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Menopause management: How you can do better

Let patients know that hot flashes, vaginal dryness, and other common menopausal symptoms can be treated successfully with hormonal and nonhormonal agents.

PRACTICE RECOMMENDATIONS

› *Hormone replacement therapy should be considered only for women who are <60 years old and within 10 years of menopause.* **(B)**

› *Selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors may reduce the frequency of hot flashes within 1 to 2 weeks of initiating treatment.* **(B)**

› *Local estrogen preparations should be first-line therapy for atrophic vaginitis.* **(B)**

› *Spirolactone may improve menopause-related hair loss.* **(B)**

Strength of recommendation (SOR)

- (A)** Good-quality patient-oriented evidence
- (B)** Inconsistent or limited-quality patient-oriented evidence
- (C)** Consensus, usual practice, opinion, disease-oriented evidence, case series

CASE ▶ During a routine well-woman visit, 54-year-old Barbara P becomes tearful and confides that she's afraid her marriage of 20 years is falling apart. She and her husband argue frequently, Barbara says, and she alternates between being tearful and angry for no apparent reason. Barbara's last menstrual period was 2 years ago. When asked about menopausal symptoms, she reports having 6 or 7 hot flashes daily—which disrupt her sleep several nights a week. She also reports that intercourse is painful and that her interest in sex has diminished as a result. A pelvic exam reveals thin, pale vaginal epithelium; the rest of her physical exam is normal.

Many women with menopausal symptoms that significantly impair their quality of life never report them to their physicians—or do so only if they're asked, as I have discovered in my practice. The mistaken belief that there are few effective treatments for menopausal symptoms, coupled with concern about adverse effects of hormone replacement therapy (HRT), prompts many women to suffer in silence. That's a problem you can do much to change.

Broaching the subject with perimenopausal women, rather than waiting for them to initiate the discussion, is an important first step. Let them know that common menopausal symptoms, including hot flashes, atrophic vaginitis, insomnia, diminished libido, and hair loss, can be treated successfully with a variety of hormonal and nonhormonal agents. And when a patient reveals, as Barbara did, that she's troubled by mood swings or uncharacteristic behavior, it may help to let her know that many women find it challenging to deal with both the physical and emotional ramifications of this new phase of life.

Hot flashes: How often? How severe?

Hot flashes are experienced by up to 75% of menopausal women, and tend to be most severe in the first 2 years of



Limiting the duration of HRT, prescribing a low-dose regimen, and using a patch rather than oral therapy can help to minimize the risk.

menopause.¹ There is a broad spectrum of frequency and severity, however, so it's important to question patients about both. Risk factors for greater severity and higher frequency include surgically or chemically induced menopause, an elevated body mass index, a history of tobacco use, and African American ethnicity.^{2,3} There are multiple treatments for hot flashes, including HRT, antidepressants, antiepileptics, antihypertensives, acupuncture, herbal remedies, and even physical activity (TABLE 1).^{4,5}

A critical look at HRT

HRT (an estrogen-progesterone combination for women with an intact uterus, and estrogen alone for those who've had a hysterectomy) is highly effective, alleviating hot flashes and other menopausal symptoms 80% to 90% of the time.⁶ But widely publicized reports from the Women's Health Initiative of an increased risk of breast cancer, coronary heart disease, stroke, and venous thromboembolism in women taking both estrogen and progesterone prompted many patients to taper

off HRT, or decline to start it.^{7,8} That initial report was a decade ago, however, and further analyses and additional research have since found that for some women and under some circumstances, HRT may, in fact, be safe and effective.⁹

■ **Age and time of menopause** are key criteria. For women who are <60 years old and within 10 years of the onset of menopause, HRT appears to be a safe short-term treatment.⁹ While the risks may be most significant after 10 years of use, physicians should attempt to limit HRT whenever possible.

Women who are ≥60 years of age and those at high risk for cardiovascular disease or breast cancer, or both, should not take HRT. When prescribing HRT for patients without these contraindications, there are things you can do to minimize the risk:

- Limit the duration of HRT to the shortest treatment required.⁹
- Use a transdermal delivery system. Compared with oral administration, the patch appears to lower the risk of thromboembolism.¹⁰
- Prescribe a low-dose HRT regimen. The

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In patients taking HRT, a transdermal delivery system is associated with a reduced risk of thromboembolism compared with oral therapy.

