Combination Drug Therapy for the Treatment of Alzheimer's Disease

X Antón Álvarez,[1] Carlos Linares[2] and Eliezer Masliah[3]

1. Director of Research, Fundación Antidemencia Al Andalus, A Coruña, Spain; 2. Assistant Professor, Medicine Department, School of Medicine, Málaga, Spain; 3. Professor, Departments of Neurosciences and Pathology, School of Medicine, University of California San Diego, La Jolla, California, US

Abstract

Alzheimer's disease (AD) is a complex and progressive neurodegenerative disorder resulting in continuous deterioration of cognition, daily living abilities and motor functions and consequently has a huge social and familial burden. To date, the drugs approved for AD treatment provide only modest symptomatic effects. At present, the combined therapy with memantine plus one cholinesterase inhibitor (ChEI) is the best option for the treatment of moderate-to-severe AD. This combination has demonstrated higher clinical efficacy than monotherapy with ChEIs, with similar safety and tolerability in several randomised-controlled clinical trials (RCTs). Recent long-term observational studies have shown that combination therapy slows the rate of cognitive and functional deterioration, delays the placement of patients in nursing homes and also provides evidence that it is more effective when initiated early. None of the drugs for AD tested in Phase III trials show evidence of disease modification. A few studies have shown that the newer drugs, particularly anti-amyloid and neurotrophic agents, may provide improved disease-modifying treatments of AD in the near future. Meanwhile, combination therapy with available drugs is the most effective AD treatment.

Keywords

Alzheimer's disease, combination therapy, memantine, disease-modifying treatments, cholinesterase inhibitor

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Correspondence: X Antón Álvarez, Fundación Antidemencia Al Andalus, PO Box 7010, 15002-A Coruña, Spain. E: xantonal@yahoo.es

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Alzheimer's Disease – A Complex Neurodegenerative Disorder with a Multifactorial Pathogenesis

Alzheimer's disease (AD), the main cause of dementia, is a neurodegenerative disorder characterised by a progressive decline of cognitive functions (memory, language, praxis, judgement and thinking, orientation and executive functions), increasing disabilities in daily living function and the presence of behavioural and psychological symptoms.[1–3] In the late to end-stages of AD, motor functions also deteriorate and thus AD causes a continuous loss of mental and physical autonomy in patients and produces a parallel increase in dependency and burden on carer-givers as the disease progresses.

The pathogenic process of AD is complex and may start decades before the condition is diagnosed (see *Figure 1*). Early molecular alterations give rise to structural changes, which precede the onset of the first symptoms and the later development of the full clinical picture, usually required for diagnosis and treatment. AD aetiopathogenesis is multifactorial and may include genetic mutations and/or risk factors,[4,5] abnormal processing and deposition of beta-amyloid (Abeta) and tau proteins,[6,7] inflammation mechanisms,[8–10] deficits of neurotrophic factors,[8,11,12] metabolic dysfunctions,[13–15] oxidative stress,[15,16] excitotoxicity[17,18] and alterations in neurotransmitters such as acetylcholine, noradrenaline, serotonine and glutamate.[18–20] These pathogenic factors influence the development of the typical AD neuropathology (senile plaques, neurofibrillary tangles, synaptic loss and neuronal apoptosis-degeneration) underlying cognitive impairment and other dementia symptoms (see *Figure 1*).[21,22] Progressive impairment of cognition reduces the abilities of AD patients to recall events, to deal with complex mental activities, to stay orientated, to plan and execute tasks and to communicate and interact with others.

The Need for Multimodal Intervention in Alzheimer's Disease

Drugs currently approved for the treatment of AD, i.e. cholinesterase inhibitors (ChEIs) and memantine, are intended to counteract the pathological consequences of neurotransmitter alterations associated with the disease. Donepezil, galantamine and rivastigmine (ChEIs) enhance cholinergic neurotransmission by inhibiting cholinesterase activity and constitute the first-line standard therapy for mild-to-moderate AD.[23,24] The uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist memantine, however, is recommended for the treatment of moderate-to-severe AD,[23–25] either as monotherapy or in combination with ChEIs

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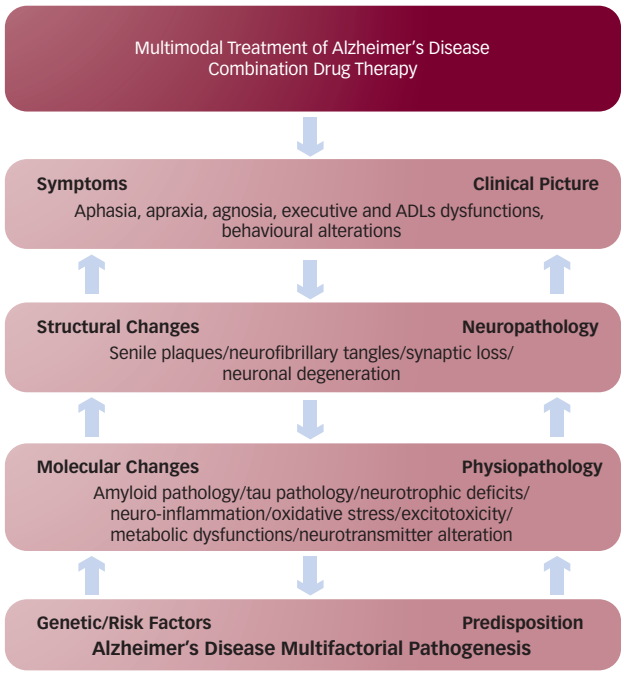
and seems to protect neurons from excitotoxicity induced via glutamate-mediated pathological activation.[26,27]

Although these AD treatments are widely prescribed for chronic use, their therapeutic benefits are limited to significant but modest symptomatic improvements with no evidence of disease modification.[23,24,28,29] Improvements of cognition and global outcome and less consistent effects on behaviour and activities of daily living (ADL), have been reported in randomised placebo-controlled clinical trials (RCTs).[30–32] In spite of treatment with ChEIs and/or memantine, AD patients show a progressive decline in cognitive, functional, behavioural and global assessments as demonstrated in long-term follow up studies.[33,34]

At present, implementation of effective treatment strategies represents an essential and unmet clinical need. The priorities in AD research are development of disease-modifying drugs to be used in early or prodromal phases of the disease and optimisation of symptomatic treatment particularly for more advanced disease stages.[28,29,35] Since the pathogenesis of AD is multifactorial, a multimodal therapeutic intervention addressing several of the molecular targets underlying the pathophysiological pathways involved in AD seems to be the most realistic strategy to modify the course of disease progression.[36–38] Thus, the use of drugs having a multimodal mode of action and/or a combination of drugs targeting a single molecular mechanism constitutes a promising alternative for effective AD therapy (see *Figure 1*).

