Contemporary Issues in the Treatment of Alzheimer's Disease: Tangible Benefits of Current Therapies

Pierre N. Tariot, M.D.

Because of the mild symptomatology associated with its earlier stages, Alzheimer's disease (AD) is most commonly diagnosed in an intermediate to late stage of progression. Patients with moderate to severe AD at diagnosis have already experienced appreciable losses in cognition and functioning. However, such patients may still benefit greatly from the use of antidementia agents such as cholinesterase inhibitors (ChEIs) and the *N*-methyl-D-aspartate (NMDA) receptor open-channel antagonist memantine. Monotherapy regimens involving a ChEI or memantine have been shown to slow the progression of cognitive symptoms in patients with moderate to severe AD, although memantine is currently the only agent approved for use in this setting. Furthermore, combination therapy involving memantine and a ChEI has been shown to yield increased cognitive benefits relative to ChEI monotherapy, a result that is believed to be attributable to the distinct therapeutic mechanisms associated with NMDA receptor open-channel antagonists and ChEIs. Nonetheless, recent findings indicate that the therapeutic effects of these antidementia agents are not limited to cognition. For example, emerging data highlight the efficacy of ChEIs and memantine, used either alone or in combination, in improving outcomes related to patient functioning and behavior, 2 domains that may have a great deal of significance for patients and caregivers. Furthermore, recent clinical trial data suggest that antidementia agents may significantly delay nursing home placement, a unique endpoint that can be tremendously distressing to patients with AD and their caregivers. Thus, it is clear that the ChEIs and memantine provide substantial benefits that extend across the spectrum of symptoms of AD, improving outcomes for those who are affected, either directly or indirectly, by this debilitating condition.

(J Clin Psychiatry 2006;67[suppl 3]:15–22)

Alzheimer's disease (AD) is a condition whose neurodegenerative nature is paralleled by its progressive symptomatic course.[1] Cognitive impairments, which represent the core symptom of AD, are typically mild in the early stages of the disease (i.e., up to approximately 3 years from the appearance of clinical signs). However, as the disease progresses to its moderate stages (approximately 3–6 years from the appearance of clinical signs), symptomatic deterioration occurs more rapidly, so that cognitive dysfunction becomes more readily evident and the affected patient experiences a loss of functional independence. Furthermore, while behavioral disturbances such as agitation and hallucinations may arise at any stage of disease, they frequently emerge in moderate AD. Behavioral symptoms continue to be seen with increasing frequency in late-stage AD (beginning approximately 6 years from the appearance of clinical signs), and cognition and function continue to deteriorate as well, leaving patients almost completely dependent on others for their care.

Presumably because of the mild symptomatology associated with early AD, many affected individuals are not diagnosed until the disease has reached its moderate to severe stages, when substantial losses in cognition and functioning have already occurred. Despite these losses, there are a variety of therapeutic agents that can provide significant symptomatic benefit to patients with moderate to severe AD. Because AD is a progressive condition, the goals of treatment of moderate to severe AD sometimes differ from the goals of treatment of mild AD. For instance, in early AD, when cognitive and functional deterioration typically occur at a relatively slow rate, the frequent aim of therapeutic interventions is to maintain cognitive and functional capacity. There is hope that early treatment may delay the emergence of psychopathology as well, although there is currently no evidence to support this hypothesis. Nonetheless, as AD advances and the rate of symptomatic progression increases, the focus of therapeutic efforts tends to shift to slowing cognitive and functional decline and to ameliorating behavioral symptoms or possibly delaying their emergence.

From the Memory Disorders Center, Banner Alzheimer's Disease Institute, Phoenix, Ariz.

This article was derived from a faculty discussion convened on August 23, 2005, and supported by an educational grant from Forest Pharmaceuticals.

Corresponding author and reprints: Pierre N. Tariot, M.D., Memory Disorders Center, Banner Alzheimer's Disease Institute, 901 E. Willetta St., Phoenix, AZ 85006 (e-mail: pierre.tariot@bannerhealth.com).

EFFICACY OF CURRENT TREATMENT OPTIONS FOR MODERATE TO SEVERE AD

Cognition and Functioning

Selegiline/vitamin E. Among the earliest large clinical trials to study the impact of AD pharmacotherapy was one involving the use of selegiline and/or α-tocopherol (vitamin E) to treat moderate AD.[2] Both agents were selected for investigation on the basis of their putative ability to prevent free radical–mediated neurodegeneration (and thus forestall AD-related cognitive deterioration) via their antioxidant activity. In addition, it was postulated that the neurostimulatory activity of selegiline—specifically, its proven ability to potentiate catecholaminergic neurotransmission—might also lead to cognitive benefits in patients with AD.

