SERMs revisited: Can they improve menopausal care?

While most clinicians are very familiar with older SERMS like tamoxifen and raloxifene, newer agents such as ospemifene and bazedoxifene offer other beneficial properties that can—and should—encourage their more widespread use to treat menopausal symptoms.

Steven R. Goldstein, MD, NCMP, CCD

Selective estrogen receptor modulators (SERMs) are unique synthetic compounds that bind to the estrogen receptor and initiate either estrogenic agonistic or antagonistic activity, depending on the confirmational change they produce on binding to the receptor. Many SERMs have come to market, others have not. Unlike estrogens, which regardless of dose or route of administration all carry risks as a boxed warning on the label, referred to as class labeling, various SERMs exert various effects in some tissues (uterus, vagina) while they have apparent class properties in others (bone, breast).

The first SERM, for all practical purposes, was tamoxifen (although clomiphene citrate is often considered a SERM). Tamoxifen was approved by the US Food and Drug Administration (FDA) in 1978 for the treatment of breast cancer and, subsequently, for breast cancer risk reduction. It became the most widely prescribed anticancer drug worldwide.

Subsequently, when data showed that tamoxifen could produce a small number of endometrial cancers and a larger number of endometrial polyps, there was renewed interest in raloxifene. In preclinical animal studies, raloxifene behaved differently than tamoxifen in the uterus. After clinical trials with raloxifene showed uterine safety, the drug was FDA approved for prevention of osteoporosis in 1997, for treatment of osteoporosis in 1999, and for breast cancer risk reduction in 2009. Most clinicians are familiar with these 2 SERMs, which have been in clinical use for more than 4 and 2 decades, respectively.

Ospemifene: A third-generation SERM and its indications

Hormone deficiency from menopause causes vulvovaginal and urogenital changes as well as a multitude of symptoms and signs, including vulvar and vaginal thinning, loss of rugal folds, diminished elasticity, increased pH, and most notably dyspareunia. The nomenclature that previously described vulvovaginal atrophy (VVA) has been expanded to include genitourinary syndrome of menopause (GSM). Unfortunately, many health care providers do not ask patients about GSM symptoms, and few women report...
Subsequent studies allowed for a broadened indication to include treatment of moderate to severe dryness due to menopause.11 The ospemifene label contains a boxed warning that states, “In the endometrium, [ospemifene] has estrogen agonistic effects.”12 Although ospemifene is not an estrogen (it’s a SERM), the label goes on to state, “There is an increased risk of endometrial cancer in a woman with a uterus who uses unopposed estrogens.” This statement caused The Medical Letter to initially suggest that patients who receive ospemifene also should receive a progestational agent—a suggestion they later retracted.13,14

To understand why the ospemifene labeling might be worded in such a way, one must review the data regarding the poorly named entity “weakly proliferative endometrium.” The package labeling combines any proliferative endometrium (“weakly” plus “actively” plus “disordered”) that occurred in the clinical trial. Thus, 86.1 per 1,000 of the ospemifene-treated patients (vs 13.3 per 1,000 of those taking placebo) had any one of the proliferative types. The problem is that “actively proliferative” endometrial glands will have mitotic activity in virtually every nucleus of the gland as well as abundant glandular progression (FIGURE 1), whereas “weakly proliferative” is actually closer to inactive or atrophic endometrium with an occasional mitotic figure in only a few nuclei of each gland (FIGURE 2).

In addition, at 1 year, the incidence of active proliferation with ospemifene was 1%.15 In examining the uterine safety study for raloxifene, both doses of that agent had an active proliferation incidence of 3% at 1 year.2 Furthermore, that study had an estrogen-only arm in which, at end point, the incidence of endometrial proliferation was 39%, and hyperplasia, 23%!5 It therefore is evident that, in the endometrium, ospemifene is much more like the SERM raloxifene than it is like estrogen. The American College of Obstetricians and Gynecologists (ACOG) endorsed ospemifene (level A evidence) as a first-line therapy for dyspareunia, noting absent endometrial stimulation.16

**FIGURE 1** Proliferative endometrium

A Hysterectomy specimen in the proliferative phase of a cycle that shows abundant endometrial thickness. B Higher-power view of proliferative endometrium; notice that virtually every nucleus is undergoing mitotic activity, hence the concept of “active proliferation.”

**FIGURE 2** Inactive or atrophic endometrium

A Hysterectomy specimen from a menopausal patient that shows inactive atrophic endometrium. The surface epithelium is a single layer of low cuboidal epithelium, and there are virtually no mitotic figures. B Hysterectomy specimen with a diagnosis of “weakly proliferative” endometrium. This is a misnomer, closer to inactive than true proliferation. Note: there is a very rare mitotic figure in any of the glandular nuclei.

their symptoms to their clinician.7 Furthermore, although low-dose local estrogens applied vaginally have been the mainstay of therapy for VVA/GSM, only 7% of symptomatic women use any pharmacologic agent,9 mainly because of fear of estrogens due to the class labeling mentioned above.