Figure 1: Flow Chart Representation of the Interaction of a Multimodal Treatment with Multiple Levels of the Alzheimer's Disease Pathogenic Process



ADLs = activities of daily living.

Potential Benefits of Combination Therapies to Improve Alzheimer's Disease Treatment

Monotherapy has several limitations in AD regarding disease modification, efficacy and safety. It seems unlikely that any agent acting on a single molecular mechanism may induce changes in AD pathophysiology sufficient to modify disease progression. In addition, treatment with a single drug is usually more effective at high doses, which produces greater or more severe side effects. This is the case with ChEIs; their efficacy increases whereas tolerability declines in a dose-dependent manner.

Treatment with a combination of drugs having different modes of action may provide advantages over monotherapy for the effective pharmacological management of AD.[28,29,39–42] Combination therapy may enhance efficacy by inducing additive or synergistic effects; improving safety and tolerability potentially allowing lower doses to be used;[43] and rendering additional neuroprotective effects prolonging the symptomatic benefits and ultimately delaying disease progression. This article reviews clinical research evidence on the use of combination drug therapies in AD.

Combination Therapy with Cholinesterase Inhibitors and Memantine

Concomitant treatment with ChEIs and memantine is the combination drug therapy most widely studied and to date, the only one with demonstrated clinical efficacy in AD.[41,42] The effects of this combined therapy in AD have been evaluated in RCTs, in open-label trials and in long-term observational studies. RCTs evaluating drug efficacy in AD usually involve assessments of four main categories (global clinical outcome, cognition, functioning in ADL, and neuropsychiatric symptoms) and are considered demonstrative of clinical efficacy. Results of these studies indicate that combination therapy with ChEIs and memantine reduces the rate of cognitive and functional decline, diminishes the emergence and severity of neurobehavioural symptoms such as agitation/aggression and delays nursing home admission as compared with either no treatment or monotherapy with ChEIs (see *Table 1*).[44–55] There is also evidence that combined treatment is more effective when initiated early.[56]

Clinical Efficacy

In clinical trials, combination therapy with a ChEI and memantine has demonstrated higher efficacy than monotherapy in patients with moderate-to-severe AD.[54,57–59] For patients with mild-to-moderate disease, this superiority was not demonstrated in a RCT of short duration (24 weeks).[51] Observational studies in probable AD patients, however, provided supportive evidence on the long-term effectiveness of combination therapy in reducing cognitive decline and the level of dependence (see *Figure 3*)[44] and in delaying nursing home admission of patients across multiple disease stages.[50]

A pivotal RCT, (the MEM-MD-02 study) demonstrated the efficacy of combination therapy with donepezil and memantine in moderate-to-severe AD (see *Figure 2*).[54] Combination therapy was associated with a significantly higher rate of study completion (p=0.01) compared with monotherapy. Significant benefits of the combination therapy with memantine extended-release (28 mg/day) versus monotherapy with ChEIs were reported for both cognition and global function in a more recent RCT involving moderate-to-severe AD patients.[58–60]

Cognitive Effects

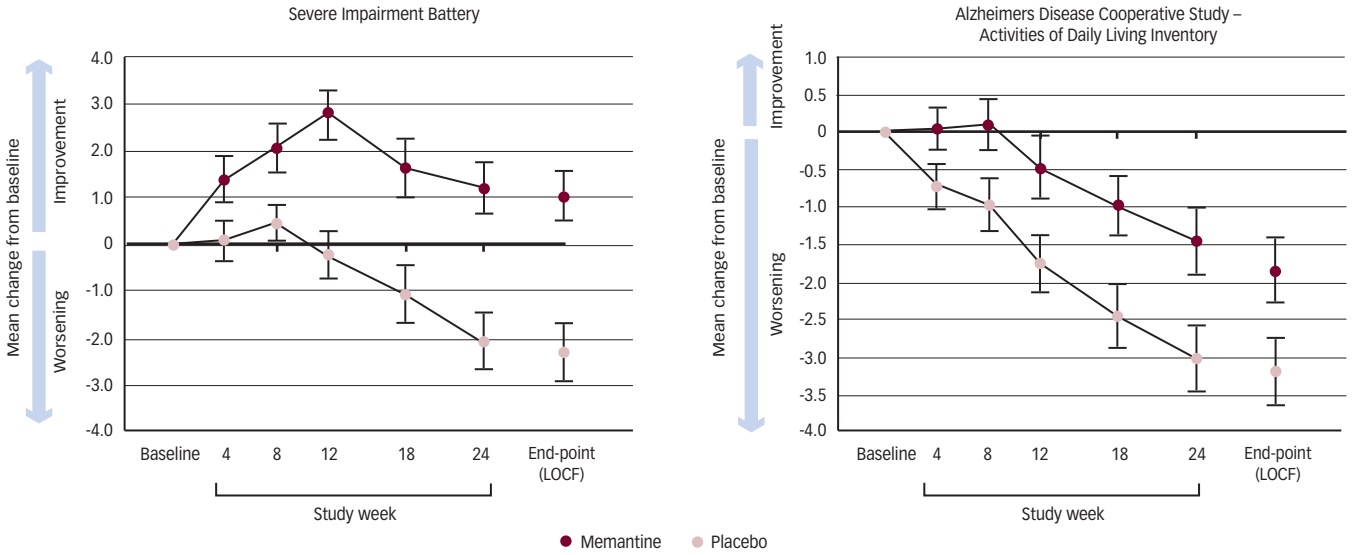
Several studies have demonstrated beneficial effects of the combination therapy with ChEIs and memantine on cognition in moderate-to-severe AD patients. The MEM-MD-02 study showed an improvement in cognitive performance (see *Figure 2*).[54] A *post-hoc* analysis found

