

# Treating postmenopausal osteoporosis in women at increased risk of fracture – critical appraisal of bazedoxifene: a review

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**Abstract:** Several categories of drugs to treat osteoporosis exist in the form of bisphosphonates, strontium, parathyroid hormone, and selective estrogen receptor modulators (SERM). Advantages and disadvantages exist for each category as some patients may, for example, not tolerate bisphosphonates for gastrointestinal side effects, and especially in women in whom osteoporosis is frequent, several options for treatment are needed. The objectives of this review were to critically appraise the effects of bazedoxifene on risk of fractures especially in women at high risk of fractures. A systematic literature search was conducted for studies, especially randomized controlled trials with fractures as end-points. Bazedoxifene is a new member of the SERM group. The literature search identified one randomized controlled trial with fractures as end-point. This was a 3-year randomized double-blind placebo controlled trial in which 7492 postmenopausal women aged 55 to 85 years were randomly allocated to 1) bazedoxifene (20 [n = 1886] or 40 [n = 1872] mg/day); 2) raloxifene (60 mg/day, n = 1849); or 3) placebo (n = 1885). The risk of vertebral fractures decreased with both 20 (HR 0.58, 95% CI 0.38 to 0.89) and 40 (HR 0.63, 95% CI 0.42 to 0.96) mg of bazedoxifene per day compared to placebo. There was no reduction in non-vertebral fractures. A subgroup of women with *a priori* high risk of fractures was identified post hoc. In this subgroup there was a reduction in the risk of non-vertebral fractures with the 20 mg dose of bazedoxifene compared to placebo (HR 0.50, 95% CI 0.28 to 0.90). In the 40 mg bazedoxifene group no significant reduction in non-vertebral fractures was seen in this subgroup (HR 0.70, 95% CI 0.40 to 1.20). In general post-hoc defined subgroup analyses should be interpreted with caution. However, the results indicate that bazedoxifene may be effective in preventing vertebral fractures in postmenopausal women with osteoporosis.

**Keywords:** bazedoxifene, fracture, bone mineral density

## Introduction

Several categories of drugs to treat osteoporosis exist in the form of bisphosphonates, strontium, parathyroid hormone, and selective estrogen receptor modulators (SERM). Advantages and disadvantages exist for each group as some patients may, for example, not tolerate bisphosphonates for gastrointestinal side effects, and especially in women in whom osteoporosis is frequent, several options for treatment are needed. This is particularly important because of the involvement of estrogen deficiency in the pathogenesis of osteoporosis in women. The objectives of this review were to critically appraise the effects of bazedoxifene on risk of fractures especially in women at high risk of fractures. A systematic search of the literature was conducted for studies, especially randomized controlled trials with fractures as end-points.

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The paper evaluates the effects of estrogen and the effects of SERM on estrogen, and the pharmacokinetics and pharmacodynamics of bazedoxifene and its effects on clinical end-points, especially fractures but also other important end-points linked to the estrogen system such as breast cancer and endometrial cancer. The literature was searched systematically and the effects of bazedoxifene were critically appraised and compared to the effects of other drugs not just in the SERM class of drugs but also with other classes of drugs against osteoporosis. The paper thus summarizes not just the effects from randomized controlled trials of bazedoxifene, but also assesses its effect in comparison with other drug classes. It also assesses the effects on bone mineral density in relation to the effects on fracture risk.

Bazedoxifene is a third-generation SERM.<sup>1</sup> Tamoxifen was the first-generation, and raloxifene the second. Significant differences have been shown between the generations in terms of effects especially on the uterus and the breast tissue.<sup>2</sup> The SERM class of drugs are drugs with selective effects on the estrogen receptor. In contrast to estrogens and estrogen receptor agonists, these are partial agonists/antagonists. Development of newer generations with more selective effects may thus prove advantageous in terms of effects on bone and side effects.

