Menopause

Fall 2023

Did you know?

- If higher doses of estrogen are needed to control vasomotor symptoms, higher doses of progestogen are required to **adequately protect the uterus from endometrial cancer** (in women who have not had a hysterectomy). See page 3 for doses (e.g. **ESTRACE** 2mg daily pairs with medroxyprogesterone 5mg daily). **Low dose vaginal estrogen does not require a progestogen.**
- The **levonorgestrel IUD MIRENA** has data for 5 years of endometrial protection (off-label).[6,7] Candidates include those who require contraception, do not tolerate an oral progestogen, prefer the convenience, or have perimenopausal heavy menstrual bleeding. It can be used for patients on any estrogen dose.
- Vaginal estrogen is minimally absorbed at commercially available low doses. **Vaginal estrogen does not appear to increase the risks of harms such as breast cancer, endometrial cancer, or cardiovascular disease.**[11] Therapy can be continued for as long as benefit is perceived by the patient.[10] See page 7 for more info.
- **The buttocks** is a preferred application site for an estradiol transdermal patch due to ↑ privacy & ↓ skin irritation.[5]
- Although less effective than hormones, **select SSRIs and SNRIs** have shown benefit for treating vasomotor symptoms (see page 4). **The dose needed is typically lower** than for anxiety or depression (& higher doses are often no more effective).

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90% of women enter menopause between the ages of 45 to 56 years.[8]
50% of women believe that menopause is still a taboo subject (and awareness of the full spectrum of symptoms – such as urinary tract infections – is low).[9]

Who is a candidate for systemic menopausal hormone therapy (MHT)?

Women (40+ yrs) who used hormone therapy in **1999**:[USA,4] **~22%**

WHI trial published in 2002 on potential benefits & harms of hormones

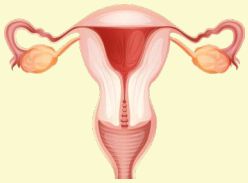
Women (40+ yrs) who used hormone therapy in **2010**:[USA,4] **~5%**

Systemic hormone therapy is **very effective** for treating vasomotor symptoms (e.g. ↓ hot flashes by 70-95%);[12] however, there are potential harms.[13] Canadian 2021 guidelines recommend hormone therapy as first line for women under the age of 60 or within 10 years of their last menstrual period (if no contraindications).[1] The back page of this newsletter helps weigh the benefits and risks of treatment.

Estrogens & Progestogens: Individualizing Systemic Therapy

- Starting at a low initial estrogen dose has fewer side effects and can ↓ cost, but may take 4-6 weeks to show benefit.[1] If severe symptoms, starting at a moderate dose can be an option for faster benefit (e.g. 2-4 weeks);[1] after treatment success, attempt to **find the lowest effective dose to reduce the risk of harm.**[14]
- **Continuous dosing** of a progestogen is generally preferred in women who have had at least 12 months of amenorrhea. **Cyclic dosing** (12-14 days/month) may be preferred during the menopause transition (to reduce breakthrough bleeding).
- **Combination products** (estrogen + progestogen) are useful to ↑ adherence, but can limit dose flexibility.
- **Micronized progesterone** PROMETRIUM can be sedating, which is desirable for some, but problematic to others. Patients should usually take it at bedtime.

Turn to page 3 for more



HORMONE THERAPY FACTS

Ask about vaginal health in women aged 45+ years.

Women who have genitourinary menopause symptoms:[1] **~50%**

Women who ask a healthcare provider for help with these symptoms:[3] **~25%**

At least half of patients do not realize that genitourinary symptoms of menopause (such as vaginal dryness, pain during sex, or recurrent UTIs) are treatable/preventable.[3] Normalize asking about vaginal health; one opportunity is when someone aged 45+ years is being screened with a Pap test. For treatment options, see page 3.

MHT=menopause hormone therapy **UTI**=urinary tract infection **WHI**=Women's Health Initiative

MENOPAUSE: Overview

Jessica Visentin PHARMD © www.RxFiles.ca/menopause Sept 2024

Definitions[4,5]

- **Perimenopause**: years leading up to menopause, often characterized by irregular menses +/- VMS and other symptoms (see **Table 1** and MQ6 below). May begin up to 10yrs before last menstrual period (LMP).
- **Menopausal transition**: perimenopause + the first 12 months post-LMP.
- **Menopause (or post-menopause)**: ≥12 months of amenorrhea.

Statistics[4,16]

- The average age of menopause onset is 51yrs.
- Menopause occurs in 90% of ♀ between the ages of 45-56yrs.
- GSM effects 45-77% of ♀; symptoms often ↑ over time & persist if untreated.
- VMS effects ~80% of ♀ (severe in ~20%); VMS persist for average 7-11yrs.
- Use of systemic MHT ↓ from 22% to 5% since **WHI** published in 2002.[USA]

Diagnosis[5]

- **<40yrs (premature ovarian failure)**: work-up for secondary causes of amenorrhea is recommended.
- **40-45yrs (early menopause)**: consider labs (hCG, prolactin, TSH, FSH).
  → Estrogen/progesterone/LH levels are not recommended.
- **>45yrs**: diagnose based on symptoms alone (labs/imaging not needed).

Clinical Pearls

Vaginal (local) Estrogen: ❶ GSM is under-recognized/ under-treated; normalize asking about vaginal health (dryness, pain, sexual concerns). ❷ Low-dose vaginal estrogen (e.g. **VAGIFEM** 10mcg, **ESTRING Ring** 2mg, **PREMARIN Cream** or **ESTRAGYN Cream** ≤ 1g/d) can be used even if **CI** to systemic estrogen[SOGC '21] (black box warnings for breast CA/CHD generally do not apply). ❸ Low-dose vaginal estrogen does not require a progestogen for endometrial protection. ❹ Low-dose vaginal estrogen can be added to systemic MHT for ♀ with GSM + VMS.

Systemic Estrogen: ❶ ♀ with an intact uterus require a progestogen (e.g. **MIRENA** IUD[off-label], **PROMETRIUM**, **PROVERA**) to prevent endometrial CA. ❷ Contraception is needed during the menopause transition for sexually active ♀; consider progestin-only contraceptive (+ systemic estrogen if needed for VMS) or low-dose CHC (e.g. **LOLO**, **ALESSE**). ❸ Avoid CHCs for treatment of VMS in post-menopausal ♀, as the estrogen dose is ~3-6x higher vs MHT (see **Box 1**).[23] ❹ Measuring serum estradiol, estrone, or SHBG is not recommended as they do not correlate with menopausal symptoms.[NAMS '22]

Menopause Quick 6 (MQ6)

1. Any changes in your *periods*?
2. Are you having *hot flashes*?
3. Any *vaginal* dryness, pain or sexual concerns?
4. Any *bladder* issues or incontinence?
5. How is your *sleep*?
6. How is your *mood*?

Useful Links and Resources

For providers:
- SIGMA Pocket Guide
- MHT Counselling List
- Menopause Rating Scale

For patients:
- NAMS MenoNotes
- Gynaecology QI Collaboration
- SOGC Menopause & U

An Approach to Therapy [SOGC '21, NAMS '22] See page 10 for MQ6 Treatment Algorithm.

Genitourinary Symptoms (GSM)

1st line: vaginal moisturizers (regular administration [e.g. ~3x/wk] of **REPLENS**, **REPAGYN**, **GYNATROF**, etc.) See **page 3** for formulations.

2nd line: vaginal estrogen [allow 3 months for full benefit]; **1st line if** moderate to severe symptoms or recurrent UTIs. ↓ *GSM by ~60-80%.*[4]

Vasomotor Symptoms (VMS) (moderate to severe)

1st line: systemic menopause hormone therapy (MHT) if no contraindications. ↓ *VMS by ~70-95%.*[12,92] See **page 3** for formulations.

Start with low-moderate dose. Expect response in 2-6wks; titrate q4-8wks. Aim to ↓ VMS by ≥ 70% with few AEs. Use lowest effective dose.[1,5]

✓ Consider MHT

- Age <60yrs or <10yrs since LMP and low risk (no cautions or contraindications)

Discuss benefits & risks of MHT (see **Figures 1 & 2**).

? MHT Cautioned

- Moderate risk of CHD* and/or CV risk factors (smoking, HTN, DM, dyslipidemia, obesity) in ♀ age <60yrs or <10yrs since LMP
- Migraine with aura
- Hx of gallstones

→ **Consider transdermal estrogen.** *Expert opinion. Observational data suggest transdermal may ↓ risk of VTE (RR 0.61; 0.53-0.71), stroke (RR 0.81; 0.68-0.97) and gallstones (RR 0.79; 0.74-0.84) vs oral estrogen.* [NAMS '22, 20-22]

- Moderate risk of breast CA** in ♀ age <60yrs or <10yrs since LMP

→ **Consider non-hormonal tx.** *MHT 2nd line after individualized risk assessment.* [Expert opinion. NAMS '22, 69, 70]

- Age ≥60yrs and ≥10yrs since LMP

→ **Consider non-hormonal tx.** *MHT 2nd line after individualized risk assessment.* [Expert opinion. NAMS '22]

✕ MHT Contraindicated

- Unexplained vaginal bleeding
- Acute liver disease
- Clotting disorder (e.g. factor V Leiden)
- Hx of CHD (CAD, stroke, TIA, unprovoked VTE, PAD) or at high-risk of CHD*
- Personal hx of estrogen-dependent CA (breast, endometrial, ovarian) or at high-risk of breast CA**
- Moderate risk of CHD*/breast CA** and age ≥60yrs and ≥10yrs since LMP

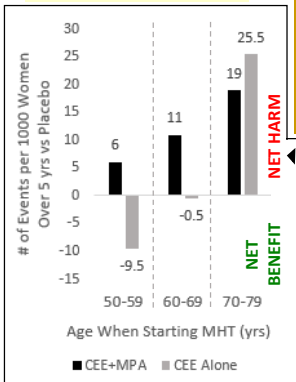


Figure 1. Global index by age group. Global index estimates net harm/ benefit. The index accounts for *CHD, breast CA, endometrial CA, stroke, PE, colorectal CA, hip fracture, and all-cause mortality*. Note: these subgroup analyses are not statistically significant.

~800 in every 1000 women on MHT will note ↓ VMS by ≥50%[12,15]

*Framingham Cardiovascular Risk Score (FRS) 10yr risk: low <10% | moderate 10-20% | high >20%
**Breast Cancer Risk Assessment Tool (BCRAT) 5yr risk: low <1.67% | moderate 1.67-5% | high >5%[76]
These risk calculators may support decision making but were not designed or validated for MHT.

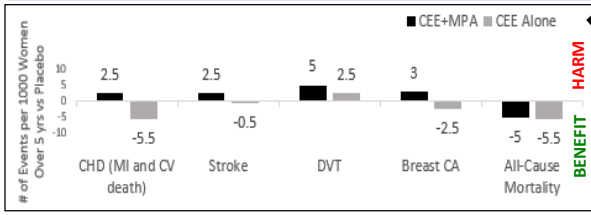


Figure 2. Benefits & Harms of MHT for ♀ aged 50-59 (subgroup analysis)[7] Data is from the WHI intervention phase (2013 analysis). Note: these subgroup analyses are not statistically significant; however, they are the best available estimates at present.

2nd line: non-hormonal therapy (**1st line if** contraindications to hormone therapy). See **page 4** for formulations.

Table 1. Specific Symptom Management.

Symptom	Consider:
GSM (vaginal dryness, irritation, urinary urgency, recurrent UTIs)	See **Approach to Therapy**.
VMS (hot flashes, night sweats)	See **Approach to Therapy**.
Sexual Concerns (↓ desire, ↓ arousal, dyspareunia, anorgasmia) See RxFiles Sexual Dysfunction	**↓desire:** psychotherapy; transdermal testosterone off-label; fibanserin; ?bupropion; MHT not proven helpful. **↓arousal:** psychotherapy; PDE5i off-label; pelvic physio. **Dyspareunia:** vaginal moisturizer/estrogen; pelvic physio; psychotherapy. **Anorgasmia:** psychotherapy; PDE5i off-label.[2]
Mood changes See RxFiles Depression / Anxiety	Same tx approach as MDD/anxiety. MHT may benefit peri- and early post-menopausal ♀ with low mood irrespective of VMS.[3,17,18]
Sleep Disturbances See RxFiles Sleep Disorders	Treat underlying cause (e.g. VMS, OAB, OSA). Sleep hygiene; CBT-I; aerobic exercise; medications (e.g. venlafaxine 75mg/day; gabapentin 300mg QHS); may try menopause herbal product (e.g. black cohosh 20mg/day; valerian root 530mg BID).[6] Link: RxFiles Sleep Diary.
↓ Memory / Concentration	↑ aerobic exercise and vegetable intake; MHT not proven helpful; possible role for ?lisdexamfetamine off-label.[6,19,73]

Box 1: When to Stop Contraception. [1, MQ6.ca, expert opinion]

- Lab tests (e.g. FSH) are typically not recommended, as they fluctuate in perimenopause and can be misleading. No lab test shows definitive loss of fertility.
- In ♀ ≥ 50yrs, stop hormonal contraceptive; use non-hormonal contraception and monitor return of menses/emergence of VMS. Continue non-hormonal contraception until amenorrhea for > 12mo.
- In ♀ ≥ 55yrs, stop contraceptive. Spontaneous conception very rare.

Box 2: Systemic MHT Treatment Adjustments. [1,11, NAMS '22, expert opinion]

- **Vaginal bleeding (e.g. breakthrough bleeding, prolonged menses on cyclical regimen, etc.):** May occur within first 6mo of MHT. Assess adherence; may ↓ estrogen dose; ↑ progestogen dose; switch to **DUAVIVE**; switch progestogen regimen (continuous → cyclical). Investigate AUB if new onset after 6mo on tx or if abnormal uterine bleeding persists > 6mo.
- **Breast pain:** ↓ estrogen dose; switch progestogen; switch to **DUAVIVE**.
- **Hot flashes persist:** assess adherence/medication administration; ↑ estrogen dose.
- **Mood changes, bloating, acne, drowsiness:** switch progestogen; switch progestogen regimen (cyclical ↔ continuous).
- **Headaches:** try transdermal estrogen; switch progestogen; switch progestogen regimen (cyclical → continuous).

