

Memantine combined with an acetylcholinesterase inhibitor – hope for the future?

Chris Fox¹
 Ian D Maidment²
 Malaz Boustani³
 Cornelius Katona⁴

^{1,2}East Kent NHS and Social Care Partnership Trust, Kent Institute of Medicine and Health Sciences, University of Kent at Canterbury, UK; ³Regenstrief Institute and Indiana University Center for Aging Research, Indianapolis, IN, USA; ⁴Kent Institute of Medicine and Health Sciences, University of Kent at Canterbury, UK

Background: Memantine and cholinesterase inhibitors (ChEI) have distinct pharmacological actions, and interest in the use of combination therapy for Alzheimer's disease (AD) is increasing.

Objective: To assess the available data on the use of memantine–ChEI combination and to develop evidence-based recommendations.

Method: A systematic literature review with detailed discussion of the current evidence base.

Results: Available data are limited: five studies of which two were randomized, double-blind, placebo-controlled trials. One study indicated that memantine–ChEI combination is not significantly more effective than placebo–ChEI in mild to moderate AD, but data were published in abstract and poster form only. A second study indicated that the memantine–ChEI combination is significantly more effective than placebo–ChEI in moderate to severe AD. The calculated effect sizes of 0.36 on cognition and 0.12 on function, which were the primary outcomes, were small, indicating a clinically minimal effect on cognition and no effect on function. No data are available on whether combination treatment is more effective than memantine monotherapy.

Conclusion: The available data do not justify the use of combination therapy. Future studies should include three arms (memantine–placebo, placebo–ChEI, and memantine–ChEI), be of an adequate size and duration, and use pragmatic measures. Clinicians should have full access to data from any future trials.

Keywords: memantine, cholinesterase inhibitors, combination, Alzheimer's disease, randomised control studies, open-label studies

Introduction

Alzheimer's disease (AD), the most common form of dementia, is a neurodegenerative disorder that adversely affects memory, comprehension, judgment, thinking, orientation, language, and calculation. Alzheimer's disease places a considerable progressive burden on the principal caregiver (Schneider et al 1999). The number of people with AD in the USA is 4 million and is predicted to more than treble by 2050 (Sloane et al 2002). Kukull and Bowen (2002) estimated that AD comprises more than 50% of total dementia cases. The economic impact of this illness is enormous, exceeding US\$100 billion annually in the USA (Boustani et al 2003).

In AD, degeneration of basal forebrain cholinergic pathways linked with the cortex is thought to cause the cognitive deficiencies (Bartus et al 1982). Two pharmacological treatments are available: memantine and the cholinesterase inhibitors (ChEI). These affect different neurotransmitter systems. ChEIs block enzymes that metabolise acetylcholine and therefore increase its levels (Becker 1991). Donepezil, galantamine, and rivastigmine inhibit acetyl cholinesterase (Lane et al 2004). Inhibition of both

Correspondence: Chris Fox
 Folkestone Health Centre, 15–25 Dover Road, Folkestone, Kent CT20 1JY, UK
 Tel +44 1303 228836
 Fax +44 1303 228837
 Email gfox@doctors.org.uk

butyrylcholinesterase and acetyl cholinesterase for rivastigmine (Giacobini 2004), and nicotinic modulation for galantamine (Samochocki et al 2000) may contribute to the efficacy of these ChEIs.

The overactivation of glutamate, particularly N-methyl-D-aspartate (NMDA)-selective receptors, has been associated with the degeneration of cholinergic function seen in AD (Francis 2003). Memantine may prevent glutamate-induced neuronal damage by noncompetitive antagonism of the NMDA receptor (Hartmann and Mobius 2003).

Current treatments may lack a clinically significant effect and new treatment strategies are essential to assist in disease management (AD2000 2004; NICE 2005). Combining memantine's potential neuroprotective effect with the improvement in cholinergic functioning noted with a ChEI may lead to additional therapeutic benefits (Wenk et al 2000). Recent animal studies have indicated a ceiling effect on benefit in memory impairment and additive or synergistic effects of combining memantine with a ChEI (Yamada et al 2005), which is the basic science rationale. We set out to review the research evidence on combination.

Method

A computerized literature search of Medline (1966–July 2005), PsycINFO (1972–September 2005), Embase (1980–July 2005), Cinhal (1982–September 2005) and the Cochrane Collaboration was conducted. Keywords used were: AD, randomized controlled trials (clinical trial, single-blind method, double-blind method, random allocation), open-label studies, cholinesterase inhibitors (donepezil, rivastigmine, galantamine, galanthamine, and tacrine), and memantine. The reference section of studies identified was scrutinized, the relevant pharmaceutical manufacturers were contacted for any unpublished studies, and the US trials database (<http://www.clinicalstudyresults.org/search/>) was examined. Single cases and non-AD studies were excluded.

