

Selective Estrogen Receptor Modulators

From bench, to bedside, and back again

► Julie M. Hall, PhD, and Donald P. McDonnell, PhD

When the search began for estrogen receptor (ER) ligands that could treat and prevent osteoporosis while reducing the risk and incidence of gynecologic cancers, it seemed unlikely that a single drug would exhibit clinically useful selectivity. In the meantime, it has become clear that the ER does not function in the same manner in all cells. This observation led to the development of a new class of molecules, selective estrogen receptor modulators (SERMs), which manifest estrogenic activities in a cell-selective manner.

As effective as the current SERMs are for conditions associated with long-term estrogen deprivation, new SERMs with more clinically useful

activities are likely to emerge in the near future. The science that is driving this quest for the perfect SERM will be discussed in detail below.

Why target estrogen action in a tissue-specific manner?

Estrogen is a key regulator of the processes involved in the growth, differentiation, and function of a wide variety of tissues. Estrogen is important in sustaining overall health: as evidence, consider that estrogen deficiency in postmenopausal women has adverse effects that can be alleviated with estrogen therapy (ET).

The beneficial effects of ET on menopausal symptoms have been well established. However, estrogen can facilitate the growth of breast tumors in some circumstances, and unopposed estrogen is an established risk factor for uterine cancer. Thus there is a clear

unmet medical need for drugs which, acting through the ER, manifest estrogenic activities in a tissue- or process-selective manner.

Key molecular mechanisms in ER pharmacology

The molecular pharmacology of estrogens and SERMs is complex. It is clear, however, that all of these compounds mediate their biological activities through 2 intracellular ERs (ER α and ER β), which function as ligand-inducible transcription factors in target cell nuclei. These receptors are ligand-activated transcription factors that, when activated, facilitate an up-regulation or down-regulation of specific genes at the messenger RNA (mRNA) level. The mRNAs are then translated into proteins that function within the cells of hormone-responsive tissues to regulate proliferation, differentiation, and homeostasis.¹

Classic receptor theory: On and off

Ligand binding initiates ER signaling. According to classic receptor theory, agonists (such as endogenous estrogens) act as molecular switches, converting ERs from an inactive to an active form. Anti-estrogens—synthetic compounds developed to oppose the action of the natural hormone—were

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FROM THE EDITOR



WHAT WOULD BE THE PERFECT

selective estrogen receptor modulator (SERM) for a menopausal woman? First, it would have to be effective at symptom relief—and function like estrogen. Second, it would have to antagonize estrogen action in the uterus and breast and function as an anti-estrogen. Oh, and it also needs to be osteoprotective! It would probably also be beneficial if it did not induce liver protein synthesis, thereby avoiding some of the clotting complications of estrogen therapy. And, of course, it should prevent vaginal atrophy. An extra bonus would be maintaining the vasodilatory effects of estradiol on the coronary vasculature.

Is it possible to achieve this perfect blend with a single compound? This issue of *Menopausal Medicine* features 3 articles that provide the answers: yes, maybe, and no. Drs Hall and McDonnell provide the scientific background that describes the search for this perfect SERM. They are so inspiring, it makes you feel as if this seemingly impossible dream can be realized. Dr Clark provides an overview of SERMs that are available or in development, giving a practical overview of what's out there and providing us with a definite “maybe” that a near-perfect SERM may be on the way. Finally, Dr Pickar describes a different strategy: instead of searching for the perfect SERM, he shows how an existing SERM can be complemented with estrogen to produce the desired effects. I hope you find this issue as enjoyable and educational as I did!

Nanette F. Santoro, MD

thought to competitively inhibit agonist binding and, in doing so, were able to lock the receptor in an inactive state. Thus, it was considered that when corrected for affinity, all agonists were functionally indistinguishable and, likewise, antagonists were qualitatively similar.

The “tamoxifen paradox”

The clinical profiles of SERMs, such as tamoxifen and raloxifene, indicate that the classic model is oversimplified.² Studies of patients who received tamoxifen as adjuvant therapy for estrogen-dependent breast tumors provided some of the first evidence that these “anti-estrogens” do more than freeze ERs in a latent state. Strikingly, while tamoxifen blocked the actions of estrogen in breast cancer cells, it was shown to function as an agonist in the bone and uterus, mimicking the actions of estrogen.³ The observation that tamoxifen displays tissue-specific agonist/antagonist activities was inconsistent with the classic definition of antagonist action and, furthermore, suggested that this compound may alter ERs in such a way that the liganded receptors could be recognized differently in distinct cell types.

These early findings led to reclassification of these agents, additional research, and new indications. Tamoxifen, originally considered an “anti-estrogen,” was reclassified as a SERM to reflect its complex pharmacologic activity. Raloxifene, another SERM, has been approved for the prevention and treatment of osteoporosis. And both have been approved for use as preventatives (early treatment) in patients at high risk of breast cancer.

Mediation of diverse responses

Two major discoveries in the past 10 years have helped us understand the molecular basis of SERM action. The first was that ERs do not merely exist in an on or off form, but rather, the overall conformation of the receptors in the presence of different ligands is not identical. The second discovery

was that of cofactors, proteins that are required for ER signaling but whose interactions with the receptor are influenced by receptor conformation. These proteins—termed coactivators and corepressors—bind the liganded ER and enhance or decrease ER-mediated transcription of target genes, respectively.¹

The ability of different ER ligands to induce different conformations of the receptors influences their ability to interact with coactivators and corepressors. We now know that different ligands induce unique structural changes in ERs and that this results in differential recruitment of coactivators and corepressors, leading to diversity in biological response. This provides a mechanism by which different ligands, acting through the same receptor, can mediate unique biological effects. For example, estrogen induces coactivator recruitment to ERs, whereas when bound to the pure anti-estrogen ICI 182780 (fulvestrant), the conformation of the ERs is compatible with corepressor (but not coactivator) binding. Correspondingly, estrogen is a full agonist of ER, whereas ICI functions as a pure antagonist on the receptor. In contrast, when bound to the SERM tamoxifen (which displays both agonist and antagonist activities), the ER is capable of interacting with either coactivators or corepressors. Therefore, it is likely that ligand-induced changes in receptor shape and the relative expression of functionally distinct coactivators or corepressors in different target cells are sufficient to explain the tissue-specific agonist/antagonist activities of tamoxifen and other SERMs. Thus, it will be important to identify the cofactor proteins present in different ER target cells in order to allow mechanism-based screening for new tissue-targeted SERMs.^{1,2,4}

Clinical implications of mechanistic differences

ER “antagonists” comprise 2 broad categories: pure anti-estrogens and SERMs, which are further divided by generation. **TABLE 1** presents a summary of the different biological functions

associated with some of the known ER-targeted pharmaceutical agents.