Box 3: Duration of Therapy & Discontinuing MHT. [6-10,13, 74-75, expert opinion]

- Anticipate 3-5yrs of MHT for many; however, some ♀ may require shorter or longer durations. There is no set age at which MHT must be discontinued. Re-evaluate need for MHT annually and with any changes in health status.
- MHT can be stopped abruptly or tapered (VMS re-emergence rates similar irrespective of discontinuation method). If tapering: ↓ dose preferred over alternate day dosing due to MHT pharmacokinetics.
- Vaginal estrogen should be continued at the lowest effective dose for as long as benefit is noted (may be continued indefinitely). Discontinuation leads to the vaginal mucosa returning to a hypoestrogenic state.

AUB=abnormal uterine bleeding **CA**=cancer **CBTi**=cognitive behavioural therapy for insomnia **CEE**=conjugated equine estrogens **CHD**=coronary heart disease **CHC**=combined hormonal contraceptive **D/C**=discontinue **DM**=diabetes mellitus **E2**=estradiol-17β **FSH**=follicle stimulating hormone **GSM**=genitourinary syndrome of menopause **HA**=headache **hCG**=human chorionic gonadotropin **HTN**=hypertension **Hx**=history **IUD**=intrauterine device **LH**=luteinizing hormone **LMP**=last menstrual period **LT4**=levothyroxine **MA**=meta-analysis **MDD**=major depressive disorder **MHT**=menopause hormone therapy **MP**=micronized progesterone **MPA**=medroxyprogesterone acetate **NAMS**=North American Menopause Society **N/V**=nausea/vomiting **OAB**=overactive bladder **OSA**=obstructive sleep apnea **PAD**=peripheral artery disease **PDE5i**=phosphodiesterase inhibitor **PE**=pulmonary embolism **po**=oral **pt**=patient **RCT**=randomized controlled trial **SERM**=selective estrogen receptor modulator **SHBG**=sex hormone binding globulin **SOGC**=Society of Obs & Gyn of Canada **TIA**=transient ischemic attack **TSH**=thyroid stimulating hormone **tx**=therapy **VMS**=vasomotor symptoms **VTE**=venous thromboembolism **WHI**=Women's Health Initiative

MENOPAUSE: Menopause Hormone Therapy (MHT)

Alex Crawley BSP © www.RxFiles.ca/menopause Sept 2024

Genitourinary Symptoms = dyspareunia, vaginal dryness/discomfort, dysuria, urinary frequency/urgency, recurrent UTIs. Vaginal estrogen ↓ dryness/dyspareunia in 60-80% of patients;[4] moisturizers and lubricants ?similar benefit.[71,84]

Genitourinary Symptom Treatment

Generic / TRADE	Usual (Equivalent) Dose	Cost/30d	Comments
Vaginal Moisturizer OTC ✗ ⊗ **REPLENS** gel $16; **GYNATROF** gel $19; **REPAGYN** ovule $37	Apply vaginally HS 2-3x/ week	$16-37 [10 applications]	**First line** before estrogens for less severe genitourinary symptoms.[8] Use routinely (i.e. not just before sex). Some patients will prefer the viscosity of one agent over another (e.g. **GYNATROF** thicker than **REPLENS**).
Vaginal Lubricant OTC ✗ ⊗ e.g. **KY JELLY** gel $8	Apply vaginally PRN before sex	$5-10/tube	**First line** before estrogens for less severe genitourinary symptoms.[8] ?Option to apply regularly 2-3x/week.[71]
Vaginal Estrogen			
CREAM: **Conjugated equine estrogen PREMARIN** 0.625mg/g vaginal cream (rose-scented)	0.5-2g vaginally HS x 2 weeks, then ↓ to 1-3x per week	$10 ($34/30g)	
CREAM: **Estrone ESTRAGYN** 1mg/g vaginal cream (unscented)	0.5-2g vaginally HS x 2 weeks, then ↓ to 1-3x per week	$10 ($48/45g)	
RING: **Estradiol-17β ESTRING** 2mg vaginal ring (releases 7.5mcg/day) Note: USA **FEMRING** releases 50-100mcg/day for VMS	Insert 1 ring vaginally q 90 days	$32 ($96/ring)	
TAB / SOFTGEL: **Estradiol-17β VAGIFEM** 10mcg vag tab	1 tab vaginally HS x 2 weeks, then ↓ to 1-3x per week	$30-70	
TAB / SOFTGEL: **Estradiol-17β IMVEXXY** 4mcg, 10mcg softgel		$27-58	
Ospemifene OSPHENA 60mg tab ✗ ⊗	60mg po daily with food	$66	SERM; improves GSM 30-50%;[4] potential role for pts who desire oral tx. **AE**: ↑ hot flash, ?VTE. **DI**: 3A4.
Prasterone (DHEA) **INTAROSA** 6.5mg vaginal ovules ✗ ⊗	6.5mg vaginally HS	$58	Converted to estrogen + testosterone; improves GSM 40-80%;[4] unknown safety if breast CA hx. **AE**: vag discharge.

Which vaginal estrogen should I choose?

- → **Efficacy**: all are similar.[84] Creams have an initial advantage if severe vaginal atrophy/dryness, to help heal (may feel initial tingling). Creams can also be applied externally off-label (e.g. to clitoris, labia). Can be used at any age, during the menopause transition or post-menopause.
- → **Systemic exposure**: minimal for all options, but likely cream > tab ≈ ring.[52]
- → **Cost**: creams typically lowest cost (e.g. 1gram 2x/week ≈ $10/month on average).
- → **Convenience**: vaginal ring q3 months an advantage. Tab can be less messy than a cream.
- → Rose-scented **PREMARIN** can be irritating to vaginal mucosa for some patients.

- Vaginal estrogen does **not** appear to be associated with ↑ breast cancer, endometrial cancer, VTE, or CVD risk.[8,49] Guidelines suggest it can be used in breast cancer survivors with oncologist consultation.[NAMS'22]
- **IMVEXXY** manual admin (no applicator). • If vaginal tab expulsion, scheduled moisturizer can help tab adhere.
- Vaginal estrogen may ↓ recurrent UTIs (e.g. meta-analysis **NNT=7** in post-menopausal ♀ over 6-12 months).[72]

Vasomotor Symptoms = hot flashes, night sweats. Estrogens ↓ frequency and severity of symptoms by 70-95%;[92] all estrogens can be equally effective. Some evidence for mood/sleep benefit in perimenopause / early menopause.

Vasomotor Symptom Treatment

Systemic Estrogen

[**PREMARIN** 0.3mg ≈ **ESTRACE** 0.5mg ≈ **patch** 25mcg][85]

	Generic / TRADE	Initial & Max Dosing	Cost/30d
ORAL	**Conjugated equine estrogen PREMARIN** 0.3, 0.625, 1.25mg tab	**Initial**: 0.3-0.625mg po daily **Max**: 1.25mg po daily	$17-18 $18
ORAL	**Micronized Estradiol-17β ESTRACE, g** 0.5ᶜ, 1ᶜ, 2ᶜ mg tab	**Initial**: 0.5-1mg po daily **Max**: 2mg po daily	$10-13 $18
TRANSDERMAL PATCH	**Estradiol-17β** [matrix patch – can cut to ↓cost] ☎ ▼ **ESTRADOT** 25, 37.5, 50 g, 75 g, 100 g mcg/day patch **OESCLIM** 25, 50mcg/day patch	**Initial**: 25-50mcg 2x/wk (e.g. M&F) **Max**: 75-100mcg patch 2x/wk *ESTRADOT = smallest patch size*	$36-37 $39-40
TRANSDERMAL PATCH	**Estradiol 17β CLIMARA** [matrix patch – can cut] 25, 50, 75mcg/day patch ☎ ▼	**Initial**: 25-50mcg patch weekly **Max**: 75mcg patch weekly	$33-34 $36
TRANSDERMAL GEL	**Estradiol-17β DIVIGEL** ☎ ▼ 0.25, 0.5, 1mg gel sachets (0.1%) **DO NOT** apply to breast. **AVOID** skin-to-skin transfer.	**Initial**: 0.25mg [1 sachet] daily to right or left upper thigh (alternating) **Max**: 1mg [1 sachet] daily	$40 $40
TRANSDERMAL GEL	**Estradiol-17β ESTROGEL** 0.06% gel pump ☎ ▼	**Initial**: 1 pump [0.75mg estradiol] to one or both arms daily (wait 2 min before putting on clothes)	$56

Which systemic estrogen should I choose?

- Observational data suggests **transdermal** (gel & patch) may have ↓VTE risk, ↓gallbladder disease, ?improved sleep, & ?↑sex drive vs oral estrogen.[20-22] SK coverage ☎: intolerant to oral estrogen or fasting TG ≥4.5mmol/L.
- **Oral estradiol** may have ↓VTE risk vs conjugated equine estrogen.[93]

Estrogen Dosing

- **Lowest effective doses** will ↓vaginal bleeding, ↓breast tenderness, & ↑safety.[93] Often start low & if needed ↑ q4-8 weeks (if severe sx, option to start higher & trial ↓ in 4-8 wks).
- Following premature ovarian failure, high doses of estrogen are needed (e.g. start at full dose and continue until the average age of menopause).

± Progestogen

A **progestogen is required** for all ♀ with a uterus & on systemic estrogen to ↓ endometrial cancer.

	Generic / TRADE	Usual Dosing	Cost/30d
ORAL	**Medroxyprogesterone PROVERA, g** 2.5ᶜ, 5ᶜ, 10ᶜ mg tab	**If under the max estrogen dose**: 2.5mg po daily or cyclic: 5mg daily first 12-14 days each month **If on max estrogen dose**: 5mg po daily or cyclic: 10mg daily first 12-14 days each month	$9
ORAL	**Micronized progesterone PROMETRIUM, g** 100mg ☎ ▼ cap peanut oil in g Teva, Reddy, Auro. sunflower oil in **PROMETRIUM** & g PMS, Sanis.	**If under the max estrogen dose**: 100mg po HS or cyclic: 200mg HS first 12-14 days each month **If on max estrogen dose**: 200mg po HS or cyclic: 100mg po AM + 200mg po HS first 12-14 days each month	$18-30
IUD	**Levonorgestrel MIRENA** 52mg intrauterine device	**Off-label**: insert q5yrs.[50,51,87] Extended intervals unstudied. (Approved in Europe for women on any estrogen dose.)	$7 ($400 up front)

Which progestogen should I choose?

- Micronized progesterone **PROMETRIUM** ↑drowsiness and may ?↓VTE, ?↓CV , ?↓breast cancer risk vs medroxyprogesterone.[NAMS'22, 93, 102-104]
- **MIRENA** useful if oral progestogen not tolerated/inconvenient, contraception desired, or to help reduce heavy bleeding in perimenopause.

Continuous or cyclical progestogen?

- **Continuous dosing** avoids withdrawal bleed & often results in amenorrhea after 12 months → often preferred if last menstrual period >1yr prior. Switch to cyclic dosing if breakthrough bleeding persists throughout first 6 months.
- **Cyclic dosing** causes a monthly withdrawal bleed → useful during the menopause transition as helps reduce breakthrough bleeding. If heavy/erratic bleeding, ↑dose or switch to continuous.

Combination Therapies (for patients with an intact uterus)

	Generic / TRADE	Strength	Usual Dose	Cost/30d	Comments
ORAL	**Estradiol-17β + micronized progesterone BIJUVA**	1/100mg cap	1/100mg po HS	$40	• Less flexibility with titrating/tapering doses vs individual products. • **DUAVIVE** (🇺🇸 **USA**: DUAVEE): Bazedoxifene is a tissue selective estrogen complex (TSEC). No progestogen needed; risk of endometrial cancer mitigated by TSEC. Useful if breast tenderness or if progestogen not tolerated.
ORAL	**Estradiol-17β + drospirenone ANGELIQ**	1/1mg tab ✗ ⊗	1 tab po daily	$31	
ORAL	**Estradiol-17β + norethindrone ACTIVELLE**	1/0.5mg tab, 0.5/0.1mg **LD** tab ✗ ⊗	1/0.5mg po daily	$97	
ORAL	**Bazedoxifene + conjugated estrogen DUAVIVE**	20/0.45mg tab ✗ ⊗	1 tab po daily	$115	
PATCH	**Estradiol-17β + norethindrone ESTALIS**	50/140mcg, 50/250mcg patch ☎ ▼	1 patch twice/week	$43	• Matrix patch, but avoid cutting as unstudied if adequate progestogen protection.

Tibolone TIBELLA ✗ ⊗ 2.5mg tab daily $118/30d; synthetic steroid for ♀ with intact uterus; does not require addition of progestogen; ↓efficacy vs estrogen + progestogen; ↑bone mineral density; amenorrhea 71%. **AE**: ↑stroke, ↑recurrent breast cancer in pts with a history of breast cancer,[96,139] ?↑endometrial cancer, hair growth, acne, breast tenderness, ↑weight. **DI**: 3A4.

Testosterone: Not helpful for vasomotor sx. **Off label**: may ↑ desire/libido/arousal[94] e.g. 1% gel **ANDROGEL** ½ pump applied on posterior calf (≈1/10 male dose); $37.6 **AE**: ↑ weight, acne, hair growth **NNH=10**.[95] Lacks long-term safety data.

MENOPAUSE: Non-Hormonal Therapy for Vasomotor Symptoms (VMS) — Taisa Trischuk PHARMD © www.RxFiles.ca/menopause Sept 2024

Note: Non-hormonal therapy options have no effect on genitourinary syndrome of menopause (GSM); for GSM therapy options see MHT drug comparison chart.

