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Alternative Medicine and Alzheimer's Disease

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Abstract

Background—Alternative medicine has an extensive worldwide history and is commonly used by older patients. A number of different alternative medicines are used by patients having Alzheimer's disease. It is both desirable and expected for clinicians to be acquainted with these medications.

Review Summary—This paper discusses the available clinical trial evidence regarding eight agents commonly used by people having Alzheimer's disease. We provide an overview of the history and basic scientific evidence available for each agent, followed by a critical analysis of the evidence available from clinical trials, including the number of participants, trial duration and specific outcomes evaluated.

Conclusion—While many of these compounds have been associated with interesting basic science, none has shown clear clinical benefit to date. Data available for some, such as ginkgo biloba, curcumin and huperzine A, suggest that further evaluation is warranted. Familiarity with this literature will allow clinicians to provide meaningful recommendations to patients who wish to use these agents.

Keywords

Alzheimer's disease; alternative medicine; ginkgo biloba; huperzine A; piracetam

Introduction

“Don't Let Your Doctor Give You Horse Urine!”¹

Alternative medicine has an extensive worldwide history.² and perhaps is more properly regarded as “traditional medicine.” As of 1997, 43% of Americans used some form of complementary and alternative medicine (CAM), generating 629 million visits and \$36 to \$47 billion expenditure per year.^{3, 4} CAM usage is reported to be even higher among the elderly.^{5, 6} Included under this umbrella are chiropractic, dietary supplements, spiritual healing, imagery, massage, and relaxation therapies. Investigators have found similar overall rates of CAM use, but differing preferences for CAM modalities among different ethnic groups.⁷

The pejorative definition of CAM as therapies not conforming to the standards of the mainstream medical community is increasingly false. Historically, CAM has been delivered outside of the mainstream healthcare system, but increasingly it is offered within hospital settings and taught as part of traditional medical school curricula. A 1997 survey reported that 64% of US medical schools offered CAM instruction as part of their curricula.⁸ CAM is often not covered by insurance (insurance may cover acupuncture, chiropractic, and massage in conjunction with PT/OT) and 60% of patients pay entirely out of pocket. CAM is typically provided by non-MD practitioners.

The role of medical doctors in CAM is evolving. Many patients do not report use of CAM at office visits, often due to their perception that medical doctors will view such practices with derision. This degrades the doctor-patient relationship and is a missed opportunity to discuss potential drug interactions. The quote preceding this text refers to estrogen and is used to illustrate an increasing distrust of more conventional medicine, possibly due in part to issues such as these. Increasingly, it is felt that the medical community has a responsibility to advise patients at some level about CAM.⁹

Ginkgo biloba

The Ginkgo tree is indigenous to Korea, Japan, and China, but can be found worldwide. It may grow to 40 m, and live for over 1,000 years. Fossils of the Ginkgo tree date back to 250 million years ago.¹⁰ Extracts from Ginkgo biloba have been used medicinally for thousands of years to treat circulatory problems, asthma, vertigo, fatigue and tinnitus, in addition to being used for cognitive disturbances. Ginkgo biloba is generally taken as an extract (GbE), which is regarded as a “food supplement” and not regulated by the FDA. GbE is typically standardized to contain 24% ginkgo-flavone glycosides and 6% terpenoids, although concentrations and extraction methods vary.

Numerous mechanisms have been proposed for GbE on the basis of animal studies which have suggested effects on cerebral blood flow, neurotransmitter systems, cellular redox state, nitric oxide levels, and antagonism of platelet activating factors.^{11, 12} Some recent studies also suggest a direct role in modulating amyloid aggregation and pathology.¹³⁻¹⁵

A 1997 study enrolled 309 participants with uncomplicated Alzheimer's disease (AD) or multi-infarct dementia (MID) in a 52-week randomized placebo-controlled trial of GbE 120 mg daily. Primary outcome measures were the Alzheimer's Disease Assessment Scale cognitive (ADAS-cog), the Geriatric Evaluation by Relative's Rating Instrument (GERRI) - a caregiver inventory, and the Clinical Global Impression of Change (CGIC). A significant number of patients withdrew from both the GbE and placebo arms of this trial, with only 137 individuals completing the 52-week visit. Overall, 236 subjects having AD were included in the intention-to-treat analysis. The authors reported a statistically significant benefit for GbE on the ADAS-cog and the GERRI. It should be noted that the magnitude of this observed difference is unlikely to be clinically relevant (a difference of 1.4 points on a 70-point scale for the ADAS-cog and a difference of 0.14 on the 5-point scale used for the GERRI).¹⁶

