Hot Flashes – A Review of the Literature on Alternative and Complementary Treatment Approaches

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Abstract

Hot flashes are a common experience for menopausal women, with an 85-percent incidence in the West. With the increased knowledge of side effects attributable to conventional treatment options, more women are exploring natural alternatives. Although more definitive research is necessary, several natural therapies show promise in treating hot flashes without the risks associated with conventional therapies. Soy and other phytoestrogens, black cohosh, evening primrose oil, vitamin E, the bioflavonoid hesperidin with vitamin C, ferulic acid, acupuncture treatment, and regular aerobic exercise have been shown effective in treating hot flashes in menopausal women.

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Introduction

Because of a gradual increase in life expectancy during the last century, women are now living nearly one-third of their lives beyond menopause. 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 that the size of this group will be 46 million.[1]

Menopause is a normal biological process, not an estrogen deficiency state, occurring naturally at an average age of 50.[2] A transitional period occurs prior to menopause termed the climacteric or perimenopause. A diagnosis is often difficult during the perimenopausal period because it can be made only after menses have ceased for at least 12 uninterrupted months.

With the widely reported risks of conventional therapies for hot flashes, many women are exploring as an alternative the use of botanical medicine and dietary supplements.[3] In 2000 the retail sales of natural products in the United States surpassed $15 billion,[4] with sales of products for menopause accounting for approximately $600 million.[5] In one study based on an interview with 100 menopausal women attending a San Francisco health conference,[6] the women using dietary supplements alone perceived their quality of life highest, followed by those taking dietary supplements plus hormone replacement therapy. The former group also had a greater sense of overall control of their symptoms. This, coupled with the perception that dietary supplements have significantly fewer side effects than hormone replacement therapy, may have contributed to their reported higher quality of life. This sense of empowerment that accompanies the use of dietary supplements is echoed throughout the literature.[7]

Symptoms of menopause range from mild to severe, with the classic symptom being the hot flash. The prevalence of symptoms is subject to wide cultural differences, being appreciably higher in Western women. For example, women in the United States report more hot flashes[8,9] than women from developing countries, where menopause generally seems to be associated with fewer complaints.[10,11]

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A hot flash is experienced as a warm or hot sensation that often begins at the top of the head and progresses toward the feet. The scalp, face, and neck are primarily affected, but an entire body sensation is sometimes experienced. Objective signs of cutaneous vasodilation such as flushing and sweating are observed, followed by drop in core body temperature, leaving some women feeling chilled after the event. Concomitant symptoms include palpitations, anxiety, irritability, and night sweats. Hot flashes may last from seconds to as long as an hour,[12] and may occur as often as hourly.[13]

Hot flashes can begin prior to the last menstrual period, with nearly 60 percent of women reporting them before any menstrual changes are experienced.[14,15] Patterns may change over time, with some women experiencing hot flashes less frequently and intensely with time, while others continue to experience discomfort well into their later years.[12] Hot flashes may be triggered by surgical menopause as soon as one week post-surgery,[14] and are typically more frequent and severe at night (often awakening a woman from sleep) or during times of stress. One of the major complaints associated with hot flashes is insomnia, which can have a domino effect on the woman's overall quality of life.[16] In cooler environments, hot flashes are fewer, less intense, and shorter in duration.[17]

Table 1. *Differential Diagnosis of Hot Flashes*[21,22]

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

Risk Factors, Triggers, and Differential Diagnoses for Hot Flashes

Risk factors for hot flashes include a maternal history,[18] cigarette smoking,[18] menopause before age 52,[19] alcohol use,[19] menarche before age 12,[19] and a history of irregular menses.[19] Low levels of estradiol and high levels of follicle stimulating hormone (FSH) have been associated with hot flashes before menopause, whereas high levels of thyroid stimulating hormone (TSH) have been related to hot flashes during menopause.[20] On the other hand, high levels of testosterone and dehydroepiandrosterone (DHEA) after menopause appear to protect against hot flashes.[20] Triggers include spicy foods, exercise, hot or humid weather, and confined spaces.[21]

Not all hot flashes are hormonally induced, and it is essential other medical conditions, medications, and food additives that can cause hot flushing be considered in the differential diagnosis (Table 1).[21,22]

Pathophysiology of Hot Flashes

Despite multiple theories, the exact pathophysiology of hot flashes remains unknown.[23,24] Even though hot flashes are most likely multifactorial in origin, dysfunction of the central thermoregulatory centers due to decreased levels of estrogen has long been thought to be the primary cause.[25] Figure 1 illustrates potential physiological triggers of hot flashes. In addition, it may be that estrogen withdrawal, rather than low circulating estrogen levels, leads to hot flashes.[26] Changes in levels or function of the neurotransmitters norepinephrine (which lowers the thermoregulatory set point, triggering a heat loss mechanism)[26,27] and serotonin,[28,29] changes in gonadotropin release through the hypothalamus,[30] and interactions among prostaglandins, catecholamines, endorphins and other neuropeptides[25] have all been implicated.

Conventional Pharmacological Treatment Options

Conventional hormonal treatment options for hot flashes include estrogen with our without progestins or selective estrogen receptor modulators (SERMs – e.g., raloxifene, tamoxifen). Nonhormonal pharmacological treatments include serotonin reuptake inhibitors (SSRIs – e.g., venlafaxine) or antihypertensives (e.g., clonidine).