The efficacy of selegiline and vitamin E was tested in a double-blind, placebo-controlled trial in which 341 patients with moderate AD (as indicated by a Clinical Dementia Rating [CDR] score of 2) were randomized to receive selegiline 5 mg b.i.d. (N = 87), vitamin E 1000 IU b.i.d. (N = 85), selegiline 5 mg plus vitamin E 1000 IU b.i.d. (N = 85), or placebo (N = 84).[2] In that trial, all 3 active treatment regimens were found, after controlling for baseline Mini-Mental State Examination (MMSE) score, to prolong significantly the time to primary endpoint, which was defined as the loss of 2 basic activities of daily living (ADLs) out of a possible 3 (eating, grooming, and toileting), death, or the onset of severe dementia (CDR score = 3). Patients treated with vitamin E alone appeared to fare the best, having their median time to primary endpoint delayed by 230 days relative to the placebo arm ($p = .001$), while the corresponding median delay times were 215 days ($p = .012$) for patients treated with selegiline alone and 145 days ($p = .049$) for those receiving selegiline plus vitamin E. However, the functional benefits associated with vitamin E and selegiline were not accompanied by cognitive benefits, as mean changes in scores on the MMSE and the Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-Cog) between baseline and final assessment (mean time to final assessment: MMSE, 15.6 months; ADAS-Cog, 12.4 months) did not differ significantly among the 4 treatment arms ($p = .83$ and $p = .17$, respectively).

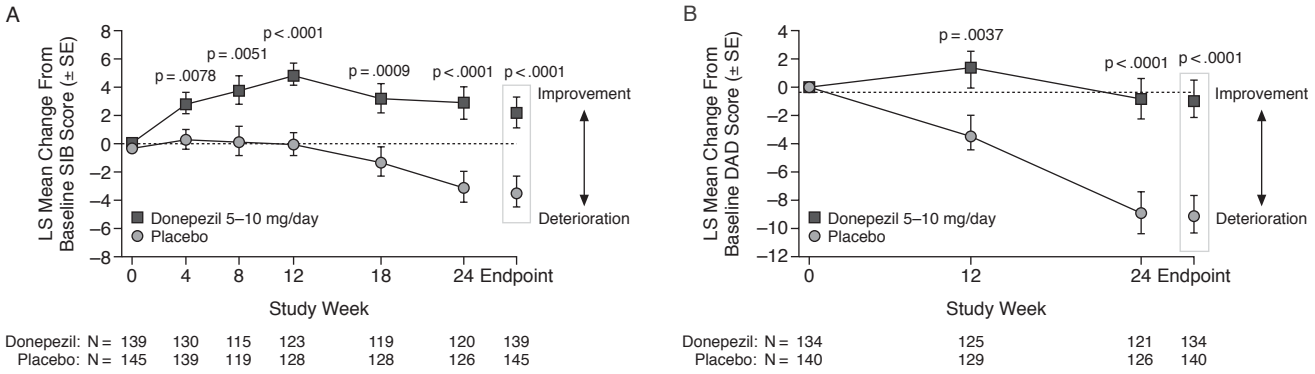
This finding of functional benefit in the absence of cognitive benefit is somewhat surprising, given that cognitive status has been identified as the key determinant of functional capabilities in AD.[3,4] In addition, the likelihood of becoming unable to perform a given ADL within a specified time frame appears to be positively correlated with the affected patient's MMSE score at the beginning of that time frame, as well as with the subsequent rate of cognitive decline.[4] However, since the ability to perform ADLs is also affected by age-related changes in sensory perception, physical condition, and behavior,[3] it is possible that the benefits seen with selegiline and vitamin E are attributable to the effects of these agents on such noncognitive determinants of patient functioning.

Cholinesterase inhibitors. Cholinesterase inhibitors (ChEIs) have been shown to provide cognitive benefits to patients with AD by blocking the activity of the enzyme cholinesterase, which mediates the degradation of the neurotransmitter acetylcholine in the synaptic cleft. Agents of this type stimulate cholinergic neurotransmission and thus help to counteract the cholinergic signaling deficits that are believed to be responsible, in part, for the loss of cognition seen in AD.

Based on the cognitive efficacy of ChEI therapy and the known relationship between cognitive status and functional capabilities in patients with AD, it has been hypothesized that the cognitive benefits of ChEIs may be accompanied by favorable functional outcomes. Consistent with this hypothesis, and despite the fact that ChEI therapy is not currently indicated for the treatment of moderate to severe AD, the ChEI donepezil has shown significant cognitive and functional benefits in patients with late-stage AD. In a 24-week, randomized, placebo-controlled study involving community-based patients with moderate to severe AD (MMSE scores, 5–17),[5] patients treated with donepezil 5 to 10 mg/day (N = 139) experienced a significant benefit relative to those receiving placebo (N = 145) in terms of least squares mean changes in Severe Impairment Battery (SIB) score between baseline and endpoint (donepezil, +2.0 points [improvement] vs. placebo, –3.6 points [deterioration]; $p < .0001$), and this cognitive benefit was accompanied by a reduced rate of functional decline as measured by the mean change between baseline and endpoint on the Disability Assessment for Dementia (DAD) scale (donepezil, –0.7 vs. placebo, –9.0; $p < .0001$) (Figure 1).

