REVIEW ARTICLE

Counseling Patients About Hormones and Alternatives for Menopausal Symptoms

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Menopause typically begins in the early fifties, although the exact age of menopause will vary from woman to woman. There are several symptoms associated with menopause that can be bothersome, and prompt women to seek treatment from their primary care provider. The purpose of this review is to describe the currently available therapies, as well as the evidence that provides support for their use. The most effective therapy for menopause symptoms is hormone therapy (HT); however, while effective for menopausal symptom relief there are several potential risks to consider prior to initiating HT. Some evidence suggests that HT can increase the risk of certain types of cancers and should be avoided in women who are at high risk for ovarian cancer or breast cancer. Non-hormonal conventional therapies include selective serotonin reuptake inhibitors (SSRIs), clonidine and gabapentin. Bioidentical hormone therapy has also been shown to be effective in the relief of symptoms, but requires further research to elucidate the potential risks associated with it. Complementary and alternative (CAM) therapies include phytoestrogen, botanical and herbal treatments, acupuncture, osteopathic manipulation therapy and behavioral interventions.

Menopause is the process of permanent cessation of menstrual periods in women.[1] For the majority of women, menopause begins in the early fifties, although some women experience menopause earlier due to surgery, chemotherapy or other causes. The onset of menopause is usually heralded by the slowing and eventual cessation of menses, as well as other physical and mental symptoms which vary widely (Table 1). Hot flash is the most common complaint in women in the US and UK, while joint pain is more common among Asian women.[2] Most women report spontaneous resolution of symptoms within about five years. Women with menopause induced by surgery, chemotherapy, or other causes tend to report more severe, prolonged symptoms. Treatment for any woman with bothersome symptoms should be offered to improve quality of life.

There are various treatment options for menopausal symptoms (Table 2). These options can be categorized as conventional hormone replacement, conventional non-hormone treatment, and pharmacological and non-pharmacological complementary and alternative medicine (CAM). Conventional hormone therapy consists of treatments that include the use of estrogen and progestin. Conventional non-hormone treatments consist of a variety of non-hormonal drugs. Pharmacological CAM treatments consist of bioidentical hormone therapy, phytoestrogen and other botanical products whereas non-pharmacological CAM treatments include behavioral intervention, acupuncture, and osteopathic manipulation therapy (OMT). Symptomatic women who can take estrogen can choose treatment options from all the above groups. For those women who cannot take estrogen, the conventional hormone treatments are not an option.

This article reviews a variety of treatment options that exist for symptomatic menopausal women. For hormone therapy (HT), data about the risks of HT on cancers and coronary events (including both reanalysis of Women's Health Initiative (WHI) data and the results of recent studies) are presented in this review. With respect to bioidentical hormone therapy, phytoestrogen and other botanicals (for instance, soy isoflavones and black cohosh), as well as non-hormonal conventional therapy, the possible mechanisms, results of recent clinical studies, side effects, and safety issues are reviewed. Clinical studies about behavioral therapy interventions, for example, yoga and cognitive behavioral therapy (CBT), are also presented. In addition, effectiveness of acupuncture and potential administration of OMT on menopause symptoms are discussed in this article.

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Table 1: Menopausal Symptoms and Their Prevalence.*

Menopausal Symptoms	Prevalence (%)			Strength of association
	Pre-menopause	Peri-menopause	Post-menopause	
Vasomotor symptoms (hot flash, night sweat)	14-51	35-50	30-80	Strong
Vaginal symptoms (dryness, dyspareunia)	4-22	7-31	17-30	Strong
Sleep disturbance	16-47	39-47	35-60	Moderate
Mood symptoms (depression, anxiety, irritability)	8-37	11-21	8-38	Limited evidence
Urinary incontinence	10-36	17-39	15-36	Mixed evidence
Cognitive disturbances	No data available			Insufficient
Somatic symptoms				

*Data from National Institutes of Health State-of-the-Science Conference Statement: Management of Menopause-Related Symptoms 2005.

