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Donepezil in Severe Alzheimer's Disease

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In the severe stages of Alzheimer's disease, functional autonomy is lost, psychiatric and behavioral symptoms become increasingly troublesome, and cognitive deficits increase until most patients require complete care, usually in specialized nursing homes. Consequently, some health care professionals question the benefits of pharmacologic intervention during these later stages. Since primary care physicians are often first to see these patients, they have key roles in recognizing the benefits of treatment and initiating appropriate management and referral. Three prospective randomized clinical trials of donepezil in severe Alzheimer's disease have been conducted; these show donepezil treatment is associated with functional and cognitive benefits, although behavioral benefits were not consistently observed. Donepezil was well tolerated; side effects were transient, mild to moderately severe, and cholinergic in nature. Donepezil has strong data throughout the Alzheimer's disease spectrum and, therefore, represents a first-line monotherapy that can provide benefits to patients in all stages of Alzheimer's disease.

Keywords: Alzheimer's disease; severe; donepezil; primary care

Introduction

Alzheimer's disease (AD) is a progressive, degenerative disorder. As patients enter the severe stages of AD, functional autonomy is lost, psychiatric and behavioral symptoms become increasingly troublesome, and cognitive deficits increase until the majority of patients require complete care, usually in specialized nursing homes.[1]

The population with severe AD is often considered to be beyond the point at which pharmacologic intervention will be beneficial, and indeed some specialists and treatment guidelines recommend discontinuing treatment in these patients.[2] However, given that a reported 20% of patients with AD have severe dementia,[3] it is not surprising that a large proportion of patients first presenting to physicians with symptoms of AD are already in the moderate to severe stages of the disease.[4] It is therefore important to recognize the benefits of initiating treatment and continuing to treat those patients with severe AD.

Donepezil is a cholinesterase inhibitor (ChEI) widely used for the treatment of AD and, following its approval for severe AD by the US Food and Drug Administration (FDA) in 2006, it is now licensed in the United States for all stages of AD: mild, moderate, and severe.[5] For patients initiating donepezil treatment during the mild to moderate phase of AD, persistent treatment can provide cognitive benefits,[6,7] slow functional decline,[8] help behavioral symptoms,[9] and allow them to stay at home longer[10] as the disease progresses toward the severe stage.

In a survey of caregivers, the primary care specialist physician was identified as the physician with whom AD patients/caregivers most frequently (two thirds of the time) first discuss AD symptoms, while diagnosis is more often made by hospital-based specialists.[11] The primary care specialist physician therefore has a key role to play in recognizing the benefits of treatment for patients with severe AD and in initiating appropriate management and referral of these patients.

This article reviews compelling evidence from large-scale randomized clinical trials with donepezil

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that supports the treatment of patients in the severe stages of AD.

Pharmacologic and Nonpharmacologic Treatment Options for Patients With Severe AD

Pharmacologic therapies widely used for the treatment of AD include the ChEIs donepezil, rivastigmine, and galantamine, and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine. Treatment guidelines for AD developed in Italy suggest that treatment with ChEIs should be considered in patients with moderate to severe AD and continued in patients who have derived benefit, even in those with a Mini-Mental State Examination (MMSE) score < 10.[12] A recent US consensus paper by Fillit et al,[13] and the latest guidelines from the European Federation of Neurological Societies,[14] advocate the treatment of patients with severe AD (MMSE score < 10) with memantine in combination with a ChEI as required. The US consensus paper also recommends that treatment should be discontinued only when a patient reaches the profound stage of AD (MMSE score of 0/unobtainable), that is, when a patient experiences a complete loss of cognitive and functional abilities, and only if there is no evidence of continued benefit in the profound stage.[13]

Recent evidence from 3 randomized, double-blind, placebo-controlled clinical trials provides strong support for the use of donepezil for the treatment of severe AD.[15-17] Donepezil is the only ChEI approved by the FDA for use in patients with severe AD. Rivastigmine[18-20] and galantamine[21,22] also have data supporting their use in moderate to severe AD; however, these data are not derived from large-scale trials nor are the trials specifically designed to assess efficacy in a severe population. Memantine, as a monotherapy, has previously shown positive effects on measures of cognition, activities of daily living (ADL), and global function in moderate to severe AD[23] and on measures of global function and function in severe AD,[24] although results from a recent study have suggested that memantine is not always effective as monotherapy in patients with moderate to severe disease.[25] Nevertheless, memantine has been shown to be a useful add-on agent in patients with moderate to severe AD already receiving donepezil.[26]

