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# Guideline No. 422a: Menopause: Vasomotor Symptoms, Prescription Therapeutic Agents, Complementary and Alternative Medicine, Nutrition, and Lifestyle

*(En français : Ménopause : symptômes vasomoteurs, agents thérapeutiques d'ordonnance, médecines douces et complémentaires, nutrition et mode de vie)*

The English document is the original version. In the event of any discrepancy between the English and French content, the English version prevails.

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This document reflects emerging clinical and scientific advances as of the publication date and is subject to change. The information is not meant to dictate an exclusive course of treatment or procedure. Institutions are free to amend the recommendations. The SOGC suggests, however, that they adequately document any such amendments.

**Informed consent:** Everyone has the right and responsibility to make informed decisions about their care together with their health care providers. In order to facilitate this, the SOGC recommends that health care providers provide patients with information and support that is evidence-based, culturally appropriate, and personalized.

**Language and inclusivity:** The SOGC recognizes the importance to be fully inclusive and when context is appropriate, gender-neutral language will be used. In other circumstances, we continue to use gendered language because of our mission to advance women's health. The SOGC recognizes and respects the rights of all people for whom the information in this document may apply, including but not limited to transgender, non-binary, and intersex people. The SOGC encourages health care providers to engage in respectful conversation with their patients about their gender identity and preferred gender pronouns and to apply these guidelines in a way that is sensitive to each person's needs.

## RECOMMENDED CHANGES IN PRACTICE

1. Menopausal hormone therapy can be safely initiated in women without contraindications who are less than 10 years post-menopause and younger than 60 years of age.
2. There is no specific time frame for duration of systemic menopausal hormone therapy, and treatment duration should be individualized.

## KEY MESSAGES

1. Vasomotor symptoms can negatively affect a woman's quality of life.
2. Menopausal hormone therapy is the most effective option for managing moderate to severe vasomotor symptoms.
3. Non-hormonal prescription therapies are options to treat vasomotor symptoms in women who have contraindications or choose not to use menopausal hormone therapy.
4. Duration of menopausal hormone therapy should be based on the individual woman's ongoing benefits, such as symptom relief, and personal risks.
5. New options for menopausal hormone therapy are now available on the Canadian market providing a wide variety of products for menopause management.
6. For cultural traditional therapies, women should be offered the opportunity to work with a cultural leader; health care providers should discuss this option in partnership with women, in order to ensure cultural humility and cultural safety.

## ABSTRACT

**Objective:** Provide strategies for improving the care of perimenopausal and postmenopausal women based on the most recent published evidence.

**Target Population:** Perimenopausal and postmenopausal women.

**Benefits, Harms, and Costs:** Target population will benefit from the most recent published scientific evidence provided via the information from their health care provider. No harms or costs are involved with this information since women will have the opportunity to choose among the different therapeutic options for the management of the symptoms and morbidities associated with menopause, including the option to choose no treatment.

**Evidence:** Databases consulted were PubMed, MEDLINE, and the Cochrane Library for the years 2002–2020, and MeSH search terms were specific for each topic developed through the 7 chapters.

**Validation Methods:** The authors rated the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. See online Appendix A (Tables A1 for definitions and A2 for interpretations of strong and weak recommendations).

**Intended Audience:** physicians, including gynaecologists, obstetricians, family physicians, internists, emergency medicine specialists; nurses, including registered nurses and nurse practitioners; pharmacists; medical trainees, including medical students, residents, fellows; and other providers of health care for the target population.

**SUMMARY STATEMENTS:**

1. The vast majority of women in mid-life experience menopausal symptoms, the hallmark being vasomotor symptoms. A significant portion of these women have severe symptoms that greatly affect their quality of life (*high*).
2. For the management of vasomotor symptoms, menopausal hormone therapy is the most effective option and can be safely initiated in women without contraindications who are younger than 60 years of age or less than 10 years post-menopause (high).
3. Options for menopausal hormone therapy for vasomotor symptoms in women with a uterus include estrogen-progestogen therapy, a tissue-selective estrogen complex, or tibolone. Estrogen alone can be used in women who have had a hysterectomy (*high*).
4. The safety and efficacy of compounded bioidentical hormone therapy have not been assessed with the same rigour as those of menopausal hormone therapy products approved by Health Canada (*moderate*).
5. Non-hormonal prescription therapies, including certain antidepressant agents, gabapentinoids, clonidine, and oxybutynin, may offer some relief from hot flashes but have their own adverse effects (*moderate*).
6. There is emerging evidence that cognitive behavioural therapy may have positive effects on vasomotor symptoms (*high*).
7. There is insufficient evidence to support the effectiveness of any one natural health product for the management of moderate to severe hot flashes (*low*).
8. A healthy diet during menopause can reduce the risk of future chronic conditions, aid in weight management, and improve energy levels (*high*).

**RECOMMENDATIONS:**

1. Health care providers should offer menopausal hormone therapy as the most effective option for managing vasomotor symptoms (*strong, high*).
2. Menopausal hormone therapy can be safely initiated in women without contraindications who are younger than 60 years of age or less than 10 years post-menopause (*strong, high*).
3. Menopausal hormone therapy should be individualized after careful consideration of symptoms, medical conditions, health risks, family history, treatment goals, patient preferences, and timing of last menstrual period (*strong, high*).
4. Duration of menopausal hormone therapy should be individualized to the patient, based on ongoing symptoms, benefits, and personal risks. Periodic re-evaluation of menopausal hormone therapy is recommended (*strong, high*).
5. Women who have experienced loss of ovarian function or with decreased ovarian function before the age of 45 years should consider replacement hormone therapy until the average age of menopause (*strong, high*).
6. Estrogen-progestogen regimens can be continuous (i.e., estrogen-progestogen taken every day) or follow a cyclic regimen, with estrogen taken every day and progestogen taken for 12–14 days every month. In women with hysterectomy, estrogen alone can be taken every day (*strong, high*).
7. Options for perimenopausal women include progestogen alone, low-dose combined hormonal contraceptives, menopausal hormone therapy, or estrogen in combination with a levonorgestrel-releasing intrauterine system. (*strong, moderate*)
8. Non-hormonal prescription therapies can be considered when hormone therapy is contraindicated or not desired (*strong, moderate*).
9. For cultural traditional therapies, women should be offered the opportunity to work with a cultural leader; health care providers can discuss this option in partnership with women, in order to ensure cultural humility and cultural safety (*strong, moderate*).