Pure anti-estrogens. Pure anti-estrogens (type I), represented by ICI 182780, oppose estrogen and ER (α and β) activity in all tissues. These compounds differ considerably from SERMs in their mechanism of action and effect a more complete blockade of estrogen signaling in target cells. Specifically, these compounds induce conformations in the ERs that are permissive to corepressor (and not coactivator) association and that also lead to a proteasome-mediated decrease in cellular ER α protein. The latter observation resulted in the renaming of some members of this drug class as selective estrogen receptor downregulators (SERDs).

Type I anti-estrogens are very useful in cancer therapy because they block the mitogenic activities of estrogen in both the breast and reproductive system. However, since ICI 182780 lacks the beneficial agonist effects of estrogen in the bone, cardiovascular system, and central nervous system, the clinical use of this compound is currently limited to patients with advanced breast cancer that has become resistant to tamoxifen.

First-generation SERMs. Tamoxifen (Nolvadex) belongs to the first generation of SERMs, having been used clinically since 1971. In addition to maintaining bone mineral density (BMD) in postmenopausal women, tamoxifen decreases low-density lipoprotein cholesterol (LDL-C) levels and antagonizes estradiol-stimulated growth in the breast. Until recently, this latter effect of tamoxifen made it a standard endocrine therapy for ER-positive breast cancers in both the neoadjuvant and postoperative adjuvant settings and a first-line therapy for the treatment of pre- and postmenopausal women with estrogen-responsive advanced (stage IV) breast cancer.

A series of clinical studies has also demonstrated the efficacy of tamoxifen as a chemopreventative agent. In the Breast Cancer Prevention Trial (BCPT), which involved 13,388 pre- and

TABLE 1

Biological Activities of ER Ligands in Selected Target Tissues

	Bone	Breast	Cardiovasculature	Uterus
Estrogen	+++	+++	+++	+++
ICI 182780	-	-	-	-
Tamoxifen	+	-	+/-	+
Raloxifene	+	-	+/-	-
Lasofloxifene	++	-	+	+

"+" , agonist activity; "-" , antagonist activity; ER, estrogen receptor.

postmenopausal women, tamoxifen dramatically reduced the risk of both in situ and locally invasive breast cancers by approximately 50%.^{5,6}

A significant proportion of women develop "tamoxifen resistance" after 5 years of anti-estrogen therapy. This term refers to the phenomenon by which certain breast cancers alter their biology and recognize the compound as an agonist for growth. Further, it appears that most tamoxifen-resistant tumors possess or are capable of developing cross-resistance to structurally related compounds such as toremifene, droloxifene, and idoxifene. Thus, mechanistically distinct pharmaceuticals such as pure anti-estrogens and aromatase inhibitors are commonly used as second-line therapies for breast cancer.^{5,7}

Although tamoxifen is safe and well tolerated, it is not suitable for the treatment of the climacteric patient. Most notably, it induces hot flashes in about 40% of women.⁸ Of greatest concern, perhaps, are its uterotrophic effects—clinical trials have found a clear association between tamoxifen and endometrial cancer. In the BCPT, the risk of invasive endometrial cancer was 2.5 times greater with tamoxifen. These findings of a significant benefit of tamoxifen in breast cancer tempered by serious risk in the uterus have been verified in other trials. Regardless, tamoxifen has been a prototype for other SERMs with improved therapeutic profiles, as will be discussed below.⁹

Second-generation SERMs. Second-generation SERMs were developed

with the objective of obtaining ER-targeted pharmaceuticals that do not have the uterotrophic effects of tamoxifen. The most well-characterized second-generation SERM is raloxifene (Evista). This compound functions as an agonist in bone and the cardiovascular system but acts as a pure antagonist in the breast and uterus (TABLE 1). Mechanistic studies showed that raloxifene induces a unique conformational state of the ER that is thought to utilize distinct cofactor complexes, compared with tamoxifen and other ER ligands.^{2,10}

Raloxifene has higher efficacy in maintaining BMD compared with first-generation SERMs, which is likely due to the unique manner in which it alters the ER structure. Indeed, raloxifene is now approved for both the treatment and prevention of osteoporosis.

More recently, raloxifene has emerged as a promising breast cancer chemopreventative. The Multiple Outcomes of Raloxifene Evaluation (MORE) trial of 7705 postmenopausal women from 25 countries evaluated whether women with osteoporosis taking raloxifene have a lower risk of invasive breast cancer. Raloxifene was found to decrease the risk of all ER-positive breast cancers by 90% and invasive breast cancers by 72%.¹¹

As a result of these findings, the National Cancer Institute sponsored the Study of Tamoxifen and Raloxifene (STAR) trial, which directly compared the effects of tamoxifen and raloxifene in postmenopausal women at higher-than-average risk of breast cancer. The

positive results of this trial led a recent US Food and Drug Administration (FDA) advisory panel to recommend approval of this drug as a breast cancer preventative in high-risk patients. Interestingly, this trial indicated that tamoxifen and raloxifene did not behave in the same manner with respect to breast cancer prevention. Specifically, whereas raloxifene was found to work as well as tamoxifen in reducing risk by about 50% for invasive breast cancer in postmenopausal women, tamoxifen was also found to reduce the incidence of both lobular carcinoma in situ (LCIS) and ductal carcinoma in situ (DCIS) by 50%. On the upside, participants in STAR who were assigned to take raloxifene had 36% fewer uterine cancers than did women assigned to take tamoxifen, reflecting differences in the ability of the 2 compounds to stimulate growth in the endometrium. In fact, the generally positive effects of raloxifene in the uterus are likely to make it the agent of choice for use as a chemopreventative in postmenopausal women at high risk of breast cancer.^{5,6}

Third-generation SERMs. The goal of developing a third-generation of SERMs was to create pharmaceuticals that are structurally distinct from first- and second-generation agents of this class. These SERMs should possess the favorable qualities of raloxifene but should be more effective in enhancing BMD and in decreasing serum LDL-C levels, and should have a reduced propensity to induce hot flashes.

