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# Alzheimer's Disease: The Pros and Cons of Pharmaceutical, Nutritional, Botanical, and Stimulatory Therapies, with a Discussion of Treatment Strategies from the Perspective of Patients and Practitioners

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### Abstract

Alzheimer's disease (AD) is characterized by dysfunctional intracellular and extracellular biochemical processes that result in neuron death. This article summarizes hypotheses regarding cell dysfunction in AD and discusses the effectiveness of, and problems with, different therapies. Pharmaceutical therapies discussed include cholinesterase inhibitors, memantine, antihypertensive drugs, anti-inflammatory drugs, secretase inhibitors, insulin resistance drugs, etanercept, brain-derived neurotrophic factor, and immunization. Nutritional/botanical therapies included are huperzine A, polyphenols, Ginkgo, *Panax ginseng, Withania somnifera*, phosphatidylserine, alpha-lipoic acid, omega-3 fatty acids, acetyl L-carnitine, coenzyme Q10, various vitamins and minerals, and melatonin. Stimulatory therapies discussed are physical exercise, cognitive training, music, and socialization. Finally, treatment strategies are discussed in light of the benefits and drawbacks of different therapeutic approaches. It is concluded that potential risks of both approved and non-approved therapies should be weighed against the potential benefits and certain consequences of disease progression. Approaches that target several dysfunctions simultaneously and that emphasize nutritional, botanical, and stimulatory therapies may offer the most benefit at this time.
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## Introduction

Although there have been numerous reviews of therapies for Alzheimer's disease (AD), most have concentrated on either pharmaceuticals or natural therapies, with only a few covering elements of both. Many papers are oriented toward researchers rather than practitioners. Although usually the emphasis has been on single-target approaches, AD is characterized by many different cellular dysfunctions, suggesting that a multi-target approach may provide more therapeutic value.

The goal of this article is to present a current review of pharmaceutical, nutritional, botanical, and stimulatory therapies. Stimulatory therapies, which include physical exercise, music, and cognitive training, have received very little attention but may prove to be important adjuncts to more traditional approaches. Since FDA-approved pharmaceuticals offer only modest short-term benefits, serious side effects, and high cost, and nutrients and botanicals often have less research backing, practitioners must weigh the potential drawbacks of all therapies against the certain consequences of AD progression.

## AD Pathology

At the most basic level, AD results from cell death that can result from many different factors. Alzheimer brains have low levels of acetylcholine (ACh), which can arise from the accumulation of beta amyloid (βA) protein fragments that form hard plaques that can in turn interfere with the ability of ACh to effect synaptic transmission and initiate inflammatory processes that produce reactive oxygen species. Research suggests that βA opens channels in cell membranes, permitting calcium ions ($Ca^{2+}$) to enter the cell and triggering several processes leading to mitochondrial dysfunction, inflammation, and cell death.[1] Some research suggests that, in the early stages of AD, βA has an

antioxidant function so that efforts to reduce it might be counterproductive. Other research has found only a weak relationship between the amounts of βA and the severity of AD. βA may be the end result of a destructive chain of events and hence more symptomatic than problematic.

Another possible cause of cell death in AD is a chemical change in a protein (tau) that keeps microtubules stable. This causes a neuron's microtubules to pair with other tubules producing tau (neurofibrillary) tangles that result in tubule disintegration and block neurotransmitters, leading to cell death.

Reactive oxygen species (oxygen ions, peroxides, and free radicals) can result in cell death by initiating a chain reaction that leads to damage of cell membranes, mitochondria, lipids, and proteins.

Damage from toxic excitatory amino acid neurotransmitters, especially glutamate, can produce excitotoxicity and cell death. Excitotoxicity can occur even with normal glutamate levels if glutamate receptor sites become overstimulated.[2] The receptor most involved in excitotoxicity is N-methyl-D-aspartic acid (NMDA). If NMDA sites are overactivated, high levels of $Ca^{2+}$ can enter the cell, causing a permanent depolarization of the post-synaptic neuron and creating reactive oxygen species and other substances that cause cell death. Potential mechanisms have also linked excitotoxicity to βA and tau tangles.[2]

Damage from toxins, chemicals, and trauma can produce inflammation, another factor in AD. Inflammation often results from persistent oxidative stress, but other determinants include βA, protease inhibitors, pentraxins, inflammatory cytokines, and prostaglandin-generating cyclooxygenases. Unhealthy neurons contain low levels of N-acetyl-aspartate (NAA), which may also be an issue. Exposure to pollutants can make the blood-brain barrier permeable to toxins, thus causing oxidative stress, inflammation, and βA accumulation.[3,4]

## Pharmaceutical Therapies
### Acetylcholinesterase Inhibitors (AChEIs)

AChEIs inhibit the action of acetylcholinesterase (AChE), thereby enabling ACh to work for a longer period of time, interact with cholinergic receptors and potassium ion channels, and affect the uptake, synthesis, and release of neurotransmitters. AChEIs include donepezil (Aricept®), rivastigmine (Exelon®), galantamine (Razadyne®), and tacrine (Cognex®) – all approved by the U.S. Food and Drug Administration (FDA) for treating AD. Meta-analyses have repeatedly found that AChEIs have a modest beneficial effect on cognition and memory.[5]

Donepezil and rivastigmine are often regarded as providing only symptomatic relief without providing neuroprotective effects. However, *in vitro* studies show that donepezil offers neuroprotection by reducing glutamate excitotoxicity, diminishing βA toxicity, and consequently increasing cell longevity.[6,7] Donepezil slowed atrophy of the hippocampus in humans, which suggests a neuroprotective effect.[8] Data also suggest that cognitive benefits from donepezil after three years are greater when treatment is started early rather than delayed one year.[9]

Galantamine, a natural AChEI (originally derived from the common snowdrop and other plants, but now synthesized), protects neurons and reduces cell death by modulating nicotinic receptors, which are significantly reduced in AD brains.[10,11] In an animal model, galantamine also increased dopaminergic neurotransmission in the hippocampus,[10] a brain area particularly important in memory.

Galantamine does not result in tolerance and only short-term efficacy characteristic of donepezil and rivastigmine.[11] A meta-analysis of 10 randomized, placebo-controlled, double-blind studies concluded that galantamine either improved or prevented decline of cognition and activities of daily living.[12] Since galantamine can produce gastrointestinal upset, researchers recommend starting with a low dose and gradually increasing to 16-24 mg daily. The beneficial effects of galantamine have been found to persist for 36 months, with 50-percent improvement over expected scores of untreated mild-to-moderate AD subjects.[13] The magnitude of the benefit increases over time.

