Clinical Medicine Insights: Women's Health

REVIEW

Safety, Efficacy and Patient Acceptability of Bazedoxifene Acetate in the Management of Postmenopausal Osteoporosis

Tayane Muniz Fighera[1], Carolina Aguiar Moreira Kulak[1,2] and Jaime Kulak Júnior[1,3]

[1]Endocrinology Division of Hospital de Clinicas, Federal University of Parana (SEMPR), Curitiba, Brazil. [2]Department of Internal Medicine, Federal University of Parana, Curitiba, Brazil. [3]Department of Obstetrics and Gynecology, Federal University of Parana, Curitiba, Brazil. Corresponding author email: jkulak@ufpr.br

Abstract: Many pharmacological agents are available for treatment of postmenopausal osteoporosis, including estrogen and the selective modulators of estrogen receptor (SERMS). Bazedoxifene is a third-generation SERM, which acts as estrogen agonist in bone and lipid metabolism and as an antagonist in the breast and endometrium. Studies demonstrated that bazedoxifene reduced significantly the risk of vertebral fractures. In a subgroup of patients at high risk (post-hoc analysis), a reduction of nonvertebral fractures risk was reported. Moreover, the combination of conjugated estrogens with bazedoxifene seems to offer an alternative to classical hormone therapy, improving the vasomotor symptoms and vaginal atrophy, without the use of a progestin. Bazedoxifene is a promising drug for the treatment and prevention of osteoporosis in postmenopausal women; however a safety concern regarding venous thromboembolic events is needed before starting treatment.

Keywords: SERMs, bazedoxifene, osteoporosis postmenopausal, TSEC

Clinical Medicine Insights: Women's Health 2012:5 9–16

doi: 10.4137/CMWH.S7308

This article is available from http://www.la-press.com.

Introduction

Osteoporosis is a systemic skeletal disease characterized by decrease of bone strength, which leads to a bone fragility and increased susceptibility to fractures.[1] It is associated with increased mortality and morbidity, reduced mobility and independence, with negative social and psychological impact.[2] Many pharmacological agents are available for treatment of postmenopausal osteoporosis, including bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid), hormone therapy, parathyroid hormone and selective modulators of estrogen receptor (SERM, raloxifene).[3–5] The most frequent cause of osteoporosis is the decline of endogenous estrogens at the time of menopause. Estrogen has an antireabsorptive effect on bone and therefore, estrogen deficiency plays a central role in the development of postmenopausal osteoporosis.[6] The loss of bone mass before menopause is small, and probably parallel to that seen in men. However, perimenopausal bone loss is accelerated, reaching 2% a year over the next 5 to 10 years, and being more significant in the early years of menopause.[7,8] On the other hand, young women with hypogonadism are also at increased risk of osteoporosis.[6]

In addition, estrogen modulates a large number of biological activities, affecting gene expression, growth and physiology of all systems.[9] Many women experience symptoms and consequences of estrogen deficiency associated with menopause, which can be severe enough to require specific therapy. The most common menopausal symptoms are the hot flashes[10] and vaginal atrophy.[11]

