Drugs, Vitamins and Supplements used in Alzheimer’s disease

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Objectives

- Define Alzheimer’s Disease and Dementia
- Illustrate how Alzheimer’s impacts society
- Examine the pathophysiology
- View the different drugs, vitamins and supplements used in Alzheimer’s disease.

What is Alzheimer’s Disease?

“A brain disease that slowly destroys memory and thinking skills and, eventually, the ability to carry out the simplest tasks.”

WHAT IS DEMENTIA?

- “A loss of thinking, remembering, and reasoning skills that interferes with a person’s daily life and activities.”

- National Institutes of Health - Senior Health

What Happens to the Brain

- Alzheimer’s disease damages neurons to where they lose connections and die.
- This damage to nerve cells effects a person’s ability to carry out daily functions.
- Two common structures appear in the brains of Alzheimer’s patients:
  - Amyloid Plaques
  - Neurofibrillary Tangles

Effects on Society

- 5.2 million Americans have Alzheimer’s Disease in the year 2014
- Alzheimer’s is the 6th leading cause of death in the United States
- Over 500,000 people die each year
- Alzheimer’s Disease is the most expensive condition in the nation
- Estimated direct cost to society in the year 2014 is $214 billion including $150 billion in costs to Medicare/Medicaid.

Amyloid Plaques

- Amyloid plaques are insoluble deposits of beta-amyloid protein fragments
- Amyloid Precursor Protein (APP) is the starting point
- APP is cleaved by alpha, beta, and gamma secretase enzymes
  - Alpha-secretase is involved in a benign pathway
  - Beta-secretase is involved in a harmful pathway
- Beta-amyloid peptides combine to form oligomers, fibrils, and eventually plaques
Neurofibrillary Tangles
- Neurofibrillary tangles are abnormal deposits of twisted protein threads inside nerve cells.
- Main component of tangles is the protein tau.
- Alzheimer’s disease exhibits hyperphosphorylation of tau protein.
- Additional phosphates lead to formation of tangles and neuronal damage.

Progression of the Disease
- Mild to Moderate AD
- Current Drug Therapy
- No treatment exists today that cures Alzheimer’s or stops the progression of the disease.
- Current therapy helps slow the loss of cognitive capability and the ability to carry out daily tasks.
- Two classes of drugs have been approved by the FDA for the treatment of symptoms of Alzheimer’s:
  - Acetylcholinesterase Inhibitors (AChE-I)
  - N-methyl-D-aspartate (NMDA) Receptor Antagonists

Acetylcholinesterase
- Acetylcholinesterase (AChE) is an enzyme located in cholinergic synapses that degrade the neurotransmitter acetylcholine.
- Patients with Alzheimer’s have a decrease in acetylcholine and nicotinic acetylcholine receptors (nAChR).
- AChE is found at increased levels surrounding beta-amyloid plaques and neurofibrillary tangles.

ACHE-Inhibitors
- Bind and deactivate AChE.
- Compensates for post-synaptic receptor loss by increasing levels of synaptic acetylcholine.
- Prolongs the signal in the synapse to continue communicating despite the decrease in receptors.
- Allosteric potentiators of nAChR bind and increase the response to acetylcholine.
- Butyrylcholinesterase (BuChE) has a minor role in regulating acetylcholine levels but increases in people with Alzheimer’s.
- Three AChE-I are used for the treatment of symptoms of Alzheimer’s in the United States today.
**Donepezil (Aricept®)**

- Approved for the use in Alzheimer’s disease in 1996
- Selective, reversible inhibitor of acetylcholinesterase
- Selectivity limits peripheral cholinomimetic side effects

**Kinetics of Donepezil**

- Reaches peak plasma concentrations in 3-5 hours
- Reaches steady state within 15 days
- 100% bioavailability
- Effects of food on absorption are minimal
- Metabolized by glucuronidation and CYP2D6 and CYP3A4
- Elimination half-life is 70 hours

**Special Populations:**
- Hepatic Impairment: Clearance reduced by 20% in alcoholic cirrhosis
- Renal Impairment and Geriatrics: No clinical significance

**Dosing and Side Effects**

**Dosing:**
- 5mg once daily at bedtime, increased to 10mg daily after 4-6 weeks if patient is tolerant
- 23mg once daily approved for advanced stages of the disease
- Therapy is continued into the severe stages as long as it shows a beneficial response

**Side Effects**
- Diarrhea (5% to 15%)
- Nausea (5% to 9%)
- Vomiting (3% to 8%)
- Cramping (3% to 8%)
- Insomnia (2% to 14%)

**Rivastigmine (Exelon®)**

- Selective, pseudoreversible inhibitor of acetylcholinesterase.
- Also inhibits butyrylcholinesterase
- Slow dissociation allows for longer duration of action.

