REVIEW ARTICLE

A Guide to Treating the Symptoms of Menopause

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Menopausal-related symptoms, which include hot flushes, night sweats, vaginal dryness, difficulty sleeping, sexual dysfunction, and depression/anxiety, among others, are experienced by roughly 80% of women and are therefore a common complaint in the primary care setting. Systemic high-dose hormone replacement therapy (HRT) was the mainstay of treatment until a large systematic review determined that the risk of HRT greatly outweighed the benefits to the patient. Since that time, women and their physicians have turned to a variety of therapies; behavioral, alternative, and off-label use of mainstream medications to treat the life-altering symptoms of menopause. Systemic HRT is still the most effective therapy on the market, although it is now prescribed in the lowest effective dose for the shortest possible duration. This article will review available mainstream, alternative and osteopathic treatments for the myriad of symptoms experienced by women during menopause and the menopausal transition.

INTRODUCTION

Menopause is defined retrospectively as absence of menses for 12 months and occurs at the median age of 51 years.[1] Perimenopause, or 'menopause transition' occurs within years of menopausal onset when the body experiences decreased levels of progesterone and estradiol with increasing levels of follicle stimulating hormone (FSH). Menses may become irregular during this period with many women experiencing menorrhagia when menses does occur. The final menstrual period occurs after the ovaries cease to produce estradiol or progestin.[2] The primary complaints during this period include vasomotor symptoms (VMS) or "hot flushes" and night sweats, and vaginal symptoms, typically related to vaginal atrophy.[3] VMS are experienced by up to 75% of women and can severely impede sleep and quality of life. Genitourinary symptoms are related to vaginal atrophy and dryness in addition to urinary symptoms of urgency, dysuria and recurrent urinary tract infections. These symptoms can interfere with relationships, sexual function, and overall quality of life.

As osteopathic primary care physicians we focus on the health of the whole individual. Menopause is a time of life when many things are changing a woman's body that affect all aspects of her life; both mental and physical. Symptoms related to vaginal atrophy are experienced by up to 60% of midlife women by the fourth year of menopause, while an estimated 7% of these women seek treatment for their symptoms.[4] What if instead of waiting for women to bring up these issues, we asked our patients about them during comprehensive exams? By proactively addressing the health problems of menopausal women we can improve their quality of life thereby improving their overall health and sense of well-being.

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METHODS:

Included in this article are major society guidelines compiled from the North American Menopause Society and the American College of Obstetrics and Gynecology. Also included are review articles of randomized controlled clinical trials. The PubMed database and Cochrane Library were searched for randomized controlled trials (RCTs) and meta-analyses of RCTs related to the study topic, with an emphasis on data published over the last 15 years. Alternative treatment studies were included for completeness sake and often included small study populations.

SYMPTOMS OF MENOPAUSE & THEIR PATHOPHYSIOLOGY

Primary Symptoms

Vasomotor symptoms typically manifest themselves as "hot flushes", aptly named for the sudden sensation of extreme heat accompanied by redness, warmth and/or sweating of the face, neck, shoulders, or chest. Each instance may last from 1-5 minutes and may be accompanied by diaphoresis, flushing, chills, clamminess, anxiety, and occasionally, by palpitations. VMS may be so severe that they interfere with sleep causing chronic fatigue. Women with hot flushes typically experience episodes for five to seven years, although some women may be afflicted with symptoms for over 15 years.[1] 87% of those affected by VMS, experience them daily, with 33% of women experiencing >10 episodes per day.[2]

Sexual symptoms, such as dyspareunia and decreased vaginal lubrication, are commonly related to vaginal atrophy. Atrophy of the vaginal mucosa is directly related to the decrease in systemic estrogen, which causes thinning of vaginal tissue, loss of vaginal rugae and elasticity and loss of subcutaneous fat in the labia majora.[2] Up to 40% of North American women will experience symptoms of vaginal dryness, discharge, itching and or dyspareunia during menopause.[5] The Women's Health Initiative (WHI) showed that women who reported sexual satisfaction in their relationships tended to have lower BMIs, be more physically active, and have fewer hot flushes and night sweats.[6] Dyspareunia is a common problem in post-menopausal women, affecting 8-22% of this population.[7] Dyspareunia often negatively affects a women's interest in sexual intercourse, and a subsequent decline in coitus frequency exacerbates vaginal dryness. Unlike vasomotor symptoms, the genitourinary symptoms of menopause typically worsen without treatment.[8]