TABLE 1
Treating hot flashes:
A look at the options^{4,5}

HRT
Estrogen-progesterone combination (estrogen only for women with hysterectomy)
Antidepressants*
SNRIs
SSRIs
Antiepileptics
Gabapentin (900 mg/d)
Antihypertensives
Clonidine (0.1 mg/d, then titrate upward) [†]
Methyldopa (200-500 mg once or twice a day)
Herbal supplements[‡]
Black cohosh [‡]
Magnesium (400 mg/d)
Omega-3 fatty acid [‡]
Red clover [‡]
St. John's wort [‡]
Lifestyle/alternative interventions
Acupuncture [‡]
Avoidance of triggers [§]
Paced respirations
Physical activity
Yoga

HRT, hormone replacement therapy; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

*Specific antidepressants and dosage are detailed in Table 2.

[†]Limited data on effect.

[‡]Optimal dose is unknown.

[§]Eg, alcohol, hot drinks, spicy foods, and caffeine.

lower dose may reduce the risk of cardiovascular disease, but it will take longer to achieve symptom relief—typically, 8 to 12 weeks vs 4 weeks for women on a standard dose.¹¹ A low-dose regimen is particularly important for women who are obese. Because of the higher serum estradiol levels found in this patient population, they need a smaller quantity of estrogen and progesterone to achieve symptom relief.¹²

•Taper slowly—over as long as 6 to 12 months—which may minimize hot flash severity and frequency.¹³

■ **Compounded hormones.** Some women prefer compounded hormones, which are often individualized based on the results of blood or saliva testing, in hopes of avoiding the risks associated with HRT. While compounds are typically marketed as a safer and more effective means of alleviating menopausal symptoms, however, there is limited evidence of their efficacy. What's more, the lack of standardization, resulting in variations in formulations and dosages from one product to another, raises questions about the safety of compounded hormones.¹⁴⁻¹⁶

Antidepressants alleviate hot flashes

Both selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), which target neurotransmitters involved in the hypothalamic thermoregulation center, have been found to reduce both the severity and frequency of hot flashes.^{4,17,18} Women who have hot flashes have a 2-fold increase in risk for depression, and antidepressant therapy may help alleviate mood disturbances in addition to providing vasomotor symptom relief,^{19,20} even in women who do not meet the criteria for clinical depression.²¹

■ **Which antidepressants are most effective?** Venlafaxine, desvenlafaxine, and paroxetine have been shown to provide the best vasomotor symptom relief, with symptom reduction of 67% vs 15% with placebo.^{15,22} It is important to note, however, that studies of individual agents have had different inclusion criteria and different means of randomization. **TABLE 2**^{17,21-30} summarizes the evidence, recommended dosing, expected onset of symptom relief, and common adverse effects of antidepressants used to treat hot flashes.

■ **Other agents have more adverse effects.** Certain antihypertensives (clonidine and methyldopa) and the antiepileptic gabapentin may alleviate hot flashes, but none is an optimal treatment. Clonidine has been shown to be effective in both oral and transdermal forms, but the drug is associated with hypotension, among other adverse ef-

TABLE 2

Antidepressants for hot flashes? Here's what to consider

Medication (usual dose)	Symptom relief	Adverse effects
SNRIs		
Desvenlafaxine (100 mg/d) ²⁴	Hot flash reduction in 1-2 wk; peak effect at 4 wk	Increased BP, decreased appetite, dry mouth, nausea
Duloxetine ^{*23}	Limited data on onset of action or adverse effects	
Venlafaxine (75 mg/d) ²²	Hot flash reduction in 1-2 wk	Constipation, decreased appetite, dry mouth, increased anxiety, nausea
SSRIs		
Citalopram (10 mg/d) ^{*21,25}	Hot flash reduction in 1-2 wk; peak effect at 4-8 wk	Dry mouth, nausea, palpitations, somnolence (may be useful for concomitant insomnia), sweating
Escitalopram (10-20 mg/d) ²⁶	Limited data on dosing, onset of action, or adverse effects	
Fluoxetine (20 mg/d) ^{21,27}	Hot flash reduction within 3 wk; peak effect at 6 mo	Appetite loss, constipation, dizziness, dry mouth, fatigue, mood changes, nausea, nervousness, sleep disturbances, sweating
Fluvoxamine (50 mg/d)	Limited data on onset of action or adverse effects	
Paroxetine (10-12.5 mg/d; may be increased to 25 mg/d after 2 wk if no relief) ^{*28,29}	Hot flash reduction in 1-2 wk	Dry mouth, headache, insomnia, nausea, somnolence; reduces the plasma concentration of active metabolite of tamoxifen, and should not be used concurrently
Sertraline (50 mg/d) ^{†17,30}	Hot flash reduction in 1-2 wk; peak effect at 3 wk	Anxiety, diarrhea, dry mouth, fatigue, nausea

