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Review

Review of Efficacy of Complementary and Alternative Medicine Treatments for Menopausal Symptoms

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Complementary and alternative medicine (CAM) treatments have been used for thousands of years around the world. There has been increased interest in utilizing CAM for menopausal symptoms since the release of results of the Women's Health Initiative elucidated long-term adverse effects associated with hormone therapy. Women looking for more natural or safer means to treat hot flushes, night sweats, and other menopausal symptoms often turn to CAM such as yoga, phytoestrogens, or black cohosh. Yet there have been few well-conducted studies looking at the efficacy of these treatments. This review examines randomized clinical trials, systematic reviews, and meta-analyses evaluating the effectiveness of commonly used CAM for the treatment of menopausal symptoms.
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INTRODUCTION

The National Center for Complementary and Integrative Health (NCCIH) defines complementary medicine as a health care approach developed outside of mainstream Western or conventional medicine that is used together with conventional medicine. Alternative health care is defined as an approach developed outside of mainstream or conventional medicine that is used instead of or in place of conventional medicine. A 2009 report from a nationwide government survey indicated that US adults spent $33.9 billion out of pocket on visits to complementary and alternative medicine (CAM) practitioners and purchases of CAM products, classes, and materials.[1] This represented 11.2% of total out-of-pocket expenditures on health care.

Hormone therapy (HT) with estrogens alone or estrogens in combination with progestins has been found to be the most effective treatment for menopausal symptoms.[2–5] However, results of the Women's Health Initiative (WHI) highlighted multiple concerns regarding the use of estrogen and progestin products in the treatment of menopausal symptoms. Treatment with prescription hormones has been associated with significant adverse effects such as coronary events, deep vein thromboembolisms, stroke, and breast cancer. Concerns regarding these adverse effects and varying opinions regarding suitability of HT for long-term use after age 60 have led to a decrease in HT use worldwide since 2002, following the release of the results of the WHI. There has been a resulting increased use and seeking of CAM therapies.[6–9]

CAM approaches for menopausal symptoms have included mind and body practices such as exercise and yoga, as well as herbal products/dietary supplements such as soy and isoflavone products, valerian, and black cohosh. The Global Consensus Statement on Menopausal Hormone Therapy endorsed by North American Menopause Society (NAMS) and The European Menopause and Andropause Society, among others, states that "menopausal hormone therapy is the most effective treatment for vasomotor symptoms associated with menopause at any age, but benefits are more likely to outweigh risks for symptomatic women before the age of 60 years or within 10 years after menopause."[3] However, the NAMS recommendations for clinical care of midlife women state that increased soy, isoflavone products, and other forms of phytoestrogens reduce menopause symptoms, although clinical trials demonstrate benefit similar to placebo.[10] In addition, the society advises that "CAM approaches, including acupuncture, herbal products, dietary soy, and isoflavone products, may be offered to treat vasomotor symptoms, although clinical trials generally demonstrate benefit for menopausal symptoms similar to that of placebo."[10] Despite such cautionary statements, consumer interest in CAM treatments remains high: 3 dietary supplements commonly used for menopause (black cohosh, flaxseed, and valerian) were among the 10 best-selling herbal dietary supplements in the United States in 2014.[11]

This review will examine the efficacy of selected CAM therapies for menopause. While not an exhaustive review, it will focus on those therapies cited most frequently in recent recommendations or guidelines from national organizations, systematic reviews, and meta-analyses.[4,5,9,10,12–15]

METHODS

Authors conducted a search of PubMed for English articles using a combination of search terms including, but not limited to, "menopause," "complementary and alternative medicine," "phytoestrogens," "herbal," and "soy," as well as the scientific names (eg, *Cimicifuga* or *Actaea racemosa* for black cohosh) of several products used to treat menopausal symptoms. Articles or books published within the previous 5 years describing randomized controlled trials, systematic reviews, and meta-analyses of CAM therapies were retrieved. The references of these resources were evaluated to identify further

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Quick Points

- Many women experiencing menopausal symptoms are turning to complementary and alternative medicine (CAM) due to concern of long-term risks with prescription hormone therapy. Yet the strength of evidence is low or insufficient overall for CAM therapies in the treatment of menopausal symptoms.
- Of CAM treatments for menopausal symptoms, soy and soy isoflavones have the strongest evidence for being effective in reducing the frequency and severity of hot flushes.
- For treatment of vasomotor symptoms, one might recommend soy-rich foods as a part of a balanced diet due to potential positive benefits on hot flush frequency and severity as well as heart health and bone mineral density with low risk of adverse effects.
- Evidence for effectiveness and safety of CAM therapies in treatment of menopausal symptoms is limited.

publications. There was minimal use of articles or studies older than 5 years, and only those identified as landmark trials (eg, Women's Health Initiative) or studies elucidating pharmacology of herbal treatments were used. This resulted in approximately 85 articles retrieved. Internet resources for CAM and herbal remedies were also reviewed and utilized in the writing of this article to identify and obtain more information about treatments and management (see Table 1). Scientific evidence levels were established based on a rubric adapted from 2 sources (Appendix 1). At least 2 of the 3 authors agreed and came to a consensus regarding the evidence level of the various therapies (see Table 2).

