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Combination Therapy in Alzheimer's Disease

A Review of Current Evidence

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Abstract

Treating dementia has become a major challenge in clinical practice. Presently, acetylcholinesterase inhibitors are the first-line drugs in the treatment of Alzheimer's disease (AD). These options are now complemented by memantine, which is approved for the treatment of moderate-to-severe AD. Altogether, a minimum of six agent classes already exist, all of which are approved for clinical use and are either already being tested or ready for phase III clinical trials for the treatment of AD. These include cholinesterase inhibitors, blockers of the NMDA receptor, antioxidants or blockers of oxidative deamination (including *Gingko biloba*), anti-inflammatory agents, neurotrophic factors (including hormone replacement therapy and drugs acting on insulin signal transduction) and antiamyloid agents (including cholesterol-lowering therapy). These approaches hold promise for disease modification and have a potential to be used as combination therapy for cognitive enhancement.

Presently, only nine clinical studies have been published that have investigated the effects of a combination regimen on cognitive performance or AD. Among those, one study was conducted in elderly cognitively intact persons; the others involved patients with AD. Only five of the treatment studies followed a randomised, controlled design. Not all studies favoured the superior efficacy of combination therapy over monotherapy. Some studies, however, showed some evidence for synergistic combination effects of symptomatic therapy, including delay or prevention of disease progression in AD patients. In addition, six studies investigated the effects of AChE inhibitor in combination with antipsychotic or antidepressant therapy on behavioural aspects of AD symptomatology. In four of those studies there were indications that combination therapy had greater efficacy over monotherapy.

The treatment of AD patients requires optimised options for all stages of illness based on the available drugs. There is a great need for further well designed studies on combination therapy in AD.

The pathophysiology of Alzheimer's disease (AD) is complex and likely to involve multiple, interconnected pathways. Data from basic and clinical research have started to elucidate the pathophysiology and have provided promising new therapeutic targets for the treatment of Alzheimer's disease.

According to the amyloid hypothesis, accumulation of β-amyloid (Aβ) in the brain is considered the primary influence driving the pathogenesis of AD. It has been proposed that the rest of the disease process, including formation of neurofibrillary tangles containing τ-protein as well as synaptic degeneration, results from the consequences of an imbalance between Aβ production and Aβ clearance.[1]

Although the amyloid hypothesis offers a broad framework to explain various aspects of AD pathogenesis, several observations do not fit with this understanding of AD pathophysiology. In considerable part, the amyloid hypothesis remains controversial because a specific neurotoxic species of Aβ and the nature of its effects on neuronal function have not been defined *in vivo*. According to this hypothesis, several therapeutic strategies have been proposed as potentially primary preventive therapy. The first strategy aims at partially inhibiting either of the two proteases, β- and γ-secretase, that generate Aβ from the amyloid precursor protein. Secondly, one attempts to prevent the oligomerisation of Aβ or to enhance its clearance from the cerebral cortex. This approach is exemplified by the use of active or passive Aβ immunisation, in which antibodies to Aβ decrease cerebral levels of the peptide. Furthermore, some anti-inflammatory drugs and cholesterol-lowering agents interact with amyloid formation in addition to their other pharmacological mechanisms of action. The fifth strategy is based on the observation that Aβ aggregation is, in part, dependent on the metal ions Cu^{2+} and Zn^{2+}. Thus, chelation of these ions *in vivo* may prevent Aβ deposition.

Another treatment strategy, which is partly independent from the amyloid cascade hypothesis but compatible with other hypotheses about the pathogenesis of AD, is to prevent the synaptotoxic and neurodegenerative effects putatively initiated by multiple events in the diseased brain. Such potentially neuroprotective strategies act on general pathogenetic cascades in the brain, which are considered pathophysiology of numerous neurodegenerative diseases. Thus, these cascades are, on the one hand, of general importance for the survival of neurons, but on the other hand potentially not specific for AD.[2]

These emerging strategies may provide treatment options for AD throughout the course of the disease, as well as possible agents for prevention. Advances in molecular pharmacology have identified multiple effective or promising, and potentially complementary, drugs for treatment of AD. Drug development for AD should consider all pathological events associated with aetiology and neurodegeneration, e.g. oxidative stress, neuroinflammation or disturbances in growth-factor signalling.

Considering the complexity of AD, and that multiple aetiologies may contribute to the disease, a combination of therapeutic agents may result in more effective strategies for treatment than one drug alone. Since the extent and topography of the neurochemical and molecular pathology of AD changes over the course of the disease, which results in a shift of symptoms over time, the efficacy of drugs may change over time as well. This might affect the choice of a rational combination of drugs. Thus, the development of an effective therapy for AD remains a great challenge for drug research. The major pathophysiological mechanisms relevant to AD and potential drug treatments are shown in table I.

To identify clinical trials that have used two or more of the above agents in order to study efficacy on cognitive measures, a systematic Medline and EMBASE search and a search with a proprietary database, R&D Insight database (Adis International Ltd) was carried out. Data range of the search was 425. Search strategies for combination therapy in AD used the following keywords: 'Alzheimer' and 'therapy' and ('combination' or 'combin*' or 'plus' or 'adjunctive' or 'dual') or 'memantine' or 'cholinesterase*' or 'acetylcholinesterase' and 'combin*'.

Table I. Conceptual approaches to pathophysiology and potential pharmacotherapy in Alzheimer's disease (AD) therapy

Pathophysiological mechanism with relevance to AD	Pharmacotherapy
Neurotransmission	Cholinesterase inhibitors
Excitotoxicity	Memantine
Oxidative stress	*Gingko biloba* Tocopherol (vitamin E) Selegiline α-Lipoid acid
Neuroinflammation	NSAIDs Peroxisome proliferator-activated receptor γ agonists
Neurotrophic factors	Estrogens Insulin
Amyloid metabolism	HMG-CoA reductase inhibitors

All clinical studies were included that investigated a combination or add-on therapy in AD or cognitive measures.

