EDITORIAL

Progestin-only systemic hormone therapy for menopausal hot flashes

Clinicians treating postmenopausal hot flashes often recommend "systemic estrogen treatment." However, progestin-only therapy also can effectively treat hot flashes and is an option for women with a contraindication to estrogen therapy.

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The field of menopause medicine is dominated by studies documenting the effectiveness of systemic estrogen or estrogen-progestin hormone therapy for the treatment of hot flashes caused by hypoestrogenism. The effectiveness of progestin-only systemic hormone therapy for the treatment of hot flashes is much less studied and seldom is utilized in clinical practice. A small number of studies have reported that progestins, including micronized progesterone, medroxyprogesterone acetate, and norethindrone acetate, are effective treatment for hot flashes. Progestin-only systemic hormone therapy might be especially helpful for postmenopausal women with moderate to severe hot flashes who have a contraindication to estrogen treatment.

Micronized progesterone

Micronized progesterone (Prometrium) 300 mg daily taken at bedtime has been reported to effectively treat hot flashes in postmenopausal women. In one study, 133 postmenopausal women with an average age of 55 years and approximately 3 years from their last menstrual period were randomly assigned to 12 weeks of treatment with placebo or micronized progesterone 300 mg daily taken at bedtime.[1] Mean serum progesterone levels were 0.28 ng/mL (0.89 nM) and 27 ng/mL (86 nM) in the women taking placebo and micronized progesterone, respectively. Compared with placebo, micronized progesterone reduced daytime and nighttime hot flash frequency and severity. In addition, compared with placebo, micronized progesterone improved the quality of sleep.[1]

Most reviews conclude that micronized progesterone has minimal cardiovascular risk.[2] Micronized progesterone therapy might be especially helpful for postmenopausal women with moderate to severe hot flashes who have a contraindication to estrogen treatment such as those at increased risk for cardiovascular disease or women with a thrombophilia. Many experts believe that systemic estrogen therapy is contraindicated in postmenopausal women with an American Heart Association risk score greater than 10% over 10 years.[3] Additional contraindications to systemic estrogen include women with cardiac disease who have a thrombophilia, such as the Factor V Leiden mutation.[4]

For women who are at high risk for estrogen-induced cardiovascular events, micronized progesterone may be a better option than systemic estrogen for treating hot flashes. Alternatively, in these women at risk of cardiovascular disease a selective serotonin reuptake inhibitor, such as escitalopram, 10 mg to 20 mg daily, may be a good option for treating postmenopausal hot flashes.[5]

Medroxyprogesterone acetate

Medroxyprogesterone acetate, at a dosage of 20 mg daily, is an effective treatment for hot flashes. In a randomized clinical trial 27 postmenopausal women with hot flashes were randomly assigned to treatment with

placebo or medroxyprogesterone acetate 20 mg daily for 4 weeks. Vasomotor flushes were decreased by 26% and 74% in the placebo and medroxyprogesterone groups, respectively.[6]

Depot medroxyprogesterone acetate injections at dosages from 150 mg to 400 mg also have been reported to effectively treat hot flashes.[7,8] In a trial comparing the effectiveness of estrogen monotherapy (conjugated equine estrogen 0.6 mg daily) with progestin monotherapy (medroxyprogesterone acetate 10 mg daily), both treatments were equally effective in reducing hot flashes.[9]

Micronized progesterone vs medroxyprogesterone acetate

Experts in menopause medicine have suggested that in postmenopausal women micronized progesterone has a better pattern of benefits and fewer risks than medroxyprogesterone acetate.[10,11] For example, in the E3N observational study of hormones and breast cancer risk, among 80,377 French postmenopausal women followed for a mean of 8 years, the combination of transdermal estradiol plus oral micronized progesterone was associated with no significantly increased risk of breast cancer (relative risk [RR], 1.08, 95% confidence interval [CI], 0.89–1.31) compared with never users of postmenopausal hormone therapy.[12] By contrast, the combination of oral estrogen plus medroxyprogesterone acetate was associated with an increased risk of breast cancer (RR, 1.48; 95% CI, 1.02–2.16) compared with never users of postmenopausal hormone therapy. The E3N study indicates that micronized progesterone may have a more favorable breast health profile than medroxyprogesterone acetate.[12]

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Norethindrone acetate

Norethindrone acetate monotherapy is not commonly prescribed for the treatment of menopausal hot flashes. However, a large clinical trial has demonstrated that norethindrone acetate effectively suppresses hot flashes in women with endometriosis treated with depot leuprolide acetate (LA). In one trial 201 women with endometriosis were randomly assigned to 12 months of treatment with[13]:

- LA plus placebo pills
- LA plus norethindrone acetate (NEA) 5 mg daily
- LA plus NEA 5 mg daily plus conjugated equine estrogen (CEE) 0.625 mg daily, or
- LA plus NEA 5 mg daily plus CEE 1.25 mg daily.

The median number of hot flashes in 24 hours was 6 in the LA plus placebo group and 0 in both the LA plus NEA 5 mg daily group and the LA plus NEA 5 mg plus CEE 1.25 mg daily group. This study demonstrates that NEA 5 mg daily is an effective treatment for hot flashes.

In the same study, LA plus placebo was associated with a significant decrease in lumbar spine bone mineral density. No significant decrease in bone mineral density was observed in the women who received LA plus NEA 5 mg daily. This finding indicates that NEA 5 mg reduces bone absorption caused by hypoestrogenism. In humans, norethindrone is a substrate for the aromatase enzyme system.[14] Small quantities of ethinyl estradiol may be formed by aromatization of norethindrone in vivo,[15,16] contributing to the effectiveness of NEA in suppressing hot flashes and preserving bone density.

Progestin: The estrogen alternative to hot flashes

For postmenopausal women with moderate to severe hot flashes, estrogen treatment reliably suppresses hot flashes and often improves sleep quality and mood. For postmenopausal women with a contraindication to estrogen treatment, progestin-only treatment with micronized progesterone or norethindrone acetate may be an effective option. ●

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Dr. Barbieri reports no financial relationships relevant to this article.

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