

**MALA S. SIVANANDY, MD**

Women's health fellow, Cleveland Clinic Women's Health Center, Department of General Internal Medicine, Cleveland Clinic

NZIAVAKE MASIMASI, MD

Women's health fellow, Cleveland Clinic Women's Health Center, Department of General Internal Medicine, Cleveland Clinic

HOLLY L. THACKER, MD*

Director, Cleveland Clinic Women's Health Center, associate professor of surgery, Cleveland Clinic Lerner College of Medicine at Case Western Reserve University

Newer hormonal therapies: Lower doses; oral, transdermal, and vaginal formulations

■ ABSTRACT

Hormonal therapy remains the gold standard for treating menopausal symptoms. In addition, some formulations are indicated for preventing and treating bone loss. In this article, we review some of the hormonal regimens that have been approved in the past 5 years.

■ KEY POINTS

The severity of postmenopausal symptoms varies widely from woman to woman. Therefore, the decision to use hormonal therapy must be highly individualized and take into account the benefits and risks.

In general, the newer hormonal products contain lower doses of estrogen and progestin than in the past and therefore cause fewer side effects.

Women who have had a hysterectomy can receive estrogen by itself; others should receive both estrogen and progestin.

Hormonal therapies are available as oral, transdermal, and vaginal products.

SEVERAL NEW PRODUCTS for hormonal therapy (also called hormone replacement therapy) became available in the last few years. Some carry an indication from the US Food and Drug Administration (FDA) only for treating vasomotor symptoms of menopause, some for preventing osteoporosis, and some for both (TABLE 1). Most of the newer products contain lower doses than the older products, and some use nonoral delivery systems, such as transdermal patches, lotions, and vaginal rings.

■ A HIGHLY INDIVIDUAL DECISION

Women have been using hormonal therapy to control postmenopausal symptoms for more than 6 decades. Since the severity of postmenopausal symptoms varies widely from woman to woman, the decision whether to use hormone therapy must be highly individualized.

For a healthy, young, recently menopausal woman who has vasomotor symptoms, the benefits of hormonal therapy usually outweigh the risks. The risks primarily involve the risk of venous thromboembolism. The risk of breast cancer is in the "rare" category of risks, and accrues after long-term use, ie, more than 5 years of estrogen-progestin therapy. The benefits of hormonal therapy include control of disruptive vasomotor symptoms, treatment of vulvovaginal atrophy, and preservation of bone mineral density.¹

There is no time limit on how long a patient can stay on hormonal therapy.¹

*Dr. Thacker has indicated that she serves as a consultant and on the speaker's bureau for Wyeth Pharmaceuticals.

TABLE 1

Approved indications for the newer hormonal therapy products

APPROVED INDICATION	ROUTE	WOMEN WITHOUT A UTERUS	WOMEN WITH A UTERUS
Vasomotor symptoms only	Oral	Femtrace Enjuvia	Low-dose femhrt Angeliq
	Transdermal	Estrasorb Estrogel	Combipatch
	Vaginal	Femring	
Osteoporosis prevention only	Transdermal	Menostar	Menostar with cycled progestin 1–2 times/year
		Vivelle-Dot (0.025 mg/day)	Vivelle-Dot (0.025 mg/day) with monthly progestin
Vasomotor symptoms and osteoporosis prevention	Oral	Premarin	Low-dose Prempro
	Transdermal	Climara Vivelle-Dot (0.375, 0.05, 0.075, and 0.025 mg/day)	Climara Pro

Most women who stop taking hormonal therapy do so because of side effects or fear of side effects

However, as with any medication, the health care provider should periodically assess the severity of the patient's symptoms, analyze the risks and benefits, and decide whether to continue the therapy.

■ A TREND TOWARD LOWER DOSES

The trend in hormonal therapy has been to use lower doses, which relieve menopausal symptoms effectively while causing fewer side effects than standard-dose therapy.^{2,3} Since most women who stop taking hormonal therapy do so because of side effects (or fear of side effects) such as uterine bleeding, breast tenderness, nausea, abdominal bloating, fluid retention, and headache, lower doses may, in theory, lead to better acceptance and long-term compliance. The dose should be individualized, with the goal of giving the lowest acceptable dose that controls the symptoms.

