REVIEW

Patient considerations in the management of menopausal symptoms: role of conjugated estrogens with bazedoxifene

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Abstract: Menopausal symptoms (eg, hot flushes and vaginal symptoms) are common, often bothersome, and can adversely impact women's sexual functioning, relationships, and quality of life. Estrogen–progestin therapy was previously considered the standard care for hormone therapy (HT) for managing these symptoms in nonhysterectomized women, but has a number of safety and tolerability concerns (eg, breast cancer, stroke, pulmonary embolism, breast pain/tenderness, and vaginal bleeding) and its use has declined dramatically in the past decade since the release of the Women's Health Initiative trial results. Conjugated estrogens paired with bazedoxifene (CE/BZA) represent a newer progestin-free alternative to traditional HT for nonhysterectomized women. CE/BZA has demonstrated efficacy in reducing the frequency and severity of vasomotor symptoms and preventing loss of bone mineral density in postmenopausal women. CE/BZA provides an acceptable level of protection against endometrial hyperplasia and does not increase mammographic breast density. Compared with traditional estrogen–progestin therapy, it is associated with lower rates of breast pain/tenderness and vaginal bleeding. Patient-reported outcomes indicate that CE/BZA improves menopause-specific quality of life, sleep, some measures of sexual function (especially ease of lubrication), and treatment satisfaction. This review looks at the rationale for selection and combination of CE with BZA at the dose ratio in the approved product and provides a detailed look at the efficacy, safety, tolerability, and patient-reported outcomes from the five Phase III trials. Patient considerations in the choice between CE/BZA and traditional HT (eg, tolerability, individual symptoms, and preferences for route of administration) are also considered.

Keywords: menopause, conjugated estrogens/bazedoxifene, hormone therapy, hot flashes, osteoporosis, safety

Introduction

Vasomotor symptoms (VMSs) of menopause occur in ~55%–90% of women,[1–5] and ~70% of women with these hot flushes and night sweats find them bothersome.[6] In addition, ~40%–70% of postmenopausal women experience vaginal/sexual symptoms (eg, discomfort, dryness, soreness, itching, burning, or pain on contact, dyspareunia, diminished libido, and avoidance of intimacy);[3,5] three-fourths of these women say vaginal symptoms have a negative impact on their lives.[3] Life expectancy is increasing,[7] and data suggest, for some women, menopausal symptoms may last many more years than previously suspected.[1,4,5,8]

This review of current and emerging pharmacologic therapies for bothersome menopausal symptoms focuses on efficacy, safety, and patient considerations regarding use of conjugated estrogens/bazedoxifene (CE/BZA). CE/BZA is a relatively new treatment

for women with a uterus who experience moderate-to-severe VMSs; CE/BZA also helps preserve bone mineral density (BMD). CE/BZA provides a progestin-free alternative to traditional estrogen plus progestin therapy for women with a uterus and seeking treatment for menopausal symptoms. As reviewed in this article, by combining estrogens with a selective estrogen receptor modulator (SERM) instead of a progestin, CE/BZA not only offers endometrial protection but may also avoid breast stimulation and have fewer adverse events typically associated with progestin use (eg, breast pain and vaginal bleeding).

Current and emerging management of menopausal symptoms
Oral hormone therapy

According to numerous international guidelines and expert consensus statements, oral hormone therapy (HT) is safe and effective to start in younger postmenopausal women (ie, those <60 years of age or those whose last menstrual period was ≤10 years ago) who have bothersome menopausal symptoms and/or require osteoporosis prevention.[9–14] The optimal duration of HT use is unknown, but the lowest effective dose should be used for the shortest time needed for symptom control;[10,11] duration should also be consistent with the patient's treatment goals. Given the long duration of menopausal symptoms, it may be appropriate to extend the duration of HT use beyond 5 years for some women who continue to require symptom relief[10,11,13–16] and osteoporosis prevention, particularly if they are not candidates for other osteoporosis therapies.[9] The decision of when to terminate HT use should be based on an individualized assessment of the risks and benefits, and should include patient counseling regarding risks of breast cancer and stroke.[15]

Much of what is known from clinical trials about the risk–benefit profile of HT for the prevention of chronic disease has been derived from the two large (N=27,347), randomized, double-blind, placebo-controlled Women's Health Initiative (WHI) trials.[17–19] These trials were conducted in postmenopausal women 50–79 years of age (mean age, ~63–64 years) who were not required to have menopausal symptoms.[17–19] (In fact, at baseline, only 12.7% of women randomized to conjugated estrogens/medroxyprogesterone acetate [CE/MPA] and 12.2% of those in the placebo group had moderate or severe VSMs.[20]).

Both the study of CE alone in hysterectomized women and the study of CE/MPA in nonhysterectomized women failed to demonstrate a reduction in coronary heart disease (CHD) in their overall population, which was the primary efficacy end point.[17,18] The CE/MPA trial was terminated early by its data safety and monitoring board based on the lack

of cardioprotection (and possible increase in CHD) coupled with increased risks of breast cancer, stroke, and pulmonary embolism.[18] The trial of CE alone was subsequently terminated early by the National Institutes of Health based on the lack of cardioprotection and increased risk of stroke, despite the fact that none of the predetermined stopping points had been met.[17] Although CE/MPA was associated with increased risks of breast cancer and related mortality,[21,22] no such increases were found in the trial of CE alone; in fact, there was a possible protective effect that became statistically significant in the postintervention period.[19,23] Thus, CE alone from a relative risk perspective appeared to be safer than CE/MPA with regard to risks of breast cancer and CHD.[19] Furthermore, progestin-related adverse effects (eg, breast tenderness and vaginal bleeding) are often poorly tolerated and may contribute to poor compliance and discontinuation of HT.[24,25] However, omitting the progestin and giving CE alone is not an option for nonhysterectomized women because unopposed estrogens can result in hyperplasia and other unwanted effects on the endometrium in a menopausal woman.[13] The inclusion of a progestin has been clearly demonstrated to counter these effects.[12,13]

Benefits of HT identified in the WHI trials include significant reductions in osteoporotic fractures,[17–19] self-reported VMSs, diabetes, joint pain, and (for CE/MPA only) colorectal cancer.[19] It should be noted that findings from the WHI trials, both positive and negative, apply specifically to CE and CE/MPA; it is unknown whether similar results would be obtained with other HT formulations.

