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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. Gloria Bachmann, MD, the Editor of *Menopause e-Consult*, encourages your suggestions for future topics. Note that the opinions expressed in the commentaries are those of the authors and are not necessarily endorsed by NAMS or Dr. Bachmann.

## Case:

46-year-old Olga had a tubal ligation in her late 30s and is now postmenopausal. She is waking twice a night drenched with night sweats. She is going to have to quit her job if she doesn't get relief. She does yoga breathing for 20 minutes twice a day, her BMI is 23, she works out on an elliptical for 30 minutes a day, and she has tried three SSRIs and multiple herbs without success. She can't take estrogen (even transdermally) because of a pulmonary embolism while on combined hormonal oral contraceptives in her 30s and an inherited clotting disorder. How would you treat her?

## Management issues by:



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Estrogen has long been the go-to treatment for vasomotor symptoms (VMS) and is well proven to be effective for VMS in randomized controlled trials (RCTs)—significantly more effective when combined with a progestogen.<sup>1</sup> Is estrogen safe even for short-term use? With it, there are increased risks of life-threatening venous thromboembolic (VTE) disease and the

rebound worsening of VMS when women try to stop treatment. Since the Women's Health Initiative hormone RCT results, other worries include increased risks of heart disease, stroke, gallbladder surgery, cognitive impairment, and incontinence.

Clinicians know that severe VMS (ones that wake women at night, involve sweating, and number more than 50 per week) require effective and safe treatment. We also know that VMS are associated with increased risk factors for cardiovascular diseases<sup>2</sup> and that there are bone health concerns because night sweats were related to more rapid bone loss in population-based data.<sup>3</sup> VMS must be effectively treated if they still make women sweat and disrupt sleep despite nonmedical measures (cognitive reframing, relaxation/meditation, yoga breathing, increased aerobic exercise, acupuncture).

I have long successfully used medroxyprogesterone acetate (MPA, 10 mg/d) to treat VMS, based both on many older RCTs and because our 1-year comparative RCT of MPA versus conjugated equine estrogen showed equivalent VMS effectiveness.<sup>4</sup> I also conducted a randomized, double-blind, placebo-controlled trial (2003-2009) in 133 healthy, early postmenopausal women using micronized progesterone.<sup>5</sup> Progesterone was significantly more effective than placebo for VMS in this 12-week RCT using micronized progesterone, 300 mg at night.<sup>5</sup> Bedtime dosing was chosen

to avoid daytime sleepiness, and the 300-mg dose was selected because it keeps the progesterone blood level at greater than or equal to luteal phase threshold for 24 hours.<sup>6</sup> Progesterone had no serious adverse effects, and it significantly improved sleep<sup>5</sup> (similar to previous RCTs<sup>7,8</sup>).

Progesterone was also effective for severe VMS in the subset of women with frequent severe hot flashes and night sweats.<sup>9</sup> Plus, there was no rebound VMS increase in progesterone-treated women over the 1 month after they stopped progesterone.<sup>9</sup> We are currently performing a Canada-wide same-design study for perimenopausal VMS. Currently, there is no therapy proven effective and safe for treatment of night sweats and hot flashes in women who have menstruated within the last year. However, before clinicians will choose oral micronized progesterone for VMS treatment, two important questions need to be answered: 1) What is the mechanism of progesterone's VMS effectiveness? and 2) Is progesterone safe in the context of the cardiovascular system and breast cancer risks?

### **How does progesterone decrease VMS?**

VMS are an estrogen-withdrawal phenomenon from an estrogen-primed brain. Estrogen withdrawal causes a narrowed thermoneutral zone in the symptomatic woman;<sup>10</sup> this thermoneutral-zone constriction is caused by the central norepinephrine release from estrogen withdrawal. Therapy with estrogen and the alpha blocker clonidine prevent this narrowed thermoneutral zone. Although progesterone therapy has not been tested in menstruating women during the luteal phase (progesterone present), the sweating threshold is significantly higher than during the follicular phase (progesterone absent).<sup>10</sup> Thus, in addition to having sleep-enhancing<sup>5,7-8</sup> and anti-oxidative brain-calming effects,<sup>11</sup> progesterone also prevents estradiol withdrawal, narrowing of the thermoneutral zone.<sup>10</sup>

### **Is progesterone safe for the cardiovascular system and breasts?**

Evidence strongly suggests that progesterone does not increase the risks of cardiac and vascular diseases based on its positive and estradiol-similar endothelial effects<sup>12</sup> and results of our 3-month RCT of cardiovascular system marker changes on progesterone or placebo.<sup>13</sup> We studied healthy postmenopausal women without initial cardiovascular risks. Results showed no significant changes with progesterone versus placebo in weight, waist circumference, systolic or diastolic blood pressure, pulse, fasting glucose, high-sensitivity C-reactive protein, D-dimer, or changes in the Framingham General Cardiovascular Risk profile.

