Update on Supplements

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Associate Professor, General Internal Medicine
A brief history of medicine:

I have an earache…

2000 BC -- Here, eat this root.
1000 AD -- That root is heathen. Here, say this prayer.
1850 AD -- That prayer is superstition. Here, drink this potion.
1940 AD -- That potion is snake oil. Here, swallow this pill.
1985 AD -- That pill is ineffective. Here, take this antibiotic.
2000 AD -- That antibiotic is artificial. Here, eat this root.

-- Anonymous
Objectives

Be able to:

– Review recent changes in supplement regulation
– Discuss the uses, mechanisms of action, and side effects of some commonly used products
– Demonstrate ability to find information on specific supplements using online resources
– Advise patients interested in supplements
Regulation

Quiz: Who was the actor in the video?
Regulatory Review

• Dietary Supplement and Health Education Act (1994).
  – No requirements for proof of safety, efficacy, quality control

• DS and Non-prescription Drug Act (2006)
  – Must report serious ADRs within 15 days

• DSHEA update (2007)
What did the DSHEA update accomplish?

✓ A. Required good manufacturing practice compliance
B. Required supplements to prove safety
C. Required supplements to prove efficacy
D. All of the above
E. None of the above
Independent Verification

United States Pharmacopeia
Which of the following groups also provide independent testing?

- NNFA/Natural Products Association
- National Sanitation Foundation
- ConsumerLab
- All of the above
- None of the above
Manufacturers More Likely to Produce Quality Products

- Nature’s Way
- Nature’s Made
- Nature’s Bounty
- Costco (Kirkland)
- Walmart (Equiline)
- Phytopharmica
- Puritan’s Pride
NHANES 2007-2008 data

“Have you used a supplement in the last 30 days?”
Top Supplements!
10 Most Common Natural Products Among Adults* - 2002

*Percentages among adults who used natural products in the last 12 months.

Which supplement was #1 in 2007?

A. Echinacea  
B. Glucosamine  
C. Fish oil  
D. Soy

✓ C. Fish oil
10 Most Common Natural Products Among Adults* - 2007

- Fish Oil/Omega-3: 37.4%
- Glucosamine: 19.9%
- Echinacea: 19.8%
- Flaxseed Oil/Pills: 15.9%
- Ginseng: 14.1%
- Combination Herb Pills: 13.0%
- Ginkgo Biloba: 11.3%
- Chondroitin: 11.2%
- Garlic Supplements: 11.0%
- Coenzyme Q-10: 8.7%

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

NCCAM “Use of CAM” survey
Which supplements were #1 with GIM faculty?

<table>
<thead>
<tr>
<th>Coenzyme Q10</th>
<th>Garlic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinacea</td>
<td>Probiotics</td>
</tr>
<tr>
<td>Fish oil</td>
<td>SAM-e</td>
</tr>
<tr>
<td>Flaxseed</td>
<td>Soy</td>
</tr>
<tr>
<td>Ginseng</td>
<td>St. Johns wort</td>
</tr>
<tr>
<td>Ginkgo</td>
<td>Vitamin D</td>
</tr>
<tr>
<td>Glucosamine</td>
<td></td>
</tr>
</tbody>
</table>
Information on Supplements

- UpToDate
- Ovid / PubMed
- Cochrane Collaboration
- Epocrates ($ for CAM content)
- Micromedex
  - Natural Medicines Comprehensive Database
  - National Center for Complementary / Alternative Medicine
  - Office of Dietary Supplements
- FDA
NMCD

Safety ratings
– Likely safe
– Possibly safe
– Possibly unsafe
– Likely unsafe
– Unsafe
– Insufficient evidence

Efficacy ratings
– Effective
– Likely effective
– Possibly effective
– Possibly ineffective
– Likely ineffective
– Ineffective
– Insufficient evidence
What is this natural product?

