CME CREDIT

LEARNING OBJECTIVE: Readers will tailor hormone therapy to the needs of the patient

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ERAAs for menopause treatment: Welcome the 'designer estrogens'

ABSTRACT

Estrogen receptor agonist-antagonists (ERAAs) selectively inhibit or stimulate estrogen-like action in targeted tissues. This review summarizes how ERAAs can be used in combination with an estrogen or alone to treat menopausal symptoms (vasomotor symptoms, genitourinary syndrome of menopause), breast cancer or the risk of breast cancer, osteopenia, osteoporosis, and other female midlife concerns.

KEY POINTS

Tamoxifen is approved to prevent and treat breast cancer. It may also have beneficial effects on bone and on cardiovascular risk factors, but these are not approved uses.

Raloxifene, a second-generation ERAA, was initially approved for preventing and treating osteoporosis and later received approval to reduce the risk of invasive estrogen receptor-positive breast cancer in postmenopausal women.

Ospemifene is approved for treatment of genitourinary syndrome of menopause.

The combination of conjugated estrogen and bazedoxifene is approved for treating moderate to severe vasomotor symptoms associated with menopause and also for preventing postmenopausal osteoporosis in women with an intact uterus.

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Estrogen receptor agonist-antagonists (ERAAs), previously called selective estrogen receptor modulators (SERMs), have extended the options for treating the various conditions that menopausal women suffer from. These drugs act differently on estrogen receptors in different tissues, stimulating receptors in some tissues but inhibiting them in others. This allows selective inhibition or stimulation of estrogen-like action in various target tissues.[1]

This article highlights the use of ERAAs to treat menopausal vasomotor symptoms (eg, hot flashes, night sweats), genitourinary syndrome of menopause, osteoporosis, breast cancer (and the risk of breast cancer), and other health concerns unique to women at midlife.

SYMPTOMS OF MENOPAUSE: COMMON AND TROUBLESOME

Vasomotor symptoms such as hot flashes and night sweats are common during perimenopause—most women experience them. They are most frequent during the menopause transition but can persist for 10 years or more afterward.[2]

Genitourinary syndrome of menopause is also common and often worsens with years after menopause.[3] It can lead to dyspareunia and vaginal dryness, which may in turn result in lower libido, vaginismus, and hypoactive sexual desire disorder, problems that often arise at the same time as vaginal dryness and atrophy.[4]

Osteopenia and osteoporosis. A drop in systemic estrogen leads to a decline in bone mineral density, increasing the risk of fractures.[5]

TABLE 1

Designer estrogens and their uses

Agent	Approved uses	Other possible benefits	Adverse effects
Tamoxifen	To treat metastatic breast cancer and ductal carcinoma in situ To reduce the risk of estrogen receptor-positive breast cancer in women at high risk	Positive effect on bone Positive effect on cardiovascular risk	Venous thromboembolism Uterine neoplasia Vasomotor symptoms
Raloxifene	To prevent and treat osteoporosis To reduce the risk of invasive estrogen receptor-positive breast cancer in postmenopausal women	Reduction in breast cancer risk	Venous thromboembolism Stroke
Ospemifene	To treat genitourinary syndrome of menopause	Positive effect on bone	Venous thromboembolism
Conjugated estrogen-bazedoxifene	In women with a uterus: to prevent osteoporosis and treat vasomotor symptoms of menopause	Positive effects on uterus, genitourinary syndrome of menopause	Venous thromboembolism

ERAAs have extended the options for treating the various conditions menopausal women suffer from

ESTROGEN-PROGESTIN TREATMENT: THE GOLD STANDARD, BUT NOT IDEAL

The current gold standard for treating moderate to severe hot flashes is estrogen, available in oral, transdermal, and vaginal formulations.[6] Estrogen also has antiresorptive effects on bone and is approved for preventing osteoporosis. Systemic estrogen may also be prescribed for genitourinary syndrome of menopause if local vaginal treatment alone is insufficient.

If women who have an intact uterus receive estrogen, they should also receive a progestin to protect against endometrial hyperplasia and reduce the risk of endometrial cancer.

