EDITORIAL

Continuing donepezil produces cognitive benefits in Alzheimer's

AUTHOR
Dr Phillip Bland
BA BM BCh MRCGP DRCOG
GP with an interest in mental health, Dalton-in-Furness

PATIENTS WITH MODERATELY SEVERE OR SEVERE ALZHEIMER'S DISEASE BENEFIT FROM CONTINUED treatment with donepezil, a UK study published in the *New England Journal of Medicine*, has found.[1] Patients who carried on with treatment had better scores, which were clinically significant on the Mini-Mental State Examination (MMSE) than those who discontinued treatment, at the end of the year-long study.

A total of 295 community residents were recruited to the study from secondary care clinics in England and Scotland. Participants had been receiving treatment with donepezil for at least 3 months and had an MMSE score between 5 and 13. Moderately severe Alzheimer's disease is defined by an MMSE score of 10-14 and severe Alzheimer's disease by an MMSE score of less than 10.[2]

'Continued treatment with donepezil had a clinically significant benefit on cognitive function'

Participants were randomised to one of four groups: continued treatment with donepezil, replacement with placebo, replacement with memantine and combination treatment with both donepezil and memantine. The study treatment was given for 52 weeks.

At one year follow-up, the MMSE scores for patients who had continued to take donepezil were on average 1.9 points higher than the scores of those whose treatment had been stopped (95% CI: 1.3-2.5, $P < 0.001$). The continued treatment group also had significantly better scores on the Bristol Activities of Daily Living Scale (BADLS): average difference 3.0 (95% CI: 1.8-4.3, $P < 0.001$). Compared with the placebo group, patients treated with memantine had MMSE scores which were an average of 1.2 points higher (95% CI: 0.6-1.8, $P < 0.001$) and BADLS scores which were 1.5 points better (95% CI: 0.3-2.8, $P = 0.02$). Combination treatment conferred no additional benefits.

The MMSE is a widely used measure of cognitive function which tests orientation, attention, short-term memory, language and praxis. Cognitive decline in Alzheimer's disease is non-linear but there is an average decline on the MMSE of three points per year over the typical ten-year course of the illness. Treatment with cognitive enhancers slows the rate of decline: untreated patients lose half their maximum MMSE score one and a half years earlier than those who receive treatment.[3]

The authors of the present study define clinical significance as an MMSE score difference of 1.4 and a BADLS score difference of 3.5. According to these criteria, continued treatment with donepezil had a clinically significant benefit on cognitive function, whereas treatment with memantine did not. Neither treatment had a clinically significant benefit on self-care.

There is no consensus as to what constitutes a clinically important change in the MMSE score. A difference of 1.9 is well short of the 3 point difference which the American College of Physicians would regard as significant.[4] Given an average decline of 3 points per annum, it is equivalent to a 7 month delay in the progression of dementia. However, as the author of an accompanying editorial in the journal points out the difference in score, 1.9 points lower in patients who discontinued donepezil, 'is potentially important because many of the patients were severely impaired, on the cusp for needing nursing home care, and slightly worse cognitive function could affect their ability to remain at home.'[5]

This benefit needs to be offset against the adverse effects of cognitive enhancers. An observational study has suggested an increased risk of syncope, pacemaker insertion and hip fracture. The absolute risks, however, are small: 13 admissions with syncope, 1 pacemaker insertion and 2 hip fractures per 1,000 patient/years.[6]

NICE originally recommended that cognitive enhancers should be stopped once the MMSE score fell below 10; they have subsequently revised their guidance to state that treatment should only be continued if it is considered to be having a 'worthwhile effect.'[2] The present study suggests that community residents with an MMSE score between 5 and 13 may derive a modest but potentially important benefit from continued treatment.

REFERENCES
1 Howard R, McShane R, Lindesay J et al. Donepezil and memantine for moderate-to-severe Alzheimer's disease. *N Engl J Med* 2012;366:893-903
2 National Institute for Health and Clinical Excellence. TA217. Donepezil, galantamine, rivastigmine and memantine for the treatment of Alzheimer's disease. NICE. London. 2011
3 Nelson PT, Kryscio RJ, Abner EL et al. Acetylcholinesterase inhibitor treatment is associated with relatively slow cognitive decline in patients with Alzheimer's disease and AD + DLB. *J Alzheimers Dis* 2009;16:29-34
4 Qaseem A, Snow V, Cross T et al. Current pharmacologic treatment of dementia: a clinical practice guideline from the American College of Physicians and the American College of Family Physicians. *Ann Intern Med* 2008;148:370-8
5 Schneider LS. Discontinuing donepezil or starting memantine for Alzheimer's disease. *N Engl J Med* 2012;366:957-58
6 Gill SS, Anderson GM, Fischer HD et al. Syncope and its consequences in patients with dementia receiving cholinesterase inhibitors: a population-based cohort study. *Arch Intern Med* 2009;169:867-73