Results

In total, five studies were identified. One trial is published only in summary format online (FLI 2003) and in a poster meta-analysis (Doody et al 2005). This poster, however, contains only limited data (Doody et al 2005), and Forest Laboratories were unable to provide more detailed information (Forest Laboratories Inc 2005 July 7, pers comm). One study was published in a peer-reviewed journal (Tariot et al 2004). Three similar prospective studies have been published only in abstract format (Pass et al 2004; Patel et al 2004; Shua-Haim et al 2004).

Trial design

Two studies were multicenter, randomized, double-blind, placebo-controlled (FLI 2003; Tariot et al 2004; Doody et al 2005), and three studies were open label (Pass et al 2004; Patel et al 2004; Shua-Haim et al 2004). The randomized, controlled trials (RCTs) (FLI 2003; Tariot et al 2004; Doody et al 2005) were not designed to determine the relative efficacy compared with placebo of memantine monotherapy, donepezil monotherapy, or combination therapy, but whether memantine would provide additional benefit in a patient already on a ChEI.

Study duration varied from 24 to 26 weeks. Tariot et al (2004) randomized 203 patients to memantine and 201 to placebo. The sample sizes of the open studies varied from 12 to 25 (Pass et al 2004; Patel et al 2004; Shua-Haim et al 2004). Patient numbers were not available for one study (FLI 2003) except in a poster meta-analysis ($n=433$) (Doody et al 2005).

FLI (2003) maintained patients on a stable dose for a ChEI (exact details not stated) for at least 6 months prior to entry. Tariot et al (2004) maintained patients on donepezil for at least 6 months, and at a stable dose of 5–10 mg daily for at least 3 months prior to the study. None of the open studies stated how long patients had been taking a ChEI before memantine was begun (Pass et al 2004; Patel et al 2004; Shua-Haim et al 2004).

Diagnostic criteria were: National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer Disease and Related Disorders Association (NINCDS–ARDA) diagnosis of probable AD (FLI 2003; Tariot et al 2004; Doody et al 2005); DSM-IV (APA 1994); and NINCDS–ARDA for possible Alzheimer's disease (Pass et al 2004; Patel et al 2004; Shua-Haim et al 2004). Disease stage ranged from mild to moderate AD in one RCT (FLI 2003; Doody et al 2005) to moderate to severe AD in the other (Tariot et al 2004). The three open studies did not specify the stage (Pass et al 2004; Patel et al 2004; Shua-Haim et al 2004).

Assessment measures

Tariot et al (2004) assessed efficacy with the Severe Impairment Battery (SIB) (Panisset et al 1994), a modified 19-item AD Cooperative Study–Activities of Daily Living Inventory (ADCS–ADL19) (Galasko et al 1997), the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus) (Schneider et al 1997), the Neuropsychiatric Inventory (NPI) (Cummings et al 1994), and the Behavioral Rating Scale for Geriatric Patients (BGP)

(van der Kam et al 1971). FLI (2003) assessed global outcomes (CIBIC-Plus) and Alzheimer's Disease Assessment Scale cognitive outcomes (ADAS-Cog); secondary outcomes were the NPI and the ADCS-ADL23 (Doody et al 2005). Three studies assessed memory objectively (exact scale not stated) and used caregiver report to assess effect on cognition and functioning (Pass et al 2004; Patel et al 2004; Shua-Haim et al 2004). None of the studies utilised outcome instruments such as time to residential admission or death.

Caregivers rated tolerability and adverse events in three studies (Pass et al 2004; Patel et al 2004; Shua-Haim et al 2004). One study assessed emergent adverse events by patient report and vital sign, physical examination, laboratory, and electrocardiogram testing (Tariot et al 2004). FLI (2003) reported adverse events in a pooled analysis of six trials (Doody et al 2005).

Efficacy

Tariot et al (2004) reported that at week 24 using last observation carried forward (LOCF) and observed cases (OC), memantine with donepezil produced a statistically significant improvement in the SIB, ADCS-ADL, CIBIC-Plus, NPI, and BGP in patients with moderate to severe AD compared with donepezil and placebo (see Table 1 for full details).

It may be difficult to relate results from psychometric scales to a clinical setting (Fox et al 2003; AD2000 2004) and the clinical significance of combination therapy is unclear. The effect size of 0.36 on cognition, although small (Cohen 1988), is of comparable magnitude to that of the ChEIs (Rockwood 2004). The effect size for function at 0.12 is very small and raises the issue of clinical relevance. The relative improvements were limited when the full range of each scale is considered, making it impossible to assess response rates, and data were not made available despite requests. Floor effects may have influenced the NPI and BGP results, as the baseline readings indicated only mild impairment.