**Kinetics of Rivastigmine**

- 40% weakly bound to plasma protein.
- Primarily metabolized at CNS receptor sites by cholinesterases.
- Minimally effected by cytochrome P450 enzymes.
- Titrated based on tolerability in hepatic and renal impairment patients.
- Plasma half-life is 1 to 2 hours

**Route Specific**:
- **Oral:**
  - Peak Plasma Concentration in 1 hour.
  - 36% bioavailable.
  - Administration with food increase AUC by 30% and increase tolerability.
- **Transdermal:**
  - Peak Plasma Concentration in 8 hours.
  - 50% of the drug load is released from the transdermal system.
  - Body weight affects exposure.

**Dosing**

- **Oral:**
  - 1.5mg BID with food, increased to 3 mg BID after 2 weeks if tolerated.
  - May continue to increase to 4.5mg BID and 6mg BID in 2 week intervals.
  - Max of 12mg/day
  - Only 30% tolerate 12mg/day

- **Transdermal:**
  - 4.5mg/24hr once daily, increased to 9.5mg/24hr in 4 weeks if tolerated.
  - May increase to 13.5mg/24hr
  - Patient’s below 50kg (110lbs) have more adverse effects, titrate dose cautiously
Adverse Effects

- **Oral:**
  - Diarrhea (7% to 19%)
  - Nausea (29% to 47%)
  - Vomiting (13% to 31%)
  - Decrease in appetite (6% to 17%)
  - Dizziness (6% to 21%)
  - Tremor (4% to 23%)
  - Headache (4% to 17%)

- **Transdermal:**
  - Diarrhea (5% to 7%)
  - Nausea (3% to 12%)
  - Vomiting (3% to 10%)
  - Decrease in appetite (1% to 6%)

Galantamine (Razadyne®)

- Approved for use in 2001
- Selective, reversible acetylcholinesterase inhibitor
- AllostERICALLY modulates nicotinic acetylcholine receptors

Kinetics of Galantamine

- Reaches peak plasma concentrations in 2 hours.
- 90% bioavailability.
- Food delays absorption but does not decrease it.
- 75% metabolized CYP2D6 and CYP3A4. 25% excreted unchanged in the urine.
- Elimination half-life is 7 to 8 hours.

- Special Populations:
  - Hepatic Impairment: Clearance reduced by 25% with moderate impairment
  - Renal Impairment:
    - Moderate: AUC increased by 37%
    - Severe: AUC increased by 67%
    - Avoid in patients with CrCl <30 ml/min

Dosing and Side Effects

- **Immediate Release:**
  - 4mg BID with food, increase to 8mg BID after 4 weeks if tolerated. May increase to 12mg BID.

- **Extended Release:**
  - 8mg QD with food, increase to 16mg QD after 4 weeks if tolerated. May increase to 24mg QD.

- **Side Effects:**
  - Nausea (25%)
  - Vomiting (12.8%)
  - Diarrhea (9%)
  - Dizziness (8.9%)
  - Headache (7.6%)

Comparison of ACHE-I

- A study in 2004 showed no statistically significant differences between Donepezil, Rivastigmine, and Galantamine.

- A study in 2010 showed no significant difference between the effects of the three drugs on ApoE-genotyped patients.

Glutamate and NMDA Receptor

- Glutamate is an excitatory.
- NMDA receptor is activated by glutamate.
- NMDA channel opens upon activation, allowing an influx of calcium.
- In Alzheimer's, there is an excessive exposure of neurons to glutamate, ultimately leading to calcium toxicity.
Memantine (Namenda®)

- Approved in 2003.
- Namenda is the only NMDA receptor antagonist.
- Uncompetitive, low affinity, open-channel blocker.
- Prevents excessive excitation but does not interfere with normal synaptic function.

Kinetics of Namenda

- Reaches peak plasma concentrations in 6-8 hours.
- 100% bioavailability.
- May take with or without food.
- 42-45% protein bound.
- Elimination half-life is 60-80 hours.

Special Populations:
- Hepatic Impairment: No dose adjustment needed
- Renal Impairment:
  - Moderate: No dose adjustment needed.
  - Severe: Decrease dose to max of 5mg BID of IR formulations and 14mg/day of XR formulations.

Dosing and Side Effects

- Immediate Release:
  - 5mg QD, titrate up by 5mg per week until dose is 10mg BID.

- Extended Release:
  - 7mg QD, titrate up by 7mg per week until taking 28mg QD.

- Side Effects:
  - Diarrhea (2% to 5%)
  - Dizziness (5% to 7%)
  - Headache (6%)

Combination Therapy

- Study in 2008 showed a significantly lower rate of decline in those taking a combination of Namenda and a cholinesterase inhibitor.
- Combination is usually used in moderate to severe stages of the disease.