## INTRODUCTION

Vasomotor instability—namely, hot flashes and night sweats—is the hallmark of menopause, occurring in up to 80% of women. Severe, bothersome symptoms, with up to 20 to 30 episodes daily, affect up to 20% of women.

### SUMMARY STATEMENT 1

A hot flash is experienced as an unwanted sensation of heat, typically starting in the chest and rising upwards, lasting an average of 3 to 4 minutes. A hot flash is sometimes preceded by anxiety or palpitations. Other common symptoms of menopause include sleep disturbances; mood, memory, and concentration difficulties; joint aches and pain; vulvovaginal dryness; and urogenital and sexual concerns. Quality of life can significantly deteriorate as a result of these symptoms.[1]

Vasomotor symptoms (VMS) are experienced by women in all walks of life.[2] However, women of lower socioeconomic status and education may be more affected than those with higher incomes and levels of education. Women with obesity, especially those with increased abdominal adiposity, tend to have more VMS than women who are not obese.[3] Black and Hispanic women have higher incidences of VMS, followed by White women and Asian women, who have the lowest incidence.[4, 5]

Onset and duration of VMS are variable. Findings from the Study of Women's Health Across the Nation (SWAN) show that VMS last an average of 7.4 years.[6] However, 4 distinct patterns of symptoms have been described: "onset early (11 years prior to the final menstrual period (FMP)) with decline after menopause (Early onset, 18.4%); onset near the FMP with later decline (Late onset, 29.0%), onset early with persistently high frequency (High, 25.6%); and persistently low frequency (Low, 27.0%)."[7] Early onset and persistently high VMS, have been associated with more adverse health and psychosocial issues than low VMS.[7]

The pathophysiology behind VMS remains incompletely understood. A narrowing of the thermoneutral zone has been described, with more opportunity for sweating, due to excess heat, and shivering, as a result of temperature lowering.[8] The exact mechanisms result from an interplay among the central nervous system, endocrine components, and the peripheral vascular system.[1]

One component of the mechanism of VMS is the interaction of kisspeptin, neurokinin B, and dynorphin (KNDy) neurons within the hypothalamus.[9–11] These neurons are affected by low levels of circulating estrogens and gonadotropins; they become hypertrophied post-menopause.[9–11] KNDy neurons have connections to estrogen-sensitive thermoregulatory centres in the brain. Emerging studies show that blocking this KNDy neuron system can be effective in treating VMS.[12] As more is understood about the components of a hot flash, novel therapies will evolve to target specific mechanisms.

VMS are proving to be more than simply bothersome symptoms; they are also a marker for disease. VMS have been independently linked with cardiovascular disease, since affected women seem to have less favourable cardiovascular disease risk profiles and greater burdens of subclinical disease.[13, 14] This knowledge may eventually lead to a change in practice, as VMS treatment shifts from symptom management to disease prevention.[13, 14]

### ABBREVIATIONS

| | |
|---|---|
| BHT | bioidentical hormone therapy |
| CBT | cognitive behavioural therapy |
| DHEA | dehydroepiandrosterone |
| EPT | estrogen-progestogen therapy |
| ER | estrogen receptor |
| GSM | genitourinary syndrome of menopause |
| LNG-IUS | levonorgestrel intrauterine system |
| MHT | menopausal hormone therapy |
| NHP | natural health products |
| SERM | selective estrogen receptor modulator |
| SNRI | serotonin-norepinephrine uptake inhibitor |
| SSRI | selective serotonin reuptake inhibitor |
| TSEC | tissue selective estrogen complex |
| VMS | vasomotor symptoms |

## MENOPAUSAL HORMONE THERAPY

Menopausal hormone therapy (MHT) is the most effective option for the management of VMS.[15, 16] In a Cochrane systematic review of randomized controlled trials, MHT, either estrogen alone or estrogen plus a progestogen, was found to significantly reduce hot flash frequency by 75% (95% CI 64.3−82.3) compared with placebo, as well symptom severity (odds ratio [OR] 0.13; 95% CI 0.07−0.23).[16] MHT can be safely initiated in healthy women without contraindications who are younger than 60 years of age or less than 10 years post-menopause.[17–19]

## SUMMARY STATEMENT 2 AND RECOMMENDATIONS 1 AND 2

Several MHT regimens are used in Canada. In women with a uterus, estrogen is provided along with a progestogen; for women who have had a hysterectomy, estrogen therapy is used alone. The estrogen component serves to alleviate bothersome symptoms, whereas the progestogen component provides protection against the increased risk of endometrial cancer seen with estrogen alone.

## SUMMARY STATEMENT 3

### General Principles of Prescribing Hormone Therapy

MHT should be individualized after careful consideration of symptoms, medical conditions, health risks, family history, treatment goals, patient preferences, and timing of last menstrual period. The initial assessment should include screening for MHT contraindications (Table 1) as well as consider the woman's unique benefit-to-risk profile. Balanced communication of MHT benefits and risks is important to facilitate informed decision-making.

## RECOMMENDATION 3

MHT doses should be titrated to effect when managing VMS, starting with low to standard estrogen doses (see Table 2 for the MHT doses), which can be adjusted based on symptom improvement or side effects. Higher starting doses may be needed in younger women with early or premature menopause.[20] VMS can be relieved with standard MHT doses as soon as 2 weeks after beginning therapy, but benefit usually takes about a month. Lower doses may take a slightly longer, up to 6 weeks, to show benefit. In women with contraindications to estrogen therapy, progestogen alone can be used to control VMS.[21, 22] Progestogens, including medroxyprogesterone (20 mg/d) or micronized progesterone (300 mg/d), have been shown to be superior to placebo in reducing VMS, although they may not be as effective as estrogen.[21, 22]

There is no specific time frame or duration for systemic MHT use. These treatments should be individualized, based on ongoing symptoms, benefits, and personal risks. Periodic re-evaluation of a patient's MHT prescription is recommended.