Nonpharmacologic therapies such as memory training, reality orientation therapy, and aromatherapy have undergone some testing in randomized clinical trials and may provide benefits for cognitive performance and/or behavioral problems; however, evidence is limited and these therapies are not the mainstay of AD treatment.[12]

Donepezil Treatment for Patients With Severe AD

Efficacy

Efficacy data from 3 large, prospective, randomized clinical trials[15-17] and a post hoc analysis[27] show that initiation of donepezil treatment in patients with severe AD can provide small, but significant, benefits in terms of short-term improvement and/or maintenance of cognition and function. The Swedish Nursing Home Severe AD study[15] was the first large-scale randomized controlled trial of a ChEI in an exclusively severe AD patient population. The trial was a 6-month, double-blind, parallel-group, placebo-controlled study in patients with severe AD (MMSE, 1-10) who were living in assisted-care nursing homes in Sweden. Patients treated with donepezil 10 mg/d showed significantly greater improvements in cognition (Severe Impairment Battery [SIB]) and declined less in function (Alzheimer's Disease Cooperative Study–Activities of Daily Living modified for severe AD [ADCS-ADL-sev]) than patients receiving placebo (Figure 1). Although there was numerically greater improvement with donepezil, there was no significant difference between treatment groups on the measure of behavior, the Neuropsychiatric Inventory (NPI).

The second trial was a multinational, 24-week, randomized, double-blind, placebo-controlled study of donepezil in patients with severe AD (MMSE scores 1-12 and Functional Assessment Staging [FAST] scores ≥ 6).[16] Participating centers were predominantly based in the United States, but patients were also enrolled in Canada, France, the United Kingdom, and Australia. In this study, patients receiving donepezil 10 mg/d had significantly better cognitive (SIB and MMSE) and global function (collapsed 3-category analysis of the Clinician's Interview-Based Impression of Change-plus caregiver interview [CIBIC-plus]) outcomes compared with those receiving placebo (Figure 2). Both the donepezil and the placebo groups showed a trend toward an improvement in behavior (NPI) from baseline but differences were not significant between groups. Changes in function (ADCS-ADL-sev)

