COURSE TITLE: Risks and Benefits of Dietary Supplement Use

COURSE INSTRUCTOR: Ann Eshenaur Spolarich, RDH, PhD

COURSE CREDIT HOURS: 3.0 CEUs

COURSE DATE: March 4, 2016

COURSE DESCRIPTION: The purpose of this course is to provide oral health care professionals with current information about the assessment, treatment and management of clients taking selected vitamins, minerals and herbal supplements. Specific course content will focus on current knowledge of the risks and benefits of supplements. Potential applications for supplement use in dentistry will be reviewed.

COURSE OBJECTIVES: Upon completion of this continuing education program, the dental professional will be able to:

1. Discuss potential benefits and harms associated with use of vitamins and minerals.
2. Identify strategies to reduce risks when managing patients taking supplements.
3. Discuss drug/dietary supplement interactions of significance to dentistry.
4. Discuss potential applications of supplement use to improve oral health.

*This material may not be duplicated without the written permission of the author.*
National Health Interview Survey
According to a nationwide government survey released in December 2008, approximately 38 percent of U.S. adults aged 18 years and over and approximately 12 percent of children use some form of CAM.


Dietary supplement: As defined by the U.S. Congress in the Dietary Supplement Health and Education Act, which became law in 1994, a dietary supplement is a product (other than tobacco) that is intended to supplement the diet; contains one or more dietary ingredients (including vitamins, minerals, herbs or other botanicals, amino acids, and other substances) or their constituents; is intended to be taken by mouth as a pill, capsule, tablet, or liquid; and is labeled on the front panel as being a dietary supplement.

- Multivitamins/multiminerals are the most commonly used dietary supplements (taken by 39% of all adults)
- Women are more likely to take dietary supplements than men
- Use of supplemental calcium increased from 28% during 1988–1994 to 61% during 2003–2006 among women aged 60 and over.
- Use of dietary supplements containing vitamin D increased from 1988–1994 through 1999–2002 for men and women in most age groups.
- Dietary supplements can contain nutrients in amounts as high as or higher than the Institute of Medicine's Recommended Dietary Reference Intakes, therefore contributing substantially to total nutrient intake.


- 50% of Americans routinely use dietary supplements
- Annual spending > $20 billion on these products

• Dietary supplements contain a variety of ingredients, such as vitamins, minerals, amino acids, and herbs or other botanicals. Research has confirmed health benefits of some dietary supplements but not others.

• To use dietary supplements safely, read and follow the label instructions, and recognize that “natural” does not always mean “safe.” Be aware that an herbal supplement may contain dozens of compounds and that all of its ingredients may not be known.

• Some dietary supplements may interact with medications or pose risks with medical problems or are going to have surgery. Most dietary supplements have not been tested in pregnant women, nursing mothers, or children.

• Herbal supplements are one type of dietary supplement. An herb is a plant or plant part (such as leaves, flowers, or seeds) that is used for its flavor, scent, and/or potential health-related properties. “Botanical” is often used as a synonym for “herb.” An herbal supplement may contain a single herb or mixtures of herbs. The law requires that all of the herbs be listed on the product label.


Dietary Supplement Use in the United States

17.7 percent of American adults had used these types of products in the past 12 months. The most popular of these products used by adults in the past 30 days were:

• fish oil/omega 3/DHA (37.4 percent)
• glucosamine (19.9 percent)
• echinacea (19.8 percent)
• flaxseed oil or pills (15.9 percent)
• ginseng (14.1 percent)

• Despite the widespread use of supplements and the strong consumer beliefs about benefits, convincing scientific data to support efficacy are lacking.

