OBG MANAGEMENT

Nonestrogen therapies for menopausal symptoms

How gabapentin, MPA, black cohosh, and other options stack up, plus 3 challenging cases from a women's midlife center

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With more women steering clear of estrogen in the wake of the Women's Health Initiative and other trials,[1,2] the menopause armamentarium seems increasingly bare.

Into the vacuum have come a host of therapies, most of them unproven. This article focuses on what we know so far about menopausal symptoms and the few alternative therapies shown to be effective:

- **Evidence is weak.** Recommendations for nonestrogen treatments are generally based on weak supporting evidence. For example, many published studies had small populations (<200) and short durations (<1 year). We also lack long-term safety data on the few nonprescription therapies shown to be effective.
- **Not all symptoms are menopause-related.** Symptoms with a moderate-to-strong link to menopause: hot flashes, night sweats, sleep disturbances, and vaginal dryness (TABLE 1). Evidence linking mood and cognitive problems, somatic symptoms, urinary incontinence, bleeding, and sexual dysfunction specifically to menopause is weak or nonexistent.
- **Large placebo effect.** In studies of alternative therapies for vasomotor symptoms, the placebo response is robust.
- **Some therapies offer short-term relief,** including gabapentin (Neurontin), medroxyprogesterone acetate (MPA) (Provera), black cohosh, physical exercise, and soy protein.

Gabapentin is a first-line agent because it has known benefits and few, minor adverse effects. MPA is a good alternative, but its side effect profile should be taken into account.

Black cohosh and soy products have estrogenic effects and should be avoided in women with contraindications to estrogen.

Selective serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs) have yielded inconsistent results when prescribed for vasomotor symptoms in postmenopausal women. They are most effective in women being treated for cancer and those taking tamoxifen.

- **No therapy specifically targets sleep disturbances.** This complaint should be treated similarly to general insomnia.
- **Vaginal symptoms can be treated over the counter.** A vaginal moisturizer (Replens) is a safe and effective therapy for vaginal dryness.

A few prescription agents ease vasomotor symptoms

Gabapentin

A double-blind, 12-week study[3] of 900 mg daily showed a reduction in hot-flash frequency of 45%, versus 29% in the placebo group ($P<.05$), and a decrease in the hot-flash composite score (the product of hot-

IN THIS ARTICLE

Is hormone-free treatment

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CASE 1 Perimenopausal, daily hot flashes

THERAPY

Exercise, soy products, vitamin E, and black cohosh

THE PATIENT: "V.S.," 51, has been a patient for some time. At her latest visit, she reports that her menstrual periods are irregular, occurring every 3 to 12 weeks. She also has as many as 5 hot flashes a day, wakes in the very early morning, and occasionally experiences mild night sweats. Because she underwent bilateral tubal ligation many years ago, there is no need for contraception. She has no family history of breast cancer, but prefers to avoid drugs and asks if there are any herbal remedies and/or lifestyle changes that will ease her transition through menopause. She has a body mass index (BMI) of 31.6, and her breast and pelvic examinations are negative.

INTERVENTION: We discuss several simple options. For example, regular exercise may reduce vasomotor symptoms, although intense exertion with sweating can provoke hot flashes. Soy products and soy extracts have had mixed results, but appear to have some benefit. I suggest adding 1 soy dietary product per day. Vitamin E also may reduce hot flashes very modestly. The most promising product is black cohosh; I advise V.S. to take 20 mg twice a day.

OUTCOME: V.S. begins exercising regularly and sets a weight loss goal of 10%. She also begins taking 400 IU of vitamin E daily, adds soy nuts to her diet, and starts taking black cohosh. Three months later, she reports that her hot flashes have decreased to about 3 per day and are tolerable. She has had 1 menstrual cycle in the interim. If her symptoms worsen, she will consider medical therapy.

CASE 2 Severe symptoms, mood effects

THERAPY

Venlafaxine and vaginal moisturizers

THE PATIENT: "A.B.," 54, a cancer survivor, is menopausal and has 10 to 20 hot flashes a day and soaking night sweats. She also reports low mood, frequent crying, and irritability. Before her cancer diagnosis, A.B. took hormone therapy for 6 months for severe menopausal symptoms. She recently underwent lumpectomy, axillary node dissection, radiation, and chemotherapy for a 3-cm, grade 3, invasive lobular carcinoma that was estrogen- and progesterone-receptor positive, and she is about to begin an aromatase inhibitor for chemoprevention. She and her husband have attempted intercourse since her chemotherapy ended, but the experience was painful. She would prefer to restart hormone therapy, but is willing to try nonhormonal options first. Her examination is unremarkable except for significant atrophy, with a vaginal pH of 7.0.

