Natural Medications (Herbs, Vitamins, and Supplements) for Menopausal Symptoms

Walt Larimore, M.D.

Family Physician, Author, and Medical Journalist
Monument, Colorado

Medical Director
DiscoveryHealth.com, DiscoveryHospital.com, HealthTeacher.com

Assistant Clinical Professor of Family Medicine
University of Colorado Health Sciences Center
Department of Family Medicine
Denver, Colorado

Visiting Faculty and Clinical Instructor
In His Image Family Medicine Residency Program
Tulsa, Oklahoma

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Introduction

In the past, menopausal symptoms were not a problem for most women. Even 100 years ago, women in the U.S. only lived, on average, to about 50 years of age, while the average age of menopause was 51.

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<tr>
<td>Today the average woman will spend about 1/3 of her lifespan in menopause.</td>
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In the year 2000, 31 million women in the United States were estimated to have reached menopause, and by the year 2020, it is estimated there will be 46 million.²

A conjugated equine estrogen (Premarin) was introduced in 1942, but didn’t become popular until the late 1960s. The association between estrogen and uterine cancer was identified in the 1980s and resulted in the addition of a progestin to Premarin (Prempro).

In the early 1990s, long-term “hormone replacement therapy” (HRT – now called “hormone therapy” or “HT”) was being used by millions of women for menopausal symptoms and in the hope of preventing osteoporosis, osteoporotic fractures, cardiovascular disease, dementia, Alzheimer’s disease, and a variety of other disorders.

In 2000, when results from the huge Women’s Health Initiative (WHI) and the Heart and Estrogen/Progestin Replacement Study (HERS II) studies were published, the entire landscape of HT shifted. These studies reported estrogen/progestin increased the risk of myocardial infarction, stroke, venous thromboembolism, and breast cancer.³,⁴,⁵,⁶ Later studies added an increased risk for dementia and urinary incontinence.⁷,⁸ Still another evaluation found HT with estrogen/progestin did not improve quality of life in older postmenopausal women without menopausal symptoms.⁹

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<td>So, conventional HT is NO longer considered a drug for ALL seasons or ALL reasons. And, HT is no longer recommended for long-term disease prevention – but rather, for the short-term for control of menopausal symptoms – in the lowest dose possible.¹⁰</td>
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Most experts recommend HT not be used for more than four years.¹¹ However, vasomotor symptoms have an approximate 50% chance of recurring when therapy is discontinued, independent of age and duration of HT use.¹²

Lots of women and their physicians have abandoned HRT. As a result, many women are exploring non-pharmacological therapies fro menopause, especially “natural” health products.

In fact, even before the WHI and HERS studies, many women were using natural products to treat menopausal symptoms. In 2000, before results from the big studies were known, women spent $600
million on these products.\textsuperscript{13} Since HRT has fallen out of favor, natural approaches have become even more popular. Women who take natural products often consider them safer than other approaches.\textsuperscript{14,15}

**Menopausal Changes**

Menopause is defined as the cessation of menstrual cycles for 12 consecutive months. The age of natural menopause ranges from about 40 to 58 years. The transition phase between fertility and menopause is technically called perimenopause or the climacteric. But to many of our patients, it’s usually just called “menopause.”\textsuperscript{11}

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**Practice Pearl**

A 2005 systematic review by the Agency for Healthcare Research and Quality (AHRQ) of forty-eight studies evaluating symptoms among menopausal women concluded that vasomotor symptoms and vaginal dryness were most consistently associated with menopause. Sleep disturbance, somatic complaints, urinary complaints, sexual dysfunction, mood, and quality of life were inconsistently associated with menopause.\textsuperscript{16}

Menopausal symptoms can persist for weeks to years and the severity of symptoms can vary from woman to woman. Vasomotor symptoms (hot flashes [in up to 85% of menopausal women] and night sweats [hot flashes with drenching sweats]) and vaginal dryness are the most common menopausal complaints.\textsuperscript{11}

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**Differential Diagnosis of Hot Flashes**\textsuperscript{17,18}

<table>
<thead>
<tr>
<th>Hot Flashes Associated with Systemic Diseases</th>
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<tr>
<td>Carcinoid syndrome</td>
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<tr>
<td>Mastocytosis</td>
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<tr>
<td>Pheochromocytoma</td>
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<tr>
<td>Medullary carcinoma of the thyroid</td>
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<tr>
<td>Pancreatic islet-cell tumors</td>
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<td>Renal cell carcinoma</td>
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<tr>
<td>Neurological Flushing</td>
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<tr>
<td>Spinal cord injury</td>
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<tr>
<td>Migraine</td>
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<tr>
<td>Parkinson’s disease</td>
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<tr>
<td>Brain tumors</td>
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<td>Emotional flushing and somatic stress-related disorders (e.g., anxiety)</td>
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<th>Hot Flashes Associated with Drugs/Vitamins and Alcohol</th>
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<tr>
<td>Calcium channel blockers</td>
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<tr>
<td>Selective serotonin reuptake inhibitors (SSRIs)</td>
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<td>Cholinergic drugs</td>
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<td>Cephalosporins</td>
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<tr>
<td>Anti-estrogens (Selective estrogen receptor modulators – SERMs)</td>
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<tr>
<td>Luteinizing hormone-releasing hormone (LHRH) agonists or antagonists</td>
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<tr>
<td>Niacin</td>
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<td>aromatase inhibitors</td>
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<tr>
<th>Hot Flashes Associated with Eating and Food Additives</th>
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### Dumping syndrome
- Hot beverages
- Spicy foods
- Monosodium glutamate
- Sodium nitrate
- Sulfites

#### Some women report “triggers” that affect the frequency and/or severity of hot flashes that include:
- Alcohol
- Caffeine
- Hot or spicy foods
- Stress
- Hot drinks
- Warm environment

#### Women can also experience many other non-vasomotor symptoms.
- Vaginal dryness
- Insomnia
- Headaches
- Joint pain
- Tiredness
- Anxiety
- Irritability
- Mood swings
- Depression
- Loss of libido
- “Brain fog”
  - Difficulty with memory
  - Difficulty with concentration
  - Difficulty with decision making

### Kupperman Index
This assessment tool of climacteric symptoms, summarized in a menopausal index, is based on the most common complaints, which include:
- Hot flashes
- Sweating
- Sleep disturbances
- Nervousness
- Depression
- Fatigue
- Vertigo
- Arthralgias
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- Headache
- Tachycardia
- Vaginal dryness

The symptom findings are converted into a summary numerical figure based on severity (graded 0-3). The severity score is adjusted by multiplying by two for sweating, sleep disturbances, and nervousness, and by four for hot flashes. The highest possible score is 51.

Lifestyle Modifications

Lifestyle modification is the first step in managing menopausal symptoms. Women who are obese (with a body mass index [BMI] > 30) are more than twice as likely to experience moderate to severe hot flashes as women whose BMI < 25. Cigarette smoking also increases the frequency and severity of hot flashes.

Women who increase daily exercise, change to a healthy diet (eating fruits and vegetables, while decreasing saturated fat intake), and stop smoking can see a reduction in menopausal symptoms, an increase in their sense of well-being, and also have a lower the risk for cardiovascular disease, breast cancer, and osteoporosis.21,22

A Cochrane Review concluded, “Only one very small trial involving symptomatic women has assessed the effectiveness of exercise in the management of vasomotor menopausal symptoms. Exercise was not as effective as HRT in this trial … No conclusions regarding the effectiveness of exercise as a treatment for vasomotor menopausal symptoms could be made due to a lack of trials.”23

Paced breathing and relaxation techniques as behavioral approaches to addressing hot flashes have shown promise in several studies and were found to be safe – warranting further investigation.19

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In most women, hot flashes will abate over time without any intervention. Nevertheless, many our patients seek more rapid therapies for their symptoms and family physicians and our patients have used a wide variety of therapies.

