Complementary and Alternative Therapies for the Management of Menopause-Related Symptoms

A Systematic Evidence Review

Anne Nedrow, MD; Jill Miller, MD; Miranda Walker, BA; Peggy Nygren, MA; Laurie Hoyt Huffman, MS; Heidi D. Nelson, MD, MPH

Background: Nearly half of adults in the United States use complementary and alternative therapies each year for a variety of reasons. These therapies are increasingly popular among women seeking alternatives to treatment with estrogen for managing menopausal symptoms. The objective of this review was to assess the effectiveness of complementary and alternative therapies in the management of menopausal symptoms.

Data Sources: MEDLINE, PsychINFO, Cochrane Library database, MANTIS, and AMED.

Study Selection: Full-text, English-language, randomized controlled trials and meta-analyses comparing a complementary or alternative therapy with placebo or control for treatment of menopausal symptoms.

Data Extraction: All eligible trials were reviewed, abstracted into evidence tables, and rated for quality.

Data Synthesis: Seventy randomized controlled trials met inclusion criteria. Forty-eight studies of phytoestrogens and other biologically based agents showed mixed results. Smaller numbers of studies using mind-body, energy, manipulative, and body-based therapies and whole medical systems showed little benefit in treating menopausal symptoms.

Conclusions: Although individual trials suggest benefits from certain therapies, data are insufficient to support the effectiveness of any complementary and alternative therapy in this review for the management of menopausal symptoms. Many of these potential therapies warrant further study in trials with rigorous scientific designs to determine benefit and safety.

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Approximately 40% of women seek medical advice for the management of menopausal symptoms that include hot flashes, night sweats, vaginal dryness, and sleep disorders. The Women’s Health Initiative influenced many women to discontinue estrogen therapy, leading more health care professionals and their patients to consider alternatives to estrogen. The 25 million women who will move through menopause during the next decade face an increasingly complex array of alternative therapies for their symptoms.

Previous surveys indicate that 42% of US adults have used alternative medicine during the past year (excluding prayer). Several hundred menopausal women in Seattle, Wash, took part in a survey that listed stress management, herbal remedies, and massage as popular approaches. Seventy percent of them did not reveal to their physicians the use of dietary supplements for menopausal symptoms. Millions of dollars are spent on over-the-counter products for menopausal symptoms by women who have little knowledge of their quality, safety, or effectiveness. The National Institutes of Health invests over $200 million annually in research on alternative therapies.

The National Center for Complementary and Alternative Medicine has divided complementary and alternative medicine into the following 5 categories: biologically based, mind-body, energy, manipulative and body-based therapies, and whole medical systems.

Biologically based therapies, purchased over the counter or through specialized health professionals, include botanicals, animal-derived extracts, vitamins, minerals, fatty acids, amino acids, proteins, probiotics, whole diets, and functional foods. Mind-body therapies focus on the interactions among the mind, body, and behavior and the ways in which emotional, mental, social, spiritual, and behavioral factors can directly affect health. The mind-body approach respects and enhances each person’s capacity for self-knowledge and self-regulation.
osteopathic manipulation, manipulative or body-based therapies include chiropractic and therapeutic touch and Reiki. Popular examples include in the physical body to influence this energy, using it to effect changes claim that they can see and work with a subtle form of energy. Therapists that human beings are infused with energy fields are based on the concept of modalities. Therapies involving these energy fields are frequently measured by reproducible methods. Veri-

Putative energy fields have defied measurement by reproducible methods. Therapies involving these energy fields are based on the concept that human beings are infused with a subtle form of energy. Therapists claim that they can see and work with this energy, using it to effect changes in the physical body to influence health. Popular examples include therapeutic touch and Reiki.

Manipulative and body-based therapies include chiropractic and osteopathic manipulation, massage, and techniques such as the Feldenkrais method and Rolfing.

Whole medical systems involve complete systems of theory and practice that have evolved independently from allopathic medicine and that are often culturally based. Eastern whole medical systems include those from China (traditional Chinese medicine) and India (ayurvedic medicine). Western whole medical systems include homeopathy and naturopathy. Additional examples can be found in Native American, African, Middle Eastern, Tibetan, and Central and South American cultures.

This systematic review evaluates alternative therapies for the management of menopausal symptoms classified using these categories. A summary of the complete review has been published separately.

**METHODS**

We identified studies from multiple searches of MEDLINE (1966 to March 2005), PsychINFO (1974 to March 2005), the Cochrane Library database (1966 to March 2005), systematic reviews, reference lists, experts, and Web sites. Searches of MANTIS and AMED revealed no relevant studies. Articles were selected based on predetermined inclusion and exclusion criteria. Randomized placebo-controlled trials and meta-analyses published in English, using alternative therapies categorized by the National Center for Complementary and Alternative Medicine, were included. Trials enrolling women with breast cancer were included; trials of nonmenopausal women and studies using animals were excluded.

Data were abstracted into evidence tables and summarized descriptively; we did not perform statistical analysis because of the heterogeneity of trials. Outcomes included hot flash frequency and severity, sleep disturbance, vaginal dryness, vaginal bleeding, urinary frequency or incontinence, quality-of-life changes, depression, anxiety, sexual dysfunction, and cognitive function, most frequently measured by the Kupperman Index and the Greene Climacteric Scale. The Kupperman Index measures the self-reported severity of hot flashes on a scale of 0 to 3 and 10 other symptoms: paresthesias, insomnia, nervousness, melancholia, vertigo, weakness, arthralgia or myalgia, headache, palpitations, and lassitude. The Greene Climacteric Scale assesses the severity of 21 self-reported symptoms on a 4-point scale and includes psychological, somatic, vasomotor, and sexual dysfunction symptoms.

A best-evidence approach was applied to eligible trials; trials with the highest-quality and most rigorous design are emphasized. Two reviewers (A.N. and J.M.) independently rated the quality and external validity of trials using criteria specific to randomized controlled trials developed by the US Preventive Services Task Force (see the Appendix available online at www.obstet.org). When reviewers disagreed, a final rating was reached through consensus. Characteristics of poor-quality trials include enrollment of fewer than 20 subjects, study duration of less than 12 weeks, and not reporting group differences or ages of subjects.

