MENOPAUSE 101

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Speaker disclosure

- I have/had an affiliation (financial or otherwise) with a pharmaceutical, medical device or communications organization:
  - I am a member of an Advisory Board or equivalent with a commercial organization: Astellas, Pfizer, Biosyent, Lupin, Searchlight, Duchesnay, Eisai, Idorsia, Knight, Sanofi, Bayer
  - I have received a grant(s) or an honorarium from a commercial organization: Astellas, Abbvie, Pfizer, Biosyent, Hologic, Bayer, Eisai, Lupin, Organon, Searchlight, Knight
  - I am currently participating in or have participated in a clinical trial within the past two years: ***Health Canada***
- *I do intend to make therapeutic recommendations for medications that have not received regulatory approval (i.e. "off-label" use of medication).*

Objectives

- Understand the landscape of menopause management in 2024
- Explore how developments in hormonal and non hormonal options can be used to individualize therapy

Defining Menopause: STRAW+10 Staging System

Menarche

Final Menstrual Period (FMP)

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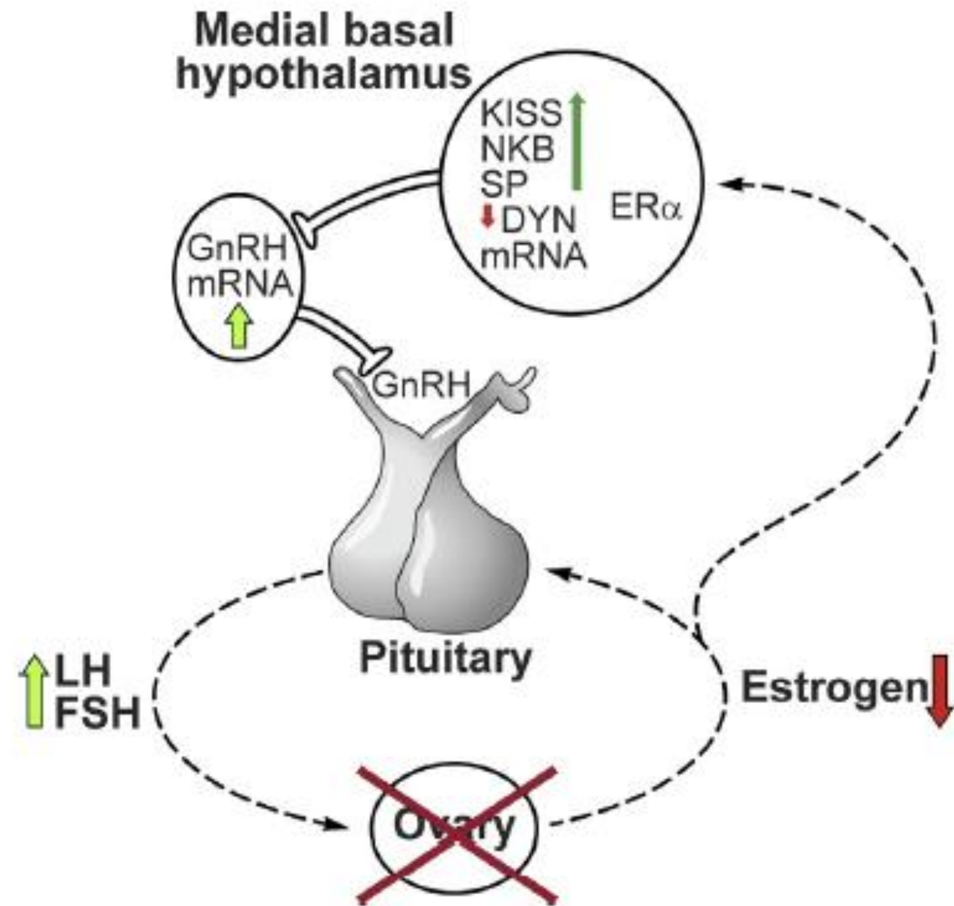
STAGES	-5	-4	-3b	-3a	-2	-1	+1a	+1b	+1c	+2
Terminology	REPRODUCTIVE				MENOPAUSAL TRANSITION		POSTMENOPAUSE			
	Early	Peak	Late		Early	Late	Early			Late
					PERIMENOPAUSE					
Duration	Variable				Variable	1-3 yrs	2 yrs (1+1)		3-6 yrs	Remaining lifespan
PRINCIPAL CRITERIA										
Menstrual cycle	Variable to regular	Regular	Regular	Subtle changes in flow/length	Variable length Persistent ≥7-day difference in length of consecutive cycles	Interval of amenorrhea of ≥60 days				
SUPPORTIVE CRITERIA										
Endocrine										
FSH				Variable	↑ Variable	↑>25 IU/L*	↑ Variable		Stabilizes	
AMH			Low	Low	Low	Low	Low		Very low	
Inhibin B			Low	Low	Low	Low	Low		Very low	
Antral Follicle Count			Low	Low	Low	Low	Very low		Very low	
DESCRIPTIVE CHARACTERISTICS										
Symptoms						Vasomotor symptoms (VMS) *likely*	Vasomotor symptoms (VMS) *most likely*			Increasing symptoms of genitourinary syndrome of menopause (GSM)