TREATMENT OPTIONS FOR SYMPTOMATIC WOMEN WHO CAN TAKE ESTROGEN

1. Hormone therapy (HT)

HT is the most effective FDA approved therapy for menopause symptoms. However, the results of the WHI published in 2002 had an immediate and lasting negative effect on use of HT around the world. HT for menopause refers to the use of semisynthetic or synthetic hormones to treat menopausal symptoms. Semisynthetic conjugated equine estrogen (CEE), such as Premarin, is used alone or in combination with a synthetic progestin, such as Provera. The addition of progestin is used to prevent estrogen-induced endometrial hyperplasia and reduce the risk of endometrial cancer in a woman with an intact uterus. Various forms, doses, and regimens are available.[3]

Prior to 2002, HT was commonly used to relieve menopausal symptoms as well as prevent chronic conditions, such as cardiovascular disease, dementia, and osteoporosis. However, the initial results of WHI showed increased risks in invasive breast cancer, coronary heart disease, stroke, thromboembolic events, and dementia among women treated with HT.[4,5] These unexpected findings caused concerns among women considering HT for menopausal symptoms and dramatically decreased the application of HT.

Since the release of WHI results, reanalysis of WHI data and additional studies have populated the medical literature with updated information on risks of HT. The increased risk of cancers, especially breast cancer, is thought to be the main concern for symptomatic women avoiding HT. Surprisingly, further reanalysis of data from the estrogen-alone group in the WHI study demonstrated a significant reduction in the risk of invasive breast cancer if estrogen was started more than five years from onset of menopause (relative risk, 0.58; 95% confidence interval (CI), 0.36–0.93).[6] A second study of 67,000 postmenopausal women in the United States also showed no increased risk with the use of estrogen alone,[7] and a similar phenomenon was found in an observational study of 533,310 postmenopausal women in France when HT was initiated more than three years from onset of menopause (hazard ratio (HR), 1.00; 95% CI, 0.68–1.47).[8] A Finnish study of 221,551 menopausal women who used combination therapy demonstrated that both sequential and continuous administration resulted in an elevation of breast cancer risk; however, the elevation of risk was greater in the group that received continuous therapy.[9] This differential increase in risk of breast cancer was most apparent among women who had been using combination therapy for greater than 5 years. Alternatively, the use of newer tissue-selective estrogen complex (TSEC) therapies has shown to be as effective as conventional HT without the breast cancer risk.[10-12] TSEC preparations, such as Duavee, combine low dose estrogen with a selective estrogen receptor modulator, such as basedoxifene.

With regards to other cancers, WHI showed increased risks of ovarian and lung cancers among women receiving estrogen and progestin. Ovarian cancer risk declines after cessation of HT, while the lung cancer risk continues.[13,14] Providers should be particularly cautious before considering HT for patients who are smokers or who have other risk factors for lung cancer.

The increase in coronary events revealed in the initial WHI results was unexpected and contrasted with the protective effects of HT on cardiovascular diseases observed in animal models and other observational studies. Further analysis of WHI data showed that the timing of initiation of HT is crucial, that is, starting treatment at or shortly after menopause is cardioprotective, whereas at a time remote from menopause may be harmful.[4,15-17] Several studies have recently been completed, or are underway to test this hypothesis. A Bayesian meta-analysis of 19 randomized clinical trials (RCTs) among 16,000 women supported the hypothesis (relative risk of

Table 2: Currently Avaliable Treatment Options for Menopausal Symptoms

Category		Treatments	Effectiveness	Side effects	Safety (use in women with breast cancer)
Conventional	Hormone	HT	Consistently	Cancer, CVD, stroke, thromboemboli c events	No (increased risks of breast cancer)
	Non-hormone	SSRI	Moderate effective/ short-term	Related to SSRI	Yes
		Clonidine	Effective	Related to clonidine	Yes
		Gabapentin	Effective	Related to gabapentin	Yes
Complementary and alternative	Pharmacological	Bioidentical hormones	Mixed evidence	Similar to HT	No
		Phytoestrogen and botanical products	Mixed evidence	May similar but light to HT, Different based on products	Not clear
	Non-pharmacological	Behavioral therapy (paced respiration training, relaxation training, yoga, and lifestyle changes)	Mixed evidence	None	Yes
		Acupuncture	Promising	Rare	Yes
		OMT	Possible but no data available	Possible but no data available	Possible but no data available

mortality, 0.73; 95% CI, 0.52–0.96).[18] The Kronos Early Estrogen Prevention Study (KEEPS) and the Early vs. Late Intervention Trial with Estradiol (ELITE), two ongoing clinical trials, should provide more defined details about the effect of early intervention with HT on development and progression of atherosclerosis.[19]

In summary, HT, as a confirmed effective therapy for menopausal symptoms, should not be used for prevention of chronic diseases in women during the menopausal transition. For those who are more than 10 years from their last menstrual period or at high baseline risks of cardiovascular diseases or cancers, alternative therapies should be considered in order to provide relief of menopausal symptoms.

