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Novel Treatment Options For Menopausal Symptoms

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Introduction

The world of menopause is undergoing a renaissance. In recent years, medical experts have taken to social media, igniting a long overdue surge of information on the subject that helps debunk the fear of menopausal hormone therapy (MHT), which stems from the 2002 Women's Health Initiative (WHI) study.[1] The devastating consequences on health and wellness were profound: an entire generation of women was suddenly deprived of symptom relief and quality of life (QOL) due to the marked decline in hormone prescriptions in North America. These effects continue to echo today. The near extinction of medical education on mature women's health and wellness in our academic institutions since 2002 has left healthcare professionals ill-equipped to guide the next generation of menopausal women who seek contemporary medical advice and refuse to "live their mothers' menopause." The creation of the Menopause Foundation of Canada in 2022, recent sold-out menopause conferences, and renewed interest from pharmaceutical companies is convincing evidence that menopause is finally receiving the recognition and attention it deserves.

Recent Guidelines

Since the publication of the WHI study, guidelines have undergone regular updates to incorporate evolving evidence on safety and benefits. The latest version, published in 2022 by the North American Menopause Society (NAMS), is summarized in **(Table 1)**.

Contraindications to MHT

There is still considerable misunderstanding regarding contraindications to MHT. Symptomatic women who are generally healthy and within 10 years of menopause onset or below age 60 are ideal candidates. Women within this 'window of opportunity' who smoke, or have mild, well-controlled medical conditions not listed below who are negatively affected by menopausal symptoms should be offered MHT. Enhancing wellness and QOL may optimize their ability to

modify lifestyle factors to benefit health and reduce risks associated with chronic illnesses.

Hormone Therapy for Systemic Symptoms

Prior to the publication of the WHI study, most MHT prescriptions in North America consisted of conjugated equine estrogen (CEE) with medroxyprogesterone acetate (MPA) for those requiring endometrial protection. Findings from the WHI study suggested potential increased health risks associated with CEE and MPA,[1] which resulted in a marked reduction in prescribing habits in North America.[4] Over time, as concerns slowly subsided, innovative MHT formulations deemed safer were introduced and adopted.

Transdermal estrogen preparations, available as patches in Canada since the late 1970s, and as gels approved by Health Canada in 2011, quickly gained popularity. Their advantages include bypassing first-pass hepatic metabolism, reducing the risk of thromboembolic events,[5] absence of metabolites, improved absorption and bioavailability, and more stable systemic delivery compared to oral preparations. Despite that both formulations have shown to be equivalent in their efficacy to relieve VMS,[6] transdermal options continue to be favoured by women and prescribers to this day.

Micronized progesterone, developed in Europe in the late 1970s, became available in Canada in 1999 and quickly replaced MPA as the progestogen of choice for women on estrogen with a uterus. It metabolizes into allopregnanolone, which has a strong affinity for Gamma-aminobutyric acid (GABA) receptors, contributing beneficial effects on sleep.[7] In addition, findings from the French E3N study suggest that micronized progesterone may have a more favourable breast cancer risk profile compared to other progestogens.[8]

A novel MHT combining CEE with bazedoxifene, a tissue selective estrogen complex (TSEC), has been available in Canada since 2017. This formulation of CEE and a TSEC that acts as an antagonist on endometrial and breast tissue and an agonist for bone, is beneficial for osteoporosis prevention. This combination offers a unique formulation appropriate for most women, including those with specific considerations.[9]

Tibolone, a selective tissue estrogenic tissue regulator (STEAR), available in Europe since 1985, made its debut in Canada in 2020. This complex molecule metabolizes into components with estrogenic, progestogenic, and androgenic properties, making tibolone an oral preparation equipped to address distinct symptoms of menopause such as mood changes and hyposexual desire disorder (HSDD).[10] It has also demonstrated a favourable risk profile with regards to breast and colon cancer.[11]

Lastly, since early 2024, estradiol and micronized progesterone have been combined into

• Hormone Therapy remains the most effective treatment for vasomotor symptoms (VMS) and the genitourinary syndrome of menopause (GSM) and has been shown to prevent bone loss and fracture.
• The risks associated with hormone therapy differ depending on factors such as type, dose, duration of use, route of administration, timing of initiation, and whether a progestogen is used.
• For women younger than 60 years or within 10 years of menopause onset without contraindications, the benefit-risk ratio is favourable for treating bothersome VMS and preventing bone loss.
• For women initiating hormone therapy more than 10 years from menopause onset or over age 60, the benefit-risk ratio appears less favourable because of the greater absolute risks of coronary heart disease, stroke, venous thromboembolism, and dementia.
• Longer durations of therapy should be for documented indications such as persistent VMS, with shared decision-making and periodic re-evaluation.
• For bothersome GSM symptoms not relieved with over-the-counter therapies, low-dose vaginal hormonal therapies are recommended.

Table 1. Hormone Therapy Position Statement; *Adapted from Faubion et al., 2022*[2]

a single oral preparation.[12] Although both therapies have been available for decades, this new combination simplifies administration, improves compliance, and reduces dispensing fees by consolidating treatment into a single product.