There have been several small clinical trials of Ginkgo. A 1998 meta-analysis¹⁷ of randomized placebo-controlled trials in patients diagnosed with Alzheimer disease identified four studies which met their established inclusion criteria and provided sufficient data for analysis, resulting in analyzable data for 212 patients treated with GbE and 212 with placebo. Dosage was either 120 mg or 240 mg of GbE per day in all four studies. The authors concluded that treatment with a standardized GbE provided a modest improvement in cognitive measures, with an effect size comparable to that reported in a meta-analysis of cholinesterase inhibitors.¹⁸ Limitations of this data include the changing diagnostic criteria for AD, variability in the outcome measures used, the small study sizes (from 27 to 207 patients) and the short duration of the studies (from 12 to 26 weeks).

Similarly, a 2002 meta-analysis of five studies reported a “modest improvement” in cognition for Ginkgo as compared with placebo.¹⁹ There was no restriction of dementia subtype in this meta-analysis. The authors noted that more recent and methodologically sound studies showed little or no benefit for GbE.

A subsequent randomized placebo-controlled study enrolled 513 patients with AD in a 6 month trial of GbE.²⁰ Patients having significant neuropsychiatric symptoms were excluded from

enrollment. Participants were allowed to continue using vitamin E or non-steroidal anti-inflammatory drugs (NSAIDs), but could not use cholinesterase inhibitors or memantine. The primary outcomes of this study were the ADAS-Cog and the CGIC. 80% of the enrolled subjects completed the study, and GbE was well tolerated. No significant adverse events were reported.

No benefit was found at either dose of GbE. However, the placebo group declined less than would be expected for the natural course of AD. This may have been due to the exclusion of patients with prominent neuropsychiatric symptoms, an enrollment bias against those declining more rapidly (since standard medical therapy would not be given) and enrollment of treatment failures (10% of participants had participated in previous experimental trials, and 12% had been on cholinesterase inhibitors previously). Subgroup analysis of 140 subjects having neuropsychiatric symptoms found benefit to GbE at either dose on ADAS-Cog. This placebo subgroup declined more similarly to placebo groups in other clinical trials. A 24-week randomized study of subjects having AD and/or vascular dementia with neuropsychiatric features supports this finding.²¹

A large five-year double blind randomized trial in Europe evaluating Ginkgo extract as a preventative agent for AD is expected to be completed in 2010.²² A similar study in the US using all-cause dementia (rather than AD) as the primary outcome is also ongoing.²³

None of the studies discussed reported any serious adverse events.

Ginkgo biloba – The Bottom Line

Overall, there is weak evidence that GbE may provide modest cognitive benefit in some patients with Alzheimer's disease. Although pooling several small (and less rigorous) clinical trials of Ginkgo extract suggested a modest benefit, the recently published large, well-designed, clinical trial that employed current diagnostic criteria and outcome measures showed no overall benefit. No long-term data exist comparing Ginkgo with cholinesterase inhibitors or memantine, or evaluating GbE use in combination with those agents. Although case reports of bleeding problems exist, as well as a theoretical interaction with platelet inhibiting medications, it is currently widely used and seems to have a good safety profile.

Acetyl-L-carnitine (ALC)

Acetyl-L-carnitine (ALC) is the most common natural short-chain acetyl carnitine ester of L-carnitine. It plays roles in energy and lipid metabolism, membrane composition and transport, and may modulate enzyme and hormone activity. It is suggested that ALC may modulate the activity of neurotrophic factors and ameliorate the effects of a variety of toxins.²⁴ Animal studies have suggested a central nervous system neuroprotective effect.²⁵ ALC was demonstrated to have a neuroprotective role in chemotherapy-induced peripheral nerve toxicity in several pilot studies.²⁶⁻²⁸ ALC acts as a partial direct cholinergic agonist and can be converted to acetylcholine. It is actively transported across the blood-brain barrier, and administration decreases cerebrospinal fluid levels of β -endorphins and plasma cortisol levels.²⁹ On the basis of these proposed mechanisms, it has been investigated in Alzheimer's disease.