The North American Menopause Society (NAMS) recommends, “When therapy is desired, various nonpharmacologic and pharmacologic options are available. The recommended clinical management approach includes lifestyle modification followed by nonprescription and/or prescription therapies, when needed.”24 The chart below indicates some of the most commonly used treatments:

<table>
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<tr>
<th>Commonly used treatments for menopausal symptoms25</th>
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<tbody>
<tr>
<td><strong>Hormonal</strong></td>
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<tr>
<td>Conventional Medications</td>
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<tr>
<td>estrogens</td>
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<tr>
<td>estrogen/progestin</td>
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<tr>
<td>medroxyprogesterone acetate (MPA)</td>
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<tr>
<td>depo-medroxyprogesterone acetate (DMPA – Depo-Provera)</td>
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<tr>
<td>megestrol acetate (Megace)</td>
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### Natural Products

**Unopposed Transdermal progesterone**  
**Bioidentical hormones**  
**Testosterone**  
**Phytoestrogens**  
- soy (*Glycine max*)  
- red clover (*Trifolium pratense*)  
- flaxseed (*Linum usitatissimum*)  
- chasteberry (*Vitex agnus-castus*)  
- kudzu (*Pueraria lobata*)  
- alfalfa (*Medicago sativa*)  
- hops (*Humulus lupulus*)  
- licorice (*Glycyrrhiza glabra*)

**Possible phytoestrogen-like activity**  
- Chinese ginseng (*Panax ginseng*)

**Steroid precursor**  
- dehydroepiandrosterone (DHEA)

### Centrally-acting Agents

**Conventional Medications**  
- venlafaxine at dosages of 37.5-75 mg/day (*Effexor*)  
- gabapentin (*Neurontin*)  
- clonidine (*Catapres*)  
- methylldopa (*Aldomet*)  
- SSRIs (*Prozac, Paxil*)  
  - paroxetine at dosages of 12.5-25 mg/day  
  - fluoxetine at a dose of 20 mg/day

**Natural Products**  
- valerian for sleep (*Valeriana officinalis*)  
- St. John’s wort for mild to moderate depression (*Hypericum perforatum*)  
- ginkgo for cognition (*Ginkgo biloba*)

### Natural medicines with miscellaneous or unknown activity

- black cohosh (*Actaea racemosa*)  
- dong quai (*Angelica sinensis*)  
- evening primrose (*Oenothera biennis*)  
- wild yam (*Dioscorea villosa*)  
- vitamin E  
- hesperidin with or without vitamin C  
- Ferulic acid  
- Pycnogenol (pine bark extract)

### Other therapies

- Paced breathing  
- Relaxation techniques  
- Acupuncture  
- Magnet Therapy
*Note: Many natural products are tried for menopausal symptoms, but very few have reliable evidence that they work. Inclusion in this list does NOT imply that these products are effective for menopausal symptoms.

**Hormonal Treatments (HT)**

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Conventional HT with estrogen/progestin will likely maintain a major role in treatment. It is very effective for hot flashes.\(^ {26,27}\)

Other less-used HT include megestrol acetate (*Megace*), medroxyprogesterone acetate (MPA, i.e. *Provera*), and depo medroxyprogesterone acetate (DMPA – *Depo-Provera*).

Several new estrogen formulations have come out, including plant-derived conjugated estrogens (*Cenestin, Enjuvia*). Some women think of them as being more natural, but they are only plant-derived and are actually synthesized in a laboratory to mimic the hormones contained in *Premarin*.

NAMS recommends, “Prescription progestogen alone can be used to treat hot flashes of varying severity. In clinical trials, DMPA, MPA, and megestrol acetate have demonstrated efficacy. Short-term use of these drugs seems reasonable in women without contraindications who do not wish to try estrogen but who are not opposed to trying another hormone, although progestogens have been linked to breast cancer risk in some studies.”\(^ {24}\)

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Yet, many women have been researching and using natural products to treat menopausal symptoms. And most don’t discuss this with their physician(s).

In 2000 the retail sales of natural products in the United States surpassed $15 billion\(^ {28}\) with sales of products for menopause accounting for approximately $600 million.\(^ {29}\) And, it is suspected, these numbers are increasing rapidly.

In 2006, Nedrow and colleagues reported that 42% of Americans used some kind of alternative medicine in the previous. Menopausal symptoms were one of the most common reasons for seeking these treatments.

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Seventy percent of menopausal women using them did not tell their doctors.\(^ {30}\) The *Natural Medicines Comprehensive Database* (NMCD) lists more than 40 products used for hot flashes and other menopausal symptoms.\(^ {11}\)

The reasons women use natural therapies for menopause are numerous.

- Many women refuse prescription HT for fear of breast cancer or side effects.\(^ {11}\)
- Others consider using conventional HT as the equivalent of turning a “natural process” into a “medical disorder.”
- Many who take natural products consider them safer than conventional HT.\(^ {31,32}\)
As a result, less than one in three menopausal women currently choose conventional HT.\textsuperscript{33}

**Unopposed Transdermal Progesterone**

In 1974, John Lee, a Californian general practitioner with a background in pharmacology, developed a cream containing bioidentical progesterone.\textsuperscript{34} The cream was intended to deliver 10–12 mg progesterone daily. Lee has reported that most patients using the cream experienced an improved sense of well-being.\textsuperscript{35}

On the basis of these anecdotal responses, Lee developed and promoted progesterone cream as a commercial product.\textsuperscript{35,36,37} Pharmaceutical companies in the United States, France, and Australia market these creams in health food stores and via the Internet as an alternative to synthetic forms of progesterone (progestins) and testosterone (androgen). They often claim these products build bone, increase sexual desire, prevent endometrial and breast cancer, and substitute for conventional HT. In 2004, the American College of Obstetrics and Gynecology concluded, “At this point, no formal studies have been published to substantiate the safety of these products.”\textsuperscript{38}

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A 2005 systematic review by Wren in the *Medical Journal of Australia* agreed that currently available progesterone creams cannot be recommended for treatment of symptoms associated with menopause.\textsuperscript{34} However, he pointed out “a number of double-blind RCTs” that evaluated unopposed transdermal progesterone” that “have failed to show an improvement in vasomotor, psychosexual or mood symptoms. In addition, progesterone cream has not been shown to induce a positive response in bone metabolism or lipid levels.”\textsuperscript{34}

According to Wren, “The claims for transdermal progesterone creams and the hypothesis on which they are based have been founded on anecdotal information rather than on sound scientific research.”\textsuperscript{34} He also found, “Eight studies of transdermal progesterone have been published in peer-reviewed journals. Their results are not generally supportive of the therapy.”\textsuperscript{34}

Wren concludes, “Creams containing progesterone in the doses currently available for clinical use do not fulfill the criteria necessary for them to be endorsed as a therapeutic agent to treat menopausal hormone deficiency.”\textsuperscript{34}

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The use of saliva to monitor levels of progesterone has been shown to be based on erroneous assumptions and should be abandoned as a means of managing postmenopausal women.\textsuperscript{34}

Although Wren looked at the data on progesterone-containing products, it’s important to know that many so-called “natural” progesterone creams do not contain substances that the human body can use as progesterone. These products are often derived from wild yam extracts and contain a substance, diosgenin, that only plants can metabolize into active progesterone.\textsuperscript{11}
Other such products contain these plant extracts plus chemically-synthesized progesterone, which is added to the plant extract in the cream. It is not always possible for a woman to tell exactly how much progesterone is available to her body by using these creams.

As for using transdermal progesterone with estrogen, there’s no evidence to date that progesterone creams can prevent the over-stimulation of the uterine lining by estrogen or reduce the risk of endometrial cancer. Thus, choosing to prescribe this therapy may “attract medicolegal scrutiny.”

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The bottom line according to ACOG’s Task Force Report on Hormone Therapy is, “Review of studies to date has found no evidence that treatment with (unopposed transdermal progesterone) has any significant effect on hot flashes.”

NAMS agrees, concluding, “Scientific data are lacking regarding the efficacy and safety of topical progesterone creams for relief of hot flashes. Contents and concentrations vary widely in different brands of nonprescription progesterone creams. Additionally, safety concerns regarding systemic progestogen preparations may also apply to topical progesterone preparations. Therefore, NAMS does not recommend use of progesterone creams for hot flash relief.”

Bioidentical HT
“Bioidentical hormones,” particularly estrogen and progesterone, have been promoted as safer and more effective alternatives to more traditional hormone therapies, often by people outside of the medical community.

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In fact, little or no scientific and medical evidence exists to support such claims about “bioidentical hormones.”

Additionally, many “bioidentical hormone” formulations are not subject to FDA oversight and can be inconsistent in dose and purity. As a result of unfounded but highly publicized claims, patients have received incomplete or incorrect information regarding the relative safety and efficacy of hormone preparations that are referred to as “bioidentical.”

“Bioidentical hormones” are defined as compounds that have exactly the same chemical and molecular structure as hormones that are produced in the human body. Though any hormone can be made to be “bioidentical,” the term is often used to describe formulations containing estrogens, progesterone, and androgens.