*Approximate expected level based on assays using current international pituitary standard; ↑ = elevated.
AMH, anti-Müllerian hormone; FSH, follicle-stimulating hormone
Adapted from: Harlow et al. *Menopause*. 2012;19(4):387-95.

Physiology of a hot flash



When Does Menopause Occur?

- Average age of natural menopause in white women from industrialized countries is 50 to 52 years (global range 45-53)[1]
- Onset varies by race, ethnicity, demographic and lifestyle factors, genetics, and social determinants[1]
- In 2019, nearly 7.5 million women in Canada were age 50 and over (40% of all women)[2]

Reminder:

Menopause is defined as the cessation of menstruation and is confirmed when 1 year has passed since the LMP.[3]

1. Gold. *Obstet Gynecol Clin North Am*. 2011;38(3):425-40; 2. Statistics Canada. Population estimates on July 1, 2019;
3. Harlow et al. *Menopause.* 2012;19(4):387-95.

An Update on Terminology

- Menopausal hormone therapy (MHT)
  - Also known as hormone therapy (HT)
  - Hormone replacement therapy (HRT) is now more commonly used to describe MHT in women with premature ovarian insufficiency (POI)

- Genitourinary syndrome of menopause (GSM)*
  - Describes signs and symptoms associated with reduced estrogen and involving changes to the labia major/minora, clitoris, vestibule/introitus, vagina, urethra, and bladder

Reminder:

"Progestogen" includes both natural progesterone and synthetic progestins that act on the progesterone receptor.

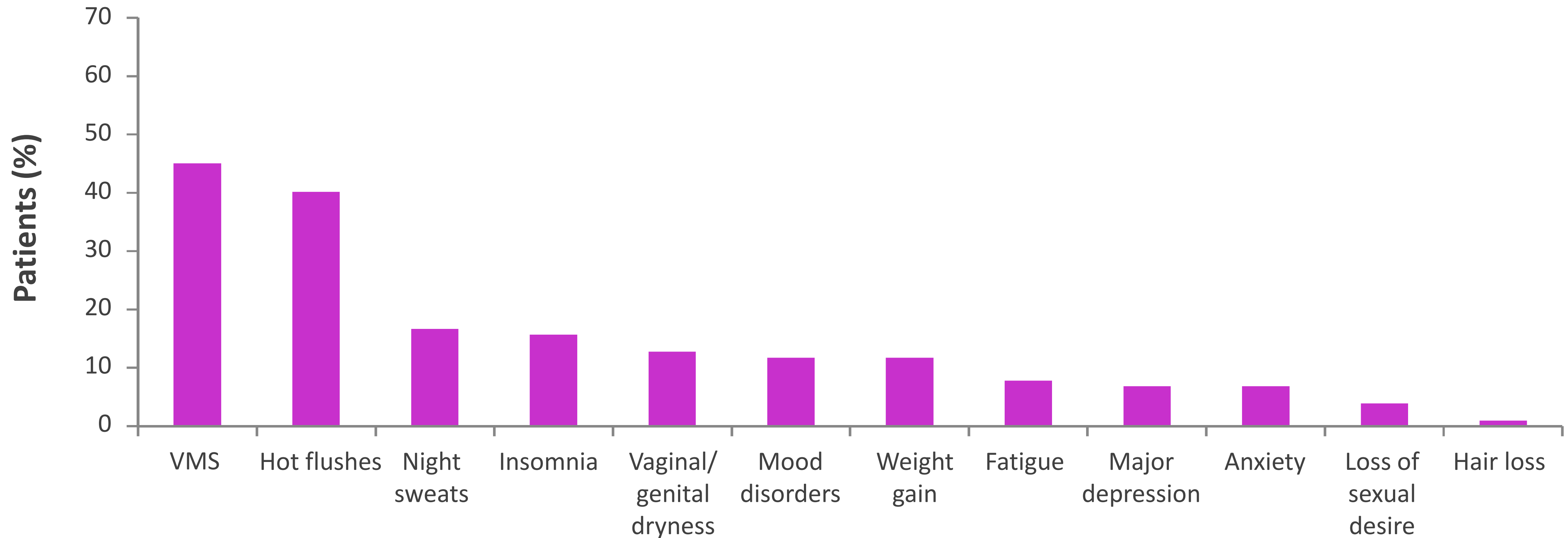
*Adopted by the International Society for the Study of Women's Sexual Health and the North American Menopause Society (NAMS).
Portman et al. *Menopause*. 2014;21:1063-8.

