Vitamin E: An Alzheimer’s Breakthrough or Bust?

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Learning Objectives:
1. Summarize the presentation and pathophysiology of Alzheimer’s Disease (AD)
2. Define current medications used in the treatment of AD
3. Identify the theoretical role of vitamin E in AD pharmacotherapy
4. Formulate evidence-based recommendations for use of vitamin E in AD
I. Dementia

A. Definition of dementia
   a. Progressive neurodegenerative disease
   b. Deterioration of memory, thinking, behavior and abilities to perform activities of daily living

B. Prevalence
   a. 47.5 million afflicted people worldwide
   b. 7.7 million new cases each year
   c. 75.6 million people by 2030

C. Social and economic burdens
   a. Total 2016 cost of all dementias in U.S. is $236 billion
      i. Out-of-pocket expenses is 19% of total cost ($46 billion)
   b. Less than 20% due to medical costs
   c. Greater than 80% due to institutionalization and loss of productivity in caregivers
      i. Nursing home admission by age 80 is expected for 75% of AD patients
         1. Only 4% for the general population
      ii. Over 15 million Americans are unpaid caregivers for AD patients

D. Different forms of dementia have their own distinct symptoms and brain abnormalities (Table 1)

<table>
<thead>
<tr>
<th>Dementia Type</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alzheimer’s Disease (AD)</td>
<td>50-80%</td>
<td>Caused by neuronal destruction via amyloid plaques and neurofibrillary tangles</td>
</tr>
<tr>
<td>Vascular Dementia (VaD)</td>
<td>20-30%</td>
<td>Caused by infarcts in the brain due to blocked or damaged blood vessels</td>
</tr>
<tr>
<td>Frontotemporal Dementia (FTD)</td>
<td>5-10%</td>
<td>Caused by progressive nerve cell loss in frontal and/or temporal lobes</td>
</tr>
<tr>
<td>Dementia with Lewy Bodies (DLB)</td>
<td>5%</td>
<td>Caused by Lewy bodies in the cortex, midbrain, and brainstem</td>
</tr>
<tr>
<td>Mixed Dementia</td>
<td>&gt;50%</td>
<td>Most commonly AD with VaD, then AD with DLB</td>
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</tbody>
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E. Differential diagnoses commonly include, but are not limited to:
   a. Depression
   b. Delirium
   c. Thyroid dysfunction
   d. Vitamin deficiencies
   e. Alcohol abuse
   f. Infections

II. Alzheimer’s Disease

A. Most common type of dementia, making up 50-80% of cases
   a. Affects over 5 million Americans
      i. Estimated to increase to 13.8 million by 2050
   b. Approximately 82% of patients are ≥ 75 years old
      i. Not a part of the normal aging process

B. AD related complications leading to hospitalizations (Table 2)

<table>
<thead>
<tr>
<th>Reason for Hospitalization</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Syncope, fall, trauma</td>
<td>26%</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
<td>17%</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>9%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>6%</td>
</tr>
<tr>
<td>Delirium</td>
<td>5%</td>
</tr>
<tr>
<td>Other</td>
<td>37%</td>
</tr>
</tbody>
</table>

C. Fifth leading cause of death in Americans > 65 years old
   a. Estimated 700,000 Americans die from AD and related complications
D. Pathogenesis
   a. Preclinical
      i. Measurable changes in the brain, cerebrospinal fluid and/or biomarkers
      ii. May occur 20+ years before symptoms appear
   b. Mild cognitive impairment (MCI)²
      i. 15-20% of people ≥ 65 years old
      ii. 32% of cases will develop AD within 5 years
      iii. Not exclusive to AD and does not always progress to AD
   c. Dementia due to AD (Figure 1)
      i. Functioning declines with disease progression

![Figure 1. Normal Aging vs. Dementia Progression](image)

E. Presentation (Table 3)²⁻⁷

<table>
<thead>
<tr>
<th>Mild (early stage)</th>
<th>Moderate (middle stage)</th>
<th>Severe (late stage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory loss – forgetting familiar words</td>
<td>Withdrawal from work or social activities</td>
<td>Loss of awareness to surroundings and ability to communicate</td>
</tr>
<tr>
<td>Losing or misplacing location of everyday objects</td>
<td>Changes in mood, personality and/or sleep patterns</td>
<td>Behavioral symptoms (anxiety, delusions, hallucinations)</td>
</tr>
<tr>
<td>Increasing trouble with planning or organizing</td>
<td>Confusion about where they are or what day it is</td>
<td>Motor impairment (lose ability to walk and/or swallow)</td>
</tr>
<tr>
<td>Impaired judgment</td>
<td>Increased risk of wandering and becoming lost</td>
<td>Vulnerable to infections and decline</td>
</tr>
</tbody>
</table>

F. Duration of disease
   a. Average survival time after diagnosis is 4 to 8 years
   b. Survival time up to 20 years has also been seen
   c. 61% of AD patients are expected to die before age 80 vs. 30% in those without AD²
      i. Primary causes of death are related to consequences of AD

III. Pathophysiology
   A. Healthy brains contain over 100 billion neurons and 100 trillion synapses which facilitate memories, thoughts, sensations, emotions, movements and skills²
   B. An AD brain shows inflammation, atrophy and debris from dead or dying neurons (Figure 2)²
      a. Disrupts transfers in synapse information causing cognitive and motor impairment

![Figure 2. Healthy Brain vs. Brain with AD](image)
C. Primary hypotheses (Figure 3)²-⁴
   a. Accumulation of protein fragment beta-amyloid (Aβ) plaques outside neurons
   b. Increased neurofibrillary tangles (NFT) containing tau protein inside neurons

![Figure 3. Hypothetical Pathophysiological Cascade][]{fig}

D. Genetic mutations are estimated to account for <1% of AD cases²-⁴
   a. Amyloid precursor protein (APP)
   b. Presenilin-1 and -2 (PS-1 and PS-2)
   c. Additional full or partial copy of chromosome 21 (Down syndrome)