Estrogen withdrawal is responsible for atrophy and decreased lubrication of the vaginal tissue, predisposing the now fragile epithelium to trauma during intercourse.[9] The sex steroid precursor hormone dehydroepiandrosterone (DHEA) produced by the adrenal glands also drops throughout a woman's life beginning around age 30. An important step in the maturation of vaginal cells responsible for vaginal elasticity is intracellular conversion of DHEA into estrogen. DHEA can only be used by tissues in possession of receptors capable of converting the sex steroid precursor into its active form; a capacity that is lost by endometrial cells after menopause. When compared to placebo, intravaginal DHEA (Prasterone) decreased all subjective vaginal symptoms of menopause when compared to placebo without increasing endometrial thickness.[4]

Important to note are pathological causes of vulvovaginal symptoms. Vulvar dystrophies such as lichen sclerosis, lichen planus, and squamous cell hyperplasia should be ruled out in any individual complaining of vaginal pain. A careful pelvic exam should be performed including biopsies of any areas of thickening, lesions or discoloration to rule out any pre-malignant/malignant conditions.[2]

Urinary incontinence is experienced by nearly 50% of women in the menopause transition and increases with age. Weak pelvic floor muscles and poor urethral support lead to stress incontinence, which is not directly related to menopause, although it is the most common cause of incontinence in middle age females.

Secondary Symptoms

Additional symptoms related to menopause and aging include weight gain, heart disease, insomnia, mood changes, cognitive decline and osteoporosis. Vaginal pH, which is typically acidic to prevent overgrowth of fungi and bacteria and subsequent inflammation and infection tends to increase during the menopause transition resulting in recurrent inflammatory vulvovaginitis.[25]

Weight gain during the menopause transition is typically around 5 lbs. and can be attributed to lifestyle and activity changes, as opposed to hormonal causes. Weight gain is associated with cardiovascular disease and worsening of vasomotor symptoms. First line treatment for weight gain should be adherence to low fat diet high in fruits and vegetables and increased physical activity. Medical treatments include phentermine, diethylpropion, orlistat, lorcaserin and phenterine/topiramate. Bariatric surgery generally results in better long-term weight loss in morbidly obese patients (BMI >40 kg/m^2 or >35 kg/m^2 with comorbid conditions) with resolution of comorbid conditions than lifestyle changes or pharmacologic therapy and should be considered in patients that have failed these therapies.[2]

Women in menopause and the menopause transition are often affected by insomnia related to disrupted sleep triggered by hot flushes and night sweats. Poor sleep is also related to decreased sexual activity and sexual satisfaction; in the WHI trial women with self-reported insomnia and sleep duration under 6 hours nightly tended to have fewer sexual encounters and experience decreased sexual satisfaction.[6] Effective options to treat insomnia include hormonal and non-hormonal therapy in addition to cognitive behavioral therapy specially geared toward insomnia treatment.[10]

Depression is a common complaint experienced by women both post menopause and during the menopause transition. Women with depression self report decreased quality of life independent of the number of hot flushes experienced.[11] It is therefore important to screen women in this stage of life for psychological comorbidities, as treating depression may improve overall sense of well-being.

Many women feel a subjective decline in cognitive function throughout the menopausal transition and into menopause, which can be related to a variety of factors prevalent during this period including insomnia, depression, and medication use.[2] The Study of Women's Health Across the Nation (SWAN) revealed that women actually experience a linear decline in cognitive function throughout the menopausal transition and into menopause. Over the ten year study period, processing speed was found to be the harbinger of cognitive decline, although not all women experienced cognitive loss in other areas and there was great variability between individuals when it came to decline in cognitive function with some improving over time.[12]

TREATMENT OPTIONS FOR VASOMOTOR SYMPTOMS

Hormone Replacement Therapy (HRT)

Oral HRT was the initial treatment of choice for women experiencing menopause-related symptoms as it is the most effective means of controlling vasomotor symptoms related to menopause. Systemic HRT fell out of favor when the WHI, a double blind placebo controlled trial, was terminated early after data showed an increased risk of MI, CVA, DVT/PE, and breast cancer in women taking combined estrogen/progesterone therapy for vasomotor symptoms.[1] Since that time, treatment has been targeted towards specific menopausal symptoms, using the lowest effective dose of HRT when required, for the shortest possible duration *(see Table 1, page 22)*.