Guidelines Recommend MHT as the First-line Treatment for Symptoms of Menopause

- HT is the most effective treatment for vasomotor symptoms and genitourinary symptoms of menopause and has been shown to prevent bone loss and fracture[1]
- Duration of MHT should be individualized with **no mandatory limit on duration of use[1-3]**

1. NAMS 2017 Position Statement. *Menopause*. 2017;24(7):728-53; 2. Reid R et al. *J Obstet Gynecol Can*. 2014;36(suppl.1):S31-4; 3. Canadian Menopause Society. *Pocket Guide Menopause Management*. Available at: https://sigmamenopause.com.

Menopause: More Than Hot Flushes



Retrospective data from 102 randomly selected women on menopausal hormone therapy (MHT) from an American health plan from 2006 to 2011.
VMS, vasomotor symptoms
Sussman, et al. *BMC Women's Health*. 2015;15:58.

Indications for systemic MHT

SOGC guidelines: indication for treatment is vasomotor symptoms[1]

NAMS guidelines: treatment of VMS and prevention of osteoporosis[2]

IMS guidelines: other menopause related complaints such as joint and muscle pains, mood swings, sleep disturbances and sexual function may improve during MHT[3]

All guidelines reflect that ***initiation*** prior to the age of 60, or less than 10 years from the FMP carries the least risk and greatest benefit

1. SOGC Clinical Practice Guideline No. 422a J Obstet Gynaecol Can 2021;43(10):1188-1204 2. NAMS Position Statement Menopause 2022;29(7):767-794 3. IMS Guidelines Climacteric 2016;19(2):109-150

Clinical Factors That Can Inform Treatment Choices

- Presence of:
  - Contraindications to menopausal hormone therapy (MHT)
  - Comorbidities
  - Other menopausal symptoms
- Presence/absence of a uterus
- Patient preferences and insurance coverage

- Menopause is clinically diagnosed on the basis of menstrual history, symptoms, and age
- Measuring sex steroids or gonadotrophins routinely is not helpful, since they may fluctuate daily

Goldstein. *Can Fam Physician.* 2017;63:295-8; National Institute for Health and Care Excellence (NICE). *Menopause Full Guideline No. 23*. Available at: https://www.ncbi.nlm.nih.gov/books/NBK327156/; Australasian Menopause Society. *Diagnosing Menopause Information Sheet*. Available at: https://www.menopause.org.au/images/stories/infosheets/docs/AMS_Diagnosing_menopause.pdf.

Endometrial Protection Required in Women With a Uterus

- Unopposed estrogen increases the risk of endometrial hyperplasia and cancer
- Addition of systemic or intrauterine progestogen reduces endometrial cancer risk
- Guidelines advocate use of adequate dose and duration of endometrial protection in women with a uterus receiving **systemic** estrogen therapy

Options include:

- Micronized progesterone (MP)
- Progestins
- SERM (BZA) combined with CE

Did you know that…

- Since tibolone is a synthetic hormone with progestogenic effects, there is no need to take a progestogen with this type of MHT
- Progesterone skin creams may not be adequate for endometrial protection

NAMS 2017 Position Statement. *Menopause*. 2017;24(7):728-53; SOGC Guidelines. *J Obstet Gynaecol Can*. 2014;36(9):830-3; Australasian Menopause Society. *Tibolone for Postmenopausal Women Information Sheet.* Available at: https://www.menopause.org.au/hp/information-sheets/1287-tibolone-as-menopausal-hormone-therapy; Australasian Menopause Society. *Combined Menopausal Hormone Therapy (MHT) Information Sheet*. Available at: https://www.menopause.org.au/images/infosheets/AMS_Combined_MHT.pdf.pdf.