Lifestyle Modifications for Vasomotor Symptoms: SOGC'21, NAMS'23

***Demonstrated efficacy for VMS**: Mostly small, short-term RCT data.*

Cognitive Behavioural Therapy (CBT) *See 2023 patient info sheet: CBT for Menopause Symptoms*	Behavioural & psychological interventions ↓ **severity** of bothersome VMS **but not frequency**.[27]	Effective for decreasing the impact (bother) of VMS and associated sleep disturbances: • **MENOS1** (6 CBT group sessions) & **MENOS2** (4 CBT group sessions or self-guided CBT) showed a clinically significant improvement of troublesome VMS in 65-78% of women vs placebo.[55,56] • **CBT-Meno** sessions (psychoeducation and CBT strategies) vs waitlist: ↓ self-reported VMS, sleep, depressive symptoms and sexual concerns after 3 months.[57] • Telephone-based CBT for insomnia (CBTi): 6 sessions over 8 weeks, resulted in a clinically meaningful insomnia score reduction vs standard menopause education control groups. ➔ CBTi ↓ hot flash bother but not frequency.[25] CBTi is the most effective treatment for insomnia in perimenopause and post-menopause.[1] See: U of S Sleep Clinic: Medication Assessment Centre.
Mindfulness		• Mindfulness-based stress reduction RCT (n=110): ↓ bother from hot flashes over 3 months, but did not affect frequency and severity.[26] Limited by need for intensive training.
Hypnosis	Limited evidence with varying procedures. May be effective for short term ↓ VMS: two small RCTs that studied hypnosis over 5 weeks showed a ↓ hot flash severity and frequency.[59,60]	
Weight Loss	Obesity is associated with ↑ VMS. Weight loss from behavioural interventions may ↓ VMS, with ↓ hot flashes a major motivator for weight loss; this effect was greater earlier in the menopausal transition.[61,62]	

***Insufficient supporting evidence for VMS**, but reasonable to recommend:*		***No evidence of efficacy for VMS**, but have health benefits:*
Cooling Techniques	Wearing breathable and layered clothing, utilizing fans, using cold packs under pillow.	**Physical activity** (see RxFiles: Activity Rx; weight bearing exercise can help maintain muscle mass & ↓ OP), **yoga**, **dietary modification**, **paced respiration**, **relaxation**, **acupuncture**, and **smoking cessation** (smoking can ↑ VMS).
Avoiding Triggers	Limiting alcohol, caffeine, spicy/hot foods, and stressful situations. Consider using diary.	

Prescription Options for Vasomotor Symptoms: SOGC'21, NAMS'23

May be considered for those who are not candidates for MHT (i.e. contraindicated) or those with a preference for non-hormonal options. All non-hormonal prescription options are less effective than MHT; few trials have been published and generalizability is limited. There are no head-to-head trials of these agents, and efficacy is confounded by the large placebo effect (which can ↓ hot flashes 20-50%).[28,77] Potential side effects may restrict use for some women. When choosing therapy, consider comorbidities such as depression, insomnia, neuropathy, and urinary incontinence.

	Generic Name; TRADE Name	Dosing for VMS	$/30d	Adverse Events AE Drug Interactions DI	Efficacy for VMS vs placebo	Evidence & Comments Start low and titrate to ↓ AE. Review need for therapy annually.
SSRI	**Paroxetine** PAXIL, g USA: 7.5mg cap HS BRISDELLE	10-20mg po daily	$20	See Rxfiles: Antidepressants, pg 178 • AE: nausea, HA, drowsiness, dizziness, dry mouth, ↓ libido, (SNRI ↑ AE vs SSRI). • DI: paroxetine & fluoxetine: ↓ tamoxifen levels due to CYP2D6 inhibition (contraindicated).	SSRI/SNRI **↓ by 27-65%** composite of hot flash severity & frequency.[4,28] Often onset in days (vs weeks for depression).[31]	• Low doses often sufficient, higher than studied doses unlikely to offer further VMS reduction benefits. • If one SSRI/SNRI is ineffective or not tolerated, another SSRI/SNRI with evidence of efficacy can be tried before moving onto another class of medication. May also improve mood and/or sleep. • Fluoxetine & sertraline: Not usually recommended as no difference vs placebo for hot flash efficacy.[28] • Paroxetine: Most well studied; **↓ VMS by ~40-65%**.[4,29] Discontinue slowly to avoid withdrawal sx. • Escitalopram: Reasonable to initiate at 5mg/day, but this dose is not studied for VMS efficacy.[NAMS'23] • Venlafaxine: **↓ VMS by ~40-65%**.[4] 37.5mg daily improved VMS in ~1 wk; 75mg daily improved sleep.[29,30] 1st line non-hormonal in breast CA pts,[SOGC'21] due to superiority vs gabapentin.[91] D/C slowly to ↓withdrawal. • Duloxetine 60mg:↓ VMS similar to escitalopram 20mg; but small, short term RCT (12 weeks).[82]
SSRI	**Citalopram** CELEXA, g	10-20mg po daily	$14			
SSRI	**Escitalopram** CIPRALEX, g	10-20mg po daily; See comments.	$20			
SNRI	**Venlafaxine** EFFEXOR XR, g	37.5-75mg po daily	$15			
SNRI	**Desvenlafaxine** PRISTIQ ER, g ✗ ⊗	100-150mg po daily	$92			
Gabapentinoid	**Gabapentin** NEURONTIN, g	Initiate 100-300mg HS, ↑ 100mg q3-4 days up to 900mg HS.[SOGC'21]	$13-15	See RxFiles: Seizures, pg 164 • AE: dizziness, drowsiness. • DI: ↑ risk of respiratory depression with opioids.[42]	Gabapentin **↓ by 45-71%** hot flash frequency;[34,35] onset within 1 week.[35]	• Gabapentin: Useful if hot flashes causing insomnia or night awakenings, as HS dosing can cause drowsiness and facilitate return to sleep. AE most pronounced during first 1-2 weeks, improves within 4 weeks.[34,36] Dosing up to 900mg/d used in clinical trials,[83] but titrate to lowest effective dose. • Pregabalin: Not generally recommended due to limited evidence (one 6 week RCT).[37,NAMS 2023]
Gabapentinoid	**Pregabalin** LYRICA, g	150-300mg po HS	$24			
Other	**Oxybutynin** DITROPAN, g	2.5-5mg po BID	$14	• AE: dry mouth 52%,[39] GI upset, constipation, blurred vision.	**↓ by 60-77%** hot flash frequency, onset ~1 wk.[40]	• Oxybutynin: Small RCTs show efficacy over 6 and 12 weeks.[39,40] AE common (e.g. anticholinergic); observational data suggests concerns about cognitive decline in older women.[41]
Other	**Clonidine** CATAPRES, g	0.025-0.05mg po BID	$15	• AE: dizziness, dry mouth, hypotension, sedation, HA.	**↓ by 20-40%;**[4] limited evidence; mixed results.	• Clonidine: Not generally recommended due to AE & less effective than SSRI, SNRI, and gabapentin for relief of VMS.[28,38, SOGC'21, NAMS'23] Discontinue slowly to avoid withdrawal symptoms.

USA: **Fezolinetant** VEOZAH ✗ ⊗ 45mg po daily; neurokinin 3 (NK3) receptor antagonist; FDA approved for moderate to severe VMS; ↓ VMS ~60% over 12 weeks.[SKYLIGHT-1 (Phase 3)] AE: abdominal pain, diarrhea, insomnia. DI: CYP1A2.

Herbal Products for Vasomotor Symptoms:

There is insufficient efficacy and safety evidence to support the use of herbal products for VMS due to inconsistent trial results.[NAMS'23, SOGC'21] All herbal products are less effective than MHT, with uncertain dosing and many drug interactions. Systematic reviews have not found any herbal products to be effective for moderate to severe hot flashes.[78] Lack of regulation of compounded products may be a concern (e.g. purity, consistency). The herbal products below have limited, weak evidence (small size, poor study designs, short duration and mild patient symptoms); see online extras 💻 for more info.

Common Name	Dosing for VMS	$/30d	Adverse Events AE / Drug Interactions DI	Efficacy for VMS	Evidence & Comments	
Soy isoflavones (phytoestrogens) [Some ♀ unable to metabolize to active metabolite **S-equol**.]	15-60g po daily soy protein[86] (≈34-100mg of soy isoflavones)	Many products ~$20	• AE: diarrhea, constipation, bloating, flatulence, nausea. • DI: ↑ effect of theophylline; ↓ effect of LT4. ?May ↓ effect of estrogen, tamoxifen, & warfarin.[86]	Mixed results and variable effects on VMS.[43-45,SOGC'21]	Isoflavones have both estrogen agonist and estrogen antagonist properties.[SOGC'21] ?Avoid in hormone sensitive conditions (i.e. breast, uterine and ovarian CA).	Many trials but evidence inconclusive; limitations: variation of interventions, small sample sizes, varying outcomes and short term (~12 week). Supplements containing ↑ proportions of genistein may ↓VMS frequency vs placebo, further investigation needed.[48] Food sources may be preferred: 3 cups soy milk=18-27g soy protein; 300g tofu=24-42g soy protein.
Soy metabolite equol USA: EQUELLE	10mg-30mg po daily[47]	USA only		MA suggests ↓ VMS frequency, but limitations.[47]		Limitations of MA: Combining data difficult due to small trial sizes (i.e. ≤50 patients/group); variability in methods, outcomes, dosage, dietary soy intakes and equol-producer status.[47]
Black cohosh (Actaea racemosa) REMIFEMIN, NUFEM, g	20mg po BID[46] 20mg/d may improve sleep.[6]	$40	• AE: breast tenderness, dizziness, GI upset, headache, irritability, rash, ?hepatotoxicity.[79]	Not recommended; likely no better than placebo.[SOGC'21, NAMS'23]	A Cochrane review (N=16 RCTs) showed no difference in frequency of VMS vs placebo after 23 weeks.[46] No conclusive evidence for ↓ frequency and severity of VMS. Active ingredients unknown and mechanism of action unclear: possible activity similar to SERM or modulation of serotonergic pathways, and antioxidant or anti-inflammatory effects.[SOGC'21,NAMS'23]	
Siberian Rhubarb (ERr 731)	4mg po daily[88]	$40	• AE: diarrhea, GI upset, N/V.	Has estrogenic properties. May ↓ VMS after 12 weeks; conclusions limited due to low retention rate in small RCT[89] and open-label design in another study.[90]		

The following have **insufficient efficacy data** to recommend as treatment for VMS: red clover, flaxseed, chasteberry, milk thistle, wild yam, crinum, dong quai root, evening primrose oil, ginseng, pollen extract, hops, maca, omega-3 fatty acid, vitamin E, cannabinoids, pine bark, puerpuria, and labisia pumila/eurycoma longifolia.[NAMS'23, SOGC'21]

Efficacy and Safety of Menopause Hormone Therapy (MHT): Trial Evidence Summary

Taisa Trischuk PHARMD, Jessica Visentin PHARMD © www.RxFiles.ca Oct 2023

Benefit | Possible Benefit | No difference/Neutral | Possible Harm | Harm | No evidence/unknown

Benefits and Harms of Systemic MHT (Oral and Transdermal): For available products see MHT drug comparison chart; see online extras for expanded evidence summary.