In this article, the presently available drugs for use in combination therapy are discussed individually in the context of their pathophysiological background (the purpose of which is to identify and illustrate the relevance of these pathophysiological cascades for the treatment of AD; the provision of a comprehensive and systematic review of the available clinical trials on individual agents is outside the scope of this review). The main focus of this article discusses the available published evidence on clinical effects of combination regimens, from which suggestions for further studies are proposed.

1. Overview of Drug Classes Tested as Combination Therapies For Alzheimer's Disease (AD)

Large-scale clinical trials have demonstrated positive effects for two agent classes in providing symptomatic effects and potentially slowing the progression of AD. In addition, epidemiological studies have identified a number of promising agents in widespread clinical use that may offer neuroprotective effects in delaying the development and progression of AD. There are a minimum of six agent classes (see table I) already in or ready for phase III clinical trial testing for retarding AD development or progression, including cholinesterase inhibitors, antagonists of the NMDA receptor, *Gingko biloba*, antioxidants or antagonists of oxidative deamination, NSAIDs, hormone replacement therapy, cholesterol-lowering therapy and drugs acting on insulin signal transduction.

1.1 Cholinesterase Inhibitors

The main drugs that are available for the symptomatic treatment of AD are cholinesterase inhibitors, which increase the availability of acetylcholine at cholinergic synapses. The efficacy of acetylcholinesterase (AChE) inhibitors is documented at different levels: (i) clinical global impression of the physician; (ii) cognitive performance assessed by neuropsychological testing; and (iii) competence in daily life of the patient as estimated by the impression of caregivers. AChE inhibitors are the first group of substances for which an indisputable and relevant efficacy in treatment of the cognitive disturbances in AD was demonstrated and extended over a period of time in the natural course of the disease. Regarding the clinical efficacy of galantamine, donepezil and rivastigmine, excellent meta-analyses can be found in the Cochrane Library.[3-5]

In summary, according to Cummings,[6] the following conclusions can be derived from clinical studies concerning the use of AChE inhibitors in practice:

- All AChE inhibitors show a reproducible efficacy for patients with AD.
- Compared with placebo, positive effects of AChE inhibitors are shown with regard to cognition and global impression of the physician.
- In placebo-controlled studies, significant differences in activities of daily living and behaviour are shown, mostly in favour of AChE inhibitors.
- Significant differences in the efficacy of different AChE inhibitors are not known.
- In patients who experience insufficient effectiveness or intolerable adverse effects, a change from one AChE inhibitor to another may help up to 50% of these patients; the change from one AChE inhibitor to another shows loss of effectiveness over the period between washout and new administration.

- Adverse effects of AChE inhibitors are more frequent in the titration phase, rather than in maintenance phase; they include nausea, diarrhoea and anorexia.

Studies have not shown that AChE inhibitors can prevent disease progression, and only a subanalysis from combined clinical trials supports their use in advanced or severe stages of AD.[7,8]

1.2 NMDA Receptor Antagonist

Memantine, available in the US and Europe for use in AD in 2003/4, is the first and only NMDA receptor antagonist to be registered for the treatment of moderate-to-severe AD. Glutamate is the most abundant excitatory neurotransmitter in the CNS. In addition to disturbances of the cholinergic system, disturbances in the glutamatergic system play a decisive role in acute and chronic neurodegenerative disorders, such as AD, and also vascular dementia. For the pathophysiology of primary dementias, the glutamate-controlled, voltage-dependent NMDA receptor is of high relevance. Whereas the physiological short-term release of glutamate is involved in cellular processes for learning, memory and the development of synaptic plasticity, chronically released glutamate leads to a continuous neuronal calcium influx and excitotoxicity associated with destruction of cortical and subcortical neurons. With memantine, which functions as a noncompetitive and low-affinity NMDA receptor antagonist, neurons are protected from calcium-mediated neurodegeneration under experimental conditions.

In two placebo-controlled, double-blind studies over a period of 6 months, patients with moderate-to-severe AD showed a significantly better outcome in the global Clinician's Interview-Based Impression of Change-Plus (CIBIC-Plus), in cognition, measured with the Severe Impairment Battery (SIB), and in activities of daily living, measured with a scale that was adapted for the impairments of severe dementias.[9,10]

1.3 *Gingko Biloba*

Gingko biloba is a dry extract from the leaves of the *Gingko biloba* tree. Different extracts do not have the same pharmacological properties because the composition of the extracts varies. Most of the clinical studies were conducted with the extract Egb761, so conclusions regarding the effects of *Gingko biloba* extracts are restricted to Egb761. *Gingko biloba* shows the following effects in animal models and *in vitro*:

- scavenger of free oxygen radicals;[11]
- platelet-activating factor antagonism;[12]
- stabilising of membranes;[13]
- normalisation of the cerebral energy metabolism after hypoxic damage;[14] and
- neuromodulatory effects on transcription factors and growth factors.[15]

The study of Kanowski et al.[16] on 216 patients with AD or vascular dementia shows positive results on cognitive performance and Clinical Global Impression (CGI) scale with Egb761; however, no significant effect on activities of daily living was shown. Le Bars et al.[17] conducted a trial on 309 patients with mild-to-moderate AD and vascular dementia who were treated with Egb761 for 1 year. Only 137 patients (42% of the initial sample) completed the study according to protocol. However, the withdrawal rate after 6 months was fairly low (approximately 28%). An analysis of AD cases showed a significant superiority in Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog) and Geriatric Evaluation by Relative's Rating Instrument (GERRI), but not for CGI scale[17] for *Gingko biloba* treatment. A placebo-controlled study of 214 patients with different diagnoses (AD, vascular dementia, acute anterior myocardial infarction, and a variety of dementias) for 24 weeks did not find statistically significant differences in mean change of outcome scores between *Gingko biloba* and placebo. Neither the dementia subgroup (n = 36) nor the acute anterior myocardial infarction subgroup (n = 87) experienced a significant effect from *Gingko biloba* treatment.[18] In summary, the three most recent trials mentioned in this paragraph show inconsistent results. There is a need for a large trial using well designed methodology and permitting an intention-to-treat analysis to provide robust esti-

mates of the size effect and mechanism of any treatment effect.[19]

