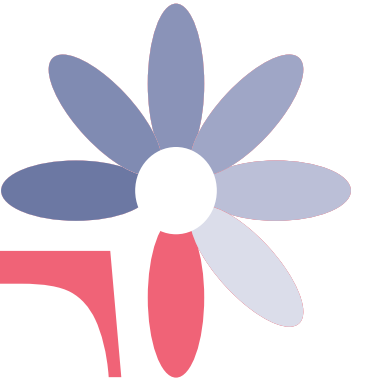
CANADIAN MENOPAUSE SOCIETY
SOCIÉTÉ CANADIENNE DE MÉNOPAUSE



POCKET GUIDE MENOPAUSE MANAGEMENT

A practical tool for healthcare professionals

2nd Edition 2023

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INTRODUCTION

The menopausal transition can be a time of significant disruption and stress for women. Symptoms associated with menopause may have a major effect on a woman's quality of life. Providing safe and effective management of these symptoms, and mitigating potential health risks in the postmenopausal years, are critical roles for health care providers.

In this pocket guide we summarize the recommendations made in the guidelines for management published by five professional associations: the Canadian Menopause Society/ Society of Obstetricians and Gynaecologists of Canada (CMS/ SOGC 2021), the International Menopause Society (IMS 2016), the North American Menopause Society (NAMS 2022), and the Endocrine Society (ES 2015).

- The publication of the report on the combined estrogen-progestin arm of the Women's Health Initiative (WHI) in 2002 led to great uncertainty about the management of menopausal women. The report caused a media firestorm because it concluded that use of conjugated estrogens and medroxyprogesterone acetate in postmenopausal women was associated with increased risks of breast cancer, coronary heart disease, and stroke. Use of menopausal hormone therapy (MHT) in postmenopausal women was largely abandoned in the years that followed.

- Reanalysis of the results of this study, and subsequent

publication of the results of the WHI estrogen-only study, suggested that the initial negative response to the WHI findings was excessive. It is critical to note that the WHI hormone therapy studies were not designed to assess the risks of MHT in symptomatic women. Instead, they were designed to find out whether the benefits of MHT seen in observational studies of younger menopausal women (chiefly cardiac benefits) applied to older women as well. As it turned out, they did not.

- In general, MHT in postmenopausal women should only be initiated in women < 60 years of age or < 10 years past menopause. The NAMS statement notes that women who initiate MHT aged older than 60 years or more than 10 or 20 years from menopause onset are at higher absolute risks of CHD, VTE, and stroke than women initiating MHT in early menopause.

Indications for menopausal hormone therapy

- All four guidelines advise that MHT (estrogen plus progestogen in women with a uterus, estrogen alone in women without a uterus) is the most effective treatment for bothersome vasomotor symptoms, with or without additional climacteric symptoms, in menopausal women.

INTRODUCTION (CONT.)

- NAMS also notes that MHT is approved by the United States FDA for four indications: bothersome VMS; prevention of bone loss; hypoestrogenism caused by hypogonadism, castration, or premature ovarian insufficiency; and genitourinary symptoms.

Choice of treatment

- The guidelines agree that MHT must be individualized and tailored according to each woman's symptoms, her need for disease prevention, her personal and family history, the results of relevant investigations, and her own preferences and expectations. The choice of treatment should be reassessed periodically.

Dosing

- The guidelines acknowledge that in choosing a dose for MHT, the "appropriate" dose is one which minimizes risk while still providing benefit. For older women, lower doses reduce cardiovascular risk.

- For women at higher risk of venous thromboembolism or CV disease, a transdermal form of estrogen at the lowest effective dose is recommended.

- In women with a uterus, the proliferative effects of systemic estrogen on the endometrium must be countered by an appropriate dose of progestogen (or a SERM,

INTRODUCTION (CONT.)

in the case of the TSEC).

Duration of treatment

- The guidelines agree that the duration of MHT for women should be individualized, because long-term follow-up data regarding use of MHT and risk are complicated. This individualization should take into account the level of symptom control and effect on quality of life, and a woman's individual risk of cancer, CVD, and venous thromboembolism.

- Each guideline recommended that the decision to continue MHT be revisited at least annually. There appear to be no reasons to place mandatory limitations on the duration of MHT.

- Longer duration courses of estrogen-alone therapy (ET) may be more appropriate because of the more favourable risk profile.

- The guidelines also universally recommended that women who undergo early menopause (before age 45) be advised to use MHT, at least until the average age of menopause. This is because of proven health benefits for menopause symptoms, prevention of bone loss, cognition and mood issues, and (in observational studies) heart disease.

IMPACT OF MENOPAUSE

Vasomotor symptoms (VMS)

- Vasomotor symptoms (hot flashes and night sweats) are a common reason for women to seek medical attention. 60-80% of women will experience VMS during the menopausal transition. Although the exact physiology of VMS is not well understood, they are thought to represent altered thermoregulatory functioning, possibly due to alterations in reproductive hormones. Hypothalamic activity of KNDy neurotransmitters, and especially neurokinin B appears to be involved. Antagonists to the neurokinin B receptor show promise as hormone-free suppressors of VMS.

- VMS are associated with physiologic circulatory changes, with initial vasodilatation followed by vasoconstriction.

- Although 50% of women experience VMS for 7 years or less, 15% may experience VMS for 15 years or longer.

- VMS are associated with diminished sleep quality, irritability, difficulty concentrating, and reduced quality of life, as well as poorer health status. Women with VMS have less favourable markers of CV health than those without VMS, and may have an increased risk of developing coronary heart disease.

IMPACT OF MENOPAUSE (CONT.)

- Menopausal hormone therapy (systemic estrogen alone in women without a uterus, or systemic estrogen with appropriate endometrial protection in women with a uterus or tibolone) is the current standard therapy for reduction of VMS. Use of a progestogen alone may be effective in treating VMS, but the safety of long term use has not been established. For those with contraindications to MHT or a desire to avoid it, SSRI/SNRIs, gabapentinoids, clonidine or oxybutynin may reduce VMS in some women.

- When MHT is discontinued, vasomotor symptoms return in approximately 50% of women, irrespective of years since menopause or duration of MHT use. There is no consensus about whether stopping MHT "cold turkey" or tapering is preferable.