As women seek safer treatments, they often request “bioidentical hormones” from their physicians.

The terms “natural” or “bioidentical” HT are usually used to describe HT with individually compounded recipes of certain hormones – commonly estrogens, progesterone, testosterone and DHEA. Preparations are compounded into troches (tablets absorbed through the cheek), vaginal suppositories, or topical cream or gel.
“Bioidentical hormones” is a term usually used to refer to hormones that are biochemically similar or identical to those produced by the ovaries or body and are typically prepared, mixed, assembled, packaged, and labeled as a drug by a “compounding pharmacist.” These preparations can be custom made for patients according to a physician’s specifications.39

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<td>The claim that Bioidentical HT is “natural” is misleading since they are synthetically manufactured from plant substrates, and include some of the same hormones used in conventional HT (some of which are similarly manufactured from plant substrates).39</td>
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It has been claimed that users of bioidentical HT experience minimal side effects. One review concluded, “Not only is there no evidence to support or refute this claim, but it is logical to assume that patients exposed to compounded estrogens and progestins would be at risk of dose-related side effects.”39 For example, studies comparing “bioidentical” micronised progesterone with “synthetic” MPA in women using HT have failed to demonstrate any significant difference in the side effect profiles of the two hormones.41

One review by family physicians suggested, “…a woman using an estradiol-containing preparation at a dose sufficient to relieve menopausal symptoms is exposed to a similar level of risk as a woman who is using an estradiol-containing conventional hormone preparation. The risk for estriol-only preparations in humans is unknown.”39

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<tr>
<td>Patients prescribed bioidentical HT often claim that the prescribing doctor and pharmacist have failed to issue any warning regarding potential safety issues with the use of HT.39</td>
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Patients prescribed hormonal treatments should be informed about the current safety issues pertaining to all HT.

<table>
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<th>Commonly prescribed bioidentical estrogen therapies include:</th>
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<tr>
<td>1. Estriol only</td>
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<tr>
<td>2. Estradiol (20%) and estriol (80%) – Biest</td>
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<tr>
<td>3. Estradiol (10%), estriol (80%) and Estrone (10%) – Triest</td>
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Proponents of bioidentical HT claim superiority to conventional HT due to decreased risk of breast and endometrial cancers. However, there is no evidence to support this claim.39

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<tr>
<td>To date, there are no double-blind, placebo-controlled studies available to assess the efficacy and safety of bioidentical HT in the treatment of hot flashes or other menopausal symptoms.19</td>
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One review evaluated two small, short term studies that examined the effectiveness of transdermal progesterone for endometrial protection. The results were conflicting and problematic due to small sample sizes. Furthermore the absorption and pharmacokinetics of individually compounded transdermal or buccal progesterone is uncertain.\(^{19}\)

Of even more concern to practicing family physicians is this conclusion: “Combined bioidentical estrogen/progesterone preparations are not recommended. Prescribing doctors are advised that any endometrial carcinoma arising in a woman using bioidentical HT is likely to attract medicolegal scrutiny.”\(^{39}\)

A 2005 Committee Opinion of ACOG concluded, “Most compounded products, including bioidentical hormones, have not undergone rigorous clinical testing for either safety or efficacy.”

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<td>ACOG points out, “There is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progesterone regimens prepared by compounding pharmacies.”(^{42})</td>
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ACOG’s opinion also reminded clinicians, as did Wren, that salivary hormone level testing used to “tailor” HT is not meaningful because salivary hormone levels vary within each woman depending on her diet, the time of day, the specific hormone being tested, and other variables.\(^{42}\)

Also, ACOG had concerns regarding the purity, potency, and quality of compounded products. They point out that in 2001, the U.S. Food and Drug Administration (FDA) analyzed a variety of 29 product samples from 12 compounding pharmacies and found that 34% of them failed one or more standard quality tests. Additionally, 9 of the 10 failing products failed assay or potency tests, with all containing less of the active ingredient than expected. In contrast, the testing failure rate for FDA-approved drug therapies is less than 2%.\(^{42}\)

The Endocrine Society released a position statement on “Bioidentical Hormones” in October 2006, which was endorsed by NAMS\(^{43}\) and concluded: \(^{44}\)

> No medical or scientific evidence exists to support the idea that the adverse and/or beneficial effects found in the WHI resulted from the molecular structure of the synthesized hormones, nor is there any sound scientific evidence to show that a different or “customized” dose of hormones would have changed the outcome. If dosage and purity were equal, then all estrogen-containing hormone therapies, “bioidentical” or “traditional,” would be expected to carry essentially the same risks and benefits. Therefore, regardless of the source or structure of the hormone administered therapeutically, all hormone therapy regimens—even those that are so-called “customized”—must be carefully controlled.

The controversies surrounding the safety and efficacy of “bioidentical hormones” illustrate the need for further scientific and medical scrutiny of these substances. Until such studies are completed, physicians should exercise caution when prescribing “bioidentical hormones” and counsel their patients about the controversy over the use of these preparations.

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The Endocrine Society is concerned that patients are receiving potentially misleading or false information about the benefits and risks of “bioidentical hormones.” Therefore, the Society supports FDA regulation and oversight of all hormones—“bioidentical” and traditional—regardless of chemical structure or method of manufacture.\(^{44}\)

NAMS has further information for healthcare professionals\(^{45}\) and for patients\(^{46}\) on bioidentical hormones.

The FDA requires manufacturers of FDA-approved products that contain estrogen and progestogen to include a black box warning that reflects the findings of the WHI. However, compounded products, including bioidentical hormones, are not approved by the FDA and therefore, compounding pharmacies are exempt from including warnings and contraindications required by the FDA in class labeling for HT.

Given the lack of well-designed and well-conducted clinical trials of these compounded hormones, ACOG recommends that all bioidentical hormones should be considered to have the same safety issues as those hormone products that are approved by the FDA. Furthermore, bioidentical hormones may have additional risks unique to the compounding process.\(^{42}\)

**Testosterone**

A Cochrane meta-analysis on testosterone in menopause concluded, “There is evidence that adding testosterone to HT has a beneficial effect on sexual function in postmenopausal women. There was a reduction in HDL cholesterol associated with the addition of testosterone to the HT regimens. The meta-analysis combined studies using different testosterone regimens. It is, therefore, difficult to estimate the effect of testosterone on sexual function in association with any individual hormone treatment regimen.”\(^{47}\)

However, unresolved safety issues led to the FDA to reject the testosterone patch in December 2004, citing substantial concerns over cardiovascular safety and breast cancer risk.

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<tr>
<td><strong>One review concluded, “Don’t recommend testosterone products to women with menopausal symptoms.”</strong>(^{48})</td>
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In a 2005 Position Statement on testosterone therapy in postmenopausal women, NAMS concluded:\(^{39}\)

Postmenopausal women with decreased sexual desire associated with personal distress and with no other identifiable cause may be candidates for testosterone therapy.

**Testosterone treatment without concomitant estrogen therapy cannot be recommended because of a lack of evidence. When evaluating a woman for testosterone therapy, recommendations are to rule out causes not related to testosterone levels (eg, physical and psychosocial factors, medications) and to ensure that there is a physiologic cause for reduced testosterone levels (eg, bilateral oophorectomy).**
Laboratory testing of testosterone levels should be used only to monitor for supraphysiologic levels before and during therapy, not to diagnose testosterone insufficiency. Monitoring should also include subjective assessments of sexual response, desire, and satisfaction as well as evaluation for potential adverse effects.

Transdermal patches and topical gels or creams are preferred over oral products because of first-pass hepatic effects documented with oral formulations. Custom-compounded products should be used with caution because the dosing may be more inconsistent than it is with government-approved products.

Testosterone products formulated specifically for men have a risk of excessive dosing, although some clinicians use lower doses of these products in women. Testosterone therapy is contraindicated in women with breast or uterine cancer or in those with cardiovascular or liver disease. It should be administered at the lowest dose for the shortest time that meets treatment goals. Counseling regarding the potential risks and benefits should be provided before initiating therapy.

