Evidence for the Continuing Use of Acetylcholinesterase Inhibitors (AChEIs) for Moderate-to-Severe Alzheimer's Disease

The DOMINO study showed that there were modest cognitive and functional benefits of continuing donepezil over the course of 12 months.

**Key results:**
- There were benefits to cognitive function of taking donepezil (about 32% less cognitive decline than those on placebo)
- The functional benefits of continuing donepezil showed about 23% less deterioration than those on placebo
- There were also small reductions in caregivers' psychological symptoms with donepezil, although these were not statistically significant

**Reference:**

**DOMINO study**

**Abstract**

**BACKGROUND:**

Clinical trials have shown the benefits of cholinesterase inhibitors for the treatment of mild-to-moderate Alzheimer's disease. It is not known whether treatment benefits continue after the progression to moderate-to-severe disease.

**METHODS:**

We assigned 295 community-dwelling patients who had been treated with donepezil for at least 3 months and who had moderate or severe Alzheimer's disease (a score of 5 to 13 on the Standardized Mini-Mental State Examination [SMMSE, on which scores range from 0 to 30, with higher scores indicating better cognitive function]) to continue donepezil, discontinue donepezil, discontinue donepezil and start memantine, or continue donepezil and start memantine. Patients received the study treatment for 52 weeks. The coprimary outcomes were scores on the SMMSE and on the Bristol Activities of Daily Living Scale (BADLS, on which scores range from 0 to 60, with higher scores indicating greater impairment). The minimum clinically important differences were 1.4 points on the SMMSE and 3.5 points on the BADLS.
RESULTS:

Patients assigned to continue donepezil, as compared with those assigned to discontinue donepezil, had a score on the SMMSE that was higher by an average of 1.9 points (95% confidence interval [CI], 1.3 to 2.5) and a score on the BADLS that was lower (indicating less impairment) by 3.0 points (95% CI, 1.8 to 4.3) (P<0.001 for both comparisons). Patients assigned to receive memantine, as compared with those assigned to receive memantine placebo, had a score on the SMMSE that was an average of 1.2 points higher (95% CI, 0.6 to 1.8; P<0.001) and a score on the BADLS that was 1.5 points lower (95% CI, 0.3 to 2.8; P=0.02). The efficacy of donepezil and of memantine did not differ significantly in the presence or absence of the other. There were no significant benefits of the combination of donepezil and memantine over donepezil alone.

CONCLUSIONS:

In patients with moderate or severe Alzheimer's disease, continued treatment with donepezil was associated with cognitive benefits that exceeded the minimum clinically important difference and with significant functional benefits over the course of 12 months. (Fundied by the U.K. Medical Research Council and the U.K. Alzheimer's Society; Current Controlled Trials number, ISRCTN49545035).

Evidence for the Use of Memantine with AChEIs as Combination Therapy in Dementia

- The DOMINO study provided evidence that adding memantine to donepezil treatment showed improvement in behaviour but no additional improvement in cognition or function.

- The British Association for Psychopharmacology (BAP) has produced a second, revised, consensus statement on Clinical Practice with Antidementia Drugs, citing 3 relevant studies:
  “The effect of adding memantine to cholinesterase inhibitors is not clear. An initial study showed clear benefit in cognitive and non-cognitive symptoms (again agitation and irritability responding best) when memantine was added to donepezil therapy (Tariot et al., 2004). However, a more recent study investigating memantine add-on to all three cholinesterase inhibitors failed to demonstrate any clear cognitive or non-cognitive benefit (Porsteinsson et al., 2008). Open label observational data suggest that treatment with antidementia drugs may slow admission to residential care with the greatest benefits seen in those on combination therapy (Lopez et al., 2009).”
Rationale for Combining Glutamatergic and Cholinergic Approaches in the Symptomatic Treatment of Alzheimer’s Disease


This review article contains the following expert commentary:

“The use of combination therapy with a cholinomimetic (AChEI) and a glutamatergic (memantine) agent for the treatment of AD is justified by findings from biochemical studies, and preclinical investigations in established animal models of AD. This is borne out by most clinical experience and, indeed, combination therapy is already considered standard treatment practice in many countries throughout the world. Despite this extensive use, the clinical evidence support for combination therapy is not complete, as it is based solely on the addition of memantine to existing AChEI treatment, with no data on the opposite order of initiation or the simultaneous treatment de novo with memantine and an AChEI. These appear to be gaps, but the available data actually reflect the real-world situation in which AChEIs (licensed for mild to moderately severe AD) are given early in the disease course, while memantine (licensed for moderate-to-severe AD) is initiated later. Therefore, the natural order of events is that patients who receive combination therapy will have started their treatment with AChEI monotherapy.”

**Tolerability**

A post-marketing surveillance study suggests that this combination therapy is safe and well-tolerated.

+ **Reference:**

International Clinical Psychopharmacology: *March 2003 - Volume 18 - Issue 2 - pp 81-85*

Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy

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**Abstract:**

Memantine, a moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to be effective in dementia, including Alzheimer disease (AD). Therefore, its combination with acetylcholinesterase inhibitors (AChEIs) is anticipated. We report a post marketing surveillance study conducted among German physicians who, during routine clinical practice, treated demented patients with memantine in combination with an AChEI. Most of the 158 surveyed patients (mean age, 74 years) were diagnosed with AD but other dementias were included. Memantine was prescribed at a wide range of daily doses (median, 20 mg/day) and was combined with donepezil for most patients (84%). Combination therapy was well tolerated for nearly all patients (98%) for an average observation period
of 4 months at stable doses of both antidementia agents. No serious adverse drug reaction (ADR) was reported. No ADR or change in blood chemistry was experienced by most patients (96% and 81%, respectively); the six reported ADRs resolved without sequelae and without drug discontinuation. Global clinical status of most patients was judged as improved (54%) or stable (39%) over the observation period. These findings particularly suggest that memantine in combination with AChEIs is safe and well tolerated.

Comment

On balance, the above evidence indicates that AChEI/Memantine combination therapy is better than AChEI monotherapy in both general and specific measures of cognition, function, behaviour and global status in patients with moderate-to-severe Alzheimer’s Disease. There is also evidence that combination therapy may reduce behavioural symptoms including agitation/aggression. Safety and tolerability was observed in Phase III and post-marketing studies of combination therapy to date.

Feedback from SABP Older Adult Consultants Group

The available research studies indicate that combination treatment is better than AChEI monotherapy in both general and specific measures of cognition, function, behaviour and global status in patients with moderate-to-severe Alzheimer’s Disease. Furthermore, there is evidence that combination therapy may reduce behavioural symptoms including agitation/aggression and a favourable safety profile was observed in Phase III and post marketing studies of combination treatment to date.

Combination therapy for Dementia is widely followed in US and many European nations. They usually start both together, but in the UK it is mainly done later on the treatment regime. NICE did not endorse the combination therapy when they changed their guidelines due to lack of definitive evidence.

Recommendation

SABP Medicines Management Committee supports the use of combination therapy of as an option for people with dementia who present with challenging behaviour and this has been reflected in the revised shared care agreement.