European Journal of Neurology 2005, **12** (Suppl. 3): 11–16

Alzheimer's disease: the benefits of early treatment

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Keywords:
Alzheimer's disease, cognition, dementia, donepezil, early treatment, mild cognitive impairment

The purpose of this review was to summarize research on the clinical benefits of early treatment for Alzheimer's disease via a focused discussion of data on donepezil. Well-controlled clinical trials demonstrate that donepezil is effective in stabilizing or slowing progressive decline in cognition, function, and behavior. Several studies reveal statistically significant and clinically meaningful advantages to initiating treatment early in the course of the disease. Benefits of donepezil treatment include behavioral stabilization and preserved independence, in addition to slowed cognitive decline. Epidemiologic studies and evidence from histopathology underlie a rationale for treating patients who are cognitively impaired but do not have dementia. Clinical trials in such patients indicate that treating patients with mild cognitive impairment (MCI) may delay the onset of Alzheimer's dementia. Substantial evidence favors initiating treatment early in the course of dementia and reinforces the necessity to assess behavior and activities of daily living to accurately evaluate treatment response. Results of early studies of donepezil in MCI are promising and suggest directions for further research.

Introduction

There is a wealth of clinical experience to support early treatment for Alzheimer's disease (AD). Much of this evidence comes from clinical studies of donepezil, a cholinesterase inhibitor (ChEI) that has been the mainstay of AD treatment since its introduction in 1996. For the purposes of this review, we shall distinguish between timely treatment, i.e. treatment initiated as soon as the diagnosis is made, and early treatment, which is initiated early in the disease course. Timely treatment, although important, may not suffice because diagnosis often lags behind disease progression. Denial, fear, and lack of awareness amongst caregivers and physicians hinder detection and diagnosis (Bond *et al*., 2005). The recent pan-European Facing Dementia Survey found that 70% of physicians believe primary care providers have trouble detecting early AD. As a result, caregivers state that an average of 2 years passes between the onset of recognizable symptoms and a formal diagnosis (Bond *et al*., 2005). The challenges facing those who treat the elderly are to look for early warning signs, screen patients, identify those with possible or probable dementia, and initiate treatment as early as possible.

The amnestic subtype of mild cognitive impairment (MCI) is increasingly being recognized as a precursor to AD in a substantial subset of individuals (Ganguli *et al*., 2004). The term, amnestic MCI, describes patients who complain of memory problems with evidence of memory deficits in neuropsychiatric tests, but who have minimal or no impairment in function or activities of daily living. In other words, MCI appears to be intermediate between the cognitive changes of normal aging and dementia (Ganguli *et al*., 2004). Although some MCI patients revert to normal cognitive function in a few months upon subsequent testing, MCI patients have a fourfold increased risk of AD relative to unimpaired individuals (Ganguli *et al*., 2004) and 10–15% per year convert to AD (Salloway *et al*., 2004). Moreover, recently published studies show that cholinergic deficits in AD exist early, when patients are experiencing the symptoms of MCI or early AD (Herholz *et al*., 2004; Mesulam *et al*., 2004). With clinical and basic science providing a rationale for early treatment, this short review will highlight compelling data illustrating the benefits of this strategy.

Because AD is a progressive disorder, reasonable treatment expectations include short-term improvement, stabilization, or a slower than expected rate of decline. To clarify the goals and expectations for AD treatment, it is useful to compare standard AD management with that of another progressive neurodegenerative disease. In multiple sclerosis (MS), stabilization and reduced rates of decline are recognized treatment goals in the absence of a cure. In fact, the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology asserts that the most important therapeutic aim of MS

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therapy is 'to prevent or postpone long-term disability' (Goodin *et al*., 2002). Consequently, medication is not withdrawn because a patient's condition declines. Rather, it is started early and continued for as long as possible to maximize the benefit of treatment (Miller *et al*., 2002). This too should be the objective of treatment in AD. An international working group convened at the World Alzheimer Congress in 2000 recommended that the definition of treatment responders be expanded to include those who experience a delay in progressive decline (Winblad *et al*., 2001a). Postponing or slowing cognitive, functional, and behavioral decline is undoubtedly a legitimate goal of AD treatment.