Table 1: Clinical Studies on the Combination Therapy with Cholinesterase Inhibitors and Memantine in Alzheimer's Disease

Combination Therapy	Study Characteristics	Treatment Regime	Main Outcome(s)	References
Donepezil + memantine	Phase III RCT Moderate-to-severe AD MMSE score: 5–14 n=404 Duration: 24 weeks	Patients on stable doses of donepezil for approximately 2 years were randomly assigned to receive: Donepezil (5/10 mg/day) + memantine (20 mg/day, after titration); or Donepezil (5/10 mg/day) + placebo	As compared with monotherapy, combination showed significant improvement in SIB (p<0.001), less decline decline in ADCS-ADL (p=0.028) and improvement in CIBIC+ (p=0.03)	Tariot et al., 2004[54] Cummings et al., 2006[46] Feldman et al., 2006[49] Schmitt et al., 2006[53]
Rivastigmine + memantine	Open-label, multicentre study Moderate-to-severe AD MMSE <18 n=202 Duration: 28 weeks	Patients failing on donepezil or galantamine received rivastigmine (3–12 mg/day) for 16 weeks Non-responders to rivastigmine at week 16 received memantine (5–20 mg/day) + rivastigmine for 12 weeks	46.3 % showed equal or improved MMSE scores with rivastigmine monotherapy (week 16) versus 77.9 % with rivastigmine + memantine (week 28)	Dantoine et al., 2006[47]
Rivastigmine + memantine	Open-label, pilot study Mild-to-moderate AD n=90 Duration: 12 weeks	Patients on stable doses of rivastigmine (6–12 mg/day) received memantine for 12 weeks	Significant improvements in ADAS-cog memory subscale, MMSE, digit span and semantic fluency scores with combination therapy	Riepe et al., 2007[52]
ChEI + memantine	Long-term real-world observational study Mild-to-moderate AD n=382 Duration: 4 years	CoT: ChEI + memantine ChEI alone: donepezil, galantamine, rivastigmine Standard care: no ChEI or memantine	Significantly lower mean annualised rates of deterioration in cognition (BDS) and functioning (ADL) with combination versus monotherapy or standard care (p<0.001)	Atri et al., 2008[44]
ChEI + memantine	Phase III RCT Mild-to-moderate AD MMSE score: 10–22 n=433 Duration: 24-week	Patients on stable doses of ChEI for more than 1 year on average were randomly assigned to receive: ChEI + memantine (20 mg/day, after titration) or ChEI + placebo	CoT with memantine did not show superiority over monotherapy on primary or secondary outcomes in patients with mild to moderate AD on stable ChEI regimens	Porsteinsson et al., 2008[51]
ChEI + memantine	Phase III RCT Moderate-to severe AD n=676	Patients on stable doses of ChEI for at least 3 months were randomly assigned to receive ChEI + memantine (28 mg/day, extended release) or ChEI plus placebo. 2-week single-blind period of placebo administration followed by a 24-week double-blind period of treatment	Significant improvements in SIB, CIBIC+ and verbal fluency	Grossberg et al., 2008[58–60]
ChEI + memantine	Long-term real-world observational study Probable AD n=943 Duration: >1-year follow-up	CoT: ChEI + memantine (n=140) ChEI alone: donepezil, galantamine, rivastigmine (n=387) No medication (n=416)	As compared with patients receiving no medication, patients on ChEIs had a significant delay in nursing home admission and those on CoT showed an additional significant increase in this delay compared to users of ChEIs	Lopez et al., 2009[50]
Memantine + rivastigmine	Prospective, open-label, parallel-group study Mild-to-moderate AD n=176 completers Duration: 24–25 weeks	Patients on donepezil were switched to rivastigmine patches (9.5 mg/day for 20 weeks after 4–5 weeks titration) Previous memantine was maintained Memantine + rivastigmine versus rivastigmine alone	Rivastigmine transdermal patch in patients on established memantine appears to be well-tolerated and did not seem to affect cognition or global functioning adversely	Farlow et al., 2010[48]
Rivastigmine + memantine	Open-label Phase IV Mild-to-moderate AD n=172 Duration: 24 weeks	After an 8-week titration period patients received for 16 weeks: rivastigmine 10 cm^2 patch + memantine or rivastigmine 10 cm^2 patch alone	No significant differences in tolerability and safety between the treatment groups. No differences in efficacy	Choi et al., 2011[45]
ChEIs + memantine	Single-arm, delayed-start exploratory study Mild-to-moderate AD n=47 Duration: 48 weeks	Patients on stable treatment with ChEIs entered an observational 24-week led-in period and then received add-on treatment with memantine for another 24 weeks	Combined treatment was associated with a significantly slower right hippocampal atrophy (-5.5 % ± 12.0 % versus -10.8 % ± 7.2 %; p=0.038). Memantine treatment was also associated with superior performances on the Boston Naming Test (p=0.034) and the Trail Making Test, Part B (p=0.001), but also with a higher number of errors on the California Verbal Learning Test	Weiner et al., 2011[55]

AD = Alzheimer's disease; ADAS-cog = Alzheimer's Disease Assessment Scale-Cognitive Subscale; ADCS-ADL = AD Cooperative Study-Activities of Daily Living Inventory; BDS = Blessed Dementia Scale; ChEI = cholinesterase inhibitor; CIBIC+ = clinician's interview-based impression of change plus caregiver input; CoT = combination therapy; MMSE = mini-mental state examination; RCT = randomised controlled clinical trial; SIB = severe impairment battery (a measure of cognition).