1.4 Antioxidants and Antagonists of Oxidative Deamination

In studies on post-mortem brains of patients with AD, several markers of oxidative damage are found, including increased lipid peroxidation, increased protein and DNA oxidation and a decline in the levels of polyunsaturated fatty acids.[20]

There are data that indicate an association of AD with mitochondrial mutations. For the two mitochondrial genes CO1 and CO2 that are coding for the catalytic centre of cytochrome-oxidase, specific mutations are found more frequently in patients with AD. Those are five missense mutations and one silent mutation in the mitochondrial genome that occurred mutually in most cases.[21] In 60% of AD patients examined, >20% of the mitochondrial genome showed these mutations, whereas this proportion of mutations was only found in 20% of controls.[21] *In vitro*, it was shown that different mutations can result in disturbances of the respiration chain that manifests as an increased release of free oxygen radicals. Such oxidative stress to the tissue increases the intracellular accumulation of Aβ.[21-23]

1.4.1 Tocopherol (Vitamin E)

Tocopherol (vitamin E) is an essential element of nutrition; its physicochemical properties as a radical scavenger result in a protective function against oxidative stress.

Antioxidants have been investigated as possible preventive therapies for AD and epidemiological studies suggest that tocopherol and ascorbic acid (vitamin C) may reduce the risk for the disease in the elderly.[24,25] A combination of tocopherol and ascorbic acid showed an effect on lipoprotein oxidation in ten patients with AD.[26] Further conclusions from this are limited by the small number of patients and the lack of control group. There is only one double-blind, randomised, controlled study investigating the efficacy of tocopherol (and selegiline) in AD.[27] This study showed differences in clinical progression of the dementia for patients with moderate dementia in favour of tocopherol. A survival analysis, including the baseline score of the Mini-Mental State Examination (MMSE) as a covariate, was used for interpretation of the data, since the two groups were different with respect to baseline severity of dementia. There were increased falls and syncopes in the treatment groups, especially in the group receiving combined treatment.[28] Additional studies are necessary to assess the possible efficacy of tocopherol. There was also an excess of falls in the tocopherol group compared with placebo that requires further evaluation.[28]

1.4.2 Selegiline

Selegiline is a selective, irreversible inhibitor of monoamine oxidase type B (MAO-B). It decreases the degradation of catecholamines in the brain and thus reduces the production of oxygen free radicals in mitochondria. Through the reduction of free radicals, selegiline may have neuroprotective effects. MAO-B activity is increased in patients with AD and is thought to contribute to neurotransmission defects and oxidative stress associated with AD. The only comparative study showing the efficacy of selegiline in delaying functional deterioration in AD patients also suggested an equal efficacy of tocopherol.[28] A survival analysis, including the baseline score of the MMSE as a covariate, was used for interpretation of the data. The conventionally parallel group comparison between selegiline and placebo group was not significant. As mentioned in section 1.4.1, adverse events may require special attention.

A recent review concluded that there is no evidence of a clinically meaningful benefit for the use of selegiline in AD and selegiline was not recommended as part of an evidence-based therapy.[27]

1.4.3 α-Lipoic Acid

α-Lipoic acid (ALA), an essential cofactor in mitochondrial dehydrogenase reactions, functions as an antioxidant and reduces oxidative stress in aged animals. In dissociated primary hippocampal cultures treated with Aβ-peptide (Aβ25-35) and iron/hydrogen peroxide (Fe/H_2O_2), pretreatment with dihydrolipoic acid (DH-LA) significantly protected against Aβ and Fe/H_2O_2 toxicity. These data suggest that the oxidation state of ALA is critical to

its function and that, in the absence of studies of ALA/DH-LA equilibrium in human brain, the use of ALA as an antioxidant in disorders such as AD may be of questionable efficacy.[29] To date, there is an absence of randomised, double-blind, placebo-controlled trials investigating ALA for dementia.[30]

1.5 Non-Steroidal Anti-Inflammatory Agents

Inflammatory processes involving cytokines, prostaglandins, free radicals and glia cells play an important and complex role in the pathogenesis of AD. In the border zone of early diffuse plaques, astrocytes can be found functioning as antigen-presenting cells under specific conditions. In this stage no signs of neurodegeneration are apparent, but primary synaptic changes are perceptible. Damage of neurites is associated with an activation of complement cascade. As a result, the membrane attack complex is activated, damaging the integrity of the cell membrane. The simultaneous expression of different cytokines, including tumour necrosis factor-α, interleukin (IL)-6, IL-1 as well as protease inhibitors (e.g. α-2 macroglobulin), can be interpreted as a secondary reaction resulting from an acute phase reaction. Altogether, the neuroimmunological data point to a pivotal role of glial reactions in the development of AD pathology.[31] However, the precise role of astrocytes and microglia regarding the development of neurodegeneration is not yet entirely clear. The significance of polymorphisms in *IL-1* and *IL-6* genes as risk factor for sporadic AD also indicates the relevance of inflammatory mechanisms.[32-34] In addition to the anti-inflammatory effect of NSAIDs, direct effects on amyloid formation could be relevant for selecting them as potential treatment in AD.[35] The recognition that NSAIDs can bind to and activate the nuclear receptor peroxisome proliferator-activated receptor (PPAR)-γ, has offered an additional explanation for the action of these drugs in AD.[36] PPAR-γ agonists were shown to play a critical role in regulating the inflammatory responses of microglia and monocytes to Aβ.[37,38]

To date, treatment of patients in the stage of manifest AD has been without success.[39] Rogers et al.[40] described in a small study on 44 patients with mild-to-moderate AD a delay of disease progression by indomethacin. Gastrointestinal adverse effects limit those results so that in general, NSAIDs cannot be recommended for treatment of mild-to-moderate AD.[41]