Two of the most advanced third-generation SERMs, bazedoxifene and lasofloxifene, have completed registration trials. The initial New Drug Application (NDA) for lasofloxifene received an unapprovable letter from the FDA. The ongoing Postmenopausal Evaluation and Risk Reduction with Lasofloxifene (PEARL) trial should resolve this issue. The second of this generation of SERMs, bazedoxifene, has recently received an approvable letter from the FDA and should be commercially available soon.

Both of these drugs have improved pharmaceutical properties and differ mechanistically from each other and from existing SERMs. How this translates into clinical benefit remains to be seen. Of note, however, are the observations from a 2-year randomized, double-blind treatment study in postmenopausal women. Lasofoxifene was found to be similar to raloxifene with regard to maintaining BMD in the hip; yet in the lumbar spine, lasofoxifene increased BMD by 2%. Comparatively, there was no mean improvement in spine BMD in patients assigned to raloxifene and a 2% decrease in density in patients assigned to placebo.

Bazedoxifene exhibited an improved vasomotor profile in phase 3 clinical trials compared with tamoxifen or raloxifene.^{12,13} However, the clinical significance of any of the differences between the second- and third-generation SERMs remains to be determined.

Fourth-generation SERMs. A list of desired properties for a fourth generation of SERMs was recently presented (TABLE 2). In general, future SERMs must oppose endogenous hormone action in the breast and reproductive system while displaying salutary estrogenic effects in the cardiovascular, bone, and central nervous system. Specifically, these agents must relieve hot flashes and both lower LDL-C and raise high-density lipoprotein cholesterol levels. Fourth-generation SERMs should possess superior bioavailability compared with existing ER modulators and should have additional indications in men for bone protection and cardioprotection. The science that will drive the search for drugs of this class is discussed below.

A new paradigm: Tissue selective estrogen complex

The tissue selective estrogen complex (TSEC) is a new concept that has recently received some attention and is likely to be available in the near future. The most advanced drug in this class, Aprela, is a combined therapy that

TABLE 2

Criteria for Fourth-Generation SERMs

1. Antagonize estrogen action in the breast; reduce breast cancer risk
2. Display no uterotrophic activity
3. Protect bone to the full extent of estrogen
4. Possess better cardiovascular and central nervous system profiles than current SERMs
5. Possess superior bioavailability than current SERMs
6. Offer potential benefits for men in protection against age-related bone loss and increases in cholesterol levels, without displaying estrogenic proliferative effects in the prostate

SERMs, selective estrogen receptor modulators.

partners the third-generation SERM bazedoxifene with conjugated estrogens. A 2-year study has demonstrated efficacy of TSEC medications in offering the benefits of estrogen while minimizing the most concerning side effects and risks of traditional ET. The TSEC provides a blend of both tissue selectivity and favorable physiologic profiles, including increases in BMD superior to those seen with SERMs, and substantial improvement in hot flashes and genitourinary atrophy, without the common side effects of hormonal therapy such as endometrial hyperplasia, bleeding, and breast pain. Interestingly, the outcome is not just that of one medication added to the other but, rather, a brand new profile, as for example, no adverse cardiovascular events have been reported.¹⁴ The mechanism(s) underlying the complex pharmacologic effect of the TSECs remain to be determined. The NDA submission for this new drug is expected in the near future, and it will be interesting to see if it is perceived in the marketplace as the “perfect” menopausal therapy.

The future of SERMs: Mechanism-based drug discovery

In the future, classic drug discovery approaches that rely primarily on ligand-receptor binding assays are unlikely to identify agents that provide favorable biology in most or all estrogen target tissues. Rather, efforts focused toward understanding the molecular determinants of ER pharmacology may lead

to incorporation of functional assays as primary drug screens. This “mechanism-based” approach to drug discovery should, in theory, permit identification of novel classes of modulators.^{4,15} Three mechanism-based approaches to new SERM discovery that are currently being put into practice are described in brief below: Cofactoromics, ER subtype-selective modulators, and pathway-targeted SERMs.

Cofactoromics. More than 50 co-activators and corepressors that bind the ER and alter its activities have been identified. The relative and absolute expression of these factors, however, can differ significantly among different cell and tissue types. Thus, a new type of mechanism-based approach to SERM discovery involves screening for compounds that facilitate particular ER-cofactor interactions in specific tissues.⁴ Clearly, this approach will require an understanding of the expression levels and biological roles of relevant ER cofactors in estrogen target tissues, a tremendous task in which our laboratory and others are currently engaged.⁴

ER subtype-selective modulators. Estrogens manifest their biological effects through 2 distinct receptors, ER α and ER β . Both ERs possess similar affinities for estrogens and most of the currently available SERMs; however, they display significant sequence and structural differences in their ligand-binding domains and have dissimilar biological activities. This observation, together with the apparent selective tissue distribution of the

2 ERs, suggest that it might be possible to pharmacologically separate estrogen biology by targeting a single ER.

To date, in vivo studies have been limited to animals, but these agents have sufficient efficacy to prompt exploration of the clinical utility of ER β -selective agonists in inflammatory diseases, including arthritis, endometriosis, inflammatory bowel disease, and sepsis.¹⁶

Pathway-targeted SERMs. Not only do estrogen-activated ERs bind to their specific target gene promoters and subsequently activate gene transcription, but ERs can manifest cellular actions independent of DNA binding by associating with other transcription factors (such as AP-1, Sp1, progesterone receptor, and others) and interfering with their activities.¹⁵ If specific biological outcomes of estrogens could be ascribed to a particular ER-transcription factor pair, it might be possible to develop agents that target the relevant interaction in order to achieve process selectivity and “pathway-targeted SERMs.”

