Combination Therapies for Treating Alzheimer's Disease

a report by

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The pathobiology of Alzheimer's disease (AD) is extremely complex and not yet fully understood. AD is characterized by the clinical syndrome of a slowly progressive dementia and the classic neuropathological findings of amyloid plaques, neurofibrillary tangles, and neuronal death.[1] These histological features develop in heterogeneous patterns and in people with varying genetic predisposition, nutritional histories, and exposure to either potentially harmful or helpful environmental agents.[1]

The precise chain of events leading to the characteristic pathology is not known, but it is likely to involve a cascade of events, including oxidative stress, excitotoxic damage, altered cell-cycle regulation, pathological inflammation, oxidative and excitotoxic damage, failure of trophic responses, demyelination, apoptosis, and the failure of neurotransmitter function, among others. In this context, it makes sense to consider the therapeutic potential of combining agents with different mechanisms of action in the hope that impinging on multiple aspects of the illness process may afford a greater benefit than that seen with a single agent.

What follows is a somewhat selective overview of the available clinical evidence as we see it. The reality is that relatively few studies combine what we now might consider to be the most promising strategies: most data come from earlier studies addressing putative neurotransmitter dysfunction. It is important to note that some studies were true 'combination' studies, in which multiple agents were co-administered simultaneously, and others were 'add-on' designs, in which case a second agent was administered some time after a prior therapy was initiated. This distinction is methodologically important.

Cholinergics

The earliest and most obvious efforts addressed what might happen if different cholinergic therapies were combined. There is compelling evidence for structural and functional cholinergic impairment in AD, and emerging evidence that cholinergic therapeutics might confer clinically discernible benefit.

Tacrine and Lecithin

What may have been the first combination study in AD addressed the effects of tetrahydroaminoacridine (THA) combined with lecithin.[2] Ten patients diagnosed with 'primary progressive dementia' were studied in four trials of random order: placebo, lecithin alone, THA alone, or a combination of lecithin and THA. Medications were administered in divided doses of THA 90mg and/or lecithin 180mg at three intervals over a 14-hour period. Cognitive testing was performed two hours after the final dose. Each of the four studies was separated by a minimum of 56 hours. While highly topical for its time, the study was essentially negative.

In a double-blind, cross-over study with two sequential randomized periods of treatment lasting for eight weeks each, Gauthier et al. evaluated the combination of the maximal tolerated dose of THA (up to 100mg/day) plus lecithin 4.7g/day in 52 AD patients.[3] This study showed no clinical benefit to combination use of THA and lecithin as measured by global ratings, a functional scale, and a behavioral scale. A double-blind cross-over study with four-month follow-up by Chatellier and Lacomblez randomized 67 AD patients to tacrine (dose ranging from 50 to 125mg/day) and tacrine (1,200mg/day) versus placebo.[4] There was no significant improvement on the Mini Mental State Examination (MMSE) or the Stockton geriatric rating scale. A fourth, small, double-blind study in 10 patients showed no therapeutic effect.[5]

Acetylcholinesterase Inhibitors and Acetyl-L-Carnitine

Acetyl-L-carnitine (ALC), an intracellular carrier of acetyl groups that are necessary for acetylcholine synthesis (which was thought to have the potential to enhance the effect of acetylcholinesterase inhibitors [AChEIs]), was tested in combination with an AChEI (either donepezil or rivastigmine).[6] After a three-month period on an AChEI only, 38% of patients were classified as 'responders' and 48% as 'non-responders' as determined by changes in the MMSE and Alzheimer's Disease

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Assessment Scale-Cognitive (ADAS-Cog). The 21 patients who were non-responders entered a three-month open-label study of ALC 2g/day in addition to the AChEI. The proportion of responders increased from 38% after treatment with AChIE alone to 50% on combination therapy. This study reports a positive response rate after the addition of ALC, but further studies have not yet been performed.

Hormone Replacement Therapy

Substantial epidemiological and experimental evidence suggested that estrogen therapy might benefit women with AD. Rigaud et al. examined whether hormone replacement therapy (HRT) could show benefit when combined with the cholinesterase inhibitor rivastigmine in menopausal women with mild to moderate AD.[7] One hundred and seventeen patients treated with rivastigmine were randomized to HRT (estrogen and progesterone) versus placebo for 28 weeks. Outcome measures included the ADAS-Cog, MMSE, Global Deterioration Scale (GDS), Clinical Global Change-plus (CGC-Plus), Neuropsychiatric Inventory (NPI), and Instrumental Activities of Daily Living (IADL). There was no discernable benefit to combining HRT with rivastigmine.

Antioxidants

Antioxidant therapy held considerable interest as a potential form of therapy for AD. Several studies attempted to examine its benefits in various combinations with other agents.