IV. Risk Factors of AD

   A. Advancing age²
      a. 15% of patients are 65-74 years old
      b. 44% of patients are 75-84 years old
   B. Family history²
      a. First-degree relative
   C. Female gender⁴
      a. Approximately 2:1
      b. AD cases in the U.S by gender
         i. Women - 3.2 million vs. Men - 1.8 million
   D. Race and ethnicity²
      a. African-Americans - 2 times increased risk compared to whites
      b. Hispanics - 1.5 times as likely as whites
   E. Apolipoprotein E (APOE) gene, on chromosome 19²-⁴
      a. Three APOE alleles: e2, e3, or e4
         i. One allele inherited from each parent
            1. 61% inherit both e3 (does not affect risk)
            2. 0.5% inherit both e2 (decreased risk)
            3. 25% inherit one e4 (3-fold increased risk)
            4. 2% inherit both e4 (8-12 fold increased risk)
      b. The only common genetic risk factor for non-familial, late-onset AD identified
   F. Low birth weight/head circumference³
      a. Low birth weight may affect brain development
      b. Small head circumference may be a marker for lower number of neurons and synapses
   G. Sedentary lifestyle and cardiovascular disease²-⁴
      a. Brain health is related to heart and blood vessel health
b. Inflammation and blood vessel damage increase risk
   i. Smoking, obesity, hypertension and diabetes

H. Education
   a. Lower levels of education are associated with an increased incidence of dementia
   b. Higher formal education may have protective effects
      i. EClipSE collaborative studies
         1. Evaluated over 800 brain autopsies
         2. Higher education did not protect people from neurodegenerative disorders, but did
            diminish the clinical expression of disease

V. Diagnosis

A. No diagnostic biomarkers of dementia-related brain changes
B. Diagnostic and Statistical Manual of Mental Disorders (DSM) fourth edition describes diagnostic criteria
   for AD, but this was not updated in the DSM fifth edition
C. Clinical diagnosis made by thorough, comprehensive medical evaluation (Table 4)
   a. Rule out differential diagnoses via blood tests and brain imaging
   b. Obtain medical and family history
   c. Conduct cognitive, physical and neurologic examinations
D. Cognitive tests
   a. Common cognitive screening tests (Appendix 1)
E. Cognitive staging systems (Appendix 2)

Table 4. National Institute on Aging and Alzheimer’s Association Diagnostic Criteria

<table>
<thead>
<tr>
<th>Core Clinical Criteria</th>
<th>Probable AD</th>
<th>Possible AD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Core criteria PLUS</td>
<td>Core criteria PLUS</td>
</tr>
<tr>
<td>• Interfere with functioning at work or usual activities</td>
<td>• Insidious onset - gradual over months to years</td>
<td>• Atypical course – sudden onset or insufficient historical/objective documentation</td>
</tr>
<tr>
<td>• Decline from previous levels of functioning</td>
<td>• Obvious history of cognitive decline</td>
<td>• Etiologically mixed presentation – evidence of differential diagnosis</td>
</tr>
<tr>
<td>• Ruled out delirium or major psychiatric disorder</td>
<td>• Presentation - amnestic vs. nonamnestic</td>
<td></td>
</tr>
<tr>
<td>• Positive patient history and cognitive assessment</td>
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<td></td>
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<tr>
<td>• Impairment involving ≥ 2 of the following:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Acquire/remember new information (repetitive speech, misplacing items)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Reasoning, handling complex tasks, poor judgment (finances)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Visuospatial (recognize faces/common objects)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>o Language functions</td>
<td></td>
<td></td>
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<tr>
<td>o Changes in personality or behavior</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

VI. Management of AD

A. There is no cure for AD
   a. Pharmacologic therapies may help manage cognitive, motor and psychiatric symptoms
B. Goals of therapy
   a. Improve quality of life
   b. Maximize function in activities of daily living (ADLs)
   c. Maintain cognition
   d. Reduce behavioral symptoms
C. Cognitive Symptoms
   a. Memory loss, confusion, thinking and reasoning impairment
   b. Cholinesterase inhibitors (Table 5)
      i. FDA approved for mild to moderate AD
      ii. Mechanism of action: reversibly inhibit centrally active acetylcholinesterase
      iii. Modest benefits for cognition, activities of daily living and behaviors
iv. Duration of therapy is unknown
1. Significant increased risk of bradycardia, syncope and related consequences (i.e. hip fractures) with long term therapy
2. Discontinuation may cause loss of cognitive and functional benefit not previously evident
3. Avoid abrupt withdrawal

Table 5. Cholinesterase Inhibitor Drug Information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosages/Titration</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Donepezil (Aricept®)</td>
<td>PO: 5, 10, 23 mg Daily</td>
<td>GI: 3-19%</td>
<td>• Additionally approved for severe AD&lt;br&gt;• No significant differences between 23 mg and 10 mg except ↑side effects in 23 mg&lt;br&gt;• ↑MMSE by 1.9 points (p&lt;0.001)⁹&lt;br&gt;• Improved ability for ADL and reduced nursing home placement by 20%⁹</td>
</tr>
<tr>
<td></td>
<td>ODT: 5, 10 mg Daily</td>
<td>Insomnia: 2-14%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 mg dose is effective</td>
<td>Dizziness: 2-8%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ to 10 mg after 4-6 weeks</td>
<td>Bradycardia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>↑ to 23 mg after 3 months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivastigmine (Exelon®)</td>
<td>PO: 1.5, 3, 4.5, 6 mg BID TD: 4.6, 9.5, 13.3 mg Daily</td>
<td>GI: 17-47%</td>
<td>• TD 13.3 mg improved ability to perform ADL compared to 9.5 mg patch, but no cognitive benefit⁹</td>
</tr>
<tr>
<td></td>
<td>↑ every 4 weeks if needed</td>
<td>Dizziness: 6-21%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Falling: 6-12%</td>
<td></td>
</tr>
<tr>
<td>Galantamine (Razadyne®)</td>
<td>PO: 4, 8, 12 mg BID ER: 8, 16, 24 mg Daily</td>
<td>GI: 11-21%</td>
<td>• Renally adjust dose&lt;br&gt;• Minimal clinical benefit; some improved cognitive function, but no ADL benefit⁹</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness: 8%</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PO (by mouth), ODT (oral disintegrating tablet), GI (gastrointestinal), TD (transdermal), BID (twice daily), ER (extended release)

c. N-Methyl-D-Aspartate (NMDA) Receptor Antagonist (Table 6)⁷
   i. FDA approved for moderate to severe AD
   ii. Mechanism of action: noncompetitive antagonist of glutamate receptor
   iii. Modest benefit for cognition, but may help reduce behavioral symptoms⁹