INTERVENTION: After a discussion of the data on SSRIs, SNRIs, and gabapentin, A.B. decides to try venlafaxine, 37.5 mg daily. If she has no improvement after 2 weeks, she will increase the dosage to

IMAGE: KIMBERLY MARTENS

flash frequency and severity) of 54%, versus 31% for placebo ($P<.05$) (TABLE 2).

An open-label, 5-week extension study[4] found larger gabapentin doses (2,700 mg/day) to be more effective, with reductions of 54% in hot-flash frequency and 67% in the hot-flash score, compared with baseline values.

Dizziness and somnolence early in therapy were the commonest adverse effects.[4]

Overall, gabapentin is modestly effective, and most patients will tolerate it if the dose is titrated slowly.

Medroxyprogesterone acetate

A number of progestin products have been

effective? 3 women's stories

75 mg daily. For the vulvovaginal atrophy, she will try both vaginal moisturizers and vaginal lubricants, recognizing that this will not rethicken the epithelium. She also will exercise 5 days per week.

OUTCOME: After 3 months and an increase to 75 mg daily venlafaxine, the patient reports a 50% decrease in hot flashes and a more stable mood. The dyspareunia remains a problem. She decides to try a small amount of estradiol cream—somewhere between the size of a pea and the size of a dime—applied externally around the introital opening. She will start by applying it daily for 2 weeks, then reduce to twice a week.

CASE 3 Severe symptoms after TAH/BSO

THERAPY

Unsatisfactory improvement, a return to estrogen

THE PATIENT: "A.G.," 46, complains of severe vasomotor symptoms. Two months ago she underwent total abdominal hysterectomy with bilateral salpingo-oophorectomy for bilateral complex masses, which turned out to be endometriomas. At that time, endometriosis was observed along the left ureter, with residual peritoneal implants and a small nodule within the rectovaginal septum. A.G. was offered leuprolide acetate (Lupron Depot) postoperatively, but declined. She did well for about 2 months and then began having vasomotor symptoms. Her physician was hesitant to prescribe estrogen because of fear of reactivating endometriosis. A.G. toughed it out for 3 months, but now reports "misery." She is moody, cries easily, and has not had sex with her husband since her surgery. An examination reveals a small, 8-mm nodule within the rectovaginal septum, decreased vulvar color, vaginal pallor, and levator ani spasm with exam. Vaginal pH is 6.5.

INTERVENTION: Although I suggest systemic progesterone therapy—oral, vaginal, or intramuscular—and explain that it would decrease any residual endometriosis and relieve the hot flashes, the patient does not want to take any hormonal therapy and is concerned about worsening her mood. Despite reassurance that hormone therapy would have less than a 5% chance of reactivating the endometriosis, A.G. decides to try an antidepressant first. Since she had taken paroxetine (Paxil) for postpartum depression, with no major side effects, she decides to try it again, starting with 10 mg daily.

OUTCOME: A.G. continues to have at least 5 bothersome hot flashes per day, which interrupt her work with profuse sweating. She also wakes at night for the same reason. However, she is less irritable. It has been 7 months since her surgery, and both she and her husband want her to try hormone therapy. She elects to begin a low-dose combined estrogen–progesterone product, as well as estradiol vaginal cream twice daily.

Three months later, she reports no pain, a gradual reduction in hot flashes, and significant improvement overall. Her vaginal color has returned, her pH is 5.5, and intercourse is no longer painful. She decides to continue taking oral hormone therapy at a low dose despite occasional vasomotor symptoms, and to keep using vaginal estrogen, but will stop the paroxetine.

investigated as therapies for menopausal vasomotor symptoms, among them megestrol acetate, medroxyprogesterone acetate (MPA), and transdermal progesterone. The most significant findings come from MPA trials.[3] Oral MPA reduced hot-flash frequency as much as 85.7%. Adverse effects were reported in 23% of patients, including weight gain, constipation, lowered libido, and vaginal spotting.[5]

Intramuscular depot medroxyprogesterone acetate (DMPA) has demonstrated similar efficacy, eliminating or significantly reducing hot-flash frequency in 89.5% of women, compared with 25% of women in the placebo group ($P<.0001$).[6] Adverse

EVIDENCE RECAP

How does one hot flash

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Nelson HD, Vesco KK, Haney E, et al. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. JAMA. 2006;295:2057–2071.

