News Flash Meets Hot Flash:

Update on Pharmacotherapy for Menopause

Maria Migas MD, CCFP, FCFP, MSCP Dalhousie Family Medicine Grand Rounds January 9, 2025

Disclosures

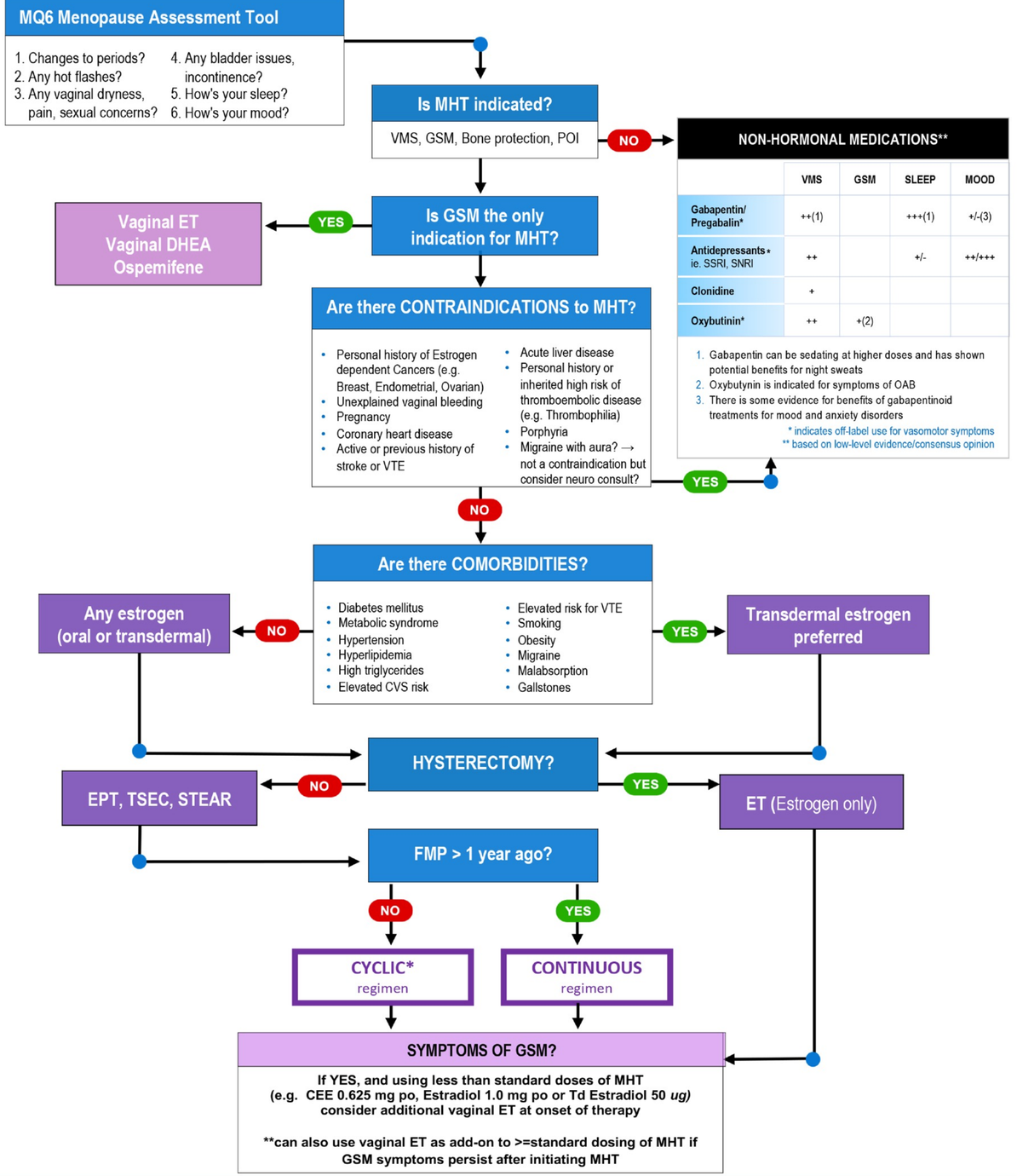
- **Faculty:** Maria Migas, MD, CCFP, FCFP, MSCP