Non-hormonal Treatment Options for Special Considerations

Following the WHI publication, MHT prescriptions rapidly declined, and a new trend quickly emerged to meet the needs of menopausal women afflicted with ongoing symptoms. Non-hormonal medications previously approved for other indications such as selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), gabapentin, pregabalin, clonidine, and oxybutynin became popular options to target specific symptoms such as VMS, insomnia, and mood disorders. However, these options often produced unpleasant side-effects and lacked the efficacy offered by MHT.[14] Despite this, concerned healthcare professionals and menopausal women reluctantly accepted these 'safer' alternatives. Today, as MHT has regained its place as a first-line treatment for menopausal symptoms, non-hormonal options have remained valid alternatives for women who have contraindications to hormonal formulations.[15]

The discovery of neurokinin 3 receptors (NK3R) as key players in the generation of menopausal VMS offered a unique opportunity to develop a truly novel non-hormonal treatment option dedicated to the relief of the most common menopausal symptom. Thermoregulation in the mammalian hypothalamus is mediated by kisspeptin-neurokinin B-dynorphin (KNDy) neurons, which are normally inhibited by estrogen. During the menopause transition, declining estrogen levels lead to KNDy neuron overstimulation, eliciting shifts in the thermoneutral zone and triggering vasomotor symptoms.[16] Fezolinetant (an NK3R antagonist) and elinzanetant (an NK-1,3 receptor antagonist), have both shown efficacy comparable to MHT with few side-effects. Both were approved in Canada within the last year for the treatment of menopausal VMS in women who have contraindications to, or prefer not to use, MHT.[14]

Local Treatment Options for GSM

For women experiencing vulvovaginal and bladder symptoms, local vaginal treatments, available for years as estrogen creams, tablets, and rings, are deemed safe for use by all given their negligible systemic absorption. Recently, an estradiol vaginal suppository has been introduced, designed to adhere to the mucosa only centimetres beyond the introitus. This targeted placement improves symptom relief where it matters most, compared to existing products inserted deeper into the vaginal canal.

Prasterone, a Canadian innovation, is a vaginal suppository containing dehydroepiandrosterone (DHEA), which converts into estrogen and testosterone intracellularly, addressing the hormonal needs of all local receptors. It is currently the only vaginal product without boxed warnings.[17] Finally, ospemifene, an oral selective estrogen receptor modulator, specifically targets vulvovaginal estrogen receptors to relieve GSM.[18] It is especially convenient for women with mobility limitations or who wish to avoid vaginal applications.

The Future Looks Bright

Discovered in 1965, estetrol was initially explored as a promising menopausal hormonal treatment option that was abandoned following the WHI publication. Later, estetrol was combined with drosperinone and introduced as an oral

Contraindications to systemic estrogen therapy	• unexplained vaginal bleeding • acute liver dysfunction • estrogen-dependent cancer • coronary heart disease • previous history of stroke • history of thromboembolic disease
Contraindications to progestogen therapy	• unexplained vaginal bleeding • breast cancer

Table 2. Contraindications to MHT; *Adapted from Yuksel et al., 2021*[3]

Type of Estrogen Standard Doses	Trade Names
Oral Conjugated estrogen (CE) 0.3–0.625 mg daily	Premarin
17β estradiol 0.5–1.0 mg daily	Estrace/generics
Transdermal 17β estradiol 25, 37.5, 50 ug patch twice weekly 25, 50 ug patch once weekly	Estradot/generics Climara
17β estradiol 1-2 pumps of gel daily 0.25, 0.5, 0.75 mg gel, one sachet daily	Estrogel Divigel
Type of Progestogens **Standard Doses**	**Trade Names**
Oral Micronized progesterone 100 mg capsule x 1-2 daily every night at bedtime	Prometrium/generics
Medroxyprogesterone acetate 2.5–5 mg daily	Provera/generics
Combination Products **Standard Doses**	**Trade Names**
17β estradiol + norethindrone acetate (NETA) 0.5 mg + 0.1 mg tablet daily	Activelle LD
17β estradiol + NETA 1.0 mg + 0.5 mg tablet daily	Activelle
17β estradiol + drosperinone 1 mg + 1 mg drosperinone tablet daily	Angeliq
17β estradiol + micronized progesterone 1 mg + 100 mg capsule every night at bedtime	Bijuva
17β estradiol + NETA 140 ug NETA + 50 ug estradiol patch twice weekly 250 ug NETA + 50 ug estradiol patch twice weekly	Estalis Estalis
CE + bazedoxifene 0.45 mg CE + 20mg bazedoxifene tablet daily	Duavive
Tibolone 2.5 mg tablet daily	Tibella

Table 3. Systemic MHT products in Canada; *Adapted from Canadian Menopause Society MHT products in Canada publication. 2025*[13]

contraceptive in 2022. Estetrol distinguishes itself by its lack of first-pass hepatic metabolism, absence of metabolites, higher bioavailability, and a longer half-life. It offers beneficial effects on lipids, carbohydrate metabolism, and bone turnover. Estetrol induces apoptosis in breast cancer cells and, at higher doses, demonstrates antitumor effects in end-stage breast and prostate cancers while alleviating VMS often associated with other hormone receptor blockers used as adjuvant therapy. It has significant efficacy for managing VMS and GSM and should become available in Canada in 2026 as a stand-alone estrogen therapy, to be combined with a progestogen for women in need of endometrial protection.[19]

Conclusion

In Canada, there are currently 10 million women over the age of 40, and on average, they will spend 40% of their lives beyond menopause. Most will experience symptoms impacting their wellness and QOL for a decade, and for others these symptoms will persist indefinitely. The impact and cost of unresolved symptoms, on personal health, wellbeing, relationships, productivity at work, and on community and society at large, cannot be overstated.[20] With a deeper understanding of hormonal physiology over the last two decades, the development of a broad range of safe treatment options for all, and renewed interest in this field, medical professionals are now better equipped than ever to provide adequate care and support for all menopausal women.

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