Despite its status as the gold standard, estrogen-progestin therapy presents challenges. In some women, progestins cause side effects such as breast tenderness, bloating, fatigue, and depression.[7] Estrogen-progestin therapy often causes vaginal bleeding, which for some women is troublesome or distressing; bleeding may be the reason for repeated evaluations, can increase anxiety, and can lead to poor adherence with hormonal treatment. Women who carry a higher-than-normal risk of developing breast cancer or fear that taking hormones will lead to breast cancer may show decreased adherence to therapy. Women who have estrogen receptor-positive breast cancer cannot take estrogen.

Individualized options are needed for women who have progestin-related side effects, unwanted vaginal bleeding, or a higher risk of breast cancer.

WELCOME THE ERAAs

An ideal treatment for menopause would relieve vasomotor symptoms and genitourinary syndrome of menopause and increase bone mineral density without causing breast tenderness, vaginal bleeding, or endometrial proliferation.

The "designer estrogens," or ERAAs, have specific positive effects on the bone, heart, and brain with neutral or antagonist effects on estrogen receptors in other tissues such as the breasts and endometrium.[8] While not entirely free of adverse effects, these agents have been developed with the aim of minimizing the most common ones related to estrogen and progestin.

Several ERAAs are currently approved by the US Food and Drug Administration (FDA) for various indications, each having a unique profile. Clomifene was the first agent of this class, and it is still used clinically to induce ovulation. This article highlights subsequently approved agents, ie, tamoxifen, raloxifene,

ospemifene, and the combination of conjugated estrogens and bazedoxifene (**Table 1**).

All ERAAs increase the risk of venous thromboembolism, and therefore none of them should be used in women with known venous thromboembolism or at high risk of it.

TAMOXIFEN: CANCER TREATMENT AND PREVENTION

After clomiphene, tamoxifen was the second ERAA on the market. Although researchers were looking for a new contraceptive drug, they found tamoxifen to be useful as a chemotherapeutic agent for breast cancer. First used in 1971, tamoxifen continues to be one of the most commonly prescribed chemotherapeutic medications today.

The FDA has approved tamoxifen to treat breast cancer as well as to prevent breast cancer in pre- and postmenopausal women at risk. It may also have beneficial effects on bone and on cardiovascular risk factors, but these are not approved uses for it.

Trials of tamoxifen for cancer treatment

The Early Breast Cancer Trialists' Collaborative Group[9] performed a meta-analysis and found that 5 years of adjuvant treatment with tamoxifen is associated with a 26% reduction in mortality and a 47% reduction in breast cancer recurrence at 10 years. In absolute terms, we estimate that 21 women would need to be treated to prevent 1 death and 8 would need to be treated to prevent 1 recurrence.

The ATLAS Trial (Adjuvant Tamoxifen Longer Against Shorter)[10] and later the UK **ATTOM** (Adjuvant Tamoxifen Treatment to Offer More)[11] trial confirmed an even greater reduction in recurrence and mortality after a total of 10 years of treatment.

Trials of tamoxifen for cancer prevention

Cuzik et al[12] performed a meta-analysis of 4 trials of tamoxifen's effectiveness in preventing breast cancer for women at elevated risk. The incidence of estrogen receptor-positive breast cancer was 48% lower with tamoxifen use, but there was no effect on estrogen-negative breast cancer. From their data, we estimate that 77 women would need to be treated to prevent 1 case of breast cancer.

The IBIS-I trial (International Breast Cancer Intervention Study I)[13] found that, in healthy women at high risk of breast cancer, the benefit of taking tamoxifen for 5 years as preventive treatment persisted long afterward. The investigators estimated that at 20 years of follow-up the risk of breast cancer would be 12.3% in placebo recipients and 7.8% in tamoxifen recipients, a 4.5% absolute risk reduction; number needed to treat (NNT) 22.