This mechanism has been explored with regard to one alternate pathway of ER action that provides for the anti-inflammatory actions of estrogens. Chadwick

et al recently identified a pathway-selective ER ligand, WAY-169916. This agent, devoid of classic estrogenic activity, can inhibit NF- κ B activity and function as a potent anti-inflammatory agent in animal models of inflammatory bowel disease.¹⁷ The clinical utility of this class of compound remains to be determined.

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SERMs in practice: An idea whose time has come

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When the results of large, randomized trials cast a shadow on the use of hormone therapy (HT), particularly for secondary

prevention of cardiovascular disease,¹⁻³ some research shifted to finding a selective estrogen receptor modulator (SERM) that might be a better alternative. Indeed, a good profile for SERMs would include a positive effect on bone and climacteric symptoms, without negative effects on the breast, endometrium, cardiovascular system, and central nervous system (CNS) function. An ideal agent would have a positive effect

on all of those tissues and functions.

This article reviews the data on the effects of various SERMs on bone and cardiovascular health, uterine and breast stimulation, climacteric symptoms, and CNS function. The SERMs considered here include the 2 approved agents, raloxifene and tamoxifen, and 2 promising newer SERMs, ospemifene and bazedoxifene (TABLE 1).

The SERMs that are not discussed

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TABLE 1

Clinical Use of SERMs

	Raloxifene	Tamoxifen	Ospemifene	Bazedoxifene
Approved indication	Osteoporosis	Breast cancer	None currently	None currently
Probable or possible future use	Breast cancer	Unknown	Vaginal atrophy Osteoporosis	Osteoporosis Breast cancer

here—idoxifene, droloxifene, levomefloxi-fene, arzoxifene, acolbifene, and lasofoxi-fene—have less clinical impact or increased side effects (or both) and are reviewed elsewhere.⁴

Bone health

Various SERMs have positive influences on bone density and fracture rates.^{5,6} The efficacy of SERMs in this regard is evaluated using markers of bone turnover as a measure of bone health and density. This implies better results for fractures, but most of the evaluations discussed here do not include data on fracture rates.

The formation of bone is evaluated with tests for alkaline phosphatase levels (and bone-specific levels), osteocalcin levels, and type I procollagen pro-peptide levels involving the C-terminal and N-terminal ends (called PICP and PINP, respectively); serum markers are generally used.⁶

Bone resorption is evaluated with urine and serum tests. Urine tests include hydroxyproline, deoxypyridi-noline, pyridinoline, and N- and C-telo-peptide (NTX and CTX) levels. Serum tests include levels of NTX, CTX, matrix metalloproteinase (MMP), carboxy-terminal telopeptide of type 1 collagen (ICTP), and the vesicle enzyme tartrate-resistant acid phosphatase (TRAP).⁶

Raloxifene. As the only approved SERM for the treatment of osteoporosis in postmenopausal women, raloxifene is the best-studied SERM for this indi-cation. It binds well to both estrogen receptors (ER α and ER β), does not sig-nificantly stimulate the endometrium, and appears to be active against breast cancer.⁴⁻⁸ Climacteric symptoms are not alleviated by the use of raloxifene, and the risk of thrombosis is similar to the

risk with estrogen.⁴⁻⁸

In several studies, use of raloxifene significantly increased bone mineral density (BMD).⁹⁻¹² Overall, these studies showed that vertebral fractures are re-duced by approximately 40%. No stud-ies have documented decreased fracture rates at nonvertebral sites. However, structural assessment of bone at the hip using biopsy has shown that BMD and bone strength do increase with raloxi-fene use, indicating that there may be a decrease in fractures that has not yet been documented.¹²

Additionally, raloxifene may de-crease bone turnover, compared with placebo, in postmenopausal wom-en.^{11,13,14} Several authors have reported that the bone turnover markers alkaline phosphatase, osteocalcin, pyridinoline, NTX, CTX, and PINP are all altered with raloxifene use.

Raloxifene adds to the bone-spar-ing effects of calcium and vitamin D₃ and monofluorophosphate therapy.^{15,16} Raloxifene also protects against bone loss associated with exercise-induced weight loss.¹⁷ The effects of raloxifene appear to be modulated through estro-gen receptors that influence osteoblast function.¹⁸

Taken together, these data sup-port significant improvement in BMD, with reduced vertebral fracture risk, and modifications in bone turnover fa-voring increased BMD (including non-vertebral sites) with raloxifene use in osteoporotic postmenopausal women.

Tamoxifen. Tamoxifen has been ap-proved for the treatment of breast can-cer; therefore, fewer data exist regarding the effect of tamoxifen on bone health. However, increased BMD and decreased fractures have been documented in

breast cancer patients treated with tamoxifen.^{19,20}

Ospemifene. Ospemifene is under investigation and has not obtained ap-proval for any indication, although it shows promise for treatment of vagi-nal atrophy.²¹ Its bone turnover effects are similar to those of raloxifene and, similar to raloxifene, its mechanism seems to be through an estrogen-mediated influence on osteoblastic functions.^{14,18} Further testing is need-ed to analyze ospemifene's influence on bone health and to see if the effect is significant enough to consider it for treatment for osteoporosis.

Bazedoxifene. Bazedoxifene is also under investigation and shows promise for treatment of osteoporosis. In stud-ies, bone turnover decreased by ap-proximately 25%, with decreases noted in CTX, NTX, PINP, PICP, and alkaline phosphatase levels.²¹⁻²³ This decrease in bone turnover is similar to but slightly less than that seen with raloxifene. Increases in bone density have been shown in animal studies but must be fully evaluated in humans.²²

Cardiovascular health

Several end points are used to evalu-ate the cardiovascular effects of HT or SERMs, including lipid parameters, clinical events, inflammatory or other markers of cardiovascular disease, and vascular functional changes.^{1-4,9} Actual cardiovascular events are relatively rare among newly postmenopausal women, so using these clinical end points poses challenges in designing studies of adequate power within lo-gistic and financial constraints.

Recent reports show that HT has less cardiovascular impact when initi-ated close to menopause, unlike the early reported results.^{3,24} This suggests that a temporal relationship is of great impor-tance. Finally, the effects of different dos-ages, compounds, and routes of admin-istration are also factors to consider.