• Current data are insufficient to formulate public health recommendations for dietary supplement use for otherwise healthy people


• Women of childbearing potential should take a folic acid-containing supplement (prevents neural tube defects)

• Smokers should avoid use of high-dose beta carotene in supplement form (increases risk of lung cancer)


• Hypothesis: taking multivitamins might lower the risk of CVD and cancer comes from published evidence supporting a role for specific micronutrients in disease prevention

• Diets high in fruits and vegetables are associated with a lower risk of CVD and cancer

• Low serum concentrations of B vitamins, carotenoids, and tocopherols have been associated with an increased risk of colorectal cancer and CVD


• Motivations for supplement use vary, but common reasons include the belief that these preparations will prevent chronic diseases, such as cancer and cardiovascular disease
What is the association between multivitamin use and risk for cancer, cardiovascular disease and mortality in postmenopausal women?

Examined the associations between multivitamin use in the Women's Health Initiative (WHI) clinical trial (CT) and observational study (OS) cohorts and the risk of site-specific solid tumors (invasive breast, renal, endometrial, ovarian, bladder, and stomach cancers); CVD (myocardial infarction, stroke, and venous thromboembolism); and total mortality

- 161,808 participants from the Women's Health Initiative clinical trials (N = 68,132 in 3 overlapping trials of hormone therapy, dietary modification, and calcium and vitamin D supplements) or an observational study (N = 93,676)
- Data were collected on multivitamin use at baseline and follow-up time points
- Study enrollment occurred between 1993 and 1998
- Followed up for a median of 8.0 years in the clinical trials and 7.9 years in the observational study
- Disease end points were collected through 2005

Data collected through in-person clinic visits; outcomes were via self-report and documented conditions in medical records (physician adjudicated)

Multivitamins were grouped into 3 classifications based on ingredients:

- *multivitamins (alone)* were preparations with 10 or more vitamins and no minerals in which the nutrient levels were at least 100% of US RDA;
- *multivitamins with minerals* were preparations with 20 to 30 vitamins and minerals and nutrient levels of 100% or less of US RDA; and
- *stress multisupplements* were preparations with higher doses (often >200% of US RDA) of several B vitamins and often including large doses of vitamin C or selected minerals, such as selenium or zinc.

*Supplement mixtures* with fewer than 10 components, such as B complex or antioxidant mixtures, were not considered multivitamins.

Results:

- 41.5% of the participants used multivitamins
  - The most common: multivitamins with minerals (35%)
- Women who used any multivitamins were more likely also to use single supplements of vitamin E, vitamin C, or calcium than women who did not use multivitamins ($P < .001$)
- Multivitamin users:
  - more likely to be white ($P < .001$)
  - living in the western United States ($P < .001$)
  - have a lower body mass index ($P < .001$)
be more physically active ($P < .001$)
- have a college degree or higher ($P < .001$)
- more likely to consume alcohol and less likely to smoke
- reported slightly higher fruit and vegetable consumption

- **No evidence that multivitamin use either increased or decreased the risk of cancer**
- No association of any multivitamin use with the risk of cancers of the breast, colon/rectum, endometrium, ovary, kidney, bladder, stomach, or lung
- **Annualized percentages of CVD events were non-significantly lower among women taking multivitamins than among those not taking multivitamins**
- Duration of multivitamin use had no apparent association with CVD risk
- **No association of duration of multivitamin use with total mortality**
- No association of persistent multivitamin use with risk of cancer or CVD

The associations of multivitamin use with cancer and CVD risk were weakly modified by demographic, health, and lifestyle characteristics.

- Older multivitamin users ($\geq 70$ years at baseline) had a reduced risk of endometrial cancer
- Multivitamin users who were obese had a reduced risk of invasive breast cancer
- Younger women using multivitamins were at a slightly higher risk of death
- Multivitamin users who were current smokers or consumers of more than 1 alcoholic drink per day had non-significant increased risks of mortality and MI, respectively
- Non-significant increased risk of MI and ovarian cancer among women who used multivitamins
- Fruit and vegetable intake did not modify the associations of multivitamin use with disease outcomes

**Conclusions:**

- No overall associations between multivitamin use and risk of several common cancers or CVD
- No associations between multivitamin use and total mortality
- Multivitamin use does not confer meaningful benefit or harm in relation to cancer or CVD risk in postmenopausal women
- After a median follow-up of 8.0 and 7.9 years in the clinical trial and observational study cohorts, respectively, the Women's Health Initiative study provided convincing evidence that multivitamin use has little or no influence on the risk of common cancers, CVD, or total mortality in postmenopausal women

What have other studies found?