Mood and Cognition

- Depressive symptoms increase during the menopause transition (as opposed to older age and younger age groups), as does the risk for clinical depression.

- There appears to be an increased risk of depression after hysterectomy (with or without bilateral oophorectomy) and in women with POI.

- The following may influence or mediate the risk for depression during the transitional years: the presence

IMPACT OF MENOPAUSE (CONT.)

and severity of VMS, the occurrence of stressful life events, sleep problems, a history of depression, and most importantly, a history of reproductive-related mood sensitivity (premenstrual dysphoric disorder, postpartum depression, or mood alterations during pregnancy). There is currently insufficient evidence to support the use of MHT as an adjunct in the treatment of depression in postmenopausal women, but transdermal estradiol has shown antidepressant effects in perimenopausal women with a major depressive disorder.

- Forgetfulness, trouble concentrating, and other mild cognitive symptoms are common during midlife. Three large RCTs showed neutral effects of MHT on cognitive function when initiated early in the postmenopausal period.

- Observational studies have found associations between early initiation of MHT and a reduced risk of developing Alzheimer's disease. Studies involving women experiencing early surgical menopause suggest that estrogen therapy improves cognitive function.

- Women who initiated MHT after the age of 65 showed impairment in memory and increased risk of dementia. Women in the pre-clinical stages of dementia may be the most vulnerable cognitively to an adverse effect of MHT.

IMPACT OF MENOPAUSE (CONT.)

Osteoporosis and Somatic Symptoms

- Postmenopausal osteoporosis results from a failure to attain peak bone density, accelerated bone loss after menopause, age-related bone loss, or a combination of factors.

- Accelerated postmenopausal bone loss is induced by estrogen deprivation. The 10-year probability of a fracture in an individual can be estimated using a model such as FRAX or CAROC, which integrates various risk factors. Intervention thresholds for therapy can be based on 10-year fracture probability. Lifestyle changes should be part of treatment strategy. The choice of pharmacologic therapy should be based on a balance of effectiveness, risk and cost.

- Therapeutic options include MHT (in appropriately selected patients), bisphosphonates, SERMs (raloxifene), RANK-ligand inhibitors (denosumab), parathyroid hormone (teriparatide), or romosozumab.

- Standard dose MHT (ET or EPT) and tibolone prevent bone loss in most healthy postmenopausal women through inhibition of bone resorption and a reduced rate of bone remodelling mediated through the RANK/RANK-ligand interaction.

IMPACT OF MENOPAUSE (CONT.)

- RCTs and observational studies show that standard dose ET and EPT reduce the incidence of osteoporotic fractures, including spine, hip and all non-spine fractures, in postmenopausal women, even those without osteoporosis. MHT is the most appropriate therapy for fracture prevention in the early menopause.

- Unless there is a contraindication, administration of MHT, or combined hormonal contraceptives is optimal for reducing the risk of osteoporosis in women with premature or early menopause, rather than other bone-specific agents.

- Osteoarthritis increases in prevalence after menopause. There is evidence for a beneficial effect of endogenous and exogenous estrogens on joint health. Women in the CE-alone arm of the WHI had significantly fewer hip and knee joint replacements than those in the placebo arm.

Cardiovascular Disease

- Cardiovascular disease is the leading cause of morbidity and mortality in postmenopausal women.

- Primary prevention strategies include smoking cessation, weight loss, blood pressure control, regular aerobic exer-

IMPACT OF MENOPAUSE (CONT.)

cise, and diabetes and lipid control. Use of low-dose ASA and/or statins does not reduce the risk of coronary heart disease, cardiovascular mortality, or all-cause mortality in women.

- Estrogen therapy initiated at the time of menopause is likely cardioprotective. In the WHI, the hazard ratio for coronary heart disease in women who initiated MHT ≤10 years after menopause was 0.50.

- Initiation of MHT > 10 years after menopause or after age 60 is associated with increased risk.

- Use of MHT for primary prevention of cardiovascular disease is not supported in any guideline. Women at high risk of cardiovascular events should be offered non-hormonal management of menopausal symptoms. Women at moderate risk of cardiovascular events, if offered MHT, should preferentially use transdermal estrogen rather than oral. Use of micronized progesterone is preferable in higher risk women who require endometrial protection.

- In a Cochrane review, women who initiated oral MHT at < 60 years of age or within 10 years of menopause did not have an increased risk of stroke but women who initiated MHT at ≥ 60 years of age or ≥ 10 years after menopause did have an increased risk.

IMPACT OF MENOPAUSE (CONT.)

Genitourinary Syndrome of Menopause

- Genitourinary syndrome of menopause (GSM) encompasses the genital and lower urinary tract symptoms associated with postmenopausal estrogen deficiency. Symptoms may include genital dryness, burning and irritation; sexual symptoms of diminished lubrication and pain during sexual activity; and urinary symptoms of urgency, dysuria, and recurrent urinary tract infections.

- First-line management options for GSM include vaginal lubricants and/or vaginal moisturizers.

- Second-line therapies include vaginal estrogen preparations, oral SERM ospemifene, and intravaginal DHEA ovules (prasterone).

- Low-dose vaginal estrogen preparations are safe and effective treatments for vulvovaginal symptoms due to estrogen deficiency.

- Because GSM symptoms often worsen with age and time since menopause, long-term low-dose vaginal estrogen therapy may be necessary. Concomitant use of an endometrial protective agent with low-dose vaginal estrogen therapy is not required, but any woman who has vaginal bleeding should be thoroughly investigated. Specific

IMPACT OF MENOPAUSE (CONT.)

endometrial safety data with use of vaginal estrogens beyond one year are not available, although observational studies suggest no long-term risk.

- Women in whom vaginal estrogens are contraindicated, or who do not wish to use vaginal estrogen, may have relief of pain during intercourse with the use of vaginal lubricants prior to intercourse. Vaginal moisturizers or vaginal hyaluronic acid therapies may help with vaginal dryness and pain with intercourse, but do not restore normal anatomy and function.

- Low- dose vaginal estrogen therapy may provide benefit for urinary symptoms, including over-active bladder and urge incontinence, and may aid in prevention of recurrent urinary tract infections.

- Symptoms of GSM are strongly associated with sexual dysfunction in postmenopausal women. Low-dose vaginal estrogen therapy improves sexual function in these women.

