MENOPAUSE

DISEASE/CONDITION OVERVIEW

Menopause is the time in a woman's life after her menses has stopped. Many people use the term menopause to describe the years leading up to and following the last period. The time before the total cessation of menses when periods are irregular (usually 3 to 5 years before the final menstrual period) is more accurately termed the climacteric or perimenopause. Menopause may be natural, artificial, or premature. Menopause is usually identified retrospectively, when it has been over a year since the woman's last monthly period. Everything afterward is generally referred to as postmenopause, a time of estrogen-deficiency.

The average age of menopause in American women is 51 but it may begin as early as age 35 and as late as 59. Cigarette smokers tend to reach menopause earlier than non-smokers. Menopause is

an experience that is unique to each woman. Some women notice little difference in their physiology while others find the change extremely troublesome and upsetting.

Etiology

Ovarian failure and the accompanying decline in estrogen production are responsible for the changes of menopause. A gradual or erratic decline in hormone levels is thought to occur in most women during the perimenopause rather than an abrupt cessation of ovarian function. At menopause, hormone levels don't always decline uniformly. They alternately rise, and fall again, not unlike the hormonal symptoms that occur during puberty. In women undergoing gynecologic surgery or chemotherapy, an abrupt cessation of ovarian function is more typical. Menopause that occurs as a result of medications such as Danocrine, GnRH analogues, or antiestrogens, is reversible.

Risk Factors

Aging is the most obvious risk factor for menopause. Genetic factors may predispose some women to an early menopause (under age 50). The only modifiable risk factor for early menopause is smoking, with heavy smokers starting earlier than light smokers. Menopausal and postmenopausal women have a greater risk of osteoporosis, heart disease, Alzheimer's disease, colon cancer, and diabetes. The incidence of these conditions is also largely affected by genetic and lifestyle factors.

Prognosis

The overt symptoms of menopause may take 1 to 2 years to diminish but in some women can persist much longer. In women undergoing gynecologic surgery or chemotherapy menopausal symptoms such as hot flashes are generally more severe. The greater concern, from a medical perspective, is that gradual, asymptomatic development of heart disease, osteoporosis, and other degenerative conditions may lead to significant morbidity and mortality. The onset of some of these conditions may be either prevented or delayed.

Signs and Symptoms

During perimenopause the menstrual cycle can become erratic, as can the quantity and quality of the menstrual flow. Menses are often skipped, then stop altogether. Most, but not all, women experience vasomotor symptoms including hot flashes and night sweats, and/or vaginal dryness. It is also common for women to have symptoms of insomnia, anxiety, and depression. They may have difficulties with memory and concentration or feel tired or moody. These symptoms differ

from woman to woman.

With advancing age, the walls of the vagina become thinner, dryer, less elastic and more vulnerable to infection. These changes can make sexual intercourse uncomfortable or painful. A woman may experience pain or urgency with urination related to estrogen changes or have vaginal symptoms. Sexual desire may also be affected. Decreased libido is a common complaint.

Asymptomatic physiologic changes that can occur with menopause include decreases in high-density lipoprotein (HDL) cholesterol, glucose tolerance, and bone density. These changes may be accompanied by increases in homocysteine levels, blood glucose, blood pressure, low-density lipoprotein (LDL) and total cholesterol. While these changes can be totally silent they are not innocuous.

Differential Diagnosis

There are a variety of conditions that could mimic some of the symptoms of menopause. These include:

- Adrenal dysfunction
- Hypothyroidism or hyperthyroidism
- Pituitary disorders
- Polycystic ovary disease
- Uterine cancer

Monitoring Parameters

Menopausal women should plan on having regular physical exams and screening tests that monitor for cancer, risk of heart disease, diabetes, hypertension, and osteoporosis. This includes periodic screening of blood lipids, blood pressure, blood glucose, mammography, bone densitometry, sigmoidoscopy/colonoscopy, and pap smear. Women should continue to do screening breast exams once a month. If any of the screening tests show an unfavorable trend, then intervention is warranted for the specific abnormalities identified.

WESTERN MEDICAL THERAPIES

Until relatively recently, the gold standard of conventional treatment for menopause has been hormone replacement therapy (HRT). For women with an intact uterus this includes both an

estrogenic agent and a progestin. Progestins are generally indicated to offset the increased risk of endometrial cancer with the use of unopposed estrogen. For women using both an estrogenic agent and a progestin there is a choice between cyclic and continuous dosing regimens. With the cyclic dosing regimens (intermittent high dose progestin and estrogenic withdrawal), women can anticipate resuming a predicable (but artificial) menstrual cycle. With the continuous regimens (continual estrogen and low dose progestin without withdrawal), women can anticipate amenorrhea with occasional erratic spotting. For women who have had a hysterectomy progestins are usually not recommended.

Compliance with HRT has been poor with only about one in three women staying on HRT after a year. There are many reasons for non-compliance with medically recommended HRT but the most commonly cited include thrombotic complications and side effects on mood, and the tissues of the breasts. There is an increased incidence of breast and uterine cancer. HRT does not seem to definitely decrease the risk of heart disease in women.. Recent highly publicized studies have documented an increased incidence of heart attacks upon initiation of HRT (Grodstein et al, 2001). There have also been questions concerning the preventive effect of HRT on Alzheimer's disease. Both have weakened the persuasiveness of the risk-benefit argument in the barometer of public opinion.

The selective estrogen receptor modulators (SERMs), or so-called "designer estrogens," are a newer class of drugs that may offer the benefits of HRT (protection against osteoporosis and maintaining favorable lipid profiles) without some of the risks associated with standard HRT. Over the last few years there has also been a tremendous proliferation of doses, delivery systems, different hormonal agents, and combination products to increase treatment options and decrease side effects of conventional HRT. Currently there are close to thirty prescription products available for the treatment of symptoms of menopause. Information on dosing regimens for all of these products is readily available and will not be addressed in this protocol.

The net effect of all these recent developments is that both public and medical opinion appear to be transitioning from "one-size-fits-all" HRT to an approach that is individualized (based on symptoms, history, and risk factors) and uses the lowest effective doses of hormones to achieve the preventive benefits. The choice of specific hormonal agents to be used can now be a matter of preference, convenience, and tolerability.

In situations where HRT is contraindicated (hormone-dependent carcinoma, stroke, thromboembolic disease, thrombophlebitis, and undiagnosed vaginal bleeding), "off-label" use of clonidine (Lucerno & McCloskey, 1997), megestrol acetate (Lucerno & McCloskey, 1997), and paroxetine (Beebe, 2000) may help control hot flashes.

The classes of prescription products currently available for the treatment of menopause include:

<u>Estrogenic agents</u>

- Compounded bio-identical "Biest" (20% estradiol [E2] and 80% estriol [E3])

- Compounded bio-identical "Triest" (10% estrone [E1], 10% estradiol [E2], and 80% estriol [E3])
- Conjugated estrogens (Cenestin tabs and Premarin tabs)
- Dienestrol (Ortho dienestrol cream)
- Esterified estrogens (Estratab tabs and Menest tabs)
- Estradiol (Alora patches, Climara patches, Esclim patches, Estrace tabs and cream, Estraderm patches, Estring vaginal ring, and Vivelle patches)
- Estropipate (Ogen tabs and Ortho-est tabs)
- Ethinyl estradiol (Estinyl tabs)

Progestins

- Medroxyprogesterone acetate (Amen tabs, Cycrin tabs, and Provera tabs)
- Micronized natural progesterone (Prometrium caps and compounded products)
- Norethindrone acetate (Aygestin tabs)

Combination products (estrogenic agent plus progestin)

- Conjugated estrogens plus medroxyprogesterone acetate (Premphase tabs and Prempro tabs)
- Estradiol plus norethindrone acetate (Combipatch patches)
- Estradiol plus norgestimate (Ortho-prefest tabs)
- Ethinyl estradiol plus norethindrone acetate (Femhrt tabs)
- Combination products (estrogenic agent plus androgen)
- Esterified estrogens plus methyltestosterone (Estratest)

SERMs

- Raloxifene (Evista)

INTEGRATIVE MEDICINE STRATEGY

Menopause is not a disease state warranting aggressive interventions. Rather, it is a transition

amenable to less aggressive, supportive measures. While it is true that at menopause the ovaries stop manufacturing eggs to be fertilized, this is not the only function of the ovary. Aside from the obvious effects on the ovaries and uterus, ovarian hormones also affect all other tissues, including the breasts, vagina, bones, blood vessels, gastrointestinal tract, urinary tract, and skin. It is essential that the practitioner address these various organs and body systems in their evaluation of the menopausal patient. After an individual assessment of risk factors and preferences is made, supportive measures are chosen based on the degree of symptoms experienced, the risk of heart disease, breast cancer, and the risk of osteoporosis.

For most women vasomotor symptoms (hot flashes) are the chief complaints of menopause. Several natural therapies have been researched for their effectiveness in treating vasomotor symptoms. The evidence supporting the use of soy for this purpose is mixed. Soy products and other legumes contain "phytoestrogens" and bioflavonoids called isoflavones. The primary isoflavones in soybeans are genistein and daidzein. In most of the studies, the use of soy has only been as effective as placebo in alleviating hot flashes. A few studies show a minimal effect of soy on hot flashes. It is worthwhile doing a trial of soy in the treatment or prevention of hot flashes. One would recommend that a woman consume about 1/3 of her protein as soy. The least processed and the fermented soy products are preferable such as soy milk, tempeh and miso. Red clover also contains substances such as coumestrol, daidzein, and genistein and may have weak estrogenic effects. Red clover has helped reduce hot flashes in some women. Black cohosh is one of the top selling herbal medicines used in menopause. It appears to be well tolerated and may be useful for women with hot flashes. Evening primrose oil, borage oil, and black currant seed oil produce seeds that contain gamma linolenic acid. Although GLA is more commonly used in mastalgia, some women find symptomatic relief using GLA (or one of its plant sources) in the treatment of hot flashes. Dong quai is a Chinese herbal medicine that has been used to treat menopausal symptoms traditionally for thousands of years and is thought to exert estrogenic effects. Scientific evidence has not supported this assumption and a randomized, double-blind, placebo-controlled trial found no estrogen-like activity and no difference between placebo in relief of menopausal symptoms including hot flashes and vaginal dryness (Hirata et al, 1997). Vitamin E has demonstrated minimal effects in alleviating hot flashes in recent trials. Some of the trials included below are outdated. Further research, perhaps using higher doses of vitamin E, is warranted.

Mood disturbance or emotional instability is another frequent complaint of women in perimenopause. A New England Research Institute study found that menopausal women were no more depressed than the general population: about 10 percent are occasionally depressed and 5 percent are persistently depressed. The exception is women who undergo surgical menopause. Their depression rate is reportedly double that of women who have a natural menopause.