The efficacy of donepezil was also evident in a 24-week, multicenter, randomized, double-blind, placebo-controlled trial involving nursing home–based patients with mild to severe AD (MMSE scores, 5–26),[6] as donepezil monotherapy yielded significant benefits relative to placebo in terms of scores on the CDR (Nursing Home Version)-Sum of Boxes (CDR-NH-SB), a modified version of the CDR that serves as a combined measure of cognitive and functional capabilities. Although patients randomized to treatment with donepezil 5 to 10 mg/day (N = 102) did not differ significantly from patients randomized to placebo (N = 102) in terms of mean changes in CDR-NH-SB score between baseline and week 12 ($p = .09$), the difference between the 2 treatment arms in terms of mean changes on this measure did indicate a significant benefit for donepezil-treated patients at week 24 (last-observation-carried-forward [LOCF] analysis; donepezil, –0.1 [improvement] vs. placebo, +0.7 [deterioration]; $p < .05$). Breakdown of CDR-NH-SB scores into their component parts revealed that donepezil monother-

Figure 1. Changes in (A) Cognition (SIB) and (B) Functioning (DAD) Over the Course of a 24-Week, Randomized, Double-Blind, Placebo-Controlled Trial of Donepezil for Patients With Moderate to Severe Alzheimer's Disease[a]



[a]Data from Feldman et al.[5]
Abbreviations: DAD = Disability Assessment for Dementia, LS = least squares, SIB = Severe Impairment Battery.

apy provides a significant benefit relative to placebo in terms of mean changes between baseline and endpoint on the cognitive subscale of the CDR-NH-SB (donepezil, +0.2 vs. placebo, +0.2; $p < .05$), while the benefit with respect to the functional subscale of the CDR-NH-SB approached statistical significance over the same time period (donepezil, +0.05 vs. placebo, +0.4; $p = .0578$). However, there was not a significant difference between the donepezil treatment arm and the placebo treatment arm with regard to MMSE scores at week 24, indicating that the cognitive benefit of donepezil was not consistently evident.

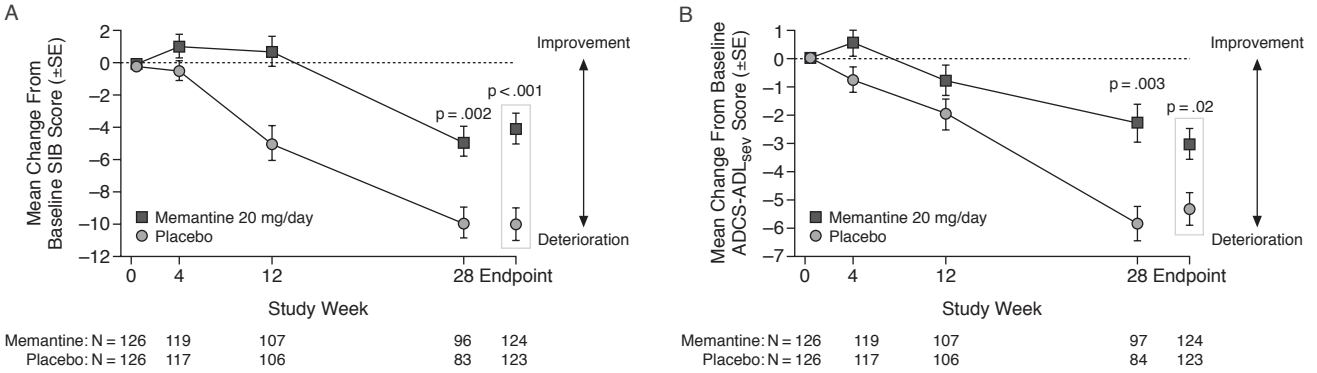
Memantine. Like ChEIs, the *N*-methyl-D-aspartate (NMDA) receptor open-channel antagonist memantine has well-established beneficial effects on cognition in patients with AD. Memantine is believed to act by targeting chronic, low-level stimulation of glutamatergic neurons, a phenomenon that is thought to result in impaired cognition and possibly also in excitotoxic neuronal death, which could further contribute to cognitive losses in AD. It has been hypothesized that the efficacy of memantine may stem in part from its ability to prevent neuronal excitotoxicity with minimal cognitive side effects, due to its low to moderate affinity for calcium ion channels associated with the glutamatergic NMDA receptor. Because of this unique affinity profile, it is believed that memantine inhibits the irregular, persistent influx of stimulatory Ca^{2+} into glutamatergic neurons while still allowing the calcium ion influx necessary for normal glutamate-mediated cognitive processes.[7]

In agreement with the documented correlation between functioning and cognition in AD, the benefits of memantine therapy were found to extend to both functional and cognitive domains in a 28-week, randomized, placebo-controlled trial involving 252 community-based patients with moderate to severe AD (MMSE scores, 3–14).[8] In that study, changes in scores on the Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory modified for more severe dementia (ADCS-ADL_{sev}) between baseline and endpoint indicated reduced mean functional decline for patients treated with memantine 20 mg/day compared with placebo-treated patients (memantine [N = 126], –3.1 vs. placebo [N = 126], –5.2; $p = .02$; LOCF), and this functional benefit was accompanied by a cognitive benefit in terms of mean changes in SIB scores between baseline and endpoint (memantine, –4.0 vs. placebo, –10.1; $p < .001$) (Figure 2).

Memantine-related functional benefits do not appear to be restricted to patients residing in the community, as indicated by findings from a 12-week, randomized, placebo-controlled trial involving nursing home residents with severe dementia (MMSE score < 10).[9] Patients in that trial who received memantine 10 mg/day were more likely than placebo-treated patients to experience favorable responses between baseline and 12 weeks (treated-per-protocol analysis; memantine, N = 75; placebo, N = 76) on each of the 16 items on the Ferm D-Scale,[10] an instrument that characterizes the extent to which a patient relies on others to perform various everyday activities. Furthermore, the difference in response rates between memantine-treated patients and placebo-treated patients reached statistical significance ($p < .05$) for 8 D-Scale items[9]—ability to stand up, ability to move, ability to wash, ability to shower/bathe, ability to dress, ability to toilet, ability to participate in group activities, and ability to partake of hobbies and interests.

