

Conjugated Estrogen Plus Bazedoxifene

A New Approach to Estrogen Therapy

This Cases in Menopause features an interview with menopause expert **JoAnn V. Pinkerton, MD**, who discusses a fairly new therapy: the combination conjugated estrogen and bazedoxifene (CE/BZA) for the treatment of moderate to severe hot flashes due to menopause and the prevention of menopausal osteoporosis.

Anne A. Moore, DNP, APN

Much of my practice has focused on the treatment of menopausal women, but which of my patients can benefit from this particular combination of conjugated estrogen (CE) 0.45 mg plus bazedoxifene (BZA) 20 mg? I asked Dr Pinkerton this question, and more.

WHICH PATIENTS CAN BENEFIT MOST?

Dr Pinkerton: CE/BZA was tested in healthy postmenopausal women with a uterus who are at risk for bone loss and were reporting 50 or more moderate to severe hot flashes per week. The combination of CE and BZA is a good choice for women who have bothersome menopausal symptoms: hot flashes, night sweats, and sleep disruption or symptomatic vulvovaginal atrophy (VVA)—although it's not approved for VVA.

Efficacy and safety data show that compared with placebo

- CE/BZA decreases the frequency and severity of hot flashes at 12 weeks, and those decreases are maintained at 12 months.^{1,2}
- Women taking CE/BZA have greater improvements in sleep, with both decreased sleep disturbance and time to fall asleep.³
- CE/BZA maintained or prevented lumbar spine

and hip bone loss in postmenopausal women at risk for osteoporosis.^{1,4,5}

Although fracture data were not captured and the drug was not tested in osteoporotic women, study results showed bone loss prevention at 12 months, which was sustained at 24 months. The improvement in bone mineral density from baseline was about 1% to 1.5%. This was compared with a bone loss of 1.8% in women taking placebo.

In clinical studies, women taking CE/BZA versus placebo also reported a lower incidence of painful intercourse⁶ and some improvement in health-related quality of life and treatment satisfaction.^{7,8}

In short, CE/BZA is a good option for symptomatic menopausal women with a uterus who have bothersome hot flashes, night sweats, and sleep disruptions and want to prevent bone loss.

WHAT ABOUT ADVERSE EFFECTS?

Dr Pinkerton: In general, CE/BZA has a favorable safety and tolerability profile, with an overall incidence of adverse events similar to placebo. The rates of cardiovascular and cerebrovascular events, cancers (breast, endometrial, and ovarian), and mortality are comparable to placebo in two-year trials. These data are limited; studies have been conducted

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in healthy postmenopausal women. Future studies need to define the full risk profile, particularly among overweight or obese women and different ethnic groups, as well as for longer-term use.

IS THERE A ROLE AMONG WOMEN WITH BREAST CANCER?

Dr Pinkerton: CE/BZA has not been tested in women at risk for or who have a history of breast cancer. In preclinical trials of up to two years' duration, involving healthy postmenopausal women, the rates for breast cancer with CE/BZA were similar to placebo. There are no long-term data, however, and there are no data in women at risk for breast cancer. I recommend that women who have or are at high risk for breast cancer consider nonhormonal treatment options.⁹⁻¹¹

HAS THERE BEEN AN ASSOCIATED INCREASE IN BREAST DENSITY WITH CE/BZA?

Dr Pinkerton: No. Data from two randomized clinical trials showed that the breast density changes with 12-month CE/BZA treatment were similar to placebo—which is markedly different from comparisons of placebo and combination estrogen-progestin therapy (EPT), where EPT increased breast density. If indeed this lack of an association translates into fewer breast cancers, it would be wonderful, but we do not have long-term data. We can tell our patients that using CE/BZA has not been shown to increase the risk for breast cancer, at least up to two years.

WHAT MAKES CE/BZA DIFFERENT FROM TRADITIONAL EPT?

