ABOUT THE AUTHOR

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Dr. Denise Black is a graduate of the University of Manitoba School of medicine and she completed residency training in OB/GYN in Manitoba as well. In a career that spans 4 decades, she has been involved in both academic and private practice. While in academia, Dr. Black served as the Director of the post graduate medical education program in Obstetrics and Gynecology and served as an examiner for the Royal College. She also was the OB/GYN consultant for the Manitoba HIV team during the early years when intrapartum AZT was first introduced as a way to reduce vertical transmission. Access to appropriate and timely contraceptive care is a professional passion, and advocacy, education, and removing barriers to access is a personal mission. Dr. Black has published in both the fields of contraception and menopause and worked as an author of the SOGC menopause guidelines.

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MENOPAUSE HORMONE THERAPY: 2023 UPDATE

Introduction

The publication of the Women's Health Initiative (WHI) study in 2002 caused a precipitous decline in use of menopause hormone therapy (MHT). Prior to publication, approximately 43% of women aged 45-74 used MHT; following publication, this number dropped to 11%.[1] Fear of breast cancer was the largest motivator behind this decline. Since the WHI study, menopause medical education has been inadequate; it is estimated that 41% of medical schools do not include menopause education in their undergraduate curriculum.[2] The same study highlighted significant knowledge gaps regarding menopause management among practicing physicians.

Menopausal women are asking questions and expecting answers. Advocacy groups such as the Menopause Foundation of Canada are empowering women to acknowledge the impact of menopausal symptoms on the workplace, personal relationships and personal health. As MHT is considered first-line therapy (in the absence of contraindications), it behooves healthcare providers to have a working knowledge of MHT.

Indications for MHT

The indications for MHT vary. In Canada, guidelines state that MHT is indicated for the management of vasomotor symptoms due to menopause, and MHT may be safely initiated in women without contraindications who are less than 60 years of age, or less than 10 years from their final menstrual period.[3] The indication from the North American Menopause Society is for treatment of bothersome vasomotor symptoms and prevention of bone loss.[4] The International Menopause Society indications are much more permissive, advocating that MHT is indicated for management of menopause-related complaints, including vasomotor symptoms, muscle and joint aches and pains, and sleep disturbances.[5]

Contraindications to MHT

Contraindications to MHT are listed in **Table 1**.

Assessing Patients for MHT

Suitability for various types of MHT depends on individual assessment of patient risks. Cardiovascular disease (CVD) risk assessment, venous thromboembolic (VTE) risk assessment, breast risk assessment, and the presence or absence of a uterus will determine the most appropriate choice of MHT.

CVD assessment includes the presence or absence of significant hypertension; hyperlipidemia (especially elevated triglycerides [TG's]); Type 2 diabetes (T2DM) or impaired glucose tolerance; obesity (BMI >35); smoking; and age >65.

VTE risk assessment includes obesity (BMI>35); past history of VTE; the presence of a prothrombotic mutation; and age >65.[6]

Contraindications to estrogen	Contraindications to progestogen
• 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 thromboembolism • Active liver disease • Known or suspected pregnancy	• Undiagnosed abnormal vaginal bleeding • Current or history of breast cancer

Table 1. Contraindications to systemic menopausal hormone therapy; adapted from Yuksel N et al, 2021.[3]

Breast risk assessment includes family history, presence of a genetic mutation and breast density.

The presence or absence of a uterus will determine the need for endometrial protection.

Selecting a therapy

For patients with an indication and no contraindications, the data support that for those with increased CVD or venous thromboembolic risk, transdermal estrogens at the lowest dose to relieve symptoms have the safety advantage. For those in this higher risk group who have a uterus, the use of micronized progesterone for endometrial protection is recommended, as it does not further increase thromboembolic risk and is viewed to be metabolically favourable for CVD risk.[7] The use of the levonorgestrel IUS 52 mg in this group is also endorsed, although it is off-label in Canada.

Observational data suggests that for women who have undergone a benign breast biopsy, have a family history of breast cancer, or for those with a BRCA 1 or 2 genetic variant who have undergone oophorectomy, hormone therapy use is not contraindicated and does not further increase their risk of breast cancer.[4] Increased breast density is a recognized risk factor for breast cancer. A recent meta-analysis, using data from digital mammography, estimates that women with BI-RADS category D breasts (highest density) have a 3.89 fold increase (2.47-6.13) in breast cancer risk vs those with BI-RADS category A breasts.[8] Estrogen-progestogen therapies further increase breast density, in a dose-dependent fashion, irrespective of the choice of progestogen.[9] For those with dense breasts, an agent that does not increase breast density (tissue selective estrogen complex [TSEC] or tibolone) may be beneficial.[10] For women using systemic estrogen who have a uterus, adequate endometrial protection is indicated.

