Potential Prevention and Treatment of Alzheimer's Disease with Natural Therapeutics

Vitamins, herbs and other substances described in this Report may cause harmful side effects if combined with perscription drugs, other types of vitamins, or if you have existing medical problems. Consult your family physician before trying any of these methods.

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Introduction

Alzheimer's disease is a brain disease that usually first occurs in older ages. It causes a decline in mental and physical functioning that gets worse over time. The most notable symptom of the disease is a form of memory loss in which patients first lose the ability to form and recall recent memories. Then, as the disease progresses over several years, memories from earlier in life become irretrievable. Late in the disease, patients lose virtually all mental functions. They become apathetic, confused, and irritable almost constantly. Aside from memory problems, patients experience increasingly severe insomnia, anxiety, depression, and disruptive behavior. Some patients will experience hallucinations later in the disease. There are severe physical problems as well—people with late stage Alzheimer's disease cannot speak clearly or walk properly.

The disease is devastating for those that suffer from it, but can also severely disrupt the lives of patient's family and caregivers. There is no cure for Alzheimer's disease and the treatments that exist, so far, are only moderately helpful. Therefore, preventative measures are key, to keep the disease at bay for as long as possible. It is important to understand the risks of developing Alzheimer's disease—both to avoid these risks (when possible) and to know when to exercise particular caution. It is also important to know about current treatments, how effective or ineffective they are, and what side effects can be expected from them.

Symptoms of Alzheimer's Disease

A certain amount of forgetfulness occurs in normal aging, but patients with Alzheimer's disease have a more profound memory loss. It is sometimes difficult to tell the difference between normal aging and the memory problems of Alzheimer's disease. Patients with Alzheimer's disease tend to forget information that they just learned. While everyone uses appointment reminders, patients with Alzheimer's disease forget many appointments and need to be reminded constantly. Healthy older people will eventually remember the appointment but patients will lose the memory forever. Another example is in using numbers. While some people have trouble balancing a checkbook, patients with the disease lose the ability to do it effectively and consistently. These same troubles extend to other activities as well. Healthy people may momentarily forget where they were going; patients with Alzheimer's disease may forget how to get there entirely. Another example is problems with time. It is not unusual to forget the day of the week or even the year in January, but patient with Alzheimer's disease lose weeks, seasons, years. While it may not start out as such, eventually they will not understand that events that took place decades ago did not occur last week, for instance.

Certain Alzheimer's symptoms seem to occur before any problems with memory at all. For example, patients with Alzheimer's disease may not be able to smell as well as healthy individuals as they age. In other words, people with the early stage Alzheimer's disease tend to lose the sense of smell as they get older.[1] While it is not routinely available in the clinic, this affect may be detected by administering a drug called atropine. In one study, 14 people with probable Alzheimer's disease, 13 people with cognitive impairment but not dementia, and 29 cognitively intact people were given atropine as a nasal spray.[2] The 14 people with Alzheimer's disease had significant impairment on tests of learning and memory after atropine while the 29 healthy people did not. The 13 remaining people had an intermediate level of performance suggesting that the atropine may have uncovered Alzheimer's disease in some people that was previously unknown. It is important to note that not everyone with a poor sense of smell has or will develop Alzheimer's disease.

Diagnosis of Alzheimer's Disease

The diagnosis of Alzheimer's disease is made by a physician when patients display or experience 1) memory impairment and 2) at least one of the following: a.) impaired ability to carry out certain physical activities, b.) have trouble speaking/forming words c.) cannot recognize or identify objects in the environment, or d.) lose the ability to plan and organize actions. In order to check for these things, the doctor will use a test called the Mini-Mental Status Examination. It is a 30-point test, conducted by doctor-patient interview, that tests for the features of memory problems. Aside from this test, physicians must make sure the problems are not caused by reversible or other irreversible causes of memory disturbances, such as Parkinson's disease, brain tumor, delirium, intoxication, infection,

HIV, etc. Most of these can be checked by standard blood tests. A computed tomography scan (CT scan) or magnetic resonance imaging (MRI) may also be performed to check for brain abnormalities. Rarely patients will have to have an electroencephalogram (EEG) to make sure epilepsy is not the cause of the memory problems.

Who Gets Alzheimer's Disease?

Alzheimer's disease is the most common form of dementia in the elderly and accounts for roughly 70% of all cases.[3] Once you reach 65, one in ten people will have some type of dementia (usually Alzheimer's disease). By the time people are 90 years old, 50% will have dementia. The risk of Alzheimer's disease is higher in women than it is in men. The most likely age range to develop the neurodegenerative disease is between 60 and 70 years old.[3] Close to 24 million people around the world are living with the disease and by 2040 the figure is expected to rise to 80 million.[3]

Problems in the Brain

Researchers have identified two main abnormalities in the brains of individuals with Alzheimer's disease; senile plaques and neurofibrillary tangles. Senile plaques contain folded sheets of a protein called beta-amyloid and occur on and outside of nerve cells. Neurofibrillary tangles, on the other hand, are found within neurons and contain high amounts of tau protein. In Alzheimer's disease, plaques and tangles appear in regions of the brain that are important for learning, memory and executive functions, namely the hippocampus and the frontal cortex. While plaques and tangles are the pathological hallmarks of the disease, the actual pathophysiology is much more complex.[4] For example, inflammation seems to play an important role in how plaques and tangles interfere with brain function.[4] One hypothesis is that abnormal protein accumulation that occurs in Alzheimer's disease is the focus of an inflammatory cascade.[5] These changes lead to oxidative stress in affected areas and ultimately dysfunctional synapses and neuron loss.

Another key finding in the brains of people with Alzheimer's disease is that neurotransmitter levels are abnormal. In general, as nerve cells die, the remaining cells cannot release as much of important neurotransmitters as they once did. To date, the neurotransmitter that has received the most attention and for which there are the greatest number of drug treatments is acetylcholine. Drugs like tacrine preventing the breakdown of acetylcholine and help support neurotransmission. Other neurotransmitters are affected by the disease also, though few have been targeted by pharmaceutical companies as intensely as acetylcholine. Importantly, these drug treatments aim to improve memory and are not intended to stop disease progression.

The hippocampus is a special area in the brain that is responsible for the formation of new memories. Researchers found that the hippocampus, as viewed using an MRI, tends to shrink in Alzheimer's disease. Moreover, it is one of the first brain changes to occur in the progression of the disease. As researchers improve upon MRI techniques, this may allow for earlier diagnosis.[6] Until then, this information aids researchers in understanding the causes and treatment of the disease.

Genetic Risk Factors

Alzheimer's disease can be inherited or it can occur spontaneously. Almost everyone that gets Alzheimer's disease (90%) will get the spontaneous form, i.e. they will not inherit it. Those that inherit the disease usually get the disease earlier than in those who get the spontaneous form--before the age of 65. Some studies suggest that mutations on chromosomes 1, 14 and 21 may cause the inherited form of Alzheimer's disease.[7] People that get the spontaneous form may have some abnormal genes that predispose them to the disease, but unlike the inherited form, just having the wrong genes does not necessarily mean that someone will get Alzheimer's disease.