Studies have also indicated that many cases of depression relate more to life stresses or "mid-life crises" than to menopause. Such stresses include: an alteration in family roles, as when your children are grown and move out of the house, no longer "needing" mom; a changing social support network, which may happen after a divorce if you no longer socialize with friends you met through your husband; interpersonal losses, as when a parent, spouse or other close relative

dies; and your own aging and the beginning of physical illness. People have very different responses to stress and crisis.

If mild to moderate depression is an issue, St. John's wort may be appropriate. SAMe may also be a good choice. *For more information on the treatment of depression, please view the AltMedDex Depression Protocol.*

One of the most important health issues for perimenopausal and postmenopausal women is the threat of osteoporosis. It is a condition in which bones become thin, fragile, and highly prone to fracture. Numerous studies over the past 10 years have linked estrogen insufficiency to this gradual, yet debilitating disease. Hormone replacement therapy has been shown to halt bone loss and certainly supplemental calcium, magnesium, ipriflavone, and vitamin D are also important. Weight bearing, impact-loading exercise is also especially important to prevent osteoporosis. *For more information on osteoporosis, please view the AltMedDex Osteoporosis Protocol.*

First line supportive measures for prevention of heart disease include dietary modification, aerobic exercise, smoking cessation, stress reduction, and control of weight, glucose, cholesterol, homocysteine levels, and blood pressure. If monitoring of risk factors reveals an unfavorable trend, specific, targeted interventions should be chosen for the risk factors in question. . *For more information, please view the any or all of the following AltMedDex Protocols: Hypercholesterolemia, Coronary Artery Disease, Hypertension, Congestive Heart Failure.*

If a woman is not already reducing her health risks by perimenopause she should begin a program of exercise, stress reduction, smoking cessation, healthy eating and nutritional supplementation to help reduce risks of heart disease, osteoporosis and cognitive decline.

The exercise program should consist of an aerobic, balance and strength training component. The aerobic component should have some impact loading such as walking or treadmill. It should be done 5 to 6 days a week, be in the woman's heart rate training zones (moderate exertion level or 60 to 70 % of the maximum heart rate) and be done without chest pain or other significant symptoms. Weight training such as biceps curls and wall push-ups can help decrease the risk of forearm fractures and be done in 2 sets of ten, 3 days a week. Balance exercises should be done to decrease the risk of falls and subsequent arm and hip fractures. Nutritional supplementation in menopause should include 400 international units (IU) of Vit E and D, 1200 mg of calcium 500 to 600mg of magnesium and other minerals to support bone health. Iron is not needed after menses has stopped unless there is an iron deficient anemia. A woman should be eating 3 meals a day with small snacks to avoid hypoglycemia and should try to eat many fruits and vegetables along with approximately 1 gram of protein per kilogram of body weight. Organic foods should be chosen when possible. Some protein may be consumed within an hour of doing some strength training to help preserve lean body mass. Soy foods should be integrated in the diet if the woman is not allergic to soy.

If many of the first line measures outlined above are ineffective, low doses of bio-identical hormones (estrone, estradiol, estriol, and micronized natural progesterone) may be initiated and titrated upward as needed for symptom control. The clinician may consider biestrogen (estradiol

plus estrone) as there might be less of a risk of cancer associated with the 2 estrogens in the formula. Topical estrogen can be applied to the vagina for vaginal dryness or thinning or painful intercourse. In situations where bio-identical hormones are not preferred or are ineffective, synthetic HRT may be used. In situations where HRT is contraindicated, "off -label" use of clonidine, megestrol acetate, and antidepressants may help reduce hot flashes.

In woman with loss of libido the testosterone level can be measured and supplemented if very low for a female.

A decrease in or loss of libido combined with a decrease in vaginal lubrication can be devastating for women. During menopause, blood supply to the vagina is decreased and the vaginal lining atrophies and becomes thinner. Some women also complain of pain with intercourse. Chaste tree, also known as Vitex or chasteberry, has been recommended for vaginal dryness. The use of a vaginal lubricant during intercourse is highly recommended during this time. Again, ginseng may be useful for these women. Some women actually feel liberated after menopause and report an increased interest in sex. They say they feel relieved that pregnancy is no longer a worry. *For more information on sexual dysfunction in women, please view the AltMedDex Sexual Dysfunction Protocol.*

Dysfunctional uterine bleeding (DUB) is another common complaint during perimenopause. Some women have irregular or heavy bleeding. Although this is considered normal during the perimenopause, it can cause considerable distress in women. Chaste tree (Vitex) is also used for this reason, as is the herb called Shepard's purse, and wild yam. None of these herbs have considerable research to support their use. *For more information, please view the AltMedDex Menorrhagia Protocol.*

For women in perimenopause, birth control can be a confusing issue. Doctors advise all women who have menstruated, even if irregularly, within the past year to continue using birth control. Unfortunately, contraceptive options are limited. Hormone-based oral and implantable contraceptives are risky in older women who smoke. Only a few IUD brands are on the market. The other options are barrier methods--diaphragms, condoms, and sponges--or methods requiring surgery such as tubal ligation.

To avoid becoming a rigid protocol that does not serve the needs of the patient, patient preference must be taken into account at every step of the evaluation process. Harnessing the power of patient preference and beliefs whenever possible can enhance outcomes.

COMPLEMENTARY AND ALTERNATIVE (CAM) THERAPIES

A wide array of products and therapies have been used to alleviate symptoms of menopause. Based on current research, black cohosh is the only herbal product that has significant documented efficacy in alleviating menopausal symptoms. Several vitamins and minerals have been shown to be important in the prevention of osteoporosis but their efficacy when used in combination remains to be determined.

Herbal Therapies

- **BLACK COHOSH (*Cimicifuga racemosa*)**
    - EFFICACY: Adult, possibly effective
    - DOCUMENTATION: Adult, fair
    - DOSE: Menopause, tablet, oral: 1 to 2 milligrams daily of 27-deoxyacteine (Murray & Pizzorno, 1998).
        - Menopause, powdered rhizome: 40 to 200 milligrams daily (Bradley, 1992).
        - Menopause, tincture (1:10 preparation in 60% alcohol): 0.4 to 2 milliliters daily (Bradley, 1992).
        - Menopause, fluid extract (1:1 preparation): 3 to 4 milliliters twice daily (Murray & Pizzorno, 1998).
        - Menopause, solid (dry powdered) extract (4:1 preparation): 250 to 500 milligrams daily (Murray & Pizzorno, 1998).
        - The dosage of black cohosh extract used in the majority of clinical studies has been based upon the level of a key marker, 27-deoxyacteine, at a dosage of 1 or 2 milligrams twice daily (Murray & Pizzorno, 1998).
        - For alcohol-based extracts, 40% to 60% (v/v), dosage should correspond to 40 mg of black cohosh (Blumenthal, 1998).
    - PRECAUTIONS: Although research is lacking, the hormonal effects of black cohosh may, in theory, produce undesirable or unpredictable effects in the face of hormone dependent tumors. Therefore, in these clinical situations caution is advised until research is available.
    - ADVERSE EFFECTS: Large doses of Black Cohosh may produce dizziness, headache, tremors, or giddiness (McGuffin et al, 1997; Tyler et al, 1988; Duke, 1985; Osol & Farrar, 1953). Large doses may cause nausea and vomiting. Mild and transient gastrointestinal complaints have also been reported (Stolze, 1982; Vorberg, 1984). There is a case report of a 45-year-old woman admitted to the emergency room after having her third nocturnal seizure within 3 months. The woman had no history of seizures but she reported taking preparations of Black Cohosh, chaste tree, and evening primrose oil for 4 months. The patient also reported having a beer or two within 48 hours of each seizure. No definitive conclusion can be drawn from this information but one or all of the herbal medicines may have played a role in seizure development (Shuster, 1997; Shuster,

1996). Hypotension, bradycardia, and vasodilation have been reported in animal studies (Tyler et al, 1988; Corsano et al, 1969; Genazzani & Sorrentino, 1962).

- INTERACTIONS: Although research is lacking, the hormonal effects of black cohosh may, in theory, interfere with antihormonal agents such as tamoxifen.
- REGULATORY/SAFETY INFORMATION: Approved for use by the German Commission E in the treatment of premenstrual syndrome (PMS), dysmenorrhea, and menopausal symptoms. The Commission E recommends its use be limited to 6 months, no other warning or contraindications (Blumenthal et al, 1998). The American Herbal Products Association rated Black Cohosh as Class 2b (not for use during pregnancy) and 2c (not to be used while nursing) (McGuffin et al, 1997). Black Cohosh is unregulated and available in the United States as a dietary supplement under the Dietary Supplement Health and Education Act of 1994 (DSHEA).
- COMPARATIVE EFFICACY: A standardized black cohosh product has been shown to be as effective as conjugated estrogens in alleviating menopausal symptoms (Lehmann-Willenbrock & Riedel, 1988; Stoll, 1987).
- LITERATURE REPORTS: Several small, double-blind and open trials support the use of Black Cohosh for the relief of menopausal symptoms including hot flashes, vaginal thinning and drying, night sweats, sleep disturbances, anxiety, and depression (Duker et al, 1991; Lieberman, 1998; Liske & Wustenberg, 1998).

- **DONG QUAI (*Angelica sinensis* (Oliv.) Diels)**
  - EFFICACY: Adult, ineffective
  - DOCUMENTATION: Adult, fair
  - DOSE: General gynecological conditions, root: 8 to 15 grams/day (Tyler, 1994).
    - Combine 100 grams (g) of dong quai with Chuanxiong Rhizoma Ligustici Chuanxiong (100 g), peony root (100 g), and Rehmannia root (100 g). Grind the mixture until a powder is formed and boil for 10 minutes in water with 15 milliliters of red wine. The dose is 9 g (3 g of dong quai) two to three times daily (Zhu, 1987).
    - Extract/Root Conversion: A 1 gram dose of 100% dong quai extract is approximately equivalent to 4 grams of raw dong quai root (Zhu, 1987).
  - PRECAUTIONS: Listed contraindications not documented in research (Zhu, 1987) include: Diarrhea due to weak digestion, hemorrhagic disease

hypermenorrhea, first trimester of pregnancy, spontaneous abortion, during colds or flu. Precautionary use is recommended during pregnancy (McGuffin et al, 1997).

- ADVERSE EFFECTS: Prothrombin times (PT) were significantly (p less than 0.0001) longer in a group receiving intravenous (IV) Radix Angelicae Sinensis (RAS) solution compared to an IV placebo (Junjie & Huaijun, 1984). The furocoumarins (psoralen and bergapten) found in dong quai are known to produce photodermatitis (Tyler, 1982). Cases of dong quai-induced photodermatitis were not found. Furocoumarins are photocarcinogenic. Safrole, found in the volatile oil, is a potential carcinogen. No specific cases of carcinogenesis due to dong quai were found (Anon, 1997).

- INTERACTIONS: Case reports suggests dong quai (or RAS (Radix Angelicae Sinensis)) may enhance the anticoagulant effect of warfarin (Page & Lawrence, 1999).

