut points on the same scale or combinations of the same four basic measures. Therefore, we considered that more restrictive values of α might run the unacceptable risk of missing important signals of treatment response.

The responder analyses in the present study may assist clinicians in evaluating the impact of memantine in a relevant clinical scenario, i.e., in patients with AD previously stabilized on a cholinesterase inhibitor. The results presented here indicate that in this setting, memantine treatment produces both improvement and stabilization of symptoms, across multiple outcome measures, and thus provides an important treatment benefit for patients with AD with moderate-to-severe disease.

These data were presented in part at the Annual Scientific Meeting of the American Geriatrics Society, May 17–21, 2004, Las Vegas, NV, and at the 44th Annual New Clinical Drug Evaluation Unit Meeting, June 1–4, 2004, Phoenix, AZ. Summary data are also reported in the article reporting the results of the trial.[14]

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