Short- and long-term benefit in mild to moderate AD

The effects of AD treatment (short-term improvement, stabilization, slowed decline) are demonstrated in the results of controlled trials and open-label extension studies of donepezil. A meta-analysis of individual patient data from phase II and III double-blind, placebo-controlled studies of donepezil unequivocally demonstrates cognitive improvement [measured via the Alzheimer's Disease Assessment Scale (ADAS-cog) instrument] for periods of at least 6 months (Whitehead *et al*., 2004). Notably, this analysis demonstrated a dose response for donepezil, showing that a dosage of 10 mg/day was statistically superior to the 5 mg/day dosage from week 18 onwards. Patients on both dosages were significantly improved compared with placebo (Fig. 1).

The Nordic Study was a 1-year, placebo-controlled trial coupled to a 2-year, open-label continuation phase that took place in multiple centers in Denmark, Finland, Norway, Sweden, and The Netherlands. The unique design of the Nordic Study illustrates cognitive stabilization (Winblad *et al*., 2001b) and elegantly demonstrates that donepezil-treated patients show less deterioration over the long term when compared with a population of untreated patients (Winblad *et al*., 2003). In this study, 286 patients with mild to moderate AD were randomized to 1 year of donepezil or placebo, after which the placebo patients were crossed over and 157 patients continued for two more years on open-label donepezil. The placebo arm of the 1-year-long, double-blind phase was used to establish a rate of decline for this patient population, which was then projected over the remaining 2 years of open-label donepezil treatment. This study, therefore, does not rely on between-study comparisons with cohorts that have different baseline characteristics. Arguably, a linear projection such as the one the authors used is a conservative estimate of the hypothetical off-treatment decline (Mortimer *et al*., 1992).

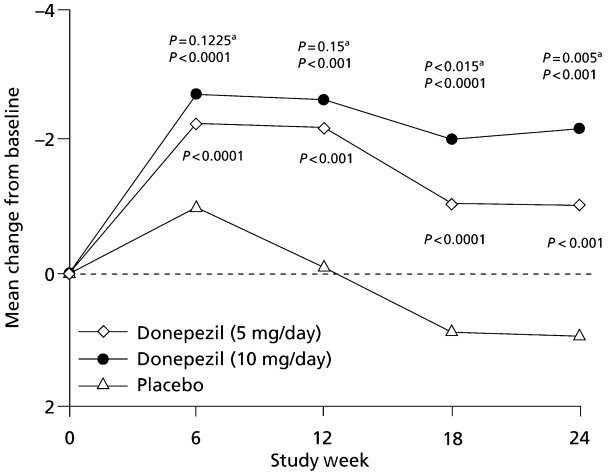

Figure 1 Mean change from baseline in Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog) scores for 5 and 10 mg/day donepezil- and placebo-treated patients with mild to moderate Alzheimer's disease [fixed effects meta-analysis of individual patient data from 10 double-blind, placebo-controlled trials of donepezil ($n = 2376$)]. [a]5 mg/day vs. 10 mg/day donepezil. Reproduced from Whitehead *et al*. (2004) with permission from John Wiley & Sons Ltd.

Cognition was measured via the Mini-Mental State Examination (MMSE), which is a more user-friendly assessment than the ADAS-cog scale. MMSE scores in the donepezil group remained close to baseline in the double-blind phase, whilst placebo patients declined approximately 2.5 points. At the end of the open-label phase, patients continuously treated with donepezil for 3 years had declined below baseline, but their MMSE scores remained approximately 2 to 3 points higher, on average, than the projected placebo scores (Fig. 2). Therefore, donepezil treatment delayed cognitive decline by about a year relative to that which would be expected without treatment. Compared with expected untreated performance, the results of the study showed that donepezil treatment retards cognitive and functional decline over periods of at least 3 years.