Women who have been using hormonal therapy in standard doses and whose symptoms are well controlled can have their dosage reduced, while their symptoms and bone status are monitored. However, lower-dose hormon-

al therapy may not be appropriate for all women, as some women may need higher doses to control their symptoms. Furthermore, although the lower doses increase bone density in many women, we do not have data on fracture reduction outcomes with these formulations as we do with conjugated equine estrogens 0.625 mg (Premarin) and the combination of conjugated equine estrogens 0.625 mg plus medroxyprogesterone acetate 2.5 mg (Prempro).

■ HORMONAL THERAPY TO PREVENT OSTEOPOROSIS

Several hormonal regimens have been approved for preventing and managing postmenopausal bone loss. Most women go through menopause (defined as the absence of menstruation for 1 year) between the ages of 45 and 55 years; women experiencing premature menopause are candidates for hormonal therapy, as they are at high risk of osteoporosis. Hormonal therapy is also indicated for women who have menopausal symptoms and are at high risk of osteoporosis.

TABLE 2

Comparable doses of different estrogens for treatment of vasomotor and urogenital symptoms

CONJUGATED SYNTHETIC ESTROGENS (ENJUVIA)	ESTRADIOL (ESTRACE)	CONJUGATED EQUINE ESTROGENS (PREMARIN)	ESTRADIOL ACETATE (FEMTRACE)
—	—	—	0.45 mg (0.39 mg estradiol)
0.3 mg	0.5 mg	0.3 mg	—
1.25 mg	2.0 mg	1.25 mg	—
0.45 mg	—	0.45 mg	0.9 mg (0.78 mg estradiol)
0.625 mg	1.0 mg	0.625 mg	—
—	—	0.9 mg	1.8 mg (1.56 mg estradiol)

Many of the hormonal products that are approved for preventing osteoporosis are transdermal patches (see below). Some of the transdermal products approved for prevention of osteoporosis are, from the lowest dose to the highest:

- Menostar (estradiol 0.014 mg/day)
- Vivelle-Dot (estradiol 0.025 mg/day)
- Climara (estradiol 0.025 mg/day)
- Climara Pro (estradiol 0.045 mg/day plus levonorgestrel 0.015 mg/day).

■ CHANGING FROM HORMONAL CONTRACEPTION TO HORMONAL THERAPY

Many women switch from hormonal contraceptives to hormonal therapy once they no longer need birth control. As long as they do not smoke, their blood pressure is controlled, and they have no documented increased risk of thromboembolism, they can remain on hormonal contraceptives until age 55 to 57, since the reported record for spontaneous unassisted pregnancy is at age 57 years.⁴

Other women do not need contraception but take hormonal contraceptives for their noncontraceptive benefits. These women usually make the transition to hormonal therapy by age 52.

Hormonal contraceptives suppress endogenous ovarian function, whereas hormonal therapy does not. However, once contraception is no longer needed, if a woman

still desires hormonal therapy to control vasomotor symptoms, improve quality of life, and maintain the genitourinary system and bones, then changing from hormonal contraception to hormonal therapy in either the standard or newer lower-dose formulations would be recommended.

■ NEWER ESTROGEN-ONLY HORMONAL THERAPIES

In general, women who have had a hysterectomy are prescribed estrogen only, while postmenopausal women with an intact uterus need both estrogen and progesterone. (The use of androgens in postmenopausal women is beyond the scope of this article.)

Femtrace: A once-a-day estrogen-only pill

Femtrace (estradiol acetate) was approved in August 2004 by the FDA for treating vasomotor symptoms. It is available in doses of 0.45 mg, 0.9 mg, and 1.8 mg (TABLE 2). It has a better pharmacokinetic profile than generic estradiol: plasma concentrations remain higher, so it can be given once daily, whereas generic estradiol is given twice daily.

Utian et al⁵ found that estradiol acetate 0.9 mg was comparable to 17-beta-estradiol 1 mg in reducing the number and severity of vasomotor and urogenital symptoms in postmenopausal women.