Given this large set of parameters, it is difficult to assess and effectively

TABLE 2

Summary of SERM Effects

	Raloxifene	Tamoxifen	Ospemifene
Bone health	<ul style="list-style-type: none"> • Increased BMD • Improved bone turnover • Decreased vertebral fractures 	In breast cancer patients ^{19,20} : <ul style="list-style-type: none"> • Increased BMD • Decreased fractures 	<ul style="list-style-type: none"> • Improved bone turnover^{14,18}
CV health	<ul style="list-style-type: none"> • Improved lipid profile • Decreased fibrinogen, antithrombin III • No clinical outcomes data^{9,13,25-28} 	<ul style="list-style-type: none"> • Improved lipid profile • Possibly decreased myocardial infarction rate³⁰⁻³⁶ 	<ul style="list-style-type: none"> • Improved markers of cardiovascular health?^{21,37-39}
Other	<ul style="list-style-type: none"> • Poor treatment of climacteric symptoms (may worsen) • Increased thromboembolic events • Increased rates of stroke • Little effect on endometrium^{4,7,8} 	<ul style="list-style-type: none"> • Increased rates of endometrial cancer • Increased incidence of polyps • Increased thromboembolic events^{4,7,29,30,35,36} 	<ul style="list-style-type: none"> • Few data • Little effect on endometrium • May improve climacteric symptoms^{21,37-39}

BMD, bone mineral density; CV, cardiovascular; SERMs, selective estrogen receptor modulators.

summarize the impact of a treatment on cardiovascular function in postmenopausal women. Despite these challenges, we will try to unravel the data available for these SERMs. In all cases, further evaluation is needed.

Raloxifene. In various studies, use of raloxifene has consistently shown to be associated with a modest decrease in total cholesterol, low-density lipoprotein cholesterol (LDL-C), lipoprotein(a) (Lp[a]), fibrinogen, and homocysteine levels, as well as a significant increase in high-density lipoprotein cholesterol (HDL-C) levels.^{9,13,25,26} These results suggest a decrease in cardiovascular risk, but importantly, no studies have shown a decrease in clinical end points. Raloxifene has not been shown to have a negative influence on echocardiographic evaluations or on plasminogen activator inhibitor-1 or C-reactive protein (CRP) levels.^{9,13,25-27}

My own evaluation showed that raloxifene has a positive effect on vasodilation similar to that of estrogen through a direct endothelial mechanism (unpublished data). Additionally, raloxifene is associated with an increased risk of venous thrombotic disease and stroke, similar to that seen with estrogen.²⁸

Overall, these data suggest a probable neutral influence of raloxifene on

cardiovascular health, but further study is needed to support this statement more concretely.

Tamoxifen. Observations that women in breast cancer trials who were treated with tamoxifen had decreased rates of myocardial infarction (MI) fueled studies of its effect on various cardiovascular end points.^{29,30}

Further evaluation has shown that tamoxifen is associated with a decrease in total cholesterol, LDL-C, CRP, homocysteine, Lp(a), and fibrinogen levels. No consistent pattern has been seen with HDL-C and triglyceride levels.^{31,32} Taken together, these data support an improved or neutral cardiovascular profile and decreased rate of MI.

Decreased intimal thickness may also play a positive role in cardiovascular outcomes. Tamoxifen use has been shown to decrease intimal thickness as well as increase flow-mediated dilation.³³ My own data suggest that tamoxifen has a minimal effect directly on the vascular endothelium, similar to that of placebo.³⁴ Unfortunately, a consistent increase in thrombotic disease has also been documented, with a risk similar to that seen with estrogens.^{35,36}

Similar to raloxifene, these data support a positive or neutral effect overall on cardiovascular risk for patients taking

this compound, but further evaluation is needed.

Ospemifene. Cardiovascular evaluations of ospemifene have been limited to nonclinical end points at this time. Decreases have been documented in total cholesterol, LDL-C, and fibrinogen levels, and increases in HDL-C and triglycerides have been noted. Neutral effects on homocysteine levels were also noted.^{21,37-39}

These data are too preliminary to draw conclusions about ospemifene's risk profile for postmenopausal women, but they do suggest that further evaluation may indeed yield a positive cardiovascular effect, and they do not suggest a negative effect.

Bazedoxifene. A very preliminary study of bazedoxifene noted a decrease in both LDL-C and fibrinogen levels.⁴⁰ Although these initial data suggest a positive influence, the current data set is far too small to reliably assess the impact that this SERM may have on cardiovascular function and risk.

Uterine and breast stimulation

Raloxifene. Raloxifene minimally stimulates the endometrial lining and has a negative influence on breast tissue growth. Trials of its use against breast cancer have shown positive results thus far.^{4,7,8}

Tamoxifen. Tamoxifen is one of the cornerstone treatments for breast cancer and is approved for this indication. However, tamoxifen stimulates the uterine lining, causing an increased incidence of uterine cancer and polyps, which has somewhat limited the drug's utility.^{4,7,29,30,35,36}

Ospemifene. Few data exist in the literature on breast stimulation with ospemifene. Minimal endometrial stimulation has been documented, similar to that of raloxifene.^{37,39}

Bazedoxifene. Evaluation in MCF-7 breast cancer cell lines suggests a negative effect of bazedoxifene on the growth of breast cancer tissue; human trials have not been performed. In both animal and human

studies, the influence of bazedoxifene on the endometrium seems negligible and it may cause beneficial thinning of the lining.²²

Climacteric symptoms

Raloxifene and tamoxifene may actually worsen hot flushing.^{4,41} Mixed data have been reported on ospemifene's effect on vasomotor symptoms, with neutral to beneficial effects seen.³⁹ Little has been reported on climacteric symptoms with bazedoxifene use.

CNS influence

Raloxifene has not been evaluated for clinical outcomes such as cognitive function, but an increase in stroke has been reported with the use of this compound.²⁸ Little has been reported on the incidence of CNS problems with the use of tamoxifen, ospemifene, or bazedoxifene.