MHT may be continued beyond the age of 65 years in some women with persistent, bothersome menopausal symptoms.[23, 24]

## RECOMMENDATION 4

Women who have experienced loss of ovarian function or with decreased ovarian function before the age of 45 years should consider replacement hormone therapy, unless contraindicated, until the average age of menopause. Premature loss of ovarian function places women at increased risk of osteoporosis, cardiovascular disease, cognitive impairment, and early mortality.[25–28]

## RECOMMENDATION 5

There is no consistent recommendation for stopping MHT; the dose can be either tapered or abruptly discontinued. Studies comparing abrupt versus taper-down discontinuation methods have shown little difference in the return of menopausal symptoms.[29, 30] In general, return of symptoms in women discontinuing MHT is about 50%.[29]

**Table 1. Contraindications to systemic menopausal hormone therapy**

| Contraindications to estrogen | Contraindications to progestogen |
|---|---|
| • Undiagnosed abnormal vaginal bleeding<br>• Known, suspected, or history of breast cancer<br>• Known or suspected estrogen-dependent cancers (i.e., endometrial, ovarian)<br>• Coronary heart disease<br>• Active or history of venous thromboembolism<br>• Active or history of stroke<br>• Known thrombophilia<br>• Active liver disease<br>• Known or suspected pregnancy | • Undiagnosed abnormal vaginal bleeding<br>• Current or history of breast cancer |

For postmenopausal women, estrogen-progestogen therapy (EPT) regimens can be either continuous or cyclic. In continuous EPT regimens, both estrogen and progestogen are taken continuously. In cyclic EPT regimens, progestogens are administered 12–14 days per month, while estrogen is taken continuously.[31, 32]

## RECOMMENDATION 6

Although vaginal bleeding is common during the first 3–6 months with a continuous EPT regimen, most women (over 75%) will become amenorrheic by 12 months.[33] With cyclic EPT regimens, a withdrawal bleed is often seen at the end of the progestogen cycle. If it has been less than a year since a woman's last menstrual period, or if the woman is in the late perimenopausal period, cyclic EPT regimens may provide more predictable bleeding profiles. While cyclic EPT regimens may be associated with a lower risk of breast cancer than continuous EPT, the continuous EPT regimens are considered safe for MHT.[34–36] In women without a uterus, estrogen therapy alone is used continuously. When prescribing combined hormone therapy consideration should be given to progestogens with lowest impact on markers for CVD.[37]

### Perimenopause

For women with symptoms in the perimenopausal period, therapeutic options include combined hormonal contraceptives, MHT, or estrogen in combination with a levonorgestrel-releasing intrauterine system (LNG-IUS).

For perimenopausal women, a cyclic regimen of EPT may be preferred to minimize the risk of breakthrough bleeding. Contraception needs should also be considered in women who are perimenopausal and for whom it is less than one year since their last menstrual period. Combined hormonal contraceptives or estrogen with LNG-IUS may be preferred over MHT in women who need contraception *or* with heavy vaginal bleeding.

### Hormonal Prescription Options

#### *Choice of Estrogen*

Estrogen is available in the form of oral pills, transdermal patches and gels, and vaginal applications. The estrogens found in Canadian products include conjugated estrogens, estradiol, and estrone. Transdermal estrogen products do not have a first-pass effect through the liver and provide more consistent estrogen levels.[38] They may be preferred over oral pills in women who are smokers or shift workers, or who have high triglyceride levels, hypertension, gall bladder disease, migraines, or malabsorption syndromes. Based on observational data alone, standard doses of transdermal estrogen may be associated with lower risk of venous thromboembolism than oral estrogen.[39–41]

#### *Choice of Progestogen*

Progestogen refers to both synthetic progestins and progesterone, and includes medroxyprogesterone, micronized progesterone, norethindrone, and drospirenone used in MHT regimens. Progestogen products are available in oral pills, transdermal formats (in combination with estrogen), and intrauterine devices. The recommended doses of progestogens to provide endometrial protection for standard doses of estrogen are provided in Table 2. In general, higher progestogen doses are required for higher estrogen doses. LNG-IUS has been shown to provide endometrial protection from hyperplasia in women on estrogen therapy, although it is not approved by Health Canada for this indication.[42] Studies that have shown endometrial protection with LNG-IUS when given with estrogen therapy have been conducted only for a dose of 52 mg for 5 years.[42]

## RECOMMENDATION 7

### Options That Do Not Require a Progestogen

Recent additions to hormonal options on the Canadian market include tissue selective estrogen complex (TSEC) and tibolone.

TSEC, a progestogen-free daily oral option, combines conjugated estrogen with a selective estrogen receptor modulator (SERM), bazedoxifene. Bazedoxifene has antagonist effects on estrogen receptors in the uterus and therefore provides endometrial protection. In trials, the conjugated estrogen–bazedoxifene combination has been found to be effective in reducing VMS when compared with placebo (significant reduction in moderate to severe hot flashes by 74% for the conjugated estrogen 0.45 mg and bazedoxifene 20 mg dose vs. 51% for placebo at 12 weeks) with no increased endometrial risk.[43,44] Regarding safety, conjugated estrogen–bazedoxifene has shown no increased risk of breast cancer in trials up to 2 years; however, longer-term studies are required to evaluate this risk.[45–47] Reassuringly, TSECs do not increase breast density.[45,46] TSECs have similar adverse effect profiles and risks as estrogen therapy, and contraindications are the same, but TSECs may be associated with less breakthrough bleeding and breast tenderness than EPT regimens.[46,48,49]

