Alzheimer's Disease: An Overview for Clinical Practice

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Abstract

Alzheimer's disease is now thought to be the fourth leading cause of death in developed nations and is estimated to affect 10% of the population over the age of 65. The cause of Alzheimer's disease is under promising investigation. The variety of theories suggests that Alzheimer's disease is multifactorial in origin. The disease is characterized by a specific enzyme deficiency and the occurrence of senile plaques, neurofibrillary tangles and granulovacuolar degeneration. The diagnosis of Alzheimer's disease should be based on a good history, physical exam and appropriate lab work. The clinical course of Alzheimer's disease lasts from 8 to 20 years and is characterized by progressive deterioration. Treatment is focused on identifying the cause and finding chemical precursors that can be used by the brain to either retard or stop the dementing process. Various nutrients, including vitamin and minerals and botanical medicines may be of some use in treating this disease.

Introduction

Alzheimer's disease (AD) has been called "the disease of the century" and is now thought to be the fourth leading cause of death in developed nations, after heart disease, cancer and stroke. Alzheimer's disease is estimated to affect 5 to 10% of the population over the age of 65 and up to 20% of the population over age 80. One of the most feared and devastating aspects of aging is the deterioration of memory and other mental processes that occurs with increasing frequency in advancing years. In 1900 only 4% of the population in Canada and the United States had attained 65 years of age. By 1990, 11% of the population was estimated to be 65 years or older. The fastest growing segment of today's population in North America is the 80 years and older group. Current demographic projections indicate that this trend will continue and the percentage of individuals 65 years old and older will increase throughout the remainder of this century and afterward as well. One of the travesties of modern medicine is that even though life expectancy has been increasing, the quality of life in the golden years, arguably, has been decreasing. The medical and social dimensions of this affliction are staggering. Alzheimer's disease is estimated to affect 1 to 3 million members of the North American population and is the major cause of institutionalization among the more than one million people in nursing homes throughout North America. Alzheimer's and other forms of dementia currently account for six billion dollars annually in nursing home costs. Many other individuals afflicted with Alzheimer's disease continue to be cared for in their homes, by both relatives and home health aides. Close relatives of the victims of Alzheimer's disease must bear a tremendous financial and emotional burden while caring for these patients. The purpose of this article is to summarize the current state of knowledge about Alzheimer's disease and to suggest natural therapies that may offer hope in treating this disease (1,2).

Definition

Dementia is the term used to describe generalized cognitive and intellectual deterioration. This term describes a clinical syndrome that can be produced at any age by numerous causes including head trauma, brain tumor, nutritional disturbances, encephalitis, heavy metal poisoning, anoxia, Alzheimer's disease and the like. The World Health Organization (WHO) classified dementia into two categories: presenile

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dementia and senile dementia. Presenile dementia refers to dementia that occurs before the age of 65 in patients with relatively rare forms of brain atrophy. Senile dementia refers to dementia that usually occurs after the age of 65 and excludes mild memory disturbances. Finally the term, Alzheimer's disease is used at present to refer to the classic clinical syndrome, with dementia of gradual onset and course, accompanied by neurological changes in the brains of affected individuals. Alzheimer's disease, as defined, may thus become manifest either before or after 65 years of age (1).

Historical Perspective

Concepts about senile dementia have varied and evolved for more than 2,500 years. Views about Alzheimer's disease have developed largely since the start of the 20th century. Hippocrates, "the Father of Medicine," was one of the first individuals who attempted to explain the degenerative processes associated with aging. It wasn't until the 19th century that the term "presenile dementia" was introduced. Then in 1906 the German physician Alois Alzheimer identified functional and structural changes in the brain of a 51 year old patient who had presenile dementia. This disease, given the name "Alzheimer's disease," was subsequently used to label senile and presenile dementia of unknown origin (1).

Cause of Alzheimer's Disease

The cause of Alzheimer's disease is not definitively understood. The variety of theories suggests that Alzheimer's disease is multifactorial in origin. Leading theories of the causes of Alzheimer's Disease include:

1. Neurotransmitter or other brain chemical deficits or imbalances (particularly acetylcholine and proteins).
2. Selective brain cell death or injury induced by viral or other transmissible disease agents in the environment.
3. Excessive accumulation in the brain of aluminum or other toxins.
4. Genetic factors (defects or predispositions).
5. An autoimmune process (i.e., anti-brain antibodies related to aging).

