

Prevention and Treatment of Alzheimer's Disease with Orthomolecular and Lifestyle Interventions

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Abstract *Alzheimer's disease (AD) is the most common form of dementia in the elderly. To date, there are no established therapies that slow or reverse the course of disease. Dozens of epidemiological associations exist between nutritional and environmental factors and the development of AD, but few studies have been done to explore whether modification of these risk factors changes the course of the disease. Affected individuals, their caregivers, and health care providers are left to choose between doing nothing and using unproven interventions. This review summarizes the orthomolecular and lifestyle interventions with the greatest benefit-to-risk ratio that are supported by the published medical literature.*

Introduction

Alzheimer's disease (AD) is the most common form of dementia in the elderly. This condition is characterized by a progressive loss of memory, increased apathy, and deterioration of a variety of intellectual functions. Emotionally and financially devastating to patients and their families,¹ the disease affects every socioeconomic and ethnic group. North America has the highest reported incidence of dementia in the world, affecting a reported 6.4% of individuals >60 years old. Less than 2% of individuals in the same age group are affected in Africa, India, and south Asia.² The disease increases dramatically with age with approximately 25% of the population older than 85 having significant cognitive impairment.³ Largely due to the aging baby boom generation, the annual total number of new cases of AD is projected to double by 2050.⁴

The prevention and management of AD with orthomolecular and lifestyle interven-

tions is as much about the strategy as it is about the agents being used. Philosophically, the goals of natural therapeutics in AD consist of prevention, disease stabilization and reversal, as well as symptom management. The nature of the disease does not lend itself well to study. Plenty of epidemiological associations exist, but few studies have been done to explore whether modification of the risk factor changes the course of the disease. Individuals are left to choose between doing nothing and using unproven interventions. This review will briefly summarize the orthomolecular and lifestyle interventions with the greatest benefit-to-risk ratio that are supported by the published medical literature.

Pathology

With age, all brains exhibit some degree of degeneration, but the process is accelerated in AD. An accumulation of protein deposits, inflammation, and loss of both structure and function are hallmarks of the disease pro-

cess. In the brain, the protein deposits accumulate and form neurofibrillary tangles and amyloid- β (A β) peptides. The presence of these plaques and tangles have been correlated with the clinical disease, but there is significant debate as to whether plaques and tangles directly cause damage, or are simply by-products of another process.⁵

In AD, the cerebral cortex, basal forebrain, and other areas of the brain have fewer synapses, fewer synaptic proteins, and reduced membrane phospholipids, which are essential for cell stability.⁶ The maintenance of appropriate lipid membrane content may prevent the production of A β peptides and subsequent neurodegeneration.⁷ The nerve cells that are particularly affected are those that are stimulated by the neurotransmitter called acetylcholine (ACh). Current pharmaceutical therapies strive to increase the availability of ACh throughout the brain. Overall, there is significant wasting of brain tissue.

Functionally, the AD brain exhibits abnormal glucose metabolism, which is in accord with the findings that diabetes, another disease of impaired glucose metabolism, is an independent risk factor for AD. This 'brain hypometabolism' is especially evident in individuals with a maternal family history of AD and in carriers of AD-related genes.⁸

Economics

In US dollars, AD cost an estimated \$183 billion in 2011, and this cost is predicted to increase to \$1.1 trillion in 2050. Because most people with AD are over age 65, Medicare and Medicaid cover approximately 70% of these costs. Individuals with AD cost Medicare almost three times as much as the same-age individuals without AD. As the incidence of AD continues to rise, there is a tremendous financial incentive to preventing and slowing the degenerative process.⁹

Signs and Symptoms

The inability to remember new information is typically the earliest manifestation of AD. Other symptoms include confusion, difficulty solving problems, problems with spatial relationships, problems speaking or

writing, poor judgment, social withdrawal, or mood changes.^{9,10} Depression occurs in approximately 50% of individuals with AD.² Death usually occurs as a result of AD-related pneumonia due to the affected individual's lack of mobility.⁹

Clinicians use diagnoses of "possible AD" or "probable AD," but pathological confirmation via autopsy is required for a diagnosis of "definitive AD." This classification system poses notable challenges for the study of early disease, as the clinical diagnosis is not always in agreement with the brain pathology and autopsy findings represent a late stage of disease.

Risk Factors

Age is the single greatest risk factor for developing AD, but it is not an inevitable course of aging. The disease is thought to be due to a combination of genetic and environmental risk factors.