Two other mutations of chromosomes 1 and 14 may be involved in the early onset Alzheimer's disease. These mutations affect proteins called presenilins. Presenilins are essential for structure and function of the brain.[8] More than 75 mutations have been reported in presenilins and they cause a particularly aggressive form of the disease—the disease starts between ages 30-50.[9] Mutations in presenilins may make harmful beta-amyloid plaques and neurofibrillary tangles form more quickly in the brain.[10] The apolipoprotein E gene (APOE) located on chromosome 19 may also cause a form of Alzheimer's disease. Those with APOE E2 allele have the lowest likelihood of develop-

ing Alzheimer's disease while individuals with the APOE E4 allele have greatly increased risk.[11] In fact, people with a higher the genetic "dose" of the APOE E4 allele seem to experience a more severe the version of the disease and one that starts earlier in life.[12] Physicians may test for the APOE type when they are considering a diagnosis of Alzheimer's disease. The APOE protein affects cholesterol and fat transport in the brain.[13] It may also be involved with inflammation in the central nervous system[14] and influence the formation of beta-amyloid plaques.[15]

Environmental/Mixed Risk Factors

Obesity

Obesity leads to a number of harmful effects on health.[16] There is mounting evidence that obesity, aside from the blood vessel problems, also causes dementia and Alzheimer's disease.[16] This is most likely because prolonged obesity causes the body to develop resistance to insulin and glucose intolerance.[17] The risk of Alzheimer's disease increases as body weight increases, as is the risk of becoming resistant to insulin.[17] Poor diet and inadequate exercise are not the only problems, however. Mutations in the fat and obesity-associated gene are also linked to Alzheimer's disease.[18] Middle-aged people with a waist to hip ratio greater than 0.8 have a 200% increased risk for both vascular and Alzheimer's related dementia.[19] In other words, people who are obese from diet and/or who are obese from genetics have an increased likelihood of developing Alzheimer's disease. Therefore maintaining a healthy body weight with good muscle tone helps reduce the risk of developing the disease.

Diabetes and Pre-Diabetes

Insulin plays a vital role in the functioning of brain, especially in memory.[17,20] When people develop Type 2 diabetes, what happens is that they become increasingly resistant to the effects of insulin. Insulin is essential to transport glucose (sugar) into cells for energy. When someone becomes "resistant to insulin," it means that the cells do not detect insulin that is in the bloodstream and glucose cannot enter cells. Therefore, insulin and glucose levels are high in the blood, but glucose is low inside of cells. The brain needs significant amounts of sugar to function properly. Long-term problems with insulin resistance in the brain are associated with age-related memory impairment and Alzheimer's disease.[20] Too much insulin in the brain increases levels of harmful beta-amyloid and increases damaging inflammation.[20] These insulin problems may also cause acetylcholine deficiency.[21]

People with Type 2 diabetes are 1.5 to 2 times more likely to develop Alzheimer's disease.[22] In fact, the relationship between Type 2 diabetes mellitus and Alzheimer's disease is so strong, that some have referred to Alzheimer's disease at Type 3 diabetes.[23] Fortunately, if one can properly control insulin and glucose levels, cognitive decline can be delayed and impaired cognitive performance will improve, to a degree.[24] Thus, it is important to avoid diabetes before it starts or, once diagnosed, to properly control blood and glucose levels with diet, exercise, and medications. This is important not only for heart health, but also for brain health and cognition.

Cholesterol

High concentrations of cholesterol have been identified as a potential risk factor for dementia and Alzheimer's disease.[25] There is a strong link between the genes/proteins that regulate cholesterol metabolism and the prevalence of Alzheimer's disease.[25] Likewise, cholesterol-reducing drugs lower the risk of developing Alzheimer's disease.[25] Statin drugs, which modulate serum cholesterol and lower triglyceride levels, may also help improve the symptoms Alzheimer's disease, though this effect may be very strong.[26] Nevertheless, it is important to maintain healthy cholesterol levels through diet, exercise, and, when needed, medication.

High Blood Pressure

Beta-amyloid protein, as is found in senile plaques, can damage both large and small blood vessels. When this harmful protein damages small blood vessels, namely capillaries, it damages the blood-brain barrier.[27] Since the blood-brain barrier is critical to the protection of the brain from things that might cross over it from the blood, all efforts should be made to preserve the blood-brain barrier. When people have uncontrolled high blood pressure for long periods of time, the capillaries adapt so that they can accommodate the increased pressure traveling through them. While this protects the brain from damaging pressures, over time this adaptation actually damages the capillaries (and the blood-brain barrier). Thus, high blood pressure and beta-amyloid

both work to destroy the blood-brain barrier. Those with high blood pressure in their 40s and 50s are 2.5 times as likely to develop cognitive problems later in life. Conversely, maintaining normal blood pressure throughout life reduces the risk of developing injury of the small blood vessels, regardless of whether one develops Alzheimer's disease later in life.[28,29] If one has Alzheimer's disease, blood pressure control is essential.[28] However, it is important not to overmedicate high blood pressure since too little blood flow to the brain (cerebral hypoperfusion) can be a problem in Alzheimer's.[28]

Aluminum

Aluminum is not essential for life, though we consume quite a bit of the metal through food and water, despite it being a known neurotoxin.[30] Aluminum can interfere with DNA, cellular functions and energy metabolism, and can inhibit neurotransmitter release.[30] In large doses, aluminum can cause memory disorders and epilepsy in humans and animals. In higher than normal doses, the metal can interfere with concentration, learning, and memory.[31] The specific link between aluminum that we normally ingest and Alzheimer's disease remains controversial. Researchers in both camps can cite a number of arguments for and against a causative link between exposure and Alzheimer's dementia.[30,32,33] Aluminum is certainly not the only causative factor in Alzheimer's disease, but it is likely one of them.[34]

Aluminum/Silica Ratio

Some experimental studies suggest that silica can reduce oral absorption of aluminum and can help the body get rid of aluminum.[35] According to an eight year study, aluminum in drinking water appeared to be a risk factor for the development of Alzheimer's disease—if you lived in a place with higher than normal aluminum in the water, you were more likely to get Alzheimer's disease.[36] In the same study, silica was potentially protective—if you lived in an area where water aluminum levels were perhaps high, but silica levels were also high, you risk of Alzheimer's disease was lower.[36] Later, more carefully controlled studies clarified some of the unresolved issues in the earlier work. Indeed high amounts of aluminum intake increase Alzheimer's disease risk while high amounts of silica intake reduce that risk.[35] A study by INSERM in France, showed that people drinking water containing with more than 0.1 mg of aluminum per liter had a 200-300% increased risk of developing Alzheimer's disease. In the future, carefully controlled studies will be needed to determine ideal yet practically feasible consumption levels of silica and aluminum. It should be emphasized that silica can be harmful when consumed in large amounts[37], therefore proper balance is key. A reasonable approach to increase silica levels is to focus on natural occurring sources of silica, such as lager beer, unrefined soy, wheat, and oats,[38] and these mineral waters are sold at grocery stores and include the brands: Fiji, Volvic, Antipodes, and Aqua pacific, mineral waters that are found in volcanic areas,[39] rather than supplements.

