

Herbal Supplementation for Women's Health: Management of Menopause and Premenstrual Syndrome

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Disclosure Declaration

- I am an employee of Rutgers University and have served as a consultant for Merck Consumer Healthcare, Inc.
- I do not have a vested interest in or affiliation with a corporate organization offering financial support or grant monies for this CE activity.
- I do not have an affiliation with an organization that has a specific interest in the therapeutic areas under discussion.

Learning Objectives – Pharmacists

- Describe the symptoms associated with menopause and premenstrual syndrome (PMS)
- Recognize the mechanism of action behind the herbal agents most commonly utilized by patients to self-treat menopausal and PMS symptoms
- Identify safety concerns, adverse events, and drug interactions associated with herbals used to treat menopause and PMS

Learning Objectives – Technicians

- Identify symptoms associated with menopause and premenstrual syndrome (PMS)
- List herbal agents most commonly utilized by patients to self-treat menopausal and PMS symptoms
- Identify safety concerns associated with herbals used to treat menopause and PMS

Why Should Pharmacists Care About Menopause?

- By the year 2020, estimated over 50 million U.S. women will be over 51 years of age
 - Increasing population of women experiencing bothersome symptoms
 - Increasing population living longer after this mid-life transition
- Controversy surrounding the risk-benefit of hormone replacement therapy

North American Menopause Society. www.menopause.org.

Review of Menopause

- Cessation of menses
 - Marks the end of a woman's childbearing capacity
 - Hormonal changes lead to irregular menses and eventual cessation of ovulation
- Average age of menopause
 - 50-51 years of age (51.3 years average)
 - Prior to age 40 is considered premature menopause
- Defined retrospectively after 12 months of amenorrhea

Stages of Menopause

- Perimenopause
- Menopause
- Postmenopause

Perimenopause

- Estrogen and follicle-stimulating hormone levels are normal to slightly elevated
 - Irregular periods and “spotting”
 - Hormonal fluctuations cause hot flashes, night sweats, and irritability
- Can last 2-5 years

Menopausal Stage

- Variable hormone levels
 - Estrogen production by ovaries decline markedly
 - Follicle-stimulating hormone levels increase and ova become resistant to it's effects
- Cessation of menses
 - Accompanied by mood swings, headaches, and hot flashes

Postmenopausal Stage

- Complete cessation of ovulation
 - Ovaries stop production of estradiol and progesterone
 - Continue to produce testosterone

Most Common Signs and Symptoms of Menopause

- Vasomotor manifestations
 - “Hot flashes” – most common
 - Occur in 75% of women, usually starting in the perimenopausal period but can occur after menopause
 - Described as a sudden sensation of heat centered on the face/upper chest and then generalized to the rest of the body
 - Associated with perspiration, followed by chills; lasts about 4 minutes or less
- Others
 - Sleep disturbances
 - Urogenital atrophy
 - Diminished libido
 - Mood alterations and depression

Lifestyle Modifications

- | | |
|---|---|
| ■ Temperature regulation <ul style="list-style-type: none">■ Dress in layers, utilize fans and lower the thermostat, open windows, and keep hydrated | ■ Avoid certain foods <ul style="list-style-type: none">■ Hot or spicy food, alcohol, or caffeinated beverages |
| ■ Daily exercise and weight loss <ul style="list-style-type: none">■ Exercise may not help with hot flashes, but will improve bone mass | ■ Avoid smoking <ul style="list-style-type: none">■ Smokers experience menopause approx. 2 years earlier than nonsmokers |
| | ■ Acupuncture, stress management and relaxation techniques |

Current Prescription Treatments

- Estrogen/progesterone
- Estrogen pill/patch (with no uterus)
- Topical estrogen
- Gabapentin
- SSRIs/SNRIs
- Clonidine (oral/patch)
- Bioidentical hormones

Women's Health Initiative (WHI) Trial

- Study that changed the treatment of menopausal symptoms with hormone therapy
- Summary
 - 15-year study of women on estrogen/progestin or estrogen alone
 - Estrogen/progestin arm stopped early (2002) due to increased risk of heart attacks, stroke, blood clots, and breast cancer
 - Benefits found in decreased risk of colorectal cancer and hip fractures

Women's Health Initiative. www.whi.org.

North American Menopause Society 2010 Position Statement

- Recently released updated position statement post-WHI trial
- Establishes strong recommendation to use hormone therapy in younger peri/postmenopausal women
- Allow patients to take hormone therapy if CV disease risks and other contraindications are ruled out
 - Younger patients, low doses, shortest time possible

North American Menopause Society. *Menopause* 2010;17:242-255.