Mild Cognitive Impairment (MCI) is a condition in which an individual experiences cognitive dysfunction severe enough to show up on cognitive tests and to be noticeable to others, but not severe enough to interfere with activities of daily living.⁹ MCI is an established risk factor for the development of AD, although not all individuals with MCI will develop AD. The diagnosis of MCI may represent a window of opportunity for intervention, should neuroprotective intervention strategies prove useful in larger scale trials.

Genetic Associations

At least six different genes have been linked to the development of Alzheimer's,² all of which result in the accumulation of protein debris described above. Individuals with a parent or sibling with AD are at increased risk of developing AD, and this risk goes up with each affected family member.⁹ Globally, Africa has the lowest reported incidence of AD² and studies support the idea that being of African descent appears to offer some protection against the disease.¹¹

The most well-established susceptibility gene for late-onset AD is the APOE gene, which is involved in cholesterol trans-

portation. The gene comes in three forms, APOE-2, -3, and -4. Individuals who inherited the APOE-4 allele from one parent have a 2 to 3-fold risk of developing AD, and six to seven years earlier, than those without the gene. Inheritance of two copies of the gene (from both parents) results in a 5-fold risk of developing the disease.² Possession of APOE-4 has been associated with dysfunctional carbohydrate metabolism in the brain,⁸ and a more pro-inflammatory state;¹² two established components of AD. Depending on the geographic region, between 37% -64% of individuals with AD possess the APOE-4 allele, with the most significant association between APOE-4 and AD found among individuals in northern Europe.¹³ While the risk of developing AD is significantly greater among individuals with one or two copies of the APOE-4 allele, not all of these individuals will develop the disease.

Modifiable Risk Factors

Each of the following is a modifiable risk factor. An individual has some influence over whether or not they have the risk factor, or the degree to which they have it. Unfortunately, few randomized controlled trials have been completed to determine whether modification affects outcome. If a patient already has AD, does changing the associated risk factors change the rate of progression of the disease? Such studies are complicated and expensive, and yet to be conducted. Since no known therapies exist to slow or reverse the disease, a reasonable strategy is to avoid the things that have been associated with disease and encourage those that have been associated with prevention.

1. Environment

Pesticides: An ecological study evaluated the relationship between environmental exposure to pesticides and the development of neurodegenerative diseases. It showed an increased risk for AD in districts with greater pesticide use.¹⁴

Aluminum: There have been repeated epidemiological correlations between alumini-

num (Al) exposure and the incidence of AD, with some studies showing a dose-response relationship.^{15,16} An established neurotoxicant, Al appears to promote AD progression. While mechanisms explaining the connection have not been fully elucidated, Al has been shown to be associated with a significant increase in markers of inflammation and the formation of plaques in animal models of AD.¹⁷ Individuals with a diagnosis of 'probable AD' have significantly higher serum levels of Al than healthy individuals or those with dementia from other causes.¹⁸ Al exposure comes from a variety of sources including deodorants, antacids, water, and food. The most significant of these sources is likely water, where Al compounds are used in many municipal water supplies as a means to purify the water from microorganisms. Thirteen studies and a meta-analysis have established an association between the incidence of AD and the Al concentration in the municipal drinking water.¹⁵

2. Cardiovascular Disease and Diabetes

Metabolic Syndrome, or Syndrome X, refers to a group of related conditions plaguing the Western world. The syndrome includes abdominal obesity, insulin resistance/ type 2 diabetes, high blood pressure, and elevated blood lipids. The syndrome, presumably associated with a high carbohydrate diet and consumption of refined sugar, is associated with increased risk of stroke, heart attacks, as well as the development of AD.^{19,20}

Mounting evidence suggests a cholesterol defect may be involved in AD, and that elevated blood levels of LDL may be an attempt at delivering cholesterol to the brain.²¹ Cholesterol is an important brain nutrient where it insulates neurons, aids communication between cells, and acts as an antioxidant.¹⁹ When cholesterol cannot reach neurons, free radicals are produced, resulting in abnormal cell function and eventually cell death.

3. Homocysteine

Elevated homocysteine is a recognized risk factor for cognitive impairment and AD.^{22,23} Homocysteine levels increase due to

a deficiency of B-vitamins, which have been shown to be low in patients with AD.²⁴ When researchers conducted a 2-year study of B-vitamin supplementation on AD progression, they found reversal of early cognitive impairment among individuals with elevated ($>11.3 \mu\text{mol/L}$) homocysteine. Most notable was a 69% higher likelihood of correct word recall compared with placebo after 2-years supplementation.²³ The therapeutic use of homocysteine-lowering vitamins (i.e., B₆, B₁₂, folic acid, betaine, and choline) should be able to maintain homocysteine levels below 10 $\mu\text{mol/L}$, and mitigate this risk factor.

