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Herbal medicine in the treatment of Alzheimer’s disease

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Abstract

Alzheimer’s disease (AD) is characterized by profound memory loss sufficient to interfere with social and occupational functioning. It is the most common form of dementia, affecting more than 20 million people worldwide. AD is characterized by an insidious loss of memory, associated functional decline, and behavioral disturbances. Patients may live for more than a decade after they are diagnosed with AD, making it the leading cause of disability in the elderly. The incidence of AD ranges from 1 to 4 percent of the population per year; rising from its lowest level at ages 65 to 70 years to rates that may approach 6 percent for those over the age of 85 years. The first neurotransmitter defect discovered in AD involved acetylcholine (ACh). As cholinergic function is required for short-term memory, the cholinergic deficit in AD was also believed to be responsible for much of the short-term memory deficit. Clinical drug trials in patients with AD have focused on drugs that augment levels of ACh in the brain to compensate for the loss of cholinergic function. These drugs have included ACh precursors, muscarinic agonists, nicotinic agonists, and acetylcholinesterase inhibitors. The most highly developed and successful approaches to date have employed acetylcholinesterase inhibition. Although some Food and Drug Administration–approved drugs are available for the treatment of Alzheimer’s disease, the outcomes are often unsatisfactory, and there is a place for alternative medicine, in particular, herbal medicine. This paper reviews the clinical effects of a number of commonly used types of herbal medicines for the treatment of AD.

Key words: Alzheimer’s disease, Ginkgo biloba, herbal medicine, Melissa officinalis, Salvia officinalis

Introduction

Alzheimer’s disease (AD) is the most common cause of severe mental deterioration (dementia) in the elderly. AD was known to occur occasionally in families but was not necessarily thought to be related to the more frequent occurrence of cognition impairment in late life. The latter condition was known as senile dementia. When results of careful pathology studies emerged in the 1970s and 1980s showing that the pathology of the brains of patients with early-onset (before the age of 65 years) and late-onset AD was the same, research into the pathologic process as well as the clinical manifestations accelerated. The incidence and prevalence of AD rose with increasing age, especially for those over the age of 65 years. The incidence of AD ranges from 1 to 4 percent of the population per year, rising from its lowest level at ages 65 to 70 years to rates that may approach 6 percent for those over the age of 85 years. Prevalence of AD has been a subject of discussion. Prevalence rates of AD also increase by half a decade or decade; reports in the literature of how many cases exist at any one period vary. Estimates of the prevalence of AD range from 3 percent of the population between the ages of 65 and 75 years to the highest reported estimate of 47 percent of people over the age of 85 years. In general, all studies report a progressive increase in the prevalence of dementia as a function of age between 65 and 85 years; more conservative estimates at the higher end are in the range of 30 to 35 percent, which is still a significant number. Whatever the current estimates, all researchers agree that the number of AD cases will probably triple over the next 30 to 40 years.
Definitions of AD

There are three widely used criteria-based approaches to the diagnosis of AD: the International Classification of Diseases, 10th revision (ICD-10); the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV); and the National Institute of Neurological and Communicative Disorders and Stroke (Alzheimer’s Disease and Related Disorders Association [NINCDS-ADRDA]) work group criteria. Not surprisingly, the three definitions share many common features.

Three common misconceptions regarding AD are: 1) that it is a global disorder, 2) that it is a diagnosis of exclusion, and 3) that it can be diagnosed only at autopsy. All are challenged by the three diagnostic frameworks that require that attention be sufficiently intact to exclude delirium as the cause of the mental status changes, whereas a global disorder would include attentional abnormalities. All the definitions specify expected findings (memory impairment, absence of focal findings), thus using inclusionary criteria in the diagnosis rather than approaching the disorder as a diagnosis of exclusion. All definitions are dependent on the feasibility of clinical diagnosis, and most series find accuracy rates of 85 to 90 percent based on these criteria. A diagnostic workup for AD should begin with detailed interviews of both the patient and an informant who is familiar with the patient. The medical history can provide relevant information, such as the timing of onset of symptoms, level of functional impairment, rate of deterioration, and any alterations in mood. A complete physical examination should include an in-office cognitive assessment, such as the Mini-Mental State Examination, and a brief neurological examination. The presence of depression should also be evaluated; useful screens include the Geriatric Depression Scale and the Zung Self-Rating Scale for Depression. Laboratory evaluations should include blood chemistry; a complete blood cell count; tests for syphilis, thyroid, kidney, and liver function; and serum levels of vitamin B12. Some neuroimaging is generally recommended. Computed tomography is usually sufficient to eliminate subdural hematoma or tumors as a potential cause; however, magnetic resonance imaging (MRI) may be necessary to detect the presence of white-matter ischemic lesions. Positron emission tomography (PET) or single-photon emission computed tomography (SPECT) are useful in distinguishing AD from other dementias through quantifying metabolism or to assess general blood flow.