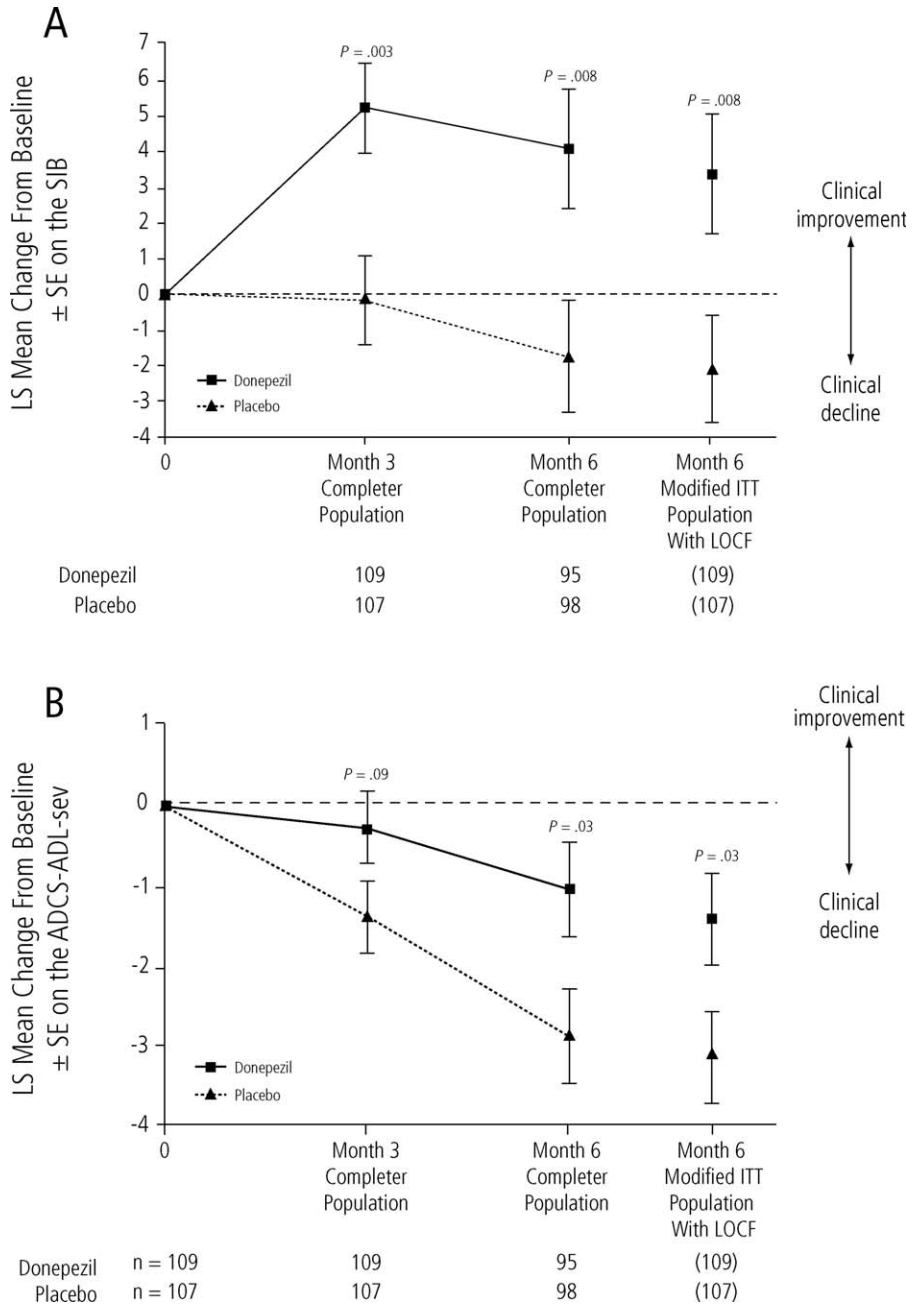

Figure 1. Swedish Nursing Home study.[15] A, Effect of donepezil treatment on Severe Impairment Battery (SIB) scores. B, Effect of donepezil treatment on Alzheimer's Disease Cooperative Study–Activities of Daily Living modified for severe Alzheimer's disease (ADCS-ADL-sev) scores. ITT = intent to treat; LOCF = last observation carried forward; LS = least squares. Figures reproduced with permission of Elsevier Limited.

were not significantly different between treatment groups.

The third study, with a design comparable to that of the multinational severe trial, but including both 5 and 10 mg/d doses, was performed in a Japanese patient population.[17] This was a 24-week, randomized, parallel, double-blind, placebo-controlled study of donepezil in patients with severe AD (MMSE scores 1-12 and FAST scores $\geq$ 6). Concurrent with the multinational severe study, Japanese patients receiving donepezil 10 mg/d had significantly better cognitive (SIB) and global function (7-category and collapsed 3-category analysis of the CIBIC-plus) outcomes compared with those receiving placebo (Figure 3). In patients receiving donepezil 5 mg/d, SIB scores were also significantly