**RESULTS**

From 1432 identified abstracts, 70 randomized controlled trials met inclusion criteria: 48 biologically based therapies, 9 mind-body therapies, 1 manipulative or body-based therapy, 2 energy therapies, and 10 whole medical systems (Figure).
### Table 1. Trials of Phytoestrogens

<table>
<thead>
<tr>
<th>Source (Condition Treated)*</th>
<th>No. of Patients in Study</th>
<th>Therapy</th>
<th>Comparison</th>
<th>Duration of Therapy, wk</th>
<th>Main Results</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Patten et al,19 2002 (breast cancer)</td>
<td>157</td>
<td>Soy beverage (IF, 90 mg/d)</td>
<td>Placebo</td>
<td>12</td>
<td>NBGD in frequency and intensity of HFs</td>
<td>Improved HF frequency and intensity in both groups</td>
</tr>
<tr>
<td>Albertazzi et al,14,15 1998, 1999</td>
<td>104</td>
<td>Soy powder, 60 g (IF, 76 mg)</td>
<td>Casein powder, 60 g</td>
<td>12</td>
<td>Improved HF frequency with soy vs casein at 12 wk (P=.01); NBGD on KI</td>
<td>Improved HF frequency in both groups (44% reduction with soy, 31% with placebo; no changes in KI)</td>
</tr>
<tr>
<td>Burke et al,18 2003</td>
<td>241</td>
<td>Soy drink, IF, 42 mg/d; or soy drink, IF, 58 mg/d</td>
<td>Soy drink with IF removed</td>
<td>96</td>
<td>NBGD in frequency and severity of HFs and night sweats (SRSD)</td>
<td>Improved HF frequency and severity in all groups (P=.001)</td>
</tr>
<tr>
<td>Han et al,17 2002</td>
<td>82</td>
<td>Soy IF (soy protein, 50 mg, and IF, 33 mg)</td>
<td>Placebo</td>
<td>20</td>
<td>NR</td>
<td>Improved HFs, insomnia, mood, and KI scores in soy group</td>
</tr>
<tr>
<td>Knight et al,18 2001</td>
<td>24</td>
<td>Soy IF powder beverage, 60 g/d (IF, 154.4 mg/d)</td>
<td>Casein powder</td>
<td>12</td>
<td>NBGD in flushing frequency or GCS scores</td>
<td>Improved flushing frequency in both groups</td>
</tr>
<tr>
<td>Morkies et al,19 1995</td>
<td>58</td>
<td>Soy flour, 45 g/d</td>
<td>Wheat flour, 45 g/d</td>
<td>14</td>
<td>NBGD for HFs and general symptom scores</td>
<td>Improved HFs and general symptom scores in both groups at 12 wk (P=.05)</td>
</tr>
<tr>
<td>St. Germain et al,20 2001</td>
<td>69</td>
<td>Soy protein (IF, 80 mg/d); or Soy protein (IF, 4.4 mg/d)</td>
<td>Soy protein (whey protein)</td>
<td>24</td>
<td>NBGD in HF frequency or severity, mood, vaginal dryness, or urinary and sexual symptoms (menopausal index)</td>
<td>Improved HFs in all groups (P=.03)</td>
</tr>
<tr>
<td>Balk et al,21 2002</td>
<td>27</td>
<td>Soy and corn flour cereal (IF, 100 mg/d)</td>
<td>Wheat cereal (Post Grape Nuts)</td>
<td>24</td>
<td>NBGD in HFs, night sweats, palpitations, headache, depression, vaginal dryness, or decreased libido over 6 mo (MSQ); soy group had more instances of insomnia than placebo (P=.02)</td>
<td>Improved HFs, night sweats, and vaginal dryness with placebo (P=.05)</td>
</tr>
<tr>
<td>Dalais et al,12 1998</td>
<td>52</td>
<td>Soy diet (high in IF); or linseed diet (high in IF)</td>
<td>Wheat diet (low in IF) crossover</td>
<td>12 Each phase</td>
<td>NR</td>
<td>Improved rate of HFs (SRSD) with linseed diet (41% decrease) or wheat diet (51% decrease) but not with soy diet</td>
</tr>
<tr>
<td>Wachburn et al,22 1999</td>
<td>51</td>
<td>Soy protein, 20 g (phytoestrogen, 34 mg/d); or soy protein, 20 g (phytoestrogens, 34 mg/d) in 2 doses</td>
<td>Placebo</td>
<td>6</td>
<td>Improved severity of HFs (SRSD) with soy vs placebo (P&lt;.001); hypoestrogenic symptom score was improved with soy vs placebo (P=.05); NBGD in number of HFs, night sweats, sleep disturbance, or general health score</td>
<td>Improved health score (P=.001); NBGD on the GCS score or in mood; improved memory with soy vs placebo (delayed recall of pictures, P&lt;.03; immediate story recall, P&lt;.06; reversal of the simple discrimination rule, P=.05; improved time to learn complex tasks, P&lt;.05)</td>
</tr>
<tr>
<td>Duffy et al,23 2003</td>
<td>36</td>
<td>Soy IF supplement, 60 mg/d</td>
<td>Placebo</td>
<td>12</td>
<td>NBGD on the GCS score or in mood; improved memory with soy vs placebo (delayed recall of pictures, P&lt;.03; immediate story recall, P&lt;.06; reversal of the simple discrimination rule, P=.05; improved time to learn complex tasks, P&lt;.05)</td>
<td>No changes in menopausal symptoms</td>
</tr>
<tr>
<td>Faure et al,24 2002</td>
<td>75</td>
<td>Soy IF extract (genistein and diadzein, 70 mg/d)</td>
<td>Placebo</td>
<td>16</td>
<td>Improved HF frequency (SRSD) with soy vs placebo (P=.01); no effect on other symptoms</td>
<td>Improved HFs in soy (61% reduction) and placebo groups (21% reduction)</td>
</tr>
<tr>
<td>Kritz-Silverstein et al,25 2003</td>
<td>56</td>
<td>Soy extract supplement (IF, 100 mg/d)</td>
<td>Placebo</td>
<td>24</td>
<td>Improved cognitive test (category fluency) for soy vs placebo (P=.05); NBGD for 2 tests of verbal memory and Trails B test</td>
<td>Improved cognitive tests for both groups</td>
</tr>
</tbody>
</table>

(continued)

**BIOLOGICALLY BASED THERAPIES**

**Phytoestrogens**

Table 1 shows results from trials of phytoestrogens. Included in the table are dietary soy isoflavones (eg, flour,19,21 beverage,14,15,20,22,23 and powder13,16-18 forms; supplement and extract forms of soy isoflavones; red clover phytoestrogens; and other phytoestrogens). A good-quality study enrolling breast cancer survivors compared 56 patients ingesting 90 mg/d of isoflavone soy drink with 55 patients who took placebo, with no differences reported between the 2 groups in hot flash frequency or intensity, yet the study found improvement in both groups from baseline.13 The largest fair-quality trial of women without breast cancer,22 showing results from trials of phytoestrogens.