While estrogen therapy has been used to treat or prevent symptoms and consequences of menopause, including hot flashes and osteoporosis, SERMs have been developed in attempt to reach the therapeutic profile of hormone therapy, but without risk to the uterine and breast tissue. So far, no drug has achieved this goal.[12] In fact, the name SERM is used to describe a class of ligands with variable estrogenic activity in different tissues, which may act as an agonist in one system and antagonist in another.[13] This idea became apparent first with tamoxifen, a triphenylethylene derivative, being its antiestrogen action first described in vitro using a human cell line of breast cancer.[14] Tamoxifen binds to estrogen receptor and acts as an antagonist of estrogen in the breast. However, long term treatment with tamoxifen increased the risk of endometrial cancer related to the partial agonist effect in the uterus.[15] Tamoxifen also has an agonist activity on bone mineral density and maintain bone mass in post menopausal women. The other SERM, raloxifene, was initially developed for treatment of breast cancer,[16] however, different from tamoxifen, it did not show the same level of stimulation on the endometrium.[17] In addition, raloxifene was shown to decrease plasma cholesterol levels and vertebral fractures. It was the first SERM to be approved by the US Food and Drug administration for the prevention and treatment of postmenopausal osteoporosis. Several new SERMs have entered clinical development in recent years.[18] Lasofoxifene has been investigated for the prevention and treatment of osteoporosis and for the treatment of vaginal atrophy in postmenopausal women. In a 2-year, randomized, double-blind study of postmenopausal women (N = 410), the mean change in lumbar spine BMD relative to placebo was significantly greater ($P < 0.05$) with lasofoxifene 0.25 and 1.0 mg/day (3.6% and 3.9%, respectively) compared with raloxifene 60 mg (1.7%), although the responses were comparable for total hip. Both lasofoxifene and raloxifene significantly reduced levels of bone turnover markers and low-density lipoprotein cholesterol compared with placebo. Evidence suggests that lasofoxifene treatment may cause increased endometrial thickness compared with placebo, although there has been no evidence of an increased risk of endometrial hyperplasia or cancer.[19] The effects of ospemifene on biochemical markers of bone turnover in postmenopausal women have also been evaluated. In phase 2 studies, ospemifene had a similar effect on most markers of bone resorption and bone formation compared with raloxifene and significantly greater changes from baseline compared with placebo ($P < 0.05$) at most doses.[20,21] Evidence suggests that ospemifene may be associated with increased endometrial thickness and uterine volume.[22] Arzoxifene was initially investigated for the treatment and prevention of breast cancer. The effects on bone mineral density, fractures, uterine safety, and overall safety were further studied in a randomized, placebo controlled trial including postmenopausal women with normal to low bone mass.[23] However, preliminary results from a five-year clinical study showed that arzoxifene met its primary

endpoints of reduction in vertebral fractures and breast cancer in postmenopausal women. However, failed to meet secondary endpoints of reduction in non-vertebral fractures and cardiovascular events and improvements in cognitive function. Based on these results, the drug company announced they are discontinuing further development of the drug.[24] Other SERMs for postmenopausal osteoporosis, like idoxifene and levormeloxifene, had their studies discontinued, in part, because of adverse uterine effects, including increased endometrial thickness.[25,26]

Bazedoxifene is a third-generation SERM, which acts as estrogen agonist in bone and lipid metabolism and as an antagonist in the breast and endometrium.[13] It was recently approved for the treatment of postmenopausal osteoporosis in Europe and Japan. The aim of this review is to describe the efficacy, safety and acceptability of bazedoxifene in women with postmenopausal osteoporosis.

Mechanism of Action of Bazedoxifene

Estrogens have a positive effect on the skeleton by inhibiting osteoclast activity,[27,28] leading to increased bone mineral density[29] and reducing the risk of fractures.[30–32] However, estrogen therapy (alone or combined with progestin) has been associated with deleterious effects on other systems. The combination of estrogen and progesterone appears to increase risk of breast cancer,[30] while the use of estrogen alone has been associated with increased risk of endometrial cancer.[33] In addition, both appear to increase cardiovascular risk.[30,32]