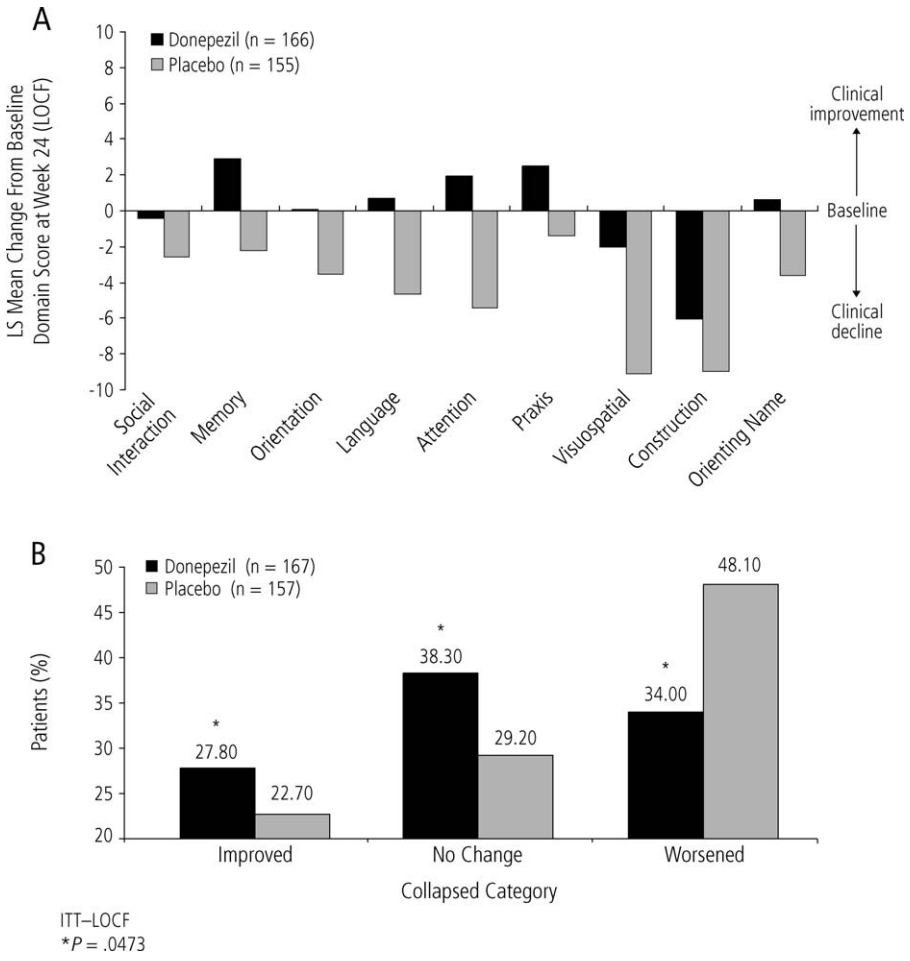

Figure 2. Multinational study.[16] A, Effect of donepezil treatment on Severe Impairment Battery (SIB) individual domain analysis scores. B, Effect of donepezil treatment on Clinician's Interview-Based Impression of Change-plus caregiver interview (CIBIC-plus) scores (3-category collapsed analysis). ITT = intent to treat; LOCF = last observation carried forward; LS = least squares. Figures reproduced with permission of Lippincott, Williams & Wilkins.

improved compared with placebo, but the distribution of CIBIC-plus scores was not statistically superior to that of the placebo group using either the 7-category or collapsed 3-category analysis. In addition, a statistically significant dose-response relationship was demonstrated on both the SIB and the CIBIC-plus. No significant differences between treatment groups were seen for measures of behavior (Behavioral Pathology in Alzheimer's Disease Rating Scale; BEHAVE-AD) or function (ADCS-ADL-sev).

Prior to these 3 studies in a severe AD population, an analysis was performed on a subgroup of patients with more severe AD (standardized MMSE [sMMSE], 5-12) within a 24-week, randomized, placebo-controlled trial in moderate to severe AD (MSAD).[27] Patients receiving donepezil had significantly better global function (CIBIC-plus), cognition (sMMSE and SIB), function (Disability Assessment for Dementia), and behavior (NPI) compared with patients receiving placebo after 24 weeks of treatment.

The 3 reported studies of donepezil in a severe AD population demonstrated robust improvements in cognition, as well as consistent positive effects on global function.[15-17] Nevertheless, statistically significant differences in favor of donepezil for the measure of function (ADCS-ADL-sev) were only seen in the Swedish Nursing Home Severe AD study.[15] The reasons for this are not clear. However, the ADCS-ADL-sev was a primary end point in the Swedish Nursing Home Severe AD study and a secondary end point in the other 2 trials, which may have influenced the respective ability to show statistically significant differences. In addition, there are likely to be inherent differences between ADL requirements in the nursing home and in the community setting, which could have affected the