A. Cranberry

✓ B. Coffee

C. Grapes (grapeseed extract)
GIM Grand Rounds
True Top Natural Product
Coenzyme Q-10 Quiz

• Is coenzyme Q-10 a vitamin?
  – Yes
  ✔– No

• How much is a 30 tab bottle of 400 mg coenzyme Q-10 at Target.com?
  – $20.99
  – $46.99
  ✔– $52.99
Coenzyme Q-10

- Found in all cells (“ubiquinone”)
- Vitamin-like cofactor, antioxidant, membrane stabilizer
- Essential for ATP production
- Deficient states: HMG CoA reductase inhibitors, beta blockers, doxorubicin, CHF, HIV…
Coenzyme Q-10 NMCD

• Effective
  – No ratings

• Likely effective
  – Coenzyme Q10 deficiency
  – Mitochondrial encephalomyopathies

• Possibly effective
  – CHF
  – HTN
  – HIV
  – Migraines
  – Secondary MI prevention
  – Parkinsons

• Insufficient evidence
  – Prevention of statin myopathy
CoQ10 for secondary prevention of myocardial infarction

- N = 144, MI within 72 hours; well stratified
- All received usual care, though study done in 1996 (prior to routine ACE-I / BB)
- Double blind, placebo controlled, randomized
- 120 mg CoQ10 / day vs 32 mg vitamin B
CoQ10 for secondary prevention of myocardial infarction

<table>
<thead>
<tr>
<th>Cardiac events</th>
<th>Coenzyme Q10 (n = 73)</th>
<th>B vitamins (n = 71)</th>
<th>Relative risk (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sudden cardiac death (&lt; 1 h)</td>
<td>3 (4.1)</td>
<td>5 (7.0)</td>
<td>0.58</td>
</tr>
<tr>
<td>Fatal myocardial infarctions</td>
<td>5 (6.8)</td>
<td>9 (12.7)</td>
<td>0.53</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>10 (13.7)*</td>
<td>18 (25.3)</td>
<td>0.54</td>
</tr>
<tr>
<td>Total cardiac deaths</td>
<td>8 (10.9)</td>
<td>14 (19.7)</td>
<td>0.55</td>
</tr>
<tr>
<td>Stroke</td>
<td>–</td>
<td>2 (2.8)</td>
<td>0.46</td>
</tr>
<tr>
<td>Angioplasty or CABG</td>
<td>1 (1.3)</td>
<td>3 (4.2)</td>
<td>0.31</td>
</tr>
<tr>
<td>Total cardiac events</td>
<td>18 (24.6)**</td>
<td>32 (45.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>Total cardiovascular events</td>
<td>18 (24.6)**</td>
<td>34 (47.8)</td>
<td>0.51</td>
</tr>
<tr>
<td>Total cardiac end points</td>
<td>19 (25.9)**</td>
<td>37 (52.0)</td>
<td>0.49</td>
</tr>
</tbody>
</table>
CoQ10 for prevention of migraines

- N = 43, 2-8 migraines/month, on no prophylactic meds
- Placebo x 1 month; randomized if had a migraine
- Double blind, placebo controlled, randomized
- 100 mg CoQ10 TID vs placebo

• Placebo: 8 increase, 8 decrease, 5 no change
• CoQ10: 1 increase, 15 decrease, 1 no change
CoQ10 for prevention of statin myopathy

- N = 32, on a statin reporting muscle pain
- Double blind, placebo controlled, randomized
- 100 mg CoQ10 daily vs 400 IU vitamin E

Pain decreased 40% in treatment group, none in vitamin E group, p<0.0001

CoQ10 for prevention of statin myopathy

- N = 33, h/o statin related muscle pain
- Double blind, placebo controlled, randomized
- 200 mg CoQ10 daily vs placebo
- Began with 10 mg simvastatin / day, increased to max of 40 mg/day as tolerated

Young JM. Am J Cardiol 2007.
Table 2
Simvastatin dose tolerated at 12 weeks

<table>
<thead>
<tr>
<th>Tolerated Dose (mg/day)</th>
<th>Coenzyme $Q_{10}$ and Simvastatin Therapy ($n = 22$)</th>
<th>Simvastatin Alone ($n = 22$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>16 (73%)</td>
<td>13 (59%)</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>0</td>
<td>6 (27%)</td>
<td>4 (18%)</td>
</tr>
</tbody>
</table>

Data are expressed as number (percentage) of patients.

$p = 0.34$ for comparison of the number of patients who tolerated simvastatin 40 mg/day (chi-square test); $p = 0.47$ for comparison of the number of patients remaining on simvastatin (chi-square test).