- REGULATORY/SAFETY INFORMATION: No German Commission E monograph has been published (Blumenthal et al, 1998). American Herbal Products Association rated dong quai as a Class 2b herb (not to be used in pregnancy unless directed to do so by an expert trained to use the herb). Canadian regulations require bilingual label warnings against use during pregnancy and do not allow it as a non-medicinal ingredient in oral use products (McGuffin et al, 1997). Angelica root oil is approved by the FDA as a food additive. The council of Europe includes Angelica root in the list of substances, spices and seasonings deemed admissible for use (Opdyke, 1975). Dong Quai is available as a dietary supplement in the United States under the Dietary Supplement Health and Education Act of 1994 (DSHEA).

- COMPARATIVE EFFICACY: Not available.

- LITERATURE REPORTS: No statistically significant estrogenic effects were observed in a group of 71 postmenopausal women who took either placebo (maltodextrin) or dong quai (4.5 grams/day). Subjective evaluation by the women determined it was no better than placebo (Hirata et al, 1997).

  Possible estrogenic effects on vaginal cells and endometrium thickness were investigated. No differences in endometrial thickness, vaginal maturation index, number of vasomotor flushes, or Kupperman index scores were detected. The women all had hot flashes and a follicle-stimulating hormone level greater than 30 milliunits/milliliter. Transvaginal ultrasonography was used to measure endometrial thickness and vaginal maturation was done on vaginal cells. The potency of the dong quai used was 1 gram of an aqueous extract combined with filler equal to one gram of root material. Subjects were seen at 6, 12, and 24

weeks after therapy was initiated. There was 75% compliance with the study protocol.

Rats fed 5% dong quai in their diet for 30 days did not have changes in ovarian tissue or nucleic acid content of the smooth muscle and endometrium of the uterus but did have increased glucose utilization and DNA synthesis. This may indicate a more functional uterus (Zhu, 1987).

- **FLAXSEED (*Linum usitatissimum* L.)**
    - EFFICACY: Adult, possibly effective for cardiovascular disease prevention
    - DOCUMENTATION: Adult, fair
    - DOSE: 25 grams flaxseed meal daily (Arjmandi et al, 1998) or 60 milliliters of flaxseed oil daily (Cunnane et al, 1995).
    - PRECAUTIONS: Contraindicated in patients with ileus (intestinal obstruction)(Blumenthal et al, 1998) or thyroid insufficiency (McGuffin et al, 1997). No support is given for this possible contraindication. Do not exceed 0.3 milligram/kilogram as linseed (flaxseed) can accumulate cadmium (Bisset & Wichtl, 1994). Flaxseed must be preswollen before use in inflammatory bowel conditions (Bisset & Wichtl, 1994).
    - ADVERSE EFFECTS: Stroke-prone rats fed rapeseed oil-supplemented diets developed severe proteinuria, accelerating renal injury (Miyazaki et al, 2000).
    - INTERACTIONS: Absorption of other drugs may be impaired because of mucilage and cellulose in flaxseed (Blumenthal et al, 1998).
    - REGULATORY/SAFETY INFORMATION: Flaxseed is approved by the German Commission E for the treatment of chronic constipation, colons damaged by abuse of laxatives, irritable colon, and diverticulitis. It is also approved as mucilage for gastritis and enteritis. Externally, it is approved as cataplasm for local inflammation (Blumenthal et al, 2000; Blumenthal et al, 1998). The American Herbal Products Association rated flaxseed as class 2d (take with at least 150 milliliters (6 ounces) liquid (McGuffin et al, 1997). Flaxseed is available as a dietary supplement in the United States under the Dietary Supplement Health and Education Act of 1994 (DSHEA).
    - COMPARATIVE EFFICACY: Not available.
    - LITERATURE REPORTS: Fifteen grams of flaxseed daily had beneficial effects on blood lipids. Platelet aggregation, measured in vitro with collagen,

demonstrated no significant changes with the use of thrombin and with or without supplementation. Adenosine triphosphate (ATP) release decreased significantly during the supplementation period (p less than 0.05) and increased significantly (p less than 0.01) by the end of the washout period (Bierenbaum et al, 1993).

Serum lipids (triglycerides, total cholesterol, and low-density lipoprotein (LDL)) were lowered approximately equivalently in groups whose diets were supplemented for two weeks with either flaxseed oil or cold-water fish; total cholesterol and LDL cholesterol decreased in a third group receiving supplementary sunflower oil. In this study healthy volunteers (n=47), men with mild essential hypertension (n=36), and patients with primary hyperlipoproteinemia (n=37) received dietary supplements of sunflower oil (60 milliliters (mL), equivalent to 45 mL/day of linoleic acid (LA)), flaxseed oil (60 mL, equivalent to 38 mL per day of alpha-linolenic acid (ALA)), or mackerel (130 grams of fish flesh in 70 grams of tomato pulp). Blood measures were taken after an overnight fast at baseline, 2 weeks of diet, and 3 months after diet end. In those receiving ALA, EPA levels rose slightly in cholesterol esters while remaining unchanged in serum triglycerides. Despite the relative lack of prostaglandin precursors, serum lipids in hypertensive patients receiving ALA showed significant decreases in triglycerides and LDL cholesterol (p less than 0.01) and in total cholesterol (p less than 0.05), similar to serum lipid decreases recorded in hypertensive patients receiving fish (Singer et al, 1986).

Plasma total and LDL cholesterol levels declined significantly (p less than 0.05) compared to baseline in one double-blind, crossover study. Five male and five female healthy volunteers were randomized to eat two muffins containing either 25 grams flaxseed meal or similar muffins with additional wheat flour substituted for flax (control muffins) daily for four weeks. After four weeks, there was a two-week washout period and the groups crossed over for four more weeks. Mean age of participants was 25 years. Though total and LDL cholesterol levels were significantly lower (p less than 0.05) after two weeks of flaxseed consumption compared to controls, by four weeks the difference was no longer significant. The comparison compared to baseline remained significant during flax consumption but was never significantly different during control periods. HDL cholesterol and triglyceride levels were not affected. This study also found no effect of flaxseed on glucose tolerance or lipid peroxidation compared to controls. During flax consumption the number of bowel movements increased significantly (p less than 0.05) compared to controls (Cunnane et al, 1995).

Flaxseed reduced serum LDL cholesterol levels significantly (p less than 0.02) compared to sunflower seeds in a double-blind, cross-over trial. Both treatments lowered total cholesterol levels compared to baseline but there was no difference between the two; flaxseed alone reduced lipoprotein(a) levels compared to

baseline but the difference from sunflower seeds was not significant. The study included 38 hypercholesterolemic (greater than 5.85 mmol/L serum total cholesterol) women with a mean age of 56 years. They were randomized to eat 38 grams flaxseed or sunflower seed baked into muffins and bread daily for six weeks. Following a two-week washout period, the groups crossed over for an additional six weeks. During the washout all values returned to baseline. High-density lipoprotein cholesterol and triglyceride levels were unaffected by treatment. No weight gain was observed during the study despite an overall increase in caloric intake. Serum estradiol and follicle-stimulating hormone levels were also unaffected (Arjmandi et al, 1998).

- **GINKGO (*Ginkgo biloba* L.)**
    - EFFICACY: Adult, possibly effective for cerebral insufficiency
    - DOCUMENTATION: Adult, fair
    - DOSE: General use, extract (standardized to contain 24% Ginkgo flavonglycosides and 6% terpene lactones), oral: 40 to 80 milligrams three times daily (van Beek et al, 1998; Kleijnen & Knipschild, 1992; DeFeudis, 1991).
    - PRECAUTIONS: The use of ginkgo with aspirin, ticlopidine, other antiplatelet drugs or anticoagulants is a relative contraindication due to the increased potential for bleeding (Kim et al, 1998). Ginkgo may potentiate pharmaceutical monoamine oxidase inhibitors (MAOI) (McGuffin et al, 1997).
    - ADVERSE EFFECTS: Bilateral subdural hematomas were found in a 33-year-old Korean woman who was chronically self-treating with ginkgo extract 120 milligrams daily for two years (Rowin & Lewis, 1996). Subarachnoid hemorrhage occurred in a 61-year-old who was taking ginkgo extract 120 to 160 milligrams daily for 6 months (Vale, 1998). Spontaneous intracerebral hemorrhage was reported in a 72-year-old woman with a six-month history of taking ginkgo biloba 50 milligrams three times daily. Dizziness and headache have occurred with the use of ginkgo preparations (Fachinfo Roekan®, 1996; Fachinfo Tebonin®, 1996a). Seizures and coma have occurred in infants fed ginkgo seed kernels. Seizures produced 25% mortality but no sequelae after recovery. The toxin is thought to be the antipyridoxine substance 4-O-methylpyridoxine (Wada et al, 1988). Gastrointestinal upset and nausea have been reported as side effects in patients using ginkgo extract therapeutically. None of the effects were serious enough to cause discontinuation of the product (Vorberg, 1985). Tenesmus and rectal burning have been reported from eating the fruit (not the herbal product made from the leaf). Persons with allergic sensitivity may exhibit pruritus (Becker & Skipworth, 1975). Perioral erythema, swollen lips, and erythema of the buccal

mucosa, tongue, and throat have been reported after ingestion of as little as two pieces of the fruit (not the herbal leaf extract) (Becker & Skipworth, 1975). Vesicular, pruritic lesions, and swollen eyelids were seen in 3 cases of contact dermatitis caused by gathering the fruit. Symptoms usually occurred within 1 to 4 days after an exposure (Tomb et al, 1988).

- INTERACTIONS: The use of ginkgo with aspirin, ticlopidine, other antiplatelet drugs or anticoagulants is a relative contraindication due to the increased potential for bleeding (Kim et al, 1998). Ginkgo may potentiate pharmaceutical MAO-inhibitors (McGuffin et al, 1997). Ginkgo counters the sexual dysfunction often experienced with the selective serotonin reuptake inhibitors (Cohen & Bartlik, 1998).

- REGULATORY/SAFETY INFORMATION: Ginkgo is approved by the German Commission E for treatment of dementia, peripheral arterial disease, and vertigo and tinnitus (Blumenthal et al, 1998). The American Herbal Products Association rated ginkgo leaf class 2d (may potentiate MAO-inhibitors) and ginkgo seed class 2d (do not exceed recommended dose; not for long-term use) (McGuffin et al, 1997). Ginkgo is rated as Pregnancy Risk Factor C (Anon, 2000). Ginkgo is available as a dietary supplement in the United States under the Dietary Supplement Health and Education Act of 1994 (DSHEA).

- COMPARATIVE EFFICACY: Not available.

- LITERATURE REPORTS: Significant subjective improvement in symptoms of cerebral insufficiency has been reported compared with placebo in several studies. Due to the subjectivity of evaluating improvement in this condition, well-designed studies are required (Kleijnen & Knipschild, 1992a).