Many women can change directly from hormonal contraceptives to hormonal therapy

TABLE 3

Comparison of doses of hormonal therapy patches

	ESTROGEN (MG/DAY)	PROGESTIN (MG/DAY)
Weekly patches		
Climara	Estradiol 0.025	None
	Estradiol 0.0375	
	Estradiol 0.05	
	Estradiol 0.06	
	Estradiol 0.075	
	Estradiol 0.1	
Climara Pro	Estradiol 0.045	Levonorgestrel 0.015
Menostar	Estradiol 0.014	None
Twice-weekly patches		
CombiPatch	Estradiol 0.05	Norethindrone acetate 0.14
	Estradiol 0.05	Norethindrone acetate 0.25
Vivelle-Dot	Estradiol 0.025	None
	Estradiol 0.0375	
	Estradiol 0.05	
	Estradiol 0.075	
	Estradiol 0.1	

Enjuvia: A plant-derived estrogen-only pill

Enjuvia is a plant-derived formulation that contains a blend of 10 synthetic estrogenic substances, including sodium delta-8,9-dehydroestrone sulfate, a potent estrogen. The other estrogenic substances are sodium estrone sulfate, sodium equilin sulfate, sodium 7-alpha-dihydroequilin sulfate, sodium 17-alpha-estradiol sulfate, sodium 17-beta-dihydroequilin sulfate, sodium 17-alpha-dihydroequilenin sulfate, sodium 17-beta-dihydroequilenin sulfate, sodium equilenin sulfate, and sodium 17-beta-estradiol sulfate.

Enjuvia was approved by the FDA in May 2004 for the treatment of moderate to severe vasomotor symptoms. Of note: Enjuvia is not approved for the management of osteoporosis, unlike Premarin, which carries both indications.

Enjuvia is available in four strengths: 0.3 mg, 0.45 mg, 0.625 mg, and 1.25 mg. It is taken once daily. Patients can be started on the lowest dose (0.3 mg), which can be adjust-

ed on the basis of the clinical response.

In a controlled study, vasomotor symptoms were significantly less frequent and less severe with Enjuvia 0.3, 0.625, and 1.25 mg compared with placebo.⁶

Transdermal estrogen-only products

Transdermal estrogen therapy has been available for more than a decade, with some newer formulations and lower doses (TABLE 3). All transdermal preparations bypass hepatic metabolism and so permit lower doses to be used. They also provide a steadier level of drug in the blood than oral products, and the once-a-week and twice-weekly patches may be easier to comply with than daily or twice-daily pills.

The most common side effect of transdermal hormonal therapy is irritation of the skin with the patches. This problem can be managed by alternating the patch site, switching to a different patch, using hydrocortisone cream, or discontinuing the patch and substituting either Estrasorb or Estrogel (see below).

Climara is available in a new dose

Climara, an estrogen-only weekly patch, has been available for some time in dosages of 0.025, 0.0375, 0.05, 0.075, and 0.1 mg/day. A new dosage, 0.06 mg/day, was approved in 2004. Like the other dosages, the new one is approved both for treating vasomotor symptoms and for preventing osteoporosis.

Menostar:

An ultra-low-dose weekly patch

Menostar is an ultra-low-dose weekly patch that delivers estradiol 0.014 mg/day. It was approved in June 2004 specifically for osteoporosis prevention only, so it would be a good option for women who are no longer having vasomotor symptoms (it was studied in women ages 60 to 80) who have T scores between -1.0 and -2.0 who need bone protection.⁷ It is currently not approved for the treatment of vasomotor or genitourinary symptoms.

Menostar delivers such a low dose of systemic estrogen that women with an intact uterus do not need regular progestin opposition when they take it. Johnson et al found that the ultra low dose of unopposed estradiol was associated with vaginal cell maturation but did not increase the rate of endometrial

hyperplasia.⁸ Nevertheless, for women with an intact uterus, 12 to 14 days of cyclic progestin once or twice a year is still suggested.

Vivelle-Dot: A smaller twice-weekly patch

Vivelle-Dot is available in five dosages (0.025, 0.0375, 0.05, 0.075, and 0.1 mg/day); the 0.025 mg/day dosage is indicated for preventing postmenopausal osteoporosis only, while the others are indicated both for symptoms and for osteoporosis prevention. The patch is placed below the waist on alternating sides of the lower abdomen and changed twice a week or every 3 1/2 days.

The patch for the most commonly prescribed dosage—0.05 mg/day—is about the size and thickness of a postage stamp. By area, it is about one third the size of Climara and about one fourth the size of Estraderm. The 0.025 mg/day patch is the size of a dime (2.5 cm²). Since Vivelle-Dot covers less skin than other patches, it may cause less skin irritation.

Estrasorb: A 17-beta-estradiol lotion

Estrasorb lotion is a soy-based emulsion that contains 17-beta-estradiol. Estrasorb was approved in October 2003 for the treatment of vasomotor symptoms.