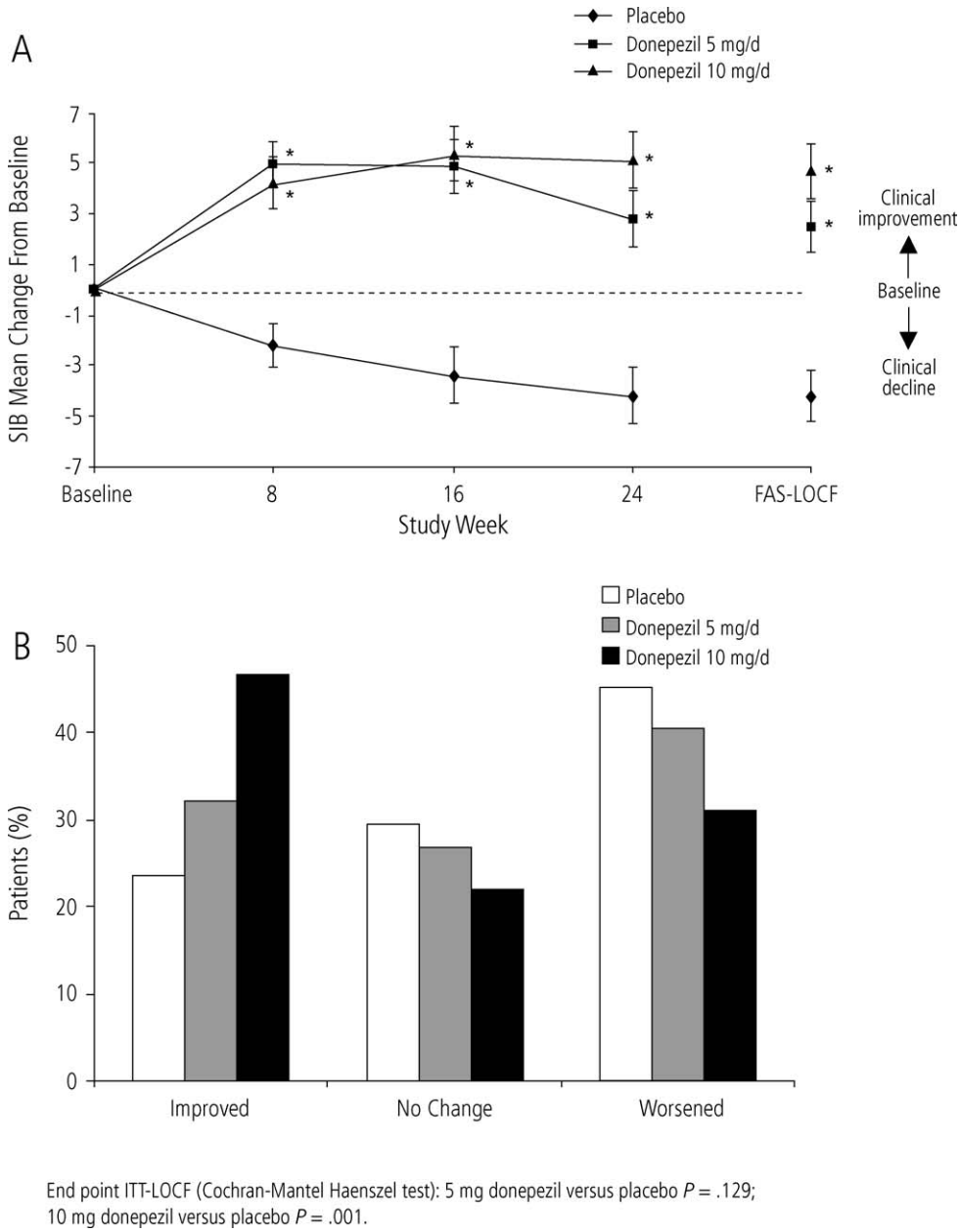

Figure 3. Japanese study.[17] A, Effect of donepezil treatment on Severe Impairment Battery (SIB) scores; error bars represent SE of the mean; data are for observed cases at weeks 8, 16, and 24, and for the FAS population at end point (LOCF); *$P < .001$ versus placebo. B, Effect of donepezil treatment on Clinician's Interview-Based Impression of Change-plus caregiver interview (CIBIC-plus) scores (3-category collapsed analysis). FAS-LOCF = full analysis set-last observation carried forward; ITT = intent to treat. Figures reproduced with permission of S. Karger AG, Basel, Switzerland.

relative sensitivity of the ADCS-ADL-sev scale in these 3 studies.