Dr Pinkerton: There are two exciting differences:

- The incidences of breast pain and tenderness were found to be similar to placebo and were significantly lower than those with the comparator EPT (conjugated estrogens 0.45 mg plus medroxyprogesterone acetate [CE/MPA] 1.5 mg).^{9,10,12}
- Bleeding and spotting rates were significantly lower than those found with CE/MPA.¹³

In addition, high rates of amenorrhea have been found—comparable to placebo.¹³

CE/BZA is similar to traditional EPT in several ways. For instance, compared with placebo, at two years, CE/BZA was not found to increase the incidence of endometrial hyperplasia, endometrial thickness (increase from baseline was < 1 mm and comparable to placebo), or endometrial cancers.¹⁴ Lastly, similar to EPT, there is probably a twofold risk

for venous thromboembolism (VTE) with BZA 20 mg alone.¹⁵ Importantly, there has been no additive effect on VTE risk when combining CE with BZA; however, we will need longer studies, in older women, to fully evaluate this risk.¹

Overall, in symptomatic postmenopausal women with a uterus, randomized controlled data show the same improvement with CE/BZA as that seen with traditional oral EPTs, with improvements in hot flashes; night sweats, with fewer sleep disruptions; and prevention of bone loss. In addition, the changes in cholesterol (an increase in triglyceride levels) and effect on the vagina are the same. Yet, CE/BZA appears to have a neutral effect on the breast and protects against endometrial hyperplasia and endometrial cancer without causing bleeding.^{9,10} CE/BZA's VTE and stroke risks are expected to be similar to traditional oral EPT.

Therefore, the major benefit of CE/BZA for women who have a uterus is the lack of significant breast tenderness, lack of changes in breast density, and lack of vaginal bleeding that is often seen with traditional EPT.¹²

THEN, IS PROGESTOGEN THE HARMFUL AGENT IN TRADITIONAL HT OPTIONS?

Dr Pinkerton: There is evidence that estrogen plus progestogen therapy has more risk for breast cancer than estrogen alone. But in women who have a uterus, you need to protect against uterine cancer so, up until now, the only option was to add progestogen. Some studies suggest the risk for breast cancer may differ depending on the type of progestogen. So it's a laudable goal to try to protect the endometrium without using a progestogen.

GIVEN ITS SAFETY PROFILE, DO YOU SEE CE/BZA BEING INDICATED FOR WOMEN WITHOUT A UTERUS?

Dr Pinkerton: CE/BZA has been tested only in women with a uterus; there is no indication for using it in hysterectomized women. In the future, unless trial data show a benefit to hysterectomized women—by a reduction in breast cancer compared with estrogen alone—there would be no reason to add BZA to the CE for these women. You would just use CE or another type of estrogen alone.

DO YOU ANTICIPATE BZA BEING USED ALONE?

Dr Pinkerton: For treating osteoporosis in postmenopausal women at increased risk for fracture,

BZA alone has greater benefits than risks. It is approved in other countries to prevent or treat osteoporosis. In 2008, Wyeth received an approval letter from the FDA for BZA alone but, for whatever reason, the drug was not brought to market. BZA reduces the number of new lumbar spine fractures by 4% (vs 2% for placebo), with efficacy better in those with a higher risk for fractures. Like raloxifene, it has not been shown effective at reducing nonvertebral fractures, although it maintains spinal bone density.¹⁶

BZA available as monotherapy could tempt clinicians to pair it with other estrogens. We must recognize that the combination of the specific estrogen and BZA dose and type need to be balanced to provide endometrial hyperplasia protection. It would not be safe or effective to take BZA as a selective estrogen-receptor modulator and pair it with any other untested systemic estrogen. I do not anticipate, in this country, that BZA will become available as monotherapy, however.

NEW OPTIONS ARE WELCOME

Dr Moore: Novel strategies for clinicians to optimally treat menopausal symptoms are always welcome. I look forward to more data from the SMART trials on CE/BZA and to moving forward as we gain experience with using this new treatment option. **CR**

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