## Estrogen effects

Estrogens have positive effects on bone by inhibiting osteoclastic resorption,<sup>3,4</sup> which leads to an increase in bone mineral density (BMD)<sup>5</sup> and a decrease in the risk of fractures.<sup>6-8</sup> In a meta-analysis, estrogen therapy in any form was associated with a decrease in the risk of non-vertebral fractures (relative risk [RR] 0.73, 95% confidence interval [CI] 0.56 to 0.94)<sup>9</sup> and vertebral fractures (RR 0.67, 95% CI 0.45 to 0.98).<sup>10</sup> A subsequent large-scale randomized controlled trial<sup>6</sup> has shown that estrogen plus progestogen were borderline significantly effective in preventing hip (hazard ratio [HR] 0.66, 95% CI 0.45 to 0.98) and vertebral fractures (HR 0.66, 95% CI 0.44 to 0.98), although this significance was not sustained after adjustment for confounders (HR 0.66, 95% CI 0.33 to 1.33 for hip fractures and HR 0.66, 95% CI 0.32 to 1.34 for vertebral fractures). For conjugated estrogens alone, a large-scale randomized controlled trial also showed a reduction in hip (HR 0.61, 95% CI 0.41 to 0.91) and vertebral fractures (RR 0.62, 95% CI 0.42 to 0.93), but again this not sustained after adjustment for confounders (HR 0.61, 95% CI 0.33 to 1.11 for hip fractures, and HR 0.62, 95% CI 0.34 to 1.13 for vertebral fractures).<sup>8</sup>

However, estrogen and estrogen plus progestogens (estrogen therapy: ET or estrogen plus progestogen therapy: EPT) have been associated with detrimental effects in other organ systems. In the breast, EPT has been associated with an increased risk of breast cancer,<sup>6</sup> whereas ET has not been associated with an increased risk of breast cancer.<sup>8</sup> For cardiovascular events, EPT has been associated with an increased risk of myocardial infarction and other cardiac events and an increased risk of cerebrovascular events.<sup>6</sup> ET has been associated with an increased risk of stroke, but not cardiac events.<sup>8</sup> ET is associated with an increased risk of endometrial cancer,<sup>11</sup> but EPT has not.<sup>12</sup> Another concern with ET and EPT is an increased risk of deep venous thromboembolism.<sup>12</sup> Some of the differences between ET and EPT may be linked to the progestogen component of EPT, as the progestogens may possess androgen effects.

The studies mentioned above have mainly been for conjugated estrogens; however similar results have been reported for the native 17-beta-estradiol.<sup>13,14</sup>

## The estrogen receptor

The estrogen receptor per se contains two subgroups: estrogen receptor alpha is located in the breast and endometrium, whereas estrogen receptor beta is located in bone, heart, endothelium and a number of other tissues.<sup>15</sup> Selective actions against subtypes of the estrogen receptor may thus modulate some of the detrimental effects of estrogen and enhance the positive effects.

## SERM

These are drugs with specific actions on subtypes of the estrogen receptor. They are typically agonist/antagonists of the estrogen receptor.

The first clinically used drug in the class was tamoxifene, which is in use as a drug to treat estrogen receptor positive breast cancer. However, tamoxifene suffers some of the same detrimental effects as estrogen such as endometrial cancer.<sup>16</sup> Tamoxifene does not seem to prevent fractures in women with breast cancer<sup>17</sup> although BMD may increase.<sup>18-20</sup>

Raloxifene was marketed as a drug to treat and prevent osteoporosis. It was shown to increase BMD<sup>21</sup> and to reduce the risk of vertebral fractures,<sup>22-26</sup> although the risk of non-vertebral fractures did not seem to decrease.<sup>27</sup> Raloxifene was associated with a significant decrease in the risk of breast cancer (estrogen receptor positive breast cancer).<sup>28,29</sup> It was associated with an increased risk of deep venous thromboembolism<sup>22</sup> and an increased risk of leg cramps.<sup>22</sup> In older women an increased risk of fatal<sup>30</sup> but not

non-fatal strokes has been reported. Raloxifene does not seem to significantly affect the rate of cardiovascular events<sup>30,31</sup> although serum cholesterol levels may decrease.<sup>21</sup> Raloxifene is associated with an increased risk of vasomotor symptoms such as hot flushes.<sup>22</sup> Raloxifene does not seem to stimulate the endometrium<sup>21</sup> although more episodes of endometrial cavity fluid have been reported.<sup>22</sup>

Other SERMs include lasofofoxifene,<sup>32,33</sup> toremifene, idoxifene, arzoxifene, acolbifene and bazedoxifene along with a number of other compounds.<sup>34</sup> For most of these only few clinical data are available.

