doi.org/ 10.58931/cwht.2024.1317

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Menopausal Symptoms in the Workplace and an Update on Treatment Options

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Introduction

Women in midlife comprise an integral component of the Canadian workforce. The Menopause Foundation of Canada (MFC) recently completed a landmark cross-national survey of Canadian women aged 40–60.[1] This study found that 46% of surveyed participants felt unprepared for perimenopause/menopause and that 4 in 10 participants felt their symptoms were undertreated by their healthcare provider. Fewer than 25% of respondents said their family physician proactively discussed menopause with them.

Impact of Menopausal Symptoms in the Workplace

A second survey by the MFC specifically investigated the impact of menopause in the workplace.[2] This survey data is the best representation of the current state of menopausal women in our workforce. The report details that of the 20 million people in the Canadian labour force, one-quarter are women over the age of 40. An analysis of the economic impact data projected $3.5 billion dollars of lost revenue due to unmanaged menopausal symptoms. The MFC's study projected $237 million dollars in annual lost productivity and 540,000 lost days of work due to unmanaged peri-menopausal symptoms. One-third of the women in the menopausal transition reported their symptoms negatively impacted their work performance and one-quarter of respondents hid their symptoms at work. Two-thirds of these women did not feel comfortable speaking to their supervisor about their concerns and 70% of surveyed women were not comfortable speaking with their Human Resources department about their symptoms. This same survey found

Contraindications to Systemic Estrogen	Contraindications to Progestogen
Unexplained abnormal vaginal bleeding	Unexplained abnormal vaginal bleeding
Personal history of breast cancer (independent of receptor status)	Personal history of breast cancer
Personal history of estrogen-dependent malignancy	
Cardiac disease	
History of thromboembolism	
History of stroke	
Active liver disease (excluding fatty liver disease)	
Pregnancy	
History of thrombophilia	

Table 1. Contraindications to menopausal hormone therapy.[3,4]

a 14% drop in the number of employed women between ages 45–55, compared to a 10% decline in male workers. Women are leaving the workforce in the prime of their careers and uncontrolled menopausal symptoms can be a significant factor. Given the magnitude of the impact that midlife women have on the Canadian workforce, Canadian women deserve counselling and up-to-date medical options for management of their symptoms.

Current Treatment Options for Vasomotor Symptoms

Hormone Therapy

Menopausal hormone therapy (MHT) is the first-line treatment option for vasomotor symptoms (hot flashes, night sweats, and resultant sleep disturbance) in women under the age of 60 or within 10 years of a woman's final menstrual period.[3,4] MHT can be delivered via the oral or transdermal route, and is the standard of care for management of vasomotor symptoms barring any specific contraindications (**Table 1**). It is important for providers to note that unlike absolute contraindications such as smoking >35 years of age, migraine, or controlled (medicated) hypertension for combined hormonal contraceptive users, due to a marked dosing difference, these are not considered absolute contraindications to the use of MHT. In general, MHT refers to the use of an estrogen-containing product (which can be used as monotherapy if a woman has had a hysterectomy) and a progestogen for endometrial protection. However, MHT can also include synthetic steroids and the tissue-selective estrogen complex. Historically, providers have followed 5- or 10-year rules and then withdrawn their patients from hormone therapy due to concern for risk. Current major menopause guidelines take into consideration the fact that the average length of the vasomotor experience is approximately 7.4 years and this varies by a person's ethnicity. This information was informed by the Study of Women Across the Nation, or SWAN study.[5] The guidelines agree that there is no maximum length of use of MHT preparations, and that a decision to dose-reduce or cease therapy (either "cold turkey" or via tapering) is a decision that should be made following discussion between a patient and her provider.[3,4]

