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Menopause e-Consult®

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This clinical e-newsletter from The North American Menopause Society (NAMS) presents questions and cases commonly seen in a menopause specialist's practice. Recognized experts in the field provide their opinions and practical advice. Nicole Jaff, PhD, NCMP, the editor of *Menopause e-Consult*, encourages your suggestions for future topics. The opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or by Dr. Jaff.

Case

A 64-year-old white woman presented to my office for her well-woman examination. She brought her medical file from her primary care provider, and I reviewed her recent dual-energy x-ray absorptiometry (DXA) scan. The T-score of her left hip was −2.7; her lumbar spine was −3.0. She has had a DXA scan every 2 years since her menopause at age 52. She has never taken hormone therapy.

The T-scores have decreased progressively over the past 10 years. She has no significant medical history and receives no prescription medications. She takes a multivitamin that includes calcium and vitamin D and exercises three to four times a week. She has never smoked and drinks three to four units a week. She has a body mass index of 28.50 kg/m^2.

I told her that she has osteoporosis and should be taking a prescription medication. She refused because her primary care provider told her that these medications have too many adverse effects (AEs). What is the quantifiable risk of fracture, and what would be the rationale for taking medication to reduce fracture risk if there are possible adverse effects with the medication?

Also, because gastrointestinal (GI) absorption of bisphosphonates may present challenges, are the generic options equivalent to branded therapies? Are there medications that may be effective and have fewer AEs than bisphosphonates? The primary goal of therapy is to prevent the first fracture. Waiting to see whether a patient suffers a fracture is a poor measuring stick for a generic medication's effectiveness.

Suggested by Mark Firestone, MD, FACOG, NCMP, Aventura, Florida

Commentary by

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Pharmacologic treatment is recommended for postmenopausal women with osteoporosis, defined either by a bone mineral density (BMD) T-score of −2.5 or less at the femoral neck, total hip, or lumbar spine or by the presence of a low-trauma hip or vertebral fracture.

In addition, treatment is recommended in those with a low BMD (T-score between −1 and −2.4, with a 10-y probability of hip fracture ≥ 3% or 10-y probability of major osteoporosis-related fracture > 20%, based on the US adaptive fracture-risk algorithm [FRAX]).

This patient had T-scores of −2.5 or less at both spine and hip. She should start on osteoporosis therapy. She has not had a first fragility fracture, and our goal is to prevent her first fracture.

Most recommendations suggest that initial osteoporosis treatment should include either a bisphosphonate (alendronate, risedronate, ibandronate, or zoledronic acid) or a RANK ligand inhibitor (denosumab). My commentary will focus on the use of bisphosphonates.

This woman is not unique in her concerns about AEs with osteoporosis therapies. There is a perception by many patients that osteoporosis medications are dangerous, because a medicine that one must stop taking at 5 years for a drug holiday must be dangerous.

Patients often do not understand that the benefit of reducing fracture risk is far greater than the risk of AEs. The consequence is that the prevalence of bisphosphonate use has declined by about 50% since 2008. Unfortunately and possibly related, the steady decline in hip fracture incidence over the past 25 years has stopped since 2012.

In a Kaiser study looking at medical records in which there was no cost to patients to fill their bisphosphonate prescription, approximately one-third of patients with osteoporosis did not fill their bisphosphonate prescriptions.[1]

The problem is that major AEs associated with bisphosphonates, atypical femoral fracture and osteonecrosis of the jaw, have received significant media attention and engendered significant concern by patients. These AEs are perceived as manmade and catastrophic.

Atypical femoral fracture has an incidence of between 2 and 78 cases per 100,000 person-years with 2 and 8 years of oral bisphosphonates, respectively.[2] Osteonecrosis of the jaw has an estimated incidence of 10 cases per 10,000 person-years in patients with osteoporosis taking oral bisphosphonates, which may increase to 21 cases per 10,000 person-years with more than 4 years of oral bisphosphonate exposure.[3] The risk of future fractures in this patient is far greater than the incidence of these major AEs.

Common AEs with bisphosphonates include upper GI AEs such as dyspepsia or abdominal pain.[4] The highest level of evidence, randomized controlled trials, suggest little or no increase in upper GI problems if the bisphosphonates are administered appropriately.[5] Upper GI events also may be reduced by less frequent dosing; for example, monthly or IV injection (zoledronic acid) is preferred in patients with significant acid reflux.

It will be important for this woman who is at increased risk of future fracture to be assessed for balance and fall risk. The woman should be encouraged to continue regular weight-bearing and strengthening exercise not only to improve bone strength but also to reduce fall risk. Some patients may become fearful of exercising after being told that they are at increased risk of fracture and should be counseled accordingly.

Lifestyle modifications include tobacco cessation and avoidance of excess alcohol intake. As a physician, I would educate her about osteoporosis and the risk of related fractures, particularly hip and vertebral fractures that have been associated with excess mortality. Nutritional counseling for adequate calcium and vitamin D intake also is important.