## Fracture risk

The major determinants of fracture risk are age and gender.<sup>35</sup> Other major determinants include reduced bone mineral density,<sup>36</sup> prior fractures,<sup>37</sup> corticosteroid use,<sup>38,39</sup> smoking,<sup>40,41</sup> alcohol intake,<sup>42</sup> and a number of other factors such as low body weight,<sup>43</sup> reduced eye sight,<sup>44</sup> reduced physical performance,<sup>44</sup> and use of psychotropic drugs.<sup>45–47</sup>

Special scores have been constructed to identify women at high risk of fractures using clinical risk factors<sup>48</sup> in addition to low BMD. This is particularly important as it may be more difficult to show significant fracture risk reductions in randomized controlled trials in women at low risk (say, with low BMD but no prior fractures equivalent to a secondary preventive scenario) than in women at high risk of fractures (women with, say, a prior spine fracture – a tertiary preventive scenario).<sup>49</sup>

A special algorithm, the FRAX algorithm<sup>48</sup> has been constructed to predict expected 10-year risk of fractures (hip or major osteoporotic fractures) based on age (only valid in the range 40 to 90 years), gender, weight, height, prior fracture, parental fracture history, current smoking, glucocorticoid use, rheumatoid arthritis, secondary osteoporosis, alcohol intake, and femoral neck BMD.

## Bazedoxifene

### Methods

The effects of bazedoxifene were reviewed using a systematic search of Pubmed, Embase, and Web of Science on June 19, 2009, using the term ‘bazedoxifene’. This produced a total of 213 unique references (46 from Pubmed, 148 from Embase, and 120 from Web of Science).

### Pharmacokinetics

Bazedoxifene is rapidly absorbed<sup>50</sup> with a  $t_{max}$  of approximately 2 hours and exhibits a linear increase in plasma concentrations for single doses from 0.5 mg up to 120 mg.

Following intravenous administration of a 3 mg dose of bazedoxifene, the volume of distribution is  $14.7 \pm 3.9$  L/kg. Bazedoxifene is highly bound (95.8% to 99.3%) to plasma proteins *in vitro*. Bazedoxifene is extensively metabolized in women. Glucuronidation is the major metabolic pathway. Little or no cytochrome P450-mediated metabolism is evident. Bazedoxifene-5-glucuronide is the major circulating metabolite. The concentrations of this glucuronide are approximately 10-fold higher than those of unchanged active substance in plasma. Bazedoxifene is eliminated with a half-life of approximately 30 hours. Steady-state concentrations are achieved by the second week of once-daily administration. The apparent oral clearance of bazedoxifene is approximately 4 to 5 L/h/kg. The major route of excretion of radio-labeled bazedoxifene is the feces, and less than 1% of the dose is eliminated in urine.<sup>32</sup>

### Pharmacodynamics

The SERMs differ significantly in terms of tissue specificity.<sup>51</sup> Bazedoxifene seems to have less effect on the uterus than estradiol and raloxifene in animal experiments<sup>52</sup> due to lower estrogen receptor alpha agonistic effects.<sup>53</sup> In a study on rats<sup>52</sup> the uterine weight differed significantly between bazedoxifene 0.5 mg/kg (mean  $\pm$  SEM:  $32.7 \pm 2.40$ , 135% of control weight), raloxifene 0.5 mg/kg ( $45.0 \pm 1.23$  mg, 185% of control weight), and conjugated estrogens ( $98.7 \pm 6.30$  mg, 406% of control weight). In human studies bazedoxifene was associated with a decreased thickness of the endometrium at doses of 30 to 40 mg/day compared to placebo or conjugated estrogen plus medroxyprogesterone (mean  $\pm$  SEM increase:  $0.04 \pm 0.12$  mm for 30 mg,  $0.12 \pm 0.11$  mm for 40 mg,  $0.58 \pm 0.21$  mm for placebo, and  $1.60 \pm 0.23$  mm for conjugated estrogen plus medroxyprogesterone acetate after 168 days).<sup>54</sup> This is in contrast to effects of other SERMs such as tamoxifen<sup>16</sup> and raloxifene.<sup>22</sup> In the mammary gland in animals bazedoxifene was more antagonistic to conjugated estrogens than raloxifene and lasofofoxifene.<sup>53</sup> Bazedoxifene thus has more more tissue-specific effects than other SERMs.

