ABSTRACT

As cholinesterase inhibitors and N-methyl-D-aspartate antagonists become part of the standard of care for Alzheimer's disease (AD), pharmacists are now encountering new approaches to AD treatment by physicians, in addition to patients experimenting with over-the-counter agents, dietary supplements, and nutraceuticals. Clinicians and researchers are considering combination therapy for AD treatment, with the hope and expectation of additional benefits beyond monotherapy (eg, additive or synergistic effects). This article discusses the published data on combination pharmacologic therapies, including dietary supplements (or nutraceuticals) that are frequently used by patients but may not be reported to the physician or pharmacist. The most commonly used nutraceutical is Ginkgo biloba. Several other types of therapies have been tested in recent years, in an attempt to address other aspects of the amyloid cascade (eg, metal chelators, β- and γ-secretase inhibitors, amyloid antiaggregants, and dietary changes). These treatments have not yet shown success in the treatment or prevention of AD or are in preclinical studies. While we attempt to use drugs or synthetic analogs to address the many components of the AD pathophysiology, medical technology now brings several other avenues to address the pathophysiology of AD through more sophisticated means, such as vaccination against Aβ, gene therapy, and surgical intervention. (Adv Stud Pharm. 2005;2(5):191-198)

NEW DIRECTIONS IN THE PREVENTION AND TREATMENT OF ALZHEIMER'S DISEASE

Manju Beier, PharmD, FASCP*

As cholinesterase inhibitors and N-methyl-D-aspartate (NMDA) antagonists become part of the standard of care for Alzheimer's disease (AD), pharmacists are now encountering new approaches to AD treatment by physicians, in addition to patients experimenting with over-the-counter herbal agents/dietary supplements (sometimes referred to as nutraceuticals). Clinical researchers are attempting to study the effects of these combinations in a systematic way, but the literature to date is more anecdotal or descriptive than methodical. Nonetheless, the studies and reports of combination therapies provide some insight into possible new approaches to AD treatment.

COMBINATION THERAPIES

With the safety and efficacy of the cholinesterase inhibitors and memantine well established, it is not surprising that clinicians and researchers are considering combination therapy for the moderate to severe stages of AD. Combination therapy would be expected to have additional benefits beyond monotherapy for several reasons. The mechanisms of action of the cholinesterase inhibitors are different from memantine, thus combination therapy may have additive or even synergistic effects on AD pathogenesis. The cholinesterase inhibitors are approved for mild to moderate AD, whereas memantine is approved for moderate to severe AD, thus they could be used together during the more moderate to advanced stages of the disease. Combination therapy may also allow for dose reduction of a poorly tolerated drug by adding on a second drug to complement it, as is sometimes done with other psychiatric disorders. This attempt at “rational comedication” is an established strategy for many other chronic illnesses, such as human immunodeficiency virus infection, hypertension, certain types of cancer, and migraine.

Several new classes of drugs are under investigation for treating different aspects of the β-amyloid cascade,
as reviewed by Cummings—amyloid metabolism, excitotoxicity, oxidative stress, neuroinflammation, neurotransmission, and nerve growth. Examples are shown in Table 1. Some of the drugs (eg, nonsteroidal anti-inflammatory drugs, statins, vitamin E, antidepressants, antipsychotics, and mood stabilizers) are discussed earlier in this monograph by Drs Levin and Jackson-Siegel.

**COMBINATION: PHARMACOLOGIC PLUS PHARMACOLOGIC AGENTS**

The most frequent pharmacologic combination for AD is memantine in combination with a cholinesterase inhibitor. A postmarketing surveillance study was conducted in Germany of patients receiving memantine in combination with any cholinesterase inhibitor (although donepezil was used in 84% of the study patients). Most of the patients (77%) had AD, but those patients with other types of dementia were also included. The drug combinations were well tolerated in 98% of the study patients over 4 months of observation; no serious drug reactions were reported. Physician records of global benefit were rated as improved (54%) or stable (39%) in most of the patients, supporting the safety of this combination and suggesting an additive benefit.