Dual therapy. The putatively distinct mechanisms of action ascribed to ChEIs and memantine in the treatment of AD bolster the belief that additive or synergistic therapeutic effects may be seen with combination therapy involving a ChEI and memantine. This belief is supported at least in part by findings from a 24-week, randomized, double-blind, placebo-controlled trial examining the effi-

Figure 2. Changes in (A) Cognition (SIB) and (B) Functioning (ADCS-ADL$_{sev}$) Over the Course of a 28-Week, Randomized, Double-Blind, Placebo-Controlled Trial of Memantine for Patients With Moderate to Severe Alzheimer's Disease[a]



[a]Data from Reisberg et al.[8]
Abbreviations: ADCS-ADL$_{sev}$ = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (modified for more severe dementia), SIB = Severe Impairment Battery.

cacy of memantine given in addition to donepezil in patients with moderate to severe AD (MMSE scores, 5–14).[11] In that trial, patients receiving stable donepezil monotherapy at baseline were randomized to additional treatment with either memantine 20 mg/day or placebo. At study endpoint, patients randomized to memantine (N = 198) had superior cognitive and functional outcomes when compared with patients randomized to placebo (N = 196 or 197), as evidenced by mean changes (LOCF) in scores on the SIB (memantine, +0.9 [improvement] vs. placebo, –2.5 [deterioration]; $p < .001$) and the ADCS-ADL$_{sev}$ (memantine, –2.0 vs. placebo, –3.4; $p = .03$) between baseline and endpoint (Figure 3). In addition, patients treated with memantine experienced a significant benefit relative to placebo-treated patients in terms of mean global improvement as measured at study endpoint using the Clinician's Interview-Based Impression of Change Plus Cognitive Input (CIBIC-Plus) scale (memantine, 4.41 vs. placebo, 4.66; $p = .03$).

Behavior

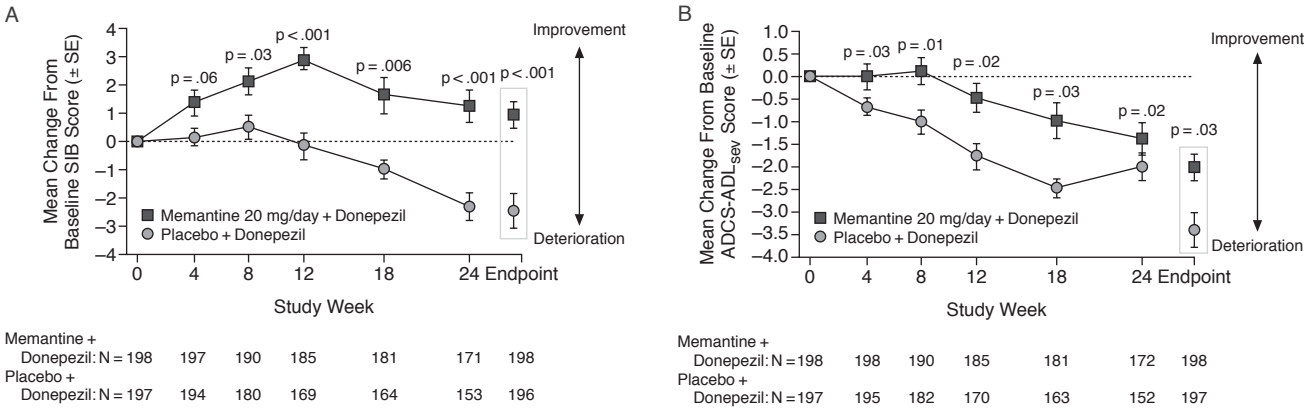
Patients with AD frequently exhibit behavioral disturbances, which may include hallucinations, delusions, depression, euphoria, agitation, aggression, abnormal vocalizations, wandering, overactivity, sexual disinhibition, sleep disturbances, and apathy.[12] One investigation of 50 consecutive outpatients with mild (N = 17), moderate (N = 20), or severe (N = 13) AD revealed the presence of detectable behavioral dysfunction in 88% of all affected patients, compared with 12.5% of the 40 age-matched control individuals who were assessed concurrently.[13]

Because of their detrimental effects on patients and caregivers, behavioral disturbances pose a considerable challenge in the management of AD. A variety of studies have found certain aspects of behavioral dysfunction to be correlated with patient or caregiver distress,[14] with recent data indicating that depression and agitation, respectively, have the largest negative impact on quality of life for patients and caregivers.[15] In addition, behavioral disturbances have been linked to increases in the cost of care and decreases in time to nursing home placement for patients with AD.[16–18]

Behavioral symptoms tend to increase in number and severity throughout the course of AD, bringing with them increased levels of patient and caregiver burden. Consequently, the identification of therapeutic options that can delay the emergence of new behavioral symptoms or reduce the severity of existing symptoms in advanced AD is of primary importance. To that end, a number of clinical trials have examined the use of antidementia agents to target behavioral symptoms in advanced AD, and these trials have yielded promising results.