Risks of hormone therapy when provided to healthy, symptomatic people within this window of safety are considered minimal. Risks of coronary artery disease, stroke, and venous thrombosis in the combined arm of the Women's Health Initiative study (WHI) for women aged 50–59 were 2.5, 2.5 and 5/1000 women, respectively, over 5 years of use. Specific re-analysis of data from the WHI finds a pooled hazard ratio of all-cause mortality for both the estrogen alone and combined estrogen progestin arms in women aged 50-59 to be 0.69 (95% CI, 0.51-0.94) which is reassuring to providers.[6] The main counselling point during the provision of MHT containing estrogen and a progestogen is the association with invasive breast cancer. Breast cancer risk likely depends on several factors including length of use, type of MHT used and individual patient risk factors (most notably menopausal obesity and alcohol consumption).[7] However, the breast cancer risk most often quoted is an excess of 8/10,000 women users of MHT per year which is a finding of all pooled ages, from the WHI study.[8] Our understanding of the association between breast cancer risk and MHT use continues to evolve based on specific preparations. The Post-authorization Safety Study (PASS) on the tissue selective estrogen complex ([TSEC] - containing conjugated estrogens and bazedoxifene) studied more than 75,000 women for up to 5 years (mean follow-up was 22 months). Approximately 18,000 women were studied on the TSEC and 57,000 users of estrogen and progestin MHT were studied. Eighty-eight percent of participants were <60 years of age. The study found no increased risk of breast cancer with TSEC use (RR <1) compared to users of estrogen and a progestin. This same study found lower rates of endometrial cancer and hyperplasia than expected in the population and lower rates of acute cardiovascular events than expected in a comparison untreated population.[9] A large systematic review by Formoso *et al.* in 2016 in the Cochrane database reviewed the association between tibolone use and breast cancer risk. The OR for invasive breast cancer was 0.52 (95% CI 0.21 to 1.25) for tibolone vs placebo.[10]

Women who have undergone total hysterectomy surgery (removal of the uterus and cervix) are candidates for estrogen monotherapy. An important finding from the WHI in the estrogen monotherapy arm for women with a hysterectomy was no increased association with breast cancer.[8] **Table 2a–c** describes current Health Canada approved estrogen options. MHT is a systemic treatment and while it may benefit symptoms of genitourinary syndrome of menopause (GSM), systemic MHT use is not indicated solely for treating GSM in the absence of vasomotor symptoms. GSM refers to the constellation of symptoms including vaginal dryness, dyspareunia, recurrent urinary tract infection, vulvar irritation, and lower urinary tract symptoms.[11,12] This symptom cluster can be extremely symptomatic for many menopausal women and is best treated with local or selective therapies that target the tissues of the bladder, vagina and vulva (**Table 3**). There is no maximum length of use or age limit regarding the use of medications treating GSM, and progestogens are not required for endometrial protection.

Non-hormonal Options for Management of Menopause Symptoms

For midlife women who have a contraindication to MHT or a preference to avoid hormonal medications, several medications are used off-label for the management of vasomotor symptoms. These medications are supported by several guidelines; however, as they do not have Health Canada approval for the management of menopausal symptoms, providers should document the reasons why these medications are being prescribed and that they have counselled the patient that they are being used in an off-label fashion.[3,13] Several medications such as clonidine and pregabalin have now been removed from recent guidelines due to lack of efficacy data and possible adverse effects. Important considerations in this category include avoiding oxybutynin in women at risk for cognitive decline and the elderly, and limiting paroxetine use in women on tamoxifen. Venlafaxine is the best-studied non-hormonal agent in the breast cancer survivorship literature (**Table 4**).[13]

The addition of neurokinin B antagonists to the non-hormonal options for menopausal symptoms is an exciting development. This is a novel class of non-hormonal medications with current FDA approval for fezolinetant and elinzanetant which are in advanced development.[14,15] These medications have been studied in clinical trials and have shown improvements in the frequency and severity of vasomotor events.

Estrogen Name *(Generic/Commercial)*	Dosage
17B-estradiol/Estrace	0.5, 1, 2 mg PO OD
Conjugated estrogen (CE)/Premarin	0.3, 0.625, 1.25 mg PO OD
17B-estradiol/Climara	25, 50, 75, 100 mcg patch once weekly
17B-estradiol/Estradot	25, 37.5, 50, 75, 100 mcg patch twice/week
17B-estradiol/Divigel	10, 25, 50, 100 mcg gel applied daily
17B-estradiol/Estrogel 0.06%	2 pumps = 1.5 mg of E2 gel applied daily
17B-estradiol/Oesclim	25, 37.5, 50, 75, 100 mcg patch twice weekly

Table 2a. Estrogen therapy available in Canada (can be used as monotherapy in women who have had a hysterectomy); *courtesy of Kelsey E. Mills, MD, FRCSC, MSc HSEd, MSCP.*