Summary

The variety of responses is a hallmark of SERMs (TABLE 2). The differential tissue responses show that their mechanism of action is variable, relating to the interaction with the receptor and subsequent modifications of transcription ability within different tissues.

Currently, the perfect SERM does not exist, but continued work in this area will undoubtedly yield improved compounds. With a promising future, the perfect SERM may someday be available to optimize postmenopausal hormone therapy.

Disclosure

Dr Clark has nothing to disclose.

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Tissue selective estrogen complex: A new paradigm for menopausal therapy

► James H. Pickar, MD

Our knowledge of estrogen receptor action has developed considerably from the “lock and key” model of 40 years ago. Anti-estrogens were later called selective estrogen receptor modulators (SERMs) when it was recognized that, although working through the estrogen receptor, they possessed both agonist and antagonist activity. Estrogens were also shown to have different activity profiles, even when corrected for receptor binding affinity. Hence, it became important to understand how estrogens and SERMs, working through the same receptor, could have similar effects in one tissue and different effects in other tissues. The fact that there were 2 estrogen receptors (ER α and ER β) with their own distribution was only part of the story. The activity and distribution of coactivators and corepressors and other transcription-related events also helped to explain how conformational changes of the estrogen receptor, induced by specific receptor-ligand interactions, played a role in the tissue-related agonist/antagonist profiles of estrogens and SERMs.

The understanding that estrogens and SERMs exist on a continuum of tissue-specific, estrogen receptor-mediated agonist/antagonist activity has led to the evaluation of estrogen/SERM pairings in treating the effects of menopausal estrogen deficiency. Although hormone therapy (HT) has been proven highly effective for treating vasomotor symptoms and vulvovaginal atrophy associated with menopause and preventing postmenopausal osteoporosis,

the clinical profile of some estrogen/SERM pairings may enhance tolerability while maintaining the efficacy seen with HT. In particular, amenorrhea rates and an incidence of breast tenderness that are similar to placebo would be an improvement. This article reviews the phase 2 clinical data for a new paradigm for menopausal treatment—the tissue selective estrogen complex (TSEC), the next-generation menopausal therapy.

Tissue selective estrogen complexes

A TSEC partners a SERM with other estrogens to achieve a more favorable clinical profile than either therapy alone, based on their blended tissue selective activity profiles. The appropriate pairing of an estrogen and a SERM must provide endometrial protection and be effective for other menopausal indications. Not just any estrogen/SERM combination will provide a favorable clinical profile. This was recently illustrated in a report of oral estradiol given with raloxifene.¹ Although the combination effectively relieved hot flashes, it did not fully protect against estrogenic stimulation of the endometrium.¹

Both preclinical and clinical evidence support the pairing of the SERM bazedoxifene with conjugated estrogens (CE). On a cellular level, in the rat uterus, bazedoxifene by itself did not influence wet weight or histology, unlike raloxifene or lasofoxifene.²⁻⁶ Additionally, when bazedoxifene was added to CE, the proliferative effects of CE on the uterus were blocked.⁷ On a molecular level, estrogens and SERMs have been shown to elicit unique gene expression profiles both independently and when combined, such that when bazedoxifene

was partnered with CE, the gene expression profile was distinct from that of the individual components.⁷ Preliminary clinical data are consistent with these cellular and molecular data.

Preliminary clinical trial of a TSEC

A phase 2 study randomized 412 healthy, postmenopausal women (aged 40 to 65 years) to 6 different doses of bazedoxifene/CE for 84 days: bazedoxifene, 5 mg, 10 mg, or 20 mg with either CE, 0.3 mg or 0.625 mg. Controls included placebo, CE 0.3 mg, CE 0.625 mg, CE/medroxyprogesterone acetate (MPA) 0.625 mg/2.5 mg, and bazedoxifene 5 mg. Study participants had to experience an average of 4 hot flashes per day and have an intact uterus with an endometrial thickness less than 5 mm, as measured by transvaginal ultrasound. Participants could not have taken any hormone-containing medications within 8 weeks prior to study entry. Endometrial thickness, rates of amenorrhea, hot flush incidence and severity, vaginal maturation, and N-telopeptide levels were examined.

Demographic and baseline characteristics were similar among all treatment groups at baseline. The average age was approximately 54 years, the majority of women were white, the average body mass index was 25.4, and the mean time since their last menstrual period was 4.3 years. The results of this study are presented here.

Endometrial protection

Endometrial hyperplasia, a surrogate marker for endometrial cancer, is a well-documented side effect of unopposed estrogen therapy.^{8,9} To date, only

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FIGURE 1

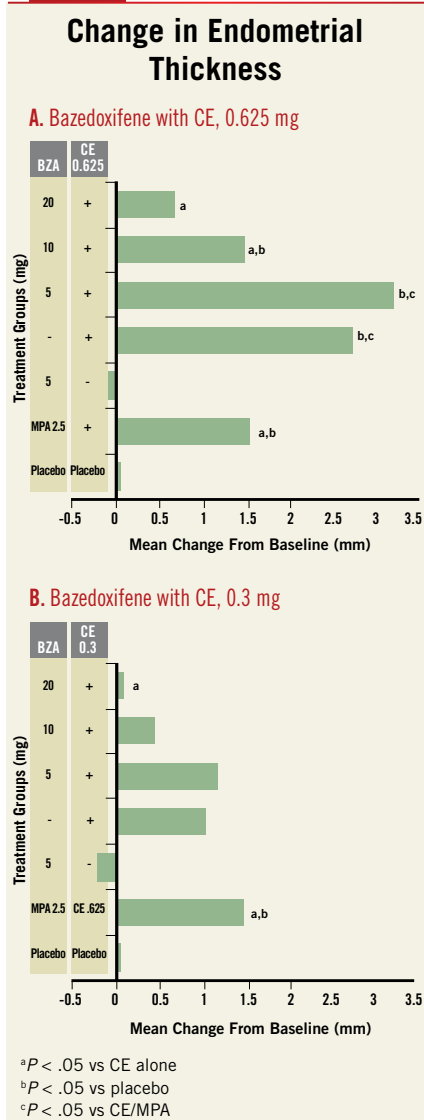
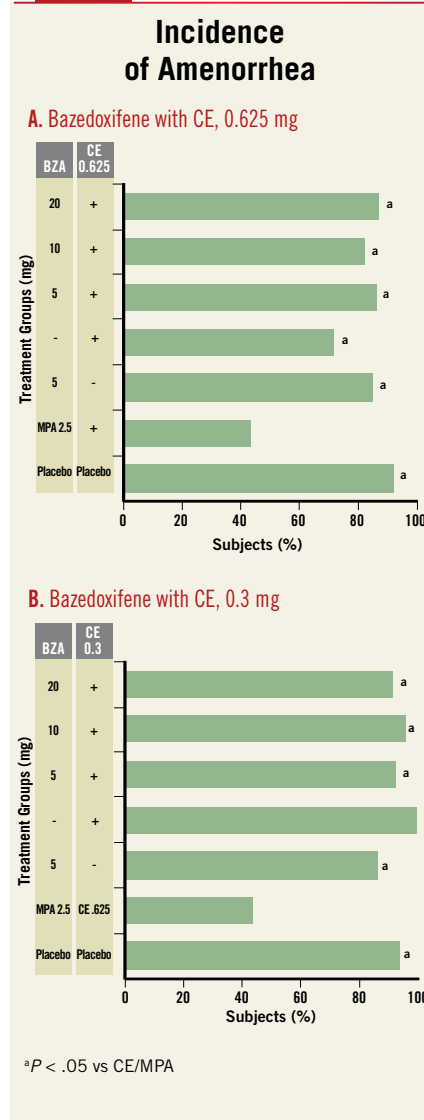