Note: *IF=Isolauronol.**

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Phytoestrogens

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Note: *IF=Isolauronol.**
cancer enrolled 241 women for 24 months and compared 2 doses of isoflavones in a soy drink (58 mg/d vs 42 mg/d) with placebo.16 No between-group differences in frequency or severity of hot flashes or night sweats were observed. Four additional trials failed to show benefit compared with placebo.18-21 Albertazzi and coauthors14,15 reported mixed results in hot flash reduction in 2 fair-quality studies. Three other trials compared 54 mg/d of genistein isoflavone with that of placebo showed significant improvement in hot flash frequency; however, no effect was seen on other menopausal symptoms.25 Poor-quality studies showed variable results.26-28 Results were mixed in 2 fair-quality studies on cognitive memory testing among women using soy supplements.24,26

Red clover was the active compound examined in 6 trials.22-27 A good-quality 12-week trial22 comparing red clover isoflavone tablets (82 mg/d vs 57 mg/d) with placebo in 252 women experiencing hot flashes showed no difference in any of the 3 groups as measured by number of hot flashes per day (P > .001). Three other trials, 1 of which enrolled 205 women,16 reported similar results.29-31 Seven studies, 2 enrolling women with breast cancer,30,31 used other phytoestrogen preparations.32-33 The longest study included 90 women using soy supplements.34-41 Results were mixed in 2 fair-quality studies of cognitive memory testing among women using soy supplements.24,26

### Table 1. Trials of Phytoestrogens (cont)

<table>
<thead>
<tr>
<th>Source (Condition Treated)</th>
<th>No. of Patients in Study</th>
<th>Therapy</th>
<th>Comparison</th>
<th>Duration of Therapy, wk</th>
<th>Between-Group Differences</th>
<th>Within-Group Differences</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penotti et al, 2003</td>
<td>62</td>
<td>Soy tablet (IF, 36 mg/d, and saponine, 48 mg/d of soy)</td>
<td>Placebo</td>
<td>24</td>
<td>NBGD in HFs (SRSD)</td>
<td>40% Reduction in HFs overall in both groups</td>
<td>Fair</td>
</tr>
<tr>
<td>Russo and Corosu et al, 2003</td>
<td>50</td>
<td>Soy-based IF, 30 mg/d with G. lucidum and red clover isoflavone</td>
<td>Placebo</td>
<td>12</td>
<td>NBGD in HF score or frequency between groups; reduced by half significantly more in the placebo group (36%) vs soy group (24%) (P = .01)</td>
<td>Improved HF symptoms in both groups</td>
<td>Poor</td>
</tr>
<tr>
<td>Russo and Corosu et al, 2000 (breast cancer)</td>
<td>177</td>
<td>Soy IF extract, 50 mg/d</td>
<td>Placebo</td>
<td>12</td>
<td>Improved average HF severity (SRSD) with soy vs placebo (P = .01); no difference in frequency of night sweats</td>
<td>Improved HF symptoms in both groups</td>
<td>Fair</td>
</tr>
<tr>
<td>Scambia et al, 2000</td>
<td>39</td>
<td>Soy extract (400 mg/d) with IF (50 mg/d) followed by CEE, 0.625 mg/d for 4 wk</td>
<td>Placebo followed by CEE, 0.625 mg/d for 4 wk</td>
<td>12</td>
<td>Improved mean number of HF/wk (score card) and GCS score with soy vs placebo at 6 wk (P &lt; .01)</td>
<td>Improved HF symptoms in both groups</td>
<td>Poor</td>
</tr>
<tr>
<td>Tice et al, 2003</td>
<td>252</td>
<td>Red clover IF tablet, 82 mg/d or red clover IF tablet, 57 mg/d</td>
<td>Placebo</td>
<td>12</td>
<td>NBGD in GCS score or number of HFs (P &lt; .001); reduction in HFs was faster for red clover compared with placebo (P = .03)</td>
<td>Improved GCS score and number of HFs in all groups</td>
<td>Good</td>
</tr>
<tr>
<td>Bartenste, 2004</td>
<td>205</td>
<td>Red clover IF tablet, 40 mg/d</td>
<td>Placebo</td>
<td>52</td>
<td>NBGD in number of HFs or menopausal symptoms score (SRSD)</td>
<td>Improved number of HFs and symptoms score in both groups</td>
<td>Poor</td>
</tr>
<tr>
<td>Baber et al, 1999</td>
<td>51</td>
<td>Red clover IF tablet, 40 mg/d</td>
<td>Placebo</td>
<td>28</td>
<td>NBGD in symptoms (GCS score, HF frequency)</td>
<td>Improved symptoms in both groups (GCS score, HF frequency)</td>
<td>Fair</td>
</tr>
<tr>
<td>Jeri, 2002</td>
<td>10</td>
<td>Red clover IF tablet, 40 mg/d</td>
<td>Placebo</td>
<td>16</td>
<td>NR</td>
<td>Improved frequency and severity of HFs in treatment group (P &lt; .001)</td>
<td>Poor</td>
</tr>
<tr>
<td>van de Weijer and Matson, 2002</td>
<td>30</td>
<td>Red clover IF tablet, 80 mg/d</td>
<td>Placebo</td>
<td>12</td>
<td>NBGD in flushing frequency or GCS score</td>
<td>Improved HF symptoms in both groups; no change in GCS score</td>
<td>Poor</td>
</tr>
<tr>
<td>Knight et al, 1999</td>
<td>37</td>
<td>Red clover IF tablet, 40 mg/d or red clover IF tablet, 169 mg/d</td>
<td>Placebo</td>
<td>12</td>
<td>NBGD in flushing frequency or GCS score</td>
<td>Improved flushing frequency decreased in all groups</td>
<td>Poor</td>
</tr>
</tbody>
</table>