Outcome Measure	Oral Estrogen (E) + Progestogen (P) Combination MHT Dose studied in WHI trial: **CEE 0.625mg + MPA 2.5mg po daily** Population: post-menopausal women with a uterus; ~**63 years old**	Oral Estrogen (E) Alone MHT Dose Studied in WHI trial: **CEE 0.625mg po daily** Population: post-menopausal women without a uterus; ~**64 years old**	Risk estimate** of using Oral MHT *for 5 years* at age 50-59[3] CEE + MPA	 CEE alone	Differences in Type of Estrogen (E) or Progestogen (P)	Route of Administration (Transdermal vs Oral)
Moderate to Severe Vasomotor Symptoms (VMS)	Most effective, 1st line treatment of VMS.[SOGC 2021, NAMS 2022] Oral MHT vs placebo: ↓ **weekly frequency of hot flashes by 75% and ↓ symptom severity: OR 0.13 (0.07-0.23)**.[4] MP monotherapy is not approved for management of VMS.[HC] Limited evidence suggests high dose MP (300 mg daily) may ↓ frequency of hot flashes, but ↑ AE vs combination E + P.[5] No long-term studies have assessed the safety of progestogen-only treatment.[2,6]		VMS efficacy was not studied as an outcome measure in the WHI trials. See limitations at bottom of page.		No evidence for superiority of one type of estrogen or progestogen over another.[NAMS 2022, 7,8]	Systemic formulations are similarly effective.[2,7,9] Oral CEE and transdermal E2 were **70-95% effective at ↓ hot flashes**.[10]
Breast Cancer *See RxFiles VMS Infographic: "Comparing Breast Cancer Risks"	CEE + MPA ↑ risk of breast CA during the intervention phase: **NNH=196**/5.2 yrs, which persisted ~8 years after discontinuing CEE + MPA.[WHI 2013] **WHI** 20 year follow-up after using MHT for ~5 years: **↑ 1.4-2.0 breast CA cases/100 women over 20 yrs**, but had no effect on breast CA mortality during this follow-up.[WHI 2020,8,13]	CEE alone did not affect the incidence of breast CA during the intervention phase.[WHI 2013] **WHI** 20 year follow-up after using MHT for ~5-7 year: **↓ 1.4 breast CA cases/100 women over 20 yrs**;[WHI 2020] however, observational data estimates **↑ 0.5 breast CA cases/100 women over 20 yrs**.[8,13] Differences may be due to different E used, older age in **WHI** trials or ↑ mammographic screening in observational studies.[8]	**↑ 3 events per 1000 women**	**↓ 2.5 events per 1000 women**	Observational data suggests MP may ↓ risk of breast CA vs MPA (OR 0.99 vs 1.28).[NAMS 2022,14,15] However, other observational data have found no difference in risk.[NAMS 2022,13] Cyclic P may have a small ↓ risk of breast CA vs continuous P (RR 1.93 vs 2.30).[13]	Observational studies have found no significant differences in risk of breast CA between formulations.[15,16]
Coronary Heart Disease (CHD= Non-fatal MI + CHD death)	CEE + MPA did not affect the incidence of CHD during the intervention phase or cumulative 13 year follow-up.[WHI 2013]	CEE alone did not affect the incidence of CHD during the intervention phase or cumulative 13 year follow-up.[WHI 2013]	**↑ 2.5 events per 1000 women**	**↓ 5.5 events per 1000 women**	MP preferred over MPA in patients with elevated CV risk, due to less negative effects on metabolic parameters such as blood pressure and triglycerides.[18,23,24]	Transdermal E may theoretically ↓ CHD risk due to less negative effects on biomarkers of CV risk (e.g. lipids, coagulation & inflammatory factors).[8,25,26]
	A Cochrane review suggests MHT initiated within 10 years of menopause ↓ risk of CHD: **NNT=125**, with no effect on CHD when initiated >10 years after menopause.[19] Due to data limitations, these findings are only hypothesis generating (i.e. help support the timing hypothesis).					
Venous Thrombo-embolism (VTE)	CEE + MPA ↑ risk of DVT: **NNH=147**/5.2 yrs and PE: **NNH=196**/5.2 yrs during the intervention phase; ~8 years after discontinuing CEE + MPA, DVT risk persisted but PE risk did not persist.[WHI 2013]	CEE alone ↑ risk of DVT during the intervention phase: **NNH=196**/6.8 yrs, this risk did not persist ~6.5 years after discontinuing CEE. CEE alone did not affect the incidence of PE.[WHI 2013]	**DVT (PE): ↑ 5 (3) events per 1000 women**	**DVT (PE): ↑ 2.5 (1.5) events per 1000 women**	Observational data suggests that oral estradiol may ↓ VTE risk vs CEE (RR 0.83; 0.76-1.91);[25,29] and MP may be less thrombogenic vs other synthetic P (OR 0.7 vs 3.9).[25,30]	Observational data suggests transdermal E may ↓ VTE risk vs oral E (RR 0.61; 0.53-0.71).[SOGC'21,NAMS'22, 25,29-34]
	A Cochrane review suggests MHT initiated within 10 years of menopause ↑ risk of VTE: **NNH=146**, and MHT initiated >10 years after menopause ↑ risk of VTE: **NNH=101**.[19] VTE risk appears highest in the first year of treatment.[28]					
Stroke	CEE + MPA ↑ risk of stroke during the intervention phase: **NNH=192**/5.2 yrs; this risk did not persist ~8 years after discontinuing CEE + MPA.[WHI 2013]	CEE alone ↑ risk of stroke during the intervention phase: **NNH=127**/5.2 yrs; this risk did not persist ~6.5 yrs after discontinuing CEE.[WHI 2013]	**↑ 2.5 events per 1000 women**	**↓ 0.5 events per 1000 women**	Insufficient evidence.	Observational data suggests transdermal E may ↓ stroke risk vs oral E (RR 0.81; 0.68-0.97).[1,2,25,31,33,35,36]
	A Cochrane review suggests MHT initiated within 10 years of menopause shows no effect on the incidence of stroke, and MHT initiated >10 years after menopause ↑ risk of stroke: **NNH=102**.[19]					
All-Cause Mortality	CEE + MPA and CEE alone did not affect all-cause mortality over ~5-7 yrs of use;[WHI 2013] this neutral effect remained after 18 years cumulative follow-up.[WHI 2017] A Cochrane review suggests MHT initiated within 10 years of menopause ↓ risk of all-cause mortality: **NNT=167**, with no effect on mortality when initiated >10 years after menopause.[19] This subgroup analysis suggesting possible mortality benefit when MHT is initiated early is only hypothesis generating.		**↓ 5 events per 1000 women**	**↓ 5.5 events per 1000 women**	Insufficient evidence.	Insufficient evidence.
Fracture See RxFiles chart: Osteoporosis Treatment.	CEE + MPA ↓ risk of hip fractures: **NNT=322**/5.2 yrs, vertebral fractures: **NNT=333**/5.2 yrs, and all fractures: **NNT=40**/5.2 yrs.[WHI 2013]	CEE alone ↓ risk of hip fractures: **NNT=217**/6.8 yrs, vertebral fractures: **NNT=217**/6.8 yrs, and all fractures: **NNT=26**/6.8 yrs.[WHI 2013]	**↓ 12 events per 1000 women**	**↓ 8 events per 1000 women**	No difference in ↓ fracture risk between all MHT regimens, dose of E, type of E or P used or cyclic vs continuous dosing.[Million Womens Study 2004]	Weak heterogeneity between formulations; differences unlikely to be clinically significant.[Million Womens Study 2004]
	All types of systemic MHT, while using, offer protection against fractures. Fracture benefit disappears after stopping MHT;[37] incidence rates return to baseline within ~1 year of stopping use.[Million Womens Study 2004]					

Extrapolation of **WHI intervention phase data.[WHI 2013] Note: The **WHI** trials were not powered for age-related subset analyses, so the stated absolute risks are best estimates and are not statistically significant.

Limitations of Women's Health Initiative (WHI) trials: The **WHI** trials were designed to address the benefits and harms of long-term hormone therapy for the prevention of chronic diseases in post-menopausal women. Generalizability to younger women with distressing VMS is somewhat limited because 2/3 of enrollment was >60 yrs old and many patients were not experiencing bothersome VMS. In addition, oral CEE ± MPA are the only hormonal treatments for which clinical trials have been designed and sufficiently powered to examine CV events, VTE, and breast cancer risk. Evidence for the safety and effectiveness of other MHT doses, formulations, regimens, and delivery methods is limited, thus guidelines often recommend using lowest effective dose and reviewing annually.

Efficacy and Safety of Menopause Hormone Therapy (MHT): Trial Evidence Summary

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Benefit | Possible Benefit | No difference/Neutral | Possible Harm | Harm | No evidence/unknown

Benefits and Harms of Systemic MHT: Other Outcomes to Consider. For available products see MHT drug comparison chart; see online extras 💻 for expanded evidence summary.	
Sleep 40-60% of women experience major sleep difficulties during the menopause transition.[8]	CBTi is the most effective treatment for insomnia during perimenopause and post-menopause.[8] See CBTi resource: U of S Sleep Clinic: Medication Assessment Centre. MHT ↑ sleep quality and satisfaction in women with bothersome VMS.[NAMS 2022,8,39] Limited evidence suggests MHT may also improve sleep independent of VMS.[NAMS 2022,39,40] E alone is less effective at improving sleep vs E + P regimens.[41] One small RCT (n=8) suggests that high dose MP monotherapy (300mg QHS) may improve sleep quality in post-menopause without VMS,[42] but further research is needed to confirm these findings. MP may improve sleep more than MPA.[8,39,41,43] Transdermal estradiol may improve sleep more than oral estradiol.[8,39,41] See RxFiles Chart: Sleep Disorders.
Cognition and Dementia Natural decline initially, but often improves after the menopause transition.[8]	E + P in perimenopause and early post-menopause appears to have neutral effects on cognitive function.[WHIMSY, KEEPS-Cog,NAMS 2022,46,47] E alone appears to have neutral effects on cognitive function, irrespective of age at initiation.[WHIMSY,NAMS 2022,47] There is no evidence to suggest benefit of early MHT initiation (within 6 years of LMP) to prevent cognitive decline.[46] E + P may ↑ risk of dementia when initiated in post-menopausal women ≥65 yrs (HR 2.05; 1.21-3.48, **NNH=114**/4 years).[WHIMS] Observational data suggests small ↑ risk of Alzheimer's Disease in long duration users for >10 yrs (OR 1.19; 1.06-1.33).[49] Another observational trial demonstrated a significant association between dementia and use of MHT in patients aged 50-60 years (HR 1.24; 1.17-1.33), although further investigation is needed to confirm causation.[50] See RxFiles Chart: Dementia.
Mood Perimenopause has a 3 fold ↑ risk of depressive events regardless of history[59] & ↑recurrences in those with a history of depression.[51]	Data on combination E + P for the treatment of depression are sparse and inconclusive.[NAMS 2022,51] Perimenopause and early post-menopause: Several small RCTs have demonstrated E2 alone (oral and transdermal) is effective for depressive disorders; effects were similar to classic antidepressants, irrespective of the presence of VMS.[SOGC 2021, NAMS 2022,8,47,51-55] One large RCT suggests women without depression or with mild to moderate depressive symptoms at baseline may benefit from oral MHT.[45] Early evidence suggests transdermal E2 + cyclical MP may prevent depressive symptoms in euthymic perimenopausal women, but further research is needed to confirm these findings.[51,56] Late post-menopause: Small RCTs suggest estrogen therapy is ineffective in treating depressive disorders.[SOGC 2021, NAMS 2022,8,47,51,57,58] See RxFiles Chart: Antidepressants.
Sexual Drive	Largely neutral effect. In a Cochrane review, MHT was found to reduce sexual pain but not directly augment sexual desire.[60] In another Cochrane review, estrogen alone slightly improved sexual function score (lubrication, pain and satisfaction) vs placebo, while E + P had uncertain effect.[61,62] Transdermal products may be preferred for women with low libido given that oral estrogen increases sex hormone binding globulin and reduces bioavailability of testosterone.[NAMS 2022] Testosterone is off label for treatment of hypoactive sexual desire. See RxFiles Chart: Testosterone.
Type 2 Diabetes Mellitus	CEE + MPA (**NNT=134**/5.2 yrs) and CEE alone (**NNT=80**/6.8 yrs) ↓ self-reported T2DM during the intervention phases of the **WHI** trials; this effect was attenuated after cumulative 13 yr follow-up when the active intervention was discontinued.[WHI 2013] A meta-analysis (N=107 RCTs, n=33,315 women) also suggests ↓ risk of T2DM with MHT use, although type of estrogen or progesterone studied not specified. This meta-analysis was not designed to determine if the ↓ risk of T2DM translates into clinical CV outcome benefits.[63] MHT should not be initiated solely for management of T2DM.
Weight	Oral and transdermal MHT have not been shown to affect weight in menopausal women, but they have been shown to ↓ visceral fat and ↑ lean body mass.[8,64,65]
Quality of Life	CEE + MPA was associated with a small but statistically significant benefit for several measures of QoL (physical functioning, role physical, bodily pain, and general health), and neutral results for other measures at 1 year.[WHI 2013]
Gallbladder Disease	CEE + MPA (**NNH=43**/5.2 yrs) and CEE alone (**NNH=34**/6.8 yrs) ↑ self-reported gallbladder disease during the intervention phase of the **WHI** trials.[WHI 2013] CEE may slightly ↑ risk of gallbladder disease vs oral estradiol.[66] Observational studies show a lower risk of gallstones with transdermal estrogens (RR 0.79; 0.74-0.84) vs oral estrogen.[66] In the event of gallstone disease, oral E may be switched to a non-oral route, although no RCT data is available to support this.[NAMS 2022]
Colorectal Cancer	CEE + MPA ↓ risk of colorectal cancer during the intervention phase of the **WHI** trial: **NNT=294**/5.2 yrs, this effect was attenuated after ~8 years of follow-up when the active intervention was discontinued.[WHI 2013] CEE alone did not affect the incidence of colorectal cancer during the intervention phase or cumulative 13 year follow-up of the **WHI** trial.[WHI 2013]
Urinary Incontinence	CEE + MPA (**NNH=24**/5.2 yrs) and CEE alone (**NNH=19**/6.8 yrs) ↑ self-reported urinary incontinence (at least once/week) during the intervention phase of the **WHI** trials. This effect was decreased, but still statistically significant after 13 year follow-up when the active intervention was discontinued.[WHI 2013] See RxFiles Chart: Treatment of Urinary Incontinence.

Benefits and Harms of VAGINAL ESTROGEN (cream, tablet and ring): For available products see MHT drug comparison chart. Note: Before initiating vaginal estrogen therapy, genitourinary syndrome of menopause (GSM) should be confirmed via physical exam to rule out other causes and/or vaginal/endometrial risk factors.[expert opinion]	
Efficacy	Treatment of moderate to severe GSM, with preference for low-dose vaginal estrogen therapy. 1st line management includes vaginal lubricants and moisturizers, especially if vaginal dryness or dyspareunia.[SOGC 2021, NAMS 2020] Treatment of GSM: All intravaginal estrogens are equally effective, improving GSM by ~60-80%.[47] Adequate vaginal estrogen therapy restores the normal vaginal acidic pH and microflora, thickens the epithelium, increases vaginal secretions, and decreases vaginal dryness and dyspareunia.[67] • A Cochrane review (N=30 RCTs) reported **vaginal estrogen as 12x more likely to improve vaginal symptoms** (OR=12) vs placebo.[68] Beneficial effects can be seen within 2-4 weeks, with full effect after 3 months.[expert opinion] • With initial administration of a low-dose vaginal estrogen, there may be some systemic absorption of estrogen due to the thin, atrophied vaginal lining more readily absorbing estradiol. As a result, vaginal estrogen treatment may decrease VMS initially, as well as ↑AE (e.g. breast tenderness, vaginal bleeding).[NAMS 2020] With continued use of vaginal estrogen, the vaginal wall undergoes "estrogenization" and thickening, resulting in less systemic absorption over time.[69] • Overall, systemic absorption with low-dose vaginal preparations generally remains within the normal post-menopausal range.[NAMS 2020] See Menopause FAQ, for information on systemic absorption of vaginal products. • Vaginal estrogen may reduce the risk of recurrent UTIs vs placebo in post-menopausal women; RR=0.42 (0.30-0.59), **NNT=7** over 6-12 months.[78] Oral estrogen was not effective at reducing recurrent UTIs vs placebo.[72,78]