There are two types of estrogen receptor (ER). Alpha receptor predominates in the breast and endometrium, while the beta receptor predominates in bone, heart, endothelium and various other tissues.[34] Estrogens, particularly 17β-estradiol, and to a lesser extent, estrogen, bind and activate ER, modulates the growth and differentiation of target cells. Each receptor activates different signaling pathways, and the result is a complex balance of different actions for each system.[35] For example, while activation of ERα (predominant in the female reproductive system) was found to stimulate cell growth, activation of ERβ (gastrointestinal, cardiovascular, respiratory and urinary system) often counteracts this process.[36] SERMs are substances with the ability to act as specific agonists\antagonists on the estrogen receptor subtypes, modulating them.[37] Bazedoxifene binds with high affinity to the ER.[38] Tamoxifen is the first generation, and raloxifene is second. The main feature that differs from the generations of SERMs it's the effects on breast tissue and the uterus.[39] In vitro studies have shown that bazedoxifene did not stimulate proliferation of breast cancer cells (MCF-7) and also suppressed the proliferation induced by 17β estradiol in a dose-dependent manner. In animal studies, treatment with bazedoxifene preserved bone mass and reduced levels of bone turnover markers.[13] Moreover, when compared to other SERMs such as raloxifene and lasofoxifene, bazedoxifene proved to be the most potent inhibitor of the increase in uterine weight induced by estrogen in ovariectomized rats.[40] Finally, studies in mice demonstrated that bazedoxifene was the most effective antagonist against the stimulation provided by estrogen on breast tissue when compared to raloxifene and lasofoxifene.[40]

Metabolism and Pharmacokinetics

Bazedoxifene is rapidly absorbed and has a long half-life as unchanged drug, up to 33 hours. The maximum plasma concentration occurs 1–2 hours after administration. It shows high plasma protein binding (99%) and volume of distribution of 248 + 34 L/kg. It is metabolized through the glucuronidation pathway, with few metabolites formed via cytochrome P450. The combination gives rise to the BZA-5-glucuronide (40%–95% of metabolites) and to a lesser extent, the BZA-4-glucuronide. The extensive metabolism and the effect of first-pass are responsible for the low oral bioavailability and high clearance of the drug. The major route of excretion is the feces (85%) with less than 1% being excreted in the urine.[41,42] Bazedoxifene is little metabolized by cytochrome P450, therefore risk of drug interactions is low.[43] Baird et al[44] evaluated the interaction between bazedoxifene 20 mg and 600 mg ibuprofen, and concluded that the use of two drugs together is safe and does not require dose adjustment.

Efficacy in Clinical Studies

Bazedoxifene represents a new drug for osteoporosis treatment with a safety profile until now.[45] Clinical studies of phase 2 and 3 assessed the behavior of the drug in different doses. In phase 2, the effect of bazedoxifene on bone turnover markers was examined.