A daily dose of Estrasorb comes in two laminated foil pouches, each containing 4.35 mg of estradiol hemihydrate. The standard dosage is two packets applied to the skin of the thigh daily, and is approximately equivalent to Climara 0.05 mg/day.

Once-daily application of this emulsion at this dose (8.6 mg of estradiol) was proven to be safe and effective for the treatment of vasomotor symptoms.⁹

Estrogel: A 17-beta-estradiol gel

Estrogel also contains 17-beta-estradiol. It comes in a nonaerosol, metered-dose pump that delivers 1.25 g of gel (0.75 mg of estradiol) per compression. It is applied once a day.

Estrogel significantly reduces vasomotor symptoms with minimal side effects.¹⁰ It was approved by the FDA in February 2004.

Femring: An estrogen vaginal ring

Femring, a vaginal ring that patients can insert themselves, delivers a steady dose of estradiol acetate for 3 months. It was

approved by the FDA in March 2003 for the treatment of vasomotor and genitourinary symptoms, and it is the only vaginal ring that produces systemic effects.

Femring delivers a higher daily dose of estradiol (50–100 µg) than the Estring (6–9 µg), which is indicated only for genitourinary symptoms.

Femring is an option for women who have had a hysterectomy who present with hot flashes and vaginal symptoms and prefer a route other than oral or transdermal.

NEWER ESTROGEN-PROGESTIN PRODUCTS

If a woman still has her uterus and needs estrogen therapy to control postmenopausal symptoms, she also needs a progestin, because unopposed estrogen poses an increased risk of endometrial cancer. The lowest dose of combination therapy should be used.

Prempro now has two new lower doses

Prempro (conjugated equine estrogens plus medroxyprogesterone acetate) now comes in two new lower doses, which were the first combination low-dose pills to be approved (in March 2003) for treating specific menopausal symptoms such as hot flashes and vulvovaginal atrophy and for preventing osteoporosis. One of the low-dose pills contains conjugated equine estrogens 0.45 mg and the other contains 0.3 mg; both contain medroxyprogesterone acetate 1.5 mg. The higher-dose Prempro pills contain 0.625 mg of conjugated equine estrogens and either 2.5 or 5 mg of medroxyprogesterone acetate.

Lower-dose femhrt now available

A lower-dose form of femhrt is now available and contains ethinyl estradiol 2.5 µg and norethindrone acetate 0.5 mg. Approved in January 2005, this form contains half of the estrogen and progestin doses contained in regular femhrt (ethinyl estradiol 5 µg and norethindrone acetate 1.0 mg).

These are the same ingredients as in the hormonal contraceptive Loestrin,¹¹ but the contraceptive has higher doses: ethinyl estradiol 20 µg and norethindrone acetate 1.0 mg (TABLE 4).

In general, women with an intact uterus should receive an estrogen-progestin product

TABLE 4

Doses in selected hormonal contraceptives and hormonal therapies

PRODUCT	ESTROGEN	PROGESTIN
Hormonal contraceptives		
Loestrin (21/7, 24/4)	Ethinyl estradiol 20 µg	Norethindrone acetate 1.0 mg
Yasmin	Ethinyl estradiol 30 µg	Drospirenone 3 mg
Yaz	Ethinyl estradiol 20 µg	Drospirenone 3 mg
Hormonal therapies		
femhrt	Ethinyl estradiol 5 µg	Norethindrone acetate 1.0 mg
femhrt (low dose)	Ethinyl estradiol 2.5 µg	Norethindrone acetate 0.5 mg
Angeliq (US)	Estradiol 1.0 mg	Drospirenone 0.5 mg
Angeliq (Europe)	Estradiol 1.0 mg	Drospirenone 2.0 mg

Angeliq: An estradiol-drospirenone pill

Angeliq, the newest of the hormonal therapy options, was approved in September 2005 and will be available in 2007 in the United States. It contains estradiol 1.0 mg and drospirenone 0.5 mg.

Drospirenone is the same progestin as in the hormonal contraceptives Yasmin and Yaz, although the dose is higher in the contraceptives: 3.0 mg (TABLE 4). Drospirenone has antimineralocorticoid and antiandrogenic effects, but poses a risk of elevated potassium. Women with renal failure or those taking medications that may raise the serum potassium level should not take drospirenone.

Angeliq has been widely used in Europe for managing menopausal symptoms since 2002. However, the European formulation contains 2 mg of drospirenone—four times as much as the US formulation. The 2-mg European dose may have antihypertensive effects that counteract the sodium-retaining effects of oral estradiol.