  Ginkgo is thought to be similar in efficacy to ergoloid mesylates. Short-term memory improvement along with statistically significant regression of vertigo, headache, tinnitus, vigilance, and mood disturbance were all reported following a one-year therapy using Ginkgo 120 milligrams leaf extract/day (Vorberg, 1985).

  Kleijen and Knipschild reviewed a variety of clinical studies evaluating the use of Ginkgo. A few demonstrated an improvement of 8 of 12 symptoms (difficulties with concentration and memory, absentmindedness, confusion, lack of energy, tiredness, decreased physical performance, depression, anxiety, tinnitus, or headache) (Vorberg, 1985).

  Improvement was reported in 10 of 12 symptoms typically affecting patients with cerebral insufficiency. This was a placebo-controlled, double-blind study of 99 outpatients who received 150 milligrams/day for 12 weeks. Symptoms did not improve until the 4th week and the reported 10 of 12 symptoms evaluated did not

improve until after 12 weeks (Schmidt et al, 1991).

Seven of 11 symptoms of cerebral insufficiency improved, as well as significant difference in the syndrome short test was noted at both 6 and 12 weeks of this randomized, double-blind, placebo-controlled trial of 50 outpatients. The trial was 12 weeks long and had 3 of the placebo group and 5 of the Ginkgo group drop out (reason not specified). The syndrome short test scores for the placebo group were 6.64 at the study onset, 5.5 at 6 weeks, and 5.32 at 12 weeks. The syndrome short test scores for the Ginkgo group were 5.25 at the start, 2.4 (p less than 0.001) at 6 weeks, and 1.1 (p less than 0.001) at 12 weeks. No statistically significant difference was measured between the Ginkgo group and the placebo group when measuring the figure-correction test or the multiple-choice vocabulary test (Halama, 1991).

A marked reduction of the theta portion of the theta/alpha ratio, shortened saccade duration, reduced latency, and an increase in the number of correct answers given in the Wiener Determination Test (WDT) and the Number Connection Test (NCT) was significant versus controls in this study of patients given 120 milligrams of ginkgo extract EGb 761 for 8 weeks. Patients were given a wash-out period, then given either the extract or an identical looking placebo. Quantified EEG, saccadic eye movements, WDT, and NCT were given at the beginning and the end of the experimental treatment. If a patient had abnormal findings on 2 of the above 4 measurements, he was included in the study. The test results of the patients on placebo remained essentially unchanged (Hofferberth, 1989).

Improved memory, positive changes in the patient's subjective performance, improved attention, improved response behavior, and stabilization of time intervals for information processing were reported in a study of 90 outpatients with cerebral insufficiency caused by old age who were tested with Ginkgo extract L1 1370. This was a placebo-controlled, double-blind, multi-center study. No patients had been affected with cerebral/myocardial infarctions within the last 6 months. The changes were noted late in treatment, mostly from the 6th week onward. The average patient age was 62.7 years; the trial was run for 12 weeks and the dose was 50 milligrams of a product which had been assayed to contain 25% flavonglycosides and 6% terpenes (Vesper & Hansgen, 1994).

Ginkgo flavone glycosides showed some protective effects against induced hypoxia in healthy volunteers. The study was a randomized, placebo-controlled, double-blind, crossover, 14-day trial of 8 healthy male volunteers. Performance measurements (tests) were oculomotor (saccadic eye movements) and complex choice reaction system. Volunteers were given the extract (Tebonin(R)) at 120 milligrams daily for 14 days. Hypoxia was measured by corneal-retinal resting

potential and cardiorespiratory parameters. Subjects were made hypoxic by administration of 10.5% oxygen and 89.5% nitrogen (Schaffler & Reech, 1985).

- **PANAX GINSENG (*Panax ginseng* C.A. Mey)**
    - EFFICACY: Adult, possibly effective
    - DOCUMENTATION: Adult, poor
    - DOSE: Climacteric: 6 grams daily (Tode et al, 1999).
    - PRECAUTIONS: Ginseng or its extracts should not be used in any patient known to be allergic to it or any of its constituents. Ginseng may lower blood sugar levels, interfering with maintenance of blood glucose levels in diabetics (Sotaniemi et al, 1995). Ginseng should be used with caution in patients who are hyperactive or taking stimulants like caffeine (Baranov, 1982).
    - ADVERSE EFFECTS: Nervousness (Ryu & Chien, 1995; Bahrke & Morgan, 1994; Siegel, 1979), gastrointestinal upset or diarrhea (Siegel, 1979), insomnia (Ryu & Chien, 1995; Bahrke & Morgan, 1994; Anon, 1980a; Siegel, 1979), edema (Siegel, 1979), dizziness, (Hammond & Whitworth, 1981), headache, euphoria, vaginal bleeding, and skin eruptions (Siegel, 1979) have been reported. Ginseng was reported to cause hypertension (153/106) in one case report. Blood pressure returned to 140/85 five days after discontinuing ginseng and remained within normal limits at a 3 month follow-up (Hammond & Whitworth, 1981). Hypertension was also reported in 22 of 133 patients following ginseng use over a 2-year period. It was reported that most patients in this study were taking Panax ginseng but some were taking other forms of ginseng. Five episodes of hypotension were also reported (Siegel, 1979). Cerebral arteritis was noted in association with ginseng in a 28-year-old female (Ryu & Chien, 1995). Ginseng has been noted to have estrogenic effects (Punnonen & Lukola, 1980). A 27-year-old male manifested signs and symptoms of erosions in the mouth and urogenital mucosa, corneal ulceration, and widespread purpuric macules. He took aspirin and an unspecified antibiotic for 4 days, 3 days before taking ginseng (dose unknown). The ginseng was continued for 3 days before symptoms were detected (Dega et al, 1996).
    - INTERACTIONS: Ginseng may interact with monoamine oxidase inhibitor as (MAOI) or diabetic medications and may increase blood pressure. MAOI drugs should not be used with ginseng (Newall et al, 1996; Jones & Runikas, 1987). Ginseng caused a reduction in the International Normalization Ratio (INR) within 2 weeks in a patient on long-term anticoagulation therapy with warfarin (Janetzky & Morreale, 1997).

- REGULATORY/SAFETY INFORMATION: Ginseng is approved by the German Commission E as a tonic for fatigue, debility, and declining concentration and during convalescence (Blumenthal et al, 1998). The American Herbal Products Association rated ginseng as class 2d (contraindicated in hypertension) (McGuffin et al, 1997). Ginseng is available as a dietary supplement in the United States under the Dietary Supplement Health and Education Act of 1994 (DSHEA).

- COMPARATIVE EFFICACY: Not available.

- LITERATURE REPORTS: Use of Korean red ginseng in postmenopausal women with climacteric syndrome appeared to alleviate some symptoms including fatigue, insomnia, and depression. Postmenopausal women with climacteric syndrome (n=12) received ginseng 6 grams daily for thirty days. Postmenopausal women without climacteric syndrome (n=8) were used as controls. After 30 days, scores on the Cornell Medical Index and the State-Trait Anxiety Inventory (A-state) were significantly reduced (p less than 0.001) as compared to before treatment and were similar to scores recorded in the postmenopausal women without climacteric syndrome. The women treated had a significant decrease in cortisol and cortisol to dehydroepiandrosterone ratio (p less than 0.05). No adverse effects were noted (Tode et al, 1999).

- **RED CLOVER (*Trifolium pratense* L.)**

  - EFFICACY: Adult, inconclusive

  - DOCUMENTATION: Adult, poor

  - DOSE: A commonly used dosage is 20 to 40 mg daily (Nestel et al, 1999).

  - PRECAUTIONS: Although research is lacking, the phytoestrogenic effects of red clover may, in theory, produce undesirable or unpredictable effects in the face of hormone-dependent tumors. Therefore, in these clinical situations caution is advised until research is available. Avoid use in patients with estrogen receptor-positive neoplasia (Fetrow & Avila, 1999). Use of red clover should be avoided in patients taking hormonal medications as competition for the same hormonal receptor sites may interfere with the effect of the medication and lead to unpredictable results. Excessive intake should be avoided due to the estrogenic constituents in red clover (Newall et al, 1996). Use with caution in patients susceptible to bleeding problems or those taking anticoagulants (Fetrow & Avila, 1999).

  - ADVERSE EFFECTS: Red clover is an established aeroallergen as demonstrated

by positive flare reactions to extract skin tests in sensitive individuals (Lucas & Buckley, 1989). An isolated case of blistering and inflammation of the eyes, mouth, and penis occurred in a patient within a few days of oral ingestion of an herbal formula containing red clover (Monk, 1986). Infertility and growth disorders have been reported in grazing animals (Frohne & Pfaender, 1984). These effects have been attributed to the estrogenic isoflavone constituents, in particular to formononetin (Kelly et al, 1979). Stimulation of estrogen-receptor positive breast cancer cells by Red Clover, equal to that of estradiol, was reported in one in vitro study (Zava et al, 1998).

- INTERACTIONS: Although research is lacking, the phytoestrogenic effects of red clover may, in theory, interfere with anti-hormonal agents such as tamoxifen.

- REGULATORY/SAFETY INFORMATION: Red clover is listed by the Council of Europe as a natural source of food flavoring (category N2). This category indicates that it can be added to foodstuffs in small quantities, with a possible limitation of an active principle (as yet unspecified) in the final product (Council of Europe, 1981). No German Commission E monograph has been published. The American Herbal Products Association has assigned a Class 2b to red clover (not to be used during pregnancy unless otherwise directed by an expert qualified in the appropriate use of this substance) (McGuffin et al, 1997).

- COMPARATIVE EFFICACY: Not available.

- LITERATURE REPORTS: Red clover has been shown to contain phytoestrogenic compounds (Kelly et al, 1979; Nestel et al, 1999). Red Clover extract failed to elicit an estrogenic effect or improve menopausal symptoms in two small human studies (Wilcox et al, 1990; Eden, 1999).

- **ST. JOHN'S WORT (*Hypericum perforatum* L.)**

    - EFFICACY: Adult, possibly effective for perimenopausal mood disturbances

    - DOCUMENTATION: Adult, excellent

    - DOSE: The standard dose is 300 milligrams three times daily of a product standardized to 0.3% hypericin (Laakmann et al, 1998; Muller & Clauson, 1997).

    - PRECAUTIONS: As with prescription antidepressants, St. John's wort may precipitate mania in patients with bipolar (manic-depressive) disorder.

    - ADVERSE EFFECTS: Photosensitivity may be experienced with the use of St. John's wort (Bove, 1998; Roots, 1996). There is one case report of neuropathy associated with St. John's wort and sun exposure (Duran & Song, 1986). Other

reported side effects include restlessness (Wheatley, 1998; Vorbach et al, 1997), fatigue (Wheatley, 1998; Vorbach et al, 1997), headache (Wheatley, 1998), mild gastrointestinal effects (Wheatley, 1998; Vorbach et al, 1997), and pruritus and exanthema (Woelk et al, 1994).