Rivastigmine, which inhibits both butyrylcholinesterase and AChE, provides two pathways for prolonging ACh and so might be expected to be more effective than donepezil or galantamine. Such an outcome, along with less cortical atrophy in the temporal parietal area, was observed in mild AD patients over a 20-week period.[14] A *post hoc* analysis of several studies suggests that rivastigmine slows the rate of decline as long as five years.[15]

AChEIs have several limitations; they are expensive, provide modest benefits, and usually have a brief period of effectiveness (sometimes partially resolved by switching to a different AChEI). AChEIs have short half-lives and may have considerable side effects (especially tacrine),

resulting from activation of peripheral cholinergic systems.[16] More emphasis is needed on clinical significance rather than statistical significance.

## NMDA Antagonists

Memantine is thought to reduce cell damage by decreasing excitotoxicity resulting from overactivation of NMDA glutamate receptors during synaptic transmission. Memantine stops overstimulation by binding to NMDA receptors, which inhibits the influx of $Ca^{2+}$ and results in a small improvement in cognition and behavior.[17] Although memantine has been FDA approved only for more severe AD, it has been found effective in phase III trials for both moderate-to-severe[18,19] and mild-to-moderate cases.[20,21] Nevertheless, the overall data suggest that clinically significant effects on cognition, mood, and performance of daily activities are seen primarily with more severe cases of AD.[22]

It is important not to completely block all glutamate-mediated synaptic transmission since cells must have some NMDA activity to function properly. Memantine meets this criterion since it selectively blocks only excessive stimulation.[2,23]

In a small study of 11 AD patients, memantine was shown to reduce tau phosphorylation, which would be expected to reduce tau tangles.[24] Other neuroprotective effects have been summarized in a recent review.[25] Memantine appears to be well tolerated.[26]

NMDA antagonists, such as memantine, have generally been regarded as neuroprotective,[2] but they have also demonstrated neurotoxic properties that diminish memory, incite neuron death, and even produce psychotic episodes in humans.[27] Memantine's neurotoxicity may be increased by AChEIs. Such an effect has been demonstrated in an animal model where the concurrent use of donepezil and memantine produced a substantial increase in neurotoxic reactions.[27] Although the clinical relevance of this in humans is unknown, the simultaneous use of both drugs merits caution. On the other hand, recent research shows that such combinations slow cognitive decline more than memantine or AChEIs alone and that the benefit of combination therapy increases over time and persists for years.[28]

## Antihypertensive Drugs

Antihypertensive drugs have potential for AD therapy. Angiotensin converting enzyme (ACE) inhibitors reduced inflammation and mental decline in AD patients by 50 percent.[29] Mild-to-moderate AD subjects with high blood pressure had less cognitive decline when given an ACE inhibitor that crossed the blood-brain barrier (perindopril or captopril) than when given an ACE inhibitor that did not (enalapril or imidapril) or a calcium channel blocker (nifedipine or nilvadipine).[30] A recent study confirmed that ACE inhibitors slow the progression of AD.[31] A potential downside of ACE inhibitors is that they may block ACE from converting $\beta A_{1-42}$ to less damaging $\beta A_{1-40}$, thereby reducing its protective function.[32]

Possible mechanisms by which ACE inhibitors work include reducing angiotensin II (a substance that interferes with memory formation by reducing ACh),[33] increasing an enzyme that breaks down βA, and increasing acetylcholine. Another possibility is that angiotensin II is converted to angiotensin III and then to angiotensin IV. Angiotensin IV binds at $AT_4$ receptor sites, which are most prevalent in the neocortex, hippocampus, and other areas important in cognition and memory. This counteracts a dysfunctional cholinergic system, resulting in more ACh and improved learning and memory.[34]

Angiotensin receptor blockers are antihypertensive drugs that block the action of angiotensin II by binding at $AT_1$ receptor sites. They have been reported to reduce AD risk and slow its progression.[35,36] These drugs include telmisartan, valsartan, losartan, and candesartan. Potential mechanisms of action include reducing angiotensin II and increasing the activation of $AT_4$ receptors.

Calcium channel blockers are another category of antihypertensive drugs. It may be that βA, mutations in presenilin proteins, or other factors open channels that permit $Ca^{2+}$ to enter and damage cells.[37] If so, calcium channel blockers might be expected to benefit AD patients. Although some research has shown that people taking calcium channel blockers were less likely to develop dementia,[38] other studies have been negative.[39] Since most research has been on hypertensive individuals, the effects of calcium channel blockers on nonhypertensive subjects are unknown.

## Anti-Inflammatory Drugs

Most research on nonsteroidal anti-inflammatory drugs (NSAIDs) has focused on prevention rather than treatment of AD. One study that examined 49,349 NSAID users for five years found the risk of acquiring AD was clearly reduced by ibuprofen and less so by indomethacin, while celecoxib and the salicylates offered no protection.[40] It was not possible to determine AD risk for many NSAIDs because of small numbers of users.

NSAIDs that reduced $\beta A_{1-42}$ were no more likely to be effective than those that did not. Studies of risk have been inconsistent and correlational in nature, making it impossible to conclude causation. Moreover, other studies have reported that NSAID use can actually increase the risk of developing dementia.[41] NSAIDs are well known for producing gastrointestinal symptoms as well as liver and kidney toxicity.

Research on the use of NSAIDs for the treatment of AD patients has also been disappointing.[42] A randomized, placebo-controlled study of people with mild-to-moderate AD found no cognitive benefit from NSAIDs.[43]

Animal models have demonstrated that anti-inflammatory cyclooxygenase-2 (COX-2) inhibitors (rofecoxib) reduced oxidative stress but non-specific COX inhibitors (flurbiprofen and ibuprofen) did not.[44] An animal model revealed that ibuprofen, naproxen, and a COX-2 inhibitor (MF-tricyclic) each restored memory, but only MF-tricyclic blocked the suppressive effects of $\beta A$ on synaptic plasticity.[45] In an 18-month human trial, celecoxib, a COX-2 inhibitor, improved memory and cognition in individuals with mild cognitive impairment.[46]

## Secretase Inhibitors

Secretases are enzymes that break amyloid precursor protein (APP), found in cell membranes, into $\beta A$ fragments that form plaques. Consequently, secretase inhibitors should slow the production of $\beta A$. Human research is very limited, but a gamma-secretase inhibitor has been shown to reduce plasma $\beta A$ by about 60 percent in a small 14-week study of mild-to-moderate AD patients; however, no significant differences in cognition were found.[47] Conclusions that the treatment was well tolerated seem false, given hair color changes, skin rashes, a bowel obstruction, nausea, vomiting, diarrhea, and more in just 36 treated subjects.

Beta-secretase inhibitors have been shown to reduce $\beta A$ in animal models and may have fewer adverse effects.[48,49] Memoquin is a beta-secretase inhibitor that also inhibits AChE, reduces $\beta A$ production, limits tau hyperphosphorylation, and fights oxidation,[50] but it is early in the developmental stage. Presently, most research involves developing secretase inhibitor molecules that will penetrate the blood-brain barrier, produce beneficial results, and not produce adverse effects.

