INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: *Menopause Treatment Guidelines*
-January 2025-

Background:

The Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) provided a review of menopause, focusing on updated treatment guidelines from the Endocrine Society (ENDO) and the National Institute for Health and Care Excellence, as well as current position statements from the North American Menopause Society (NAMS).[1,2,3,4] Medications listed on the NCF relevant to this condition include citalopram, escitalopram, estradiol, gabapentin, medroxyprogesterone, oxybutynin, paroxetine, and venlafaxine. Following clinical review and analysis, the NPTC made **no modifications** to the IHS National Core Formulary.

Discussion:

Menopause affects more than one million women annually, with the average age of onset being 51-52 years old.[5] The most prominent symptoms of menopause include vasomotor symptoms [VMS], sleep disturbances, anxiety, depression and genitourinary symptoms of menopause (GSM).[6] Up to 80% of women experience VMS during the menopausal transition.[5] American Indian and Alaska Native women are most likely to report bothersome VMS, with 30% experiencing moderate to severe VMS.[7] Women who experience VMS earlier during menopause appear to be more likely to have persistent VMS late into the postmenopausal period as well.[6] Evidence demonstrates VMS may be a biomarker for chronic diseases.[7] Thus, evidence-based interventions to improve VMS and other symptoms are needed.

Estrogen therapy (ET) was historically the most effective treatment for VMS until 2002 when the Women's Health Initiative (WHI) study revealed that risks may outweigh benefits of hormone therapy (HT). The WHI included women between the ages of 50-79 years old. Notably, when distributing the data based on age, the study showed that women under 60 years of age and less than 10 years out from menopause have a very different risk profile than older women.[8] Among postmenopausal women in the WHI, HT with conjugated equine estrogen (CEE) plus medroxyprogesterone acetate (MPA) for a median of 5.6 years or CEE for a median of 7.2 years was not associated with an increased risk of all-cause, cardiovascular, or overall cancer (including breast cancer) mortality during a cumulative follow-up of 18 years.[9]

The highest quality clinical practice guidelines (CPGs) consistently recommend HT as the most effective treatment for moderate to severe VMS, GSM, premature menopause (surgical/medical/spontaneous), and prevention of osteoporosis and fracture risk in high-risk women younger than 60 years or within 10 years of menopause onset.[10] Treatment should be individualized based on the best available evidence to maximize benefits and minimize risks, with periodic reevaluation. Factors to consider include type, dose, duration, route of administration, timing of initiation, and whether a progestogen is used.[2] For the treatment of VMS, all CPGs recommend estrogen-only therapy for hysterectomized women, or with the addition of a progestogen (EPT) to protect the endometrium of non-hysterectomized women.[10]

All selected CPGs supported low-dose vaginal estrogen for GSM (vulvovaginal atrophy and dyspareunia), including potential use by cancer survivors.[10] Low-dose vaginal ET (creams, tablets, rings, soft gel vaginal insert) is preferred over systemic ET when used solely for vulvar or vaginal symptoms due to minimal systemic absorption. Low-dose vaginal estrogen may also provide benefit for urinary symptoms (i.e., prevent UTIs, overactive bladder, and urge incontinence), but HT does not have FDA approval for any urinary health indication. Both systemic HT and low-dose vaginal ET increase lubrication, blood flow, and sensation of vaginal tissues, but only vaginal ET improves sexual function, interest, arousal, and orgasmic response. Nonhormonal alternatives that are FDA approved for dyspareunia include ospemifene and intravaginal DHEA. Transdermal ET may be preferable over oral ET for sexual function or libido concerns as it has minimal effect on sex hormone-binding globulin and free testosterone levels.[2] Consider testosterone as a potential therapeutic option for postmenopausal women with low libido when HT alone is not effective.[4]

Most CPGs, except ENDO, recommend HT for the prevention of osteoporosis.[10] Women with primary ovarian insufficiency (POI) experience long-term adverse events related to bone density, in addition to other health risks. The strongest evidence from meta-analyses and systemic reviews links early loss of ovarian function to decreased quality of life and increased risk of fracture, CVD, heart failure, diabetes mellitus, and overall mortality. Other significant issues may include persistent VMS, loss of fertility, bone loss, GSM, sexual dysfunction, cognitive and mood changes, and increased risk of dementia, ophthalmic conditions, and depression. Higher-than-standard doses of HT may be needed to provide protection against bone density loss in younger women, particularly in those <40 years and thus lower future osteoporotic fracture risk.[2] Effective management of POI and premature or early menopause may include appropriate doses of HT, calcium with vitamin D, exercise, and screening to detect medical issues, as well as fertility counseling and mental health services. HT is recommended at least until the average age of menopause. Oral contraceptives may be an alternative form of HT, because spontaneous pregnancy may occur in about 5% of women with POI.