1.6 Hormone Replacement Therapy

The CNS, including the basal nucleus of Meynert, contains estrogen receptors; estrogens under certain physiological conditions increase cerebral blood flow and have an antioxidant effect. Studies in rodents demonstrate a promotional effect of estrogen on various measures of brain activity, including acetylcholine levels, and reveal the presence of high-affinity estrogen binding sites on neurons in brain regions affected by AD.[42,43] Taken together, this evidence may suggest that estrogen withdrawal (e.g. resulting from menopause) may promote neurodegeneration. While the biological basis for estrogen replacement therapy as a cognition enhancer is strong and multiply mediated, the clinical evidence for its use is not as compelling and must be weighed against possible adverse effects.[44] The results of two recent studies[45,46] revealed no benefit for hormone replacement therapies or combination therapies with estrogens and progesterone in women with AD, and even showed a potentially deleterious effect. More studies are necessary in order to determine whether estrogen therapy can delay the onset of dementia.[47] In summary, the timing of estrogen initiation and the neurological status of the brain at this time contribute to the efficacy of estrogen in preventing neurodegenerative disease and sustaining neurological health and function.[48]

1.7 Cholesterol-Lowering Therapy

The production of Aβ depends on the availability of cholesterol in nerve cells. Balance of α- and β-secretase activity is linked with the cellular lipid composition.[49] High cellular cholesterol levels increase amyloidogenic processing of amyloid precursor protein (APP) by β-secretase,[49] whereas low cholesterol levels increase the physiological metabolism of APP by α-secretase.[50] By this mechanism,

a depletion of cholesterol from neuronal membranes could be a therapeutic approach for the treatment of AD.[51] Epidemiological studies have shown that treatment with cholesterol-lowering drugs, e.g. HMG-CoA reductase inhibitors, reduce the prevalence of dementia in comparison with the normal population.[52,53] In a recent study, treatment of AD patients with simvastatin led to a slight improvement in cognitive performance compared with placebo.[54] There is no reliable evidence to recommend HMG-CoA reductase inhibitors for reducing the risk of AD, but there is limited evidence that lowering serum cholesterol may retard the pathogenesis of AD.[55] In a case-control study on elderly patients without dementia, the authors provide evidence that HMG-CoA reductase inhibitors affect cerebral cholesterol metabolism; however, these changes were not associated with altered amyloid-peptide secretion in human CSF.[56]

1.8 Insulin Signal Transduction

An emerging body of evidence suggests that an increased prevalence of insulin abnormalities and insulin resistance in AD may contribute to the disease pathophysiology and clinical symptoms. It is now well known that insulin and insulin receptors are densely but selectively expressed in the brain, including the medial temporal regions that support the formation of memory. It has recently been demonstrated that insulin-sensitive glucose transporters are localised to the regions that support memory, and that insulin plays a role in memory functions. The function of the neuronal insulin/insulin receptor signal transduction cascade is important for maintaining normal blood flow and oxidative energy metabolism in the human brain. By this mechanism, several aspects of cell metabolism, including a normal function of the endoplasmic reticulum/Golgi apparatus and the induction of cell cycle in terminally differentiated neurons, are controlled. Insulin may also play a role in regulating the amyloid precursor protein and its derivative Aβ. It has been proposed that insulin can accelerate the intracellular trafficking of Aβ and interfere with its degradation. These findings are consistent with the notion that insulin abnormalities may potentially influence levels of Aβ in brains affected by AD.[57] Furthermore, by influencing the conversion of glycogen synthase kinase (*GSK*)-*3* to *GSK-3b*, insulin may induce the hyperphosphorylation of τ-proteins in AD.[58] These processes as a whole increase the vulnerability of the ageing brain and facilitate the pathogenesis of late-onset sporadic AD.[59] The increased occurrence of insulin resistance in AD and the numerous mechanisms through which insulin may affect clinical and pathological aspects of the disease suggest that improving insulin effectiveness may have therapeutic benefit for patients with AD.

Recently, the thiazolidinediones, a novel class of agents, have been approved for human use; they influence insulin sensitivity and possibly also pancreatic β-cell function.[60,61] The thiazolidinediones are synthetic ligands that bind to the PPAR-γ and exert their action by activating transcription of genes that, among others, regulate adipocyte differentiation and adipogenesis as well as glucose and lipid metabolism. To date, the precise mechanisms underlying the actions of thiazolidinediones are largely unknown.[62] When given as monotherapy or in combination with sulphonylureas, metformin or insulin in patients with type 2 diabetes mellitus, the currently available thiazolidinediones (rosiglitazone and pioglitazone) ameliorate glycaemic control, by lowering fasting and postprandial blood glucose levels, and improve insulin sensitivity in placebo-controlled trials.[63,64] Mainly in preclinical studies, rosiglitazone and pioglitazone have demonstrated beneficial effects on cardiovascular risk factors associated with the insulin resistance syndrome, anti-inflammatory and other vascular effects.[62,64] Studies in AD have not been published as yet, but are underway.

2. Clinical Trials of Combination Therapy in AD

Although single-agent therapy has the advantage of simplicity, fostering patient compliance and allowing straightforward identification of the source of adverse effects, monotherapy also has substantial limitations. Many diseases are products of multiple

pathophysiological pathways. One drug blocking a single step in a complex pathogenic network often cannot block all crucial disease-propagating mechanisms. Combination therapy permits deployment of agents that block multiple targets, thus increasing the likelihood of arresting or delaying the pathogenesis of a disease. In addition, administering a single agent at high doses may lead to adverse effects and to stimulation of compensatory mechanisms that attenuate effectiveness, in contrast to administering combinations of agents at potentially lower doses. However, as a general summary, a drug that fails as monotherapy may be of benefit as a combination regimen. Also, in contrast to additive and synergistic beneficial effects, drugs in combination may show additive or synergistic adverse effects and/or unexpected antagonistic effects. The most conclusive method to determine whether a theoretically attractive combination of agents actually confers net added benefit *in vivo* is to conduct a phase III randomised, controlled, clinical trial in patients with the relevant disease.