Optimal Timing of Initiation of MHT

- "The safety profile of MHT is most favourable when it is initiated by women aged younger than 60 years or within 10 years of menopause onset"[1]

- MHT should be initiated in women with premature ovarian insufficiency (menopause before age 40) and should also be considered for "early menopause" (i.e. before age 45), and continued until age of natural menopause[1]

in general, there is no age limit for prescribing MHT,
but the benefit-risk profile is most favourable for women aged
50 to 59 years or within 10 years of menopause.

1. NAMS 2017 Position Statement. *Menopause*. 2017;24(7):728-53; 2. IMS Recommendations on Midlife Women's Health and Menopause Hormone Therapy. Climacteric. 2016 Apr;19(2):109-50.

No Mandatory Limit to Duration of Use of MHT

Like most long-term treatment regimen…

“treatment should be individualized using the best available evidence to maximize benefits and minimize risks, with periodic re-evaluation for the benefits and risks of continuing HT.”[1]

Reminders:

- Use the appropriate dose for the appropriate patient for the appropriate period of time
- No indication to routinely discontinue after age 60 or 65 years
- No mandatory 5-year limit on duration of use
- Decision to continue therapy at discretion of well-informed patient and her HCP

HCP, health-care professional

1. NAMS 2017 Position Statement. *Menopause*. 2017;24(7):728-53; 2. IMS Recommendations on Midlife Women’s Health and Menopause Hormone Therapy. *Climacteric*. 2016 Apr;19(2):109-50.

Discontinuing Hormone Therapy?

- 25- 50% of women will continue to have vasomotor symptoms after stopping HT
- Most women will stop HT when VM benefits cease
- Stopping ‘cold turkey’ vs ‘slow tapering’ does not seem to influence likelihood of symptom return
- Decision to stop therapy needs to be made by patient and physician after a trial off hormones to see severity of symptoms…then based on individual determination of benefits vs potential risks.

Ness et al, Maturitas 2006;53(3):356-61
Haimov-Kochman et al, Menopause 2006;13:370-376

Individualizing Treatment for Menopausal Women

Women with a uterus who choose hormone therapy for management of menopausal symptoms have a choice to discuss with their physician:

- Estrogens paired with a progestogen
- Tibolone
- CE paired with BZA

EPT

- Combines an estrogen (oral or transdermal, depending on risk) with a progestogen (synthetic or micronized progesterone)
- Available as combination or individually
- Breast tenderness in 25% of women in first few months
- If used continuously, amenorrhea rates increase with duration of therapy, but unscheduled bleeding rates of about 10% still persist after 12 months of therapy

1. Crandall CJ, Aragaki AK, Chlebowski RT, et al. Arch Intern Med. 2009;169(18):1684-91.
2. Lobo RA et al. Obstet Gynecol. 2018;132(1):161-170.

MHT Products in Canada: Estrogens

Type of MHT	Trade Names	Strengths Available	Comments
Oral Estrogen			
17β-estradiol	ESTRACE®	0.5, 1, 2 mg tablets	1 tablet daily
Conjugated estrogens (CE)	PREMARIN®	0.3, 0.625, 1.25 mg tablets	1 tablet daily
Transdermal Estrogen Gel			
17β-estradiol	DIVIGEL®	0.25, 0.5, 1 mg packets	Daily application
	ESTROGEL®	0.75 mg estradiol per 1.25 g metered dose (1 actuation)	Daily application, use in same area
Transdermal Estrogen Patches			
17β-estradiol	CLIMARA®	25, 50, 75, 100 μg	Once weekly application
	ESTRADOT®	25, 37.5, 50, 75, 100 μg	Twice weekly application
	OESCLIM®	25, 50 μg	Twice weekly application
	Sandoz Estradiol Derm (generic)	50, 75, 100 μg	Twice weekly application

Canadian Menopause Society. *Pocket Guide Menopause Management*. Available at: https://sigmamenopause.com; Individual product monographs.

Selecting a Progestogen

Synthetic progestins	Micronized progesterone
Link to thrombosis when used with estrogen (dose dependent)	Less thrombogenic
Blood pressure neutral	Lowers blood pressure slightly
Robust endometrial protection	Endometrial protection dose dependent
Breast cancer risk?	Less breast cancer risk?
Absorbed orally, some preparations transdermally	Absorbed orally or vaginally, but not transdermally in sufficient quantity
Choices of agent, dose and regimen	Choice of dose and regimen, oil additives

MHT Products in Canada: Progestogens

Type of Progestogen	Trade Names	Strengths Available	Comments
Levonorgestrel Intrauterine System (IUS)			
Levonorgestrel IUS	MIRENA®*	52 mg/IUS, for 5 years*	Off-label use
Oral Progestogen			
Medroxyprogesterone acetate (MPA)	PROVERA, generics	2.5, 5, 10, 100 mg tablets	
Norethindrone acetate	NORLUTATE®	5 mg tablet	
Progesterone, micronized	PROMETRIUM®, generics	100 mg capsule	Take at bedtime because of sedating effect. Note: generics may contain peanut oil.