Single Prescription Name *(Generic/Trade)*	Dosage
Conjugated estrogen and bazedoxifene/Duavive	1 tab PO OD (0.45 mg CE and 20 mg bazedoxifene)
Tibolone/Tibella	1 tab PO OD
17B-estradiol and norethindrone acetate (NETA)/Activelle	1 tab PO OD (1 mg estradiol and 0.5 mg of NETA)
17B-estradiol and norethindrone acetate (NETA)/Activelle LD	1 tab PO OD (0.5 mg estradiol and 0.1 mg of NETA)
17B-estradiol and drospirenone/Angeliq	1 tab PO OD (1 mg estradiol and 1 mg drospirenone)
17B-estradiol and micronized progesterone/Bijuva	1 tab PO OD (1 mg estradiol and 100 mg progesterone)
17B-estradiol and levonorgestrel/Climara Pro	1 patch changed weekly (45 mcg estradiol and 15 mcg levonorgestrel)
17B-estradiol and norethindrone acetate (NETA)/Estalis (two dosing options)	1 patch changed twice weekly (50 mcg estradiol and 140 mcg NETA); (50 mcg estradiol and 250 mcg NETA)

Table 2b. Combined estrogen/progestogen and other single-prescription therapies available in Canada (no additional progestogen required for this category); *courtesy of Kelsey E. Mills, MD, FRCSC, MSc HSEd, MSCP.*

Progestogen Name *(Generic/Trade)*	Dosage
Levonorgestrel intrauterine system/Mirena	52 mg intrauterine system (IUS) for 5 years **Note**: Currently the 19 mg IUS is not recommended for endometrial protection
Medroxyprogesterone acetate/Provera	2.5, 5, 10 mg PO OD
Micronized progesterone/Prometrium	100 mg PO/PV OD
Norethindrone acetate/Norlutate	5 mg PO OD
Drospirenone/Slynd	1 tab PO OD
Norethindrone acetate/Movisse	1 tab PO OD

Table 2c. Progestin therapies available in Canada for endometrial protection; *courtesy of Kelsey E. Mills, MD, FRCSC, MSc HSEd, MSCP*.

Medication Name *(Generic/Commercial)*	Dosage
Conjugated estrogen cream (Premarin)	0.5 mg PV x 14 days, then twice weekly
0.1% Estrone cream (Estragyn)	0.5-4 g PV x 14 days then twice weekly
17 B-estradiol suppositories (Vagifem)	10 mcg tab PV x 14 days then twice weekly
17 B-estradiol vaginal ring (Estring)	1 ring PV change q 3 months
17 B-estradiol vaginal suppositories (Imvexxy)	4 or 10 mcg suppository PV x 14 days then twice weekly
Prasterone (Intrarosa)	6.5 mg vaginal ovules PV QHS
Ospemiphene (Osphena) (oral estrogen agonist/antagonist)	60 mg PO OD

Table 3. Genitourinary syndrome of menopause therapies available in Canada; *courtesy of Kelsey E. Mills, MD, FRCSC, MSc HSEd, MSCP*.

Medication Name *(Generic/Commercial)*	Dosage
Paroxetine/Paxil	10–25 mg PO OD
Citalopram/Celexa	10–20 mg PO OD
Escitalopram/Lexipro	10–20 mg PO OD
Desvenlafaxine/Pristiq	25–150 mg PO OD
Venlafaxine/Effexor	37.5–150 mg PO OD
Gabapentin/Neurontin	100–2400 mg PO OD
Oxybutynin/Ditropan	2.5–15 mg XR PO OD

Table 4. Non-hormonal therapies available in Canada for the management of menopausal vasomotor symptoms (all are off-label usage); *courtesy of Kelsey E. Mills, MD, FRCSC, MSc HSEd, MSCP.*

Conclusion

Now, more than ever, the literature is clear that supporting women experiencing menopause by inquiring about and then addressing their symptoms is the standard of care. There are several algorithms for providers that aid in the assessment and treatment of menopausal women.[16,17] Lack of provision of menopausal treatment is resulting in an enormous unmet health need in Canadian women and others experiencing menopause, with very significant health and economic impact. Menopause hormone therapy is the first-line treatment for systemic symptoms, and local or targeted hormonal therapy is the mainstay of GSM therapy. Treatment options exist for women who cannot or will not use MHT and this area of medicine is rapidly evolving. There are many novel hormonal and non-hormonal options either in advanced development or newly brought to market, which increase the range of options available to menopausal women in Canada.

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Financial Disclosures

Speakers bureaus /advisory committees:
Astellas, Abcellera, Biosyent, Knight, Lupin, Duchesnay, Eisai, Pfizer, Bayer.

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