In the literature to date, donepezil has been the most frequently used cholinesterase inhibitor with memantine. In healthy volunteers, the combination of memantine and donepezil incurs no significant pharmacokinetic interaction. Tariot et al conducted the first randomized, double-blind, placebo-controlled study of memantine in combination with donepezil. Patients with moderate to severe AD who were on stable doses of donepezil (mean dose of 9.25 mg/day or 9.49 mg/day in the memantine and placebo groups, respectively) received memantine up to 20 mg/day for 24 weeks (n = 322). Those patients in the memantine treatment group experienced significantly better outcomes than the placebo group in measures of cognition, activities of daily living, global outcome, and behavior. Measures of cognitive impairment were above baseline during the entire study for the memantine group, whereas those patients in the placebo group deteriorated (Figure). Measures of activities of daily living declined in both groups, but significantly more in the placebo group. A total of 55% of

**Table 1. Alzheimer’s Disease Treatments Under Investigation and Their Respective Therapeutic Targets**

<table>
<thead>
<tr>
<th>AD Pathophysiologic Mechanism as Therapeutic Target</th>
<th>Drug Treatment</th>
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<tr>
<td>Neurotransmission</td>
<td>Cholinesterase inhibitors</td>
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<tr>
<td>Excitotoxicity</td>
<td>Memantine</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td><em>Ginkgo biloba</em>, vitamin E; selegeline</td>
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<tr>
<td>Neuroinflammation</td>
<td>NSAIDs</td>
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<tr>
<td>Neurotrophic factors</td>
<td>Estrogen; nerve growth factor</td>
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<tr>
<td>Amyloid metabolism</td>
<td>HMG CoA reductase inhibitors (statins); β- and γ-secretase inhibitors</td>
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</tbody>
</table>

AD = Alzheimer’s disease; HMG CoA = 3-hydroxy-3-methylglutaryl coenzyme A; NSAIDs = nonsteroidal anti-inflammatory drug.

Adapted with permission from Schmitt et al. CNS Drugs. 2004;18:827-844.

**Figure. Measures of Cognition and Activities of Daily Living in the Memantine Plus Donepezil Clinical Trial**

LS = least squares; SIB = severe impairment battery (a measure of cognition). Reprinted with permission from Tariot et al. JAMA. 2004;291:317-324.
the memantine group was rated as improved or unchanged versus 45% of the placebo group. Dropout rates also favored memantine (15% vs 25% with placebo). Interestingly, several of the adverse events were more frequent in the placebo group than the memantine group, such as agitation, dizziness, accidental injury, upper respiratory tract infection, diarrhea, and fecal incontinence (Table 2). It is also interesting that more patients in the placebo group than in the memantine group discontinued prematurely because of adverse events (12.4% vs 7.4%). Confusion and headache were listed as the 2 most common adverse events. Confusion occurred more frequently in the memantine group (7.9% vs 2.0%; \( P = .01 \)). However, 75% (3 of 4) of placebo patients who experienced confusion discontinued treatment because of this adverse event compared to 25% (4 of 16) in the memantine group. In the memantine group, confusion was rated as mild, occurred at a median of 32 days, and remitted within 2 weeks. By comparison, in the placebo group, confusion was more likely to be rated as severe, tended to occur later in treatment (median of 55 days), and did not remit. No patients discontinued because of headache, which usually lasted 1 day.\(^5\) Although not yet published, Riepe et al presented the results of a 3-month pilot open-label study in which memantine was added to stable doses of rivastigmine (6–12 mg/day).\(^6\) There was a statistically significant improvement in cognition scores (Alzheimer's disease assessment scale-cognitive [ADAS-cog], Mini-Mental State Examination [MMSE], verbal fluency test, and digit span test), but no significant changes in 3 other measures, including activities of daily living. Most patients showed improvement in the ADAS-cog score. The most common adverse events were nervous system (10.5%) and gastrointestinal disorders (4.2%).\(^6\) Therefore, these results suggest that rivastigmine in combination with memantine may not only be well tolerated but also provide clinical benefit, as seen with donepezil plus memantine.

These limited studies have evaluated memantine as an add-on treatment. Other studies are needed to test memantine with a cholinesterase inhibitor as combination treatment from the beginning of the study. If the progression rate and nature of AD pathophysiology varies between the 2 therapeutic strategies (ie, cholinergic neuronal death begins before low-level overstimulation of glutamate NMDA receptors), the efficacy of each drug may be limited to that particular stage of disease progression (ie, cholinesterase inhibitors in mild to moderate AD, NMDA-receptor antagonists in moderate to severe AD). Conversely, if the irregularities in NMDA-receptor activation begin early in the AD process, memantine may be a possible drug for treatment in earlier stages of the disease.

