Chapter 31: Hormone Therapy in Women

INTRODUCTION

- *Perimenopause* begins with the onset of menstrual irregularity and ends 12 months after the last menstrual period, which marks the beginning of menopause. *Menopause* is the permanent cessation of menses caused by the loss of ovarian follicular activity. Women spend about 40% of their lives in postmenopause.

PHYSIOLOGY

- The hypothalamic–pituitary–ovarian axis controls reproductive physiology. Follicle-stimulating hormone (FSH) and luteinizing hormone (LH), produced by the pituitary in response to gonadotropin-releasing hormone from the hypothalamus, regulate ovarian function. Gonadotropins are also influenced by negative feedback from the sex steroids estradiol (produced by the dominant follicle) and progesterone (produced by the corpus luteum). Other sex steroids are androgens, primarily testosterone and androstenedione, secreted by the ovarian stroma.
- As women age, circulating FSH progressively rises, and ovarian inhibin-B and anti-Mullerian hormone declines. In menopause, there is a 10- to 15-fold increase in circulating FSH, a 4- to 5-fold increase in LH, and a greater than 90% decrease in circulating estradiol concentrations.

CLINICAL PRESENTATION

- Symptoms of perimenopause and menopause include vasomotor symptoms (hot flushes and night sweats), sleep disturbances, depression, anxiety, poor concentration and memory, vaginal dryness and dyspareunia, headache, sexual dysfunction, and arthralgia.
- Signs include urogenital atrophy in menopause and dysfunctional uterine bleeding in perimenopause. Other potential causes of dysfunctional uterine bleeding should be ruled out.
- Additionally, loss of estrogen production results in metabolic changes; increase in central abdominal fat; and effects on lipids, vascular function, and bone metabolism.

DIAGNOSIS

- Menopause is determined retrospectively after 12 consecutive months of amenorrhea. FSH on day 2 or 3 of the menstrual cycle greater than 10–12 IU/L indicates diminished ovarian reserve.
- The diagnosis of menopause should include a comprehensive medical history and physical examination, complete blood count, and measurement of serum FSH. When ovarian function has ceased, serum FSH concentrations exceed 40 IU/L. Altered thyroid function and pregnancy must be excluded.

TREATMENT

- Goals of Treatment: The goals are to relieve symptoms, improve quality of life, and minimize medication adverse effects.

Nonpharmacologic Therapy

- Mild vasomotor and/or vaginal symptoms can often be alleviated by lowering the room temperature; decreasing intake of caffeine, spicy foods, and hot beverages; smoking cessation; exercise; and a healthy diet.

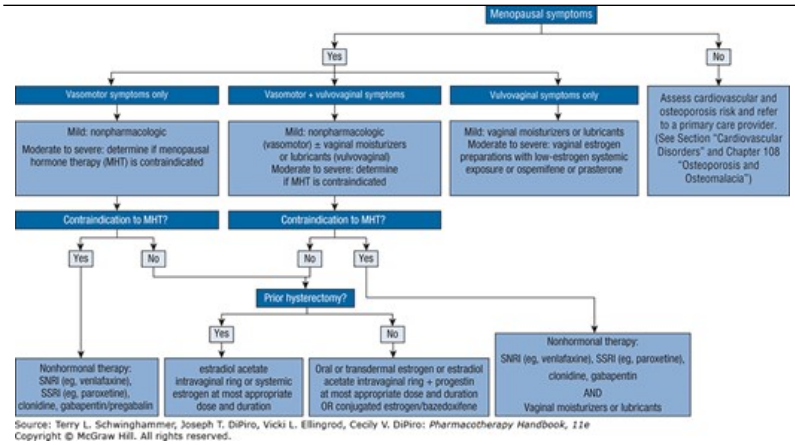
- Mild vaginal dryness can sometimes be relieved by nonestrogenic vaginal creams, but significant vaginal dryness often requires local or systemic estrogen therapy.

