Complementary and Alternative Treatments for Cognition

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Objectives

- Define complementary and alternative medicine (CAM) and discuss its role in the treatment and/or prevention of cognitive decline
- Recognize common dietary supplements used by patients to improve cognition
- Analyze the current literature on the use of dietary supplements for cognitive disorders
- Provide pertinent information to patients utilizing or planning to utilize dietary supplements for cognitive disorders
Complementary and Alternative Medicine (CAM)

- What is CAM?
  - Group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine
  - Complementary Medicine: used in conjunction with conventional
  - Alternative Medicine: used in place of conventional
- Integrative Medicine combines conventional and CAM treatments for which there is evidence of safety and effectiveness

NHIS 2007 Survey Results

- 23,393 adults
- CAM use greater among:
  - Women
  - American Indian/Alaska Native (50.3%), Whites (43.1%) and Asians (39.9%)
  - Higher levels of education
  - Higher incomes
NHIS 2007 Survey Results

CAM Use by Age - 2007


NHIS 2007 Survey Results

10 Most Common CAM Therapies Among Adults - 2007

Therapies with significant increases between 2002 and 2007 are:

<table>
<thead>
<tr>
<th>Therapy</th>
<th>2002</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep breathing</td>
<td>11.6%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Meditation</td>
<td>7.6%</td>
<td>8.4%</td>
</tr>
<tr>
<td>Massage</td>
<td>5.9%</td>
<td>8.3%</td>
</tr>
<tr>
<td>Yoga</td>
<td>5.1%</td>
<td>6.1%</td>
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</tbody>
</table>

Herbal Supplements

- Herbal use in U.S. growing at about 20% per year
  - Use stable when comparing 2002 to 2007 NHIS results
- Expenditure > $3 billion per year
- 15-20% of individuals on prescription medications also use herbal supplements
- < 40% disclose the usage of herbals


Why Herbals?
Use of Herbal Products

- Dissatisfaction
- Control
- Values/beliefs
- “Natural” or “Safe”
- Avoid appointments
- Cost of prescriptions

Figure 7. Reasons People Use CAM

NHIS 2007 Survey Results

Diseases/Conditions for Which CAM Is Most Frequently Used Among Adults - 2007

- Psychiatric Illnesses


Herbal Regulation
Background

- Dietary Supplement Health and Education Act of 1994
  - Restricts FDAs authority over any herb or supplement
    - “no claim” to affect a “disease state”
  - Presumed safe until FDA receives numerous reports of adverse effects
  - NO standardization of manufacturing is required
- June 22, 2007 – FDA final rule
  - Established regulations to require current good manufacturing practices (CGMPs) for dietary supplements

Dietary Supplement Use for Cognitive Disorders

- Ginkgo biloba
- Vitamin E
- Huperzine A
- Lecithin
- Vinpocetine
- Acetyl-L-Carnitine
- Piracetam
- Curcumin
- Phosphatidylserine
**NHIS 2007 Survey Results**

### 10 Most Common Natural Products Among Adults* - 2007

- **Nature's Blend** 17.4%
- **Carotene** 19.9%
- **Echinacea** 16.8%
- **Bacopa (Centella)** 15.9%
- **Ginseng** 14.1%
- **Boswellia** 13.0%
- **Garlic Supplementation** 11.3%
- **Chromatides** 11.2%
- **Ginger** 11.0%
- **Ginkgo biloba** 8.7%

*Percentages among adults who used natural products in the last 30 days.


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**Ginkgo biloba**

- Sold as a drug and regulated in Germany
- In 1999, total US sales exceeded $249 million
- Generally taken as an extract (GBE)
- Used medically for thousands of years to treat circulatory problems, asthma, vertigo, fatigue, tinnitus and cognitive disturbances
- Typical dose = 120-240 mg/day

Ginkgo biloba

- Numerous mechanisms proposed
  - Normalize the Ach receptors in the hippocampus area of the brain in aged animals
  - Direct role in modulating amyloid aggregation and pathology
  - Antioxidant – scavenger for free radicals