Rates of HT use have declined dramatically since the WHI trials, such that HT is now used by <10% of postmenopausal women in most developed countries in Europe (Figure 1A) and the USA (Figure 1B).[26,27] Given the high prevalence of bothersome symptoms,[1,6] low rates of HT use suggest undertreatment of menopausal symptoms. Indeed, a survey of postmenopausal women in the USA, conducted by the Endocrine Society, revealed that nearly three-fourths of women with menopausal symptoms had not been treated for them.[28] Untreated VMSs are associated with greater absenteeism and health care costs, as well as impaired quality of life and personal relationships.[29,30] A recent survey of Australian women determined that moderate-to-severe VMSs have an adverse impact on psychological well-being that is comparable to that of housing insecurity and greater than that of obesity or being a caregiver for a family member with special needs.[31] Vaginal discomfort related to menopause can interfere with libido, intimate relationships, self-esteem, and quality of life.[3,32,33]

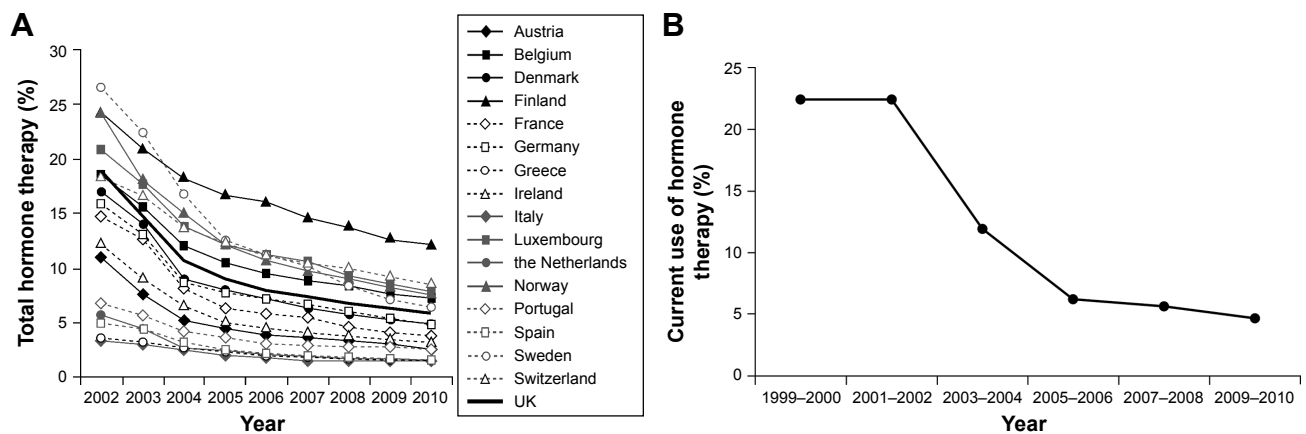The decline in use of traditional HT has been accompanied by increasing popularity of custom-compounded

Figure 1 Changes in estimated proportion of women aged 45–69 years using menopausal hormone therapy in 17 European countries from 2002 to 2010 (**A**). Changes in estimated proportion of women aged ≥40 years reporting current use of oral postmenopausal hormones from 1999 to 2010 in the USA (**B**).
Notes: (**A**) Reprinted from *Maturitas*, 2014;79(3), Ameye L, Antoine C, Paesmans M, de Azambuja E, Rozenberg S, Menopausal hormone therapy use in 17 European countries during the last decade, Pages 287–291,[26] Copyright ©2014, with permission from Elsevier. (**B**) Data from Sprague et al.[27]

bioidentical HT, which is used by an estimated 1–2.5 million US women annually.[34] This trend is troublesome given the lack of evidence supporting the efficacy and safety of compounded bioidentical HT and the potential for additional risks due to variable purity, potency, and quality.[35]

Benefits and safety of HT for treatment of menopausal symptoms in younger women shortly after menopause were not addressed by the WHI results. Reanalyses of the WHI trials suggested lower risks of CHD, stroke, and a global index of events (ie, CHD, stroke, pulmonary embolism, breast cancer, colorectal cancer, endometrial cancer, hip fracture, or all-cause mortality) among women in their 50s and/or women closer to menopause compared with older women and women who have been postmenopausal longer.[36] For example, in the trial of CE alone, although not statistically significant, the hazard ratio (95% confidence interval [CI]) for CHD was 0.63 (0.36–1.09) in women 50–59 years indicating a possible protective effect, whereas it was 0.94 (0.71–1.24) in women aged 60–69 years and 1.13 (0.82–1.54) in women 70–79 years of age.[36] Breast cancer risk with CE/MPA, however, was not lower in this younger group.[22]

Other forms of hormonal therapy

HT formulations with vaginal or transdermal routes of administration are also available. Selection of the route of administration should take into account the individual woman's symptoms and preferences. Vaginal estrogens are recommended if the only bothersome menopausal symptoms are genitourinary in nature.[11,13,37] This is likely to be a small proportion of younger postmenopausal women because a majority of such women have VMSs.[2]

It has been hypothesized based on observational data that transdermal estrogens' avoidance of first-pass hepatic metabolism

may result in reduced risk of venous thromboembolism (VTE), and that lower doses used with transdermal administration may also result in lower rates of dose-related adverse effects (eg, breast tenderness and vaginal bleeding).[38] However, most of these safety and tolerability outcomes have not been compared in head-to-head randomized trials of transdermal versus oral HT, so these claims are as yet unproven.