Climara Pro: An estradiol-levonorgestrel weekly patch

Climara Pro, a patch that is changed once a week, delivers estradiol 0.045 mg/day and levonorgestrel 0.015 mg/day. It was approved in November 2003. This combination patch could be prescribed for women with a uterus who need hormonal therapy and who want a transdermal route. It is the only once-a-week combination estrogen-progesterone patch approved for preventing postmenopausal

osteoporosis and treating vasomotor symptoms.

CombiPatch: A twice-a-week patch

CombiPatch contains a slightly higher dose than Climara Pro (estradiol 0.05 mg/day and norethindrone acetate in strengths of either 0.14 or 0.25 mg/day). It is applied twice a week, and is indicated only for treating vasomotor symptoms (TABLE 3).

TIPS FOR SELECTING A HORMONAL PRODUCT

- If a woman has high triglyceride levels or diabetes or experiences nausea with oral agents, or if you do not want to lower her androgen levels, one of the transdermal products can be used. The risk of venous thromboembolism appears to be much lower with transdermal than with oral agents.¹²
- If the patient is concerned about symptoms of androgen excess such as acne, hair loss, or deepening of voice, you can choose one of the oral products, which raise sex hormone-binding globulin levels and subsequently lower androgen levels.
- If the patient is on a hormonal contraceptive such as Yaz, has tolerated it well, doesn't need contraception anymore, but still needs hormone therapy, Angeliq can be used.
- If the patient doesn't have a uterus, has hot flashes and vaginal dryness, and prefers a route other than oral or transdermal, the Femring intravaginal ring can be used (TABLE 1). ■

Drospirenone has antimineralocorticoid and antiandrogenic effects

■ REFERENCES

1. **The North American Menopause Society (NAMS).** Estrogen and progestogen use in peri- and post-menopausal women: March 2007 position statement of the North American Menopause Society. *Menopause* 2007; 14:1–17.
2. **Mattsson LA, Skouby SO, Heikkinen J, et al.** A low-dose start in hormone replacement therapy provides a beneficial bleeding profile and few side-effects: randomized comparison with a conventional-dose regimen. *Climacteric* 2004; 7:59–69.
3. **Ettinger B.** Vasomotor symptom relief versus unwanted effects: role of estrogen dosage. *Am J Med* 2005; 119:118(suppl 12B):74–78.
4. **Tarlatzis BC, Zepiridis L.** Perimenopausal conception. *Ann NY Acad Sci* 2003; 997:93–104.
5. **Utian WH, Speroff L, Ellman H, Dart C.** Comparative controlled trial of a novel oral estrogen therapy, estradiol acetate, for relief of menopause symptoms. *Menopause* 2005; 12:708–715.
6. **Utian WH, Lederman SA, Williams BM, et al.** Relief of hot flashes with new plant-derived 10-component synthetic conjugated estrogens. *Obstet Gynecol* 2004; 103:245–253.
7. **Ettinger B, Ensrud KE, Wallace R, et al.** Effects of ultralow-dose transdermal estradiol on bone mineral density: a randomized clinical trial. *Obstet Gynecol* 2004; 104:443–451.
8. **Johnson SR, Ettinger B, Macer JL, et al.** Uterine and vaginal effects of unopposed ultra low-dose transdermal estradiol. *Obstet Gynecol* 2005; 105:779–787.
9. **Simon JA.** Estradiol in micellar nanoparticles: the efficacy and safety of a novel transdermal drug-delivery technology in the management of moderate to severe vasomotor symptoms. *Menopause* 2006; 13:222–231.
10. **Naunton M, Al Hadithy AF, Brouwers JR, et al.** Estradiol gel: review of the pharmacology, pharmacokinetics, efficacy, and safety in menopausal women. *Menopause* 2006; 13:517–527.
11. **Masimasi N, Sivanandy MS, Thacker HL.** Update on hormonal contraception. *Cleve Clin J Med* 2007; 74:186–198.
12. **Canonico M, Oger E, Plu-Bureau G, et al;** Estrogen and Thromboembolism Risk (ESTHER) Study Group. Hormone therapy and venous thromboembolism among post-menopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. *Circulation* 2007; 115:840–845.

ADDRESS: Holly L. Thacker, MD, Women's Health Center, A10, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH 44195; e-mail thackeh@ccf.org.