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Memantine ER Maintains Patient Response in Moderate to Severe Alzheimer's Disease

Post Hoc Analyses From a Randomized, Controlled, Clinical Trial of Patients Treated With Cholinesterase Inhibitors

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Abstract: Memantine extended release (ER) significantly outperformed placebo on co-primary endpoints of Clinician's Interview-based Impression of Change Plus Caregiver Input (CIBIC-Plus) and baseline to endpoint changes on the Severe Impairment Battery (SIB) in a 24-week, randomized trial (NCT00322153) in patients with moderate to severe Alzheimer's disease taking a cholinesterase inhibitor (ChEI). A post hoc analysis compared patients receiving memantine ER/ChEI to placebo/ChEI for time to onset of response and if the response was maintained (achieving improvement at weeks 8, 12, or 18 and maintaining through endpoint/week 24) on the SIB, the Neuropsychiatric Inventory (NPI), CIBIC-Plus, and Activities of Daily Living (ADL) using Fisher exact test. A second post hoc analysis compared percentages of patients for all possible combinations of 2 to 4 assessments with either no decline or clinically notable response using Wald χ^2. Significantly greater percentages of memantine ER/ChEI patients achieved an early response that was maintained on SIB, NPI, and CIBIC-Plus ($P < 0.05$) versus placebo/ChEI. Significantly greater percentages of memantine ER/ChEI-treated patients achieved and maintained a clinically notable response on ADL/NPI, SIB/ADL/NPI,

and SIB/ADL/CIBIC-Plus, compared with placebo/ChEI ($P < 0.05$). Memantine ER results in early, maintained improvement in patients with moderate to severe Alzheimer's disease concurrently taking ChEIs, compared with cholinesterase treatment alone.

Alzheimer's disease (AD) is a progressive neuro-degenerative brain disease affecting millions worldwide. Patients with moderate and severe AD experience progressively declining cognition and function. AD progression increases dependence upon caregivers, and is associated with increased nursing home placement, higher direct and indirect costs of care, and increased mortality.[1–4] Patient symptoms can be aggravated by poor medication adherence.[5–7]

Memantine is an uncompetitive antagonist of N-methyl-D-aspartate receptors approved for the treatment of moderate to severe AD. Memantine, administered twice daily in the immediate-release formulation (10 mg bid) has been shown to benefit behavioral and cognitive symptoms in moderate to severe AD.[8–10] An extended release (ER) formulation of memantine (memantine ER 28 mg) once daily is approved in the United States for the treatment of moderate to severe AD. Memantine ER (28 mg) may potentially increase ease of use and adherence in patients with AD.

This study demonstrated that memantine ER was efficacious and well tolerated in patients with moderate to severe AD being treated concomitantly with cholinesterase inhibitors (ChEIs).[11] Memantine ER treatment resulted in statistically significant improvement in patient performance on the Severe Impairment Battery (SIB), the Clinician's Interview-based Impression of Change Plus Caregiver Input (CIBIC-Plus), the Neuropsychiatric Inventory (NPI), and verbal fluency tests, compared with placebo; a trend toward improvement that did not reach statistical significance was seen on the Alzheimer's Disease Cooperative Study-Activities of Daily Living (ADCS-ADL$_{19}$). The only adverse events with a frequency of $\geq 5.0\%$ and higher than placebo were headache (5.6% vs. 5.1%) and diarrhea (5.0% vs. 3.9%). As all patients were treated concomitantly with ChEI, these improvements and safety profile demonstrate the efficacy and tolerability of memantine ER when added to the standard of ChEI treatment in patients with AD; however, it is sometimes difficult to fully elucidate the benefits of add-on treatments.

Further post hoc analyses were conducted to examine the effects of memantine ER added to ChEI treatment in patients with moderate to severe AD. Patients were identified from each treatment group (memantine ER/ChEI vs. placebo/ChEI), who achieved improvement on the SIB, the NPI, the CIBIC-Plus, and the ADCS-ADL$_{19}$ at weeks 8, 12, or 18 and maintained that level of response through all subsequent weeks up to and including endpoint (week 24). Further, patients who achieved improvements on multiple measures at endpoint were compared between treatment groups of memantine ER/ChEI or placebo/ChEI.