Because patients in the placebo arm of the double-blind phase initiated donepezil treatment 1 year later than their counterparts in the donepezil arm, the Nordic Study also allows us to examine the effects of delayed treatment. In the open-label phase, patients for whom treatment was delayed did experience cognitive benefit compared with placebo, although at the end of the 3-year study, the mean MMSE total scores still showed a significant difference, favoring early and continuous treatment (Winblad *et al*., 2003).

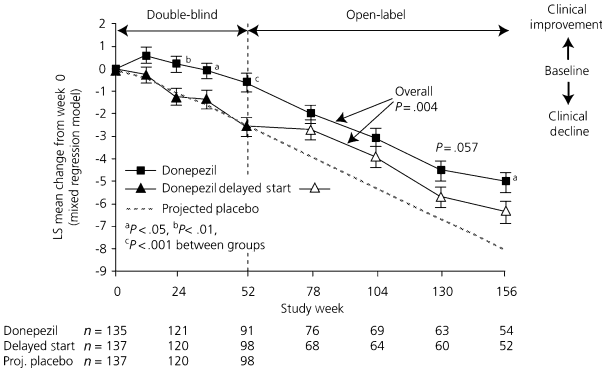

Figure 2 Least-squares mean (±SE) change from baseline in Mini-Mental State Examination (MMSE) score for patients treated with donepezil and placebo. Results from a 1-year double-blind, placebo-controlled donepezil trial and 2 years of open-label treatment. [a]$P < 0.05$; [b]$P < 0.01$; [c]$P < 0.001$ between groups. Overall treatment difference: $P = 0.004$ (Winblad *et al.*, 2003).

Defining treatment benefit in AD: beyond cognition

These and other studies demonstrate cognitive and functional benefits in patients with mild to moderate AD (Winblad *et al.*, 2001b, 2003; Whitehead *et al.*, 2004) but other symptom domains are also important to physicians, patients and caregivers (Winblad *et al.*, 2001a). If physicians rely solely on MMSE scores to make treatment decisions, a substantial number of patients may be undertreated. In addition to cognitive tests limited questions to the caregiver during follow-up visits regarding the patient's behavior, activities of daily living, and global function will provide a more complete picture of effectiveness. Initial cognitive decline does not preclude benefits in other areas, and does not necessarily indicate a lack of response to treatment. This notion is supported by a recent study in which mild to moderate AD patients with uncertain clinical benefit in open-label donepezil treatment (10 mg/day) were randomized to continue treatment or receive placebo in a double-blind phase (Fig. 3). Of 817 patients enrolled, 202 patients completing 24 weeks of open-label treatment were judged to have uncertain clinical benefit. At the end of the 12-week, double-blind phase, significant treatment differences between donepezil and placebo were observed on the neuropsychiatric inventory (NPI; a 12-item caregiver-rated measure of problem behaviors, agitation, and anxiety) and the MMSE, although not on the ADAS-cog (Johanssen *et al.*, 2003). The improvement in problem behaviors may be especially important to caregivers, as these have been shown to be a major factor in the caregiver's decision to institutionalize patients (Haupt and Kurz, 1993; Hope *et al.*, 1998; Smith *et al.*, 2001).

The behavioral benefits of donepezil in moderate to severe AD are well established (Feldman *et al.*, 2001; Gauthier *et al.*, 2002a,b). Holmes *et al.* (2004) conducted a landmark study on the behavioral effects of donepezil in mild to moderate AD. In summary, their method was a 12-week, open-label donepezil treatment phase, during which patients were titrated from 5 to 10 mg/day donepezil, followed by a 12-week randomization to 10 mg/day donepezil or placebo. The primary outcome measure was the NPI. Donepezil-treated patients maintained the behavioral improvement seen during open-label therapy and placebo-treated patients experienced behavioral deterioration in the double-blind phase. This study design would no longer be considered ethical, however, due to data showing that drug holidays of 6 weeks or longer may irreversibly wash out the effect of treatment (Doody *et al.*, 2001). In addition to providing evidence of behavioral benefit associated with donepezil treatment, the Holmes *et al.* data serve to further caution physicians against extended drug holidays.