Pathophysiology of AD

Neuroimaging of the patient with AD or other dementias may reveal atrophy of the brain, such as enlarged ventricles and sulci and narrowed gyri, although these features are not always present. Neuronal loss is the main neuropathologic feature underlying the symptoms of AD. Microscopically, AD is characterized by the presence of senile plaques and neurofibrillary tangles (NFTs). Plaques are extracellular deposits of filamentous β-amyloid, a protease cleavage product of amyloid precursor protein. NFTs are formed intracellularly by the abnormal rearrangement of microtubule-associated proteins, such as tau. Both NFTs and senile plaques, although diagnostic of AD when observed in large numbers, are also present to some degree in the brains of normal elderly persons. However, the plaques seen in normal brains or early-stage AD are diffuse and relatively benign deposits of β-amyloid, whereas at later stages, the plaques assume a compact b-pleated conformation and subsequently become associated with dystrophic neuritis. These later-stage plaques are thought to represent a more neurotoxic form.

Cholinergic Hypothesis

The first neurotransmitter defect discovered in AD involved acetylcholine (ACh). Because cholinergic function is required for short-term memory function, it was determined that cholinergic deficit in AD was also responsible for much of the short-term memory deficit. Markers for cholinergic neurons such as choline acetyltransferase and acetycholinesterase, which are enzymes responsible for synthesis and degradation of ACh, respectively, are decreased in the cortex and hippocampus, areas of the brain involved in cognition and memory. The earliest loss of neurons occurs in the nucleus basalis and the entorhinal cortex, where cholinergic neurons are preferentially affected. As the illness progresses, up to 90 percent of cholinergic neurons in the nucleus basalis of Mynter may be lost. Animal studies have demonstrated that loss of cholinergic function in these areas is associated with declines in learning capacity and memory. The resultant decrease in ACh-dependent neurotransmission is thought to lead to the functional deficits of AD, much as dopaminergic deficits underlie Parkinson’s disease and its clinical manifestations. Clinical drug trials in patients with AD have focused on drugs that augment levels of ACh in the brain to compensate for losses of cholinergic function in the brain. These drugs have included ACh precursors, muscarinic agonists, nicotinic agonists, and cholinesterase inhibitors. The best-developed and most successful approaches to date have used cholinesterase inhibition. The first drug approved for general clinical use in AD was tacrine. However, three new cholinesterase
inhibitors are currently available: donepezil (Aricept®), rivastigmine (Exelon®), and galantamine (Reminyl®). All of these drugs have been tested primarily in patients with AD, with most trials studying treatment in patients with mild to moderately severe illness. The newest drug for AD breaks out of the ACh-enhancing mode and focuses on a different receptor complex. Memantine (Namenda®) was approved for the US market in October 2003 and has been used in Europe for many years. Memantine is marketed for patients at the moderate to severe stages of the disease.

**Pharmacologic treatment**

While no drug has been shown to completely protect neurons, agents that inhibit the degradation of ACh within the synapse are the mainstay of treatment for AD. Acetylcholinesterase/cholinesterase inhibitors and memantine are the only agents approved by the Food and Drug Administration for the treatment of AD. Other drugs, such as selegiline, vitamin E, estrogen, and anti-inflammatory drugs have been studied, but their use remains controversial. Various other agents have been used in an attempt to modify the course or improve the symptoms of AD, including Ginkgo biloba. The cholinesterase inhibitor tacrine is used rarely because of potential liver toxicity and the need for frequent laboratory monitoring. Nevertheless, donepezil, rivastigmine, and galantamine have low incidences of serious reactions, but they commonly have cholinergic side effects such as nausea, anorexia, vomiting, and diarrhea.

