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Managing menopause Part 1: Vasomotor symptoms

This first article in a two-part series reviews the Society of Obstetricians and Gynaecologists of Canada's 2021 clinical practice guideline on managing vasomotor symptoms associated with menopause.

ABSTRACT: Menopause symptoms, experienced by most women during their lifetime, can significantly hinder their quality of life. When counseling menopausal women, it is essential that care providers are up-to-date on hormone therapy recommendations. This article is the first of a two-part review of the Society of Obstetricians and Gynaecologists of Canada's 2021 *Managing Menopause* clinical practice guideline and focuses on vasomotor symptoms and their management via hormone therapy and nonpharmacologic measures. Estrogen remains the most effective means for treating vasomotor symptoms, with progestogen added as required to prevent endometrial hyperplasia. Hormone therapy regimens are individualized based on preference, contraindications, and treatment goals. Drugs recently approved by Health Canada include the tissue selective estrogen complex and tibolone. There is limited evidence for many lifestyle and alternative treatments, but clinical hypnosis, cognitive-behavioral therapy, and weight loss appear to be effective.

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In 2021, the Society of Obstetricians and Gynaecologists of Canada and the Canadian Menopause Society jointly published a new *Managing Menopause* guideline, which officially replaced the 2014 guideline.[1] The updated version includes seven guidelines within it:

A. Menopause: Vasomotor Symptoms, Prescription Therapeutic Agents, Complementary and Alternative Medicine, Nutrition, and Lifestyle[2]
B. Menopause and Genitourinary Health[3]
C. Menopause: Mood, Sleep, and Cognition[4]
D. Menopause and Sexuality[5]
E. Menopause and Cardiovascular Disease[6]
F. Menopause and Breast Cancer[7]
G. Menopause and Osteoporosis[8]

The *Managing Menopause* guideline can be accessed from the College of Physicians and Surgeons of BC Library. To do so, you must first log into the College website with your username and password, then paste the following URL into your browser: www.clinicalkey.com/#!/browse/journal/17012163/latest or search for the *Journal of Obstetrics and Gynaecology Canada* through the Library's website.

This two-part review summarizes the key recommendations from the 2021 guideline and highlights clinically relevant changes from the 2014 guideline in order to inform health care providers who prescribe menopausal hormone therapy. This article focuses on guideline A: the treatment of vasomotor symptoms via prescriptive agents, alternative medicines, and lifestyle measures. Part 2 focuses on guidelines E and F: the effect of hormone therapy on breast cancer, cardiovascular disease, and premature ovarian insufficiency. Although the other sections (B, C, D, and G) are important and informative, this two-part review focuses on updates in hormone therapy.

Overview

Menopause can be declared retrospectively after 12 months of nonpathologic amenorrhea.[9] In developed countries, the mean age of menopause is 51 years (95% CI, 41.9-57.8).[10] Perimenopause is a period of menopausal transition during which significantly fluctuating levels of estrogen disrupt menstrual cyclicity. The Stages of Reproductive Aging Workshop (STRAW) criteria, a standardized staging system for reproductive aging, defines perimenopause as the time from which there is a minimum 7-day change in cycle length to 12 months after the final menstrual period.[9]

Menopausal symptoms affect 80% of women.[2] Furthermore, the prevalence of symptoms is increasing as Canada's population ages. The sudden onset of vasomotor symptoms and alterations in mood, cognition, and physical appearance can be very distressing for women who are in a demanding time of their life as they balance careers and family obligations. It is important that providers who care for mature women are well prepared to counsel them in order to optimize their quality of life.[11]

Vasomotor symptoms

Section A of the 2021 guideline emphasizes the high prevalence of vasomotor symptoms, such as hot flashes and night sweats, and the

burden they may cause women in midlife.[2] A hot flash is an unwanted sensation of heat that typically starts in the chest, rises upward, and lasts an average of 3 to 4 minutes.[12] Up to 20% of women experience severe symptoms, with as many as 20 to 30 episodes daily.[2] Vasomotor symptoms tend to be more prevalent among women who are obese or of Black or Hispanic origin.[13,14] Data from the Study of Women's Health Across the Nation that were published after the 2014 guideline was written suggest that the median duration of vasomotor symptoms during menopausal transition is 7.4 years.[15] The 2021 guideline reflects this updated information.

Much about the pathophysiology of hot flashes remains poorly understood. The 2021 guideline notes that in addition to the currently accepted narrowing of the thermoneutral zone, there appears to be a role for hypothalamic hormones, including kisspeptin, neurokinin B, and dynorphin (KNDy). The neurons that release these hormones hypertrophy in the postmenopausal low-estrogen environment. New medications that block the KNDy neuron receptors are being tested as therapy for vasomotor symptoms.[16] Beyond symptom management, the 2021 guideline notes the independent link between vasomotor symptoms and cardiovascular disease, thus raising the important point that women with vasomotor symptoms should also be counseled for disease prevention.[17] Cardiovascular disease in menopause is discussed in detail in Part 2 of this review.

