دانشگاه علوم پزشکی
و خدمات بهداشتی درمانی تهران

ژورنال کلاب

دوشنبه ۲۹ آبان

ارائه دهنده: پردیس زمانی- اینترن زنان

استاد راهنما : دکتر فاضل

Vasomotor symptoms during menopause : A practical guide on current treatments and future perspectives

- International journal of women’s health
- Published 14 February 2023
- Mayo clinic , USA
- Khan SJ, Kapoor E, Faubion SS, Kling JM. Vasomotor Symptoms During Menopause: A Practical Guide on Current Treatments and Future Perspectives. Int J Womens Health. 2023 Feb 14;15:273-287. doi: 10.2147/IJWH.S365808. PMID: 36820056; PMCID: PMC9938702.

Abstract

- Vasomotor symptoms affect as many as 80% of midlife women, but only about one in four women receive treatment due to many factors. Menopausal hormone therapy remains the most effective treatment for vasomotor symptoms, and current professional guidelines conclude that the benefits of treatment typically outweigh the risks for healthy, symptomatic women under age 60 years and those within 10 years from their final menstrual period. For women with medical comorbidities, an individualized approach to treatment is recommended. For women who cannot use or choose not to use menopausal hormone therapy, there are many evidence-based non-hormonal options available including pharmacologic therapies. This review aims to summarize treatment options for bothersome vasomotor symptoms to guide clinicians caring for midlife women.

Introduction

- Definition of menopause : Menopause is defined as 12 months of amenorrhea, occurring at a median age of 51.3 years in the United States (US)

- VMS persist for a median duration of 7 years

- Data show that women who experience frequent VMS (>6 days in the previous 2 weeks) also experience higher rates of anxiety, depression, difficulty sleeping, and overall impaired quality of life.

Introduction

- Hormone therapy (HT) has been the cornerstone of VMS management and has been shown to be effective in reducing VMS severity and improving quality of life

- the current guidelines suggest that the benefits of HT typically outweigh the risks for most symptomatic women under 60 years of age and within 10 years of their final menstrual period (FMP)

Physiology of VMS

- VMS can begin during the perimenopausal stage, during which hormones have started to fluctuate, and last years past the FMP.

- Estrogen withdrawal during the menopause transition (MT) is associated with alterations in the hypothalamic thermoregulatory neutral zone, a group of neurons that regulate body temperature.

- Feelings of flushing, warmth sensation, skin reddening, and perspiration

Hormone therapy

- HT is the most effective treatment for VMS. HT use not only reduces symptom frequency but also intensity by nearly 90%, usually within one month of initiation.
- Considerations :
- Cardiovascular disease
- Venous thromboembolism
- Stroke
- Breast cancer

Cardiovascular disease

- In contrast to HT that is initiated in older women who are farther from the MT, when HT is started in women who are under the age of 60 years and within 10 years of menopause onset, CAD risks do not appear to be increased and there may be a cardioprotective effect. For women with a history of CAD, the risks of HT may exceed benefit, and non- hormonal options are recommended for VMS treatment.

- CVD outcomes may also be affected by different HT routes, with transdermal estradiol being associated with lower CAD-related mortality compared to oral estrogens.

Venous thromboembolism

- Unlike CVD, risk of VTE was not found to differ by age at initiation.

- Non-oral formulations with lower doses of estrogen(less than 0.625mg CEE or 1mg estradiol for oral formulations and less than 50 µg for transdermal formulations) are associated with lower risk of VTE.
- Synthetic progestogens, including MPA and norpregnane, are associated with an increased risk of VTE, while micronized progesterone and dydrogesterone do not appear to increase risk of VTE.
- these risks may be increased in women that are overweight or obese.

Stroke

- An increased risk of ischemic stroke was identified during the intervention phases of both the CEE plus MPA and CEE- alone WHI trials for women aged 50 to 79 years of age.

- If HT is initiated in women less than 60 years of age or within 10 years of menopause, meta-analysis of RCTs shows no increased risk of stroke . Unlike oral estrogen which has an increased risk of ischemic stroke, transdermal estrogen does not confer the same risk . Risk of stroke appears dose-dependent with oral estrogens, with high doses (>0.625mg CEE, >2mg estradiol) being associated with greatest risk.