Nedrow A, Miller J, Walker M, Nygren P, Huffman LH, Nelson HD. Complementary and alternative therapies for the management of menopause-related symptoms. Arch Intern Med. 2006;166:1453–1465.

The hot flash, long synonymous with menopause, is the bane of many women facing the midlife transition. Despite the intensity of the sensation, hot flashes appear to be triggered by small elevations in core body temperature within a greatly reduced thermoneutral zone.[1–4] If the core temperature crosses the upper threshold, a hot flash with sweating and peripheral vasodilation occurs. If the lower threshold is crossed, shivering results. Core temperature elevations occur in both symptomatic and asymptomatic women.

The difference:
In symptomatic women, the thermoneutral zone is narrowed.

2 randomized trials attest to mostly modest efficacy

In their rigorous study of nonhormonal therapies for hot flashes, Nelson et al reviewed MEDLINE, PsycINFO, and the Cochrane Clinical Trials Register Database for randomized, double-blind, placebo-controlled trials of oral nonhormonal treatments for hot flashes, ultimately selecting 43 trials. These included 10 trials of antidepressants, 10 trials of clonidine, 17 trials of isoflavones, and 6 trials of other prescription drugs. They found at least some evidence of efficacy for SSRIs, SNRIs, clonidine, and gabapentin, but all were considerably less effective than estrogen.

Nedrow and colleagues searched the same databases plus MANTIS and AMED, selecting 70 trials for inclusion. Overall, the data were insufficient to support the effectiveness of any complementary or alternative therapy. For example, a good-quality study enrolling breast cancer survivors compared 56 patients ingesting 90 mg daily of isoflavone soy drink with 55 patients who took placebo, with no differences reported between the groups

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Hot flashes may be triggered by small elevations in core body temperature in a greatly reduced thermoneutral zone

events include uterine bleeding, depression, headache, and vaginal dryness.[6]

There were no reports of DVT or pulmonary embolism in either of these studies. However, current or past thromboembolic disorders are a contraindication to MPA and DMPA.

Antidepressants

Controlled release paroxetine (Paxil) was studied in menopausal women experiencing 2 to 3 hot flashes per day.[8] Hot-flash composite scores were significantly reduced in women taking paroxetine (62.2% with 12.5 mg/day, 64.6% with 25 mg/day), compared with placebo (37.8%) ($P<.05$). Therapy was fairly well-tolerated, with headache, nausea, and insomnia the most commonly reported adverse effects.

Citalopram (Celexa) and fluoxetine (Prozac) were investigated in a 9-month double-blind study.[9] Hot-flash reduction of more than 80% was observed in 29%, 39%, and 36% of the placebo, fluoxetine, and citalopram groups, respectively. In addition, the Kupperman index, which measures multiple symptoms, including sweating, improved in all groups. However, neither the improvements in hot-flash frequency nor those in the Kupperman index were statistically significant. Nausea and dry mouth were the most common adverse effects.

differ from another?

in hot flash frequency or intensity, yet both groups improved over baseline.

The placebo effect and other challenges

Randomized, controlled trials of alternative medicines and nonhormonal prescription therapies have found a placebo effect that ranges from about 1% to as high as 77%.[5,6] In estrogen trials, the mean placebo response is 50.8%.[7] The study of nonhormonal therapies involves several challenges, such as difficulty locating a proper control or placebo, and double-blinding is often impossible.

A big problem faced in both studies was the lack of consistency in inclusion criteria. Study samples differed in age range, menopausal status, type of menopause, inclusion of breast cancer survivors, or use of antiestrogen therapy such as tamoxifen, raloxifene, or aromatase inhibitors—drugs that are associated with hot flashes.

Studies also varied in the degree of hot-flash severity required for enrollment. Some studies of alternative therapies enrolled women with 1 or 2 hot flashes per day, or 14 per week, whereas the US FDA requires women in hormone-therapy trials to have at least 7 moderate to severe hot flashes daily, or 50 to 60 per week, with specific definitions of severity.