Ospemifene, a newer SERM, improved superficial cells and reduced parabasal cells as seen on a maturation index compared with placebo, according to results of multiple phase 3 clinical trials9,10; it also lowered vaginal pH and improved most bothersome symptoms (original studies were for dyspareunia). As a result, the FDA approved ospemifene for treatment of moderate to severe dyspareunia from VVA of menopause.
While women who need treatment for osteoporosis should not be treated primarily with ospemifene, women who use ospemifene for dyspareunia can expect positive activity on bone metabolism. The same beneficial direction of activity in breast could also be expected.

Ospemifene effects on breast and bone

Although ospemifene is approved for treatment of moderate to severe VVA/GSM, it has other SERM effects typical of its class. The label currently states that ospemifene “has not been adequately studied in women with breast cancer; therefore, it should not be used in women with known or suspected breast cancer.” We know that tamoxifen reduced breast cancer 49% in high-risk women in the Breast Cancer Prevention Trial (BCPT). We also know that in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial, raloxifene reduced breast cancer 77% in osteoporotic women, and in the Study of Tamoxifen and Raloxifene (STAR) trial, it performed virtually identically to tamoxifen in breast cancer prevention. Previous studies demonstrated that ospemifene inhibits breast cancer cell growth in vitro cultures as well as in animal studies and inhibits proliferation of human breast tissue epithelial cells, with breast effects similar to those seen with tamoxifen and raloxifene.

Thus, although one would not choose ospemifene as a primary treatment or risk-reducing agent for a patient with breast cancer, the direction of its activity in breast tissue is indisputable and is likely the reason that in the European Union (unlike in the United States) it is approved to treat dyspareunia from VVA/GSM in women with a prior history of breast cancer.

Virtually all SERMs have estrogen agonistic activity in bone. Bone is a dynamic organ, constantly being laid down and taken away (resorption). Estrogen and SERMs are potent antiresorptives in bone metabolism. Ospemifene effectively reduced bone loss in ovariectomized rats, with activity comparable to that of estradiol and raloxifene. Clinical data from 3 phase 1 or 2 clinical trials found that ospemifene 60 mg/day had a positive effect on biochemical markers for bone turnover in healthy postmenopausal women, with significant improvements relative to placebo and effects comparable to those of raloxifene. Actual fracture or bone mineral density (BMD) data in postmenopausal women are lacking, but there is a good correlation between biochemical markers for bone turnover and the occurrence of fracture.

Once again, women who need treatment for osteoporosis should not be treated primarily with ospemifene, but women who use ospemifene for dyspareunia can expect positive activity on bone metabolism.

Clinical application

Ospemifene is an oral SERM approved for the treatment of moderate to severe dyspareunia as well as dryness from VVA due to menopause. In addition, it appears one can safely surmise that the direction of ospemifene’s activity in bone and breast is virtually indisputable. The magnitude of that activity, however, is unstudied. Therefore, in selecting an agent to treat women with dyspareunia or vaginal dryness from VVA of menopause, determining any potential add-on benefit for that particular patient in either bone and/or breast is clinically appropriate.

The SERM bazedoxifene

A meta-analysis of 4 randomized, placebo-controlled trials showed that another SERM, bazedoxifene, can significantly decrease the incidence of vertebral fracture in postmenopausal women at follow-up of 3 and 7 years. That meta-analysis also confirmed the long-term favorable safety and tolerability of bazedoxifene, with no increase in adverse events, serious adverse events, myocardial infarction, stroke, venous thromboembolic events, or breast carcinoma in patients using bazedoxifene. However, bazedoxifene use did result in an increased incidence of hot flushes and leg cramps across 7 years. Bazedoxifene is available in a 20-mg dose for treatment of postmenopausal osteoporosis in Israel and a number of European Union countries.

Enter the concept of tissue-selective estrogen complex (TSEC)

Some postmenopausal women are extremely intolerant of any progestogen added to estrogen therapy to confer endometrial protection in those with a uterus. According to the...
According to results of a clinical trial of postmenopausal women, bazedoxifene is the only SERM shown to decrease endometrial thickness compared with placebo. This is the basis for thinking that perhaps a SERM like bazedoxifene, instead of a progestogen, could be used to confer endometrial protection.

A further consideration comes out of the evaluation of data derived from the 2 arms of the Women’s Health Initiative (WHI). In the arm that combined conjugated estrogen with medroxyprogesterone acetate through 11.3 years, there was a 25% increase in the incidence of invasive breast cancer, which was statistically significant. Contrast that with the arm in hysterectomized women who received only conjugated estrogen (often inaccurately referred to as the “estrogen only” arm of the WHI). In that study arm, the relative risk of invasive breast cancer was reduced 23%, also statistically significant. Thus, the culprit in the breast cancer incidence difference in these 2 arms appears to be the addition of the progestogen medroxyprogesterone acetate.