The 2021 guideline reaffirms that hormone therapy containing estrogen is the most effective treatment for vasomotor symptoms during menopause. Both the 2014 and 2021 guidelines reference a 2004 Cochrane systematic review of randomized controlled trials, which found that estrogen alone or estrogen plus a progestogen significantly reduced the frequency of hot flashes by 75% (95% CI, 64.3-82.3) compared with placebo.[18,19] Estrogen is the main agent responsible for reducing vasomotor symptoms, whereas progestogen is required only to prevent endometrial hyperplasia in women with a uterus. Before beginning hormone therapy, a careful risk assessment should be undertaken. The guideline includes sections on assessment and risk management of menopausal women, and special considerations (e.g., vaginal bleeding, premature menopause, endometriosis). The contraindications to systemic estrogen-containing hormone therapy listed in the 2021 guideline are similar to those in the 2014 guideline; they include:

- Undiagnosed abnormal vaginal bleeding.
- Known, suspected, or history of breast cancer.
- Known or suspected estrogen-dependent cancers.
- Coronary heart disease.
- Active or history of venous thromboembolism.
- Active or history of stroke.
- Known thrombophilia.
- Active liver disease.
- Known or suspected pregnancy.

New additions to the contraindications list are:

- Known thrombophilia.
- Known or suspected pregnancy.

The 2021 guideline lists many scenarios in which transdermal estrogen is preferred. It appears to have a lower risk of venous thromboembolism than oral formulations, does not have a first-pass effect through the liver, and provides more consistent estrogen levels.

The 2021 guideline also modified the wording of venous thromboembolism to include *past* and active venous thromboembolism (previously, only *active* venous thromboembolism).

The key contraindications to the use of progestogens are undiagnosed abnormal vaginal bleeding and current or previous breast cancer. In terms of systemic androgen therapy, off-label use of transdermal testosterone is newly endorsed in the 2021 guideline for improving sexual function in menopause, but it is not recommended for treating vasomotor symptoms. Contraindications to testosterone therapy include pregnancy, severe acne, hirsutism, androgenic alopecia, and high baseline free testosterone levels.[5]

Prescribing hormone therapy

Hormone therapy can be prescribed to menopausal women, using either a cyclic or continuous regimen. In both regimens, estrogen is taken daily to manage vasomotor symptoms. In the continuous regimen, progestogen is also used daily, which eliminates a withdrawal bleed by continually opposing the proliferative effects of estrogen on the endometrium. In the cyclic regimen, progestogen is taken for 12 to 14 days per month, which induces cyclic endometrial shedding (withdrawal bleeding).

The 2014 guideline included tables of prescription therapeutic agents for hormone therapy, separated into estrogens, progestogens, and combination products. The 2021 guideline lists all individual and combination hormone therapy products in one table **[Table]**, which practitioners can print or screenshot for easy reference.

Available formulations of estrogen can be delivered in many ways, including oral, transdermal, and vaginal routes. The guideline lists each formulation's generic name, trade name(s), available strength, and suggested starting dosage.

Symptom improvement is usually apparent within 2 to 4 weeks of starting therapy. The 2021 guideline recommends periodic re-evaluation of patients on hormone therapy, although similar to the 2014 guideline, there is no specific time frame or duration of use. Women may continue beyond age 65 if they have persistent bothersome symptoms. The old adage that hormone therapy should be given in the lowest effective dose for the shortest amount of time is controversial and not endorsed by the 2021 guideline. There is insufficient evidence that lower dose and shorter duration therapy is any safer or better than average dose and medium- to long-term therapy [**Table**].

Although a range of estrogen products is available, the 2021 guideline lists many scenarios in which transdermal estrogen is preferred. It appears to have a lower risk of venous thromboembolism than oral formulations, does

TABLE. Systemic hormone therapy options in Canada.