- As there is minimal systemic absorption, the standard contraindications for systemic MHT do not apply to vaginal estrogen therapy.

- Use of vaginal estrogen therapy is not contraindicated in women with a past history of breast cancer, but consultation with their oncologist is recommended. In women with current breast cancer who are being treated with an aromatase inhibitor, the decision to use low-dose vaginal estrogen therapy should be made, in consultation with their oncologist, only after non-hormonal methods have been unsuccessful in relieving symptoms.

ESSENTIALS OF MANAGEMENT

Vasomotor symptoms

Mild hot flashes: lifestyle strategies only

- keeping core body temperature cool: (light clothes, air conditioning, ventilation)
- participating in regular exercise
- avoiding alcohol intake and cigarette smoking
- following a healthy diet
- behavioural modification (avoid stressful situations)

Moderate to severe hot flashes: MHT is the gold standard and best therapy for reduction of VMS (Tables 1-6), followed by non-hormonal prescription medications (Table 7) as a second choice. Cognitive behavioural therapy may be helpful. If these strategies are ineffective or unacceptable, complementary and alternative medicine may be used, although efficacy for natural health products are unproven.

ESSENTIALS OF MANAGEMENT (CONT.)

Menopausal hormone therapy

- Women without a uterus can use systemic estrogen-alone therapy (ET).

- Women with a uterus can use systemic estrogen combined with a progestogen (EPT), the tissue-selective estrogen complex (conjugated estrogens and bazedoxifene), or tibolone.

- Combined low-dose hormonal contraceptives can be used in perimenopausal women.

- Progestogens alone may be used in women with contraindications to estrogen therapy.

Contraindications to MHT

Estrogens

- undiagnosed abnormal vaginal bleeding
- known, suspected, or history of breast cancer
- known or suspected estrogen-dependent cancers (i.e. endometrial, ovarian)
- coronary heart disease
- active or history of venous thromboembolism
- active or history of stroke
- known thrombophilia
- active liver disease

ESSENTIALS OF MANAGEMENT (CONT.)

- known or suspected pregnancy

Progestogens

- undiagnosed abnormal vaginal bleeding
- current or history of breast cancer

Complementary and alternative medicine options

- Natural health products
  - phytoestrogens: soy foods, red clover, isoflavone supplements, flaxseed
  - black cohosh
  - dong quai
  - evening primrose oil
  - ginseng
  - ginko
- Cognitive Behavioral Therapy
- Mindfulness stress reduction
- Acupuncture

Urogenital Health

- Systemic MHT for treatment of VMS may be sufficient to relieve symptoms; other options can be added to systemic MHT or used alone
  - Maintain sexual activity
  - Lubricants
    - water-based - silicone-based - oil-based

ESSENTIALS OF MANAGEMENT (CONT.)

- Moisturizers
  - hyaluronic acid
  - adhesive polycarbophil polymer
- Low-dose vaginal estrogen therapy (no additional progestogen required)
  - tablets
  - creams
  - ring
- Intravaginal DHEA (prasterone) - vaginal ovule
- Ospemifene - oral tablet

Osteoporosis

- Weight-bearing and high impact exercise (brisk walking, climbing stairs, dancing, etc)
- Nutrition and supplements
  - calcium: 1200 mg of daily intake combination of diet and supplements, preferably mostly from diet (i.e., 3 servings of milk/dairy)
  - vitamin D: over 50 years of age: 800-2000 IU daily
- Menopausal hormone therapy (ET or EPT)
- Bisphosphonates
  - alendronate (oral, weekly), risedronate (oral, weekly, monthly)
  - zoledronic acid (intravenous, yearly)
- RANKL inhibitor
  - denosumab (subcutaneous injection, every 6 months)

ESSENTIALS OF MANAGEMENT (CONT.)

- Parathyroid hormone (PTH)
  - teriparatide (subcutaneous injection, daily)
- Sclerostin inhibitor
  - romosozumab (subcutaneous injection, monthly)
- Selective estrogen receptor modulator (SERM)
  - raloxifene (oral, daily)

CHOOSING THERAPY

Clinical indications for initiation of systemic MHT

- Vasomotor symptoms (i.e. hot flashes/night sweats)
- Prevention of bone loss
- Reduction in fracture risk in women at increased risk of osteoporosis or fracture
- Early menopause (< age 45) or premature ovarian insufficiency
- Sleep disturbance
- Mood change: MHT often used in conjunction with an SSRI/SNRI

CHOOSING THERAPY (CONT.)

Therapeutic goal: in each woman, to choose the optimal therapy that will alleviate symptoms with minimal side effects

- The appropriate initial choice of therapy is the first step in preventing problems.

- Choice of therapy will depend on any contraindications, the woman's symptoms, age, time since menopause, medical risks, family history, personal preferences, and insurance coverage for medications.

Therapeutic options for systemic MHT (Tables 1-6)

- In women with a uterus:
  - Estrogen and progestogen (EPT);
  - TSEC (tissue selective estrogen complex) containing conjugated estrogen and bazedoxifene (a selective estrogen receptor modulator);
  - Tibolone

- In women without a uterus: estrogen alone

- Systemic estrogen options: oral tablets, transdermal patches and transdermal gels

- Progestogen options: oral tablets, transdermal patch (combined with estrogen) or intrauterine system

CHOOSING THERAPY (CONT.)

- Schedules:
  - EPT:
    - Continuous EPT regimen: continuous estrogen and continuous progestogen
    - Cyclic EPT regimen: continuous estrogen and cyclic progestogen taken 12 - 14 days every month
  - ET: continuous estrogen
  - TSEC: single daily dose
  - Tibolone: single daily dose

General principles

- Higher doses of estrogen require higher doses of progestogens for endometrial protection, and higher doses result in more side effects.
- Younger women (premature ovarian insufficiency) require higher estrogen doses for bone protection and to help with symptoms.
- Lower doses of estrogen and progestogen reduce breast discomfort and vaginal bleeding.

Regimen Decisions

- Continuous EPT regimens in postmenopausal women usually results in amenorrhea in 3 - 6 months.
- Cyclic EPT regimens in postmenopausal women usually produces regular withdrawal bleeding at the end of the progestogen cycle.