- **Relationships with financial sponsors: None**

- **<u>Potential for conflict(s) of interest</u>:**
- ***Co-founder of the Menopause Society of Nova Scotia, a not-for-profit society whose purpose is to provide education about Menopause, and resources for individuals, families, health care providers and employers.***
- ***Co-founder of Three Wise Women Ltd., a new company focused on wellness and lifestyle strategies for women in midlife.***

Learning Objectives

- Identify common and uncommon symptoms associated with the menopause transition.
- Summarize evidence-based therapies to treat menopausal symptoms.
- Apply current guidelines on menopause hormone therapy to patients with moderate to severe symptoms.



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

Pause for Menopause

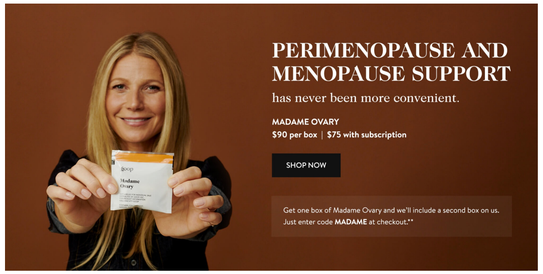
Gen X is over having their menopause and sex concerns brushed aside
The Globe and Mail. July 7, 2023

Hormone replacement therapy should be first line of treatment for menopausal women under 60, study says
The Globe and Mail. May 15, 2023

"The Menopause Talk" with Oprah, Drew Barrymore, and Maria Shriver"

Silent Suffering

Menopause has long been a taboo topic. Talking about it can help women learn more about an overlooked treatment.