Cost Comparison

- Cost to order a 1 month supply from McKesson:
  - Donepezil 10mg QD: $2.30
  - Rivastigmine 3mg BID: $110.80
  - Exelon 9.5mg/24hr QD: $341.61
  - Galantamine 8mg BID: $88.21
  - Galantamine XR 16mg QD: $83.73
  - Namenda 10mg BID: $307.80
  - Namenda XR 28mg QD: $289.46

Vitamins and their Role in the Prevention of Alzheimer’s Disease
What can be done?

- No definitive preventative measures
- Vitamins may reduce risk

Vitamins believed to reduce risk

- Pyridoxine (Vitamin B6)\(^4\)
- Folate (Methyltetrahydrofolate) (Vitamin B9)\(^5\)
- Cobalamin (Vitamin B12)\(^4\)
- Thiamine (Vitamin B1)\(^3\)
- Vitamin C\(^6\)\(^9\)
- Vitamin D\(^7\)

*Vitamins are not intended to diagnose, treat, cure or prevent any condition.

Homocysteine

- Modified Amino Acid
- Inflammation Marker\(^{27}\)
- Risk Factor for Alzheimer’s Disease\(^{14}\)
  - Possible mechanisms\(^{26}\)
    - Inflammation\(^{47}\)
    - Lead to increase in phosphorylated τ
    - Inhibits methylation reactions
      - Prevents histone methylation

Pyridoxine Deficiency

- Often seen with B9 and B12 deficiencies\(^{23}\)
- Elevated Homocysteine Levels:
  - Increased Risk of Dementias\(^{21}\)
    - Including Alzheimer’s Dementia\(^{10}\)
  - Increased risk of stroke\(^{20}\)
- Cysteine Deficiency
  - Potential protein dysfunction.

How homocysteine is eliminated

![Homocysteine Elimination Diagram](image)

Folate

- Vitamin B9
- Active Form
  - 5-methyltetrahydrofolate (5-MTHF)
- Biological methylene (–CH\(_2\)–) transfer reagent
- Folate Cycle
  - Methionine Synthase
    - Converts Homocysteine back to Methionine
    - Remethylation

![Folate Cycle Diagram](image)
Folate Deficiency

- Decrease Remethylation
  - Increase Homocysteine levels
    - Increase Risk of Alzheimer’s Disease

Cobalamin

- Vitamin B12
  - Cofactor for Folate cycle
  - Assists in Remethylation of Homocysteine.
  - Assists in 5-MTHF to THF conversion
  - Main function in brain is methylation

Cobalamin Deficiency

- Decreased methylation
  - Impairs neuronal cell proliferation
- Decreased Remethylation
  - Increase Homocysteine levels
    - Increase Risk of Alzheimer’s Disease
- Can be masked by large amounts of Folate.
  - High Plasma Folate and Cobalamin deficiency may increase risk of AD.

Thiamine

- Vitamin B1
  - Links Glycolysis to Citric Acid Cycle
  - Cofactor for Pyruvate Dehydrogenase
    - Takes Pyruvate to Acetyl Coenzyme A (AcCoA)

Vitamin C

- Ascorbic Acid
- Anti-oxidant
- Vital Role in Brain
  - Development
  - Protection
  - Norepinephrine Biosynthesis
  - Acetylcholine release

Vitamin C’s Role in Alzheimer’s

- Cholinesterase Inhibition
  - Could be used as Adjuvant therapy
    - Appears to boost Cholinergic system functioning
- Oxidative stress
  - Key role in pathogenesis
  - Cholinergic system
    - Forebrain cholinergic cell death
- Low Plasma levels
  - Found in Patients with Alzheimer’s
**Vitamin C Deficiency**
- Referred to as Scurvy
  - Brain Retains during deficiency
- Decreased Antioxidant ability
  - Increased risk of Alzheimer’s
- Use of Vitamin C
  - Showed protective advantage

**Vitamin D**
- Active form
  - 1,25dihydroxy-vitamin D₃ (1,25-D₃)
- Multiple uses in body
  - Calcium absorption
  - Modulates cell growth
  - Gene modulating
    - Apoptosis
    - Differentiation

**Vitamin D Deficiency**
- Increased risk of Alzheimer’s Disease
- Potential Mechanisms
  - Vitamin D receptors located throughout brain.
  - Regulates Nerve Growth Factor
  - Stimulate Macrophages

**Ginkgo Biloba**
- Contains two major active compounds, flavonoids and terpenoids
  - Flavonoids are plant-derived antioxidants, which can protect cells from free radicals and oxidative damage
  - Terpenoids can increase blood flow by vasodilation and anti-platelet effects
  - These combined effects can protect neurons and allow them to be better perfused

**Ginkgo Biloba continued**
- Can stimulate neuron activity
- Can protect neuronal membranes
- Can improve neurotransmitter function
- There are conflicting studies on Ginkgo’s efficacy
- However, some studies show that it works as well as some Rx medications at delaying symptoms of dementia