### Effects on BMD

In a 2-year, randomized, placebo-controlled, double-blind trial 1434 postmenopausal women ( $\geq 45$  years and  $\geq 1$  year postmenopausal) were randomly allocated in a dose-dependent manner to bazedoxifene (10 [n = 321], 20 [n = 322] or 40 mg/day [n = 319]), raloxifene (60 mg/day, n = 311) or placebo (n = 310).<sup>55</sup> The inclusion criteria were: 1) osteopenia (lumbar spine or femoral neck T-score

between  $-1$  and  $-2.5$ ); or 2) clinical risk factors for osteoporosis (family history of fracture, bilateral oophorectomy, current smoking, weight  $<58$  kg, inadequate calcium intake, or low physical activity).<sup>55</sup> Bazedoxifene was significantly more efficient in increasing BMD than placebo and was equally effective as raloxifene in increasing BMD. There was no significant trend with bazedoxifene dose and BMD.<sup>55</sup> However, at 12 to 24 months bazedoxifene 20 to 40 mg was more efficient in increasing hip BMD than 10 to 20 mg.<sup>55</sup> The patients in this study on bazedoxifene and BMD were in general at low risk of fractures,<sup>55</sup> as they were only osteopenic and had additional risk factors which did not place them at high risk of fractures.

BMD was unchanged at 24 months compared to baseline with bazedoxifene in contrast to a decline with placebo,<sup>55</sup> in contrast to other drugs against osteoporosis, which significantly increase BMD in the range of 3% in the femoral neck and 6.5% in the lumbar spine with alendronate after 24 months.<sup>56</sup> The difference in BMD at 24 months of around 1.5% between bazedoxifene and placebo (around 0.1 Z-scores) would translate into a fracture risk reduction of  $1.5^{-0.1} = 0.95$  (5%) for overall fracture risk and  $2.3^{-0.1} = 0.90$  (10%) for spine fractures using the risk estimates of Marshall et al.<sup>36</sup>

## Effects on fracture risk

In a 3-year, randomized, double-blind, placebo-controlled trial 7492 postmenopausal ( $\geq 2$  years after last menstruation) women aged 55 to 85 years were randomly allocated to 1) bazedoxifene (20 [n = 1886] or 40 [n = 1872] mg/day), 2) raloxifene (60 mg/day, n = 1849), or 3) placebo (n = 1885).<sup>57</sup> The inclusion criteria were: 1)  $\geq 1$  radiologically confirmed spine fracture ( $\geq 20\%$  compression) and lumbar spine and femoral neck T-scores  $> -4$ ; or 2) in the absence of vertebral fractures lumbar spine or femoral neck T-scores should be between  $-2.5$  and  $-4$ .<sup>57</sup> Overall, around two thirds of the included patients completed the trial.<sup>57</sup>

The risk of vertebral fractures decreased with both 20 (HR 0.58, 95% CI 0.38 to 0.89) and 40 (HR 0.63, 95% CI 0.42 to 0.96) mg of bazedoxifene per day compared to placebo.<sup>57</sup> The reduction was in the same range as with raloxifene 60 mg (HR 0.58, 95% CI 0.38 to 0.89).<sup>57</sup> There was no reduction in the risk of non-vertebral fractures.<sup>57</sup>

