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CLINICAL REVIEW

Menopausal Hot Flashes and Non-hormonal Management in Women

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Hot flashes present a unique opportunity for physicians to offer a wide selection of treatment options that can be tailored to a patient's past medical history, presentation severity, and personal beliefs. These remedies include classic hormone replacement; complementary medicine (e.g. herbs, acupuncture); prescriptions such as serotonergics, anticonvulsants, central alpha agonists; and lifestyle changes (e.g. meditation, exercise).

Estrogen replacement was the mainstay of hot flash treatment until the publication of the Women's Health Initiative, which deepened the complexity of treatment, requiring patients and physicians to discuss risks of cancer and cardiovascular disease. Although hot flashes can occur in men and women, usually in association with declines in the level of sex hormones (i.e. estrogen in women and testosterone in men), women are the primary complainants, affecting the majority of women going through menopause. Women with identified risk factors such as clotting disorders, cardiovascular disease and breast cancer will need alternatives to hormone replacement, as do women fearful of such complications. For this reason, non-hormonal treatments have gained popularity and will be primarily addressed. Treatment will depend on severity of symptoms and their impact on daily function, as well as personal preferences of the patient. While mild symptoms may be ignored or merely tolerated, disruptive symptoms may require more aggressive interventions.

Symptoms of hot flashes typically include: an abrupt sensation of warmth or internal heat, measured as a small rise in core temperature; cutaneous vasodilatation; diaphoresis primarily involving the upper body and face; and often followed by a subsequent lowering of body temperature, when chills and shivering can occur. Episodes can last seconds to hours, with variable intensity and frequency over days or weeks and can occur even years before menopause. Diurnal variations have been noted, with nighttime symptoms referred to as "night sweats".[1,2] The presence and severity of hot flashes often but not always correlates with estrogen levels, and other influencing factors including smoking, alcohol intake, BMI, race, and exercise have been identified. Smoking, for example, increases the intensity of symptoms but has no effect on estrogen levels.[3] Disruption of sleep and quality of life can be discouraging and disabling, and primary care physicians play an important role in managing hot flashes to help maintain quality of life.

Menopause is defined as the lack of a menstrual cycle for one year due to the cessation of ovarian estrogen production or a consistent rise in FSH over 30[4]. Alternatively, AMH (anti-müllerian hormone) less than 200 indicates minimal to no ovarian oocytes, strongly suggestive of menopause.[5] Hot flashes in women are pathognomonic of menopause when there is depletion of reserve oocytes resulting in amenorrhea for 12 or more months. Yet, hot flashes are also characteristic of perimenopause, the years preceding menopause when serum estrogen and AMH levels begin to decline, FSH (follicle-stimulating hormone) rises and menses begin to change. Per the American College of Obstetrics and Gynecology (ACOG) and others, symptoms of menopause can occur even in the 30s and 40s, while the average age of menopause is 52 years. Women with identifiable menstrual changes (i.e. uterus intact) or with vasomotor symptoms consistent with hot flashes are candidates for treatment if warranted.[1,5,6] The use of non-hormonal therapies for the treatment of hot flashes is applicable to both menopause and perimenopause.

Lifestyle changes

Smoking is associated with increased reports of hot flash severity. Increased activity level, lower waist circumference, and lower BMI have been associated with decreases in frequency and severity of hot flashes, particularly in early menopause.[2,3,7] Women who underwent biofeedback and relaxation techniques (paced breathing, controlled muscle relaxation, mental focusing) had decreased frequency of hot flashes over a six-week period of time. This is consistent with the known role of sympathetic activation in enhancing or inducing hot flashes.[1] High body fat percentage or body mass index (BMI) have been associated with increased severity of hot flashes. Weight loss in suitable candidates may prove to be an effective though challenging treatment—10-20 lbs. weight loss over 1 year was needed to reduce or eliminate moderate to severe hot flashes.[8] Smoking cessation, weight loss, and relaxation techniques provide good options for patients as a first line intervention for those who wish to avoid medications or herbs.

Herbals

Black cohosh and soy are the most well known and most often used botanicals to manage hot flashes. Soy and soy products remain the most popular of this group for the presumed benefits of phytoestrogens. Phytoestrogens are naturally occurring compounds found in some foods that have estrogen and anti-

estrogen properties. Red clover extracts also contain phytoestrogens, though are not as popular. Other botanicals like black cohosh are commonly used solo or in combination. Black cohosh (*Cimicifuga*) has not been shown to be affective in some studies and hepatoxicity has been suggested but not definitively connected to its use.[9] Other unsubstantiated herbal remedies include: flaxseed, linseed, ginseng, St. John's wort, and gingko biloba. A Cochrane review on phytoestrogens, while critical of the trials determined that "some trials reported a slight reduction in hot flushes and night sweats with phytoestrogen-based treatment," especially in those women experiencing more than five daily episodes. In the same review, but independent of the main meta-analyses, high dose genistein extracts, a soy derivative (or isoflavone), 30-60 mg or greater, were associated with improvement in hot flashes. No endometrial or vaginal changes were detected with any of these phytoestrogen agents after 2 years of use.[10] Despite multiple trials of these supplements, no benefit has been consistently seen.[1,2,10] None are FDA-approved.