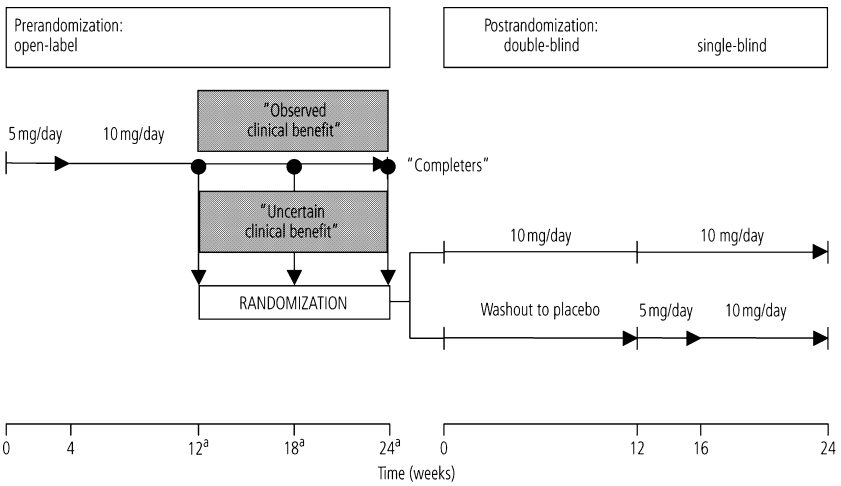

Figure 3 Design of the AWARE study. After a 12-week, open-label trial of donepezil, patients who showed uncertain benefit were randomized in a double-blind fashion to continued donepezil treatment or a placebo washout. The placebo patients were crossed over after 12 weeks and restarted on donepezil. [a]Clinical benefit was assessed at 12, 18, and 24 weeks in the prerandomization phase (Johanssen *et al.*, 2003).

Assisting patients with activities of daily living is another major element of caregiver time and focus. Preserving as much functional ability as possible should, therefore, be a treatment goal. A 1-year preservation of function study (Mohs *et al*., 2001) used a Kaplan–Meier survival to endpoint design to monitor functional decline in AD patients taking donepezil (10 mg/day) or placebo. Patients with AD of moderate severity (i.e. MMSE scores of 12–20 points, inclusive) were included, exiting the study when they met one of three criteria for clinically evident functional decline: clinically significant decline in two instrumental activities of daily living; clinically significant decline in one basic activity of daily living; or worsening of overall dementia severity, as measured by the Clinical Dementia Rating Scale. Most patients experienced a decline in function during the 54 weeks of the study, but donepezil treatment extended the median time to functional decline compared with placebo by approximately 5 months ($P = 0.002$; Fig. 4). Donepezil-treated patients were 38% less likely to decline over a 1-year period.

Treatment of AD, especially if initiated early, has the potential to dramatically influence the patient's experience toward the end of their life. A long-term observational study from a US clinic (Lopez *et al*., 2002) showed that ChEI treatment may substantially affect nursing home placement. In this study, 135 patients with probable AD taking ChEIs for at least 9 months (predominantly donepezil) and an equal number of controls were followed for 8 years. The control patients were never exposed to ChEIs and were strictly matched to the ChEI-treated patients by age, education, duration of symptoms, and baseline cognitive status. Treated patients were significantly less likely to enter a nursing home. At the end of the study nearly all controls were in nursing homes whilst less than one-quarter of treated patients had been institutionalized. An important caveat to these results is that nursing home placement may be influenced by varying levels of caregiver support, for which it is difficult or impossible to control. However, rigorous matching ensured that the study was well controlled for baseline disease severity.