Figure 2: Effect of Combined Memantine and Donepezil Therapy versus Donepezil Monotherapy for Patients with Moderate to Severe Alzheimer's Disease



Number of patients							
Memantine	198	197	190	185	181	171	198
Placebo	197	194	180	169	164	153	196
LS mean difference		-1.2	-1.5	-3.1	-2.7	-3.4	-3.4
p value		0.06	0.03	<0.001	0.006	<0.001	<0.001

Number of patients							
Memantine	198	198	190	185	181	172	198
Placebo	197	195	182	170	163	152	197
LS mean difference		-0.8	-1.1	-1.3	-1.4	-1.6	-1.4
p value		0.03	0.01	0.02	0.03	0.02	0.03

LOCF = last observation carried forward. Source: Tariot et al., 2004.[54] Copyright © (2004) American Medical Association. All rights reserved.

statistically significant differences between the memantine and placebo groups for memory, language and praxis domains of cognition.[53] Significant benefits on cognition were also reported for the therapy with extended-release memantine in moderate-to-severe AD patients receiving stable doses of ChEIs.[58–60] Cognitive benefits were also found with rivastigmine and memantine combination therapy in AD patients showing no response to rivastigmine alone after failing on donepezil or galantamine treatment.[47]

Data on the cognitive effects of this combination therapy in mild-to-moderate AD are less consistent. The MEM-MD-12 study showed no advantage over monotherapy regarding cognitive performance.[51] In a recent multicentre, randomised, open-label Phase IV trial combination therapy of memantine plus rivastigmine patch did not show improved efficacy over rivastigmine patch monotherapy.[46] Changes in cognition after switching from donepezil to rivastigmine transdermal patches were also found to be similar in mild-to-moderate AD patients with or without prior and concomitant memantine treatment.[48] Results of this trial, however, are limited by the fact that the two experimental groups are not comparable because patients receiving previous memantine therapy had significantly longer disease duration and more severe cognitive and functional impairments.

In contrast, a recent study, designed to assess changes in brain volume and cognitive abilities, showed that add-on memantine treatment in mild-to moderate AD patients treated with acetyl-cholinesterase-inhibitors (AChEIs) improved language and executive functions.[55] These findings are in line with results from a previous open-label trial showing that treatment with memantine significantly improved cognition in mild-to-moderate AD patients on stable rivastigmine therapy.[52] Cognitive improvements reported in these two studies suggest there are some positive effects of combination therapy on attention, language and executive functions in mild-to-moderate AD.

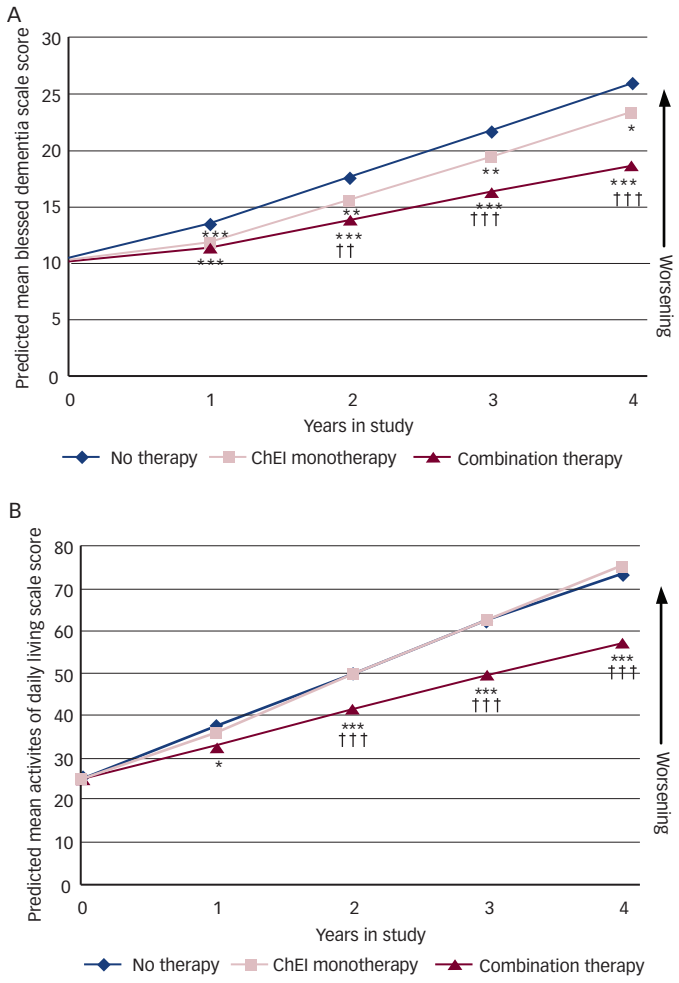
Finally, in a long-term real-world observational study[44] it was found that combination therapy with ChEIs and memantine reduced the mean annualised rate of cognitive deterioration in mild-to-moderate AD compared with ChEI monotherapy or no treatment ($p<0.001$ for both). Interestingly, the effect size favouring combination therapy increased during the four-year observation period (see *Figure 3*). This additive effect indicated that treatment benefits are maintained over time.

Effects on Functioning in Activities of Daily Living

Functional deterioration is the main cause of dependence and increasing care-giver burden in AD. One important therapeutic objective is to improve and/or maintain the capacity of the patients to perform ADLs and to co-operate with care-givers. This will contribute to preserve the autonomy of the patients, to reduce care-giver burden and to delay institutionalisation.

Moderate-to-severe AD patients in the MEM-MD-02 trial showed significantly reduced decline of ADLs function and a significantly smaller increase in care dependency scores compared with patients on donepezil monotherapy.[54] A *post-hoc* analysis revealed statistically significant benefits of combination over monotherapy on grooming, toileting, conversing, watching television and being left alone, which seems to reflect improvements in high-level functions and autonomy.[49] A significantly lower mean annualised rate of deterioration in ADL compared with monotherapy or standard care was also found in mild-to-moderate AD patients who were included in a long-term observational study.[44] The delay to nursing home admission found in another observational study provides additional indirect support to the positive effects of combination therapy on disability in mid-to-late disease stages.[50]

Figure 3: Effects of Memantine in Combination with a Cholinesterase Inhibitor, Compared with Cholinesterase Inhibitor Alone or Placebo on the Rates of Decline in Cognitive (Blessed Dementia Scale) (A) and Functional (Activities of Daily Living) (B) Abilities of Patients with Alzheimer's Disease



*p values are for the difference in Cohen's d effect size estimates at each time point. *p<0.05 versus no medication. **p<0.01 versus no medication. ***p<0.001 versus no medication. ††p<0.01 versus cholinesterase inhibitor (ChEI) monotherapy. †††p<0.001 versus ChEI monotherapy. Source: graph plotted from data given in Atri et al., 2008.[44]*

Benefits of combination therapy on functioning were not evident in short duration trials performed with mild-to-moderate AD patients.[45,51] One study reported a higher deterioration of ADL functioning in patients receiving memantine compared with those not receiving memantine,[48] but as mentioned before, the two groups investigated in the study were significantly different at baseline.