Table 6. NMDA Drug Information

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosages/Titration</th>
<th>Side Effects</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memantine (Namenda®)</td>
<td>PO: 5, 10 mg ER: 7, 14, 21, 28 mg ↑ after 1 week if needed</td>
<td>Dizziness: 5-7% Confusion: 6% Constipation: 3-5%</td>
<td>• No evidence of benefit in mild-moderate&lt;br&gt;• Doses ≥ 10 mg/day should be taken BID&lt;br&gt;• Renally adjust dose&lt;br&gt;• ↑MMSE by 1.2 points (p&lt;0.001)⁹&lt;br&gt;• No additional effect with donepezil 23 mg</td>
</tr>
</tbody>
</table>

D. Behavioral and Psychiatric Symptoms
a. Over 90% of AD patients experience behavioral and/or psychiatric symptoms⁹
   i. Apathy, depression, wandering, agitation, anxiety, hallucinations and sleep disturbances
b. Management
   i. Rule out other causes⁹
      1. Medication adverse effects, infections, or hearing and vision disturbances
   ii. Nonpharmacologic management³¹
      1. Help prevent or deescalate psychiatric symptoms
      2. Strategy examples: sleep hygiene, redirection, distraction, environmental modifications
   iii. Pharmacologic management (Table 7)⁹
      1. Use when nonpharmacologic options fail
      2. Therapeutic selection based upon symptoms
### Table 7. Pharmacologic Management of AD Symptoms*[^9,18,20]

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Treatment</th>
<th>Comments</th>
</tr>
</thead>
</table>
| **Depression**        | Selective serotonin reuptake inhibitors (SSRIs)[^9]  
  - Escitalopram  
  - Sertraline  
  Non-SSRIs[^9]  
  - Bupropion  
  - Venlafaxine  
  - Mirtazapine | Escitalopram and sertraline are well tolerated in elderly[^9]  
May additionally benefit patients with anxiety  
May take several weeks to reach peak efficacy  
Bupropion: do not use in agitated patients  
Venlafaxine: monitor blood pressure  
Mirtazapine: low dose well tolerated in elderly & promotes sleep |
| **Anxiety and Agitation** | Benzodiazepines (BZD)[^18]  
  - Temazepam  
  - Lorazepam  
  - Alprazolam  
  - Anxiolytic  
  - Buspirone | Benzodiazepines[^7,18]  
Avoid all BZD if possible  
Use at lowest effective dose  
Use as needed for intermittent, severe anxiety  
↑risk of sedation, confusion, falls, disinhibition  
Buspirone:  
May be useful in mild-moderate agitation  
May take 2-4 weeks to become effective |
| **Insomnia**          | Non-benzodiazepines (Non-BZD)[^18]  
  - Zolpidem  
  Other[^9]  
  - Melatonin  
  - Mirtazapine  
  - Trazodone | Avoid BZD due to rebound insomnia which may occur within 1-2 weeks of use  
Non-BZD have similar side effects as BZD  
Trazodone: as effective as zolpidem at one week, slightly less effective by week two[^9] |
| **Psychosis**         | Atypical (2[^nd] generation)  
  - Preferred  
  - Risperidone[^9]  
  - Olanzapine[^9]  
  - Quetiapine[^19]  
  Cognition agents:  
  - Cholinesterase inhibitors  
  - Memantine | Both typical and atypical antipsychotics black boxed warning - increased mortality in elderly with dementia-related psychosis[^9,20]  
Reserve for severe psychosis (problematic delusions, hallucinations, severe psychomotor agitation and combative ness)  
Initiate and use cautiously due to side effects  
Sedation, increased stroke risk, metabolic symptoms and extrapyramidal symptoms |

*List is not comprehensive of all pharmacologic options

### VII. Vitamin E

- **A.** Vitamin E is a lipophilic antioxidant that may protect cells from this damage[^21]  
  a. DNA fragmentation and cytotoxicity is suppressed by antioxidants[^22]  
  b. Low serum vitamin E levels have been associated with memory loss and AD[^23,24]
- **B.** Proposed mechanism and role of vitamin E  
  a. Pathophysiological processes may involve oxidative stress (Figure 4)[^25]  
  i. Imbalance of antioxidants and free radicals causes oxidative stress leading to cell damage  
     1. Aging causes increased free radical formation  
  ii. Altered amyloid precursor protein (APP) processing causing excessive Aβ aggregation  
     1. Aβ plaques contain denatured proteins (require reactive oxygen species)[^24]
C. Safety profile of vitamin E
   a. Doses > 3,000 IU/day are toxic\(^\text{21}\)
      i. Increase in bleeding risk
         1. Antiplatelet effect\(^\text{28}\)
            a. High doses (>1,000 IU/day) inhibit platelet aggregation
            b. Increase in risk of hemorrhagic stroke by 22\%\(^\text{21}\)
            c. Signs and symptoms of toxicity include fatigue, GI cramps, diarrhea\(^\text{21}\)
   b. Drug interactions\(^\text{28}\)
      i. Antiplatelet and anticoagulant therapies – increased risk for bleeding
      ii. Simvastatin and niacin – may stop the rise of high-density lipoprotein
      iii. Chemotherapy and radiotherapy – may reduce effectiveness by inhibiting cellular oxidative damage in cancerous cells
   c. Syncope/falls\(^\text{28,32}\)
      i. Sano et al. evaluated vitamin E vs. placebo\(^\text{32}\)
         1. Significantly higher incidence of syncope (p=0.031) and falls (p=0.005)
   d. Increased mortality
      i. Demonstrated in meta-analyses by Miller et al.\(^\text{29}\) and Bjelakovic et al.\(^\text{30}\)
         1. Risk ratio 1.04; 95\% confidence interval, 1.01-1.07\(^\text{30}\)
   e. Increased risk for prostate cancer\(^\text{31}\)
      i. SELECT trial showed vitamin E 400 IU/day may be harmful in men
         1. Hazard ratio, 1.13; 99\% confidence interval, 0.95-1.35
   f. Increased risk for heart failure\(^\text{36}\)
      i. HOPE-TOO trial extension sensitivity analysis of all heart failure outcomes
         1. Risk ratio 1.19; 95\% confidence interval, 1.05-1.35, p=0.007