Genetic predisposition to Alzheimer's disease varies. There are a few families in which the disease appears to be genetically transmitted as an autosomal dominant trait and in these families the incidence of the disease approaches 50 percent. In more typical cases, if one parent is affected, fewer than 10 percent of the children will develop the disease. If both parents are affected, the incidence in the offspring increases to about 25 percent. The apparently higher incidence of Alzheimer's in women than in men is probably a reflection of the greater longevity of females and there is no clear evidence of a predilection for one sex over the other (2).

One condition in which Alzheimer's disease occurs with great regularity on an inherited basis is Down syndrome or trisomy 21 and there is a possible association with thyroid dysfunction in women with this form of dementia (3).

One interesting study showed that individuals with Alzheimer's disease showed specific fingerprint patterns. Patients with Alzheimer's disease showed a significantly increased frequency of ulnar loops on their fingertips and a decreased frequency of whorls and arches. The fingerprint patterns observed in patients with Alzheimer's disease are similar to patterns repeatedly found in patients with Down syndrome, and support the known associations between these two diseases (4).

Kuru and Creutzfeldt-Jakob disease are relatively rare degenerative diseases affecting the brains of infected individuals. There are many clinical and pathological similarities between Kuru and Creutzfeldt-Jakob disease and Alzheimer's disease. Since the discovery that certain slow viruses were responsible for the development of Kuru and Creutzfeldt-Jakob disease, there has been much speculation as to the possible role of slow viruses in the development of Alzheimer's disease. It has been speculated, that like Kuru and Creutzfeldt-Jakob disease, Alzheimer's disease may be the result of previous viral disease or infection with a slow virus (2).

Toxic response has also been postulated as a causative mechanism. Aluminum and silicon deposits have been detected in the affected portions of the brains of patients with Alzheimer's disease. However, these deposits may be the result of the disease, rather than a causative factor (5).

One intriguing theory attempts to link Alzheimer's disease to aging immune mechanisms. This conjecture is supported by the phenomenon of immuno-incompetence and the increased number of auto-antibodies that appear late in the course of the disease.

Pathology of Alzheimer's Disease

Alzheimer's disease is characterized by the loss of the enzyme choline acetyltransferase (CAT) which is responsible for the formation of the neurotransmitter acetylcholine. A 30 to 50% loss of CAT activity has been measured in affected brain tissue (1).

Microscopic analysis of brain tissue demonstrates the classic findings that were described by Alois Alzheimer more than 80 years ago. Three characteristic lesions of Alzheimer's disease include senile plaques (amyloid deposits), neurofibrillary tangles (paired helical filaments) and granulovacuolar degeneration (1).

Senile plaques are spherical deposits, classically consisting of a central amyloid core surrounded by degenerative nerve cell processes and connective tissue. Amyloid is a protein complex having a starch-like characteristic produced and deposited in tissues during certain disease states. Eventually the plaques develop into solid amyloid spheres and may finally become unidentifiable. Senile plaques tend to accumulate deep in the gray matter and dominate in the superficial cortical layers, although they can, especially in advanced cases, be found diffusely and in all layers (1). The beta-amyloid precursor protein is encoded on the 21st chromosome, which is triplicated in Down Syndrome, and may account for the prevalence of Alzheimer's Disease in Downs adults (personal communique to Ed., W. Mitchell, ND).

Neurofibrillary tangles or paired helical filaments are hairlike hooks or loops within nerve cells. Neurofibrillary tangles consist of bundles or masses that become looped or hooked over each other. Neurofibrillary tangles are primarily seen in the central nerve cell body, but can be seen even at distant parts of the nerve cell (1).

Granulovacuolar degeneration is usually restricted to a specific portion of the brain called the hip-

pocampus. Granulovacuolar degeneration consists of inclusions within cells called vacuoles. Affected nerve cells often appear in the stages of terminal degeneration, and granulovacuoles are believed to consist of parts of destroyed nerve cells (1).

The brain may appear normal in early cases of Alzheimer's disease. When more advanced, the disease causes a widespread atrophy of the cerebral hemispheres. Although brain atrophy is a normal consequence of aging, cerebral atrophy may be accelerated in Alzheimer's disease. In extreme cases the generalized atrophy results in a reduction of brain weight to 800 grams or less, a loss of 400-500 grams of brain tissue. This loss of substance is due to a reduction of gray matter and white matter, white matter atrophy presumably being secondary and a late event. Though generalized, atrophy is more marked in certain areas of the brain. The temporal lobe and the post-central parietal region, are particularly involved, as well as, to a somewhat lesser extent, the frontal lobes (1).