More recently, researchers from Boston’s Brigham and Women’s Hospital and Harvard Medical School analyzed data on more than 120,000 women in the Nurses’ Health Study and found the more than 800 women who had taken estrogen with testosterone – which was targeted at boosting depressed mood and sex drive and lessen bone deterioration – faced an even higher risk of breast cancer.\(^{50}\)

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<td>In the Boston study, the combination of estrogen and testosterone raised the risk of developing breast cancer by 77 percent compared to women not taking hormones. Estrogen therapy alone carried a 15 percent higher risk and estrogen combined with progesterone – taken to cut the attendant risk of ovarian cancer – carried a 58 percent higher risk.(^{51})</td>
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**Phytoestrogens**

The most commonly used group of natural products for vasomotor symptoms are phytoestrogens or “plant estrogens.” The three mains kinds are isoflavones, lignans, and coumestans. Isoflavones are the most potent and the most common in supplements. Phytoestrogens are also found in many common food sources.\(^{52}\)

<table>
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<tr>
<th>Phytoestrogen Class</th>
<th>Food Source(^{53})</th>
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<tr>
<td><strong>Isoflavones</strong></td>
<td>Soybean products (tofu, soy meal, soy grits, soy flour, soy milk) and legumes (soybeans, chickpeas or garbanzo beans, red clover, lentils, beans)</td>
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<tr>
<td><strong>Lignans</strong></td>
<td>whole grains (wheat, wheat germ, barley, hops, rye, rice, brans, oats) and fruits, veggies and seeds (apple, pear, cherry, carrot, fennel, onion, garlic, sunflower seed, flaxseed, vegetable oils [flax, olive]) with</td>
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Phytoestrogens are not structurally related to estrogen, but phytoestrogens contain a phenolic ring that allows them to bind to estrogen receptors. And, phytoestrogens are 100 to 10,000 times weaker than endogenous estrogen.11

Depending on the tissue type and location in the body phytoestrogens can act as estrogens or antiestrogens. In fact, some experts suggest that phytoestrogens have activity similar to selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene (Evista).11 For example, the estrogenic activity of soy varies with the level of endogenous estrogen. In premenopausal women with normal endogenous estrogen levels, soy phytoestrogens may have an antiestrogen effect since soy isoflavones can displace endogenous estrogen from receptors. In postmenopausal women with low endogenous estrogens, soy phytoestrogens are more likely to act as weak estrogens.11

Interest in phytoestrogens for vasomotor symptoms began when researchers noticed that only 10% of Asian women experienced hot flashes. The Asian diet contains 20 to 50 mg per day of soy protein, compared with only about 1 mg per day in the U.S. Some researchers suspect that Asian women are less likely to have hot flashes due to their high soy consumption.11

Since phytoestrogens have estrogenic effects women often wonder if phytoestrogens also increase the risk of breast cancer and have other adverse effects similar to prescription estrogen. There is a lot of debate about the potential risks associated with phytoestrogens. Research findings are conflicting.

Research has shown both protective and stimulatory effects of phytoestrogens on breast cancer. But most of this research is in Asian populations. There's not much evidence in Western women. Some evidence suggest soy intake does not reduce breast cancer risk in Western women.54

Population studies suggest that consuming phytoestrogens in the diet might decrease the risk of breast cancer. Other research suggests phytoestrogens reduce breast cancer risk in pre-menopausal women, but not post-menopausal women. However, laboratory evidence suggests that phytoestrogens can stimulate proliferation of normal human breast tissue.11

Some women also ask if phytoestrogens “unopposed” by a progestin will increase the risk of endometrial cancer just like conventional estrogens. There’s not much known about this, but there is preliminary clinical research that suggests phytoestrogens do not stimulate endometrial growth.56,57 There’s also some evidence that women in countries with a diet high in isoflavones have a lower incidence of endometrial cancer.55,58
Concentrated isoflavone-containing supplements providing 120 mg/day of isoflavones for 6 months also does not seem to stimulate endometrial thickening.\(^5^9\) But taking 150 mg/day for 5 years does seem to increase the risk of endometrial hyperplasia.\(^6^0\)

### Practice Pearl

The NMCD concludes, “Tell women that the safest bet is to stick with foods containing phytoestrogens rather than concentrated supplements.”\(^1^1\)

**Soy** (*Glycine max*) and soy isoflavones are the most commonly used phytoestrogens...and the best studied. The NMCD review concludes, “Consuming soy protein, 20 to 60 grams per day, containing 34 to 76 mg of isoflavones, seems to *modestly* decrease the frequency and severity of hot flashes in menopausal women.”\(^1^1\)

Soy extracts in tablet form, providing 35-120 mg of isoflavones daily, also seems to have beneficial effects. Soy supplements appear to be helpful in about 30% of postmenopausal women.\(^1^1\) One review concluded that isoflavone preparations seemed to be less effective than soy foods.\(^6^1\)

Soy extracts have been compared to conventional estrogens in preliminary trials. In one trial, a soy extract providing 54 mg/day of the isoflavone genistein reduced hot flashes by 22% to 29% compared to about 53% with 17beta-estradiol 1 mg daily.\(^6^2\)

Another trial suggests that a soy extract providing 60 mg of isoflavones twice daily might be comparable to conjugated estrogens (*Premarin*) 0.625 mg daily; however, conjugated estrogens work more quickly.\(^6^3\)

Obviously, more evidence is needed to accurately compare the effectiveness of soy extracts to conventional estrogens.

### Practice Pearl

Some research suggests that constituents in soy, genistein and daidzein, may stimulate existing breast tumor growth and antagonize the effects of tamoxifen.\(^6^4\) The NMCD says, “Tell women with breast cancer who take tamoxifen not to use soy.”\(^1^1\)

However, the most recent systematic review of soy was less positive. This 2005 Systematic Review evaluated twenty-five RCTs involving 2,348 participants concluded, “The available evidence suggests that phytoestrogens available as soy foods (and) soy extracts…do not improve hot flushes or other menopausal symptoms….Of the 8 soy food trials reporting hot flush frequency outcomes, 7 were negative. Of the five soy extract trials reporting hot flush frequency, three (including the two largest trials) were negative.”\(^6^5\)

According to the NMCD, “The reason for these conflicting findings is not clear. But it may be due to high placebo response rates in some trials. Patient expectations of treatments can significantly impact perceived benefits.”\(^1^1\)

Nevertheless, NAMS recommends “for women with frequent hot flashes, clinicians may consider recommending soy foods or soy isoflavone supplements. Most hot flash studies used isoflavone amounts
of 40 to 80 mg/day…Effects, if any, may take several weeks. Isoflavones exhibit a low incidence of side effects, although caution is advised when estrogenicity is a concern.”^{24,55}

ACOG concludes, “Soy and isoflavones may be helpful in the short-term (≤2 years) treatment of vasomotor symptoms.”^{40}

NAMS adds, “Soy and isoflavone intake over prolonged periods may improve lipoprotein profiles and protect against osteoporosis. Soy in foodstuffs may differ in biological activity from soy and isoflavones in supplements.”^{24} In addition, a 2007 RCT showned increased BMD with genistein in postmenopausal women.^{66}

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<td>Caution patients on warfarin to be cautious about adding soy to their diet. Soy can reduce the international normalized ratio (INR) and decrease warfarin effectiveness.^{67}</td>
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When ConsumerLab.com (an independent quality testing lab that requires a subscription to access their full test results^{68}) tested soy isoflavones in 2005, two of twelve supplements failed testing because they contained, respectively, 50% and 59% of their listed total isoflavones and were low in specific isoflavones (daidzin/daidzein and glycitin/glycitein).

A soy/red clover isoflavone product also failed because it would not break apart properly, suggesting that some of its ingredients might pass through the body unused. The other products passed the testing — they contained their key ingredients, had no contaminants, and broke apart properly for absorption.

Some women might ask about ipriflavone. It’s a synthetic soy derivative. Some research suggests that it reduces bone loss. But, unfortunately, it does not have any effect on hot flashes.^{11}

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<td>Breast cancer survivors often have significant problems with hot flashes. Although soy seems to be helpful for some with hot flashes, it doesn’t seem to be effective for women who have hot flashes related to breast cancer treatment.^{11}</td>
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Red clover (Trifolium pratense) is widely promoted and used for hot flashes. It contains isoflavones similar to soy, but red clover it not nearly as well studied as soy.

There is some evidence that it might provide modest improvement for some women^{69,70} — approximately 25-30 percent more effective than placebo for menopausal symptoms, including hot flashes.^{71}

But more recent and higher quality published evidence contradicts these older findings.^{72} As a result, a 2005 systematic review concluded, “The available evidence suggests that phytoestrogens available as…red clover extracts do not improve hot flushes or other menopausal symptoms. Red clover trials showed no improvement in hot flush frequency.”^{65}
The NMCD says, “Taking red clover extract does not seem to significantly reduce hot flashes compared to placebo. Don't recommend it.”