A 12 month multicenter randomized double-blind placebo controlled trial enrolled 431 patients with probable AD. The primary outcome measures were the Clinical Dementia Rating scale (CDR) and ADAS-Cog. Secondary outcome measures included the Non-cognitive measures of the ADAS (ADAS-NonCog), mini mental state examination (MMSE), CGIC and scales assessing activities of daily living (ADLs). No benefit was found in any primary or secondary outcome measure.³⁰ Subgroup analysis suggested a possible benefit (slower decline) in younger patients, and a follow-up study of ALC in early-onset AD was performed. This was

again a 12 month double-blind placebo controlled randomized trial which studies 197 patients with probable early-onset AD (age 45–65, mean 58).³¹ The primary outcomes were the same and secondary outcomes were similar, with the Clinician-Based Impression of Change (CIBIC) replacing the CGIC. No benefit was demonstrated. Over 75% of enrolled subjects completed these studies, and adverse events resembled those reported by the placebo group.

A 2003 meta-analysis of 21 randomized placebo-controlled trials of ALC in mild cognitive impairment (MCI) and/or mild AD identified 1204 subjects with outcome data adequate for analysis (591 received ALC and 613 placebo).³² Dosing was 1.5 to 3.0 g per day. Study duration varied from 3 to 12 months, with only 6 studies of 1 year duration. The authors combined the widely variable outcome measures into a single “all scales” category encompassing all clinical and neuropsychological test data into a single parameter. The effect size for “all scales” was 0.201, just at the cutoff for a clinically detectable effect. They also evaluated the global assessment of change (available in 13 studies), and found an effect size of 0.32, and a pooled effect size of 0.214 for neuropsychological measures. They concluded that this meta-analysis found significant benefit in MCI and mild AD in all measures, although modest in size. Secondary analysis indicated ALC provided more benefit for memory and higher cognitive functions. CGIC seemed to reach its maximum improvement within 3 months, while “all scales” achieved maximum after 6 months.

A Cochrane meta-analysis of ALC in dementia identified sixteen studies for inclusion, all of which investigated ALC in AD and made attempts to exclude patients with other diagnoses. The authors found no overall benefit for ALC in measures of clinical severity, daily activities, or cognitive measures.³³

No significant adverse events were reported in the studies reviewed in the meta-analyses or in the two studies reported above. Minor adverse gastrointestinal effects, restlessness, and headache have occasionally been reported.

Acetyl-L-carnitine – The Bottom Line

Two large, well-designed studies in patients with probable AD that employed current diagnostic definitions and outcome measures found no benefit for ALC. There is no good evidence to recommend ALC beyond mild AD, and the evidence advocating its use in mild disease is based on a meta-analysis of studies spanning over 20 years with varying clinical definitions, inclusion criteria, durations, and outcome measures. No “add-on” studies of ALC in combination with current standard treatments have been conducted. No serious side effects have been reported in clinical trials or as individual cases.

Lecithin

Lecithin, a choline-containing phospholipid, is the major dietary source of choline and has been shown to increase serum choline levels. It has been postulated that lecithin may accelerate acetylcholine synthesis in the brain through enhanced availability of the substrate choline.³⁴ A meta-analysis of ten trials which studied patients with AD analyzed data on 265 subjects.³⁵ Doses of lecithin ranged from 1 g/day to 35 g/day, although the concentration varied between 25% and 95%. All trials reported equivocal results for cognitive testing and there was no significant effect on behavior or ADLs. Two trials reported on some measure of global impression of change. They produced a pooled odds ratio estimate of 3.0 in favor of placebo, which almost reached significance.

Huperzine A

Huperzine A (HupA) is an extract of *Huperzia serrata* (Chinese club moss, *Lycopodium serrata*, Qian Ceng Ta, Shuangyiping), a hardy plant which grows in a variety of temperate habitats, preferring semi-to-full shade, and sandy, well-drained soil. It has been used for centuries in China to treat fever, swelling and blood disorders.