BP, blood pressure; SNRIs, serotonin-norepinephrine reuptake inhibitors; SSRIs, selective serotonin reuptake inhibitors.

*Can be given with HRT.

†Mixed efficacy data; use as second-line treatment only.

fects. Methyldopa has not been well studied and is not viewed as a first-line agent.⁵ And, although gabapentin at doses ≥ 900 mg/d reduces the frequency of hot flashes, many women cannot tolerate the nausea, headache, dizziness, and confusion that are common adverse effects.³¹⁻³³

Exercise: Little help for hot flashes, but it may boost mood

Data on physical activity's effect on hot flashes are rather limited. Overall, exercise has not been found to improve or worsen hot flashes,⁵ but it does improve mood swings associated with menopause.³⁴ Any type of exercise may be beneficial.

Small studies have found that specific activities, such as paced respiration and yoga, improve hot flashes, but larger studies are needed to clarify effect size.⁵ Other lifestyle interventions, such as limiting alcohol consumption, decreasing spicy food intake, avoiding hot drinks, and eliminating caffeine, may alleviate hot flashes, as well.

What to expect from alternative treatments

Acupuncture. While acupuncture does appear to reduce the frequency of hot flashes in the short term, such benefits have not been sustained.^{35,36} What's more, clinical studies have found sham acupuncture and true acu-



Studies suggest that an HRT regimen will alleviate vaginal dryness only if it contains estriol.

puncture to be beneficial, so the placebo effect may be an important factor in the success of this modality.³⁵

■ **Herbal remedies.** A number of herbal preparations have been touted to improve hot flash frequency and severity: Black cohosh, red clover, St. John's wort, and omega-3 fatty acids have shown some benefit, although more research is needed to determine optimal dosing and ensure safety of use.^{5,21,37-39} Magnesium (400 mg/d), with its minimal adverse effects and low cost, has also recently emerged as an attractive option for hot flash control.⁴⁰ No randomized double-blind clinical trials have been done, however, to test the effectiveness of these preparations.

Kava kava, vitamin E, evening primrose oil, and dong quai should be avoided. All have shown little or no benefit and have potentially serious adverse effects.⁵

Question patients about other menopausal symptoms

Treating hot flashes alone is not enough. It is important to address the full spectrum of menopausal symptoms, including insomnia, atrophic vaginitis, impaired sexual function, and hair loss.

Is she getting a good night's sleep?

Insomnia—a common complaint of menopausal women—may be unrelated to, or a consequence of, hot flashes. Sedating hypnotics, and at least one herbal remedy, may help with both.

■ **Eszopiclone** (3 mg, taken at bedtime) has been shown to alleviate insomnia-related hot flashes. With sufficient sedation, night sweats and hot flashes go unnoticed, and both sleep and mood typically improve.⁴¹ Other sedating hypnotics have not been studied in this patient population, but would likely have similar effects.

■ **Magnolia bark supplements** may be a preferred sleep aid for women who hesitate to take a sedating hypnotic medication. This herbal remedy has been found to decrease anxiety, irritability, and insomnia related to menopause,⁴² although there is limited research regarding long-term benefits and adverse effects.

Is she experiencing vaginal dryness?