Pharmacologic Therapy

- **Figure 31-1** outlines the pharmacologic treatment of women with menopausal symptoms. Food and Drug Administration (FDA)-approved indications and contraindications for menopausal hormone therapy (MHT) are shown in **Table 31-1**.
- The decision to use MHT and the type of formulation used must be individualized based on several factors, including personal preference, age, menopause onset, the severity of menopausal symptoms, and MHT-associated risks.
- Combined hormonal contraceptives (CHCs) provide contraception and vasomotor symptom relief but should not be used in perimenopausal women if they smoke or have a history of estrogen-dependent cancer, cardiovascular or cerebrovascular disease, hypertension, diabetes with vascular disease, or risk factors for thromboembolism, liver disease, or migraine headaches (see **Chapter 30**).
- MHT remains the most effective treatment for moderate and severe vasomotor symptoms, impaired sleep quality, and vulvovaginal symptoms of menopause.
- Several national and international guidelines and consensus statements on the management of menopause are available (eg, United States Preventive Services Task Force, American Association of Clinical Endocrinologists, North American Menopause Society).
- When urogenital symptoms, such as vaginal dryness and dyspareunia, are the only menopausal complaint, **intravaginal estrogen cream, tablet**, or **ring** should be considered before oral therapy. Intravaginal estrogen minimizes systemic absorption and is more effective for vaginal symptoms than oral therapy. **Ospemifene**, a selective estrogen receptor modulator, is another option. Intravaginal estrogen reduces the risk of recurrent urinary tract infections and may improve urge incontinence and overactive bladder.
- MHT is the most effective treatment for moderate-to-severe vasomotor symptoms, and impaired sleep quality. **Estrogen-only** therapy may decrease heart disease and all-cause mortality in 50- to 59-year-old women with a history of hysterectomy.
- MHT is effective and appropriate for prevention of osteoporosis-related fractures in recently menopausal women at risk.
- In women with an intact uterus, MHT consists of an **estrogen plus a progestogen** or **estrogen agonist/antagonist** (eg, **bazedoxifene** see **Fig. 31-1**). In women who have undergone hysterectomy, estrogen therapy is given unopposed by a progestogen. Concomitant progestogen therapy is unnecessary when low-dose vaginal estrogen is used.
- Women with vasomotor symptoms taking MHT have better mental health and fewer depressive symptoms compared with those taking placebo, but hormone therapy may worsen quality of life in women without vasomotor symptoms.

FIGURE 31-1

Algorithm for pharmacologic management of menopause symptoms.



Source: Terry L. Schwinghammer, Joseph T. DiPiro, Vicki L. Ellingrod, Cecily V. DiPiro: *Pharmacotherapy Handbook, 11e*

TABLE 31-1

FDA-approved Indications and Contraindications for Menopausal Hormone Therapy with Estrogens and Progestins

Indications	
For systemic use	Treatment of moderate-to-severe vasomotor symptoms (ie, moderate-to-severe hot flashes)
For intravaginal use (low systemic exposure)	Treatment of moderate-to-severe symptoms of vulvar and vaginal atrophy (ie, moderate-to-severe vaginal dryness, dyspareunia, and atrophic vaginitis)
Contraindications	
Absolute contraindications	Undiagnosed abnormal genital bleeding Known, suspected, or history of cancer of the breast Known or suspected estrogen- or progesterone-dependent neoplasia Active deep vein thrombosis, pulmonary embolism, or a history of these conditions Active or recent (eg, within the past year) arterial thromboembolic disease (eg, stroke, myocardial infarction) Liver dysfunction or disease
Relative contraindications	Elevated blood pressure Hypertriglyceridemia Impaired liver function and past history of cholestatic jaundice Hypothyroidism Fluid retention Severe hypocalcemia Ovarian cancer Exacerbation of endometriosis Exacerbation of asthma, diabetes mellitus, migraine, systemic lupus erythematosus, epilepsy, porphyria, and hepatic hemangioma

Estrogens

- Estrogen products and doses for MHT are shown in **Table 31-2**. The oral and transdermal routes are used most frequently and are considered

equally effective.