## Insulin

Insulin has many roles in normal cell functioning. Nasal administration of insulin improved several cognitive measures in subjects with early AD or mild cognitive impairment.[51] Nasal administration allows insulin to reach the brain quickly without affecting insulin levels elsewhere in the body. Nasal administration has also improved verbal memory but only for persons with a specific genetic makeup (the apolipoprotein E4 [APOE ε4] allele).[52] The latter study used only three doses of insulin (versus 42 in the previous study) and tested 15 minutes after administration (versus after 21 days).

Insulin resistance can affect the brain as well as other organs, making it difficult for the brain cells to acquire energy for cell maintenance and synaptic connections; thus, cell death can occur.[53] Also, hyperinsulinemia has been found to increase inflammation and $\beta A_{1-42}$ in healthy adults.[54]

A possible mechanism underlying insulin resistance in the central nervous system is the formation of toxic protein fragments called beta-amyloid derived diffusible ligands (ADDLs). According to this view, ADDLs bind to synaptic receptor sites, where they prevent insulin from working, causing synaptic dysfunction and eventual dementia. Other possible mechanisms of action are described elsewhere.[55]

## Etanercept (Enbrel®)

Etanercept has recently generated interest because it produced dramatic cognitive improvement. AD brains have elevated levels of the cytokine tumor necrosis factor-alpha (TNF-α). Since TNF-α regulates neural transmission, lowering it by spinal injections of etanercept might restore the brain to more normal functioning. A dramatic cognitive improvement was evidenced in one moderate-to-severe AD subject within minutes.[56] The author reported this finding was commonly observed on multiple patients over three years of clinical practice. An open-label pilot study with mild-to-severe AD found once weekly treatments of 25-50 mg etanercept produced improvement over a six-month period.[57] Etanercept is FDA approved for immune disorders but not for AD.

## Brain Derived Neurotrophic Factor (BDNF)

BDNF is a protein produced in the brain that helps existing neurons survive, facilitates the growth of new neurons and synapses, and reverses neuronal atrophy and behavior deficits;

intracellular signaling is also facilitated. BDNF is active in the hippocampus and cortex and low levels of it are associated with poor memory. In some areas of the brain, BDNF stimulates neurogenesis. BDNF levels decline with age and are lower in AD brains than in those without dementia.[58]

In various mouse, rat, and primate models, BDNF has reversed synaptic damage, partially normalized genetic errors, improved cell signaling, reversed learning and memory deficits, reversed cognitive decline, and reduced oxidative stress and cell death.[59] These changes did not result from changes in βA.

A major problem is that the BDNF molecule is too large to penetrate the blood-brain barrier. Human trials, mostly investigating Parkinson's disease, have used a micro pump to directly infuse BDNF into the brain through a cannula inserted into the skull. This risky procedure accounts for the lack of human trials.[60] In addition, too large a dose can produce serious side effects. Although *in vitro* and animal data are promising, it is unlikely that BDNF therapy will be in use anytime soon. However, physical exercise and diets rich in omega-3 fatty acids have been found to normalize BDNF without the difficulties associated with brain infusions.[61,62]

### Immunization

βA has been reduced by injecting AD patients with a synthetic form of βA called AN1792. Although this reduces βA, the effect on AD is unclear. Some people respond to immunization with a slowing of disease progression even after 4.6 years,[63] but other studies have found a clearing of βA without any cognitive benefit.[64] It may be that βA accumulation starts a chain of events that cannot be stopped by merely clearing βA deposits.[65] Three phase II studies have been reviewed elsewhere.[66] It is unlikely that immunization therapy will be practical for some time.

The advantages and disadvantages of pharmaceutical therapies are summarized in Table 1.

### Antipsychotics and Sedatives Warning

Antipsychotics and sedatives have accelerated the progression of AD, defined as an increase of one or more points in the Global Deterioration Scale,[67] and produced a 50-percent decrease in cortical plasticity in cats.[68] Thus, care should be exercised in using such drugs for AD patients.

## Flavonoids and other Novel Plant Constituents
### HuperzineA (HupA)

HupA is an extract from the Chinese moss *Huperzia serrata* that has been used for centuries in Chinese folk medicine to treat a wide range of diseases. A review of *in vitro* and animal studies found HupA preserves ACh longer than tacrine, galantamine, or donepezil.[69] HupA reduces βA-induced neuronal degeneration in the hippocampus and cortex, decreases oxidative damage from free-radical induced βA plaques, protects neurons from cytotoxins and apoptosis induced by βA and free radicals, and inhibits glutamate toxicity. The research and potential mechanisms of action underlying these effects have been reviewed in detail.[69,70]

Acetylcholinesterase exists in different molecular forms referred to as G1, G2, G3, and G4. Human brains have mostly the G4 form with a smaller amount of G1. Hence, inhibition of G4 is more germane in terms of prolonging ACh and facilitating synaptic transmission in humans. In the striatum and hippocampus (areas important in learning and memory), HupA primarily inhibits G4, whereas donepezil primarily inhibits G1. HupA penetrates the blood-brain barrier better than donepezil, rivastigmine, or tacrine.[70]

Two Chinese randomized, double-blind, placebo-controlled trials with 103 AD patients for eight weeks[71] and 202 mild-to-moderate AD patients for 12 weeks[72] used 400 mcg HupA daily. In both cases, there was statistically and clinically more improvement in several measures of cognition, memory, and activities of daily living in the HupA group than in placebo controls. A recent meta-analysis of four Chinese studies found 300-500 mcg HupA produced a marked improvement in cognition.[73]

A U.S. phase II clinical trial of 210 mild-to-moderate AD patients over 16 weeks found 800 mcg of HupA, but not 400 mcg, resulted in cognitive enhancement.[74] A Cochrane review concluded that, although HupA improves cognition, there are too few studies of sufficient quality to recommend its use.[75] Similar conclusions were reached in another review.[76] At this point, HupA appears to be effective and better tolerated than FDA-approved AChEIs, but larger studies with longer treatment periods would be desirable.