Behavioural Effects

Some of the neuropsychiatric symptoms more commonly associated with moderate-to-severe AD, such as agitation, psychosis and night-time disturbances are highly troublesome and a major cause of distress for care-givers. Thus, therapeutic interventions reducing behavioural alterations in AD represent a relief for the care-givers and may help to maintain independence of patients and their adherence to treatment.

Combination therapy with donepezil and memantine resulted in a significant reduction of the worsening of neuropsychiatric symptoms compared with donepezil monotherapy in moderate-to-severe AD.[54] A further data analysis of this trial revealed significant effects in favour of the combination therapy on agitation/aggression, eating/appetite and irritability/lability NPI items.[46] Under combination therapy, patients who were agitated at baseline showed reduced agitation/aggression scores and those who were free of agitation at baseline experienced a significant delay in its emergence. These findings are in agreement with results of the pooled analyses of the behavioural effects of memantine in moderate-to-severe AD. These show that memantine reduces severity or emergence of agitation/aggression and the accelerated progression of global, cognitive and functional decline which are exhibited by the agitated/psychotic patients treated with placebo.[57,61,62] Other studies, however, did not find significant effects for ChEI and memantine combination therapy on neuropsychiatric symptoms in patients with mild-to-moderate[45,51] or moderate-to-severe AD.[47]

Alzheimer's Disease Biomarker Effects

There is only one literature report of a study comparing the effects of ChEI and memantine combination therapy with those of ChEI monotherapy on relevant AD-related biomarkers. A significantly lower rate of atrophy was found in the right hippocampus during the combination therapy period compared with the monotherapy period and no significant differences between study periods for the rates of change in total brain volume (TBV), ventricular volume or left hippocampal volume.[55] Although limited by the low number of patients and the short treatment duration, findings of this study are consistent with those of a previous trial in which patients treated with memantine (20 mg/day for 52 weeks) showed a substantially smaller loss of hippocampal volume (2.4 versus 4.0 %) and less decline in brain glucose metabolism than placebo-treated patients.[63] These results suggest a protective effect of memantine against the degeneration of hippocampal neurons in AD patients.

Long-term Effectiveness Studies

Three recent publications provide complementary evidence on the long-term clinical effectiveness of combination therapy with ChEIs and memantine in AD.[44,50,64]

The effects of the persistence (defined as total drug-use years divided by total symptom-years) of treatment with antidementia drugs (ChEIs and/or memantine) on the annual rates of change in clinical measures were evaluated in an observational study involving the follow-up of 641 probable AD patients over 20 years.[64] Patients with more persistent exposure to antidementia drugs over the course of their illness showed significantly slower rates of decline on key measures of cognition (MMSE, p<0.001), global function (CDR-SB, p<0.001), and instrumental ADL (p<0.001). Greater antidementia drug use was also associated with a slower rate of decline on the ADAS-Cog for the first 3.3 years, but not afterwards. Treatment benefits were cumulative over time, as in the study by Atri and colleagues.[44] Although the study did not enable a direct comparison of the effects of combination therapy and monotherapy, it provides additional support for the long-term effectiveness of antidementia treatments.

Safety and Tolerability

Overall, combined therapy in AD is well tolerated with no additional safety concerns compared with monotherapy. A review of safety of memantine and ChEIs concluded that both agents were fairly well tolerated. Both drugs commonly produce dizziness and/or headache. AChEIs are associated with more types of AEs than memantine,

particularly in the gastrointestinal category, and agitation. Withdrawals in memantine-treated groups are comparable to placebo and more common in AChEI-treated groups compared with placebo. Overall, drug-drug interactions, contraindications and warnings were fewer for memantine than AChEIs. Due to vagotonic effects, AChEIs are contraindicated in patients with cardiovascular conditions. They should be used with caution in patients with asthma, obstructive pulmonary disease, seizures, those at risk of peptic ulcers and patients with urinary outflow obstruction. Memantine is contraindicated in patients with known hypersensitivity to the drug and in those with severe renal impairment; and it is recommended to use it with caution in patients with cardiovascular disease or a history of seizure.[65] Safety analyses of the main studies mentioned in the clinical safety section showed no relevant differences between memantine plus ChEI combination therapy and monotherapy with ChEIs.[44,50,51,58–60]

In patients with moderate-to-severe AD, treated with donepezil monotherapy or in combination with memantine, there was a lower rate of treatment discontinuations due to adverse events (AEs) in the combination group (7.4 %) than in the donepezil monotherapy group (12.4 %).[54] There was also a lower incidence of some gastrointestinal AEs in the patient group receiving combination therapy compared with those on donepezil (diarrhoea: 4.5 versus 8.5 %; faecal incontinence: 2.0 versus 5.0 %; nausea: 0.5 versus 3.5 %). AEs that occurred in at least 5 % of the memantine combination group and with an incidence of at least twice that of the donepezil monotherapy group were confusion (7.9 versus 2.0 %; p=0.01) and headache (6.4 versus 2.5 %; p=0.09). Constipation was also more frequent in patients on combination therapy (3.0 versus 1.5 %).

The incidence of AEs was reported to be similar in mild-to-moderate patients treated with memantine plus ChEIs and in those receiving ChEI monotherapy.[51] AEs occurring in more than 5 % of combination-treated patients included falls, accidental injury, agitation, dizziness, influenza-like symptoms, depression, gait abnormalities, diarrhoea, confusion, upper respiratory tract infection, fatigue and hypertension. The rate of discontinuation due to AEs was also similar in combination (6 %) and monotherapy (7.9 %) groups. Laboratory tests, vital sign measurements, or electrocardiogram (ECG) parameters showed no clinically significant group differences.