Breast cancer

- women taking CEE plus MPA had a cumulative increased incidence of breast cancer over time, increasing after about 3 years for women with prior HT use and 5 years for women without prior HT use. However, unlike CEE plus MPA, estrogen alone in women without a uterus did not appear to increase breast cancer risk if taken for less than 5 years.
- For women with a prior history of breast cancer, HT should be avoided.
- Though the risk is overall low, HT formulation may impact conferred risk of breast cancer. For women on estrogen alone, there does not appear to be an increased risk of breast cancer in the short term (<5 years). In women with an intact uterus requiring combined estrogen plus progestogen, cyclic dosing of micronized progesterone or dydrogesterone may confer the least risk of breast cancer. (synthetic progestogens may have the highest risk)

HT Formulation and Route of Administration

- For women with an intact uterus, systemic estrogens must be paired with a progestogen or selective estrogen receptor antagonist (for example, bazedoxifene) to prevent the risk of endometrial hyperplasia and endometrial cancer associated with unopposed estrogen use
- Low dose vaginal estrogens, which are effective for management of genitourinary symptoms related to menopause, are insufficient for vasomotor symptom management.
- When comparing the various available formulations of systemic estrogen, transdermal formulations remain the preferred route of administration for women with obesity and a higher risk of VTE, and those with diabetes mellitus or increased risk of CVD.

Table 1 Common HT Formulations

HT Type	Formulation	Common Brand Names	Route of Administration	Dosing	Additional Considerations
Estrogens	17β-estradiol	Activella, Mimvey, Estrace	Oral	1–2mg/day	
		Alora, Climara, CombiPatch, Minivelle, Vivelle-Dot	Transdermal	0.025mg-0.1mg; one patch every 3–7 days	May confer less risk of VTE vs oral estrogens
		Elestrin, Divigel	Topical/Lotion	1.74g/day	Can transfer to other individuals, clothing, et cetera without proper precautions; possible alternative to transdermal patch for adhesive allergies
		Estrace	Vaginal cream	500mg-1g daily x2 weeks; then 500mg-1g 1–3x weekly	Preferred for genitourinary but not systemic symptoms
		Femring	Intravaginal ring	0.05mg/day x3 months; 0.1mg/day x3 months	
	Conjugated equine estrogen (CEE)	Premarin, Prempro	Oral	0.3mg-1.25mg/day	In women post-hysterectomy: may be associated with reduced breast cancer mortality
		Premarin	Vaginal Cream	Daily x 2 weeks; then 2x weekly	Preferred for localized genitourinary symptoms; does not treat systemic VMS
	Estrone	Estragyn	Injection	0.1–0.5mg 2–3x weekly	
	Esterified estrogens	Menest	Oral	0.3–1.25mg/day	
	Ethinyl Estradiol	FemHrt	Oral	0.02–0.05mg 1–3x daily	Dose-dependent increased risk of coagulopathy such as VTE

Progestogens	Medroxyprogesterone (MPA)	Premphase, Prempro (CEE + MPA)	Oral	30-day cycle: 5–10mg/ day x10-14 days Daily: 2.5–5mg/day	
	Micronized Progesterone (MP)	Prometrium, Endometrin	Oral	28-day cycle: 200mg/ day x12 days Daily: 100mg/day	Continuous dose reduces unwanted vaginal bleeding; cyclical dose more favorable for endometrial protection and reduced breast cancer risk
	Norethindrone acetate	FemHrt (ethinyl estradiol + norethindrone acetate)	Oral	5mg/day	
		CombiPatch (estradiol + norethindrone acetate)	Transdermal	0.14mg 2x weekly	
	Levonorgestrel	Climara (estradiol + levonorgestrel)	Transdermal	0.015mg weekly	
	Dydrogesterone	Duphaston	Oral	28-day cycle: 10mg/day Daily: 2.5mg-5mg/day	Nonandrogenic
Synthetic Steroids	Tibolone	Tibella	Oral	2.5mg/day	Not recommended for women with history of breast cancer

Contraindications

- Current guidelines support the use of HT in symptomatic menopausal women with consideration of age, time since menopause, and individual risk factors.

- Clinicians should be aware of several contraindications for HT. Women with a prior history of CAD, stroke, myocardial infarction, unprovoked VTE, or those who are at high risk for CVD should avoid HT. Unexplained vaginal bleeding should be evaluated prior to consideration of HT. In the setting of prior estrogen-sensitive cancers, such as breast cancer, systemic HT should be avoided.

Long-Term Management of HT

- Currently, data are insufficient to suggest an optimal way to discontinue HT, but gradual tapering is generally favored over stopping abruptly.

- Regardless of age or treatment duration, at the time of HT cessation, approximately 50% of women experience recurrence of VMS.

Non hormone Therapies

- Although HT is the mainstay of VMS treatment, nonhormone options should be made available for women who have medical contraindications to HT use or a personal preference to avoid it.