The extract most researched (Promensil [Novogen, Australia], a standardized product containing 40 mg isoflavones) was independently tested by ConsumerLab.com and did pass quality testing.

**Practice Pearl**

Caution patients on warfarin (Coumadin) about using red clover. Red clover contains coumarins which can have anticoagulant effects. Red clover might have additive effects with warfarin and potentially increase the risk of bleeding.

Flaxseed (*Linum usitatissimum*) is a rich source of lignan phytoestrogens, as well as omega-3 fatty acids, alpha-linolenic acid, and fiber. Some research suggests that dietary flaxseed used in place of other dietary fats might be as effective as estrogen for mild menopausal symptoms.

The NMCD says, “This is promising, but preliminary. There isn't enough convincing evidence to recommend this approach for all women. But flaxseed is a healthy alternative to other fats and very safe. Some women may be interested in giving it try.”

**Practice Pearl**

The NMCD recommends, “Explain to women that 40 grams of flaxseed contains 16 grams of fat and lots of calories. Tell women to use flaxseed instead of other dietary fats, not in addition to them, to avoid weight gain.”

However, flaxseed oil has no well-documented specific medical uses. Flaxseeds themselves contain fiber and lignans that are phytoestrogens; however, flaxseed oil contains little or no lignan because lignans are bound to the fiber, which is lost when the oil is pressed from the seeds.

**Practice Pearl**

Caution patients on warfarin (Coumadin) about using flaxseed. High doses of flaxseed can decrease platelet aggregation and could increase the risk of bleeding in patients who also take warfarin.

Chasteberry (*Vitex agnus-castus*) is a well-known "women's herb." It has a variety of effects on neurotransmitters including dopamine and acetylcholine. It also appears to have estrogen and progestin activity.

**Practice Pearl**

There is some evidence that chasteberry might help for symptoms of premenstrual syndrome. But there's no reliable evidence that it helps for menopausal symptoms.
Furthermore, chasteberry appears to stimulate the growth of experimental breast cancer cells.\textsuperscript{77} The NMCD recommends, “Like other phytoestrogens, tell women with a history of breast cancer that chasteberry might not be safe.”\textsuperscript{11}

**Kudzu** (*Pueraria lobata*), **alfalfa** (*Medicago sativa*), **hops** (*Humulus lupulus*), and **licorice** (*Glycyrrhiza glabra*) are herbs that have estrogenic activity and are used to treat menopause. They each have varying degrees of estrogenic activity.\textsuperscript{78,79} The NMCD concludes, “Tell patients there’s no reliable evidence these are effective for menopausal symptoms.”\textsuperscript{11}

**Chinese ginseng** (*Panax ginseng*, *Panax schinseng*), also called “Asian,” “Japanese,” or “Korean ginseng,” is sometimes recommended for vasomotor symptoms due to suspected estrogenic effects. “American ginseng” (*Panax quinquefolius*) and “Siberian ginseng” (*Eleutherococci senticosus, Acanthopanax senticosus, Hedera senticosa*), which isn’t in the *Panax* genus at all, are not usually used for menopausal symptoms.\textsuperscript{11}

But whether ginseng has any estrogenic effect is controversial.\textsuperscript{80,81} Ginseng does appear to stimulate breast cancer cells. And some women who take ginseng can have estrogen-like side effects.\textsuperscript{82} The NMCD concludes, “For now, tell women to think of ginseng as possibly having estrogenic effects and tell women with a history of breast cancer to avoid ginseng.”\textsuperscript{11}

Even though ginseng might have some estrogenic effects, it doesn’t seem to help for hot flashes.\textsuperscript{80} But there is preliminary research that suggests it might help menopausal symptoms such as fatigue, insomnia, and depression.\textsuperscript{83} But it does not seem to help for hot flashes.\textsuperscript{84} According to the NMCD, “Until more is known, don’t recommend it.”\textsuperscript{11}

Furthermore, ConsumerLab.com\textsuperscript{68} has found problems in many ginseng supplements over the years. In a 2006 review, six of thirteen products failed to pass testing due to lead contamination, lack of ingredient, or inadequate labeling. One product had less than 10% of its claimed amount of ginsenosides despite its “Extra Strength” label. A major store brand product was contaminated with lead.

**Dehydroepiandrosterone (DHEA)** is hyped as a “miracle hormone” to prevent aging. DHEA is an endogenous weak androgen and a precursor to other sex steroids. Low doses of DHEA (50 mg per day) increase testosterone levels and may very slightly increase estrogen levels.\textsuperscript{11}

One University systematic review of DHEA for menopause concluded, “Although circumstantial evidence might suggest potential benefits of DHEA therapy, until large randomized controlled trials using validated scales and hard safety endpoints have been conducted, the prescription of DHEA therapy for treatment of any specific symptoms cannot be recommended.”\textsuperscript{85}

In a 2002 Product Review, ConsumerLab.com\textsuperscript{68} found that 3 of the 17 DHEA supplements it tested contained less than their claimed amounts of this hormone – one having less than one-fifth of what it claimed. One product boasted it was “Pharmaceutical Quality” and “produced and packaged in [an] OTC approved facility” despite having only 19% of the DHEA claimed. Another product with only 79% of its claimed DHEA stated that its raw material met USP standards. A third product contained only 84% of the DHEA claimed.
### Practice Pearl
DHEA hype far exceeds DHEA research. For menopausal symptoms, DHEA probably won’t help much, if at all.\(^{86,87}\)

There is contradictory evidence on the effects of DHEA on menopausal symptoms. Some evidence suggests that taking DHEA orally 25 mg/day decreases hot flashes, as well as psychological symptoms.\(^{88}\) But other evidence suggests no benefit of DHEA 50 mg/day on mood, fatigue, cognition, or sense of well-being in perimenopausal women.\(^{89}\)

### Practice Pearl
The NMCD says, “Tell women that it is too soon to recommend DHEA for menopausal symptoms.”\(^{11}\)

Since DHEA can be converted to estrogen, there are also concerns about breast cancer. In fact, epidemiological studies associate higher serum concentrations of DHEA with increased breast cancer risk in postmenopausal women.\(^{90}\) So, the NMCD advise us to “Tell women with hormone responsive tumors such as breast cancer not to use DHEA.”\(^{11}\)

### Practice Pearl
Since DHEA can be converted to androgens such as testosterone, it can sometimes cause unwanted cosmetic side effects such as an increase in facial hair, acne, and deepening of the voice.\(^{11}\)

### Centrally-Acting Treatments
Alternatives to hormonal treatments are now becoming more popular due to the negative studies associated with HRT. Venlafaxine (Effexor), gabapentin (Neurontin), clonidine (Catapres), and methyldopa (Aldomet) have all been used.\(^{24}\) Selective serotonin-reuptake inhibitors (SSRIs) and other antidepressants are also used, but none of these treatments seems to be as effective as estrogen for hot flashes.\(^{91}\) Also, SSRIs sometimes have bothersome side effects such as drowsiness, dry mouth, constipation, and sexual dysfunction.\(^{24}\)

Nevertheless, NAMS recommends, “If there are no contraindications, NAMS recommends the antidepressants venlafaxine (at dosages of 37.5-75 mg/day), paroxetine (12.5-25 mg/day), or fluoxetine (20 mg/day) as options for women with hot flashes who are not candidates for hormone therapy, including breast cancer survivors.”\(^{24}\)

Gabapentin is another nonhormonal option recommended by NAMS for treating hot flashes. Therapy can be initiated at a daily dose of 300 mg (although starting at 100 mg/day may be advisable in women older than age 65). Bedtime administration is advised, given the initial side effect of dizziness. In women who continue to have hot flashes, the dose can be increased to 300 mg twice daily and then to three times daily, at 3- to 4-day intervals. Increased efficacy may be seen at even higher doses, although this has not been well studied.\(^{24}\)
Clonidine is sometimes used to treat mild hot flashes, although it is less effective than the newer antidepressants or gabapentin. In addition, clonidine has a side effect profile that limits its use in many women. The initial oral dose for hot flash treatment is 0.05 mg twice daily, but women may require at least 0.1 mg twice daily. The clonidine patch, delivering 0.1 mg/day, can also be considered. When discontinuing higher-dose therapy, the dose should be gradually tapered to avoid adverse side effects.\textsuperscript{24}