The proportion of participants having a clinically significant weight increase, however, was greater in the memantine combination group (9.7 %) than in the ChEI monotherapy group (5.0 %) In a study of combined treatment with memantine and rivastigmine in moderate-to-severe AD patients there was a slight weight loss on rivastigmine alone followed by a slight regaining of weight on combined therapy.[47]

The addition of memantine to rivastigmine was well tolerated and only one treatment-related AE was reported in a study of moderate-to-severe AD patients.[47] Other studies adding memantine to rivastigmine, found no significant differences in tolerability and safety between combination and monotherapy groups.[45,48]

Other Options of Combination Therapy in Alzheimer's Disease

During the past decade, despite an enormous scientific effort, a disease-modifying therapy able to delay or halt the progression of AD has not been forthcoming. Numerous drugs aimed at interfering with the major AD pathophysiological pathways have entered research phases, and different combination treatment strategies have been investigated. Clinical study data on combination therapy options are summarised in *Table 2*.

It has been proposed that combined treatment with disease-modifying and symptomatic agents will be the optimal therapy for AD patients.[28] To date, however, all the Phase III RCTs conducted in AD with this combination approach have failed to show significant clinical benefits over standard therapy. There is still hope that some of the drugs being tested in ongoing trials may be successful.

Anti-amyloid Therapy

Anti-amyloid therapy has been the major focus of AD research during the past twelve years. Strategies to reduce brain amyloid pathology include active immunisation with different anti-Abeta vaccines, passive immunisation with monoclonal anti-Abeta antibodies, DNA vaccines, inhibitors of the amyloidogenic enzymes γ-secretase and β-secretase, activators of the α-secretase physiologic pathway and several other interventions that can reduce amyloid production, aggregation and deposition or to enhance its clearance. The first anti-amyloid approach was active immunisation with the AN1792 vaccine using synthetic Abeta42 as antigen.[66] Unfortunately, the initial Phase II trial was discontinued prematurely because some of the vaccinated patients developed aseptic meningoencephalitis. *Post mortem* neuropathological studies confirmed a considerable reduction of the amyloid deposition and some effects on tau-related pathology within the brains of some of the immunised patients,[67,68] but data on the clinical efficacy remains unclear. A recent follow-up study found that, after 4.6 years of the immunisation with AN1792, those patients originally defined as antibody responders showed a significantly lower functional decline (p=0.015) compared with placebo-treated patients.[69]

Preliminary clinical data are also available for passive immunisation with humanised monoclonal antibodies against Abeta (bapineuzumab) and intravenous immunoglobulins (IVIGs). A Phase II RCT with bapineuzumab found no significant effects in the primary efficacy analysis and suggested potential treatment differences for cognitive and functional endpoints in the subgroup of patients without the Apolipoprotein E (APOE) epsilon4 allele completing the study.[70] Treatment with bapineuzumab reduced cortical fibrillar Abeta levels, as measured through carbon-11-labelled Pittsburgh compound B (11C-PIB) retention, compared with baseline and placebo.[71] The highest dose of bapineuzumab (2 mg/kg) had to be discontinued owing to the occurrence of adverse events (vasogenic oedema with sulcal effusions and microhaemorrhages with haemosiderin deposits) associated with the treatment dosage and the presence of APOE4.[72] Several IVIG preparations are under investigation in Phase II–III trials.[73] Two exploratory uncontrolled studies reported reduced cerebrospinal fluid (CSF)/increased serum levels of total Abeta and some improvements in cognition in AD patients treated with IVIG[74] and reduced CSF Abeta levels and cognitive stabilisation in patients with mild AD.[75]

The development of semagacestat, a gamma-secretase inhibitor,[76,77] was recently discontinued because preliminary analysis of two large Phase III trials showed that patients treated with the semagacestat add-on combination therapy compared with those on placebo plus regular anti-dementia treatment showed significant clinical deterioration and had an increased risk of skin cancer.[78]

Table 2: Other Combination Therapy Options Investigated in Alzheimer's Disease – Clinical Studies with Agents Targeting Different Pathophysiologal Pathways

Pathophysiology Target • Therapeutic Intervention	Therapeutic Agent (Mechanism of Action)	Combination Therapy Type Study Characteristics	Current Status Main Outcome	References
Amyloid Pathology				
• Active immunisation	AN1792 (Abeta removal)	Add-on Phase IIa Mild-to-moderate AD; n=372; 15 months (interrupted)	Discontinued SAEs: aseptic ME Unclear Efficacy ADL function	Shenck et al., 1999[66] Holmes et al., 2008[67] Vellas et al., 2009[69] Serrano-Pozo et al., 2010[68]
• Passive immunisation	Bapineuzumab (Abeta mAb: Abeta removal)	Add-on Phase II Mild-to-moderate AD n=234; 78 weeks	Ongoing (Phase III) No efficacy AEs: VE, MH 2 mg/kg dose discontinued	Salloway et al., 2009[70] Rinne et al., 2010[71] Sperling et al., 2012[72]
	IVIG: Gammagard, Octagam, Flebogamma (Natural human Abeta Abs)	Add-on Open-label, dose-ranging Mild AD; n=8; 18 months	Ongoing (Phases II–III) Stabilisation MMSE scores Reduction of CSF Abeta levels	Dodel et al., 2004[74] Klaver et al., 2010[73] Relkin et al., 2009[75]
• γ-secretase/β-secretase inhibitors	Semagacestat (LY450139) (γ-secretase inhibitor)	Add-on Phase III RCTs Mild-to-moderate AD; n>2,600; 76 weeks	Discontinued Clinical worsening Increased risk skin cancer	Alzforum.org, 2012[78] Fleisher et al., 2008[76] Henley et al., 2009[77]
• α-secretase activators	Etazolate (EHT0202) (alpha-secretase enhancer)	ChEIs Phase II Mild-to-moderate AD; n=159; 12 weeks	Ongoing Improved ADCS-ADL Dose-dependent AEs	Vellas et al., 2011[79]
• Amyloid-lowering agents	Tramiprosate (Antifibrillar)	Add-on Phase III RCT Mild-to-moderate AD; n=1,052; 78 weeks	Discontinued No clinical efficacy Reduced hippocampal atrophy Safe	Aisen et al., 2011[80] Gauthier et al., 2009[81]
	Tarenflurbil (SALA γ-secretase modulator)	Add-on Phase III Mild AD; n=1,649; 18 months	Discontinued No clinical efficacy	Green et al., 2009[82] Wilcock et al., 2008[83]
	ELND005, Scyllo-inositol (Inhibits oligomer formation)	Add-on Phase II Mild-to-moderate AD; n=353; 78 weeks	Inactive No efficacy Reduced CSF Abeta42 Toxicity at high doses. At 250 mg dose, brain ventricular volume showed a small increase (p=0.049), scyllo-inositol concentrations increased in CSF and brain, and CSF Aβx-42 decreased compared to placebo (p=0.009)	Salloway et al., 2011[87]
	Simvastatin (HMG-CoA reductase inhibitor)	Add-on Phase III Mild-to-moderate AD; n=406; 18 months	Discontinued No clinical efficacy Safe	Sano et al., 2011[84]
	Atorvastatin (HMG-CoA reductase inhibitor)	Add-on Phase III Mild-to-moderate AD; n=640; 72 weeks	Discontinued No clinical efficacy Safe	Feldman et al., 2010[85]
	Rosiglitazone (PPAR-γ agonist) ChEIs	Phase III (2) Mild-to-moderate AD; n=1,496 + 1,485; 48 weeks	Discontinued No clinical efficacy	Harrington et al., 2011[86]
TAU Pathology				
• Tau phosphorylation inhibitors	Divalproex sodium (GSK3-beta inhibition)	Add-on Phase III Moderate AD without previous agitation or psychosis; n=313; 24 months	Discontinued No clinical advantage over monotherapy Greater rates of brain atrophy	Fleisher et al., 2011[88] Tariot et al., 2011[89]
Neurotrophic Deficits				
• Mimetic neuropeptides	Cerebrolysin (Neurotophic-like effects)	Donepezil Phase III Mild-to-moderate AD; n=200; 28 weeks	Ongoing Combination superior to donepezil on global function	Alvarez et al., 2011[93]