Mercury

Mercury causes various psychiatric and neurological problems.[40] For instance, the phrase "mad as a hatter" came from numerous reports of mental disease among hat makers who routinely used felt laced with mercury. Mercury concentrations are higher in certain regions of the brain and blood in some patients with Alzheimer's disease.[41] Even low levels of inorganic mercury cause Alzheimer's disease-typical deterioration in nerve cells in *in vitro* studies and in animal models.[41,42] A recent study has also shown that mercury affects the accumulation of harmful tau protein fragments.[43] Since mercury is associated with immediate and long-term health issues, exposure to and use of mercury should be tightly regulated and reduced, not only for the development of Alzheimer's disease, but other medical and neurological problems that it causes.[42]

Copper

The liver easily processes organic copper, that is, the copper found in food; however, the liver cannot manage *inorganic* copper, the type found in some drinking water and dietary supplements. [44] This inorganic copper is potentially toxic and may contribute to the development of Alzheimer's disease.[44,45] Copper is part of harmful beta-amyloid plaques and it also produces highly toxic oxygen radicals when it contacts amyloid plaques in brain.[46,47] Some have argued that copper being used as a plumbing material and in certain multivitamins is responsible for the increase in the number of cases of Alzheimer's disease, but the association is difficult verify.[46] Nevertheless, it may be prudent to limit copper exposure when practical. Moreover, zinc (found in oysters, liver, seeds, and dark chocolate) may be partially protective by reducing free (inorganic) copper levels.[47]

Zinc Deficiency

Zinc is important in the normal functioning of brain and is involved in a wide variety of cellular processes. Deficiency in zinc can lead to certain brain disorders and brain cell death.[47] In addition, zinc deficiency has been cited as a factor in the development of Alzheimer's disease.[48] Investigators have found that Alzheimer's patients have decreased levels of zinc in the cerebrospinal fluid and brain compared to healthy individuals. A study of ten Alzheimer's patients who were given 27 milligrams of zinc daily found that eight patients had definite improvement in social behavior, memory performance, comprehension ability, and communication skills.[48] Zinc may also acts in a positive way in treating patients with Alzheimer's disease by lowering the overall toxicity caused by copper.[47] In small trials, six months of zinc therapy improved performance on two cognitive measuring systems in patients with Alzheimer's disease.[47] Further research is needed to determine the proper dietary levels of zinc to prevent Alzheimer's disease since it may have a negative effect at high concentrations.[49]

Lead

While lead is directly toxic to the developing brain, some have argued that exposure early in life may be associated with the later development of Alzheimer's disease.[50] When primates and rodents are exposed to various heavy metals such as lead early in life, it enhances the expression of genes associated with Alzheimer's disease.[50] Early exposure to lead even during the stages of brain development interferes with certain genes that affect Alzheimer's disease later in life.[50] While it is unlikely that lead is the principal cause of Alzheimer's disease, exposure to this heavy metal may contribute to the disease. Thus, efforts should be taken to avoid it, especially in early ages.[50]

Head Trauma

Traumatic brain injury may contribute to Alzheimer's disease.[51] It can lead to swelling in the brain, disruption of the blood-brain barrier function, inflammation, free radical formation, and brain cell death.[51,52] One important consideration moving forward is whether head trauma is a primary or secondary mechanism of Alzheimer's disease development.[53] In other words, does traumatic brain injury accelerate the development of Alzheimer's disease in people already destined to have it or does head injury set off a series of events that turn into Alzheimer's disease that the person would not have otherwise experienced? While every reasonable person attempts to avoid traumatic brain injury, certain endeavors and careers make the chance of head injury quite high (e.g. race car drivers, boxers, athletes in contact sports, combat personnel, etc.).

Other Potential Causes and Markers of Alzheimer's disease

In one study, 93 nuns who could write a grammatically complex sentence at age 20 did not get Alzheimer's disease 60 years later while those who could only communicate using simple sentences got Alzheimer's disease. This sentence test was 90% accurate. A number of other studies have indicated individuals who are more educated are less likely to get Alzheimer's disease. Scientists at Rush University gave stress and anxiety tests to 1064 elderly men and women with normal brain function. Three to six years later these same individuals were then given a memory test. Those individuals initially tested as being prone to worry, anxiety and stress had a 240% greater chance of being diagnosed with Alzheimer's disease than those who were tested as being not anxious or stressed.[54]

A spinal tap test involves taking fluid from the spine. It has been hypothesized that when this fluid contains traces of the protein tau it can be an early sign of Alzheimer's disease. High levels of *Helicobacter pylori*, the bacteria causing stomach ulcers, have also been shown to be a possible early marker for Alzheimer's disease because this virus is found in many Alzheimer's disease patients. Another early sign of Alzheimer's disease is when an individual shows disruption in circadian rhythms, a process in the brain that tells you when to wake up and when to fall asleep. Magnetic resonance imaging (MRI) of the brain that shows the hippocampus section of the brain shrinking has also been shown to be a possible marker of early Alzheimer's disease. If an individual has been given anesthetic gas such as isoflurane or halothane on multiple occasions it is hypothesized this may lead to clumping of amyloid in the brain and potentially cause Alzheimer's disease.

Diet and Alzheimer's disease

A Diet to Prevent Alzheimer's Disease

Fortunately, the diet that seems most effective in reducing the risk of developing Alzheimer's disease is also one that also reduces the risk of Type 2 diabetes, heart disease, stroke, and some forms of cancer. In essence, a diet that is rich in fruits and vegetables, dietary fiber, fish (omega-3 fatty acids), antioxidants, unsaturated fatty acids, folic acid, Vitamins C, E and B12; and low amount of saturated fats are all associated lower chances of getting Alzheimer's disease.[55] While some of the above dietary components may sound like supplements, getting them in their natural form is always better than taking them as a pill or capsule, when possible.

Several lines of scientific evidence suggest that the above diet is virtually ideal in the prevention of Alzheimer's disease. Vegetarians or people that eat few animal proteins may be able to delay the onset of Alzheimer's disease by as many as 6.7 years.[56,57] Giem and colleagues showed an increase in the cases of dementia amongst heavy meat eating populations, in comparison to vegetarian populations.[57] Vegetables seem to provide more protein than fruit.[56] Various studies have demonstrated that the risk of people getting Alzheimer's is higher among the consumers of a high-cholesterol and low-fiber diet,[58,59] which is essentially the opposite of the type of diet a vegetarian consumes (i.e. high natural fibers and few animal fats). Fruits and vegetables are also an excellent source of natural and potent antioxidants. As opposed to strict vegetarianism, however, fish is also good since it is an excellent source of omega-3 fatty acids. One of the most important omega-3s for healthy brain is docosahexaneoic acid (DHA), since it is found in the fatty membranes that surround the brain cells.[60] A number of studies have found that fish/omega-3 poly-unsaturated fatty acids consumption partially protects against the development of Alzheimer's disease[61,62]; however, most of the interventional studies using omega-3 poly-unsaturated fatty acid supplements have been disappointing.[63] Therefore, eating fish is likely better for Alzheimer's disease prevention that supplements. Likewise, patients with Alzheimer's disease typically have lower levels of omega-3 fatty acids and several types of vitamins.[64]

Individuals consuming the lowest amount of calories have a minimal risk of Alzheimer's disease.[58] In fact, several research groups have shown that high caloric intake based on a diet high in saturated fat increases the degree and extent of harmful beta-amyloid proteins in the brains of animals.[65,66] It is important to bear in mind, however, that patients *who already have Alzheimer's disease* need extra care with nutrition. Weight loss and malnutrition are common in Alzheimer's disease[67,68,69] and when they occur, they reduce patient and caregiver quality of life and hastens death.[70]

A diet that is very low in all kinds of fat is not necessarily the best diet for Alzheimer's disease or for health in general. That is because the brain needs fat and cholesterol in order to function properly. While the human brain represents only about 2% of total body mass, it contains one-fourth of the total cholesterol present in body.[71] Cholesterol is a functional part of cell membranes and plays an important role in the formation and functioning of synapses.[72] Interestingly, most cholesterol in the body does not come from the cholesterol that we eat. Most cholesterol in the body is actually produced by the liver in response to the fat that we eat. Thus, avoiding all fat is not helpful in preventing Alzheimer's disease; what is important is getting the right kinds of fat. Those that follow the Mediterranean diet have a lower risk of Alzheimer's disease and mild cognitive impairment.[55,73,74,75 76] The Mediterranean diet is largely similar to the diet described above and mimics what people in Southern Europe eat, namely lots of olive oil, legumes (beans and nuts), unrefined cereals, fruits, vegetables, fish, cheese and yogurt, wine with minimal consumption of meat and meat products.