While hormone replacement therapy has historically been prescribed for hot flashes, partly because of purported protection from long-term chronic degenerative disease, studies are currently calling this practice into question. Randomized trials of conjugated estrogens plus progestins (HRT) have found no benefit from these compounds for either primary or secondary prevention of heart disease.[31] In fact, HRT appears to be associated with increased risk of heart attacks, stroke, deep venous thrombosis (DVT), pulmonary embolism (PE), and gallbladder disease.[32] A 26-percent increase in breast cancer was noted in women who took HRT, resulting in discontinuation of that arm of the 8.5 year study after five years.[32,33] Progestins alone may produce vaginal bleeding, thromboembolic events, bloating, weight gain,[24] and increased risk of primary or recurring breast cancer.[34,35]

Other adverse effects of HRT include headache, nausea, water retention, phlebitis, breast tenderness, irritability,[36] and withdrawal vaginal bleeding, which is the main reason women stop taking HRT.[37,38]

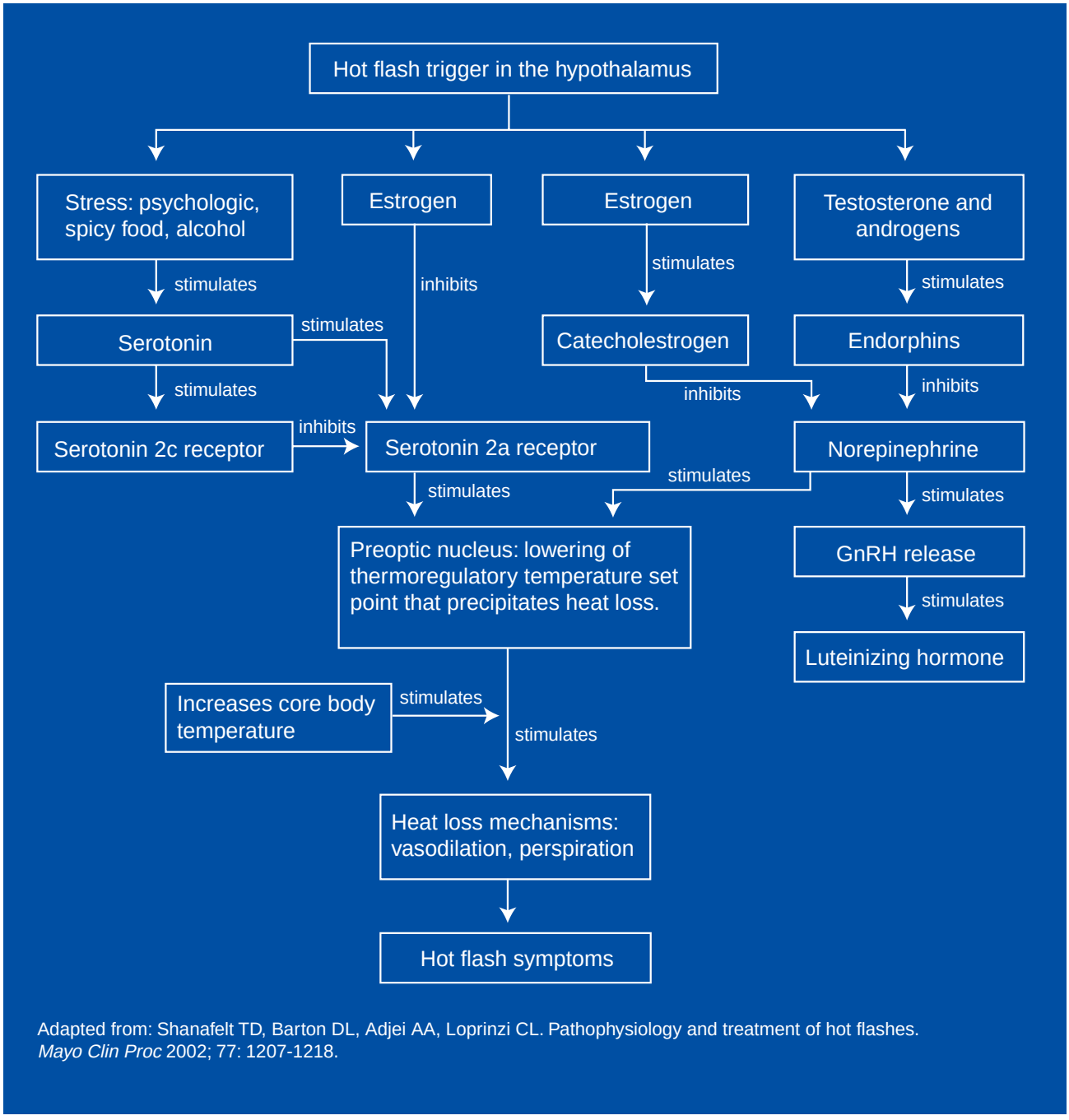
Botanical Medicine in the Treatment of Hot Flashes

Due to the side effects and risks associated with conventional approaches to hot flashes, many women are turning to alternatives. Botanical medicine offers some of the most-thoroughly researched options.