Pathophysiology Target • Therapeutic Intervention	Therapeutic Agent (Mechanism of Action)	Combination Therapy Type Study Characteristics	Current Status Main Outcome	References
Neurotrophic Deficits				
• Other	MK-677 (GH secretagogue IGF-I increase)	Add-on Phase II Mild-to-moderate AD; n=563; 12 months	Discontinued No clinical efficacy No effect on the rate of AD progression	Sevigny et al., 2008[90]
	Xaliproden (5-HT1A receptor agonist. NGF-like effects)	Add-on Phase III Mild-to-moderate AD; n=1,455; 18 months	Discontinued No clinical efficacy	Martel et al., 2009[91] Sabbagh et al., 2009[92]
Neuroinflammation				
• NSAIDs	Naproxen/Rofecoxib (NSAID/COX-2 inhibitor)	ChEIs Phase III. Mild-to-moderate AD; n=351; 52 weeks	Discontinued No clinical efficacy Safety concerns	Aisen et al., 2003[94]
	Celecoxib (COX-2 inhibitor)	Add-on Phase III Mild-to-moderate AD; 52 weeks	Discontinued No clinical efficacy Safe	Soininen et al., 2007[95]
	Ibuprofen (Anti-inflammatory)	Add-on Phase III Mild-to-moderate AD; n=132; 12 months	Discontinued No clinical efficacy Safe	Pasqualetti et al., 2009[96]
Oxidative Stress				
• Omega-3 fatty acids	DHA/EPA (Omega-3 fatty acids)	ChEIs Phase III Mild-to-moderate AD; n=204; 6 months (+6 extent)	Definitive No clinical efficacy Safe	Freund-Levi et al., 2006[97]
	DHA (Omega-3 fatty acid)	Add-on Phase III Mild-to-moderate AD; n=402; 18 months	Definitive No clinical efficacy Safe	Quinn et al., 2010[98]
• Vitamins	Folate/B6/B12 (Reduction homocysteine)	Add-on Phase III Mild-to-moderate AD; n=409; 18 months	Definitive No effects on cognition Reduction homocysteine	Aisen et al., 2008[99]
	Vitamin E, Selegiline (Antioxidant, MAOI)	Combined versus monotherapy Phase III Moderate AD; n=341; 2 years	Definitive No superiority of combination to monotherapy	Sano et al., 1997[100]
Excitotoxicity				
• Metal Chelators	PBT2 (Inhibits metal-protein toxicity)	ChEIs Phase IIa Early AD; n=78; 12 weeks	Ongoing Dose-dependent effects on executive function, CSF Abeta Acceptable tolerance	Lannfelt et al., 2008[102] Faux et al., 2010[101]
Metabolic Alterations				
• Hormone therapy	Insulin (Enhances insulin signalling)	Add-on Open-label Mild-to-moderate AD and DM-2; n=104; 12 months	Ongoing Insulin reduced cognitive (MMSE) and global (CGI-C) decline significantly	Plastino et al., 2010[104]
	HRT (Restores hormonal deficits)	Rivastigmine RCT Menopausal AD women; n=117; 28 weeks	Discontinued No significant superiority of the combination	Rigaud et al., 2003[103]
Neurotransmitter Deficits				
	Atomoxetine (NA re-uptake inhibitor)	ChEIs Phase II–III Mild-to-moderate AD; n=92; 6 months	Phase II in MCI No clinical efficacy Safe	Mohs et al., 2009[105]

Abs = antibodies; Abeta = beta-amyloid; AD = Alzheimer's disease; ADCS-ADL = AD Cooperative Study-Activities of Daily Living Inventory; AEs = adverse events; CGI-C = clinician's global impression of change; ChEIs = cholinesterase inhibitors; COX-2 = cyclo-oxygenase-2; CSF = cerebrospinal fluid; DHA = docosahexaenoic acid; DM-2 = type 2 diabetes; EPA = eicosapentaenoic acid; GH = growth hormone; GSK3-beta = glycogen synthetase kinase 3 beta; HMG-CoA = 3-hydroxy-3methyl-glutaryl-coenzyme A; HRT = hormone replacement therapy; 5-HT = 5-hydroxytyiptamine (serotonin); IGF-I = insulin-like growth factor type I; IVIG = intravenous immunoglobulins; MAOI = monoamine oxidase inhibitor; mAb = monoclonal antibody; MCI = mild cognitive impairment; ME = meningoencephalitis; MH = microhaemorrhages; MMSE = mini-mental state examination; NA = noradrenaline; NGF = nerve growth factor; NSAIDs = non-steroidal anti-inflammatory drugs; PPAR-γ = peroxisome proliferator-activated receptor-gamma; RCT = randomised-controlled clinical trial; SAEs = severe adverse events; SALA = selective abeta42-lowering agent; VE = vasogenic oedema.