Serotonergics

The role between brain neurochemicals and hot flashes has been noted for some time, whether playing a role in setting the thermoregulation zone (for sweating and shivering) or in countering sympathetic activation.[1] Though still inferior compared to hormone replacement therapy, SSRIs (selective serotonin reuptake inhibitors) and SSNRIs (selective serotonin-norepinephrine reuptake inhibitors) have been shown to be effective in hot flash treatment in women. On the other hand, supplementation with 5-hydroxytryptophan, a metabolic precursor to serotonin, does not show any benefit.[1] Fluoxetine, escitalopram, venlafaxine and desvenlafaxine have all demonstrated reductions in hot flashes of up to 60%, often in a dose related response. In breast cancer survivors, venlafaxine was preferred over gabapentin in the management of hot flashes.[1] An ACOG (American College of Obstetrics and Gynecology) practice management article published in 2014 updated in 2018, supported the role of SSRIs and SSNRIs as alternatives to hormones.[11]

At this time, only paroxetine 7.5 mg (*Brisdelle*) is FDA approved for the treatment of hot flashes with moderate to severe vasomotor symptoms. However its use in breast cancer patients is limited by its inhibition of the CYP2D6 isoenzyme which is necessary for the activation of tamoxifen. Antidepressants are convenient for the dual management of depression and hot flashes in breast cancer patients. In patients taking tamoxifen, if an antidepressant is chosen for hot flash management, choosing medications that have no CYP2D6 inhibition would be preferred. SSRIs like sertraline, citalopram, escitalopram, and fluvoxamine do not appear to significantly inhibit this isoenzyme and would be preferred over fluoxetine and especially paroxetine, which has significant CYP2D6 inhibition. Of the SNRIs, venlafaxine would be preferred over desvenlafaxine because of the same drug interaction.[12] When compared escitalopram 20 mg daily versus duloxetine 60 mg daily, both improved hot flashes in breast cancer patients after 12 weeks.[13]

Anticonvulsants

Gabapentin has also shown efficacy in reducing hot flashes over a 6-12 weeks treatment period, requiring titration of doses from 900-2400 mg/day in order to reduce hot flashes 30-70%.[1] Doses of gabapentin 600 mg/day were still effective, but less effective than low-dose transdermal estrogen replacement.[11] When gabapentin and venlafaxine treatments were compared, patients reported equal relief of hot flashes with both agents but reported greater satisfaction with venlafaxine.[10] Pregabalin may be another option, though not as well studied.

Alpha-2 Agonist

Clonidine in both the pill and transdermal (patch) form decreases hot flashes, but as with most other therapies is still inferior to estrogen hormone replacement. Doses of 0.1 mg/day were superior to placebo and these low doses did not adversely affect blood pressure.[11] Clonidine appears to work by resetting and widening the temperature thresholds for shivering and sweating, consistent with its role of counteracting the adrenergic activation that would normally narrow the temperature ranges. Yohimbine, an alpha-2 adrenergic antagonist, worsens hot flashes in menopausal women.[1] Clonidine also is not FDA approved for the treatment of hot flashes.

Choice of hot flash treatment is affected by co-existing factors such as depression and anxiety, insomnia, cancer history, personal beliefs, and drug interactions. Women who cannot, or choose not, to use estrogen will particularly benefit from such counseling. Hot flashes can be managed through multiple non-hormonal treatments and it is reasonable to start simply with lifestyle changes whenever possible. Smoking cessation, as an example, would be reasonable to address, both for risk reduction and as a means of improving hot flashes. Although not all treatments have shown benefit, the side effects especially with prescription medications can be anticipated and even used to advantage. Gabapentin may help for sleep or restless leg syndrome in a patient with hot flashes.

The length of treatment can vary from patient to patient, averaging anywhere from a few years to a decade. The severity of hot flashes and the menopausal status at first onset of symptoms appear to correlate with the lifetime duration of hot flashes. Women with surgically induced menopause had the highest reported incidence of hot flashes (90%). When hot flash frequency increased or occurred in *premenopausal* women, hot flashes persisted a median of 11 years (9 years postmenopausal), while women who experienced their first hot flashes when in menopause experienced an average of 3 years of symptoms.[7]

On a case-by-case basis, physicians can address a range of therapeutic options best suited to the patient's vasomotor symptoms and unique needs with the aim of improving quality

of life. Lifestyle changes are the easiest and most practical means of addressing and initiating hot flash treatment while hopefully also addressing risk reduction, such as weight management and tobacco cessation. If symptoms are not adequately treated with such measures and quality of life issues predominate, then it is appropriate to identify the patient's preferences and provide education on the risks and benefits of therapy, be it hormonal or non-hormonal treatment. The insufficient quality and number of studies and, especially in the case of herbals, the lack of FDA oversight, limit the options for non-hormonal treatment. SSRI and SSNRIs are the preferred alternative when hormone replacement and lifestyle changes are ineffective or contraindicated.