A subgroup of women with *a priori* high risk of fractures was identified post-hoc. This group had femoral neck T-score ( $-3.0$  or lower) and/or the presence of at least one moderate or severe vertebral fracture or multiple mild vertebral fractures at baseline, result in a subgroup of 1772 women. Restricting the analysis to a post-hoc analysis of these 1772 women with

high risk of fractures showed a 50% reduction in the risk of non-vertebral fractures with the 20 mg dose of bazedoxifene compared to placebo (HR 0.50, 95% CI 0.28 to 0.90).<sup>57</sup> In the 40 mg bazedoxifene group no significant reduction in non-vertebral fractures were seen in this subgroup of women at high risk of fractures (HR 0.70, 95% CI 0.40 to 1.20).<sup>57</sup> In the 20 mg bazedoxifene group at high risk of fractures (n = 1772) the risk of non-vertebral fractures was borderline significantly lower than with raloxifene (HR 0.56, 95% CI 0.31 to 1.01). Also in the 40 mg bazedoxifene group a non-significant trend towards a decrease in non-vertebral fractures compared to raloxifene was seen (HR 0.78, 95% CI 0.45 to 1.35).<sup>57</sup>

At 3 years the absolute risk of morphometric fractures was 4.1 with placebo, 2.3% with 20 mg of bazedoxifene, and 2.5% with 40 mg bazedoxifene.<sup>57</sup> This yields numbers needed to treat of 56 for 20 mg of bazedoxifene and 63 for 40 mg of bazedoxifene for morphometric vertebral fractures, ie, 56 and 63 women have to be treated for 3 years to prevent one morphometric vertebral fracture.<sup>57</sup> For non-vertebral fractures the corresponding numbers needed to treat were 167 for 20 of bazedoxifene and 143 for 40 mg of bazedoxifene (6.3% cumulated risk of non-vertebral fractures after 3 years vs 5.7 and 5.6% respectively).<sup>57</sup> In the high risk group the number needed to treat was 24 and 38 respectively with 20 and 40 mg of bazedoxifene.<sup>57</sup> The latter lower number reflects a 3-year cumulated risk of non-vertebral fractures of 9.1% in the placebo group vs 4.9% and 6.5% with 20 and 40 mg of bazedoxifene, respectively, ie, a much higher absolute risk of fractures.<sup>57</sup> This also reflects that it is much easier to obtain statistical significance with a high absolute fracture risk than with a low risk of fractures.<sup>57</sup> When small differences in absolute risk are converted to compute the numbers needed to treat, seemingly large differences in number are not significant owing to wide confidence intervals because small differences may convert into large numbers.

Kanis et al.<sup>58</sup> re-analyzed the data from the study by Silverman et al.<sup>57</sup> Kanis et al did a post-hoc analysis based on the 10-year modeled risk of major osteoporotic fractures using the FRAX algorithm as co-variate. At a modeled 10-year risk of major osteoporotic fractures above 16%, bazedoxifene was associated with a significant decrease in both morphometric vertebral and clinical fractures.<sup>58</sup> At a 10-year risk of morphometric vertebral of 22%, the hazard ratio for morphometric vertebral fractures was 0.49, 95% CI 0.31 to 0.79 for bazedoxifene vs placebo and for clinical fractures the hazard ratio was 0.68, 95% CI 0.49 to 0.93.<sup>58</sup>

The patients in this trial were thus at significantly higher risk of fractures than the above mentioned trial with BMD as end-point.<sup>55</sup>

## Adverse effects

In the study by Miller et al,<sup>55</sup> deep venous thromboembolism was rare with bazedoxifene (0% to 0.6% with various doses after 2 years) and in the same range as placebo (0.3%). Leg cramps were in the same range as with raloxifene and as with placebo.<sup>55</sup> Hot flushes were in the same range as raloxifene, but a little higher than with placebo.<sup>55</sup> In the study by Silverman et al<sup>57</sup> leg cramps (10.9% to 11.7% with various doses after 3 years) and deep venous thromboembolism (0.4% to 0.5% with various doses after 3 years) were significantly more frequent with bazedoxifene than with placebo (8.2 for leg cramps and 0.2% for deep venous thromboembolism), while breast cyst/fibrocystic breast disease was significantly less frequent.