- **Conjugated equine estrogens** are composed of estrone sulfate (50%–60%) and other estrogens such as equilin and 17α-dihydroequilin.
- **Estradiol** is the predominant and most active form of endogenous estrogens. Given orally, it is metabolized by the intestinal mucosa and liver, and resultant estrone concentrations are three to six times those of estradiol.
- **Ethinyl estradiol** is a semisynthetic estrogen that has similar activity following oral or parenteral administration.
- **Non-Oral estrogens**, including transdermal, intranasal, and vaginal products, avoid first-pass metabolism and result in a more physiologic estradiol:estrone ratio (ie, estradiol concentrations greater than estrone concentrations). Transdermal estrogen is also less likely to increase sex hormone–binding globulin, triglycerides, blood pressure, or C-reactive protein levels. Transdermal dosage forms may also have a lower risk for deep vein thrombosis, stroke, and myocardial infarction.
- Variability in absorption is common with the percutaneous preparations (gels, creams, and emulsions).
- **Estradiol pellets** (unavailable in the United States) contain pure crystalline 17β-estradiol and are placed subcutaneously (abdomen or buttock). They are difficult to remove.
- **Vaginal creams**, **tablets**, and **rings** are used for treatment of urogenital atrophy. Most tablets and rings provide local estrogen, but Femring is designed to achieve systemic estrogen concentrations and is indicated for moderate-to-severe vasomotor symptoms.
- New evidence indicates that lower doses of estrogens are effective in controlling postmenopausal symptoms and reducing bone loss. Low-dose estrogen regimens include 0.3–0.45 mg conjugated estrogens, 0.5 mg micronized 17β-estradiol, and 0.014–0.0375 mg transdermal 17β-estradiol patch. Topical gels, creams, and sprays are also available in low doses. Lower doses typically have fewer adverse effects, and may have better benefit to risk profiles than standard doses. The lowest effective dose should be used.

  ✔ Adverse effects of estrogen include nausea, headache, breast tenderness, and heavy bleeding. More serious adverse effects include increased risk for stroke, venous thromboembolism (VTE), and gall bladder disease. Transdermal estrogen is less likely to cause breast tenderness, gallbladder disease, and deep vein thrombosis.

  ✔ The Women's Health Initiative (WHI) trial showed an overall increase in the risk of coronary heart disease in healthy postmenopausal women ages 50–79 years taking estrogen–progestogen therapy compared to placebo. The estrogen-alone arm showed no effect (either increase or decrease) in the risk of coronary heart disease.

  ✔ The more recent Early versus Late Intervention Trial with Estradiol (ELITE) trial suggests that the benefits of hormone therapy are dependent on the timing of initiation and hormone therapy may be cardioprotective if started around the time of menopause (within 6 years) and therapy may be harmful when initiated in late postmenopausal women (after 10 years). MHT should not be initiated or continued solely for prevention of cardiovascular disease.

  ✔ Risk of VTE and stroke increases with oral MHT containing estrogen, but the absolute risk is low in women below 60 years of age. Transdermal MHT and low-dose oral estrogen therapy appear to have a lower risk of VTE and stroke compared to standard-dose oral estrogen regimens. The norpregnane progestogens also appear to be thrombogenic. MHT should be avoided in women at high risk for thromboembolic events (eg, those with Factor V Leiden mutation, obesity, or history of previous thromboembolic events).

  ✔ MHT is contraindicated in women with a personal history of breast cancer. In the WHI, the risk of MHT-related breast cancer appears to be associated with the addition of progestogen to estrogen after 3 years of combined use.

  ✔ The WHI trial suggests that combined oral MHT does not increase endometrial cancer risk compared with placebo, but estrogen alone given to women with an intact uterus significantly increases uterine cancer risk.

  ✔ While the WHI trial suggested that oral combined MHT does not increase the risk of ovarian cancer, more recent research now suggests that MHT are associated with an increased risk of ovarian cancer regardless of the type or the regimen used. More research is needed.

✔ The WHI study found that postmenopausal women 65 years or older taking estrogen plus progestogen therapy had twice the rate of dementia, including Alzheimer disease, than those taking placebo. Combined therapy did not prevent mild cognitive impairment. The estrogen-alone arm showed similar findings.