Data on tamoxifen and osteoporosis

The Breast Cancer Prevention Trial revealed a 19% reduction in the incidence of osteoporotic fractures with tamoxifen, but the difference was not statistically significant.[14] The 1-year rates of fracture in women age 50 and older were 0.727% with placebo and 0.567% with tamoxifen, an absolute difference of 0.151%; therefore, if the effect is real, 662 women age 50 or older would need to be treated for 1 year to prevent 1 fracture. Tamoxifen is not FDA-approved to treat osteoporosis.

Data on tamoxifen and cardiovascular risk reduction

Chang et al,[15] in a study in women at risk of breast cancer, incidentally found that tamoxifen was associated with a 13% reduction in total cholesterol compared with placebo.

Herrington and Klein,[16] in a systematic review, noted similar findings in multiple studies of tamoxifen, with decreases in total cholesterol ranging from 7% to 17% and decreases in low-density lipoprotein cholesterol ranging from 10% to 28%. However, they found no change in high-density lipoprotein cholesterol concentrations or in the cardiovascular mortality rate.

The ATLAS trial[10] revealed a relative risk reduction of 0.76 (95% confidence interval [CI] 0.60–0.95, $P = .02$) in ischemic heart disease for women who took tamoxifen for 10 years compared with 5 years. We calculate that ischemic heart disease occurred in 163 (2.5%) of 6,440 women who took tamoxifen for 5 years compared with 127 (1.9%) of 6,454 women who took it for 10 years, a 0.6% absolute risk reduction, NNT = 167.

Adverse effects of tamoxifen

Uterine neoplasia. Women taking tamoxifen have a 2.5-fold increased risk of endometrial

Women with a uterus who receive estrogen should also receive a progestin

cancer.[14] Tamoxifen also increases the risk of benign uterine disease such as endometrial hyperplasia and polyps. As many as 39% of women taking tamoxifen will have evidence of benign uterine changes on pathology.[17] Other adverse effects:

Venous thromboembolism (the risk of pulmonary embolism is increased approximately threefold[14])

Cataracts (there is a slight increase in cataract diagnosis in tamoxifen users)

Vasomotor symptoms, which limit the use of tamoxifen in many women.

Ideal candidate for tamoxifen

The ideal candidate for tamoxifen is a woman with breast cancer that is estrogen receptor-positive and who has a history of osteopenia or osteoporosis and no risk factors for venous thromboembolism.

RALOXIFENE: FOR OSTEOPOROSIS AND FOR CANCER PREVENTION

Raloxifene, a second-generation ERAA, was first approved for preventing and treating osteoporosis and later for reducing the risk of invasive estrogen receptor-positive breast cancer in postmenopausal women.

An ideal menopause therapy would stimulate bone but inhibit estrogen action in breast and uterine tissue

Trials of raloxifene for osteoporosis

The MORE trial (Multiple Outcomes of Raloxifene)[18] was a large multicenter randomized double-blind study. Raloxifene recipients showed a significant increase in bone mineral density in the lumbar spine and femoral neck at year 3 ($P < .001$) compared with those receiving placebo. Even after only 1 year of treatment, raloxifene significantly reduced the risk of new fractures, despite only modest gains in bone mineral density. After 3 years of treatment, new clinical vertebral fractures had occurred in 3.5% of the placebo group compared with 2.1% of the group receiving raloxifene 60 mg.[19] Relative risk reductions were similar in women who had already had a clinical vertebral fracture at baseline, whose absolute risk is higher. However, no significant effect was seen on the incidence of hip or nonvertebral fractures.

The CORE trial (Continuing Outcomes Relevant to Raloxifene)[20] extended the treatment of the women enrolled in the MORE trial another 4 years and found that the benefit of raloxifene with regard to bone mineral density persisted with continued use.

Trials of raloxifene for breast cancer prevention

The MORE trial,[21] in postmenopausal women with osteoporosis included breast cancer as a secondary end point, and raloxifene was shown to decrease the incidence of invasive breast cancer. At a median of 40 months, invasive breast cancer had arisen in 13 (0.25%) of the 5,129 women assigned to raloxifene and 27 (1.0%) of the 2,576 women assigned to placebo. The authors calculated that 126 women would need to be treated to prevent 1 case of breast cancer.