A second trial failed to demonstrate that combination therapy is significantly more effective than ChEI monotherapy in patients with mild to moderate AD (FLI 2003; Doody et al 2005). Combination therapy did not produce a statistically significant difference on global or cognitive outcomes compared with placebo-ChEI. Over 24 weeks there was no change in cognition in the memantine-ChEI group and the decline in cognition in the placebo-ChEI group was less than expected. The small group

Table 1 Efficacy outcomes (least squares mean score [SE]) baseline to week 24 change – memantine–donepezil vs placebo–donepezil (Tariot et al 2004)

Rating scale	LOCF	Observed cases
SIB	0.9 (0.67) vs -2.5 (0.69); p < 0.001	1.0 (0.70) vs -2.4 (0.74); p < 0.001
ADCS-ADL	-2.0 (0.50) vs -3.4 (0.51); p = 0.03	-1.7 (0.51) vs -3.3 (0.55); p = 0.02
CIBIC-Plus	4.41 (0.074) vs 4.66 (0.075); p = 0.03	4.38 (0.081) vs 4.64 (0.087); p = 0.03
NPI	-0.1 (0.98) vs 3.7 (0.99); p = 0.002	-0.5 (0.99) vs 2.9 (1.06); p = 0.01
BGP dependency care subscale	0.8 (0.37) vs 2.3 (0.38); p = 0.001	0.6 (0.37) vs 2.2 (0.40); p = 0.001

Abbreviations: ADCS-ADL, Alzheimer's disease Cooperative Study-Activities of Daily Living Inventory (Galasko et al 1997); BGP, Behavioral Rating Scale for Geriatric Patients (van der Kam et al 1971); CIBIC-Plus, Clinician's Interview-Based Impression of Change Plus Caregiver Input (Schneider et al 1997); LOCF, last observation carried forward; NPI, Neuropsychiatric Inventory (Cummings et al 1994); SIB, Severe Impairment Battery (Panisset et al 1994).

difference was not statistically significant (exact p value not stated).

The three open studies noted improvements in carer-rated cognition, but failed to demonstrate objective memory improvements (Pass et al 2004; Patel et al 2004; Shua-Haim et al 2004). Furthermore any effect noted in the open studies should be treated cautiously because of the potential for false positive outcomes owing to random variability, placebo effects, and bias (Khan et al 2001).

Adverse events

Significantly more patients on memantine–donepezil compared with placebo–donepezil completed one study (85.1% [n = 172] vs 74.6% [n = 150], p = 0.01) (Tariot et al 2004), suggesting that the combination was not associated with significantly greater side effect burden than the ChEI alone. Adverse events that occurred twice as frequently with memantine were: confusion (7.9% vs 2.0%; p = 0.01), and headache (6.4% vs 2.5%; p = 0.09) (Tariot et al 2004). Adverse events occurred in 78% of patients on memantine, and 72% of patients on placebo (p not stated) (Tariot et al 2004). This high rate of adverse events may provide an accurate reflection of adverse events in the wider population of nonstudy patients. Future trials should take into account the fact that the patient selection criteria of placebo-controlled studies may overestimate the incidence of adverse events associated with placebo (Bandolier 2003) owing to the nature of the underlying disorder.

One study has not mentioned tolerability to date except as a pooled figure, which makes specific commentary impossible (FLI 2003; Doody et al 2005). Discontinuation rates of 7.9% with placebo and 6% with memantine may indicate that memantine lacks efficacy in the milder stages of AD (Doody et al 2005). No patients discontinued treatment or reported adverse events in the open studies (Pass et al 2004; Patel et al 2004; Shua-Haim et al 2004).

Conclusion

On the current available evidence, the use of memantine–ChEI combination therapy cannot be recommended as there is no evidence that combination therapy is more effective than memantine monotherapy (Tariot et al 2004). On common outcome measures, Reisberg et al (2003) demonstrated a larger memantine monotherapy–placebo signal than the memantine–donepezil combination/placebo–donepezil signal (Tariot et al 2004). The negative mild AD study (FPI 2003; Doody et al 2005) in our opinion backs the US Food and Drug Administration decision not to allow license extension to mild AD (FDA 2005).

The difficulty in obtaining full access to relevant studies is of concern and makes developing evidence-based recommendations problematic. Clinicians should have full access studies as directed by new US legislation (<http://www.clinicalstudyresults.org/search/>). The publication of a meta-analysis that includes dementia at various stages in advance of full publication or full data disclosure may obscure negative results (Lexchin et al 2003; Doody et al 2005).