A recent report on a Phase II trial with the alpha-secretase enhancer etazolate (EHT0202) showed promising results.[79] Although the study was not powered to show drug efficacy, significant improvements in functioning were reported. Safety and tolerance data were encouraging and support further development of EHT0202.

Several other amyloid-lowering agents were discontinued owing to the lack of efficacy at the Phase III stage, including the antifibrillar compound tamiprosate,[80,81] the selective Abeta42 lowering agent tarenflurbil,[82,83] the two statins simvastatin[82–84] and atorvastatin[85] and the peroxisome proliferator-activated receptor-gamma agonist rosiglitazone.[86] A Phase II trial with the scyllo-inositol (ELND005), a drug-inhibiting Abeta oligomer formation, reported acceptable tolerance only with the lowest dose tested (250 mg twice per day) and no significant effects on primary endpoints in the overall study population.[87] A significant increase of brain ventricular volume and a significant reduction of CSF Abeta42 were found in the group of patients treated with the 250 mg dose.[87]

Drugs Targeting Tau-related Pathology

Strategies targeting tau-related pathology include drugs inhibiting tau phosphorylation such glycogen synthase kinase 3 (GSK-3) inhibitors, and compounds or antibodies reducing tau aggregation. The only Phase III study published on the combination therapy with anti-tau agents investigated the effects of flexible-dose valproate in patients with moderate AD without previous agitation or psychosis.[88,89] Valproate treatment did not delay emergence of agitation or psychosis or slow cognitive or functional decline in patients with moderate AD, and was associated with significant toxic effects.[89] Furthermore, valproate-treated patients showed greater loss in hippocampal and whole-brain volume, greater ventricular expansion ($p<0.001$) and a more rapid decline of MMSE scores ($p=0.037$) at month 12.[88,89]

Neurotrophic Agents

A downregulation of nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), insulin-like growth factor-I (IGF-I) and IGF-I receptors has been reported in AD and mild cognitive impairment (MCI).[8,11,12] These reductions in neurotrophic signalling influence the degeneration of basal forebrain cholinergic neurons and constitute an early event in AD pathogenesis.[11] Neurotrophic alterations are also associated with Abeta- and tau-related pathology, apoptosis, reduced neural plasticity, synaptic loss and cognitive impairment.[11,12] Therefore, drugs and mimetic peptides able to increase brain neurotrophic signalling are a promising alternative for AD treatment.

Three studies using this approach were recently published. The growth hormone secretagogue MK-677[90] and Xaliproden,[91,92] a 5-HT1A receptor agonist with NGF-like activity, showed no clinical efficacy; whereas combined treatment with donepezil and the peptidergic drug cerebrolysin[93] showed some advantage over donepezil monotherapy in terms of improvements in global outcome. Further research into this combined treatment is recommended.

Anti-inflammatory Drugs and Anti-oxidative Factors

All Phase III trials on combination therapy with anti-inflammatory drugs have failed to show clinical efficacy. Naproxen and rofecoxib,[94] celecoxib[95] and ibuprofen[96] had no advantage over placebo in the combined treatment of AD. Omega-3 fatty acids,[97,98] group B vitamins[99] and vitamin E[100] were also devoid of efficacy in combination trials.

Interventions Based on Excitotoxicity, Metabolic and Neurotransmitter Alterations

An early Phase II study was completed with PBT2, a metal chelator drug intended to reduce toxicity of metal–protein complexes like those formed by Abeta oligomers with copper and zinc. In early AD patients, the combination of PBT2 with ChEIs dose-dependently improved executive functions and reduced CSF Abeta42 levels significantly compared with ChEIs alone.[101, 102] These positive findings are preliminary and need further confirmation. Treatments for metabolic alterations have had mixed results. Hormone replacement therapy did not enhance the clinical response to rivastigmine when administered to menopausal women with AD.[103] However, a recent open-label study found that add-on treatment with insulin reduced the rates of cognitive and functional decline significantly compared with regular therapy without insulin in patients with mild-to-moderate AD and diabetes type 2.[104] Finally, the combined treatment with atomoxetine (a noradrenaline re-uptake inhibitor) and ChEIs showed no effects in improving the clinical efficacy of monotherapy in mild to moderately severe AD.[105]

Conclusions and Future Developments

At present, combined drug therapy with memantine and ChEIs represents the best available option for the effective treatment of moderate-to-severe AD patients. This therapeutic approach showed higher clinical efficacy than monotherapy with similar safety and tolerability. Results of RCTs and observational studies[44,50,54] support the benefits of this combination therapy to retard the rate of cognitive and functional deterioration, to reduce the severity and emergence of neuropsychiatric symptoms such as agitation and to delay nursing home admission compared with no treatment or ChEI monotherapy.

The utility of the memantine–ChEI combination therapy in patients with mild-to-moderate AD, however, has not been conclusively demonstrated. RCTs showed similar short-term efficacy for combination therapy and monotherapy;[51] whereas long-term observational studies support the effectiveness of the combination therapy to reduce the rate of cognitive decline and the level of dependence and indicate that combined treatment is more effective when initiated early and maintained.[44,50,56,64] Therefore, long-duration RCTs are needed to confirm whether combination therapy in early AD stages retards disease progression. The potential long-term benefits should be more evident after two years of combined treatment when the rate of deterioration is more prominent.[34] It will be important to assess the efficacy of the combined treatment with the high-dose new formulations of memantine. The combined therapy should also be assessed in terms of cost-effectiveness, potential neuroprotective effects and a more detailed assessment of its potential benefits on motor impairment in end-stage disease.

Although most add-on trials with potential disease-modifying drugs failed, there are data to suggest that success with this approach may be achieved in future, particularly for anti-amyloid strategies and neurotrophic agents. Anti-Abeta vaccines, cerebrolysin and insulin, may be potentially beneficial agents that warrant further investigation. Combinations of anti-amyloid and/or anti-tau interventions with neurotrophic agents have not been studied and may give synergistic or additive effects. Future drug studies in prodromal or early AD stages will require long follow-up periods to demonstrate efficacy because the rates of disease progression and clinical deterioration of these patients are highly variable and rather slow. ■

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