Dietary Interventions

The Mediterranean diet: The Mediterranean diet (MeDi) refers to the diet traditionally consumed throughout Southern Europe, near the Mediterranean Sea. The diet is high in plant foods, including vegetables, fruits, grains, beans, nuts, and seeds. Fish, poultry, dairy, and red wine are consumed in low-to-moderate amounts, and red meat consumed infrequently. The major source of fat in the MeDi comes from olive oil and the diet is low in saturated fat overall.²⁵ The diet has been associated with reduced incidence of AD and related cardiovascular diseases. It is unclear if there is a particular nutrient or combination of nutrients that confers protection.

A well-conducted study in Greece sought to determine whether dietary and lifestyle variables affected cognitive function in the elderly.²⁶ The researchers found that adherence to the MeDi were not found to be associated with cognitive function. Rather, physical activity and height were associated with improved cognitive performance whereas increased risk of dementia was associated with depression, diabetes, and age.

A large study, The Chicago Health and Aging Project (CHAP), found an association between intake of saturated fat and cognitive decline.²⁷ Alternatively, unsaturated oils from plants were shown to be protective against age-related cognitive decline and AD in large longitudinal studies conducted throughout Europe.^{28,29} The findings from the CHAP study also support a role for unsaturated oils,

as they found that frequent consumption of fish, a rich source of polyunsaturated oil, was associated with better cognitive function. Individuals who ate fish at least once weekly had cognitive scores decline about 10% more slowly than those who avoided fish.³⁰

Low-carbohydrate diet: AD is associated with insulin resistance, elevated cholesterol, and obesity. It should come as no surprise that AD has been termed “type 3 diabetes.”³¹ Elevated sugars interfere with the brain’s ability to access essential fats and contribute to insulin resistance.

Nutrient-dense foods: Epidemiological studies have shown that individuals who consume diets high in antioxidants are afforded cognitive protection.³² Cherries,³³ grape juice, berries, and walnuts³⁴ have been shown to enhance resistance to oxidative stress and improve verbal memory performance.³⁴ Curcumin is isolated from the spice turmeric, often used to make yellow curries and mustards. Its antioxidant properties are especially suited for the brain. Studies in mice demonstrate curcumin decreases inflammation and reduces oxidative damage in the brain.³⁵

Orthomolecular Interventions

Omega-3 Fatty Acids: The omega 3 polyunsaturated fatty acids are major constituents of neuronal lipids,⁷ and docosahexanoic acid (DHA) is thought to be the most neuroprotective form of fat. DHA has been shown to improve membrane fluidity, decrease inflammation, prevent oxidative damage, reduce tau aggregation, discourage amyloid formation, improve signal transduction, and facilitate neural re-growth.^{1,3,36}

A randomized controlled trial of 2 grams of DHA daily for 18 months did not slow the rate of cognitive decline in patients with mild to moderate AD.³⁷ It was suggested that a year and a half of DHA supplementation does not accurately replicate the effects of a lifetime of fish consumption. In addition, this protocol neglected to include other nutrients found in seafood, such as trace minerals,³⁸ which may account for some of the protection afforded by fish consumption in epidemiological studies.

Based on current evidence, oily fish³⁶ should be consumed several times per week. Sardines, pickled herring, and smoked salmon (lox) require no preparation and can be found relatively inexpensively. Fish oil supplements are widely available and should be considered, although the ideal dose has not been determined. Daily doses as high as 4,000 mg of DHA may be required.

Creatine: Creatine is a naturally occurring nitrogenous organic acid that plays an essential role in cellular energy supply. It is manufactured endogenously from L-arginine, glycine, and L-methionine and therefore not considered an essential nutrient. That brain energy capacity may influence cognitive performance has led to the hypothesis that supplemental creatine may have therapeutic value in the treatment of dementia. This idea is supported by the findings that brain creatine levels, measured via magnetic resonance spectroscopy, have been shown to be associated with some aspects of memory.³⁹