HupA is a potent, reversible and selective inhibitor of acetylcholine esterase, with rapid absorption and penetration into the brain in animal studies.³⁶ Compared to the currently available cholinesterase inhibitors, HupA has a longer duration of action, and some studies have suggested better tolerability due to fewer peripheral cholinergic side effects.³⁶ HupA was reported to reduce glutamate-induced toxicity in neurons, possibly through modulation of glutamate–NMDA receptor interaction, or of the passage of Ca^{2+} through associated ion channels.³⁷ In addition to the hypothesized reduction in excitotoxicity, other neuroprotective and antioxidant properties have been suggested as well.³⁸

To date, all reported clinical trials of huperzine have been performed in China. An 8 week double-blind placebo-controlled study that evaluated huperzine A in 103 people with AD reported that 58% receiving HupA showed improvements in memory, thinking, and behavioral functions compared to 36% of the placebo group.³⁹ A study of 60 patients with probable AD compared capsule and tablet administration of HupA. The investigators found no difference between the two groups, but did report a statistically significant difference on psychological evaluations between ‘before’ and ‘after’ participants began the 60 day trial.⁴⁰

A phase II clinical trial of HupA funded by NIA and the Alzheimer's Disease Cooperative Study (ADCS) will enroll 150 patients into three arms (placebo, 200 mcg BID or 400 mcg BID) looking for cognitive and/or functional improvement.⁴¹ The primary outcome measure will be the ADAS-cog and secondary outcome measures include the CGIC, ADLs scales and the Neuropsychiatric Inventory. This will be a 24 week study, with optional 6 month open-label extension.

The animal data and clinical safety tests to date have not identified any unexpected toxicity.⁴² As would be expected given its proposed mechanism of action, gastrointestinal complaints were reported by some subjects.

Huperzine A – The Bottom Line

The limited available data, including human and animal studies conducted in China, suggest that HupA may compare favorably in symptomatic efficacy to the cholinesterase inhibitors currently in use. The purported antioxidant and neuroprotective properties of HupA provide a hypothetical basis for a disease-modifying role in AD. This agent is currently under investigation in a small, well designed clinical trial.⁴¹ Given its proposed mechanism of action, clinicians should probably caution patients against concomitant use of HupA and a prescribed cholinesterase inhibitor.

Piracetam

Piracetam is a derivative of GABA which was first marketed for the treatment of vertigo and events associated with ageing in 1971. In 1973 it was christened the first of a new class of pharmaceuticals, the “nootropics,” on the basis of proposed telencephalic activity, activation of higher integrative mechanisms and facilitation of nervous activity.⁴³ It is currently approved in over 120 countries for use in adults and the elderly at doses up to 24 g per day, for a variety of disorders including stroke, cortical myoclonus, psycho-organic syndromes, alcoholism, fetal distress during labor, dyslexia, and sickle cell anemia. Although not FDA approved in the US,

piracetam is available by mail without a prescription. In 2006, piracetam sales totaled 99 million Euro, representing 4.5% of the pharmaceutical company UCB's net sales.⁴⁴

Piracetam has no proven action at GABA receptor sites, on dopaminergic, serotenergic, adrenergic transmission, or any other known receptor, enzyme, or transporter system, with the exception of weak interaction at L-glutamate binding sites. A variety of biochemical effects have been observed in many systems after piracetam administration, but these vary between experiments. Others report that piracetam improves cell membrane fluidity. Many different mechanisms have been suggested, reflecting that evidence for an exact mechanism is still not well established in the scientific community.⁴⁵ A review of proposed mechanisms of action, supported by UCB, is available.⁴⁶

A 12 month double-blind placebo-controlled study of 8 g of piracetam per day enrolled 33 patients with early probable AD.⁴⁷ Thirty subjects completed the study, which found no overall benefit to piracetam. Although both groups declined and there was no significant difference on global measures (such as the MMSE), the authors concluded that performance on individual neuropsychological tests supported the hypothesis that long-term administration of high doses of piracetam might slow the progression of cognitive deterioration in patients with AD.

In 2002, the pharmaceutical company UCB sponsored a meta-analysis of 9 published and 10 unpublished placebo-controlled studies that ranged in duration from 6–52 weeks (15 studies $\leq$ 8 wks, 3 12 wks, 1 52 wks) with doses of piracetam ranging from 2.4–8 g/day.⁴⁸ The most recent study included in this meta-analysis was the small trial from 1993 which is discussed above, and most included studies enrolled ill-defined dementia populations. The CGIC was extracted for analysis, and the authors report that using CGIC, 60.9% dementia patients taking piracetam (vs. 32.5% for placebo) improved, although the term “improved” is undefined. They estimate the number needed to treat to provide benefit as 4.8. It should also be noted that the CGIC underwent significant changes in definition over the time period spanned by these studies.