CHOOSING THERAPY (CONT.)

- Symptomatic perimenopausal women (with continuing menstrual cycles) will have less unscheduled bleeding with use of combined oral contraceptives, estrogen with a progestin-releasing IUS or estrogen with a cyclic progestogen.

Route of Administration

- Transdermal estrogen therapy may be preferable in women who are smokers or shift workers or who have high triglycerides, hypertension, migraines, malabsorption syndromes, metabolic syndrome, diabetes mellitus, gall bladder disease or are at elevated risk for venous thromboembolism or CVD.

MENOPAUSAL HORMONE THERAPY AND CANCER

MHT and Breast Cancer

In women, mortality from breast cancer is far less than from cardiovascular disease.

- ET (for women without a uterus) has minimal effect on the risk of breast cancer. Observational studies suggest a small increase in risk on long term ET. In the WHI, CE-only therapy resulted in a significantly reduced risk of breast cancer.

- EPT (CE+MPA) in both observational studies and the WHI resulted in a small increase in breast cancer risk after 5 years of use (the absolute risk is very small). Women using

EPT for the first time showed no increase in breast cancer incidence. In the WHI, EPT accounted for less than 1 additional breast cancer diagnosis per 1,000 women per year of use.

- Different progestogens may exert different effects on the breast, but there is no conclusive evidence to suggest a differential effect on breast cancer risk.

- The recently introduced TSEC combines conjugated estrogen with a SERM (bazedoxifene) that blocks any stimulatory effect on the breast. Longer term data on whether this will reduce or eliminate breast cancer risk are not yet available.

Family History of Breast Cancer

- There is a marginal increase in personal risk with a single relative who develops breast cancer after menopause.

- A woman with two first-degree relatives who develop breast cancer after age 50 or one first-degree relative who develops breast cancer before age 50 has approximately double the lifetime risk.

- Lifetime risk quadruples in women with two first-degree relatives affected before age 50 (these women should be assessed for genetic mutation).

MENOPAUSAL HORMONE THERAPY AND CANCER (CONT.)

- Observational studies have shown no further increase in risk with the use of MHT in women with a family history of breast cancer.

- BRCA mutation increases the risk of breast and ovarian cancer, and surgery to remove the tubes and ovaries is common in these women. Subsequently, MHT may be required to alleviate vasomotor symptoms; no increased risk of MHT has been identified in several observational studies.

MHT after Treatment of Breast Cancer

- Most observational studies found no increase in breast cancer recurrence with MHT use (possibly due to selection bias).

- Two RCTs came to opposite conclusions about the effect of systemic MHT after treatment of breast cancer. Both trials were terminated prematurely because of worrisome findings in one of them.

- Tibolone should not be used in women with a history of breast cancer because of increased recurrence rates in studies.

- If quality of life is significantly affected and the breast cancer has a favourable prognosis, women may elect to use

MHT after careful counselling about the uncertainty in the available data. For women with more advanced breast cancers, avoiding use of MHT is prudent.

- Observational data suggest that low-dose vaginal estrogen therapy has no effect on breast cancer recurrence.

- Women on aromatase inhibitors should use vaginal estrogen therapy with caution.

MHT and Endometrial Cancer

- ET in women with a uterus has a stimulatory effect in the endometrium and increases the risk of endometrial cancer. Addition of a progestogen (EPT) will counteract this effect.

- Treatment with the TSEC or tibolone does not increase the risk of endometrial cancer.

- Use of MHT in women after treatment of early stage endometrial cancers (grade 1 and 2 with negative estrogen and progesterone receptors) does not increase the risk of recurrence or mortality.

MHT and Ovarian Cancer

- The WHI showed no significant effect of MHT on the risk of ovarian cancer.

MENOPAUSAL HORMONE THERAPY AND CANCER (CONT.)

- A few observational studies suggest an increased risk of epithelial and endometrioid ovarian cancers with long term MHT; the absolute risk is rare (<1/1,000).

- MHT use after treatment of ovarian cancer has not been shown to affect rates of recurrence or survival.

MHT and Colorectal Cancer

- A protective effect of MHT has been shown on the incidence of colorectal cancer in some preclinical observation and observational studies; this was also observed in the WHI EPT arm.

- However, follow-up of the WHI found no evidence to support the use of MHT to reduce the risk of colorectal cancer.

MHT and Lung Cancer

- In non-smokers, MHT may reduce or have no effect on lung cancer risk.

- In the EPT arm of WHI, current and former smokers over age 60 were shown to have a small increase in the risk of death from non-small cell lung cancer (4/10,000 per year).

WHEN TO REFER

A number of symptomatic challenges may arise as women approach menopause. While many presentations are easily addressed by the primary care provider, there are times when a referral to a specialist is indicated:

Perimenopausal vaginal bleeding

Although common and expected, further assessment is required for:

- Prolonged heavy bleeding – initial investigations such as a CBC, vulvovaginal inspection, Pap smear, bimanual examination, pelvic/transvaginal ultrasound and endometrial biopsy should be done. If the history is suggestive, von Willebrand's disease should be ruled out.

Postmenopausal bleeding

- Bleeding more than one year after the final menstrual period requires investigation consisting of vulvovaginal inspection, Pap smear, bimanual examination, pelvic/transvaginal ultrasound, and endometrial biopsy if endometrial thickness > 4 mm.

- If there is no abnormality but bleeding recurs, refer for hysteroscopy. Unscheduled bleeding more than 6 months after initiating EPT should be investigated.

WHEN TO REFER (CONT.)

Concerns about MHT

- A referral may be helpful when there are concerns or uncertainty about comorbidities, risk factors due to personal or family history, or if the MHT regimens prescribed are poorly tolerated.

- A referral can also be useful if there is uncertainty about prolonged MHT, use of MHT at advanced age, or difficulty having patients discontinue MHT.

Premenstrual syndrome/Premenstrual dysphoric disorder

- When lifestyle recommendations for PMS/PMDD (regarding diet, exercise, use of caffeine or alcohol, and sleep) fail and/or herbal or pharmaceutical treatments are ineffective, careful evaluation of the cyclic nature of these complaints should be documented and referral initiated.

Breast changes

- Complaints of breasts becoming fibrous and/or having recurrent cystic changes can be further evaluated by mammography ± ultrasound.