Drew Barrymore's Hot Flash on live TV

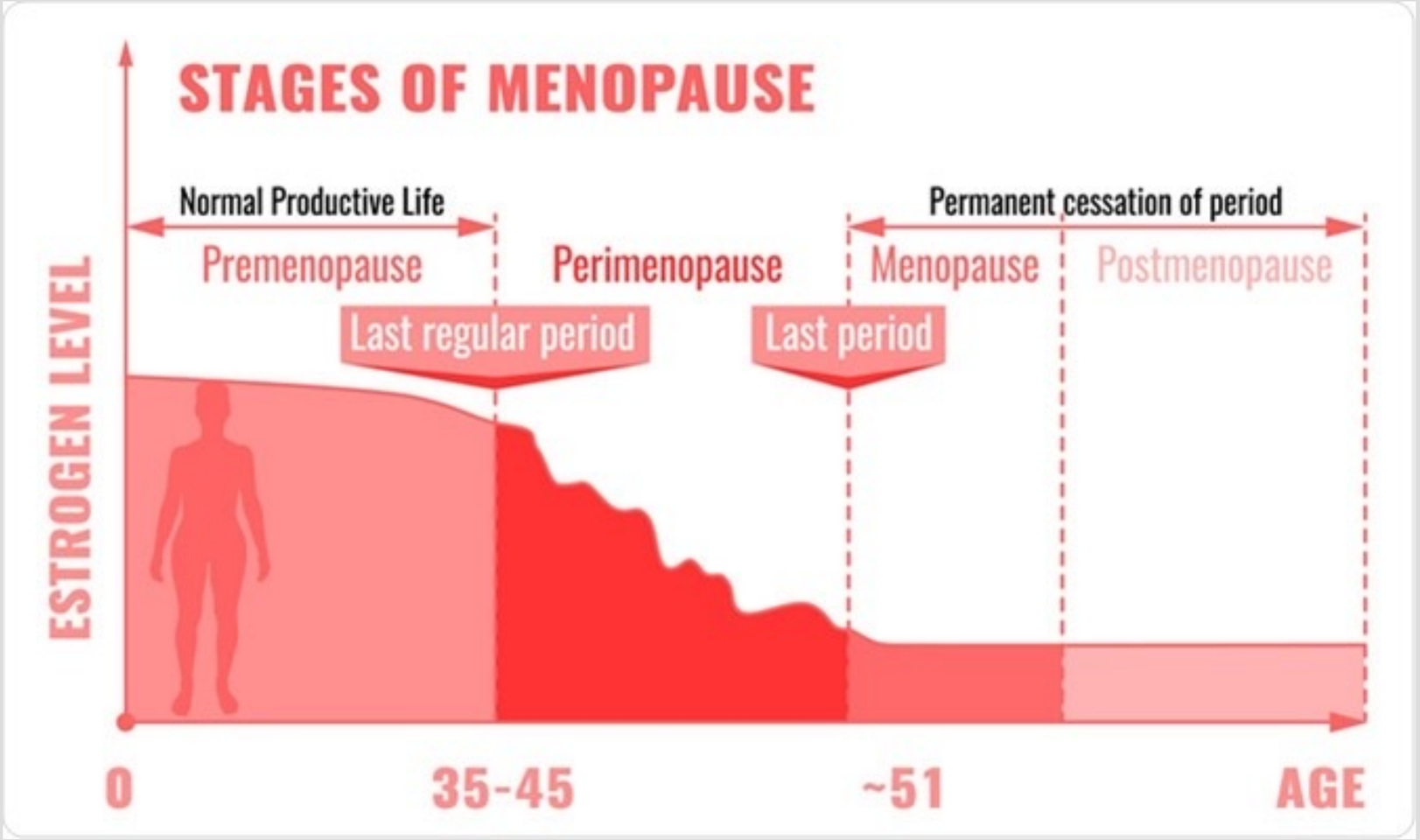
Menopause Matters

- **100** % of adult females will experience menopause, regardless of race, culture, ethnicity or gender.
- 50 % of Cdn women who feel unprepared for this life stage*
- 77 % of Cdn women who turn to their health care provider as the preferred source of advice*
- 75 % who sought out advice felt no help or somewhat helpful*
- 50 % seek out extended health care, 13% exclusively extended health care (e.g. massage therapists, naturopaths)**
- 43 % of Cdn women who will be at least 50 yrs old in 2038.
- $3.3 Billion the estimated lost income due to reduced hours or pay due to *un*managed menopause symptoms*

* *Menopause Foundation of Canada reports : "The Silence and the Stigma" released October 2022, and "Menopause and Work in Canada" released October 16, 2023*.

** *HER_BC_Report - Health and Economics Research on Midlife Women in BC Report.* Women's Health Research Institute, Vancouver BC. November 1, 2024.

The Menopause Transition




Symptoms
Progesterone
Estradiol
Puberty
Reproductive Years
Peri Menopause
Post Menopause