Products Available in Canada

In Canada, there are a variety of products, dosages and routes of administration available. Oral estrogens are available as stand-alone therapy, or can be used in combination with endometrial protective agents. Transdermal estrogens are available as patches (changed once or twice weekly) or daily use gels. Progestogens are available as natural micronized progesterone or synthetic progestins, and are available as part of a combination or as stand- alone therapy. The use of the progestin IUS for endometrial protection as part of an MHT regimen is off-label in Canada; however, there is evidence of endometrial protection with the levonorgestrel-releasing intrauterine system (LNG-IUS) 52 mg for up to 5 years for MHT use, even with higher doses of estrogen administration **(Table 2)**.[11]

Innovative Therapies

Two novel non-estrogen progesterone/progestin hormone therapy (EPT) therapies are available in Canada. Both of these are fixed-dose, single oral tablet combination therapies.

Tibolone is a synthetic steroid. The parent compound has no metabolic effect; however, once ingested, it performs different actions in various tissues due to tissue selective metabolism. Some metabolites have estrogenic effects on the bone, vagina and brain (for vasomotor symptoms), while one isomer has progestogenic (endometrial protective) activities and mild androgenic properties. The breast is not stimulated due to local enzyme activity which inhibits formation of active estrogens at the breast.[12] In a clinical study, the use of tibolone over a six-month period did not increase breast density.[13] During the first six months of use, approximately 20% of users with a uterus will experience unscheduled bleeding or spotting; by twelve months this declines to approximately 10%.[14] These are results similar to those seen with estrogen/progestogen therapy.

Conjugated estrogens with bazedoxifene (CE/BZA) is the first product to provide relief of hot flushes and endometrial protection without a progestogen. It is considered a tissue selective estrogen complex (TSEC) and uses a selective estrogen receptor modulator (SERM) to provide endometrial protection. The bazedoxifene (SERM component) provides potent antagonistic activity at the endometrium. The unique combination of this estrogen and this SERM provides relief of vasomotor symptoms, with reported unscheduled bleeding rates of 10% during the first six months, and 1.8% thereafter; this incidence is very similar to that of placebo.[15]

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 β-estradiol (micronized)	Estrace Lupin-estradiol	0.5, 1, 2 mg tablets 0.5, 1, 2 mg tablets	0.5–1 mg once daily
Transdermal patch			
Twice weekly 17 β-estradiol patches	Estradiol Derm Estradol Oesclim	50, 75, 100 µg patches 25, 37.5, 50, 75, 100 µg patches 25, 50 µg patches	25–50 µg twice weekly
Once weekly 17 β-estradio patches	Climara	25, 50, 75, 100 µg patches	25–50 µg once weekly
Transdermal gel			
17 β-estradiol gel	Estrogel	0.06% gel 0.75 mg estradiol per 1.25 g metered dose(= 1 actuation)	1–2 metered doses/actuation once daily
	Divigel	0.1% gel Sachets contain 0.25, 0.5, 1 mg	0.5–1 mg sachets once daily
Progestogens			
Oral			
Medroxyprogesterone	Provera Apo-medroxy Pro Doc Limitee Teva-medroxyproges-terone	2.5, 5, 10 mg tablets 2.5, 5, 10 mg tablets 2.5, 5, 10 mg tablets 2.5, 5, 10 mg tablets	2.5 mg daily for continuous regimen 5mg daily for 12–14 days/month for cycle regimen
Progesterone (micronized)	Prometrium PMS-progesterone Reddy-progesterone Teva-progesterone	100 mg capsules 100 mg capsules 100 mg capsules 100 mg capsules	100 mg daily for continuous regimen 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	52 mg per IUS	For 5 years
	Kyleena	19.5 mg per IUS	For 5 years
Combination hormone therapy preparations			
Oral			
17 β-estradiol (E2) and NETA	Activelle Activelle LD	1mg E2 and 0.5 mg NETA tablet 0.5 mg E2 and 1 mg DRSP tablet	1 tablet daily
17 β-estradiol (E2) and DRSP	Angeliq	1 mg E2 and 1 mg DRSP tablet	1 tablet daily
Transdermal patch			
17 β-estradiol (E2) and NETA	Estalis 140/50 Estalis 250/50	50 µgE2 and 140 mg NETA patch 50 µgE2 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

Table 2. Systemic menopausal hormone therapy products in Canada; adapted from Yuksel N et al, 2021.[3]

* Not approved for menopausal hormone therapy by Health Canada.
* Mirena is the only LNG-IUS marketed in Canada that has evidence for endometrial protection.
CE: conjugated estrogen; DRSP: drospirenone; IUS: intrauterine system; INETA: inorethindrone acetate; SERM: selective estrogen receptor modulator; TSEC: tissue selective estrogen complex.