Other physiological aspects of Alzheimer's disease include a diffusely slow electroencephalogram, reduced brain blood flow, and particular patterns noted on positron emission tomographic scanning. A common characteristic of EEG changes after the age of 65 is the slowing of the dominant alpha frequency and the appearance of slow waves. Diffuse slow waves are associated with progressive degenerative dementia. In addition, both brain blood flow and brain metabolism have been shown to be decreased in patients suffering from Alzheimer's disease (1).

Diagnosis of Alzheimer's Disease

The definitive diagnosis of Alzheimer's disease is made by examination of brain tissue. Unless a brain biopsy is performed, the diagnosis becomes certain only after an autopsy. However, the diagnosis can be made with relative certainty on the basis of the history and physical examination, together with laboratory tests and computed tomography (CT) scanning to exclude other, potentially reversible causes of dementia. Although approximately 80 percent of dementia is irreversible and is caused by either Alzheimer's disease or other forms of dementia, the remaining 20 percent is potentially reversible. Obtaining an accurate medical history is therefore crucial to the diagnosis (6).

Author's Note: A thorough physical and mental status examination is necessary in the evaluation of any patient with suspected memory problems. As general practitioners it is vital we perform a good exam. Do not forget the details of a thorough mental status exam. Review *Bates Guide to Physical Examination and History Taking*. Remember to look at the following steps of the mental status exam:

1. Appearance and Behavior
2. Speech and Language
3. Mood
4. Thought Processes
5. Thought Content
6. Perceptions
7. Cognitive Function
8. Higher Intellectual Function

Recommended Tests for the Evaluation of Dementia

Testing and Rationale

1. Urine drug screen for sedatives: Unknown drug use or accumulated metabolites
2. Complete Blood Count: Anemia, infection, leukemia
3. Serum Electrolytes: Lung, kidney or endocrine dysfunction, occult malignancy, alcoholism, drug abuse, dehydration.
4. BUN/Creatinine: Kidney dysfunction, dehydration
5. Liver Function Tests: Liver dysfunction, cancerous lesions, nutritional status
6. Thyroid hormones (T3, T4, TSH) Hyperthyroidism, Hypothyroidism
7. Erythrocyte Sedimentation Rate (ESR): Collagen vascular disease, occult malignancy, inflammation
8. Vitamin B12/Folate: Deficiency, Pernicious anemia
9. VDRL: Syphilis
10. Electroencephalogram (EEG): Focal or diffuse brain dysfunction
11. Computed tomographic scan (CT scan): Intracranial masses, epidural or subdural hematoma, old areas of tissue death, hydrocephalus, focal or diffuse brain atrophy

Additional Studies as Indicated

12. Urinalysis: Kidney, liver or endocrine disease
13. Chest X-ray: Infection, chronic lung disease, primary or metastatic tumor
14. Electrocardiogram (EKG): Arrhythmias, heart block
15. Drug levels: Drug intoxication
16. Heavy metal screen: Heavy metal poisoning
17. Lumbar puncture: Infection, cancer, inflammation
18. Arteriography: Subdural hematoma
19. Serum Cortisol and DHEA: Adrenal gland excess or deficiency
20. Blood cultures: Infections, sepsis
21. Arterial Blood Gases: Lung disease, hypoxia

Hair mineral analysis can be useful in assessing whether the patient has aluminum or silicon overload or other heavy metal toxicity (7,8).

CT scanning has revolutionized the diagnosis of dementia. A CT scan should be obtained early in the evaluation because more than half of potentially reversible causes of dementia may have CT abnormalities.

The electroencephalogram (EEG) may be useful in diagnosing Alzheimer's disease, particularly if the presence of partial complex seizures or Creutzfeldt-Jakob disease is a concern. It is important to remember, however, that the effect of psychoactive drugs may confound the EEG evaluation.

Author's Note: One can perform the following tests to assess for age-related dementia: CBC, comprehensive blood chemistry (chem-23 or larger), thyroid function, routine urinalysis and hair analysis. If you have access to CT scans, EEG, MRI and ABG and have any suspicion of any underlying disorder that may be confirmed by more complicated laboratory testing, refer out. As a routine diagnostic test for aluminum, silicon or heavy metal toxicity consider ordering hair mineral analysis. These tests are reliable and relatively cost effective tests for heavy metal toxicty. In lieu of evaluating B12/folate levels consider giving a therapeutic trial of B12 and folate to see if it is beneficial.