In fact, in a subset analysis of the Kronos Early Estrogen Prevention Study (KEEPS), one of the few comparative trials, the authors concluded that there was no significant difference between transdermal 17-β-estradiol 50 µg/d with oral micronized progesterone 200 mg/d, oral CE 0.45 mg/d with oral micronized progesterone 200 mg/d, or placebo with regard to the occurrence or the severity of breast pain.[39] Although the incidence of breast pain (collected at baseline and yearly with the Mayo Clinic Breast Pain Questionnaire) before and during treatment was not significantly different across the treatment groups (*P*=0.78 before treatment; *P*=0.18 during treatment), a numerically higher proportion of women developed new-onset breast pain during treatment in the transdermal group (18 out of 31 women without baseline pain [58%]) than in the oral HT group (12 out of 32 women without baseline pain [38%]) or the placebo group (15 out of 39 women without baseline pain [38%]) (Figure 2).[39] The transdermal and oral formulations both had neutral effects on endothelial dysfunction (measured via pulse volume digital tonometry) and, compared with placebo, both significantly improved VMSs to a similar extent.[40]

The KEEPS study was not designed to evaluate differences between the treatments with regard to VTE rates. However, KEEPS did evaluate effects on platelet count and function (as a marker of thrombotic risk) in a subgroup of 117 women and found that neither formulation had a significant effect on general platelet characteristics, including platelet
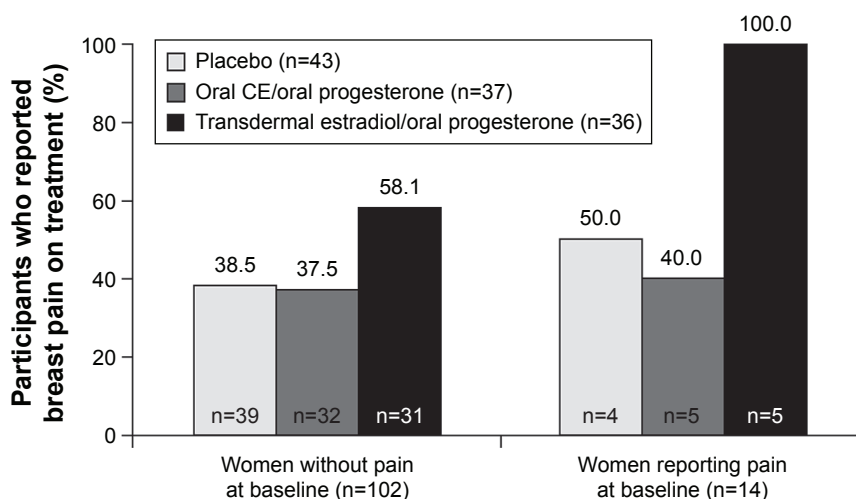
Figure 2 Incidence of breast pain during treatment with transdermal estradiol/oral micronized progesterone, oral CE/oral micronized progesterone, or placebo in women with and without baseline pain in KEEPS.
Note: P=0.18 for Pearson's chi-square test of differences among treatment groups versus baseline.
Abbreviations: CE, conjugated estrogens; KEEPS, Kronos Early Estrogen Prevention Study.

count, spontaneous micro-aggregation (a test of platelet sensitivity), or expression of surface receptors for P-selectin or fibrinogen.[41] Both oral and transdermal estrogens had comparable effects on platelet proteins, and transdermal estrogens (but not oral estrogens) increased the number of tissue factor-positive microvesicles and platelet-derived microvesicles, indicative of cellular activation and a proco-agulant environment.[41]

Ospemifene, a SERM, is an oral therapy indicated for dyspareunia.[42] In two 12-week Phase III clinical trials, ospemifene at the approved dose of 60 mg/d significantly improved the vaginal maturation index (P<0.001) and vaginal pH (P<0.001) and reduced dyspareunia (P<0.05) compared with placebo in postmenopausal women with vulvar-vaginal atrophy,[43,44] which is now considered a component of the genitourinary syndrome of menopause.[45] Hot flushes were an adverse event,[43,44,46] typical of SERMs,[47–49] so ospemifene may not be an ideal choice for women who are already experiencing bothersome VMSs. Endometrial effects of ospemifene were reported to be negligible[43] or not clinically meaningful,[44] although minor increases in endometrial thickness were observed, along with a couple of cases of active endometrial proliferation. There were no cases of endometrial hyperplasia or carcinoma observed in the core studies or a 40-week extension of the first trial.[43,46]

Finally, as noted earlier, CE/BZA is the first successfully developed progestin-free, estrogen-based therapy for nonhysterectomized women consisting of a combination of estrogens and a SERM. CE/BZA is reviewed in detail beginning on the next page.

Nonhormonal therapies

The selective serotonin reuptake inhibitor paroxetine is the first nonhormonal prescription therapy approved by the US Food and Drug Administration for treatment of moderate-to-severe menopausal VMSs.[50] In two randomized Phase III clinical trials, paroxetine reduced moderate-to-severe VMSs by ~0.9/d and 1.4/d relative to placebo at week 12 (P<0.01 and P=0.0001, respectively).[51] As the average daily number of hot flushes at baseline was 11.8 and 10.8, this amounts to a 7.6% and 13.0% reduction in hot flush frequency for paroxetine relative to placebo. VMS severity was also significantly reduced at week 12 in one study (P<0.05).[51] Paroxetine did not adversely affect weight or sexual function.[52] No comparative data are available, but the magnitude of effect paroxetine has on VMSs appears to be less than what is typically seen with HT. Paroxetine has no favorable bone effects (unlike estrogens), and despite the low dose (7.5 mg/d) used for this indication, it may have adverse effects characteristic of selective serotonin reuptake inhibitors (eg, fatigue and somnolence).[50] Thus, paroxetine should be considered an alternative for women who are not candidates for HT.