Safety	• There are no long-term RCTs evaluating the safety of vaginal estrogen, however, observational data has not shown any increased risk of breast or endometrial cancer, CHD, stroke or VTE: [NAMS 2020,13,73]
	  • A long-term (18 year), prospective cohort study (n=54,000) of post-menopausal women using vaginal estrogen in the **Nurses' Health Study**, showed no increased risk of CVD (MI, stroke and VTE), hip fracture or cancer (invasive, breast, endometrial, ovarian and colorectal).[NAMS 2020,74]
	  • The **WHI** Observational Study, a prospective cohort study (n=45,000, median follow-up 7.2 years) examining the risks of post-menopausal women who used vaginal estrogen, did not show an increased risk of breast cancer, VTE or CV risk.[75]
	• A 2016 Cochrane review (N=30 RCTs) and 2020 systematic review (N=15) of randomized and non-randomized trials did not show any increase in endometrial hyperplasia or endometrial cancer after 1 year of therapy.[68,76]
	• Low-dose vaginal estrogens can be considered in breast cancer survivors in consultation with their oncologist; clinical trials are ongoing to establish safety in those taking aromatase inhibitors.[77] See Menopause FAQ.
	• Adverse events are uncommon. Vaginal estrogens are contraindicated if unexplained vaginal bleeding occurs, and this should be investigated.[NAMS 2020]
	Note: Despite overwhelming safety data, vaginal estrogen products currently have the same black box warnings as systemic MHT. Inform patients to avoid unnecessary concern if reading the product monograph.[expert opinion]

AE=adverse events **BP**=blood pressure **CA**=cancer **CBTi**=cognitive behavioral therapy for insomnia **CEE**=conjugated equine estrogen **CHD**=coronary heart disease **CIMT**=carotid artery intima-media thickness **CRC**=colorectal cancer **CV**=cardiovascular **CVD**=cardiovascular disease **DVT**=deep vein thrombosis **E**=estrogen **E2**=estradiol-17β **GSM**=genitourinary syndrome of menopause **HR**=hazard ratio **LMP**=last menstrual period **MA**=meta-analysis **MHT**=menopause hormone therapy **MI**=myocardial infarction **MP**=micronized progesterone **MPA**=medroxyprogesterone acetate **NETA**=norethisterone acetate **NNH**=number needed to harm **NNT**=number needed to treat **OR**=odds ratio **P**=progestogen **PE**=pulmonary embolism **po**=oral **QoL**=quality of life **RCT**=randomized controlled trial **RH**=relative hazard **RR**=relative risk **SE**=summary estimate **SR**=systematic review **TG**=triglycerides **TIA**=transient ischemic attack **UTI**=urinary tract infection **VMS**=vasomotor symptoms **VTE**=venous thromboembolism **WHI**=Women's Health Initiative

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The Menopause Transition & Post-Menopause FAQs

Vaginal Estrogen for the Treatment of Genitourinary Syndrome of Menopause (GSM)

1. What is the vaginal estrogen safety data and why is there a FDA black box warning for vaginal estrogen?

Despite overwhelming safety data, low-dose vaginal estrogen products (e.g. **VAGIFEM** 10mcg, **ESTRING Ring** 2mg, **PREMARIN Cream** or **ESTRAGYN Cream** ≤1g/d) currently have the same FDA mandated black box warning as systemic estrogen products. The product monograph for vaginal estrogen notes risks associated with systemic hormone therapy (i.e. oral CEE ± MPA),[WHI 2013] including CHD, stroke, VTE, breast cancer and endometrial cancer.[FDA 2003, NAMS 2020] However, these risks are negligible when using low-dose vaginal estrogen due to minimal systemic absorption and reassuring findings from clinical trials and observational studies.[NAMS 2020] Clinicians can proactively inform patients about the warning's **inapplicability** when prescribing vaginal estrogen to avoid unnecessary alarm.

The safety of vaginal estrogen is supported by the following data and guideline recommendations:

- Clinical guidelines no longer recommend using high-dose, cyclic vaginal estrogen regimens. In women with a uterus, progestogens are not indicated for endometrial protection when using low-dose vaginal estrogen products, as clinically significant hormone absorption does not occur.[SOGC 2021]
    - A 2016 Cochrane review (N=30 RCTs, n=6,235) and 2020 systematic review (N=15) of randomized and non-randomized trials did not show any increase in endometrial hyperplasia or endometrial cancer after 1 year of therapy.[43,54]
- There are no long-term RCTs evaluating the safety of vaginal estrogen, however, observational data has not shown any increased risk of breast or endometrial cancer, coronary heart disease, stroke or VTE: [NAMS 2020,56,57]
    - A long-term (18 year), prospective cohort study (n=54,000) of post-menopausal women using vaginal estrogen in the **Nurses' Health Study**, showed no increased risk of CVD (MI, stroke and VTE), hip fracture or cancer (invasive, breast, endometrial, ovarian and colorectal).[NAMS 2020,58]
    - The **WHI** Observational Study, a prospective cohort study (n=45,000, median follow-up 7.2 years) examining the risks of post-menopausal women who used vaginal estrogen, did not show an increased risk of breast cancer, VTE or CVD risk.[67]

2. What are the differences between vaginal products in terms of systemic absorption?

Available data suggests that vaginal estrogen tablets and rings, as well as prasterone (vaginal DHEA ovule), all have comparably low serum estradiol absorption; vaginal estrogen creams may have a higher potential for increasing serum estradiol. Overall, **systemic absorption with any low-dose vaginal preparation** (e.g. **VAGIFEM** 10mcg, **ESTRING Ring** 2mg, **PREMARIN Cream** or **ESTRAGYN Cream** ≤ 1g/d) **is minimal**, and generally remains within the normal post-menopausal range (e.g. <50pg/mL).[NAMS'22,60] **Use of a low-dose vaginal estrogen does <u>not</u> require a progestogen for endometrial protection.**

- When starting vaginal estrogen therapy, there may be an initial increase in serum absorption depending on the degree of vaginal atrophy. As healing and thickening of the vaginal lining occur with continued local therapy, systemic absorption tends to decrease over time.[64]
- Comparing the systemic absorption of different vaginal estrogen dosage forms is challenging due to the heterogeneity of studies in terms of doses used, treatment timeframe, hormone measurement assays used, and units of measurement.[48-51,62,63,65]
- A note on vaginal estrogen creams: most data evaluating systemic absorption includes use of high-dose estrogen cream, where historically the aim was to achieve systemic absorption for management of VMS. This is no longer recommended practice, and serum absorption data for low-dose vaginal estrogen to treat genitourinary symptoms is limited.

3. Can vaginal estrogens be used to treat GSM in those with a history of breast cancer?

Observational data shows no increased risk of breast cancer recurrence with use of low-dose vaginal estrogens in individuals with a history of breast cancer. However, non-hormonal options (i.e. vaginal moisturizers and lubricants) should be offered first-line, before considering vaginal estrogen therapy in consultation with the oncologist.[NAMS 2020, ACOG 2016, BMS 2020, KSM 2020, 44]

- Observational trials investigating the use of vaginal estrogens in patients with a history of breast cancer have shown no increased risk of breast cancer recurrence.[69,70] These results appear consistent for patients who are receiving tamoxifen.[40-42]
- Clinical trials are currently ongoing to assess the safety of vaginal estrogen products in those taking aromatase inhibitors.[66]
- There is a lack of long-term safety data for vaginal estrogen use in patients with a history of breast cancer; a shared decision-making approach should be used involving both the patient and their health care team.[47]

4. What is meant by the term "bioidentical hormone therapy" (BHT)?

Bioidentical refers to a hormone with the same molecular structure as a hormone that is endogenously produced or "body identical" (see Table 1).[SOGC 2021, NAMS 2022] The term "bioidentical hormone therapy" in popular culture, is often used to describe custom-compounded formulations created by specialized pharmacies. These custom-compounded therapies may contain untested combinations of hormones (e.g. estradiol, estrone, progestogen, testosterone and DHEA),[3] and may be administered via unstandardized routes such as subdermal implants, pellets or troches.[NAMS 2022]

- Compounded BHT is often promoted as plant-derived or "natural"[5] when in reality these products undergo the same process of chemical extraction and stabilization as government regulated hormone formulations.[SOGC 2021] Initiation of BHT compounds and dosage adjustments are often based on serial hormone monitoring, which uses unreliable salivary and urine hormone testing.[NAMS 2022, 6] Hormone testing is not recommended during menopause to confirm diagnosis or to make dosage adjustments to hormone therapy.[SOGC 2021, NAMS 2022]
- Non-regulated, BHT compounds are not recommended due to lack of quality control (e.g. chance of overdosing/underdosing, presence of impurities), and lack of evidence to support their safety and efficacy.[3-6] Shared decision-making is important, but patient preference alone should not be used to justify the use of compounded bioidentical hormone preparations, particularly when government regulated bioidentical hormone preparations are available.[NAMS 2022]

Table 1: Regulated hormone products

Synthetic Hormones	Bioidentical Hormones
Progestogens:	
➢ Medroxyprogesterone acetate (MPA) **PROVERA**, **g**	➢ Micronized progesterone (MP) **PROMETRIUM**, **g**
Estrogens:	
➢ Conjugated equine estrogen (CEE) **PREMARIN**	➢ Estradiol-17β (E2) e.g. **ESTRACE**, **g**; **ESTRADOT**, **g** ➢ Estrone **ESTRAGYN**

5. Can MIRENA IUD (levonorgestrel) be used off-label for endometrial protection in women with an intact uterus who are on systemic estrogen for VMS?

MIRENA has been shown to **provide endometrial protection** for women on any dose of systemic estrogen. Although data supports the extended use of **MIRENA** **up to 8 years for contraception**,[19] data only supports the use of **MIRENA** **up to 5 years for endometrial protection** in women on estrogen therapy.

- **MIRENA** markedly decreases menorrhagia commonly seen in perimenopause, often leading to complete amenorrhea.
- **MIRENA** is often the preferred contraceptive (vs combined hormonal contraceptives) in perimenopausal women to mitigate estrogen-related cardiovascular risks that increase with age, such as stroke and VTE.
- Many prospective cohort studies demonstrate no endometrial thickening or abnormal endometrial histology after 5 years of **MIRENA** IUD + continuous systemic estrogen use. Endometrial protection has been consistently reported across studies with high estrogen doses (e.g. estradiol 2mg po daily) and various routes of administration (e.g. oral, transdermal patch/gel). ~90% of perimenopausal women on **MIRENA** + systemic estrogen achieve amenorrhea at 5 years.[20-22]
- What about other progestogen-only contraceptives?
  - **KYLEENA** IUD is not suitable for perimenopausal women experiencing menorrhagia and does not provide adequate endometrial protection for women on systemic estrogen.[1,18]
  - DMPA injections (**DEPO-PROVERA**) have been shown to provide endometrial protection in women using systemic estrogen for VMS;[23] however, DMPA is not routinely recommended in perimenopausal women as it has been associated with bone loss and may exacerbate the natural decline in bone mineral density, which is greatest in menopause.[25]
  - The etonogestrel implant (**NEXPLANON**) and progestin-only pills (e.g. **MICRONOR**) lack evidence to support their use as progestogen options for endometrial protection in women on systemic estrogen for VMS.[26]

6. Is there a risk of dementia associated with menopause hormone therapy (MHT)?

There appears to be **no increased risk** of dementia or cognitive decline associated with MHT in patients under the age of 65 years who receive MHT.[WHIMSY] In post-menopausal women ≥65 years, there may be an increased risk of dementia associated with continued use of estrogen plus progestogen MHT (HR: 2.05, 95% CI 1.21-3.48; **NNH=114** over 4 years).[WHIMS]

- A recent nested case-cohort study reported an association between MHT and dementia in patients aged 50-60 years (HR: 1.24; 95% CI 1.17-1.33);[11] although further evidence is needed to support a causative relationship in this population.
- Post-hoc RCTs have consistently found no increased risk of dementia or cognitive decline in patients <65 years receiving MHT when compared to placebo, and did not show significant improvements in cognitive assessments following several years of MHT.[WHIMSY, KEEPS-Cog, ELITE-Cog]
- There is no evidence to suggest benefit of early MHT initiation (within 6 years of LMP) to prevent cognitive decline.[10]
- In the absence of more definitive findings, menopause hormone therapy is not recommended at any age to prevent or treat a decline in cognitive function or dementia.[NAMS 2022] See RxFiles Chart: Dementia.

7. Can MHT be used in patients who experience migraines?

Limited evidence suggests that MHT **appears to be safe** for use in patients who experience migraines with or without aura, despite hormonal contraception being contraindicated in patients who experience migraines with aura. The doses used for MHT are 3-6x lower than those used for contraception and appear to pose no increased risk of stroke.[17]

- Currently, available data investigating MHT use in patients with migraines comes from small observational studies or sub-analyses of larger RCTs where MHT use with migraines was not a pre-specified target of the study:
    - **Estrogen:** One small observational study (n=50), reported a small but statistically significant increase in the frequency of migraine attacks in patients on oral estrogen therapy compared to transdermal estrogen.[15] Additionally, a RCT subgroup analysis has shown no statistically significant increase in the risk of stroke or TIA compared to placebo.[13] Although data is limited, using transdermal formulations at the lowest effective dose may mitigate risks in this patient population.[17]
    - **Progestogen:** Continuous dosing regimens are preferred over cyclical, if migraines are triggered by hormonal fluctuations.[17] Theoretically, this may lead to fewer occurrences of progestogen-associated migraine attacks. One small observational trial (n=38), appears to support this theory, although no other data is currently available studying the effect of progestogen use in MHT on migraines.[14]
    - **Tibolone:** One small observational study (n=40), has reported a significant reduction in the duration of migraine symptoms when compared to EPT. No other data is currently available on tibolone and its use in patients with migraines.[15]

8. Does MHT help with depressive symptoms during the menopause transition or in post-menopausal women?

Limited evidence suggests estrogen therapy **may be effective** in the management of depressive disorders (e.g. MDD, sub-clinical depression, dysthymia) **during perimenopause**. Estrogen therapy is ineffective in treating depressive disorders in post-menopausal women. Data on estrogen plus progestogen MHT are sparse and inconclusive. Proven therapeutic options for depression (e.g. antidepressants, psychotherapy) remain first-line treatments for perimenopausal and post-menopausal depression.[32,38,61] See RxFiles Chart: Antidepressants.