A prospective, randomized, double-blind study compared bazedoxifene in doses of 5 mg, 10 mg and 20 mg to raloxifene 60 mg or placebo. A total of 494 postmenopausal women were enrolled and treated for 3 months. The investigators reported a reduction in levels of bone turnover markers in bazedoxifene and raloxifene groups, even with low doses of bazedoxifene as 5 mg.[46] Still in phase 2 studies, the effect of bazedoxifene on the endometrium was evaluated in a prospective and double-blind manner, with 6 months follow-up. 497 healthy postmenopausal women were randomized to receive doses bazedoxifene 2.5, 5.0, 10, 20, 30 and 40 mg daily, and were compared with patients receiving conjugated estrogen combined with medroxyprogesterone acetate (0.625 mg and 2.5 mg, respectively). Doses of up to 40 mg a day bazedoxifene were well tolerated and did not stimulate the endometrium. There was a significant reduction in endometrial thickness and uterine bleeding with doses of 30 and 40 mg/day compared to placebo, suggesting an antagonistic effect of the drug on the endometrium.[47] Two large studies have evaluated the behavior of bazedoxifene in phase 3. One study, with 2 years follow-up, multicenter, evaluated 1434 postmenopausal women aged ≥45 years with T score in lumbar spine or femoral neck between −1.0 and −2.5 and/or risk factors for osteoporosis (family history of fractures, smoking, bilateral oophorectomy, menopause before 40 years of age, inadequate calcium intake). The objective of this study was to evaluate the efficacy and safety of bazedoxifene in preventing bone loss. Patients were randomized into 5 groups: bazedoxifene 10, 20 or 40 mg daily, placebo or raloxifene 60 mg daily, and all received calcium carbonate 600 mg daily. All doses of bazedoxifene and raloxifene prevented the loss of bone mass, while in the placebo group there was a significant loss of bone mass at all sites evaluated. The mean differences in percent change in lumbar spine BMD from baseline after 24 months was 1.8% ± 0.28%, 1.41% ± 0.28%, 1.49% ± 0.28%, and 1.49% ± 0.28% for bazedoxifene 10, 20, and 40 mg and raloxifene 60 mg, respectively ($P < 0.001$ for all comparisons). A similar response was observed at other sites. There was a significant reduction in the levels of osteocalcin and C-telopeptide comparing the treated and control groups. Thus, this study demonstrated that treatment with bazedoxifene prevented bone loss and reduced bone turnover as well as raloxifene, and shows good tolerance.[48] Another large randomized, double-blind study evaluated 6847 postmenopausal women with osteoporosis treated with bazedoxifene 20 or 40 mg/day, raloxifene 60 mg/day or placebo for 3 years. The patients were aged between 55 and 85 years, with menopause for at least 2 years. All patients received 1,200 mg calcium and 400–800 IU of vitamin D per day. The incidence of new vertebral fractures was significantly lower in the groups receiving bazedoxifene 20 mg (2.3%), bazedoxifene 40 mg (2.5%), and raloxifene 60 mg (2.3%) compared to placebo (4.1%) ($P < 0.05$), with relative risk reduction of 42%, 37% and 42%, respectively. The incidence of nonvertebral fractures was not different between groups. In a post hoc analysis of a subgroup of patients (n = 1772) with a high risk of fractures bazedoxifene 20 mg showed a 50% reduction in risk of nonvertebral fractures compared with placebo ($P = 0.02$) and raloxifene 60 mg ($P = 0.05$) (hazard ratio, 0.50; CI, 0.28–0.90). Furthermore, bazedoxifene also significantly improved BMD and reduced of bone turnover markers compared with placebo.[49]

Safety and Adverse Effects

The most common adverse effects reported were headache, infection, arthralgia, back pain, abdominal pain, hypertension, hot flushes, and flu syndrome.[48–50] A group of researchers evaluated the safety and tolerability of bazedoxifene on the basis of phase 3 clinical studies. Were evaluated 3146 patients who received bazedoxifene 40 mg, bazedoxifene 20 mg or placebo, with recruitment for a period of seven years, starting in 2001. After five years, the incidence of adverse events, serious adverse events and discontinuation due to adverse events was similar between groups. The group receiving bazedoxifene had a higher incidence of hot flushes and cramps compared with placebo. Most of these effects were mild to moderate in severity and did not result in study discontinuation. In addition, clinical laboratory tests indicated no clinically relevant safety findings.[51] Regarding thromboembolic events, Miller et al[48] found no difference in the incidence of deep vein thrombosis between the groups receiving bazedoxifene (0% to 0.6% with various doses after 2 years) and the placebo group (0.3%). However, in the study by Silverman et al[51] the incidence of deep vein thrombosis was higher

among the bazedoxifene groups (0.5% and 0.6% for bazedoxifene 20 and 40 mg, respectively) than the placebo group (0.2%; overall $P < 0.05$), consistent with what was observed in other studies of SERMs. The incidence of pulmonary or retinal vein thrombosis was similar among groups. None of these studies[48,51] showed a higher incidence of adverse effects on the cardiovascular system with bazedoxifene, including myocardial infarction and stroke. Also there seems to be a favorable effect (or at least without adverse significant effect) on the lipid profile. Finally, bazedoxifene does not seem to stimulate the endometrium and breast tissue.[50] After five years, the incidence of breast cancer with bazedoxifene was low and similar to that with placebo. There were fewer cases of fibrocystic breast disease and breast cysts with bazedoxifene 20 and 40 mg compared with placebo. There was one report of endometrial hyperplasia in each group. No cases of endometrial carcinoma were reported with bazedoxifene 20 mg; the number of endometrial carcinoma cases was lower with bazedoxifene 40/20 mg (n = 3) compared with placebo (n = 6; overall $P = 0.05$). There was one report of lung carcinoma in the study (placebo group).[51]

