

COURSE TITLE: Risks and Benefits of Dietary Supplement Use

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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.

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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.

Barnes PM, Bloom B, Nahin R. *CDC National Health Statistics Report #12. Complementary and Alternative Medicine Use Among Adults and Children: United States, 2007*. December 10, 2008

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.

- **Use of dietary supplements is common among the U.S. adult population.** Over 40% used supplements in 1988–1994, and 53% in 2003–2006.
- **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 supplements containing folic acid among women aged 20–39 did not increase since 1988–1994. In 2003–2006, 34% of women aged 20–39 used a dietary supplement containing folic acid.**
- **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.**

Centers for Disease Control. National Health and Nutrition Examination Survey (NHANES) data collected from 2003 to 2006. <http://www.cdc.gov/nchs/data/databriefs/db61.htm>

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

Slesinski MJ, Subar AF, Kahle LL Trends in use of vitamin and mineral supplements in the US. *J Am Diet Assoc* 1995;95 (8) 921- 923; NIH State-of-the-Science Panel, National Institutes of Health State-of-the-Science Conference Statement: multivitamin/mineral supplements and chronic disease prevention. *Ann Intern Med* 2006;145 (5) 364- 371

- **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.

National Center for Complementary and Integrative Health. Using Dietary Supplements Wisely. Available at: <https://nccih.nih.gov/health/supplements/wiseuse.htm>

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**

Nesheim MC. What is the research base for the use of dietary supplements? *Public Health Nutr* 1999;2 (1) 35- 38; Hendrich S, Fisher K. What do we need to know about active ingredients in dietary supplements? summary of workshop discussion. *J Nutr* 2001;131 (4) ((suppl)) 1387S- 1388S; Fairfield KM, Fletcher RH. Vitamins for chronic disease prevention in adults: scientific review. *JAMA* 2002;287 (23) 3116- 3126

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

NIH State-of-the-Science Panel, National Institutes of Health State-of-the-Science Conference Statement: multivitamin/mineral supplements and chronic disease prevention. *Ann Intern Med* 2006;145 (5) 364- 371; Morris CD, Carson S. Routine vitamin supplementation to prevent cardiovascular disease: a summary of the evidence from the U.S. Preventive Services Task Force. *Ann Intern Med.* 2003;139(1):56-70.

- **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)**

American Academy of Pediatrics Committee on Genetics, Folic acid for the prevention of neural tube defects. *Pediatrics* 1999;104 (2, pt 1) 325- 327; Bentley JR, Ferrini RL, Hill LL. American College of Preventive Medicine public policy statement: folic acid fortification of grain products in the U.S. to prevent neural tube defects. *Am J Prev Med* 1999;16 (3) 264- 267; Omenn GS. Chemoprevention of lung cancer: the rise and demise of beta-carotene. *Annu Rev Public Health* 1998;1973- 99

- **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**

Fuchs CS, Willett WC, Colditz GA. et al. The influence of folate and multivitamin use on the familial risk of colon cancer in women. *Cancer Epidemiol Biomarkers Prev* 2002;11 (3) 227- 234; Harnack L, Jacobs DR, Nicodemus K, Lazovich D, Anderson K, Folsom AR. Relationship of folate, vitamin B-6, vitamin B-12, and methionine intake to incidence of colorectal cancers. *Nutr Cancer* 2002;43 (2) 152- 158; Giovannucci E, Stampfer M, Colditz GA. Multivitamin use, folate and colon cancer in women in the Nurses' Health Study. *Ann Intern Med* 1998;129 (7) 517- 524; Wei EK, Giovannucci E, Selhub J, Fuchs CS, Hankinson SE, Ma J. Plasma vitamin B6 and the risk of colorectal cancer and adenoma in women. *J Natl Cancer Inst* 2005;97 (9) 684- 692; Comstock GW, Alberg AJ, Huang HY, et al. The risk of developing lung cancer associated with antioxidants in the blood: ascorbic acid, carotenoids, alpha-tocopherol, selenium, and total peroxy radical absorbing capacity. *Cancer Epidemiol Biomarkers Prev* 1997;6 (11) 907- 916; Dorgan JF, Sowell A, Swanson CA, et al. Relationships of serum carotenoids, retinol, alpha-tocopherol, and selenium with breast cancer risk: results from a prospective study in Columbia, Missouri (United States). *Cancer Causes Control* 1998;9 (1) 89- 97; Losonczy KG, Harris TB, Havlik RJ. Vitamin E and vitamin C supplement use and risk of all-cause and coronary heart disease mortality in older persons: the Established Populations for Epidemiologic Studies of the Elderly. *Am J Clin Nutr* 1996;64 (2) 190- 196; Knecht P, Aromaa A, Maatela J, et al. Serum selenium and subsequent risk of cancer among Finnish men and women. *J Natl Cancer Inst* 1990;82 (10) 864- 868