Phytoestrogens

Phytoestrogens are plant substances functionally similar to 17β-estradiol or that produce estrogenic effects.[39] They have a structure

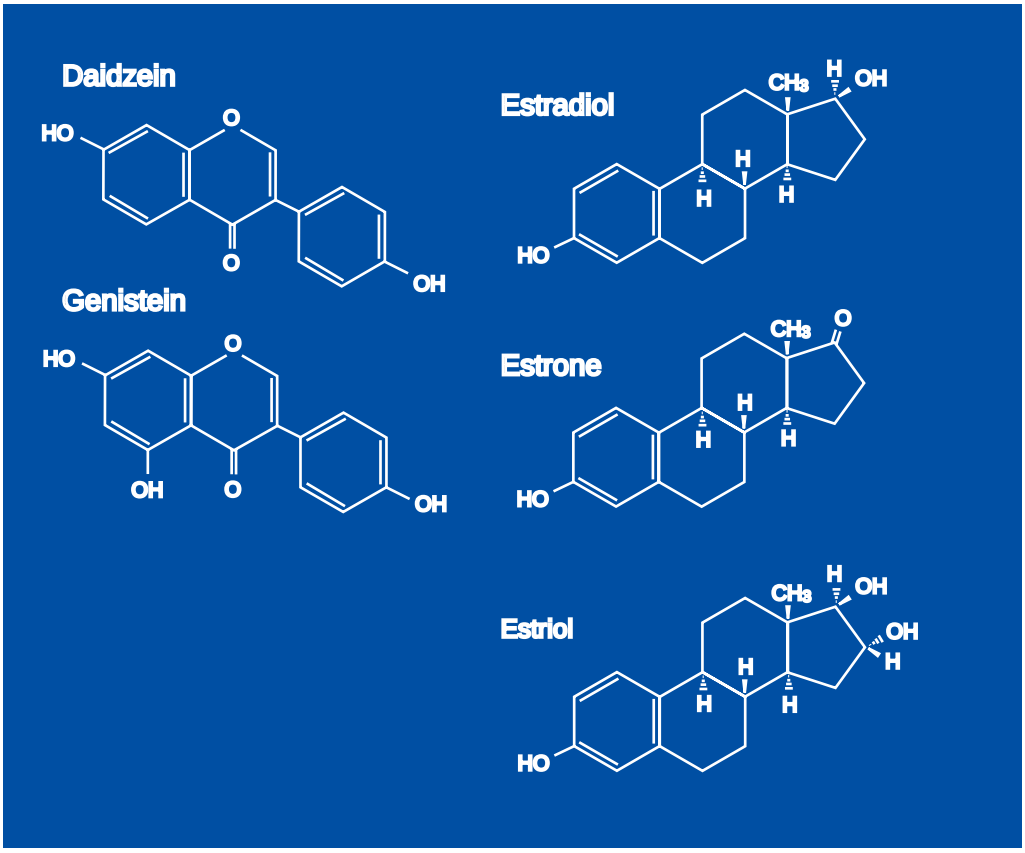
Figure 1. *Potential Triggers for Hot Flashes*



Adapted from: Shanafelt TD, Barton DL, Adjei AA, Loprinzi CL. Pathophysiology and treatment of hot flashes. *Mayo Clin Proc* 2002; 77: 1207-1218.

similar to estrogen (Figure 2), which enables them to bind to estrogen receptors (ER), but are 100-1,000 times weaker than estradiol.[40] The three main classes of phytoestrogens are isoflavones, lignans, and coumestans. Isoflavones are the most widely studied class of phytoestrogens, with genistein (4'5,7-trihydroxyisoflavone) and daidzein (4',7-dihydroisoflavone) and their

Figure 2. *Comparison of the Chemical Structures of Estrogen and Isoflavones*



respective β-glycosides, genistin and daidzin, providing the most data to date.[40,41]

Phytoestrogens are derived from dietary and botanical sources (Table 2). Major sources of dietary lignans include flaxseed and whole grain cereals, while legumes, such as soybeans and chickpeas, are major sources of isoflavones, and clover, alfalfa, and soybean sprouts are sources of coumestans. [5] Phytoestrogens are currently the most popular alternative to HRT.[42]

A relatively small but growing number of clinical trials have evaluated the role of phytoestrogens in relieving hot flashes associated with menopause. Most randomized, double-blind, placebo-controlled trials indicate favorable reductions in the frequency, duration, and/or severity of hot flashes.

Soy Isoflavones and other Soy Products

Several published studies report improvements in hot flashes with soy protein, soy foods, or soy isoflavone extract. In a randomized, double-blind, placebo-controlled study, 75 postmenopausal women (55 completed the study) experiencing at least seven hot flashes daily received either soy isoflavone extract (total of 70 mg genistin, the aglycone form of genistein, and daidzin, the aglycone form of daidzein, per day) or placebo.[43] After 16 weeks, women taking the soy extract had a 61-percent reduction in daily hot flashes, versus a 21-percent reduction in the placebo group. "Responders" (defined as patients whose hot flashes were reduced by at least 50 percent at the end of the treatment period) included 66 percent in the soy extract group and 34 percent in the placebo group.