Healthcare provider guidelines need to consider the economic impact of combination prescribing in a situation where the cost benefits of cognitive is already controversial (NICE 2005; Maidment et al 2006).

No adequate study has yet been presented to determine whether ChEI combined with memantine has a synergistic effect. Further studies including three arms: memantine–placebo, placebo–ChEI, and memantine–ChEI, are required to develop the evidence base. Studies should concentrate on patients with moderate to severe AD and include a 12-month extension arm to determine if efficacy is sustained. Active treatments should be assessed for a clinical effect in addition to a statistically significant effect. Future studies should evaluate the efficacy of combination therapy in non-AD dementia and include formal economic evaluations and pragmatic efficacy assessments such as time to residential facility.

Key points

On the current dataset the use of memantine–ChEI combination therapy cannot be endorsed.

Future studies should include three arms: memantine–placebo, placebo–ChEI, and memantine–ChEI.

Before adding in memantine, ChEIs should be discontinued or, once on therapeutic dose of memantine, be discontinued in a tapered manner with regular review.

Clinicians should be granted full access to the data at the earliest opportunity.

Disclosures

CF and CK have received funding for a project on screening for memory problems from Eisai, Lundbeck, Novartis, Pfizer, and Shire. CF and IDM have not been involved in trials of memantine or ChEIs. CF and IDM have received honoraria and meeting travel costs from Eisai, Lundbeck, Novartis, Pfizer, and Shire.

MB has been involved in trials of ChEIs funded by Pfizer.

CK has received funding for a project with people with AD from Lundbeck and has also participated in a memantine clinical trial. He has received honoraria and meeting travel costs from Lundbeck and honoraria from Shire and Pfizer. CK has also been involved in trials of ChEIs.

References

- [AD2000] AD2000 Collaborative Group. 2004. Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomized double-blind trial. *Lancet*, 363:2105–15.
- [APA] American Psychiatric Association 1994. Diagnostic and statistical manual of mental disorders. 4th ed (DSM-IV). Washington DC: APA.
- Bandolier. Adverse nondrug reactions [online]. Accessed 20 Sept 2003. URL: <http://www.jr2.ox.ac.uk/bandolier/band115/b115-4.html>.
- Bartus RT, Dean RL, Beer B, et al. 1982. The cholinergic hypothesis of geriatric memory dysfunction. *Science*, 217:408–17.
- Becker RE. 1991. Therapy of the cognitive deficit in Alzheimer's disease: the cholinergic system. In Becker RE, Giacobini E (eds). *Cholinergic basis for Alzheimer therapy*. Boston: Birkhauser.
- Boustani M, Peterson B, Hanson L, et al. Screening for dementia. systematic evidence review [online]. Rockville, MD: Agency for Healthcare Research and Quality. Accessed 23 Sept 2003. URL: <http://www.ahrq.gov/clinic/uspstfix.htm>.
- Cohen J. 1988. *Statistical power analysis for the behavioral sciences*. 2nd ed. Hillsdale, NJ: Erlbaum.
- Cummings JL, Mega M, Gray K, et al. 1994. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*, 44:2308–14.
- Doody R, Tariot PN, Pfeiffer E, et al. 2005. Metanalysis of 6-month memantine clinical trials in Alzheimer's disease [abstract] [online]. New Clinical Drug Evaluation Unit 45th Annual General Meeting. 2005 June 6–9; FL, USA. Accessed 14 Dec 2005. URL: <http://www.nimh.nih.gov/ncdeu/posterabstracts.cfm>.
- Folstein MF, Folstein SE, McHugh PR. 1975. Mini-mental state: a practical method for grading the mental state of patients for the clinician. *J Psychiatr Res*, 12:189–98.