Her insurance plan may only pay for a generic bisphosphonate. Generic bisphosphonates are closely equivalent in efficacy to branded bisphosphonates.[6,7] Generic and brand bisphosphonates produce similar gains in BMD and reduction in bone turnover markers but, depending on the generic formulation, may have greater GI AEs (possibly because of pill-shape differences or lack of wax coating). In fact, some patients who are doing well on branded bisphosphonates may exhibit intolerance when switched to generics.

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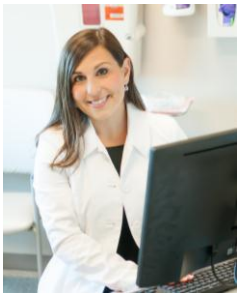
Question

After she recently screened positive for *BRCA2* mutation, a 42-year-old woman in my practice underwent risk-reducing salpingo-oophorectomy (RRSO). Now that she is postmenopausal, she suffers from significant night sweats, poor sleep, and vaginal dryness. She has tried over-the-counter lubricants with no relief. She then opted to try a low-dose selective serotonin reuptake inhibitor for hot flash relief, but this did not resolve her symptoms. What is the role of hormone therapy (HT) in symptomatic postmenopausal *BRCA* carriers without known cancer who have had RRSO?

Suggested by Michael Blumenfeld, MD, FACG, Columbus, Ohio

Commentary by



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Current guidelines recommend RRSO for *BRAC1* and *BRCA2* mutation carriers before age 40 or after a woman has reached her reproductive goals.[1] This highly personal decision reduces the risk of ovarian cancer by approximately 80% while reducing breast cancer risk by about 50%. However, quality of life (QOL) may be greatly affected in these women because of the effects of surgical menopause at a relatively younger age than when they may have naturally transitioned into menopause.

Vasomotor symptoms (VMS) and genitourinary syndrome of menopause (GSM) are the most commonly reported post-menopause symptoms and are often exacerbated by the abrupt nature of surgical menopause. Moreover, in women with early menopause, which is more typical for women undergoing RRSO, women not treated with HT are vulnerable to elevated risks of

cardiovascular disease, osteoporosis, and other chronic diseases.[2]

It is imperative that menopause QOL issues and risks of long-term chronic disease in this population are balanced with the risks of HT. Long-term data on HT in women with *BRCA* mutations who have elected RRSO are limited.

A systematic review consisting of 13 observational studies showed that HT after RRSO improved menopause-related QOL issues, specifically demonstrating clear benefits for reducing VMS and improvements in GSM.[1] The risk of breast cancer remains unclear, however, because of the short mean duration of follow-up in these studies (2.6 y). Other studies show that HT does not appear to confer an elevated risk of breast cancer.[3]

Data from the long-term Women's Health Initiative (WHI) for the use of oral conjugated equine estrogen (CEE) alone in women posthysterectomy show a statistically significant decrease in breast cancer development,[4] and this decreased breast cancer risk persisted in 18-year follow-up WHI data.[5]

Although these data cannot be directly applied to women with *BRCA* mutations after RRSO, the findings are still encouraging for *BRCA* carriers without active cancer who have had RRSO and are considering estrogen because of severe menopause symptoms.

Another option to consider is Duavee, a combination of oral CEE with bazedoxifene (CEE 0.45 mg/BZA 20 mg). Bazedoxifene functions as an estrogen receptor (ER) agonist/antagonist (ERAA), a unique compound that acts directly on the ER and having different actions in various target tissues, allowing for the possibility to selectively inhibit or stimulate estrogen-like action in these target tissues.[6] Although women who have had RRSO no longer have an intact uterus, the bazedoxifene appears to act as an antagonist at the breast, similar to other ERAAs such as tamoxifen and raloxifene, and may be of benefit in this specific population,[7] although long-term studies are essential.

In those women who prefer not to subject themselves to the possible risks of systemic estrogen, another option to consider for GSM would be ospemifene, an ERAA that has been shown to improve GSM and bone health. In further support of its use in this population, ospemifene has been shown to act as an antagonist at the level of the breast in animal studies. This option, however, would not improve other menopause-related OQL issues such as VMS or poor sleep because of night sweats and in some cases may even exacerbate VMS.[7] Vaginal prasterone, or topical dehydroepiandrosterone, would be another nonestrogen option for bothersome GSM but again would have limited systemic benefits.

Because of the rapid expansion and availability of genetic testing, it is imperative that longer-term studies are undertaken in women with *BRCA* mutations who have had RSSO and elect to use HT for severe menopause symptoms

This also highlights the need for more NAMS-certified practitioners in large academic settings to work closely with gynecologic and medical oncologists to ensure that women consider "both sides of the coin" when faced with an elevated genetic risk of breast or ovarian cancer

Finally, if a woman is considering or planning for prophylactic mastectomy, yet another significant and personal decision, this would further alleviate potential risks of HT on breast cancer development.

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What do you do when a patient is unwilling to take a medication because of adverse events that have gained media attention? Do you work to convince her that the medication is worth taking, or do you work on finding alternative therapies? Visit our Member Forum to discuss the September *Menopause e-Consult*.

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