A Diet to Treat Alzheimer's Disease?

It is important to note that the above diet is considered the ideal for *preventing* Alzheimer's disease. It is also considered to be healthy for those with mild and moderate Alzheimer's disease (if not severe, too). However, several research groups have tried to use specialized diets to *treat* Alzheimer's disease after the diagnosis. One of the most extensively studied diets is the ketogenic diet.

People on the ketogenic diet eat large amounts of fat and very little carbohydrates (with average to high amounts of protein. When the body gets so little carbohydrates, it "thinks" it is in a state of fasting or near-starvation. In fact, in a medically supervised ketogenic diet, the patient starts by eat-

ing nothing to produce a state of near-starvation. Instead of using glucose (sugar) as its main fuel, the body uses fat in the form of ketone bodies (ketones).[77]

Physicians have successfully used the ketogenic diet to treat people with epilepsy for decades. Normally, the brain is one of the most metabolically active organs and requires a constant supply of glucose.[78] Under a ketogenic diet, up to 60% of the total energy being provided to brain is made up of ketone bodies.[77] In this state, the overall electrical activity of the brain is reduced, which is key to halting/preventing the seizures that occur in someone with epilepsy. In Alzheimer's the benefits of a ketogenic diet are less clear.

One variant of the ketogenic diet uses medium-chain triglycerides as the primary fat source (most fats from the diet are long-chain).[79] Some studies suggest it is an easier diet to start and maintain this type of diet than the traditional ketogenic diet. Medium-chain triglycerides and fatty acids are found in particular oils and fats, such as coconut oil and palm oil. It is also the main component of the medical food known as caprylidene. Caprylidene is essentially three molecules of the Medium-chain triglyceride, caprylic acid, joined together. Caprylidene is metabolized into ketone bodies and facilitates an overall ketogenic diet approach. The medical food is approved by the FDA to treat mild to moderate Alzheimer's disease.

The traditional or medium-chain triglyceride ketogenic diet may decrease the amounts of beta-amyloid protein brain[80] and reduce the protein's toxic effect on brain cells.[76] Clinical studies in Alzheimer's disease are mixed, but seem to suggest that a ketogenic diet can improve cognitive function.[81] More research is needed before the diet can be considered effective or as a standard treatment. A health care professional should prescribe, initiate, and monitor any ketogenic diet.

Conventional Therapies

Tacrine, Rivastigmine, Donepezil, Galantamine

Conventional therapy for Alzheimer's disease are designed to control some of the symptoms of the disease. Tacrine, rivastigmine, donepezil, and galantamine are grouped together because the enhance the effect of the neurotransmitter acetylcholine. The drugs have some effect of slowing the decline of learning and memory in Alzheimer's disease, but they do nothing to slow the rate at which brain cells die. They are effective in patients with mild to moderate dementia and perhaps delay cognitive decline by a few months—certainly less than one year.[82] The side effects from these drugs can be very harsh. These agents may cause anorexia, nausea, vomiting, weight loss, increased frequency of bowel movements, dizziness, daytime drowsiness, headache, nighttime insomnia, and muscle cramping.[83,84]

Memantine

Memantine, one of the newest Alzheimer's disease drugs, works by blocking the major excitatory neurotransmitter in the brain, NMDA. Unlike acetylcholinesterase inhibitors, memantine is designed to slow brain cell death, i.e., it is the only conventional therapy that tries to slow progression. It can be used in moderate to severe Alzheimer's disease and is often combined with tacrine, rivastigmine, or donepezil.[85] Memantine slightly improved patient's performance on activities of daily living after 28 weeks of used compared to placebo[86] and this improvement persisted after an additional 24 weeks.[87] It should be noted that the difference between treatment and placebo, while statistically significant, it may not be noticeable to patients or their caregivers. In general, the drug is well tolerated but may cause constipation, dizziness, and headache.[86]

Estrogen

Several research groups have noted that women who use estrogen replacement therapy have a decreased risk of developing Alzheimer's disease while those that have their ovaries removed without replacing estrogen have an increased risk.[88] At least ten studies found that postmenopausal women who were taking estrogen hormone replacement therapy had lower rates of Alzheimer's disease than those who did not use such therapy.[89] For example, a placebo-controlled, double-blind, parallel-group trial of estrogen hormone therapy for one year showed that estrogen could improve visual and sematic memory in patients with mild dementia.[90] While this impressive effect was considered a very promising treatment option in the 1990s and 2000s, estrogen therapy has been shown to increase the risk of developing breast

cancer, heart attack, and stroke. Therefore, estrogen is not considered a treatment option for Alzheimer's disease; however, women who are prescribed estrogen for other reasons (hot flashes) may enjoy the benefit of reduced occurrence of dementia. Estrogen only seems to have a protective benefit when it is started just after the start of menopause[91], suggesting there might be an opportunity to use estrogen therapy in women for a brief period of time, but halting it before the risk of heart attack and stroke become too great.[92]

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Brains of patients who died of Alzheimer's disease show signs of chronic inflammation.[93] NSAIDs are drugs such as ibuprofen (i.e. Advil), naproxen (i.e. Aleve), and celecoxib (i.e. Celebrex), and aspirin. Because inflammation is considered a key part of Alzheimer's disease, attempts have been made to counteract this inflammation with NSAIDs. NSAIDs displayed some promising early clinical trials.[94,95,96,97] In one of the largest studies of its kind, NSAID use was compared using the medical records of 49,349 patients with Alzheimer's disease and 196,850 without the disease. Patients that used NSAIDs over a long period of time were significantly less likely to develop Alzheimer's disease.[98] Unfortunately, long-term use of NSAIDs use can cause abnormal bleeding, gastrointestinal, and kidney problems. More potent and selective NSAIDs called COX-2 inhibitors have fewer bleeding and kidney problems, but they increase the risk of heart attack and stroke. The use of NSAIDs is promising, though it will probably be necessary to find one that is safe for use over a long period of time.[99] One promising NSAID is aspirin. In people that require a daily "baby" aspirin for heart disease, they may have the additional benefit in terms of Alzheimer's disease. The reason that aspirin is not routinely recommended for patients without cardiovascular problems is the increased risk of hemorrhagic stroke.[100]

Alternative Therapies

Ginkgo Biloba

Ginkgo biloba is an herbal medicine that has been used to treat a variety of ailments in China for thousands of years. Extracts from this plant has been used for the treatment of various health conditions such as circulatory problems, vertigo, asthma, weakness, fatigue and cognitive disturbances.[101] It has also been used as a memory enhancer since ancient times.[101] Ginkgo is considered to be a food supplement and is not under the regulation of FDA.[101] In animal studies, Ginkgo enhanced blood flow to the brain.[101] It may also block blood clot formation and the formation of amyloid protein found in Alzheimer's disease senile plaques.[101,102] Some of this work has been reproduced in humans.[103]

