

Is Complementary and Alternative Therapy Effective for Women in the Climacteric Period?

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Vasomotor symptoms start about 2 years prior to menopause in women who are approaching menopause, and early menopause symptoms appear including emotional disturbance and anxiety, followed by physical changes such as vaginal dryness, urinary incontinence and skin wrinkles. As time progresses, osteoporosis, cardiovascular diseases, and dementia occur consecutively. Hormone therapy is primarily considered for the relief of menopause symptoms in postmenopausal women. However, as hormone replacement has emerged as a therapy that increases the potential risk of thrombosis, cerebral infarction and breast cancer, complementary and alternative medicine has drawn much attention. This study aimed to examine the types and effects of evidence-based complementary and alternative therapies that are currently used. (**J Menopausal Med 2015;21:28-35**)

Key Words: Climacteric, Complementary therapies, Postmenopause

Introduction

The National Center for Complementary and Alternative Medicine (NCCAM) classifies complementary and alternative medicine (CAM) therapies into five major groups: traditional medical practices such as Chinese medicine, mind-body interventions, biological substance based practices, manipulative and body-based practices such as finger pressure and massage, and energy medicine such as qi-gong.¹ In relation to CAM, a wide range of methods have been used to relieve menopause symptoms including phytohormones, various herbal therapies, homeopathy, antidepressants, anticonvulsants, dehydroepiandrosterone (DHEA) and exercise.^{2,3} This study aimed to investigate the effects of those practices with evidence-based medicine.

Phytoestrogens

Phytoestrogens are secondary metabolites of plants and characterized by a polyphenolic structure with phenol rings. Phytoestrogens have similar structures with 17- β -estradiol produced by the ovaries, and bind to estrogen receptors.⁴ Phytoestrogens demonstrate higher affinity for estrogen receptor- β than receptor- α ,^{5,6} and possess either estrogenic or antiestrogenic activity. Moreover, flavones are mainly divided into flavonoids with the basic structure such as isoflavone and coumestrol, and non-flavonoids without the basic structure such as lignan.⁴ Currently, phytohormones have been identified in about 300 plants,⁷ and have 1/1000 the binding affinity of estradiol.⁸ Phytoestrogens exist in the form as glycosides conjugated with sugars, and they are absorbed after being hydrolyzed to the aglycone forms by bacteria in the intestine on enterohepatic circulation.⁹⁻¹¹ For example, a large quantity

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of hydrolyzed aglycones are already present in fermented soybean paste.¹²

1. Isoflavones

Isoflavones are abundant in soy, red clover and others. According to systematic review, isoflavones have been identified to be effective in the relief of hot flashes, but ineffective in some studies, showing inconsistent results.¹³ In a meta-analysis conducted by Tempfer et al.,¹⁴ isoflavone was effective in mild-to-moderate hot flashes in women at early menopause. The conversion of daidzein to equol has drawn attention as a critical factor that induces favorable effect on hot flashes. About 30% to 50% of Western women have ability to convert daidzein to equol.¹⁵

In a systematic review of 15 clinical studies on the effect of isoflavones on bone mineral density (BMD), isoflavones are identified to decrease bone loss. A daily dose of 80 mg or higher is recommended in Asian diets.¹⁶ Furthermore, a meta-analysis of 9 randomized comparative studies showed that isoflavones are effective in reducing bone loss.¹⁷ With respect to cardiovascular diseases, there has been increasing interest since the U.S. Food and Drug Administration (FDA)¹⁸ addressed that soy foods lower the risk of heart disease in 1999. Rudkowska¹⁹ performed a meta-analysis of 74 randomized comparative studies in 2008. Soy protein was effective in lowering diastolic blood pressure and serum low-density lipoprotein (LDL) cholesterol, but did not change high-density lipoprotein (HDL) cholesterol. In addition, foods containing soy protein were found to have no influence on systolic and diastolic blood pressure.¹⁹ Since no studies have investigated the effect to isoflavones on the morbidity and mortality of cardiovascular diseases, isoflavones are not recommended as the primary therapy for prevention purpose.

The contradicting results of studies on phytoestrogens are attributable to the facts that the amounts of isoflavones in soybeans vary according to regions and seasons, and intestinal bacteria involved in the conversion of daidzein to equol vary according to races. Meanwhile, Asians are anticipated to have a relatively low risk of developing cardiovascular diseases, menopause symptoms, breast cancer, diabetes, obesity and others because they consume considerably large quantities of soy foods compare to Western populations.