TABLE 31-2

FDA-Approved Estrogen Products for Menopausal Hormone Therapy

Drug	Brand Name[a]	Initial Dose/Low Dose	Usual Dose Range	Comments
Systemic Estrogen Products (for the treatment of moderate and severe vasomotor symptoms ± urogenital symptoms)				
Oral estrogens[b]				
Conjugated equine estrogens	Premarin	0.3 or 0.45 mg once daily	0.3–1.25 mg once daily	Dosage form available as 0.3, 0.45, 0.625, 0.9, 1.25 mg
Esterified estrogens (75%–85% estrone + 6%–15% equilin)	Menest	0.3 mg once daily	0.3–1.25 mg once daily	Administer 3 weeks on and 1 week off
				Dosage form available as 0.3, 0.625, 1.25 mg
Estradiol acetate	Femtrace	0.45 mg once daily	0.45–1.8 mg once daily	Dosage form available as 0.45, 0.9, 1.8 mg
Micronized 17β-estradiol	Estrace Generics	1 mg once daily	1 or 2 mg once daily	Administer 3 weeks on and 1 week off
				Dosage form available as 0.5, 1, 2 mg
Transdermal estrogens patches				
17β-estradiol	Alora	0.025 mg/day (patch applied twice weekly)[c]	0.025–0.1 mg/day (patch applied twice weekly)[c]	Dosage form available as 0.025, 0.05, 0.075, 0.1 mg/day
	Climara	0.025 mg/day (patch applied once weekly)[c]	0.025–0.1 mg/day (patch applied once weekly)[c]	Dosage form available as 0.025, 0.0375, 0.05, 0.06, 0.075, 0.1 mg/day
	Menostar	0.014 mg/day (patch applied once weekly)[c,d]	0.014 mg/day (patch applied once weekly)[c,d]	Dosage form available as 0.014 mg/day
	Estraderm	-	0.05 or 0.1 mg/day (patch applied twice weekly)[c]	Dosage form available as 0.05, 0.1 mg/day
	Minivelle, Vivelle, Vivelle Dot	0.025 mg/day (patch applied twice weekly)[c]	0.025–0.1 mg/day, 0.05 is standard dose (patch applied twice weekly)[c]	Dosage form available as 0.025, 0.0375, 0.05 (standard dose), 0.075, 0.1 mg/day
Other topical forms of estrogen				
17β-estradiol topical	Estrasorb	–	Two pouches once daily	Apply to legs

emulsion	0.25% emulsion		(which delivers 0.05 mg of estradiol per day)	
17β-estradiol topical gel	EstroGel 0.06% metered-dose pump	–	1.25 g/day once daily (contains 0.75 mg estradiol)	Apply from wrist to shoulder
	Elestrin 0.06% metered-dose pump	–	1–2 unit doses once daily (1 unit dose: 0.87 g, which contains 0.52-mg estradiol)	Apply to upper arm
	Divigel 0.1% (topical once daily)	0.25 g once daily	0.25–1 g (provides 0.25–1 mg of estradiol)	Apply to upper thigh; dosage form available as 0.25, 0.5, 0.75, 1 mg
17β-estradiol transdermal spray	Evamist	1 spray once daily	1–3 sprays once daily (1.53 mg of estradiol per spray)	Apply to inner surface of forearm
Implanted estrogens[e]				
Implanted 17β-estradiol	Estradiol pellets	25-mg implanted subcutaneously every 6 months	50–100 mg implanted subcutaneously every 6 months	
Vaginal estrogens				
Estradiol acetate vaginal ring	Femring	12.4 mg every 3 months	12.4-, 24.8-mg ring (delivers 0.05- or 0.1-mg estradiol/day)	
Intravaginal Estrogen Products (for the treatment of urogenital symptoms only/low systemic exposure)				
Conjugated equine estrogens (CEE) vaginal cream	Premarin		0.5–2 g/day (contains 0.625 mg CEE per g)	Administer 21 days on and 7 days off
17β-estradiol vaginal cream	Estrace	2–4 g daily for 1 or 2 weeks then gradually reduced to ½ initial dosage for similar period	Maintenance dose of 1 g, one to three times weekly	Dosage form available as tube containing 1½ oz with calibrated applicator for delivery of 1, 2, 3, or 4 g
17β-estradiol vaginal ring	Estring	2 mg replaced every 90 days	2 mg ring (delivers 0.0075 mg/day) replaced every 90 days	
17β-estradiol vaginal insert	Imvexxy	1 vaginal insert daily for 2 weeks, then 1 insert twice weekly	4 or 10 mcg twice weekly	
Estradiol hemihydrate vaginal tablet	Vagifem Yuvafem	10 mcg once weekly for 2 weeks, then twice weekly	10 mcg twice weekly	

	Generics	

[a]US brand names.