Nurses' Health Study:

- Multivitamin use was associated with lower colon cancer incidence but only when use lasted for 15+ years
- Weak, non-significant protective association for breast cancer with 5 to 9 years of multivitamin use
- Increased risk for fatal non-Hodgkin lymphoma with long-term (>10 years) use
- Inverse association between multivitamin use and risk of MI or any coronary heart disease death, but the analysis was focused on use of B vitamins, including folic acid


The Women’s Health Study:

- A randomized, placebo-controlled trial of vitamin E and aspirin in 39,876 female health professionals. Since the end of the trial in 2004, participants have been followed up as a cohort.
- No association of baseline multivitamin use with subsequent breast cancer risk after an average follow-up of 10 years, nor association by duration of use, but they did report a modest suggestion of effect modification of breast cancer risk by alcohol intake.


What are the effects of multivitamin use in men aged 50 years and older?

The Physicians' Health Study II is a randomized, double-blind, placebo-controlled trial testing whether a standard multivitamin (Centrum Silver) will reduce the incidence of cancer, CVD, eye disease, or cognitive decline among 14,641 US male physicians aged 50 years and older. Findings were medical record confirmed.

• During median follow-up of 11.2 years, daily multivitamin use was associated with a modest reduction in total cancer
• No significance effect of daily multivitamin use on prostate, colorectal or other site-specific cancers
• Vitamin E and C supplementation had no immediate or long-term effects on risk of total cancers, prostate or other site-specific cancers
• Taking a multivitamin did not reduce major cardiovascular events (MI, stroke) or mortality after 10+ years of use
• Alternate day use of 400 IU of vitamin E or placebo and/or daily use of 500 mg vitamin C had no beneficial or harmful effect on risk of diagnosis of age-related macular degeneration
• Long-term alternate use of 400 IU of vitamin E and daily use of 500 mg of vitamin C had no notable beneficial or harmful effect on risk of cataracts
• Long-term daily multivitamin use modestly and significantly decreased risk of cataracts but had no significant effect on visually significant age-related macular degeneration (11.2 years of treatment and follow-up)


• In 35,533 men, aged 50 and older, long-term daily supplementation with selenium (200 mcg) and/or vitamin E (400 IU) is not likely to have a large beneficial effect on age-related cataracts (lens opacity, decreased visual acuity, cataract extraction)


HERBAL SUPPLEMENT USE AND SAFETY

• Study of 10,480 adults found that 1 in 3 adults in the United States take both prescription drugs and dietary supplements
Multivitamins with added ingredients (herbs or fish oil) were most common form of supplement mixed with medications.

47% diagnosed with major medical conditions (asthma, arthritis, CHF, CHD, angina, MI, stroke, HTN, high cholesterol, emphysema, chronic bronchitis, cancer, weak bones, or liver, thyroid or kidney problems) used both prescription medication and supplements.

Cardiovascular medications were most likely to be used along with dietary supplements, followed by CNS agents, hormones, metabolism-related drugs, psychotherapeutic agents, antibiotics or antivirals.

Supplement use was most common among people with osteoporosis, thyroid disease, cancer, arthritis, cardiovascular disease, kidney, diabetes, respiratory and liver conditions.

Concern is for altered liver metabolism caused by some herbal supplements and potential to increase/weaken medication potency.