Selegiline and Alpha-tocopherol (Vitamin E)

Selegiline, a monoamine oxidase inhibitor, inhibits oxidative deamination and therefore may reduce neuronal damage and have other positive effects on AD. Alpha-tocopherol (vitamin E) is a lipid-soluble vitamin that interacts with cell membranes, traps free radicals, and is thought to interrupt the sequence of reactions that damages cells.

One of the larger combination studies that has been conducted, the Alzheimer's Disease Co-operative Study, addressed whether selegiline, alpha-tocopherol, or a combination of the two could slow the course of clinical decline in AD.[8] AD patients of moderate severity, as measured by a Clinical Dementia Rating score of 2, from 23 participating sites were randomized to one of four groups (selegiline 10mg, alpha-tocopherol 2,000IU, a combination of selegiline and alpha-tocopherol, or placebo) over a two-year period. The primary outcome measure for these 341 patients was the time to reach one of four possible end-points: death, institutionalization, severe dementia defined as a Clinical Dementia Rating score of 3, or loss of the ability to perform at least two of three basic activities of daily living (eating, grooming, and using the toilet).

The results of undjusted comparisons of selegiline with placebo, alpha-tocopherol with placebo, and combined treatment with placebo were not statistically significant. When the baseline score on the MMSE was included as a co-variate, a significant delay in the primary outcome was found with seleginile (risk ration 0.57; p=0.012), alpha-tocopherol (risk ratio 0.47; p=0.001), and combination therapy (risk ratio 0.69; p=0.049). There was no additive benefit in the combined treatment group. The estimated increase in median survival was 230 days for the patients receiving alpha-tocopherol, 215 days for those receiving selegiline, and 145 days for those receiving both compared with the patients receiving placebo. There was no improvement in cognition in any of the groups.

Numerous clinical trials with selegiline have been performed with variable results and insufficient evidence to justify routine clinical use in AD.[9] A 2005 meta-analysis[10] suggested an increase in all-cause mortality with alpha-tocopherol. Together with the results of the Alzheimer's Disease Co-operative Study trial, these findings have led to a marked reduction in the use of these agents, and the combination has not been advocated by any major consensus statements.

Donepezil and Alpha-tocopherol

A retrospective study[11] investigating 40 AD patients who were on combination therapy with donepezil ≥5mg daily and vitamin E ≥1,000IU daily for at least one year were compared with historical data of patients with no AD treatment obtained from the 1986–1996 Consortium to Establish a Registry for Alzheimer's Disease (CERAD)[12] database, which was created prior to the availability of these treatment options. The average MMSE of patients on donepezil and vitamin E declined at a significantly lower rate at the one-, two, and three-year follow-up compared with historical data from the CERAD. This study had significant inherent limitations.

Multivitamins

The combination of vitamin B_{12} 0.5mg and an over-the-counter nutritional supplement containing folic acid 1mg and vitamin B_6 5mg (other vitamins and iron were also included) was tested as an adjunct to an AChEI in mild to moderate AD in 89 patients over 26 weeks.[13] The aim was to determine whether oral multivitamin supplementation containing vitamins B_6 and B_{12} and folic acid would improve cognitive function and reduce serum homocysteine levels in patients with mild to moderate AD. Although no statistical significance was found on primary or secondary outcome measures, there was a significant decline in the serum homocysteine concentration in the treatment group.

Selective Serotonin Re-uptake Inhibitors

Sertraline

Sertraline has been assessed as an adjunct to donepezil in the treatment of behavioral symptoms in outpatients with AD (MMSE between 8 and 23).[14] AD patients with an NPI total score >5 (minimum severity score 2 in at least one domain) were treated with donepezil 5–10mg for eight weeks, and then randomized to 12 weeks with sertraline 50–200mg or placebo. The primary outcome measures were the 12-item NPI and the Clinical Global Impression Improvement (CGI-I) and Severity (CGI-S) scales. The treatment group consisted of 124 patients, and 120 patients received placebo. There were no statistically significant differences on outcome measures. *Post hoc* analysis suggested a 'modest' improvement on the CGI-I score in patients in the treatment group. Additionally, in a sub-group of patients with moderate to severe behavioral and psychological symptoms—as defined by a Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD) three-item aggressiveness, affective disturbance, and anxiety/phobias score ≥6—of those on sertraline, 60% achieved a positive response compared with 40% (p=0.006) of those on placebo. A positive response was defined as a ≥50% reduction in a four-item NPI-behavioral subscale. Sertraline was generally well tolerated. Diarrhea was significantly more common (p<0.05) in the donepezil plus sertraline group compared with the donepezil plus placebo group. This study was insufficient to define best practice with respect to the use of this combination strategy.