### Polyphenols

Polyphenols are a group of plant-derived chemical substances with more than one phenol unit. They protect plants from stress induced by

**Table 1. Advantages and Disadvantages of Pharmaceuticals for AD**

| Pharmaceutical | Advantages | Disadvantages |
|---|---|---|
| Acetylcholinesterase inhibitors* | Prolong ACh; some evidence for neuroprotection; FDA approved | Often short-term efficacy; severe side effects; high costs; modest benefits |
| Memantine* | Decreases glutamate excitotoxicity; possible other neuroprotective effects; well tolerated; FDA approved for moderate-to-severe AD, but also helps mild-to-moderate AD | Possible neurotoxicity; some severe adverse effects; primarily recommended for moderate-to-severe AD; high cost |
| Antihypertensive drugs | Reduce inflammation; may block $Ca^{2+}$; may reduce $\beta A$ and increase ACh | Most human research on hypertensive individuals and animals |
| Anti-inflammatory drugs | May reduce neural inflammation | Most research focused on risk of acquiring AD and not on treatment; human research correlational in nature, making causation impossible to determine; effects on intestinal tract, liver, and kidneys; therapeutic benefit questionable |
| Secretase inhibitors | May reduce $\beta A$ and inhibit AChE | Little human research; severe adverse effects; insufficient data |
| Insulin drugs | Improve energy production and cellular functions; may reduce ADDLs and oxidative stress; reduce cell death | Must be administered nasally to prevent insulin changes in non-brain areas; little human data |
| Etanercept | Produces dramatic improvement within minutes | Little research; risky spinal injections required |
| BDNF | Stimulates neurogenesis; reverses synaptic damage; improves signaling; reduces oxidative stress and cell death | Molecule too large to penetrate blood-brain barrier; risky administration via a cannula in the skull; can produce serious side effects; little human research. |
| Immunization | Reduces $\beta A$ | Often ineffective; clearing of $\beta A$ not always accompanied by symptom reduction; early in the development stage |

*Denotes therapies with the most research backing and therapeutic potential for AD

ultraviolet radiation, disease, pests, and physical damage. Polyphenols also protect animals by activating a number of intracellular processes that preserve neurons.

### Curcumin

Curcumin is extracted from the plant *Curcuma longa* (turmeric). Reviewers suggest curcumin may be a promising therapy for AD because it has at least 10 neuroprotective properties, including anti-inflammatory, antioxidant, inhibition of βA formation, clearance of existing βA, and copper and iron chelation.[42,77,78]

Curcumin readily penetrates the blood-brain barrier, but oral administration may produce barely detectable blood levels at doses of 2 g and low levels at 8 g.[79] The reasons for bioavailability problems appear to be low absorption, rapid metabolism, quick elimination, and the inherent instability and hydrophobic nature of curcumin.

Efforts to increase bioavailability have been covered in an extensive review.[80] One approach is to use adjuvants, such as piperine, that increase bioavailability by blocking metabolic pathways. Adding 20 mg of piperine to 2 g of curcumin increased bioavailability by a factor of 20 in humans.[81] Quercetin may also enhance bioavailability.[82] Bioavailability has been significantly enhanced by combining curcumin with phosphatidylcholine or other lipophilic formulations.[83] Other approaches combine curcumin with turmeric oil or use nanoparticles.[84]

Turmeric is a widely used spice in India, which may explain why India has a much lower incidence of AD than the United States.[85,86] Bioavailability may not be a problem for Indians because it is combined with oil in cooking. A randomized, double-blind, placebo-controlled clinical trial tested nine subjects from old-age homes and 24 from dementia clinics over six months. A daily dose of 1 g or 4 g curcumin without bioavailability enhancers produced no cognitive benefit relative to a placebo.[87] No significant effects were found on several cognitive tests in another randomized, double-blind, placebo-controlled trial that used 2 g or 4 g curcumin enhanced by piperine and green tea extract (Curcumin C3 Complex®) in 36 mild-to-moderate AD patients.[88]

### Resveratrol

Resveratrol, a polyphenol found in red wine, peanuts, and other plants, reduces oxidative stress, decreases inflammation, reduces βA, protects DNA, decreases cell death, and modulates various other systems that protect cells.[77,89] Animal models suggest that resveratrol mimics the effects of caloric restriction on longevity and negates the harmful effects of a high-fat diet,[90] doubles resistance to muscle fatigue,[91] reduces neurotoxicity, decreases cell death, reduces degeneration of the hippocampus, and prevents learning impairment.[92] Several studies have shown that moderate consumption of red wine reduces the risk of developing AD.[93]

Resveratrol is similar to curcumin in that oral bioavailability is low because it is quickly metabolized and excreted. Attempts have been made to increase bioavailability by the use of quercetin, catechin, apigenin, fisetin, myricetin, and kaempferol.[94] Whether resveratrol will slow the progression of AD awaits the outcome of trials currently underway.[95]

## Herbal Supplements
### Ginkgo biloba

*Ginkgo biloba* contains compounds that have antioxidant and anti-inflammatory properties that protect neuron membranes, regulate neurotransmitters, and retard cell degeneration. It is sold as a supplement in the United States, dispensed as a pharmaceutical in Europe, and has been used for centuries in traditional Chinese medicine. *In vitro* data show that *Ginkgo biloba* extract EGb 761 reduces βA and neuron death.[96,97] Elderly mice fed EGb 761 exhibit hippocampal neurogenesis.[98] Numerous other animal and *in vitro* studies support Ginkgo's neuroprotective benefits.

Many early human studies found that Ginkgo improved cognition in AD patients. However, these studies often used few subjects and had methodological problems. More recently, a number of randomized, double-blind, placebo-controlled trials have produced positive results. Ginkgo produced more cognitive benefits than placebo for 156 AD patients receiving 240 mg daily for 24 weeks,[99] for 202 AD patients receiving 120 mg daily over 52 weeks,[100] in a 2003 re-analysis of Kanowski et al 1999 data using previously unpublished data,[101] for 214 patients with probable AD given 240 mg Ginkgo daily for 22 weeks,[102] and for a *post hoc* analysis of LeBars et al showing that Ginkgo improved cognition for mild to very mild impairment and reduced deterioration in subjects with more severe dementia.[103]

In contrast, recent randomized, double-blind, controlled studies, using subjects without dementia, concluded that Ginkgo did not slow dementia onset. One study gave 120 mg Ginkgo twice daily

to 2,587 healthy subjects and 482 subjects with mild cognitive impairment over a period of 6.1 years, with testing at six-month intervals. Ginkgo was no better than placebo at preventing the onset of dementia or AD.[104] A second study examined 3,069 healthy individuals given 120 mg Ginkgo twice daily for 6.1 years. There was no effect on cognitive decline.[105] Another study of 240 mg Ginkgo daily to 118 subjects with no cognitive impairment for 42 months found no effect on cognitive decline.[106] Thus, it appears that Ginkgo aids cognition when subjects have AD but does not prevent the onset of AD.

A study that is an exception to this conclusion failed to find benefit from 120 mg Ginkgo daily for six months.[107] This study recruited 176 participants with mild-to-moderate dementia by ads and by a clinical diagnosis of dementia from the individuals' physicians rather than by uniform, objective criteria. Although individuals were excluded if they admitted taking AChEIs, the authors mentioned there was some noncompliance. Other interventions were allowed, which could have masked the effect of Ginkgo. A final study found a benefit for Ginkgo only for a subset of AD patients who also had behavioral disturbances.[108] As the authors concluded, this outcome can be questioned because the placebo group failed to decline over the course of the study, as would have been expected, thereby potentially masking any effect of Ginkgo.