Association of bazedoxifene and conjugated estrogens

The classical hormonal therapy, a combination of estrogen with progestin, raises concerns about possible negative effects of progesterone. The "tissue selective estrogen complex" (TSEC) is the term used to describe a new kind of therapy, which has been investigated in recent years in an attempt to develop effective new therapies with a more favorable tolerability profile.[52] In recent publications, the combination of bazedoxifene and conjugated estrogens (BZA\EC) showed to reduce the frequency and severity of hot flushes, vaginal atrophy and the symptoms associated, maintain or increase bone density, with an incidence of amenorrhea and pain in breast cancer at least equivalent to placebo, without stimulating the endometrium.[18,53–55] In a phase 3 clinical study[53] 3397 postmenopausal women were evaluated for the effects of bazedoxifene 10, 20 or 40 mg in combination with conjugated estrogen 0.45 mg or 0.625 for 2 years, compared to raloxifene 60 mg or placebo. This study was divided into two subgroups: women with menopause between 1–5 years or >5 years. In two subgroups, regardless of time of menopause, there was significant improvement in BMD in the lumbar spine in the group receiving BZA\CE compared to placebo ($P < 0.001$). In addition, there was improvement in BMD at the lumbar spine ($P < 0.05$) for all doses of BZA\CE compared to raloxifene, except in women with menopausal for >5 years who received 40 mg bazedoxifene. In women with menopausal for >5 years, the annual percentage change in BMD was 0.51% to 0.59%, 0.79% and −1.08%, respectively, for different doses of BZA\CE, raloxifene and placebo. Similarly, in women with menopause between 1–5 years, the changes were 0.55% to 1.60% −0.07% and −1.41%, respectively.[53] Thus, based on the data presented, the combination BZA\CE seems to be a promising therapeutic option, with effects on bone and endometrium similar to that of conventional hormone therapy, but without the need of a progestin.[52]

Place in therapy and patient preference

So far the only SERM approved for the treatment and prevention of osteoporosis is raloxifene, which has demonstrated effectiveness in preventing bone loss and fractures, with the added benefit in preventing breast cancer. The development of a new SERM should bring attributes that represent an improvement over drugs already established. Bazedoxifene was shown to be effective in maintaining or improving BMD, reduce bone turnover and reduce the risk of fractures in postmenopausal women with no evidence of stimulation on the endometrium and breast tissue.[56] Moreover, although the optimal dose has not yet been established, the bazedoxifene has the convenience of taking a single daily dosage, a safe metabolic profile and minimum drug interaction with other drugs.

Conclusions

Bazedoxifene is a promising drug for the treatment and prevention of osteoporosis in postmenopausal women. In Phase 3 studies, bazedoxifene reduced the risk of vertebral fractures by 37% to 42% in women with osteoporosis compared to placebo. In addition, reduced risk of nonvertebral fractures in a subgroup of patients at high risk (post-hoc analysis) was reported. It also seems to have a safe profile on lipid metabolism, endometrial and breast tissue. Thromboembolic

events, although they were more common than in placebo, seems to be similar to raloxifene. Therefore, a safety concern regarding the development of venous thromboembolic events is need before start treatment in postmenopausal women. Based on the data presented, the bazedoxifene appears to be a good candidate for the next generation of osteoporosis treatment. Moreover, the combination of conjugated estrogens with bazedoxifene seems to offer an alternative to classical hormone therapy, with preservation of bone mass, improvement of vasomotor symptoms and vaginal atrophy, without the use of a progestin.