**Table 2. Systemic menopausal hormone therapy products in Canada**

| Generic | Trade name | Strengths available | Starting dosage |
|---|---|---|---|
| Estrogens | | | |
| Oral | | | |
| Conjugated estrogens | Premarin | 0.3, 0.625, 1.25 mg tablets | 0.3–0.625 mg once daily |
| 17$\beta$-estradiol (micronized) | Estrace<br>Lupin-estradiol | 0.5, 1, 2 mg tablets<br>0.5, 1, 2 mg tablets | 0.5–1 mg once daily |
| Transdermal patch | | | |
| Twice weekly 17$\beta$-estradiol patches | Estradiol Derm<br>Estradot<br>Oesclim | 50, 75, 100 $\mu$g patches<br>25, 37.5, 50, 75, 100 $\mu$g patches<br>25, 50 $\mu$g patches | 25–50 $\mu$g twice weekly |
| Once weekly 17$\beta$-estradiol patches | Climara | 25, 50, 75, 100 $\mu$g patches | 25–50 $\mu$g once weekly |
| Transdermal gel | | | |
| 17$\beta$-estradiol gel | Estrogel | 0.06% gel<br>0.75 mg estradiol per 1.25 g metered dose (= 1 actuation) | 1–2 metered doses/actuation once daily |
| | Divigel | 0.1% gel<br>Sachets contain 0.25, 0.5, 1 mg | 0.5–1 mg sachets once daily |
| Progestogens | | | |
| Oral | | | |
| Medroxyprogesterone | Provera<br>Apo-medroxy<br>Pro-Doc Limitee<br>Teva-medroxyprogesterone | 2.5, 5, 10 mg tablets<br>2.5, 5, 10 mg tablets<br>2.5, 5, 10 mg tablets<br>2.5, 5, 10 mg tablets | 2.5 mg daily for continuous regimen<br>5 mg daily for 12–14 days/month for cyclic regimen |
| Progesterone (micronized) | Prometrium<br>PMS-progesterone<br>Reddy-progesterone<br>Teva-progesterone | 100 mg capsules<br>100 mg capsules<br>100 mg capsules<br>100 mg capsules | 100 mg daily for continuous regimen<br>200 mg daily for 12–14 days/month for cyclic regimen |
| Norethindrone acetate | Norlutate | 5 mg tablets | 5 mg once daily |
| Intrauterine | | | |
| Levonorgestrel IUS | Mirena[a,b] | 52 mg per IUS | For 5 years |
| | Kyleena[a,b] | 19.5 mg per IUS | For 5 years |
| Combination hormone therapy preparations | | | |
| Oral | | | |
| 17$\beta$-estradiol (E2) and NETA | Activelle<br>Activelle LD | 1 mg E2 and 0.5 mg NETA tablet<br>0.5 mg E2 and 0.1 mg NETA tablet | 1 tablet daily |
| 17$\beta$-estradiol (E2) and DRSP | Angeliq | 1 mg E2 and 1 mg DRSP tablet | 1 tablet daily |
| Transdermal patch | | | |
| 17$\beta$-estradiol (E2) and NETA | Estalis 140/50<br>Estalis 250/50 | 50 $\mu$g E2 and 140 mg NETA patch<br>50 $\mu$g E2 and 250 mg NETA patch | For 140/50 patch, twice weekly application |
| TSEC | | | |
| CE and bazedoxifene | Duavive | 0.45 mg CE and 20 mg bazedoxifene tablet | 1 tablet daily |
| Synthetic steroid | | | |
| Tibolone | Tibella | 2.5 mg oral tablet | 1 tablet daily |

[a] Not approved for menopausal hormone therapy by Health Canada

[b] Mirena is the only LNG-IUS marketed in Canada that has evidence for endometrial protection.

CE: conjugated estrogen; DRSP: drospirenone; IUS: intrauterine system; NETA: norethindrone acetate; SERM: selective estrogen receptor modulator; TSEC: tissue selective estrogen complex.

Tibolone (Tibella), a 2.5-mg daily tablet, was recently approved by Health Canada for the treatment of VMS in postmenopausal women, but it has been available in various countries worldwide for over 30 years.[50] Tibolone is a synthetic steroid analogue of the progestin, norethynodrel. Tibolone is converted to 3 active metabolites in the body, with weak estrogenic, progestogenic, and androgenic properties. Additional progestogen therapy is not required. In a recent Cochrane review of randomized controlled trials, tibolone was more effective than placebo, but slightly less effective than EPT, in reducing VMS in postmenopausal women.[51] The most common adverse effects were fatigue, breast tenderness, fluid retention, stomach upset/nausea, and increased appetite. Tibolone is associated with more vaginal bleeding than placebo, but lower than EPT.[51] Tibolone may not increase breast density; however, it should not be used in patients with a history of breast cancer, as it has been shown to increase recurrence rates.[52,53] Tibolone has a cardiovascular risk profile similar to that of EPT and carries the same black box warning and contraindications in the product monograph for its estrogen class effect.[54]

Current systemic MHT products available in Canada can be found in Table 2.

### Treatment options for genitourinary syndrome of menopause

Treatment options for genitourinary syndrome of menopause (GSM) are fully discussed in Guideline No 422b: Menopause and Genitourinary Health,[55] in summary:

Local vaginal estrogen therapy is appropriate for treatment of genitourinary syndrome of menopause (GSM). The doses used in vaginal estrogen are so low that they produce little to minimal increase in serum estradiol levels. They may be used in women with contraindications to systemic estrogen. Concurrent progestogen therapy is not needed when using recommended doses of vaginal estrogen for genitourinary symptoms.

The Canadian market has 2 new therapeutic options for the treatment of GSM: prasterone, a vaginal dehydroepiandrosterone (DHEA; Intrarosa), and ospemifene, a SERM (Osphena).