- **Motivations for supplement use vary, but common reasons include the belief that these preparations will prevent chronic diseases, such as cancer and cardiovascular disease**

Neuhouser ML. Dietary supplement use by American women: challenges in assessing patterns of use, motives and costs. *J Nutr* 2003;133 (6) 1992S- 1996S; Neuhouser ML, Patterson RE, Levy L. Motivations for using vitamin supplements. *J Am Diet Assoc* 1999;99 (7) 851- 854

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 (≥ 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

Neuhouser ML, Wassertheil-Smoller S, Thomson C, Aragaki A, Anderson GL, Manson JE, Patterson RE, Rohan TE, van Horn L, Shikany JM, Thomas A, LaCroix A, Prentice RL. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. *Arch Intern Med.* Feb 2009;169(3):294-304.

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

Giovannucci E, Stampfer M, Colditz GA. Multivitamin use, folate and colon cancer in women in the Nurses' Health Study. *Ann Intern Med* 1998;129 (7) 517- 524; Zhang S, Hunter DJ, Forman M. Dietary carotenoids and vitamins A, C and E and risk of breast cancer. *J Natl Cancer Inst* 1999;91 (6) 547- 556; Zhang SM, Giovannucci EL, Hunter DJ, et al. Vitamin supplement use and the risk of non-Hodgkin's lymphoma among women and men. *Am J Epidemiol* 2001;153 (11) 1056- 1063; Rimm EB, Willett WC, Hu FB, et al. Folate and vitamin B6 from diet and supplements in relation to risk of coronary heart disease among women. *JAMA* 1998;279 (5) 359- 364

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.

Lee I-M, Cook NR, Gaziano JM, et al. Vitamin E in the primary prevention of cardiovascular disease and cancer: the Women's Health Study: a randomized controlled trial. *JAMA* 2005;294 (1) 56- 65; Ishitani K, Lin J, Manson JE, Buring JE, Zhang SM. A prospective study of multivitamin supplement use and risk of breast cancer. *Am J Epidemiol* 2008;167 (10) 1197- 1206

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.

Christen WG, Gaziano JM, Hennekens CH. Design of Physicians' Health Study II—a randomized trial of beta-carotene, vitamins E and C, and multivitamins, in prevention of cancer, cardiovascular disease, and eye disease, and review of results of completed trials. *Ann Epidemiol* 2000;10 (2) 125- 134

- 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)

Gaziano JM, Sesso HD, Christen WB, Bubes V, Smith JP, MacFadyen J, Schvartz M, Manson JE, Glynn RJ, Buring JE. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 2012;308(18):1871-80; Wang L, Sesso HD, Glynn RJ, Christen WG, Bubes V, Manson JE, Buring JE, Gaziano JM. Vitamin E and C supplementation and risk of cancer in men: posttrial follow-up in the Physicians' Health Study II randomized trial. *Am J Clin Nutr* 2014;100(3):915-23; Sesso HD, Christen WG, Bubes V, Smith JP, MacFadyen J, Schvartz M, Manson JE, Glynn RJ, Buring JE, Gaziano JM. Multivitamins in the prevention of cardiovascular disease in men: the Physicians' Health Study II randomized controlled trial. *JAMA* 2012;308(17):1751-60; Christen WG, Glynn RJ, Sesso HD, Kurth T, MacFadyen J, Bubes V, Buring JE, Manson JE, Gaziano JM. Vitamins E and C and medical record-confirmed age-related macular degeneration in a randomized trial of male physicians. *Ophthalmology* 2012;119(8):1642-9; Christen WG, Glynn RJ, Sesso HD, Kurth T, MacFadyen J, Bubes V, Buring JE, Manson JE, Gaziano JM. Age-related cataract in a randomized trial of vitamins E and C in men. *Arch Ophthalmol* 2010;128(11):1397-405; Christen WG, Glynn RJ, Manson JE, MacFadyen J, Bubes V, Schvartz M, Buring JE, Sesso HD, Gaziano JM. Effects of multivitamin supplement on cataract and age-related macular degeneration in a randomized trial of male physicians. *Ophthalmology* 2014;121(2):525-34.

- 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)

Christen WG, Glynn RJ, Gaziano JM, Darke AK, Crowley JJ, Goodman PJ, Lippman SM, Lad TE, Bearden JD, Goodman GE, Minasian LM, Thompson IM Jr, Blanke CD, Klein FA. Age-related cataract in men in the selenium and vitamin e cancer prevention trial eye endpoints study: a randomized clinical trial.

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**

Jegtvig S. One third of Americans mixing supplements with meds: study. Medscape. April 29, 2014; J Acad Nutr Diet 2014.