The CORE trial,[22] as noted, extended the treatment of the women enrolled in the MORE trial another 4 years. The risk of any invasive breast cancer in postmenopausal women with osteoporosis was significantly reduced by 59% after 8 years, and the risk of estrogen receptor-positive invasive breast cancer was reduced by 66%.

There is evidence that raloxifene's effect on breast cancer risk persists after discontinuation of use.[23]

Does raloxifene reduce mortality?

Grady et al[24] studied the effect of raloxifene on all-cause mortality in a pooled analysis of mortality data from the MORE, CORE, and Raloxifene Use for the Heart (RUTH)[25] trials. In older postmenopausal women, the rate of all-cause mortality was 8.65% in those taking placebo compared with 7.88% in those taking raloxifene 60 mg daily—10% lower. The mechanism behind the lower mortality rate is unclear, and Grady et al recommend that the finding be interpreted with caution.

Trials of raloxifene for heart protection

The RUTH trial[25] was a 5.6-year study undertaken to study the effects of raloxifene on coronary outcomes and invasive breast cancer in postmenopausal women. Results were mixed. Active treatment:

- Did not significantly affect the risk of coronary artery disease compared with placebo
- Significantly decreased the risk of invasive breast cancer
- Significantly decreased the risk of clinical

vertebral fractures
- Increased the risk of fatal stroke (59 vs 39 events, hazard ratio 1.49, 95% CI 1.00–2.24) and venous thromboembolism (103 vs 71 events, hazard ratio 1.44, 95% CI 1.06–1.95).

The STAR trial (Study of Tamoxifen and Raloxifene)[26,27] compared raloxifene and tamoxifen in postmenopausal women at increased risk of breast cancer. Women were randomized to receive either tamoxifen 20 mg or raloxifene 60 mg for 5 years. Results:
- No difference in the number of new cases of invasive breast cancer between the groups
- Fewer cases of noninvasive breast cancer in the tamoxifen group, but the difference was not statistically significant
- Fewer cases of uterine cancer in the raloxifene group, annual incidence rates 0.125% vs 0.199%, absolute risk reduction 0.74%, NNT 1,351, relative risk with raloxifene 0.62, 95% CI 0.30–0.50
- Fewer thromboembolic events with raloxifene
- Fewer cataracts with raloxifene.

Adverse effects of raloxifene

Raloxifene increases the risk of venous thromboembolism and stroke in women at high risk of coronary artery disease.[19]

Ideal candidates for raloxifene

Postmenopausal women with osteopenia or osteoporosis and a higher risk of breast cancer who have minimal to no vasomotor symptoms or genitourinary syndrome of menopause are good candidates for raloxifene. Raloxifene is also a good choice for women who have genitourinary syndrome of menopause treated with local vaginal estrogen. Raloxifene has no effect on vasomotor symptoms or genitourinary syndrome of menopause.

OSPEMIFENE: FOR GENITOURINARY SYNDROME OF MENOPAUSE

Although ospemifene does not have the steroid structure of estrogen, it acts as an estrogen agonist specifically in the vaginal mucosa and an antagonist in other tissues.[28] It has been shown on Papanicolaou smears to reduce the number of parabasal cells and increase the number of intermediate and superficial cells after 3 months of treatment.[29]

Ospemifene 60 mg taken orally with food is approved by the FDA to treat genitourinary syndrome of menopause.

Why ospemifene is needed

First-line treatment options for genitourinary syndrome of menopause include over-the-counter lubricants. However, there is no evidence that these products reverse vaginal atrophy,[30] and many women report no relief of symptoms with them.

While various local estrogen preparations positively affect genitourinary syndrome of menopause, some of them can be messy, which can limit-long term adherence.

In one of the largest surveys on genitourinary syndrome of menopause (the REVIVE survey—the Real Women's View of Treatment Options for Menopausal Vaginal Changes[29]), 59% of women reported that their vaginal symptoms negatively affected sexual activity. The problem affects not only the patient but also her sexual partner.[31] Another large study showed that 38% of women and 39% of male partners reported that it had a worse-than-expected impact on their intimate relationships.[31]

Genitourinary syndrome of menopause also makes pelvic examinations difficult, may worsen or exacerbate cystitis, and may increase urinary tract infections.