- Two small RCTs demonstrated estradiol alone may improve mood in perimenopausal women with a depressive disorder; effects were similar to classic antidepressants and were observed irrespective of the presence of VMS.[30,31] Limitations include short trial duration and small sample sizes.
    - Schmidt et al. (2001): n=36 perimenopausal women with a depressive disorder; transdermal estradiol 50mcg/d vs placebo x6wks. Full or partial response occurred in 80% receiving estradiol vs 22% receiving placebo.[31]
    - Soares et al. (2001): n=50 perimenopausal women with a depressive disorder; transdermal estradiol 100mcg/d vs placebo x 12wks. Remission occurred in 68% receiving estradiol vs 20% receiving placebo.[30]
- One large RCT suggests peri- and early post-menopausal women without depression or with mild to moderate depressive symptoms at baseline may benefit from oral MHT.[9]
    - Gleason et al. (2015): n=693 peri- and early post-menopausal women (within 36 months of LMP) without depression (~10%) or with mild-moderate depressive symptoms (~90%) at baseline; ❶ oral CEE 0.45mg/d with oral micronized progesterone 200mg/d x12d every month vs ❷ transdermal estradiol 50mcg/d with oral micronized progesterone 200mg/d x12d every month vs ❸ placebo x4yrs.[9] Women receiving oral CEE with micronized progesterone had lower depression and anxiety scores than those receiving either transdermal estradiol with micronized progesterone or placebo. The reason for the discrepancy in results for transdermal estrogen in this trial vs the two trials above is unclear.
- Early evidence suggests that MHT (transdermal estradiol 100mcg/d with oral micronized progesterone 200mg/d x12d q3mos) may prevent the onset of depressive symptoms in euthymic perimenopausal women.[34] Further research is needed to confirm these findings.

9. Does MHT help improve sexual desire?

Systemic MHT generally does not improve sexual desire. Transdermal estrogen (e.g. gel or patch) is preferred over oral estrogen when treating VMS in women with libido concerns. Therapeutic options for sexual dysfunction (e.g. psychotherapy, transdermal testosterone$^{\text{off-label}}$, etc.) remain first-line treatments. See RxFiles Chart: Sexual Dysfunction.

- Available evidence suggests MHT has a largely neutral effect on sexual desire.[27-29]
- In women with vaginal atrophy, MHT may lead to reduced sexual pain which may indirectly improve sexual interest (note: low-dose vaginal estrogen is preferred over systemic MHT if vaginal atrophy is the only menopausal symptom present); likewise, in women with significant VMS, MHT may improve overall quality of life, which may indirectly benefit relationships with romantic partners and sexual desire.
- Transdermal products may be preferred for women with low libido given that oral estrogen could reduce bioavailability of testosterone (by increasing sex hormone binding globulin).[NAMS 2022]

BHT=bioidentical hormone therapy **CA**=cancer **CEE**=conjugated equine estrogen **CHD**=coronary heart disease **CI**=confidence interval **CV**=cardiovascular **CVD**=cardiovascular disease **DHEA**=dehydroepiandrosterone **DMPA**=depot medroxyprogestereone acetate **E2**=estradiol-17β **EPT**=estrogen plus progestogen therapy **FDA**=Food and Drug Administration **GSM**=genitourinary syndrome of menopause **HR**=hazard ratio **IUD**=intrauterine device **LMP**=last menstrual period **MDD**=major depressive disorder **MHT**=menopause hormone therapy **MI**=myocardial infarction **mos**=months **MP**=micronized progesterone **MPA**=medroxyprogesterone acetate **NNH**=number needed to harm **NNT**=number needed to treat **pg/mL**=picograms per millilitre **po**=oral **RCT**=randomized controlled trial **TIA**=transient ischemic attack **VMS**=vasomotor symptoms **VTE**=venous thromboembolism **WHI=**Women's Health Initiative

MQ6 Menopause Assessment Tool

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www.MQ6.ca

MQ6 Treatment Algorithm
Adapted from and reproduced with permissions: Jan 2023
Goldstein, S. An efficient tool for the primary care management of menopause
Can Fam Physician. 2017 Apr; 63(4):295-298

MQ6 Menopause Assessment Tool

1. Changes to periods?
2. Any hot flashes?
3. Any vaginal dryness, pain, sexual concerns?
4. Any bladder issues, incontinence?
5. How's your sleep?
6. How's your mood?

Is MHT indicated?

VMS, GSM, Bone protection, POI

NO → **NON-HORMONAL MEDICATIONS****

	VMS	GSM	SLEEP	MOOD
Gabapentin/ Pregabalin*	++(1)		+++(1)	+/-(3)
Antidepressants* ie. SSRI, SNRI	++		+/-	++/+++
Clonidine	+			
Oxybutinin*	++	+(2)		

1. Gabapentin can be sedating at higher doses and has shown potential benefits for night sweats
2. Oxybutynin is indicated for symptoms of OAB
3. There is some evidence for benefits of gabapentinoid treatments for mood and anxiety disorders

* indicates off-label use for vasomotor symptoms
** based on low-level evidence/consensus opinion

Is GSM the only indication for MHT?

YES → **Vaginal ET**
Vaginal DHEA
Ospemifene

Are there CONTRAINDICATIONS to MHT?

- Personal history of Estrogen dependent Cancers (e.g. Breast, Endometrial, Ovarian)
- Unexplained vaginal bleeding
- Pregnancy
- Coronary heart disease
- Active or previous history of stroke or VTE
- Acute liver disease
- Personal history or inherited high risk of thromboembolic disease (e.g. Thrombophilia)
- Porphyria
- Migraine with aura? → not a contraindication but consider neuro consult?

YES

NO

Are there COMORBIDITIES?

- Diabetes mellitus
- Metabolic syndrome
- Hypertension
- Hyperlipidemia
- High triglycerides
- Elevated CVS risk
- Elevated risk for VTE
- Smoking
- Obesity
- Migraine
- Malabsorption
- Gallstones

NO → **Any estrogen (oral or transdermal)**

YES → **Transdermal estrogen preferred**

HYSTERECTOMY?

NO → **EPT, TSEC, STEAR**

YES → **ET (Estrogen only)**

FMP > 1 year ago?

NO → **CYCLIC*** regimen

YES → **CONTINUOUS** regimen

SYMPTOMS OF GSM?

If YES, and using less than standard doses of MHT (e.g. CEE 0.625 mg po, Estradiol 1.0 mg po or Td Estradiol 50 *ug*) consider additional vaginal ET at onset of therapy

****can also use vaginal ET as add-on to >=standard dosing of MHT if GSM symptoms persist after initiating MHT**

MHT = Menopausal Hormone Therapy, EPT=Estrogen + Progestogen therapy, ET=Estrogen therapy
Td =Transdermal, POI=Premature Ovarian Insufficiency
GSM = Genitourinary Syndrome of Menopause

VMS =vasomotor symptoms
TSEC =Tissue Selective Estrogen Modulator, STEAR=Selective Tissue Estrogenic Activity Regulator
*Cyclic regimen = a daily estrogen with a progestogen added 12-14 days of the month

Acknowledgements and Key References

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Gender Terminology:

Our resources are most relevant for people born with ovaries. To remain consistent with the research we reference, we will use the term "women;" however, we acknowledge that this term does not capture all those people who experience menopause. More research is needed to explore how diverse genders experience menopause, and we hope that the information contained in our materials will help any person experiencing this life transition.

Disclaimer:

Symbols and Abbreviations:

✗ =non-formulary in SK ☎=Exception drug status in SK ⊗=not covered by NIHB ✆=prior approval required by NIHB ▼=covered by NIHB **$=** retail *Cost to Consumer* based on acquisition cost, markup & dispensing fee in SK (lowest generic price used) ç=tablet is scored g=generic available ♀=biological female ↓/↑=decrease/increase 💻= check our website for online extras (www.RxFiles.ca) =dose ↓ may be required for liver dysfunction =dose ↓ may be required for renal dysfunction **AE**=adverse events **AUB**= abnormal uterine bleeding **BHT**=bioidentical hormone therapy **BID**=twice daily **BP**=blood pressure **CA**=cancer **CBT**=cognitive behavioural therapy **CBTi**=cognitive behavioral therapy for insomnia **CEE**=conjugated equine estrogen **CHC**=combined hormonal contraceptive **CHD**=coronary heart disease **CI**=confidence interval **CIMT**=carotid artery intima-media thickness **CRC**=colorectal cancer **CT**=computed tomography **CV**=cardiovascular **CVD**=cardiovascular disease **D/C**=discontinue **DHEA**=dehydroepiandrosterone **DI**=drug interaction **DM**=diabetes mellitus **DMPA**=depot medroxyprogesterone acetate **DVT**=deep vein thrombosis **E**=estrogen **E2**=estradiol-17β **EPT**=estrogen plus progestogen therapy **FDA**=Food and Drug Administration **FSH**=follicle stimulating hormone **GI**=gastrointestinal **GSM**=genitourinary syndrome of menopause **HA**=headache **hCG**=human chorionic gonadotropin **HR**=hazard ratio **HS**=bedtime **HTN**=hypertension **IUD**=intrauterine device **LH**=luteinizing hormone **LMP**=last menstrual period **LT4**= levothyroxine **MA**=meta-analysis **MDD**=major depressive disorder **MHT**=menopause hormone therapy **MI**=myocardial infarction **mos**=months **MP**=micronized progesterone **MPA**=medroxyprogesterone acetate **NAMS**=North American Menopause Society **NETA**=norethisterone acetate **NNH**=number needed to harm **NNT**= number needed to treat **N/V**= nausea/vomiting **OAB**=overactive bladder **OP**=osteoporosis **OR**=odds ratio **OSA**=obstructive sleep apnea **OTC**=over the counter **P**=progestogen **PAD**=peripheral artery disease **PDE5i**=phosphodiesterase inhibitor **pg/mL**=picograms per milliliter **PE**=pulmonary embolism **pt**=patient **po**=oral **PRN**=as needed **QoL**=quality of life **RCT**=randomized controlled trial **RH**=relative hazard **RR**=relative risk **SE**=summary estimate **SERM**=selective estrogen receptor modulator **SHBG**=sex hormone binding globulin **SNRI**=serotonin norepinephrine reuptake inhibitor **SOGC**=Society of Obs & Gyn of Canada **SR**=systematic review **SSRI**=selective serotonin reuptake inhibitor **sx**=symptoms **TG**= triglycerides **TIA**=transient ischemic attack **TSH**=thyroid stimulating hormone **tx**=treatment **UTI**=urinary tract infection **VMS**=vasomotor symptoms **VTE**=venous thromboembolism **WHI**=Women's Health Initiative

Vasomotor Symptom Therapies
Quick Reference

For women without contraindications
(e.g. have not experienced a heart attack, stroke, or breast cancer)

September 2024

Rx FILES

Hormones

- Around **800 out of 1000** women will have their hot flashes improve by ≥50%.[15,32,12] This can mean hot flashes are less frequent and/or less bothersome. **Patients with the most severe symptoms tend to receive the largest benefit.** Some patients will also report improved mood or sleep.
- Below are some evidence-based estimates of how risks and benefits of hormones change depending on the individual:[7]

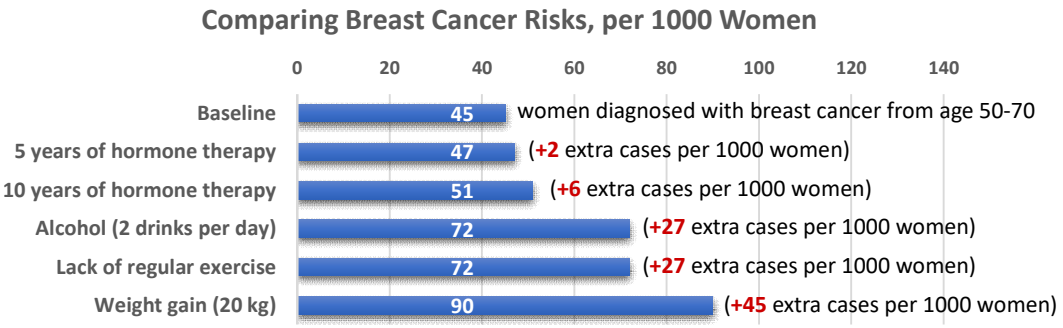
Women WITH a uterus (progestogen required)	
If < 60 years old:	If ≥ 60 years old:
Estrogen + Progestogen	**Estrogen + Progestogen**
Around **11 in 1000** (NNH=91) women will have a **major harm** (such as a stroke, a blood clot, or breast cancer) after 5 years.	Around **16 in 1000** (NNH=63) women will have a **major harm** (such as a stroke, a blood clot, or breast cancer) after 5 years.
Around **7 in 1000** (NNT=143) women will receive a **major benefit** (such as preventing a hip fracture or preventing colorectal cancer) after 5 years.	Around **7 in 1000** (NNT=143) women will receive a **major benefit** (such as preventing a hip fracture or preventing colorectal cancer) after 5 years.

Women WITHOUT a uterus	
If < 60 years old:	If ≥ 60 years old:
Estrogen	**Estrogen**
Around **3 in 1000** (NNH=333) women will have a **major harm** (such as a blood clot) after 5 years.	Around **13 in 1000** (NNH=80) women will have a **major harm** (such as a blood clot or stroke) after 5 years.
Around **15 in 1000** (NNT=64) women will receive a **major benefit** (such as preventing colorectal cancer) after 5 years.	Around **10 in 1000** (NNT=95) women will receive a **major benefit** (such as preventing a hip fracture or preventing colorectal cancer) after 5 years.