Author Contributions

TMF, CAMK and JK. Jr have equally contributed in this paper and have also reviewed and approved the final manuscript.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

References

1. Marcus R. The nature of osteoporosis. *J Clin Endocrinol Metab*. 1996; 81:1–5.
2. Atik OS, Gunal I, Korkusuz F. Burden of osteoporosis. *Clin Orthop Relat Res*. 2006;443:19–24.
3. North American Menopause Society. Management of osteoporosis in postmenopausal women: position statement of The North American Menopause Society. *Menopause*. 2010;17:25–54.
4. Miller PD, Derman RJ. What is the best balance of benefits and risks among anti-reabsortive therapies for postmenopausal osteoporosis? *Osteoporos Int*. 2010;21:1793–802.
5. Lewiecki EM. Current and emerging pharmacologic therapies for the management of postmenopausal osteoporosis. *J Womens Health*. 2009;18: 1615–26.
6. Popat VB, Calis KA, Vanderhoof VH, et al. Bone Mineral Density in Estrogen-Deficient Young Women. *J Clin Endocrinol Metab*. 2009;94: 2277–83
7. National Osteoporosis Foundation. America's Bone Health. The State of Osteoporosis and Low Bone Mass in Our Nation. Washington, DC: *National Osteoporosis Foundation*. 2002:1–55.
8. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Technical report series no 843. Geneva: *World Health Organization*. 1994:1–129.
9. Kim KH, Bender JR. Membrane-initiated actions of estrogen on the endothelium. *Molecular and Cellular Endocrinology*. 2009;308:3–8.
10. Staropoli CA, Flaws JA, Bush TL, Moulton A. Predictors of menopausal hot flashes. *J Womens Health*. 1998;7:1149–55.
11. Bachmann GA, Cheng RJ, Rovner E. Vulvovaginal complaints. *Treatment of the Postmenopausal Woman*. In: Lobo RA, editor. 3rd ed. Burlington, MA: Academic Press; 2007:263–9.
12. Komm BS. A new approach to menopausal theraphy: the tissue selective estrogen complex. *Reproductive Sciences*. 2008;15:984–92.
13. Komm BS, Kharode YP, Bodine PVN, Harris HA, Miller CP, Lyttle CR. Bazedoxifene acetate: a selective estrogen receptor modulator with improved selectivity. *Endocrinology*. 2005;146:3999–4008.
14. Fisher B, Constantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project: P-1 study. *J Natl Cancer Inst*. 1998;90:1371–88.
15. Pritchard K. Breast cancer prevention with selective estrogen receptor modulators: a perspective. *Ann NY Acad Sci*. 2001;949:89–98.
16. Buzdar AU, Marcus C, Holmes F, Hug V, Hortobagyi G. Phase II evaluation of Ly156758 in metastatic breast cancer. *Oncology*. 1998;45:344–5.
17. Black LJ, Sato M, Rowley ER, et al. Raloxifene (LY156758) prevents bone loss and reduces serum cholesterol without causing uterine hypertrophy in ovariectomized rats. *J Clin Invest*. 1994;93:63–9.
18. Kulak JJ, Kulak CA, Taylor H. SERMs in the prevention and treatment of postmenopausal osteoporosis: an update. *Arq Bras Endocrinol Metabol*. 2010;54:200–5.
19. McClung MR, Siris E, Cummings S, Bolognese M, Ettinger M, Moffett A, et al. Prevention of bone loss in postmenopausal women treated with lasofoxifene compared with raloxifene. *Menopause*. 2006;13(3):377–86.
20. Komi J, Lankinen KS, DeGregorio M, Heikkinen J, Saarikoski S, Tuppurainen M, et al. Effects of ospemifene and raloxifene on biochemical markers of bone turnover in postmenopausal women. *J Bone Miner Metab*. 2006;24(4):314–8.
21. Komi J, Heikkinen J, Rutanen EM, Halonen K, Lammintausta R, Ylikorkala O. Effects of ospemifene, a novel SERM, on biochemical markers of bone turnover in healthy postmenopausal women. *Gynecol Endocrinol*. 2004;18(3):152–8.
22. Rutanen EM, Heikkinen J, Halonen K, Komi J, Lammintausta R, Ylikorkala O. Effects of ospemifene, a novel SERM, on hormones, genital tract, climacteric symptoms, and quality of life in postmenopausal women: a double-blind, randomized trial. *Menopause*. 2003;10(5):433–9.
23. Bolognese M, Krege JH, Utian WH, Feldman R, Broy S, Meats DL, et al. Effects of arzoxifene on bone mineral density and endometrium in postmenopausal women with normal or low bone mass. *J Clin Endocrinol Metab*. Jul 2009;94(7):2284–9.
24. Company ELa. Lilly Reperts on outcome of Phase III of Arzoxifene, press release; 2009.
25. Fleischer AC, Wheeler JE, Yeh IT, Kravitz B, Jensen C, MacDonald B. Sonographic assessment of the endometrium in osteopenic postmenopausal women treated with idoxifene. *J Ultrasound Med*. 1999;18(7):503–12.
26. Warming L, Christoffersen C, Riis BJ, Stakkestad JA, Delmas PD, Christiansen C. Adverse effects of a SERM (Levormeloxifene). Safety parameters and bone mineral density 12 months after treatment withdrawal. *Maturitas*. 2003;44(3):189–99.
27. Alexeeva L, Burkhardt P, Christiansen C, Cooper C, Delmas P, Johnell O, et al. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO Study Group. WHO Technical Report Series 843, Geneva, 1994.