2.1 Combination Therapy or Add-On Therapy for Treating or Preventing AD

Experimental investigations show that AChE inhibitors keep their therapeutic effect in combination with memantine. Furthermore, no interactions between the two substance groups of AChE inhibitor and memantine were observed.[65] Hartmann and Mobius[66] reported a surveillance study conducted among German physicians who, during routine clinical practice, treated patients with dementia with memantine in combination with an AChE inhibitor. The findings suggest that memantine in combination with AChE inhibitors has a good safety profile and is well tolerated. At present, the German Competence Network on Dementias, a research initiative supported by the German Ministry of Education and Research, is systematically investigating whether a combination therapy of galantamine and memantine is superior to monotherapy with galantamine or placebo regarding the prevention or slowing of the progression from mild cognitive impairment (MCI) to manifest AD. The study is a nationwide, multicentre, prospective, double-blind, randomised study with parallel group design. A second study is planned to investigate the efficacy of the same combination therapy in comparison with monotherapy with galantamine for mild-to-moderate AD. Results can be expected by 2007.

In the following subsection, the existing clinical trials of combination therapy or add-on therapy for treating or preventing AD are described. All these studies have been included in table II.

- A first US prospective randomised controlled study in patients with moderate to severe AD that investigated the effects of an add-on therapy with memantine to long-term ongoing donepezil medication reported positive effects on cognitive performance as measured by the SIB (table II).[67,68]
- Combined tacrine and estrogen replacement therapy in patients with AD was researched by Schneider and Farlow[69] (table II). The results provide evidence that prior and continuing estrogen replacement therapy may enhance responses to tacrine in women with AD.
- In a 28-week, randomised, double-blind study, 117 women with mild to moderately severe Alzheimer-like dementia (MMSE between 10 and 26) were randomly assigned to continuous hormone therapy (n = 59) or placebo (n = 58), while all receiving continuous treatment with rivastigmine (table II).[70] No significant difference was observed in the parameters assessing efficacy (cognitive function, global assessment, functioning and neuropsychiatric symptoms) and tolerance between the two groups. These data do not confirm the results of Schneider and Farlow[69] that suggested that estrogen might enhance the effect of cholinergic therapy in elderly women with AD.
- A placebo-controlled trial of selegiline, α-tocopherol, or a combination of both as treatment for AD was conducted by Sano et al.[28] (table II). Statistical analyses, which included the baseline score on MMSE as a covariate, showed a significant delay in the time to the primary outcome composite score (time to occurrence of any of the following: death, institutionalisation, loss of abil-

Table II. Studies of combination therapy or add-on therapy for treating or preventing Alzheimer's disease (AD). Only studies that assessed the effects of treatment on cognitive performance, Clinical Global Impression of Change (CGIC) or measures of activities of daily living (ADL) and behaviour are included in this table

Combination therapies	Sample size and design	Outcome variables	Study duration	Dose schedule	Effects	Comments
Memantine, donepezil[67,68]	403 patients with moderate to severe AD; RCT, add-on design	SIB, ADCS-ADL	24wk	Donepezil at stable doses (5 or 10 mg/day) + memantine 20 mg/day (10mg bid titrated over a 4-wk period) or Donepezil at stable doses (5 or 10 mg/day) + placebo	At wk 24, patients treated with memantine plus donepezil showed significant improvement ($p < 0.001$) in cognitive function (SIB), compared with patients treated with donepezil plus placebo, and showed significantly less decline ($p = 0.028$) in daily function (ADCS-ADL) [2-way analysis of covariance]	Patients were receiving donepezil for the immediate preceding 3mo (and throughout the study period) and were randomised to receive memantine or placebo
Tacrine, estrogen[69]	343 female patients with AD (MMSE: 10–26); RCT; add-on design	ADAS-cog, CIBIC	30wk	Placebo or ERT + placebo or Tacrine 40–160 mg/day + placebo or Combination of ERT and tacrine 40–160 mg/day	ITT analysis (two sample t test, adjusted by baseline scores): ADAS-cog: $p = 0.01$ (ERT and tacrine vs tacrine alone) CIBIC: $p = 0.15$ (ERT and tacrine vs tacrine alone)	Tacrine treatment as the only randomisation/ nonrandomised ERT treatment, differences in age and education among ERT users
Rivastigmine, HRT[70]	117 menopausal women with AD (MMSE: 10–26); RCT; add-on design	ADAS-cog, IADL, MMSE, NPI	28wk	Rivastigmine (up to 12 mg/ day) + HRT or Rivastigmine (up to 12 mg/ day) + placebo	No significant changes in favour of HRT were noted on any efficacy parameters (ITT analysis of HRT vs placebo in menopausal women treated with rivastigmine, Wilcoxon test)	Patients were receiving rivastigmine and were randomised to receive HRT or placebo
α-Tocopherol, selegiline[28]	341 patients with moderate severity of AD (CDR: 2); RCT; combination design	Time to the occurrence of any of the following: death, institutionalisation, loss of ability to perform basic ADL, or severe dementia (defined as a CDR of 3)	2y	Selegiline 5mg bid (n = 87) or α-Tocopherol 1000IU bid (85) or Combination of selegiline 5mg bid and α-tocopherol 1000IU bid (85) or placebo (84)	In analyses that included the MMSE baseline score as a covariate, there were significant delays in the time to the primary outcome for the patients treated with selegiline ($p = 0.012$), α-tocopherol ($p = 0.001$) and combination therapy ($p = 0.049$), compared with the placebo group (Kaplan-Meier estimation)	Combination therapy with α-tocopherol plus selegiline did not provide an additional benefit compared with either treatment alone
Donepezil, tocopherol[71]	130 patients with AD (MMSE: 10–24); retrospective chart review; combination therapy	MMSE	3y	Donepezil 5 mg/day (at least) + tocopherol 1000 IU/day (at least)	Average cumulative change in MMSE at the 1-yr follow-up ($p = 0.0097$), at the 3-yr follow-up ($p = 0.0382$) [independent samples t test]	Retrospective chart review