Major Causes of Dementia

1. Blood Vessel Disorders: Stroke, hypertension, cerebral vasculitis, cerebral embolism
2. Space-occupying lesions: Chronic subdural hematoma, tumor, abscess
3. Toxicity: Medications, alcohol, arsenic
4. Metabolic Disorders: Organ dysfunction including liver, kidney, lung and heart, electrolyte imbalance, hypothyroidism, or other endocrine disorder
5. Nutritional Deficiencies: Vitamin B12, Niacin, Thiamine (Korsakoff's syndrome)
6. Infections: Syphilis, tuberculosis, cryptococcosis, viral disease
7. Specific Neurologic Syndromes: Alzheimer's disease, Parkinson's disease, Wilson's disease, Huntington's disease, Multiple sclerosis, Cerebral amyloid angiopathy, Pick's disease, Creutzfeldt-Jakob disease, cerebrocerebellar degeneration, Marchiafava-Bignami disease, normal pressure hydrocephalus

Clinical Course of Alzheimer's Disease

The clinical course of Alzheimer's disease lasts from 8 to 20 years. It is useful to stage Alzheimer's disease to the patient's behavior and clinical problems. Alzheimer's disease is classified into three distinct stages of progression (2).

Stage 1. The first stage of Alzheimer's disease lasts three to four years. It is characterized by the onset of memory failure, which progresses insidiously from what appears to be normal forgetfulness. Because these changes occur subtly over a span of one to four years, patients and their families tend to deny their significance.

Stage 2. The transition from the first stage to the second stage of Alzheimer's disease is heralded by the appearance of neurologic symptoms. Because of the deterioration in motor skills and the development of exaggerated behavior, the patient may become difficult to manage. Wandering behavior can be troublesome because the patient may become lost. This stage of the disease lasts two to twelve years. Individuals at this stage of Alzheimer's disease may exhibit inappropriate behavior, aggressive behavior, sleep disturbances, urinary incontinence, fecal incontinence, appetite disturbances, and many neuromuscular disturbances. Approximately 75% of patients with Alzheimer's disease develop seizure activity.

Stage 3. The third stage of Alzheimer's disease may last from several months to five years. The patient commonly needs total care, is bedridden and catheterized, and frequently develops contractures and skin problems.

Treatment

The cause of Alzheimer's disease is unknown and the current treatment is focused on identifying the cause and finding chemical precursors that can be used by the brain to either retard or to stop the dementing process. Various nutrient deficiencies are associated with the development of Alzheimer's disease and should be identified and treated accordingly. Treatment should also consist of developing ways of effectively supporting the families of patients with this disease.

Diet

A well balanced diet emphasizing whole, unprocessed and unrefined foods is recommended. Refined carbohydrates, sugar, fat and alcohol should be decreased. Complex carbohydrates, fruit and vegetables and fiber should be increased. The diet should include a wide variety of foods to maintain proper nutrition and prevent nutritional deficiencies (9).

Author's Note: Foods rich in choline, so-called brain foods, may be helpful. Foods to emphasize include whole grains, legumes, egg yolk, liver, meat, broccoli family vegetables and nuts.

Vitamins and Minerals

Individuals with dementia are more likely to be deficient in various vitamins and minerals than are members of their cohort (9).

Folic acid deficiency is associated with organic brain syndrome and dementia. Deficiency is associated with apathy, disorientation, poor concentration and memory deficits. (10) Deficiency is common among elderly psychiatric patients and supplementation may be beneficial (11).

Vitamin B1 (Thiamine) is often deficient in elderly patients suffering from Alzheimer's disease and supplementation may be beneficial in slowing progression of mental deterioration (12).

Vitamin B6 (Pyridoxine) is often deficient in elderly patients suffering from Alzheimer's disease and parallels an age-related decline in dopamine receptors (13).

Vitamin B12 deficiency is associated with depression, confusion, memory deficits and mental slowness, along with neurologic deficits (14). Vitamin B12 levels were significantly lower and deficiency was more frequent in individuals with Alzheimer dementia (15). Vitamin B12 supplementation may be effective in improving the symptoms associated with this deficiency.