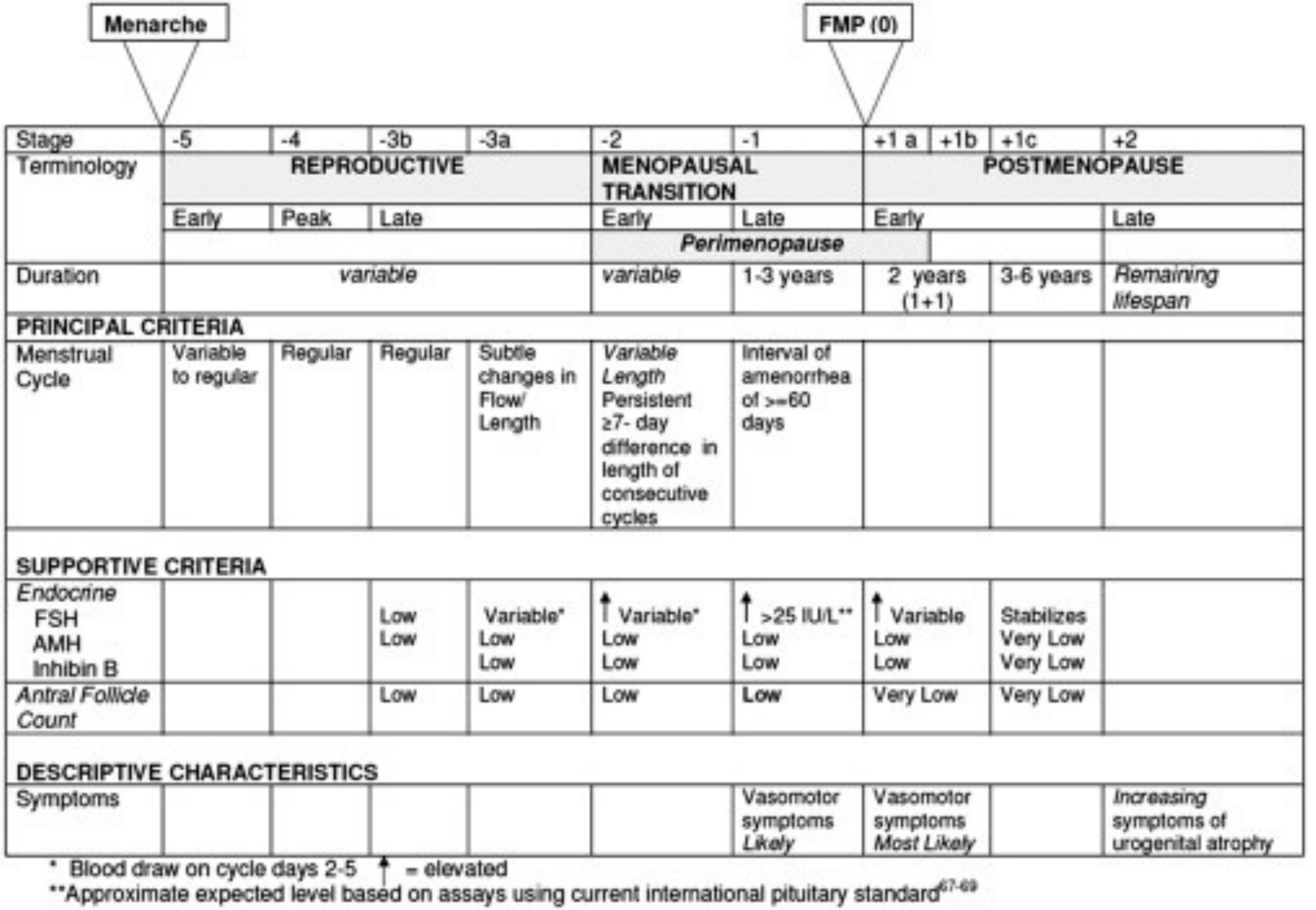


Diagram from Harlow S. D. et al. Executive Summary of the Stages of Reproductive Aging Workshop +10: addressing the unfinished agenda of staging reproductive aging. *Fertility and Sterility*. Vol 97, Issue 4. April 2012

Common Symptoms of Menopause

Vasomotor Symptoms
(HOT FLASH):