No difference in number of patients able to tolerate 40 mg simvastatin
CoQ-10 Safety

- Used safely in studies up to 30 months
- GI side effects in <1%; minimized by dividing doses over 100 mg
- Allergic rash in one study
- Drug interactions (theoretical) – warfarin (vitamin K-like), chemotherapy (antioxidant), antihypertensives (additive effect)
Glucosamine Quiz

• Does glucosamine raise glucose levels?
  – Yes
  ✔– No

• Which of the following is also marketed for osteoarthritis?
  – Lactobacillus
  – Feverfew
  ✔– S-adenosyl methionine (SAMe)
Glucosamine

- Glucosamine hydrochloride, glucosamine sulfate, N-acetyl glucosamine all likely active
- Required for production of glycosaminoglycans
- Derived from marine exoskeletons or synthesized
- Stimulates chondrocytes, synovial cells
Glucosamine - NMCD

- Insufficient evidence to rate
  - Osteoarthritis
    - Knee
    - Low back
    - Hip
  - Rheumatoid arthritis
Glucosamine for chronic LBP

- N = 250, adults over age 25, chronic low back pain and degenerative lumbar osteoarthritis
- Double blind, placebo controlled, randomized
- 1500 mg glucosamine / day vs placebo x 6 months

Wilkens P. JAMA 2010
Glucosamine for LBP
Glucosamine +/- Chondroitin for Knee Pain

- N=1583
- Randomized; stratified by severity
- 1500 mg glucosamine, 1200 mg chondroitin, both, 200 mg celecoxib, or placebo x 24 weeks
- Primary outcome – 20% decrease in knee pain

## GAIT trial – Endpoint Reached

### All patients
- Placebo: 60%
- Glucosamine: 64%
- Chondroitin: 65%
- Combo: 67%
- Celecoxib: 70%*

### Mod / severe OA
- Placebo: 54%
- Glucosamine: 66%
- Chondroitin: 61%
- Combo: 79%**
- Celecoxib: 69%

*p=0.008 **p < 0.002
Glucosamine for OA – Cochrane 2009

Review: Glucosamine therapy for treating osteoarthritis
Comparison: 1 Glucosamine versus placebo
Outcome: 1 Pain