A Cochrane review of 36 trials concluded that the effect of Ginkgo is inconsistent, except in subjects having dementia with neuropsychiatric features, and that further clinical trials are unwarranted.[109] This meta-analysis combined studies on dementia patients with studies of subjects with little cognitive impairment or just age-related cognitive decline. A subsequent meta-analysis avoided such confounding by including only studies with a diagnosis of mild-to-moderate AD or AD plus vascular dementia, including several more recent studies and excluding older, methodologically problematic studies.[110] The screening yielded nine randomized, double-blind trials ranging from 12-52 weeks and totaling 2,372 subjects; all but one study was placebo-controlled. Ginkgo was moderately more effective than placebo and the difference was statistically significant.

Ginkgo and donepezil appeared equally effective in a 24-week, randomized, placebo-controlled, double-blind study of 76 mild-to-moderate AD subjects given 160 mg Ginkgo, 5 mg donepezil, or a placebo daily.[111] Similar results were obtained in

another study of 96 subjects with probable AD over 22 weeks, comparing daily doses of 240 mg Ginkgo, 5 mg donepezil increasing to 10 mg after four weeks, or placebo. Although the groups did not differ significantly, there was a suggestion that a combination of the two might be better than either alone.[112]

There are indications from a small placebo-controlled, double-blind study of 28 healthy young adults that 120 mg Ginkgo is more effective when combined with 360 mg phosphatidylserine (PS) as a phytosome (Virtiva®). Subjects were given cognitive tests at intervals of from 1-6 hours after dosing and were tested every seventh day for five sessions. Ginkgo improved performance from baseline when complexed with phosphatidylserine, but not as a standardized extract alone or complexed with phosphatidylcholine.[113] Whether this outcome would apply for AD patients is unknown.

Although concern has been raised about increased bleeding with Ginkgo, a review of the clinical-trial literature lends no credence to this hypothesis.[114]

### *Panax ginseng*

*Panax ginseng* (Chinese, Asian, or Korean ginseng) has been studied for its effects on cognition. Although an early review of randomized, placebo-controlled clinical trials on ginseng found three of four studies produced cognitive benefits, the reviewers nevertheless concluded that its effectiveness was in doubt because of methodological deficiencies.[115] In a placebo-controlled, double-blind, crossover design, a single dose of 200, 400, or 600 mg *Panax ginseng* enhanced memory in 20 young healthy adults, with 400 mg providing the most benefit.[116] Subjects were tested at intervals from 1-6 hours following dosing.

The active components in ginseng are thought to be steroid-like compounds called ginsenosides. Ginsenoside Rg3 reduced $\beta A_{1-42}$ by 84 percent *in vitro* and by 31 percent *in vivo*.[117]

Despite promising results, there have been few studies on AD. A recent review found only two studies that met the inclusion criteria. Although those studies found significant cognitive benefits, the authors concluded that methodological shortcomings rendered the evidence inconclusive.[118] A recent trial examined the effect of 4.5 g *Panax ginseng* powder daily for 12 weeks on 58 patients with probable AD, with 39 patients serving as controls. The ginseng group gradually improved over the 12 weeks of treatment, whereas the placebo group gradually declined.[119] During a

12-week follow-up period without treatment, the ginseng group gradually declined to the level of the control group.

### *Withania somnifera*

*Withania somnifera*, a small evergreen shrub commonly called ashwagandha or Indian ginseng, has been used in India for thousands of years to treat many different diseases. A recent review enumerated many neuroprotective properties of ashwagandha, including anti-inflammatory, antioxidant, inhibition of βA, inhibition of calcium, inhibition of AChE, and reduction of cell death.[120] *In vitro* research has demonstrated that ashwagandha regenerates damaged axons, dendrites, and synapses.[121,122] Oral administration of ashwagandha to mice reversed damage to the hippocampus and cortex by decreasing neurite atrophy, restoring synapses, and improving memory.[122] At least 18 withanolides, the active components in ashwagandha, have been identified. Withanolides have different neuroprotective properties; for example, withanolide-A preserves axons whereas withanolides IV and VI preserve dendrites.[123]

There is no published research on possible therapeutic effects of ashwagandha on AD. However, a recent double-blind, randomized, placebo-controlled study of the effects of ashwagandha on stress found that it reduced symptoms of stress, including forgetfulness and inability to concentrate, in a dose-dependent manner, with 500 mg/day more effective than 250 mg/day. No adverse effects were found.[124]

## Nutrients
### Phosphatidylserine

Phosphatidylserine is important in neurotransmission, mitochondria function, and cell metabolism. It has also been implicated in the enhancement of nerve growth factor. *In vitro* research demonstrates PS increases ACh[125] and provides neuroprotection by inhibiting βA and inflammation.[126]

Supplemental PS was originally derived from bovine brains, and research using bovine PS typically found cognitive benefits. The largest double-blind, multi-center, placebo-controlled study investigated 494 patients with moderate-to-severe cognitive decline, 69 of whom dropped out. They were given a placebo or 300 mg bovine PS daily for six months. The PS groups showed cognitive improvement relative to the placebo.[127] Other early positive studies have been reviewed elsewhere[128] and will not be covered here because

bovine PS is no longer available.

There is very little research on soy-based PS for AD. An open study found cognitive benefit for 18 healthy elderly subjects with age-associated memory impairment treated with 100 mg soy-based PS three times daily for 12 weeks. Testing at six and 12 weeks showed cognitive gains relative to baseline performance (there was no control group).[129] In a second randomized study, 120 elderly subjects with age-associated memory impairment received 300 mg or 600 mg soy PS or placebo daily for 12 weeks. Various cognitive tests were given after six, 12, and 15 weeks. No significant effects or interactions were found.[130] The lack of recent research and convincing data on soy-based phosphatidylserine presents a confusing picture requiring more research.

### alpha-Lipoic acid (ALA)

ALA, a fatty acid found in all cells and in some foods, is manufactured in the body. It is a powerful antioxidant that readily penetrates the blood-brain barrier, chelates metals, reduces inflammation, and increases ACh. The potential mechanisms underlying these and other neuroprotective effects are reviewed elsewhere.[131-133]

Despite potential benefits, there has been a paucity of human studies. In one open study, nine patients with AD and similar dementias were given 600 mg ALA daily for an average of 337 days. Before ALA supplementation, cognitive test scores had continuously declined; however, after onset the scores remained constant.[134] This study was extended to 48 months for 43 subjects with the same result.[135] Although promising, these studies had few subjects, no control group, were not double-blind, and came from only one lab.