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Practice Pearl \\
Given their toxicity, NAMS does not recommend \textbf{methyl dopa} or \textbf{Bellergal-S} as hot flash treatments for most women.\textsuperscript{24} \\
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Women also use many centrally acting natural products...mostly for non-vasomotor menopausal symptoms. The NMCD recommends that \textbf{Valerian (Valeriana officinalis)} is “possibly effective” for insomnia and that \textbf{Ginkgo (Ginkgo biloba)} may be effective for memory or cognition problems.\textsuperscript{11}

The NCMD reports that \textbf{St. John’s wort (Hypericum perforatum)} is “possibly effective” for mild to moderate depression.\textsuperscript{11} ACOG agrees, concluding, “St. John’s wort may be helpful in the short-term (<2 years) treatment of mild to moderate depression in women.”\textsuperscript{40}

Nevertheless, NCMD points out that “Although valerian can be effective for insomnia and St. John’s wort can be effective for mild to moderate depression, there’s no reliable evidence that they help for these conditions when they are associated with menopause.”\textsuperscript{11}

\textbf{Miscellaneous}

\textbf{Black cohosh (Actaea racemosa, formerly Cimicifuga racemosa)} is among the top-selling herbs in the U.S. It is sometimes referred to as a phytoestrogen, but this is an improper designation. Researchers used to think that black cohosh had estrogenic effects, but newer evidence suggests that black cohosh does \textit{not} affect estrogen receptors and it doesn’t seem to affect endometrial or breast tissue.\textsuperscript{77,92}

It’s not clear how black cohosh might work for menopausal symptoms.\textsuperscript{11} It has been suggested black cohosh might act as an agonist at serotonin receptors and it appears to increase markers of bone formation.\textsuperscript{93,94} In addition, there is speculation that black cohosh has SERM-like activity.

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Practice Pearl \\
Do not confuse black cohosh with two unrelated plants, blue cohosh (\textit{Caulophyllum thalictroides}) and white cohosh (\textit{Actaea alba}) as these have toxic effects.\textsuperscript{11} \\
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Despite the popularity of black cohosh, research supporting its use for hot flashes is \textit{not} impressive. One study comparing black cohosh to estrogen found similar efficacy.\textsuperscript{95} But this study didn’t include a placebo. This is a big concern since the placebo response rate for menopausal symptoms can be 20 to 30%. Another study found both estrogen and black cohosh relieved hot flashes better than placebo.\textsuperscript{96}
Natural Medications (Herbs, Vitamins, and Supplements) for Menopausal Symptoms
AAFP Annual Scientific Assembly – San Diego, CA – September 19 and 20, 2008

Practice Pearl
The German Commission E approved the use of 40 mg/day of black cohosh (Remifemin brand) for 6 months for relief of menopausal symptoms, as well as for premenstrual syndrome (PMS) and dysmenorrhea.

Most sources recommend a dose of 40-80 mg per day, and at least 4-12 weeks of treatment may be required before therapeutic benefits may be apparent.97

A 2002 review concluded that “black cohosh may be effective for menopausal symptoms, especially hot flashes,” but added, “the lack of adequate long-term safety data (mainly on estrogenic stimulation of the breast or endometrium) precludes recommending long-term use.”61

Another review concluded, “Studies have concluded black cohosh is nontoxic, nonmutagenic, noncarcinogenic, and suitable for long-term treatment.”98

Practice Pearl
Virtually all clinical trials on black cohosh have been conducted with a proprietary formula of black cohosh root extract developed in Germany (Remifemin) and standardized to contain 20 mg of the root extract, including 1 mg triterpene glycoside 27-deoxyactein (now known as 26-deoxyactein), per tablet.97

In three of four of the most recent trials of black cohosh, the results have been negative.30 The single large RCT showed a benefit for vasomotor symptoms with the black cohosh extract used in Remifemin.59 The effect size was 0.03 to 0.05 Menopause Rating Scale units (which is statistically identical to recent hormone replacement therapy study results of 0.036 Menopause Rating Scale units) and may therefore be considered clinically relevant. In this study, women in the early climacteric phase benefited more than in the late phase. Also, the hot flush subscore was the most effective measure of the black cohosh extract’s efficacy.

Of the three recent studies that showed no benefits from black cohosh, two “were confounded by concurrent use of tamoxifen, known to exacerbate hot flashes,” while another used a “more unusual (research) preparation, BN01055.”30

According to the NMCD, “Studies using other non-commercial black cohosh extracts have been mostly negative. In fact, one of the most recent, and highest quality studies found that a non-commercial black cohosh extract 160 mg daily standardized to 2.5% triterpene glycosides did not significantly reduce hot flash frequency or other vasomotor symptoms after 3, 6, or 12 months of treatment.100 The problem is, this product is different than all of the others, which makes it difficult to make an apples-to-apples comparison of the findings.”11

For example, a three-month RCT that compared Remifemin and low-dose transdermal estradiol found them to be comparable in reducing hot flashes and vasomotor symptoms and also for alleviating anxiety and depression.101 In addition, older, smaller trials102,103,104 and trials from Germany have shown some efficacy for hot flashes using Remifemin. One of these groups104 repeated their study in 2005 with a

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different brand of black cohosh and did not find any beneficial results for the reduction of menopause symptoms.\textsuperscript{105}

Therefore NAMS recommends, “With its low incidence of side effects, a black cohosh supplement (two 20-mg tablets daily of a 27-deoxyactein standardized preparation) taken for less than 6 months is likely to do no harm and may provide relief of mild hot flashes.”\textsuperscript{24}

The NMCD agrees, “Black cohosh seems to be safe and well tolerated. Tell women that black cohosh might be worth a try.”\textsuperscript{11} ACOG also concludes, “Black cohosh may be helpful in the short-term (\textless 6 months) treatment of women with vasomotor symptoms.”\textsuperscript{40}

When ConsumerLab.com tested nine black cohosh supplements in 2005, they found that all passed testing, providing at least 1 mg of triterpene compounds per daily serving as recommended by the German Commission E Expanded Monographs.\textsuperscript{68}

However, a 2006 article reported that three of eleven black cohosh supplements purchased and tested in the United States did not even contain black cohosh. Instead, the three contained less expensive extracts of Chinese \textit{cimicifuga} (specific other \textit{Actaea} species) that do not have all the same chemical compounds or clinical uses as the native North American plant. A fourth product indicated a probable mixture of the two plants.\textsuperscript{106}

Even though black cohosh might help some patients with hot flashes, like soy, black cohosh does \textit{not} seem to be effective for relieving hot flashes in breast cancer survivors.\textsuperscript{11}

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<td>Past news reports raised concerns that black cohosh may be unsafe by suggesting that it increases breast cancer risk. This all stems from an animal study that showed mice that received black cohosh that eventually developed cancer had tumors that were more likely to spread.\textsuperscript{107} The NMCD concluded, “It’s way too soon to say that black cohosh is unsafe for most women. But tell women with a history or family history of breast cancer to avoid black cohosh.”\textsuperscript{11} A 2007 population-based, case-controlled study found that black cohosh and Remifemin “had a significant breast cancer protective effect.”\textsuperscript{108}</td>
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<td>Some published reports have suggested possible hepatotoxicity with black cohosh. However, experts from the NIH who participated in a black cohosh workshop in November 2004 concluded that although there is no known mechanism with biological plausibility that explains any hepatotoxic activity of black cohosh, that women be informed of the possibility and that future studies evaluate this potential side effect.\textsuperscript{109} A subsequent large RCT found no evidence of hepatotoxicity.\textsuperscript{99} NMCD says there is no “conclusive evidence that black cohosh is responsible for liver disease. Until more is known, monitor liver function in patients who take black cohosh.”\textsuperscript{11} ICSI agrees saying, “Until more is known, consider monitoring liver function in patients who take black cohosh.”\textsuperscript{110}</td>
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Dong quai (*Angelica sinensis*) is used in traditional Chinese medicine, usually in combination with other herbs. In the U.S. dong quai is often used as a single-ingredient remedy for hot flashes. There’s contradictory evidence regarding whether or not dong quai has estrogenic effects. There is some evidence that it does stimulate the growth of breast cancer cells like estrogen. But dong quai, when used alone, does not seem to be effective for relieving hot flashes.