*Note: Mirena is the only levonorgestrel-IUS marketed in Canada that has evidence for endometrial protection; it is not indicated for menopausal symptom relief but is recognized as an option for endometrial protection for up to 4 to 5 years of continuous use in other jurisdictions (British Menopause Society).

Canadian Menopause Society. *Pocket Guide Menopause Management*. Available at: https://sigmamenopause.com; Panay et al. *Menopause Int.* 2013;19(2):59-68;
Individual product monographs.

What Is Tibolone?

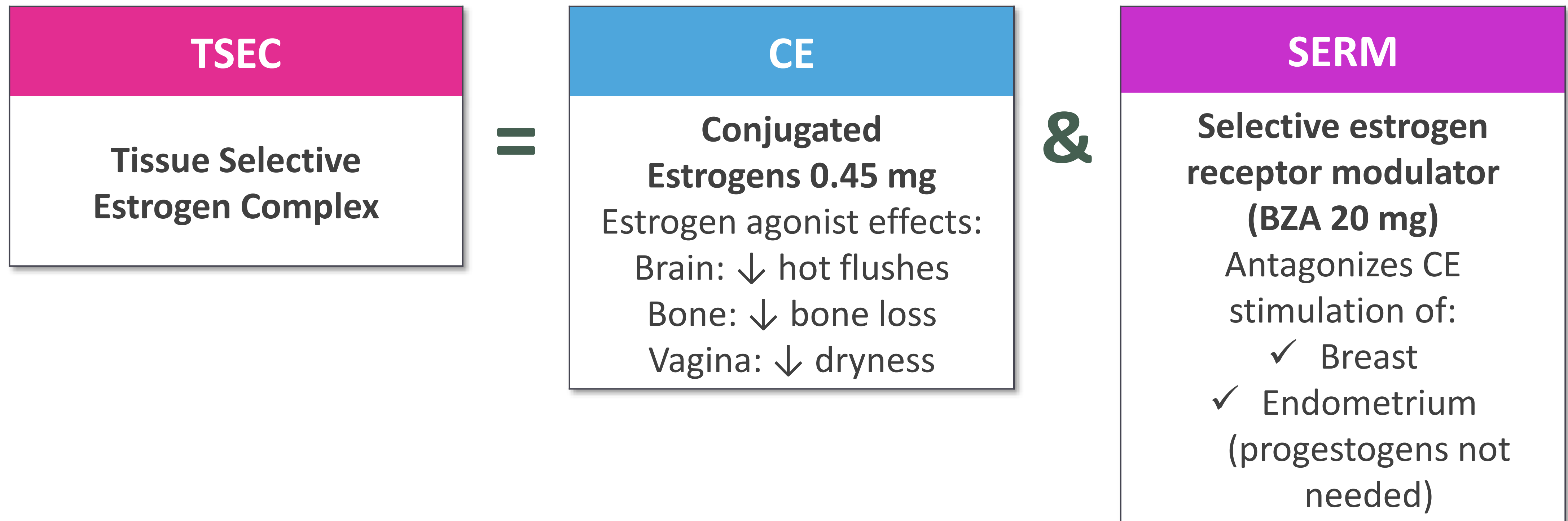
- A synthetic steroid hormone derived from Mexican yam
- Its metabolites have hormonal effects

Estrogenic Effects	Progestogenic Effects	Androgenic Effects
Brain: ↓ hot flushes Bone: ↓ bone loss Vagina: ↓ dryness	Uterus: ↓ endometrial thickening and bleeding	May enhance mood and libido

Australasian Menopause Society. *Tibolone for Postmenopausal Women Information Sheet*.
Available at: https://www.menopause.org.au/hp/information-sheets/1287-tibolone-as-menopausal-hormone-therapy.

What Is a Tissue Selective Estrogen Complex (TSEC)?

Pharmacology that is distinct from CE or SERM components alone



Komm, Mirkin. *Int J Women's Health.* 2012;4:129-40.