BACKGROUND

Menopause is defined as the cessation of menstrual periods or the final menstrual period confirmed when a woman has been without a menstrual period for 12 consecutive months.[10] The average age of menopause is 52 years, but the age of natural menopause can vary significantly from 40 to 58 years.[10] As a result of aging, there is reduced ovarian function, which leads to lower levels of estrogen and other hormones like androgens and progestogens. It has been proposed that abruptly lowered estrogen levels during menopause cause a changed thermoregulation set point of the hypothalamus, which leads to vasomotor symptoms consisting of hot flushes (flashes) and night sweats. The interaction of estrogen with neurotransmitters such as norepinephrine, endogenous opioids, and serotonin is also thought to alter temperature regulation set point in the hypothalamus. Decreased estrogen and changes in other hormone levels as well as dysregulation of neurotransmitters results in non-vasomotor symptoms associated with menopause such as anxiety, depression, difficulty concentrating, headaches, insomnia, irritability, loss of libido, and vaginal dryness.[2,4,9] For example, decrease in estrogen and androgen production in peripheral target tissues is thought to result in vulvovaginal atrophy or genitourinary syndrome of menopause. Symptoms include vaginal dryness, pain during sexual activity, irritation, and itching. Pain and burning during urination and urinary tract infections with vaginal discharge also commonly present with vulvovaginal atrophy. Furthermore, changes in serotonergic activity have been associated with depressive and other psychological symptoms in menopause.

It is estimated that as many as 50% to 75% of perimenopausal and postmenopausal women experience adverse symptoms related to menopause.[16] The most studied menopausal symptoms are vasomotor symptoms of hot flushes. It is estimated that 70% to 80% of postmenopausal women in the United States experience hot flushes, while 40% are affected enough to seek medical attention. The duration of vasomotor symptoms is believed to range from one to 7 years, with approximately 10% of women experiencing these symptoms for at least 10 years. The impact of menopausal symptoms on humanistic and economic outcomes is substantial. Symptoms associated with menopause lead to a significant decrease in health-related quality of life for postmenopausal women.

CAM TREATMENTS FOR MENOPAUSAL SYMPTOMS

Mind and Body Practices

Exercise

Exercise is inexpensive and has many health benefits such as improved cardiovascular and bone health. A sedentary lifestyle, defined as less than 3 weekly periods of physical activity lasting 30 minutes or longer, has been associated with a higher severity of menopausal symptoms including vasomotor and/or other symptoms.[18] Concentration of endorphins is thought to decline as estrogen production declines, and thus exercise may improve menopausal symptoms through increased endorphin production, a mechanism shared by hormone therapy.[19] However, current evidence is limited and does not totally support this theory. A 2014 Cochrane review, which included a total of 762 women from 5 randomized studies, found no effect of exercise on the frequency and intensity of vasomotor symptoms.[20] One small study (14 women) included in the analysis compared exercise with HT and found significantly fewer hot flushes reported in the HT group per 24 hours after 12 weeks (mean difference, 5.80; 95% confidence interval [CI], 3.17-8.43). The authors rated the quality of the evidence as low due to poor description of methods and inconsistent results, meaning that further research is needed.

A randomized controlled trial published in 2014 by Reed and colleagues examined the effect of 12 weeks of exercise, yoga, and omega-3 fatty acids on menopause quality of life

Table 1. Resources for Information Regarding Treatments for Menopausal Symptoms

Resource	Site Information and Content	Website Address (URL)
American Botanical Council	Independent, nonprofit, international member-based organization providing education on herbal medicines including monographs and articles regarding science-based and traditional information.	http://abc.herbalgram.org/site/PageServer
HerbMed	An interactive, electronic herbal database; provides hyperlinked access to the scientific data underlying the use of herbs for health. The public site provides access to 20 of the most popular herbs.	http://www.herbmed.org/
National Center for Complementary and Integrative Health (NCCIH)	The US agency for scientific research on the diverse medical and health care systems, practices, and products that are not generally considered part of conventional medicine.	https://nccih.nih.gov/
Natural Medicines	Provides monographs on dietary supplements, natural medicines, and complementary, alternative, and integrative therapies. Includes interaction checker, effectiveness checker, and information about pregnancy and lactation.	https://naturalmedicines.therapeuticresearch.com/
Natural Standard	Provides monographs with information on indications, effectiveness with grades, adverse effects, and an interactions checker. Recently taken over by Natural Medicines.	http://3rdparty.naturalstandard.com/frameset.asp
The North American Menopause Society (NAMS)	Official website of NAMS that includes resources for health care practitioners such as clinical recommendations and guidelines and resources for consumers such as links and answers to frequently asked questions.	https://www.menopause.org/home
United States (US) Food and Drug Administration (FDA)	Provides information regarding regulatory issues such as recalls, alerts, approvals, and clearances for foods, drugs, medical devices, etc.	http://www.fda.gov/default.htm