Prasterone, available as a 6.5-mg ovule, is an inactive sex steroid precursor that is converted to estrogen and androgen in the vaginal cells. The efficacy of prasterone on moderate to severe dyspareunia and vaginal dryness has been demonstrated in two 12-week controlled efficacy trials and in a 52-week, open-label safety study.[56–58] Endometrial safety has been shown with prasterone, with women in the study maintaining an atrophic or inactive endometrial lining over 52 weeks.[56–59] One ovule is inserted every night into the vagina with the provided reusable applicator or with a finger. Progestogen therapy is not needed while taking prasterone. Overall, prasterone is well tolerated. Vaginal discharge, partly from melting of the hard-fat excipient in the ovule, is the most common adverse effect reported in clinical trials.[60]

Ospemifene is a SERM with specific estrogen receptor (ER) agonist activity in the vagina. It also has ER agonist activity on the bones and is a partial ER agonist in the uterus. Ospemifene has recently received approval by Health Canada for the treatment of GSM; it has been available in the United States and in several European countries since 2013. Ospemifene is taken as a once-daily 60-mg oral tablet, which some women consider an advantage over vaginal administration. Several 12-week randomized controlled trials have shown significant improvement in dyspareunia and vaginal dryness.[61–63] The most common adverse effects with ospemifene are hot flashes, increased sweating, muscle spasms, and vaginal discharge. Safety trials with ospemifene have lasted up to 52 weeks.[64] In a meta-analysis, although ospemifene was associated with greater endometrial thickness of 1 mm compared with placebo at 12 and 52 weeks, this finding was not considered clinically significant.[65] No cases of endometrial cancer have been reported.[65] Concomitant progestogen is not needed when taking ospemifene. In a pooled analysis of 6 trials, the cardiovascular treatment-emergent adverse effects (including venous thromboembolism, cerebrovascular accident, and cerebral hemorrhage) were low in both the ospemifene (0.3%) and placebo (0.1%) groups.[66] There are limited human studies evaluating ospemifene in patients with breast cancer.[67] Table 3 lists current prescription products available in Canada for the treatment of GSM.

### Adverse Effects with MHT

Breakthrough bleeding is the most common adverse event with MHT and is often cited as the reason for discontinuation within the first 3 to 12 months.[68–70] Patients should be informed that it is normal to see breakthrough bleeding up to 6 months after starting continuous MHT, with most women having amenorrhea by 12 months (<10% of women report ongoing breakthrough bleeding).[31,70] Heavy vaginal bleeding or continued breakthrough bleeding beyond 6 months should be investigated. Women on cyclic EPT regimens may continue to have withdrawal bleeding.

Estrogen-related adverse effects include nausea, fluid retention, breast tenderness, and headaches. These

**Table 3. Pharmacologic options for genitourinary syndrome of menopause**

| Generic | Trade name | Strengths available | Dosage |
|---|---|---|---|
| Vaginal estrogen | | | |
| Conjugated estrogens | Premarin vaginal cream | 0.625 mg/g vaginal cream with refillable applicator | 0.5 g (0.3 mg) vaginally daily × 14 days, then 0.5 g (0.3 mg) 2–3 times weekly |
| 17$\beta$-estradiol | Vagifem vaginal tablets | 10 $\mu$g vaginal tablet with individual applicator | 1 tablet vaginally daily × 14 days, then 1 tablet twice weekly |
| | Estring vaginal ring | 2 mg/ring | One vaginal ring inserted every 3 months |
| | Imvexxy vaginal ovules | 4, 10 $\mu$g vaginal ovules | 1 ovule vaginally daily x 14 days, then 1 ovule twice weekly |
| Estrone | Estragyn 0.1% vaginal cream | 1 mg/g vaginal cream with refillable applicator | 0.5–4 g (0.5–4 mg) vaginally daily cyclic (3 weeks on, one week off) or 2–3 times weekly |
| Intravaginal DHEA | | | |
| Prasterone | Intrarosa vaginal ovules | 6.5 mg vaginal ovules with reusable applicators | 1 ovule vaginally every night |
| Oral SERM | | | |
| Ospemifene | Osphena | 60 mg oral tablet | One tablet daily |

effects are usually dose related and improve with time. Vaginal estrogens are associated with fewer adverse effects than systemic estrogen formulations, the most common being increased vaginal discharge, which is an expected outcome of local therapy. Adverse effects of progestogen include bloating, fluid retention, breast tenderness, and mood changes, such as depression or anxiety. Micronized progesterone causes drowsiness through the mediated effects of progesterone metabolites (i.e., allopregnanolone) on gamma-aminobutyric acid (GABA)-ergic receptors; consequently, it should be taken at bedtime.[69] If patients experience excessive drowsiness, they can take micronized progesterone vaginally.[32,71] Options for women who are intolerant of oral progestogens or who continue to have heavy vaginal bleeding or breakthrough bleeding after 6 months include switching to a different progestogen, using an LNG-IUS for endometrial protection, or switching to a TSEC. For micronized progesterone, the brand Prometrium now contains sunflower oil, and some generic formulations may contain peanut oil. As a result, these formulations should be used with caution in women with peanut allergies. Transdermal patches may cause skin irritation. MHT doses can be reduced or formulations changed if adverse effects become bothersome.

### Compounded Bioidentical Hormone Therapy

*Bioidentical* is a term used to refer to any hormones that are identical in molecular structure to human hormones, but there is no true scientific definition of *bioidentical*.[72] Bioidentical hormones include estrogens (such as estradiol, estriol, and estrone), micronized progesterone, testosterone, and DHEA. Bioidentical hormone therapy (BHT) is often used to refer to compounded formulations; however, many commercially available products approved by Health Canada would be considered bioidentical or "body identical." Compounded BHT is often promoted as "natural," implying that these preparations are safer and more efficacious than commercial MHT.[73] In reality, the use of the word "natural" is a misnomer, as these preparations, although derived from plant sources, need to undergo a process of chemical extraction and stabilization to produce the same chemical structure as human hormones. The safety and efficacy of compounded BHTs have not been assessed with the same rigour as those of Health Canada–approved products. Unfortunately, many claims for the safety of compounded BHT are misleading and not substantiated by evidence.[73] Furthermore, there is a lack of data to support the use of salivary hormone levels to initiate or adjust dosing of MHT, and these levels may not be reliable in a clinical setting.[74] The National Academies of Sciences, Engineering, and Medicine recently released key recommendations addressing the clinical utility of compounded BHT.[75] In their report evaluating the safety, effectiveness, and use of compounded BHT, they recommended restricting the use of compounded BHT to women with a documented allergy or requiring a specific dosage form, as well as conducting further research to assess the use of compounded BHT.[75]

### SUMMARY STATEMENT 4

## NON-HORMONAL PRESCRIPTIONS

For patients with contraindications to hormone therapy or those who prefer alternatives to MHT, non-hormonal prescription options have shown some efficacy in the relief of VMS. These include selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine uptake inhibitors (SNRIs), gabapentinoids, clonidine, and oxybutynin. None are as effective as estrogen, and the response rate among women is variable.