Moreover, botanical products may have milder effects overall or take longer to elicit a response. Most studies are of short duration with small numbers of women, increasing the potential for confounding by the placebo effect.

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In RCTs of alternative therapies and nonhormonal prescription drugs, the placebo effect ranges from 1–77%

Venlafaxine (Effexor), an SNRI, was evaluated in a placebo-controlled trial involving postmenopausal women with hot flashes.[10] There was a trend toward improvement but no significant difference in hot-flash severity recorded by patient-kept diaries. However, there was a significant difference in the subjective assessment of the impact of hot flashes on daily living, with an improvement of 51% in venlafaxine-treated patients and 15% in placebo-treated patients ($P<.001$). Dry mouth, sleeplessness, and decreased appetite were more common in the women receiving venlafaxine.

Antidepressants overall. A metaanalysis[7] of 6 trials of SSRIs and SNRIs showed a mean reduction in hot-flash frequency of -1.13 (CI -1.70 to -0.57). These findings were not reproducible when trials of cancer patients and tamoxifen-treated women were excluded; the result was a mean difference in hot-flash frequency of -0.17 (CI -1.41 to 1.07).

Clonidine (Catapres)

A metaanalysis[7] concluded that clonidine has a positive impact on hot flashes. The mean difference in the number of daily hot flashes was -0.95 (confidence interval [CI] -1.44 to -0.47) for 4-week studies and -1.63 (-2.73 to -0.50) for 8-week studies. However, 2 of the trials showing

TABLE 1

Symptoms can show up well before the menopausal transition is complete

TYPE OF SYMPTOM	PREMENOPAUSE	PERIMENOPAUSE	POSTMENOPAUSE	COMMENTS
Vasomotor symptoms (includes hot flashes and night sweats)	14–51%	35–50%	30–80%	Higher incidence with high body mass and younger age at onset of menopause
Sleep disturbances	16–42	39–47	35–60	Role of vasomotor symptoms is unclear
Vaginal dryness and painful intercourse	4–22	7–39	17–30	May persist indefinitely in some women

a positive effect included breast cancer patients taking tamoxifen. When these trials were excluded, the mean difference in hot-flash frequency was an insignificant -0.53 (CI -2.09 to 1.04).

Among the adverse events associated with clonidine therapy were dry mouth, insomnia, and drowsiness, but there were no significant changes in blood pressure.[7] Nevertheless, blood pressure should be monitored when the drug is given to normotensive women.

Overall, clonidine appears most effective in women with cancer.

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Whenever possible, use the specific brand of botanical agent studied in clinical trials

Few over-the-counter agents make the grade

Many products claim to alleviate vasomotor symptoms, but few have the clinical evidence to support their claims. Not only are efficacy data lacking for botanicals, but safety data are scarce, too. Because the Food and Drug Administration (FDA) has looser controls on botanicals than on pharmaceutical products, product ingredients are often not standardized and lack strict federal oversight.[3] Therefore, these agents require an extra degree of caution. When possible, the specific brands studied in clinical trials should be used in practice.

Black cohosh

This herbal product is a selective estrogen receptor modulator (SERM). The German Commission E (equivalent to our FDA) has substantial data on its use to treat vasomotor symptoms—data that support its efficacy and safety, with few adverse effects and no known drug interactions.[11]

A recent study[12] compared 40 mg of black cohosh (Remifemin) daily with 25 µg transdermal estradiol (Estraderm) weekly for 3 months. Estrogen users were also given dihydrogesterone (Dufaston), 10 mg daily, for the last 12 days of the 3-month treatment. Both treatment groups exhibited significant reductions of more than 50% in the daily number and severity of hot flashes, compared with baseline (P<.001). Adverse effects—mostly nausea—were mild.

Another trial[13] evaluated standard-dose (39 mg) versus high-dose (127.3 mg) black cohosh. Remifemin was the active ingredient in the preparation given. The median Kupperman index decreased significantly in both groups, compared with baseline values, with a response rate of 70% in the standard-dose group and 72% in the high-dose group (CI 59–80% and 61–82%, respectively). There was no added benefit of high doses, compared with standard dosing (P=.73). Adverse effects were similar in both groups, and gastrointestinal and central nervous system complaints were the most common.

Long-term effects are unknown.