Cholinesterase inhibitors. With regard to ChEIs, a prospective, 52-week, open-label trial investigating the effects of rivastigmine 3 to 12 mg/day on behavioral dysfunction in 173 nursing home residents with moderate to severe AD (MMSE scores, 6–15)[19] revealed favorable outcomes as measured using the nursing home version of the Neuropsychiatric Inventory (NPI-NH).[20] Although the mean improvement in total NPI-NH scores relative to baseline for patients receiving rivastigmine was not statistically significant at study endpoint, significant improvements were seen in 10 of the 12 items that make up the NPI-NH, including delusions ($p = .002$), hallucinations ($p < .001$), anxiety ($p = .014$), euphoria ($p = .006$), apathy ($p = .008$), disinhibition ($p < .001$), irritability ($p = .001$), aberrant motor behavior ($p < .001$), nighttime behavior disturbances ($p < .001$), and appetite irregularities ($p = .012$). In addition, of the 134 study participants who had detectable behavioral symptoms at baseline, 60 (45%)

Figure 3. Changes in (A) Cognition (SIB) and (B) Functioning (ADCS-ADL$_{sev}$) Over the Course of a 24-Week, Randomized, Double-Blind, Placebo-Controlled Trial of Memantine Plus Donepezil Versus Donepezil Alone for Patients With Moderate to Severe Alzheimer's Disease[a]



[a]Data from Tariot et al.[11]
Abbreviations: ADCS-ADL$_{sev}$ = Alzheimer's Disease Cooperative Study–Activities of Daily Living Inventory (modified for more severe dementia), SIB = Severe Impairment Battery.

experienced clinically significant responses to treatment (as indicated by a reduction of ≥ 30% in NPI-NH total score) between baseline and endpoint. Nonetheless, the ability to draw inferences regarding the therapeutic effect of rivastigmine on behavioral symptoms in AD is limited, due to the lack of blinding and the absence of a placebo treatment arm in this trial.

Another nursing home–based study, a 24-week, randomized, placebo-controlled trial involving 208 patients with mild to severe AD (MMSE scores, 5–26), also revealed improvements in behavioral outcomes for patients receiving ChEI monotherapy.[6] Donepezil, the agent under investigation in the trial (dose range, 5–10 mg/day), did not yield a significant benefit relative to placebo with regard to the mean change in total NPI-NH score between baseline and endpoint, the trial's primary behavioral outcome, nor did it yield a significant benefit in terms of changes in scores on any of the 12 individual NPI-NH items over the same time period. However, a secondary analysis demonstrated that the within-group distribution of responses between baseline and endpoint on the agitation/aggression item of the NPI-NH was superior for patients who were treated with donepezil compared with those treated with placebo (p = .0442). Furthermore, a larger difference in the likelihood of symptomatic reduction was noted when only patients with detectable agitated/aggressive symptoms at baseline were considered (donepezil [N = 69], 67% vs. placebo [N = 63], 46%; p = .017).

Favorable behavioral outcomes were also documented in a secondary analysis performed as part of a clinical trial designed to establish the cognitive benefits of donepezil monotherapy. In that trial, which examined the use of donepezil in community-dwelling patients with moderate to severe AD (MMSE scores, 5–17)[5] over a period of 24 weeks, treatment with the study drug at a dose of 5 to 10 mg/day (N = 139), when compared with placebo treatment (N = 145), yielded a significantly larger mean improvement (p = .0005) in NPI total score between baseline and endpoint (donepezil, –4.6 [improvement] vs. placebo, +1.0 [deterioration]). With regard to changes in scores on individual NPI items between baseline and endpoint, donepezil monotherapy was associated with statistically significant improvements relative to placebo in the domains of depression, anxiety, and apathy (p < .05), as well as with nonsignificant improvements in all other NPI domains.

Memantine. A 28-week, randomized, placebo-controlled trial examining the therapeutic efficacy of the NMDA open-channel antagonist memantine in community-residing patients with moderate to severe AD (MMSE scores, 3–14) found no significant treatment effect on total NPI scores.[21] A secondary analysis, however, revealed superior outcomes (either improvement or slowed deterioration) in 2 separate NPI domains for patients treated with memantine 20 mg/day (N = 126) when compared with placebo-treated patients (N = 126). Specifically, memantine-treated patients experienced significant benefits in the domains of agitation/aggression (p = .008) and delusions (p = .039) as measured by mean changes in scores on the corresponding NPI items between baseline and endpoint.

Dual therapy. Behavioral benefits were also seen in the same 24-week, randomized, placebo-controlled trial that demonstrated the cognitive and functional benefits of therapy with memantine and donepezil for patients with moderate to severe AD.[22] Patients randomized to memantine 20 mg/day added to an ongoing course of done-

pezil 5 to 10 mg/day (N = 198) had superior responses in terms of overall behavioral symptom severity compared with patients for whom placebo was added to donepezil (N = 196), as evidenced by significant differences between the 2 treatment arms with respect to mean changes in total NPI scores between baseline and week 12 (combination, –2.5 [improvement] vs. donepezil, +1.7 [deterioration]; $p < .001$; LOCF analysis) and between baseline and endpoint (combination, –0.1 [improvement] vs. donepezil, +3.7 [deterioration]; $p = .002$). Patients randomized to memantine also had superior outcomes in 3 separate NPI domains—agitation/aggression ($p = .001$), irritability/lability ($p = .005$), and appetite irregularities ($p = .045$)—between baseline and endpoint when compared with patients randomized to have placebo added to their ongoing donepezil regimen.