- Unexplained breast pain, a rash, or a persistent palpable lump should be referred for evaluation because mammography may (rarely) not detect a malignancy.

WHEN TO REFER (CONT.)

Dyspareunia

- GSM that results in dyspareunia can be diagnosed during careful vulvovaginal inspection. It may be treated with lubricants/moisturizers, vaginal estrogen, ospemifene and intravaginal DHEA.

- Pain that is unresponsive to this treatment requires further evaluation to rule out vaginismus, deep pain related to pelvic pathology or past surgical treatment, infections, and skin conditions such as lichen sclerosus, eczema, and Behcet's disease. Referral for evaluation of skin lesions is appropriate. Referral to a pelvic floor physiotherapist can be helpful for myofascial pain and incontinence.

Insomnia

- Sleep disturbance is common in perimenopausal and postmenopausal women. Sleep patterns often improve with treatment of vasomotor symptoms and micronized progesterone improves the efficiency of sleep.

- If persistent, disorders such as obstructive sleep apnea, fibromyalgia and restless legs syndrome need to be excluded or managed by means of a sleep study and/or specialist referral.

WHEN TO REFER (CONT.)

Relevant family history

- Referral may be appropriate for women with a family history of breast cancer, or of thrombophilias such as Protein C and Protein S deficiency or Factor V Leiden mutation.

Osteoporosis

- Fracture risk assessment is critical in postmenopausal women. Referral to an osteoporosis clinic for women with increased risk is often helpful.

TROUBLESHOOTING

Vaginal bleeding

- Unscheduled bleeding is the most common problem for women on MHT. Some bleeding for up to 6 months after beginning MHT is acceptable. If bleeding is heavy or frequent, investigations should be carried out sooner.

- The incidence of endometrial cancer in women on EPT using continuous progestogen is not increased above the incidence in the general population. Women on EPT with cyclical progestogen have a slight increase in endometrial cancer risk.

- Investigations should include history, physical examina-

tion, vulvar and vaginal inspection, Pap smear, directed cultures, and bimanual examination. Ensure that the bleeding is vaginal and not urethral or rectal.

- Pelvic/transvaginal ultrasound to check for endometrial thickness can be carried out before performing an endometrial biopsy. An endometrial thickness ≤ 4 mm is reassuring.

- If bleeding recurs, endometrial biopsy, diagnostic hysteroscopy, or sonohysterogram should be performed.

- Therapeutic options are to switch from continuous progestogen use to cyclical progestogen, to reduce the dose of estrogen or the route of administration, or to switch to use of a TSEC or tibolone.

Breast Pain

- Breast symptoms are least likely to occur with the lowest doses of MHT.

- Women who used a TSEC for 2 years had no increase in breast density or discomfort.

Mood Change

- Women who experience depression or irritability with use of progestogens may benefit from changing the

type of progestogen or the regimen used (cyclical or continuous).

- If this is unsuccessful, discontinuing use of the progestogen may be necessary. If continuing with unopposed ET, endometrial monitoring with ultrasound or biopsy is required.

- Use of a TSEC avoids use of a progestogen and any associated mood change.

Headaches

- Headache in women on MHT may be tension headache, migraine headache with or without aura, or cluster headache.

- Tension headache will frequently respond to lifestyle modifications, stress management, and use of non-narcotic analgesics.

- Migraine headache is usually managed with use of triptans, beta-blockers, anti-depressants or anticonvulsants. However, because the frequency and severity of migraine may be affected by fluctuations in hormone levels, MHT may be helpful. Migraine frequency may increase in the perimenopause and decrease after menopause.

TROUBLESHOOTING (CONT.)

- Menstrual migraine may improve with use of transdermal estradiol beginning in the week before menses and continuing to the end of menses.

- Women who have migraine headaches without aura may have improvement with MHT. Transdermal estradiol and micronized progesterone may be preferred because oral estrogen provides less stable serum estradiol levels and synthetic progestins may aggravate headache.

- Women who have migraine headaches with aura may be adversely affected by MHT. If auras worsen, MHT doses should be reduced and possibly discontinued.

- Migraine headache with aura is associated with double the risk of stroke.

- When in doubt, a headache expert should be consulted.

Progestogen Intolerance

- Some women may have specific intolerance to a progestogen, with symptoms including bloating, breast tenderness, and mood changes. Micronized progesterone can also cause excess drowsiness in some patients.

- These symptoms may improve with switching from cycli-

cal to continuous progestogen use, switching to another progestogen, administering micronized progesterone vaginally, insertion of a progestogen-releasing IUS, a reduction in the doses of both estrogen and progestogen, or switching to use of a TSEC.

- If these options are not effective and estrogen therapy is required, the effects of unopposed estrogen therapy on the endometrium must be monitored with transvaginal ultrasound and endometrial biopsy.

Vaginal Symptoms

- Systemic low-dose estrogen therapy may not relieve symptoms of vaginal mucosal atrophy alone and may additional require vaginal administration of estrogen (creams, tablets, or estradiol-releasing silastic ring), or intravaginal DHEA.

- If symptoms persist with vaginal therapy, consider applying vaginal cream to the introitus and non-hair bearing vulvar tissues.

- Attempting intercourse in the presence of mucosal atrophy may lead to secondary vaginismus.

- In women with persistent vulvovaginal burning and chronic itching, vulvar dermatoses including lichen

TROUBLESHOOTING (CONT.)

sclerosus, chronic dermatitis, psoriasis, and cancer must be ruled out.

- Women with persistent vulvar pain may have sexual dysfunction. Sexual counselling may be appropriate.

SPECIAL CONSIDERATIONS

Hypertension

- Hypertension is not a contraindication to use of MHT.

- Hypertension in menopausal women (including a history of pregnancy-induced hypertension) indicates an increase in the future risk of cardiovascular complications. The INTERHEART study found that women with hypertension had a 97% increase in risk of CV disease over normotensive women.

- Reversible risks for hypertension (obesity, poor dietary habits, high sodium intake, sedentary lifestyle, and high alcohol consumption) should be carefully assessed and reduced where possible during assessment of the newly menopausal woman.