[b]Orally administered estrogens stimulate synthesis of hepatic proteins and increase circulating concentrations of sex hormone-binding globulin, which in turn may compromise the bioavailability of androgens and estrogens. Women with elevated triglyceride concentrations or significant liver function abnormalities are candidates for nonoral estrogen therapy.

[c]Do not apply estrogen patches on or near breasts. Avoid waistline as patch may rub off with tight-fitting clothing.

[d]FDA-approved for prevention of postmenopausal osteoporosis only.

[e]Not available in the United States.

Progestogens

- In women who have not undergone hysterectomy, a **progestogen** or tissue-selective estrogen complex (estrogen/bazedoxifene) should be added for endometrial protection.
- Several progestogen regimens to prevent endometrial hyperplasia are shown in **Table 31-3**. **Combination estrogen–progestogen** regimens are shown in **Table 31-4**.

TABLE 31-3

Progestogen Dosing for Endometrial Protection (Cyclic Administration)

Progestogen	Dosage
Medroxyprogesterone acetate	5–10 mg/day for 12–14 days per calendar month (oral dosage form available as 2.5-, 5-, 10-mg tablets)
Micronized progesterone	200 mg/day for 12–14 days per calendar month (oral dosage form available as 100- and 200-mg tablets)
Norethindrone acetate	5 mg/day for 12–14 days per calendar month (oral dosage form available as 2.5-, 5-mg tablets)

TABLE 31-4

Common Combination Menopausal Hormone Therapy Regimens

Regimen	Brand name	Dosage
Oral Regimens		
Conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA)	Prempro (continuous)	0.625 mg CEE/2.5 mg MPA, 0.625 mg CEE/5 mg MPA daily Low-dose: 0.3 mg CEE/1.5 mg MPA, 0.45 mg CEE/1.5 mg MPA daily
	Premphase (continuous sequential)	0.625 mg CEE daily only in the first 2 weeks of a 4-week cycle, then 0.625 mg daily, CEE + 5 mg MPA daily in the last 2 weeks of a 4-week cycle

Conjugated equine estrogen (CEE) + bazedoxifene	Duavee (continuous)	0.45/20 mg daily
Ethinyl estradiol (EE) + norethindrone acetate (NETA)	Generic, Femhrt (continuous) Fayvolv (continuous)	Femhrt: 2.5 mcg EE/0.5 mg NETA daily Fyavolv: 2.5 mcg EE/0.5 mg NETA daily, 5 mcg EE/1 mg NETA daily
Estradiol (E) + drospirenone (DRSP)	Angeliq (continuous)	1 mg E/0.5 mg DRSP daily Low dose: 0.5 mg E/0.25 mg DRSP daily
Estradiol (E) + norgestimate	Prefest (estrogen/intermittent progestogen)	1 mg E daily for first 3 days, then 1 mg E/0.09 mg norgestimate daily for next 3 days; this pattern is repeated continuously
Estradiol (E) + norethindrone acetate (NETA)	Activella (continuous) Mimvey (continuous) Mimvey Lo (continuous) Amabelz (continuous) Lopreeza (continuous)	1 mg E/0.5 mg NETA daily Low-dose: 0.5 mg E/0.1 mg NETA daily
Estradiol (E) + progesterone	Bijuva (continuous)	1 mg E/100 mg progesterone daily
Transdermal Regimens		
Estradiol + norethindrone acetate patch	CombiPatch (continuous) CombiPatch (continuous sequential)	Continuous: 0.05/0.14 mg, 0.05/0.25 mg (apply 1 patch twice weekly) Continuous sequential: 0.05 mg of an estradiol only patch (apply 1 patch twice weekly) in the first 2 weeks of a 4-week cycle, then either dose of the CombiPatch (apply 1 patch twice weekly) in the last 2 weeks of a 4-week cycle
Estradiol (E) + levonorgestrel patch	Climara Pro (continuous)	0.045 mg E/0.015 mg/day (apply 1 patch once weekly)

CEE, conjugated equine estrogen; DRSP, drospirenone; E, estradiol; EE, ethinyl estradiol; NETA, norethindrone acetate; MPA, medroxyprogesterone acetate.