General adverse effects of systemic HRT during treatment include breast tenderness, vaginal bleeding, bloating and headaches. These effects tend to be experienced less frequently in women taking low dose or ultra-low dose therapy, although the effectiveness of treatment of VMS may be diminished.

Other formulations of systemic HRT with FDA approval for treatment of VMS include a combination conjugated estrogen plus the

TABLE 1:

Available Formulations of Estrogen

	Ultra-Low Dose*	Low Dose	Standard Dose
Conjugated Estrogen	N/A	0.3-0.45 mg/d	0.625 mg/d
Micronized Estradiol	0.25 mg/d	0.5 mg/d	1 mg/d
Transdermal Estradiol	0.014 mg/d	0.025 mg/d	0.0375-0.05

**Mixed evidence as to effectiveness in reducing VMS,[13,14] currently not FDA approved for this use*

selective estrogen receptor modulator bazedoxifene (brand name Duavee), and progestin. The combination of estrogen and bazedoxifene, has a black box warning that includes increased risk of dementia in patients over 65 years, endometrial cancer, stroke and DVT, although it was not found to cause endometrial hyperplasia and has lower risk of vaginal bleeding when compared to conjugated estrogen/medroxyprogesterone.[15] Progestin is generally prescribed in combination with Estrogen preparations in women with a uterus to prevent endometrial hyperplasia and endometrial cancer. Studies have shown that progestin is an effective treatment for VMS, however; progesterone is generally not prescribed alone.[16] This is due to the WHI's finding of increased risk of breast cancer in those patients on estrogen/progesterone combination compared to those on estrogen alone; leading to the belief that the progesterone component was the culprit in these situations.

Non-Hormonal Medical Treatments

The selective serotonin reuptake inhibitor (SSRI), paroxetine, is the only SSRI with FDA approval for the treatment of VMS in menopause. Although less effective than systemic HRT, it effectively reduced the frequency of VMS within four weeks of initiating treatment across study populations.[17] The most common adverse effects experienced during treatment were nausea and dizziness, which generally resolved with time and dose adjustment. About one third of women will experience a relapse in VMS symptoms within three weeks of discontinuation of SSRI therapy.[18] The starting dose of paroxetine is 7.5mg daily and should be considered in women complaining of concomitant depression.

Clonidine is a centrally-active α2 agonist and anti-hypertensive used off-label at a dose of 0.1 mg/day for the treatment of VMS. It is less effective than HRT, SSRIs and gabapentin and only modestly more effective than placebo in decreasing VMS.[3] Due to its multitude of adverse effects including hypotension, headache, light-headedness, xerostomia, sedation and constipation and the risk of developing rebound hypertension upon cessation of therapy, clonidine is not commonly prescribed for VMS.[3] Clonidine may be considered in hypertensive women complaining of symptoms related to VMS.

Gabapentin used at 900 mg daily (300mg TID) resulted in a 51% decrease in hot flush frequency and improved the overall quality of life of study participants.[19] Side effects included dizziness, unsteadiness and drowsiness, although these symptoms improved over the course of treatment. Gabapentin does not currently hold FDA approval for this indication, although practitioners intending to treat peripheral neuropathy may monitor patients for a concomitant decrease in hot flush frequency.

Stellate ganglion block is performed by locating the anterior tubercle of C6 while the patient is lying in the supine position. A needle is inserted into the pre-vertebral fascial plane, contrast dye is injected, and fluoroscopy is used to confirm proper needle positioning. The area is then injected with 0.5% bupivacaine and the needle is removed. Patients are evaluated for a positive Horner's sign (which includes miosis, ptosis and anhydrosis) to determine the success of the ganglion block. Stellate ganglion block decreases frequency and intensity of moderate to severe hot flushes over a six month period, but not in a statistically significant manner when compared to sham injections.[20] The role of the stellate ganglion in VMS is not well understood.