Although behavioral benefits over placebo were observed in the MSAD trial post hoc analysis,[27] they were not evident in the 3 randomized clinical trials of donepezil for severe AD. This is, however, concurrent with studies of memantine monotherapy in moderate to severe AD in which behavioral benefits were also not observed.[23] Behavioral and psychological symptoms of AD can be particularly disruptive at the severe stage of the disease and are said to be responsible for the majority of distress experienced by the patient and their family/caregiver.[28] Assessing the effect of antidementia agents on these behavioral symptoms may be confounded by the variety of behaviors assessed in the overall NPI and BEHAVE-AD scales (eg, agitation, depression, hallucination, aggressiveness, and so on) and by the

fact that the symptoms vary between patients in terms of presentation and pattern. In addition, the sensitivity of the scales could be further compromised by the often widespread use of psychoactive medications among the severe AD population, as has been demonstrated in a previous study of donepezil.[29] Indeed, it is noteworthy that in the Swedish Nursing Home Severe AD study, for example, in excess of 80% of the patients used concomitant psychoactive medication, which likely would have influenced the NPI outcomes in that study. At present, whether the lack of behavioral benefits in these studies can be attributed to the actual efficacy of the agents or to a lack of sensitivity of behavioral instruments among the severe population remains unknown.

Safety and Tolerability

Donepezil is safe and well tolerated in the severe AD population.[15-17,27] The safety and tolerability data from patients receiving donepezil in the cited studies were comparable to those in patients receiving placebo and did not differ substantially from data obtained in patients with mild to moderate AD. Side effects were typical of ChEI therapy, for example, diarrhea and hallucinations, and were primarily transient and mild to moderate in severity.

Impact on Caregivers

Alzheimer's disease treatment has also been shown to reduce caregiver stress and burden for patients with moderate to severe AD.[30] In the MSAD study, donepezil-treated patients had a significantly slower decline in both instrumental and basic ADL compared with patients receiving placebo. These donepezil-mediated benefits in ADL were associated with a saving of approximately 1 hour a day of caregiver time (based on a 16-hour day).[30] Moreover, donepezil treatment resulted in stabilized scores on a measure of caregiver stress (Caregiver Stress Scale [CSS]), whereas placebo patients showed a worsening in CSS scores over the 24-week study period. Treatment may therefore also provide benefit for those caring for patients with severe AD.

Donepezil in Combination Therapy

As mentioned previously, 1 study has assessed the efficacy and safety of administering memantine to patients with moderate to severe AD (MMSE scores 5-14) already receiving stable donepezil therapy.[26] Patients who received donepezil plus memantine had significantly better outcomes on measures of cognition (SIB), function (standard ADCS-ADL), global function (CIBIC-plus), and behavior (NPI), compared with patients receiving donepezil plus placebo. In this study, both treatment regimens were well tolerated and the incidence of individual adverse events was generally similar in the 2 groups. These results suggest that the addition of memantine to donepezil therapy may be particularly effective in patients with advanced disease, with few additional tolerability issues.

Conclusions

Donepezil has strong efficacy data in AD from the mild to the severe stage[6-9,15-17,31,32] and has been shown to be effective for treating all domains of AD.[8,9,15-17,29-32] The data reviewed here highlight that, in addition to improvement, an important outcome of treatment of patients with severe AD is the maintenance of baseline levels or less-than-expected decline in cognition and function. Donepezil has consistent data throughout the AD spectrum from patients with mild AD through to severe AD, even when initiated in severe AD. It therefore represents a treatment that can provide benefit to patients throughout all stages of the disease. However, many patients presenting with AD in the severe stage are not started on a treatment regimen. Because many patients initially present to primary care practices with symptoms of AD, the primary care arena is well placed to ensure that patients, when they eventually reach the severe AD stage, receive this beneficial treatment.

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