MEDICAL MANAGEMENT OF MENOPAUSE SYMPTOMS

INDICATION FOR HORMONE THERAPY

Systemic hormone therapy should be considered for management of troublesome vasomotor symptoms (hot flashes and night sweats) during perimenopause and menopause[1]. Despite historical concerns, hormone therapy is **safe** and effective and is the first line treatment for people younger than 60 years of age ***or*** less than 10 years post-menopause without contraindications[1]. Hormone therapy may also be effective in treating other symptoms of menopause, which include brain fog, sleep disturbances and mood changes. See Table 1 for further details.

Perimenopausal and menopausal individuals may also experience symptoms such as vaginal dryness, irritation, discomfort during intercourse as well as urinary urgency, dysuria and recurrent urinary tract infections. These symptoms collectively are referred to as the genitourinary syndrome of menopause (GSM)[2]. For GSM symptoms, first-line therapies include vaginal moisturizers and lubricants whereas second-line therapies consist of local vaginal estrogen preparations (vaginal creams, vaginal tablets or a vaginal ring) (Table 2). Vaginal estrogen preparations are not systemic and therefore do not require progesterone for endometrial protection, even in individuals with a uterus[2].

Table 1: Indications and contraindications for systemic hormone therapy

Common symptoms of menopause	When hormone therapy should be considered the 1st line option	Caution should be taken when any of the following are present	Contraindications to systemic hormone therapy
Vasomotor symptoms Hot flashes Night sweats Other systemic symptoms Mood changes Sleep disturbances Weight gain Brain fog Decreased libido	Troublesome vasomotor symptoms AND Less than 60 years of age ***or*** less than 10 years post-menopause and no contraindications	Moderate cardiovascular risk Migraines with aura History of gallstones Above 60 years of age ***or*** more than 10 years since last period	Unexplained vaginal bleeding Acute liver dysfunction History of estrogen-sensitive cancer (breast, endometrial, and/or ovarian) High risk for cardiovascular disease[3] Previous history of stroke History of thromboembolic disease * High blood pressure is not a contraindication to hormone therapy, but may affect cardiovascular risk

ASSESSMENT AND DIAGNOSIS

Take a careful history to exclude other causes of hot flashes and sleep disturbances, which may include thyroid disorders, medication side effects, mental health issues and chronic pain.

There is no blood test required to diagnose perimenopause or menopause, treatment can be started based on history alone. However routine blood work to screen for risk factors such as cardiovascular disease and diabetes may be warranted[4].

It is important to approach menopause support broadly. Not all individuals who experience menopause will identify as a woman, and gender diverse and transgender members may also be affected by menopause. Menopause may affect younger people and may be the result of surgery or illness. Each person's experience with menopause will be unique and should be considered during your assessment and treatment plan.

Everyone can be affected by menopause. Some firsthand, and others indirectly both within the workplace and at home. This is an inclusive subject that everyone needs to know about[5].

CHOOSING THE RIGHT REGIMEN

To address the systemic symptoms of perimenopause and menopause, effective management involves the administration of systemic estrogen, whether through transdermal or oral route. Transdermal estrogen is safer, better tolerated and has a lower thrombosis risk profile than oral estrogen. For individuals with a uterus, concurrent progesterone is essential to protect the endometrium, while those without a uterus do not require progesterone for symptom management (Graphic 1).