Many of today’s synthetic drugs originated from the plant kingdom, and only about two centuries ago the major pharmocopeias were dominated by herbal drugs. Herbal medicine went into rapid decline when basic and clinical pharmacology established themselves as leading branches of medicine. Nevertheless, herbal medicine is still of interest in many diseases, in particular, psychiatric and neurological disorders. There are some reasons for this issue: 1) patients are dissatisfied with conventional treatment, 2) patients want to have control over their healthcare decision, and 3) patients see that herbal medicine is congruent with their philosophical values and beliefs. There are several studies and documents that indicate a unique role of herbal medicines in the treatment of AD.

**Galantamine**

An alkaloid cholinesterase inhibitor originally derived from European daffodils or common snowdrops, this drug is a competitive and selective acetylcholinesterase inhibitor. Galantamine also allosterically modifies nicotinic ACh receptors, potentiating the presynaptic response to ACh. Like donepezil and rivastigmine, galantamine is brain selective. Galantamine has a half-life of five to six hours and is metabolized by the same CYP-450 enzymes as donepezil. Galantamine has not been associated with hepatotoxicity in clinical trials. Pooled data from four randomized trials of patients with mild AD indicate that patients who received galantamine 24 mg/d for six months had improved cognition more often than those who received placebo, and that a higher proportion receiving galantamine were globally improved. This suggests that patients with mild AD benefit from galantamine treatment.

**Ginkgo biloba**

Ginkgo biloba is an herbal medicine that has been used to treat a variety of ailments for thousands of years in China. An extract of Ginkgo biloba has been found in several studies to improve the symptoms and slow the progression of AD. A study of 309 patients with mild dementia was performed. The patients were given either 120 mg of Ginkgo biloba extract (GBE) or placebo every day for up to a year. At the six-month point, 27 percent of those using Ginkgo biloba had moderate improvement on a variety of cognitive tests. Only 14 percent of those using placebo had an improvement on these tests. In a separate trial, 112 patients with chronic cerebral insufficiency received 120 mg/d of GBE. The researchers found that the use of this extract led to significant improvements in blood and oxygen flow. Restricted blood and oxygen flow to the brain may be an important factor in the development of AD.

GBE appears to be most effective in the early stages of AD. This could potentially mean that patients with early AD may be able to maintain a reasonably normal life. GBE has been shown to have the ability to normalize the ACh receptors in the hippocampus area of the brain (the area most affected by the disease) in aged animals. GBE has also demonstrated the ability to increase cholinergic activity and to provide improvements in other aspects of the disease. A double-blind study of 216 patients with AD or dementia caused by small strokes found that 240 mg of GBE daily led to significant improvements in a variety of clinical parameters when compared to placebo. The most effective form of GBE is one that is standardized to a concentration of 24 percent Ginkgo flavoglycosides.

A study compared the effectiveness of the most common AD drugs, such as donepezil and rivastigmine, to that of a Ginkgo biloba extract called EGb761. The researchers determined that EGb761 was as effective as...
any of these commonly prescribed drugs in treating the symptoms of AD patients. In general, various forms of Ginkgo biloba have been found to be safe, but in individuals who take aspirin or other anticoagulant drugs, Ginkgo biloba should be taken with great caution and with the advice of a physician. Ginkgo biloba is sold as a drug and regulated in Germany, and it is used in many other parts of the world to slow the progression of various forms of dementia. The most commonly sold form of Ginkgo biloba in Europe is EGb761 (80 to 120 mg/d).

A different study found that EGb761 prevents β-amyloid toxicity to brain cells, a key part of the development of the disease. All forms of Ginkgo biloba need to be taken consistently for at least 12 weeks, a potentially difficult task for AD patients, to determine whether the supplement is working. A recent double-blind placebo-controlled randomized study of patients with AD found that EGb761 produced significant improvements in cognitive function compared to a placebo group. Other recent comprehensive surveys of multiple clinical trials found similar results with EGb761 in these patients. An additional study found that EGb761 produced cognitive improvement compared to placebo over a 26-week period using a variety of research measures. This study also demonstrated that EGb761 was as safe as placebo during the study period. Nevertheless, the clinical trial data for cholinesterase inhibitors, reported in reviews by the Cochrane Collaboration, appear to be more consistent and robust than those for Ginkgo biloba, and also show greater effects on cognition. Considering the evidence, it is suggested that cholinesterase inhibitors should be used in preference to Ginkgo biloba in patients with mild to moderate AD.