VIII. Controversy

A. Some studies report positive effects from vitamin E use (Appendix 3)\(^\text{12-34}\)
   a. Correlations between vitamin E users and better cognitive performance and delay in AD progression
   b. Only one randomized controlled trial evaluating vitamin E monotherapy use in patients with AD\(^\text{13}\)

B. Several studies and reviews report neutral or negative effects from vitamin E use (Appendix 4)
   a. Cochrane review from 2014 evaluated 3 studies\(^\text{21}\)
      i. Concluded there is no convincing evidence vitamin E benefits patients with AD or MCI
   b. Increased mortality and risk of prostate cancer and heart failure\(^\text{31,36}\)

C. Clinical Questions
   a. Does vitamin E have any efficacy for use in AD?
   b. Is vitamin E safe to use?
## Literature Review


### Purpose
To perform a meta-analysis of the dose-response relationship between vitamin E supplementation and total mortality by using data from randomized, controlled trials.

### Design
All randomized, controlled trials testing effect of vitamin E supplementation in humans.

### Population
**Inclusion criteria:**
- Randomized allocation of participants
- Use of vitamin E supplementation alone or combined with other vitamins/minerals
- Limited to men or nonpregnant women
- Duration of vitamin E supplementation and follow-up longer than 1 year
- Occurrence of at least 10 deaths in the trial

**Exclusion criteria:**
- No original data
- Not a randomized, controlled trial
- No control group without vitamin E
- Vitamin E administration or follow up < 1 year
- Trials in children or in pregnant or lactating women
- Secondary publications of included trials
- < 10 deaths in the trial
- No mortality data available or mortality data not separated from a composite end point

### Outcomes
**Primary outcome:** all-cause mortality with daily high-dose vitamin E use

### Methods
**Search strategy:**
- MEDLINE search using Medical Subject Heading (MeSH) terms vitamin E, antioxidant vitamins, alpha tocopherol, tocopherol and clinical trials from 1966-2004
- Cochrane database of randomized controlled trials; reviewing reference lists from original research, review articles and previous meta-analyses

**Study description:**
- Included 19 trials involving 135,967 participants
  - Low dosage (<400 IU/day) trials: 8
  - High dosage (≥ 400 IU/day) trials: 11

**Statistics:**
- Used intention-to-treat principle and 2-level hierarchical logistic regression model for all trials with a factorial design with 2-way analyses (treatment vs. placebo)
- Defined high dose vitamin E as ≥ 400 IU/day to evaluate dose-response analyses
- Sensitivity analyses
  - Different knot values (100, 200, 300, 400, or 500 IU of vitamin E per day) for the quadratic-linear, dose-response model
  - Evaluated effect of variables: sex distribution, mean age, use of other vitamins/minerals combined with vitamin E and average duration of follow-up

### Results
**Study description:**
- All-cause deaths = 12,504
- Reported mean age 47-84 years
- Average follow up ranged from 1.4-8.2 years
- Vitamin E dosage varied from 16.5-2000 IU/daily

**Vitamin E combined effect:**
- Average death risk = 1022 per 10,000 persons
- Vitamin E supplementation increased all-cause mortality (Figure 5)
  - All-cause mortality increased in dose-response analysis for doses >150 IU/day
    - No residual heterogeneity after consideration of different dosages (p=0.15)
  - Authors separated into low and high dose groups to control for heterogeneity
    - Significant heterogeneity (p=0.02) due to differences in high and low dosage trials
    - Low dose pooled risk difference was -16 per 10,000 persons (CI,-41-10 per 10,000 persons) and risk ratio 0.98 (CI, 0.96-1.01; p>0.2)
    - High dose pooled risk difference 39 per 10,000 persons (CI, 3-74 per 10,000 persons) and risk ratio 1.04 (CI, 1.01-1.07; p=0.035)
Figure 5. Risk difference in all-cause mortality for vitamin E supplementation and pooled results for low and high vitamin E trials

Sensitivity analyses:
- Different knot values curve was essentially unchanged
- Overall pooled risk differences
  - 4-way analysis overall = 8 per 10,000 persons (CI, 23-39 per 10,000 persons; p>0.2)
  - 2-way analysis had significant heterogeneity (p=0.039)
  - Low-dosage -33 per 10,000 persons (CI, -60 to -5; p=0.021)
  - High-dosage 34 per 10,000 persons (CI, 5-63 per 10,000 persons; p=0.022)
- No significant change after adjusting for sex distribution, mean age, or average follow-up
- Increased mortality risk with high dose trials after adjusting for concomitant use of other vitamins/minerals (pooled risk difference 63 per 10,000 persons, CI 6-119 per 10,000 persons)
- Statistically significant increase in mortality for high doses remained after exclusion of the 11 high-dose trials
  - Pooled all-cause mortality risk difference ranging from 28-55 per 10,000 persons

Authors’ Conclusions
Authors identified all-cause mortality progressively increased for dosages > 150 IU/day. Vitamin E ≥ 400 IU/day is unjustified as it far exceeds intake from the diet. Recommendations to give vitamin E are premature as larger, randomized, controlled trials evaluating safety and efficacy of high-dose vitamin E in patients with AD are warranted.