Methods of administration include the following:

- **Continuous-cyclic estrogen-progestogen (sequential)** results in scheduled vaginal withdrawal bleeding in approximately 90% of women. The progestogen is administered 12–14 days of the 28-day cycle.
- **Continuous-combined estrogen-progestogen** causes endometrial atrophy but prevents monthly bleeding. It may initially cause unpredictable spotting or bleeding. Use of conjugated equine estrogens [0.625 mg/day] plus medroxyprogesterone acetate [2.5 mg/day]) lead to a decreased risk of endometrial cancer in the WHI study.
- **Continuous long-cycle estrogen-progestogen (cyclic withdrawal)**. Estrogen is given daily, and progestogen is given six times yearly (every

other month) for 12–14 days, resulting in six periods per year. Bleeding may be heavier and last for more days than with sequential use.

- **Intermittent-combined estrogen-progestogen (continuous pulsed)** consists of 3 days of estrogen therapy alone, followed by 3 days of combined estrogen and progestogen, repeated without interruption. It causes fewer side effects than regimens with higher progestogen doses and lowers the incidence of uterine bleeding.

  ✔ Adverse effects of progestogens include irritability, headache, mood swings, fluid retention, and sleep disturbance. See previous estrogen section for additional adverse effects associated with estrogen and progesterone in combination.

Compounded Bioidentical Hormone Therapy (CBHT)

- CBHTs are hormone therapy formulations custom-prepared (ie, compounded) for individual patients, often involving the use of measuring and monitoring hormone levels in blood and/or other body fluids such as saliva. Hormones commonly used in CBHT include estrone, estradiol, estriol, progesterone, testosterone, DHEA, and thyroid hormone. Bioidentical hormones appear to carry the same risks as traditional hormone therapy products and several major medical organizations have released statements against this practice.

Non-Hormonal Treatments

- For women with contraindications to or who cannot tolerate estrogens and/or progestogens, other treatment options for hot flushes can be considered (**Table 31-5**). Some clinicians consider **selective serotonin reuptake inhibitors** (eg, paroxetine, fluoxetine, citalopram, escitalopram) or serotonin-norepinephrine reuptake inhibitors (eg, venlafaxine and desvenlafaxine) to be first-line agents. **Clonidine** can be effective, but side effects are often problematic (eg, sedation, dry mouth, hypotension). **Gabapentin** has beneficial effects for reducing the frequency and severity of vasomotor symptoms but side effects may limit dosing. It may be a reasonable option for women with disrupted sleep and hot flashes when administered in the evening.

TABLE 31-5

Alternatives to Estrogen for Treatment of Hot Flashes[a]

Drug	Brand Name[b]	Initial Dose	Usual Dose Range	Comments
Tibolone[c]	Livial (not available in the United States)	2.5 mg	2.5 mg/day	Tibolone is not recommended during the perimenopause period because it may cause irregular bleeding
Venlafaxine	Effexor, Effexor XR	37.5 mg	37.5–150 mg/day	Adverse effects include nausea, headache, somnolence, dizziness, insomnia, nervousness, xerostomia, anorexia, constipation, diaphoresis, weakness, and hypertension
Desvenlafaxine	Pristiq	100–150 mg	100–150 mg/day	Adverse effects include nausea, headache, somnolence, dizziness, insomnia, xerostomia, anorexia, constipation, diaphoresis, and weakness
Paroxetine[d]	Brisdelle[e], Paxil, Paxil CR, Pexeva	7.5 mg/day (paroxetine)[e], 10 mg/day (paroxetine), or 12.5 mg/day (paroxetine CR)	7.5 mg/day[e], 10[e]–20 mg/day or 12.5–25 mg/day	Adverse effects include nausea, somnolence, insomnia, headache, dizziness, xerostomia, constipation, diarrhea, weakness, and diaphoresis