### Omega-3 Fatty Acids

Omega-3 fatty acids have many beneficial effects that make them investigative prospects for AD. A recent study followed 5,395 healthy adults for an average of 9.6 years to assess the relationship between dietary omega-3 intake and risk of developing AD. Dietary intake of omega-3s was the same for the 365 subjects who developed AD as for those who did not.[136]

Another study showed no effect of 2 g/day docosahexaenoic acid (DHA) on 402 subjects with mild-to-moderate AD, but there was a slower rate of cognitive decline among those without the APOE ε4 allele.[137] Although 1.7 g DHA plus 0.6 g of EPA did not slow the rate of cognitive decline in 204 mild-to-moderate AD patients, a subset with

very mild AD did benefit.[138] A randomized, double-blind, six-month study of 485 subjects with age-related cognitive decline found 900 mg algal DHA daily improved performance on learning and memory tests relative to a placebo.[139] These data suggest that the benefits of omega-3 fatty acids are limited to those with very mild cognitive impairment.

### Acetyl L-Carnitine (ALCAR)

ALCAR, derived from the amino acid L-carnitine, works synergistically with ALA to transport acetyl groups and fatty acids into the mitochondria for energy production. ALCAR is a small molecule that readily penetrates the blood-brain barrier and promotes biosynthesis of ACh while clearing mitochondria of toxic fatty-acid metabolites.[140] Its effect on APP helps prevent the buildup of amyloid plaque and preserves synaptic function.[141] ALCAR also increases nerve growth factor.[142]

ALCAR has been found to produce cognitive benefits for AD patients. A small double-blind study of seven probable AD patients and five placebo controls found that 3 g ALCAR daily resulted in less cognitive decline over the course of one year.[143] A meta-analysis of 21 double-blind, randomized, placebo-controlled studies lasting from three months to one year showed that ALCAR either improved cognitive deficits or delayed the progression of cognitive decline.[144] These effects were both statistically and clinically significant with the magnitude of the effects increasing over time. Most studies used daily doses from 1.5-2 g, which were well tolerated.

### Coenzyme Q10 (CoQ10; Ubiquinone)/Idebenone

Coenzyme Q10 is essential for mitochondrial energy production. Mitochondrial dysfunction can result in generation of reactive oxygen species and oxidative stress.[145] Many mitochondrial dysfunctions occur in AD brains, including disruption of energy production, apoptosis deregulation, altered calcium homeostasis, and others (reviewed elsewhere).[146] For these reasons, mitochondria are viewed as promising therapeutic targets.[147]

CoQ10 reduced oxidative stress and tau pathology in mice,[148] and metabolized βA and inhibited its formation *in vitro*.[149] The reduction of βA found in a mouse model was attributed to the antioxidant properties of CoQ10.[150]

CoQ10 has other neuroprotective virtues, including protection of mitochondria, reduction of apoptosis, extension of life, reduction of brain atrophy, promotion of energy production, and protection against ischemia, as reviewed.[151-153] Data on CoQ10 have been obtained from *in vitro* studies, animal models, and human research on neurodegenerative diseases other than AD. The one trial to examine the effect of CoQ10 on AD has not yet been published.[154] CoQ10 has been found to be safe and well tolerated at doses as high as 3,600 mg/day, although maximum plasma levels are reached at a dose of 2,400 mg/day.[153]

Idebenone is a synthetic variant of CoQ10 that protects cell membranes and mitochondria from oxidative stress, preserves adenosine-triphosphate, stimulates nerve growth factor,[155] and protects from βA toxicity.[156] A two-year, randomized, double-blind study with 450 mild-to-moderate AD subjects found that each of two idebenone groups (90 and 120 mg three times daily) scored significantly better than the placebo group in several cognitive measures, with the 120-mg group scoring better than the 90-mg group.[157] A six-month, randomized, double-blind, placebo-controlled study of 300 mild-to-moderate AD patients compared idebenone (30 or 90 mg three times daily) with placebo. At the end of six months, only the 90-mg group performed better than the placebo on several cognitive tests.[158] However, not all studies have been positive. A randomized, double-blind, one-year study of 536 subjects with probable AD compared idebenone (120, 240, or 360 mg three times daily) with placebo. There were no significant differences among the four groups, although one cognitive test showed a small but significant difference between the placebo and the three idebenone groups combined. The authors concluded that the difference was too small to be of practical import.[159]

## Vitamins and Minerals
### B Vitamins

Low levels of vitamin $B_{12}$ and folate appear to be associated with an increased rate of cognitive decline.[160,161] Also, in a study of 107 normal elderly individuals, those with low-normal vitamin $B_{12}$ had the greatest five-year loss of brain volume.[162] Since AD patients typically have high levels of homocysteine,[163] researchers have examined the possibility that lowering homocysteine would be therapeutic. A combination of vitamins $B_{12}$ and $B_6$ and folate lowered homocysteine both in normal seniors[164] and in those with mild-to-moderate AD,[165,166] but had no effect on cognition. Homocysteine levels appear to correlate with aging but not with cognition.[167]

### Vitamin A

Vitamin A has received attention because it is essential for learning, memory, and cognition, and because vitamin A levels in the brain decline with age and are lower still in individuals with AD.[168] A metabolic product of vitamin A, retinoic acid, is known to slow cell death and offer protection from βA.[169]

### Vitamin E

Antioxidants have been examined extensively as therapeutic possibilities, although questions exist regarding whether oxidative stress produces AD or vice versa. Vitamin E is low in AD patients.[170] Although in vitro and animal data have been encouraging, human trials have produced conflicting results.[171] The reason for this may be that most studies have used only α-tocopherol. A study that followed 3,718 individuals over six years examined dietary consumption (excluding vitamin E supplement intake, which showed no effect) of all four tocopherols (α, β, γ, and δ) as determined by questionnaires. The authors concluded that α-tocopherol alone may not be as protective as the combined tocopherols.[172] In addition, the risk of AD was inversely related to the intake of α, γ, and δ but not β tocopherol. In general, higher levels of dietary vitamin E lowered the risk of AD and slowed cognitive decline over the six-year course of the investigation.

### Multiple Nutrients

Since AD patients often have multiple deficiencies, it makes sense to use multiple supplements. A mixture of alpha-lipoic acid, acetyl-L-carnitine, DHA, phosphatidylserine, and glycerophosphocholine prevented cognitive decline in aged mice.[173] A recent study found long-lasting cognitive improvement in elderly beagles with the daily use of one capsule/5 kg body weight of a complex with 25 mg phosphatidylserine, 50 mg Ginkgo biloba, 33.5 mg d-alpha tocopherol, and 20.5 mg pyridoxine.[174]

A study of 14 individuals with early AD found that a multiple formulation (400 mcg folic acid, 6 mcg vitamin B12, 30 IU vitamin E, 400 mg S-adenosylmethionine, 600 mg N-acetylcysteine, and 500 mg acetyl-L-carnitine per tablet, with a daily dose of two tablets) improved all measures of cognition, although the increase in memory was not statistically significant. The improvement persisted throughout the 12-month study.[175]

### Lithium

Lithium is a naturally occurring mineral found in small amounts in many foods. Lithium got a bad reputation in the 1940s when its use as a salt substitute produced toxicity and even fatalities. The lithium salts orotate and aspartate are sometimes recommended for neurogenerative disorders.