Depressive symptoms worsen as women transition through menopause. Menopause-associated mood disturbances were identified as potential indications for HT by all CPGs, but most recommend against HT for the treatment of clinical depression.[10] None recommend HT for cognitive symptoms or for prevention of dementia, primary or secondary CVD prevention, or prevention of diabetes mellitus or sarcopenia, although most noted that HT reduced incident diabetes mellitus.[10]

During the menopause transition, women with VMS are more likely to report disrupted sleep. Poorer sleep quality has been associated with mood fluctuations, memory problems, metabolic syndrome, obesity, and other CV risk factors. HT does improve sleep in women with bothersome nighttime VMS by reducing nighttime awakenings. Transdermal estrogen may have some evidence of sleep benefit, independent of VMS.[2]

HT does not need to be routinely discontinued in women older than 60 or 65 years and can be considered for continuation beyond age 65 for persistent VMS, quality-of-life issues, or prevention of osteoporosis after appropriate evaluation and counseling of benefits and risks.[2] None of the CPGs specified an age or time limit to the duration of use.[10] VMS symptoms return in about 50% of women when HT is discontinued.[2] Gradually stopping HT may limit recurrence of symptoms in the short term, but neither option makes a difference to symptoms in the longer term.[4] Absolute contraindications to HT include CVD (CHD, stroke, VTE), estrogen-sensitive cancer (breast cancer, endometrial cancer), undiagnosed vaginal bleeding, and liver disease.[2]

Nonhormonal therapy (NHT) is recommended for the treatment of VMS in women who are not candidates for HT due to contraindications or personal preference. All the CPGs recommend selective serotonin/norepinephrine reuptake inhibitors (SSRIs/SNRIs), but most considered them not to be first line.[10] Paroxetine mesylate is the first FDA approved NHT for moderate to severe VMS with improvements in VMS severity and frequency for up to 24 months. Sertraline and fluoxetine have not shown statistically significant improvements.[3] Other recommended NHT options for VMS by most of the CPGs included gabapentin and clonidine.[1,3,10] However, NAMS does not recommend clonidine mainly due to the presence of other more effective therapies with fewer adverse effects.[3,10] Oxybutynin and fezolinetant are recommended for the treatment of VMS, with NAMS acknowledging that long-term use of oxybutynin might be associated with cognitive decline in older adults.[3] Complimentary and alternative therapies were less well addressed. NAMS alone definitively recommended cognitive behavioral therapy (CBT) and hypnosis for VMS.[3] The remaining CPGs variably stated CBT could be considered for low mood, sleep disturbance, and VMS, and hypnosis could be considered for VMS.[10]

Fezolinetant is a first-in-class NK3 receptor antagonist which received FDA approval for use in the treatment of moderate to severe VMS. Fezolinetant was shown to reduce VMS frequency by about 2.5 hot flashes per day vs. placebo, meeting the FDA's clinical threshold for a reduction of at least 2 VMS per day (or 14 per week).[11,12] FDA issued a warning that fezolinetant can cause rare but serious liver injury and requires increased frequency of liver blood testing. It is unclear how fezolinetant compares to other NHTs due to lack of head-to-head studies. While the use of fezolinetant is supported by guidelines, the use of this agent in a larger population will help further define the role of fezolinetant in menopause.

Findings:

Hormone therapy remains the most effective treatment for VMS and should be considered in menopausal women <60 years old and within 10 years of their final menstrual periods. For women who are poor candidates for HT because of contraindications or personal preference, there are several NHT options for reducing VMS that are supported by evidence. Fezolinetant may be considered an alternative to other NHTs including SSRIs (paroxetine, citalopram, escitalopram), SNRIs (venlafaxine or desvenlafaxine), gabapentin, or oxybutynin when there is a contraindication, intolerance, or inadequate response.

References:

1. Stuenkel C, Davis SR, Gompel A, et al. Treatment of Symptoms of the Menopause: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*, 2015, 100(11):3975-4011.
2. North American Menopause Society. The 2022 hormone therapy position statement. *Menopause* 2022; 29(7):767-94.
3. North American Menopause Society. The 2023 nonhormone therapy position statement. *Menopause:* 2023; 30(6):573-90.
4. National Institute for Health and Care Excellence. Menopause: identification and management. NICE guideline [NG23].07 Nov 2024.
5. World Health Organization. FACT SHEET: Menopause. Published Oct 16, 2024.
6. Neal-Perry, G. Menopause Presentation. Healio. 2024 July 22. Accessed January 6, 2025.
7. Taylor L, Kent J, Austin S, et al. Developing a Menopausal Transition Health Promotion Intervention with Indigenous, Integrative, and Biomedical Health Education: A Community-Based Approach with Urban American Indian/Alaska Native Women. Glob Adv Integr Med Health. 2024 Aug 13:
8. Roussouw JE, Prentiss RL, Manson JE, et al. Postmenopausal hormone therapy and risk of cardiovascular disease by age and years since menopause. *JAMA.* 2007; 297(13):1465-77.
9. Manson JE, Aragaki AK, Rossouw JE, et al. Menopausal Hormone Therapy and Long-term All-Cause and Cause-Specific Mortality: The Women's Health Initiative Randomized Trials. *JAMA*. 2017; 318(10):927-38.
10. Hemachandra C, Taylor S, et al. A systematic review and critical appraisal of menopause guidelines. *BMJ Sex Reprod Health.* 2024; 50:122-38.
11. Johnson K, Martin N, Nappi RE, et al. Efficacy and Safety of Fezolinetant in Moderate to Severe Vasomotor Symptoms Associated with Menopause: A Phase 3 RCT. *J Clin Endocrin Metab*. 2023; 108:1981-97.
12. Bonga KN, Mishra A, Maiti, R, et al. Efficacy and Safety of Fezolinetant for the Treatment of Menopause-Associated Vasomotor Symptoms: A Meta-analysis. *Obstet Gynecol*. 2024; 143(3):393-402.