A Cochrane meta-analysis of available trials of piracetam in dementia or cognitive impairment found no benefit in cognition, mood, or dependency.⁴⁹ This meta-analysis primarily included studies of poorly-defined dementia populations. The authors concluded that the existing published evidence does not support the use of piracetam in dementia or cognitive impairment.

Piracetam has been well-tolerated in the clinical trials to date, and no serious adverse events have been reported in clinical trials or in post-marketing surveillance.⁵⁰ Occasional reports of headache, dizziness, agitation, insomnia, fatigue and gastrointestinal disturbance are noted in clinical trials, but generally are remarked upon as being transient or minor.

Piracetam – The Bottom Line

In summary, piracetam was developed in 1964 and has been marketed for a variety of indications. A well-designed study of a high dose of piracetam and a rigorous meta-analysis found no benefit for patients with AD. There is not currently sufficient evidence to recommend use of this agent in AD or MCI. It appears to be safe, and was well tolerated in clinical trials at doses up to 8 g/day.

Curcumin

Curcuma longa is a member of the ginger family indigenous to South and Southeast Asia, where it is grown commercially. Turmeric is derived from the rhizome (root) of the plant, whose most important commercial application is curry. Curcumin was isolated in 1815, initially named diferuloylmethane.

Preparations made from *Curcuma longa* have been used for centuries in Ayurvedic medicine to treat a variety of ailments. These may be taken orally for dyspepsia, liver disease, flatulence, urinary tract disease, and as a “blood purifier” or used topically for a variety of skin ailments. Components of turmeric are currently under investigation as anti-inflammatory agents (particularly in inflammatory bowel disease) and in the treatment and prevention of cancer, HIV infection, myelodysplastic syndromes, and cystic fibrosis. Eleven clinical trials are currently recruiting participants, including two in Alzheimer disease.

Experimental evidence has suggested several possible mechanisms of action relevant to AD. *In vitro* and *in vivo* evidence suggests anti-oxidant and anti-inflammatory properties as well as a direct effect against β -amyloid aggregation.⁵¹⁻⁵³ *In vivo* data has demonstrated curcumin passes the blood-brain barrier, and that it possesses cholesterol-lowering properties.⁵³ Several animal studies suggest that this agent may reduce oxidative damage and amyloid pathology in Alzheimer transgenic mice and may modulate amyloid-induced cytopathology or macrophage processing of amyloid.^{54, 55}

No clinical trials of curcumin in AD have been completed. A NIA-funded phase II trial of curcumin will enroll 33 subjects to determine the safety and tolerability of two doses (2 g/day and 4 g/day) of curcumin C3.⁵⁶ The primary outcome is a side-effect checklist, with serum, CSF, cognitive and behavioral measures used as secondary outcomes.⁵³ A separate Chinese study will examine the safety and tolerability of curcumin in combination with ginkgo.⁵⁷

Curcumin is generally accepted as safe, although some animal studies have suggested risks of gastric ulceration, thyroid follicular cell hyperplasia and hepatotoxicity at very high doses. In human studies to date, doses of 1200 mg/d were well tolerated in general, although one study noted gastric irritation in 2 of 19 subjects receiving this dose. Another study found that doses up to 8 g/d were well tolerated, and that higher doses were not tolerated simply due to the bulk of the agent.

Curcumin – The Bottom Line

Although the use of curcumin as a treatment for AD is currently under investigation, no clinical trial data is currently available. Several mechanisms of action have been proposed which may be relevant to AD, based upon preliminary *in vitro* and *in vivo* data. Curcumin has been well-tolerated in clinical trials investigating its use in other diseases. It is generally accepted as safe, however some animal studies have suggested possible toxicities.