There have been a number of studies of Ginkgo in both healthy humans and those with certain neurological disorders. In general the supplement is not associated with severe adverse events.[101] While a number of small trials seemed to show that Ginkgo had a positive outcome in Alzheimer's disease, larger clinical trials have not shown this to be true.[104,105,106] It is not at all clear why the extract works well in laboratory studies and in animals but has not improved measures in human studies. In a 2005 randomized placebo-controlled study carried out by Schneider, *et* al. on 513 patients suffering with Alzheimer's disease[105], it was observed that no benefit of Ginkgo was observed after 6 months; however, the placebo group declined less than would be expected. While this suggests that some of the discrepancy is due to patient population and selection, meta-analysis of several trials that combine the results of all known, high-quality studies indicates that there is little evidence to suggest that Ginkgo has an appreciable effect on Alzheimer's disease.[107]

Turmeric

Turmeric belongs to the same family as ginger and is abundant in regions of South and Southeast Asia.[101] The root of the plant is used for the extraction of turmeric.[101] Turmeric is widely used as a main ingredient in curry paste, however, it has also been used for medicinal applications for centuries.[101] Researchers became interested in turmeric as a possible treatment for Alzheimer's disease when it was discovered that people in India, whose diet contains a large amount of turmeric in curry have the lowest Alzheimer's rates in the developed world and are over four times less likely than people in the United States and Western countries to get Alzheimer's disease. Results from a number of studies have suggested that turmeric plays an active part in the prevention of Alzheimer's disease.[101]

Turmeric acts as an antioxidant and anti-inflammatory properties as well as activity against beta-amyloid aggregation.[108,109,110] It also reduces serum cholesterol levels and has long been used as a remedy and as a food additive with an excellent safety record.[101,109] A number of animal studies indicate turmeric drastically reduces free radical damage and the problems that arise from harmful beta-amyloid protein in mice with Alzheimer's disease.[101] Prospective clinical trials on turmeric have been less favorable and the spice has not yet been shown to have a positive influence on cognition, dementia, or Alzheimer's disease been documented yet.[101,111] Researchers at ULCA performed a 24-week randomized, double blind, placebo-controlled study in 36 people with mild to moderate Alzheimer's disease. Even though the same researchers found turmeric to be the most potent compound and reduced the markers of Alzheimer's disease in mice, the clinical trial resulted in no clinical or biochemical evidence of effect.[111] Nevertheless, clinical trials of turmeric are ongoing.

Acetyl-L-Carnitine

Acetyl-L-carnitine has been studied extensively as a potential treatment for age-related memory problems, senile depression, and Alzheimer's disease. Acetyl-L-carnitine is produced naturally in the brain and is the most commonly occurring form of L-carnitine.[101] Acetyl-L-carnitine is more effective than standard carnitine in affecting brain function.[112] It plays a vital role in metabolism of fats in the body, it is used by the body to make cell membranes and effects enzyme and hormone activity.[101] Acetyl-L-carnitine is also related to the neurotransmitter, acetylcholine.[101] Acetyl-L-carnitine has been investigated as a tool for increasing acetylcholine neurotransmission, a process that is damaged in Alzheimer's disease.[101] Various animal studies have shown that Acetyl-L-carnitine is protects against brain cell damage[113] and nerve cell damage.[114] In clinical trials, Acetyl-L-carnitine was helpful in reduced damaging senile plaques and to improve thinking and memory (though this was in a very small study).[115] In a larger study of 130 patients, long term Acetyl-L-carnitine treatment helped patients improve on the Blessed Dementia Scale, logical intelligence, verbal critical abilities, long-term verbal memory, and selective attention.[116] Although another study was not favorable. A one-year, multicenter, double-blind, placebo-controlled randomized study of 112 Alzheimer's patients and 117 healthy controls showed that Acetyl-L-carnitine did not slow cognitive decline.[117] The key factor may be using Acetyl-L-carnitine in younger patients and earlier in the disease process. A longitudinal, double-blind, parallel group, placebo-controlled study of 334 patients with Alzheimer's disease showed that Acetyl-L-carnitine slowed the progression of disease symptoms in younger subjects.[118] The compound is well tolerated even at high doses (2.2 to 3 grams per day) and may be helpful in some cases (perhaps in younger patients?).[119] Larger, controlled trials are needed to make definitive recommendations about Acetyl-L-carnitine, however.

Phosphatidylcholine and Phosphatidylserine

One of the most commonly used dietary supplements for elderly people with memory deficits are the phospholipids: phosphatidylserine and phosphatidylcholine.[120] These phospholipids are found in cell membranes and play a vital role in the functioning of brain cells.[121] Supplementation with phospholipids such as phosphatidylserine and phosphatidylcholine has been suggested as a possible treatment, since phosphatidylcholine breaks down at a faster rate in Alzheimer's patients than in healthy persons.[122] Thus far, supplementation with phosphatidylcholine has not had a major impact on Alzheimer's disease patients. Nevertheless, a combination of vitamin E, pyruvate, and phosphatidylcholine provides more protection against brain oxidation processes in dementia-type diseases than vitamin E alone.[123]

Phosphatidylserine, and related compound, was shown to have beneficial effects on Alzheimer's disease and dementia.[124,125,126,127,128] The largest of these trials involved 494 elderly patients between the ages of 65 and 93 years with moderate-to-severe senility.[125] The researchers assessed the patients' cognitive function, behavior, and mood before the therapy began and at the end of the trial. They determined that the group receiving phosphatidylserine had significant improvements in all of these measures. The beneficial effects of phosphatidylserine are larger when the supplement is combined with cognitive training (e.g. brain teasers, mental exercises).[129] While a large trial would help better establish dosing and duration of treatment parameters and help identify which Alzheimer's

disease patients would benefit from treatment, phosphatidylserine is a promising addition to a comprehensive Alzheimer's disease treatment strategy.

Citocoline

Citocoline (also known as cytidine 5'-diphosphocholine) is a supplement related to choline that may help protect brain cells by increasing the rate at which they replenish themselves.[130] In a meta-analysis of trials with the compound, citocoline improved memory and behavior in patients with cognitive impairment in short and medium term endpoints.[130] The daily administration of 600-1000 mg of citocoline reduced the emotional and behavioral impairment experienced by patients with dementia.[130] No severe side effects were reported.

NADH

In a randomized, placebo-controlled, double-blind trial lasting six month, 26 patients with probable Alzheimer's disease either received oral NADH (10 mg/day) or placebo.[131] Patients treated with NADH had no further decline in their brain functioning, but those in the placebo group did. People that received treatment were more verbally fluent and had better reasoning skills. There were no differences, however, in measures of attention or memory. This small study has not been replicated, so it is difficult to know how applicable NADH use is on a larger scale.

Resveratrol

Resveratrol is a compound that is found in grapes and, by extension, in red wine.[132] Resveratrol has the ability to reduce blood clotting and inflammation when studied on brain and blood in the laboratory.[133] Clinically, resveratrol seems to be able to improve heart and blood vessel disease, diabetes, arthritis, and age-related disorders.[134] Resveratrol's role in has shown preventing or improving symptoms of Alzheimer's disease is less clear.[133] The compound is also a potent antioxidant and seems to protect brain cells from free radicals.[132] Moreover, resveratrol delays the damage caused by beta-amyloid protein neuronal cell culture models.[135,136] It may do so by blocking inflammation in the brain.[137] Clearly clinical trials are needed to assess the efficacy and degree of effect that resveratrol has in cognitive decline and Alzheimer's disease.