- The WHI EPT arm found that oral CE, with or without added MPA, was associated with an increased risk of hypertension in older postmenopausal women, but a 2014 review found that oral MHT had a largely neutral effect

on blood pressure in normotensive women and a neutral effect in hypertensive women.

- Chronic (but not acute) administration of transdermal estradiol has been shown to reduce ambulatory blood pressure in normotensive postmenopausal women. Use of transdermal estradiol may therefore be preferable to oral estrogen in hypertensive postmenopausal women.

Endometriosis

- A history of endometriosis is not a contraindication to use of MHT in symptomatic menopausal women, but the lowest effective estrogen dose should be used.

- There is no convincing evidence that women with a history of endometriosis who have undergone hysterectomy should be routinely treated with EPT rather than estrogen alone.

- Similarly, in women who have undergone surgery for endometriosis, there is no evidence that subsequent progestogen-only therapy, or delaying use of estrogen for 6 months, reduces the risk of recurrence of endometriosis or the development of malignancy in residual or recurrent endometriotic deposits.

SPECIAL CONSIDERATIONS (CONT.)

- Use of progestogens in postmenopausal women without a uterus and with a history of endometriosis remains a matter for clinical judgement and informed choice.

Premature ovarian insufficiency

- Women without contraindications should receive MHT until the average age of menopause (51 years).

- Women with surgical POI have more severe symptoms.

- Typical daily doses for MHT in women with POI are 100 µg transdermal estradiol, 2 mg oral micronized estradiol, or 1.25 mg CE, with 10mg MPA or 300 mg progesterone for 12 days per month. Younger women need higher doses of hormones.

- Meta-analyses have shown that women with POI at age <40 and even <45 have a greater incidence of early death, cardiac disease, Parkinson's disease, lowered cognitive function, increased affective disorders, GSM and sexual dysfunction in the absence of MHT. Rates of osteoporosis may also be increased.

- Healthy ovaries should not be removed electively in women aged < 50 unless they are at high risk for ovarian cancer.

SPECIAL CONSIDERATIONS (CONT.)

Previous endometrial ablation

- There is no common recommendation for use of MHT in symptomatic postmenopausal women with a history of endometrial ablation.

- Because endometrial ablation procedures are unable to reliably remove all of the endometrium, EPT should be used in these women.

Thrombophilia

- The incidence of venous thromboembolism (deep vein thrombosis and pulmonary embolism) in women on MHT is generally estimated at 1-2 cases per 1000 woman-years. This incidence is significantly increased in women with thrombophilia.

- Women with high-risk thrombophilia (deficiency of anti-thrombin, Protein C, Protein S, Factor V Leiden mutation) should generally avoid use of MHT.

- The risk of VTE is increased with use of oral estrogen, but observational studies have not found any increased risk with use of transdermal estradiol.

- Observational studies have suggested that the risk of VTE is higher with use of synthetic progestins than with micronized progesterone.

SPECIAL CONSIDERATIONS (CONT.)

- Postmenopausal women with an increased risk of VTE who require MHT will have least risk with use of transdermal estradiol and micronized progesterone.

- Population screening for thrombophilia prior to MHT use is not justified.

Diabetes

- Diabetes is not a contraindication to use of MHT.

- RCTs and observational studies suggest MHT reduces the prevalence of diabetes by 14-19% while taking the medication.

- A few short-term RCTs have shown either no effect or improved control for women with diabetes on MHT.

- The approach to therapy therefore should be individualized - preferably transdermal estradiol with micronized progesterone should be used.

- If diabetes occurs with concurrent CV disease, non-hormonal therapies for menopausal symptoms are preferred.

SPECIAL CONSIDERATIONS (CONT.)

Uterine fibroids

- MHT is not contraindicated in women with fibroids.
- Fibroids may enlarge or remain stable on MHT.
- The location of fibroids (submucous, intramural, serosal) may affect the incidence of breakthrough bleeding on MHT.

Long-term MHT

- MHT should not usually be initiated more than 10 years after menopause or after 60 years of age as there are greater risks of coronary heart disease, VTE and stroke.
- Long-term use should be individualized for persistent vasomotor symptoms, prevention of bone loss or fracture, and quality of life.
- It is advisable for women to use the lowest dose possible to control symptoms as they age.
- It is not necessary to stop MHT at age 65.
- 50% of women will experience symptoms when they stop MHT. Of these, 50% will subsequently restart MHT. When stopping, there is no evidence to suggest greater success

SPECIAL CONSIDERATIONS (CONT.)

with sudden stoppage or tapering of therapy.

- Low-dose vaginal estrogen therapy can be used life-long.
- Bone loss and GSM will continue with aging.
- The incidence of breast cancer may increase with longer use of MHT, especially with continuous combined estrogen-progestogen.
- The incidence of DVT and PE increases with age.
- There is currently insufficient evidence on benefits and risks for long term users. One large Finnish database has found increased risk of CV mortality, coronary heart disease and stroke death in the year after discontinuation of MHT.

Professional associations currently recommend greater flexibility for longer MHT use if there are no contraindications and the balance of risk and benefit is evaluated annually.

COMPLEMENTARY AND ALTERNATIVE MEDICINE

- More than 50% of perimenopausal and postmenopausal women use some form of complementary and alternative medicine, including natural health products, dietary changes, massage, acupuncture, and stress therapies for management of midlife and menopausal symptoms.

- Natural health products are regulated by the Natural Health Products Directorate (NHPD), a division of the Health Products and Food Branch of Health Canada, and, following approval, are assigned an NPN number. Choosing products with an NPN number is therefore advisable.

- Of "natural" and "alternative" products, phytoestrogens (especially phytoestrogen supplements) have been the most extensively studied. Phytoestrogens comprise two major categories: (1) isoflavones (particularly genistein), which have shown benefit in treating mild vasomotor symptoms, and (2) flaxseed, which has not.

- Soy diets rich in isoflavones have been claimed to show some benefit in managing mild vasomotor symptoms and GSM, as well as providing bone and breast protection, but results are not definitive.

COMPLEMENTARY AND ALTERNATIVE MEDICINE (CONT.)

- St John's Wort has been shown to improve sleep and quality of life in menopausal women.

- Acupuncture and mind-body techniques (yoga, relaxation, tai chi, meditation) have not been shown to be effective in reducing vasomotor symptoms and other menopausal symptoms.