- INTERACTIONS: Concurrent use of St. John's wort and cyclosporine, indinavir, and theophylline can result in subtherapeutic drug levels due to stimulation of the hepatic P-450 enzyme system (Piscitelli et al, 2000; Ruschitzka et al, 2000; Nebel et al, 1999). Concomitant use of St. John's wort and drugs metabolized by cytochrome P450 3A4 may potentially result in decreased drug concentrations and subsequent loss of drug effectiveness (Roby et al, 2000). St. John's Wort should not be combined with the SSRI class of antidepressants (which include Celexa, Paxil, Prozac, and Zoloft) as this could lead to a syndrome of dangerously high serotonin levels (Lantz et al, 1999; Gordon, 1998). An undocumented, theoretical concern is that St. John's wort should not be combined with the MAOI class of antidepressants (which include Marplan, Nardil, and Parnate) as this could lead to a hypertensive crisis (Hoelzl & Ostrowski, 1986; Suzuki et al, 1984). Given the large number of potential interactions it may be prudent to not use St. John's Wort while using any prescription medications.

- REGULATORY/SAFETY INFORMATION: St. John's wort is approved by the German Commission E positive for the internal treatment of postvegetative disturbances, depressive moods, anxiety and/or nervous unrest, and dyspeptic complaints (oily preparation only), externally (oily preparation only) for treatment and post-therapy of acute and contused injuries, myalgia, and first-degree burns (Blumenthal et al, 1998). The American Herbal Products Association rated St. John's wort class 2d (may potentiate pharmaceutical MAO-inhibitors) (McGuffin et al, 1997). St. John's wort is available as a dietary supplement in the United States under the Dietary Supplement Health and Education Act of 1994 (DSHEA).

- COMPARATIVE EFFICACY: St. John's wort appears to be equally effective as amitriptyline (Wheatley, 1997; Bergmann et al, 1993), fluoxetine (Harrer et al, 1999), imipramine (Wheatley, 1998; Vorbach et al, 1997), maprotiline (Harrer & Sommer, 1994), and sertraline (Brenner et al, 2000) in the treatment of mild to moderate depression.

- LITERATURE REPORTS: St. John's wort has been studied extensively and found to have beneficial effects in depression (Josey & Tackett, 1999; Kim et al, 1998; Ernst, 1995; Harrer & Sommer, 1994; Vorbach et al, 1994).

  St. John's wort in 3 different daily doses effectively treated the symptoms of mild to moderate depression. Two- hundred and sixty patients were evaluated using primarily the abbreviated Hamilton Depression Scale (HAMD-17) in this double-

blind, randomized trial and were randomized to receive daily doses of St. John's wort standardized to 0.17 milligram (mg) hypericin, 0.33 mg, or 1 mg hypericin content (Hyperiforce(R)). Following 2 weeks of therapy, HAMD-17 scores were reduced by 30% (from 16 to 11 points) and by 50% after 6 weeks (from 16 to 8 points). Relative efficacy was higher by 4% in the highest dose group but this difference did not reach statistical significance. After 14 days of treatment, 39% of patients were classified as responders, compared to 62% to 68% after 6 weeks; responder rates did not differ significantly between the 3 groups. Physician and patient-assessed tolerability was good for all three doses; 2% of adverse reactions reported could be causally related to St. John's wort. The investigators note that the hypericum preparation used in this trial was prepared from only the fresh shoot tips of St. John's wort and may thus be more potent on a mg-to-mg basis than preparations used in other trials (Lenoir et al, 1999).

Hyperforin 5% was more effective in treating depression than hyperforin 0.5% or placebo in a randomized, double-blind, placebo-controlled study. Patients with mild to moderate depression (n=147) were divided into three groups that received 1 tablet three times daily of a placebo, 300 milligrams (mg) hypericum extract WS5573 (0.5% hyperforin), or 300 mg hypericum extract WS5572 (5% hyperforin) for 6 weeks. The Hamilton Rating Scale for Depression (HAMD) was measured at the start and days 7, 14, 28, and at the end of the study. There was no significant difference between the placebo group and treatment with WS5573 (0.5% hyperforin). Treatment with WS5572 (5% hyperforin) was superior to the placebo group (p=0.004). The study concluded the therapeutic effect is dependent on hyperiforin content (Laakmann et al, 1998).

Hypericum extracts were more effective than placebo and equally effective as standard synthetic antidepressants in a meta-analysis of 23 randomized trials with a total of 1757 outpatients with mild to moderate depression. Many of the studies were of short duration, used widely different extract preparations, and had a poorly defined patient population. The tests were done against imipramine, desipramine, diazepam, bromazepam, and maprotiline (Linde et al, 1996).

St. John's wort extracts are more effective than placebo in the treatment of mild to moderate depression according to multiple clinical controlled trials. Many of the clinical studies conducted with St. John's wort were of short duration, used widely different extract preparations, and had poorly defined patient populations. The sheer number of trials with positive outcomes must be taken into consideration and may outweigh these shortcomings. Clinical trials using St. John's wort in the treatment of seasonal affective disorder, fatigue, and to improve sleep quality and cognitive function have reported primarily positive results.

Dietary Supplements

- **DHEA**
    - EFFICACY: Adult, possibly effective
    - DOCUMENTATION: Adult, fair
    - DOSE: Systemic lupus erythematosus, oral: 200 milligrams daily (van Vollenhoven et al, 1995). Patients should use a pharmaceutical grade DHEA product to reduce the risk of contaminants. A number of products sold as DHEA only contain ground wild yam.
    - PRECAUTIONS: Contraindicated in patients who have or are at risk for breast cancer (McNeil, 1997), prostate cancer, and ovarian cancer (Skolnick, 1996). DHEA replacement therapy with the intent to obtain physiological levels found in young adults should not exceed 50 milligrams/day, unless otherwise indicated (Koo et al, 1983). Smoking significantly increases endogenous DHEA levels (Khaw, 1996). Contraindicated during pregnancy (Yen et al, 1995; Sasaki et al, 1982) and lactation (Yen et al, 1995).
    - ADVERSE EFFECTS: DHEA may stimulate the growth of prostate cancer (Jones et al, 1997). Arrhythmias (Sahelian & Borken, 1998), acne (van Vollenhoven et al, 1995; van Vollenhoven et al, 1994), hirsutism (van Vollenhoven et al, 1994), and hepatitis (Buster et al, 1992) have been reported with the use of DHEA.
    - INTERACTIONS: No human drug interaction data is available.
    - REGULATORY/SAFETY INFORMATION: DHEA is available as a dietary supplement in the United States under the Dietary Supplement Health and Education Act of 1994 (DSHEA) and also as a prescription drug.
    - COMPARATIVE EFFICACY: No studies available.
    - LITERATURE REPORTS: The effect of 12-month dehydroepiandrosterone (DHEA) replacement therapy was evaluated in fourteen 60- to 70-yr-old women who received daily applications of a 10% DHEA cream. Vaginal epithelium maturation was stimulated by DHEA administration in 8 of 10 women who had a maturation value of zero at the onset of therapy, whereas a stimulatory effect was also seen in all three women who had an intermediate vaginal maturation index before therapy. The estrogenic effect of DHEA observed in the vagina was not observed in the endometrium, which remained atrophic in all women. The bone mineral density significantly increased at the hip from 0.744 +/- 0.021 to 0.759 +/- 0.025 g/cm2 after 12 months of treatment (p less than 0.05). These changes in bone mineral density were associated with a significant 20% decrease (p less than 0.01) in plasma bone alkaline phosphatase and a 28% decrease in the urinary

hydroxyproline/creatinine ratio. A 2.1-fold increase over the control value (p less than 0.01) in plasma osteocalcin was concomitantly observed. The data describe for the first time a series of medically important beneficial effects of DHEA therapy in postmenopausal women through transformation of the precursor steroid DHEA into androgens and/or estrogens in specific peripheral intracrine tissues without significant adverse effects. The stimulatory effect on the vaginal epithelium in the absence of stimulation of the endometrium is of particular interest because it eliminates the need for progestin replacement therapy. On the other hand, the stimulatory effect on bone mineral density accompanied by an increase in serum osteocalcin, a marker of bone formation, suggests stimulation of bone formation by the androgenic action of DHEA, a finding of particular interest for both the prevention and treatment of osteoporosis.

Twenty-two post-menopausal women were divided into three groups. Group 1 (n=8) was treated with 50 milligrams (mg) DHEA-S daily. Group 2 (n=8) received DHEA-S 50 mg and a 50-microgram estradiol patch. Group 3 (n=6) received 50 micrograms estradiol daily. At the start and after 3 months of treatment, a Kupperman score and multiple hormone levels were evaluated. Both groups receiving DHEA-S experienced significant increases in mean basal serum DHEA, DHEAS, androstenedione, and testosterone, while no change was seen in those receiving estradiol alone. Kupperman scores were similar and progressively improving for all treatments (Stomati et al, 1999).

- **IPRIFLAVONE**
    - EFFICACY: Adult, possibly effective for postmenopausal osteoporosis
    - DOCUMENTATION: Adult, good
    - DOSE: 200 milligrams (mg) three times daily (Agnusdei et al, 1992).
    - PRECAUTIONS: Renal insufficiency (creatinine clearance less than 40 milliliter/minute) (Rondelli et al, 1991).
    - ADVERSE EFFECTS: The only significant adverse effects of oral ipriflavone in studies to date have been gastrointestinal (GI) in nature, including epigastric pain or "burning" and diarrhea (Agnusdei et al, 1989).
    - INTERACTIONS: Elevated serum theophylline concentrations were seen in a 65-year-old patient who was concurrently taking ipriflavone (Takahashi et al, 1992). The bioavailability of ipriflavone may be enhanced when given with food (Shino, 1985).

- REGULATORY/SAFETY INFORMATION: Ipriflavone is unregulated in the United States and is available as a dietary supplement under the Dietary Supplement Health and Education Act (DSHEA). Ipriflavone is commercially available in Japan for the treatment of bone loss (Hyodo et al, 1991).

- COMPARATIVE EFFICACY: Oral ipriflavone 600 mg/day was as effective as salmon calcitonin nasal spray 200 International Units (IU)/day in relieving bone pain in 15 patients with senile osteoporosis. The study was randomized and double-blind and treatment was evaluated for 28 days. Both treatments were well-tolerated (Scali et al, 1991). Ipriflavone was more effective in increasing bone mineral density (BMD) than salmon calcitonin. Forty postmenopausal, osteoporotic patients with a BMD more than 2 standard deviations below the mean value for healthy age matched controls participated in this open, randomized, parallel group trial. Patients received either ipriflavone 200 mg three times daily by mouth (Osteofix(R)) or salmon calcitonin 100 IU daily intranasally for 12 months. Ipriflavone administration resulted in a significantly greater increase in BMD after 6 and 12 months compared to calcitonin (4.3% versus 1.9%; p less than 0.001) and at 12 months a significant difference in urinary calcium and hydroxyproline/creatinine excretion (p less than 0.05). Gastralgia was reported by 4 ipriflavone patients. Pruritus was reported in 2 and epistaxis in 1 patient(s) from the calcitonin group (Cecchettin et al, 1995). When the effects of KCA-098 and ipriflavone were compared in animal models, KCA-098 was a stronger inhibitor of artificially stimulated bone resorption than ipriflavone. Effective concentrations for ipriflavone were 10 to 100 times higher than those of KCA-098 (Tsutsumi et al, 1994).