**COMBINATION: PHARMACOLOGIC PLUS HERBAL AGENTS**

As noted in Table 1, several herbal agents/dietary supplements are under investigation for the treatment of AD and have garnered a lot of attention. In the United States, dietary supplement usage is increasing substantially, especially in older adults, although the extent varies by geographic region. For example, in Oregon, a review of supplement usage by older adults revealed that most of the study participants (70.6%) used dietary supplements. Women used them more frequently than men, and the frequency in both sexes decreased with age (perhaps because of financial limitations). The greatest usage (89.7%) was in metropolitan “young-olds” (in this study, defined as those patients aged 65–85 years vs oldest-old who were \( \geq 85 \))

<table>
<thead>
<tr>
<th>Table 2. Adverse Events Reported in at Least 5% of Patients in the Memantine Plus Donepezil Clinical Trial</th>
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<tbody>
<tr>
<td><strong>Adverse Event, n (%)</strong></td>
</tr>
<tr>
<td>Agitation</td>
</tr>
<tr>
<td>Confusion</td>
</tr>
<tr>
<td>Fall</td>
</tr>
<tr>
<td>Influenza-like symptoms</td>
</tr>
<tr>
<td>Dizziness</td>
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<tr>
<td>Headache</td>
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<tr>
<td>Urinary tract infection</td>
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<tr>
<td>Urinary incontinence</td>
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<tr>
<td>Accidental injury</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
</tr>
<tr>
<td>Peripheral edema</td>
</tr>
<tr>
<td>Diarrhea</td>
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<tr>
<td>Fecal incontinence</td>
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</tbody>
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The placebo column is actually placebo plus donepezil. Reprinted with permission from Tariot et al. *JAMA*. 2004;291:317-324.\(^5\)
years), with no significant correlation between usage and body mass index or educational level. Multivitamins were the most common source.\textsuperscript{7} Similarly, the Resources for Enhancing Alzheimer’s Caregiver Health Project tracked use of cognitive-enhancing medication among people with dementia and their caregivers.\textsuperscript{8} The most common cognitive-enhancing drug by far was donepezil, followed by \textit{Ginkgo biloba}, and their combination was the most common of all combinations reported. Use of these drugs was more likely in patients who were married to their caregivers and under age 74 years and if the caregivers were male and older, better educated, and had higher incomes. Although there was again substantial geographic variability in these trends, the results highlight the importance of the caregiver in whether and what type of cognitive-enhancing medication is given to the patient with AD.\textsuperscript{8}

Combination treatments of pharmacologic agents (prescription or herbal/nutraceuticals) may pose several risks. Any combination of agents increases the risk of adverse events and drug-drug interactions, to which the elderly are already highly sensitive. Taking increasing numbers of agents also tends to reduce compliance, even when the dietary supplement is added with good intentions. Combination treatment also increases the risk for medication errors, particularly when dosages are different (eg, twice daily vs once a day) or the names are similar. For example, confusion between Amaryl (glimepiride; Sanofi-Aventis, Bridgewater, NJ) and Reminyl (galantamine; Ortho-McNeil Neurologics, Inc, Titusville, NJ) led to reports of severe adverse events, including hypoglycemia and death, and prompted an advisory letter from the US Food and Drug Administration (FDA), in addition to a brand name change from Reminyl to Razadyne.\textsuperscript{9} Because dietary supplements fall outside the realm of FDA regulation, adverse reactions are not routinely monitored and the amount of active ingredients in each preparation is not necessarily standardized, thus the true dose is often never fully known. This also affects study results when these agents are analyzed in clinical trials. The pharmacist should be aware of these potential pitfalls.

\textbf{Herbal Therapies}

\textit{Ginkgo biloba} is an herb that has been used in traditional Chinese medicine for thousands of years for several purposes. The medically active compound is extracted from the dried leaves and is thought to have

\textbf{Case Study}

AN 87-YEAR-OLD WOMAN WITH ALZHEIMER’S DISEASE

Martha is an 87-year-old female resident of a nursing home. She was diagnosed with Alzheimer’s disease (AD) 2 years ago and placed in the skilled nursing facility 1 year ago, although her daughters live nearby and visit frequently.

Her current Mini-Mental State Examination (MMSE) score is 12/30 (moderate to severe AD); 1 year ago it was 16/30.

Her previous medical history includes osteoarthritis, hypertension, and a history of falls. Her psychiatric history includes wandering, which has increased (and was the initial reason for nursing home placement), recent appetite changes, and aggression toward the certified nurse assistant (ie, hitting the nurse assistant 2–3 times each week while showering).

Her current medications include enalapril 5 mg every day, hydrochlorothiazide 50 mg every day, potassium chloride 20 mEq every day, acetaminophen 500 mg twice daily, donepezil 10 mg every day since diagnosis, and vitamin E 800 IU/day since diagnosis.

\textbf{Discussion}

Martha is clearly experiencing a change in progression of her disease state, thus a review of her current AD treatments and overall medication profile is warranted. Her cognition has worsened by 4 points on the MMSE in the past year, in the context of continuous donepezil treatment (10 mg every day) and vitamin E for the past 2 years. Behavioral and psychological symptoms have emerged (eg, appetite changes, increased wandering, and physical aggression). She is now in the moderate to severe stages of dementia compared to moderate dementia 1 year ago.