- Cognitive behavioural therapy and, to a lesser extent, mindfulness-based stress reduction and clinical hypnosis have been shown to be effective in reducing vasomotor symptoms.

RECENT THERAPEUTIC DEVELOPMENTS

Tibolone

- Tibolone (Tibella®), a 2.5 mg daily tablet, is approved for the treatment of vasomotor symptoms in postmenopausal women.

- Tibolone is a synthetic analogue of the progestin norethynodrel. Tibolone is converted to three active metabolites, two of which have estrogenic activity and the third a mix of progestogenic and androgenic effects.

- Additional progestogen therapy (for endometrial protection) is not required.

- Adverse effects include fatigue, breast tenderness, fluid retention, stomach upset/nausea, and increased appetite. Tibolone use is associated with more vaginal bleeding than placebo, but less than with use of estrogen-progestogen therapy.

- Tibolone carries the same black warning and contraindications in the product monograph because of its estrogen class effects.

RECENT THERAPEUTIC DEVELOPMENTS (CONT.)

Prasterone (intravaginal DHEA)

- Prasterone (Intrarosa®), a 6.5 mg vaginal ovule, is a sex steroid precursor that is converted in vaginal cells to estrogen and androgen.

- Prasterone's effectiveness in reducing moderate to severe dyspareunia and vaginal dryness has been shown in two 12-week controlled efficacy trials, and endometrial safety has been shown in a 52-week open label study.

- Prasterone is administered by inserting one ovule daily, preferably in the evening, into the vagina using either a finger or the provided reusable applicator.

- Concomitant progestogen therapy is not required.

- Prasterone therapy is well-tolerated overall; the most common adverse effect is vaginal discharge, likely attributable to the melting of the hard-fat excipient in the ovule.

RECENT THERAPEUTIC DEVELOPMENTS (CONT.)

Ospemifene

- Ospemifene (Osphena®), a 60 mg oral tablet, is a selective estrogen receptor modulator with specific estrogen receptor (ER) agonist activity in the vagina. It also has ER agonist activity in bone and partial ER agonist activity in the endometrium.

- Several randomised controlled trials have demonstrated significant reductions in vaginal dryness and dyspareunia. Safety trials of up to 52 weeks have shown no cases of endometrial cancer.

- It is taken as a once-daily tablet.

- Concomitant progestogen therapy is not required.

- Studies of women with breast cancer and treated with ospemifene are limited, and no conclusions can be drawn at present.

ABBREVIATIONS

ASA	acetylsalicylic acid
CE	conjugated estrogens
CHD	coronary heart disease
CV	cardiovascular
DHEA	dehydroepiandrosterone sulphate
DVT	deep vein thrombosis
ET	estrogen (alone) therapy
EPT	estrogen-progestogen therapy
FDA	Food and Drug Administration
GSM	genitourinary syndrome of menopause
IUS	intrauterine system
MHT	menopausal hormone therapy
MPA	medroxyprogesterone acetate
PE	pulmonary embolism
PMS	premenstrual syndrome
PMDD	premenstrual dysphoric disorder
POI	premature ovarian insufficiency
RCT	randomized controlled trial
SERM	selective estrogen receptor modulator
SNRI	selective norepinephrine reuptake inhibitor
SSRI	selective serotonin reuptake inhibitor
TSEC	tissue selective estrogen complex
VMS	vasomotor symptoms
VTE	venous thromboembolism
WHI	Women's Health Initiative

MHT PRODUCTS IN CANADA

Table 1: Systemic Estrogen Products in Canada

Type of Estrogen	Trade Names	Strengths Available	Comments
Oral estrogen			
conjugated estrogen (CE)	Premarin®	0.3, 0.625, 1.25 mg tablets	One tablet daily
17β estradiol	Estrace®	0.5, 1, 2 mg tablets	One tablet daily
Transdermal estrogen patches			
17β estradiol patch	Estradot®, generics	25, 37.5, 50, 75, 100 µg patches	Twice weekly application
	Sandoz Estradiol Derm® (generic)	50, 75, 100 µg patches	Twice weekly application
	Oesclim®	25, 50 µg patches	Twice weekly application
	Climara®	25, 50, 75 µg patches	Once weekly application
Transdermal estrogen gel			
17β estradiol gel	Estrogel®	0.75 mg estradiol per 1.25 g metered dose(=one actuation)	Daily application, use in same area (do not rotate sites)
	Divigel®	0.25, 0.5, 1 mg individual packets	Daily application

MHT PRODUCTS IN CANADA (CONT.)

Table 2: Progestogen Products in Canada

Type of Progestogen	Trade Names	Strengths Available	Comments
Oral progestogen			
progesterone, micronized	Prometrium®, generics	100 mg capsule	Take at bedtime because of sedating effect. Note: generics may contain peanut oil
medroxyprogesterone acetate	Provera®, generics	2.5, 5, 10 mg tablets	
norethindrone acetate	Norlutate®	5 mg tablets	
Levonorgestrel intrauterine system (IUS)			
levonorgestrel IUS	Mirena®*	52 mg/IUS, for 5 years	Off-label use

*Mirena is the only LNG-IUS marketed in Canada that has evidence for endometrial protection

MHT PRODUCTS IN CANADA (CONT.)

Table 3: Combination MHT Products in Canada

Type	Trade Names	Strengths Available	Comments
Oral combination estrogen and progestogen products			
17B estradiol/ norethindrone acetate	Activelle® Activelle® LD	1 mg estradiol/0.5 mg norethindrone tablet LD - 0.5 mg/0.1 mg tablet	One tablet daily
17B estradiol/ drospirenone	Angeliq®	1 mg estradiol/1 mg drospirenone tablet	One tablet daily
Transdermal combination estrogen and progestogen products			
17B estradiol/ norethindrone acetate	Estalis® patch 140/50	140/50 (50 µg estradiol/140 µg norethindrone) 250/50 (50 µg estradiol/250 µg norethindrone)	Twice weekly application

MHT PRODUCTS IN CANADA (CONT.)