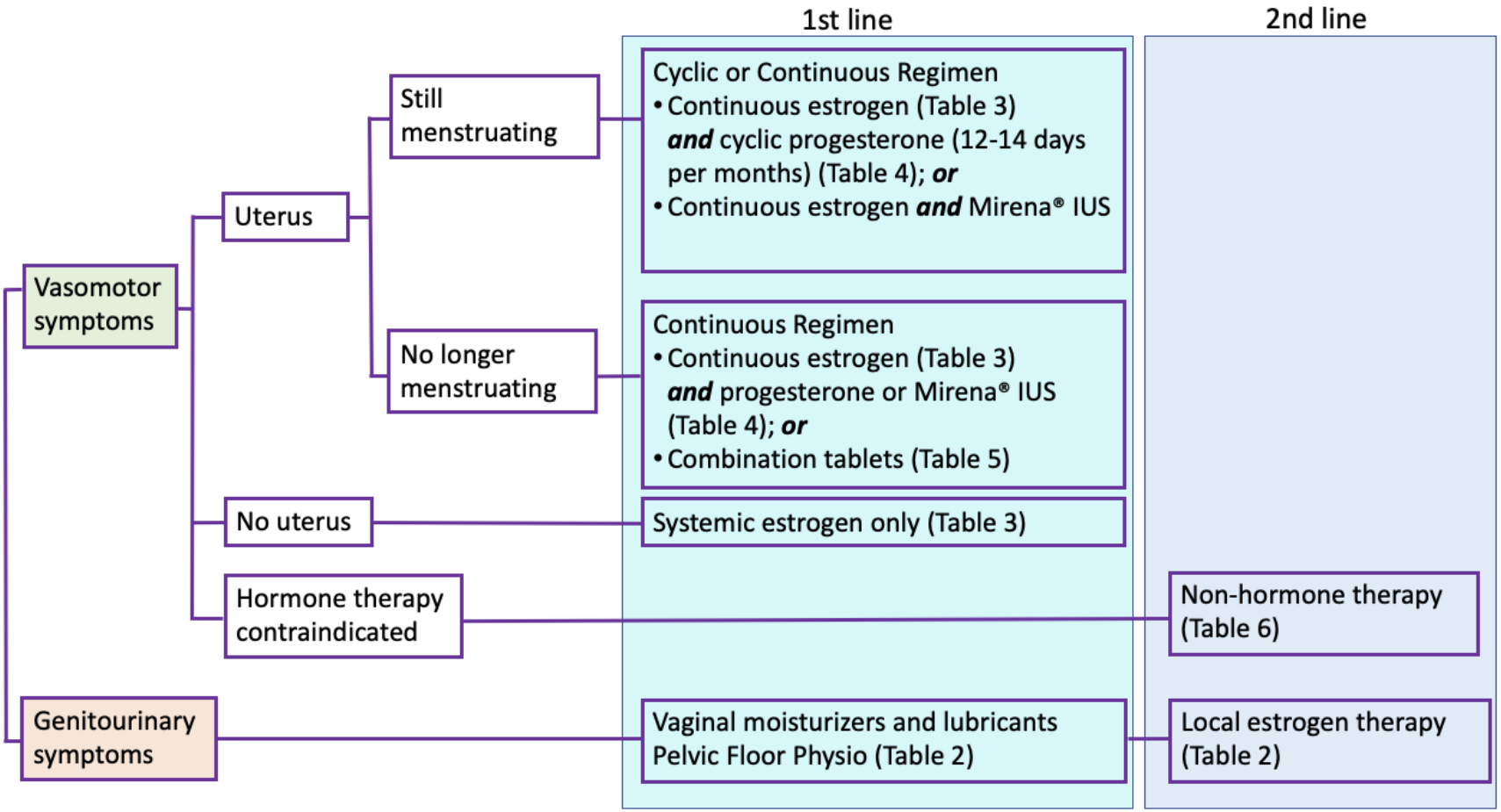
HORMONAL THERAPY (CONTINUOUS OR CYCLIC):

Continuous combined regimen – Continuous estrogen and progesterone therapy (Tables 3-5) typically induces amenorrhea in persons who are menstruating. Estrogen and progesterone are usually given separately, but there are combination preparations available with both estrogen and progestin contained in one product. A 52 mg levonorgestrel-releasing intrauterine system (Mirena®) can also be used as a form of continuous progesterone therapy for endometrial protection.