- LITERATURE REPORTS: Ipriflavone prevented rapid bone loss in a 2-year placebo-controlled study of 56 postmenopausal women with low bone mineral density (BMD) and at least two risk factors for osteoporosis (smoking, low calcium intake, sedentary lifestyle). Patients were randomized to receive placebo or ipriflavone 200 milligrams (mg) three times daily with meals. All patients received concomitant calcium supplementation of 1000 mg daily (Gennari et al, 1998). In limited controlled studies involving patients with established postmenopausal osteoporosis, oral ipriflavone 600 mg daily for up to one year (plus calcium supplementation 1 gram/day) has been associated with conservation or slight increases of bone mineral density (distal radius, lumbar spine, femoral shaft) (Agnusdei et al, 1992). Ipriflavone decreased bone remodeling and prevented rapid bone loss following ovariectomy. Thirty-two evaluable patients were followed for 1 year after receiving calcium (CA) 500 mg daily or CA 500 mg/day plus ipriflavone (IP) 600 mg daily starting 10 to 30 days after surgery (Gambacciani et al, 1993).

- **NATURAL PROGESTERONE**
    - EFFICACY: Adult, possibly effective
    - DOCUMENTATION: Adult, good
    - DOSE: Perimenopause, capsule: 100 to 300 milligrams daily (Balasch et al, 1996; Chen et al, 1998; Freeman et al, 1995).
    - PRECAUTIONS: Use is contraindicated in the following conditions: carcinoma of the breast or genital organs, known or suspected (Prod Info Crinone (R), 2000); diagnostic test for pregnancy (Prod Info Prometrium (R), 2000); liver dysfunction or disease (Prod Info Crinone (R), 2000); missed abortion (Prod Info Crinone (R), 2000), peanut allergy (Prometrium(R) capsules contain peanut oil) (Prod Info Prometrium (R), 2000); pregnancy or suspected pregnancy (Prod Info Prometrium (R), 2000); thrombophlebitis, thromboembolic disorders, cerebral apoplexy, or past history of these disorders (Prod Info Prometrium (R), 2000); undiagnosed vaginal bleeding (Prod Info Crinone (R), 2000). Before treatment conduct a pelvic exam, breast examination, and Pap smear (Prod Info Prometrium (R), 2000). The use of progesterone may complicate epilepsy, migraine, asthma, cardiac dysfunction, or renal dysfunction (Prod Info Prometrium (R), 2000). Use with caution in patients with a history of psychic depression (Prod Info Crinone (R), 2000; Prod Info Prometrium (R), 2000). Glucose tolerance may be impaired (Prod Info Crinone (R), 2000; Prod Info Prometrium (R), 2000). Progesterone use may mask the onset of the climacteric (Prod Info Crinone (R), 2000; Prod Info Prometrium (R), 2000). Pathologists should be advised of therapy when specimens are submitted (Prod Info Crinone (R), 2000)
    - ADVERSE EFFECTS: Progesterone may cause edema (Prod Info Prometrium(R), 2000). Progesterone may cause fatigue, sleepiness, or sedation (Freeman et al, 1995; Frishman et al, 1995). Progesterone therapy has been associated with abdominal pain, abdominal distention, constipation, nausea, vomiting, and diarrhea (Prod Info Prometrium(R), 2000; Prod Info Crinone(R), 2000). Oral progesterone has been associated with a 5% incidence in upper respiratory tract infections (Prod Info Prometrium(R), 2000; Prod Info Crinone(R), 2000).
    - INTERACTIONS: Concurrent oral administration of progesterone capsules and conjugated estrogens to 29 postmenopausal women over a 12-day period resulted in an increase in the total estrone and total equilin concentrations (Prod Info Prometrium(R), 1999). Increased doxorubicin-induced neutropenia and thrombocytopenia have been observed when intravenous progesterone (up to 10 grams over 24 hours) was administered concurrently with intravenous doxorubicin (60 milligrams per meter squared bolus) to patients with advanced malignancies (Prod Info Adriamycin RDF(R), 1999). Ketoconazole, an inhibitor

of cytochrome P450 3A4 enzymes, was shown to inhibit the metabolism of progesterone in vitro, which may result in an increase in the bioavailability of progesterone. The clinical significance of this interaction is unknown (Prod Info Prometrium(R), 1999). The bioavailability of progesterone 200 milligrams (mg) capsules was increased by the concomitant ingestion of food relative to a fasting state in postmenopausal women. However, it is recommended that progesterone be administered in the evening (Prod Info Prometrium(R), 1999). Use of progesterone can result in false elevations of digoxin as measured by the Abbott TDx method (Soldin et al, 1984). The metyrapone test may be altered by progesterone (Prod Info Prometrium(R), 1999).

- REGULATORY/SAFETY INFORMATION: Micronized progesterone was approved by the United States Food and Drug Administration for use in secondary amenorrhea and hormone replacement therapy in 1998 (Wetzel, 1999). Progesterone cream is available without a prescription in the United States as a dietary supplement under the Dietary Supplement Health and Education Act of 1994 (DSHEA). Oral micronized progesterone is available by prescription at compounding pharmacies.

- COMPARATIVE EFFICACY: NET decreased estradiol, FSH, HDL cholesterol, and triglyceride levels compared to progesterone therapy which produced no changes (Saarikoski et al, 1990).

- LITERATURE REPORTS: Estrogen had a positive effect on lipoprotein metabolism that was blunted by both progesterone (micronized) and medroxyprogesterone acetate in a prospective clinical study of 123 postmenopausal women. Study participants had been amenorrheic for one year or more without evidence of gynecologic disorders, had not been treated with estrogen for at least 3 months prior to the study, and had no contraindications to hormone replacement therapy. Women with a history of bleeding from undiagnosed cause, oncotic colpocytology, possible malignant breast disease or estrogen-dependent tumors, alcoholism, liver and kidney disorders, endometrial hyperplasia or severe hypertension were excluded from the study. Group 1 (41 women, post-hysterectomy) received conjugated estrogens 0.625 milligrams (mg) daily, group 2 (43 women) received conjugated estrogens 0.625 mg daily with medroxyprogesterone acetate (MPA) 5 mg daily for 25 days per month, and group 3 (39 women) received conjugated estrogens 0.625 mg daily with progesterone (micronized) 100 mg daily for 25 days per month. Total cholesterol, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), very low density lipoprotein cholesterol (VLDL-C), total cholesterol/HDL-C ratio, LDL/HDL ratio and triglyceride levels were measured before the study and after 6 months. Unopposed estrogen increased HDL-C by 14.4% (p less than 0.05 compared to initial values), estrogen combined with MPA or progesterone nonsignificantly increased HDL values. Unopposed estrogen and MPA both

decreased LDL concentrations significantly (6.6 and 9% respectively, p less than 0.05) while progesterone did not significantly change LDL values. Total cholesterol levels were decreased on MPA (5%, p less than 0.05) but were not changed by unopposed estrogen or progesterone. Triglyceride levels increased significantly in group 3 (21%, p less than 0.05). Blood fat ratios were significantly decreased by unopposed estrogen and MPA, and were decreased by progesterone but without statistical significance. The authors concluded that estrogen replacement therapy has a beneficial effect on lipid profiles in postmenopausal women, an effect that is diminished but not eliminated by the addition of progesterone. The authors suggested that it is not necessary to use the more expensive progesterone in combined hormone replacement therapy as MPA had an equal or better effect on lipid profiles (Chen et al, 1998).

Daily vaginal administration of micronized progesterone for 10 days achieved useful blood levels of progesterone and induced clear secretory changes in the endometrium. Nine menopausal women self-administered progesterone (100 milligrams micronized progesterone, 200 milligrams benzyl alcohol and ethyloleate to a volume of 2 milliliters) in the morning. They then received 0.1 milligrams per day of Estraderm(R). Progesterone was administered daily on the last 10 days of estrogen treatment. At the first and second progesterone administrations, blood samples were taken and progesterone levels determined. At the end of treatment, endometrial samples were taken and assessed microscopically. Progesterone levels increased rapidly and were significantly higher than baseline 15 minutes after administration (p less than 0.0005), decreased starting 4 hours later, and returned to normal within 24 hours. In the second administration, progesterone levels remained significantly higher than baseline at 24 hours (p less than 0.0003). The endometrial samples showed a secretory pattern corresponding to postovulation days 4 to 7. No systemic side effects were noted although 5 of the volunteers reported a mild vaginal burning sensation that quickly resolved. The authors suggest that this type of daily progesterone administration may be useful in postmenopausal hormone replacement therapy (Cicinelli et al, 1996).

Vaginally administered progesterone (micronized) is preferentially distributed to the uterus, the so-called "first uterine pass effect." Twenty women undergoing transabdominal hysterectomy for uterine prolapse and/or pelvic floor repair who were in spontaneous menopause and who had not been on any type of hormone replacement therapy participated in the study. A dose of 100 milligrams of micronized progesterone, 200 milligrams of benzyl alcohol and ethyl oleate to a volume of 2 milliliters was administered as deeply as possible into the vagina 45 minutes before surgery. After laparotomy, simultaneous blood samples were drawn from the uterine and radial arteries. Progesterone levels were significantly higher in the uterine artery samples with a mean difference of 4.6

nanograms/milliliter. The authors noted that these results suggest that vaginal delivery may be preferred in cases where a target effect on the uterus is desired, as in the case of hormone replacement therapy or the treatment of endometrial abnormalities (Cicinelli et al, 1998).

Oral micronized progesterone did not attenuate the favorable effect of estradiol on endothelium-dependent vasodilation in postmenopausal women. Seventeen healthy, non-smoking postmenopausal women with mild hypercholesterolemia participated in this double-blind, crossover trial. The treatment group received 8 weeks of estradiol alone followed by estradiol in combination with 2 week cycles of progesterone (weeks 9, 10, and 13 to 14). Estradiol was administered as 0.2 milligram estradiol transdermal patch; micronized progesterone (300 milligrams daily) was administered vaginally. Vascular reactivity was evaluated during placebo treatment (week 8), during estradiol treatment (week 8), and during estradiol plus progesterone treatment (week 10). Only modest decreases in total and low-density lipoprotein cholesterol concentrations were achieved with the active treatments. The authors suggested that these results may allay fears about abrogating cardiovascular risk reduction by adding progesterone to estrogen replacement therapy (Gerhard et al, 1998).