Because her disease state has worsened, the clinician should consider discontinuing donepezil or adding memantine to the regimen and assessing for stabilization and/or improvement in cognition, behavior, and function. If combination therapy is elected, memantine should be initiated at 5 mg/day for 1 week and titrated thereafter by 5 mg/week to a maximum dose of 10 mg twice daily. The clinician or pharmacist should also discuss with her family whether Martha should continue with high-dose vitamin E in light of the increasingly negative evidence pertaining to high doses of vitamin E.\textsuperscript{1}

(continued on page 195)
several pharmacologic effects, including antioxidant properties (scavenging free radical species). In recent decades, *Ginkgo biloba* has gained popularity among the general public for myriad uses, including memory impairment, tinnitus, and intermittent claudication. It has been studied to some length in AD and/or dementia, but the studies’ quality lack the rigor of well-controlled trials, standardized measures of cognition, and well-defined populations (eg, AD only, rather than a general diagnosis of dementia). An early review of the literature indicated that *Ginkgo biloba* could offer small but significant effects (ie, 3% difference) in objective cognitive measures with 120 mg to 240 mg over 3 to 6 months of treatment. A recent review of the Cochrane meta-analyses shows that *Ginkgo biloba* offers a small but significant (*P = .03*) benefit in measures of cognition, but only when the data from all studies are pooled together. The effect is not nearly as compelling as for the cholinesterase inhibitors, which were also reviewed. The proportion of patients discontinuing with *Ginkgo biloba* during the trials for any reason was similar to placebo. The National Center for Complementary and Alternative Medicine, along with the National Institute on Aging and the National Heart, Lung, and Blood Institute, are conducting a clinical trial to study whether *Ginkgo biloba* (240 mg/day) is effective in preventing AD, in addition to vascular and mixed dementia. Healthy men and women aged 75 years or older are participating; the trial is due to end soon. Given its apparent safety, pharmacists need not discourage use of *Ginkgo biloba* if patients (or caregivers) wish to try it for AD symptoms, but they should inform their physician if they are using it. *Ginkgo biloba* is also known to act as an anticoagulant, potentially leading to increased risk of bleeding (eg, spontaneous hemorrhage), especially if *Ginkgo biloba* is taken in combination with other blood-thinning drugs, such as aspirin and warfarin.

Huperzine A is another natural cholinesterase inhibitor derived from the Chinese herb *Huperzia serrata*. Clinical trials in China suggest that huperzine A has antioxidant and neuroprotective properties that can relieve memory deficits in patients with AD and other types of dementia. The drug is available as a nutraceutical in this country, and is being used by some US clinicians to treat AD. The National Institute on Aging is presently conducting a phase II, randomized, controlled study of huperzine A for the treatment of AD. Nausea, vomiting, and diarrhea are the most common adverse effects, and patients who use huperzine A should be cautioned to monitor for bradycardia, particularly with concurrent use of medications that slow heart rate, such as β blockers. Huperzine A should not be combined with other cholinesterase inhibitors. A synthetic analog of huperzine A, termed huprine X, has a binding affinity to acetylcholinesterase that is 180 times that of huperzine A and 40 times that of donepezil, based on in vitro assays. It may prove to be a candidate for clinical investigation in AD.

It is interesting to note that in both combination studies with memantine (donepezil and rivastigmine), participants were allowed to take concomitant vitamin E, *Ginkgo biloba*, or estrogen.

**Other Experimental Therapies**

Several other types of therapies have been tested in recent years, in an attempt to address yet other aspects of the amyloid cascade. The therapies discussed in this section have not yet shown success in the treatment or prevention of AD or are in preclinical studies.

**Metal Chelators**

Aβ acts as a metalloprotein by binding with high affinity to copper and zinc. These metals are thought to cause the production of reactive oxygen species when bound to Aβ. Chelators of copper and zinc have been shown to solubilize Aβ plaques in autopsied brains of patients with AD. In mice, administration of oral clioquinol (a copper/zinc chelator that crosses the blood-brain barrier) resulted in substantial deple-
tion of Aβ plaques after 9 weeks. However, clioquinol was withdrawn from the market in the 1970s because of its association with subacute myelo-optic neuropathy (when it was used as an antiamoebic agent).