Current role of antidementia agents in the treatment of behavioral symptoms. Although the behavioral data from the clinical trials described here are encouraging, none of these trials was designed specifically to prove the behavioral efficacy of the antidementia agents being tested, meaning that the evidence available to date is not sufficient to define best clinical practice. Nonetheless, given the available data, recent practice guidelines do recommend the use of antidementia agents for treatment of behavioral symptoms in dementia.[23]

Nursing Home Placement

Nursing home placement is an important endpoint in AD, resulting from the deterioration of patient cognition, functioning, and/or behavior to such an extent that the family caregiver (after taking into account factors such as his or her own health, available resources, and alternative options) decides that the affected patient's needs would be better met in an institutionalized care setting. Decisions regarding nursing home placement may be a source of considerable distress, as caregivers frequently prefer to avoid institutionalizing loved ones for whom they have been providing care, while patients themselves may desire to remain in a community setting for as long as possible. In addition, family caregivers who do ultimately decide to place an elderly patient in a nursing home may be burdened by feelings of failure as a provider of care, as well as guilt over relinquishing the bulk of the caregiving duties to a third party.

A variety of factors have been found to exert an influence over decisions regarding nursing home placement. One is the use of caregiver-targeted interventions, as the randomization of caregivers to undergo a 6-session counseling course and then join a caregiver support group was shown to reduce the incidence of nursing home placement by one third ($p = .02$) in a volunteer sample of 206 patient-caregiver pairs who were followed for up to 8 years from the time of randomization.[24] In the same study, patient income was also found to play an important role in decisions regarding institutionalization, as individuals with greater financial resources were shown to have a reduced incidence of nursing home placement, presumably due to their increased ability to afford the services of trained, in-home helpers.

Other variables related to the symptomatic status of the affected patient have also been recognized as key determinants of nursing home placement. For example, a positive correlation has been reported between the severity of cognitive symptoms and the likelihood of institutionalization.[24] Likewise, functional disability and behavioral symptoms have been identified as significant predictors of the need for nursing home placement.[25,26] In fact, a retrospective analysis of a random sample of 204 patients with dementia found that behavioral disturbances were associated with a median decrease of almost 2 years (655 days) in time to nursing home placement.[17] In addition, while caregiver depression has been linked to an increased incidence of nursing home placement, the primary driving force behind this correlation has been identified as depression resulting from troubling behavior on the part of the affected patient.[24] The association between risk of nursing home placement and cognitive, functional, and behavioral symptoms in AD suggests a possible role for antidementia agents in prolonging the length of time for which affected patients can remain in a community setting, and the validity of this role has been tested in a number of clinical trials.

Cholinesterase inhibitors. The utility of ChEIs as a class in prolonging time to nursing home placement was explored in an observational case-control study involving 270 patients with probable AD.[27] Patients in the study were divided into two 135-patient cohorts, which were balanced according to age, education, duration of symptoms, and cognitive status. One cohort consisted of patients who had been exposed to ChEI therapy (predominantly donepezil; mean MMSE score, 18.7), while the other consisted of patients with no history of ChEI exposure (mean MMSE score, 18.8). Analysis of the 2 patient cohorts, with ChEI exposure treated as a time-dependent covariate in a Cox proportional hazards model, revealed a significant negative association between ChEI use (past or present) and risk of nursing home placement over the course of observational follow-up (risk ratio [RR], 0.33; $p = .004$; mean follow-up duration, approximately 3 years in both patient cohorts).

The putative ability of ChEIs to delay institutionalization is also supported by findings from an observational follow-up study of 671 patients who had previously been enrolled in 1 of 3 randomized, double-blind, placebo-controlled trials (two 12-week trials and one 24-week trial) and who had the option to participate in 1 of 2 subsequent open-label trials investigating the efficacy of donepezil in mild to moderate AD (mean MMSE score, 19.4).[28] Time to first dementia-related nursing home placement (whether temporary or permanent), time to first nursing home placement (whether temporary or permanent) for any reason,

and time to permanent nursing home placement were selected as principal study outcomes, and patients were stratified according to their donepezil use patterns throughout the double-blind and open-label treatment periods. Under this stratification scheme, patients who had received effective donepezil therapy (≥ 5 mg/day; ≥ 80% compliance) for the entire duration of double-blind treatment plus at least 24 weeks of open-label treatment (N = 310) were found to have longer median times to first dementia-related institutionalization (66.1 months vs. 44.7 months) and permanent institutionalization (63.0 months vs. 45.5 months) when compared with patients classified as minimal users of donepezil (N = 113)—that is, patients who did not receive an entire course of effective donepezil therapy (including patients treated with placebo or with subtherapeutic donepezil doses) during double-blind treatment and who subsequently did not participate in an open-label study or received less than 24 weeks of effective open-label treatment. Furthermore, when compared with these minimal users of donepezil, patients who had received an entire course of effective double-blind donepezil therapy plus at least 24 weeks of effective open-label donepezil therapy had a significantly reduced risk of experiencing their first dementia-related institutionalization (RR, 0.574; $p < .01$), as well as a significantly reduced risk of permanent nursing home placement (RR, 0.642; $p < .01$) over the course of the observational follow-up period.