compared with usual care in 355 women.[21] The exercise intervention consisted of three 40- to 60-minute cardiovascular training sessions per week supervised by a certified trainer, with a weekly expenditure goal of 1000 to 1500 kcal. The primary objective was measured by the Menopausal Quality of Life (MENQOL) questionnaire,[22] which consists of 29 items distributed throughout 4 domains: vasomotor, physical, psychosocial, and sexual. Symptoms are rated as present or not present. If present, symptoms are rated using a Likert scale, from not bothersome to extremely bothersome. Mean scores are calculated for each domain and range from one to 8, with higher scores indicating worse symptoms. No improvements were seen on the total MENQOL score in the study, but a small reduction in the mean score for the physical domain was observed (−0.2; 95% CI, −0.5 to 0; $P < .02$). One criticism of this study is that the MENQOL questionnaire's correlation with a symptom diary for the vasomotor domain has been found to be only moderately good.[23] A similar publication by the same research group found no difference in vasomotor symptoms according to patient daily logs; however, exercise slightly improved the secondary endpoint of sleep quality compared with usual care.[24] In summary, there are theoretical benefits of exercise on menopausal symptoms, but the benefits seen in studies have been limited to physical symptoms, including sleep quality.

Yoga

Yoga practice most commonly consists of physical postures, controlled breathing, and meditation.[25] Studies evaluating the effects of yoga on menopausal quality of life have had mixed results. Many studies have had methodological issues reducing the impact and generalizability of the results. Many studies were uncontrolled; with small samples; varied by the type, frequency, and duration of practice; or included only a selected population of patients.[26–28] Furthermore, one study with

Table 2. Treatments for Menopausal Symptoms and Related Evidence Levels

Treatment Category	Treatments	Evidence Levels[a]
Mind-body practices	Acupuncture	C
	Exercise	C
	Clinical hypnosis[b]	B
	Mindfulness meditation	C
	Relaxation	C
	Reflexology	C
	Yoga	C
Natural herbal or food treatments		
Hormonal	Chasteberry/chaste tree (*Vitex agnus-castus*)	C
	DHEA[c] (dehydroepiandrosterone or prasterone) [Intrarosa]	C
	Ginseng (*Panax ginseng*)	C
Phytoestrogens	Flaxseed (*Linum usitatissimum*)	C
	Red clover (*Trifolium pratense*)	C
	Soy/soy isoflavones (Glycine max)	B
Neuromodulating agents	Black cohosh[d] (*Cimicifuga racemosa*) [Remifemin]	B/C
	Sage (*Salvia officinalis*)	C
	St. John's wort (*Hypericum perforatum*)[e]	C
	Valerian (*Valeriana officinalis*)	C
Other	Dong quai (*Angelica sinensis*)	D
	Evening primrose	C
	Wild yam	C
Combinations	Black cohosh/St. John's wort	C
	Soy isoflavones/lignans from linseed oil [Femarelle]	C

[a]Scientific evidence levels: A = strong evidence of efficacy and/or generally considered effective (may recommend); B = good evidence of efficacy or likely effective (may recommend); C = unclear or conflicting evidence of efficacy or possibly effective (too little quality or quantity of evidence to recommend); D = fair negative evidence of efficacy and/or some evidence of ineffectiveness (discourage use of product); F = strong negative evidence of efficacy or ineffective (discourage use of product).
[b]Good evidence found with clinical hypnosis, and it is recommended for vasomotor symptoms in menopause by the North American Menopause Society.[41] Use may be limited by barriers such as time commitment and access to appropriately credentialed practitioners.
[c]There is unclear or conflicting evidence of efficacy with most preparations. Prasterone or DHEA (Intrarosa) intravaginal formulation has FDA labeled indication to treat women experiencing moderate to severe pain during sexual intercourse (dyspareunia).
[d]Randomized controlled trials with standardized extracts show good effectiveness of black cohosh with evidence level of B. The majority of trials done and published to date have not been with the standardized extracts, and therefore evidence level for those preparations is C.
[e]St. John's wort is evidence level A for mild to moderate depression. NAMS recommends, "St John's wort may be advised for mild mood symptoms in midlife women."[7]

positive results had very high dropout rates, which may have led to an exaggeration of benefit.[26]

In the study by Reed and colleagues, the yoga intervention consisted of "cooling breathing exercises, 11-13 poses, and guided meditation."[21] Patients received a 90-minute yoga class weekly and were expected to engage in 20 minutes of home practice on all other days. A statistically significant but small reduction in the mean total MENQOL score was seen in the yoga group (−0.3; 95% CI, −0.6 to 0; $P < .02$) due to minor improvements in the vasomotor and sexual domains. No differences were observed in the psychosocial or physical domains. In a similar publication, the same investigators found no difference in vasomotor symptoms but found a statistically significant improvement in the secondary endpoint of insomnia symptoms in the yoga group compared to usual care.[29]

A recent study conducted in Brazil compared the effects of yoga, stretching exercises, and no intervention on menopause symptoms after 12 weeks.[30] The yoga intervention included 75 minutes of guided yoga twice a week. Each session consisted of 45 minutes of postures, followed by 10 minutes each of respiratory exercises, relaxation, and meditation. The primary outcome was change in the total Menopause Rating Scale (MRS) score.[31] The MRS consists of 11 symptoms with 3 domains: 4 psychological, 4 somato-vegetative, and 3 urogenital. Each symptom is rated on a Likert scale from 0 (asymptomatic) to 4 (extremely bothersome). Composite scores range from 0 to 44. The study found statistically significant reductions in total MRS scores compared to baseline ($P < .01$), compared to the control group ($P < .01$), and compared to the stretching group ($P < .05$). They found statistically significant improvements within the 3 domains of the MRS: somatic-vegetative (flushes, sleep, cardiac, and musculoskeletal/joint complaints); psychological (depressed, irritable, anxious, exhausted) and urogenital (sexual problems, urinary complaints, vaginal dryness). These results should be applied cautiously due to the high rate of attrition in the control group compromising the power of the study. This study cannot be directly compared to the study by Reed et al due to use of a different scale to assess the primary outcome. It is currently unknown if the increased frequency of guided practice in this study, twice weekly, compared to once weekly in the study by Reed et al, is the reason for the positive

results. Therefore, additional studies showing positive effects of yoga practice are needed to confirm its potential benefits.