Herbals and Menopause

- 36% of American adults report utilizing complementary or alternative medicine
 - Women are more likely to utilize products
 - Easy access
 - Comfortable self-prescribing
 - Perceptions of safety
 - Feel symptoms don't warrant seeking medical advice
 - Lack of efficacy and safety concerns with hormonal replacement therapies

Barnes PM. Adv Data 2004;343:1-19.; Dog TL. Menopause 2007;14(3):347-349.

Herbal Supplements Used to Treat Menopause

| | |
|------------------------|---------------|
| ■ Black cohosh | ■ DHEA |
| ■ Soy isoflavones | ■ Alfalfa |
| ■ Flaxseed | ■ Chasteberry |
| ■ Red clover | ■ Flaxseed |
| ■ Dong quai | ■ Hops |
| ■ Vitamin E | ■ Kudzu |
| ■ Evening primrose oil | ■ Licorice |
| ■ Kava | ■ Wild yam |

Products That May be Effective

- Soy and soy isoflavones
- Black cohosh
- Flaxseed

Phytoestrogens

| Phytoestrogen Class | Food Source |
|---------------------|---|
| Isoflavones | Soy, chickpeas or garbanzo, red clover, lentil, beans |
| Lignans | Flaxseed, whole grains, beans, fruits, vegetables |
| Coumestans | Red clover, sunflower seeds, sprouts |

Soy Isoflavones



www.menopauserx.com; www.21food.com

Soy Isoflavones

- Mechanism of action
 - Phytoestrogen
 - Weak estrogenic activity
 - Potency has been estimated to be only 1/1,000 to 1/100,000 that of estradiol
- Dosage
 - Oral: 500-1000 mg of soy extract daily containing a minimum of 100 mg of total isoflavones per 1000 mg
- FDA approved health claim
 - 25 g/day in conjunction with a diet low in saturated fat and cholesterol reduces the risk of heart disease

Soy Isoflavones

- Difficult to reach recommended daily intake
- Tablets/capsules do not contain omega 3 fatty acids and phytosterols that food sources supply
- Tofu, soybeans, and soy flour are good sources of isoflavones
 - Contain iron, protein, fiber, and calcium
 - Dried soy beans contain approx. 200 mg soy isoflavones per 100 g soy beans

Evidence for Soy

- Clinical trial results are mixed
 - Hot flashes reduced in 45% of women consuming 60 grams of soy per day versus 30% in placebo arm
 - Contradictory results because of variety of products, doses, and length of treatments
 - Long-term safety is unknown

Albertazzi P. *Obstet Gynecol* 1998;91:6-11.

Contraindications and Safety Concerns

- | | |
|--|---|
| ■ Contraindications <ul style="list-style-type: none">■ Allergy to soy beans or soya lecithin■ Children and infants | ■ Hormone-responsive breast cancer survivors |
| ■ Pregnancy and lactation <ul style="list-style-type: none">■ Women receiving fertility treatments■ Avoid if breast-feeding | ■ May accumulate in renal failure |
| | ■ Caution in hepatic impairment |
| | ■ Drug-drug interaction <ul style="list-style-type: none">■ Reduce efficacy of warfarin |

Drug Interactions

- Drugs with estrogenic activity
 - Caution in patients taking estrogens or combination oral contraceptives
- Selective estrogen receptor modulators
 - Clomiphene, raloxifene, tamoxifen, or toremifene
- Thyroid hormone supplements
- Additive effects with red clover products

Question

- How would you describe the efficacy of using soy for hot flashes to a patient?

Black Cohosh



www.menopauserx.com

Black Cohosh

- Synonyms
 - *Actaea racemosa*
 - *Cimicifuga racemosa* – most commonly used sources in OTC agents
 - Black snakeroot
 - Bugwort
 - Macrotys
 - Rattle root
 - Rattle weed

Mechanism of Action

- Unknown
- Purported to have mild estrogenic binding effects
 - Negligible concern as a risk for causing breast cancer
 - Not recommended for women with a history of breast cancer
- Isoferulic (constituent) reported to have anti-inflammatory effects
- Salicylic acid found in small amounts
 - Anti-inflammatory and analgesic properties?