Oral micronized progesterone induced antiproliferative changes in the human endometrium at doses lower than those required for transformation of the endometrium to a full secretory state. Twelve healthy, estrogen-primed, progestin-challenged, postmenopausal women participated in this controlled, open, parallel group pilot study. Each subject took 300 milligrams of micronized Progesterone in the morning, and half the group took a second dose in the evening. Frequent blood samples were taken and endometrial biopsies were performed on day 1 and day 14. There was minimal accumulation of progesterone with a once per day dosing and consumption of either a high fat or a high fiber diet dramatically increased absorption of progesterone. Pre-therapy endometrial biopsies showed moderate to marked proliferation of the endometrium. The endometria of the once per day group showed incomplete secretory conversion in the second biopsy while 5 of 6 showed full secretory conversion in the twice per day group. A dose-dependent response was seen in both groups, especially in glycogen increase, ribonucleic acid content decrease, and decrease of nuclear estrogen receptors in glandular epithelial and stromal cells. Eleven of the 12 volunteers reported sleepiness with the medication at some time during the study. The authors stated that sustained low concentrations of progesterone are probably sufficient to inhibit endometrial overgrowth, hyperplasia, and/or cancer but that further studies are needed to determine the lowest effective dose of progesterone to prevent endometrial overgrowth from unopposed estrogen and minimize the hypnotic and sedative effects of oral progesterone (Kim et al, 1996).

Oral estrogen combined with micronized progesterone had a favorable effect on a soluble marker of vascular inflammation, perhaps explaining the cardioprotective effect of hormone replacement therapy among healthy postmenopausal women. Soluble intracellular adhesion molecule 1 (ICAM1) may be a predictor of cardiovascular disease. Thirty-seven healthy menopausal women were randomly assigned to receive one of the following protocols: Cyclic oral estradiol valerate (2 milligrams (mg) per day or transdermal 17-beta estradiol (2.5 mg/day), both combined with micronized progesterone (200 mg/day from days 14 to 25) or no hormonal treatment for 6 months. Total serum cholesterol and low-density lipoprotein cholesterol decreased significantly in women on estradiol valerate (p less than 0.02 to 0.05) and decreased, but without significance, in women on transdermal estrogen compared to baseline values. Significant decreases in ICAM1 values were also seen in the women on estradiol valerate (p less than 0.05). The authors suggested that the results show a hepatic first pass effect of oral estrogen and that estrogen may have a cardioprotective effect by decreasing the inflammatory response that is associated with atherosclerosis (Scarabin et al, 1999).

Increased fractional catabolism of low-density lipoprotein (LDL) may be responsible for the LDL-lowering effect of continuous conjugated estrogen and micronized progesterone in postmenopausal women. Six postmenopausal women, one of whom was hypothyroid and treated with l-thyroxine, captopril, and hydrochlorothiazide, maintained a low fat diet (29% fat) and their regular exercise regimens throughout the study. The women were treated for 7 weeks with continuously administered conjugated equine estrogens (CEE; 0.625 milligrams per day (mg/day)) and micronized progesterone (200 mg/day). Prior to hormone replacement therapy and at 4 weeks, the women were injected with 131I-labeled very low-density lipoprotein (VLDL) and 125I-labeled low density lipoprotein (LDL) to assess the kinetics of VLDL and LDL apolipoprotein (apo) B turnover. The combined hormones significantly lowered plasma LDL apoB by increasing the mean catabolic rate of LDL apoB by 20% (p less than 0.03). VLDL kinetic parameters were unchanged while plasma high density lipoprotein cholesterol levels rose significantly compared to base values (p less than 0.02). The authors concluded that combined hormone therapy reduces LDL by increasing the fractional catabolism of LDL (Wolfe et al, 2000).

- **SOY**
    - EFFICACY: Adult, possibly effective
    - DOCUMENTATION: Adult, fair
    - DOSE: Menopause: 200 milligrams soy isoflavone daily (Messina & Barnes,

1991).

- PRECAUTIONS: Contraindicated in known hypersensitivity or history of allergic reactions to soy or any of its components.

- ADVERSE EFFECTS: A prospective cohort study of 3734 Japanese-American men found that those who consumed higher amounts of tofu in midlife were significantly more likely to demonstrate poor cognitive test performance, enlargement of ventricles, and low brain weight (White et al, 2000). Lower estrogen levels and longer menstrual cycles have been reported with soy-rich diets. Dietary intervention with soy led to significant changes in the regulation of the menstrual cycle of six premenopausal women (21 to 29 years of age) with regular ovulatory cycles in a controlled study. A significant increase of follicular phase length, plasma estradiol concentrations, and cholesterol concentrations (9.6%), a significant suppression of midcycle surges of luteinizing hormone and follicle-stimulating hormone, and delayed menstruation were observed. These effects were thought to be due to nonsteroidal estrogens of the isoflavone class which are supposed to possess partial estrogen agonistic and antagonistic effects (Cassidy et al, 1994). Increased soy intake has been correlated with an increased number of hyperplastic epithelial cells in breast fluid (Finkel, 1998). Animal studies have suggested that soy proteins are diabetogenic (Virtanen & Aro, 1994). Some human studies have suggested a lower iron absorption from meals containing soy but animal studies which measured hemoglobin of rats given various low level amounts of iron in their diet have not shown any changes in absorption. The iron status of the animals did not affect iron uptake from various foods (Schricker et al, 1983). A 48-year-old woman developed contact dermatitis after applying a facial moisturizer containing maleated soybean oil. Symptoms disappeared after discontinuing use of the product (LeCoz & Lefebvre, 2000).

- INTERACTIONS: Evaluation of a case series of 22 infants with congenital hypothyroidism found that administration of soy formula increased requirements of levothyroxine by approximately 20%. Withdrawal of soy feeding required an 18% to 25% decrease in levothyroxine dosing requirements. Similar findings are expected for dietary supplements containing soy (Jabbar et al, 1997).

- REGULATORY/SAFETY INFORMATION: Soy is available as a food source and as a dietary supplement in the United States under the Dietary Supplement Health and Education Act of 1994 (DSHEA).

- COMPARATIVE EFFICACY: Not available.

- LITERATURE REPORTS:

- <u>General Estrogenic Effects</u>
  A four-week soy diet did not produce estrogenic effects in 97 postmenopausal

women given a soy diet or normal diet for 4 weeks. Changes in urinary isoflavone concentrations were measured. Measures of estrogen response included serum follicle stimulating hormone (FSH), luteinizing hormone (LH), sex hormone binding globulin (SHBG), and vaginal cytology. No significant differences were found in any of the measures. Subjects who obtained significant increases in isoflavone concentrations did not show higher estrogenic effects than those with lower isoflavone concentrations. Body weight and endogenous estradiol concentration did not change significantly (Baird et al, 1995).

Twenty-five postmenopausal women were given 6 weeks of soya (isoflavones) and linseed (lignins) and developed maturation of vaginal epithelia cells (Wilcox et al, 1990).

The diet of Japanese women is much higher in isoflavones than that of American women. In a study of Japanese, American, and Finnish women isoflavonoids in the urine were 100 to 1000-fold greater in Japanese women than in the other two groups. The higher isoflavonoid levels in their diet may contribute to a decreased incidence of menopausal symptoms in the Japanese women (Seidl & Stewart, 1998).

Premenopausal women fed a diet containing 60 grams of soy protein per day (equivalent to about 45 milligrams of isoflavones) were noted to have reduced luteinizing and follicle-stimulating hormone levels during their mid-cycles (Wardle, 1998).

Women who increased their consumption of soy foods demonstrated an increase in the number of superficial cells that line the vagina. In a controlled trial of postmenopausal women, the women who consumed enough soy foods to provide approximately 200 milligrams of soy isoflavone demonstrated signs of estrogenic activity in comparison to a control group (Messina & Barnes, 1991).

Isoflavones were shown to alter estrogen metabolism, lowering production of genotoxic metabolites and increasing production of inactive metabolites. Eighteen postmenopausal women were given three diets for 93 days each, separated by a 25-day washout period between the diets. The three diets contained soy protein isolate in concentrations of 0.1 milligram/kilogram/day (mg/kg/d), 1 mg/kg/d, or 2 mg/kg/d (Xu et al, 2000).

Hot Flashes

Soy flour and wheat flour proved effective in reducing hot flushes in 47 postmenopausal women who were treated with supplements of either soy flour (n=23) or wheat flour (n=24) for 12 weeks in a randomized, double-blind study. The soy group had a 40% reduction and the wheat group a 25% reduction (p less

than 0.001 for both groups when compared to previous number). There was no significant difference between the two flours. The soy response usually occurred within 6 weeks which was earlier than the wheat group. Other menopausal symptoms (sweats, palpitations, headache, sleep disturbances, depression, irritability, urinary frequency, vaginitis dyspareunia, and libido loss) were measured and found to be decreased in both groups. Compliance was assured by measurement of the isoflavone daidzein. Serum follicle stimulating hormone (FSH) decreased and hydroxyproline increased statistically significantly from baseline in the wheat group only. There was no statistical difference between the two flour groups in these 2 measures. Vaginal cell maturation, plasma lipids, and urinary calcium were not significantly altered in either group (Murkies et al, 1995). Patients included in the study were without periods for at least 12 months, had more than 14 hot flushes per week, had a FSH greater than 25 milli-international units/milliliter, did not smoke, were not on antibiotics, and had no hormone therapy for the previous 3 months. Prior to the study there was a 2 week baseline period where diet and number of hot flushes were recorded. Women were evaluated versus their pre-trial behavior and no placebo effect was measured. The soy or wheat flour was allocated randomly and was to be taken raw in a beverage or cooked if that was not possible. The dose of the flours was not specified.

A double-blind, placebo-controlled, parallel, multicenter, randomized study of postmenopausal women who took either 60 grams of soy protein isolate or 60 grams of casein for 12 weeks showed a 26% reduction in hot flushes by the 3rd week, a 33% reduction by week 4 (p less than 0.001), and a 45% reduction by week 12. The casein group had a 30% reduction at the end of 12 weeks. There were 51 patients (age 48 to 61) in the soy group initially but 11 dropped out. The casein group started with 53 patients (age 45 to 62) but 14 dropped out. There was no statistical difference in the baseline measurements of the two groups. At baseline the median number of hot flushes was 11.4 flushes/24 hours for the soy group and 10.9/24 hours for the casein group. Compared to the casein (placebo) group, soy produced a 1.59 flush/24 hours reduction in moderate to severe hot flushes. The flushes/24 hour drop in the soy group was 5.01 flushes and in the control group 3.42 flushes (Albertazzi et al, 1998).

Hot flushes were reduced in frequency and severity in postmenopausal women treated with a soy isoflavone extract containing 50 milligrams of genistein and daidzein per day in a double-blind, randomized, placebo-controlled study. Subjects were randomized to receive the soy extract treatment (n=89) or placebo (n=86) daily for 12 weeks. The soy group experienced a significant decrease in hot flush severity (p=0.01) in comparison to the placebo group. The treatment group also experienced a moderately significant decrease in number of hot flushes compared with placebo (p=0.078) over the 12 week period. Both the control and

treatment groups had a significant reduction in hot flush severity and frequency in comparison to baseline values (p less than 0.05) (Upmalis et al, 2000).