The serotonin–norepinephrine reuptake inhibitor desvenlafaxine is approved for treatment of menopausal symptoms in Mexico, the Philippines, and Thailand, but not the USA or most of Europe. In a randomized controlled trial, desvenlafaxine 100 mg/d reduced the frequency of moderate-to-severe hot flushes by 2–3/d relative to placebo (P<0.001), and also significantly reduced hot flush severity (P<0.01); these effects were well maintained for 12 months.[53]

Emerging treatments

A number of investigational therapies are in late-stage clinical trials. TX-004HR is a vaginal estradiol suppository that is currently in Phase III development.[54] TX-001HR is an oral HT that combines 17-β-estradiol and progesterone into a single peanut-oil-free capsule, whereas these hormones are currently available only separately or through pharmacy compounding.[55,56] Pharmacokinetic results show that the bioavailability of estradiol and progesterone with the new combination product is similar to that of commercially available formulations of the separate components.[56] A Phase III trial of TX-001HR is ongoing.[55,57]

Nonhormonal psychotropic therapies (eg, escitalopram,[58] sertraline,[59] venlafaxine,[60] and gastroretentive gabapentin[61]) have shown modest reductions in hot flushes in clinical studies of postmenopausal women. However, with the exception of gastroretentive gabapentin, they generally have not been studied in large populations of women with at least seven moderate-to-severe hot flushes per day, or 50/wk, as required by the Food and Drug Administration.

Rationale for development of CE/BZA

In an attempt to develop a safe, well-tolerated, progestin-free option for nonhysterectomized women, it was hypothesized that combining estrogens with a SERM might retain beneficial estrogenic effects on VMSs and bone while blocking the known estrogenic effects of estrogens on the endometrium and breast tissue.[62,63]

The combination CE/BZA has proven uniquely suitable for development. CE has a long history of use and has been well studied. At a dose of 0.625 mg/d, CE was extensively investigated in the WHI trials because it was the most commonly used estrogen formulation.[19] Although estradiol is sometimes touted as a more natural or bioidentical hormone, it is unclear whether there is an actual advantage to one estrogen formulation over another. Observational studies largely report little to no statistically significant difference in their relative effects on VTE, CHD, and stroke risk,[64–66] and no randomized comparative trials with adequate power to evaluate these endpoints have been conducted. The KEEPS study, described earlier, is the only direct comparison of their relative safety.

BZA is a unique SERM in that it degrades the estrogen receptors in breast and endometrial tissue, similar to fulvestrant.[67–72] Preclinical investigations showed that BZA countered the stimulating effects of estrogens in the endometrium and breast when they were coadministered, whereas

other SERMs provided less protection against stimulation of these tissues.[67,68,70,71,73,74] In fact, a clinical trial of 17-β-estradiol/raloxifene found this combination to result in significant increases in endometrial thickness; in addition, among 91 women who underwent postbaseline endometrial biopsy, cases of endometrial proliferation (estradiol/raloxifene: n=7; raloxifene alone: n=3) and hyperplasia (estradiol/raloxifene: n=2; raloxifene alone: n=0) were found.[75]

After selection of CE and BZA as the best combination for development, it was necessary to identify the optimal dose ratio that would allow for both endometrial protection and therapeutic efficacy. Based on results of Phase II and III dose-finding studies,[76–78] combinations of BZA 20 mg with either CE 0.45 mg or 0.625 mg were determined to best achieve this balance. A series of Phase III trials named the Selective estrogens, Menopause, And Response to Therapy (SMART) trials provide data on the efficacy and safety of these two doses of CE/BZA.

Efficacy of CE/BZA in the SMART trials

The first two SMART trials, SMART-1 and SMART-2, demonstrated significant reductions in hot flush frequency and severity in generally healthy postmenopausal women who had at least seven moderate or severe hot flushes per day or 50/wk at baseline.[78,79] In these two trials, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg reduced the mean number of moderate-to-severe hot flushes by ~8–9/d at 12 weeks of treatment compared with being reduced by ~2.5 and 5 in the placebo groups of SMART-1 and SMART-2, respectively (all $P<0.001$ vs placebo); improvements were sustained throughout 2 years of treatment in SMART-1.[78,79] (It should be noted that placebo response rates are typically high [eg, 52% at week 12 in SMART-2[79]] and may be sustained in treatment of menopausal hot flushes.)[80] Similarly, in SMART-1 and SMART-2, respectively, the mean daily hot flush severity rating (1= mild, 2= moderate, and 3= severe) decreased by 1.0 and 0.9 in the CE 0.45 mg/BZA 20 mg arms and 1.1 and 1.2 points in the CE 0.625 mg/BZA 20 mg arms compared with reductions of 0.21 and 0.26 in the placebo arms (all $P<0.001$ vs placebo) (data on file).[78,79] A post hoc analysis of these two trials confirmed that women with both <5 and ≥5 years since menopause achieved significant reductions in hot flush frequency and severity.[81]

CE/BZA (CE 0.45 mg/BZA 20 mg; Duavee®) is approved for the prevention of postmenopausal osteoporosis in the USA and Korea. CE/BZA was shown to reduce bone loss in SMART-1, SMART-4, and SMART-5, whereas patients in

the placebo groups lost BMD; CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg were associated with gains in nearly all BMD outcomes, albeit more modest ones compared with CE/MPA (Table 1).[82–84] CE/BZA also significantly reduced bone turnover compared with placebo based on changes in serum levels of osteocalcin and C-telopeptide.[82–84]

CE/BZA has not been approved for treatment of vulvar-vaginal symptoms of menopause. However, women taking CE/BZA for other indications may experience some benefits with regard to vaginal health. The SMART-3 trial enrolled postmenopausal women with <5% superficial cells on vaginal cytological smear; a vaginal pH >5; and vaginal dryness, itching/irritation, or pain with sexual intercourse were their most bothersome symptom.[85] At 12 weeks, both doses significantly increased superficial cells, decreased parabasal cells, alleviated vaginal dryness, and improved self-reported sexual function, especially ease of lubrication.[85,86] The higher dose (which is not commercially available) also significantly decreased vaginal pH and improved the most bothersome vaginal symptom.[85]