Upmalis et al examined the safety and efficacy of an oral soy isoflavone extract on 177 postmenopausal women (mean age 55 years) experiencing five or more hot flashes per day.[44] In this double-blind, placebo-controlled study the women were randomized to receive either soy isoflavone extract (total of 50 mg genistin and daidzin per day) or placebo. Analysis after 12 weeks showed a statistically significant reduction

Table 2. *Classification and Food Sources of Phytoestrogens*

Isoflavones		Lignans		Coumestans
Soybean products Tofu Soy meal Soy grits Soy flour Soy milk	Legumes Soybean Lentils Beans Chickpea	Whole grains Wheat Wheat germ Barley Hops Rye Rice Brans Oats	Fruits, Veggies, Seeds Apple Pear Cherry Carrot Fennel Onion Garlic Sunflower seed Flax Vegetable oils (including flax, olive)	Bean sprouts Alfalfa Soybean Clovers

Adapted from: Murkies AL, Wilcox G, Davis SR. Phytoestrogens. *J Clin Endocrinol Metab* 1998;83:297-303.

in average hot flash severity and frequency in the soy isoflavone group compared with the placebo group. In addition, decreases in the incidence and severity of hot flashes occurred as soon as two weeks in the soy group; whereas, the placebo group experienced no relief the first four weeks. Endometrial thickness, measured by ultrasound, did not change in either group.

In another randomized, double-blind, crossover study, a statistically significant decrease in hot flashes occurred in 51 menopausal women consuming 20 g soy protein (containing 34 mg isoflavones) in single or split dosages compared to placebo (20 g complex carbohydrates).[45] After six weeks, a significant improvement was observed for the perceived severity of vasomotor symptoms (i.e., hot flashes) in both soy groups compared with placebo, although in the "twice daily" group the effect was greater. This suggests having consistent circulating levels of phytoestrogens may be more efficacious than a single higher dose. In addition, significant improvements in lipid and lipoprotein levels, as well as blood pressure, were noted in the treatment groups.

Albertazzi et al conducted a randomized, double-blind, placebo-controlled trial to assess the effect of daily dietary supplementation of soy protein isolate powder on hot flashes in postmenopausal women.[46] Age in the treatment group (n=51) was 48-61 years, while in the control group (n=53) it ranged from 45-62 years. The diets of the 104 women were supplemented with either 60 g soy powder (40 g isolated soy protein) or 60 g placebo (casein) daily for 12 weeks. By the end of the 12th week, women taking the soy protein isolate had a 45-percent reduction in daily hot flashes compared to a 30-percent reduction obtained with the placebo.

A randomized, double-blind, 12-week study in Australia with 58 postmenopausal women compared soy flour, which contains daidzin, to wheat flour, which contains lignans.[47] Both groups experienced a significant reduction in the frequency of hot flashes – 40 percent in the soy flour group and 25 percent in the wheat flour group.

The reduction from soy flour occurred six weeks earlier than that produced by wheat flour. Vaginal cell maturation, plasma lipids, and urinary calcium remained unchanged.

Two other studies investigating the effects of soy isoflavones showed no statistically significant changes in the frequency of hot flashes between the treated and control groups.[48,49]

Breast cancer patients may experience worsening of vasomotor symptoms due to chemotherapy, tamoxifen, and/or discontinuation of HRT. One randomized, double-blind, placebo-controlled clinical trial with 123 postmenopausal breast cancer survivors with hot flashes showed no significant difference in vasomotor symptoms between the soy (90 mg isoflavones daily) and placebo groups after 12 weeks; however, both groups had a significant reduction in hot flashes (30-percent reduction with soy; 40-percent reduction with placebo.)[50] These results may not be extrapolated to a normal menopausal population due to the presence of chemotherapeutic medication.

A review of soy studies suggests an appropriate intake of 10-15 g of soy protein or 50 mg isoflavones (range of 30-100 mg) per day.[41]

An important consideration with respect to the use of soy is its potential benefit in regard to other common risk factors in menopausal women. Whereas studies have shown estrogen replacement increases endometrial cell proliferation (increasing the risk of endometrial cancer)[51] and serum triglyceride levels,[52] isoflavone-rich soy protein[53] and isolated isoflavones[54] do not affect endometrial cell proliferation,[55] may help prevent various cancers,[56] and have been found to inhibit thrombin formation and platelet aggregation, possibly preventing atherosclerosis.[57] Soy protein and soy isoflavones either do not affect or slightly decrease serum triglyceride levels, offering further protection against cardiovascular disease.[58,59]

Black Cohosh (Cimicifuga racemosa; Actaea racemosa)

Black cohosh, advocated as an alternative to HRT, has been used by Western doctors in the United States for the treatment of hot flashes and other menopausal symptoms for more than 100 years,[60] and was an official drug in the *U.S. Pharmacopoeia* from 1820-1926.

The characteristic chemical constituents of the roots and rhizomes of black cohosh include cycloartenol-type triterpenoids, such as actein, 23-epi-27-deoxyactein (now known as 26-deoxyactein), cimicifugoside, and cinnamic acid derivatives (i.e., ferulic acid, isoferulic acid, and piscidic and fukiic acid esters).[61,62] Although the estrogenic isoflavone formononetin is reportedly a chemical constituent of black cohosh, its presence has not been detected in alcoholic extracts of the root/rhizome.[63,64]

Some of the triterpenes fractions have been thought to act as *in vivo* precursors to steroids.[5] The German Commission E has endorsed the use of black cohosh for the treatment of menopausal symptoms, including hot flashes,[65] and stated in its monograph that black cohosh has an estrogen-like action, suppresses luteinizing hormone (LH), and binds to estrogen receptors.[66] However, the estrogen modulation effects of black cohosh are controversial, and the more recent data indicate black cohosh extracts may have anti-estrogenic activity.[60] This area remains controversial and the herb's action may depend on the hormonal status of the individual. In addition, black cohosh may alleviate hot flashes by actions discrete from estrogen-receptor regulation.[67] Further research is needed to elucidate the mechanisms of action of black cohosh.