Progesterone, in contrast to MPA, does not cause breast cell proliferation or act through the glucocorticoid receptor.<sup>14</sup> Rather, acting through the progesterone receptor, it decreased breast cell proliferation and counteracted estradiol's proliferative effects in two same-design 11-day comparative RCTs of transdermal estradiol, progesterone, estradiol-progesterone, or placebo in women who had breast biopsies for benign nodules.<sup>15-16</sup> The 8-year prospective observational results of the E3N epidemiological cohort study in more than 80,000 postmenopausal French women reported that estrogen plus progesterone had no increased breast cancer risk versus significantly increased risk with estrogen alone or estrogen with progestogens.<sup>17</sup>

### **In summary**

RCT data show that oral micronized progesterone, in a luteal phase-equivalent dose of 300 mg at bedtime, is effective for VMS treatment in general as well as in women with frequent, severe hot flashes and night sweats. Furthermore, progesterone, in contrast to estrogen, does not cause a VMS rebound when it is stopped. Progesterone also improves sleep, has beneficial effects on endothelial function, and shows short-term cardiovascular safety. In addition, progesterone does not cause breast cell proliferation and, based on large-cohort prospective observational data, does not increase breast cancer risk. Thus, progesterone

is a safe and effective therapy for daytime and nighttime VMS.

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### References

1. MacLennan AH, Broadbent JL, Lester S, Moore V. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. *Cochrane Database Syst Rev.* 2004(4):CD002978.
2. Gast GC, Grobbee DE, Pop VJ, et al. Menopausal complaints are associated with cardiovascular risk factors. *Hypertension.* 2008;51(6):1492-1498.
3. Pinto MM, Prior JC, Tomlinson G, Cheung AM. Are night sweats related to bone change? A prospective population-based study in women 40-60 from the Canadian Multicentre Osteoporosis Study [abstract]. *Endocrine Society Abstracts.* 2007;P2-143.
4. Prior JC, Nielsen JD, Hitchcock CL, Williams LA, Vigna YM, Dean CB. Medroxyprogesterone and conjugated oestrogen are equivalent for hot flushes: a 1-year randomized double-blind trial following premenopausal ovariectomy. *Clin Sci (Lond).* 2007;112(10):517-525.
5. Hitchcock CL, Prior JC. Oral micronized progesterone for vasomotor symptoms in healthy postmenopausal women—a placebo-controlled randomized trial. *Menopause.* 2012;19(8):886-893.
6. Simon JA, Shangold MM, Andrews MC, Buster JE, Hodgen GD. Micronized progesterone therapy: the importance of route of administration and pharmacokinetics on clinical outcome. *Contracept Fertil Sex.* 1992;20(11):1031-1037.
7. Friess E, Tagaya H, Trachsel L, Holsboer F, Rupprecht R. Progesterone-induced changes in sleep in male subjects. *Am J Physiol.* 1997;272(5 pt 1):E885-E891.
8. Schussler P, Kluge M, Yassouridis A, et al. Progesterone reduces wakefulness in sleep EEG and has no effect on cognition in healthy postmenopausal women. *Psychoneuroendocrinology.* 2008;33(8):1124-1131.
9. Prior JC, Hitchcock CL. Progesterone for hot flush and night sweat treatment—effectiveness for severe vasomotor symptoms and lack of withdrawal rebound. *Gynecol Endocrinol.* 2012;28 (suppl 2):7-11.
10. Freedman RR, Subramanian M. Effects of symptomatic status and the menstrual cycle on hot flash-related thermoregulatory parameters. *Menopause.* 2005;12(2):156-159.
11. Gibson CL, Coomber B, Rathbone J. Is progesterone a candidate neuroprotective factor for treatment following ischemic stroke? *Neuroscientist.* 2009;15(4):324-332.
12. Mather KJ, Norman EG, Prior JC, Elliott TG. Preserved forearm endothelial responses with acute exposure to progesterone: a randomized cross-over trial of 17-beta estradiol, progesterone, and 17-beta estradiol with progesterone in healthy menopausal women. *J Clin Endocrinol Metab.* 2000;85(12):4644-4649.
13. Prior JC, Elliott TG, Norman E, Stajic V, Hitchcock CL. Progesterone therapy, endothelial function and cardiovascular risk factors: a 3-month randomized, placebo-controlled trial in healthy early postmenopausal women. *PLoS One.* 2014;9(1):e84698.
14. Courtin A, Communal L, Vilasco M, et al. Glucocorticoid receptor activity discriminates between progesterone and medroxyprogesterone acetate effects in breast cells. *Breast Cancer Res Treat.* 2012;131(1):49-63.
15. Chang KJ, Lee TT, Linares-Cruz G, Fournier S, de Lignieres B. Influence of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo. *Fertil Steril.* 1995;63(4):785-791.
16. Foidart J, Collin C, Denoo X, et al. Estradiol and progesterone regulate the proliferation of human breast epithelial cells. *Fertil Steril.* 1998;69(5):963-969.
17. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. *Breast Cancer Res Treat.* 2008;107(1):103-111.