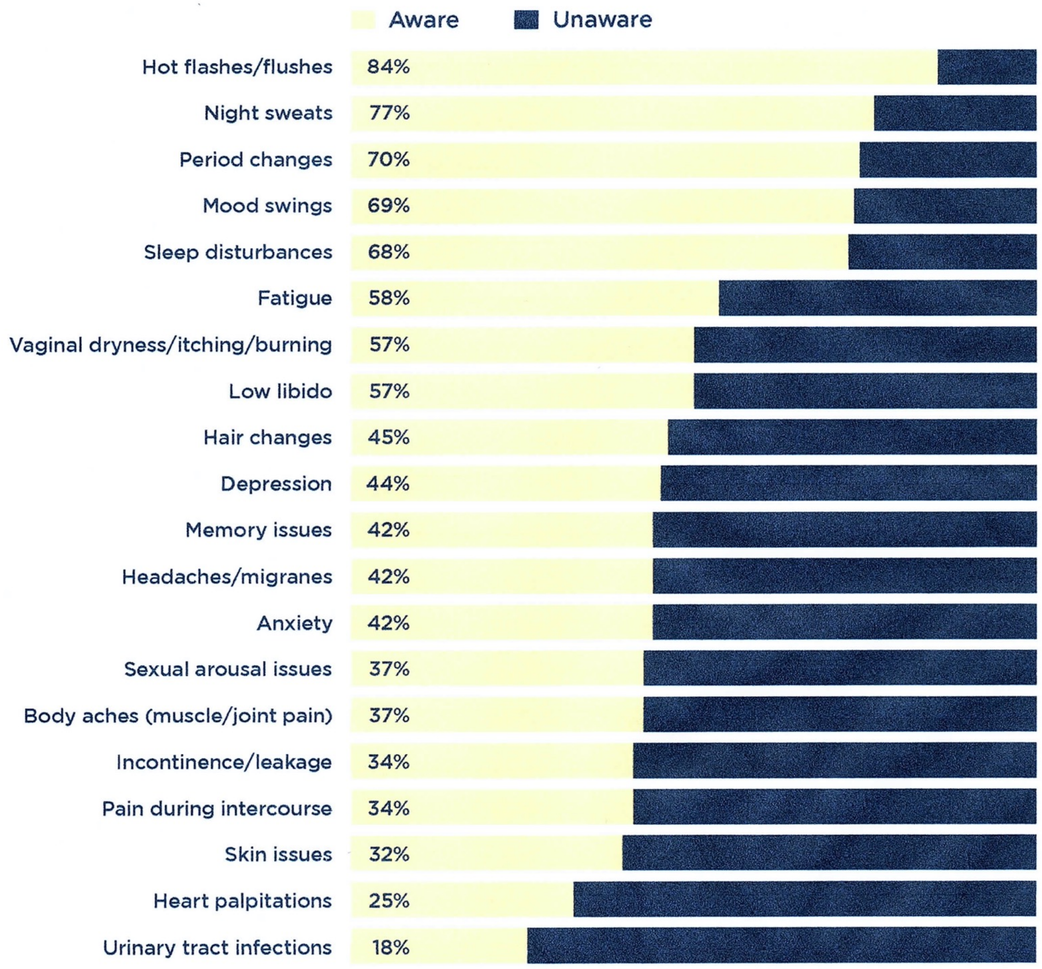
- 80% of women
- Interruption of thermoregulatory system
- Plateaus with time but can persist for decades (15%)
- Can vary by race/ethnicity (US data)
- Can be a red flag for medical conditions (e.g. B symptom)
- Very treatable.

Genitourinary Syndrome of Menopause (GSM):