Since the progestogen was used only for endometrial protection, could such endometrial protection be provided by a SERM like bazedoxifene? Preclinical trials showed that a combination of bazedoxifene and conjugated estrogen (in various estrogen doses) resulted in uterine wet weight in an ovariectomized rat model that was no different than that with placebo.

In terms of effects on breast, preclinical models showed that conjugated estrogen use resulted in less mammary duct elongation and end bud proliferation than estradiol by itself, and that the combination of conjugated estrogen and bazedoxifene resulted in mammary duct elongation and end bud proliferation that was similar to that in the ovariectomized animals and considerably less than a combination of estradiol with bazedoxifene.

Five phase 3 studies known as the SMART (Selective estrogens, Menopause, And Response to Therapy) trials were then conducted. Collectively, these studies examined the frequency and severity of vasomotor symptoms (VMS), BMD, bone turnover markers, lipid profiles, sleep, quality of life, breast density, and endometrial safety with conjugated estrogen/bazedoxifene treatment. Based on these trials with more than 7,500 women, in 2013 the FDA approved a compound of conjugated estrogen 0.45 mg and bazedoxifene 20 mg (Duavee in the United States and Duvive outside the United States).

The incidence of endometrial hyperplasia at 12 months was consistently less than 1%, which is the FDA guidance for approval of hormone therapies. The incidence of bleeding or spotting with conjugated estrogen/bazedoxifene (Figure 3, page 34) in each 4-week interval over 12 months mirrored that of placebo and ranged from 3.9% in the first 4-week interval to 1.7% in the last 4 weeks, compared with conjugated estrogen 0.45 mg/medroxyprogesterone acetate 1.5 mg, which had a 20.8% incidence of bleeding or spotting in the first 4-week interval and was still at an 8.8% incidence in the last 4 weeks. This is extremely relevant in clinical practice. There was no difference from placebo in breast cancer incidence, breast pain or tenderness, abnormal mammograms, or breast density at month 12.

In terms of frequency of VMS, there was a 74% reduction from baseline at 12 weeks compared with placebo (P<.001), as well as a 37% reduction in the VMS severity score (P<.001). Statistically significant improvements occurred in lumbar spine and hip BMD (P<.01) for women who were 1 to 5 years since menopause as well as for those who were more than 5 years since menopause.

Packaging issue puts TSEC on back order

In May 2020, Pfizer voluntarily recalled its conjugated estrogen/bazedoxifene product after identifying a “flaw in the drug’s foil laminate pouch that introduced oxygen and lowered the dissolution rate of active pharmaceutical ingredient bazedoxifene acetate.” The manufacturer then wrote a letter to health care professionals in September 2021 stating, “Duavee continues to be out of stock due to an unexpected and complex packaging issue, resulting in manufacturing delays. This has nothing to do with the safety
The combination of conjugated estrogen/bazedoxifene, when it is once again clinically available, may well provide a new paradigm of hormone therapy that is progestogen free and has a benefit/risk ratio that tilts toward its benefits.

Other TSECs?
The conjugated estrogen/bazedoxifene combination is the first FDA-approved TSEC. Other attempts have been made to achieve similar results with combined raloxifene and 17β-estradiol. That study was meant to be a 52-week treatment trial with either raloxifene 60 mg alone or in combination with 17β-estradiol 1 mg per day to assess effects on VMS and endometrial safety. The study was stopped early because signs of endometrial stimulation were observed in the raloxifene plus estradiol group. Thus, one cannot combine any estrogen with any SERM and assume similar results.

Clinical application
The combination of conjugated estrogen/bazedoxifene is approved for treatment of VMS of menopause as well as prevention of osteoporosis. Although it is not approved for treatment of moderate to severe VVA, in younger women who initiate treatment it should prevent the development of moderate to severe symptoms of VVA.

Finally, this drug should be protective of the breast. Conjugated estrogen has clearly shown a reduction in breast cancer incidence and mortality, and bazedoxifene is a SERM. All SERMs have, as a class effect, been shown to be antiestrogens in breast tissue, and abundant preclinical data point in that direction.

This combination of conjugated estrogen/bazedoxifene, when it is once again clinically available, may well provide a new paradigm of hormone therapy that is progestogen free and has a benefit/risk ratio that tilts toward its benefits.

Potential for wider therapeutic benefits
Newer SERMs like ospemifene, approved for treatment of VVA/GSM, and bazedoxifene/conjugated estrogen combination, approved for treatment of VMS and prevention of bone loss, have other beneficial properties that can and should result in their more widespread use.
References


2. Goldstein SR. Not all SERMs are created equal. Menopause. 2006;13:325-327.