2. Lignan

Lignans are abundant in flaxseeds. Among 4 clinical trials on the effect of lignan on hot flashes, its effect has not been proved in 3 studies and has been insignificantly observed in the other one.²⁰⁻²³ Thus, its effect still remain controversial. In a study of Pan et al.,²⁴ lignans have been shown to reduce total and LDL cholesterol.

Herbs

1. Black cohosh

Black cohosh was widely used by the American Indians for relief of dysmenorrhea and menopause symptoms. The action of black cohosh is known to be mediated by opioid or dopamine receptors,²⁵ and to block the reabsorption of serotonin.²⁶ According to Borrelli and Ernst²⁷ black cohosh is effective in mild-to-moderate vasomotor symptoms associated with sleep and emotional disturbances in early menopause. Black cohosh has been used in Germany since the 1940s, and has been commercialized in the products GYNO-Plus, Feramin-Q and others.

2. St. John's wort

St. John's wort has been used to relieve depression and menopause symptoms. In a comparative study on 47 postmenopausal women administered with St. John's wort for three months, the quality of life, sleep disturbances and others were improved, but the frequency and severity of hot flashes remained the same.²⁸

3. Dan quai

Dan quai containing coumarin, phytosterol, flavonoid, minerals, vitamins and others has been widely accepted as a tonic for women, and traditionally used for menstrual regulation and dysmenorrhea in East Asia. In a previous study performed on 74 subjects using dan quai alone for two years, there was no effect of dan quai on the relief of menopause symptoms.²⁹ On the other hand, positive effects were found in a previous study on concurrent administration of dan quai and chamomile for 12 weeks in 55 postmenopausal women. Significant decreases were observed in hot flashes, sleep disturbances, fatigue and others.³⁰ In a

recent randomized controlled study on the effect of mixed extract (EstroG–100) of *Cynanchi Wilfordii Radix*, *Phlomis umbrosa* and *dan quai* on menopause symptom relief, Kupperman menopause index (KMI) decreased markedly in the EstroG–100 group compared to the placebo group.³¹

4. Ginseng

Ginseng containing saponin, amino acid, vitamins, alkaloids and flavonoid is recognized as a tonic herb for men because of its aphrodisiac properties, and has been used to improve sexual dysfunction and menopause symptoms. According to the result of previous study on ginseng administered to 384 subjects for two years, ginseng was effective in improving depression and physical well-being, but it had no influence in alleviating vasomotor symptoms.^{31,32} In a recent systematic review on 11 randomized controlled studies on the effect of ginseng on menopause symptom relief, there was no change in the frequency of hot flushes in 3 studies. In contrast, the ginseng group showed more improvement in sexual dysfunction, overall health status, depression and physical well-being compared to the placebo group in the other 4 studies, suggesting limited relief effect of ginseng on menopause symptoms.³³

5. Evening primrose oil

Evening primrose oil containing omega–6 fatty acids has been used for treating atopic dermatitis, rheumatoid arthritis, mastalgia, menopause symptom relief, induced delivery and others. However, no studies have verified that evening primrose oil is effective in relieving hot flushes.

6. Ginkgo

Ginkgo containing flavonoid, terpenoid and omega–6 fatty acids is used for circulatory disturbance, memory improvement and others, and this has been particularly used in enhancing memory and concentration abilities. However, ginkgo had no effect in improving menopause symptoms, emotional and sleep disturbances, and memory and concentration abilities in two randomized controlled studies.^{34,35}

7. Hops

Hops containing terpenoid, flavonoid glycoside and catechin are widely used herbal medicine to treat sleep disturbances, tension headache, seizure, edema and others. In a 6–week randomized clinical trial on the efficacy of hops, hot flushes, sweating, insomnia, palpitation and other symptoms were identified to be reduced.^{36,37}

Homeopathy

Homeopathy is the notion that symptoms are best treated by agents believed to induce the same reaction as a “fight fire with fire” approach. Homeopathic medicine is based on ideas that humans are believed to have an inherent capacity to grow and heal, and their own natural responsiveness to drugs in response to specific physiological triggers after administering a minimum quantity of diluted substances. Commonly used substances are lachesis, pulsatilla, sepia and others.³⁸ Hot flushes was relieved by about 40% to 50% in a observational study on homeopathy. Moreover, Bordet et al.³⁹ reported that significant improvement was seen during both day and night hot flushes in their study performed in 2008. However, the results of randomized controlled study on homeopathy was insufficient to prove its positive effects on improvement of vasomotor symptoms.^{40–42}