2. Bioidentical hormone therapy (BHT)

With the concerns about the risks related to semisynthetic or synthetic HT, the use of "natural" bioidentical hormones has gained popularity as an alternative to HT in recent years. BHs are derivatives of plant extracts chemically modified to be structurally identical to human endogenous hormones. BHs include estrone, estropipate, 17β-estradiol, estriol, progesterone, testosterone, and dehydroepiandrosterone. Based on a patient's salivary hormone level, BHT is available commercially as standardized hormone or compounded hormone (with different dosages and for different administration routes).[20] The most popular and commonly prescribed compounded formulations of BHT in the United States are Biest (estriol + 17β-estradiol) and Triest (estriol + 17β-estradiol + estrone).[21] For example, Biest (80:20) 2.5 mg refers to a preparation containing 2 mg of estriol and 0.5mg of 17β-estradiol. Currently, the FDA has only approved standardized bioidentical estrone, estropipate, 17β-estradiol, and progesterone, but not estriol, testosterone or DHEA for relieving menopausal symptoms. Evidence about the efficacy and safety of FDA approved bioidentical hormones used for relieving menopausal symptoms is well reviewed.[22,23] In summary, there were sufficient clinical trial data for the efficacy of 17β-estradiol and progesterone for relieving menopausal symptoms, but no WHI-equivalent study for safety of long-term use.[22] Observational data from the French Etude Epide´miologique aupre`s de femmes de l'Education Nationale cohort suggested that bioidentical progesterone may be safer than synthetic progestogen (relative risk of breast cancer, 1 vs 1.69).[23] However, there are no large RCTs directly comparing the efficacy and safety of the bioidentical and synthetic/semisynthetic hormones.[22] Theoretically, hormones with similar biochemical structures would have similar benefits/risks/side effects. Therefore, the application of bioidentical estrogen and progesterone for relieving menopausal symptoms should adhere to the same guideline for HT; that is, "lowest effective dose for shortest time."[22]

There are two special situations where compounded progesterone may be preferable. FDA-approved micronized progesterone is available only as a peanut oil suspension, and

would be contraindicated for a patient with peanut allergy. The other appropriate application occurs if the patient's progesterone requirement is smaller than the available FDA-approved product.[24] No compounded formulation is approved by the FDA, because FDA approval would not be possible for each compounded product made for an individual consumer with many variables affecting efficacy, and for compounded products containing unapproved products. Thus, it is understandable that there is no substantiated support for the application of compounded products, and that it would be difficult to design a systematic study of the efficacy or side effects of compounds.

3. Phytoestrogen and other botanicals

Phytoestrogens are plant-derived substances with structure and/or function similar to estrogens or their active metabolites. The most important groups of phytoestrogen and plant origins are listed in Table 3. A substantial number of studies of phytoestrogens and other botanical products have been conducted; however, there is no convincing evidence supporting their efficacy in alleviating menopausal symptoms. Since the majority of the data is about soy isoflavones and black cohosh, they will be discussed as a representative of phytoestrogens and botanical products, respectively.

Soy isoflavones have been investigated in numerous trials because of the epidemiologic data showing less frequency and severity of hot flashes reported in Asian women with high dietary intake of soy.[25] However, results have been conflicting, with some studies showing statistically significant improvement in vasomotor symptoms while others showed no overall difference compared to placebo.[26,27] The contradictions may be due to variations in soy preparations, dosages and durations of treatment, and ethnic differences in isoflavone metabolism.[28-30] Concerns about application of soy isoflavones in relieving menopausal symptoms include risks of cancers in hormone-sensitive tissue, allergies, and undesirable effects from unknown mixed ingredients within the products.