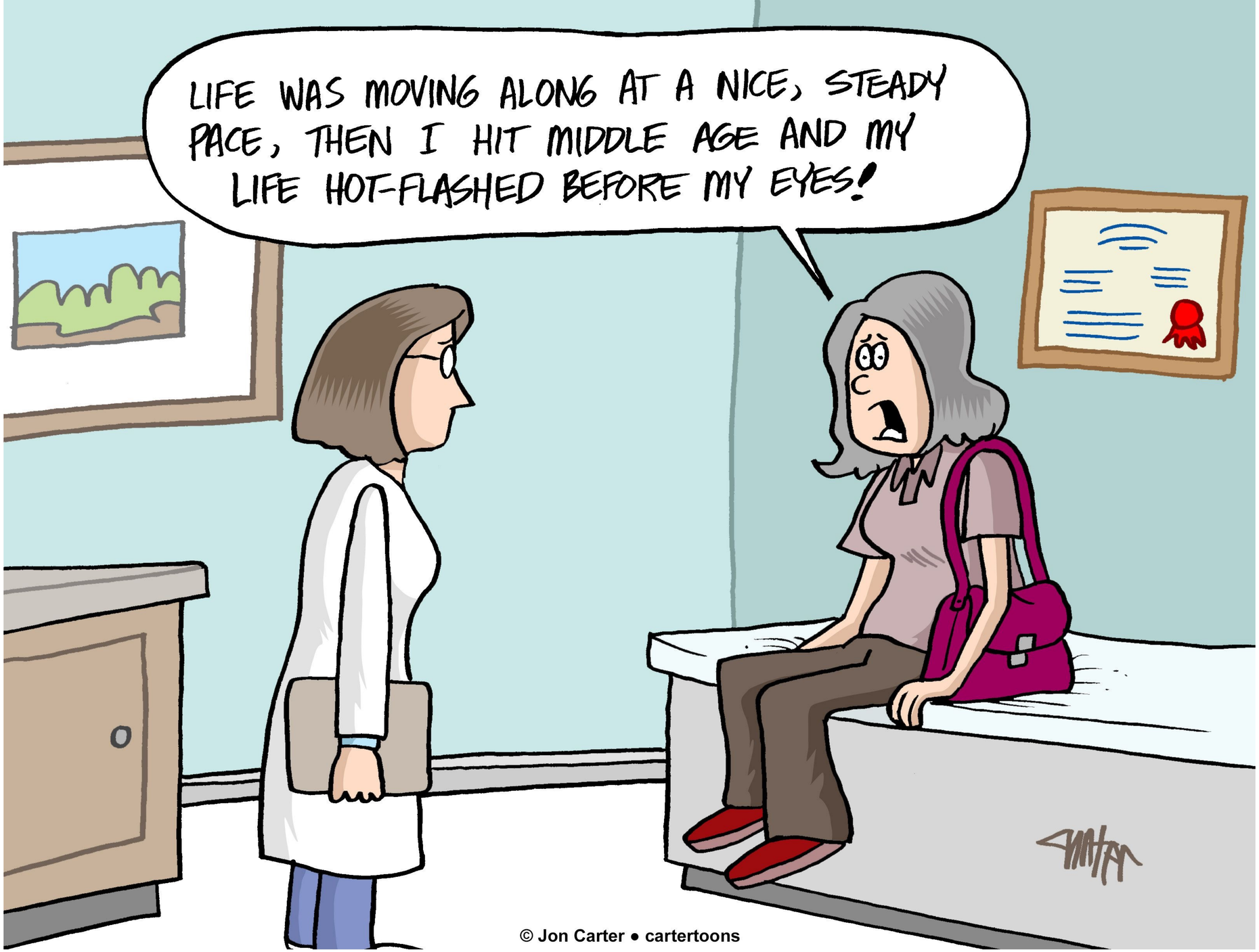
- Collection of signs/symptoms involving the GU tract
- 50-70% of postmenopausal women
- Significant negative impact on sexual function (80%)
- Symptoms are progressive.
- Underdiagnosed yet very treatable <u>at any age</u>.

Knowledge of Symptoms

There are more than 30 symptoms associated with the hormonal changes that occur through menopause. While many respondents were aware of common menopausal symptoms like hot flashes, night sweats and period changes, many other common symptoms had very low awareness.



Source: The Silence and the Stigma - report from the Menopause Foundation of Canada (October 2022)