Antidepressants (SSRIs/SNRIs) and Anticonvulsants

Norepinephrine and serotonin are neurotransmitters involved in complex neurotransmission process that regulates thermoregulatory zone in the brain.⁴³ It is assumed that the increased levels of norepinephrine acts to narrow the thermoregulatory zone,⁴ and the activation of specific serotonin receptor may incur hypothermia or high fever.⁴⁴ The occurrence of hot flushes has been hypothesized that estrogen deficiency lowers serotonin levels and increases norepinephrine levels that narrow the thermoneutral zone.⁴³ Selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) are known to improve hot flashes by increasing the amount of serotonin

in the synaptic cleft by blocking reuptake of presynaptic neuron of serotonin and norepinephrine from the synapse in the central nervous system.

1. SSRIs

Since SSRIs have been identified to reduce hot flashes in the 1990s,⁴³ a large number of related studies have been conducted. Fluoxetine, paroxetine, sertraline, citalopram and others have been identified to reduce hot flashes. Of these, paroxetine is found to be most effective in targeting hot flashes. In a comparative randomized controlled study on 156 subjects, hot flashes were reduced by 62% and 65% in two groups administered with 12.5 mg/day and 25 mg/day of paroxetine, respectively, for 6 weeks.⁴⁵ Moreover, the frequency of hot flashes was significantly lowered in the experimental groups after being administered with 20 mg and 10 mg of paroxetine for 4 weeks compared to the placebo group in another randomized controlled study.⁴⁶ In a recent multicenter, randomized controlled study, the experimental group administered with 7.5 mg/day of paroxetine for 12 weeks was compared with the placebo group. As a result, the frequency and severity of vasomotor symptoms were reduced markedly in the experimental group.⁴⁷ The low-dose of paroxetine has been approved by the FDA as an effective agent to control hot flashes.⁴⁸

Furthermore, according to the result of randomized controlled study after administration of 20 mg/day fluoxetine for 4 weeks, hot flashes was reduced by 50% and 36% in the fluoxetine and placebo groups, respectively.⁴⁹

According on the 2003 report on the effect of citalopam on hot flashes relief, 26 patients with breast cancer were administered with 10 mg/day of citalopam on the first week and 20 mg/day for the next 3 weeks, and hot flashes was decreased by 53%.⁵⁰ Moreover, in a study on 254 subjects grouped into placebo, 10 mg/day, 20 mg/day and 30 mg/day of citalopram groups, hot flashes was lowered by 20%, 46%, 43% and 50%, respectively.⁵¹

2. SNRIs

SNRIs have the ability to affect neurotransmitters according to dose. These antidepressants were developed more recently than SSRIs and fewer subtypes have been reported. The most common SNRIs are venlafaxine

and desvenlafaxine. In particular, venlafaxine has been recognized to be effective in reducing hot flashes.⁵² In a randomized controlled study on patients with breast cancer, venlafaxine groups were compared with the placebo group after being administered with 37.5 mg/day, 75 mg/day and 150 mg/day of venlafaxine for 4 weeks. The 75 mg/day group had most favorable results in hot flashes reduction compared to the placebo and 37.5 mg/day groups and fewer side effects compared to the 150 mg/day group.⁵³ Depo-medroxy progesterone acetate (DMPA) was administered as a single intramuscular injection of 400 mg in a group, and 37.5 mg/day of venlafaxine on the first week and 75 mg/day for the following 5 weeks were administered to another group. In this comparative study, hot flashes was reduced by 79% and 55% in two groups, respectively.⁵⁴

3. Tamoxifen and SSRIs/SNRIs

Tamoxifen is the most commonly used therapy for the treatment of breast cancer, and is converted to the active metabolites, 4-hydroxytamoxifen (4-OHT) or endoxifen in drug metabolic processes by the cytochrome p450 enzyme (CYP2D6).⁵⁵ CYP2D6 can be inhibited by some antidepressants such as paroxetine and fluoxetine. However, venlafaxine with a lesser extent of CYP2D6 inhibition is better alternative antidepressant for concurrent administration with tamoxifen.⁵⁶

4. Gabapentin

Gabapentin acts as a regulator of seizure or neuropathic pain. After the first identification of gabapentin's effect on hot flashes in 2000,⁵⁷ a comparative randomized controlled study was performed on 59 postmenopausal women grouped into placebo and gabapentin groups. After a 12-week follow-up, the frequency of hot flashes was lowered by 29% and 45% in each group, respectively.⁵⁸ Moreover, 420 patients with breast cancer were divided into three groups of placebo, 30 mg/day gabapentin and 900 mg/day gabapentin groups in a randomized controlled study performed for 4 weeks. Consequently, severity index of hot flashes was reduced by 21%, 33% and 49% in each group, respectively.⁵⁹ The above findings of recent studies suggest that administration of gabapentin at 900 mg/day is more effective in relieving hot flashes, and increasing dose is desirable after the initial use

of gabapentin at 300 mg/day.