Following 24 months of use, there was a small **decrease** in breast density, similar to that of placebo.[16]

Managing Side Effects

The most commonly-reported side effects are mastalgia and unscheduled bleeding. Rates vary between MHT preparations.

With continuous estrogen/progestogen therapy and tibolone, unscheduled bleeding in the first six months of use is reported at approximately 20-25%. In the absence of increased risk of endometrial cancer, no investigations are mandated during this period. Any bleeding following the first six months of therapy needs to be adequately investigated.[17] If thorough investigations are negative and bleeding persists, switching to CE/BZA (in patients not considered at increased VTE or CVD risk) may alleviate the bleeding issues.[18]

Mastalgia is a common side effect during the initial three months of EPT use, with rates approaching 25%. With tibolone or CE/BZA, mastalgia rates are similar to those of placebo.

Initial Fears

When the original WHI publication first appeared, the headlines sensationalized the increased cardiovascular (CV) and breast cancer risks.

Since that publication, numerous scientific works have provided clarity concerning CV risks. A Cochrane Review which stratified CV risk according to age at the initiation of MHT showed a statistically significant 48% reduction in coronary heart disease (CHD) among individuals who initiated MHT prior to age 60 or less than 10 years from their final menstrual period.[19] This data has played a significant role in allaying the fears of CV risk.

The breast cancer fears are difficult to undo, and breast cancer risk due to MHT is difficult to quantify. Guidelines recognize that the relationship between MHT and breast cancer is complex. Attention to lifestyle modification is emphasized. Certain regimens may be considered more "breast friendly" than others, specifically, micronized progesterone rather than synthetic progestins, and perhaps CE/BZA.[10]

Duration of Use

Following the publication of the WHI study, it became entrenched in popular culture that duration of MHT use should be limited to five years or less. Current guidelines reflect that the average duration of hot flushing is 7.4 years. Extended use is permissible, provided that initiation of MHT occurred prior to age 60 or less than 10 years from the final menstrual period. In women > 65 who have opted to continue MHT, it is recommended that oral estrogen users switch to a transdermal estrogen at the lowest effective dose. The current thinking is that MHT should be used in the appropriate patient, at the appropriate dose, for the appropriate length of time.[4]

Annual follow up is recommended to discuss the patient's desire to either continue or discontinue MHT, and to assess for new co-morbidities.

There are no long-term, randomized, controlled trials to assess the impact of long-term hormone therapy use on rates of breast cancer. One study showed progressively increasing risk with extended use; however, the overall applicability of this data is difficult, as the preparations used in the study are not the regimens currently in use, with very few study patients using micronized progesterone, and none using CE/BZA.[20] It is important to counsel patients about the lack of robust data to predict the impact of prolonged MHT use on breast cancer risk.

Summary

Significant advances have been made in our scientific understanding concerning the risks and benefits of MHT since the WHI study. The lessons learned have been these:

1. **Initiation less than 10 years from the patient's final menstrual period, or prior to age 60, confers the greatest advantages with the least amount of risk.**
2. **In the absence of contraindications, women with increased CV or VTE risk should use a transdermal estrogen at the lowest dose to effectively relieve symptoms. If endometrial protection is necessary, micronized progesterone or LNG-IUS 52 mg should be used (off-label in Canada).**
3. **Dense breasts are a risk factor for breast cancer. Women with dense breasts should use an agent that doesn't further increase density, such as CE/BZA or tibolone.**
4. **There is no "five-year rule" for duration of MHT use. Use of the appropriate therapy, at the appropriate dose, for the appropriate duration is the new rule.**
5. **Although short-term use of MHT (especially "breast-friendlier" options) does not appear to increase breast cancer risk, there is a lack of quality evidence concerning the risks of long-term therapy. Patients are capable of making their own decisions about uncertain outcomes.**
6. **The most common nuisance side effects are unscheduled bleeding and mastalgia. Lowering the medication dose or switching to an agent with a different bleeding or tenderness profile may be beneficial.**

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