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*)

Tsai HH, Lin HW, Simon Pickard A, Tsai HY, Mahady GB. Evaluation of documented drug interactions and contraindications associated with herbs and dietary supplements: a systematic literature review. *Int J Clin Pract.* 2012;66(11):1056-1078.

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

Ulbricht CE. *Natural Standard Herbs & Supplement Reference: Evidence-Based Clinical Review.* St Louis, MO: Mosby/Elsevier, 2005.

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

Cassileth BR. *Herb-Drug Interactions in Oncology.* Lewiston, NY: BC Decker, Inc., 2003; Mahady GB. *Botanical Dietary Supplements: Quality, Safety and Efficacy.* Lisse, The Netherlands: Swets & Zeitlinger Publishers, 2001.

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

Ulbricht CE. *Natural Standard Herbs & Supplement Reference: Evidence-Based Clinical Review.* St Louis, MO: Mosby/Elsevier, 2005; National Center for Complementary and Alternative Medicine. *Herbs at a Glance.* <http://nccam.nih.gov/health/herbsataglance>

Drug-Herb Interactions of Significance to Dentistry

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

Source: American Society of Anesthesiologists. Considerations for Anesthesiologists: What you should know about your patients' use of herbal medicines and other dietary supplements. 2003. Available at: www.ASAhq.org.

Medication Effect	Drug	Herb	Interaction
Stimulants	caffeine, decongestants (Sudafed, Actifed, etc.)	ephedra, yohimbe, guarana, ginseng	Potentiate stimulation
Sedatives	alcohol, benzodiazepines, barbituates	valerian, kava, St. John's wort	Potentiate sedation

Platelet aggregation	warfarin, aspirin, clopidogrel, dipyridamole, ticlopidine	garlic, ginger, ginkgo, 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	Potentiate lowering of glucose levels
Immunostimulant	anabolic steroids, amiodarone, HIV drugs	echinacea, astragalus	Decrease action of corticosteroids; may interfere with immunosuppression

Source: Society of Gastroenterology Nurses and Associates, Inc. Patient Safety Issues with Use of Herbal Supplements. Available at: <http://www.sgna.org/GINurseSedation/PatientCareSafety.aspx>

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

Melville N. Polyherbacy: a common challenge in pain patients. Medscape. Sep 23, 2014.

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)
 - 85% (11/13) of sports enhancement supplements
 - 67% (6/9) of weight loss supplements
 - 20% (1.5) of sexual enhancement supplements

Hand L. Many recalled supplements remain on the market months later. Medscape. Oct 22, 2014; JAMA 2014;321:1691-1693.

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

Kelly JC. Liver injuries from supplements up 3-fold in 10 years in large study. Medscape. Sep 8, 2014; Hepatology. August 25, 2014 (Abstract)

ANTIOXIDANT SUPPLEMENT USE AND CANCER

It is estimated that > 50% of patients with chronic diseases or cancers use HDS

Miller MF, Bellizzi KM, Sufian M, Ambs AH, Goldstein MS, Ballard-Barbash R. Dietary supplement use in individuals living with cancer and other chronic conditions: a population-based study. J Am Diet Assoc. 2008;108:483-94.

- **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 of 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**

Bjelakovic G, Nikolova D, Simonetti RG, Gluud C. Antioxidant supplements for prevention of gastrointestinal cancers: a systematic review and meta-analysis. *Lancet* 2004;364:1219-1228.

- 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

Bairati I, Meyer F, Jobin E, Gélinas M, Fortin A, Nabid A. Antioxidant vitamin supplementation and mortality: a randomized trial in head and neck cancer patients. *Int J Cancer* 2006; 119:2221-2224.

- **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

Doyle K. Extra antioxidants may make little difference in lifespan. *Medscape*. Jan 8, 2015; *Am J Epidemiol* 2014.

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:

Reddy RS, Swapna LA, Ramesh T, Rajesh Singh T, Vijayalaxmi N, Lavanya R. Bacteria in oral health-probiotics and prebiotics a review. *Int J Biol Med Res.* 2011;2(4):1226-1233.

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

Hempel S, Newberry SJ, Maher AR, et al. Probiotics for the prevention and treatment of antibiotic-associated diarrhea: a systematic review and meta-analysis. *JAMA* 2012;307:1959-1969; Johnston BC, Ma SS, Goldenberg JZ, et al. Probiotics for the prevention of Clostridium difficile-associated diarrhea: a systematic review and meta-analysis. *Ann Intern Med* 2012;157:878-888.

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?**

Allen SJ, Wareham K, Wang D, et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and Clostridium difficile diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet* 2013;382:1249-1257.

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**

Rodriguez S, Hernandez MB, Tarchini G, et al. Risk of Clostridium difficile infection in hospitalized patients receiving metronidazole for a non-*C difficile* infection. *Clin Gastroenterol Hepatol* 2014;12(11):1856-61.