Periwinkle –Vinca minor (Vinpocetine)

Periwinkle has historically been used to treat a wide variety of diseases. It was used as a folk remedy for diabetes in Europe for centuries. In India, juice from the leaves was used to treat wasp stings. In Hawaii, the plant was boiled to make a poultice to stop bleeding. In China, it was used as an astringent, diuretic and cough remedy. In Central and South America, it was used as a homemade cold remedy to ease lung congestion and inflammation as well as sore throats. Throughout the Caribbean, an extract from the flowers was used to make a solution to treat eye irritation and infections. It also had a reputation as a magic plant; Europeans thought it could ward off evil spirits, and the French referred to it as “violet of the sorcerers.”

Numerous mechanisms of action have been proposed for vinpocetine; it will improve cerebral metabolism, increase glucose and oxygen consumption by the brain, and improve brain resistance to hypoxia.⁵⁸ It has been shown to improve cerebral microcirculation and to reduce cerebral vascular resistance.⁵⁹ It has been shown to inhibit platelet aggregation and improve red blood cell deformability.⁶⁰ A neuroprotective effect has been claimed through blocking

voltage-gated sodium channels, modulating neurotransmitter release, and potentiating the effect of adenosine in cytotoxic hypoxia.⁶¹

In the only clinical trial of vinpocetine in AD, 15 patients were treated with increasing doses of vinpocetine (30, 45, and 60 mg per day) in a 1-year open-label pilot study.⁶² Vinpocetine failed to show a positive impact at any dose tested on cognition, neuropsychological testing, or overall functioning as measured by the clinical global impression. When compared to a matched control group, study participants followed the natural course of disease. There were no significant adverse events reported.

A Cochrane meta-analysis of vinpocetine in dementia identified three studies with sufficient data to be analyzed. All were performed before the 1990's and enrolled poorly-defined dementia populations. Very few patients were followed for 6 months or more. This analysis suggested a possible benefit on CGI, but insufficient data was available to draw a definitive conclusion and the study populations were very loosely defined. They conclude: "Although the basic science is interesting, the evidence for beneficial effect of vinpocetine on patients with dementia is inconclusive and does not support clinical use."⁶³

No serious adverse events have been reported. Gastrointestinal complaints and vertigo have been reported at higher rates than placebo groups, with some suggestions of dose-dependence.⁶³⁻⁶⁵

Vinpocetine – The Bottom Line

Vinpocetine has been reported to have a variety of actions that would hypothetically be beneficial in AD. The only study investigating this agent in a well-defined cohort of AD patients found no benefit. Meta-analysis of older studies of vinpocetine in poorly-defined dementia populations concluded that there is insufficient evidence to support its clinical use at this time. Vinpocetine has been well tolerated at doses up to 60 mg/d in clinical trials of dementia and stroke, and no significant adverse events have been reported in these studies.

Phosphatidylserine

Phosphatidylserine (PS) is one of five phospholipids that contribute to the structural matrix of all cell membranes. Endogenous synthesis requires a complex series of reactions and substantial energy expenditure, and most PS is obtained from dietary sources. In the past, supplements were derived from bovine cerebral cortex, which differ in composition from PS obtained from soy. When the bovine cortex origin of this agent became a source of concern in the 1990's, clinical investigations ceased.

PS accounts for a minor percentage of the membranes, but may be important in determining neuronal membrane surface potential and ionic environment. The functions of PS include cell-cell recognition and communication, and membrane PS expression is implicated in the early phases of apoptosis.⁶⁶ It has a proposed role as a tumor necrosis factor inhibitor.⁶⁷ PS influences levels of neurotransmitters (including acetylcholine, dopamine, and norepinephrine), and modulates their receptors.⁶⁸ PS is also involved in regulation of key proteins in neuronal membranes, including sodium-potassium-exchanging ATPase, calcium-magnesium ATPase, and isoforms of protein kinase and adenylyl cyclase.⁶⁸ Age-related loss of dendritic spines is ameliorated by dietary PS supplementation in rats.⁶⁹ Treatment with PS has also been reported to counteract the reduction in release of neurotransmitters (e.g., ACh, dopamine, and norepinephrine) that occurs with aging.⁷⁰

There have been six trials in humans with cognitive impairment; two of which identified people with “probable AD”. All six studies were short; one lasted six months, three lasted three months and two lasted two months. All used bovine cortex-derived PS (BC-PS).