Herbal Dietary Supplement (HDS) and Medication Interactions and Contraindications

- Identified 1,491 pairs of HDS-drug interactions
  - 213 HDS
  - 509 medications
- Greatest number of documented interactions with medications:
  - St. Johns wort
  - magnesium
  - calcium
  - iron
  - ginkgo
- Of a total of 509 drugs, most were used for:
  - CNS disorders (100)
  - cardiovascular system disorders (90)
  - systemic anti-infectives (75)
- Greatest number of reported interactions with HDS:
  - warfarin: most HDS interactions (100+)
    - insulin
    - aspirin
    - digoxin
    - ticlopidine
- HDS products containing herbs were more likely to have documented interactions with medications and contraindications than vitamins, minerals and other types of dietary supplements.
- 152 identified contraindications
- Most frequent contraindications involves:
  - gastrointestinal (16.4%)
• neurological (14.5%)
• renal/genitourinary diseases (12.5%)
• 59 HDS were contraindicated for use among patients with specific disease states
• Highest number of documented contraindications:
  • flaxseed ( *Linum usitatissimum*
  • echinacea ( *Echinacea purpurea*
  • yohimbe ( *Pausinystalia yohimbe*


• Flaxseed contraindications:
  o acute/chronic diarrhea
  o esophageal stricture
  o inflammatory bowel disease
  o hypertriglyceridemia
  o prostate cancer


• Echinacea contraindications:
  o rheumatoid arthritis
  o systemic lupus erythematosus
  o leukosis
  o multiple sclerosis
  o tuberculosis
  o HIV infection


• Yohimbe contraindications:
  o anxiety
  o bipolar disorder
  o depression
  o mania and schizophrenia
  o benign prostate hypertrophy
  o kidney disease

Drug-Herb Interactions of Significance to Dentistry

<table>
<thead>
<tr>
<th>HERB</th>
<th>COMMON USES</th>
<th>SOME SIDE EFFECTS AND INTERACTIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echinacea</td>
<td>Common cold; cough and bronchitis; wound and burn care; urinary tract infection</td>
<td>Hepatotoxic, especially when used with other hepatotoxic drugs; may decrease effectiveness of corticosteroids</td>
</tr>
<tr>
<td>Feverfew</td>
<td>Migraine prophylactic; fever reduction; see above</td>
<td>Inhibits platelet activity; avoid use with warfarin; 5-15% of users may develop aphthous ulcers or GI tract irritation</td>
</tr>
<tr>
<td>Garlic</td>
<td>Anti-lipidemic, antimicrobial, anti-asthmatic, anti-inflammatory</td>
<td>Potentiates effects of warfarin; May decrease effectiveness of certain HIV protease inhibitor drugs</td>
</tr>
<tr>
<td>Ginseng</td>
<td>Anti-cancer, slows aging, prevent heart attack, improve digestion, reduce hypertension, strengthen immunity, CNS stimulant</td>
<td>Antiplatelet properties; Avoid use with other stimulants: risk for tachycardia and hypertension</td>
</tr>
<tr>
<td>Kava-Kava</td>
<td>Anxiolytic</td>
<td>Serious risks for hepatotoxicity; potentiates alcohol, benzodiazepines, barbiturates = caution with sedation and general anesthesia</td>
</tr>
<tr>
<td>Licorice</td>
<td>Gastric disorders; cough and bronchitis</td>
<td>Glycyrrhizic acid in licorice may cause hypertension and hypokalemia; contraindicated with chronic liver disease, renal insufficiency, hypokalemia</td>
</tr>
<tr>
<td>St. John’s wort</td>
<td>Depression and anxiety</td>
<td>Decreases effectiveness of drugs for HIV: protease inhibitors and non-nucleoside reverse transcriptase inhibitors; induces liver enzymes (altered drug metabolism); prolongs effects of general anesthesia (anecdotal reports)</td>
</tr>
<tr>
<td>Valerian</td>
<td>Mild sedative; mild anxiolytic</td>
<td>Potentiates effects of barbiturates</td>
</tr>
<tr>
<td>Vitamin E</td>
<td>Antioxidant; CVD prevention; wound healing; fibrocystic breast syndrome</td>
<td>Increased bleeding risk with other antiplatelet and anticoagulant medications; may affect thyroid function in otherwise healthy person; may enhance hypertension in hypertensive patients (≥ 400 IU per day)</td>
</tr>
</tbody>
</table>