Black cohosh (Actaea racemosa, Cimicifuga racemosa) is a plant native to North America and recently has gained popularity as a remedy for menopausal symptoms. There are several preparations of black cohosh, including infusions, capsules, tablets, and tinctures. One commercially available products, Remifemin, contains 20mg of black cohosh per tablet.[26] While the true mechanism of effect is poorly understood, black cohosh potentially has a mild central estrogenic effect, and may inhibit luteinizing hormone levels, or act as a partial agonist of the serotonin receptor.[26,31-33] Study results are mixed on whether black cohosh effectively relieves menopausal symptoms. Herbal Alternatives for Menopause Trial (HALT) found that black cohosh, whether used alone or with other botanicals over 12 months, was ineffective in relieving hot flashes or night sweats in postmenopausal women or those approaching menopause.[34] A meta-analysis of six double blind, randomized, clinical trials with a total of 1,112 peri- and post-menopausal subjects did not consistently demonstrate an effect of black cohosh on menopausal symptoms.[35] There is a lack of evidence supporting an association between black cohosh and increased risk of breast cancer.[36] In general, mild side effects, such as stomach discomfort, headache, and rash, were found in clinical trials of black cohosh use for menopausal symptoms.[26,37] However, there are several individual reports of hepatotoxicity associated with black cohosh, ultimately requiring liver transplantation. Thus, women with liver disorders or risk factors for liver disorders should be advised to avoid or discontinue black cohosh. The safety of long-term use of black cohosh for menopausal symptoms needs further evaluation, since most studies to date were limited to less than six months.

Table 3: Important Groups of Phytoestrogen, Their Plant Origins, and Other Botanical Products

Category		Plant Origins
Phytoestrogen	Isoflavones (including genistein and daidzein)	Soybeans, chickpeas, other legumes (beans and peas), red clover
	Lignans (including enterolactone and enterodiol)	Oilseeds (flaxseed), cereal bran, whole cereals, vegetables, legumes and fruit
Other botanical products	North American Herb	Black cohosh, rosemary, evening primrose,etc.
	Chinese Herb	Dong quai, ginseng, gingko, licorice, schisandra, and other combinations
	Indian Herb	Ayurveda, fenugreek, etc.

TREATMENT OPTIONS FOR SYMPTOMATIC WOMEN WHO CANNOT TAKE ESTROGEN

1. Non-hormonal conventional therapies

Several conventional medications used to treat other diseases have been confirmed to be effective in reducing vasomotor symptoms in women who cannot take estrogen (Table 2).

Among these conventional medications, antidepressant medications, especially selective serotonin reuptake inhibitors (SSRIs), are recommended as first-line treatment. Venlafaxine, paroxetine and fluoxetine are the most commonly used SSRIs for treatment of vasomotor symptoms.[38] They have been shown to concurrently increase serotonin levels and decrease

luteinizing hormone levels, although the latter effect is short term and not as effective as estrogen.[27,39] Several small, RCTs confirmed this moderate effect on vasomotor symptoms.[39-43] These agents are also helpful in regulating sleep disturbance and mood instability during menopausal transition.[43] Adverse effects include gastrointestinal or central nervous system symptoms, which were reported as "tolerable."[42] Additionally, paroxetine should not be given to women with breast cancer who are taking tamoxifen because of concerns for reduced efficacy of tamoxifen when combined with paroxetine.

Clonidine and gabapentin are the two other medications with solid evidence of efficacy for vasomotor symptoms.[44] Clonidine is an alpha2 adrenergic agonist used to treat hypertension and migraine headaches. It reduces peripheral and central vascular reactivity.[44] When used for 8-12 weeks, it may help decrease hot flash frequency and associated symptoms such as sleep difficulty.[38,1,27,44] Gabapentin, commonly prescribed for seizure disorder or neuropathic pain, is a gamma-aminobutyric acid analogue and has a direct effect on the temperature regulation center of the ventromedial hypothalamus.[45] One randomized control trial showed that gabapentin can reduce the severity and frequency of hot flashes as effectively as estrogen in post-menopausal women.[46] This effect also existed in women with breast cancer.[47,48] However, severe and intolerable side effects of high-dose gabapentin, such as headache, dizziness, and disorientation cluster, reduce its application in symptomatic menopausal women.[46,47,49]

For those who can take neither estrogen nor conventional medications mentioned above, some non-pharmacological CAM options are available for management of menopausal symptoms, such as behavioral interventions, acupuncture, and OMT.

2. Behavioral interventions

There are several behavioral interventions available for management of menopausal symptoms, including cognitive behavioral therapy, paced respiration training, relaxation training, yoga, and lifestyle changes such as exercise and dietary adjustments.[2] While these behavioral interventions will benefit patients' overall health status, their efficacy in relieving menopausal symptoms is controversial and needs investigation with more clinical trials of good methodological quality. Yoga is one of the most commonly used complementary therapies for menopausal symptoms, but the evidence is conflicting. In a randomized controlled study in 2011, yoga statistically significantly reduced menopausal symptoms,[50] while a 2012 meta-analysis including four RCTs among 545 patients showed no evidence for yoga in overall relief of menopausal symptoms.[51] Another behavioral intervention especially useful in the context of patient-centered care is cognitive behavioral therapy (CBT). CBT goals include patient understanding of menopausal symptoms, management of symptoms and the belief that lifestyle changes can improve health status. In addition to two case reports supporting this therapy, one RCT showed comprehensive menopausal assessment and counseling by a nurse significantly improved menopausal symptoms.[52-54] Again, further clinical studies are warranted.