METHODS

Study Design

Methods from this 24-week, double-blind, parallel group, placebo-controlled, randomized study (NCT00322153) are described in detail elsewhere[11] and summarized here. Briefly, patients with moderate to severe AD [Mini Mental State Examination (MMSE) range, 3 to 14] who were receiving stable, ongoing ChEI treatment were eligible. Following a 2-week lead-in with single-blind placebo, patients were randomized (1:1) to double-blind treatment with placebo or ER memantine (qd) for 24 weeks. Memantine ER was titrated weekly in 7 mg increments to reach 28 mg/d by week 4. The SIB, CIBIC-Plus, and ADCS-ADL$_{19}$ were administered at weeks 4, 8, 12, 18, and 24; NPI was administered at weeks 8, 12, 18, and 24 (not week 4).

Outcomes and Assessments

Efficacy parameters included change from baseline to each time point for the SIB, NPI, CIBIC-Plus, and ADCS-ADL$_{19}$. The SIB is a 40-item, 100-point scale designed to assess cognitive performance in patients with moderate to severe AD, with higher scores indicating more preserved cognitive function.[12] The NPI is a 12-item, 144-point scale instrument based upon a caregiver interview, designed to measure the frequency and severity of behavioral disturbances in patients with dementia[13] in which higher scores indicate greater impairment. The CIBIC-Plus is a 7-point scale (1 = marked improvement; 4 = no change; 7 = marked worsening), designed to assess global clinical status of a patient.[14] The ADCS-ADL$_{19}$ is a 54-point scale that assesses daily functional abilities in patients with moderate to severe AD, with lower scores indicating greater impairment.[15]

Maintenance of Response

The percentages of patients who achieved and maintained response were compared between randomized groups of patients receiving memantine ER or placebo in addition to stable dosages of ChEI. Maintenance of response was defined as patients who achieved a specified level of improvement at weeks 8, 12, or 18 and then maintained that response at all subsequent weeks through endpoint (week 24) for each of the following outcomes: SIB, NPI, CIBIC-Plus, and ADCS-ADL$_{19}$. To characterize the responder rates, evenly spaced interval scores were chosen for each of the outcomes. That is, SIB score changes of ≥ 0, ≥ 5, ≥ 10, ≥ 15, and ≥ 20 points were used to define positive response levels to treatment. NPI score changes of ≤ 0, ≤ -3, ≤ -6, ≤ -9, ≤ -12 were used to define positive response levels to treatment. CIBIC-Plus endpoint scores of ≤ 4, ≤ 3, ≤ 2, ≤ 1, correspond to no change up to marked improvement. ADCS-ADL$_{19}$ score changes of ≤ 0, ≤ -2, ≤ -4, ≤ -6, ≤ -8 were used to quantify stabilization/improvement.

Combined Outcomes Analysis

The percentage of patients who achieved and maintained response for all possible combinations of 2, 3, or 4 efficacy assessments were compared between memantine ER/ChEI versus placebo/ChEI. Two levels of response were defined: no decline or clinically notable response. No decline was a change from baseline to endpoint of ≥ 0 points for SIB and ADCS-ADL$_{19}$, ≤ 0 points for NPI, and an endpoint score of ≤ 4 points for CIBIC-Plus (improvement or stabilization). On the basis of clinical expertise, clinically notable response was defined as a change from baseline to endpoint of ≥ 3 points for SIB and ADCS-ADL$_{19}$, ≤ -3 for NPI, and an endpoint score of ≤ 3 for the CIBIC-Plus. In the clinic, 3-point score changes are generally large enough for patients and caregivers to note the improvement.