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Glucosamine N</th>
<th>Glucosamine Mean(SD)</th>
<th>Placebo N</th>
<th>Placebo Mean(SD)</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
<th>Weight</th>
<th>Std. Mean Difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cibere 2004</td>
<td>71129.72 (113.23)</td>
<td>66 129.62 (118.02)</td>
<td></td>
<td></td>
<td></td>
<td>6.4 %</td>
<td>0.00 [-0.33, 0.34]</td>
</tr>
<tr>
<td>Clegg 2006</td>
<td>317 149.3 (115.9)</td>
<td>313 151 (113.1)</td>
<td></td>
<td></td>
<td></td>
<td>7.0 %</td>
<td>-0.01 [-0.17, 0.14]</td>
</tr>
<tr>
<td>Croll 1980</td>
<td>15 0.21 (0.43)</td>
<td>15 1.13 (0.89)</td>
<td></td>
<td></td>
<td></td>
<td>4.1 %</td>
<td>-1.28 [-2.08, -0.49]</td>
</tr>
<tr>
<td>D’ambrosio 1981</td>
<td>15 0.33 (0.12)</td>
<td>15 1.2 (0.19)</td>
<td></td>
<td></td>
<td></td>
<td>1.8 %</td>
<td>-5.33 [-6.94, -3.71]</td>
</tr>
<tr>
<td>Drova 1980</td>
<td>40 0.95 (0.82)</td>
<td>40 1.88 (0.44)</td>
<td></td>
<td></td>
<td></td>
<td>5.6 %</td>
<td>-1.40 [-1.89, -0.91]</td>
</tr>
<tr>
<td>Herrero-Beaumont  2007</td>
<td>106 5.1 (3.03)</td>
<td>104 6 (3)</td>
<td></td>
<td></td>
<td></td>
<td>6.6 %</td>
<td>-0.30 [-0.57, -0.03]</td>
</tr>
<tr>
<td>Houpt 1999</td>
<td>45 7.14 (4.01)</td>
<td>53 7.65 (4.13)</td>
<td></td>
<td></td>
<td></td>
<td>6.1 %</td>
<td>-0.12 [-0.52, 0.27]</td>
</tr>
<tr>
<td>Hughes 2002</td>
<td>39 7.5 (4.81)</td>
<td>39 7.35 (4.38)</td>
<td></td>
<td></td>
<td></td>
<td>5.8 %</td>
<td>0.03 [-0.41, 0.48]</td>
</tr>
<tr>
<td>McAllindon 2004</td>
<td>101 6.8 (3.3)</td>
<td>104 6.6 (4.2)</td>
<td></td>
<td></td>
<td></td>
<td>6.6 %</td>
<td>0.05 [-0.22, 0.33]</td>
</tr>
<tr>
<td>Pavelka 2002</td>
<td>101 4.61 (3.45)</td>
<td>101 5.03 (3.13)</td>
<td></td>
<td></td>
<td></td>
<td>6.6 %</td>
<td>-0.13 [-0.40, 0.15]</td>
</tr>
<tr>
<td>Pujal 1980</td>
<td>10 1.25 (0.25)</td>
<td>10 2.36 (0.79)</td>
<td></td>
<td></td>
<td></td>
<td>3.0 %</td>
<td>-1.81 [-2.89, -0.74]</td>
</tr>
<tr>
<td>Reginster 2001</td>
<td>106 156.1 (101.9)</td>
<td>106 164.2 (104.5)</td>
<td></td>
<td></td>
<td></td>
<td>6.6 %</td>
<td>-0.08 [-0.35, 0.19]</td>
</tr>
<tr>
<td>Rindone 2000</td>
<td>49 3.2 (2.5)</td>
<td>49 3.4 (2.5)</td>
<td></td>
<td></td>
<td></td>
<td>6.1 %</td>
<td>-0.08 [-0.48, 0.32]</td>
</tr>
<tr>
<td>Rovati 1997</td>
<td>79 24.3 (19.3)</td>
<td>77 50 (22)</td>
<td></td>
<td></td>
<td></td>
<td>6.3 %</td>
<td>-1.24 [-1.58, -0.89]</td>
</tr>
<tr>
<td>Rozendaal 2008</td>
<td>111 35.2 (26.8)</td>
<td>111 34.4 (25.6)</td>
<td></td>
<td></td>
<td></td>
<td>6.7 %</td>
<td>0.03 [-0.23, 0.29]</td>
</tr>
<tr>
<td>Usha 2004</td>
<td>30 0.65 (0.71)</td>
<td>28 1.16 (0.76)</td>
<td></td>
<td></td>
<td></td>
<td>5.4 %</td>
<td>-0.68 [-1.22, -0.15]</td>
</tr>
<tr>
<td>Vajrajad 1981</td>
<td>28 0.18 (0.16)</td>
<td>26 0.69 (0.92)</td>
<td></td>
<td></td>
<td></td>
<td>5.3 %</td>
<td>-0.78 [-1.33, -0.22]</td>
</tr>
<tr>
<td>Zenk 2002</td>
<td>13 74.7 (26.3)</td>
<td>10 76.5 (25.1)</td>
<td></td>
<td></td>
<td></td>
<td>4.0 %</td>
<td>0.07 [-0.76, 0.89]</td>
</tr>
</tbody>
</table>

Total (95% CI): 1276 1267

Heterogeneity: Tau² = 0.22; Chi² = 136.13, df = 17 (P<0.00001); I² = 88%
Test for overall effect: Z = 3.76 (P = 0.00017)
Glucosamine Safety

• Side effects
  – Mild GI upset

• Theoretical drug interactions
  – Warfarin (heparin-like; antiplatelet activity)

• Glucose control in DM – no change
Fish Oil Quiz

• Why is fish oil preferred over cod liver oil?