- [FLI] Forest Laboratories Inc. 2003. Combined therapy of memantine and acetylcholinesterase inhibitors for the treatment of mild to moderate Alzheimer's disease did not demonstrate statistically significant effects on cognitive or global outcome compared to placebo/acetylcholinesterase treat. [Press release available online]. Accessed 25 July 2005. URL: <http://www.frx.com>.
- [FDA] Food and Drug Administration 2005. Mild Alzheimer's disease licence extension rejection [announcement]. 2005 Aug 5.
- Francis PT. 2003. Glutamatergic systems in Alzheimer's disease. *Int J Geriatr Psychiatry*, 18:S15–21.
- Fox GC, Boustani M, Edwards C. 2003. Good practice in appraising trials. International Guideline and Approaches. *Int Psychogeriatr*, 15(Suppl 2):S27.
- Galasko DR, Bennett D, Sano M et al. 1997. An inventory to assess activities of daily living for clinical trials in Alzheimer's disease. *Alzh Dis Assoc Disord*, 11:S33–9.
- Giacobini E. 2004. Cholinesterase inhibitors: new roles and therapeutic alternatives. *Pharmacol Res*, 50:433–40.
- Hartmann S, Mobius SJ 2003. Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy. *Int Clinical Psychopharmacology*, 18: 81–5.
- Khan KS, Riet GT, Popoay J, et al. 2001. Stage 11 conducting the review phase 5 study quality assessment York Centre for Reviews and Dissemination. York: York Publishing Services Ltd, NHS Centre for reviews and dissemination, University of York.
- Kukull WA, Bowen JD. 2002. Dementia epidemiology. *Med Clin North Am*, 86:573–90.
- Lane RM, Kivipelto M, Greig N. 2004. Acetylcholinesterase and its inhibition in Alzheimer disease. *Clin Neuropharmacol*, 27:141–9.
- Lexchin J, Bero LA, Djulbegovic B, et al. 2003. Pharmaceutical industry sponsorship and research outcome and quality: systematic review. *BMJ*, 326:1167.
- Maidment I, Fox C, Livingston G, et al. 2006. Drug treatment for Alzheimer's disease: the way forward. *Int J Geriatr Psychiatry*, 21: 6–8.
- National Institute for Clinical Excellence. Donepezil, rivastigmine and galantamine for the treatment of Alzheimer's disease [online]. Accessed 23 January 2006. URL: <http://www.nice.org.uk/article.asp?a=14487>.
- Panisset M, Roudier M, Saxton J, et al. 1994. Severe impairment battery: a neuropsychological test for severely demented patients. *Arch Neurol*, 51:41–5.
- Pass MD, Shua-Haim JR, Patel P, et al. 2004. Tolerability and caregiver's impressions of combination therapy with galantamine and memantine for the treatment of Alzheimer's disease [abstract]. *Neurobiol Aging*, 25(Suppl):S210.
- Patel S, Shua-Haim JR, Pass MD, Lee P. 2004. Safety, tolerability and caregiver's impressions of combination therapy with donepezil and memantine for the treatment of Alzheimer's disease [abstract]. *Neurobiol Aging*, 25(Suppl):S204–5.
- Reisberg B, Doody R, Stoffler A, et al. 2003. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med*, 348(14):1333–41.
- Rockwood K. 2004. Size of the treatment effect on cognition of cholinesterase inhibition in Alzheimer's disease. *J Neurol Neurosurg Psychiatry*, 75:1086.
- Samochocki M, Zerlin M, Jostock R, et al. 2000. Galantamine is an allosterically potentiating ligand of the human alpha 4/ beta 2 nAChR. *Acta Neurol Scand*, 176(Suppl):S68–73.
- Schneider LS, Olin JT, Doody RS, et al 1997. Validity and reliability of the Alzheimer's Disease Cooperative Study – Clinical Global Impression of Change. *Alzheimer Dis Assoc Disord*, 11:S22–32.
- Schneider J, Murray J, Banerjee S, et al. 1999. EURO CARE: a cross-national study of co-resident spouse carers for people with Alzheimer's disease: I-Factors associated with carer burden. *Int J Geriatr Psychiatry*, 14:651–61
- Shua-Haim JR, Pass MD, Patel S, et al. 2004. Safety, tolerability and caregiver's impressions of combination therapy with rivastigmine and memantine for the treatment of Alzheimer's disease [abstract]. *Neurobiol Aging*, 25(Suppl):S205.
- Sloane PD, Zimmerman S, Suchindran B. 2002. Impact of Alzheimer's disease, 2000-2050: potential implication of treatment advances. *Annu Rev Public Health*, 23:213–31.
- Tariot PN, Farlow MR, Grossberg GT, et al. 2004. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil – a randomized controlled trial. *JAMA*, 291:317–24.
- van der Kam P, Mol F, Wimmers M. 1971. Beoordelingsschaal voor Oudere Patienten (BOP). Deventer, The Netherlands: Van Loghum Slaterus.
- Wenk GL, Quack G, Moebius HJ, et al. 2000. No interaction of memantine with acetylcholinesterase inhibitors approved for clinical use. *Life Sci*, 66:1079–83.
- Yamada K, Takayanagi M, Kamei H, et al. 2005. Effects of memantine and donepezil on amyloid beta-induced memory impairment in a delayed-matching to position task in rats. *Behav Brain Res*, 162: 191–9.