These risk estimates are the best that are available, but do have some uncertainty. For example, the estrogen studied was conjugated equine estrogen (**PREMARIN**) 0.625mg per day for 5 years; a lower dose or duration may result in lower risk.

In general, **women at lowest risk are those under the age of 60 or within 10 years of their last menstrual period**.[6,9] Some patients may find it helpful to see how the breast cancer risk of hormones compares to other common risk factors for breast cancer (see graph to the right).[136]

- Doses of hormones used in systemic menopause hormone therapy are 1/3 to 1/6 lower than doses used for birth control.
- The cost of systemic menopause hormone therapy is usually between $20-70 per month (depending on the product & dose).



Note: for women without a uterus and taking only estrogen, the WHI trial showed no increase in breast cancer.[7]

Non-Hormonal Drugs (such as paroxetine, venlafaxine, gabapentin, or others)

- Around **500 out of 1000** women will have their hot flashes improve by ≥50%.[28,32,137,138] This can mean hot flashes are less frequent and/or less bothersome.
- Non-hormonal drugs can also help with **mood and/or sleep problems**.
- Side effects such as drowsiness, nausea, or appetite changes can lead to discontinuation.
- The cost of these medications is usually $20-30 per month (depending on the product & dose).

Non-Drug Treatment (such as cognitive behavioural therapy or lifestyle measures)

- Cognitive behavioural therapy (CBT) can help hot flashes feel less bothersome, but does NOT reduce their frequency. There are no side effects from CBT. Cost and availability vary depending on jurisdiction.
- Link to patient info sheet, *CBT for Menopause Symptoms*: tinyurl.com/BMS-menopause

Notes

- Our resources are most relevant for people born with ovaries. To remain consistent with the research we reference, we use the term "women;" however, we acknowledge that this term does not capture all those people who experience menopause.
- The most common Canadian choices are listed (but list is not exhaustive).
- Medications for menopause can take up to a month to show full benefit; dose titration may also be needed.
- Regardless of medication chosen, once per year an effort may be made to lower the dose to see if treatment is still needed. Mild rebound symptoms can occur during the first few weeks after stopping therapy.
- The placebo response rate in menopause clinical trials is around 20-50%.[28]
- **Herbal options** are popular, but not recommended by guidelines due to a lack of evidence for efficacy.[8] **Compounded "bioidentical" hormone therapies** are also not recommended due to a lack of evidence, regulation, & quality control.

MENOPAUSE Cover Page

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MENOPAUSE: Overview, MHT, Non-Hormonal Therapy, and VMS Quick Reference

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💻 Online Extras: Menopause Herbal Chart

Common name *botanical name*	**EFFICACY / SELECTED DOSES # / MECHANISM OF ACTION / CAUTIONS / ADVERSE EFFECTS AE / DRUG INTERACTIONS DI**
Black cohosh *Actaea racemosa* NUFEM, generics	• Likely no better than placebo and worse than hormone therapy for VMS.[97-101] ?Estrogenic effects.[131,102] May consider dose of **20mg po BID**.[67,106] Onset: 2-**4** weeks. Most studies ≤6 months.[67,131] • AE: headache, dizziness, GI upset, weight gain, heaviness in legs, cramping, ?seizures,[67,108] ?safe if history of breast cancer,[109] rare: liver toxicity case reports.[Health Canada '05 & '10] AKA *cimicifuga racemosa*. • DI: ? ↑ effect of tamoxifen and antihypertensives;[131] ? ↓ absorption of iron;[110] ?↓ effect of cisplatin. ?Avoid concurrent use with other hepatotoxic drugs. Most consistent evidence for **REMIFEMIN**.[67]
Chasteberry *Vitex agnus-castus*	• Although possibly effective (20-40mg/day) for **PMS**, insufficient evidence to support use in post-menopausal women.[111] Phytoestrogen, ?may affect FSH, LH, dopamine. Studied up to 1.5yrs.[67] AKA chaste tree berry. • AE:[4] headache, GI upset, itching, urticaria, rash, acne, irregular menstrual bleeding, ?seizures.[108] ?avoid in hormone sensitive conditions*.[67] DI: ? ↑ effect of dopamine agonists, neuroleptics, hormone therapy, OCs.
Dong quai *Angelica sinensis*	• Likely no better than placebo for VMS.[112] ?Estrogenic effects.[67] Studied up to 24 weeks.[67] • AE: Generally well toleratedshort term,?photosensitization,[113] ?carcinogenic, ?mutagenic (avoid long-term use), ?antiarrhythmic;[114] ?avoid in hormone sensitive conditions.*[67] DI: ↑effect of **anticoagulants**, ?antiplatelets.[115,116]
Evening primrose oil	• Likely no better than placebo for VMS.[117] ?gamma-linolenic acid may be active ingredient.[110] ?**Dose**: 4-6g/day. AKA *oenothera biennis*. Studied up to 6 months.[67] • AE:[Error! Bookmark not defined.] Generally safe; headache, indigestion, nausea, soft stools. ?may ↓ seizure threshold.[108] DI: ? ↑ effect of anticoagulants, antiplatelets.
Fennel	• Small, 10 week study suggests ↓ in menopausal symptoms.[132] ?Estrogenic effects. **Dose**: 100mg po BID. AE: uncommon; allergic reactions, GI upset. DI: ? ↑ effect of anticoagulants, antiplatelets. AKA *foeniculum vulgare*
Red clover (isoflavone source) *Trifolium pratense*	• Likely no better than placebo for VMS.[97] Phytoestrogen, contains isoflavones, ?estrogenic effects.[67] May ↑ HDL, but insufficient evidence.[101,118] **Bone loss:** may ↑ BMD.[67,111] • **Dose**: 4g flower tops po TID.[67] **PROMENSIL** 20-40mg isoflavones (200-400mg trifolium pretense) daily (vasomotor). • AE: rash, ?avoid in hormone sensitive conditions.*[67] DI: ? ↑ effect of anticoagulants, antiplatelets, fexofenadine, azole antifungals, lovastatin, & triazolam; ? ↓ effect of estrogen, OCs, tamoxifen, letrozole.[67]
Soy Active ingredient unclear; some ♀ may be **unable** to convert to ?active metabolite S-equol.	• Mixed evidence for VMS.[119,120] Not effective in breast cancer survivors.[113] ?no benefit in heart disease, lipids, bone loss, or fractures.[43,121-124 ,SPARE] • Phytoestrogen with ?estrogenic effects; may block thyroid hormone production.[67] Isoflavones may be active ingredient (25g soy protein = 50mg isoflavones). Ipriflavone → synthethic isoflavone. S-equol → isoflavone metabolite. • **Food source may be preferred over supplements**. Dose: **20-60g** po daily soy protein (e.g. **3 cups soy milk per day** = 18-27g soy protein; **300g tofu per day** = 24-42g soy protein).[67] • AE: constipation, bloating, mood,[134] nausea, ?avoid in hormone sensitive conditions*.[125,126,135] Studied up to 2 months.[67] • DI: ↑ effect of theophylline; ↓ effect of levothyroxine.[67,127] ?Antibiotics may ↓ effect. ?May ↓ effect of estrogen, tamoxifen, & warfarin.[12]
Wild yam *Dioscorea villosa*	• Insufficient evidence to support use for libido or vaginal dryness.[101] Progesterone precursor; since conversion to progesterone does not occur in the human body, prescribed progesterone may be more useful.[107,67] • AE: Generally well tolerated; emesis (large doses); ?avoid in hormone sensitive conditions.* Some yam creams tested had adulterated steroids or does not contain any yam extract (YAM SCAM!).[NAMS'15'23] No DI.[67]
Valerian *Valeriana officinalis*[127]	• Conflicting evidence if effective for insomnia.[128] ?mediates GABA release.[24] **Dose**: 400-800mg po HS {**NYTOL NATURAL SOURCE**, **UNISOM NATURAL SOURCE**}. Onset: several days to one month. Studied up to 1 month.[67] • AE: withdrawal symptoms (cardiac failure, delirium),[129] ataxia, hallucination, ↑ muscle relaxation, hypothermia,[118] restlessness & palpitations (paradoxical).[118] DI: ? ↑ CNS effects of alcohol, barbiturates, benzos, opiates.[120]

* **hormone sensitive conditions** = breast, uterine, or ovarian cancer; endometriosis; uterine fibroids.[130] # **Doses** provided only for products which **may** be more effective than placebo.

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Efficacy and Safety of Menopause Hormone Therapy (MHT): Trial Evidence Summary

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Online Extras: Expanded Trial Evidence Summary

Detailed Evidence Summary and Supplementary Notes

Vasomotor Symptoms

- Most effective, first line treatment of moderate to severe vasomotor symptoms of menopause.[SOGC 2021, NAMS 2020]
- Oral MHT vs placebo: ↓ weekly symptom frequency by 75% and ↓ symptom severity: OR 0.13 (0.07-0.23).[4]
- Progesterone monotherapy is not FDA or Health Canada approved for VMS, and there is minimal data to support its effectiveness. An RCT of 133 women with vasomotor symptoms aged 44-62 years showed a 55% reduction in symptoms after treatment with 300 mg of micronized progesterone nightly for 12 weeks, compared with a 29% reduction in the placebo group.[5] This high dose is associated with more side effects than estrogen. No long-term studies have addressed the safety of progestogen-only treatment of menopause symptoms.[2,6]

Route of Administration:

- In recently menopausal women (within 3 yrs), systemic oral and transdermal formulations are similarly effective for VMS compared to placebo:[9] (KEEPS f/u)

Baseline	**At 6 months:**			
	Oral: CEE 0.45mg od + MP 200mg 12d/mos	Transdermal E2 50µg + MP 200 mg po 12d/mos	Placebo	P value
Mod-severe hot flashes (44%)	4.2%	7.4%	28.3%	P<0.001
Mod-severe night sweats (35%)	4.7%	5.3%	19%	P<0.001

- In a meta-analysis of RCTs, both oral CEE and transdermal estradiol were 70-95% effective at reducing hot flashes.[10]

Breast Cancer

- Oral CEE + MPA ↑ risk of breast CA during the intervention phase: HR 1.24 (1.01-1.53), **NNH=196**/5.2 yrs, which persisted after cumulative 13 years of follow-up: HR 1.28 (1.11-1.48).[WHI 2013]
- Oral CEE alone did not significantly affect the incidence of breast CA during the intervention phase or 13 year cumulative follow-up.[WHI 2013]
- WHI 20 year follow-up trial looking at breast cancer risk and breast cancer mortality:[WHI 2020]
  - Oral CEE + MPA ↑ risk of breast CA: HR 1.28 (1.13-1.45); absolute risk extrapolation: 1.8 cases per 100 women over 20 years.[8]
    - Oral CEE +MPA did not significantly affect the incidence of breast CA mortality.
  - Oral CEE alone ↓ risk of breast CA: HR 0.78 (0.65-0.93); absolute risk extrapolation: ↓ 1.4 cases per 100 women over 20 years.[8]
    - Oral CEE alone ↓ risk of breast CA mortality: ↓ risk HR 0.60 (0.37-0.97; absolute risk extrapolation: ↓ 0.4 cases per 100 women over 20 years.[8]
- Over 20 years of observational follow-up: absolute risk estimate for those who had 5 years of MHT starting at age 50:[8,13]
  - Estrogen + continuous progestogen: ↑ 2 cases/100 women over 20 years
  - Estrogen + cycled progestogen: ↑ 1.4 cases/100 women over 20 years
  - Estrogen alone: ↑ 0.5 cases/100 women over 20 years
- Based on observational data, breast cancer risk appears to increase steadily with longer duration of systemic MHT use:[13]

	Systemic Estrogen + Progestogen		Systemic Estrogen Alone	
	1-4 year of use	5-9 years of use	1-4 years of use	5-9 years of use
Current use	↑ risk (RR 1.60; 1.52-1.69)	↑ risk (RR 1.97; 1.90-2.04)	↑ risk (RR 1.17; 1.10-1.26)	↑ risk (RR 1.22; 1.17-1.28)
Past use	↑ risk (RR 1.10; 1.05-1.16)	↑ risk (RR 1.21; 1.16-1.26)	NS	↑ risk (RR 1.09; 1.03-1.15)

- Mixed evidence exists regarding the risk of breast cancer and type of progestogen use. Some observational data suggests MP may have a lesser association with breast cancer than MPA (OR 0.99 vs 1.28).[2,14,15] However, other observational data have found no difference in risk.[2,13] A cyclic progestogen regimen may have a small decreased risk of breast CA vs a continuous progestogen regimen (RR 1.93 vs 2.30).[13]

Route of administration

- There is no RCT data available comparing efficacy and safety of transdermal vs oral estrogen. Observational studies have found no significant differences in risk of breast cancer between formulations.[15,16]

Coronary Heart Disease	• MHT is not recommended for the primary or secondary prevention of CVD.[SOGC'21, NAMS'22]
	• Oral CEE + MPA and CEE alone did not significantly affect the incidence of CHD events (non-fatal MI or CHD death) during the intervention phase or 13 year cumulative follow-up.[WHI 2013]
	  o Post hoc, subgroup analysis by 10 year age groups, suggests that early initiation (aged 50-59 years) of CEE alone has CHD benefits: ↓ CHD (HR 0.65; 0.44-0.96) after 13 years cumulative follow-up. CEE + MPA showed no significant differences when analyzed by age group.[WHI 2013]
	• Oral MHT initiated <10 years of menopause suggests a ↓ risk of CHD (non-fatal MI or CHD death): RR 0.52 (0.29-0.96), **NNT=125**. However, when initiated >10 years after menopause there was no effect on CHD.[19] This subgroup analysis suggests a possible benefit when initiating MHT early, however, this data is only hypothesis generating (i.e. timing hypothesis).
	• Oral MHT initiated early after menopause↓ risk of the composite of death, MI and HF hosp: HR 0.48 (0.26-0.87) without an increase in stroke, VTE or cancer. There is an increased risk of bias because of no placebo group and use of a composite outcome not described in study protocol.[DOPS 2012]
	• Primary endpoints for these trials are surrogate markers of CV risk (e.g., carotid artery intimal-medica thickening [CMIT]). All were underpowered to compare clinical event rates.
	  o Oral MHT vs transdermal vs placebo showed no difference in CMIT with MHT vs placebo in early-menopausal women.[KEEPS 2014]
	  o Oral E2 ± progesterone is associated with less progression of atherosclerosis (CMIT) vs placebo when initiated <6yrs years post-menopause, but not when initiated ≥10yrs post-menopause.[ELITE 2016]
	• MPA negatively impacts lipid parameters to a greater degree than MP.[23]
	• MP is preferred over MPA in moderate cardiovascular risk, due to less untoward effect on metabolic parameters such as BP and TG.[18,24]
	<u>Route of administration</u>
	• There is no available data comparing risk. Transdermal estrogens have less effect on surrogate markers (coagulation factors, inflammatory markers, and lipids), and are therefore theorized to potentially have lower risk of CHD.[8,25,26] Transdermal formulations are preferred in women with hyperlipidemia, diabetes, hypertension, or other risk factors for CVD.[27]