28. Riggs BL, Melton LJ III, eds. *Osteoporosis: Etiology, Diagnosis, and Management*. Philadelphia: Lippincott-Raven Publishers; 1995.
29. Christiansen C, Christensen M, McNair P, Hagen C, Stocklund K, Transbøl I. Prevention of early bone postmenopausal loss: controlled 2-year study in 315 normal females. *Eur J Clin Invest*. 1980;10:273–9.
30. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–33.
31. Cauley J, Robbins J, Chen Z, Cummings S, Jackson R, LaCroix A, et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: The women's health initiative randomized trial. *JAMA*. 2003;290:1729–38.
32. Anderson GL, Limacher M, Assaf AR; Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291:1701–12.
33. Beresford SA, Weiss NS, Voigt LF, McKnight B. Risk of endometrial cancer in relation to use of estrogen combined with cyclic progestagen therapy in postmenopausal women. *Lancet*. 1997;349:458–61.
34. Couse JF, Lindzey J, Grandien K, Gustafsson JA, Korach KS. Tissue distribution and quantitative analysis of estrogen receptor-alpha (ERalpha) and estrogen receptor-beta (ERbeta) messenger ribonucleic acid in the wild-type and ERalpha-knockout mouse. *Endocrinology*. 1997;138:4613–21.
35. Dahlman-Whight K, Cavailles V, Fuqua SA, et al. International Union ofPharmacology, LXIV. Estrogen receptors. *Pharmacol Rev*. 2006;58:773–81.
36. Gustafsson JA. What pharmacologists can learn from recent advances in estrogen signaling. *Trends Pharmacol Sci*. 2003;24:479–85.
37. Thomsen SS, Vestergaard P. Treating postmenopausal osteoporosis in women at increased risk of fracture – critical appraisal of basedoxifene: a review. *International Journal of Women's Health*. 2009;1:97–103.
38. Bazedoxifene: bazedoxifene acetate, TSE 424, TSE-424, WAY 140424. *Drugs RD*. 2008;9:191–6. (No authors listed in pubmed.)
39. Vogel V, Costantino J, Wickerham D, Cronin W, Cecchini R, Atkins J, et al. Effects of tamoxifen vs raloxifene on the risk of developing invasive breast cancer and other disease outcomes: the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 trial. *JAMA*. 2006;295:2727–41.
40. Peano BJ, Crabtree JS, Komm BS, Winneker RC, Harris HA. Effects of various SERMs with or without conjugated estrogens on mouse mammary gland. *Endocrinology*. 2009;150:1897–903.
41. Ermer J, McKeand W, Sullivan P, Parker V, and Orczyk G. Bazedoxifene acetate dose proportionality in healthy, postmenopausal women. (Abstract). *Clin Pharmacol Ther*. 2003;73:P46
42. Patat A, McKeand W, Baird Bellaire S, Ermer J, LeCoz F. Absolute Bioavailability of bazedoxifene acetate in healthy postmenopausal women. (Abstract). *Clin Pharmacol Ther*. 2003;73:P43.