Statistical Analyses

Analyses were performed using data from all patients who completed the trial and had data at each time point (observed cases). Descriptive statistics (n, %) summarized responders for individual outcomes; Fisher exact test compared maintenance of response between memantine ER/ChEI-treated and placebo/ChEI-treated patients. For response on multiple outcome measures, treatment groups were compared using the Wald χ^2 test ($\alpha = 0.05$). Sensitivity analyses were performed by (1) using the last observation carried forward approach and (2) counting patients with missing data as nonresponders. No corrections for multiple comparisons were performed as all analyses were post hoc.

RESULTS

Baseline Characteristics

The patient population was described in full elsewhere,[11] and is summarized here. A total of 676 participants were included in the current analyses; 341 in the memantine ER/ChEI group and 335 in the placebo/ChEI group. Baseline characteristics were similar between memantine ER/ChEI and placebo/ChEI groups (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/WAD/A200). Most participants were female and white, and had baseline MMSE scores from 3 to 17. All patients were receiving a background ChEI at stable dosages throughout the study.

Maintenance of Response

SIB

Significantly greater percentages of patients maintained score increases of ≥ 5 or ≥ 10 when treated with memantine ER/ChEI compared with placebo/ChEI from weeks 8 to 24 and for the other time periods [ie, weeks 12 to 24, weeks 18 to 24 (≥ 10 only); Fig. 1]. Compared with placebo/ChEI, significance was reached for patients receiving memantine ER/ChEI with improvements of ≥ 15 points on the SIB from weeks 12 to 24 and weeks 18 to 24. Memantine ER/ChEI treatment was associated with numerically larger proportions of participants with improvement on the SIB for each response level, except for score of ≥ 0 from weeks 8 to 24 (Fig. 1). Sensitivity analysis with missing data counted as nonresponders found similar results (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/WAD/A201).
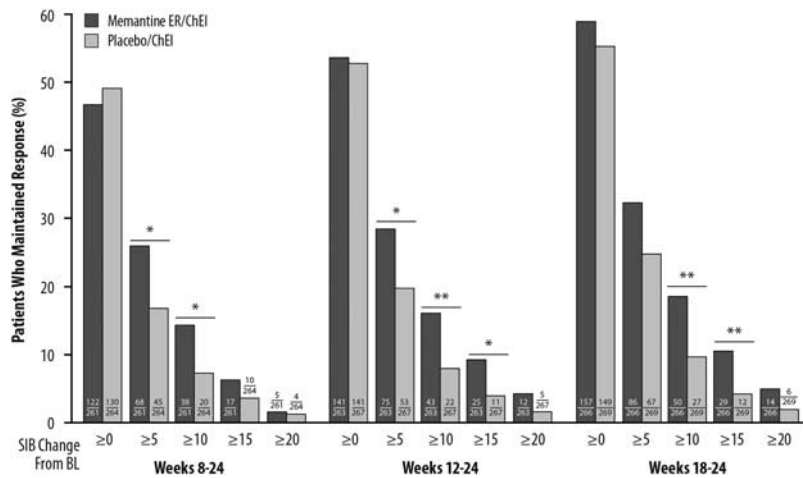
FIGURE 1. SIB maintenance of response (OC). Fisher exact test. BL indicates baseline; ChEI, cholinesterase inhibitor; ER, extended release; OC, observed cases; SIB, Severe Impairment Battery. *$P < 0.05$, **$P < 0.01$.

NPI

More patients treated with memantine ER/ChEI showed a maintained response on the NPI than patients treated with placebo/ChEI, although these differences did not always reach statistical significance (Fig. 2). From weeks 8 to 24, significantly greater percentages of memantine ER/ChEI-treated patients maintained score decreases of ≤ −3, ≤ −9, ≤ −12, compared with ChEI alone. For cut offs ≤ −9 and ≤ −12, these significant changes were maintained for all additional time points (ie, weeks 12 to 24 and weeks 18 to 24; Fig. 2). For the ≤ −3 cut off, significance was maintained at weeks 12 to 24 but lost at weeks 18 to 24. Further, for the scores ≤ −6, significantly greater proportions of memantine ER/ChEI-treated patients maintained scores ≤ −6, from weeks 12 to 24 and weeks 18 to 24, compared with patients treated with ChEI alone. Sensitivity analysis with missing data counted as nonresponders found similar results (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/WAD/A201).