Safety of CE/BZA in the SMART trials
Endometrial safety

CE/BZA's effect on the risk of endometrial hyperplasia at 12 months was evaluated as a primary end point of SMART-1 and SMART-5.[77,84] Without a progestin, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg were associated with a <1% incidence of hyperplasia with an upper limit of the 95% CI <2%, which was similar to placebo.[77,84] This low rate of endometrial hyperplasia meets the US and European Union regulatory requirements for endometrial safety.[87,88] Of note, CE/BZA formulations containing only 10 mg of BZA in SMART-1 and a formulation of CE 0.625 mg/BZA 20 mg used only in SMART-4 that was found to have reduced BZA bio-availability were associated with potentially inadequate endometrial protection, which attests to the importance of utilizing the currently approved combination of CE/BZA to ensure that the optimal dose ratio is maintained.[77,83] BZA is believed to block estrogen-stimulated proliferation in the endometrium by inhibiting estrogen-mediated expression of proliferative genes while maintaining expression of antiproliferative genes;[89] this

Table 1 Effects of CE/BZA on BMD at month 12 in SMART-1,[&] SMART-4,[#] and SMART-5[$] (data on file)

	BMD, adjusted mean (SE) percentage change from baseline at month 12			
	CE 0.45 mg/ BZA 20 mg	CE 0.625 mg/ BZA 20 mg	CE 0.45 mg/ MPA 1.5 mg	Placebo
SMART-1 substudy I[a]				
Lumbar spine	1.45 (0.25)*	1.59 (0.25)*	–	−1.14 (0.25)
Total hip	1.06 (0.17)*	1.10 (0.17)*	–	−0.44 (0.17)
Femoral neck	0.65 (0.21)*	0.58 (0.21)*	–	−0.67 (0.21)
Femoral trochanter	1.86 (0.28)*	1.72 (0.28)*	–	−0.09 (0.28)
SMART-1 substudy II[a]				
Lumbar spine	1.08 (0.28)*	1.05 (0.29)*	–	−1.78 (0.29)
Total hip	0.64 (0.20)*	0.26 (0.21)*	–	−0.86 (0.21)
Femoral neck	−0.16 (0.29)**	0.12 (0.30)*	–	−1.27 (0.29)
Femoral trochanter	0.79 (0.27)*	0.85 (0.28)*	–	−1.07 (0.28)
SMART-4				
Lumbar spine	0.80 (0.24)*	0.80 (0.24)*	2.22 (0.37)*	−1.56 (0.35)
Total hip	0.62 (0.19)*	0.84 (0.19)*	1.47 (0.29)*	−0.99 (0.27)
Femoral neck	0.53 (0.24)*	0.69 (0.24)*	0.20 (0.36)*	−1.95 (0.34)
Femoral trochanter	1.20 (0.24)*	1.18 (0.24)*	2.29 (0.36)*	−1.05 (0.34)
SMART-5				
Lumbar spine	0.24 (0.29)*	0.60 (0.27)*	1.30 (0.39)*	−1.28 (0.28)
Total hip	0.50 (0.20)*	0.89 (0.18)*	0.71 (0.26)*	−0.72 (0.18)
Femoral neck	−0.07 (0.26)**	0.84 (0.24)*	0.52 (0.34)*	−1.00 (0.24)
Femoral trochanter	1.31 (0.31)*	1.57 (0.29)*	1.35 (0.41)*	−0.29 (0.29)

Notes: [a]SMART-1 substudy I: women >5 years postmenopausal; SMART-1 substudy II: women 1–5 years postmenopausal. Both substudies enrolled women with lumbar spine or total hip BMD T-scores between −1 and −2.5 (inclusive) and at least one additional osteoporosis risk factor at screening. Risk factors included Caucasian or Asian race, early menopause (≤40 years of age), family history of osteoporosis, current smoking, low-calcium diet, history of excessive alcohol use, inactive lifestyle, and a thin and/or small frame (weight <50 kg and/or BMI <18 kg/m²). *P<0.001 versus placebo. **P<0.01 versus placebo. [&]Reprinted from *Fertil Steril*, 2009;92(3), Lindsay R, Gallagher JC, Kagan R, Pickar JH, Constantine G, Efficacy of tissue-selective estrogen complex of bazedoxifene/conjugated estrogens for osteoporosis prevention in at-risk postmenopausal women, pages 1045–1052,[82] Copyright ©2009, with permission of Elsevier. [#]Effects of bazedoxifene/conjugated estrogens on endometrial safety and bone in postmenopausal women, Mirkin S, Komm BS, Pan K, Chines AA, *Climacteric*, 2013;16(3):338–346,[83] reprinted by permission of the publisher (Taylor and Francis Ltd, http://www.tandfonline.com). [$]Adapted with permission of Endocrine Society, from Effects of bazedoxifene/conjugated estrogens on the endometrium and bone: a randomized trial, Pinkerton JV, Harvey JA, Lindsay R, et al; SMART-5 Investigators, *J Clin Endocrinol Metab*, 2014;99(2):E189–E198,[84] Copyright © 1952; permission conveyed through Copyright Clearance Center, Inc.
Abbreviations: CE, conjugated estrogens; BZA, bazedoxifene; BMD, bone mineral density; SMART, Selective estrogens, Menopause, And Response to Therapy; SE, standard error; MPA, medroxyprogesterone acetate; BMI, body mass index.

differs from progestins, which counter estrogenic activity in the endometrium by inducing epithelial differentiation as well as downregulation of estrogen receptors.[90]

In a pooled analysis of gynecologic safety data from all five SMART trials,[91] there was only one case of endometrial cancer, which occurred in a woman taking CE 0.45 mg/BZA 20 mg. The incidence rate for endometrial cancer among women taking CE 0.45 mg/BZA 20 mg was determined to be 0.4 per 1,000 woman-years (95% CI, 0.0–2.4) with a relative risk compared with placebo of 0.9 (95% CI, 0.2–4.8). (A relative risk of 1 would indicate equivalent risk between the two treatments, whereas a relative risk <1 suggests a protective effect and a relative risk >1 suggests an association with increased risk).