Ginkgo biloba

Treatment of Cognitive Disorders
**Ginkgo biloba**

- **Meta-analysis**
  - 1998: Four RPC studies (N=424) in Alzheimer’s disease (AD)
    - Dose = 120 or 240 mg GBE
    - Conclusion: Modest benefit on cognitive measures
    - Limitations: Variability of outcome measures and diagnostic criteria used for AD
  - 2009: Cochran Review of 36 trials (N = 4,423) in dementia/cognitive impairment
    - Dose = 80-600 mg GBE (typically less than 240 mg)
    - Conclusion: Benefit in individuals with dementia not convincing; most recent trials more methodologically sound and show little to no benefit for GBE
    - Limitations: Early trials used unsatisfactory methods, small sample size, small length of trial and possibility of publication bias.


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**Ginkgo biloba**

- N = 60
- GBE (160 mg) vs. donepezil (5mg) vs. PLB
  - Authors conclusions: Study suggests that there is no evidence of relevant differences in the efficacy of GBE and donepezil in the treatment of mild to moderate AD, so both substances can be justified
  - Limitations: Lack of power/sample size, no statistically significant differences from placebo, dose of donepezil, statistical tests used (parametric when non-parametric more appropriate)
- Evidence for cholinesterase inhibitors still more consistent and robust

Ginkgo biloba

Prevention of Cognitive Disorders

Prevention

- Pilot Study (42-months)
  - N = 118; Normally aged individuals
  - GBE (240 mg daily) vs. PLB
- Results:
  - No reduced risk of progression to cognitive impairment (ITT analysis)
  - Reduced risk of progression (p=0.02) and a smaller decline in memory scores (p=0.04) in GBE group vs. PLB group when controlled for medication adherence
  - Significantly more ischemic strokes and TIAs in GBE group (p=0.01)

Ginkgo Evaluation of Memory (GEM) Study

- N = 3,069
  - Age >75 years
  - Normal cognition or Mild Cognitive Impairment (MCI)
- GBE dosing = 120 mg twice daily
- Primary outcome
  - Diagnosis of dementia by DSM-IV criteria


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Ginkgo Evaluation of Memory (GEM) Study

- <1% dementia rate in first year regardless of treatment
- 523 participants diagnosed with dementia
  - 277 (17.9%) GBE vs. 246 (16.1%) PLB
- Cognitive status known for 93.6% of participants
  - 195 drop-outs

Ginkgo Evaluation of Memory (GEM) Study

- Results:
  - GBE showed no benefit over placebo for reducing all-cause dementia (p=0.39) or AD (p=0.51)
  - No statistically significant difference in rate of serious adverse events including bleeding, CHD, stroke
- Conclusion:
  - GBE not recommended for the purpose of preventing dementia.


Ginkgo biloba

Tolerability and Safety Considerations
Ginkgo biloba

- Reported to inhibit platelet aggregation
  - Bleeding complications w/ and w/out concomitant drug therapy
  - Associated with increased bleeding time, subdural hematoma and retinal hemorrhage
    - ASA, warfarin, NSAIDs
  - GEM Study – discontinuation of study medication if warfarin therapy initiated

Ginkgo biloba

- Seizures
  - Enzyme induction
  - Ginkgo nuts contain a potent neurotoxin
- Other adverse effects – headache, dizziness
- Pregnancy
  - Prolongation of bleeding during delivery
- Lactation - no available information

Vitamin E

- Previously possible benefit > risk
  - Limited evidence for benefit
- No longer recommended for the treatment of cognitive symptoms of dementia
  - Meta-analysis
    - Increased dose-dependent mortality
  - Cancer and Heart Disease Prevention Trial
    - Increased rate of heart failure

Lonn E, et al.  JAMA 2005;293:1338-1347

Huperzine A

- Authorized for treating AD and benign memory deficits since 1994 in China
- Natural cholinesterase inhibitor (ChEI)
  - Highly specific and reversible
- Derived from club moss
  - Alkaloid
- Dietary supplement – memory loss and mental impairment
- Dose = 200-400 µg BID
- Common SE: mild dizziness, abdominal distention, nausea
Huperzine A