REFERENCES

1. **Freedman RR**. Menopausal hot flashes: mechanisms, endocrinology, treatment. *J Steroid Biochem Mol Biol*. 2014 Jul;142:115-20. doi: 10.1016/j.jsbmb.2013.08.010. Epub 2013 Sep 4. Review. PubMed PMID: 24012626; PubMed Central PMCID: PMC4612529.
2. **Kronenberg F**. Hot flashes: epidemiology and physiology. *Ann N Y Acad Sci*. 1990;592:52-86; discussion 123-33. Review. PubMed PMID: 2197954.
3. **Smith RL, Gallicchio LM, Flaws JA**. Understanding the complex relationships underlying hot flashes: a Bayesian network approach. *Menopause*. 2018 Feb;25(2):182-190. doi: 10.1097/GME.0000000000000959. PubMed PMID: 28763402; PubMed Central PMCID: PMC5771829.
4. https://www.menopause.org/for-women/menopause flashes/menopause-symptoms-and-treatments/how-do-i-know-i'm-in-menopause
5. **Gold EB, Crawford SL, Avis NE, Crandall CJ, Matthews KA, Waetjen LE, Lee JS, Thurston R, Vuga M, Harlow SD**. Factors related to age at natural menopause: longitudinal analyses from SWAN. *Am J Epidemiol*. 2013 Jul 1;178(1):70-83. doi: 10.1093/aje/kws421. Epub 2013 Jun 20. PubMed PMID: 23788671; PubMed Central PMCID: PMC3698989.
6. https://www.acog.org/Patients/FAQs/The-Menopause-Years?IsMobileSet=false#is
7. **Gold EB, Crawford SL, Shelton JF, Tepper PG, Crandall CJ, Greendale GA, Matthews KA, Thurston RC, Avis NE**. Longitudinal analysis of changes in weight and waist circumference in relation to incident vasomotor symptoms: the Study of Women's Health Across the Nation (SWAN). *Menopause*. 2017 Jan;24(1):9-26. doi: 10.1097/GME.0000000000000723. PubMed PMID: 27749738; PubMed Central PMCID: PMC5177513.
8. **Kroenke CH, Caan BJ, Stefanick ML, Anderson G, Brzyski R, Johnson KC, LeBlanc E, Lee C, La Croix AZ, Park HL, Sims ST, Vitolins M, Wallace R**. Effects of a dietary intervention and weight change on vasomotor symptoms in the Women's Health Initiative. *Menopause*. 2012 Sep;19(9):980-8. PubMed PMID: 22781782; PubMed Central PMCID: PMC3428489.
9. **Avis NE, Crawford SL, Greendale G, Bromberger JT, Everson-Rose SA, Gold EB, Hess R, Joffe H, Kravitz HM, Tepper PG, Thurston RC; Study of Women's Health Across the Nation**. Duration of menopausal vasomotor symptoms over the menopause transition. *JAMA Intern Med*. 2015 Apr;175(4):531-9. doi: 10.1001/jamainternmed.2014.8063. PubMed PMID: 25686030; PubMed Central PMCID: PMC4433164.
10. **Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J**. Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database Syst Rev*. 2013 Dec 10;(12):CD001395. doi: 10.1002/14651858.CD001395.pub4. Review. PubMed PMID: 24323914.
11. ACOG Practice Bulletin No. 141: management of menopausal symptoms. *Obstet Gynecol*. 2014 Jan;123(1):202-16. doi: 10.1097/01.AOG.0000441353.20693.78. Erratum in: *Obstet Gynecol*. 2016 Jan;127(1):166. *Obstet Gynecol*. 2018 Mar;131(3):604. PubMed PMID: 24463691.
12. **Juurlink D**. Revisiting the drug interaction between tamoxifen and SSRI antidepressants. *BMJ*. 2016 Sep 30;354:i5309. doi: 10.1136/bmj.i5309. PubMed PMID: 27694573.
13. **Biglia N, Bounous VE, Susini T, Pecchio S, Sgro LG, Tuninetti V, Torta R**. Duloxetine and escitalopram for hot flushes: efficacy and compliance in breast cancer survivors. *Eur J Cancer Care (Engl)*. 2018 Jan;27(1). doi: 10.1111/ecc.12484. Epub 2016 Mar 3. PubMed PMID: 26936232.