(continued)
**Table 1. Trials of Phytoestrogens (cont)**

<table>
<thead>
<tr>
<th>Source (Condition Treated)*</th>
<th>No. of Patients in Study</th>
<th>Therapy</th>
<th>Comparison</th>
<th>Duration of Therapy, wk</th>
<th>Between-Group Differences</th>
<th>Within-Group Differences</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crisafulli et al,38 2004</td>
<td>90</td>
<td>Genistein, 54 mg/d</td>
<td>Placebo; or estradiol (1 mg/d) combined with norethisterone</td>
<td>52</td>
<td>Genistein group: HF score decreased by 22% vs placebo at 3 mo ($P&lt;.01$); 29% at 6 mo ($P&lt;.001$); and 24% at 12 mo ($P&lt;.01$); estrogen group: HF score decreased by 33% vs placebo at 3 mo ($P&lt;.001$) and maintained at 6 and 12 mo; improvement with estrogen greater than with genistein at all measurements ($P&lt;.05$)</td>
<td>NR</td>
<td>Fair</td>
</tr>
<tr>
<td>Nikander et al,39 2003 (breast cancer)</td>
<td>62</td>
<td>3 Phytoestrogen tablets, 114 mg, twice daily</td>
<td>Placebo crossover 12 Each phase</td>
<td>Prior to crossover: NBGD in KI or HFs</td>
<td>Improved KI in both groups; improved HF intensity with placebo; no effect on anxiety, working ability, or self-confidence in either group</td>
<td>Improved KI score with genistein ($P&lt;.05$)</td>
<td>Fair</td>
</tr>
<tr>
<td>Sammartino et al,40 2003†</td>
<td>70</td>
<td>Genistein, 36 mg/d</td>
<td>Placebo</td>
<td>52</td>
<td>Improved KI score with genistein vs placebo ($P&lt;.05$)</td>
<td>Improved KI score with genistein ($P&lt;.05$)</td>
<td>Poor</td>
</tr>
<tr>
<td>Secreto et al,41 2004 (breast cancer)</td>
<td>262</td>
<td>IF, 40 mg midday, and IF, 40 mg, with 5 mg melatonin in the evening; IF, 40 mg at midday and evening; or placebo at midday, and melatonin, 5 mg, in the evening</td>
<td>Placebo midday and evening</td>
<td>12</td>
<td>NBGD in the total score or subscores or GCS score</td>
<td>Improved GCS scores in all groups; 38% placebo; 26% melatonin alone; 38% IF alone; and 39% IF and melatonin</td>
<td>Poor</td>
</tr>
<tr>
<td>Brzezinski et al,42 1997</td>
<td>145</td>
<td>Phytoestrogen-rich diet (tulsi, soy drink, miso, flax seed, daxi, about 182 mg; genistein, 255 mg; and lignans, 4 mg)</td>
<td>Regular Israeli diet</td>
<td>12</td>
<td>Improved HF severity ($P=.004$) and vaginal dryness severity ($P=.002$) with phytoestrogen vs control; NBGD in MSQ score</td>
<td>Both groups improved on the MSQ score</td>
<td>Poor</td>
</tr>
<tr>
<td>Carranza-Lira et al,43 2001</td>
<td>30</td>
<td>Phytoestrogen cream, 4 mg/d</td>
<td>Placebo (identical-looking cold cream)</td>
<td>4</td>
<td>NBGD in KI between groups</td>
<td>Improved KI score in both groups ($P&lt;.01$)</td>
<td>Poor</td>
</tr>
<tr>
<td>Komesaroff et al,44 2001</td>
<td>50</td>
<td>Wild yam cream preparation; 1 teaspoonful twice daily applied to arms, legs, or abdomen</td>
<td>Placebo crossover</td>
<td>12</td>
<td>NBGD (SRSD) including flushing frequency, severity, mood, breast tenderness, libido, and energy level</td>
<td>Improved flushing symptom scores, and energy in both groups; improved mood with wild yam cream</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Abbreviations: BC, black cohosh; CEE, conjugated equine estrogen; GCS, Green Climacteric Scale; HF, hot flash or hot flush; IF, isoflavones; KI, Kupperman Index; MSQ, Menopause Symptoms Questionnaire; NBGD, no between-group differences; NR, not reported; SRSD, self-reported symptoms diary.

*If breast cancer survivors are included, this was noted.
†Not double-blinded (open).

Other Biologically Based Therapies

Other biologically based studies (Table 2) included black cohosh, dehydroepiandrosterone, vitamin E, kava, phospholipid liposomes, s-adenosyl-L-methionine, melatonin, guar gum, vaginal lubricants, and combination therapies.

Four trials of black cohosh (Cimicifuga racemosa) met our criteria,45-48, 2 included women with breast cancer who were taking tamoxifen.45,46 The most recent and largest trial enrolled 304 women randomized to either 40 mg/d of a black cohosh supplement or placebo for 12 weeks.46 Improvement was observed in the treatment group for a variety of menopausal complaints as measured by the Menopause Rating Scale48 and included mood, sleep disorders, sexual disorders, sweating, and hot flashes. These results are in contrast to a smaller study that used a different botanical formulation and that did not show significant reduction in hot flashes compared with placebo.47 One poor-quality study45 and one fair-quality study46 suggested no improvement in hot flashes in breast cancer survivors.
The 2 dehydroepiandrosterone studies were of fair and poor quality. The fair-quality trial did not demonstrate a significant benefit of dehydroepiandrosterone compared with placebo for menopausal symptoms or quality of life, and the poor-quality trial did not report between-group differences.

Eleven trials of other agents met our criteria, 8 of which were of poor quality. One fair-quality trial enrolled 125 women with prior breast cancer and compared the effectiveness of 800 IU/d of vitamin E with placebo. There were no between-group differences in hot flash frequency or severity. Two fair-quality studies, 1 of a trial with kava and 1 with phospholipid liposome injections, showed measurable improvement in anxiety over the placebo. Women using phospholipid liposomes, but not kava, also had improvement in menopausal symptoms.