Citalopram		10 mg/day	10–20 mg/day	Adverse effects include drowsiness, insomnia, diaphoresis, nausea, xerostomia, dose-dependent QTc prolongation
Escitalopram		10 mg/day, start with 5 mg/day in sensitive or older women and titrate up	10–20 mg/day	Adverse effects include headache, insomnia, nausea, increased sweating, fatigue, and somnolence; decreased libido and anorgasmia
Clonidine	Catapres and generic tablets (oral)	0.1 mg/day	0.1 mg/day	Adverse effects include drowsiness, dizziness, hypotension, and dry mouth, especially with higher doses
	Catapres-TTS (transdermal)			
	Kapvay tablets (extended release; oral)			
Pregabalin	Lyrica	150 mg/day	150–300 mg/day	Adverse effects include drowsiness, dizziness, dry mouth, edema, blurred vision, weight gain, impaired concentration
Gabapentin	Gralise, Neurontin	300 mg at bedtime	900 mg/day (divided in three daily doses), doses up to 2400 mg/day (divided in three daily doses) have been studied	Adverse effects include somnolence and dizziness; these symptoms often can be obviated with a gradual increase in dosing

[a]Treatment of postmenopausal hot flashes is an off-label indication in the United States for all medications listed except for one formulation of paroxetine (paroxetine mesylate).

[b]US brand names.

[c]Not available in the United States.

[d]Other selective serotonin reuptake inhibitors (eg, citalopram, escitalopram, fluoxetine, and sertraline) have also been studied and may be used for the treatment of hot flashes.

[e]The brand Brisdelle contains 7.5 mg of paroxetine and is FDA-approved to treat moderate-to-severe vasomotor symptoms of menopause. This specific product is not FDA-approved for treating psychiatric conditions.

Androgens

- **Testosterone** use in women, although controversial, is becoming more common, even in the absence of androgen deficiency. Testosterone, with or without estrogen, may improve the quality of the sexual experience in postmenopausal women.
- Absolute contraindications to androgen therapy include pregnancy or lactation and known or suspected androgen-dependent neoplasia.

- Excessive dosage may cause virilization, fluid retention, and adverse lipoprotein lipid effects, which are more likely with oral administration. Evidence on the efficacy and safety of testosterone in women is lacking, and its use is currently not recommended.
- Adverse effects include virilization, fluid retention, and potentially adverse lipoprotein lipid effects, which are more likely with oral administration.
- **Dehydroepiandrosterone** (DHEA) is a precursor hormone in the synthesis of estrone, estradiol, and testosterone. Intravaginal DHEA (Prasterone) has FDA approval for the treatment of moderate-to-severe dyspareunia at a dose of 6.5 mg once daily at bedtime, which does not appear to convey the same systemic risks seen from other oral hormonal products.

Selective Estrogen Receptor Modulators (SERMs)

- SERMs are nonsteroidal compounds that act as estrogen agonists in some tissues such as bone and as estrogen antagonists in other tissues such as breast through high-affinity binding to the estrogen receptor.
- **Tamoxifen** is an antagonist in breast tissue and an agonist on the bone and endometrium (see Chapter 60).
- **Raloxifene** is approved for prevention and treatment of postmenopausal osteoporosis and reduction in risk of invasive breast cancer. The dose is 60 mg once daily.
- The third-generation SERM, **bazedoxifene**, is used in conjunction with **conjugated estrogen**, and is FDA-approved for moderate-to-severe vasomotor symptoms and prevention of osteoporosis.
- **Ospemifene** is approved for moderate-to-severe dyspareunia from menopausal vulvar and vaginal atrophy. It has a boxed warning for increased risk of endometrial cancer in women with a uterus who use ospemifene (an estrogen agonist in the endometrium) without a progestogen to reduce endometrial hyperplasia. It also has a boxed warning about the possible risk of stroke and VTE.