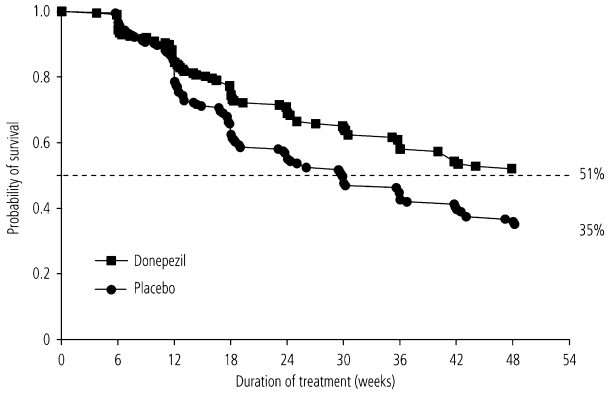

Figure 4 Kaplan–Meier survival estimates of time to clinically evident functional decline, as judged by the investigator (intent-to-treat population, $n = 431$). The survival curves for the donepezil- and placebo-treated groups were significantly different ($P = 0.002$). Reproduced from Mohs *et al*. (2001) with permission from Lippincott Williams and Wilkins.

Results of an observational follow-up study of AD patients who had previously participated in three placebo-controlled trials and two open-label extensions (Geldmacher *et al*., 2003) also suggest that donepezil treatment delays nursing home placement. Nevertheless, a study published by the AD2000 Collaborative Group (Courtney *et al*., 2004) has recently generated attention and controversy by challenging the long-term benefits of ChEI treatment. Although the effect of donepezil on cognition (MMSE change from baseline) over the first 2 years was highly significant ($P < 0.0001$) and patients improved in basic activities of daily living, no significant differences were observed on the primary endpoints, institutionalization and progression of disability, or on the secondary endpoints of the Neuropsychiatric Inventory, caregiver psychopathology, formal care costs, unpaid caregiver time, adverse events, or death. Despite much attention in the medical and lay press, the AD2000 study had several weaknesses. First, sufficient numbers of patients to draw meaningful conclusions were only maintained through the first 2 years of the study. A negative result (no significant difference on primary endpoints) would be more convincing if the sample size were closer to the original target of 3000 patients than the 194 who remained after the first 2 years. Secondly, the requirement that physicians were uncertain about the potential benefit of the drug may have biased the sample in favor of a negative result. Thirdly, it is now recognized that interrupting donepezil treatment may irreversibly undermine its beneficial effects. (Doody *et al*., 2001; Holmes *et al*., 2004) Thus, the 6-week washout period and subsequent 4-week washouts were likely to have had deleterious effects on donepezil-treated patients. Finally, although death and nursing home placement contributed to sample attrition, a substantial number of patients were withdrawn to open-label donepezil treatment.

The potential of treatment in MCI

The aforementioned studies demonstrate the benefits of early treatment in populations of patients with mild to moderate AD. These benefits might be even more pronounced if patients could be identified and treated

before the onset of frank dementia. The amnestic form of MCI may be a symptom of early cholinergic deficit leading to AD. A recently published study comparing postmortem brains of four elders with MCI and one with early AD with those of seven age-matched cognitively normal subjects found that the cognitively impaired patients had significantly more neurofibrillary tangles and tau antibody staining in the nucleus basalis than controls (Mesulam *et al*., 2004). The degree of cholinergic damage was significantly correlated with worse total scores on the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) word list delayed recall trial. These results are amongst the first to show that damage to the central cholinergic pathways is a very early event in the MCI-AD continuum. If cholinergic damage begins early, then early cholinergic intervention is potentially beneficial and treatment of MCI with ChEIs may indeed be warranted.