Even though the limited data we have suggests that, used alone, dong quai is no more helpful than placebo in relieving menopausal symptoms, one reviewer pointed out that “practitioners of Traditional Chinese Medicine (TCM) counter that (they) do not use the herb alone, nor in a dosage as low as 4.5 grams daily. Typically, dong quai is used in conjunction with at least four other herbs, at a dose of 9-12 grams, and traditional formulas containing dong quai are highly successful in clinical practice, suggesting there is a synergistic effect among the herbs that was not detected in this single herb study.”

Practice Pearl

However, there’s also a concern that some of dong quai’s constituents might be carcinogenic. The NMCD recommends, “Whether taking dong quai supplies enough of these constituents to cause cancer is not known. Tell women not to use it.”

Evening primrose oil (*Oenothera biennis*) is sometimes promoted to relieve hot flashes. It’s sometimes advertised as an “estrogen promoter,” but there’s no evidence of any effect on estrogen levels in humans and it doesn’t seem to be effective for relieving hot flashes. Even though a 2005 Product Review by ConsumerLab.com found that all four evening primrose oil products passed quality testing, until there’s better evidence supporting its use for menopausal symptoms, the NMCD concludes, “Don’t recommend it.”

Wild yam (*Dioscorea villosa*) is often promoted as a source of “natural hormones.” It is often used as a topically applied cream for menopausal symptoms. Promoters falsely claim that a component of wild yam, diosgenin, is converted by the body to progesterone and/or dehydroepiandrosterone (DHEA). Diosgenin can be converted to hormones in the laboratory, but not in the body. Wild yam does not have estrogenic effects and is not effective for hot flashes.

Practice Pearl

The NMCD bluntly concludes, “Tell women not to waste their money on wild yam creams.”

Vitamin E supplements are sometimes recommended for menopausal symptoms. There’s preliminary evidence that vitamin E might have a modest benefit for reducing hot flashes in breast cancer survivors, although older trials found no benefit for vitamin E over placebo.

For menopausal women without a history of breast cancer, Vitamin E, 800 IU/day, is an option to try for hot flash relief, although clinical evidence is mixed. One RCT found, “There’s no reliable evidence that vitamin E helps menopausal women.”
After reviewing all available data, NAMS concluded, “Because vitamin E seems to be nontoxic at low doses, inexpensive, and available without a prescription, it is a reasonable option for a trial. Effects, if any, may take weeks.”

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<td>However, the NMCD came to a different conclusion, “There's no reliable evidence that vitamin E helps menopausal women.”</td>
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Like all natural medicines (herbs, supplements and vitamins – which are unregulated in the U.S.), there can be manufacturing issues. In 2004, ConsumerLab.com found that five of fifteen vitamin E products failed to pass their quality testing by having either too little vitamin E and/or for containing synthetic vitamin E when claiming to be natural.

**Hesperidin**, according to one review, is becoming more popular. The review reported, “In one clinical study, 94 menopausal women with hot flashes were given a daily formula for one month containing 900 mg hesperidin, 300 mg hesperidin methyl chalcone, and 1,200 mg vitamin C. After one month, symptoms of hot flashes were completely relieved in 53 percent and reduced in 34 percent of the women. No signs of toxicity have been observed with the intake of hesperidin or related compounds.”

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<td>Nevertheless, the NMCD concludes, “There is insufficient reliable information available about the effectiveness of hesperidin for (menopausal symptoms).” Therefore, it’s too early to recommend this product.</td>
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**Ferulic** acid, this same review claims, “was found, in the early 1960s, to be effective for reducing menopausal symptoms, including hot flashes. Ensuing studies have substantiated its effectiveness. In one small study, eight menopausal women and 13 women who had their ovaries surgically removed were given 300 mg ferulic acid daily. At the end of the one-month trial 67 percent of the women had at least a 50-percent reduction in menopausal symptoms. In a later study, ferulic acid at a dose of 300 mg daily was also found effective, with 85 percent of 13 women reporting an improvement in menopausal symptoms. Of interest, ferulic acid is not reviewed in the NMCD. Therefore, I would need more data to evaluate this product.

**Pycnogenol** (pine bark extract) is an extract of the bark of the French maritime pine tree (*Pinus pinaster*). Research suggests that the extract acts as an anti-inflammatory and may improve blood flow by enhancing blood vessel dilation. Researchers in Taiwan have hypothesized that all of these attributes might ease the common symptoms of menopause and have reported one small RCT in which 155 women, starting menopause, between the ages of 45 and 55 were randomized to placebo or to take 100 mg of Pycnogenol, twice a day for six months. The Pycnogenol group reported improvements in symptoms ranging from hot flashes and sexual dysfunction to fatigue and depression. In addition, blood tests showed that the women's antioxidant levels climbed, while their cholesterol levels improved slightly. In contrast, women who took the placebo generally showed no change, or sometimes worsening symptoms. In multiple studies, Pycnogenol has been safely used in doses of 50-450 mg daily for up to six months.
The Bottom Line

According to the NMCD: 11

Explain to women that these supplements are not "big guns." They seem to provide only modest relief, if any. Explain to women that natural products with estrogenic effects might not be any safer than conventional estrogenic drugs. Women with a history of breast cancer should avoid supplements containing a phytoestrogen or suspected of having estrogenic effects.

Soy has the most evidence for effectiveness and some women might benefit from taking it. Soy protein-containing foods are preferred over soy extract supplements which have concentrated isoflavones. There is less known about the long-term safety soy extracts.

Black cohosh might also help some women. Due to concerns about potential liver damage, women taking black cohosh should consider getting liver function tests. Don't recommend red clover, DHEA, flaxseed, chasteberry, kudzu, alfalfa, hops, licorice, evening primrose, ginseng, wild yam, or vitamin E. There's not enough evidence that these are beneficial. Steer patients away from dong quai due to potential safety concerns.
ACOG’s Recommendations for Counseling Patients about Complementary and Alternative Medicine

- All patients should be asked about their use of herbal therapies and dietary supplements. Use of these products should be documented in the patient’s chart.

- "Natural" is not an assurance of safety or efficacy.

- Potentially dangerous drug-herb interactions occur.

- Lack of standardization of botanicals may result in variability of content and efficacy from batch to batch, from a single manufacturer, or between manufacturers.

- Lack of quality control and regulation may result in contamination, adulteration, or potential misidentification of plant products.

- Errors in compounding may result in toxic or lethal outcomes in custom-blended herbal preparations.

- Botanicals should not be taken in larger than recommended doses or for longer than recommended duration.

- Several botanicals have known adverse effects and toxicities.

- Because the expected placebo response for menopausal treatment ranges from 10% to 30%, a small positive response to any treatment, conventional or alternative, may not necessarily represent a pharmacologic effect.

- Anecdotal experience is not a substitute for well-constructed clinical trials.

- Nonetheless, the effect of support, counseling, and empathetic care should not be discounted or dismissed.
Take Home Points

- No therapy for menopausal symptoms is more effective than conventional HT.
- **Lifestyle changes** can be highly effective for menopausal vasomotor symptoms.
- The NAMS consensus recommendation is: “In women who need relief for mild vasomotor symptoms, (we recommend) first considering lifestyle changes, either alone or combined with a nonprescription remedy, such as **dietary isoflavones** or **black cohosh**...Prescription systemic estrogen-containing products remain the therapeutic standard for moderate to severe menopause-related hot flashes. Recommended options for women with concerns or contraindications relating to estrogen-containing treatments include prescription progestogens, venlafaxine, paroxetine, fluoxetine, or gabapentin.”
- There is little evidence of effectiveness and safety of most natural medicines (herbs, vitamins and supplements) for the treatment of menopausal symptoms. Furthermore, these products are not regulated in the U.S.
- ACOG states, “Given the general lack of standardization of products, the relatively short duration of therapy and follow-up in the available data, and the difficulty of interpreting the available clinical data, **few recommendations can be made with confidence**.”
- A 2004 systematic review from NAMS concluded, “When lifestyle changes are not adequate to achieve the desired level of relief from mild hot flashes, adding a nonprescription remedy may be considered. A trial of **dietary isoflavones** or supplements containing **black cohosh** or **vitamin E** may be an option, primarily because these remedies are not associated with serious side effects. However, because of inconclusive efficacy data, this is not a consensus recommendation.”
- A 2006 systematic review recommends a trial of **soy isoflavones**, **black cohosh** or **red clover isoflavones** along with **lifestyle modifications** for “mildly” or “moderately” symptomatic women.
- The most recent systematic review and meta-analysis on the topic of nonhormonal therapies for menopausal hot flashes, published in JAMA in 2006, found 43 trials that met their inclusion criteria, including 10 trials of antidepressants, 10 trials of clonidine, 6 trials of other prescribed medications, and 17 trials of isoflavone extracts.
- The authors concluded that “The frequency of vasomotor symptoms in menopause was not reduced in meta-analysis of trials of **red clover** isoflavone extracts and results were mixed for **soy isoflavone** extracts. Evidence of the efficacy of other therapies is limited due to the small number of trials and their deficiencies. Trials do not compare different therapies head-to-head and relative efficacy cannot be determined.”
- They also found, “The SSRIs or SNRIs, clonidine, and gabapentin trials provide evidence for efficacy; however, effects are less than for estrogen, few trials have been published and most have methodological deficiencies, generalizability is limited, and adverse effects and cost may restrict use for many women. These therapies may be most useful for highly symptomatic women who cannot take estrogen but are not optimal choices for most women.”
- **“Soy”** the NMCD recommends, “has the most evidence for effectiveness and may be worth trying for some women. Soy foods are preferred over soy supplements which have concentrated isoflavones.” Another review agrees: “Less is known about the safety of soy supplements.”
• Women with a history of breast cancer should avoid any supplement containing a phytoestrogen or suspected of having estrogenic effects.