Commonly prescribed continuous regimen: 17β-estradiol gel (Estrogel), 1 actuation to each arm or conjugated estrogen (Premarin), 0.625mg tablets, once daily. For individuals with a uterus Micronized progesterone (Prometrium) 100mg at bedtime or a 52 mg levonorgestrel-releasing intrauterine system (Mirena®) needs to be added[6].

Cyclic Regimen – For individuals in the perimenopausal stage who are still experiencing menstruation, a continuous treatment plan may result in unpredictable bleeding. For such individuals, we suggest opting for a cyclic regimen for example: continuous/daily administration of transdermal or oral estrogen and cyclic administration of oral micronized progesterone (200mg per day for 12 – 14 days of each calendar month) (Table 4)[6].

Graphic 1: Choosing the right regimen



NON-HORMONAL THERAPY

When non-hormonal therapy is recommended or preferred, venlafaxine is typically the initial consideration, starting at 37.5mg daily for one week, then increase to 75mg daily[1].

STARTING DOSE AND ADJUSTMENTS OF HORMONE THERAPY

Standard dosing for estrogen and progesterone are included in Tables 3 - 5. Typically, relief from hot flashes is experienced within the initial three to four weeks of treatment. In cases where bothersome hot flashes persist beyond this period, increasing the estrogen dose is appropriate. For individuals with severe symptoms, initiating therapy at a higher estrogen dose is recommended for more prompt relief, such as starting doses of 1.25mg of conjugated estrogen or 3-4 actuations of transdermal estradiol. If higher doses of estrogens are used, higher doses of progestogens should also be used[1]. The goal is to have the lowest doses possible that obtain symptom relief.

TAPERING

If vasomotor symptoms are alleviated and the hormone therapy is well-tolerated, the same regimen may be maintained over several years. While there is no definitive restriction on the duration of menopause hormone therapy, it is customary to wait at least five years before considering the initial taper. The taper's objective may be to reduce the dosage rather than cease hormone therapy entirely. Factors like patient age, cardiovascular risk, additional benefits such as preventing bone loss, and collaborative decision-making should all be carefully considered in this context[1].

Non-hormone systemic therapies found in Table 6 will often require tapering of the medication when discontinuing.

SIDE EFFECTS AND TROUBLESHOOTING OF HORMONE THERAPY

Vaginal bleeding: Unscheduled bleeding is the most common side effect for persons on hormone therapy. Some vaginal bleeding for up to 6 months after initiating hormone therapy is acceptable. If bleeding is heavy, frequent or persists beyond 6 months, investigations, such as endometrial biopsy, should be initiated. Consideration should be given to inserting a Mirena® IUS to prevent unscheduled bleeding, once investigated[4].

Mood changes: Persons who experience depression or irritability with the use of progestogens may benefit from changing the type of progesterone or regimen (cyclic versus continuous)[4].

Headaches: Frequency and severity of migraines may fluctuate with hormone levels. Migraines may improve with the use of transdermal estrogen and micronized progesterone. Individuals who experience migraine headaches with auras have an increased risk of stroke. If migraines or auras worsen while on hormone therapy, the dose should be decreased, or the medications discontinued[4].

The following tables provide details on the type of therapy, dosing and additional information that may be helpful when treating symptoms of perimenopause and menopause. Note that if a checkmark ✓ is located in the first column, this indicates that the medication is available in the CAF Drug Benefit List as a regular benefit.

Table 2: Treatment options for genitourinary symptoms

Listed on CAF Drug Benefit List	Vaginal Moisturizer	Trade names	Use	Comments
✓	Polyacrylic	Replens™	Regular vaginal application, 2 to 3 times per week for long lasting efficacy	Includes an applicator
	Hyaluronic Acid and Vitamin E	Gynatrof		Includes an applicator. Hyaluronic Acid may possess anti-inflammatory properties
Special Authorization	Hyaluronic Acid	Repagyn®		No applicator ovules. Hyaluronic Acid may possess anti-inflammatory properties
	Vaginal Lubricant	**Use**		
✓	Water-based	Use as needed to reduce friction during intercourse Note: Oil-based lubricants can damage latex condoms and sex toys		
	Silicone-based			
	Oil-based			