Author's Note: Consider therapeutic injections of B12 alone or in combination with other vitamins and minerals and see if they are helpful. Usually one to three sessions are sufficient to determine if therapeutic B12 is helpful. There seem to be no negative side effects of B12 shots. They either help improve mood, memory and well being or no change is appreciated. Of course with any injection there is the risk of allergic reaction.

FOOD	CHOLINE (mg)
Wheat germ (1/2 cup)	2,820
Peanuts (1/2 cup)	1,113
Peanut Butter (1/2 cup)	966
Calf's Liver (3.5 ounces)	850
Ham (3.5 ounces)	800
Lamb Chops (3.5 ounces)	753
Whole wheat flour (1/2 cup)	613
Whole rice (1/2 cup)	586
Trout (3.5 ounces)	580
Beef (3.5 ounces)	453
Whole egg (1 large)	394
White flour (1/2 cup)	354
Pecans (1/2 cup)	333

Vitamin C deficiency is not uncommon among elderly psychiatric patients and deficiency is marked among individuals with senile dementia (13).

Vitamin E is often deficient in Alzheimer's patients (16). Individuals with Down syndrome, who are prone to neurologic degeneration and are at high risk of developing dementia, have increased superoxide dismutase (SOD), which may damage cell membranes because of increased free radicals. (17) Since vitamin E is a free radical scavenger, supplementation may reduce associated cell membrane damage.

The role of aluminum and silicon in the development of Alzheimer's disease is still controversial. Elevated aluminum and silicon levels have been found in brains of patients with Alzheimer dementia. Aluminum inhibits choline transport in nerve endings, reduces choline acetyltransferase (CAT) activity and is associated with the development of neurofibrillary tangles (18). It is believed that elevated brain aluminum levels in Alzheimer's dementia may contribute to the neurologic degeneration associated with this disease. If this is the case, then it is advised that aluminum exposure is kept to a minimum.

Excess accumulation of calcium in localized brain tissue is believed to contribute to dementia and the development of Alzheimer's disease. Excess calcium is deposited in brain tissue and blood vessels. The prevalence of vascular ischemia in localized brain tissue leads to poor memory and cognitive decline (19).

Excess copper accumulation is known to cause mental deterioration and brain injury (20).

Excess iron accumulation in brain tissue can act as a pro-oxidant and accelerate free radical damage and brain injury (21).

Chronically excessive exposure of manganese is associated with an increased risk of dementia (22).

Most of the enzymes primarily concerned with DNA replication, repair and growth are zinc dependent. Zinc may be deficient in individuals with Alzheimer's disease and administration of zinc could prevent or delay the onset of dementia in subjects genetically at risk (23).

NUTRIENTS

Lecithin (phosphatidyl choline) is required for the formation of the neurotransmitter, acetylcholine (24). Alzheimer's disease is marked by decreased levels of choline acetyltransferase (CAT), the enzyme required for production of acetylcholine. It is logical to assume that supplying the precursors necessary for acetylcholine synthesis would improve Alzheimer's disease. The use of lecithin in treating Alzheimer's disease is still controversial. Lecithin supplementation does not appear to improve the symptoms associated with Alzheimer's disease, but rather appears to be useful in retarding the rate of disease progression (25). The percentage of phosphatidyl choline varies between 10 to 95% in commercially available "phosphatidyl choline" and "lecithin."

Author's Note: Although the scientific literature is inconsistent in terms of the therapeutic value of lecithin supplementation for Alzheimer's disease, it is relatively inexpensive, safe and provides the choline necessary to make acetylcholine. Remember phosphatidyl choline is actually two fatty acids plus choline. The average daily consumption of choline is about 6 grams per day. Commercially available lecithin is about 10 to 35% phosphatidylcholine. A good therapeutic starting dose is about 10 to 25 grams of lecithin per day for about two to four weeks. Thereafter a maintenance dose is 5 to 10 grams per day. However, some unpleasant side effects of lecithin supplementation include nausea, gas, bloating, diarrhea and GI upset. Additionally, choline is poorly if at all converted to acetylcholine, especially in the Nucleus Basalis of Maynard. It is choline acetyltransferase that is dysfunctional in Alzheimer's disease. Lecithin therefore does no good in the middle to later stages of the disease (personal communique to Ed., W. Mitchell, ND).