Bexarotene

Bexarotene, commercially available as Targretin™, is an FDA approved skin cancer drug. However, researchers have discovered that it has a number of useful features in animals with experimental Alzheimer's disease and so it is being tested in a small number of patients.[138] When animals genetically altered to have Alzheimer's disease are given bexarotene for as little as three days, the animals have much lower levels of the harmful Alzheimer's disease protein, beta-amyloid deposition.[146] The mice also stop displaying the abnormal behaviors that the Alzheimer's disease mutation causes.[138] Bexarotene is thought to block the effect of a certain type of cell in the brain (microglia) and strongly suppress inflammation in the brain.[139,140,141] Even though bexarotene does not cause the side effects one would expect from a cancer chemotherapeutic, it is still a cancer treatment and will require regulatory clearance and additional safety and efficacy trials in humans before any meaningful conclusions can be made about its potential use in Alzheimer's disease.

Deferoxamine

Deferoxamine is a substance, when injected into the body, removes aluminum and iron from blood and tissue. When a small group of patients with Alzheimer's disease was treated with this substance it cut the rate of decline in daily functioning skills by 50% as compared to those who did not receive the treatment.[142] Deferoxamine is currently a treatment for iron overdose or aluminum toxicity. The drug may not be suitable for Alzheimer's disease treatment because of side effects of long term use; however, it provides a path to producing other, safer aluminum-reducing drugs that may be of use in Alzheimer's disease.[143]

Huperzine A

Huperzine A is substance that is derived from a plant and is available in supplement form, though it has been used as a remedy in China for centuries. Huperzine A has two interesting properties that may be of use in Alzheimer's disease. It has the ability to prevent the breakdown of the neurotransmitter acetylcholine and it can block the NMDA receptor. More acetylcholine in the brain (less breakdown) helps improve cognition. In fact, it is the main way that drugs like tacrine (Cognex) and donepezil

(Aricept) work. Additionally, blocking the NMDA receptor may help prevent the destruction of nerve cells in the brain. Incidentally, blocking NMDA receptors is how the drug Memantine (Namenda) works. Treatment with Huperzine A was better than placebo in a trial of 103 patients with Alzheimer's disease.[144] Patients taking the supplement performed better on several tests of memory.[144] This beneficial effect was confirmed in a larger study (202 patients) in 2002.[145] Moreover, patients experienced benefits in behavior, mood, and activities of daily living as well. This study also showed that the supplement did not cause serious side effects.[145]

Insulin

In recent years, Alzheimer's disease has been referred to as "diabetes of the brain" or even Type 3 diabetes. People suffering from diabetes have a significantly higher risk of developing Alzheimer's disease. In a recent study patients suffering from dementia and Alzheimer's disease were given insulin through a nasal spray. Those participants who took 20 IU (International Units) of insulin had stabilized and improved cognition as compared to those who did not take the insulin nasal spray.[146] This study demonstrates the potential of insulin as a treatment for Alzheimer's disease symptoms and for the use of nasal sprays technology as a potentially more effective method to deliver medications to the brain.

DHEA

Dehydroepiandrosterone (DHEA) is the most common hormone in the body. It is also found in large quantities in the brain. DHEA levels decrease in the blood and the brain with age and are thought by many to be associated with many of the symptoms of aging. The precise role of DHEA is unknown other than its role as a source for other steroid hormones in the body. In recent years, several studies have demonstrated an association between decreasing levels of DHEA and the development of age-related conditions such as arthritis, heart disease, diabetes, and obesity. Two separate studies suggest DHEA can improve memory and enhance cognitive function in elderly persons with cognitive problems. A case-control study found that a group of 14 persons with Alzheimer's disease had significantly lower levels of DHEA sulfate in the plasma compared to 13 matched healthy controls.[147] A study of 52 patients with Alzheimer's disease found that those with higher plasma DHEA sulfate levels scored higher on a variety of cognitive tests than those with lower DHEA sulfate level.[148] DHEA has also been found to have the ability to protect cells from oxidative damage to the hippocampus part of the brain.[149] This is among the regions of the brain most affected by Alzheimer's disease. A small, randomized, double-blind, placebo-controlled trial of DHEA in patients with Alzheimer's disease showed that the hormone showed a trend toward improvement in cognitive test scores at three months, but failed to meet statistical significance.[149] A new study of patients with Alzheimer's disease found that the administration of DHEA sulfate combined with insulin improved a variety of physiologic factors associated with the disease.[150]

Periwinkle

Periwinkle (also known as Vinpocetine) has been used historically in various countries for the treatment of a number of diseases.[101] It was used in European countries as a folk remedy against diabetes; in India as a topical treatment of wasp stings; in China as a cough remedy; in the central and South American countries, it was used as a remedy for colds; and in the Caribbean, it is used to treat irritation and infections of the eye.[101] Periwinkle appears to support brain cell function by enhancing the use of sugar (glucose) and oxygen consumption. Periwinkle also seems to make the brain more resistant to oxygen deprivation (that may occur during stroke).[101,151] An analysis of several trials in the 1990s and 2000s a modest clinical benefit of periwinkle on tests of learning, memory, and mental functioning.[152] Fortunately, periwinkle appears to cause very few side effects even at relatively high doses of 60 mg per day.[152] It should be noted that larger clinical trials using well-defined treatment groups are needed in order to make a definitive recommendations about the use of periwinkle in Alzheimer's disease.

Anatabine

Anatabine is a plant alkaloid that occurs in foods such as tomatoes, eggplants, and peppers. When anatabine was placed in cell culture with brain cells, it reduced the formation of beta-amyloid protein. Moreover, the plant product reduced harmful levels of the protein in an animal model of Alzheimer's disease-like neuropathology.[153] Roskamp Institute is studying the role of anatabine

in fighting Alzheimer's disease and other inflammatory diseases (Anatabloc). A pharmaceutical company is currently recruiting participants with mild and moderate Alzheimer's disease to test the effect of an anatabine-containing compound on beta-amyloid levels and cognitive tests, however no clinical trials of anatabine in Alzheimer's patients have been published.

Muira Puama (Marapuama)

Almost all the parts of both the trees found in the genus *Muira Puama* are used for medicinal purposes, however the most commonly used parts are the bark and roots of *Ptychopetalum olacoides.* These contain long-chain fatty acids, plant sterols, lupeol and other bioactive molecules.[154] Muira Puama is able of inhibit acetylcholinesterase activity in brain, which is the enzyme that breaks down acetylcholine after it is released by presynaptic neurons.[155] While it has not been rigorously tested in humans, *Ptychopetalum olacoides* has promensic effects (improves memory; opposite of amnesia) and enhances memory retrieval in mice.[155,156,157,158]

Vitamin A

Vitamin A is an essential vitamin for the proper functioning of the eye and brain.[159] Vitamin A and beta-carotene levels in blood and brain are lower in patients suffering from Alzheimer's disease and this may influence the progression and severity of the disease.[159,160] Vitamin A in the form of retinol, retinal, retinoic acid and beta-carotene slow the formation and extension of beta-amyloid and may even break up the harmful proteins.[161,162] Wilcock and coauthors were able to decrease plaques and tangles in mice with Alzheimer's disease by administering injections of Vitamin A.[163]

These experimental examples certainly suggest that Vitamin A may be a key molecule for the prevention and perhaps treatment of Alzheimer's disease. Unfortunately, Vitamin A is a fat-soluble vitamin; the body cannot remove excess Vitamin A like it can with water-soluble vitamins. High intake of Vitamin A is associated with poor bone mineral density and other negative effects.[164] Because of these issues, no formal clinical studies using Vitamin A in Alzheimer's disease have been pursued. Nevertheless, any Vitamin A deficiency should be corrected. It is also reasonable to consume a diet rich in food that contain Vitamin A such as green, leafy greens, carrots, apricots, and cantaloupe.