MIND-BODY AND BEHAVIORAL THERAPIES

Nine trials (Table 3) met our criteria in the mind-body and behavioral therapy category and included exercise, relaxation breathing, progressive muscle relaxation, audiotape relaxation, stress management and menopause education, and counseling support for women with breast cancer.

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**Table 2. Trials of Other Biologically Based Therapies**

<table>
<thead>
<tr>
<th>Source (Condition Treated)</th>
<th>No. of Patients in Study</th>
<th>Therapy</th>
<th>Comparison</th>
<th>Duration of Therapy, wk</th>
<th>Between-Group Differences</th>
<th>Within-Group Differences</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobson et al. 2001 (breast cancer)</td>
<td>85</td>
<td>BC, 1 tablet twice daily</td>
<td>Placebo</td>
<td>9</td>
<td>Improved sweating in BC vs placebo group ( P = 0.04 ); NBGD in mean number of HFs, HF severity, sleep, irritability, nervousness, depression, headaches, and palpitations</td>
<td>Improved sleep, irritability, nervousness, depression, headaches, palpitations, excessive sweating in both groups; global rating of well-being did not change in either group</td>
<td>Fair</td>
</tr>
<tr>
<td>Osmers et al. 2005</td>
<td>304</td>
<td>Cimicifuga racemosa, 2.5 mg of isopropanolic extract</td>
<td>Placebo</td>
<td>12</td>
<td>Improved HFs, sweating, sleep disorders, depressive mood, other psychological disorders, sexuality disorders, urinary tract complaints, and vaginal dryness in the treatment group vs placebo group based on the Menopause Rating Scale; NBGD found for cardiac complaints or joint and muscle symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wuttke et al. 2003</td>
<td>62</td>
<td>C racemosa preparation, 40 mg/d, herbal drug</td>
<td>Placebo; or CEE, 0.6 mg/d</td>
<td>12</td>
<td>No differences between the C racemosa group and placebo on HFs; improved HFs (menopause rating scale) with estrogen vs placebo ( P = 0.046 )</td>
<td>Improved symptoms for all groups (menopausal rating scale)</td>
<td>Fair</td>
</tr>
<tr>
<td>Hernandez Munoz and Pluchino 2003 (breast cancer)</td>
<td>136</td>
<td>BC, 20-mg, 1 tablet twice daily</td>
<td>Usual care</td>
<td>9</td>
<td>Improved HFs with treatment (47% of patients free of HFs) vs usual care (0% free of HFs) ( P &lt; 0.01 )</td>
<td></td>
<td>Poor</td>
</tr>
<tr>
<td>Barnhart et al. 1999</td>
<td>60</td>
<td>DHEA, 50 mg/d</td>
<td>Placebo</td>
<td>12</td>
<td>NBGD in HFs, vaginal dryness, sleep, mood, cognition, somatic symptoms, urinary tract symptoms, sexual symptoms, and quality of life</td>
<td>Improved total symptoms and health-related quality of life in both groups</td>
<td>Fair</td>
</tr>
<tr>
<td>Stornati et al. 1999</td>
<td>22</td>
<td>DHEA, 50 mg/d; or DHEA, 50 mg/d, and estradiol, 50 mg/d, transdermally</td>
<td>Estradiol, 50 mg/d, transdermally</td>
<td>12</td>
<td>NR</td>
<td>Similar improved K1 score with all groups ( P &lt; 0.01 )</td>
<td>Poor</td>
</tr>
<tr>
<td>Barton et al. 1998 (breast cancer)</td>
<td>125</td>
<td>Vitamin E succinate, 800 IU/d</td>
<td>Placebo and crossover</td>
<td>4 Each phase</td>
<td>Prior to crossover and in summary: no between-group differences in HF frequency or severity (SRSD questionnaire)</td>
<td>Improvements within groups were not significant</td>
<td>Fair</td>
</tr>
<tr>
<td>Cagnacci et al. 2003</td>
<td>80</td>
<td>Kava, 100 mg/d + calcium, 1 g/d; kava, 200 mg/d + calcium, 1 g/d</td>
<td>Calcium, 1 g/d</td>
<td>12</td>
<td>Improved anxiety with treatment vs placebo; NBGD in GCS score or depression score</td>
<td>Improved GCS score, anxiety, and depression score in both treatment groups</td>
<td>Fair</td>
</tr>
<tr>
<td>Rachev et al. 2001</td>
<td>64</td>
<td>Phospholipid liposomes, 28 mg/2 mL, intramuscular injection every other day</td>
<td>Placebo injection every other day</td>
<td>9</td>
<td>Improved GCS score ( P = 0.001 ) and anxiety (Hamilton Anxiety Scale) ( P &lt; 0.001 ) with treatment vs placebo</td>
<td>Improved GCS score and anxiety for both groups ( P &lt; 0.001 ) for both</td>
<td>Fair</td>
</tr>
</tbody>
</table>

(continued)
A fair-quality trial randomized 173 women to aerobic exercise therapy 225 min/wk compared with controls undertaking stretching 45 min/wk. There were no between-group differences in hot flash frequency, sleep disturbance, mood, or cognitive function. Another fair-quality trial compared women undertaking aerobic exercise 3 times per week with women under usual care that included menopause hormonal therapy for 6 weeks. The exercise group showed improved quality of life compared with the control group.

Four poor-quality studies evaluated benefits of relaxation therapy. Two studies trained participants in breathing therapies but did not report between-group differences. Six months of progressive muscle relaxation suggested a delayed onset of hot flashes in the treatment group compared with a control biofeedback group. A study involving 60 minutes per week of audiotape sound wave therapy had no impact on menopausal, somatic, or psychological symptom outcomes.

A stress and menopause management education intervention was compared with usual care in 86 women older than 50 years.