Clinical Hypnosis

Clinical hypnosis induces a deeply relaxed state and has been used to reduce chronic symptoms such as pain. The NAMS position statement of 2015 states that clinical hypnosis may be recommended as relatively risk-free therapy. This recommendation was based on a recent study that found clinical hypnosis to be superior to structured attention control for the management of hot flushes.[32] Participants in the treatment group received hypnosis induction by a trained therapist and instruction on self-hypnosis for daily practice. The active control group received 5 sessions including discussion of symptoms, attentive listening, interpersonal exchange, avoidance of negative suggestions, monitoring, measurements, and encouragement provided by a trained clinician. Results were reported for 165 patients, 78 in the study group and 87 in the active control. A mean reduction in hot flushes after 12 weeks of 55.82 (74.16%) in the clinical hypnosis group was found compared to 12.89 (17.13%) in the structured attention group. The mean difference in hot flush frequency at 12 weeks was significant ($P < .001$; 95% CI, 36.15-49.67). The results are both statistically and clinically significant.

In summary, exercise and yoga have limited data for efficacy in treatment of vasomotor symptoms in menopause, and the NAMS position statement indicates that exercise and yoga should not be recommended for management of vasomotor symptoms. It is important to consider that women may find exercise and yoga helpful for other menopausal symptoms such as insomnia and sexual issues. While clinical hypnosis has limited but good evidence for vasomotor symptoms, barriers such as time commitment and availability of appropriately credentialed practitioners must also be considered.

Foods and/or Dietary Supplements

Phytoestrogens

Given the efficacy shown by estrogen and combined estrogen and progestin medications, it is not surprising that the most commonly used group of natural products for vasomotor symptoms would be plant estrogens, also known as phytoestrogens. Phytoestrogens are naturally occurring estrogen-like compounds found in plants, fruits, or vegetables.[33,34] Phytoestrogens are believed to be converted enzymatically in the gut to heterocyclic phenols: isoflavones to aglycones, genistein, and daidzen (metabolized to S(-)-equol); lignans to secoisolariciresinol-diglucoside (SDG); and coumestans to coumestrol. The phenolic rings in these breakdown products can compete for binding to the estrogen receptors. Phytoestrogens have 100 to 1000 times less activity than human estrogens. Phytoestrogens seem to show greater affinity for estrogen receptor beta (ERβ) than for classical estrogen receptor alpha (ERα). The products structurally resemble estrogen and may have weak estrogenic activity that is expressed in the central nervous system, blood vessels, bone, and skin without causing similar stimulation of breast or uterus.[9,33] Therefore, phytoestrogens may reduce vasomotor symptoms by impacting the vascular system without causing unwanted estrogenic effects in other body systems. However, they have also been shown to be selective estrogen receptor modulators, and in some situations may exhibit anti-estrogenic activity. Whether they have estrogenic or anti-estrogenic activity appears to depend on the amount of circulating endogenous estrogen. Phytoestrogens appear to exert anti-estrogenic effects in a high-estrogen environment and estrogenic effects in a low-estrogen environment like that of postmenopause.[9,33]

Multiple foods have been shown to contain phytoestrogens. Phytoestrogens are commonly divided into 3 main classes: isoflavones, lignans, and coumestans.[34] Isoflavones are commonly found in beans from the legume family. A major dietary source of isoflavones is soybeans and/or soy products. Lignans are commonly found in high-fiber foods such as unrefined grains, cereal brans, and beans. Flaxseed is a major dietary contributor of lignans. Coumestan-containing foods include alfalfa and clover sprouts, with lesser amounts in split peas, pinto beans, and lima beans.[34] One could obtain a significant amount of phytoestrogens from diet alone. There has been an increase in production of dietary supplements that would provide an even more concentrated and higher dose of phytoestrogens.

A recent meta-analysis by Chen and colleagues[13] evaluated the efficacy of phytoestrogens for the relief of menopausal symptoms with outcome measures including Kupperman index (KI)[13,35] changes, daily hot flush frequency, and the likelihood of side effects (Table 3). The KI measures menopausal symptoms including hot flushes, paresthesia, insomnia, nervousness, melancholia, headache, palpitations, vertigo, weakness, arthralgia or myalgia, and formication. Each symptom is rated on scale of 0 to 3 for no, slight, moderate, or severe complaints, with the highest score being 51.[13,35] While isoflavones were the phytoestrogens utilized in the majority of studies, phytoestrogens from other sources were also included in this analysis. The authors concluded that phytoestrogens did not cause a decrease in KI compared to placebo. Phytoestrogen use was associated with a reduction in hot flush frequency, and their side effects were no more common than those with placebo.