Continued next page

Table II. Contd

Combination therapies	Sample size and design	Outcome variables	Study duration	Dose schedule	Effects	Comments
Selegiline and tacrine, physostigmine[72]	10 patients with AD; case series, crossover design, add-on therapy	ADAS-cog, MMSE	4wk	Tacrine + selegiline 5mg bid or physostigmine + selegiline 5mg bid; then Tacrine + placebo or physostigmine + placebo; or Tacrine + placebo or physostigmine + placebo; then Tacrine + selegiline 5mg bid or physostigmine + selegiline 5mg bid	ADAS-cog: p = 0.04 (Wilcoxon test), first period effect for selegiline compared with placebo; MMSE: p = 0.55 (nonsignificant Wilcoxon test)	Small number of patients; change scores were analysed for the comparison of the groups that first received selegiline with all groups that first received placebo
AChE inhibitor and α-lipoic acid[73]	9 patients with AD and related dementias; case series; open, uncontrolled study; add-on design	MMSE, ADAS-cog	337 ± 80 d	AChE inhibitor + α-lipoic acid 600mg	Stabilisation of cognitive functions (constant scores in MMSE and ADAS-cog) for at least 337 days	α-Lipoic acid was added to patients' existing standard treatment with AChE inhibitors; small sample size, short duration, lack of placebo control group, unblinded dosage
Donepezil and d-cycloserine[74]	5 patients with AD; case series; open uncontrolled study; add-on design	MMSE, ADAS-cog, IADL, CGIC	4wk	Long-term donepezil 5–10 mg/day treatment for at least 8 months + D-cycloserine 100 mg/day	No statistically significant effect found with any outcome measures examined at follow-up (MMSE p = 0.1, ADAS-cog p = 0.08; related sample t-test)	D-cycloserine was added to patients' existing treatment with donepezil; small sample size, short duration, lack of placebo control group, unblinded dosage
Pravastatin, tocopherol[75]	41 men and women with low-density lipoprotein cholesterol, cognitively intact, aged ≥70y; RCT, add-on therapy, crossover study	GHPQ, GDS, IADL, Digit Symbol Test, SDS	12mo	Pravastatin 20 mg/day for 6mo followed by pravastatin 20 mg/day + tocopherol 400 IU/day Tocopherol 400 IU/day + placebo for 6mo, followed by tocopherol 400 IU/day + pravastatin 20 mg/day	No significant changes occurred in any of the health-related quality of life or cognition measures after 6 or 12mo of therapy with pravastatin, tocopherol or their combination (assessed by nonparametric U-statistics)	No AD patients

AChE = acetylcholinesterase; **ADAS-cog** = Alzheimer's Disease Assessment Scale – cognitive subscale; **ADSC-ADL** = Alzheimer's Disease Cooperative Study-ADL Inventory; **bid** = twice daily; **CDR** = Clinical Dementia Rating; **CIBIC** = Clinician's Interview-Based Impression of Change; **ERT** = estrogen replacement therapy; **GDS** = Geriatric Depression scale; **GHPQ =** Global Health Perception Question; **HRT** = hormone replacement therapy; **IADL** = Instrumental Activities of Daily Living measured on the Assessment of Living Skills and Resources questionnaire; **ITT** = intention to treat; **IU** = international units; **MMSE** = Mini-Mental State Examination; **NPI** = Neuropsychiatric Inventory; **RCT** = randomised controlled clinical trial; **SDS** = Sleep Dysfunction Scale; **SIB** = Severe Impairment Battery.

ity to perform basic activities of daily living, or severe dementia) for patients treated with selegiline, α-tocopherol or combination therapy of both compared with the placebo group. Interestingly, there was a smaller, but not significantly smaller, effect with the combination therapy than with each compound alone.

- A retrospective chart review was performed on 130 patients from a memory disorders clinic to examine the long-term effects of combination therapy with donepezil and tocopherol on patients with AD (table II).[71] Patients were included if they met the Alzheimer's Disease and Related Disorders Association criteria for probable AD and had taken at least 5mg donepezil and at least 1000IU tocopherol daily. In the MMSE, taken annually, patients declined at a significantly lower rate compared with the Consortium to Establish a Registry for Alzheimer's Disease data. Prospective trials comparing combination therapy of donepezil and tocopherol with single drugs are necessary.
- Schneider et al.[72] designed a double-blind crossover pilot study of selegiline combined with a cholinesterase inhibitor (tacrine or physostigmine) in ten patients with AD. Selegiline was associated with significant improvement in scores on the ADAS-cog, suggesting possible additive effects of 1-deprenyl to the effects of cholinesterase inhibitors.
- In a case series by Hager et al.,[73] ALA 600mg was given daily to nine patients with AD and related dementias who were receiving a standard treatment with AChE inhibitors over an observation period of, on average, 337 ± 80 days. The treatment led to a stabilisation of cognitive functions in the combination therapy group, demonstrated by constant scores in two neuropsychological tests (MMSE and ADAS-cog). Despite the fact that this study was small and not randomised, this provided a first indication that treatment with ALA might be an add-on therapy option for AD and related dementias.
- Falk et al.[74] reported a case series of D-cycloserine added to donepezil in the treatment of AD. D-cycloserine alone had been associated with improvement in scores on the ADAS-cog in AD patients when given 100 mg/day.[76] Falk et al.[74] presented a small, open-label case series of five patients with AD treated for 1 month with D-cycloserine as add-on therapy to donepezil. Each patient had taken donepezil for at least 8 months. There was no statistically significant effect with any outcome measures examined at follow-up (e.g. MMSE, ADAS-cog, CGI and Instrumental Activities of Daily Living [IADL] measured on the Assessment of Living Skills and Resources questionnaire). The study is very limited in size and duration and its lack of placebo group and unblinded dosage precludes any firm conclusions being drawn.
- Carlsson et al.[75] investigated health-related quality of life and long-term therapy with pravastatin and tocopherol in older adults with hypercholesterolaemia. Investigating the relationship between the use of HMG-CoA reductase inhibitors and quality-of-life measures in older adults is becoming increasingly important as the potential indications for HMG-CoA reductase inhibitor therapy expand. Measures of health perception, depression, physical functioning, cognition (Digit Symbol Substitution Score) and sleep did not change after 12 months' therapy with pravastatin and tocopherol (table II). This trial is not a study of AD patients, but it is important for the potential role of HMG-CoA reductase inhibitor and tocopherol in the prevention of AD, since epidemiological studies have shown that treatment with HMG-CoA reductase inhibitors may reduce the prevalence of dementia in comparison with the normal population.[52,53]