### Question:

How do I decide when to treat the moderate-risk patient for osteoporosis?

### Commentary by:



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The consequences of underdiagnosing and undertreating osteoporosis are significant. In women with hip fracture, 40% are known to have had a previous fracture,<sup>1</sup> 40% will require assistance with walking in the future, 18% will enter a long-term care facility, and as many as 23% will die within 1 year.<sup>2</sup>

A history of fragility fracture is critical information. Often we erroneously attribute a fracture to causes other than osteoporosis. The definition of a fragility fracture is one that happens after a minor trauma such as falling from a standing height, a fall from a sitting or

lying position, or a fall after having missed the last few steps in a staircase.

### **How is risk defined?**

An easy way to determine risk is to use the online FRAX tool. The low-risk patient is one who has a 10-year risk of fracture below 10%. For these patients, we would agree that lifestyle modification is important, including exercise, fall prevention, and optimization of calcium and vitamin D. Encourage all smokers to stop. A high-risk patient has more than a 20% risk of fracture in the next 10 years and should be treated with level 1 evidence-based pharmacologic treatment. The question that many clinicians face is what to do with the moderate-risk patients who have a fracture risk somewhere between the low- and high-risk patient. Is lifestyle modification enough, or do they merit a course of pharmacotherapy?

### **How do I assess the moderate-risk patient?**

It is imperative that we complete a thorough history and physical exam. Questions about broken bones since the last visit, falls, prolonged and unusual back pain, and cortisone are important to risk stratification. Examining for kyphosis and asking your patient to do a Get-Up-and-Go test to assess speed and balance are all useful strategies. Measure weight and height at every visit. Osteoporosis Canada suggests that useful biochemical tests should include calcium corrected for albumin, a complete blood count, creatinine, alkaline phosphatase, TSH, serum protein electrophoresis in those patients with vertebral fractures, and a 25-OH vitamin D (drawn after 3-4 months of adequate supplementation; should not be repeated if an optimal measure is achieved).

### **When do I order a BMD?**

All men and women should have a bone mineral density (BMD) test at age 65—however, in women and men from ages 50 to 64 years, one can consider an earlier bone density if there is a fragility fracture after age 40, prolonged use of steroids or other high-risk

medication, parental hip fracture, high alcohol intake or current smoking, a body weight less than 60 kg, or major weight loss (>10% since age 25).

### **What might shift the balance to treating the moderate-risk patient?**

In the physical examination, be sure to measure an annual height, the rib-to-pelvis distance, and the occiput-to-wall distance as a measure for kyphosis. If there has been height loss, a lateral spine x-ray can identify occult vertebral fracture and that would speak to poor bone quality and have the patient go up a class from moderate risk to high risk meriting pharmacotherapy. The next area for consideration is rapid bone loss, and although that is not precisely defined, it would represent a significant drop in a patient's BMD since the last visit. A patient who has a propensity to fall (two or more falls in the last year) could be at higher risk for fracture and that too might encourage a consideration of pharmacotherapy.

In addition, concurrent high-risk disorders or high-risk medications would indicate that pharmacotherapy is appropriate. Long-term repeated use of glucocorticoids, hypogonadism, premature menopause, untreated hyperthyroidism, primary hyperparathyroidism, rheumatoid arthritis, and the use of aromatase inhibitor therapy should all prompt consideration for intervention. Other conditions that might prompt a treatment intervention include chronic malnutrition or malabsorption, chronic liver disease, and chronic inflammatory conditions.