For about 50% of menopausal women, symptoms associated with atrophic vaginitis impair sexual function and quality of life.⁴³ Clinical signs such as thinning of the vaginal epithelium and loss of rugae can be seen 2 to 3 years after the onset of menopause, but many women do not report symptoms until 4 to 5 years postmenopause.⁴³ Sexually active women tend to have fewer menopausal symptoms in general, and less atrophic vaginitis in particular.⁴⁴

Common symptoms include vaginal dryness (affecting 75% of menopausal women); dyspareunia (38%); and itching, unusual vaginal discharge, and pain (15%).⁴³ Urinary tract infections secondary to atrophic vaginitis are common, as well. Yet only 25% of women with atrophic symptoms report them to their physicians—and nearly 70% say that their health care provider has never asked about them.⁴³ Failure to diagnose and treat atrophic vaginitis leads to unnecessary suffering, as many effective treatments exist (TABLE 3).^{43,45-49}

■ **Topical estrogen** is the most effective treatment for atrophic symptoms. Up to 25% of women on HRT continue to suffer from vaginal dryness and may benefit from topical estrogen. Research suggests that only regimens containing estriol alleviate vaginal symptoms.⁴³

Conversely, while women using HRT for vasomotor symptoms may find that their vaginal dryness improves, HRT should not be considered for atrophic vaginitis alone in view of safety concerns and limited efficacy.⁴³

Available as conjugated equine estrogens and estriol, estrone, or estradiol, topical estrogen may be delivered via cream, tablet, ring, or pessary. Adverse effects include itching, pain, vaginal discharge, and vaginal bleeding,⁴³ but a switch to a different preparation may reduce or eliminate these problems. Endometrial proliferation has not been found to occur within 24 months of continuous use, so concomitant progesterone use is not recommended.⁴⁵

Up to 90% of patients using local estrogen show improvement in atrophic symptoms within 3 weeks.⁴³ Alternative diagnoses, such as vaginal candidiasis, contact irritation, or other vaginosis, should be considered if the

TABLE 3
Treating atrophic vaginitis^{43,45-49}

HRT
Estrogen-progesterone combination (estrogen only for women with hysterectomy)
Lubricants and moisturizers (water-based are most effective)
Topical estrogen (5-10 mcg/d)
<ul style="list-style-type: none"> • Creams • Pessary • Tablets • Vaginal ring
Herbal remedies/vitamins
<ul style="list-style-type: none"> • Soy* • Black cohosh* • Red clover* • Vitamin D† • Vitamin E (100-600 IU/d orally, or topically)
Other agents
<ul style="list-style-type: none"> • DHEA • Gabapentin (300-900 mg/d) • Pilocarpine† • Tibolone (2.5 mg/d) • Topical lidocaine (PRN)

DHEA, dehydroepiandrosterone; HRT, hormone replacement therapy.

*Limited data on effect.

†Optimal dose is unclear.

condition fails to improve. Systemic absorption of estrogen—which is minimal to begin with—declines with use, as the thinness of the vaginal epithelial layer resolves. Doses can be reduced over time as less estrogen is needed to maintain healthy epithelium. The lowest effective dose should always be chosen for a patient.⁴³

The only contraindication to topical estrogen use is allergy to an ingredient in the preparation. Because of its limited systemic absorption and low doses, it can be prescribed for virtually any woman with vaginal symptoms, including those who would not be candidates for systemic therapy. That said, few studies have addressed the use of local estrogens by women with a history of breast

cancer. While it is likely a safe option for treatment of atrophic vaginitis, more research involving breast cancer survivors is needed.⁴³

■ **Dehydroepiandrosterone (DHEA)** may provide the same benefits as local estrogens, but without any systemic effects.⁴³

■ **Water-soluble lubricants and moisturizers** provide short-term relief.⁴³ A variety of over-the-counter (OTC) lubricants are effective at alleviating dyspareunia. However, moisturizers often have limited long-term benefit and may have adverse effects. A hypersensitivity reaction to components of specific formulations is one potential adverse effect. Women need to be aware that some OTC lubricants may damage condoms, as well. (Pregnancy may still be possible for women who have occasional menstrual cycles; condoms also provide protection from sexually transmitted infection.)