A significant increase in plasma levels of sex hormone-binding globulin (from 55.8 nanomoles/liter (nmol/L) to 71.2 nmol/L, p less than 0.003) occurred after 12 weeks in 78 women fed a phytoestrogen-rich diet. Symptoms of hot flashes and vaginal dryness decreased significantly (p=0.004 and p=0.005, respectively) in the treatment group as compared with the control group (n=36). No significant difference in total menopausal symptoms was found between the two groups although the treatment group showed an improvement that did not reach statistical significance (Brzezinski et al, 1997).

Limited increases in bone density and mineralization occurred in 66 hypercholesterolemic, postmenopausal women who were given 40 grams/day of moderate to higher isoflavone containing soy protein in this 6 month, double-blind, parallel-group study. Patients ate a step 1 low fat, low cholesterol (less than 300 milligrams/day) National Cholesterol Education Program diet with either casein and nonfat dry milk (control (C)), soy proteins containing 1.39 milligrams/gram (mg/gram) of isoflavones (moderate isoflavone) (MID), or soy protein containing 2.25 mg/gram of isoflavones (high isoflavone)(HID). Subjects were not taking any medications known to alter lipid, bone, or calcium metabolism. Bone density and mineralization increased in the HID soy group in the lumbar spine only; total body density and mineralization was not altered (Potter et al, 1998).

Treatment with soy protein decreased bone loss from the lumbar spine in postmenopausal women in a randomized, double-blind trial. Participants were randomized into three treatment groups: isoflavone-rich soy (80.4 milligrams (mg) aglycone components per day, n=24), isoflavone-poor soy (4.4 mg aglycone components per day, n=24), or whey protein as a control (n=21). The isoflavone-rich group demonstrated a positive change in bone mineral density (BMD) (5.6% change, p=0.023) and bone mineral content (BMC) (10.13%, p=0.0032). Loss of BMD and BMC occurred only in the control group (-1.28% change, p=0.0041 and -1.73%, p=0.0037, respectively) (Alekel et al, 2000).

In a randomized, cross-over study of 14 premenopausal and 17 postmenopausal women, soy isoflavones showed only a small, clinically irrelevant effect on bone turnover. Subjects were assigned to three dietary groups: control (0.13 milligram/kilogram/day (mg/kg/day) isoflavones), low isoflavone (1.0 mg/kg/day), or high isoflavone (2.01 mg/kg/day) for three months. The investigators concluded that isoflavone use did not demonstrate a significant change in bone turnover and a long-term benefit is unlikely (Wangen et al, 2000).

- **VITAMIN E**
    - EFFICACY: Adult, inconclusive
    - DOCUMENTATION: Adult, poor
    - DOSE: 800 International Units (IU) orally daily (Barton et al, 1998).
    - PRECAUTIONS: Bleeding time should be monitored in patients with blood clotting disorders or those taking anticoagulant medication (Kappus & Diplock, 1992).
    - ADVERSE EFFECTS: Vitamin E had no effect on hemostasis in two studies. High doses of Vitamin E (800 IU to 900 IU daily) had no effect on bleeding time, prothrombin time, or other biochemical parameters associated with bleeding (Meydani et al, 1998; Kitagawa & Mino, 1989). Vitamin E (tocopherol) has been implicated in the development of thrombophlebitis and pulmonary embolism (Roberts, 1979; Roberts, 1981). These effects are controversial since prior literature has proposed that Vitamin E be used for the prevention of thromboembolic disease (Kanofsky & Kanofsky, 1981). A severe inflammatory response occurred in 3 patients using topical Vitamin E after chemical peel or dermabrasion of the face (Hunter & Frumkin, 1991). The Vitamin E and vitamin A in a cosmetic cream were thought responsible for eczematous lesions experienced by a 19-year-old woman (Bazzano et al, 1996).
    - INTERACTIONS: Vitamin E has been shown to enhance the response to oral anticoagulants, perhaps due to an interference with the effect of vitamin K in clotting factor synthesis (Hansten, 1981; Hansten & Horn, 1989; Anon, 1982; Corrigan & Ulfers, 1981). Concomitant administration of cholestyramine resin and fat-soluble vitamins may cause malabsorption of these vitamins (Prod Info Questran®, 1989). Although colestipol may interfere with absorption of fat-soluble vitamins, several studies have demonstrated only minor decreases in vitamin A and Vitamin E concentrations during colestipol therapy (Probstfield et al, 1985; Schlierf et al, 1985; Anon, 1980; Schwarz et al, 1980).
    - REGULATORY/SAFETY INFORMATION: United States Food and Drug Administration (FDA) Pregnancy Category A (Briggs et al, 1998). Vitamin E is available in the United States as a dietary supplement under the Dietary Supplement Health and Education Act of 1994 (DSHEA).
    - COMPARATIVE EFFICACY: Not available.
    - LITERATURE REPORTS: One randomized study of vitamin E (800 IU daily) demonstrated a marginal but statistically significant reduction in hot flashes (Barton et al, 1998).

Twenty-five percent of patients receiving vitamin E 50 to 100 milligrams daily (n=82) reported a moderate to excellent response measured by the Menopausal Index, a numerical conversion of the severity of the 11 most common menopausal symptoms. However, this response was no greater than that reported by subjects (n=298) taking placebo. Vasomotor symptoms accounted for a maximum of only one-third of the total possible score (Blatt et al, 1953).

Patients with vasomotor symptoms (n=66), most of whom were ineligible for estrogen therapy, were given an average of 30 milligrams (range 20 to 100 milligrams) vitamin E daily for an average of 31 days (range 10 days to 7 months). Good to excellent responses were reported by 31 subjects and fair responses by 16. Placebo was substituted in 17 patients, which resulted in recurrence of symptoms that remitted again when active treatment was resumed (Finkler, 1949).

Patients with vasomotor symptoms after surgical or irradiation menopause who responded to estrogens, but not to barbiturates or placebo (n=17), were given vitamin E 75 milligrams daily. Fourteen responded adequately to vitamin E and 6 attained complete relief (Rubenstein, 1948).

Complementary Therapies

Types of complementary therapies that have been widely used for menopausal symptoms include Ayurveda (a system of healing from India), homeopathy, and TCM (Traditional Chinese Medicine, including acupuncture and herbs). While anecdotal reports abound, potential interactions, safety, and the efficacy of these therapies for treatment of menopausal symptoms has not yet been adequately documented through scientific studies.

Acupuncture has helped reduce hot flashes significantly in controlled trials (Kraft & Coulon, 1999; Wyon et al, 1994).

Homeopathic medicine may support a woman's transition into menopause. If a woman is interested in using homeopathy, a referral to a qualified practitioner is recommended. Alternating sitz baths are useful to relieve uterine congestion and ease the symptoms of hot flashes.

Wellness Recommendations

Regular, weight-bearing physical exercise at least 30 minutes three or more times weekly can improve mood (Slaven & Lee, 1997), reduce hot flashes (Slaven & Lee, 1997), and help prevent osteoporosis (Burghardt, 1999; Coupland et al, 1999; Kelley, 1998), heart disease (Burghardt, 1999), and diabetes (Burghardt, 1999).

Aside from the well-known associations with heart disease, lung disease, and cancer (American Thoracic Society, 1996; Barendregt et al, 1997; Schoenbaum, 1997) smoking has an antiestrogenic effect (Spangler, 1999) in the body which can worsen menopausal symptoms and osteoporosis.

Patients should strive to maintain an ideal body weight is important (Harris et al, 1997; James, 1998; Jensen & Rogers, 1998).

Studies suggest that an active social network (Achat et al, 1998; Kouzis & Eaton, 1998; Yasuda et al, 1997), a spiritual life (Braam et al, 1997; McBride et al, 1998; McKee & Chappel, 1992), and an optimistic outlook (Robinson-Whelen et al, 1997; Scioli et al, 1997), are beneficial for the menopausal patient.

Consume a diet high in fiber (Johnson et al, 1980; Stellfeld & Helms, 1990; Wolk et al, 1999), fruits (Steinmetz et al, 1994; Steinmetz et al, 1993), whole grains and vegetables (Steinmetz et al, 1994; Steinmetz et al, 1993; Stellfeld & Helms, 1990), and low in fat. Avoiding red meat and dairy products as well as saturated oils is also important. A high-saturated fat diet can increase risk of heart disease and obesity in women of all ages, but particularly menopausal women.

Healthy essential oils from fish, raw seeds, and nuts can be extremely beneficial for menopausal women. Essential fatty acids help to relieve tissue dryness and protect the heart as well.

Decrease salt and sugar intake and avoid caffeine. Eating more soy products (tofu, tempeh, soy cheese, soy milk, soy burgers) will also help (Washburn et al, 1999). Other therapeutic foods include organic, free-range animal products, fish, apples, cherries, brown rice, oats, nuts, seeds, carrots, and yams. Excess sugar can increase anxiety, irritability and nervous tension that many women feel as they transition into menopause.

Avoid alcohol, fried foods, fatty foods, rich foods, salty foods, coffee, caffeine, sugar, white bread, refined foods, smoking, and spicy foods (if hot flashes are an issue).

A daily multivitamin (with extra amounts of antioxidants and folic acid (Carr & Frei, 1999; Stahelin, 1999; Stahl & Sies, 1997) may provide several health benefits such as improved immune function (Beharka et al, 1997), and reduced risks of heart disease (Davey et al, 1998; den Heijer et al, 1998; Ridker et al, 1999), stroke, cancer (Giovannucci et al, 1998), Alzheimer's disease (Behl, 1999; Morris et al, 1998), and cataracts (Jacques, 1999; Leske et al, 1998; Lyle et al, 1999a, Lyle et al, 1999b).

Taking 1500 milligrams daily of elemental calcium (Reid, 1996; Ullom-Minnich, 1999) along with vitamin D 400 to 800 IU daily (Bunker, 1994; Kamezawa, 1999), boron (Bunker, 1994; Nielsen, 1990; Volpe et al, 1993), magnesium (Boncimino et al, 1999; Bunker, 1994; Durlach et al, 1998; Kotkowiak, 1997), copper (Klevay, 1998), and vitamin K (Bunker, 1994; Caraballo et al, 1999; Kamezawa, 1999) can be useful in preventing osteoporosis. While the importance of these nutrients has been documented, their efficacy in the prevention of osteoporosis when used in combination remains to be determined.

Advise patients to dress in layers so they can remove as necessary as hot flashes come on. A glass of cold water or juice at the onset of a flash may also be helpful. Recommend that patients keep a thermos of ice water or an ice pack by their bed. The use of cotton sheets, lingerie and clothing will help the skin be cool at night.

To help prevent urinary tract infections, advise the patient to urinate before and after intercourse, empty her bladder regularly, drink plenty of fluids, and keep her genital area clean. Douching is not thought to be effective in preventing infection.

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