<table>
<thead>
<tr>
<th>Source (Condition Treated*)</th>
<th>No. of Patients in Study</th>
<th>Therapy</th>
<th>Comparison</th>
<th>Duration of Therapy, wk</th>
<th>Between-Group Differences</th>
<th>Within-Group Differences</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bellipanni et al,54 2001</td>
<td>79</td>
<td>Melatonin, 3 mg/d Placebo</td>
<td>BC</td>
<td>26</td>
<td>Improved mood and morning depression (questionnaire) in melatonin vs placebo group (P&lt;.05); NBGD for other symptoms</td>
<td>NR</td>
<td>Poor</td>
</tr>
<tr>
<td>Blatt et al,55 1953</td>
<td>748</td>
<td>Vitamin E, 50-100 mg 3 times daily; ethinyl estradiol, 0.05 mg/d; CEE, 1.25 mg/d; or phenobarbital, 15 mg 3 times daily Placebo</td>
<td>156</td>
<td>NR</td>
<td>Improved HF symptoms with CEE and ethinyl estradiol (67% of women), phenobarbital (24%), vitamin E (13%), and placebo (16%)</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Bygdeman et al,56 1996†</td>
<td>39</td>
<td>Vaginal moisturizer 3 times per week Dienoestrol vaginal cream, 0.5 mg/d, for 2 wk, then 3 times per week</td>
<td>12</td>
<td>Improved vaginal dryness index with dienoestrol vs moisturizer (P = .001)</td>
<td>Improved vaginal dryness index in both groups</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Chenoy et al,57 1994</td>
<td>56</td>
<td>Evening primrose oil (gamma-linolenic acid), 2000 mg/d, with natural vitamin E, 10 mg/d Placebo</td>
<td>26</td>
<td>Improved maximum number of daytime HFds (SRSD) with placebo vs treatment (P&lt;.05).</td>
<td>NR</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Hudson et al,58 1998</td>
<td>13</td>
<td>Botanical formula, 2 500-mg capsules 3 times per day (combined dry herb including burdock root [2 parts], licorice root [2 parts], motherwort [1 part], dong quai root [2 parts], and Mexican wild yam root [1 part]) Placebo</td>
<td>12</td>
<td>NBGD in number and severity of HFds (SRSD)</td>
<td>Improved number and severity of HFds for both groups (SRSD)</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Makkonen et al,59 1993</td>
<td>30</td>
<td>Guar gum, 5 g 3 times daily</td>
<td>Placebo</td>
<td>26</td>
<td>NBGD in KI scores</td>
<td>Improved KI scores in both groups (P&lt;.001)</td>
<td>Poor</td>
</tr>
<tr>
<td>Nachtigall,60 1994†</td>
<td>30</td>
<td>Vaginal moisturizer, 3 times per week CEE vaginal cream, 2 g/d</td>
<td>12</td>
<td>NR</td>
<td>Improved vaginal elasticity, pH, fluid volume, and moisture in both groups</td>
<td>Poor</td>
<td></td>
</tr>
<tr>
<td>Salmaggi et al,61 1993</td>
<td>80</td>
<td>S-adenosyl-L-methionine, 1600 mg/d Placebo</td>
<td>4</td>
<td>Improved depression in treatment vs placebo group (Hamilton Depression Rating Scale; Rome Depression Inventory; Clinical Global Impression Improvement Scale; Psychoasthenia Scale of the Minnesota Multiphasic Personality Inventory)</td>
<td>NR</td>
<td>Poor</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BC, black cohosh; CEE, conjugated equine estrogen; DHEA, dehydroepiandrosterone; GCS, Green Climacteric Scale; HF, hot flash or hot flush; KI, Kupperman Index; NBGD, no between-group differences; NR, not reported; SRSD, self-reported symptoms diary.

*If breast cancer survivors are included, this was noted.
†Not double-blinded (open).
Table 3. Trials of Mind-Body and Behavioral Therapies

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients in Study</th>
<th>Therapy</th>
<th>Comparison</th>
<th>Duration of Therapy, wk</th>
<th>Between-Group Differences</th>
<th>Within-Group Differences</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aiello et al.62, 2004</td>
<td>173</td>
<td>Aerobic exercise, 225 min/wk</td>
<td>Stretching, 45 min/wk</td>
<td>52</td>
<td>NBGD in HF frequency, sleep, depressive mood, or cognitive function; a subset of women with recent menopause showed improved memory in aerobic vs stretching group</td>
<td>NR</td>
<td>Fair</td>
</tr>
<tr>
<td>Ganz et al.63, 2000</td>
<td>76</td>
<td>Counseling by nurse practitioner, tailored therapy, and support; therapy includes any of the following: HFs (includes belligerent, chlondien patch, megestrol); behavioral symptoms (slow abdominal breathing); vaginal dryness (moisturizer or lubricant); urinary symptoms, phenylpropanolamine; psychosocial (referral for counseling or group support)</td>
<td>Usual care</td>
<td>20</td>
<td>Improved adjusted mean change in menopausal symptoms (P = .004) and adjusted mean change in sexual functioning with intervention vs usual care (P = .04); NBGD for vitality score</td>
<td>NR</td>
<td>Fair</td>
</tr>
<tr>
<td>Hunter and O’Dea,64 1999</td>
<td>86</td>
<td>Health/menopause and stress relief education</td>
<td>Usual care</td>
<td>260 Follow-up</td>
<td>Control group more likely to contribute aches and pains to menopause than the intervention group (P &lt; .01); NBGD on mood, health, vaginal dryness, or sexual relationships; knowledge of menopause increased in the intervention group</td>
<td>Improved maintenance of knowledge, less concern with menopause, more exercise, and less estrogren use in intervention group; more women in the control group lost interest in sex</td>
<td>Fair</td>
</tr>
<tr>
<td>Teoman et al.65, 2004</td>
<td>81</td>
<td>Aerobic exercise 3 times/wk</td>
<td>Usual care (taking hormone therapy)</td>
<td>6</td>
<td>NR</td>
<td>Exercise group showed changes in quality of life; no changes for control group</td>
<td>Fair</td>
</tr>
<tr>
<td>Freedman et al.66, 1995</td>
<td>24</td>
<td>Paced respiration training in 8 1-h biweekly treatment sessions</td>
<td>Alpha-wave EEG biofeedback in 8, 1-h biweekly treatment sessions</td>
<td>4</td>
<td>NR</td>
<td>Decreased HF frequency for the paced-respiration group (P &lt; .001) but not for the alpha-wave biofeedback group</td>
<td>Poor</td>
</tr>
<tr>
<td>Germaine and Freedman,67 1984</td>
<td>14</td>
<td>Progressive muscle relaxation training in 6, 1-h weekly sessions</td>
<td>Alpha-wave EEG biofeedback training in 6, 1-h weekly sessions</td>
<td>26</td>
<td>Improved time for onset of HF (P &lt; .01) (physiological laboratory testing) in progressive muscle relaxation vs biofeedback group</td>
<td>Reduced HF frequency in relaxation group at 6-mo follow-up (P &lt; .01)</td>
<td>Poor</td>
</tr>
<tr>
<td>Irvin et al.68, 1996</td>
<td>45</td>
<td>Relaxation (diaphragmatic breathing, 20 min/d) and charting HFs</td>
<td>Reading and charting HFs; or charting HFs only</td>
<td>10</td>
<td>NR</td>
<td>Significant improvement in HF intensity, tension/anxiety, and depression for the relaxation group (P &lt; .05); reduction in trait anxiety and confusion in the reading group (P &lt; .05); no differences in HF frequency in any groups; no changes in control group</td>
<td>Poor</td>
</tr>
<tr>
<td>Linth-Astrand et al.69, 2004</td>
<td>30</td>
<td>Exercise, 3 sessions/wk</td>
<td>Estradiol, 2 mg/d for 12 wks minimum; or wait list controls*</td>
<td>38</td>
<td>NR</td>
<td>Improved HFs, KI score, symptom list, Visual Analog Score, and Mood Scale with estrogen; improved KI score, symptom list, and Visual Analog Score with exercise</td>
<td>Poor</td>
</tr>
<tr>
<td>Rankin,70 1989</td>
<td>40</td>
<td>Low-frequency sound wave audiotape; 20 min 3 times/wk for 2 wk</td>
<td>Usual care</td>
<td>2</td>
<td>NBGD in menopausal, somatic, and psychological symptoms</td>
<td>Improved frequency of menopausal (Neugarten-Kraines Menopausal Index Scale), somatic, and psychological symptoms with sound waves in menopausal group</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Abbreviations: EEG, electroencephalographic; HF, hot flash or hot flush; KI, Kupperman Index; NBGD, no between-group differences; NR, not reported.