Black cohosh also contains isoflavonoids, beta-carotene, ascorbic acid, butyric acid, calcium, zinc, thiamine, chromium, selenium, and salicylic acid.[66] Therefore, it is possible that the combination of the essential fatty acids, phytosterols, proteins, vitamins and minerals, and chemical constituents together result in its numerous physiological effects.[5]

Table 3. *Kupperman Index*

This assessment tool of climacteric symptoms, summarized in a menopausal index, is based on the most common complaints, which include:

Hot flashes	Vertigo
Sweating	Arthralgias
Sleep disturbances	Headache
Nervousness	Tachycardia
Depression	Vaginal dryness
Fatigue	

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.

This index is often modified, depending on the outcomes being measured in the study and, although there is some debate about the absolute validity of this tool, is still widely used in clinical studies measuring menopausal changes.

Most clinical trials have been conducted with a proprietary formula of black cohosh root extract developed in Germany (Remifemin; Shaper & Brummer, GmbH & Co KG, Salzgitter, Germany) and standardized to contain 20 mg of the root extract, including 1 mg triterpene glycoside 27-deoxyactein (now known as 26-deoxyactein), per tablet.[60,65] This is the only commercial black cohosh extract to date to be tested clinically for safety and efficacy.

Black cohosh has been used safely in well-designed studies lasting up to six months,[68-71] and has been commonly prescribed in Europe as an effective alternative to HRT for menopausal symptoms.[72]

Since 1982, at least 11 clinical trials have assessed the efficacy of the aforementioned standardized formulation of black cohosh for the symptomatic treatment of menopausal symptoms, such as anxiety, hot flushes, profuse sweating, insomnia, and vaginal atrophy. Most studies assessed symptoms using the Kupperman index (KI), a standard measurement of menopausal symptoms (Table 3). Of the 11 trials, six were randomized, controlled or comparison trials,[68,70,71,73-75] and the other five were uncontrolled studies.[76-80]

In a six-month, controlled, randomized, double-blind clinical trial involving 152 peri- and postmenopausal women with hot flashes and other menopausal symptoms, the effects of two different doses of black cohosh extract (39 mg versus 127.3 mg daily) were compared.[68] A positive decrease in the KI was observed in both treatment groups after two weeks, with similar therapeutic efficacy and safety profiles. In addition, no effects on LH and FSH levels, sex-hormone binding globulin, prolactin, estradiol, or vaginal cytology were observed, indicating the black cohosh extract at these doses was associated with improvement in hot flashes and other menopausal symptoms without any evidence of estrogen-like activity.

A 12-week, double-blind, placebo-controlled trial with 80 postmenopausal women (ages 45-58) compared 8 mg black cohosh extract (equivalent to approximately 40-140 mg of dried herb) daily to either 0.625 mg conjugated estrogens or placebo.[71] Outcome measures included the KI for menopausal symptoms, the Hamilton Anxiety Rating Scale, and the vaginal maturation index. The black cohosh group had a statistically significant improvement in both menopausal vasomotor symptoms (i.e., hot flashes, sweating) and the proliferative status of the vaginal epithelium after 12 weeks, compared to both the estrogen and placebo groups. However, contrary to previous studies on estrogen and hot flashes, this study found the estrogen group fared no better than placebo, calling into question the overall quality and validity of the study.

Jacobson et al, in a randomized, double-blind, placebo-controlled trial, assessed the efficacy of the same proprietary formula of black cohosh root extract in 85 breast cancer survivors (69 completed the trial).[70] The women were assigned to black cohosh (40 mg of extract daily) or placebo for two months and, in addition to assessing symptomatology, FSH and LH levels were measured in a subset of the women at the first and final visits. Both treatment and placebo groups evidenced significant declines in number and intensity of hot flashes over time, but the differences between the two groups were not statistically significant. There was, however, a statistically significant decline in sweating for the black cohosh group. Changes in blood levels of FSH and LH did not differ between the two groups. This study, however, may not be applicable to women without a breast cancer history. The major limitations of this study include the high dropout rate (19 percent) and the short treatment period. In addition, 59 of the 85 women were on tamoxifen. The nine women who were taking the black cohosh extract alone experienced marked reduction in symptoms. Because the mechanism of action of black cohosh is not fully understood, the confounding effects of tamoxifen, an estrogen agonist/antagonist, may have influenced the results by dampening the effectiveness of black cohosh.