• Why is fish oil preferred over plant sources of omega 3 fatty acids?
Fish Oil Quiz

• Why is fish oil preferred over cod liver oil?
  – Too much vitamin A in cod liver oil

• Why is fish oil preferred over plant sources of omega 3 fatty acids?
  – Body must process alpha-linoleic acids in plants to the DHA / EPA omega 3 fatty acids
Fish Oil

- Omega 3 fatty acids (Eicosapentaenoic acid (EPA), Docosahexaenoic acid (DHA))
  - Long chain, polyunsaturated fats
  - Cannot be made by the body
  - Antiinflammatory, vasodilatory, antiplatelet
  - Inhibit growth factors, angiogenesis
- Which fish?
  Herring, kipper, mackerel, menhaden, pilchard, salmon, sardine, trout
- Plants?
  Alpha-lineoleic acid, *precursor* for DHA/EPA – some similar clinical effects but not on cholesterol
Fish Oil - NMCD

• Effective
  – Hypertriglyceridemia

• Likely effective
  – Cardiovascular disease
    (primary and secondary prevention)

• Possibly effective
  – 29 listings

• Possibly / likely ineffective
  – 9 listings

• Insufficient evidence
  – 22 listings
Omega 3 FA for Secondary Prevention

- N=11323 with MI within 3 months
- N-3 PUFAs (1 gm), vitamin E (300 mg), both, neither
- All received optimal med and lifestyle tx
- Reduced many endpoints

Omega 3 for CHF

• 7046 patients with class II-IV CHF
• 1 gm n-3 PUFA vs placebo
• NNT to prevent 1 death in 4 years = 56

GISSI-HF investigators. Lancet 2008
Fish Oil Safety

– Inhibition of coagulation / bleeding
– Fishy taste, GI effects
  • Minimize with food or freezer
– Immunosuppression at high doses
– Mercury concern likely negligible; concentrates in meat > oils
– May lower blood pressure
– May decrease pulmonary function if aspirin sensitive
Advising patients

• “Natural” ≠ safe, “test-of-time” ≠ safe
• Tradition or anecdotal successes are not proof of safety or efficacy
• Supplements used for health purposes should be treated with the same cautions as other medications
• Supplements are not required to be shown safe or effective before marketing
Advising Patients

- Maximize benefits and minimize risks by:
  - Discussing with your health care provider
  - Stop taking the product if you notice side effects, and report them to your provider
  - Avoid combination and MLM products
  - Look for well-labeled products (scientific name of the plant, information about the manufacturer, dosing guidelines, expiration, and possible side effects)
  - Look for USP or other quality designation
“What we know for sure is the United States secretes the richest urine in the world”

--Victor Herbert, MD
Resources – General Information

- FDA Dietary Supplements 101 (www.fda.gov/food/dietarysupplements/default.htm)
- UpToDate (www.uptodate.com)
- PubMed (www.ncbi.nlm.nih.gov/pubmed/)
- Cochrane Collaboration (www.cochrane.org)
- Epocrates (www.epocrates.com)
- Micromedex (www.micromedex.com/)
- Natural Medicines Comprehensive Database (naturaldatabase.therapeuticresearch.com/home.aspx?cs=475965)
- National Center for Complementary / Alternative Medicine (nccam.nih.gov/health/supplements/)
- Office of Dietary Supplements (ods.od.nih.gov/)
Resources – Safety / Standardization

- Adverse event reporting (www.fda.gov/Food/DietarySupplements/Alerts/ucm111110.htm)
- United States Pharmacopeia (www.usp.org/USPVerified/dietarySupplements/)
- NNFA/Natural Products Association (www.npainfo.org/)
- National Sanitation Foundation (www.nsf.org/business/dietary_supplements/index.asp?program=DietarySups)
- ConsumerLab (www.consumerlab.com/)
Getting familiar with NMCD

• The following slides are for you to practice finding information using the NMCD

1. Begin on the Health Sciences Library home page: http://hslibrary.ucdenver.edu/
2. Select “Natural Medicines” on left under “Top Resources”
Getting familiar with NMCD

• Questions to answer
  1. Which product(s) are “likely effective” for osteoarthritis?
  2. What dose of SAMe is suggested for osteoarthritis?
  3. Are there any USP grade SAMe products?
  4. Which of the following medications may have interactions with SAMe: fluoxetine, levodopa, digoxin, MAO inhibitors, coumadin?
  5. For which conditions has marijuana been shown “possibly effective”?

Answers on last slide
Getting familiar with NMCD

• Answers
  1. SAMe, glucosamine
  2. 200 mg TID
  3. No
  4. fluoxetine, levodopa,, MAO inhibitors
  5. Glaucoma, spasticity / tremor in MS, HIV-related weight loss

Answers on last slide