Does donepezil treatment for MCI yield clinical benefits? To date, two studies have been completed that address this important question. The first, a 24-week, randomized, double-blind, placebo-controlled trial in patients with predefined evidence of MCI, used cognitive outcome measures including the NYU Paragraph Test Delayed and Immediate Recall portions and a 13-item modified ADAS-cog suitable for MCI patients. The NYU Paragraph Test Delayed Recall was the primary efficacy measure. Interestingly, although investigators supposed that the modified ADAS-cog would not be sensitive enough to detect a treatment difference, there was a significant difference favoring donepezil at endpoint (ITT-LOCF analysis as well as fully evaluable patients) on the modified ADAS-cog. Surprisingly, it was the NYU Paragraph Test that failed to show a treatment effect in the ITT-LOCF analysis. Amongst fully evaluable patients, however, those treated with donepezil were significantly improved compared with placebo (Salloway *et al*., 2004).

The Alzheimer's Disease Cooperative Study on MCI (Petersen *et al*., 2005) was a double-blind, placebo-controlled study that compared the effects of 10 mg/day donepezil, 2000 IU/day vitamin E, and placebo in delaying the progression from MCI to AD. A total of 769 patients were followed for 3 years. Donepezil provided symptomatic benefits and decreased the probability of conversion to AD for as long as 18 months. However, neither vitamin E nor donepezil had a statistically significant effect on conversion over the full 3-year period. An important finding was the observation that patients with ApoE ε4 alleles converted at a much faster rate than other MCI patients. Therefore, future studies on MCI conversion are likely to use a population enriched for the ApoE ε4 genotype.

Conclusions

Data from donepezil trials in mild to moderate AD clearly show that early and continuous treatment confers a therapeutic advantage relative to patients for whom treatment initiation is delayed or disrupted. Benefits are observed not only in cognition, but also in function and behavior, underlining the importance of assessing these domains at follow-up visits. Questioning the caregiver about activities of daily living and any problem behaviors is imperative; it is not sufficient to rely on the MMSE alone to evaluate treatment success.

Recently, MCI has generated a great deal of interest. Evidence is emerging to support that cholinergic deficit is a very early event in AD as it is associated with the same kinds of cholinergic deficits as AD and has overlapping symptoms (i.e. memory loss). The rationale of ChEI therapy is to maximize remaining cholinergic function; treating MCI with ChEIs is a promising strategy. The limited clinical data available suggest that donepezil improves cognition amongst MCI patients and may delay (though not prevent) the progression to AD.

Delaying the onset of an inevitable outcome is certainly not the ideal form of treatment. However, in the absence of a cure, maintaining patients' cognitive abilities, functional independence, and appropriate behavior as long as possible are worthy goals. These goals are best achieved when treatment is initiated early in the course of the disease. Challenges for physicians include helping to overcome the fear and stigma of dementia through patient and caregiver education, and improving the early detection of AD so that treatment may be initiated early for maximum benefit.

References

Bond J, Stave C, Sganga A, O'Connell B, Stanley RL (2005). Inequalities in dementia care across Europe: key findings of the Facing Dementia Survey. *Int J Clin Prac* **59**(Suppl. 146)**:**8–14.

Courtney C, Farrell D, Gray R *et al*. (2004). Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* **363:** 2105–2115.

Doody RS, Geldmacher DS, Gordon B, Perdomo CA, Pratt RD (2001). Open-label, multicenter, phase 3 extension study of the safety and efficacy of donepezil in patients with Alzheimer disease. *Arch Neurol* **58:**427–433.

Feldman H, Gauthier S, Hecker J, Vellas B, Subbiah P, Whalen E (2001). A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease [published erratum appears in Neurology 2001;57:2153]. *Neurology* **57:**613–620.

Ganguli M, Dodge HH, Shen C, DeKosky ST (2004). Mild cognitive impairment, amnestic type: an epidemiologic study. *Neurology* **63:**115–121.

Gauthier S, Feldman H, Hecker J *et al*. (2002a). Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *Int Psychogeriatr* **14:**389–404.

Gauthier S, Feldman H, Hecker J, Vellas B, Emir B, Subbiah P (2002b). Functional, cognitive and behavioral effects of donepezil in patients with moderate Alzheimer's disease. *Curr Med Res Opin* **18:**347–354.