A short (8 weeks of active treatment) double-blind placebo-controlled crossover study of BC-PS (300 mg/d) in 33 German patients with mild-to-moderate AD (MMSE between 15 and 27) found no improvement on cognitive measures or the Mattis Dementia Rating Scale (DRS).⁷¹ They found a small but statistically significant improvement on their clinical global improvement rating in patients receiving BC-PS during treatment phase one, but this was not observed in those receiving BC-PS after crossover. The authors felt this improvement carried over to the subsequent wash-out and treatment phases.

A 12 week randomized double-blind placebo-controlled trial of 300 mg/day of BC-PS in 51 patients with probable AD used a 12-item clinical global impression (CGI) scale and two behavioral scales as primary outcome measures and neuropsychological testing as a secondary outcome.⁷² The authors reported small but statistically significant improvements on 2 of the 12 CGI items and on 3 of the 25 items assessed in the clinician-reported behavior scale. No difference was found on the total CGI scale or on the behavioral scale as a whole. No difference was found on the family-reported behavior scale (the third primary outcome measure), or on any of its individual items. No significant differences were found on neuropsychological testing.

A multicenter randomized double-blind placebo-controlled study of 152 loosely diagnosed “AD” patients examined the effect of BC-PS 200 mg/day for 3 months, with proposed follow-up at 6, 12, 18, and 24 months.⁷³ They proposed nine co-primary outcome measures: the Blessed Dementia Scale (BDS), the Clifton Assessment Scale for the Elderly, and seven neuropsychological tests. At the 3 month assessment, they reported a trend for two neuropsychological measures and for a single item of the BDS in favor of BC-PS, only in the subgroup of the most severely affected patients, which reached statistical significance at the 6 month follow-up. Eight patients receiving BC-PS were in this subgroup. No analysis of the data from the moderately affected group was presented, but the tabular data reported did not demonstrate any meaningful difference between the placebo and BC-PS groups. Twelve, 18, and 24 month follow-up data were never published.

The only reported study of plant-source phosphatidylserine, enrolled 18 patients with “age associated memory impairment” in an 12 week open trial of 300 mg/day.⁷⁴ No primary endpoint was specified. Fifteen participants completed the study, which reported subjective memory improvement and some improvement from baseline to 6 weeks on several neuropsychological tasks. There was no improvement in testing from 6 weeks to 12 weeks, and a practice effect could not be excluded.

In the few clinical trials conducted with PS, no significant adverse events were reported. Stomach upset has been reported at higher dosages, and some subjects complained of flatulence related to plant-source PS.^{74, 75} Theoretical concerns regarding transmissible spongiform encephalopathy halted research with BC-PS.

Phosphatidylserine – The Bottom Line

Two trials of BC-PS in AD and one larger trial of BC-PS in poorly defined dementia patients failed to show convincing evidence of cognitive improvement and were too short to evaluate any neuroprotective effect. No longer-term studies of PS in AD patients are currently underway. No adverse events were reported in the clinical trials to date. Concerns regarding the safety of BC-PS relate directly to the cattle from which it the agent is derived.

CONCLUSION

Numerous alternative medicines are touted as being beneficial for Alzheimer's disease. Due to space limitations, we are unable to discuss every agent which has been proposed to be of benefit and have restricted our attention to several which have been the best studied and/or most popularly used. While the basic science underlying many of these agents provides interesting hypothetical effects, to date these have not been manifest in well-designed clinical trials, with the possible exception of huperzine A, which is currently under investigation. The modest improvements reported in some older studies of these agents these have not been replicated in recent more rigorously designed trials that enrolled well-characterized AD populations.

None of these agents provides clearly documented meaningful improvement or modulation of the natural course of AD in the trials conducted to date. This is an important point, as many patients may expect such a response based upon the advertisements for these agents. In general, they appear to be safe, with few significant adverse events occurring during clinical trials and only rare case reports of adverse events temporally associated with their use. The available evidence for the eight agents discussed in this review does not clearly recommend any of them as being efficacious. Nonetheless, they continue to be widely used. The use of alternative medicines is an exercise in shared medical decision-making, with the ultimate decision resting with the patient and their family. While there is clearly insufficient evidence to *recommend* any of these agents at this time, it is not clear whether clinicians should actively *discourage* their use. It is our hope that this review provides sufficient detail to inform discussions between clinicians and their patients regarding use of these substances.

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