Table 4: MHT Products Which Do Not Require Progestogen

Type	Trade Names	Strengths Available	Comments
Tissue Selective Estrogen Complex (TSEC) – Estrogen and selective estrogen receptor modulator (SERM)			
conjugated estrogen (CE)/ bazedoxifene	Duavive®	0.45 mg CE/20 mg bazedoxifene tablet	One tablet daily
Selective Tissue Estrogenic Activity Regulator (STEAR)			
tibolone	Tibella®	2.5 mg tablet	One tablet daily

MHT PRODUCTS IN CANADA (CONT.)

Table 5: Pharmacologic Options for GSM

Type	Trade Names	Strengths Available	Comments
Vaginal hormone therapy			
conjugated estrogen (CE)	Premarin® Vaginal Cream	0.625 mg/gram vaginal cream Refillable applicator	0.5 gm (0.3 mg) vaginally daily for 14 days, then 0.5 gm (0.3 mg) 2 – 3 times weekly
17β estradiol	Vagifem® vaginal inserts	10 µg vaginal tablet with applicator	one tablet vaginally daily for 14 days, then one tablet twice weekly
17β estradiol	Estring® vaginal ring	2 mg/vaginal ring	Inserted every 3 months
estrone	Estragyn® 0.1% vaginal cream	1 mg/gm vaginal cream Refillable applicator	0.5 – 4 gm (0.5 – 4 mg) daily cyclic (3 weeks on, one week off) or 2 – 3 times weekly*
Dehydroepindrosterone (DHEA), prasterone	Intrarosa® vaginal ovules	6.5 mg ovule	One ovule inserted vaginally daily
Oral selective estrogen receptor modulator (SERM)			
ospemifene	Osphena® oral tablets	60 mg tablet	One tablet daily by mouth

*note: the product monograph for Estragyn® recommends cyclic (three weeks on, one week off) and concomitant progestogen therapy

Table 6: Suggested Doses in MHT Regimens

Type of Product	Starting Doses
Estrogen*	
Oral estrogen: conjugated estrogen (CE) 17ß-estradiol oral	 0.3 - 0.625 mg tablet daily 0.5 – 1 mg tablet daily
Transdermal estrogen: 17ß-estradiol (patch) 17ß-estradiol (gel)	 25 – 50 µg patches once or twice weekly (see transdermal estrogen products) 1 - 2 metered doses/actuation daily (Estrogel®) 0.5 – 1 mg packets daily (Divigel®)
Progestogen	
Oral progestogens: progesterone micronized medroxyprogesterone acetate	 100 mg daily for continuous regimen* 200 mg daily for 12 – 14 days/month for cyclic regimen* 2.5 mg daily continuous regimen* 5 mg cyclic regimen (12 -14 days/month)*
Combined patches: 17ß-estradiol/norethin-drone acetate	50/140 µg continuous regimen twice weekly patch

*higher doses of progestogens will be required when higher estrogen doses are used

NON-HORMONAL MEDICATIONS FOR MENOPAUSE IN CANADA

Table 7: Non-hormonal Medications for Menopausal Vasomotor Symptoms (VMS)

Drug	Trade Names/ Strengths Available	Doses	Comments
Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)			
venlafaxine*	Effexor XR®, generics 37.5, 75, 150 mg caps	37.5 mg – 150 mg	Start 37.5 mg daily x 1 week, then increase to 75 mg daily. Taper to discontinue.
desvenlafaxine*	Pristiq®, generics 50, 100 mg tabs	100 - 150 mg daily	Start with 50 mg, then increase to 100 mg over a few days. Taper to discontinue.
Selective Serotonin Reuptake Inhibitors (SSRI)			
paroxetine*	Paxil CR®, generics 12.5, 25 mg tabs	12.5 – 25 mg daily	Taper to discontinue
citalopram*	Celexa®, generics 20, 40 mg tabs	20 mg daily	Taper to discontinue.
escitalopram*	Cipralex®, generics 10, 20 mg tabs	10 – 20 mg daily	Taper to discontinue

*off-label use (not approved by Health Canada for this indication)

NON-HORMONAL MEDICATIONS FOR MENOPAUSE IN CANADA (CONT.)

Table 7: Non-hormonal Medications for Menopausal Vasomotor Symptoms (VMS) (CONT.)

Drug	Trade Names/Strengths Available	Doses	Comments
Alpha-adrenergic agonists			
clonidine	generics 0.025 mg tabs	0.05 mg bid	Some women may require higher doses (ie 0.05 mg tid), but side effects may limit use. Taper slowly to discontinue.
Gabapentinoids			
gabapentin*	Neurontin®, generics 100, 300, 400 mg caps 600, 800 mg tabs	Start 300 mg daily, then increase to 300 mg tid at 3 – 4 day intervals**	May take 1 – 2 weeks to see effective dose for VMS.
pregabalin*	Lyrica®, generics 25, 50, 75, 100, 150, 200, 225, 300 mg caps	150 – 300 mg daily	Less well studied in menopause.
Anticholinergic Agent			
oxybutynin*	generics 2.5, 5 mg tabs	2.5 – 5 mg twice daily	Reductions in VMS also demonstrated with 15 mg extended-release daily dose; this dose is not currently available in Canada.

*off-label use (not approved by Health Canada for this indication)**gabapentin can also be used as a nightly dose to help with sleep. It is recommended to start with 300 mg nightly and increase in increments of 100mg to doses of 600–900mg nightly.

ACKNOWLEDGEMENTS

Canadian Menopause Society/Société Canadienne de Ménopause (CMS/SCM) would like to thank the following health care experts for the development of this pocket guide.

Development 1st edition 2019:
Denise Black, MD, FRCSC; Céline Bouchard, MD, FRCSC; Christine Derzko, MD, FRCSC; Michel Fortier, MD, FRCSC; Susan Goldstein, MD, CCFP, FCFP, NCMP; Vicki Holmes, MD, NCMP; Elaine Jolly, MD, FRCSC; Robert Reid, MD, FRCSC; Timothy Rowe, MB BS, FRCSC, FRCOG; Wendy Wolfman, MD, FRCSC, FACOG, NCMP; Chui Kin Yuen, MD, FRCSC, FACOG, MBA; Nese Yuksel, BScPharm, PharmD, FCSHP, NCMP

Revised 2nd edition 2023:
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CMS/SCM also wishes to thank our readers who have been very supportive and help distribute to others.

Layout and Design: Lini Qiao
Publisher: CMS/SCM