### SUMMARY STATEMENT 5 and RECOMMENDATION 8

### Antidepressants

Many SSRIs and SNRIs have been tested for the treatment of VMS.[76] Successful placebo-controlled trials of antidepressants paroxetine, venlafaxine, desvenlafaxine, citalopram, and escitalopram have been reported.[76] Efficacy of antidepressants for the reduction of hot flashes may vary from 27% to 61%.[77] Although antidepressants are moderately effective for the treatment of VMS, they have side effects[78] and afford none of the other health benefits of hormone therapy that directly affect quality of life (e.g., prevention of urogenital atrophy and osteoporosis).[79] Antidepressants may be used concurrently with hormone therapy in menopause for the treatment of coexisting depression.[77, 80] Although not available in Canada, paroxetine 7.5 mg (previously called "low-dose mesylate salt of paroxetine") is the first and only non-hormonal option for the treatment of moderate to severe VMS associated with menopause approved by the U.S. Food and Drug Administration.[81]

Adverse effects of SSRIs and SNRIs include nausea, headache, dizziness, dry mouth, insomnia, and nervousness. Contraindications to SSRIs and SNRIs include prior neuroleptic syndrome or serotonin syndrome and concurrent use of monoamine oxidase inhibitor. Caution is also advised in regard to possible interaction with other medications and concurrent use of other SSRIs or SNRIs. In women receiving tamoxifen, coadministration of paroxetine and fluoxetine, which are potent inhibitors of the enzyme cytochrome P2D6, may reduce the formation of the active metabolite of tamoxifen (endoxifen).[82] A subsequent review did not show increased risk of cancer recurrence with paroxetine,[83] but safer options for women receiving tamoxifen may include venlafaxine or citalopram or their derivatives. Canadian product monographs for antidepressants include a warning about their potential association with behavioural and emotional changes, including self-harm, which may occur in the first several weeks of use, although this side effect is uncommon.

### Gabapentinoids

Gabapentin, an antiepileptic drug, has been found in trials to improve bothersome VMS reducing hot flash frequency by 45% to 71% from baseline.[84,85] Adverse effects include dizziness, unsteadiness, and drowsiness, which tend to improve within 1 to 2 weeks. Gabapentin may be a good option for women with sleep disturbances from VMS, because drowsiness is a side effect. The suggested dosage for gabapentin, based on clinical trials, is 900 mg daily in 3 divided doses. In practice, some clinicians start gabapentin at 200−300 mg at night and increase the dosage in increments of 100 mg every 3−4 days, until a maximum of dosage of 900 mg nightly is reached. Another gabapentinoid, pregabalin, may be effective in relieving hot flashes, but it is less well studied and less commonly used for VMS.[86] Health Canada has advised of an increased risk of respiratory depression in patients who use gabapentin or pregabalin in combination with opioids.[87]

### Clonidine

Clonidine is a centrally active alpha-adrenergic agonist that has been shown to be modestly more effective than placebo, but less effective than SSRIs, SNRIs, and gabapentin, for the relief of VMS.[76,77] Clonidine may be administered orally at a dosage of 0.025 mg or 0.05 mg twice daily. Adverse effects include dizziness, dry mouth, and hypotension.

### Oxybutynin

Oxybutynin is an anticholinergic agent, typically used for urinary incontinence, that has also been shown to reduce VMS.[88] Significant reductions in VMS (efficacy estimate) were seen in a randomized controlled trial of extended-release oxybutynin 15 mg once daily in naturally postmenopausal women.[88] In another study (available only in abstract form), immediate-release oxybutynin at a dosage of 2.5 mg or 5 mg twice daily significantly reduced severe VMS in patients with breast cancer.[89] Adverse effects of oxybutynin include dry mouth, gastrointestinal upset, constipation, and blurred vision; there are also some therapeutic concerns about the drug's effects on cognition in older women.[90]

Suggested dosages of non-hormonal prescriptions are listed in Table 4.

**Table 4. Suggested dosages in non-hormonal prescription therapy regimens**

| Type | Starting dosages |
|---|---|
| SNRIs | |
| Venlafaxine | 37.5–75 mg oral daily |
| Desvenlafaxine | 100–150 mg oral daily |
| SSRIs | |
| Paroxetine | 10–20 mg oral daily |
| Citalopram | 10–20 mg oral daily |
| Escitalopram | 10–20 mg oral daily |
| Gabapentinoids | |
| Gabapentin | 900 mg oral daily in divided doses[a] |
| Pregabalin | 150–300 mg oral daily |
| Clonidine | 0.05 mg oral twice daily |
| Oxybutynin | |
| Oxybutynin Immediate-Release | 2.5 mg or 5 mg oral twice daily |
| Oxybutynin XL | 15 mg daily[b] |

[a] In clinical practice, gabapentin can also be prescribed as 300 mg oral at night and increased in increments of 100 mg up to a maximum dose of 900 mg oral nightly.

[b] Oxybutynin XL 15 mg day has also been studied in clinical trials; the 15 mg doses are no longer marketed in Canada, although the 5 and 10 mg doses are still available.

SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor.

## NON-PRESCRIPTION OPTIONS

Between 50% and 80% of women in North America use non-hormonal therapies for VMS.[91,92] Choosing among these methods can be challenging. Many women report they do not feel informed or have concerns about treatment options related to interactions, dosage, and use.[92]

### Lifestyle Changes and Complementary Therapy

Lifestyle modifications that have been used for alleviating VMS are summarized in Table 5. Cognitive behavioural therapy (CBT) has been shown in several studies as an effective strategy to manage VMS.[93–98] MENOS1 and MENOS2 are cognitive behaviour therapy protocols that may have a positive effect on VMS.[95,96] In a recent study, CBT-Meno was effective in reducing the combination of self-reported VMS symptoms, sleep, depressive symptoms, and sexual concerns.[94] Clinical hypnosis per the Elkins Protocol has shown positive effects on VMS.[99,100] However, behavioural modifications such as yoga, weight loss, and exercise, although they may provide other health benefits, cannot be recommended for the treatment of moderate to severe bothersome VMS because of lack of evidence for efficacy.