Drug name	Route	Brand name	Strengths	Starting dosage
Estrogens				
Conjugated	Oral	Premarin	0.3, 0.625, 1.25 mg	0.3–0.625 mg (1×/day)
17 β estradiol	Oral	Estrace	0.5, 1, 2 mg	0.5–1 mg (1×/day)
		Lupin-Estradiol	0.5, 1, 2 mg	
17 β estradiol	Transdermal patch	Estradiol Derm	50, 75, 100 µg	25–50 µg (2×/week)
		Estradot	25, 37.5, 50, 75, 100 µg	
		Oesclim	25, 50 µg	
		Climara	25, 50, 75, 100 µg	25–50 µg (1×/week)
17 β estradiol	Gel	Estrogel	0.06% gel 0.75 mg estradiol per 1.25 g metered dose	1–2 metered doses (1×/day)
		Divigel	0.1% gel 0.25, 0.5, 1 mg sachets	0.5–1 mg sachet (1×/day)
Progestogens				
Medroxyprogesterone	Oral	Provera	2.5, 5, 10 mg	2.5 mg daily for continuous use or 5 mg daily for 12–14 days/month for cyclic use
		Apo-Medroxy	2.5, 5, 10 mg	
		Pro-Doc Limitee	2.5, 5, 10 mg	
		Teva-Medroxyprogesterone	2.5, 5, 10 mg	
Progesterone (micronized)	Oral	Prometrium	100 mg	100 mg daily for continuous use or 200 mg daily for 12–14 days/month for cyclic use
		PMS-Progesterone	100 mg	
		Reddy-Progesterone	100 mg	
		Teva-Progesterone	100 mg	
Norethindrone acetate	Oral	Norlutate	5 mg	5 mg (1×/day)
Levonorgestrel intrauterine system	Intrauterine	Mirena	52 mg per intrauterine system	5 years' duration
		Kyleena	19.5 mg per intrauterine system	
Combined therapies				
17 β estradiol + norethindrone acetate	Oral	Activelle	1 mg estradiol + 0.5 mg norethindrone acetate	1 tablet/day
		Activelle LD	0.5 mg estradiol + 0.1 mg norethindrone acetate	
17 β estradiol + norethindrone acetate	Transdermal patch	Estalis 140/50	50 µg estradiol + 140 mg norethindrone acetate	2×/week application
		Estalis 250/50	50 µg estradiol + 250 mg norethindrone acetate	1×/week application
17 β estradiol + drospirenone	Oral	Angeliq	1 mg estradiol + 1 mg drospirenone	1 tablet/day
Tissue selective estrogen complex				
Conjugated estrogen + bazedoxifene	Oral	Duavive	0.45 mg conjugated estrogen + 20 mg bazedoxifene	1 tablet/day
Synthetic steroid				
Tibolone	Oral	Tibella	2.5 mg	1 tablet/day

Adapted with permission from guideline A of the Society of Obstetricians and Gynaecologists of Canada's 2021 *Managing Menopause* guideline.

not have a first-pass effect through the liver, and provides more consistent estrogen levels.[20] Use of transdermal estrogen is preferable in smokers, shift workers, and women with high triglyceride levels, hypertension, gall bladder disease, migraines, or malabsorption syndromes.[21-23] In the 2014 guideline, transdermal estrogen was also specifically recommended for women with a high risk of venous thromboembolism, metabolic syndrome, or sexual dysfunction.[24,25]

In women with a uterus who use estrogen therapy, either a progestogen or a selective estrogen receptor modulator is required to oppose the proliferative effects of estrogen on the endometrium and prevent hyperplasia. Either micronized progesterone or a synthetic progestin (medroxyprogesterone acetate, norethindrone, or drospirenone) can be prescribed in a continuous or cyclic fashion. A progestin-releasing intrauterine system also provides endometrial protection, but it has not yet been approved by Health Canada for this indication.[26] The 2021 guideline includes suggested doses for endometrial protection with standard doses of estrogen but notes that higher progestogen doses may be indicated when the estrogen dose is higher.

In some situations, patients cannot or do not wish to take estrogen. The 2014 guideline had a subsection on progestogen-only therapy, androgen therapy, and dehydroepiandrosterone, but it is not included in the 2021 guideline.

The 2021 guideline introduces some new options in Canada for menopausal therapy: the tissue selective estrogen complex and tibolone. Neither of these options requires endometrial protection with a progestogen. The tissue selective estrogen complex is a daily tablet that contains both conjugated estrogen and bazedoxifene, a selective estrogen receptor modulator. The estrogen component works to control vasomotor symptoms, while the estrogen receptor modulator antagonizes estrogen receptors in the endometrium to prevent hyperplasia. The number of moderate to severe hot flashes declined by 74% at 12 weeks in women who received a 0.45 mg conjugated estrogen and 20 mg bazedoxifene dose, with no increased endometrial risk, versus 51% for those who received a placebo.[27,28] The risks and adverse events with the tissue selective estrogen complex are similar to those for estrogen, and while long-term studies are needed, there does not appear to be an increased risk of breast cancer with up to 2 years of use.[27]

Tibolone is new to the Canadian market, but as the guideline points out, it has been available for decades in other countries. Tibolone is a synthetic agent similar to progestin. It is taken as a daily tablet and, once ingested, is converted into three metabolites with weak estrogenic, progestogenic, and androgenic properties. A 2016 Cochrane review concluded that tibolone was effective against vasomotor symptoms but was not as effective as estrogen.[29]

The 2021 guideline introduces some new options in Canada for menopausal therapy: the tissue selective estrogen complex and tibolone.