An extensive and comprehensive review was performed by the Evidence-Based Practice Center for the Agency for Healthcare Research and Quality.[5] This review examined 283 trials evaluating comparative effectiveness of treatments for menopausal symptoms, along with potential long-term benefits and harms of the treatments[5] (Table 3). The most commonly studied agents were estrogens, isoflavones, and selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs). Estrogens were found to be the most efficacious in relieving vasomotor symptoms and were accompanied by improved quality-of-life scores. The authors concluded that there was low strength of evidence that isoflavones improve vasomotor symptoms compared with placebo. In analyses comparing and ranking effectiveness of treatments for alleviating vasomotor symptoms (scale of 1 to 9, with 1 being best and 9 being worst), standard-dose estrogens were best at 1.3, isoflavones ranked 5.9, black cohosh ranked 6.7, and ginseng as 7.0.[5] There has been some positive evidence of isoflavones alleviating sleep issues, but the strength of evidence is low and more studies are needed.[5,34]

Table 3. Recent (Within Last 5 Years) Review and Meta-analysis Studies of Herbal Treatments of Menopausal Symptoms

Author, Year	Review Type, Sample Size	Treatment	Outcome Measures	Findings and Conclusions	Limitations
Chen[13] 2015	Systematic review and meta-analysis 15 trials 3762 participants	Isoflavones, S-(-) equol, trifolium	KI, daily hot flush frequency and likelihood of side effects	Phytoestrogens did not result in significant decrease in KI scores. Four of 10 studies reporting hot flush frequency reported significant reduction in the phytoestrogen group. Meta-analysis showed significant reduction in hot flushes with use of phytoestrogens as compared to placebo.	Variety of isoflavones and doses. Included studies that looked at Trifolium and combinations of isoflavones and lignans as well as isoflavones from red clover with other isoflavones.
Dew[42] 2013	Systematic review 11 trials 632 participants	Ground flaxseed. Some studies measured secoisolarciresinol or lignans total	Menopausal symptoms, sex hormones, bone biomarkers	Four studies reported statistically significant decreases in hot flush frequency or combined hot flush/severity scores, but these were not significantly different from changes in the control arms. One study reported that hot flush severity was significantly lower in flax-treated volunteers compared to placebo.	Varying doses of flaxseed were used. Study looked at dietary flaxseed consumption, but studies did not control for other dietary factors. Some studies reported grams of flaxseed, others also included grams of lignans.
Franco[12] 2016	Systematic review and meta-analysis 62 trials 3762 participants	Dietary soy isoflavones, supplements and extracts of soy isoflavones, red clover, black cohosh	Number of hot flushes in 24 hours Number of night sweats in 24 hours Vaginal dryness score	Soy supplementation led to modest reduction in hot flashes and vaginal dryness. Red clover associated with improvements in night sweats but not with frequency of hot flushes. No significant association between black cohosh supplementation and menopausal symptoms.	Assessments based on limited studies, quality of included studies was limited. Supplements used in studies may vary in quality and composition.

(*Continued*)

Table 3. Recent (Within Last 5 Years) Review and Meta-analysis Studies of Herbal Treatments of Menopausal Symptoms

Author, Year	Review Type, Sample Size	Treatment	Outcome Measures	Findings and Conclusions	Limitations
Ghazanfarpour[44] 2015	Systematic review 11 trials 907 participants	Red clover	Primary outcomes: hot flush frequency, hot flush intensity, and sweating at night Secondary: Effects on FSH, LH, SHBG, estradiol, and testosterone. Effect on endometrial thickness	Greater decline in hot flush frequency seen in 6 trials of red clover versus placebo. Intensity of hot flushes seemed to decrease with red clover; however, authors suggested that more studies with consistent statistical methodology be used.	Included studies looking at perimenopausal and postmenopausal women. Large heterogeneity among trials due to isoflavone bioavailability, amount of administered red clover, and isoflavones received by other food sources.
Grant[5] 2015	Systematic review 211 trials More than 53,000 women	Estrogen, SSRIs, SNRIs, gabapentin, progestogens. Nonprescription agents: isoflavones (40 trials), black cohosh, vitamin E, flax seed, St. John's wort, ginseng, and variety of herbs and other agents.	Hot flush frequency, hot flush severity, night sweats, combined hot flush and night sweats, Greene vasomotor scale, Kupperman vasomotor, MENQOL vasomotor, WHQ vasomotor, MRS	Low strength of evidence that isoflavones alleviate vasomotor symptoms more than placebo.	Enrolled women could be perimenopausal or postmenopausal. Large number of calculations were required across multiple arms of multiple trials. Large variety of outcome measures.
Leach[47] 2012	Cochrane review 16 trials 2027 perimenopausal and menopausal women	Black cohosh versus placebo, hormone therapy, red clover, and fluoxetine	Primary outcomes: vasomotor symptoms, vulvovaginal symptoms, menopausal symptom scores, and adverse effects	There were no statistically significant differences between black cohosh and placebo in frequency of vasomotor symptoms or in menopausal symptom scores. Results in terms of adverse effects were inconclusive due to poor reporting.	Heterogeneity between trials, poor quality of trials, poor reporting, and small treatment groups.