CIBIC-Plus

A numerically greater proportion of the memantine ER/ChEI group was observed for each response level on the CIBIC-Plus scale of ≤ 4, ≤ 3, ≤ 2 (corresponding to no change to marked improvement) (Fig. 3). From weeks 8 to 24, significantly greater percentages of memantine ER/ChEI-treated patients maintained a score of ≤ 3 than placebo/ChEI-treated patients; this effect was maintained for all additional time groups (ie, weeks 12 to 24 and weeks 18 to 24; Fig. 3). From weeks 12 to 24, memantine ER/ChEI patients who maintained a score of ≤ 4 also reached statistical significance versus ChEI alone; however, there was only a trend for this group of patients from weeks 18 to 24. From weeks 18 to 24, significantly higher proportions of patients treated with memantine ER/ChEI maintained a score ≤ 2 versus ChEI alone. Sensitivity analysis with missing data counted as nonresponders found similar results (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/WAD/A201).

ADCS-ADL$_{19}$

A smaller proportion of patients treated with memantine ER/ChEI had sustained worsening in ADL from weeks 12 to 24 and weeks 18 to 24 versus placebo. From weeks 8 to 24, a smaller proportion of patients treated with memantine ER/ChEI had sustained worsening in ADL for
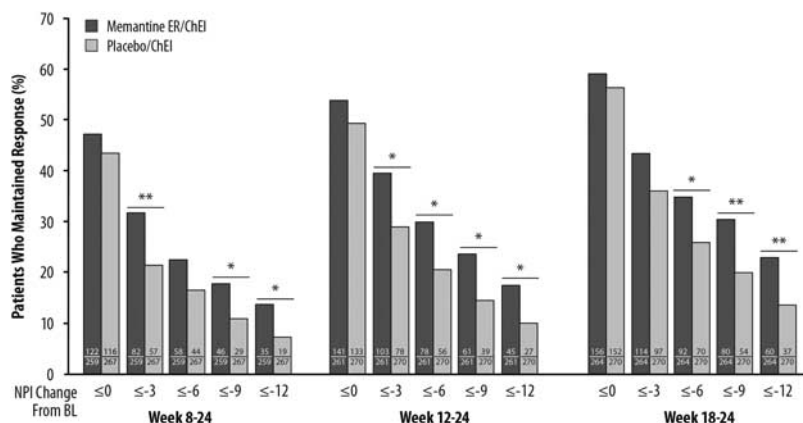

FIGURE 2. NPI maintenance of response (OC). Fisher exact test. BL indicates baseline; ChEI, cholinesterase inhibitor; ER, extended release; NPI, Neuropsychiatric Inventory; OC, observed cases. *$P < 0.05$, **$P < 0.01$.
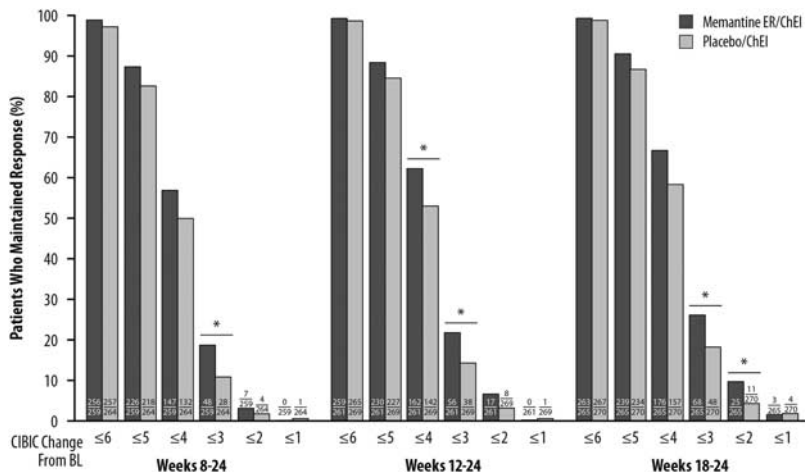
FIGURE 3. CIBIC-Plus maintenance of response (OC). Fisher exact test. BL indicates baseline; ChEI, cholinesterase inhibitor; CIBIC-Plus, Clinician's Interview-based Impression of Change Plus Caregiver Input; ER, extended release; OC, observed cases. *$P < 0.05$.