Huperzine A

Huperzine A is a chemical derived from a particular type of club moss (Huperzia serrata). Like caffeine and cocaine, huperzine A is a medicinally active plant-derived chemical that belongs to the class known as alkaloids. This substance is really more a drug than an herb, but it is sold over the counter as a dietary supplement for memory loss and mental impairment.

According to three Chinese double-blind trials enrolling a total of more than 450 people, use of huperzine A can significantly improve symptoms of AD and other forms of dementia. One double-blind trial failed to find evidence of benefit, but it was relatively small.

Vinpocetine

Vinpocetine is a chemical derived from vincamine, a constituent found in the leaves of common periwinkle (Vinca minor) as well as the seeds of various African plants. It is used as a treatment for memory loss and mental impairment.

Developed in Hungary more than 20 years ago, vinpocetine is sold in Europe as a drug under the name Cavinton. In the United States, it is available as a “dietary supplement,” although the substance probably does not fit that category by any rational definition. Vinpocetine does not exist to any significant extent in nature. Producing it requires significant chemical work performed in the laboratory.

Several double-blind studies have evaluated vinpocetine for the treatment of AD and related conditions. Unfortunately, most of these studies suffered from significant flaws in design and reporting. A review of the literature found three studies of acceptable quality, enrolling a total of 728 individuals. Perhaps the best of these was a 16-week double-blind placebo-controlled trial of 203 people with mild to moderate dementia that found significant benefit in the treated group. However, even this trial had several technical limitations, and the authors of the review concluded that vinpocetine cannot yet be regarded as a proven treatment. Currently, several better-quality trials are underway.

Melissa officinalis and Salvia officinalis

It has been reported that Melissa officinalis (lemon balm) improves cognitive function and reduces agitation in patients with mild to moderate AD. M. officinalis is known to have ACh receptor activity in the central nervous system with both nicotinic and muscarinic binding properties. A recent study has shown that this plant modulates mood and cognitive performance when administered to young, healthy volunteers. In addition, a parallel, randomized, placebo-controlled study assessed the efficacy and safety of M. officinalis in 42 patients with mild to moderate AD. Subjects were treated for four months. The main efficacy measures were the cognitive subscale of the Alzheimer’s Disease Assessment Scale (ADAS-cog) and the Clinical Dementia Rating-Sum of the Boxes (CDR-SB) scores. The CDR-SB provides a consensus-based global clinical measure by summing the ratings from six domains: memory, orientation, judgment, problem solving, community affairs, home and hobbies, and personal care. The results revealed that patients receiving M. officinalis extract experienced significant improvements in cognition after 16 weeks of treatment. Improvements were seen on both the ADAS-cog and CDR-SB scores. The changes at the end-point compared to baseline (mean [SD]) were -1.92 (1.48) and 1.03 (0.54) for Melissa extract and placebo, respectively, on the CDR-SB scores. The researchers observed no significant difference in the
frequency of side effects between the placebo group and those receiving the herb extract. However, the frequency of agitation was higher in the placebo group compared to those receiving active treatment. Moreover, another study showed that patients with mild to moderate AD receiving Salvia officinalis (sage) extract experienced statistically significant benefits in cognition after 16 weeks of treatment. The clinical relevance of these findings was emphasized by the improvements seen in both the ADAS-cog and CDR-SB measures in the S. officinalis extract group on both observed case and intention-to-treat analyses. The changes at the endpoint compared to baseline (mean [SD]) were -1.60 (1.35) and 0.73 (0.41) for Salvia extract and placebo, respectively, on the CDR-SB scores. The side effects associated with Salvia in this study were generally those expected from cholinergic stimulation and were similar to those reported with cholinesterase inhibitors. Frequency of agitation appeared higher in the placebo group, and this may indicate an additional advantage for M. officinalis in the management of patients with AD.

In conclusion, treatment strategies will have to include a variety of interventions directed at multiple targets. So far, the outcomes with available Food and Drug Administration–approved medications for AD are often unsatisfactory, and there is a place for alternative medicine, in particular herbal medicine. As described for many of these herbs, there is, in fact, a putative pharmacological target such as a receptor or neurotransmitter; none of the herbs can be said to treat the "whole disorder."

References