  ✔ Depending on tissue selectively, the SERMs are associated with hot flashes and leg cramps. They can also increase the risk of VTE and stroke similar to oral estrogen, but the degree of risk is agent specific. Additional side effects of bazedoxifene include muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, oropharyngeal pain, dizziness, and neck pain. Adverse effects of ospemifene include hot flashes, vaginal discharge, muscle spasm, genital discharge, and hyperhidrosis.

Tibolone

- Tibolone (unavailable in the United States) has combined estrogenic, progestogenic, and androgenic activity and improves mood, libido, menopausal symptoms, and vaginal atrophy. It protects against bone loss and reduces the risk of vertebral fractures. It reduces total cholesterol and triglycerides, but may decrease high-density lipoprotein concentrations. It decreases the risk of breast and colon cancer in women ages 60–85 years.

  ✔ Adverse effects include weight gain and bloating, increased risk of stroke in older women, and possible breast cancer recurrence. It may increase endometrial cancer risk.

Complementary and Alternative Agents

Phytoestrogens

- Phytoestrogens are plant compounds with estrogen-like biologic activity and relatively weak estrogen receptor-binding properties, resulting in physiologic effects in humans.
- Although some data support their use, clarity regarding, dosing, biological activity, safety, and efficacy is needed before they can be considered as an alternative to MHT in postmenopausal women.

  ✔ Common adverse effects include constipation, bloating, and nausea.

Others

- Other herbals and alternative treatments that may be used by women include **black cohosh, dong quai, red clover leaf** (contains phytoestrogens), and **ginseng**. Complementary and alternative therapies should not be recommended to treat menopausal symptoms as their efficacy and safety have not been completely established.

EVALUATION OF THERAPEUTIC OUTCOMES

- Management of patients taking hormone therapy is summarized in **Table 31-6**.
- In order to adequately assess treatment effect, women should be encouraged to continue their MHT regimen for at least 1 month with dosages being modified to balance adverse effects and efficacy. Women receiving MHT should be seen annually for monitoring.
- Many women have no difficulty stopping MHT, while some develop vasomotor symptoms after discontinuation, regardless of discontinuation rate (ie, gradual or sudden withdrawal).

TABLE 31-6

Management of Patients Taking Hormone Therapy Regimens

Initiation of Hormone Therapy			
Hormone therapy should be used only as long as vasomotor symptom control is necessary			
Six-Week Follow-up Visit			
To discuss patient concerns about hormone therapy			
To evaluate the patient for symptom relief, adverse effects, and patterns of withdrawal bleeding (if continuous sequential hormone therapy is given)			
Drug	**Adverse Drug Reaction**	**Monitoring Parameter**	**Suggested Change**
Estrogen		Persistence of hot flashes	Increase estrogen dose
Estrogen	Breast tenderness		Reduce estrogen dose; switch to a transdermal regimen
Progestogen	Bloating	Switch to another progestogen or bazedoxifene	
	Premenstrual-like symptoms		
Annual Follow-up Visit			
Annual monitoring: Medical history, physical examination (including pelvic examination), blood pressure measurement, and routine endometrial cancer surveillance (as indicated). Additional follow-up is determined based on the patient's initial response to therapy and the need for any modification of the regimen.			
Breast examinations: Annual mammograms (scheduled based on patient's age and risk factors).			
Osteoporosis prevention: BMD should be measured in women 65 years and older and in women younger than 65 years with risk factors for osteoporosis. Repeat testing should be performed as clinically indicated.			
In women taking sequential hormone therapy	Transvaginal ultrasound, and where indicated an endometrial biopsy should be performed if vaginal bleeding occurs at any time other than the expected time of withdrawal bleeding or when heavier or more prolonged withdrawal bleeding occurs (if endometrial pathology cannot be excluded by endovaginal ultrasonography, further evaluation may be required, such as hysteroscopy).		
In women taking continuous combined hormone therapy	Endometrial evaluation should be considered when irregular bleeding persists for more than 6 months after initiating therapy.		

BMD, bone mineral density.

See Chapter 98, Hormone Therapy in Women, authored by Devra K. Dang, Kathryn E. Wheeler, and Judy T. Chen, for a more detailed discussion of this topic.