(*Continued*)

Table 3. Recent (Within Last 5 Years) Review and Meta-analysis Studies of Herbal Treatments of Menopausal Symptoms

Author, Year	Review Type, Sample Size	Treatment	Outcome Measures	Findings and Conclusions	Limitations
Lethaby[9] 2013	Cochrane review 43 trials 4084 participants	Soy isoflavones (flour, powder, or beverages), soy isoflavone extracts, red clover extracts, genistein extracts, flaxseed dietary supplements, hop extract, S-(-) equol and *Rheum rhaponticum* root extract	Daily frequency of hot flushes	Some trials reported slight reduction in hot flushes and night sweats with phytoestrogens. Extracts containing genistein (from soy) appeared to reduce number of daily hot flushes. No evidence that other phytoestrogens work any better than placebo.	Many of the trials were small, of short duration and questionable quality. Wide variance in type of phytoestrogens used. Only 5 studies qualified for meta-analysis.

Abbreviations: FSH, follicle-stimulating hormone; KI, Kupperman index; LH, luteinizing hormone; MENQOL, Menopause Quality of Life; MRS, Menopause Rating Scale; SHBG, sex hormone–binding globulin; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; WHQ, Women's Health Questionnaire.

Bedell and colleagues reviewed efficacy and safety of phytoestrogens as divided into subgroups of isoflavones, lignans, and coumestans.[34] This review not only examined effects on vasomotor symptoms but also looked at efficacy in alleviating vaginal atrophy, insomnia, and osteoporosis. There were encouraging findings of the proprietary blend of isoflavones and lignans (Femarelle) being favorable to genital tissues. Isoflavones appeared to have a protective effect in short-term use, and positive effects became more apparent with more prolonged (6 months) usage. Despite these positive findings, the comparative effectiveness review found that there is low strength of evidence that isoflavones improve symptoms of urogenital atrophy.[5]

Safety concerns with phytoestrogens include the idea that these substances, in having estrogenic effects, may lead to increased risk of breast cancer and endometrial hyperplasia. Examination of findings regarding safety of phytoestrogens has shown that the most common and significant adverse effect with phytoestrogens is gastrointestinal irritation. One review noted that endometrial cancer risk was not increased with the use of phytoestrogens, with some studies suggesting a possible protective effect with isoflavone and lignan combination use.[34,36,37] One case-control study examined dietary information from 500 women aged 35 to 79 years who were diagnosed with endometrial cancer and 470 age- and ethnicity-matched control women.[38] Isoflavone and lignan consumptions were inversely related to the risk of endometrial cancer. The associations were slightly stronger in postmenopausal women. The highest risk of endometrial cancer was found in postmenopausal women who were obese and consumed relatively low amounts of phytoestrogens.[38]

Soy

Among phytoestrogens, soy (*Glycine max*) and soy isoflavones are the most commonly used and studied agents for treatment of menopausal vasomotor symptoms. Many studies have looked at the effectiveness of isoflavones from foods (mainly soy) and isoflavone supplements. A recent systematic review and meta-analysis by Franco et al looked at 62 trials of plant-based therapies that were further subcategorized into isoflavones (dietary, supplements, and extracts), red clover, black cohosh, and Chinese medicinal herbs.[12] In the evaluation of the 24 trials of soy isoflavones, it was found that soy isoflavones led to modest reduction in hot flushes and vaginal dryness but no significant reduction of night sweats. A Cochrane review found that very few trials provided data suitable for inclusion in meta-analysis.[9] Four trials that were not part of the meta-analysis suggested that extracts with high (>30 mg/d) genistein (a soy isoflavone) levels consistently reduced the frequency of hot flushes. Other trials of dietary soy (6 of 13) and soy extracts (9 of 12) included in the Cochrane review found that soy isoflavones alleviated the frequency and severity of hot flushes and night sweats, but many of these trials were small and determined to be at high risk of bias.[9]

Recent studies have indicated that the metabolite of daidzein, S-equol, has efficacy in treating vasomotor symptoms.[9,39,40] One double-blind, placebo-controlled trial looked at 77 postmenopausal Japanese women consuming 10 mg/day S-equol compared to 83 women in the placebo

group. After a 12-week intervention, the S-equol group had a greater decrease from baseline in hot flush frequency compared with the placebo group. Severity of hot flushes and neck or shoulder muscle stiffness significantly decreased in the S-equol group as compared to the placebo group.[39] The NAMS 2015 position paper says it may be recommended with caution.[41]

Flax and Flaxseed

A recent systematic review points to some positive evidence for flaxseed (*Linum usitatissimum*) decreasing frequency of hot flushes.[42] Pruthi et al evaluated the effect of consumption of flaxseed bars (410 mg of lignan) versus placebo bars for 6 weeks and determined that in both groups approximately a third of women reported a 50% decrease in hot flushes.[43] Dew et al[42] determined that while 4 of 5 studies looking at the effect of flaxseed consumption in decreasing hot flush frequency or combined hot flush frequency and severity scores showed positive effects, the changes were not significantly different from similar changes in the control arms. It was concluded that of the 5 studies, none reported benefit for hot flush frequency and/or severity beyond placebo.[42]