- Meta-analysis – Alzheimer’s Disease
  - 6 placebo-controlled trials (N=454)
    - Results:
      - Beneficial effects on the improvement of general cognitive function measures (MMSE, ADAS-cog, functional performance measured by ADL)
      - Adverse events mild and similar to placebo
    - Limitations: sample size, methodology
    - Conclusion: Some beneficial effect on improvement of cognitive function and low incidence of adverse events

- Vascular dementia
  - Trials limited and more flawed than for AD – not recommended
  - Conclusion: Evidence does not to support use

Acetyl-L-Carnitine

- Most common natural short-chain acetyl carnitine ester of L-carnitine
- Animal studies suggest CNS neuroprotective effects
- Acts as a partial direct cholinergic agonist and can be converted to acetylcholine – actively transported across the blood-brain barrier.
- Typical dose = 1.5-3 g/day
- SE: GI, restlessness, headache

References:

Acetyl-L-Carnitine

- 12-month RDBPC trial (N=431) showed no benefit in primary or secondary outcome measures in patients with probable AD
- Meta-analysis – 21 trials
  - N=1204 (MCI or mild AD)
  - Modest benefit in outcome measures
- Meta-analysis – Cochrane – 16 trials
  - No benefit in outcome measures
- Conclusion: No evidence to support use


Lecithin

- Choline-containing phospholipid
- Major dietary source of choline – increase choline levels
- Theory = accelerate acetylcholine synthesis through enhanced availability of the substrate choline
- Dose range = 1-35g/d
- Meta-analysis – Cochrane - 10 trials (N=265)
  - No benefit on behavior or ADLs in patients with AD

**Vinpocetine**

- Chemically derived from vincamine
  - Seeds of the periwinkle
- Claim: memory loss and mental impairment
  - MOA unknown – numerous proposed
- Drug in Europe – Cavinton
- Dietary supplement in U.S.
  - Does not really exist in nature
- Dose = 30-60 mg/day
- SE: GI complaints, vertigo
  - May be dose dependent

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**Vinpocetine**

- Open-label in AD over one year showed no benefit
- Meta-analysis – Cochrane – 3 trials in dementia
  - Studies significantly flawed
    - Poorly defined dementia population
    - Length of studies <6 months
    - Insufficient data to draw conclusions
  - No significant adverse events reported
- Conclusion: No evidence to support use

Szatmari SZ, Whitehouse PJ. Cochrane Database Syst Rev. 2003:CD003119
Piracetam

- Derivative of GABA although no proven action at GABA receptor sites
  - MOA not established
- Approved in >120 countries and available in US without a prescription via mail order
- Dose = 24 g/day
  - 2.4 to 8 g/day studied in AD and MCI trials
- SE: HA, dizziness, insomnia, fatigue, GI

Piracetam

- DBPC trial – 12 months (N=33)
  - Early probable AD
  - Results: No benefit on outcome measures
- Meta-analysis in trials of dementia or cognitive impairment found no benefit – trials significantly flawed
- Conclusion: Existing literature dose not support recommended use in cognitive disorders

Curcumin

- *Curcuma longa* – member of the ginger family
- Suggested antioxidant and anti-inflammatory properties as well as a direct effect against β-amyloid aggregation
- Variable dosing – most human studies
  - 1200mg/day
    - Up to 8g/day well tolerated
- No current trials completed in AD

Phosphatidylserine (PS)

- One of the five phospholipids that contribute to the structural matrix of all cell membranes
- Most obtained from dietary sources
- Supplements obtained from bovine cerebral cortex (BC-PS)
  - Composition differs when obtained from soy
- Dosage = 200-300 mg/day
- SE:
  - Stomach upset, flatulence – plant source
  - Spongiform encephalopathy (theoretical) – BC-PS
Phosphatidylserine (PS)

- Trials:
  - Previous trials in BC-PS show mixed results in AD
    - Limitations:
      - Poorly defined patient populations
      - Too short in length to evaluate neuroprotective effects
    - Studies halted in 1990s
  - One study in plant-source PS (N=19)
    - Short – 12-week open label trial in “age associated memory impairment”
- Conclusion: Evidence does not support benefit in cognition