<table>
<thead>
<tr>
<th>Medication Effect</th>
<th>Drug</th>
<th>Herb</th>
<th>Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulants</td>
<td>caffeine, decongestants (Sudafed, Actifed, etc.)</td>
<td>ephedra, yohimbe, guarana, ginseng</td>
<td>Potentiates stimulation</td>
</tr>
<tr>
<td>Sedatives</td>
<td>alcohol, benzodiazepines, barbituates</td>
<td>valerian, kava, St. John's wort</td>
<td>Potentiates sedation</td>
</tr>
</tbody>
</table>
### Platelet Aggregation

| Platelet aggregation | warfarin, aspirin, clopidogrel, dipyridamole, ticlopidine | garlic, ginger, gingko, feverfew, ginseng | Potentiate anticoagulant effect |

### Antidepressant

| SSRI drugs, phenelzine sulfate, sertraline, citalopram, bupropion, tranylcypromine sulfate | St. John's wort | Serotonin syndrome, Monoamine oxidase inhibitors (MAOI) interaction potentially leading to mental effects such as confusion, as well as shivering, sweating, fever, muscle twitching |

### Hypoglycemics

| insulin, all antidiabetics | bilberry, bitter melon, dandelion, garlic | Potentiates lowering of glucose levels |

### Immunostimulant

| anabolic steroids, amiodarone, HIV drugs | echinacea, astragalus | Decrease action of corticosteroids; may interfere with immunosuppression |


### Polyherbacy

Especially common in patients trying to relieve chronic pain

- **Avocado-soybean unsaponifiables** – 4 studies have shown that 300 to 600 mg of avocado sterol compounds per day are associated with reduced knee/hip pain and swelling after 3 to 6 months of use
- **Omega-3 fatty acids** – fatty acids, especially 2 to 4 g of marine-based docosahexaenoic acid and eicosapentaenoic acid may be helpful for arthritis
- **Tumeric** – low quality evidence; curcumin 1 to 2 g per day may be beneficial for joint pain; best taken with fatty meal and absorption may be improved if taken with black pepper
- **Cat’s claw** (Uncaria tomentosa) – may be helpful for joint pain; pentacyclic and tetracyclic alkaloids in cat’s claw are associated with immunostimulant properties, increased phagocytosis, anticancer, antioxidant and anti-inflammatory effects
- **Ginger** – best with dried formulation; anti-inflammatory effects


### Recalled Supplements Remain on Market
• Supplements recalled by the FDA because they contained banned pharmaceutical ingredients
• Investigators purchased recalled supplements 8 to 52 months after issued recall
• Tested 27 supplements of the 274 supplements recalled during that time; 20 of the 27 were from U.S. manufacturers
• 66.7% (18/27) supplements tested contained one or more adulterant: majority (63%) contained same adulterant listed in FDA recall; 22.2% contained one or more additional banned ingredients not identified in FDA recalls: (sibutramine [Meridia], sildenafil [Viagra], fluoxetine, anabolic steroids)
  o 85% (11/13) of sports enhancement supplements
  o 67% (6/9) of weight loss supplements
  o 20% (1.5) of sexual enhancement supplements


Liver Injury
• Use of unregulated herbal or dietary supplements associated with liver injury
• Prospective study using 8 sites within the Drug-Induced Liver Injury network found 839 people with drug-induced liver injury caused by HDS or conventional medications (excluding acetaminophen cases)
• During 10 year study period, proportion of cases linked to HDS use increased from 7% to 20%
• Products commonly used for bodybuilding or weight loss in middle-aged women
• HDS products associated with death or need for transplant included energy boosters, herbal “Viagra,” Chinese herbal mixtures, ayurvedic compounds, colon and “cleanse” products
• Liver injury associated with HDS use is more likely to require transplantation than with hepatotoxicity associated with conventional medications