Combination Hormone Therapy Differences

	EPT	Tibolone	TSEC
Unscheduled bleeding	25% first 6 months, 10% at end of first year	15-20% first six months, 10% at end of first year	4% first six months, less than 2% at one year
Breast tenderness	25% in first 3 months, 10-15% at end of first year	Similar to placebo	Similar to placebo
Breast density	Increased, in a dose dependent fashion	Similar to placebo	Similar to placebo

Balancing the Benefits and Risks of MHT

Symptom relief:

- ✓ VMS, GSM
- ✓ Bone (and fracture) protection
- ✓ May improve mood, sleep, joint pain, quality of life

May increase risk of:

- ✓ Cancer
- ✓ Cardiovascular disease (CVD) (women >60 years)
- ✓ VTE

VTE, venous thromboembolism

NAMS 2017 Position Statement. *Menopause*. 2017;24(7):728-53.

Practical Tool for Discussing Menopausal Symptoms: Menopause Quick 6 (MQ-6)

1. Have you and any changes in your periods?
2. Are you having any hot flushes?
3. Are you having any vaginal dryness or pain, or sexual concerns?
4. Are you have any bladder issues or incontinence?
5. How is your sleep?
6. How is your mood?

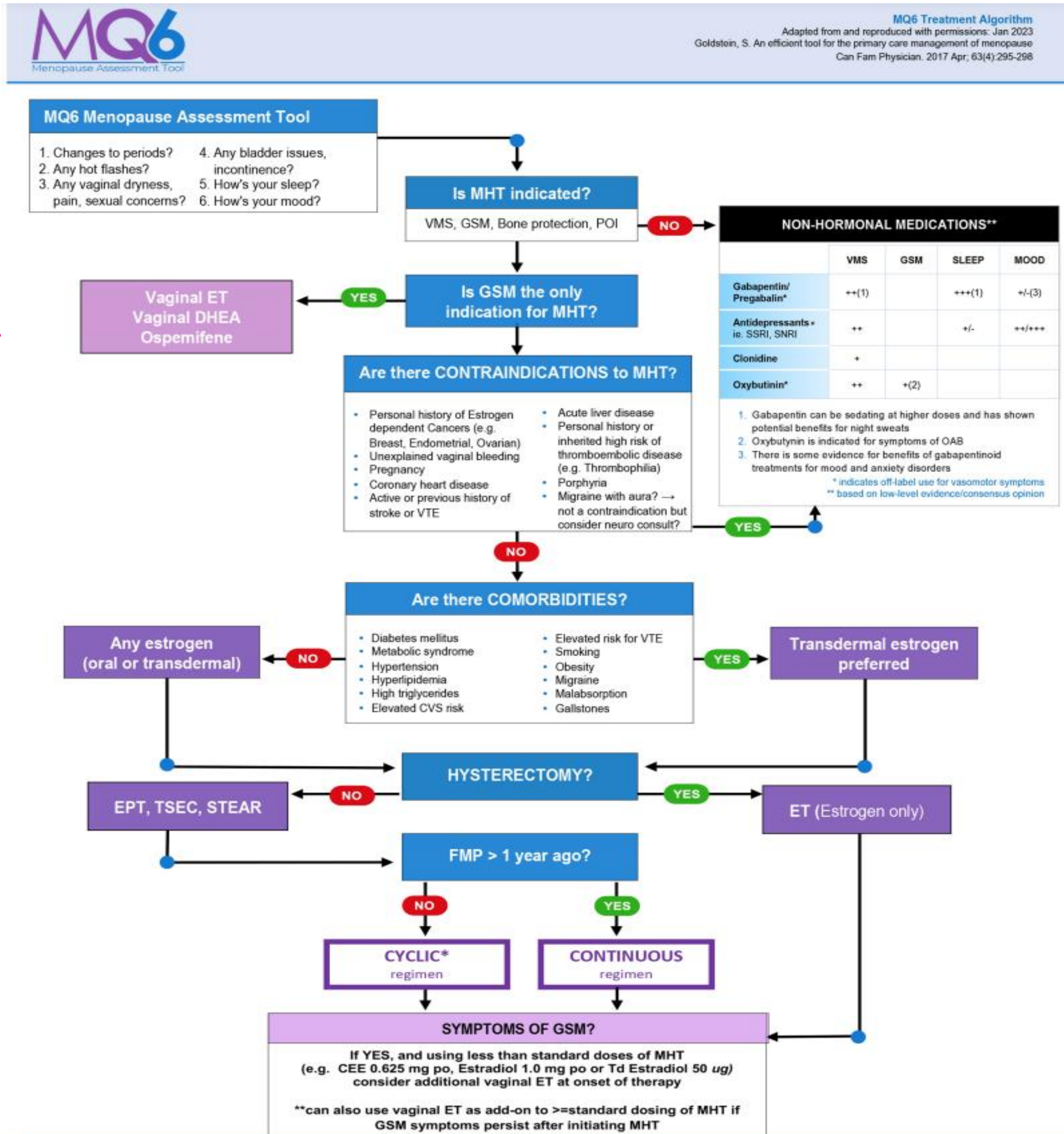
The SOGC & International Menopause Society guidelines recommend that questions 2 to 6 be asked of all perimenopausal women.