The collective clinical and observational experience suggests black cohosh may be approximately 25-30 percent more effective than placebo for menopausal symptoms, including hot flashes.[7] Studies have concluded black cohosh is nontoxic, nonmutagenic, noncarcinogenic, and suitable for long-term treatment.[81] Its use in Europe for more than 40 years in over 1.5 million cases demonstrates excellent tolerability and low risk of side effects.[81,82] The German Commission E has approved the use of black cohosh for menopausal symptoms at daily doses of 40-200 mg. The current recommended dose is 40-80 mg per day, and at least 4-12 weeks of treatment may be required before therapeutic benefits may be apparent.[60]

*Red Clover (*Trifolium pratense*)*

Red clover extracts are frequently prescribed for the treatment of menopausal symptoms.[83] Like soy it is a legume and provides a number of phytoestrogens, including formononetin, biochanin A, daidzein, genistein, and coumestrol, all of which are weak estrogens.[84] It is a rich source of coumestans (a phytochemical with steroid-like activity) and is the richest source of isoflavones.[21] Red clover extract is marketed as Promensil (Novogen, Australia), a standardized product containing 40 mg isoflavones.

Two double-blind, randomized, controlled trials involving a total of 100 menopausal women evaluated, via a symptom checklist, the ability of Promensil (40 mg) to manage hot flashes. The red clover extract was not found to be significantly more effective than placebo,[85,86] nor did the groups differ in vaginal cytology, endometrial thickness as measured by ultrasonography, or serum hormone levels.

Currently it is unknown whether long-term use of red clover would have an estrogenic effect on the human female breast or endometrium, but data suggest it is weakly estrogenic in the ovariectomized rat model.[87] Because of the presence of coumarins in some clover species, including *Trifolium pratense*, tests of clotting factors in future trials may be prudent.[83] In addition, red clover has been shown to improve systemic arterial compliance and elasticity in postmenopausal

women,[88] potentially decreasing risk of cardiovascular disease.[3] Currently there are several larger trials of red clover in progress.

*Wild Yam (*Dioscorea villosa*)*

Topical wild yam and progesterone creams, readily available over-the-counter, are promoted for menopausal symptoms, including hot flashes.[89] While one of the components in wild yam, diosgenin, can be converted in the laboratory to steroidal compounds including progesterone, this synthesis does not occur in the human body.[90] Therefore, patients need to be advised that wild yam extract will not increase their progesterone levels.[91,92] Wild yam may have some estrogenic activity, but this possibility has not been adequately investigated.[93]

A double-blind, placebo-controlled, crossover study tested the effects of a wild yam cream against placebo for three months in 23 healthy women complaining of menopausal symptoms, including hot flashes.[94] Both the treatment and placebo groups improved slightly in subjective experience of hot flashes and night sweats, but there were no changes from baseline in FSH, estradiol, or serum or salivary progesterone. Additional baseline measures, including body weight, blood pressure, levels of serum total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and glucose did not change.

*Dong Quai (*Angelica sinensis*)*

Dong quai is an herb native to Eastern Asia and China, used for more than 2,000 years as a tonic, spice, and medicine in traditional Chinese medicine (TCM). It is known as the "female ginseng" and is currently the second-best selling herb in China.[95] Traditionally it has been indicated for menstrual disorders, as a supportive herb for menopausal complaints,[96] and for its vasodilatory and antispasmodic effects.[3] Its effectiveness in relieving hot flashes may be due to a combination of a mild estrogenic effect and other components acting to stabilize blood vessels.[97] Dong quai contains ferulic acid,[98] which has also been shown to decrease hot flashes.[99,100]

A randomized, double-blinded, placebo-controlled study of 71 postmenopausal women evaluated the effectiveness of 4.5 g dong quai or placebo daily.[101] Menopausal symptoms (i.e., hot flashes and vaginal atrophy) decreased to a similar degree in both the treatment and control groups, and the dong quai did not cause endometrial thickening or an increase in the vaginal maturation index. In addition, estradiol, estrone, and sex hormone-binding globulin levels were unchanged by the dong quai treatment. Dong quai was well tolerated and no serious side effects were noted.

This study would suggest that, used alone, dong quai does not produce estrogen-like responses and is no more helpful than placebo in relieving menopausal symptoms. However, a chief concern with this study among practitioners of TCM is that dong quai was used alone; practitioners of TCM 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,[102] suggesting there is a synergistic effect among the herbs that was not detected in this single herb study.

*Evening Primrose Oil (*Oenothera biennis*)*

Evening primrose oil (EPO) comes from the seeds of the yellow primrose, a North American wildflower. The seeds contain oils rich in alpha-linolenic acid (an omega-3 fatty acid) and gamma-linolenic acid (GLA; omega-6 fatty acid), both precursors of eicosanoids, which are constituents of cell membranes. The biochemical pathway for metabolism of dietary GLA eventually leads to prostaglandin E1, which has potent anti-inflammatory activity and is often recommended for inflammatory and autoimmune conditions.[21]

EPO is also used to treat premenstrual syndrome (PMS) and menopausal symptoms. A single six-month, randomized, double-blind, placebo-controlled study examined EPO for menopausal hot flashes and night sweating in 56 women.[103] There was a statistically significant reduction in nighttime flushing in the treatment

group compared to the control group, but not of daytime hot flashes. Further studies are warranted to examine the possible therapeutic effects of evening primrose oil for hot flashes.