FIGURE 2



the addition of a progestin to estrogen therapy has been shown to prevent estrogen-induced endometrial hyperplasia.^{8,9} In this preliminary study, the effect of 84 days of bazedoxifene/CE on endometrial thickness (as a measure of endometrial stimulation) was assessed by transvaginal ultrasound (FIGURE 1).

As expected, endometrial thickness increased in women who received CE 0.3 mg or CE 0.625 mg alone, which was statistically significant versus placebo at a dose of 0.625 mg (*P* < .05).⁸ Also as expected, CE/MPA significantly reduced the CE-induced increase in endometrial thickness (*P* < .05), although the change from baseline with CE/MPA was still

higher than that with placebo (*P* < .05).

By itself, bazedoxifene at 5 mg did not increase endometrial thickness but, rather, resulted in a non-significant decrease in uterine thickness. When added to either CE 0.3 mg or CE 0.625 mg, bazedoxifene dose-dependently inhibited the CE-induced increase in endometrial thickness. A dose of bazedoxifene 20 mg significantly lowered the increases in endometrial thickness observed with CE alone at 0.3 mg or 0.625 mg (*P* < .05). In fact, bazedoxifene 20 mg almost completely blocked the endometrial increase observed with CE 0.3 mg alone.

When bazedoxifene 20 mg was

added to CE 0.625 mg alone, the increase in endometrial thickness was less than half that observed with CE/MPA. Likewise, the increase in endometrial thickness with bazedoxifene 10 mg plus CE 0.625 mg was comparable to that with CE/MPA, and was significantly lower (*P* < .05) than that with CE 0.625 mg alone. When bazedoxifene 10 mg was paired with CE 0.3 mg, the CE-induced increase in endometrial thickness was less than half, but not significantly less, than that with CE 0.3 mg alone. Bazedoxifene at 5 mg was not enough to reduce an increase in endometrial thickness observed with either CE 0.3 mg or CE 0.625 mg.

Collectively, these effects of bazedoxifene with and without CE on the endometrium are consistent with preclinical and clinical studies examining the effects of bazedoxifene alone, and preclinical studies of bazedoxifene/CE in the rat.^{2,7,10} When tested in the rat uterus, or when tested at various doses in studies of postmenopausal women, bazedoxifene alone did not elicit a proliferative endometrial response.^{2,10} Also in a model of the rat uterus, bazedoxifene blocked CE-induced increases in uterine wet weight.⁷ However, raloxifene significantly increased uterine wet weight versus control.² Preclinical results with raloxifene, then, are consistent with the recently reported finding that raloxifene did not fully prevent endometrial stimulation with estradiol plus raloxifene.¹

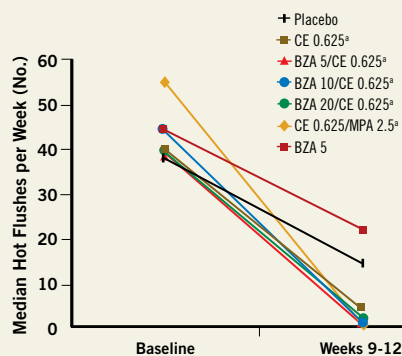
Achieving amenorrhea

Additional effects on the endometrium can be indicated by endometrial bleeding. Irregular bleeding is one of the limitations of HT as menopausal treatment. Comparing bleeding incidence between different therapies is difficult based on inconsistent bleeding definitions with each study. However, irregular bleeding has been consistently demonstrated with various HTs, although bleeding incidence has improved with the advent of lower doses of HT.¹¹⁻¹⁶ Bleeding

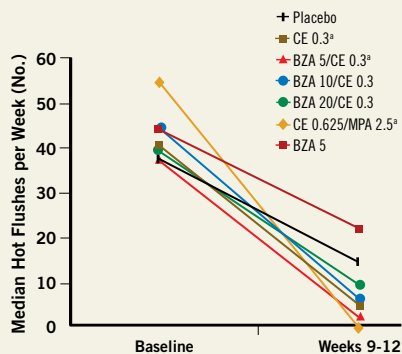
FIGURE 3

Incidence of Hot Flashes

A. Bazedoxifene with CE, 0.625 mg



B. Bazedoxifene with CE, 0.3 mg



* $P < .05$ vs placebo at weeks 9-12.

is also a common reason that women discontinue HTs—approximately 12% to 23% of women discontinue HT because of bleeding.^{17,18} An improved menopausal therapy would have a rate of amenorrhea (no bleeding or spotting) comparable to that in either untreated postmenopausal women or women given placebo.