3. Acupuncture

Among current CAM modalities for menopausal symptoms, acupuncture has become popular because of its rare adverse side effect profile. However, the effectiveness of acupuncture needs to be confirmed with additional well-controlled placebo trials. A recent review, restricted to RCTs, examined the effectiveness of acupuncture therapy on menopausal symptoms and evaluated its adverse effects. A total of 764 individual cases in 11 studies from USA, Sweden, Korea, and China were systematically reviewed. Each study included a control group of no treatment, placebo treatment, pharmacological treatment, or non-pharmacological treatment. Five studies showed significant difference in reduction of hot flashes within groups but not between groups. An analysis of the outcomes of the trials showed that acupuncture was superior to hormone therapy or oryzanolin in alleviating vasomotor symptoms. There were minimal acupuncture-related adverse events reported in the six RCTs, such as temporary skin rash and pruritus which disappeared within a day, suggesting acupuncture is a relatively safe treatment option.[55] In women with breast cancer and menopausal symptoms, acupuncture appeared to be equivalent to drug therapy as a safe, effective and durable alternative treatment for vasomotor symptoms secondary to long-term antiestrogen hormone use.[56,57] Considering the promising results in initial studies, the authors recommend further investigation via well-designed trials to determine the efficacy of acupuncture for relieving menopausal symptoms.

4.Osteopathic manipulation therapy (OMT)

As an integrative treatment, OMT may be of benefit in the management of menopausal symptoms. However, to my knowledge, there are very few clinical trials to support this. As previously mentioned, a major complaint from menopausal women is hot flashes. Hot flashes are vasodilatory, and therefore parasympathetic, in nature. OMT has been shown to be effective on sympathovagal balance.[58] Stimulation to the thoracolumbar region may be helpful in promoting sympathetic triggers of vasoconstriction. In addition, since there are obvious changes in the musculoskeletal system during aging and menopause, somatic dysfunction of the musculoskeletal system should be evaluated, particularly that of the sacrum and pelvis. OMT techniques such as muscle

energy, balanced ligamentous tension, counterstrain, or myofascial release techniques may improve circulation and menopausal symptoms through optimization of posture and locomotion, increased range of joint motion, and reduction of joint pain. In 1994, a randomized controlled osteopathic study of 30 women in the United Kingdom demonstrated osteopathic techniques designed to treat the spin, peripheral joint and ribs improved the mobility and significantly reduced menopausal symptoms in the treatment group compared to the placebo group. In addition, there was an unexpected significant reduction in testosterone level in the treated group.[59] Furthermore, Angelika Muckler, a Vienna Doctor of Osteopathic Medicine, showed in her thesis "osteopathic treatment during transition of perimenopause" that even two osteopathic treatments induced a clear trend towards improvement of menopausal symptoms and quality of life of 13 women in 2005. The effects showed in her study seemed to be individually different, thus the mechanisms involved may include specific effects of OMT on particular areas (for example, effects on hormonal changes in aging process or on the central nervous system), general improvement of compensatory capacity of the whole body, or the combination of both.[60] However, the sample sizes of these two studies were small. More well-designed studies are essential to confirm the positive effects of OMT on menopausal symptoms and to define the possible mechanisms of these effects.

CONCLUSION

Bothersome menopause symptoms are common and affect quality of life for many women, whether menopause is natural or medically induced. Any woman with symptoms should be considered for treatment. Good communication between physicians and patients regarding menopausal symptoms and risks/benefits of available therapies is essential. Conventional hormone therapy is the only effective treatment consistently confirmed in randomized control trials; however, it is not appropriate in all situations. BHT appears to have some benefit, especially in a woman with an intact uterus requiring progesterone. In women who are not candidates for hormone therapy or who do not want a hormonal approach to treatment, CAM therapies should be considered, as potential benefits have been demonstrated. Acupuncture appears to be a promising treatment with rare adverse events. OMT seems to have some benefits which need to be explored in depth. Further evaluation of the effectiveness and safety of CAM therapies based on well-designed RCTs is warranted.

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