Breast safety

Effects of any menopausal hormonal therapy on breast safety must be carefully evaluated. CE and BZA each separately have demonstrated good breast safety in clinical trials. In the WHI trial, CE alone in hysterectomized women did not adversely affect the breast; in fact, it was associated with a reduction in breast cancer incidence and related mortality that persisted even after discontinuation.[23] In a 7-year clinical trial of postmenopausal women with osteoporosis, BZA alone had a neutral effect on the breast, with a low breast cancer incidence and breast stimulation similar to that of placebo.[92]

CE/BZA did not significantly affect the percentage of dense breast tissue on mammography compared with placebo in substudies of SMART-1 and SMART-5.[93,94] In contrast, CE/MPA (an active comparator in SMART-5) did significantly ($P<0.001$) increase breast density compared with placebo,[94] as it also did in the WHI trial.[95] These findings are potentially clinically relevant because higher breast density is associated with reduced ability to detect breast cancer on mammography and may be an independent risk factor for breast cancer.[96–98]

In a pooled analysis of all five SMART trials,[91] the incidence of breast cancer was 0.3% with CE 0.45 mg/BZA 20 mg, 0.0% with CE 0.625 mg/BZA 20 mg, and 0.2% with placebo. The incidence rate per 1,000 woman-years was estimated to be 1.0 (95% CI, 0.0–3.2), 0.0 (95% CI, 0.0–1.5), and 1.4 (95% CI, 0.0–4.2), respectively. Relative risk of breast cancer with CE 0.45 mg/BZA 20 mg compared with placebo was 1.1 (95% CI, 0.3–3.8). The longest SMART trials were 2 years, so longer term safety, including breast cancer risk, remains to be confirmed. CE alone was given to hysterectomized women in the WHI trial for a median of ~6 years, and in another study BZA alone was given to women with

postmenopausal osteoporosis for up to 7 years, both without evidence of an increase in breast cancer incidence.[23,99] CE/BZA has not been studied in women at high risk for breast cancer.

Thromboembolic, cerebrovascular, and cardiovascular safety

An increased risk of VTE has been reported in users of estrogens as well as users of clinically available SERMS, and this association has been independently found with CE and BZA. In the WHI trial, CE alone was associated with an increased risk of deep vein thrombosis (hazard ratio [HR] 1.48, 95% CI, 1.06–2.07) and pulmonary embolism, although the latter did not achieve statistical significance (HR 1.35, 95% CI, 0.89–2.05).[19] In postmenopausal women with osteoporosis, BZA 20 mg was associated with a statistically significant increase in the risk of deep vein thrombosis over 7 years (HR 3.38, 95% CI, 1.01–11.39); pulmonary embolism occurred in 2% of both the BZA and placebo groups.[92]

When CE and BZA are combined, the risk does not appear to be additive.[100] In a pooled analysis of the five SMART trials, the incidence of VTE was 0.2% in the CE 0.45 mg/BZA 20 mg group, 0.0% in the CE 0.625 mg/BZA 20 mg group, and 0.1% in the placebo group, and all of the VTEs were deep vein thromboses.[100] In the CE 0.45 mg/BZA 20 mg group, the rate per 1,000 woman-years was 0.3 (95% CI, 0.0–2.0) and the relative risk versus placebo was 0.9 (0.2–4.1).[100] Given the low number of VTE events in the SMART trials and the incomplete understanding as to the mechanism by which estrogens and SERMs may contribute to VTE risk, the true risk of VTE with CE/BZA remains unknown. Because the increased risk of VTE associated with CE has been shown to occur early, particularly in the first 2 years of treatment, with modest increases thereafter,[101] the low rate of VTE in the 2-year SMART-1 trial (relative risk of VTE for CE/BZA vs placebo: 0.48 [95% CI, 0.05–4.66]) is reassuring.[78]

Stroke occurred in one SMART trial participant treated with CE 0.45 mg/BZA 20 mg (0.06%) and one treated with CE 0.625 mg/BZA 20 mg (0.06%) compared with none in the placebo group.[100] The rate per 1,000 woman-years was 0.4 (95% CI, 0.0–2.4) and 0.2 (95% CI, 0.0–1.9) for the approved dose and higher dose of CE/BZA, respectively, and for both doses, the relative risk versus placebo was 0.9 (95% CI, 0.2–4.8).[100] As with VTE, the low number of events prohibits definitive conclusions regarding the effect of CE/BZA on stroke risk.

In the pooled analysis of the SMART trials, the rate of any CHD event was 0.3% with either dose of CE/BZA compared

with 0.2% in the placebo group, and the rate of myocardial infarction was 0.2% for both CE 0.45 mg/BZA 20 mg and placebo and 0.1% with CE 0.625 mg/BZA 20 mg.[100] The rate of any CHD event per 1,000 woman-years was 2.6 (95% CI, 0.0–5.6) with CE 0.45 mg/BZA 20 mg, 1.4 (95% CI, 0.0–3.9) with CE 0.625 mg/BZA 20 mg, and 2.0 (95% CI, 0.0–5.2) with placebo.[100] The relative risk versus placebo was 0.9 (95% CI, 0.3–2.9) for the approved dose and 1.0 (95% CI, 0.3–3.1) for the higher dose.[100] A pooled analysis of 12- and 24-month data from the three longest trials (SMART-1, SMART-4, and SMART-5) reported that CE/BZA significantly ($P<0.001$) decreased total cholesterol and low-density lipoprotein cholesterol, and increased high-density lipoprotein cholesterol and triglycerides compared with placebo – a pattern that is consistent with the effects of traditional HT.[102]

Patient considerations: tolerability of CE/BZA versus other HT

Breast pain/tenderness and vaginal bleeding are common complaints of women using traditional HT. Based on data from the WHI, users of HT are more than four times as likely to experience breast tenderness or vaginal bleeding compared with nonusers.[24] In contrast, in SMART-1 and SMART-5, the incidence of breast pain/tenderness with CE/BZA was comparable to placebo, whereas significantly ($P<0.001$) higher rates of breast tenderness were observed with CE/MPA than CE/BZA in SMART-5 (Figure 3).[78,84,94] Similarly, in SMART-1 and SMART-5,[84,103] CE/BZA was associated with high rates of amenorrhea and low rates of bleeding/spotting, similar to placebo, whereas bleeding/spotting rates were significantly ($P<0.001$) higher with CE/MPA than CE/BZA in SMART-5 (Figure 4).[104] These adverse events may be more than just nuisance effects. Breast pain/tenderness has been reported to be associated with an increase in breast density on mammography[95] as well as increased risk of breast cancer.[105] Breakthrough bleeding is not only inconvenient but can also lead to endometrial sonograms, biopsies, and hysteroscopies, which result in unnecessary anxiety and costs.