Behavioral Changes

Behavioral techniques are generally aimed at self-cooling or avoidance of foods that are thought to trigger VMS. 50-80% of women use non-hormonal therapies for VMS associated with menopause. Self-cooling techniques include wearing layers, using a fan between sheets at night, or application of cold packs during hot flush. Triggers include alcohol, caffeine, spicy food, or hot liquids/foods. Clinical evidence does not support the effectiveness of these measures.[2]

Exercise has not been shown to decrease frequency or severity of VMS, although one study showed improved quality of life in menopausal women who participated in aerobic exercise three times weekly when compared to those who did not.[21] When comparing yoga to aerobic exercise and placebo in a factorial design randomized controlled trial, yoga was found to decrease interference of hot flushes on quality of life, although it did not affect overall frequency of VMS, while exercise was found to increase physical functionality without having any bearing on VMS.[22] Studies have also not proven yoga or aerobic exercise to be of benefit in the treatment of insomnia.[23]

The Women's Health Initiative Dietary Modification trial studied over 17,000 post-menopausal women who were randomized to either a low-fat, high fruits, vegetables and whole grain diet or the study control group. VMS were measured at baseline and at one year from a 34 item survey. Women with mild symptoms at baseline who lost weight were more likely to eliminate VMS at one year. Participants who lost ≥ 10% of body weight were 56% more likely to no longer report hot flushes and night sweats after one year, although women who followed the low fat diet were more likely to eliminate VMS irrelevant of weight loss.[24]

Alternative Medicine

Many women pursue acupuncture as an alternative to systemic medical treatments, due to their myriad of side effects, for the life-disrupting symptoms of menopause. While modest benefit in hot flush frequency and severity has been noted in randomized controlled trials, acupuncture is not more effective than sham needle treatments across study populations.[25] The North American Meno-

pause Society therefore recommends against acupuncture for the treatment of menopause-related symptoms.

Although Black Cohosh is the most commonly prescribed over the counter medication for the vasomotor symptoms of menopause, very little is known about its mechanism of action.[3] A Cochrane review concluded that black cohosh does not reduce either frequency or intensity of VMS and had insufficient evidence to support improvement in vaginal symptoms or overall quality of life in menopausal women.[26] The average dose used in studies was 40mg daily. Although there were initially concerns over hepatotoxicity caused by the supplement,[27] those claims have since been determined to be unfounded.[28]

Other commonly prescribed supplements in menopause include evening primrose and ginseng. While evening primrose is a good source of prostaglandin E and γ-linolenic acid, it has not been found to have any effect on menopausal VMS.[29] Ginseng has been used for centuries in Asia to treat a variety of conditions. While commonly prescribed for treatment of menopausal symptoms, no randomized controlled trials have shown it to be an effective treatment. There is also concern over the potential side effect of postmenopausal bleeding found in case studies due to its estrogen-like effect on the vaginal mucosa.[30]

Pycnogenol is a pine bark extract available on the market in a variety of dosages. When compared to placebo in a trial of 156 perimenopausal participants, 30mg of pycnogenol was found to significantly improve vasomotor symptoms after both four and 12 weeks of treatment. Interestingly, it was additionally found to improve insomnia in study participants over the 12 week study period.[31] It is unknown whether other pine bark extracts are effective in the treatment of menopausal symptoms.

Pollen extract has a high level of the antioxidant superoxide dismutase. It does not contain pollen shells which are the allergenic component of pollen, so it is safe to give in patients with a reported pollen allergy. 64 women were followed for one month before initiation of the trial to determine frequency and intensity of hot flushes and then for three months after starting daily pollen extract supplementation in the form of Femal pills. Femal was found to decrease frequency of hot flushes by 22%. Study participants did not experience any change in vaginal dryness or bleeding or fluctuation in levels of FSH, estrogen, testosterone or sex-hormone binding globulin.[32] The North American Menopause Society concludes that while pollen extract does not have estrogen activity and was effective in reducing VMS and increasing quality of life in one study, more studies are needed to determine safety and efficacy.

TREATMENT OPTIONS FOR GENITOURINARY SYNDROME OF MENOPAUSE

Hormone Replacement Therapy

Systemic estrogen treatment is actually considered less effective than topical estrogen for vaginal symptoms of menopause. Topical estrogen need not be combined with progesterone to prevent endometrial hyperplasia or cancer.[14] Topical estrogen (available in cream, ring, and vaginal tablets) leads to plumping of the vaginal mucosa and increased lubrication and sensation during intercourse, which may improve patient sexual satisfaction.[33] Intravaginal estrogen can improve urinary urgency and dysuria in women with over-active detrusor muscles leading to urge incontinence. It is indicated for treatment of vaginal symptoms unresponsive to conservative measures.