■ **Vitamin E**, taken orally (100-600 IU/d) or used as a topical preparation, has also been shown to improve symptoms of vaginal dryness.⁴⁶ Early studies of vitamin D in cell culture have shown benefit to atrophic tissues, although limited clinical studies have been performed.⁴⁷

■ **Soy, red clover, and black cohosh** have been shown to provide some relief of atrophic symptoms.⁴³ However, each of these agents uses estrogenic pathways, which may be a concern for some patients. Limited safety data and variation in preparations are potential problems, as well.⁴³ Placebo-controlled trials of numerous other herbal products—including bryonia, belladonna, lycopodium, nettle, dong quai root, motherwort, chickweed, and wild yam—have found them to be neither safe nor effective.⁴⁸

■ **Other medications** that may have limited use in treating atrophic vaginitis include tibolone, a weak estrogenic steroid, and oral pilocarpine,⁴⁹ but limited data regarding their efficacy and adverse effects curtail their use. Topical lidocaine and oral gabapentin may work as analgesics, but little improvement in tissue integrity can be expected.⁴³

Is intercourse painful?

Has she lost interest in sex?

Many menopausal women notice a decline in libido, which is often related to frequent hot



Because of limited systemic absorption and lower doses, local estrogen can be used by virtually all women with atrophic vaginitis associated with menopause.

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Magnolia bark has been found to decrease anxiety, irritability, and insomnia related to menopause, but little is known about long-term benefits or adverse effects.

flashes or dyspareunia secondary to atrophic vaginitis. In these instances, treatment of the underlying condition, as detailed earlier, should be first-line therapy.

■ **Sustained-release bupropion** (300 mg/d) has been shown to increase both sexual arousal and satisfaction in women who are not depressed.⁴⁴

■ **Testosterone therapy** is another treatment; in some cases, it can be added to an existing HRT regimen to improve libido. However, testosterone supplementation should be offered only after all other causes of low libido have been excluded. It is not recommended for women who are not on HRT, as its safety in this population is unknown. Long-term clinical trials are needed to assess the effectiveness of medications such as phosphodiesterase-5 inhibitors, although early research has shown encouraging results.⁴³

Is her hair thinning?

Up to 26% of women develop thinning hair at the onset of menopause. This is thought to be the result of the relative increase in circulating androgens that occurs as estrogen production decreases.⁵⁰ Spironolactone has been shown to be a safe and effective intervention. Acting as an antiandrogen, spironolactone is thought to restore the balance between estrogen and androgen, thereby halting hair loss—and, in some women, resulting in partial hair regrowth. A variety of doses have been used, but 100 to 200 mg/d is recommended.⁵¹

■ **Topical minoxidil** may also be helpful in women with hair loss, but up to one year of treatment may be necessary before effectiveness can be accurately assessed. The US Food and Drug Administration has approved only the 2% minoxidil solution for use in women,

although a 5% solution is available and may be more effective.

Adverse effects of minoxidil include facial hypertrichosis over the cheeks and forehead. This is more likely to occur if the 5% solution is used, but may be reversible within 4 months of discontinuing therapy.⁵² Emerging evidence suggests that a combination of topical minoxidil and topical spironolactone may be helpful for women, without the adverse effects associated with systemic therapy.

■ **Cyproterone acetate**, which has also been shown to be effective, is usually administered as an oral contraceptive regimen: The patient takes 100 mg/d on Days 5 to 15 and 50 mcg ethinyl estradiol on Days 5 through 25. Up to 88% of women either have no progression of hair loss or actually experience hair regrowth with the use of cyproterone.⁵³ However, the risks associated with exposure to ethinyl estradiol may limit use of this therapy.

CASE ▶ After an extensive discussion about treatment options, Barbara decided to start taking venlafaxine for her hot flashes and mood swings. She also began using an estrogen-containing vaginal ring (the device contains 2 mg estradiol and must be replaced every 90 days) to alleviate atrophic vaginitis symptoms. When she returned to the office 6 months later, the patient reported that the frequency of her hot flashes was down to only one or 2 per week, and they rarely disrupted her sleep. She also noted that her mood had improved, she was arguing with her husband far less often, and her pain during intercourse had resolved. **JFP**

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➤ Long-term clinical trials are needed to assess the effectiveness of medications such as phosphodiesterase-5 inhibitors for female loss of libido, although early research has shown encouraging results.