Red Clover

Red clover (*Trifolium pratense*) contains phytoestrogens from isoflavone and coumestan groups. In many of the studies of phytoestrogens in general and isoflavones specifically, various forms and formulations of red clover have been utilized. Notably, in the Cochrane review of phytoestrogens for vasomotor symptoms of menopause,[9] 5 studies that used a proprietary formula containing red clover extract (Promensil) were included in the meta-analysis. No significant difference overall was noted in the number of hot flushes per day between study participants taking this product and those given placebo (mean difference, −0.93; 95% CI, −1.95 to 0.10). No evidence indicated a difference in percentage reduction in hot flush frequency in 2 trials between the proprietary formula containing red clover extract (Promensil) and placebo (mean difference, 20.15; 95% CI, −12.08 to 52.38).[9]

One systematic review of trials of red clover included 11 studies.[44] This review had primary outcome measures of hot flush frequency and intensity and night sweats. Red clover had a positive effect on alleviating hot flushes in menopausal women. Yet the significance of these positive results is tempered by limitations such as lack of control of dietary intake of other phytoestrogens or failure to measure isoflavones (in urine or otherwise). The trials included perimenopausal and postmenopausal women with varying hormone statuses, which limited the strength of evidence.

In summary, there is insufficient evidence to recommend soy or soy isoflavones, flax or flaxseed, or red clover dietary supplements.[41] One might recommend soy-rich foods as a part of a balanced diet due to potential positive effects on menopausal symptoms as well as heart health and bone mineral density with low risk of adverse effects.[33]

Neuromodulating Agents

There has been much attention recently given to the effects of agents such as SSRIs/SNRIs and gabapentin on menopausal symptoms.[45] Herbal agents such as black cohosh, St. John's wort, and valerian, acting on similar neurotransmitters or by similar mechanisms, have been tried with some positive results.

Black Cohosh

Black cohosh (*Cimicifuga racemosa*) is one of the most widely studied and popular herbal remedies for menopausal symptoms.[12] Black cohosh was originally thought to be a phytoestrogen containing isoflavones, which have an estrogenic effect on the release of luteinizing hormone (LH) in women. The pulsed release of LH has been linked to the occurrence of hot flushes. Recent studies have shown black cohosh to have no direct effect on estrogen receptors and have demonstrated dopaminergic, serotonergic, and GABAergic effects.[46] It is hypothesized that the synergistic effects of these components may be the key to their effectiveness in treating hot flushes.[46] In vitro and animal studies on cancer tissue from the mammary gland and endometria have demonstrated no carcinogenic effect.[46]

In a Cochrane review of the effectiveness of black cohosh in treating symptoms of menopause, the authors concluded that there was "insufficient evidence to support its use." However, the authors did recommend further investigation due to the questionable quality of the trials conducted up to that point.[47] Since this review, it appears that the methodology of clinical trials (eg, blinding, statistical testing, reporting results) has improved. However, heterogeneity between studies still exists due to the use of varying extracts, different plant species, various doses, different outcomes measures, and different patient populations.

Schellenberg and colleagues investigated whether there was a dose-dependent response to the *Cimicifuga racemos*a extract Ze 450.[48] The study involved 166 postmenopausal women in 4 outpatient clinics in Germany. The primary outcome was improvement on the KI. The women were randomized to a low dose (6.5 mg Ze 450), a high dose (13 mg Ze 450), or placebo for 12 weeks. They found a significant change from baseline in reducing the KI in both treatment groups versus placebo (low dose, −8.47%; 95% CI, −11.30 to −5.55; high dose, −17; 95% CI, −19.35 to −14.65).[48] Statistically significant reduction in individual items such as hot flushes and sweating were seen only in the high-dose group.[48] A second group of researchers used the same black cohosh standardized extract in an observational study in Switzerland. They suggested treating physicians use the high dose (13 mg Ze 450) for the first phase (3 months) and then let the physician decide whether to change the dose during the second phase to a lower dose (6.5 mg Ze 450) or continue on the higher dose. The study included 440 women with menopausal complaints. The primary outcome was a decrease in total KI scores. They found statistically significant decreases in those patients treated with high dose, low dose, and double the high dose at 3 months ($P < .0001$). At 6 months KI scores were further reduced in both the high- and low-dose groups but were significantly more reduced in those that continued the high-dose treatment.[49]

Two randomized, placebo-controlled trials done in Iran looking at vasomotor symptoms found statistically significant decreases at 8 weeks using 6.5 mg of dried extract of black cohosh root.[50,51] A study in China compared black cohosh to

2 different estrogen and progesterone regimens for 3 months in 89 participants. KI scores were significantly reduced in all groups, but the scores in the black cohosh group were reduced less than in the 2 hormone-treated groups. However, there was not a statistically significant difference between groups.[52]

One randomized, placebo-controlled trial performed in Thailand found a black cohosh extract of 40 mg/day non-superior to placebo in reducing KI scores, frequency of hot flushes, and quality of life. The authors suggest that the dose they used had less of the active ingredient (1.28 mg) compared with other reports, which may have affected their outcomes.[53]