2.2 Combination Regimens For Behavioural and Neuropsychiatric Symptoms of AD

Depending on the stage of disease, patients with dementia show considerable changes in behaviour, including anxiety, grief, depression, aggressiveness, agitation, hyperactivity, delusions, and hallucinations. Such behavioural disturbances may result directly from neurodegeneration, but may also be a

psychological reaction to cognitive loss and subsequent loss of competence. Milieu therapeutic attempts as well as psychopharmacological treatment (including medication that improves cognition) can influence symptoms positively.[77,78] Antipsychotics are among the most frequently used psychotropic drugs in AD, but they are also assumed to be misused.[79] Psychotic symptoms are common in AD, but essential questions remain about the nature of 'psychosis' in these patients. Given an already increased risk of tardive dyskinesia in this population, conventional antipsychotics have been overused in managing AD. The newer atypical antipsychotics should have a much lower risk for tardive dyskinesia, but in some patients cardiac problems might complicate the use of these atypical antipsychotics.[80]

Concomitant use of antipsychotics and antidementia drugs are common in elderly dementia patients.[81] However, generally favourable effects of such a combination still needs to be demonstrated.

A small open-label study with 12 inpatients with dementia of the Alzheimer's type investigated donepezil as add-on treatment to perphenazine for psychotic symptoms.[82] This trial revealed significant differences between perphenazine 16mg alone and perphenazine 8mg plus donepezil 5mg in the Positive and Negative Symptoms scale, CGI and MMSE. Donepezil augmentation of antipsychotics may be appropriate for those patients with AD and psychotic symptoms. There is a need for larger, longer-term studies with double-blind control to confirm the efficacy of donepezil for AD patients with psychotic symptoms.

A combination of donepezil and gabapentin helped to control behavioural symptoms in two patients with AD.[83] This effect of gabapentin in controlling behavioural symptoms in AD should be confirmed by well designed, controlled studies.

To explore the steady-state pharmacokinetic profile after coadministration of galantamine and risperidone, an open-label, randomised drug-drug interaction study was conducted in 16 healthy elderly subjects, aged ≥60 years.[84] The results showed that risperidone, when administered with galantamine, did not change the bioavailability of galantamine at steady state. Galantamine and risperidone were both well tolerated when administered either alone or together. It is concluded that no dose adjustment for either risperidone or galantamine is necessary when these two drugs are coadministered.

Extrapyramidal symptoms (EPS) due to the combination of risperidone and donepezil have been investigated by Liu et al.[85] in a case report. In the described case, the patient, who had been receiving donepezil 5 mg/day for 12 days, developed severe EPS abruptly following the coadministration of risperidone 1 mg/day for 3 days. The balance between acetylcholine and dopamine in the striatum is important in controlling EPS. Therefore, increased acetylcholine might lead to an imbalance between acetylcholine and dopamine and subsequent increased susceptibility to dopamine blockade.

A randomised, open-label trial assessing safety and pharmacokinetic parameters of coadministration of rivastigmine (3–12 mg/day) with risperidone (0.5–2 mg/day) in AD patients (n = 65) with behavioural disturbances was described by Weiser et al.[86] The preliminary results indicate that coadministration of rivastigmine and risperidone is safe. Although increased cholinergic transmission is expected to worsen EPS in coadministration of antidopaminergic drugs, this did not occur in this open-label study. Confirmation of these results in large clinical studies is required.

Finkel et al.[87] investigated sertraline augmentation in outpatients treated with donepezil. Combining the two drugs in a population of nondepressed AD patients with behavioural impairment was well tolerated and had a good safety profile. A *post hoc* analysis showed significant improvement in scores on the CGI-Improvement (CGI-I) scale for donepezil plus sertraline compared with donepezil plus placebo, based on a linear mixed model analysis.

2.3 Combination Regimens in Mild Cognitive Impairment

MCI is defined as primary decline in episodic memory, isolated or associated with a decline in

intellectual abilities without functional disabilities. The efficacy of any pharmacological therapy in patients with MCI has not been proven; however, there are several phase III studies with different classes of agents underway. Equally, it has not yet been investigated whether a combination therapy, that aims at modifying several parts of the complex pathophysiological cascades in the brains of patients with AD who are clinically in the state of MCI, may be more beneficial than the generally unsatisfactory effects of the secondary preventive AD treatment options tested to date. In Germany, the Competence Network of Dementias is running a project in which the effects of a combination therapy of memantine and galantamine will be compared not only with placebo, but also with galantamine effects alone. To corroborate a potential 'disease-modifying effect', and to separate it more reliably from a purely symptomatic effect, the disease progression will be tracked by clinical measures (Clinical Dementia Rating) and also by using volumetric magnetic resonance imaging techniques and proton magnetic resonance spectroscopy.

3. Conclusion

The possibility of developing a 'cocktail' of effective or maybe even neuroprotective agents for AD has gained widespread attention among researchers and the lay public.[88] However, the difficulty in determining which agents to include in such a 'cocktail' shows the limitations of a simple empirical as well as an experimental approach to the problem. We have described six pathophysiological cascades with potential relevance to disease progression in AD, for which drugs are already approved for human use and available. Several more pathways may be assumed to act in the pathophysiology of AD for which drugs are not yet available, e.g. drugs acting on amyloid formation or τ-hyperphosphorylation.