SOGC, Society of Obstetricians and Gynaecologists of Canada

Baber et al. *Climacteric.* 2016;19:109-50; Goldstein. *Can Fam Physician.* 2017;63:295-8; Reid et al. *J Obstet Gynaecol Can.* 2014;36:830-8.

Resources

- https://mq6.ca/mq6-interactive-algorithm/
- https://www.sigmamenopause.com/sites/default/files/pdf/publications/Final-Pocket%20Guide.pdf
- SOGC/CMS guidelines 2021
- TMS position statements 2022/2023
- https://www.imsociety.org/wp-content/uploads/2024/10/2024-WMD-Leaflet_English.pdf



Optimal Management of Menopause 2024

Symptomatic Menopausal Management

- Take symptoms seriously
- Safety for HT in younger symptomatic women
- Options: Hormonal and non-hormonal

Asymptomatic Management

- Pay attention to asymptomatic problems that occur after menopause
- 8 optimal AHA 8 Healthy Heart Habits
- BMI, BP, Glucose, exercise ,diet, Lipids no smoking
- Changes in fat deposition
  - Risk of diabetes

Hasban N , Circulation 2022;145:808-818

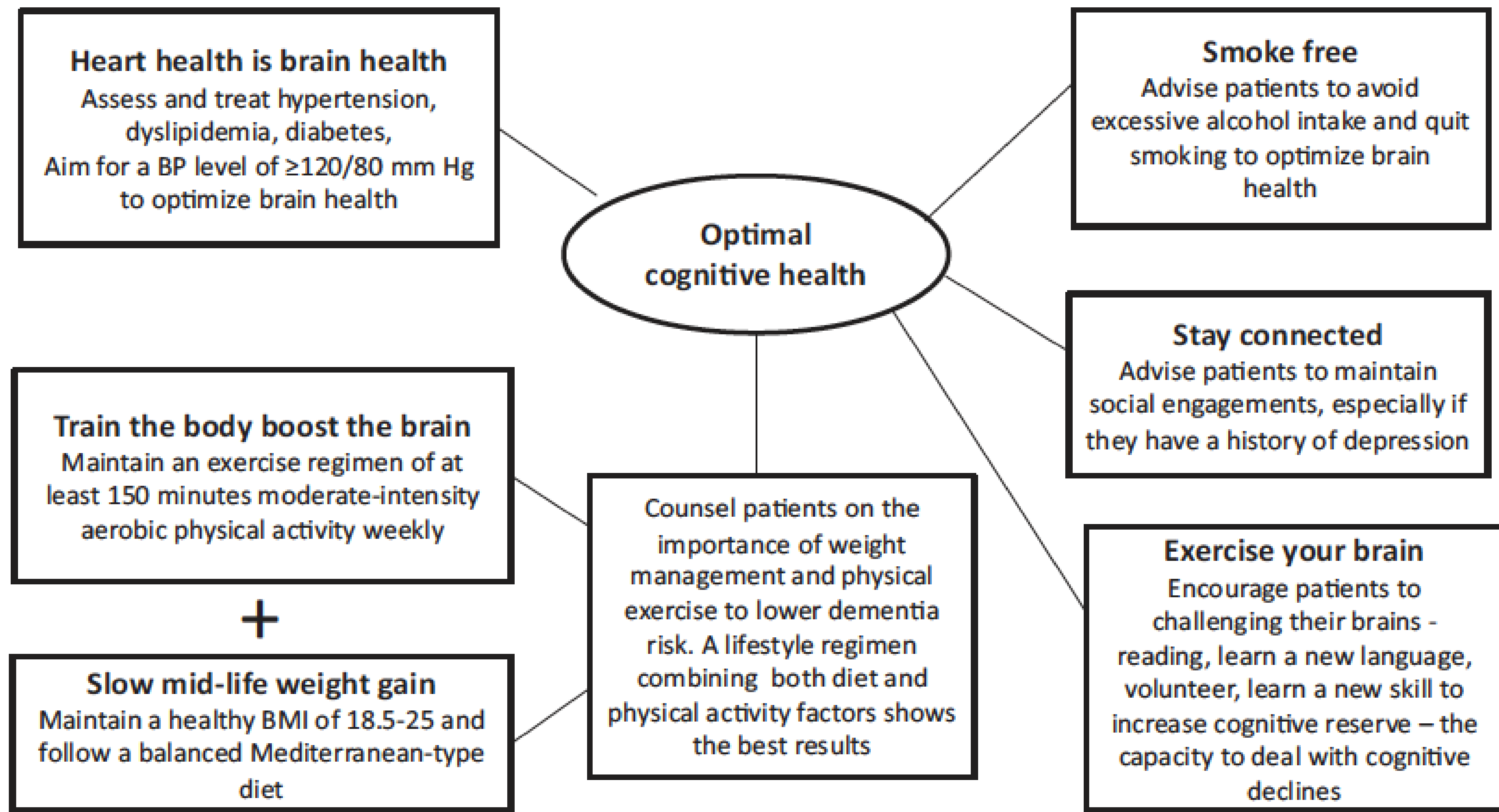


Figure 3. Patient tips to optimize brain health based on modifiable risk factors for dementia. From modifiable risk factors for dementia prevention from the World Health Organization (WHO) 2019 guidelines and the 2020 Lancet Commission [56,57]. BMI, body mass index; BP, blood pressure.

Contraindications to Systemic MHT

Table 1. Contraindications to systemic menopausal hormone therapy

Contraindications to estrogen	Contraindications to progestogen
• Undiagnosed abnormal vaginal bleeding • Known, suspected, or history of breast cancer • Known or suspected estrogen-dependent cancers (i.e., endometrial, ovarian) • Coronary heart disease • Active or history of venous thromboembolism • Active or history of stroke • Known thrombophilia • Active liver disease • Known or suspected pregnancy	• Undiagnosed abnormal vaginal bleeding • Current or history of breast cancer

Not on the list: Smoking, migraines with aura, obesity, hypertension

SOGC Clinical Practice Guideline No. 422a J Obstet Gynaecol Can 2021:43(10);1188-1204

Nonhormonal Options for VMS

Not recommended

- Cooling techniques
- Avoiding triggers
- Exercise
- Yoga
- Dietary changes
- Paced respiration
- Relaxation
- Pregabalin
- OTC supplements/herbals