**Phosphatidylserine**
- Phosphatidylserine is the major phospholipid in the brain
- Extremely important for proper neuron functioning
- Necessary for neuronal signaling, membrane fluidity, membrane protection, and efficient release of neurotransmitters
- Allows for an increased response to neurotransmitters such as acetylcholine, norepinephrine, serotonin, and dopamine
Phosphatidylserine continued

- The brain’s levels of PS being to decline around middle age
- This effect is worsened by deficiencies in essential fatty acids, folate, and vitamin B12, which aid in the synthesis of PS
- PS deficiency is linked to dementia and Alzheimer’s disease

Nerve growth factor (NGF) is associated with growth, maintenance, and survival of neurons. As with humans, older rats possess fewer and smaller brain neurons. PS supplementation in older rats was associated with an increased number of NGF receptors. It also allowed the rats to retain more neurons along with maintaining larger neurons. These rats also performed better on maze tests.

In rats, PS supplementation also stimulated dopamine release and acetylcholine release from the cerebral cortex. Human studies using PET scans revealed increased brain glucose utilization in patients supplemented with PS. PS may also function to protect cells against free radical damage, as evidenced by a decrease in oxidative damage to human fibroblasts in cultures treated with PS.

A double-blind, placebo controlled study was performed with 425 patients who had moderate-to-severe Alzheimer’s. One group was given daily doses of 200–300mg of PS for 6 months. They showed significantly improved memory, learning, motivation, and socialization compared to placebo.

There have been many other studies that show PS has positive effects on memory, mood, and behavior in the elderly. It is a very well-tolerated supplement. It does not appear to have any adverse side effects except mild GI upset.

Docohexaenoic Acid (DHA)

- It is an essential omega-3 fatty acid
- Has the highest concentration in the brain
- Composed of 35% of phosphatidylethanolamine in the brain
- May slow dementia and AD through a number of different mechanisms
DHA continued

- Possesses anti-inflammatory properties by competing with arachidonic acid for positions in phospholipids in the brain\textsuperscript{15}
- In mice brains and cultured human neurons, it reduced the production of amyloid precursor protein, the protein that eventually becomes amyloid beta\textsuperscript{15}
- Does this by several possible mechanisms: changes in membrane structure and fluidity which influence APP processing; production of anti-amyloidogenic chaperones for APP and amyloid beta\textsuperscript{15}

- Inhibits some kinases responsible for tau phosphorylation\textsuperscript{15}
- May assist in fixing insulin and neurotrophic factor signaling defects\textsuperscript{15}
- May increase brain levels of neurotrophic factors which are responsible for neural development and function\textsuperscript{15}
- May prevent oxidative damage\textsuperscript{15}
- May prevent neuroinflammation\textsuperscript{15}

DHA continued

- A randomized, double blind, placebo-controlled study was performed with 485 healthy individuals aged 55 and older with age-related cognitive decline\textsuperscript{16}
- Were given DHA or placebo for 24 weeks
- The treatment group had fewer paired associate learning test errors, as well as improved verbal recognition memory scores compared to placebo
- Very well tolerated
- Seem to be most effective when taken early and prophylactically

Vitamin E

- Alpha-tocopherol acts as a powerful antioxidant
- There exists much evidence that oxidative stress is an important factor in the pathogenesis of AD\textsuperscript{18}
- Oxidation also promotes the irreversible polymerization of tau and beta amyloid, and beta amyloid is toxic through a mechanism involving free radicals\textsuperscript{18}
- In neuronal cell cultures, vitamin E has been shown to prevent oxidative damage induced by beta amyloid\textsuperscript{18}

Vitamin E continued

- In rats, chronic vitamin E treatment resulted in a decreased concentration of oxidized proteins and fewer errors on memory tests\textsuperscript{18}
- A randomized, placebo controlled study was done with 613 patients who had mild-moderate AD at 14 Veteran’s Affairs medical centers\textsuperscript{17}
- 4 groups- one that received just 2000IU of vitamin E a day, one that received 20mg/d of memantine, one that received both, and one that received placebo
- The group treated with vitamin E showed significantly slower cognitive decline compared with placebo
- There was no significant difference in the groups that received memantine alone or memantine and vitamin E

Vitamin E continued

- In the Alzheimer’s Disease Cooperative Study, 341 patients with moderately severe AD were treated with vitamin E or placebo\textsuperscript{18}
- The time it took to reach major events/endpoints in AD were measured, such as institutionalization, loss of basic activities of daily living, developing severe dementia, and death
- The group treated with vitamin E had prolonged time to each event/endpoint; however, they showed no better improvement in cognitive tests, possibly since they already had moderately severe AD
References:


Resources continued