Critique
Strengths:
- Assessed dose-response
- Accounted for heterogeneity between studies
- Performed sensitivity analyses to account for sex, age, other vitamins/minerals
- Evaluated multiple disease states – including patients that may be on antiplatelet or anticoagulation therapy

Limitations:
- Small size of several trials
- Inconsistent reporting of events across trials
- Potential publication bias in trials
- Only included one trial for AD

Summary
Use of high dose vitamin E (≥ 400 IU/day) should be cautioned due to potential for increased mortality

Purpose
Determine whether treatment with vitamin E or donepezil could delay the clinical diagnosis of AD in subjects with the amnestic form of mild cognitive impairment

Design
Double-blind, randomized, placebo-controlled, parallel-group multicenter (69 sites) trial

Population
See Appendix 5 for full inclusion and exclusion criteria

Inclusion criteria:
- Age 55-90 years
- Amnestic MCI of a degenerative nature (insidious onset and gradual progression)
- Impaired memory
- Logical memory delayed-recall score ~1.5-2 SD below education-adjusted norm
- Clinical Depression Rating (CDR) of 0.5
- MMSE score of 24-30

Exclusion criteria:
- Significant cerebral vascular disease
- Depression
- CNS infarct, infection, or focal lesions of clinical significance on CT/MRI
- Medical diseases/psychiatric disorders
- Taking additional vitamins or supplements
- Medication restriction (potential cognitive effects)

Outcomes/Endpoints
Primary outcome:
- Clinically possible or probable AD

Secondary outcomes:
- Cognition and function

Primary endpoint:
- Time to development of possible or probable AD – if met AD criteria, participant was offered open-label donepezil until they completed the study at month 36

Secondary endpoints:
- MMSE scores
- ADAS-Cognitive subscale
- Global CDR
- CDR sum of boxes
- ADCS MCI Activities of Daily Living Scale
- GDS
- Neuropsychological battery tests (NYU paragraph-recall, symbol digit modalities, category-fluency, number-cancellation, Boston naming, digits-backward, clock-drawing, maze-tracing task)

Methods
- 790 patients underwent randomization; 769 completed baseline assessment
- Conducted between March 1999 and January 2004

Table 8. Petersen RC, et al. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n=259)</th>
<th>Donepezil (n=253)</th>
<th>Vitamin E (n=257)</th>
<th>All subjects (n=769)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – year</td>
<td>72.9±7.6</td>
<td>73.1±7.1</td>
<td>72.8±7.3</td>
<td>72.9±7.3</td>
</tr>
<tr>
<td>Female sex no. (%)</td>
<td>121 (47)</td>
<td>112 (44)</td>
<td>119 (46)</td>
<td>352 (46)</td>
</tr>
<tr>
<td>APOE e4 carrier no. (%)</td>
<td>136 (53)</td>
<td>147 (58)</td>
<td>141 (55)</td>
<td>424 (55)</td>
</tr>
<tr>
<td>ADAS Cog Original</td>
<td>11.03±4.2</td>
<td>11.28±4.5</td>
<td>11.48±4.4</td>
<td>11.26±4.4</td>
</tr>
<tr>
<td>ADAS Cog Modified</td>
<td>17.40±6.0</td>
<td>17.72±6.2</td>
<td>18.04±6.0</td>
<td>17.72±1.8</td>
</tr>
<tr>
<td>MMSE</td>
<td>27.35±1.8</td>
<td>27.25±1.8</td>
<td>27.20±1.9</td>
<td>27.27±1.8</td>
</tr>
<tr>
<td>CDR sum-of-boxes score</td>
<td>1.87±0.8</td>
<td>1.80±0.8</td>
<td>1.78±0.8</td>
<td>1.82±0.8</td>
</tr>
<tr>
<td>GDS score</td>
<td>2.72±0.6</td>
<td>2.66±0.6</td>
<td>2.64±0.6</td>
<td>2.67±0.6</td>
</tr>
<tr>
<td>ADL scale</td>
<td>45.87±5.2</td>
<td>46.49±4.3</td>
<td>45.82±4.6</td>
<td>46.06±4.7</td>
</tr>
</tbody>
</table>

Patients randomly assigned to receive
- Vitamin E 2,000 IU/daily + placebo donepezil + multivitamin daily
  - Initial vitamin E dose was 1,000 IU daily and was titrated after 6 weeks
- Donepezil 10 mg daily + placebo vitamin E + multivitamin daily
  - Initial donepezil dose was 5 mg daily, titrated after 6 weeks
- Placebo vitamin E + placebo donepezil + multivitamin daily
Results

Primary outcome measures:
- 16% per year overall rate of progression
- 214 patients progressed to dementia over 3 years
- No significant differences for incidence of progression from MCI to AD
  - Vitamin E vs. placebo (HR 1.02; 95% confidence interval, 0.74-1.41; p=0.91)
  - Donepezil vs. placebo (HR 0.80; 95% confidence interval, 0.57-1.13; p=0.42)

Progression risk (Table 9)
- 36-month analysis
  - Showed no significant differences between vitamin E and placebo at any time during study

Table 9. Petersen RC, et al. Risk of Progression to AD

<table>
<thead>
<tr>
<th></th>
<th>Placebo, n=38</th>
<th>Vitamin E, n=33</th>
<th>Donepezil, n=16</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk at 12 months</td>
<td>Placebo, n=73</td>
<td>Vitamin E, n=76</td>
<td>Donepezil, n=63</td>
</tr>
<tr>
<td>Risk at 36 months</td>
<td>Placebo, n=73</td>
<td>Vitamin E, n=76</td>
<td>Donepezil, n=63</td>
</tr>
</tbody>
</table>

- HR for progression to AD statistically decreased in donepezil group in year 1, 2 (p=0.004, 0.03)
  - No statistical difference at year 3 (p=0.21) (Figure 6)

Figure 6. Petersen et al., Progression Rate from MCI to AD

Secondary outcome measures (Appendix 6)
- Few differences in cognitive function from baseline between vitamin E and placebo

Authors’ Conclusions
Over the 3 study years, there were no significant differences in the probability of progression among vitamin E, donepezil or placebo.
Prespecified group comparisons at 6 month evaluations showed vitamin E had no significant effect during the trial regarding progression of disease and only minimal effects for secondary outcomes. Vitamin E and donepezil did not produce any unexpected side effects.

Critique

Strengths:
- Patient population included broad age range, ensured rule out of differential diagnoses
- 50% of funding from National Institute on Aging
- Intention-to-treat principle
- Statistical tests

Limitations:
- Excluded patients with depression, unspecified other medical diseases or psychiatric disorders that could interfere with participation, and medication restriction
- 50% of funding from Pfizer and Eisai (served on advisory capacity)
- Not adjusted for other covariates (some examples: comorbidities, smoking status, diet)
- Study duration

Summary
Vitamin E was well tolerated, but did not reduce disease progression. There were minimal effects on cognition and functioning based on assessment scales such as MMSE, GDS and modified ADAS-Cog, and they were not clinically significant.