Phosphatidylserine is a major phospholipid found in brain and nervous cell tissue. It accounts for up to 10% of all phospholipids in brain tissue. Its major function is to regulate cell membrane integrity and fluidity. Trace amounts of phosphatidylserine are found in soy lecithin. Low levels of phosphatidylserine are associated with poor memory, depression and impaired cognitive function. Supplementation of phosphatidylserine have been shown in some studies of animals and humans to improve mood, memory and cognitive function. The recommended dose of phosphatidylserine is 100 milligrams 3 x per day (26).

Author's Note: Very little published material is available about the use of phosphatidylserine in clinical practice. Some of the research reports and studies are intriguing; therefore, consider recommending it for some patients who haven't responded to other therapies and supplements such as ginkgo. One major drawback is its cost, which is about $75.00 per month. First try dietary changes, vitamin and mineral supplementation and ginkgo for several months. If no noticeable change then consider additional therapeutics which include phosphatidylserine.

L-carnitine is a non-essential amino acid that is necessary for the transport of long chain fatty acids into the mitochondria. L-carnitine is necessary for the proper oxidation of fats within cells. Carnitine deficiency may play a role in the abnormal utilization of fatty acids and lipids in brain tissue. Acetyl-L-carnitine is believed to act as a precursor to acetylcholine in brain tissue. Acetyl-L-carnitine supplementation in some studies has been shown to improve memory and cognitive function of some patients with Alzheimer's disease. Acetyl-L-carnitine has shown to work as well as some of the nootropic drugs in the treatment of early to moderate Alzheimer's disease. Acetyl-L-carnitine supplementation helps to slow the rate of mental deterioration in some patients with dementia (27,28).

Author's Note: This author admits to not having much experience with the use of acetyl-L-carnitine and Alzheimer's disease despite having read at least 12 clinical studies on the use of this supplement. It seems that acetyl-L-carnitine is being touted as the next natural nootropic or smart supplement.

Essential fatty acid deficiency is a common nutritional deficiency in the elderly. Manifestations of EFA deficiency include neurological signs such as poor memory and cognitive decline. Supplementation with a blend of EFAs seems to improve memory in some patients with Alzheimer's disease. This conjecture is interesting and further supports the theory that Alzheimer's disease is not caused just by acetylcholine deficiency. EFAs play such an important role in many facets of human biochemistry and EFA supplementation is a simple and

cost effective measure for prevention and nutritional support (29).

Hormones

DHEA (Dehydroepiandosterone) is touted as a master steroid hormone of the human body. It is produced primarily in the adrenal glands. It is used to make a variety of sex hormones including estrogen, progesterone and testosterone and other steroid hormones including cortisone. Normal production of DHEA peaks at about age 25 to 30 years. It declines with age. Significant decline is experienced by some elderly individuals (30). Supplementation may be beneficial in some individuals with poor memory and dementia (31).

Author's Note: DHEA is often touted as the miracle hormone that is supposed to cure all the ills of the geriatric population. However, a rational approach to the assessment and prescription of DHEA is necessary. The best way to assess whether DHEA supplementation is necessary is serum DHEA levels. Other tests including urine and saliva have also been utilized. Supplementation of physiologic doses of hormones is warranted if the hormone has been shown to be low via laboratory testing or clinical signs and symptoms indicate a therapeutic trial is justified. Like with any hormone, abnormally low levels warrant supplementation. Rampant prescription of DHEA to all patients with memory or cognitive function is not justified and may be harmful to some. DHEA supplementation has been clinically useful for some patients with poor memory and abnormal cognitive decline. For some patients it is remarkable.

DMAE (Dimethylaminoethanol) is a natural precursor to acetylcholine. It is found in small amounts in seafood. It works slowly and has been shown to increase choline levels in the brain. Supplementation has been shown to improve some parameters of short and long term memory. It also has been shown to improve moods and behavior. It is recommended for the treatment of hyperactivity in children. Large doses over time can produce agitation. The usually recommended dose of DMAE is 500 milligrams per day for children and 1000 milligrams per day for adults (32).

Author's Note: DMAE is an interesting nutrient. It was once designated a prescription drug in the United States as Deaner, for mood and memory problems. DMAE has also been marketed under a variety of other names such as Deanol. DMAE is believed to be a major component of the once touted eastern European wonder drug GH3 or Gero Vita. Upon injestion GH3 dissociates into procaine and DMAE. The DMAE is believed to cross the blood-brain barrier more effectively than choline itself. DMAE is relatively inexpensive. In clinical practice this author frequently recommends it and has found it to produce inconsistent results.