change scores ≤ 0, ≤ -6, and ≤ -8. Compared with memantine ER/ChEI-treated patients, a significantly greater proportion of patients in the placebo/ChEI group had a change score ≤ -4 (12.1% memantine vs. 20.0% placebo; $P = 0.0137$), ≤ -6 (8.0% vs. 13.3%; $P = 0.0499$), and ≤ -8 (4.9% vs. 9.6%; $P = 0.0453$) from weeks 18 to 24. Sensitivity analysis with missing data counted as nonresponders found similar results (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/WAD/A201).

Combined Outcomes Responders

When comparing memantine ER/ChEI-treated versus placebo/ChEI-treated responders for all possible combinations of 2, 3, or 4 efficacy measures, a greater proportion of memantine ER/ChEI patients showed no decline (Fig. 4) and clinically notable response (Fig. 5) versus ChEI alone. The difference between treatments for patients who showed no decline did not reach statistical significance; the combination of efficacy outcomes with the greatest difference was

SIB/CIBIC-Plus ($P = 0.0541$). Memantine ER/ChEI was associated with a greater proportion of patients achieving a clinically notable response for the 2-parameter combination of ADCS-ADL$_{19}$/NPI ($P = 0.0421$), and the 3-parameter combinations of SIB/ADCS-ADL$_{19}$/NPI ($P = 0.0271$) and SIB/ADCS-ADL$_{19}$/CIBIC-Plus ($P = 0.0302$) combinations.

DISCUSSION

Efficacy of memantine ER has been previously demonstrated in the primary analysis of this trial.[11] This post hoc analysis explored the question of early and maintained benefits of memantine ER treatment, by identifying improvements at earlier time points that were maintained to endpoint, and the efficacy of memantine ER over multiple assessment domains. Patients treated with memantine ER and ChEI achieved earlier, maintained responses at greater rates than ChEI alone, demonstrating ongoing benefit on cognitive and behavioral symptoms. Patient response for
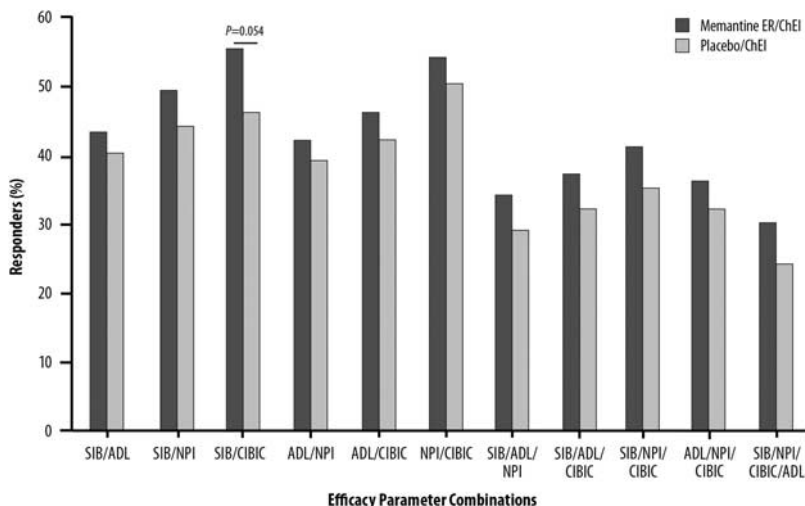

FIGURE 4. Response across multiple parameters: no decline. ADL indicates Activities of Daily Living; ChEI, cholinesterase inhibitor; CIBIC-Plus, Clinician's Interview-based Impression of Change Plus Caregiver Input; ER, extended release; NPI, Neuropsychiatric Inventory; SIB, Severe Impairment Battery.