<table>
<thead>
<tr>
<th>Purpose</th>
<th>Determine if vitamin E (α-tocopherol), memantine or both slow progression of mild to moderate AD in patients taking an acetylcholinesterase inhibitors (AChEI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Double-blind, placebo-controlled, parallel-group, randomized multicenter (14 VAs) clinical trial</td>
</tr>
</tbody>
</table>
| Population | **Inclusion criteria:**  
  - Diagnosis of possible or probable AD of mild to moderate severity  
    - Defined by MMSE score 12-26  
  - Taking a maintenance dose of AChEI  
  - Presence of a caregiver who can assume responsibility for medication compliance and rate patient’s condition  
  - Written informed consent and agreement not to take treatment drugs outside of study  
  **Exclusion criteria:**  
  - Non-AD primary dementia  
  - Current major depression, delirium, alcohol, psychoactive substance abuse or dependency, schizophrenia, delusional disorder defined by DSM-IV  
  - Uncontrolled systemic illness or life expectancy < 1 year  
  - Pregnant or intention to become pregnant  
  - Enrollment in other interventional clinical trial  
  - Current prescription with 1+ AChEI or warfarin  
  - Use of vitamin E or amantadine in past 2 weeks or memantine within past 4 weeks or intolerance  
  - CrCl < 5 mL/min |

| Outcomes | **Primary Outcome:**  
  - Change in Alzheimer’s Disease Cooperative Study/Activities of Daily Living (ADCS-ADL) Inventory  
    - Difference of 4 points defined by authors to be meaningful  
  **Secondary Outcomes:**  
  - MMSE  
  - ADAS-Cog  
  - 12-item Neuropsychiatric Inventory (NPI) – assesses psychological and behavioral issues  
  - Caregiver Activity Survey (CAS) |

| Methods | 613 veterans randomized 1:1:1:1  
  - Vitamin E (n=152), memantine (n=155), combination (n=154), placebo (n=152)  
    - Vitamin E given as 1,000 IU twice daily  
    - Memantine titrated over 4 weeks to maintenance dose of 10 mg twice daily  
  - Conducted between August 2007 and March 2012  
  - Baseline characteristics similar across treatment groups  
    - Mean age 78.8 years  
    - 97% men, 86% white  
    - 46% with ≤ 1 comorbidity (n=283/613)  
      - Diabetes 27% (n=167/613)  
      - Heart disease 24% (n=146/613)  
    - 78% high school graduates or some college education  
  - Duration ranged from 6 months – 4 years  
  - Assessments  
    - Clinic visits occurred every 6 months to monitor for falls, syncope, and heart failure  
    - Annual physical, medication review, α-tocopherol and memantine serum concentrations  
  - Adjusted power calculation  
    - To maintain 90% power  
      - Required 600 participants  
      - Increased median follow-up to 3 years |

| Results | **Primary outcome:** (Figure 7)  
  - Data analyzed from 561 participants  
    - Vitamin E = 140, memantine = 142, combination = 139, placebo = 140  
    - 52 excluded for lack of any follow-up data  
  - Vitamin E participants had significantly slower decline than placebo based on ADCS-ADLI  
    - Mean change 3.15 units less for vitamin E (95% confidence interval 0.92-5.39; p=0.03)  
  - Adherence – mean percentage of days as reported by caregivers  
    - Vitamin E 65%, memantine 68%, combination 66% |
Figure 7. Change in ADCS-ADL Between Groups Compared With Baseline

- Not completing the trial
  - Death (n=128, 50%)
  - Withdrawal of consent (n=77, 30%)
  - Adverse event possibly related to study medication (n=3, 1%)

Secondary outcome:
- None of the treatment differences were significant (Table 10)

Table 10. Mean Difference in Secondary Outcomes Compared with Placebo from Baseline

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Vitamin E</th>
<th>Memantine</th>
<th>Vitamin E + Memantine</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>0.19 (-0.54 to 0.92); p=0.84</td>
<td>0.12 (-0.61 to 0.84); p=0.84</td>
<td>0.37 (-0.36 to 1.10); p=0.84</td>
</tr>
<tr>
<td>ADAS-cog</td>
<td>-1.80 (-3.28 to -0.33); p=0.10</td>
<td>-1.39 (-2.85 to 0.07); p=0.25</td>
<td>-1.65 (-3.12 to -0.17); p=0.14</td>
</tr>
<tr>
<td>NPI</td>
<td>-1.46 (-3.55 to 0.63); p=0.94</td>
<td>-0.39 (-2.47 to 1.70); p=0.94</td>
<td>-0.47 (-2.57 to 1.63); p=0.94</td>
</tr>
<tr>
<td>CAS</td>
<td>-1.79 (-3.35 to -0.23); p=0.12</td>
<td>0.38 (-1.18 to 1.94); p=0.86</td>
<td>-0.14 (-1.70 to 1.42); p=0.86</td>
</tr>
</tbody>
</table>

Safety:
- No significant differences between groups on adverse effects
- Serious adverse events occurred in >5% of treatment groups vs. placebo
  - Falls (p=0.89), bleeding (p=0.78), pneumonia (p=0.12), urinary tract infection (p=0.66)
- Annual mortality rate: Vitamin E (7.3%), memantine (11.3%), combination (9.0%), placebo (9.4%)

Authors’ Conclusions
Vitamin E improves functional outcomes and decreases caregiver burden.
No significant increase in mortality with vitamin E was noted.