Advice for troubleshooting adverse effects such as bloating and breakthrough bleeding are outlined in the 2021 guideline. For example, micronized progesterone capsules can be administered vaginally if they induce unwanted drowsiness. Micronized progesterone preparations should be used with caution in patients with peanut allergies, because, although the preparation marketed as Prometrium is made with sunflower oil, some generic preparations contain peanut oil.

The term "bioidentical" is also addressed more thoroughly in the 2021 guideline than in the 2014 guideline: "Bioidentical hormone therapy . . . is often used to refer to compounded formulations; however, many commercially available products approved by Health Canada would be considered bioidentical or 'body identical.'" Bioidentical therapies should not be considered more natural or safer because they have not been scrutinized in the same manner as Health Canada–approved products. Many claims about their safety are misleading and not substantiated by evidence.[30]

The 2021 guideline lists additional nonhormonal options, most of which are similar to those in the 2014 guideline. They include selective serotonin reuptake inhibitors, serotonin-norepinephrine uptake inhibitors, gabapentinoids, clonidine, and oxybutynin. Bellergal was listed in the 2014 guideline but is not listed in the 2021 guideline.

Lifestyle changes and complementary therapy

At the end of guideline A of the 2021 guideline, lifestyle changes and complementary therapy for vasomotor symptoms are addressed. With the rising popularity of alternatives outside of conventional medicine, it is important for clinicians to be prepared to counsel women who often feel overwhelmed by choice and uninformed about product safety and efficacy.[31] This topic was briefly reviewed in the 2014 guideline but was in a section that was separate from the prescription agents.

Nutrition recommendations were taken from the 2019 update to Canada's food guide. A table of lifestyle modifications summarizes the evidence for a range of options for treating vasomotor symptoms. Weight loss, cognitive-behavioral therapy, and clinical hypnosis are considered to be efficacious.[32-34] Mindfulness-based stress reduction and paced respiration have also shown some evidence of benefit.[35,36] There is insufficient evidence of the efficacy of cooling techniques, avoiding triggers, and exercising,[37-39] and acupuncture and yoga do not appear to be helpful.[40,41]

The 2021 guideline presents significantly more information than the 2014 guideline about the evidence, or lack thereof, supporting the use of natural health products. The 2014 guideline stated that "Canadian legislation in January 2004 removed Natural Health Products from the food category and placed them in a special drug category to allow regulation. . . . To date, little appears to have been accomplished in the regulation of Natural Health Products in Canada."[42] The 2014 guideline also mentioned that pharmaceutical product trials require participants to have at least seven hot flashes per day, and many studies of herbal products have been open-label trials and have been conducted in women with as few as one or two hot flashes per day.[1]

The 2021 guideline outlines the mechanism of action, evidence for efficacy, and recommendations for 13 natural health products. Only two of them may be beneficial for treating vasomotor symptoms: fermented soybean extract and soy (S-equol).[43,44] There is insufficient efficacy data to recommend the use of red clover, flaxseed, black cohosh, wild yam, crinum, dong quai root, evening primrose oil, ginseng, pollen extract, hops, and maca.[45-53]

When referring to the efficacy of these natural health products, the 2014 guideline drew attention to placebo effects. In particular, a 2004 Cochrane review showed participants who received placebo as treatment had an improvement in vasomotor symptoms by up to 50%.[19] In terms of counseling patients with vasomotor symptoms, the 2021 guideline introduces the importance of a collaborative process between patients, clinicians, and cultural leads to ensure cultural safety and humility are achieved.

Summary

Overall, the 2014 and 2021 guidelines both emphasize the prevalence of vasomotor symptoms and their effect on quality of life. Estrogen-containing hormone therapy remains the most effective option for treating vasomotor symptoms. The 2021 guideline contains information on new agents (tibolone and the tissue selective estrogen complex) and tabular summaries of natural health products and lifestyle interventions. The **Table**, adapted from the 2021 guideline, lists currently available prescription hormone agents and may be helpful for practitioners. The 2021 guideline contains many more details on the topics discussed in this article and should be referenced for a deeper understanding. ■

Competing interests

Dr Rowe was involved in writing the Society of Obstetricians and Gynaecologists of Canada recommendations and is a past member of the *BCMJ* Editorial Board. He is also a current member of the advisory boards for BioSyent, Lupin Pharma Canada, Pfizer Canada, and Astellas. Dr Dunne was a member of the *BCMJ* Editorial Board when this article was written, and is now the journal's editor, but did not participate in making the publication decision regarding this article.

Bioidentical therapies should not be considered more natural or safer because they have not been scrutinized in the same manner as Health Canada–approved products.

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