FIGURE 5. Response across multiple parameters: clinically notable response. Fisher exact test. ADL indicates Activities of Daily Living; ChEI, cholinesterase inhibitor; CIBIC-Plus, Clinician's Interview-based Impression of Change Plus Caregiver Input; ER, extended release; NPI, Neuropsychiatric Inventory; SIB, Severe Impairment Battery. *$P < 0.05$.
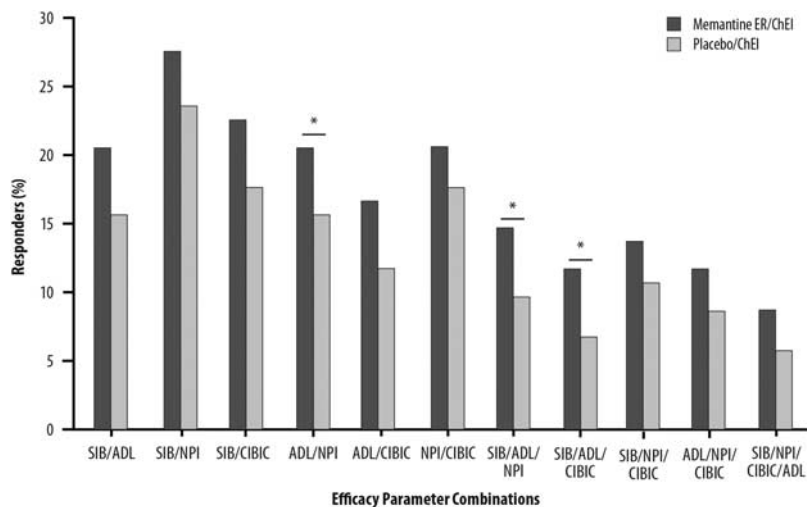
SIB and NPI was numerically greater at all improvement levels for most or all time points, respectively. Statistically significant improvements were seen on the SIB and NPI for many response levels corresponding to improvement, beginning as early as 8 weeks and maintained to week 24.

Cognitive and behavioral improvement is consistent with other data suggesting greater cognitive and behavioral benefit of combined ChEI and immediate-release memantine than ChEI treatment alone. Overall additive benefits of memantine and ChEI compared with individual monotherapies are supported by a large pooled analysis of memantine added to donepezil in clinical trials[16]; a majority of the patients here were treated with donepezil. Long-term prospective observational cohort studies also indicate combination therapy benefits over monotherapy.[17–19]

Memantine with ChEI may slightly ameliorate the inevitable decline in function in moderate to severe AD patients compared with treatment with ChEIs alone. In general, there were numerically lower percentages of patients with sustained worsening of ADL in the memantine ER group compared with placebo. The decrease in sustained worsening associated with memantine ER/ChEI treatment was significant from 18 to 24 weeks for several levels of response. Given the progressive nature of AD and the importance of maintaining ADL in patients, any delay of this decline may represent a meaningful benefit to patients and their caregivers.

Memantine was associated with improvements in global clinical change in patients with AD as well. Numerical improvements on global clinical status were seen on the CIBIC-Plus for each time group. Effects generally reached significance at scores of ≤ 3, indicating improvements on this Likert-type scale; on the CIBIC-Plus, a score of 4 is indicative of no change, whereas a score of 7 represents marked worsening. Therefore, when including only patients improving (not worsening or stable), greater proportions of patients treated with memantine ER/ChEI were improved and maintained that improvement, compared with ChEI alone.

By assessing response on multiple measures concomitantly, multiple symptoms were simultaneously considered, leading to a broader definition of success that may more fully describe the complexity of symptoms associated

with AD. In patients with moderate to severe AD receiving ChEI, memantine ER may provide simultaneous benefits on multiple clinical domains, especially stabilization of cognition and global status. Memantine ER was associated with numerically greater proportions of responders exhibiting a clinically notable improvement for every combination of parameters, including statistically significant effects for memantine/ChEI versus ChEI alone for combinations of ADCS-ADL$_{19}$/NPI; SIB/ADCS-ADL$_{19}$/NPI; and SIB/ADCS-ADL$_{19}$/CIBIC-Plus. Memantine ER/ChEI was associated with numerically greater proportions of responders with no decline compared with placebo/ChEI for every combination of multiple parameters, although this difference did not reach statistical significance.

