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Benefits of combined cholinesterase inhibitor and memantine treatment in moderate–severe Alzheimer's disease

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Abstract

Background: Clinical studies and post hoc analyses have investigated the use of combination therapy for the treatment of Alzheimer's disease (AD). We review the evidence for the short- and long-term efficacy of combination therapy in AD.

Methods: The review is based on a search of the PubMed database to identify relevant articles concerning combination treatment with memantine and cholinesterase inhibitors (ChEIs).

Results: In patients with moderate-to-severe AD, combination treatment with the *N*-methyl-D-aspartate receptor antagonist memantine and the ChEI donepezil has produced significant benefits in cognition, function, behavior, global outcome, and care dependency, compared with donepezil treatment alone. Data from long-term observational studies support these findings. Compared with ChEI monotherapy, combination treatment slowed cognitive and functional decline (a 4-year sustained effect that appeared to increase over time) and reduced the risk of nursing home admission. Preclinically, the combination of *N*-methyl-D-aspartate receptor modulation and acetylcholinesterase inhibition has been shown to act synergistically, which may explain the observed clinical effects of combination treatment.

Conclusion: Treatment with memantine/ChEI combination therapy in moderate-to-severe AD produces consistent benefits that appear to increase over time, and that are beyond those of ChEI treatment alone.

Keywords: Combination; Drugs; Alzheimer; Treatment

1. Introduction

The symptoms of Alzheimer's disease (AD) become increasingly severe over a period of years, reducing a patient's capacity for independent everyday living and raising the burden of care. In the absence of a cure, it is important that available treatments mirror this disease process by providing both immediate and sustained long-term effects and, ideally, slowing the rate of clinical worsening.

The cholinesterase inhibitors (ChEIs) donepezil, galantamine, and rivastigmine are indicated for the treatment of AD from the mild stages, and the *N*-methyl-D-aspartate (NMDA) receptor antagonist memantine for moderate AD onward. All are well-established monotherapies for AD, with symptomatic efficacy demonstrated in several clinical studies [1–3]. Combination therapy with both treatment types has also been used to treat patients in the moderate-to-severe stages of disease.

A preclinical study in a triple-transgenic mouse model of AD (homozygous 3×Tg-AD, containing mutations $PS1_{M146V}$, APP_{Swe}, and tau_{P301L}) showed that co-administration of memantine and donepezil could reverse cognitive deficits ([4], poster communication). In addition, pharmacokinetic and dynamic studies in healthy volunteers and in patients with mild-to-moderate AD indicated no specific safety concerns related to the clinical application of memantine/ChEI combination therapy [5,6]. Subsequently, two 6-month, double-blind, controlled clinical studies (one in moderate-to-severe AD, the other in mild-to-moderate AD) have investigated the clinical efficacy of memantine in patients already receiving stable treatment with ChEIs [7,8], in addition to several open-label investigations. Further to the prospective analyses, data from these studies have been assessed through pooled data analysis and specific post hoc examinations of clinically meaningful outcomes, including the reduction of occurrence of clinical worsening.

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We review the currently available study evidence regarding the use of combination therapy in AD, including clinical and observational studies. We also consider preclinical data that may help to explain the mechanism underlying the observed clinical effects.

2. Methods

Relevant journal articles concerning the efficacy, safety, and tolerability of combination treatment with memantine and ChEIs were identified using PubMed. The database was searched for (nonreview) articles in English, published up to June 2011. Terms used for the search were "Alzheimer's," "memantine," "cholinesterase inhibitor" (or donepezil, rivastigmine, or galantamine), and "combination" (or combined, concomitant, or adjunct), with the search limits set for studies in humans. Articles reviewed here include only those containing original information on the treatment effects of combination treatment in patients with AD. For completeness, articles reporting a post hoc analysis [9] and a meta-analysis [10] of the Tariot et al study of combination therapy in moderate-to-severe AD [7] were also included.