Evidence for Black Cohosh

- Clinical evidence
 - Benefit for modest symptom reduction
 - Sleep and mood disturbances
 - Hot flashes/flushes
- Supported by the American College of Obstetricians and Gynecologist guidelines for use up to 6 months

Contraindications and Safety Concerns

- Contraindications
 - Hepatotoxicity
 - Out of 155 case reports of toxicities, 30 associated with “possible” causality related to drug-induced liver damage
 - Use with caution in patients with liver disease
 - Pregnancy
 - Estrogen positive breast cancer (controversial)
 - History of cardiovascular disease (clots, stroke, etc.)
- Adverse effects
 - Gastrointestinal complaints
 - Dizziness and headache

Drug Interactions

- Hepatotoxic medications
- Blood pressure medications
- Antidiabetic medications
- Hormonal supplements or fertility treatments
 - Unknown if black cohosh potentiates estrogenic effects

Flaxseed

- *Linum usitatissimum*
- Rich source of:
 - Phytoestrogens
 - Omega-3-fatty acids, alpha-linolenic acid and fiber
- Mild improvement in menopausal symptoms
- Use caution in patients taking warfarin

Case Discussion

- PB is a 53 year old female who presents to your pharmacy
- She reports she has hot flashes and recently saw a TV commercial for *Remifemin*
- She takes no other medications and has no known drug allergies

Question #1

- Hot flashes or flushes are classified as what type of menopausal symptoms?

Question #2

- How would you counsel this woman on using black cohosh for her hot flashes?

Herbs With Questionable Safety or Efficacy

- Vitamin E

Vitamin E

- Added to many formulations with black cohosh or other herbals
- Used for antioxidant properties
- Clinical evidence
 - No study has shown decrease in vasomotor symptoms or other menopausal symptoms with vitamin E alone

Barton DL. *J Clin Oncol* 1998;16:495-500.

Side Effects and Safety Concerns

- Generally safe and well-tolerated
- Doses greater than 400 IU per day and long term use:
 - Blurred vision
 - Diarrhea
 - Dizziness
 - Headache
 - Nausea or gastrointestinal upset

Drug Interactions

- Coumarin derivatives
 - May alter vitamin K-dependent clotting factor activity
 - Increased risk of bleed when taken concomitantly with warfarin or other blood-thinning agents

Ineffective or Unsafe Herbs

- Evening primrose oil
- DHEA
- Red clover
- Wild yam
- Dong quai

Evening Primrose Oil

- *Oenothera biennis*
- Used to treat breast pain associated with menstruation, menopause and premenstrual symptoms
- Clinical evidence
 - No evidence of effect on symptoms of menopause
 - Some clinical trials have shown benefit in relieving symptoms of PMS

Red Clover

- *Trifolium pratense*
- Clinical efficacy
 - Five controlled clinical trials found no evidence in reduction of menopausal symptoms
 - Few side effects and generally well-tolerated



www.menopauserx.com

Safety Concerns and Drug Interactions

- Not recommended for women who have had breast or uterine cancer
- Caution in women taking anticoagulants
 - Coumarin constituents may increase risk of bleeding

DHEA and Wild Yam

- | | |
|---|--|
| <ul style="list-style-type: none">■ DHEA<ul style="list-style-type: none">■ “Miracle” anti-aging hormone?■ Contradictory efficacy evidence■ Not enough information to recommend routinely | <ul style="list-style-type: none">■ Wild Yam<ul style="list-style-type: none">■ The “natural” hormone■ Available as a topical cream■ Not effective for hot flashes |
|---|--|

Dong Quai

- Prepared from the root of *Angelica sinensis*
- Clinical evidence
 - Double-blind, placebo-controlled trial of 71 women treated with dong quai for 24 weeks
 - Found no benefit in menopause symptoms reduction
 - Not expected to have benefit when used as monotherapy according to principles of Chinese medicine

Hirata JD. *Fertil Steril* 1997;68:981-986.

Safety Concerns and Drug Interactions

- Carcinogenic constituents
- May cause photosensitization
- Coumarin components
 - Significant interaction with warfarin
 - Should be avoided in patients with an increased risk of bleeding
 - Avoid in patients taking concomitant medications which increase the risk of bleeding

Summary of Herbal Products for Menopause

| | Safety | Likely Safe | Possibly Safe | Insufficient Evidence | Possibly Unsafe |
|-----------------------|--------|--|---|-----------------------|-----------------|
| Efficacy | | | | | |
| Effective | | | | | |
| Likely Effective | | | | | |
| Possibly Effective | | -Flaxseed -Soy foods | -Black cohosh -Soy extracts | | |
| Insufficient Evidence | | -Chasteberry -St. John's wort -Vitamin E | -Aflato -Ginkgo -Hops -Kudzu -Licorice -Valerian | | |
| Possibly Ineffective | | -Evening primrose oil | -DHEA -Red clover -Wild yam | | -Dong quai |

www.naturaldatabase.com

Important Counseling Points

- Dietary supplements are regulated as foods, not drugs, in this country
 - Issues with manufacturing quality control
 - Supplements can interact with prescription medications and other over-the-counter products
 - Products have not undergone the same rigorous FDA review process prescription products are subject to