Other Botanicals

Other botanicals often used in multi-herbal formulations for their purported hormonal modulatory effects include ginseng, licorice, hops, alfalfa, and chaste tree berry, although no clinical research to date has been conducted to support their use for hot flashes. In addition, since herbs usually take longer than estrogen therapy to affect symptoms, the typical three-month pharmaceutical trial model may be too short to accurately assess the clinical ability of botanicals to reduce hot flashes.[104]

Nutritional Supplements for Menopause

There is increasing evidence in the scientific literature that supplementing with vitamins and minerals has potential for reducing symptoms of menopause, including hot flashes. With almost 50 percent of Americans taking some sort of botanical or nutritional supplement,[21] dietary supplements are frequently used during menopause.[6] The following provides an overview of the research of the supplements most studied.

Vitamin E

Research on vitamin E for the reduction of hot flashes, mood swings, and vaginal dryness suggests a possible benefit with supplementation. In the late 1940s, several clinical studies found vitamin E at daily doses of 50-400 IU effectively decreased hot flashes and other menopausal complaints when compared to placebo.[105-107] In one study, supplementation was shown to increase blood supply to the vaginal wall and improve menopausal symptoms.[105] These results were observed only when vitamin E was taken for at least four weeks.

The first placebo-controlled, randomized, crossover trial of vitamin E, in 105 breast cancer survivors who were experiencing an average of at least 2-3 hot flashes daily, showed a clinically small but statistically significant advantage for vitamin E (400 IU twice daily) for four weeks over placebo.[108] Vitamin E was successful, even for some women using tamoxifen, which has been shown to increase hot flashes.[109]

Vitamin E supplementation has also been shown to reduce other common symptoms of menopause, including fatigue, dizziness, palpitations, and nervousness.[105,107] Although there is scant published information demonstrating the effectiveness of higher doses of vitamin E for hot flashes and other menopausal symptoms, a daily intake of 400-1,200 IU has been observed by both conventional and CAM practitioners to be clinically beneficial.

Hesperidin and Vitamin C

Interest has increased in the possible health benefits of flavonoids owing to their potent antioxidant and free-radical scavenging activities observed *in vitro*.[110] Some flavonoids demonstrate a very weak estrogenic effect, which may be why regular use can alleviate symptoms associated with menopause.[111]

The flavonoid hesperidin, from citrus fruit, is known to improve vascular integrity and decrease capillary permeability.[112] A dietary deficiency has been linked to abnormal capillary leakiness, pain and weakness in the extremities, and nocturnal leg cramps. Both hesperidin and its aglycone hesperitin have been reported to possess a wide range of pharmacological properties.[113]

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.[114]

No signs of toxicity have been observed with the intake of hesperidin or related compounds.

Ferulic Acid (Gamma Oryzanol)

Ferulic acid is a ubiquitous plant constituent that arises from the metabolism of phenylalanine and tyrosine.[115] It is found in grains and isolated from rice bran oil,[112] occurs primarily in seeds and leaves,[115] and has potent antioxidant potential.[115] Ferulic acid has also been found in dong quai.[98]

Ferulic acid may protect against various inflammatory conditions due to its free-radical scavenging effects.[115]

In the early 1960s, ferulic acid was found to be effective for reducing menopausal symptoms, including hot flashes.[99] Ensuing studies have substantiated its effectiveness.[100] 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.[99]

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.[100]

Other Treatment Approaches

Bio-identical Hormones

Bio-identical HRT uses synthesized hormones that are exact chemical replicas of those produced in the human body (i.e., estrone, estradiol, estriol, and progesterone). Because natural progesterone is poorly absorbed and rapidly metabolized, an effective and well-tolerated micronized progesterone is available that is readily absorbed, reaching peak serum concentrations 1-4 hours after administration.[116] Available bio-identical hormones that may be prescribed for hot flashes include bi-est (80% estriol and 20% estradiol), tri-est (80% estriol, 10% estradiol, 10% estrone), and micronized progesterone. The estrogens may also be acquired individually. These hormone combinations have been prescribed for many years by European health-care providers, but are typically available only from compounding pharmacies in the United States.

To date, there are no double-blind, placebo-controlled studies available to assess the efficacy and safety of estrogen bio-identical hormones in the treatment of hot flashes. However, a randomized, double-blind, placebo-controlled trial on the effect of a transdermal progesterone cream on preventing postmenopausal bone loss examined hot flashes as a secondary outcome.[117] Healthy postmenopausal women (n=102) applied one-quarter teaspoon progesterone cream (containing 20 mg progesterone) or placebo daily for one year. The women also received daily multiple vitamins and 1,200 mg calcium. No protective effect on bone density was demonstrated after one year, but there was significant improvement in hot flashes reported by the treated group compared to the placebo group (83 percent versus 19 percent, respectively). Eight women treated with the progesterone cream reported some vaginal bleeding, and an endometrial biopsy revealed endometrial proliferation in one woman. Unfortunately, biopsies for the seven other women did not retrieve sufficient tissue for diagnosis.

A parallel, double-blind, randomized, placebo-controlled trial comparing the effect of a transdermal progesterone cream (32 mg progesterone daily) with a placebo cream was conducted on 80 symptomatic postmenopausal women over a period of three months.[118] Despite a slight elevation of blood progesterone levels, there was no detectable change in vasomotor symptoms (e.g., hot flashes), mood characteristics, or sexual feelings, nor was there any change in blood lipid levels or in bone metabolic markers from the use of transdermal progesterone at this dose.