These collected articles are reviewed in the following section on combination therapy in the treatment of AD.

3. Combination therapy in the treatment of AD

3.1. Key symptomatic domains

In a 6-month, double-blind, placebo-controlled clinical study, 404 patients with moderate-to-severe AD (Mini-Mental State Examination [MMSE] score: 5–14) were randomized to treatment with memantine or placebo, in addition to existing stable treatment with the ChEI donepezil [7]. Over the study period, combination treatment produced significant benefits across all four symptomatic domains—cognition, function, behavior, and global outcome—when compared with donepezil treatment alone (Table 1) [7]. In addition, combination treatment produced significant advantages over donepezil monotherapy in the measure of care dependency (Table 1) [7].

Examining these results in more detail, post hoc analyses identified specific areas in which combination treatment produced a significant benefit over donepezil treatment alone (results from observed cases [OC] and last observation carried forward [LOCF] analyses were generally similar; no adjustments were made for multiple comparisons). Within the cognition domain, combination treatment had a statistically superior effect on several individual cognitive items, which fell into the Severe Impairment Battery (SIB) subscales of language ($P < .01$), praxis ($P < .01$), and memory ($P < .05$) (both OC and LOCF) [11]. Consistent with this, memantine/donepezil combination treatment showed benefit over donepezil monotherapy in the higher-order SIB subscale clusters of "memory/attention/orientation/orientating to name," "language/social interaction," and "praxis/visuospatial ability/construction" ($P \leq .01$) (both OC and LOCF) [11]. In terms of functional measures, combination treatment was significantly superior to donepezil alone in Alzheimer's Disease Cooperative Study–Activities of Daily Living 19-item subscale items, including toileting (both $P \leq .05$), grooming ($P < .01$; $P < 0.05$), watching television (both $P < 0.01$), and finding belongings ($P < .05$; not significant), with significantly less deterioration in the item subgroups of "connectedness/autonomy" and "higher level

Table 1
Change in efficacy measure scores from baseline to week 24 in patients with moderate-to-severe AD [7]

	Least squares mean score (SE)					
	LOCF analysis			OC analysis		
Efficacy measure	Combination therapy*	Donepezil alone†	*P* value‡	Combination therapy*	Donepezil alone†	*P* value‡
SIB	0.9 (0.67)	−2.5 (0.69)	<.001	1.0 (0.70)	−2.4 (0.74)	<.001
Number of patients	198	196		171	153	
ADCS-ADL$_{19}$	−2.0 (0.50)	−3.4 (0.51)	.03	−1.7 (0.51)	−3.3 (0.55)	.02
Number of patients	198	197		172	152	
CIBIC-plus	4.41 (0.074)	4.66 (0.075)	.03	4.38 (0.081)	4.64 (0.087)	.03
Number of patients	198	196		172	152	
NPI	−0.1 (0.98)	3.7 (0.99)	.002	−0.5 (0.99)	2.9 (1.06)	.01
Number of patients	193	189		171	152	
BGP–care dependency	0.8 (0.37)	2.3 (0.38)	.001	0.6 (0.37)	2.2 (0.40)	.001
Number of patients	185	179		172	151	

Abbreviations: LOCF, last observation carried forward; OC, observed cases; SIB, Severe Impairment Battery; ADCS-ADL$_{19}$, Alzheimer's Disease Cooperative Study-Activities of Daily Living 19-item subscale; CIBIC-Plus, Clinician's Interview-Based Impression of Change plus caregiver input score; NPI, Neuropsychiatric Inventory; BGP, Behavioral Rating Scale for Geriatric Patients.

NOTE. Reproduced with permission from Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I; Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil. A randomized controlled trial. JAMA 2004;291(3):317–24.

*Combination therapy with memantine + donepezil.

†Monotherapy with donepezil (+placebo).

‡*P* value for comparison of combination therapy versus donepezil alone; 2-way analysis of covariance.