While these findings regarding the effect of ChEI therapy on nursing home placement are promising, results from the AD2000 trial,[29] the first placebo-controlled study to evaluate prospectively the association between AD pharmacotherapy and institutionalization, suggest that treatment with a ChEI may not have a significant impact on the ability of affected patients to continue living in a community setting. In the AD2000 trial, 565 patients who were referred to a memory clinic, subsequently judged by a physician to have met the DSM-IV criteria for a diagnosis of AD, and whose likelihood of benefiting from donepezil therapy was deemed to be uncertain were randomized to receive either placebo (N = 283) or donepezil 5 to 10 mg/day (N = 282) for the duration of a 12-week run-in period. Patients who completed this run-in phase were then rerandomized and entered into a long-term follow-up phase in which they received their randomly assigned treatment (donepezil 5–10 mg/day or placebo) for an indefinite period of time, with the decision regarding when to discontinue treatment being left to the discretion of the patient, the patient's caregiver, and the patient's physician. (All trial participants, including those who had discontinued treatment, were assessed for efficacy outcomes at least once yearly for the duration of the study.) Using this study protocol, it was found that there was no significant difference between treatment arms in terms of rates of institutionalization at 1 year (donepezil, 9% vs. placebo, 14%; $p = .15$) or 3 years (donepezil, 42% vs. placebo, 44%; $p = .4$) from the start of the initial run-in phase. Likewise, the overall risk of institutionalization was nearly identical in both treatment groups (RR, 0.97 [donepezil vs. placebo]; $p = .8$), further suggesting that this outcome was not significantly affected by donepezil therapy. It should be noted, however, that the ability to draw inferences from these results is somewhat limited, as the AD2000 study was not sufficiently powered to detect between-group differences in institutionalization-related endpoints, because trial enrollment fell well short of the 3000 patients called for in the original study design.[30]

Memantine. Possible improvements in institutionalization-related outcomes are suggested by pharmacoeconomic data from the same pivotal trial in which the cognitive and functional benefits of memantine monotherapy were established in patients with moderate to severe AD (MMSE scores, 3–14).[31] Analysis of data on the residential status of patients in the study's treated-per-protocol population revealed similar baseline institutionalization rates for patients in the memantine 20-mg/day treatment arm (N = 90) and patients in the placebo treatment arm (N = 76) (memantine, 7% vs. placebo, 13%; $p = .16$). However, by the conclusion of the study, the difference in institutionalization rates between the 2 treatment arms was significant (memantine, 8% vs. placebo, 20%; $p = .04$), as 1 memantine-treated patient and 5 placebo-treated patients moved from a community setting to an institutional setting during the 28-week treatment period. In the same study, memantine-treated patients also showed a near-significant tendency toward having a longer median time to institutionalization when compared with placebo-treated patients ($p = .052$; treated-per-protocol analysis), providing further evidence of the association between memantine monotherapy and prolonged ability to live in a community setting.

Current role of antidementia agents in delaying time to nursing home placement. In general, studies addressing delayed nursing home placement as a function of antidementia therapy have not been designed to resolve conclusively the issue or have been underpowered. A large-scale "effectiveness" trial of the type intended by the AD2000 study would therefore represent an important step toward definitive characterization of the way in which antidementia agents influence institutionalization-related outcomes.

SUMMARY

Alzheimer's disease is a progressive condition that is commonly diagnosed in the intermediate to late stages of its natural course, when the characteristic cognitive and functional symptoms associated with the disease become more readily evident. While patients with moderate to

severe AD at diagnosis have already experienced appreciable losses in cognition and functioning, they can still derive substantial benefits from a variety of pharmacotherapeutic options. In particular, antidementia agents—ChEIs and the NMDA receptor open-channel antagonist memantine—have been shown to slow the progression of cognitive symptoms in patients with moderate to severe AD (although memantine is currently the only agent approved by the U.S. Food and Drug Administration for use in this stage of the disease). Also promising is the finding from a single study[11] that therapy involving both memantine and a ChEI provides increased cognitive benefit relative to ChEI monotherapy in patients with moderate to severe AD, a result that may be related to the distinct therapeutic mechanisms ascribed to NMDA receptor open-channel antagonists and ChEIs.

While cognitive symptoms represent the core feature of AD, functional and behavioral impairments accompanying the disease are also weighty concerns, as patients and caregivers may consider impairments in these domains to be more important when compared with impairments in cognition. Thus, the emergence of evidence regarding the beneficial effects of antidementia agents on function and, possibly, behavior in patients with AD represents an encouraging development. Some (but not all) pharmacotherapy trials examining the issue of nursing home placement[27–31] suggest that these agents may play a role in prolonging time to institutionalization as well, although this point remains unproven. Nonetheless, overall, there is growing evidence to suggest that the therapeutic effects of ChEIs and memantine are not limited to cognition but may extend across the spectrum of AD symptoms, resulting in a number of tangible benefits for those whose lives are affected, either directly or indirectly, by this debilitating condition.

Drug names: donepezil (Aricept), memantine (Namenda), rivastigmine (Exelon), selegiline (Eldepryl and others).