Other medications that are not bone friendly include anticonvulsant therapy, methotrexate, and perhaps proton-pump inhibitors and selective serotonin reuptake inhibitor medications. As always, patient preference on a thorough review of their risks is important to consider. All high-risk patients as defined by a 10-year fracture risk of greater than 20%, or those with a prior fragility fracture of hip or spine, or those with more than one fragility

fracture should be offered pharmacological therapy.<sup>3</sup>

### **How do I decide what to treat with?**

Evidence-based level one medication should be chosen with respect to an individual patient's risk and benefit profile. We often underestimate the importance of patient adherence to medication. In considering treatment choices, it is imperative to consider safety and efficacy, convenience and frequency of administration, and risks associated with the medication.

Osteoporosis Canada has published the 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada.<sup>3</sup> The focus is on preventing fragility fractures and their negative consequences, rather than on treating low BMD, which is viewed as only one of several risk factors for fracture.

To develop the recommendations on therapeutic options for prevention of fracture in women with osteoporosis, a systematic review of pharmacologic therapies was conducted, focusing on the treatment of patients aged older than 50 years at increased risk for fracture and on reporting adverse events associated with these therapies as published from January 2007 to December 2009.

There is consistent evidence from randomized clinical trials that all therapies currently available in Canada reduce the risk of vertebral fractures for menopausal women with osteoporosis (as defined by a T-score  $\leq -2.5$ ). There is also evidence that some interventions prevent nonvertebral and/or hip fractures and may reduce the mortality rate among patients at high risk for fractures. Women with prior fragility fractures affecting the vertebra or hip also benefit from pharmacologic intervention. In general, pharmacotherapy reduces the risk of vertebral fracture by 30% to 70%, depending on the agent and level of adherence. The effect on nonvertebral fractures is lower and varies by fracture site. There is inconsistent evidence

regarding the benefits of pharmacologic therapy for those who have sustained a fracture at a site other than the hip or the spine (eg, the wrist) unless they also have an osteoporotic T-score. Both calcitonin and teriparatide may decrease the pain associated with vertebral fractures.

For menopausal women needing treatment of osteoporosis, the drugs alendronate, risendronate, zoledronic acid, and denosumab can be used as first-line therapies for prevention of hip, nonvertebral, and vertebral fractures [grade A].

For menopausal women requiring treatment of osteoporosis, raloxifene can be used as a first-line therapy for prevention of vertebral fractures [grade A].

In women at high risk of fragility fracture and in need of therapy for VMS, hormone therapy can be used as first-line therapy for prevention of hip, nonvertebral, and vertebral fractures [grade A].

For menopausal women intolerant of first-line therapies, calcitonin or etidronate can be considered for prevention of vertebral fractures [grade B].

### **Take-away points**

Without a doubt, the moderate-risk patient presents a challenge, and it is important to use our clinical judgment to decide on management and treatment. Patients should be monitored for factors that might reclassify them. It is important to talk to our patients about fracture risk, counsel them on the consequences of fracture, and consider patient treatment preference.

**Disclosure:** Dr. Shapiro reports: Board of Directors/ Trustees: Baycrest, Research Canada, Dairy Farmers of Canada; Employment: Consultant, CTV Canada AM, CTV National News, CTV NewsChannel, Parents Canada; Consultant/Advisory Board: Amgen, AstraZeneca, Merck, Novartis, Pfizer; Speaker's Bureau:

Amgen, Merck, Novartis, Novo Nordisk, Pfizer, Warner Chilcott; Website Writer: CTV.ca, healthandbone.ca.

### References

1. Hajcsar EE, Hawker G, Bogoch ER. Investigation and treatment of osteoporosis in patients with fragility fractures. *CMAJ*. 2000;163(7):819-822.
2. Ioannidis G, Papaioannou A, Hopman WM, et al. Relation between fractures and mortality: results from

the Canadian Multicentre Osteoporosis Study. *CMAJ*. 2009;181(5):265-271.

3. Papaioannou A, Morin S, Cheung AM, et al; for the Scientific Advisory Council of Osteoporosis Canada. 2010 practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ*. 2010;182(17):1864-1873.

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### 2014 Call for Abstracts

Don't miss the opportunity to submit your research abstracts to NAMS for presentation at the 25th Annual Meeting (October 15-18, 2014) in Washington, DC.

- Submit your abstracts through the NAMS website:  
<http://www.menopause.org/annual-meetings/2014-meeting/abstract-submission>
- Information submitted for consideration must not be identical to that presented at any meeting before the NAMS meeting, and the study must have been published as of April 30, 2014
- The abstract submission deadline is April 30, 2014
- Top abstracts will be accepted for oral presentation, and up to four poster prizes will be awarded (top prize: \$1,000)
- All accepted abstracts will be published in the NAMS journal, *Menopause*, after the meeting

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