- low-dose paroxetine is the only nonhormone treatment approved by the US Food and Drug Administration (FDA) for the treatment of VMS.
- Taken at a dose of 7.5mg daily, paroxetine has shown improvements in VMS frequency and severity, as well as improvement in sleep disruption without negative effects such as decreased libido or weight gain. Because of CYP2D6 inhibition, paroxetine should be used with caution in breast cancer patients taking tamoxifen.

Table 2 Nonhormone Pharmacologic Therapies for Menopausal VMS

Medication Name	Drug Class	Suggested Dosing	Side Effects	Additional Considerations
Gabapentin	Gamma-aminobutyric acid (GABA) analogue	100–300mg 3x/day	Dizziness, fatigue	Consider in concomitant migraine or sleep disorders
Paroxetine	SSRI	Paroxetine mesylate: 7.5mg/day Paroxetine HCl: 10–20mg/day	Nausea, dizziness	Only US FDA-approved nonhormone option. CYP2D6 inhibition; avoid in tamoxifen users; consider in concomitant mood disorders
Venlafaxine	SNRI	37.5–150mg/day	Nausea, dizziness	May be safe in tamoxifen users
Oxybutynin	Anticholinergic, antimuscarinic	2.5mg-5mg/2x daily up to 15mg/day	Dry mouth, urinary difficulties	Avoid in elderly; may benefit concomitant overactive bladder with VMS; side effects appear dose-dependent
Clonidine	Antihypertensive; α-2 adrenergic agonist	0.05–0.15mg/day	Blood pressure, drowsiness, dry mouth	Inconsistent data; less effective than SSRIs/SNRIs and gabapentinoids; significant side effects

Notes: Data from [illegible] et al[23] and [illegible] et al[73]

Non hormone Therapies

- **Venlafaxine**, an SNRI, is one of few nonhormone agents that has been studied head-to-head against HT in an RCT.The study showed that venlafaxine 75mg daily was as effective as low-dose oral estradiol (0.5 mg daily) in reducing frequency of hot flashes. it does not interact with the CYP450 system and therefore can be safely prescribed in tamoxifen users.
- **Gabapentin** is inferior to estrogen therapy in reducing hot flash frequency and severity. It may be a preferred nonhormone option in women with other indications for its use, including migraine and sleep disorders.

Non Hormone Therapies

- **Oxybutynin** should be used with caution in older women due to anticholinergic side effects including the potential risk for impaired cognition. However, use in young women experiencing VMS is a reasonable and effective option, especially for women who also suffer from overactive bladder symptoms.

- the limited efficacy and significant side effects limit the clinical use of **clonidine** for VMS management.

Lifestyle modifications

- Exercise, weight loss, and cooling techniques may be associated with improvement in VMS, although there are less conclusive data compared to other treatment modalities.

- While physical activity may not directly alleviate VMS, weight loss induced by better lifestyle choices does seem to be associated with reduced symptoms. Perimenopausal women with obesity are more likely than their normal or overweight counterparts to experience menopausal symptoms.

Mind-Body Techniques

- CBT :In an RCT assessing CBT for menopausal symptoms (CBT-Meno), symptomatic women who received CBT reported a significant improvement in their VMS symptom interference and bother compared to no active intervention.

- Clinical Hypnosis: hypnotherapy reduced hot flashes by 80%, and participants reported high treatment satisfaction.

New and Novel Therapies

- Estetrol (E4) is a natural human fetal estrogen with selective action in the tissues that works by activating nuclear estrogen receptor α (ERα) leading to a cascade of coregulator activators and repressors similar to estradiol (E2) and estriol (E3) but in a different pattern than tamoxifen or raloxifene.
- Neurokinin B Antagonism (NK3R Antagonists): Our understanding of VMS pathophysiology has expanded with the identification of specialized hypothalamic KNDy neurons that utilize neurokinin B (NKB) signaling on neurokinin 3 receptor (NK3R).This signaling pathway appears influential in the development of hot flashes within the hypothalamic thermoregulatory neutral zone. Through NK3R antagonism, the signaling pathway can be disrupted and potentially attenuate VMS.

Conclusion

- Despite the high prevalence, significant impact on quality of life, and a variety of safe and effective treatment options, VMS remain undertreated. HT remains the gold-standard, most effective treatment for VMS, but many symptomatic women do not use it for a variety of reasons, including perceived safety concerns. The benefits of HT outweigh the risks for healthy women under age 60 and/or within 10 years from their FMP. While HT use is a consideration for a majority of symptomatic, healthy, and recently menopausal women, nonhormone options may be utilized for women with contraindications to HT use, or for those who prefer to avoid HT use for any reason. Emerging therapies may provide additional options for women with bothersome VMS.

Thank you for your attention