Lithium increases the level of a neuroprotective protein called bcl-2 in the rat hippocampus and frontal cortex and inhibits glycogen synthase kinase 3β (GSK-3), which is implicated in increasing levels of phosphorylated tau[176] and is thought to be a factor leading to βA plaques and cell death.[177] There is also human evidence that lithium increases N-acetyl-aspartate (NAA) which protects cells from dysfunction and death.[178] An in vitro study found lithium's neuroprotection resulted from inhibiting $Ca^{2+}$ influx mediated by NMDA receptors.[179]

Increases in grey matter were found for 8 of 10 bipolar subjects given four weeks of lithium.[180] These neuroprotective effects have led some to suggest that lithium may have been overlooked as a therapy for dementia.[181]

No human trials have been published, but some data are relevant. One study found only five percent of bipolar patients treated with lithium had AD compared with 33 percent of untreated patients.[182] Anecdotal evidence comes from Jonathan V. Wright, MD, who claims he has used 10-20 mg lithium aspartate or orotate for over 30 years and found it effective for AD.[183] Human trials are sorely needed.

## Hormones
### Melatonin

Melatonin is a naturally occurring hormone that is produced in decreasing amounts with age. Melatonin is a powerful antioxidant, provides mitochondrial support, protects against tau tangles, and reduces βA toxicity.[184] Melatonin readily crosses the blood-brain barrier and enters all cell structures. A case study in which one identical twin was given 6 mg melatonin daily, whereas the other was not, revealed that the melatonin-treated twin had less memory loss over 36 months.[185] Another small study showed 6 mg melatonin daily improved mood and memory over six days for 10 patients with mild cognitive impairment.[186] In another study, melatonin (9 mg/day) was given to 14 sleep-disordered AD patients over 22-35 months. In the authors' judgment, the subjects did not show typical cognitive decline over the course of this experiment,[187] or in a similar

## Table 2. Summary of Botanicals and Nutrients for AD

| Nutrient or Botanical | Advantages | Disadvantages |
|---|---|---|
| Huperzine A | Prolongs ACh; reduces oxidative damage; excitotoxicity & apoptosis; penetrates the blood-brain barrier better than cholinesterase inhibitors; well tolerated; benefits cognition | Not many studies |
| Polyphenols | Curcumin has at least 10 neuroprotective properties including inhibition of oxidative stress, inflammation, and $\beta$A; benefits cognition; resveratrol has similar benefits; both are well tolerated | Curcumin has low bioavailability unless accompanied by bioavailability enhancers; need more human trials; little human research on resveratrol therapy for AD |
| *Ginkgo biloba*\* | Has antioxidant and anti-inflammatory properties; retards cell death; well tolerated; considerable research backing cognitive benefit | Appears to work for AD but not mild cognitive impairment; does not reduce risk of getting AD |
| *Panax ginseng* | Has neuroprotective effects, including reduction of $\beta$A, but mechanisms are largely unknown; cognitive benefits have been reported; well tolerated | Human studies few in number and weak in methodology |
| *Withania somnifera* | Many neuroprotective properties, including reducing inflammation, oxidation, $Ca^{2+}$, $\beta$A, AChE, and cell death; restores synapses | No research on humans with AD |
| Phosphatidylserine | Important in neurotransmission, mitochondria function, and cell metabolism; may enhance nerve growth factor; increases ACh and inhibits $\beta$A; well tolerated | Most positive research used bovine-derived PS now unavailable; the studies using soy-derived PS equivocal |
| alpha-Lipoic acid | Increases ACh and glucose; easily penetrates the blood-brain barrier; powerful antioxidant inside and outside cells; regenerates itself; reduces inflammation; well tolerated | Limited AD research; none without serious shortcomings |
| omega-3 Fatty acids | Many beneficial effects, but not specific to AD; well tolerated | Limited research; little benefit except in mild impairment |
| Acetyl L-carnitine\* | Readily penetrates the blood-brain barrier; promotes ACh and clears mitochondria of toxic metabolites; inhibits free radicals; increases NGF; preserves synaptic function; reduces $\beta$A production; considerable evidence of benefit; well tolerated | More research would be welcome, but reasonable current body of literature |
| Coenzyme Q10 | Protects mitochondria and promotes energy production; reduces oxidative stress, $\beta$A, apoptosis, and brain atrophy. The synthetic variant, idebenone, more readily penetrates the blood-brain barrier; all forms well tolerated | Research has been on neurodegenerative diseases other than AD except for one unpublished study; not all idebenone studies have shown cognitive benefits |
| Vitamins & minerals | AD patients typically have low levels; supplementation has shown benefit for E, lithium, and some nutrient combinations | Although reasonable to supplement when deficiencies exist, insufficient research to draw conclusions in most cases |
| Melatonin | Antioxidant, protects mitochondria, reduces tau tangles and $\beta$A toxicity; readily penetrates the blood-brain barrier; enters all cell structures; cognitive benefits in several studies; well tolerated | Few studies on AD subjects and those are small and poor in quality |

\*Denotes therapies with the most research backing and therapeutic potential for AD

study using 6 mg/day for four months to 45 AD patients with sleep disturbances.[188] One study failed to find cognitive benefits from 3 mg melatonin, which is a lower dose than others typically used.[189]

Despite numerous studies, few have examined its effect on AD and the ones that did were small and of poor quality. Since melatonin improves sleep, it might help memory by facilitating memory consolidation.

The advantages and disadvantages of nutritional and botanical therapies are summarized in Table 2.

## Stimulatory Therapies

Physical exercise, cognitive training, and socialization are generally thought to facilitate cognitive functioning.[190,191] Physical exercise increases the blood supply to the brain and regulates chemicals such as insulin that are necessary for a healthy brain. Recent reviews of studies on exercise indicate that exercise may facilitate learning and memory, improve vascular function, reduce inflammation, improve metabolism, elevate mood, delay age-related memory loss, speed information processing, increase brain volume, aid hippocampal neurogenesis, increase synaptic plasticity, increase brain-derived neurotrophic factor, increase dendritic spines, enhance the glutamatergic system, and reduce cell death.[192,193]

A meta-analysis of 18 studies examined the effect of exercise on healthy but sedentary older adults. Exercise had the largest effect on executive function (planning, coordination, working memory, abstract thinking, initiating appropriate actions, and inhibiting inappropriate ones), with lesser effects on skill acquisition and visuospatial tasks.[194] Executive functioning requires the greatest level of cognitive function and suffers significantly in AD.