In some studies, progestin-based therapies have also been associated with mood symptoms (eg, depression and anxiety). In a randomized, placebo-controlled trial, CE/MPA was associated with a significant ($P=0.01$) increase in depression in women who had not undergone hysterectomy, based on daily ratings on the Prospective Record of the Impact and Severity of Menstrual Symptoms calendar (though depressive symptoms were mostly considered mild and not troublesome); no such increase was found among
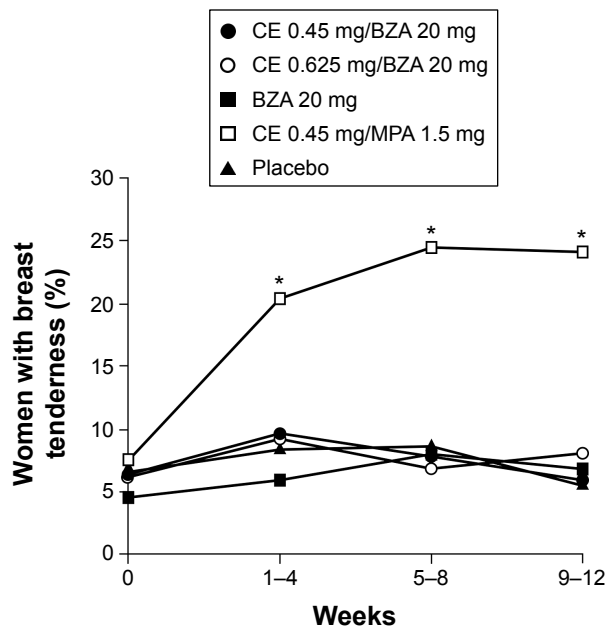

Figure 3 Percentage of women reporting ≥1 day of breast tenderness in daily diaries during 4-week intervals through 12 weeks in SMART-5.
Notes: *$P<0.001$ for CE/MPA versus all other treatment groups. There were no statistically significant differences between either dose of CE/BZA and placebo. Pinkerton JV, Harvey JA, Pan K, et al. Breast effects of bazedoxifene-conjugated estrogens: a randomized controlled trial. *Obstet Gynecol.* 2013;121(5):959–968.[94] Promotional and commercial use of the material in print, digital or mobile device format is prohibited without the permission from the publisher Wolters Kluwer Health. Please contact healthpermissions@wolterskluwer.com for further information.
Abbreviations: SMART, Selective estrogens, Menopause, And Response to Therapy; CE, conjugated estrogens; MPA, medroxyprogesterone acetate; BZA, bazedoxifene.

hysterectomized women taking CE alone.[106] A study using data from the Korean National Health and Nutrition Examination Survey V found an increased risk of depression among women who initiated HT before age 48 (vs never users; OR 3.86, 95% CI, 2.10–7.09), and the odds of depression increased with longer HT use (P-trend <0.001).[107] Not all studies of HT have shown adverse effects on mood, however. In the WHI trial, CE/MPA had a neutral effect on mood swings compared with placebo,[24] and in the randomized, placebo-controlled KEEPS-Cognitive and Affective Study (KEEPS-Cog) of perimenopausal and early postmenopausal women, oral CE with cyclical oral micronized progesterone was found to significantly reduce tension-anxiety (small to medium effect size) and depression-dejection scores (medium effect size) on the Profile of Mood States compared with placebo.[108] These benefits with regard to mood were not observed with transdermal estradiol plus oral micronized progesterone, though the formulations provided comparable benefits with regard to reduction of VMSs.[108]

Menopausal hormonal therapy may also adversely affect insulin sensitivity. In a randomized, placebo-controlled trial,
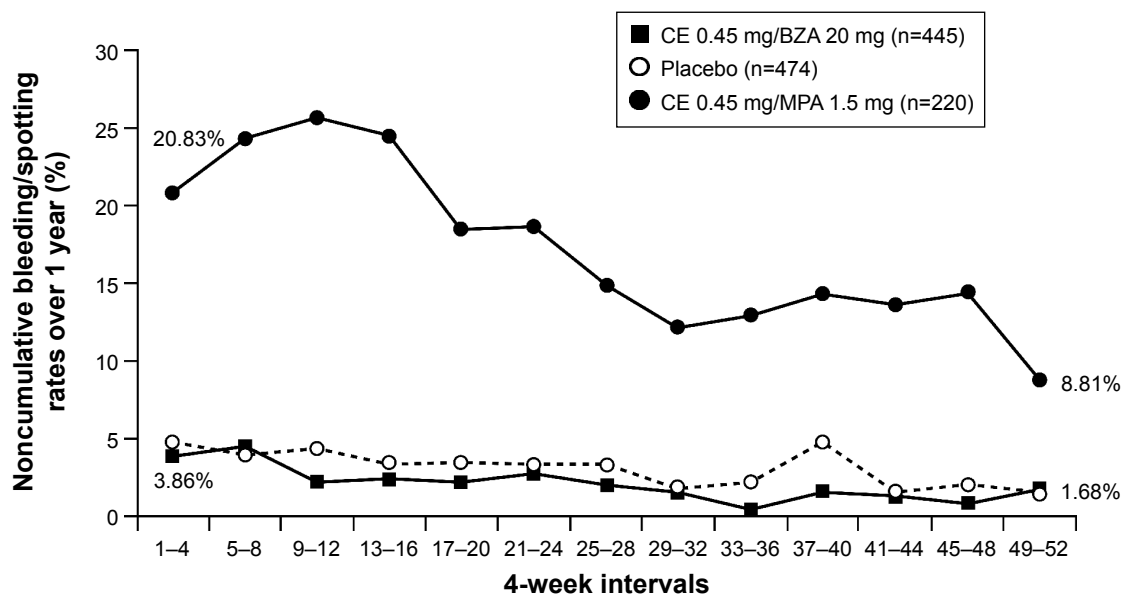
Figure 4 Bleeding/spotting rates over 1 year of treatment with CE/BZA compared to CE/MPA in SMART-5.[104]
Note: *P*<0.001 for all values versus CE/MPA.
Abbreviations: CE, conjugated estrogens; BZA, bazedoxifene; MPA, medroxyprogesterone acetate; SMART, Selective estrogens, Menopause, And Response to Therapy.