*Once the study was completed, those on the wait list were then able to go through the treatment.

Referred to in the text: Stratified that the control group more commonly attributed pain to menopause than the education group; however, no other benefit for menopausal symptoms was reported. In another fair-quality study that used counseling and emotional support in 76 women with breast cancer, an adjusted mean change in both menopausal symptoms and sexual function in the intervention group compared with the usual care group was reported.
Table 4. Trials of Manipulative, Body-Based, and Energy Therapies

<table>
<thead>
<tr>
<th>Source</th>
<th>No. of Patients in Study</th>
<th>Therapy</th>
<th>Comparison</th>
<th>Duration of Therapy</th>
<th>Between-Group Differences</th>
<th>Within-Group Differences</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cleary and Fox,71 1994</td>
<td>30</td>
<td>Low-force osteopathic manipulation of the pelvis, spine, and cranium, 10 treatments</td>
<td>Sham low-force touch in similar areas</td>
<td>10 Treatments</td>
<td>Improved HF and night sweats (questionnaire), urination frequency, depression, and insomnia treatment vs control group</td>
<td>NR</td>
<td>Fair</td>
</tr>
<tr>
<td>Williamson et al,72 2002</td>
<td>80</td>
<td>Reflexology, 9 sessions</td>
<td>Standard foot massage</td>
<td>19 wk</td>
<td>NBGD in severity of HF and night sweats (Women’s Health Questionnaire, Usual Analog Scale, and a self-completed measure of quality of life)</td>
<td>NR</td>
<td>Poor</td>
</tr>
<tr>
<td>Carpenter and Andrykowski,73 2002</td>
<td>15</td>
<td>6 Magnetic devices attached to participants’ skin over acupuncture/acupressure sites used to balance energy and treat HF</td>
<td>Placebo crossover, placebo identical but blinding; not effective because of magnet properties</td>
<td>72-h + 2-d Follow-up each phase</td>
<td>Decrease in HF frequency with placebo (from 10.5 to 6.6) vs magnets (from 9.6 to 8.3) (P = .02); decrease in bothersome HF with placebo (from 4.4 to 3.2) vs magnets (from 4.2 to 4.1) (P = .02); NBGD for HF severity, interference scale, or overall quality of life</td>
<td>NR</td>
<td>Poor</td>
</tr>
</tbody>
</table>

Main Results

**Manipulative and Body-Based Treatments**

- **Energy Medicine**
  - NBGD in severity of HF and night sweats (Women’s Health Questionnaire, Usual Analog Scale, and a self-completed measure of quality of life)
  - Decrease in HF frequency with placebo (from 10.5 to 6.6) vs magnets (from 9.6 to 8.3) (P = .02); decrease in bothersome HF with placebo (from 4.4 to 3.2) vs magnets (from 4.2 to 4.1) (P = .02); NBGD for HF severity, interference scale, or overall quality of life

**Within-Group Differences**

- NR

**Quality**

- Fair
- Poor

**Abbreviations:** HF, hot flash or hot flush; NBGD, no between-group differences; NR, not reported.

**MANIPULATIVE, BODY-BASED, AND ENERGY THERAPIES**

Table 4 lists body-based therapies. The only eligible study incorporating body-based techniques evaluated low-force osteopathic manipulation of the pelvis, spine, and cranium compared with sham low-force touch for 30 menopausal women.71 Investigators reported improvement in hot flashes, night sweats, urinary frequency, depression, and insomnia with the treatment group compared with the sham touch group.71

Two studies examined the energy therapies of reflexology72 and magnetic devices.73 A comparison of standard foot reflexology and routine foot massage reported no differences between study groups in hot flashes, night sweats, or quality-of-life measures.72 A trial enrolling 15 women with breast cancer evaluated benefits of 6 magnetic devices applied over classic Chinese acupressure points used to treat hot flashes.73 Hot flash frequency improved in the placebo group compared with the group using magnets (P = .02).