Critique

**Strengths:**
- First large scale clinical trial to assess AChEI+ vitamin E +/- memantine
- Longer duration than other studies
- Assessed adherence
- Caregiver assessments

**Limitations:**
- Undefined “uncontrolled systemic illness” in exclusions
- Did not include patients on anticoagulation therapy
- High withdrawal rates, without reason or number per group
- Adjusted power calculations
- Did not use intention-to-treat analysis
- Adherence assessed via patient and caregiver report
- Poor adherence rate to cholinesterase inhibitors and 28% of patients on AChEI for ≤ 12 weeks
- Poor generalizability (healthy, well-educated white males)

Summary
Vitamin E was well tolerated and did not show an increased mortality rate. Vitamin E may be recommended in a very select, healthy, educated, white male veteran population.
A. Alzheimer’s Disease
   a. Progressive, debilitating and fatal neurodegenerative illness
   b. Affects over 35 million people worldwide and is expected to double by 2030
   c. Significant health and economic costs
   d. No cure or reversible treatments
   e. Hypothetical pathophysiological processes include oxidative stress and inflammation

B. Vitamin E
   a. Theoretical role to help protect against free radical cell damage and inflammatory processes

C. Vitamin E use in AD
   a. Advantages
      i. Inexpensive agent
      ii. Generally well-tolerated in very low doses
   b. Disadvantages
      i. Increased risk for side effects (falls, syncope, antiplatelet effect)
      ii. Potential for drug interactions
      iii. May increase mortality rate
      iv. Minimal clinical benefit for cognition
      v. Does not reduce disease progression

Recommendations

A. Would not recommend vitamin E in all AD patients
   a. Inconsistent findings in the literature
   b. Potential risk for hazardous effects

B. Potential candidates for vitamin E therapy concurrently taking AChEI
   a. Patient population of Dysken et al.43,44
      i. White males with ≤ 1 comorbidity and a high school or college graduate

C. Further studies are warranted to evaluate vitamin E
   a. Safety with long-term administration
   b. Appropriate dose if considering
   c. Additional randomized controlled trials needed
      i. Large sample size
      ii. More applicable patient population (multiple comorbidities)
## Appendices

### Appendix 1. Cognitive Assessment Tools

<table>
<thead>
<tr>
<th>Tool</th>
<th>Scoring</th>
<th>Comments</th>
</tr>
</thead>
</table>
| Mini Mental Status Exam (MMSE) | Score out of 30  
Normal: >26  
Mild: 20-25  
Moderate: 10-20  
Severe: 0-10 | Most widely used and studied  
Administration time 10 min  
Ceiling effect (highly educated impaired people pass)  
Education/age/language bias |
| Montreal Cognitive Assessment (MoCA) | Score out of 30  
Normal: >26/30  
MCI avg 22  
AD avg 16 | Multiple languages available  
Administration time 10-15 min  
Education bias  
Validated for MCI, AD, Parkinson’s disease dementia |
| St. Louis University Mental Status Exam (SLUMS) | Score out of 30  
High school educated:  
Normal: > 27  
MCI: 21-26  
Dementia: 1-20 | No education bias  
Administration time 7 min  
Tests many separate domains  
Studied in VA geriatric clinic  
Different score cut-offs for < high school educated |
| Alzheimer’s Disease Assessment Scale’s cognitive subscale (ADAS-Cog) | Score out of 70  
Scores > 18 = greater cognitive impairment | Administration time 30-45 min  
11 sub-items ranging from 0-5  
Standard primary cognitive outcome measure  
Low sensitivity due to floor or ceiling effects in different stages |
| MiniCog | Score out of 5  
Word recall (0-3 points)  
Clock draw (0-2 points) | Administration time 3 min  
Score < 3 validated for dementia screening  
Low sensitivity |
| ADCS-ADL Inventory | Score out of 78  
Higher scores indicating less functional impairment | Administration time 20 min  
19 and 23 – item versions  
19 item version for basic ADL in more severe AD vs. 23 item for more complex ADL assessing mild-moderate AD |

### Appendix 2. Cognitive and Functional Staging Systems

**Pre-dementia: Stages 1-3**  
Stage 1: normal cognitive functioning  
Stage 2: normal aged forgetfulness  
Stage 3: mild cognitive impairment  

**Dementia: Stages 4-7**  
Stage 4: mild AD  
Stage 5: moderate AD (ADL assistance)  
Stage 6a-e: moderately severe AD  
Stage 7a-f: severe AD

| Global Deterioration Scale (GDS) | Pre-dementia: Stages 1-3  
Stage 1: normal cognitive functioning  
Stage 2: normal aged forgetfulness  
Stage 3: mild cognitive impairment  

Dementia: Stages 4-7  
Stage 4: mild AD  
Stage 5: moderate AD (ADL assistance)  
Stage 6a-e: moderately severe AD  
Stage 7a-f: severe AD |  
| CDR 0: no memory loss (ML)  
CDR 0.5-1: mild; slight-moderate ML  
CDR 2: moderate; profound ML  
CDR 3: severe ML | A 5-stage system evaluating six areas: memory, orientation, judgment and problem solving, community affairs, home/hobbies and personal care |
| Clinical Dementia Rating (CDR) | |  
| Functional Assessment Staging (FAST) | |  
| Stage 1 – no functional decline  
Stage 2 – personal awareness of some decline  
Stage 3 – early AD; noticeable deficits in demanding job situations | Stage 4 – mild AD; assistance in complicated tasks (finances)  
Stage 5 – moderate AD: assistance with attire  
Stage 6 – moderately severe; assistance in bathing, toileting  
Stage 7 – severe; speech ability declines and progressive loss of abilities to walk, sit up, smile and hold head up |
Appendix 3. Positive Vitamin E Effects on Cognition or Alzheimer’s Literature Review\textsuperscript{32-35}

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Sano M, et al. 1997\textsuperscript{32} | • Moderate severity AD  
• Free of other central nervous system diseases  
• Not on psychoactive medications | Vitamin E 1,000 IU twice daily compared to selegiline 5 mg twice daily        | • Delay to primary outcome (time to death, institutionalization, loss of ability to perform certain ADLs, and severe dementia) decreased with vitamin E (risk ratio, 0.47; p=0.001) although significantly increased falls and syncope |
| Pavlik VN, et al. 2009\textsuperscript{33} | • Probable or mixed AD                                                               | Vitamin E 1,000 IU twice daily compared to non-users                          | • Vitamin E use was associated with a 29% reduction in mortality risk (p=0.003)                                                        |
| Grodstein F, et al. 2003\textsuperscript{34} | • Women  
• Age 70-79 years old  
• Free of AD or stroke                                                                   | Users of vitamin E (dose ranged from <100-600) and/or vitamin C              | • Users of vitamin E and C and vitamin E alone had higher mean global scores  
• (p=0.07 and 0.03, respectively)                                                                 |
| Fotuhi M, et al. 2008\textsuperscript{35} | • Age ≥ 65 years old                                                                 | Vit E+C+NSAIDs compared to Vit E+Vit C compared to Vit E or Vit C alone +/-NSAID | • Combination users (Vit E+C+NSAIDs) showed less decline in cognitive status compared to all other groups; only significant among e4-carriers (p<0.01) |