Thiamine

Thiamine, one of the B vitamins, produces similar effects in the brain as acetylcholine. Acetylcholine is the primary neurotransmitters involved in normal memory function and is low in the brains of people with Alzheimer's disease.[165] Moreover, people with thiamine deficiency have an increased risk of developing Alzheimer's disease. Thiamine increases the effects of acetylcholine. The elderly are particularly vulnerable to thiamine deficiency. Two studies found that supplementation with 3 to 8 grams per days of thiamine improved mental function in patients with Alzheimer's disease and other forms of senility.[166] Administration of thiamine at these levels is generally regarded as safe.

Folic Acid

Folic acid deficiency might contribute to insidious aging effects of on the brain.[167,168] Deficiencies in folic acid and Vitamin B_{12} lead to increased levels of homocysteine. Homocysteine, in turn, is associated with increased risk of dementia and Alzheimer's disease.[169,170] A study of nuns with Alzheimer's disease aged 78 to 101 years old living in a convent found that brain atrophy, as determined at autopsy, was strongly associated with low blood levels of folic acid.[171] A case-control study of 164 Alzheimer's patients and healthy control subjects aged 55 years or older found that low levels of folic acid and vitamin B12 in the blood was associated with Alzheimer's disease.[172] However, a different study that evaluated the levels of serum folic acid, vitamin B12, and other factors in 52 Alzheimer's patients, 50 hospitalized controls, and 49 healthy elderly subjects found no significant differences in folic acid or vitamin B12 levels between the three groups.[173] A recent, population-based study found that individuals with low levels of folic acid in the blood were twice as likely to develop Alzheimer's compared to those with normal folic acid levels.[174] Newer research has found that low levels of folic acid in the blood are associated with an increased risk of developing Alzheimer's disease. This effect was reinforced when homocysteine levels in the blood were increased.[169] Low folic acid levels are also associated with an increased risk of cognitive decline in otherwise healthy older adults who do not have Alzheimer's disease.[174] Another study found that folic acid deficiencies are a risk factor for both

vascular dementia and Alzheimer's disease, and this risk is increased when increased levels of homocysteine are present.[175,176]

A number of experiments have shown that increasing dietary intake of folic acid reduces the risk of Alzheimer's disease and dementia. On the other hand, some studies have identified no association between the dietary intake of B Vitamins and Alzheimer's disease. In a recent systematic review and meta-analysis, Dangour and coauthors reviewed 33 clinical trials and observational studies testing B vitamins in the treatment and prevention of Alzheimer's Disease.[177] Although, there is much promise in the study of B vitamins as a dietary treatment method for Alzheimer's disease, there is insufficient data from high quality, long term trials to recommend their use above standard levels.[177]

Vitamin B12

Vitamin B12 deficiencies have also been linked to Alzheimer's disease. Vitamin B12 deficiencies can lead to nerve malfunction that includes numbness and pins-and-needles sensations and these sensations have been associated with Alzheimer's disease. Vitamin B12 deficiencies have also been linked with other types of impaired cognitive and neurological function in the elderly. Anyone who is displaying signs of dementia should have an analysis performed to determine vitamin B12 levels. Vitamin B12 supplementation has led to improved mental function in patients with impaired mental function and a vitamin B12 deficiency. As with many anti-Alzheimer's agents, early treatment results in the best effects. Some patients with diagnosed dementia for less than six months had a complete reversal of disease when they received supplements of vitamin B12 and/or folic acid[178] though it is not clear if the dementia was from Alzheimer's disease directly.

The most effective forms of vitamin B12 in the body are called methylcobalamin and adenosylcobalamin. Cyanocobalamin is the most commonly found form of vitamin B12 supplementation, but it requires additional reactions in the body to become effective. Elderly individuals may be less efficient in performing this conversion, so the other forms may be the most effective way to treat those with Alzheimer's disease. One study has found that low levels of vitamin B12 in the blood of dementia patients increased the risk of these patients developing hallucinations and sleep disturbances, which are two of the prominent complications of dementia-type diseases.[178] A study of folic acid and vitamin B12 found that a combination of the vitamins reduced levels of homocysteine in the blood of Alzheimer's patients.[172] Researchers have found that homocysteine is a key biochemical factor in the development of Alzheimer's disease. Moreover, people with low vitamin B12 have a faster mental decline than those with normal B12 levels.[179] This research suggests vitamin B12 supplementation could slow progression or prevent some aspects of the disease. In a double-blind study of 266 patients with mild cognitive impairment, those that received 0.8 mg of folic acid, 0.5 mg of vitamin B12 and 20 mg of vitamin B6 each day for two years did better on several tests of learning and memory than those taking placebo.[180]

Vitamin C

Vitamin C, also known as ascorbate or ascorbic acid, is an essential nutrient for human beings. Fruits and vegetables are the natural sources rich in Vitamin C, however, it is also found in the liver of meat such as beef and chicken; the richest sources being Kakadu plum and Camu Camu. It is also found in Indian gooseberry, Chili pepper, grape fruit, oranges, tangerine, guava, parsley, and acerola among other sources.

Antioxidants in the diet have long been thought to not only confer some amount of protection against oxidative damage but also to reduce the general cognitive decline caused by normal aging.[181] Vitamin C is a good free radical scavenger in that it reduces free radicals.[181] The accumulation of beta-amyloid protein is believed to induce toxicity and death in cells by oxidative stress created by peroxides and superoxide.[182] The property of Vitamin C to potently reduce the level of oxidative stress has created a lot of interest as an Alzheimer's disease/anti-aging remedy.[183]

Vitamin C is a water-soluble vitamin and therefore the levels of toxicity produced by it are also remarkably low—excess amounts are eliminated from the body. One of the main side effects caused by Vitamin C is that it enhances iron absorption and iron is actually a pro-oxidant. In general the vitamin is very safe since unused portions are rapidly excretes in the urine. This safety has been demonstrated in clinical trials.[184,185,186,187,188,189] What has not

yet been determined is the effect of Vitamin C on cognition and disease progression. Supplementation did not improve neuropsychological test scores in Alzheimer's disease patients.[187,188] Nor did it improve biomarkers associated with Alzheimer's disease usually present in cerebrospinal fluid, though there was evidence of reduced inflammation/oxidative stress.[187] Of note, Vitamin C when combined with other vitamins and supplements actually *accelerated* decline on Mini-Mental State Examination scores, raising concern for future trials and long term use in Alzheimer's disease patients.[187]