43. Chandrasekaran A, McKeand WE, Sullivan P, et al. Metabolic disposition of bazedoxifene in healthy postmenopausal women. *Drug Metab Dispos*. 2009;37:1219–25.
44. Baird SJ, McKeand WE, Ermer JC, Patat AA, Garcia-Querglas E. Lack of clinically relevant pharmacokinetic interaction between bazedoxifene and ibuprofen. *Clin Pharmacol Ther*. 2002;71:P94, WPIII-68.
45. Shen L, Ahmad S, Park S, et al. In Vitro Metabolism, Permeability, and Efflux of Bazedoxifene in Humans. *Drug Metabolism and Disposition*. 2010;38:1471–9.
46. Ronkin S, Clarke L, Boudes P, Constantine G. TSE-424, a novel tissue selective estrogen, reduces biochemical indices of bone metabolism in a dose related fashion. *J Bone Miner Res*. 2001;16:S413.
47. Ronkin S, Northington R, Baracat E, et al. Endometrial effects of bazedoxifene acetate, a novel selective estrogen receptor modulator, in postmenopausal women. *Obstet Gynecol*. 2005;105:1397–404.
48. Miller PD, Chines AA, Christiansen C, et al. Effects of bazedoxifene on BMD and bone turnover in postmenopausal women: 2-yr results of a randomized, double-blind, placebo-, and active-controlled study. *J Bone Miner Res*. 2008;23:525–35.
49. Silverman SL, Christiansen C, Genant HK, et al. Efficacy of bazedoxifene in reducing new vertebral fracture risk in postmenopausal women with osteoporosis: results from a 3-year, randomized, placebo- and active-controlled clinical trial. *J Bone Miner Res*. 2008;23:1923–34.
50. de Villiers TJ, Chines AA, Palacios S, Lips P, Sawicki AZ, Levine AB, et al. Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled phase 3 trial. *Osteoporos Int*. 2011;22(2):567–76.
51. Silverman SL, Chines AA, Kendler DL, Kung AWC, Teglbaerg CS, Felsenberg D, et al. Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. *Osteoporos Int*. 2012;23(1):351–63.
52. Lindsay R. Preventing osteoporosis with a tissue selective estrogen complex (TSEC) containing bazedoxifene\conjugated estrogens (BZA\CE). *Osteoporos Int*. 2011;22:447–51.
53. Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G. Efficacy of tissue-selective estrogen complex (TSEC) of bazedoxifene/conjugated estrogens (BZA/CE) for osteoporosis prevention in at-risk postmenopausal women. *Fertil Steril*. 2009;92:1045–52.
54. Lobo RA, Pinkerton JV, Gass MLS, et al. Evaluation of bazedoxifene/conjugated estrogens for the treatment of menopausal symptoms and effects on metabolic bone parameters and overall safety profile. *Fertil Steril*. 2009;92:1025–38.
55. Archer DF, Lewis V, Carr BR, Olivier S, Pickar JH. Bazedoxifene/conjugated estrogens (BZA/CE): incidence of uterine bleeding in postmenopausal women. *Fertil Steril*. 2009;92:1039–44.
56. Taylor HS. Designing the ideal selective estrogen receptor modulator – achievable goal? *Menoapause*. 2009;16:609–15.