	Vaginal Estrogen	Trade names	Strengths available	Comments
✓	Conjugated Estrogen (CE)	Premarin® vaginal cream (Rose scented)	0.625mg/g of vaginal cream	0.5g of vaginal cream (0.3mg dose) daily X 14 days, then twice weekly; dosage should be titrated to the lowest dose which manages symptoms Scent can be irritating for some persons Application can be messy may not be ideal for field settings with no hand washing facilities Insertion is less painful than tablets if severe atrophy present Can also be applied externally only for vulvar symptoms or recurrent urinary Tract Infections (UTIs)
✓	17β estradiol	Vagifem® vaginal tablets	10mcg tablet with applicator	Insert one vaginal tablet daily X 14 days, then one tablet twice weekly Comes with disposable applicator for each tablet, may be a good option for unsanitary or field settings Insertion can be painful if severe vaginal atrophy present
✓	17β estradiol	Estring® vaginal ring	2mg per ring	Remove current ring and insert a new vaginal ring every 3 months Requires clean hands, may be a good option for field exercises or deployments due to minimal changing requirements
✓		Imvexxy® vaginal ovules	4mcg, 10mcg ovules	1 ovule vaginally daily X 14 days, then twice weekly
✓	Estrone	Estragyn 0.1% vaginal cream	1mg/g of cream refillable applicator	0.5g of vaginal cream daily X 14 days, then twice weekly; dosage should be titrated to the lowest dose which manages symptoms

NOTE: All vaginal estrogens help to decrease urinary tract infections

Table 3: Systemic estrogen hormone therapy availability and dosing

Listed on CAF Drug Benefit List	Systemic estrogen type	Trade names	Strengths available			Comments
			Low dose	Standard dose	High dose *	
Oral estrogen (systemic) requires endometrial protection using progesterone if patient has a uterus						
✓	Conjugated estrogen (CE)	Premarin®	0.3mg	0.625mg	1.25mg	Once daily orally
✓	17β-estradiol	Estrace®	0.5mg	1mg	2mg	Once daily orally
Transdermal Estrogen (systemic) requires endometrial protection using progesterone if patient has a uterus						
✓	17β-estradiol patch Do not apply on breast	Estradot® or Oesclim®	25mcg	37.5mcg-50mcg	75mcg-100mcg patches	25-50mcg twice weekly patch application Patch can be cut to decrease dose
		Climara®	25mcg	50mcg	75mcg, 100mcg	Once weekly patch application Patch can be cut to decrease dose
✓	17β-estradiol gel Do not apply on breast	EstroGel® 0.06%	1 actuation	2 actuations	3-4 actuations	0.75mg per actuation Once daily gel application, apply regularly to same area of skin
		Divigel®	0.25mg	0.5mg	1mg	Once daily gel application, apply regularly to same area of skin

NOTE: If using high dose systemic estrogen, consider using a Mirena® IUS for endometrial protection for persons with an intact uterus which can reduce the risk of abnormal uterine bleeding

Table 4: Progestogen dosing for continuous and cyclic therapy

Listed on CAF Drug Benefit List	Progesterone type	Trade names	Strengths available	Comments	Comments
				Continuous regimen dosing	**Cyclic regimen dosing**
✓	Micronized Progesterone	Prometrium®	100mg capsule	Take 100mg orally at bedtime due to sedative effect	200mg PO daily for 12 to 14 days per month. Take at bedtime due to sedative effect
✓	Medroxyprogesterone acetate	Provera ®	2.5mg, 5mg, or 10mg tablet	2.5mg PO daily	5mg PO daily for 12 to 14 days per month
✓	Norethindrone acetate*	Norlutate ®	5mg tablet	5mg PO daily	*Off label use
✓	Levonorgestrel (LNG) intrauterine system (IUS)	Mirena®	52mg/device inserted intrauterine	Provides endometrial protection for up to 5 years. Mirena® is the only LNG-IUS marketed in Canada that has evidence of endometrial protection.	