### SUMMARY STATEMENT 6

Natural health products (NHPs) and complementary therapies for VMS have proven popular in North America, although they do not meet the rigorous testing criteria required for pharmaceutical products by Health Canada or the US Food and Drug Administration. In Canada, NHPs refer to herbal remedies, vitamins and minerals, and homeopathic and Chinese medicines. NHPs are regulated under the Natural Health Products Regulations, which fall under the direction of the Natural and Non-prescription Health Products Directorate of Health Canada. Although NHPs fall under a special regulation category, there remain deficiencies in the regulation of their manufacturing, labelling, and indications for use.[101]

Several NHPs are promoted as helping with VMS, including phytoestrogens such as soy or red clover, black cohosh, evening primrose oil, and others (Table 6).[102] Although individual trials have suggested benefits from certain NHPs, systematic reviews of these products have not found any single NHP or combination of NHPs to have proven efficacy for moderate to severe hot flashes.[103–105] A recent meta-analysis showed that supplements containing S-equol (isoflavandiol estrogen) may reduce VMS; however, further studies are needed.[106] Data on NHPs are often fraught with limitations. These limitations include small sample size, lack of a placebo or control group, short study duration, and mild patient symptoms. At this time, there is insufficient evidence to support the effectiveness of any one of these therapies for the management of menopausal symptoms. Patients should be advised of possible side effects from NHPs, which can be serious and/or unknown.

For cultural traditional therapies, women may wish to work with a cultural leader. Health care providers can discuss this option in partnership with women, in order to ensure cultural humility and cultural safety.

### SUMMARY STATEMENT 7 and RECOMMENDATION 9

Tables 5 and 6 provide a detailed list of lifestyle modifications and complementary therapies.

**Table 5. Lifestyle modifications**

| Method | Evidence | Recommendation |
|---|---|---|
| Cooling techniques[102] | Insufficient evidence supporting efficacy | Reasonable to recommend as low-risk option but uncertainty of utility |
| Avoiding triggers[125] | Insufficient evidence supporting efficacy | Reasonable to recommend as low-risk option but uncertainty of utility |
| Exercise[126] | Cochrane review concluded insufficient evidence supporting efficacy | Not currently recommended for VMS; however, provides other health benefits |
| Yoga[127,128] | Current available data does not support reduction in VMS with yoga | Not currently recommended for VMS; however, provides other health benefits |
| Weight loss[129,130] | May be efficacious in relief of VMS | Weight loss may be associated with a decrease in or elimination of VMS |
| Cognitive behavioural therapy[93,94,95,96,a] | Demonstrates efficacy in relief of VMS | CBT can be useful in the impact of VMS but not the frequency |
| Mindfulness-based stress reduction[131] | Likely to be efficacious in reducing VMS | May be efficacious in relief of VMS |
| Paced respiration[132] | Paced breathing has been shown to be no better than usual breathing for VMS | Not currently recommended for management of VMS; however, provides other health benefits |
| Relaxation[133] | Unlikely to be efficacious in reducing VMS | Not currently recommended for management of VMS; however, provides other health benefits |
| Clinical hypnosis[99,100] | Demonstrates efficacy in relief of VMS | There may be a positive impact |
| Acupuncture[134] | Unlikely to be efficacious in reducing VMS | Insufficient evidence |

[a] The focus of CBT treatment includes beliefs about control/coping with VMS, beliefs about VMS in a social context, group and self-help behaviour therapy/beliefs and ideas, and virtual telephone guided self-help/beliefs/ideas and treatment goals.[97,98]

CBT: cognitive behavioural therapy; VMS: vasomotor symptoms.

## Nutrition

A healthy diet during menopause can reduce the risk of future chronic conditions, promote weight management, and improve energy levels. The 2019 update to Canada's Food Guide shifted away from sex- and age-specific serving recommendations and instead focuses on a balanced diet.[107] For women aged 51–70 years, a healthy diet should include complex carbohydrates, protein, and healthy fats, as well as dietary fibre and calcium.[108,109]

Cross-sectional and clinical trial studies have shown an increased risk of cardiovascular disease and other chronic conditions from eating a pro-inflammatory diet (i.e., a diet high in saturated fat and simple carbohydrates).[110–113] Diets high in protein, fibre, and unsaturated fats are recommended to prevent chronic disease.[114–116] Furthermore, Health Canada recommends limiting daily intake of sodium to 1300 mg.[113,117] Women should supplement their diet with vitamin D and calcium to protect bone mineral density and prevent fractures.[118,119] The 2016 Canadian Consensus on Female Nutrition recommends a daily intake of 1200 mg of calcium and 800 IU of vitamin D, achieved through diet and/or supplements.[109] Loss of lean muscle mass accelerates after menopause and protein requirements increase; adequate protein, together with an active lifestyle, is recommended to avoid sarcopenia.[109]

Increasing fruits and vegetables and decreasing fat intake is associated with less later-life decline in cognitive and physical functioning, including mental well-being.[120–122] As energy requirements decline with age, reducing caloric intake and avoiding simple sugars is recommended, especially if weight maintenance is a goal.[109,123] Weight-loss diets should be undertaken with care and combined with an active lifestyle. Finally, research has shown that "mindless eating" and an irregular diet contribute to excess consumption.[111] Women should be encouraged to eat a variety of healthy foods throughout the day.[107] Outside of Canada, some recommendations, including the Brazilian Food Guide, encourage taking pleasure in food preparation and sharing mealtimes.[124] As mid-life frequently brings changes to family mealtime dynamics, these observations are particularly pertinent to women in menopause.