Animal muscle is the primary source of dietary creatine, putting vegetarians at risk for deficiency. While vegetarians have been shown to have significantly lower creatine levels in skeletal muscle than omnivores,⁴⁰ brain differences among these groups has not been reported. Two studies have examined the effects of creatine supplementation on cognitive function in vegetarians. The first demonstrated that 5 g/ day of creatine supplementation had a significant positive effect on two cognitive tests measuring processing speed.⁴¹ In the second study, the authors concluded that 20 g of creatine supplementation for five days resulted in improved memory for vegetarians, but not omnivores. In this short trial, supplementation did not influence measures of verbal fluency or vigilance.⁴²

In young adults, 0.03 g/kg/day of creatine supplementation did not improve cognitive processing after six weeks of supplementation.⁴³ In the elderly, however, 5 g creatine four times daily did result in improvement of four of five cognitive tasks measured. The authors concluded that creatine supplementation was effective for enhancing cognitive

function in the elderly.⁴⁴

Unfortunately, cognitive enhancement research does not necessarily translate into AD therapeutics. Both creatine and creatine kinase (CK), the enzyme responsible for the conversion of adenosine triphosphate to adenosine diphosphate, have been shown to be reduced in the brains of individuals with AD.^{39,45} In one study CK activity was 86% decreased in brain homogenates of patients with AD compared to age-matched controls.⁴⁶ While researchers have suggested that administration of creatine may prevent or delay the course of AD-related neurodegeneration, such a randomized controlled trial has not been conducted and it is difficult to predict whether the AD-specific decreases in creatine and CK may influence response to supplementation.

Physical, Mental, and Social Activity

Stress: A lifetime study of clergy members in the Catholic Church found that those exposed to high levels of chronic psychological stress were more than twice as likely to develop Alzheimer's as those with low levels of psychological stress.⁴⁷ It is known that high levels of cortisol negatively impact the hypothalamus, which is a center of learning and memory. Chronic stress is associated with metabolic and inflammatory changes that are thought to favour the development and progression of AD.⁴⁸ In clinical studies, high exposure to stress was associated with cognitive impairment among APOE-4 positive individuals.⁴⁹

Exercise: Several studies have demonstrated that physical activity is associated with improved cognitive performance²⁶ and reduced risk of AD.⁵⁰ Even among individuals who already have AD, a 12-week program that included training in balance/ coordination, joint mobility, resistance, and flexibility resulted in significant improvements in physical outcome measures and the individuals' abilities to independently perform activities of daily living.⁵¹ In addition to the purported benefits of enhanced blood flow to the brain, physical activity has been demonstrated to offer protection against the body's response to stress.⁵²

Social Activity: Withdrawal from social activities is a symptom of even mild stages of AD.⁵³ A group of Finnish researchers studied the effects of social stimulation on cognition in elderly individuals suffering from loneliness (individuals in this study did not have AD). In this randomized, controlled trial of 235 participants, individuals were exposed to active discussions and therapeutic writing, group exercise, or art experiences over three months. The study concluded that psychosocial group intervention improved cognition in lonely elderly individuals.⁵⁴

Conclusion

While the personal, social, and economic impact of AD are enormous, and a growing public health concern, few current conventional interventions offer prospects for prevention or long-term cognitive benefit. Orthomolecular and lifestyle interventions may have an important role in both the prevention and treatment of AD. Unfortunately, only a few rigorous clinical trials have been conducted to determine the safety or efficacy of several orthomolecular interventions. Furthermore, these therapies may well work in concert with one another (e.g., fish oils and dietary antioxidants), but do not lend themselves well to standard clinical trial methods. For these reasons, epidemiological studies give us clues as to what may be protective from developing dementia and/or AD.

From these studies, we know that lifestyle modifications are the most likely avenue to maintain cognitive function. These include: daily exercise (physical and mental), social involvement, attention to dietary patterns, and avoidance of known environmental risk factors. While it is easy to list these, it is well-known in medicine that lifestyle modifications are difficult for patients to adopt. Rather than a single therapy that offers a cure, it is likely that the best way to slow, stop, or reverse AD will be through a holistic combination of many interventions. There are virtually no risks to increasing one's physical and social activity, and improving diet to include nutrient-dense foods (beans, nuts, vegetables, oily fish) and fewer carbo-

hydrates. All patients, and their families, should be encouraged to adopt these habits to the greatest extent possible. While some orthomolecular interventions are supported by preliminary data and have promise in the management of AD, more study is certainly needed with respect to optimal dosing, brand, and the potential interactions with other medications. Overall, the orthomolecular and lifestyle interventions reviewed here are supported by the published medical literature, have few side effects, and, pending more clinical research, have tremendous potential for neuroprotection in AD.

Competing Interests

The author declares that she has no competing interests.

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