Physical exercise

Many prospective observational studies have found a decrease in the frequency and severity of vasomotor symptoms with regular physical activity. Some of these trials included large patient populations and evaluated women over 1 to 3 years.[3]

However, a recent randomized trial[14] involving a yearlong, moderate-intensity exercise regimen in 173 overweight, post-

menopausal women found an insignificant increase in the rate of menopausal symptoms in the exercise group. It is unclear why exercise produced such an outcome.

Most data suggest that physical activity has a positive impact on menopausal symptoms, although there is no clear indication of the intensity or amount of exercise needed.

Phytoestrogens

These plant-derived substances, which contain isoflavones, are considered SERMs. Isoflavones produce the greatest estrogenic effects, and at least 4 are known to be active: genistein, daidzein, biochanin A, and formononetin (in order of lessening activity).[3] The 2 most common sources of phytoestrogens: soy protein and red clover.

Soy protein is the most extensively studied of the phytoestrogens, largely because soy has a fairly high content of isoflavones. The various soy products marketed today contain different amounts of isoflavones. For example, 1 cup of soy milk contains 3 to 10 g of soy protein. The recommended daily dose for vasomotor symptoms is 40 to 60 g of soy protein or 50 to 80 mg of isoflavones.

The variation in soy products and composition makes it hard to compare data and extrapolate results in specific patient populations.[3] A recent metaanalysis[7] looked at 6 clinical trials involving soy. Results varied slightly with the duration of therapy. After 4 to 6 weeks of use, the mean difference in daily hot flashes was -1.48 (CI -2.49 to -0.48) in women taking soy, compared with placebo. After 12 to 16 weeks and 6 months, the respective mean differences in hot flashes daily were -0.97 (CI -1.82 to -0.12) and -1.22 (CI -2.02 to -0.42) in women taking soy, versus placebo.

Most of the adverse effects documented with soy protein are mild and tend to be gastrointestinal, but hypothyroidism and peanut anaphylaxis-type reactions have been reported.[3]

The fact that soy becomes metabolized to equol, which has potential estrogenic effects, justifies a cautious approach. Evidence suggests that soy protein is a viable alternative to estrogen for short-term management of vasomotor symptoms.

Red clover contains all 4 estrogenic isoflavones, and at least 2 brand names—Promensil and Rimostil—have been evaluated. A metaanalysis[7] reviewed 6 trials evaluating both brands and found a mean difference in daily hot flashes of -0.44 (CI -1.47 to 0.58), compared with placebo.

Adverse effects appear to be mild and include headache, nausea, and diarrhea.[3]

Initial data on red clover were promising, but the more rigorous metaanalysis does not support its use.

Sleep disturbances remain an enigma

Sleep disturbances increase as women age, with up to 60% of postmenopausal women experiencing them.[15] It is unclear whether they are a direct complication of vasomotor symptoms or have another cause, and little information exists regarding their treatment. Aside from the agents typically used to treat insomnia, such as benzodiazepines and nonbenzodiazepine hypnotics (zolpidem and related medications), other drugs have been considered, such as SSRIs and gabapentin. Some herbal therapies such as valerian root, chamomile, and soy protein claim to help with insomnia as well as menopausal symptoms, but no clinical studies have adequately assessed their use.[16]

Sleep disturbances as a secondary endpoint

Numerous studies of vasomotor symptoms have evaluated sleep disturbances as a secondary endpoint. For example, in a study evaluating citalopram and fluoxetine for menopausal symptoms,[9] the citalopram group had significant improvement in insomnia scores over the placebo group (P=.02), but the fluoxetine group did not.

A study of gabapentin[4] evaluated sleep quality as a secondary endpoint and found insignificant improvement (P=.09).