There has been some concern about hepatotoxicity with long-term use of black cohosh, yet only one trial reported elevation in liver enzymes occurring in 3 study participants (one from each study group: placebo, low dose, and high dose). The authors attributed this to heavy alcohol use in 2 of the 3 participants.[48] Yet not all studies monitored liver enzymes, and most of the trials were less than 12 weeks. Other side effects related to black cohosh use were gastrointestinal (ie, stomach pain, diarrhea, nausea), with one study reporting a slight incidence of breast tenderness and vaginal bleeding.[49] When looking at recent data, standardized extracts of black cohosh, such as those approved for use in treatment in many European countries, seem to be safe and effective to decrease vasomotor symptoms.[4]

St. John's Wort

St. John's wort (*Hypericum perforatum*) has shown efficacy for mild depression and has been utilized for depressive symptoms associated with menopause. The mechanism of action of St. John's wort is not fully understood. Monoamine oxidase inhibition, inhibition of serotonin receptor, and serotonin reuptake inhibition have been suggested as means of activity.[54,55] A meta-analysis by Liu et al concluded that St John's wort extracts and its combination with other herbs were significantly superior to placebo, and extracts of the plant proved to be more effective than placebo in the treatment of menopausal symptoms, specifically hot flushes. Interestingly, the authors did not note a significant difference in depressive symptoms following treatment. The trial had several significant limitations, which temper the strength of these results. There was high heterogeneity because the analyses were based on a very small number of studies with multiple doses and measurements being used. While the study noted that the adverse effects in the included trials did not differ significantly from placebo, there is significant concern about safety of St. John's wort due to herb-drug interactions. St. John's wort may interact with prescription antidepressants to produce serotonin syndrome. It has been noted to have inhibitory and induction effects in the cytochrome P450 system, which may lead to numerous interactions that are unpredictable.[54]

Valerian

Valerian (*Valeriana officinalis*) is an herb that has shown some promise in treatment of menopausal symptoms.[56–58] Taavoni et al conducted a randomized, placebo-controlled triple-blind study of 100 postmenopausal women experiencing insomnia.[56] The 50 women on active treatment received 530 mg of valerian root extract twice daily for 4 weeks. Improvement in sleep quality was seen in 30% of the valerian group as compared to 4% of the placebo group. Another recent double-blind, placebo-controlled study looked at the use of valerian for hot flushes in 68 menopausal women.[57] Women in the valerian group received 255 mg valerian capsules 3 times daily for 8 weeks. Valerian treatment resulted in significantly decreased severity and frequency of hot flushes as compared to the placebo group.[57] Valerian is purported to have sedative, anxiolytic, and antidepressant properties. The mechanism of action is unknown but valerian is reported to have serotonergic activity.[59] Valerian has also been suggested to act by modulation of gamma-aminobutyric acid (GABA) neurotransmission. While valerian has shown positive effects for treating insomnia and sleep issues in general, there is insufficient evidence for sleep issues associated with menopause.[5] There is insufficient evidence for valerian alleviating hot flushes.[5,58]

CONCLUSION

Many treatment modalities of CAM have studies showing positive effects, including clinical hypnosis, yoga, soy and soy isoflavones, and black cohosh. Yet there have also been studies showing effects similar to placebo, meaning that there is unclear or conflicting evidence for the effectiveness of most of these CAM treatments. Therefore, while generally not considered harmful, there is insufficient evidence of safety and efficacy to recommend most forms of CAM. While not an exhaustive review of available CAM therapies for menopausal symptoms, among the dietary supplements, soy and soy isoflavones have the strongest evidence for being effective in reducing frequency and severity of hot flushes. Dietary soy or soy isoflavones (S-equol-containing supplements) may be recommended for vasomotor symptoms. Evidence of effectiveness for black cohosh has improved, with good evidence existing for standardized preparations of this herb, which may be recommended. Clinical hypnosis may be recommended for vasomotor symptoms.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to disclose.

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Appendix 1: Rubric for Evaluating Evidence about Complementary and Alternative Therapies for Menopause

A	Strong evidence of efficacy and/or generally considered effective (may recommend). There is evidence from at least 2 randomized clinical trials or meta-analysis. Trials and/or meta-analysis are of good quality with low risk of bias.
B	Good evidence of efficacy or likely effective (may recommend). There is evidence from at least one randomized clinical trial, meta-analysis, case control, or epidemiological studies. Studies have low risk of bias. Contrary evidence of effectiveness may exist, but positive evidence outweighs the contrary evidence.
C	Unclear or conflicting evidence of efficacy or possibly effective (too little quality or quantity of evidence to recommend). Studies have low to moderate risk of bias. Contrary evidence of effectiveness may exist and is not outweighed by positive evidence.
D	Fair negative evidence of efficacy and/or some evidence of ineffectiveness (discourage use of product). There is evidence from at least 2 randomized clinical trials or meta-analysis. Trials and/or meta-analysis are of good quality with low risk of bias.
F	Strong negative evidence of efficacy or ineffective (discourage use of product). There is evidence from one randomized clinical trial, meta-analysis, case control, or epidemiological studies. Trials and/or meta-analysis are of good quality with low risk of bias. Evidence consistently indicates negative outcomes

Adapted from rubrics developed by Natural Standard[60] and Natural Medicines.[61]