Intravaginal DHEA, brand name Prosterone or Intrarosa, was shown in two double blind placebo controlled trials to improve the symptoms of vulvovaginal atrophy and improve dyspareunia. Its use was approved by the FDA in November 2016.[34]

Medical Treatment

Ospemifene, a non-steroidal estrogen receptor agonist/antagonist (ie selective estrogen receptor modulator) with greatest effect on vaginal epithelium, is the first non-hormonal treatment with FDA approval for moderate to severe dyspareunia. After 52 weeks of therapy, Ospemifene 60mg daily was well tolerated by patients and did not show adverse effect on endometrial or breast tissue. Adverse events include increase hot flushes, although in clinical studies, increased VMS were not severe enough to lead to discontinuation of therapy.[25]

Pharmacologic treatment for urge incontinence focuses on anticholinergic therapy (ie solifenacin, oxybutynin, flavoxate, hyoscyamine, tolterodine), which antagonizes acetylcholine at muscarinic receptors to relax bladder smooth muscle and inhibit involuntary detrusor contractions.[35]

Non-Medical Treatment

Vaginal moisturizers and lubricants are a readily available over the counter solution. Vaginal lubricants are shorter-acting than moisturizers, which can be applied every few days. Lubricants are intended for application before or during intercourse and are either water or silicone based; silicone-based treatments are longer-lasting in smaller amounts, although they may interfere with male erection.[36] Often, they must be applied multiple times during one encounter.

Urinary incontinence related to poor urethral support and weak pelvic floor muscles could be effectively treated with weight loss, physical therapy and pessaries. Behavioral therapies for urge incontinence include caffeine and fluid restriction and bladder retraining. Surgical treatment, most commonly mid-urethral sling, has a success rate of 85% but lacks good long-term data.[2]

INTEGRATION OF OSTEOPATHIC MANIPULATIVE THERAPY

Anatomy

The ovaries are innervated by spinal cord levels T10-11, while the uterus derives its innervation from T12-L1 and the sacral splanchnic nerve. Pain from the cervix and upper vagina is sensed by sacral levels 2-4. The pudendal nerve provides somatic efferent innervation to the skeletal muscles of the perineum and general somatic afferents from the external genitalia *(see Table 2, page 24)*.[37]

Osteopathic Manipulative Treatment (OMT)

Very few studies have been carried out to determine the effect of OMT on menopausal symptoms. One unblinded study evaluated 30 women who underwent 'Fox's low force technique', a procedure

TABLE 2:

Structure	Levels	Parasympathetic Role	Sympathetic Role
Sweat Glands	Various spinal levels contribute to sympathetic and parasympathetic tone	Sweating on palms of hands	All other sweat glands through cholinergic function
Ovaries	Parasympathetic: CN X Sympathetic: T10-11	Exact effect unknown	Exact effect unknown
Uterine Fundus	Parasympathetic: pelvic splanchnic (S2-4) Sympathetic: T10-L2	Relaxation	Constriction
Cervix	Parasympathetic: pelvic splanchnic (S2-4) Sympathetic	Constriction	Relaxation

invented by the study's author and applied to specific spinal segments that were felt to be out of alignment, and determined it be an effective treatment for VMS in menopause.[38,39] There are, however; no randomized controlled trials evaluating the effect of OMT on menopausal symptoms despite the wide array of techniques available to treat menopausal women.[40,41]

Conclusion

Menopausal symptoms are a common complaint encountered in the primary care setting. While there are a variety of pharmacologic, behavioral and alternative treatments available today, none are as effective in reducing the vasomotor and vaginal symptoms as hormone replacement therapy (systemic or topical). As is the case with most processes that effect quality of life, the physician must chose from the available treatment modalities to find the best fit for the individual patient. None are as prepared as the osteopathic physician, who can take a full-body approach to the patient and chose the treatment(s) that best fit the patient's symptoms, risk factors, medical comorbidities and lifestyle.

AUTHOR DISCLOSURE

No relevant financial affiliations.

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