Important Counseling Points

- Discuss herbal treatment options with physician or healthcare provider
 - Allows for a complete treatment plan
 - Pharmacist can address issues related to drug interactions and other safety concerns
- Select USP-Dietary Supplement Verification Program approved products



www.supplementquality.com

Bioidentical Hormone Replacement Therapy (BHT)

- Misconception of “natural” hormones compared to FDA-approved ET/EPT
 - All hormones are “synthetic” and made by a chemical process
 - No official definition or standardization of bioidentical hormones
 - Created by marketing firms
- Derived from soybeans and yams
 - Advantages over animal sources?

Bioidentical Hormones

- No large randomized controlled studies to support safety compared with hormone therapy
- No regulation of compounding pharmacies for quality control
- Saliva testing
 - No evidence to show a certain level is needed to “cure” symptoms
 - Levels are used to titrate levels of hormone therapy

Patient Counseling for Bioidentical Hormones

- Patient education
 - Scared of hormone therapy due to WHI
 - FDA-approved agents supported by safety and efficacy data and held to manufacturing standards
- Some BHT make claims about anti-aging properties, increased libido, energy and well being
 - No evidence!

Case Discussion

- KS is a 49 year old female who presents to your pharmacy counter asking about “natural” treatment options for her menopausal symptoms.
- She reports she has mild hot flashes that make sleeping through the night difficult.
- She reports taking warfarin and cardizem for atrial fibrillation.

Question #1

- What possible treatments would you recommend for this patient at this time?
 - Please consider drug interactions and safety of the various herbal products available.

Question #2

- Identify important counseling points that you would want to address during your interaction with this patient.

Question #3

- Hepatotoxicity is a reported adverse effect of which of the following herbal products used in the symptomatic management of menopause:
 - a. DHEA
 - b. Soy isoflavones
 - c. Black cohosh
 - d. Dong quai

Premenstrual Syndrome Symptoms

- Decreased interest in usual activities
- Depressed mood
- Difficulty concentrating
- Feeling overwhelmed
- Insomnia or hypersomnia
- Irritability
- Lack of energy
- Marked change in appetite
- Mood swings
- Physical symptoms
 - Bloating
 - Breast tenderness
- Tension

Treating Premenstrual Syndrome

- **Step 1**
 - Supportive therapy, dietary modification, aerobic exercise, nutritional supplementation (i.e., vitamin E, calcium, magnesium), spironolactone
- **Step 2**
 - SSRIs (fluoxetine or sertraline) and anxiolytics
- **Step 3**
 - Hormonal ovulation suppression (oral contraceptives or GnRH agonists)

Natural Medicines for Premenstrual Syndrome

- **Analgesics and anti-inflammatories**
 - Evening primrose
 - Ginkgo
- **Minerals & vitamins**
 - Calcium
 - Magnesium
 - Manganese
 - Pyridoxine (vitamin B6)
 - Vitamins D and E
- **Antidepressants**
 - 5-HTP
 - L-tryptophan
 - SAMe
 - St. John's Wort
- **Hormonal agents**
 - Black cohosh
 - Chasteberry
 - Dong quai
 - Progesterone
 - Red clover
 - Soy

The Bottom Line...

- Recommend calcium 1200 mg daily
 - Benefits make take weeks-months
 - Offers protection against osteoporosis
- Other minerals and vitamins might help
 - i.e., Magnesium, vitamin E, and pyridoxine
 - Not as much evidence as there is for calcium

The Bottom Line...

- Other herbs
 - Chasteberry, ginkgo are probably safe and likely effective
 - Evidence is poor-quality to recommend routine use
 - Evening primrose oil, progesterone, black cohosh, red clover, soy or dong quai
 - Although they are probably safe, will likely **NOT** improve symptoms

Summary of Herbal Products for Premenstrual Syndrome

| Efficacy \ Safety | Likely Safe | Possibly Safe | Insufficient Evidence | Possibly Unsafe |
|-----------------------|--|--|-----------------------|-----------------|
| Effective | -Calcium | | | |
| Likely Effective | -Calcium | | | |
| Possibly Effective | -Chasteberry -Ginkgo -Magnesium -Pyridoxine -Vitamin E | | | -L-tryptophan |
| Insufficient Evidence | -Manganese -St. John's wort -SAMe -Soy -Vitamin D | -Black cohosh -Dong quai -Red clover | | -5-HTP |
| Possibly Ineffective | -Evening primrose oil -Progesterone | | | |

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