Venous Thrombo-embolism	• Oral CEE + MPA ↑ risk of DVT: **NNH=147**/5.2 yrs and PE: **NNH=196**/5.2 yrs during the intervention phase; ~8 years after discontinuing CEE + MPA, DVT risk persisted but PE risks did not persist.[WHI 2013]
	• Oral CEE alone ↑ risk of DVT: **NNH=196**/6.8 yrs, this risk did not persist ~6.5 years after discontinuing CEE. CEE alone did not effect the incidence of PE.[WHI 2013]
	• Oral MHT initiated <10 years of menopause ↑ risk of VTE: RR 1.74 (1.11 to 2.73), **NNH=146.** When initiated >10 years after menopause this risk remained, ↑ risk of VTE: RR 1.96 (1.37 to 2.80), **NNH=101**.[19]
	• VTE risk appears highest in the first year of treatment.[28]
	• Based on observational data alone:
	  o Estradiol may be associated with a lower risk of VTE than CEE: RR 0.83 (0.76-1.91)[25,29]
	  o MP may be less thrombogenic than other synthetic progestogens: OR 0.7 vs 3.9.[25,30]
	<u>Route of administration</u>
	• Based on observational data alone, standard doses of transdermal estrogen may be associated with lower risk of VTE than oral estrogen: RR 0.61 (0.53-0.71).[1,2,25,29-34]

Stroke	• Oral CEE + MPA ↑ risk of stroke during the intervention phase: HR 1.37 (1.07-1.76), **NNH=192**/5.2 yrs.[WHI 2013] • Oral CEE alone ↑ risk of stroke during the intervention phase: HR 1.35 (1.07-1.70), **NNH=127**/6.8 yrs.[WHI 2013] • There was no effect on stroke risk during the 13 year cumulative follow-up of the WHI trials for both combined and estrogen only therapy.[WHI 2013] • Oral MHT initiated <10 years of menopause did not significantly affect the incidence of stoke, but when initiated >10 years after menopause*:* ↑ risk: RR 1.21 (1.06 to 1.38), **NNH=102**. Boardman et al '15 <u>Route of administration</u> • Based on observational data alone, standard doses of transdermal estrogen may be associated with lower risk of stroke than oral estrogen: RR 0.81 (0.68-0.97).[NAMS 2022, SOGC 2021, 25,31,33,35,36]
All-cause mortality	• Oral MHT use for ~5-7yrs had no effect on all-cause, CV or cancer mortality. o When analyzed by 10 year age groups, women aged 50-59 yrs on MHT had reduction in all-cause mortality during the intervention phase: HR 0.61 (0.43-0.87) and possibly after 18 years of cumulative follow-up, although the reduction was no longer statistically significant: HR 0.87 (0.76-1.00).[WHI 2017] • Oral MHT initiated <10 years of menopause suggests a ↓ risk of all-cause mortality: RR 0.70 (0.52-0.95), **NNT=167**. However, when initiated >10 years after menopause there was no effect on mortality.[19] This subgroup analysis suggests a possible benefit when initiating MHT early, however, this data is only hypothesis generating.

Osteoporosis and Fractures	• Hormone therapy has been shown in double-blind RCTs to prevent bone loss, and in the WHI, to reduce fractures in post-menopausal women without OP. The FDA indication includes prevention, but not treatment, of postmenopausal OP. Nonestrogen medications are preferred for treatment of existing OP.[NAMS'22]
	• CEE + MPA ↓ risk of hip fractures: HR 0.67 (0.47-0.95), **NNT=322**/5.2 yrs, vertebral fractures: HR 0.68 (0.48-0.96), **NNT=333**/5.2 yrs, and all fractures: HR 0.76 (0.69-0.83), **NNT=40**/5.2 yrs.[WHI 2013] After stopping MHT for 5 years, fracture benefit disappeared.[Watts et al 2017]
	• CEE alone ↓ risk of hip fractures: HR 0.67 90.46-0.96), **NNT= 217**/6.8 yrs, vertebral fractures: HR 0.64 (0.44-0.93), **NNT= 217**/6.8 yrs, and all fractures: HR 0.72 (0.64-0.80), **NNT= 26**/6.8 yrs.[WHI 2013] After stopping MHT for 5 years, there was a suggested residual benefit of CEE ↓ risk of all fractures: HR 0.85 (0.73-0.98).[Watts et al 2017]
	• Current users of MHT (mean duration 5.9 yrs), ↓ risk of any fracture (except fingers, toes and ribs): RR 0.62 (0.58-0.66).[Million Womens Study 2004]
	  o This decrease did not vary significantly according to MHT regimen choice (estrogen alone, combined MHT, tibolone, vaginal or not known), dose of estrogen or type of estrogen/progestin used. Among users of combined estrogen-progestin, there was no significant difference in the effect on fracture risk between those taking sequential and continuous preparations.
	  o There is weak evidence of heterogeneity between oral, transdermal and implant routes of administration (p=0.04), but difficult to interpret given the large number of statistical tests conducted. Differences are unlikely to be clinically significant.

	○ Past users of hormone therapy had no protection against fractures; incidence rates returned to those of never-users within about a year of ceasing use.
Sleep	• MHT improves sleep quality and satisfaction in perimenopausal and post-menopausal women with bothersome VMS. Cintron et al 2018, Duralde et al 2023, NAMS 2022 • Limited evidence suggests that estrogen and progestogen may also improve sleep independent of VMS. Greiger et al 2019, Cintron 2017, NAMS 2022 • Estrogen alone is less effective at improving sleep vs estrogen + progestogen regimens. Pan et al 2022 • Limited evidence (1 RCT, n=8) suggests that high dose MP alone (300 mg QHS) may improve sleep quality in healthy post-menopausal women without VMS, based on polysomnography and physiologic markers. Caufriez et al 2011 This may be due to its sedating properties, further research is needed to confirm these findings. • Both CEE and estradiol have been shown to improve sleep. MP has been shown to reduce sleep disturbances more than MPA. Nolan et al 2021, Pan et al 2022, Cintron 2018, Duralde et al 2023 <u>Route of administration</u> • Transdermal estradiol may improve sleep more than oral estradiol. Pan et al 2022, Cintron 2018, Duralde et al 2023
Cognition	• Estrogen + progestogen use in perimenopause or early post-menopause appears to have neutral effects on cognitive function. Gleason et al 2015, **WHIMSY**, Henderson et al 2016, NAMS 2022, Crandall et al 2023 • Estrogen + progestogen use may increase risk of dementia when initiated in older post-menopausal women (≥65 yrs), CEE + MPA: HR 2.05 (1.21-3.48) over a mean follow-up of 4 yrs, an additional 23 dementia cases per 10,000 person-years. Rapp et al 2003, Shumaker et al 2003 (**WHIMS**), Resnick et al 2006, Grady et al 2002 • Observational data suggests weak evidence of small increased risk of Alzheimer's Disease in long duration users (7-12.7 years) of combined MHT; Vinogradova et al 2021 ○ 7.1 years: OR 1.11 (1.04-1.20) ○ 12.7 years: OR 1.19 (1.06-1.33) • CEE alone appears to have neutral effects on cognitive function, irrespective of age at initiation. **WHIMSY**, Espeland et al 2004, NAMS 2022, Crandall et al 2023
Mood	• Data on estrogen + progestogen for the treatment of depression are sparse and inconclusive. Maki et al 2018, NAMS 2022 <u>Perimenopause & early post-menopause</u>: • Based on a single RCT, transdermal E2 (100mcg) + cyclic MP (200mg/d for 12 days) may prevent clinically significant depressive symptoms in euthymic perimenopausal and early postmenopausal women. Gordon et al 2018, Maki et al 2018 • MHT for prevention of depressive symptoms is currently not recommended due to the limited evidence to support its use. • Several small RCTs demonstrate that estradiol (oral and transdermal) is effective for the management of depressive disorders (e.g. MDD, dysthymia or minor depression) in perimenopausal or early post-menopausal women. Effects were similar in magnitude to classic antidepressants. Efficacy was observed irrespective of the presence of VMS. Maki et al 2018, Gleason et al 2015, Schmidt et al 2000, Soares et al 2001, Joffe et al 2011, NAMS 2022, SOGC 2021, Crandall et al 2023, Duralde et al 2023 <u>Late post-menopause</u>: • Several small RCTs suggest estradiol is ineffective in treating depressive disorders in late post-menopausal women. Rudolph et al 2004, Morrison et al 2004, NAMS 2022, SOGC 2021, Crandall et al 2023, Duralde et al 2023, Maki et al 2018 <u>Type of estrogen/progestogen and route of administration</u>: • Insufficient evidence comparing risk between different formulations of estrogens and progestogens or route of administration.
Sexual Drive	• Largely neutral effect. Taylor et al 2017 Estrogen was found to reduce sexual pain but not directly augment sexual desire; MHT treatment with estrogens alone or in combination with progestogens was associated with a small to moderate improvement in sexual function, particularly in pain, when used in women with menopausal symptoms or in early postmenopause (within five years of amenorrhoea), but not in unselected postmenopausal women. Nastri et al 2013 (Cochrane) <u>Route of administration</u> • Transdermal may be preferred for women with low libido given that oral estrogen increases sex hormone binding globulin and reduces bioavailability of testosterone. NAMS 2022
Diabetes Mellitus	• Oral CEE + MPA ↓ self-reported T2DM during the intervention phase of the WHI trial: HR 0.81 (0.70 to 0.94), **NNT=134**/5.2 yrs. This effect was attenuated in long-term (13-yr) follow-up after the active intervention was discontinued. **WHI 2013** • Oral CEE alone ↓ self-reported T2DM during the intervention phase of the WHI trial: HR 0.86 (0.76 to 0.98), **NNT=134**/5.2 yrs. This effect was attenuated in long-term (13-yr) follow-up after the active intervention was discontinued. **WHI 2013** • Meta-analysis data (N=107 RCTs, n=33,315 women) also suggests a ↓ risk of T2DM with MHT use (type of estrogens or progesterone studied were not specified), RR 0.7 (0.6-0.9). Salpeter et al 2006
Weight	• Oral and transdermal hormone therapy have not been shown to affect weight in menopausal women, but they have been shown to decrease visceral fat and increase lean body mass. Duralde et al 2023, Kapoor et al 2017, Mehta et al 2021
Quality of Life	• Regarding health-related quality of life (RAND 36-Item Short Form Health Survey) treatment with CEE+MPA compared with placebo was associated with a small but statistically significant benefit for physical functioning, role physical, bodily pain, and general health, and neutral results for the other subscales at 1 year. Manson et al. 2013 • Treatment with CEE alone was associated with nominally significant adverse effects for social functioning and emotional role. Manson et al. 2013
Gallbladder Disease	• Oral CEE + MPA ↑ self-reported gallbladder disease during the intervention phase of the WHI trial: HR 1.57 (1.36-1.80), **NNH=43**/5.2 yrs). **WHI 2013** • Oral CEE alone ↑ self-reported gallbladder disease during the intervention phase of the WHI trial: HR 1.55 (1.34-1.79), (**NNH=34**/6.8 yrs). **WHI 2013** • Oral CEE may be associated with a slightly greater risk of gallbladder disease than estradiol. CEE: RR 1.79 (1.72 to 1.87) vs estradiol: RR 1.62 (1.54-1.70). Liu et al 2008 <u>Route of administration</u> • Transdermal estrogen is associated with a significantly lower risk of gallbladder disease than oral estrogen. Transdermal: RR 1.17 (1.10 -1.24) vs oral: RR 1.74 (1.68-1.80). Liu et al 2008

	• Observational studies show a lower risk of gallstones with transdermal estrogens: RR 0.79.[66] In the event of gallstone disease, oral estrogen may be switched to a non-oral route, although no RCT data are available to support this.[NAMS 2022]
Colorectal Cancer	• Oral CEE + MPA ↓ risk or colorectal cancer: HR 0.63 (0.43-0.92), **NNT=294**/5.2 yrs.[WHI 2013] This effect was attenuated in long-term (13-yr) follow-up after the active intervention was discontinued.[WHI 2013] • Oral CEE alone did not significantly affect the incidence of colorectal cancer. [WHI 2013]
Urinary Incontinence	• Oral CEE + MPA ↑ self-reported urinary incontinence (at least once/week) during the intervention phase of the WHI trial: HR 1.49 (1.36-1.63), **NNH=24**/5.2 yrs. This effect was decreased, but still statistically significant after 13 year follow-up when the active intervention was discontinued: HR 1.16; 1.08-1.25.[WHI 2013] • Oral CEE alone ↑ self-reported urinary incontinence (at least once/week) during the intervention phase of the WHI trial: HR 1.61 (1.46-1.79), **NNH=19**/6.8 yrs. This effect was decreased, but still statistically significant after 13 year follow-up when the active intervention was discontinued: HR 1.24; 1.13-1.35.[WHI 2013]

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