Table 5: Combination hormone therapy availability and dosing

Listed on CAF Drug Benefit List	Combination hormone therapy preparations	Trade names	Strengths available	Comments
	Oral			
✓	17β-estradiol (E2) and drospirenone (DRSP)	Angeliq®	1mg E2 and 1mg DRSP tablet	Once daily PO
	17β-estradiol (E2) and norethindrone (NETA)	Activelle® LD	1mg E2 and 0.5mg NETA tablet; 0.5mg E2 and 0.1mg NETA tablet	Once daily PO
✓	Estradiol (E2) /micronized progesterone (MP)	Bijuva®	1mg E2 and 100mg MP tablet; 0.5mg E2 and 100mg MP tablet	Once daily PO in the evening with food Not indicated for patients without a uterus Moderate to severe Vasomotor symptoms
	Transdermal			
	17β-estradiol (E2) and norethindrone (NETA)	Estalis® 140/50 Estalis® 250/50	50mg E2 and 140mg NETA patch; 50mg E2 and 250mg NETA patch	Twice weekly application to skin Apply to buttocks or abdomen and rotate sites

Table 6: Non-hormone therapy options for vasomotor symptoms

Listed on CAF Drug Benefit List	Drug	Trade name	Strengths available	Comments
	Alpha-adrenergic agonist			
✓	Clonidine*	Catapres ®, Dixarit ® *Do not use extended-release version*	0.05mg, 0.1mg, 0.2mg, 0.3mg	Usual dose is 0.05mg PO twice daily Works well for night sweats Consider when person is already on Selective Serotonin Reuptake Inhibitors (SSRI) / Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) Some may require higher doses (e.g. 0.05mg TID) but side effects may limit use - Taper slowly to discontinue
	Serotonin-Norepinephrine Reuptake Inhibitors (SNRI)			
✓	Venlafaxine	Effexor ®	37.5mg ,75mg, 150mg	***1st choice of the non-hormone options*** Start at 37.5mg PO daily x 1 week, then increase to 75mg daily. Taper to discontinue
✓	Desvenlafaxine	PRISTIQ ®	100mg, 150mg	Start with 50mg PO daily, then increase to 100mg daily over a few days. Taper to discontinue
	Selective Serotonin Reuptake Inhibitors (SSRI)			
✓	Paroxetine	Paxil ®	10mg, 20mg, 30mg, 40mg	10mg to 20mg PO at bedtime Gradually taper over 2 to 4 weeks to discontinue
✓	Citalopram	Celexa ®	10mg, 20mg, 40mg	Usual dose is 20mg PO daily Gradually taper over 2 to 4 weeks to discontinue
✓	Escitalopram	Cipralex ®	10mg, 15mg, 20mg	Usual dose is 10mg PO daily

				Gradually taper over 2 to 4 weeks to discontinue
	Gabapentin			
✓	Gabapentin	Neurontin ®	100mg, 300mg, 400mg, 600mg, 800mg	Start at 300mg orally at bedtime, then increase in increments of 100mg every 3-4 days as tolerated to a target dose 900mg (300mg TID with last dose at HS). May take 3-4 weeks to reach effective dose for symptom improvement
✓	Pregabalin	Lyrica ®	25mg, 50mg 75mg, 100mg, 150mg, 200mg, 225mg, 300mg	150mg to 300mg PO daily
	Oxybutynin			
✓	Oxybutynin	Ditropan ®	2.5mg, 5mg	2.5mg or 5mg PO twice daily May cause cognitive decline in older women
	Oxybutynin XL	Only generic available	15mg	15mg PO daily

*Clonidine is the only non-hormone medication approved by Health Canada for treatment of vasomotor symptoms. All the other medications included in this table are being used off label.

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