ANTIOXIDANT SUPPLEMENT USE AND CANCER

It is estimated that > 50% of patients with chronic diseases or cancers use HDS
• 64% to 81% of cancer survivors take vitamin and mineral supplements, and 14% to 32% of patients begin using supplements after diagnosis
• **Antioxidant supplements do not reduce risk for cancer or prevent tumor growth; may actually increase likelihood from dying from cancer**

• 2004 meta-analysis (14 RCTs) comparing effects of antioxidant supplement use versus placebo on incidence of gastrointestinal cancers: esophageal, gastric, colorectal, pancreatic, liver cancers

• Findings: consuming vitamins A, C and E, beta-carotene, and selenium supplements increased overall mortality


• 2006 RCT of 540 patients with head and neck cancer undergoing radiation

• Patients who consumed vitamin E and beta-carotene supplements daily had significantly increased likelihood of dying compared to those who took placebo


• **Best practices: consume antioxidants in fruits and vegetables** (dose is lower and body can regulate cellular exposure; supplement dose is much higher)

• Antioxidant supplements interact with chemotherapy and radiation therapy

• Chemotherapy creates oxidative stress (kills cancer cells) = taking antioxidants may interfere with process (risk that treatment will fail)

**People who take a lot of antioxidant supplements or who consume a lot of dietary antioxidants do not live any longer than those who just eat well overall**

• No association between amount of vitamins A and C in diet, or vitamin E supplements and risk of death

• Beta-carotene in smokers increases risk of lung cancer

• High doses of vitamin E increases risk for prostate cancer and stroke

• Antioxidants cause drug interactions altering drug efficacy


**PROBIOTICS**

**Actions:** Inhibit biofilm formation by altering bacterial attachment; normalize the oral ecosystem = improves microbial balance; modulate oral immunity

• Prebiotics: non-digestible dietary supplements; enhance growth and activity of beneficial organisms and suppress growth and activity of pathogenic bacteria; stimulate the growth of probiotics (living microorganisms added to foods for ingestion to benefit the host)
Probiotics have been studied for the following oral conditions: caries, periodontal disease, halitosis, candidiasis

Probiotics are contraindicated in patients who are immunocompromised, premature infants, and patients with central venous access (central line catheters).

For a review of the literature of probiotics and oral health:

Probiotics and Antibiotic Use
2 large studies (1 meta-analysis and 1 Cochrane review) suggest that probiotics may prevent or diminish antibiotic-associated diarrhea, and potentially be helpful in avoiding C difficile infection = limitations: small study populations, heterogeneous populations


PLACIDE study (United Kingdom) = 17,000 hospitalized subjects 65+ years and older who were taking an antibiotic = randomly assigned to “probiotic” (lactobacilli/bifidobacteria for 21 days) or “placebo” (no HX prosthetic valves, IBS, C diff) = at 8 weeks, no difference in outcomes for C diff infection or antibiotic-associated diarrhea; increased flatus in probiotic group; patients with C diff diarrhea who received the probiotic reported a 3-fold increase in bloating (didn’t prevent/get better/harmful side effects) = does use of probiotics cause a dysbiosis in some patients?


Cleveland Clinic Foundation Hospitals study = 12,026 high-risk patients age 55+ who received broad-spectrum antibiotics and gastric acid suppressant during hospitalization; randomly assigned to receive metronidazole or no metronidazole before broad-spectrum antibiotics (piperacillin-tazobactam or ciprofloxacin) for a non-C diff infection: use of metronidazole resulted in 80% reduction in C diff infection in at-risk patients