Extensive monitoring of has cardiovascular side effects been performed, and no difference between bazedoxifene and placebo were observed for myocardial infarction, strokes (ischemic or hemorrhagic strokes), or retinal vein thrombosis.<sup>55,57</sup> This is particularly interesting given the tissue-specific actions of the various estrogen receptors.

## Combinations of bazedoxifene and conjugated estrogens

In general SERMs have been shown to have weaker action on BMD than conjugated estrogen or 17-beta-estradiol.<sup>59</sup> This has led to examination of combinations of bazedoxifene and estrogen. However, at present no definite data on BMD in humans are available. In animals the combination of bazedoxifene and conjugated estrogen showed that with bazedoxifene 3 mg/kg an increase in bone density similar to that for conjugated estrogen 2.5 to 5 mg/kg, but higher than that for 0.5 to 1 mg/kg.<sup>60</sup> The combination of bazedoxifene 3 mg/kg and conjugated estrogen in all doses showed an increase in bone density.<sup>60</sup> However, the increase at the doses of 3 mg/kg of bazedoxifene and 2.5 to 5 mg/kg of conjugated estrogen was a little less than with conjugated estrogen alone, although the difference was not statistically significant.<sup>60</sup> Bazedoxifene plus conjugated estrogen in animals seems to counter some of the detrimental effects seen in humans.<sup>53,54,60</sup> However, more human data are needed.

## Other drugs against osteoporosis

In accordance with the results for bazedoxifene,<sup>57</sup> raloxifene has also been shown to reduce only vertebral but not non-vertebral fractures in the intention-to-treat analysis in randomized controlled trials.<sup>22-26</sup> In contrast, the bisphosphonates alendronate,<sup>56,61</sup> risedronate,<sup>62,63</sup> and zoledronate<sup>64</sup> have been shown to reduce both vertebral and non-vertebral fracture risk in randomized controlled trials. For the other bisphosphonates,

etidronate,<sup>65</sup> ibandronate,<sup>66</sup> pamidronate,<sup>67,68</sup> and clodronate,<sup>69</sup> randomized controlled trials have demonstrated effect only on vertebral fractures. Strontium ranelate has demonstrated effects on vertebral<sup>70</sup> and non-vertebral fractures.<sup>71</sup> The parathyroid hormone teriparatide has been shown to reduce vertebral and non-vertebral fracture risk.<sup>72</sup> However, for recombinant 1-84-PTH only a reduction in vertebral and not non-vertebral fractures has been demonstrated.<sup>73,74</sup>

## Comments

Bazedoxifene has shown effects on the risk of vertebral but not non-vertebral fracture risk in the intention-to-treat analysis in randomized controlled trials, in line with the results for raloxifene.<sup>57</sup> In post-hoc analyses, high risk groups have shown a decrease in non-vertebral fracture risk. However, post-hoc subgroup analyses have been discredited in prior recommendations.<sup>75</sup> It is recommended that any subgroup analyses should be preplanned to avoid searching for significant results.<sup>75</sup> Although subgroup analyses may help to generate hypotheses and explore data, they should be performed and interpreted with caution and should not be used as definite evidence for an effect. By analyzing data in subgroups randomization is usually discouraged, and the analyses are to be graded as cohort studies in terms of level of evidence unless the randomization is stratified on the subgroups.

At present the evidence supports an effect of bazedoxifene on vertebral fractures in postmenopausal women, whereas further studies are needed to establish if an effect on non-vertebral fractures is present in high risk subgroups. The effect of bazedoxifene on the skeleton is thus in line with the effect of raloxifene, and bazedoxifene may be used on the same indications as raloxifene. The value of bazedoxifene may lie in a different risk profile than raloxifene, especially in terms of uterine safety, and bazedoxifene may thus offer an alternative for prevention and treatment of osteoporosis in some groups of women.

## Disclosures

The authors declare no conflicts of interest.

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