All ERAAs increase the risk of venous thromboembolism

Trials of ospemifene for genitourinary syndrome of menopause

To date, 3 randomized, double-blind clinical trials have demonstrated ospemifene 60 mg to be superior to placebo in treating genitourinary syndrome of menopause. Two were short-term (12-week) and showed significant positive changes in the percent of superficial cells, vaginal pH (lower is better), and number of parabasal cells, along with improvements in the Likert rating of both vaginal dryness and dyspareunia.[32,33]

A long-term (52-week) randomized placebo-controlled trial compared ospemifene and placebo and showed significant improvement in vaginal maturation index and pH at weeks 12 and 52.[34] Other outcome measures included petechiae, pallor, friability, erythema, and dryness, all of which improved from baseline ($P < .001$). At the end of the trial, 80% of the patients who received ospemifene had no vaginal atrophy.

No serious adverse events were noted in any of the clinical trials to date, and a systemic review and meta-analysis demonstrated ospemifene to be safe and efficacious.[35] The most frequently reported reasons for discontinuation were hot flashes, vaginal discharge, muscle spasms, and hyperhidrosis, but the rates of these effects were similar to those with placebo.

Trial of ospemifene's effect on bone turnover

As an estrogen receptor agonist in bone, ospemifene decreases the levels of bone turnover markers in postmenopausal women.[36] A study found ospemifene to be about as effective as raloxifene in suppressing bone turnover,[37] but ospemifene does not carry FDA approval for preventing or treating osteoporosis.

Other effects

In experiments in rats, the incidence of breast cancer appears to be lower with ospemifene, and the higher the dose, the lower the incidence.[38]

Ospemifene also has antagonistic effects on uterine tissue, and no cases of endometrial hyperplasia or carcinoma have been reported in short-term or long-term studies.[35]

The clinician has multiple options to improve quality of life in these patients

Ospemifene has no effect however on vasomotor symptoms and may in fact worsen vasomotor symptoms in women suffering with hot flashes and night sweats. Further investigation into its long-term safety and effects on breast tissue and bone would provide more insight.

Ideal candidates for ospemifene

Ospemifene could help postmenopausal women with genitourinary syndrome of menopause for whom over-the-counter lubricants fail, who dislike local vaginal estrogen, or who decline systemic hormone therapy, and who do not meet the criteria for treatment with systemic hormone therapy.

CONJUGATED ESTROGENS AND BAZEDOXIFENE COMBINATION

A combination agent consisting of conjugated estrogens 0.45 mg plus bazedoxifene 20 mg has been approved by the FDA for treating moderate to severe vasomotor symptoms associated with menopause and also for preventing postmenopausal osteoporosis in women who have an intact uterus.

Trials of estrogen-bazedoxifene for vasomotor symptoms

The Selective Estrogen Menopause and Response to Therapy (SMART) trials[39,40] were a series of randomized, double-blind, placebo-controlled phase 3 studies evaluating the efficacy and safety of the estrogen-bazedoxifene combination in postmenopausal women.

The SMART-2 trial[39] evaluated the combination of conjugated estrogens (either 0.45 mg or 0.625) plus bazedoxifene 20 mg and found both dosages significantly reduced the number and severity of hot flashes at weeks 4 and 12 ($P < .001$). At week 12, the combination with 0.45 mg of estrogen reduced vasomotor symptoms from baseline by 74% (10.3 hot flashes per week at baseline vs 2.8 at week 12); the combination with 0.625 mg of estrogen reduced vasomotor symptoms by 80% (10.4 vs 2.4 flashes); and placebo reduced them by 51% (10.5 vs 5.4 flashes).