Geldmacher DS, Provenzano G, McRae T, Mastey V, Ieni JR (2003). Donepezil is associated with delayed nursing home placement in patients with Alzheimer's disease. *J Am Geriatr Soc* **51:**937–944.

Goodin DS, Frohman EM, Garmany GP Jr *et al*. (2002). Disease modifying therapies in multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* **58:**169–178.

Haupt M, Kurz A (1993). Predictors of nursing home placement in patients with Alzheimer's disease. *Int J Geriatr Psychiatry* **8:**741–746.

Herholz K, Weisenbach S, Zundorf G *et al*. (2004). In vivo study of acetylcholine esterase in basal forebrain, amygdala, and cortex in mild to moderate Alzheimer disease. *Neuroimage* **21:**136–143.

Holmes C, Wilkinson D, Dean C *et al*. (2004). The efficacy of donepezil in the treatment of neuropsychiatric symptoms in Alzheimer disease. *Neurology* **63:**214–219.

Hope T, Keene J, Gedling K, Fairburn CG, Jacoby R (1998). Predictors of institutionalization for people with dementia living at home with a carer. *Int J Geriatr Psychiatry* **13:**682–690.

Johanssen P, Barcikowska M, Dautzenberg PL *et al*. (2003). Donepezil-treated Alzheimer's disease patients with apparent initial cognitive decline demonstrate significant benefits when therapy is continued: results from a randomized, placebo-controlled trial. *Int Psychogeriatr* **15:**106–107.

Lopez OL, Becker JT, Wisniewski S, Saxton J, Kaufer DI, DeKosky ST (2002). Cholinesterase inhibitor treatment alters the natural history of Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **72:**310–314.

Mesulam MM, Shaw P, Mash D, Weintraub S (2004). Cholinergic nucleus basalis tauopathy emerges early in the aging-MCI-AD continuum. *Ann Neurol* **55:**815–828.

Miller A, Cohen J, Eidelman B *et al*. (2002). *Expert Opinion Paper: Disease Management Consensus Statement*. National Multiple Sclerosis Society, New York, NY.

Mohs RC, Doody RS, Morris JC *et al*. (2001). A 1-year, placebo-controlled preservation of function survival study of donepezil in AD patients. *Neurology* **57:**481–488.

Mortimer JA, Ebbitt B, Jun SP, Finch MD (1992). Predictors of cognitive and functional progression in patients with probable Alzheimer's disease. *Neurology* **42:**1689–1696.

Petersen RC, Thomas RG, Grundman M *et al*. (2005). Vitamin E and donepezil for the treatment of mild cognitive impairment. *N Engl J Med* **352:**2379–2388.

Salloway S, Ferris S, Kluger A *et al*. (2004). Efficacy of donepezil in mild cognitive impairment: a randomized placebo-controlled trial. *Neurology* **63:**651–657.

Smith GE, O'Brien PC, Ivnik RJ, Kokmen E, Tangalos EG (2001). Prospective analysis of risk factors for nursing home placement of dementia patients. *Neurology* **57:**1467–1473.

Whitehead A, Perdomo C, Pratt RD, Birks J, Wilcock GK, Evans JG (2004). Donepezil for the symptomatic treatment of patients with mild to moderate Alzheimer's disease: a meta-analysis of individual patient data from randomised controlled trials. *Int J Geriatr Psychiatry* **19:**624–633.

Winblad B, Brodaty H, Gauthier S *et al*. (2001a). Pharmacotherapy of Alzheimer's disease: is there a need to redefine treatment success? *Int J Geriatr Psychiatry* **16:**653–666.

Winblad B, Engedal K, Soininen H *et al*. (2001b). A 1-year, randomized, placebo-controlled study of donepezil in patients with mild to moderate AD. *Neurology* **57:**489–495.

Winblad B, Engedal K, Soininen H *et al*. (2003). Long-term efficacy of donepezil in patients with mild to moderate Alzheimer's disease: results from a one-year placebo-controlled study and two-year follow-up study. *Int Psychogeriatr* **15:**293–294.