In this study of bazedoxifene/CE, the incidence of vaginal bleeding was recorded by study participants on daily diary cards. The incidence of amenorrhea with the various treatment regimens throughout the study is presented in **FIGURE 2**. All 6 bazedoxifene/CE combinations had amenorrhea rates similar to placebo (92%), and better than HT (43%; $P < .05$). The incidence of amenorrhea with bazedoxifene 20 mg with CE 0.625 mg or CE 0.3 mg was 89% to 92%. Thus,

amenorrhea and bleeding rates with bazedoxifene/CE approach the goal of improved tolerability for a next-generation menopausal therapy.

Treating menopausal hot flashes and vaginal atrophy

Hot flashes and symptoms of vaginal atrophy are commonly reported by postmenopausal women and are a primary reason they seek therapy. Whereas estrogen and HTs reduce hot flush frequency and severity and treat vulvar and vaginal atrophy, raloxifene—approved for postmenopausal osteoporosis prevention and treatment—can exacerbate hot flashes and vaginal atrophy.^{19,20}

The incidence of hot flashes was collected from patient daily diary cards so that occurrence of hot flashes at weeks 9 to 12 with bazedoxifene/CE could be compared with placebo. The median numbers of hot flashes per week at screening and at weeks 9 to 12 are shown in **FIGURE 3**. All treatment groups showed numeric reductions in the median number of hot flashes at weeks 9 to 12 compared with screening. As expected, both doses of CE alone and CE/MPA significantly reduced hot flashes compared with placebo ($P < .05$). Hot flush frequency also significantly decreased with all doses (5, 10, and 20 mg) of bazedoxifene added to CE 0.625 mg, and bazedoxifene 5 mg plus CE 0.3 mg compared with placebo. Bazedoxifene alone at 5 mg did not influence the median number of hot flashes compared with placebo. Overall results were similar for hot flush severity.

The vaginal maturation index (VMI) was also measured at baseline and after 84 days of treatment. Descriptive statistics were used to summarize VMI data and showed that all treatment groups, except for bazedoxifene 5 mg, bazedoxifene 20 mg plus CE 0.3 mg, and placebo, resulted in a change in VMI that was reflective of an increase in superficial cells, consistent with estrogenization.

Unlike raloxifene, bazedoxifene alone did not worsen hot flashes or

vaginal maturation, supporting its use in combination with CE. These preliminary results suggest that bazedoxifene at an appropriate dose with CE will not block the beneficial effects of CE on hot flashes or vaginal atrophy.

Bone protection

Bone loss is greatest during the initial years of menopause.²¹ About 20% of lifetime femoral neck loss and 30% of trochanteric loss occurs in the early menopausal period.²² Thus, in addition to treatment of menopausal symptoms during the early menopausal period, it may also be important to prevent bone loss.

Preliminary, short-term effects of the bazedoxifene/CE combinations on bone physiology were evaluated by examining N-telopeptide and other bone markers. The median change from baseline to day 84 for urinary N-telopeptide was analyzed. Compared with placebo, both doses of CE and CE/MPA significantly reduced urinary N-telopeptide, as expected ($P < .05$). With the addition of all doses of bazedoxifene to either CE 0.3 mg or 0.625 mg, significant reductions in N-telopeptide versus placebo were achieved ($P < .05$). With CE 0.625 mg alone and when bazedoxifene 10 or 20 mg was added to CE 0.625 mg, the reductions were slightly less than those observed with CE/MPA ($P < .05$). Similar favorable effects of bazedoxifene/CE were observed on urinary C-telopeptide, urinary deoxypyridinoline, and serum osteocalcin. These preliminary results are consistent with preclinical data in which bazedoxifene has been shown to preserve bone in rats.²

Breast tenderness

Breast symptoms are also a common reason why menopausal women (about 9% to 13%) discontinue HT.^{17,18} Breast pain or tenderness is a common treatment-emergent side effect reported in clinical studies of various HTs.^{11-13,23} In this study of bazedoxifene/CE, no significant differences in breast tenderness were observed between any of the

bazedoxifene doses with CE 0.625 mg versus placebo. Consistent with previous reports, a significant increase in breast tenderness was found with CE 0.625 mg (46%; $P = .011$) and CE/MPA (43%; $P = .020$) compared with placebo (17%). No significant differences between placebo and either bazedoxifene 5 mg or CE 0.3 mg were observed. In conjunction with the amenorrhea rates observed with bazedoxifene/CE, these results indicate an improved tolerability for this new paradigm of menopausal therapy.

Conclusion

Preliminary clinical data with bazedoxifene/CE demonstrate a favorable tissue-specific profile. The pairing of estrogens and a SERM in this TSEC protected the endometrium, and at the same time significantly reduced frequency and severity of hot flushes, improved vaginal maturation, and had favorable effects on bone physiology. Importantly, bazedoxifene/CE provided exceptional tolerability, as demonstrated by rates of amenorrhea and breast tenderness similar to that of placebo.

The effects of bazedoxifene/CE on the endometrium indicate that, at appropriate doses, its effects were comparable to those of standard HT with regard to preventing endometrial stimulation and improved amenorrhea rates. In contrast, the pairing of estradiol and raloxifene, another potential TSEC, did not protect the endometrium.¹ This study also demonstrates that the appropriate dose combination of bazedoxifene and CE is important to ensure that the therapy protects the endometrium, and at the same time treats vasomotor symptoms. For example, bazedoxifene 20 mg added to CE 0.625 mg effectively prevented endometrial stimulation and reduced

hot flush frequency and severity. Preclinical data also demonstrate the importance of the right estrogen/SERM combination and dose. In a rat model of hot flushes, bazedoxifene at its bone-sparing dose did not antagonize the lowering of tail temperature with estrogen, whereas raloxifene at its bone-sparing dose antagonized estrogen's tail temperature reduction.³

In conclusion, the unique pharmacology of this TSEC containing bazedoxifene/CE provides a clinical profile that has the potential to provide a next-generation menopausal therapy with improved tolerability and to change the way women and physicians approach menopausal therapy.

Disclosure

Dr Pickar reported the following potential conflicts of interest: he is an employee of Wyeth Research and is a board member of the International Menopause Society.

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