Pregnenolone is another "master" steroid hormone that is similar in action and function to DHEA (33). It shares the same traits and actions on human biochemistry as DHEA. It is regarded as a softer version of DHEA. Supplementation has been shown to improve memory, mood and cognitive function in some individuals (34).

Author's Note: Again, Pregnenolone is a steroid hormone. Rational use of pregnenolone in physiologic doses is recommended for some patients with poor memory and cognitive function. In clinical practice it can be beneficial in some individuals with memory, mood and cognitive dysfunction.

Other hormone deficiencies have been postulated to be related to Alzheimer's disease. Two novel hormones that may play an accessory role in the development of Alzheimer's disease are serotonin and melatonin. Supplementation with tryptophan and melatonin improves some parameters of poor memory and cognitive decline in patients with Alzheimer's disease. Most improvement was noted in terms of mood and sleep (35).

Botanical Medicines

One of the most popular, well studied and most effective geriatric medicines in the world is standardized *Gingko biloba* extract. In Europe *Ginkgo biloba* extract is one of the most frequently prescribed medicines. According to Julian Whitaker, MD, some 10 million prescriptions for this medicine were written in 1989 by about 100,000 physicians. In France, 1.5% of all prescription sales are for ginkgo leaf extract. In Germany, 1.0% of all prescription sales are for ginkgo extract (36).

The pharmacologic activity of Ginkgo leaf is related to its high content of terpenes, flavonoids, proanthocyanidins and flavoglycosides. *Ginkgo biloba* extract contains up to 24% flavoglycosides and is a widely available medicinal product throughout Europe (37).

The pharmacologic effects of *Ginkgo biloba* can be summarized as follows (38,39):

1. Ginkgo dilates blood vessels and as a result, increases blood flow and oxygen supply in the brain.
2. Ginkgo decreases blood pressure.
3. Ginkgo decreases atherosclerotic plaque formation in blood vessels.
4. Ginkgo stabilizes the blood-brain barrier.
5. Ginkgo acts as a free radical scavenger and prevents damage to cell membranes.
6. Ginkgo increases the neurotransmitter, dopamine, which is believed to enhance nerve function in the brain.
7. Ginkgo enhances the release of adrenaline from the adrenal glands and inhibits the enzyme responsible for its breakdown.
8. Ginkgo maintains venous tone.

The clinical research with *Ginkgo biloba* extract is very encouraging. In one long term study, 112 geriatric patients with chronic cerebral insufficiency were treated with *Ginkgo biloba* extract (GBE) at 120 mg/day for one year. Results showed that the patients treated with GBE had significantly improved symptoms of brain blood flow insufficiency. Improved symptoms of headache, vertigo, tinnitus, short term memory, vigilance and mood disturbance were recorded (40). In another study of 166 geriatric patients with vascular disorders due to aging, GBE improved their symptoms. The effects of GBE became significant after three months of administration. Functional changes in the EEG (Electroencephalogram) were noted and patients experienced improved mental alertness (41). In another study with 20 patients with cerebral vascular insufficiency due to arteriosclerosis, dramatic improvement of cerebral blood flow was observed after only two weeks of GBE supplementation. Researchers in a study of Alzheimer's disease concluded that GBE appears to fulfill the conditions laid down by WHO (World Health Organization)

concerning the development of a drug effective against cerebral aging (42).

Ginkgo biloba is safe and nontoxic and few adverse side effects have been reported. Stomach upset and headache have been reported in some individuals who consumed GBE in doses of up to 600 mg/day. Consumption of the fruit and pulp of Ginkgo may cause allergic reactions including a topical red, inflamed, itchy rash (38). However, curiously, Ginkgo may speed the onset of Azheimer's disease because beta-amyloid precursor protein is produced in blood vessel walls (personal communique to Ed., W. Mitchell, ND).

The dose of *Ginkgo biloba* extract most frequently used in clinical research is 120 mg/day. Doses of up to 600 mg/day have been consumed without adverse side effects. Ginkgo is usually taken at a dosage of 40 mg three times per day of *Ginkgo biloba* extract standardized for 24% Ginkgo heterosides.