These studies suggest that citalopram and gabapentin may be beneficial in the treatment of sleep disturbances in women

IMAGE: KIMBERLY MARTENS

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Avoid black cohosh and soy products in women with contraindications to estrogen

TABLE 2

Common therapies provide a range of relief

THERAPY	POSTULATED MECHANISM	COMMON DOSE	DURATION	EFFICACY
	PRESCRIPTION THERAPIES			
Clonidine (Catapres)	Reduces peripheral and central vascular reactivity resulting in reduced small vessel response to various stimuli	0.025–0.075 mg BID PO	4-8 weeks	Moderate
Gabapentin (Neurontin)	Modulation of calcium currents modifies serotonergic and adrenergic pathways affecting thermoregulatory process	300 daily–300 mg TID PO 900 mg TID PO (studied in 1 trial)	12 weeks 5 weeks	Moderate
Medroxyprogesterone acetate	Unknown	20 mg/day PO 150 mg every 1–3 months IM DMPA	12-24 weeks	High
Selective serotonin reuptake inhibitors	Increases available serotonin in the central nervous system by blocking reuptake and decreasing luteinizing hormone	Paroxetine (Paxil) CR: 12.5–25 mg/day PO Fluoxetine (Prozac): 20–30 mg/day PO Citalopram (Celexa): 20–30 mg/day PO	6 weeks 9 months 9 months	Moderate
Venlafaxine (Effexor)	Increases available serotonin and norepinephrine in the central nervous system by blocking reuptake	XR 75 mg/day PO	12 weeks	Moderate
	NONPRESCRIPTION THERAPIES			
Black cohosh (Cimicifuga racemosa)	SERM; exact mechanism is unclear	39.0–127.3 mg daily PO	24 weeks	Moderate
Exercise	Increases ß-endorphin production (thermoregulation)	>1 time per week	1 year	High
Red clover (Trifolium pretense)	SERM, phytoestrogen metabolized by gastrointestinal flora to equol structurally similar to 17ß-estradiol	40–160 mg daily PO	12 weeks	Low
Soy protein	SERM, phytoestrogen metabolized by gastrointestinal flora to equol structurally similar to 17ß-estradiol	34–92 mg isoflavone daily PO	12 weeks–2 years	Moderate

BID = twice daily; CR = controlled release; DMPA = depot medroxyprogesterone acetate; IM = intramuscular; PO = by mouth; SERM = selective estrogen receptor modulator; TID = thrice daily; XR = extended release
SOURCE: Fugate and Church[3]

who also have vasomotor symptoms. Even so, these data are preliminary; further study is needed.

Vaginal estrogen may carry same risks as oral therapy

Vaginal estrogens have been the traditional treatment for atrophy and vaginal dryness and have proved to be as effective as oral estrogen for these symptoms (see page 24). Nonetheless, many physicians and patients seek nonestrogen alternatives for this menopause-related symptom.

Over-the-counter lubricants are a mixed lot

Although many lubricants are marketed today, clinical study has been limited because they are regulated by the FDA as cosmetics. Of these products, Replens, a bioadhesive vaginal lubricant, has been studied the most intensively.

CONTINUED

A unique formulation. Replens, a polycarbophil-based polymer, attaches to the vaginal wall and can hold 60 times its weight in water. It remains against the vaginal epithelial surface for more than 24 hours before it is sloughed off. This mechanism provides longer relief and requires less frequent application than other lubricants.[17]

Replens vs estrogen. Thrice-weekly Replens was compared with 12 weeks of daily vaginal estrogen cream[18] and with vaginal estrogen cream applied daily for 2 weeks and then 3 times weekly for a total of 3 months.[19] The comparison of Replens with conjugated estrogen cream (Premarin) showed significant improvements in vaginal moisture, fluid volume, elasticity, and pH levels in both treatment groups.[18] Vaginal atrophy (assessed via Papanicolaou smear) reversed in 100% of estrogen-treated patients and 60% of Replens-treated patients.

When Replens was compared with dienoestrol vaginal cream, both therapies produced significant improvement in the vaginal dryness index (a score based on vaginal moisture, fluid volume, elasticity, and mucosa) within the first week.[19] However, dienoestrol-treated patients had greater improvement in mean vaginal dryness (21.78 vs 17.32) at 12 weeks of therapy (P=.0001), compared with baseline values of 13 (dienoestrol) and 13.45 (Replens). Vaginal symptoms and dyspareunia improved at similar rates in the 2 groups. Patient satisfaction also was high in both groups, with 60% of Replens-treated patients and 84% of dienoestrol-treated patients reporting good to excellent effects. **No serious side effects** were reported.[18,19]

Start with Replens for vaginal dryness, as it is a safe and effective alternative. If it is ineffective, vaginal estrogen may be more effective than vaginal lubricants. ■

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Initial data on red clover were promising, but the more rigorous metaanalysis does not support its use

IMAGE: KIMBERLY MARTENS

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