CE/MPA reduced insulin sensitivity by 17% without altering body composition, fat distribution, or body weight.[109] The effect persisted throughout the 2 years of treatment but was reversible after treatment discontinuation.[109] Other preclinical and clinical studies suggest that estrogens increase insulin sensitivity, but this effect is countered by progestogens, which are associated with hyperinsulinemia and decreased insulin sensitivity or glucose tolerance.[110–112] Effects of CE/BZA on mood and insulin sensitivity have not been reported; however, women who experience these effects while taking estrogen/progestin therapy may wish to consider a trial of CE/BZA as an alternative, progestin-free option.

Patient-specific outcomes

Data from the SMART trials also indicate that CE/BZA improves various patient-reported outcomes, including menopause-specific quality of life, sleep, and treatment satisfaction.

Menopause-specific quality of life was evaluated in SMART-1, -2, -3, and -5 using the Menopause-Specific Quality of Life Questionnaire.[113] Although the studies enrolled different populations (generally healthy women, women with moderate-to-severe VMSs, and women with vulvar-vaginal symptoms), both doses of CE/BZA significantly improved overall Menopause-Specific Quality of Life Questionnaire scores and vasomotor function subscale scores in all four studies at virtually all time points through 24 months.[113] In the SMART trial participants with VMSs at

baseline (SMART-2 and SMART-5), the improvements in vasomotor functioning with CE 0.45 mg/BZA 20 mg versus placebo exceeded previously established, clinically important differences.[113] Both doses of CE/BZA improved the sexual functioning domain score in SMART-1 and SMART-3, and the higher dose also improved sexual functioning scores in SMART-2 and SMART-5.[113] Women in SMART-3, who had vulvar-vaginal symptoms at baseline, experienced the greatest improvements in sexual functioning, which were statistically significant, although they did not exceed clinically important differences.[113]

The effects of CE/BZA on sleep were evaluated in SMART-2 and SMART-5 using the Medical Outcomes Study (MOS) sleep scale.[114,115] Both doses of CE/BZA significantly reduced the time it takes to fall asleep and the amount of sleep disturbance in both studies.[114,115] Both doses also improved sleep adequacy as well as scores on two sleep indices from the MOS sleep scale measuring overall sleep problems in SMART-2, whereas improvements on these outcomes were seen only with CE 0.625 mg/BZA 20 mg in SMART-5.[114,115] Effect sizes for these improvements, reported in SMART-2, were medium to large.[114] In SMART-5, CE/MPA also improved time to fall asleep, sleep disturbance, sleep adequacy, and both sleep problem indices on the MOS sleep scale compared with placebo.[115]

Using mediation modeling, Pinkerton et al[116] concluded that at week 12, a majority (78%–86%) of CE/BZA's beneficial effects on sleep disturbance in the SMART-2 population

of women with frequent moderate-to-severe hot flushes at baseline were attributable to direct effects rather than indirect effects resulting from reduction in the bothersomeness of hot flushes. However, the opposite was found in the SMART-5 population of women with less severe VMS: reduction of hot flushes accounted for 75%–92% of the effects on sleep disturbance.[116] In an analysis of a subgroup of more symptomatic women in SMART-5, results were more comparable to those of SMART-2; thus, CE/BZA appears to affect sleep more directly in women who have severe VMSs but more indirectly via improvements in VMS in women with less severe VMSs. Similarly, benefits of CE/MPA on sleep disturbance in the overall SMART-5 population were largely (96%–147%) attributable to reduction in VMSs.[116] This is consistent with results of another recent study, which found that transdermal estradiol did not improve sleep quality compared with placebo in postmenopausal women who had insomnia but not severe VMSs or hot flushes during sleep.[117]

Treatment satisfaction was assessed via the Menopause Symptoms-Treatment Satisfaction Questionnaire in SMART-2 and SMART-3.[86,114] In both trials, CE 0.45 mg/BZA 20 mg and CE 0.625 mg/BZA 20 mg were associated with significantly ($P<0.05$) greater overall treatment satisfaction compared with placebo as well as greater satisfaction with control of daytime and nighttime hot flushes and effects on quality of sleep and mood/emotions.[86,114] In the more symptomatic population in SMART-2, both doses of CE/BZA were also associated with greater satisfaction with treatment tolerability, and the approved dose was also associated with greater satisfaction with ability to concentrate.[114]

Conclusion

CE/BZA is a good option for nonhysterectomized postmenopausal women who are seeking relief from bothersome menopausal symptoms; additionally, it avoids the use of a progestin. It is associated with significant benefits with regard to reduction of VMSs and prevention of bone loss, improves sleep and menopause-specific quality of life, and may improve vaginal lubrication and vaginal maturation index. Based on up to 2 years of follow-up, it provides acceptable protection of the endometrium and breast. Women using CE/BZA report a high rate of treatment satisfaction.

The choice between traditional HT and CE/BZA should be based on safety and tolerability as well as personal preferences. HT regimens containing progestins have been associated with an increased risk of breast cancer, increased breast density, breast pain/tenderness, and vaginal bleeding. Progestin-containing HT may also have a negative effect on mood in some progestin-sensitive women. During up to 2 years of CE/BZA

use, incidence of those outcomes is comparable to that with placebo and lower than that with CE/MPA.

The success and safety of the available formulation of CE/BZA are based on the careful selection of the estrogen component (in this case, conjugated estrogens) and SERM used in this combination product, as well as the identification of a dose ratio that provides the best balance between therapeutic efficacy and endometrial safety.

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