Few other botanical medicines have the same clout and scientific documentation for treatement of poor memory and cognitive decline as *Ginkgo biloba*. One herbal extract that shows some promise is *Panax ginseng*. *Panax ginseng* is one of the most popular and most scientifically studied herbal medicines in the world. Well known as an adaptogen to help improve the body's adaptation to stress, it also improves some parameters of memory and cognitive function. Supplementation of a standardized extract reflecting specific ginsensoside content, specifically RG1 fraction, has been shown to be beneficial for some patients with Alzheimer's disease (43).

Nootropics

Nootropics or "smart drugs" are a group of experimental medicines that have shown promise in treating Alzheimer's disease and other forms of age-related cognitive decline. Nootropics include drugs like Deprenyl or Eldepryl, Dilantin or Phenytoin, Hydergine or Ergyloid Mesylate, Piracetam and Tacrine or Cognex. There are other drugs touted as nootropics, but these drugs have been reviewed and prescribed or recommended for prescription in this clinical practice. This brief introduction to these specific nootropics is by no means conclusive. A thorough review of the pharmacological literature, especially in terms of side effects, is necessary before they can be recommended.

Deprenyl or Eldepryl is an MAO inhibitor originally used in Europe on Parkinson's patients, but not necessarily in Alzheimer's disease. As an MAO inhibitor it increases dopamine, L-dopa and norepinephrine in the brain. Supplementation has been shown to improve mood and vitality and short term memory (45).

Dilantin or Phenytoin is an antiepileptic drug. Although its method of pharmacologic action has not been entirely elucidated it is believed to be a neuron cell membrane stabilizer. It prevents excitability of the cellular membrane and thereby prevents seizures in areas of the brain that are slighltly overactive. Low dose Dilantin can prevent overexcitation in nerve cells of some individuals prone to anxiety, panic attacks and obsessive-compulsive disorder. It can stabilize mood and behavior and improve short term memory (46).

Hydergine or ergyloid mesylate is an ergot rye derivative that was originally prescribed for migraine headaches. Hydergine has demonstrated antioxidant activity and prevents free radical damage in nervous tissue. It is believed to increase blood supply to the brain, which in turn increases oxygen supply. It enhances brain metabolism and slows aging pigment deposition (47).

Piracetam or pyrrolidone acetamide was originally used as a nootropic in Europe. It increases activity within nerve cells. It has antioxidant activity and prevents free radical damage. It improves oxygen utilization in nerve cells and prevents toxemia within nerve cells. It is useful in improving integration between the right and left brain hemispheres. In experimental study it has been shown to improve memory and learning (48,49).

Tacrine or Cognex (tetrahydroaminoacridine) has shown promise delaying the progressive deterioration associated with Alzheimer's disease. Tacrine inhibits acetlylcholinesterase, the enzyme responsible for breaking down the hormone acetylcholine. It helps to increase the concentration of acetylcholine in brain tissue and thereby helps to improve memory. It does not affect the underlying pathological process in Alzheimer's disease, but helps to prevent mental deterioration and cognitive decline. Other cholinesterase inhibitors have been suggested such as neostigmine and physostigmine, but due to some of their unpleasant systemic side effects their prescription has been limited. It is interesting to note that cholinesterase inhibitors have been isolated in some botanical medicines, such as the Calabar bean (*Physostigma venosum*) (50).

Recommendations

Naturopathic physicians are primary care practitioners who deal with many patients who present with poor memory, cognitive decline and Alzheimer's disease. It is our responsibility to give our patients high quality naturopathic medical care which includes a thorough medical history, physical and mental status exam, proper and accurate medical tests within our scope of practice and an accurate diagnosis. Based upon history, diagnosis and testing we can make sound and practical recommendations which include dietary and lifestyle changes, vitamin and nutritional therapy which are in the best interest of the patient.

Supplementation

	Daily unless otherwise stated
Folic acid	5-10 mg
Thiamine	5-10 mg
Vitamin B6	10-20 mg
Vitamin B12	50-100 mcg
Vitamin C	500-1000 mg
Vitamin E	200-400 IU
Zinc	25-50 mg
Lecithin (Phosphatidyl choline)	5-25 gm
Phosphatidyl serine	300 mg
Acetyl-L-Carnitine	1500-2000 mg
DHEA (if indicated)	10-50 mg
DMAE	750-1500 mg
Pregnenolone (if indicated)	10-50 mg
Ginkgo biloba extract (24% heterosides)	120 mg
Deprenyl (if indicated)	5-10 mg
Dilantin (if indicated)	50-100 mg
Hydergine (if indicated)	3-9 mg
Piracetam (if indicated)	1500-4500 mg

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