### SUMMARY STATEMENT 8

**Table 6. Natural Health Products**

| Therapy | Mechanism of action | Efficacy evidence | Recommendation |
|---|---|---|---|
| Soy[105,135] | • Phytoestrogens containing isoflavones<br>• Isoflavones bind to estrogen receptor with both agonist and antagonistic properties.<br>• Phytoestrogens bind to both ER-alpha and ER-beta (preferentially to ER-beta).<br>• Binding affinity of phytoestrogens is 100−1000 times less than estradiol.<br>• Isoflavones contain genestein, diadzein, glycitein, biochanin A, and formonoanetin. Genestein and daidzein are found in high amounts in soybeans and soy products.<br>• S-equol is metabolized from daidzein by intestinal bacteria. | • There have been extensive studies and several systematic reviews/meta-analyses, with mixed results.<br>• Supplements containing higher proportions of genistein may reduce frequency compared with placebo.<br>• Higher amounts of equol may have benefits. Recent meta-analysis showed significant benefit of S-equol in reducing VMS frequency. | • Soy isoflavonoids: no conclusive evidence that they are more effective than placebo in reducing the frequency or severity of VMS<br>• S-equol may be beneficial for VMS.<br>• Further investigation of genistein required. |
| Fermented soybean extract (Femarelle)[136] | Isolate of soybeans | One controlled trial showed reduced VMS versus control group. | Standard dose may be effective for relief of VMS. |
| Red clover (*Trifolium pretense*)[137,138] | Phytoestrogen containing high amounts of isoflavones, particularly genistein and daidzein | No evidence of any effect on VMS frequency or severity. | Insufficient efficacy data to recommend |
| Flaxseed (*Linum usitatissimum*)[139] | Phytoestrogen with a rich source of lignans | Systematic review of available studies reported no benefit for VMS over placebo. | Insufficient efficacy data to recommend |
| Black cohosh (*Actaea racemose*)[140] | Mechanism unclear — most recently thought to have activity similar to selective ER modulators / modulation of serotonergic pathways as well as antioxidant or anti-inflammatory effects | • Cochrane review showed no difference versus placebo in frequency of VMS.<br>• Safety data: inconclusive | Insufficient efficacy data to recommend |
| Wild yam (*Diosecorea villosa*)[104] | Contains diosgenin, a precursor to progesterone in vitro (but not in vivo) | Limited | Insufficient efficacy data to recommend |
| Crinum (*Crinum species*)[141] | Unknown | Unknown | Insufficient efficacy data to recommend |
| Dong quai root (*Angelica sinensis*)[104,142] | Unknown, once reported to be estrogenic; however, this is not clear | One RCT did not show a difference in VMS | • Insufficient safety and efficacy data to recommend<br>• Safety concerns: cancer risk, interaction with anticoagulants |
| Evening primrose oil (*Oenothera biennis*)[104,143] | Contains linolenic acid and gamma-linolenic acid | Single placebo-controlled trial: proved ineffective for VMS | Insufficient efficacy data to recommend |
| Ginseng[144,145] | Root with varieties found in China, Americas, Korea | Studies showed no benefit on VMS | Insufficient efficacy data to recommend |
| Pollen extract[146,147] | Flower pollen extract | One small study showed positive effect on VMS, limited evidence | Insufficient efficacy data to recommend |
| Hops (*Humulus lupulus*)[148,149] | A plant that makes a flavonoid postulated to have estrogenic activity | Limited evidence | Insufficient efficacy data to recommend |
| Maca (*Lepidium meyemmii*)[150] | Unknown, postulated to modulate sex steroid receptor | Limited evidence | Insufficient efficacy data to recommend |

ER: estrogen receptor; RCT = randomized controlled trial; VMS: vasomotor symptoms.

## CONCLUSION

Vasomotor symptoms can significantly affect a woman's quality of life. New understanding of VMS pathophysiology is paving the way for exciting developments in therapeutic approaches for VMS. Menopausal hormone therapy is the recommended therapy for the management of VMS in postmenopausal women without contraindications. Options for perimenopause include MHT, combined hormonal contraceptives, or estrogen in combination with LNG-IUS. Women who enter menopause early should consider using MHT until the average age of menopause. Non-hormonal prescription medications can be considered in women who are unable or do not desire to use MHT. Lifestyle measures such as cognitive behavioural therapy may also help manage VMS. Several new MHT products are now available on the Canadian market, widening the treatment armamentarium for menopause management. The needs of each individual woman, as well as their own personal risks and benefits, should be considered when deciding among the treatment options for managing menopausal symptoms.

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## APPENDIX A

**Table A1. Key to Grading of Recommendations, Assessment, Development and Evaluation Quality of Evidence**

| Grade | Definition |
|---|---|
| Strength of recommendation | |
| Strong | High level of confidence that the desirable effects outweigh the undesirable effects (strong recommendation for) or the undesirable effects outweigh the desirable effects (strong recommendation against) |
| Conditional [a] | Desirable effects probably outweigh the undesirable effects (weak recommendation for) or the undesirable effects probably outweigh the desirable effects (weak recommendation against) |
| Quality of evidence | |
| High | High level of confidence that the true effect lies close to that of the estimate of the effect |
| Moderate | Moderate confidence in the effect estimate:<br>The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different |
| Low | Limited confidence in the effect estimate:<br>The true effect may be substantially different from the estimate of the effect |
| Very low | Very little confidence in the effect estimate:<br>The true effect is likely to be substantially different from the estimate of effect |

[a] Do not interpret conditional recommendations to mean weak evidence or uncertainty of the recommendation.

Adapted from GRADE Handbook (2013), Table 5.1.

**Table A2. Implications of Strong and Conditional recommendations, by guideline user**

| Perspective | Strong Recommendation<br>• "We recommend that. . ."<br>• "We recommend to not. . ." | Conditional (Weak) Recommendation<br>• "We suggest. . ."<br>• "We suggest to not. . ." |
|---|---|---|
| Authors | The net desirable effects of a course of action outweigh the effects of the alternative course of action. | It is less clear whether the net desirable consequences of a strategy outweigh the alternative strategy. |
| Patients | Most individuals in the situation would want the recommended course of action, while only a small proportion would not. | The majority of individuals in the situation would want the suggested course of action, but many would not. |
| Clinicians | Most individuals should receive the course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. | Recognize that patient choices will vary by individual and that clinicians must help patients arrive at a care decision consistent with the patient's values and preferences. |
| Policymakers | The recommendation can be adapted as policy in most settings. | The recommendation can serve as a starting point for debate with the involvement of many stakeholders. |

Adapted from GRADE Handbook (2013), Table 6.1.