Appendix 4. Negative or Neutral Vitamin E Effects Literature Review\textsuperscript{36,28-40}

<table>
<thead>
<tr>
<th>Clinical Trial</th>
<th>Patient Population</th>
<th>Intervention</th>
<th>Findings</th>
</tr>
</thead>
</table>
| Lonn E, et al. HOPE Trials 2005\textsuperscript{36} | • Age ≥ 55 years old  
• History of coronary or peripheral arterial disease, prior stroke, diabetes plus at least 1 other cardiovascular risk factor  
• Not taking vitamin E or angiotensin-converting enzyme inhibitor | Vitamin E 400 IU/day with ramipril compared to matched placebo              | • Long term vitamin E supplementation does not prevent cancer or major cardiovascular events and may increase risk of heart failure (p=0.03) |
| Galasko DR, et al. 2012\textsuperscript{38} | • Probable AD with MMSE 16 or >30  
• Age 50-85 years old  
• Positive neuroimaging lacking evidence for vascular disease | Vitamin E 800 IU/day + vitamin C + alpha-lipoic acid compared to matched placebo | • Treatment group did not affect CSF biomarkers relating to Aβ or tau  
• Treatment group had an increased decline on MMSE and ADL                                                                 |
| Lloret A, et al. 2009\textsuperscript{39} | • AD patients of all severities  
• Not taking other antioxidants  
• Only taking AChEI                                                  | Vitamin E 800 IU daily vs. placebo                                           | • Not all patients respond equally to antioxidant therapy (respondents vs. non-respondents)  
• Respondents did not show loss of cognition, but some non-respondents showed decreased cognition                                      |
| Kang JH, et al. 2006\textsuperscript{40}  | • Women ≥ 45 years old  
• No major chronic illnesses  
• Substudy of cognitive function in ≥ 65 years                           | Vitamin E 600 IU every other day compared to matched placebo                  | • Long term vitamin E use did not provide any cognitive benefits in healthy older women                                                                 |

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Appendix 5. Petersen et al. Inclusion and Exclusion Criteria

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Amnestic MCI</td>
<td>• Significant cerebral vascular disease</td>
</tr>
<tr>
<td>o Memory complaint corroborated by informant</td>
<td>o Modified Hachinski &gt; 4</td>
</tr>
<tr>
<td>o Abnormal memory function</td>
<td>• Depression</td>
</tr>
<tr>
<td>• Impaired delayed recall on one paragraph from the Wechsler Memory Scale-Revised Logical Memory II</td>
<td>o Hamilton Depression Rating scale &gt; 12</td>
</tr>
<tr>
<td>• Cutoff scores:</td>
<td>• CNS infarct, infection, or focal lesions of clinical significance on CT or MRI scans</td>
</tr>
<tr>
<td>o ≤ 8 = 16 years of education</td>
<td>• Medical diseases or psychiatric disorders that could interfere with study participation</td>
</tr>
<tr>
<td>o ≤ 4 = 8-15 years of education</td>
<td>• Pregnant, lactating, or of child bear potential</td>
</tr>
<tr>
<td>o ≤ 2 = 0-7 years of education</td>
<td>• Taking vitamin supplements, other supplements or a multivitamin</td>
</tr>
<tr>
<td>o General cognition and functional performance sufficiently preserved</td>
<td>• Restrictions on concomitant medication usage, including those with significant cholinergic or anticholinergic effects or potential adverse effects on cognition</td>
</tr>
<tr>
<td>o Not demented by National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer’s Disease and Related Disorders Association Criteria by clinical judgment</td>
<td></td>
</tr>
<tr>
<td>• Age 55-90 years, inclusive</td>
<td></td>
</tr>
<tr>
<td>• Study informant available</td>
<td></td>
</tr>
<tr>
<td>• MMSE 24-30</td>
<td></td>
</tr>
<tr>
<td>• Adequate vision &amp; hearing for neuropsychological testing</td>
<td></td>
</tr>
<tr>
<td>• Normal B12 level and thyroid function studies and non-reactive RPR</td>
<td></td>
</tr>
<tr>
<td>• Electrocardiogram normal or no clinically significant abnormalities</td>
<td></td>
</tr>
<tr>
<td>• CDR 0.5</td>
<td></td>
</tr>
<tr>
<td>o Memory box score 0.5 or 1</td>
<td></td>
</tr>
<tr>
<td>o No box score greater than 1</td>
<td></td>
</tr>
<tr>
<td>• All subjects and study informants signed written consent – approved by local IRB</td>
<td></td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Test</th>
<th>Change in Score from Baseline to 36 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>-2.20±3.64</td>
</tr>
<tr>
<td>Placebo</td>
<td>-2.75±4.04</td>
</tr>
<tr>
<td>Donepezil</td>
<td>-2.31±3.72</td>
</tr>
<tr>
<td>ADL Scale</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>-5.63±8.75</td>
</tr>
<tr>
<td>Placebo</td>
<td>-6.39±8.99</td>
</tr>
<tr>
<td>Donepezil</td>
<td>-6.26±8.67</td>
</tr>
<tr>
<td>CDR sum of boxes</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>1.67±2.18</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.64±2.55</td>
</tr>
<tr>
<td>Donepezil</td>
<td>1.60±2.09</td>
</tr>
<tr>
<td>GDS</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>0.64±0.96</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.56±0.99</td>
</tr>
<tr>
<td>Donepezil</td>
<td>0.59±0.89</td>
</tr>
<tr>
<td>ADAS-Cog (Original)</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>4.59±6.54</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.74±6.97</td>
</tr>
<tr>
<td>Donepezil</td>
<td>3.68±5.95</td>
</tr>
<tr>
<td>ADAS-Cog (Modified)</td>
<td></td>
</tr>
<tr>
<td>Vitamin E</td>
<td>3.98±7.56</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.72±8.54</td>
</tr>
<tr>
<td>Donepezil</td>
<td>3.12±7.39</td>
</tr>
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</table>