Acupuncture

Acupuncture is the most common procedure practiced within traditional Chinese medicine. Acupuncture treatment involves the use of metal needles inserted into selected points in the body for the stimulation of specific sites. In a systematic review of 11 clinical studies, Cho and Whang⁶⁰ have found no effect of acupuncture on menopause symptoms. However, two recent randomized controlled studies have addressed that acupuncture combined with other treatment methods is effective in alleviating hot flashes and menopause symptoms.^{61,62}

Others

1. DHEA

DHEA is an endogenous steroid hormone secreted by the adrenal gland and serves as precursor to male and female sex hormones. Serum levels of DHEA decrease with age in women. DHEA has been reported to be effective in improving vasomotor symptoms, vaginal dryness, sexual responsiveness, BMD and others. In contrast, Elraiyah et al.⁶³ have recently suggested that DHEA is ineffective in improving sexual responsiveness and menopause symptoms.

2. Exercise

The Royal College of Obstetricians and Gynaecologists and North American Menopause Association recommend exercise to improve menopause symptoms. However, there is limited data on the association of exercise with menopause symptom relief. According to recent meta-analysis data sources on exercise and BMD, walking exercise alone is effective for preserving BMD at the femur, but ineffective at the spine. On the other hand, walking combined with weight-bearing exercises is effective for preserving BMD at both the femur and spine. This form of exercise is effective for a person who has exercised for more than a year.

Discussion

Symptoms complained by patients have to be first accurately determined whether they are menopause symptoms. When confirmed as menopause symptoms, the use of hormone therapy has to be considered first to relieve symptoms. However, the most fearful concern of hormone replacement therapy is identified as breast cancer.⁶⁴ The use of natural bio-identical progesterone that has the same structure as the hormones made by the human body decreases the risk of developing breast cancer or cardiovascular disease compared to the use of synthetic progestins. Moreover, estriol is expected to have an ability to protect breast tissues unlike conventional estrogen agents. These findings have to be taken into consideration in hormone therapy.⁶⁵

When hormone therapies cause adverse effects or contraindications, the use of non-hormonal therapies has to be taken into account. In such cases, professional knowledge and advice about non-hormonal agents mainly taken by postmenopausal women seem to be required. According to a study on the perception of hormone replacement therapy in nurses, 95% of nurses answered that they would recommend hormone replacement therapy for the treatment of menopause symptoms to themselves or their family members. Since nurses are largely women, it is better to manage postmenopausal women.⁶⁴ Therefore, the education of knowledge about menopause management in nurses is expected to more systematically manage and improve menopausal disorders.

In addition, advantages, disadvantages and proper use should be fully identified when using antidepressants or anticonvulsants for menopause symptom relief, and adequate nutritional intake and exercise should be combined at the same time.

Conclusion

To sum up the findings of randomized controlled studies or systematic reviews for CAM mainly used in relieving menopause symptoms, phytoestrogens have good effects as suggested by some studies. However, there is insufficient

evidence, and more clinical data about DHEA or homeopathy are essential. Among several herbs, black cohosh is identified to have positive effects on symptoms in women at early menopause, and St. John's wort is found to be effective in improving sleep disturbances and the quality of life. Although mixed extract of dan quai and hops have been verified to be effective for alleviating menopause symptoms in randomized controlled studies, further studies are warranted. Only a few studies have been performed to examine the effect of ginseng, dan quai or ginkgo, and no studies have investigated the effect of evening primrose oil on menopause symptom relief. When hormone therapy is contraindicated, agents acting in the central nervous system such as antidepressants or anticonvulsants are recommended. However, their side effects and interaction with other drugs should be fully understood. The recent FDA approval of paroxetine at a low dose is encouraging and the use of paroxetine is projected to increase. When exercising, walking concurrently with weight-bearing is more effective.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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