Amaducci T. Psychopharmacol Bull. 1988;24:130-134

On the Horizon...
Ginkgo biloba

- GuidAge study (Europe)
  - 5-year DBPC trial of the efficacy of GBE for prevention of Alzheimer disease in patients over 70 with a memory complaint
  - Estimated completion 2010

- Efficacy and Safety of Ginkgo Biloba Extract in Mild Cognitive Impairment and Cerebrovascular Insufficiency (Croatia)
  - Currently recruiting
  - Estimated completion – October 2009

Curcumin

- Curcumin in Patients With Mild to Moderate Alzheimer's Disease
  - Phase II – NIA funded (N=33)
  - Completed December 2007
Combination Study

- A Pilot Study of Curcumin and Ginkgo for Treating Alzheimer's Disease
  - Chinese University – Hong Kong
  - DBPC, parallel assignment
    - Primary Outcome Measures:
      - Change in isoprostane level in plasma
      - Change in β-amyloid level
    - Secondary Outcome Measures:
      - Change in cognitive function (MMSE score)
      - Change in cholesterol and triglycerides in serum

Huperzine A

- Huperzine A in Alzheimer's Disease
  - Phase II trial funded by NIA and Alzheimer's Disease Cooperative Study (ADCS)
  - N=150
  - Completed 2007
Phosphatidylserine (PS)

- The Efficacy of Phosphatidylserine-Omega3 in Elderly With Age Associated Memory Impairment (Israel)
  - Phase IV - Completed June 2008
- The Efficacy of Phosphatidylserine-Omega3 in Elderly Subjects With Memory Impairment (Israel)
  - Phase IV – Completed March 2009

Conclusion

- Americans are utilizing CAM, particularly dietary supplements/herbals, in an effort to achieve optimal outcomes
- Numerous agents are touted as being beneficial for cognitive disorders, particularly AD
- Current literature does not support the use of these agents in the treatment of cognitive disorders
  - Older studies that show improvement have numerous flaws and have not been replicated in more recent studies with superior designs/methodology
Conclusion

- A recent large DBPC trial (GEM study) found that *Ginkgo biloba* was not more effective than placebo in reducing dementia in patients with normal cognition or mild cognitive impairment.
- Most seem generally safe with few significant adverse events, however limited information on drug interactions.
- Use of dietary supplements for cognitive disorders ultimately rests with the patient and their family, therefore candid discussions about herbal use is recommended.

Post-Conference Updates
Slide Correction

- Slide #25 provided at the conference indicated GBE was recommended in prevention of dementia.
- Slide #25 should read for the conclusion statement:
  - GBE not recommended for the purpose of preventing dementia.

Follow-up Questions

- Co-enzyme Q10 in the treatment/prevention of vascular dementia
  - No literature discovered for either the prevention or treatment of vascular or Alzheimer’s dementia with co-enzyme Q10
  - Searched on ClinicalTrials.gov for pending trials
    - No trials currently underway for this indication
    - Some trials in Parkinson’s disease, but not dementia associated with PD
Follow-up Questions

- Herbal medications that interact with SSRIs
- For answer consider antidepressant (AD) as any antidepressant that has serotonin properties (i.e. SSRIs, SNRIs, trazodone, mirtazepine, etc.)
- Little documented herbal-drug interactions
  - ESTABLISHED:
    - St. John’s Wort + AD can increase risk of serotonin syndrome
    - 5-hydroxy-l-tryptophan + AD can increase risk of serotonin syndrome
- THEORETICAL:
  - Ginkgo biloba + AD can increase risk of bleeding particularly if in combination with ASA, NSAIDs, warfarin, etc.
  - Valerian + AD can cause increased sedation particularly if antidepressant causes sedation
  - Kava + AD. Due to cases of severe liver damage, Kava may decrease metabolism of ADs requiring hepatic metabolism, increasing anxiety and other SEs associated with Ads
- Other established drug-herbal interactions outside AD
  - Most common – warfarin, antiplatelet agents, antidiabetic agents
  - Recent article in American Journal of Medicine that discusses common interactions with common herbals
Helpful Sites

- National Center for Complementary and Alternative Medicine (http://nccam.nih.gov/)
  - Contains free patient friendly information
  - Basic information on common herbal products
  - Gives updates on large trials of herbal medications