**WHOLE MEDICAL SYSTEMS**

For whole medical systems (Table 5), 4 trials of acupuncture74-77 and 6 trials78-81 of traditional Chinese medicinal herbs met our criteria. All trials of acupuncture used 6 to 14 acupuncture sessions specific to menopausal symptoms over an 8- to 12-week period. Sham acupuncture using superficial needle insertion was used as the control in 3 trials,74,76,77 and acupuncture intended for general well-being was used as the control in the fourth trial.73 In the 3 trials reporting between-group differences, none showed improved hot flash frequency with acupuncture compared with sham acupuncture,74,76,77 although mood was improved in the treatment group in 1 poor-quality trial.70 A fair-quality trial of 45 women compared electroacupuncture, sham acupuncture, and a conjugated dosage of 0.625 mg of estrogen per day. Although all 3 groups reported improvement in self-reported symptom diaries over 12 weeks, only the estrogen group had significant improvement compared with the other groups (P<.001).74

Six trials78-83 of traditional Chinese medicinal herbs (half using combination therapies) met our criteria.80-82 None showed a significant benefit over controls for menopausal symptoms. Therapy with standardized (ie, quality control of what is believed to be the active ingredient to ensure consistent dosage between samples) ginseng in 384 women showed improvement in depression, well-being, and health scores compared with placebo over 16 weeks, but there were no between-group differences in hot flashes.79

**ADVERSE EFFECTS**

Adverse effects and safety data from these and other studies are limited, and most studies lacked consistent or clear reporting. A 5-year follow-up study of soy indicated that users were at a significantly increased risk for endometrial hyperplasia compared with placebo.86 Hepatotoxicity has been associated with both black cohosh85,87 and kava.86 An increased number of breast cancer metastasis as studied in MMTV-neu transgenic mice receiving black cohosh has been observed.89

**COMMENT**

Individual trials suggest a benefit for certain therapies, yet data are insufficient to recommend any complementary and alternative therapy as effective for the management of menopausal symptoms. Of the 15 fair- to good-quality trials of phytoestrogens, only 4 showed a benefit. This is consistent with a recent systematic review of phytoestrogens as treatment for hot flashes that included 25 trials and 2348 participants.80
A single large trial\(^{46}\) showed a benefit for vasomotor symptoms with the black cohosh formulation (Enzymatic Therapy Inc, Green Bay, Wis) and is consistent with the black cohosh formulation benefit for vasomotor symptoms during menopausal transition, and the variable definitions of the menopausal transition, and use of inconsistently defined populations. The large placebo effect is consistent with preexisting work of menopausal hormonal therapies. A study of estrogen compared with placebo reported a 50% improvement in frequency of hot flashes in the placebo group.\(^{94}\) The placebo effect likely plays an important role in the expanding number of dietary supplements marketed to menopausal women.

The variety of outcome measures may have contributed to the mixed results and range from sophisticated objective sternal conductance tests\(^{66-68}\) to subjective measures through daily self-reported symptom diaries. For menopause, as for pain management, subjective relief of symptoms may be the most meaningful data.\(^{95}\) The Kupperman Index and the Greene Climacteric Scale cannot be compared because they measure different symptoms.

Another limitation to interpreting trials of therapies is the variability of nomenclature describing the menopausal transition. Progress is under way in defining standard nomenclature for the menopause transition,\(^{4}\) helping to define optimal treatment for various phases.

The populations enrolled in trials varied from random samples of menopausal women to women specifically recruited through menopause or gynecological clinics. Results may not be generalizable. Clinicians caring for menopausal women recognize different symptoms in women undergoing abrupt surgical menopause, premature ovarian failure, or the natural menopause transition at midlife. In most of the studies included in this review, the cause of menopause was not correlated with therapy outcomes.

A single large trial\(^{46}\) showed a benefit for vasomotor symptoms with the black cohosh formulation (Enzymatic Therapy Inc, Green Bay, Wis) and is consistent with older German studies.\(^{91-93}\) However, the remaining 3 studies showed no benefit of black cohosh. Two\(^{45,48}\) were confounded by concurrent use of tamoxifen, known to exacerbate hot flashes, and 1 study\(^{47}\) used a more unusual (research) preparation, BNO1055.

Limitations to this review are the exclusion of many relevant articles in the field of alternative medicine written in non-English languages, difficulty in interpretation of the data owing to large placebo effects, non-standardized outcome measures, non-standardized biologically based therapies, variable definitions of the menopausal transition, and use of inconsistently defined populations. The large placebo effect is consistent with preexisting work of menopausal hormonal therapies. A study of estrogen compared with placebo reported a 50% improvement in frequency of hot flashes in the placebo group.\(^{94}\) The placebo effect likely plays an important role in the expanding number of dietary supplements marketed to menopausal women.

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Data interpretation is further complicated by the nature of research in alternative medicine. Current published trials are generally small, of short duration, and have inadequate methods, such as not reporting between-group differences. Standardization of biologic products is poor, making direct comparison difficult. Nearly half of the studies in this review were rated as being of poor quality owing to these and other methodological shortcomings. Observational data confirm that different ethnic groups of women seem to experience menopause differently. Ethnicity of the women included in trials was not routinely recorded, and, when it was, therapeutic responses were not correlated.

Many women report the onset of hot flashes, night sweats, or sleep disturbance on cessation of any therapy for their menopausal symptoms. This lack of curative benefit complicates the risk-benefit ratio of recommending therapies to women.

The most important thing that the health professionals can do for symptomatic menopausal women is to encourage open communication that allows patients to disclose treatments they are using. Women value partnership, choice, and shared decision making. Because there is no universal menopausal presentation or treatment, it is essential that health care professionals provide accurate information and options for midlife women.

The next decade will see an increasing number of women transition through menopause. Currently, patients and health care professionals are more thoughtful in considering menopausal hormonal therapy for symptom management because of safety concerns. Such caution will increase the demand for alternatives that are effective and safe. Future research should focus on large, rigorously designed trials that ensure reliable comparisons between studies, distinguishing cause and phase of menopause and ethnic differences. Lifestyle modification and mind-body techniques may have high safety profiles and result in additional health benefits. Many alternative therapies used by menopausal women, such as massage, aromatherapy, yoga, and ayurvedic therapy, need to be studied in randomized, controlled trials. It is imperative that future research be directed toward safety and efficacy of the common modalities used by women to treat their menopausal symptoms.

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