Patients with early AD who exercised showed less brain atrophy than those who did not.[195] Another study of people with mild cognitive impairment found exercise (mostly walking) led to significantly better performance than control subjects on some, but not all, cognitive measures.[196] Actual changes in the brain have also been found. Aerobically fit individuals had larger hippocampi and better spatial memory than those who were less fit.[197] On the other hand, sedentary elderly adults showed more memory decline over the course of a day than those more active.[198]

Brain stimulation and socialization are important in brain plasticity. Mild-to-moderate AD patients who engaged in socialization

interventions for more than two semesters showed no year-to-year decline in various measures of cognitive functioning.[199] In another study, 37 adults were divided into placebo versus treatment groups. The treatment group, given a variety of cognitive tasks to work on at home, showed modest gains in recall and face name recall (tasks on which they were trained), although the training did not generalize to other cognitive measures.[200]

Another study with mild-to-moderate AD patients demonstrated that the benefits of memory training lasted months after the training ended.[201] Even longer-term benefits have been observed. A total of 2,832 elderly (mean age 73.6) normal adults were randomly assigned to placebo or training on memory, reasoning, or processing speed. Training resulted in improved cognitive scores specific to the area in which they were trained that lasted five years after the first treatment.[202] In all such studies, it would be desirable to examine the amount of sleep subjects got since that is when memories are consolidated. Unfortunately, sleep quality and quantity, which are commonly poor in the elderly, are generally overlooked.

Brain exercises can improve function in those suffering from mild cognitive impairment. A randomized, controlled, double-blind study on 487 elderly subjects without significant cognitive impairment was conducted using Posit Science's Brain Fitness Program, a series of computer-based exercises that target different areas of the brain (visual, auditory, speech, motor, etc.).[203] Cognitive training was conducted for one hour daily, five days per week, for eight weeks. The control group viewed educational videos, after which they were tested for memory of the content. For all measures, cognitive training produced higher scores than educational videos; the training generalized to non-trained tasks. Other companies are pursuing similar approaches but have less research backing.

Most studies of music stimulation have examined it as a way to moderate problematic behavior in cases of moderate-to-severe AD,[204] and to reduce levels of stress, anxiety, and depression in mild-to-moderate AD.[205] However, a few studies have focused on cognitive changes. One study compared the effects of music with controls shown a movie. Once a week for eight weeks, 17 dementia subjects were randomly assigned to music or movie groups. Cognitive testing immediately after the intervention and the next morning showed superiority for the subjects given music; however, the effect did not last until the next week's session.[206]

Mechanisms that might underlie such benefits include increased natural killer cells that destroy dysfunctional cells[207] and increased serum melatonin levels.[208] A recent paper hypothesized that music increases steroid production that facilitates neurogenesis, repairs cells, and increases neural plasticity.[209] Notwithstanding these studies, music's potential for AD therapy remains largely uninvestigated.

Psychological factors that might either ameliorate or exacerbate AD have generally been overlooked because the emphasis has been on medications to treat the problem. The patient's attitude could play a key role in retarding or accelerating progression of the disease. A patient who views all as lost will likely unknowingly contribute to making that view a self-fulfilling prophecy. On the other hand, patients who have a positive attitude and engage in activities they enjoy may experience a slowing of AD progression. Such people are likely to eat better, exercise more, be more positive about life, and engage in other activities that could enhance brain function. Therapists can encourage positive attitudes by the way they interact with patients, instilling confidence and a positive attitude.

The advantages and disadvantages of stimulatory therapies are summarized in Table 3.

## Therapeutic Strategies

One therapeutic strategy is to use only FDA-approved pharmaceuticals for AD. However, it has been estimated that less than 20 percent of AD patients have even a moderate response to approved drugs.[210] Also, approved drugs offer little or no neuroprotection, are effective for only a short duration, often produce serious side effects, and are expensive. Another option is to use FDA-approved drugs off label, such as rosiglitazone and ACE inhibitors. This approach also has risks of adverse effects and no conclusive evidence of benefit.

Some nutritional and botanical therapies, although not FDA approved, have been approved for AD in Europe and other countries.

### Table 3. Stimulatory Therapies for AD

| Activity | Advantages | Disadvantages |
|---|---|---|
| Physical exercise | Increases blood to brain; improves vascular function; aids sleep; reduces inflammation; elevates mood; increases brain volume; increases synaptic plasticity; aids neurogenesis; reduces cell death; benefits some cognitive processes | None if done within one's physical capabilities; little research specifically on AD patients |
| Cognitive training | Improves many cognitive functions | More research indicated |
| Socialization | Preserves cognitive functioning; may improve mood | Little research |
| Music | Reduces stress and depression; improves cognition, perhaps by aiding the destruction of dysfunctional cells, increasing melatonin levels, facilitating neurogenesis, and increasing plasticity | Little research |
| Psychological factors | A positive attitude may stimulate patients to exercise and engage in activities that are beneficial | No research specific to AD |

Decisions faced by therapists and patients differ from those faced by researchers. It is incumbent upon researchers to require definitive and reliable results before accepting treatments as effective. However, patients and practitioners must make decisions based on the available data, knowing that failure to treat has obvious adverse consequences. Some individuals have been led to try non-approved therapies, although doing so requires that the potential benefits and risks be recognized and weighed against the known harm that accompanies continued disease progression.

Safe doses have been determined for many dietary supplements, many of which have been used for hundreds of years. As long as a treatment does not produce known or unacceptable harm, the major risks are expense and the possibility that an approach might not work, a gamble that many are willing to make. Frequently, the expense is less than patented drugs that can cost hundreds of dollars per month. Certainly, stimulatory treatments like physical exercise, brain exercises, and socialization produce no harm and are highly recommended by health professionals.

Studies of pharmaceutical, nutritional, and botanical therapies all have apparent contradictory findings. These can arise from differences among subjects based on genetics, socioeconomic status, diet, and other factors. Varying dosages and methodologies as well as failure to examine or control for such things as dietary deficiencies, supplement use, levels of βA, and tau can contribute to discrepant results. Pharmaceutical studies seldom report whether subjects are also taking nutrients or botanicals or engaging in stimulatory therapies; sometimes the reverse is true. Studies are needed that control for a wider range of variables.

Given the complexities of AD, therapies that target different mechanisms simultaneously make sense. Ideally, it would be desirable to determine specific neurochemical dysfunctions and genetic factors for each individual and tailor therapy with those targets in mind. However, in the absence of such detailed information, the next best approach might be to use a multifaceted therapy that targets βA, tau tangles, oxidative stress, excitotoxicity, and other cellular dysfunctions. This could involve using one drug that targets several processes or using several substances that collectively target multiple dysfunctions. It may also be more effective to choose therapies that act at the beginning of the pathological cascade (e.g., secretase inhibitors, nutrients, or botanicals) rather than treatments that act after the fact (e.g., removal of amyloid plaques). One point on which all agree is that therapy should begin as early as possible while reversal of cellular pathologies is still achievable.

Finally, normal cell function is maintained by nutrients from foods. Consequently, it seems reasonable to use some form of these same nutrients to correct cell dysfunctions, a concept that is especially relevant for AD brains that are particularly low in many nutrients. At the present time, nutritional, botanical, and stimulatory therapies may provide more benefit and with fewer adverse consequences than conventional medications.

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