- Acupuncture
- Clonidine
- Mindfulness
- Soy derivatives
- Cannabinoids
- Chiropractics
- Calibration of neural oscillations

Recommended [Level I-III] evidence

- **Fezolinetant**
- Selective serotonin reuptake inhibitor (SSRI)/Serotonin-norepinephrine reuptake inhibitor (SNRI)
- Gabapentin
- Oxybutynin
- Cognitive behavioural therapy (CBT)
- Hypnosis
- Weight loss
- Stellate Ganglion Block

NAMS 2023 Position Statement. Nonhormonal Management of Menopause-Associated Vasomotor Symptoms

"Natural" and Compounded Products

- >50% of menopausal women use some form of complementary and alternative medicine (CAM) for management of midlife and menopausal symptoms[1]
- Custom-compounded hormone preparations are not recommended or endorsed by Health Canada or any medical societies[2,3]
  - They are not subject to rigorous manufacturing standards, quality control, and regulatory oversight
  - They are not "natural"
  - They are associated with a risk of endometrial stimulation
  - There is no high-quality evidence for efficacy

- "Bioidentical" means having the same molecular structure as a substance produced in the body
- Estradiol and MP are pharmaceutical-grade bioidentical forms of MHT

MP, micronized progesterone

1. Canadian Menopause Society. *Pocket Guide Menopause Management*. Available at: https://sigmamenopause.com; 2. International Menopause Society. *Climacteric*. 2016;19(2):109-50;
3. NAMS 2017 Position Statement. *Menopause*. 2017;24(7):728-53.

Key Learnings

- Menopausal symptoms are common and can significantly impair quality of life
- To engage in informed decision-making, patients must be aware of the benefits and risks of menopausal hormone therapy (MHT)
- Selection of MHT should be based on an individualized, evidence-based approach that considers signs, symptoms, comorbidities, and patient preferences
- Guidelines are useful to help physicians initiate and monitor patients with MHT

Many women suffer from menopause in silence.

These woman go through many emotions (shame, distress, anxiety, fear, etc.) and need HCPs to accompany them in seeing their future bright.

There is no valid reason not to prescribe MHT to a patient exhibiting distressing menopausal symptoms.