**β- AND γ-SECRETASE INHIBITORS**

Because Aβ can only be formed after cleavage by β- and γ-secretase, inhibitors of these enzymes would be an attractive option for AD treatment. A mutant strain of mice that lacks the β-secretase gene has been developed and the animals have low Aβ concentrations. They will provide a useful vector in which to study β-secretase inhibitors. Animal models have also shown that β-secretase inhibitors reduce Aβ concentrations, and several of these agents have entered clinical trials.

**AMYLOID ANTIAGGREGANTS**

Aβ plaques are able to form because the peptides are insoluble and form aggregates. Researchers are designing synthetic peptides that can disrupt the protein structure of Aβ and thus prevent it from aggregating. Results in mice have been promising, so clinical studies may be pursued.

**DIETARY FACTORS**

There has been popular interest in dietary factors to prevent the effects of aging. Dietary components ranging from vitamins to macronutrients (fats and cholesterol) to alcohol have been studied. As reviewed by Luchsinger and Mayeux, there is no clear direct benefit of specific vitamins, low-fat or low-cholesterol diets, or reduced alcohol intake in reducing the risk of AD. However, these dietary changes are beneficial for many other chronic illnesses, thus they are worth pursuing.

**NEURONAL NICOTINIC ACETYLCHOLINE RECEPTOR AGONISTS**

As discussed in Part 1 of this series, acetylcholine binds to 2 types of postsynaptic receptors—muscarinic and nicotinic. Nicotinic agonists improve memory. Ispronicline is a nicotinic receptor agonist that has shown benefit in phase II clinical trials in patients with age-associated memory impairment. A phase II study in patients with mild to moderate AD is set to begin in early 2006 in the United States.

**FUTURE DIRECTIONS**

While we attempt to use drugs or synthetic analogs to address the many components of the amyloid cascade, medical technology now brings several other avenues to address the pathophysiology of AD through more sophisticated means.

Nerve growth factor (NGF) stimulates cholinergic function by prevention and reversal of cholinergic neuronal damage in animal models. Early clinical studies showed that NGF, delivered parenterally as a saline infusion, offered modest improvement in clinical global assessment and cognitive scores. A phase I clinical study of NGF gene therapy in 8 patients with mild AD not only showed a lack of long-term adverse effects over 22 months of follow-up but it also suggested slowed cognitive decline.

A vaccine against Aβ was developed, consisting of aggregated Aβ in adjuvant. A phase IIa study was conducted in 300 patients (receiving the vaccine) and 72 patients (receiving placebo). Injections were planned for 0, 1, 3, 6, 9, and 12 months. Unfortunately, the study was stopped prematurely because of 18 patients in the vaccine group developing meningoencephalitis. The participants were followed up for 12 months in a blinded manner, even though the vaccine was no longer being administered. Preliminary results from these data suggest that the vaccine may prove to be useful in AD. Specific measures of cognition were not different between the placebo group and the vaccinated group showing an antibody response, but a composite score from the neuropsychological testing battery did favor the antibody responders in the vaccine group \((P = .020)\). Levels of tau (the protein involved in formation of neurofibrillary tangles) in cerebrospinal fluid (CSF) were also significantly lower in the antibody responders. Analysis of changes in cerebral volume, although incomplete because of the study discontinuation, revealed a surprising increase in volume loss in the vaccine group compared to the placebo group.

A surgical approach to AD is now under investigation. COGNISHunt (Eunoe, Inc, Pleasanton, Calif) is a shunt-type pump designed to be implanted in the brains of patients with mild AD. It is similar to the shunt used to treat hydrocephalus. Its expected mechanism for treating AD is to help replenish CSF, which normally occurs but declines with age. In theory, Aβ accumulates in the CSF and, if it is not regularly flushed out, the accumulated proteins can incur toxic damage. Replenishing the CSF by draining it into the abdominal cavity, may help to abate the neuropathic damage in AD. A prospective, randomized, controlled study in 29 patients showed that after 1 year of
treatment, the surgical device appeared to be safe and cognitive scores were stabilized in the shunt group but declined in the control group (significantly according to the Mattis Dementia Rating Scale, and a trend favoring the shunt according to the MMSE). A larger clinical trial is under way.37

CONCLUSIONS

Clinicians and researchers are now turning toward more sophisticated strategies of treating AD (ie, rational comedication) and treating the disease farther into the disease process. Combination therapies are receiving greater attention with clinical research and in patients trying different herbal treatments. The pharmacist should be aware of these treatment strategies, in addition to the emerging developments involving vaccination, gene therapy, and interventions. Combination therapies may prove to offer synergistic benefits, but they may also create increased potential for complication in terms of adverse events, reduced compliance, and increased risk of medication errors. However, they can be overcome with diligence in monitoring among the healthcare team and the caregiver.

REFERENCES