REFERENCES

1. Feldman H, Gracon S. Alzheimer's disease: symptomatic drugs under development. In: Gauthier S, ed. Clinical Diagnosis and Management of Alzheimer's Disease. Boston, Mass: Butterworth-Heinemann; 1996: 239–259
2. Sano M, Ernesto C, Thomas RG, et al. A controlled trial of selegiline, alpha-tocopherol, or both as treatment for Alzheimer's disease. N Engl J Med 1997;336:1216–1222
3. Galasko D. An integrated approach to the management of Alzheimer's disease: assessing cognition, function and behaviour. Eur J Neurol 1998;5: S9–S17
4. Galasko D, Edland SD, Morris JC, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD), pt 11: clinical milestones in patients with Alzheimer's disease followed over 3 years. Neurology 1995; 45:1451–1455
5. Feldman H, Gauthier S, Hecker J, et al. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology 2001;57:613–620
6. 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;49:1590–1599
7. Danysz W, Parsons CG, Möbius HJ, et al. Neuroprotective and symptomatological action of memantine relevant for Alzheimer's disease: a unified glutamatergic hypothesis on the mechanism of action. Neurotox Res 2000;2:85–97
8. Reisberg B, Doody R, Stöffler A, et al. Memantine in moderate-to-severe Alzheimer's disease. N Engl J Med 2003;348:1333–1341
9. Winblad B, Poritis N. Memantine in severe dementia: results of the [9]M-Best Study (Benefit and efficacy in severely demented patients during treatment with memantine). Int J Geriatr Psychiatry 1999;14:135–146
10. Ferm L. Behavioural activities in demented geriatric patients: study based on evaluations made by nursing staff members and on patients' scores on a simple psychometric test. Gerontol Clin (Basel) 1974;16:185–194
11. 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
12. Beeri MS, Werner P, Davidson M, et al. The cost of behavioral and psychological symptoms of dementia (BPSD) in community dwelling Alzheimer's disease patients. Int J Geriatr Psychiatry 2002;17:403–408
13. Mega MS, Cummings JL, Fiorello T, et al. The spectrum of behavioral changes in Alzheimer's disease. Neurology 1996;46:130–135
14. Ballard C, Lowery K, Powell I, et al. Impact of behavioral and psychological symptoms of dementia on caregivers. Int Psychogeriatr 2000; 12(suppl 1):93–105
15. Shin IS, Carter M, Masterman D, et al. Neuropsychiatric symptoms and quality of life in Alzheimer disease. Am J Geriatr Psychiatry 2005; 13:469–474
16. Wolstenholme J, Fenn P, Gray A, et al. Estimating the relationship between disease progression and cost of care in dementia. Br J Psychiatry 2002;181:36–42
17. Phillips VL, Diwan S. The incremental effect of dementia-related problem behaviors on the time to nursing home placement in poor, frail, demented older people. J Am Geriatr Soc 2003;51:188–193
18. O'Brien JA, Shomphe LA, Caro JJ. Behavioral and psychological symptoms in dementia in nursing home residents: the economic implications. Int Psychogeriatr 2000;12:51–57
19. Aupperle PM, Koumaras B, Chen M, et al. Long-term effects of rivastigmine treatment on neuropsychiatric and behavioral disturbances in nursing home residents with moderate to severe Alzheimer's disease: results of a 52-week open-label study. Curr Med Res Opin 2004;20: 1605–1612
20. Wood S, Cummings JL, Hsu MA, et al. The use of the Neuropsychiatric Inventory in nursing home residents: characterization and measurement. Am J Geriatr Psychiatry 2000;8:75–83
21. Gauthier S, Wirth Y, Stöffler A, et al. Behavioural benefit by memantine treatment in moderate to severe Alzheimer's disease. Presented at the XXIV CINP Congress; June 20–24, 2004; Paris, France
22. Cummings JL, van Dyck C, Schmitt F, et al. Functional and behavioral effects of memantine in Alzheimer's disease. Presented at the 56th annual meeting of the American Academy of Neurology; April 24–May 1, 2004; San Francisco, Calif
23. Alexopoulos GS, Jeste DV, Chung H, et al. The Expert Consensus Guideline Series: treatment of dementia and its behavioral disturbances. Postgrad Med 2005;Spec Rpt:1–111
24. Mittelman MS, Ferris SH, Shulman E, et al. A family intervention to delay nursing home placement of patients with Alzheimer disease: a randomized controlled trial. JAMA 1996;276:1725–1731
25. 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
26. Cohen CA, Gold DP, Shulman KI, et al. Factors determining the decision to institutionalize dementing individuals: a prospective study. Gerontologist 1993;33:714–720
27. Lopez OL, Becker JT, Wisniewski S, et al. Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. J Neurol Neurosurg Psychiatry 2002;72:310–314
28. Geldmacher DS, Provenzano G, McRae T, et al. Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. J Am Geriatr Soc 2003;51:937–944
29. Courtney C, Farrell D, Gray R, et al. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. Lancet 2004;363:2105–2115
30. Schneider LS. AD2000: donepezil in Alzheimer's disease [comment]. Lancet 2004;363:2100–2101
31. Wimo A, Winblad B, Stöffler A, et al. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. Pharmacoeconomics 2003;21:327–340