Vitamin E

Vitamin E is a fat-soluble vitamin that is naturally available from the oil of wheat germ, sunflower, safflower, palm; nuts and nut oils; leafy vegetables such as spinach, turnip, beet; avocados; asparagus; kiwifruit. Vitamin E is an antioxidant that blocks the production of harmful oxygen free radicals.[190]

Multiple animal studies have highlighted the importance of vitamin E deficiency in the development of Alzheimer's disease.[191] In laboratory studies, Vitamin E blocks some of the damage caused by beta-amyloid proteins.[192] In humans, Vitamin E inhibits the oxidation processes that are involved in the development of beta-amyloid, one of the classic processed involved in the development of the disease.[193] Individuals who had a high dietary intake of vitamin E over a lifetime had a lower risk of developing Alzheimer's disease.[194] Vitamin E protects against harmful oxidative processes in the brain and, when combined with vitamin C, reduces the lifetime incidence of developing Alzheimer's disease by 64%.[195] Thus, these vitamins may be helpful in preventing the disease. Since Vitamin E is fat-soluble it should not be taken in excess because it is stored in body fat and can cause problems (e.g. dizziness, headache, blurred vision, diarrhea, nausea) in high concentrations. However, data from mega-trial studies have suggested that doses of Vitamin E ≥400 IU per day for 7 years in patients with pre-existing vascular diseases or diabetes increased the incidence of cardiac arrest without any other beneficial outcomes.[196] Long-term use of Vitamin E supplements may also increase the risk of stroke (hemorrhagic type). Ideally people should consume adequate amounts of Vitamin E from their diets and not from supplements.

Caffeine

There is some evidence that caffeine consumption may be useful in Alzheimer's disease. The stimulant has had numerous beneficial effects in various animal models of Alzheimer's disease.[197,198,199,200] Caffeine improved memory impairment and reduced beta-amyloid deposition in mice genetically altered to produce Alzheimer's disease-related pathology.[197] Caffeine may also improve cellular energy by aiding mitochondrial function in mice.[198] Caffeine consumption prevented cognitive decline in normal rats[200] and memory impairment and neuronal damage in Alzheimer's disease animal models.[199] The assessment of caffeine is in the observational phase currently, however mild cognitively impaired patients with high caffeine levels in blood show a slower cognitive decline than those with low blood levels.[201]

Melatonin

Researchers have found that poor sleep habits and the presence of sleep disorders is associated with an increased risk of developing various types of dementia, including Alzheimer's disease. [202] The commonly used sleep-inducing agent melatonin has also shown some positive effects in Alzheimer's disease. In laboratory studies, melatonin reduces the negative effects of amyloid beta proteins.[203] The hormone can attenuate Alzheimer's disease pathology in animal models when given early in the course of disease process.[204,205] A double blind study of melatonin showed that patients with Alzheimer's disease could benefit by taking the medication in terms of sleep-wake cycle, cognition and other behaviors.[206] Other trials have not found the same results. Singer and colleagues determined that melatonin is not a useful sleep agent in demented patients.[207] Moreover, in a double-blind randomized, placebo-controlled trial of institutionalized patients with Alzheimer's disease, melatonin produced no significant benefit on sleep or agitation using actigraphy or behavioral scales.[208]

Art Therapy

Alzheimer's disease causes anxiety and stress, among many other behavioral changes. While art therapy may not slow the progression of the disease, it may be beneficial in reducing stress and agitation that Alzheimer's disease patients often experience. Rusted, 2006 and Bonner, 2006, both have demonstrated that art therapy has a soothing effect on the patients suffering from Alzheimer's

disease and aids in keeping them stress-free and thus less agitated. Art therapy may also minimize the adverse effects associated with some Alzheimer's disease medications and generally reduce stress.[209] Multisensory stimulation, including art therapy, had a positive effect on cognitive state, depression, and anxiety in mildly-affected Alzheimer's patients.[210] In patients with severe dementia, significant support was needed such as cutting paper in advance and pre-drawing lines, yet patients who participated in art therapy responded favorably.[211] In the only controlled trial of its kind, coloring and drawing improved patient quality of life and ratings of personal vitality.[212]

Exercise Therapy

Exercise has been shown to be beneficial in mild cognitive disorder, dementia, and Alzheimer's disease through a number of putative mechanisms.[213,214,215,216,217,218] It has favorable effects on neuronal viability and function, neuroinflammation, vascularization, neuroendocrine stress response and beta-amyloid burden in the brain.[214] While the former work was done in animal models of Alzheimer's disease, exercise also reduces the risk of developing dementia in older individuals.[219,220] Generally the effects are seen only after 6 to 12 months of exercise therapy compared to sedentary controls.[221] In addition to improvements in cognitive function, patients with dementia are also more physically capable, which helps caregivers provide care, and they have better overall quality of life.[222] At this point it does not seem to matter what type of exercise is used since positive effects are observed with home-based, aerobic, structured and self-guided exercise regimens.[223,224,225,226]

Therapeutic Touch and Massage Therapy

Agitation is a common problem in patients with Alzheimer's disease. This not only affects their own health, but also affects other patients and care givers and increases costs of and access to care. Massage therapy has been used successfully for the treatment of depression related to trauma and stress and is purported to reduce agitation associated with dementia and "sundowning."[227] The basic concept is that rubbing, kneading and tapping a patient's muscles helps release tension and emotional angst.[227] The beneficial effect has been seen in a few small clinical trials[228,229,230,231,232] A study of four elderly Alzheimer's patients who received two, half-hour sessions for six months resulted in improvement in variety of measures including increased physical relaxation, improved communication, increased sleepiness, and a decrease in abnormal behaviors.[230] Researchers found that therapeutic touch therapy significantly reduced discomfort in Alzheimer's disease patients in as little as five sessions. Likewise, low-stroke massage decreased agitation in advanced cases of Alzheimer's.[231] A study that measured anxiety and dysfunctional behavior in Alzheimer's disease patients found that expressive physical touch combined with visualization led to decreased anxiety and dysfunctional behavior in advanced Alzheimer patients.[229] Moreover, therapeutic touch and hand massage reduced agitation levels in these patients.[232] This particular study found that hand massage was the more effective of the two therapies. Nevertheless, in resource-rich environments, massage and touch therapy may be an effective, non-pharmaceutical means of reducing agitation in Alzheimer's disease.

Music Therapy

Several studies have demonstrated that music therapy provides beneficial effects to Alzheimer's patients. A study of 18 elderly Alzheimer's patients aged 55 to 95 years with severe disease found that music played during bath time led to significant decreases in aggressive behavior events over a two-week period.[233] In a curious case study, an Alzheimer's disease patient found had improved cognitive scores after listening to a Mozart piano sonata.[234] A twin sibling of the patient, also with Alzheimer's, had no increase in these cognitive measures following exposure to a period of silence or popular music from the 1930s.[234] On the other hand, the content of the music may not be terribly important—researcher composed music was effective as well.[235] In patients with senile dementia, music therapy improved behavioral measures associated with irritability and also endocrinological indices associated with stress.[236] Importantly, scores on cognitive tests were unchanged in the study.[236] Problematic behaviors such as agitation decreased when Alzheimer's disease patients listened to music.[237] Music therapy improves autobiographical memory in Alzheimer's disease patients.[238] After a session of music therapy, patients of Alzheimer's disease were not only less agitated but also had increased interactions with one another.[239] One of the main advantages of music therapy over oth-

ers such as art or massage therapy is that is it less expensive and require minimal caregiver effort.

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