For bone density. The SMART-1 trial[40] showed that the estrogen-bazedoxifene combination in both estrogen dosages significantly increased mean lumbar spine bone mineral density ($P < .001$) and total hip bone mineral density ($P < .05$) from baseline at 12 and 24 months compared with placebo. Increases in density tended to be higher with the higher estrogen dose (0.625 mg), but less with higher doses of bazedoxifene.[41] At 24 months, the increase in bone mineral density was even greater than in women treated with raloxifene.[42] However, the effect of estrogen-bazedoxifene on the incidence of fractures remains to be studied.

For genitourinary syndrome of menopause. The SMART-3 trial showed that treatment with conjugated estrogens plus bazedoxifene (0.45/20 mg or 0.625/20 mg) was more effective than placebo in increasing the percent of superficial and intermediate cells and decreased the number of parabasal cells at 12 weeks compared with placebo ($P < .01$).[43] Both doses also significantly decreased the mean vaginal pH and improved vaginal dryness.

Patients treated with estrogen-bazedoxifene for a minimum of 12 weeks in a double-blind placebo-controlled study also showed a significant improvement in sexual function and quality-of-life measurements based on 3 well-defined scales, which included ease of lubrication, satisfaction with

treatment, control of hot flashes, and sleep parameters.[43]

Low rates of side effects

To evaluate this regimen's antagonistic effects on uterine tissue, endometrial hyperplasia was diagnosed by blinded pathologists using endometrial biopsies taken at 6, 12, and 24 months or more if cancer was a suspected diagnosis. At 12 and 24 months of treatment, the incidence of hyperplasia with bazedoxifene 20 or 40 mg at doses of either 0.45 or 0.625 mg of conjugated estrogens was less than 1%, which was similar to placebo rates over the 24 months.[44] The lowest dose studied, bazedoxifene 10 mg, did not prevent hyperplasia with conjugated estrogens 0.45 or 0.625 mg, and its use was discontinued.

Rates of amenorrhea with bazedoxifene 20 or 40 mg and conjugated estrogens 0.45 or 0.625 mg were very favorable (83%–93%) and similar to those with placebo.[45] For women with continued bleeding on hormone therapy requiring multiple evaluations, or for women who won't accept the risk of bleeding on hormone therapy, conjugated estrogens and bazedoxifene may be a sustainable option. However, any woman with abnormal bleeding should undergo prompt immediate evaluation.

A typical side effect of estrogen replacement therapy is breast tenderness. For women seeking vasomotor symptom treatment but who experience breast tenderness, this may be a deterrent from continuing hormone therapy. As shown in the SMART-1 and SMART-2 trials,[46] conjugated estrogens and bazedoxifene did not cause an increase in breast tenderness, which may enhance medication adherence.

Ideal candidates for conjugated estrogens plus bazedoxifene

This product could help postmenopausal women who have an intact uterus and are suffering with moderate to severe vasomotor symptoms and genitourinary syndrome of menopause who cannot tolerate the side effects of hormone therapy such as bleeding, bloating, or breast tenderness, or who prefer to take an estrogen but without a progestin. It is also ideal for women at higher risk of osteoporosis.

WHO SHOULD GET WHAT?

Not all postmenopausal women have vasomotor symptoms, genitourinary syndrome of menopause, or bone loss. For those who do, standard hormone therapy is an option.

For those who have symptoms and a lower threshold of side effects such as breast tenderness and vaginal bleeding, a combination of an estrogen plus an ERAA (eg, bazedoxifene) is an option.

For women who have no vasomotor symptoms but do have genitourinary syndrome of menopause and don't want local vaginal treatment, ospemifene is an option.

For women with no vasomotor symptoms but who have bone loss and increased risk of estrogen receptor-positive breast cancer, raloxifene is a good option.

Both premenopausal and postmenopausal women who are at increased risk for breast cancer should be considered for tamoxifen chemoprevention. Postmenopausal women with a uterus at increased risk for breast cancer should be considered for raloxifene, as it has no uterine effect. Raloxifene is *not* indicated in premenopausal women.

No woman at increased risk of venous thromboembolism is a candidate for ERAA treatment or for oral estrogen. However, the clinician has multiple options to improve quality of life and work productivity and reduce office visits of women at midlife, especially when they are individually assessed and treated.

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