Limitations of the current study include lack of statistical correction for multiple tests, the use of OC analysis which may bias the sample population, the use of the MMSE as an enrollment criterion which assesses only 1 symptom (cognition) and may not fully represent the spectrum of AD patients, and potential heterogeneity due to the pooled analysis of patients receiving treatment with 3 possible ChEIs (ie, separate analyses were not conducted for each ChEI). The study population was overwhelmingly white and most were female, possibly limiting generalizability to other populations.

This study indicates that memantine ER treatment in patients with moderate to severe AD concurrently taking ChEIs results in early and maintained improvement and stabilization of symptoms compared with cholinesterase treatment alone. Memantine ER provided benefits across multiple clinical domains considered simultaneously, indicating a clinically important benefit for patients.

REFERENCES

1. Handels RL, Wolfs CA, Aalten P, et al. Determinants of care costs of patients with dementia or cognitive impairment. *Alzheimer Dis Assoc Disord*. 2013;27:30–36.
2. Wilson RS, Li Y, Aggarwal NT, et al. Cognitive decline and survival in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2006;21:356–362.
3. Wilson RS, McCann JJ, Li Y, et al. Nursing home placement, day care use, and cognitive decline in Alzheimer's disease. *Am J Psychiatry*. 2007;164:910–915.

4. Wilson RS, Tang Y, Aggarwal NT, et al. Hallucinations, cognitive decline, and death in Alzheimer's disease. *Neuroepidemiology*. 2006;26:68–75.
5. Hughes CM. Medication non-adherence in the elderly: how big is the problem? *Drugs Aging*. 2004;21:793–811.
6. Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med*. 2005;353:487–497.
7. Small G, Dubois B. A review of compliance to treatment in Alzheimer's disease: potential benefits of a transdermal patch. *Curr Med Res Opin*. 2007;23:2705–2713.
8. McShane R, Areosa Sastre A, Minakaran N. Memantine for dementia. *Cochrane Database Syst Rev*. 2006;3:1–68.
9. Reisberg B, Doody R, Stoffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*. 2003;348:1333–1341.
10. 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.
11. Grossberg GT, Manes F, Allegri RF, et al. The safety, tolerability, and efficacy of once-daily memantine (28 mg): a multinational, randomized, double-blind, placebo-controlled trial in patients with moderate-to-severe Alzheimer's disease taking cholinesterase inhibitors. *CNS Drugs*. 2013;27:469–478.
12. Panisset M, Roudier M, Saxton J, et al. Severe impairment battery. A neuropsychological test for severely demented patients. *Arch Neurol*. 1994;51:41–45.
13. Cummings JL, Mega M, Gray K, et al. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44:2308–2314.
14. Schneider LS, Olin JT, Doody RS, et al. Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 2):S22–S32.
15. Galasko D, Bennett D, Sano M, et al. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 1997;11(suppl 2):S33–S39.
16. Atri A, Hendrix SB, Pejovic V, et al. Cumulative, additive benefits of memantine-donepezil combination over component monotherapies in moderate to severe Alzheimer's dementia: a pooled area under the curve analysis. *Alzheimers Res Ther*. 2015;7:28.
17. Atri A, Molinuevo JL, Lemming O, et al. Memantine in patients with Alzheimer's disease receiving donepezil: new analyses of efficacy and safety for combination therapy. *Alzheimers Res Ther*. 2013;5:6.
18. Atri A, Rountree SD, Lopez OL, et al. Validity, significance, strengths, limitations, and evidentiary value of real-world clinical data for combination therapy in Alzheimer's disease: comparison of efficacy and effectiveness studies. *Neurodegener Dis*. 2012;10:170–174.
19. Rountree SD, Atri A, Lopez OL, et al. Effectiveness of antidementia drugs in delaying Alzheimer's disease progression. *Alzheimers Dement*. 2013;9:338–345.