The postmenopausal bleeding noted in the previous study[117] is concerning, as are the results of three other studies showing serum concentrations of progesterone after application of transdermal creams were insufficient to prevent estrogenic stimulation of the endometrium when compared to the protection offered by progestins in women taking HRT.[119-121] Given that women may use transdermal progesterone cream instead of the progestin component of HRT, these findings warrant further research into the efficacy and outcome of transdermal progesterone creams.

Acupuncture

Acupuncture is another alternative to HRT. Two randomized, controlled studies by the same author evaluated the effects of acupuncture treatments on climacteric symptoms. The first study compared low-frequency electroacupuncture (EA) or superficial needle position (SNP) (an acupuncture technique whereby needles are inserted into the superficial layer of the derma and Qi is not typically elicited in the patient) in 24 postmenopausal women experiencing hot flashes. The women were treated twice weekly for two weeks, and then weekly for an additional six weeks. Hot flashes and Kupperman index scores decreased significantly in both groups. At three months, however, beneficial effects continued only in the EA group.[122]

Of import is the fact that, instead of using sham acupuncture, which utilizes points on the body not recognized as acupuncture points, the authors instead used shallow needle insertion at correct acupuncture points, which would be expected to have some effect; therefore, the chosen control was suboptimal.

In the second study, 30 women with menopausal complaints were studied using either EA or extremely superficial needle insertion (SNI). Again, the results revealed no significant differences in climacteric symptoms or well-being between the groups. However, the women's sense of well-being in the EA group was improved from week 4 until the end of the study at week 12; whereas, in the SNI group, well-being was not experienced until week 8. Again, correct acupuncture points were used in both groups leaving the results equivocal.[123]

Behavioral Therapies

Very few studies have examined behavioral techniques for addressing hot flashes. One study evaluated paced respiration, muscle relaxation, or biofeedback control in 33 menopausal women with frequent hot flashes. Whereas there was no change in the control group, those in the paced respiration group experienced a significant decrease in hot flashes (44 percent). No adverse reactions were noted.[124]

In a randomized, controlled, prospective study, 33 perimenopausal women experiencing at least five hot flashes daily were assigned to one of three groups (relaxation response, reading, or control) for seven weeks. The relaxation group was asked to practice relaxation techniques 20 minutes daily; the reading group read leisure material for 20 minutes; while the control group only recorded their symptoms. When compared to baseline, the frequency of hot flashes did not change in any of the groups; however, the intensity of the hot flashes decreased significantly in the relaxation group.[125]

Paced breathing and relaxation techniques as behavioral approaches to addressing hot flashes show promise in these studies, were found to be safe, and warrant further investigation.

Lifestyle Modifications

Some lifestyle changes appear to help reduce hot flashes. The practice of wearing light, "breathable" cotton clothing or layering clothing so pieces can be removed might prove beneficial. Other suggestions include keeping the ambient temperature of a room low; and avoiding hot or spicy foods, caffeine, and alcohol.

Exercise

It is difficult to perform randomized, prospective, double-blind, placebo-controlled trials on the effectiveness of exercise in prevention and treatment of disease. However, regular exercise may achieve the following: decrease the incidence and intensity of hot flashes; improve depressive symptoms, memory, quality of sleep, and sexual desire; prevent weight gain; and improve lipid profiles in postmenopausal women.[126]

Observational studies have shown regular aerobic exercise lessens the frequency and severity of hot flashes.[127,128] In a Swedish study of 1,323 postmenopausal women, 15 percent of sedentary women experienced "severe" hot flashes compared with only five percent of subjects who exercised.[128] These findings were not explained by differences in body mass index, HRT use, or smoking habits.

Similar results from exercise, including mood elevation in pre-, peri- and postmenopausal women, have been reported in other studies.[129] Considering the apparent effectiveness of physical activity to reduce the frequency and severity of hot flashes, as well as the many benefits of exercise on bone health, the cardiovascular system, and mood, regular physical exercise may enhance a woman's overall health.

Conclusion

Hot flashes are a common experience for menopausal women, and for many are severe enough to significantly compromise their overall sense of well-being and quality of life.

In contrast to HRT, soy protein and isoflavones do not appear to increase the risk of cancer, and may even decrease the risk of endometrial and breast cancers.[130] While SERMs may be an alternative to conventional HRT for cancer patients, studies show that they increase hot flashes. On the other hand, soy and other phytoestrogens, botanicals, dietary supplements, and other CAM approaches have been shown to be effective in treating hot flashes in menopausal women. Fewer than one in three menopausal women currently choose conventional HRT because of side effects and/or a fear of increased breast cancer risk.[131] Given these statistics, it becomes important to provide women with alternatives for reducing menopausal symptoms. The findings of the aforementioned research suggest there are effective alternative approaches to treating menopausal hot flashes.

Further research is certain to produce more definitive answers regarding effective treatments and potential side effects. Currently, the National Center for Complementary and Alternative Medicine is funding research on several botanicals that have shown promise for reducing menopausal symptoms, including black cohosh, red clover, hops, dong quai, flax seed, and dietary soy. The intention is to learn more about the mechanisms of action as well as the safety and effectiveness of these botanical products. Until definitive guidelines become available, an individualized approach should be applied, with careful consideration to both the benefits and risks of any treatment provided. With the information available to date, menopausal women can be encouraged to explore alternative approaches to alleviating hot flashes.

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