While the number of individual agents for a condition increases arithmetically, the number of promising agent combinations increases exponentially. Taking only one agent and one dose from the drug classes described in section 1, the number of possible combination regimens is 256 (2^8). Head-to-head testing of all combinations of one agent/dose from each category would require over 10 000 trials and over 8 million patients.[89] As a consequence, theoretical as well as practical considerations are needed to guide us in reducing the possible number of combinations and to select promising combination targets. At present, only a very small number of approaches in AD therapy have been shown to be effective in large clinical studies, and only these should be considered in combination therapies.

In numerous other chronic diseases (e.g. congestive heart failure,[90] chemotherapy of certain cancers,[91] diabetes,[92] Parkinson's disease,[93] multiple sclerosis[94] and epilepsy[95]), it has been shown that a combination of several different classes of drugs, which act on distinct aspects of the pathophysiology, is superior to one drug alone in terms of either the magnitude of symptomatic effect or duration of effect. In clinical practice, this approach has already frequently been pursued because of the lack of a curative treatment in AD, which limits life expectancy and leads to severe disability. In this context, the risks involved in polypharmacy for elderly patients (which is prevalent in this population) need to be considered. Although there are many instances of 'rational polypharmacy', any use of multiple medications may increase the risk of adverse effects, drug interactions, patient noncompliance with treatment and medication errors. Polypharmacy has also been associated with elevated mortality rates in patients with schizophrenia.[96]

In terms of practical antidementia therapy, AChE inhibitors are presently the drugs of choice for the treatment of AD. Despite pharmacological differences in their mechanism of action, there is no convincing evidence at present that one AChE inhibitor shows superior efficacy over another. Any combination therapy will most likely include only agents that have already shown some efficacy as a monotherapy (because of regulatory standards, unforeseeable pharmacological interaction and commercial interest). In the same way, newly developed drugs are primarily tested for use as monotherapy rather than as combination therapy. However, any

combination regimen will need to consider AChE inhibitors, either as part of the treatment combination or as a comparison, because they are the gold standard in AD.[6] Thus, it is highly likely that AChE inhibitors will be part of any combination regimen; this approach has in fact been followed by all except one[28] of the presently available combination therapy studies in AD patients.[28]

Furthermore, it is highly likely that any combination therapy will only consist of two classes of agents in order to relate efficacy and/or tolerability of the combination regimen to the respective monotherapy in a design that contains a manageable number of treatment arms. As guidance for a rational choice of a combination therapy consisting of two antidementia drugs, several perspectives appear important:

1. Pharmacological targets
- the combination regimen should act on most distinct pathophysiological cascades
- the combination regimen should act on most homogeneous pathophysiological cascades

2. Timing of the intervention (in close relation to the target study population)
- primary preventive (healthy elderly)
- secondary preventive (disease progression; presymptomatic or early symptomatic patients, e.g. in MCI)
- symptomatic (patients with manifest AD)

3. Targeting symptoms
- cognitive symptoms
- behavioural symptoms

Because of the incomplete understanding of the pathophysiology of AD, it appears likely that a combination regimen will contain classes of agents that act on most distinct aspects of AD pathophysiology to maximise efficacy. However, at present there are no data from either cellular models or animal models that support this hypothesis. On the other hand, it may not be irrational to choose two AChE inhibitors as a combination therapy to obtain a larger responder rate with respect to the cognitive effects of these drugs or to minimise adverse effects. Considering the timing of the intervention, it may be most attractive to aim at delaying or preventing disease progression rather than maximising symptomatic improvement for a limited period of time. Monotherapeutic approaches to delay disease progression in patients with manifest AD have generally been unsuccessful, with one potential exception (tocopherol),[28] although several promising drug candidates have been investigated. Thus, as a logical extension from these results, either a change of the study population (to investigate patients with the earliest symptoms of AD, e.g. MCI patients) or a combination therapy might be pursued in order to achieve better efficacy. Finally, considering the target symptoms in patients with manifest AD, the most important spectrum of symptomatology is generally believed to be the cognitive deficits, but behavioural (affective as well as delusional/hallucinatory or psychomotor) symptoms cause excessive impairment in competence, and therefore need to be treated with equal vigour. In psychiatric diseases, e.g. depression and schizophrenia, combination therapy is common, but not undisputed.[97-100]

All six studies that targeted behavioural symptomatology in AD show limitations in design, subject characteristics, duration of treatment and lack of detailed outcome measures.[82-87] Therefore, the initial claims need to be collaborated by larger, well designed, randomised, controlled trials.

The most common mode of polypharmacotherapy in psychiatry is 'add-on' or adjunctive pharmacotherapy. The prevalence of this practice has been reported to exist in 28–75% of diverse patient populations and study designs.[101] Most frequently, patients are treated with a stable dose of drug A, and to increase efficacy or reduce relapse probability, drug B is added. The alternative approach of a 'true' combination therapy is to initiate treatment of *de novo* patients with a combination of drugs A and B immediately. For the treatment of dementia, there are several drawbacks for an 'add-on' approach, e.g. the chronic progressive nature of the disease, which leads to an increasing destruction of neuronal networks, and the limited efficacy of available drugs in terms of magnitude of effect as well as responder rate. Thus, to best assess a potentially synergistic effect of a combination regimen

over monotherapy, a 'true' combination therapy should be pursued. Despite this, six of the available combination trials in AD to date have applied an 'add-on' design.[67-70,72-74] Among those, four have reported positive or stabilising effects of the add-on therapy on cognitive measures.[67-69,72,73]

Altogether, empirical evidence for the efficacy of combining antidementia drugs is far too limited to draw firm conclusions. The practice of augmenting AChE inhibitors with other potentially neuroprotective drugs has little empirical or theoretical support. The risks of add-on therapy strategies have not been studied systematically. No study has examined the economic impact of combination treatment. Thus, further trials of antidementia combination therapies are needed before this currently unsupported practice can be recommended. The controlled study of combination therapy in the treatment of AD may hopefully lead to the development of optimal and empirically based treatment algorithms for achieving the maximum benefit for the patients.

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