Fluoxetine

One preliminary study has been performed to assess the effect of a fluoxetine as an adjunct to an AChEI in AD for 12 weeks.[15] One hundred and twenty-two patients with mild to moderate AD (MMSE 10–24) were randomized to one of three arms: fluoxetine plus rivastigmine, rivastigmine alone, or placebo. There was a significant improvement in MMSE and Wechsler Memory Scale 3rd Edition (WMS-III) in both the combination group and the rivastigmine alone group, but there was no difference between these two groups. These two groups also significantly improved on the Lawton and Brody ADL scale,[16] with a statistical significance between the two groups favoring the combination group. On the Hamilton Depression Scale-17 (HAM-17), both treatment groups had significant benefit compared with placebo, but were not clinically significant compared with each other.

Memantine and Cholinergic Agents

Glutamatergic neurons are ubiquitous in the central nervous system (CNS) and are involved in learning, memory, and shaping neuronal architecture. They are the primary CNS excitatory neurons, and are predominantly 'projection' neurons, which provide information about one brain area to another. In AD, there is thought to be an overstimulation of the glutamatergic N-methyl-D-aspartate (NMDA) receptor. This abnormal glutamate activity leads to an excessive cellular influx of calcium and sustained low-level activation of NMDA receptors. This is thought to lead to impaired learned and neuronal death following chronic insult.[17] Memantine, an NMDA receptor antagonist, was shown to be efficacious in moderate and severe AD as monotherapy.[18,19] Pre-clinical studies show no inhibition of AChE by memantine, and no binding to muscarinic receptors.[20–22] There is no pharmacokinetic or pharmacodynamic interaction between memantine and donepezil,[23] so it was quite logical to study memantine together with various cholinergic therapies.

An open-label study suggested that the combination of memantine and cholinesterase inhibitors was well tolerated.[24] A subsequent large trial in moderate to severe AD examined the efficacy of memantine in patients already receiving stable treatment with donepezil. This double-blind, placebo-controlled trial randomized 404 AD patients with an MMSE of 5–14 to memantine versus placebo over a 24-week period.[25] The primary outcome measures were change from baseline on a cognitive measure, Severe Impairment Battery (SIB), and a modified 19-item AD Co-operative Study-Activities of Daily Living Inventory (ADCS-ADL19). Secondary outcomes included a Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC-Plus), the Neuropsychiatric Inventory, and the Behavioral Rating Scale for Geriatric Patients (BGP Care Dependency Subscale). There was statistical significance favoring memantine in all primary and secondary outcomes, showing efficacy on cognition, activities of daily living, global outcome, and behavior. Furthermore, memantine was shown to be safe and well tolerated. More participants (n=25 [12.4%]) in the placebo-treated group discontinued treatment prematurely because of adverse events than in the memantine group (n=15 [7.4%]). The most common statistically significant adverse events in the memantine group compared with placebo were confusion (p=0.01) and headache (p=0.09). In contrast, there were lower incidences of diarrhea and fecal incontinence in the memantine group compared with the placebo group.

A *post hoc* analysis of this same study examined the ADCS-ADL19 in more detail.[26] Patients receiving combination therapy had statistically significantly less decline in ADLs, with item analysis showing that effects were on grooming, using the toilet, conversing, watching television, and being left alone. The addition of memantine to an AChEI was recently studied in patients with mild to moderate AD (MMSE 10–22).[27] A total of 433 patients who were on stable doses of an AChEI (donepezil, rivastigmine, or galantamine) were randomized to placebo versus memantine 20mg once daily for 24 weeks. Although memantine was well tolerated, there were no statistically significant differences in primary (ADAS-cog and CIBIC-Plus) or secondary (ADCS-ADL(23), NPI, and MMSE) outcome measures.

Conclusions

Most of the combination or add-on studies failed to show significant benefit or define best practice. Perhaps the most widely cited data come from studies in patients with mild to moderate AD, where the available evidence indicates that memantine can be used alone or in combination with a cholinesterase inhibitor, but we do not know whether one approach is truly superior to the other (and we note that donepezil alone among the cholinesterase inhibitors is also US Food and Drug Administration [FDA]-approved for the treatment of severe AD). We also do not know whether the order in which these two classes of agents are administered is important. There are many other unanswered questions, including whether the combination of memantine with other agents might show benefit and whether benefit can be seen in non-AD dementias.

The future of the study of combination therapy will inevitably be far different from its past. More novel agents, such as those attempting to normalize aberrant amyloid processing, will be combined with currently approved neurotransmitter-based therapies, and within the next five years we will begin to see trials combining novel strategies (e.g. normalizing tau phosphorylation and regulating amyloid processing)—strategies suggested by the promising pre-clinical work of Ashe, Laferla, and others.[28,29] ■

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