Indian Health Service
National Pharmacy and Therapeutics Committee
Formulary Brief: *Menopausal Hormone Therapy*
-August 2016-

Background:
The IHS National Pharmacy & Therapeutics Committee recently reviewed menopausal hormone therapy (MHT, estrogen alone or combined with a progestin) in August 2016. Oral estradiol, conjugated equine estrogen (CEE) vaginal cream and progestin-only oral contraceptive pills (any) are currently on the National Core Formulary (NCF). **No changes were made to the NCF** following the presentation of the clinical evidence, guideline reviews and utilization data.

Discussion:
The peri/postmenopausal period can be challenging time for women who experience vasomotor symptoms (VMS) including hot flashes, genitourinary syndrome of menopause (GSM) traditionally referred to as vulvovaginal atrophy, and mood disorders such as depression and anxiety. Estrogen is an effective therapy for VMS and GSM. The hypothesis is that estrogen acts at the hypothalamus to restore thermoregulatory control.[1] Estrogen's action on the vaginal tissue restores an acidic pH and microflora, thickens the epithelium and increases vaginal secretions.[2] In women with an intact uterus, progestins when added to estrogen help prevent endometrial hyperplasia and endometrial carcinoma which can occur in unopposed estrogen therapy.

During the 1990s, systematic reviews and meta-analysis of observational studies concluded that estrogen's impact on reducing heart disease and hip fracture outweighed the risk of cancer.[3] Estrogen became the leading prescription medication, as it relieved the bothersome symptoms of menopause and prevented heart disease and fractures. The surprising results of the Women's Health Initiative (WHI), the first large clinical trial to study the effects of MHT and diseases of aging women, concluded that the risks of taking MHT were greater than the benefits. As a result, prescriptions for MHT in the United States decreased from 22% in 1999-2002 to 4.7% in 2009-2010.[4]

The CEE/medroxyprogesterone acetate (MPA) 0.625mg/2.5mg daily treatment vs. placebo arm of the WHI was terminated early after 5.2 years. Results showed an excess risk per 10,000 person-years of 7 more coronary heart disease (CHD) events, 8 more strokes, 8 more pulmonary emboli and 8 more invasive breast cancers, outweighing the benefits of 6 fewer colorectal cancers and 5 fewer hip fractures.[5] Although the CEE vs. placebo arm showed no effect on CHD events, colorectal or breast cancer, the increased risk of 12 more strokes and 6 more venous thromboembolisms (VTE) outweighed the benefit of 6 fewer bone fractures per 10,000 person-years.[6] Secondary analysis of the WHI data resulted in the "timing hypothesis"; the data for CHD was stratified by age and years since menopause. For women 50-59 years, the hazard ratio (HR) and absolute excess risk were 0.93 and (-2) per 10,000 person-years (not statistically significant). For women <10 years since menopause, the HR was 0.76 and excess risk was (-6) per 10,000 person-years (p= 0.02).[7]

The WHI studied both CEE/MPA and CEE unopposed. Transdermal estrogen does not appear to increase the risk of stroke and VTE. A population-based, nested case-control study concluded the use of low-dose estrogen patches was not associated with stroke compared to nonusers (Odds Ratio [OR] 0.81; CI: 0.62 to 1.05).[8] A case-controlled study of transdermal vs. oral estrogen users showed that transdermal estrogen did not increase risk of VTE vs. nonusers (OR 0.9; 95% CI: 0.4 to 2.1) whereas oral estrogen vs. nonusers increased the risk of VTE (OR 4.2; 95% CI: 1.5 to 11.6). The same study found no significant association of VTE with micronized progesterone (OR 0.7; 95% CI: 0.3 to 1.9). Norpregnane derivatives however were associated with a 4-fold-increased VTE risk (OR 3.9; 95% CI: 1.5 to 10.0).[9] The WHI CEE study and a population case-control study found no increased risk of breast cancer with estrogen alone.[10,11] The French E3N cohort study indicated that natural progesterone is not associated with increased risk of breast cancer (OR 1.00; 95% CI: 0.83 to 1.22) compared with synthetic progesterone (OR 1.69; CI 95%: 1.50 to 1.91).[12]

Guidelines for MHT from the Endocrine Society and the North American Menopause Society base their recommendations on the aforementioned studies and many others. Of note, only FDA-approved MHT is recommended whereas custom-compounded hormonal preparations are not.[13,14]

Menopro™, a free mobile application (with no advertising and developed without industry support), is a useful tool for busy clinicians where evidence-based guidelines are formatted into algorithms. This application is intended for women >45 years of age however it can be used for women of any age who have undergone bilateral oophorectomy.[13] Clinicians can review (and print) recommendations for behavioral modifications, contraindications, calculate cardiovascular risk, and recommended therapy for women with VMS or GSM. When risk is too high for MHT, alternative options for non-hormonal therapies such as SSRIs, SNRIs, gabapentin, and clonidine are recommended. Also included are the National Cancer Institute's breast cancer risk assessment tool, patient information, tables of the different preparations available and recommendations for treatment duration.

A tissue selective estrogen complex, which combines the selective estrogen receptor modulator bazedoxifene with conjugated estrogen, is available for the management of VMS and prevention of postmenopausal osteoporosis. This unique combination is included in guideline recommendations for women averse to bleeding and breast tenderness commonly caused by estrogen/progesterone therapy.

Findings:
As with any pharmacotherapy, the risks (breast cancer and cardiovascular) and benefit of MHT should be weighed individually prior to initiation. Age should also be considered when initiating MHT as evidence indicates favorability in women <60 years of age or <10 years from menopause. When indicated, MHT should be tailored to address patient-specific needs (VMS, GSM, mood disorders) and only for the length of time necessary to manage troublesome symptoms. Recommended medications for common peri/postmenopausal symptoms including oral estrogen, estrogen vaginal cream and progestins are currently available on the NCF. Current guidelines do not support the use of MHT in the prevention of cardiovascular disease, osteoporosis or dementia. Given the findings from the clinical and pharmacoeconomic evaluation, no changes were made to the NCF.

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

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