• “Black cohosh” the NMCD concludes, “has less evidence than soy, but might help some women.”

• There is really not enough safety or efficacy data to recommend unopposed transdermal progesterone, bioidentical hormone therapy, or testosterone.  

• The NMCD tells us, “There is really not enough safety or efficacy data to recommend red clover, DHEA, flaxseed, chasteberry, kudzu, alfalfa, hops, licorice, evening primrose, Panax ginseng, wild yam, or vitamin E. They haven’t been studied enough to recommend. Tell patients not to use dong quai due to safety concerns.”

• NAMS recommends, “Given the lack of efficacy data, (we do) not recommend dong quai, evening primrose oil, ginseng, licorice, Chinese herb mixtures, acupuncture, or magnet therapy for hot flash relief.”

• NAMS also reminds us, “Clinicians are advised to enlist women’s participation in decision making when weighing the benefits, harms, and scientific uncertainties of therapeutic options. Regardless of the management strategy adopted, treatment should be periodically reassessed as menopause-related vasomotor symptoms will abate over time without any intervention in most women.”
ACOG’s advice to our patients seems wise:\textsuperscript{38}

If you decide to use alternative therapies, be sure to tell your physician.

Some treatments have the potential to cause drug interactions with other medications you are using. Your doctor may recommend that you be monitored more closely for safety’s sake while using alternative or complementary therapies.

Remember, too, that dietary supplements, including herbal products, are not as strictly regulated by the federal government as are prescription and over-the-counter drugs. As a result, potency may vary from product to product, or even from batch to batch of the same product.

Bear in mind that just because alternative therapies are referred to as ‘natural’ remedies doesn’t mean they’re without risks or side effects. For this reason, you should take the same care when using alternative supplements or products as you would when using any over-the-counter or prescription medication.

Be sure to inform your physician that you are using these therapies, as well as any prescription medications, during medical visits.
## Recommendation Chart for Natural Medicines for Menopausal Symptoms

<table>
<thead>
<tr>
<th>Safety</th>
<th>Likely Safe</th>
<th>Possibly Safe</th>
<th>Insufficient Evidence</th>
<th>Possibly Unsafe</th>
<th>Likely Unsafe</th>
<th>Unsafe</th>
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<tbody>
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<td>Effective</td>
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<td>Likely Effective</td>
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<td>Soy foods or protein*^+</td>
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<td>Soy extracts*^+</td>
<td>Black cohosh (Remifimin)*</td>
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<td>Flaxseed*</td>
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<td>Black cohosh (Klimadynon)</td>
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<tr>
<td>Lifestyle changes*^</td>
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<td>-Testosterone^</td>
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<td>Chasteberry*</td>
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<td>-Bellergal^</td>
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<td>Licorice*^</td>
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<td>Evening primrose oil*^</td>
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<td>Red clover*</td>
<td>Wild yam*</td>
<td>Iproflavone*</td>
<td>Unopposed transdermal testosterone^+</td>
<td>DHEA*</td>
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<td>Panax ginseng*^</td>
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</table>

KEY:
- Consider recommending this product.
- Consider not recommending this product.
- Recommend against using this product.

* Based on the Safety and Effectiveness Ratings contained in *Natural Medicines Comprehensive Database* – which assumes the use of high-quality, uncontaminated products and typical doses. Some products are never appropriate for some patients due to concomitant disease states, potential drug interactions, or other clinical factors.\(^1^\)\(^1^\)

^ Based on a review by the North American Menopause Society (NAMS).\(^24^,\(^55^\)

+ Based on reviews by the American College of Obstetricians and Gynecologists (ACOG).\(^38^,\(^40^,\(^42^\)

^ Based on a review by the U.S. Food and Drug Administration.\(^45^\)

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Natural Medications (Herbs, Vitamins, and Supplements) for Menopausal Symptoms
AAFP Annual Scientific Assembly – San Diego, CA – September 19 and 20, 2008

Vasomotor Symptom Treatment Algorithm: A conservative clinical approach

Mildly symptomatic
- Lifestyle and complementary therapies
  - Lifestyle modifications
    - Core body temp
    - Exercise
    - Non-smoking
  - Relaxation
  - Complementary therapies
    - Red clover isoflavones
    - Black cohosh
    - Soy isoflavones

Moderately symptomatic
- First line
  - Lifestyle and complementary therapies
  - Review after 8-12 weeks

Severely symptomatic
- Averse to or contraindicated to HT
  - Non-HT prescription medications
-非HRT prescription therapies for symptoms
  - Antidepressants
  - Gabapentin
  - Antipsychotics
  - and/or
  - Lifestyle and complementary therapies

Patient understands risks and benefits of HT
- HT
  - Low dose estrogen
  - Progestrone

Second line
- HT
  - Low dose estrogen
  - Progesterone

Review after 3 months then annually, or as required by patient.

HT: hormone therapy.
Evidence-Based Guidelines


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Independent Testing Labs

- ConsumerLab.com is one of the leading providers of independent test results and information to help consumers and healthcare professionals evaluate health, wellness, and nutrition products. It publishes results of its tests at www.consumerlab.com, in The Guide to Buying Vitamins & Supplements, and in special technical reports. As a certification company, CL enables companies of all sizes to have their products voluntarily tested for potential inclusion in its list of Approved Quality products and bear the CL Seal. In the past seven years, CL has tested more than 1,800 products, representing over 350 different brands and nearly every type of popular supplement.

- In July 2005, ConsumerLab.com released a report on the quality of supplements used to treat symptoms of menopause, notably hot flashes. Tested were supplements containing soy isoflavones, red clover isoflavones and/or black cohosh as well as creams containing progesterone. www.consumerlab.com/results/phytoestrogens2.asp.

- USP tests the purity, potency, and quality of dietary supplement finished products. Only those that meet USP's stringent criteria are awarded use of the USP Verified Dietary Supplement Mark to display on their product labels. Finding this mark on a dietary supplement label helps to assure consumers that the supplements they buy provide the expected value. USP standards have been helping to ensure good pharmaceutical care for people throughout the world for more than 185 years. http://www.usp.org/aboutUSP/ or http://www.usp.org/USPVerified/dietarySupplements/supplements.html.

References

1. The core information used to create this handout for you was taken from an article (Natural Medicines in Clinical Management of Menopausal Symptoms) from the Clinical Management Series of the Natural Medicines Comprehensive Database – supplemented with information from the below referenced reviews, systematic reviews, evidence-based guidelines and consensus statements. The Natural Database and its Clinical Management Series are available only to subscribers of the Database. Subscriptions information can be viewed at www.naturaldatabase.com.


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66 Ann Intern Med. 2007(Jun 19);146(12):839-47.
68 www.ConsumerLab.com. Information on ConsumerLab’s testing of products, including those that pass (approved) and fail (not approved) is available to clinicians and consumers who are subscribers to the website. Subscribers can choose to access all reviews or to purchase only the reviews of a particular product.
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Complementary and hormonal therapy for vasomotor symptom relief: a conservative clinical approach.


This chart is adapted from a chart in an article, Natural Medicines in Clinical Management of Menopausal Symptoms, in the Clinical Management Series of the Natural Medicines Comprehensive Database (that is available by subscription to the Database. Subscription information can be viewed at www.naturaldatabase.com. Used with permission.