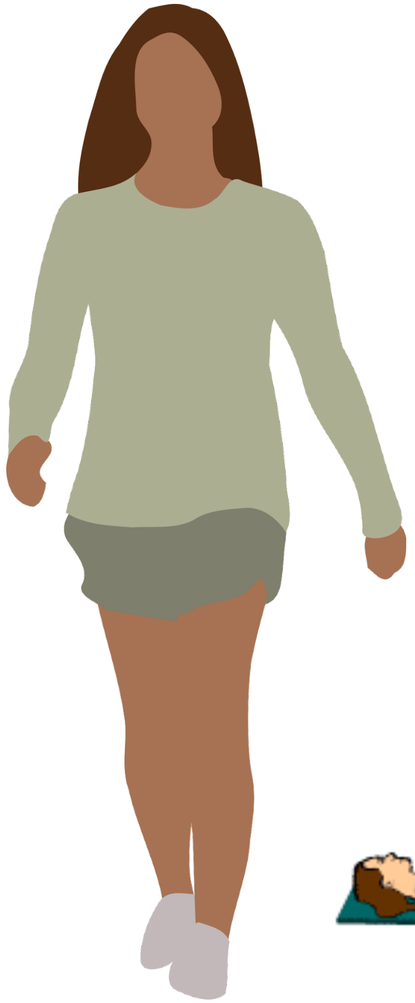
Evaluating symptoms

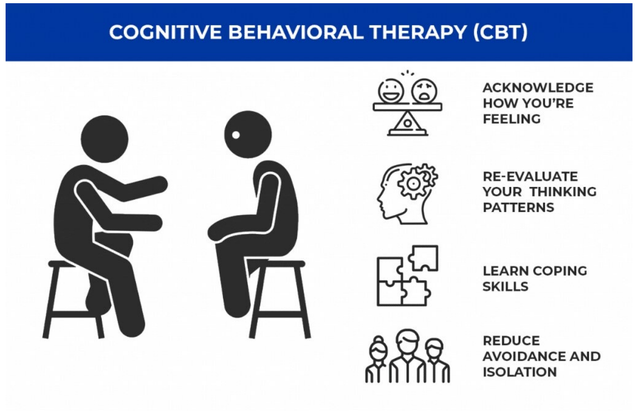
- Focused history and physical/vitals
- https://mq6.ca/mq6-assessment-tool/
- Bloodwork:
  - CBC, ferritin, B12
  - TSH
  - Anti-inflammatory markers, ANA
  - Cardiac risk factor screening - Lipid profile, diabetes
  - Hormone markers?

Management Options

Lifestyle strategies	OTC/Non-hormonal Rx	Hormone Therapy
Evidence-based strategies to continue through the lifespan.	For symptomatic relief for women who are not eligible for, or not desiring HT.	For symptomatic relief of VMS and GUSM.

Non-Pharmacologic Options & Lifestyle modification





Non-Hormonal Rx

- SSRI/SNRI: Citalopram 10-20 mg od, Paroxetine 10-20 mg, Venlafaxine 37.5-75 mg (25-65% reduction in VMS)
- Gabapentin: 100 -900 mg po hs (25-65% reduction in VMS), Pregabalin 150 -300 mg po od
- Clonidine 0.05 mg po BID **
- Oxybutinin 2.5-5 mg po BID (VMS and OAB)
- Fezolinetant 45 mg po od - NEW class - Neurokinin 3 receptor antagonist. Health Canada Approved.
- OTC products: vaginal moisturizers with hyaluronic acid, lubricants

BC NEWS

You are in: Health

Wednesday, 10 July, 2002, 11:29 GMT 12:29 UK

HRT linked to breast cancer

The study examined estrogen and progestin

Women who take hormone replacement therapy may be at increased risk of brea cancer, heart disease and stroke, a study suggests.

s Front Page
World
UK
England
N Ireland
Scotland
Wales
Politics
Business
ntertainment
ience/Nature
Technology
Health
dical notes
Education
lking Point
untry Profiles
In Depth
rogrammes

Hormone Replacement Therapy – WHI (2002) report

WHI study

- > 27,000 US women aged 50-79 (mean age 63)
- Primary Q: HRT prevent CHD?
- RCT: Uterus: CEE + MPA
  No Uterus: CEE only
- Increased risk of breast cancer, CVD, PE → Study was halted.

—> **Risk outweighed Benefit**

Lessons Learned

(*Manson et al, JAMA 2013, 2017)*

- Risks of breast cancer, CVD, and PE exist but are much lower or nil in the 50-59 yr age.
- No progression of atherosclerosis in women starting HT within 3 years of menopause (KEEPS study)

—> **Benefits outweigh Risks**

WHI - Absolute Risks

(/10000/yr)

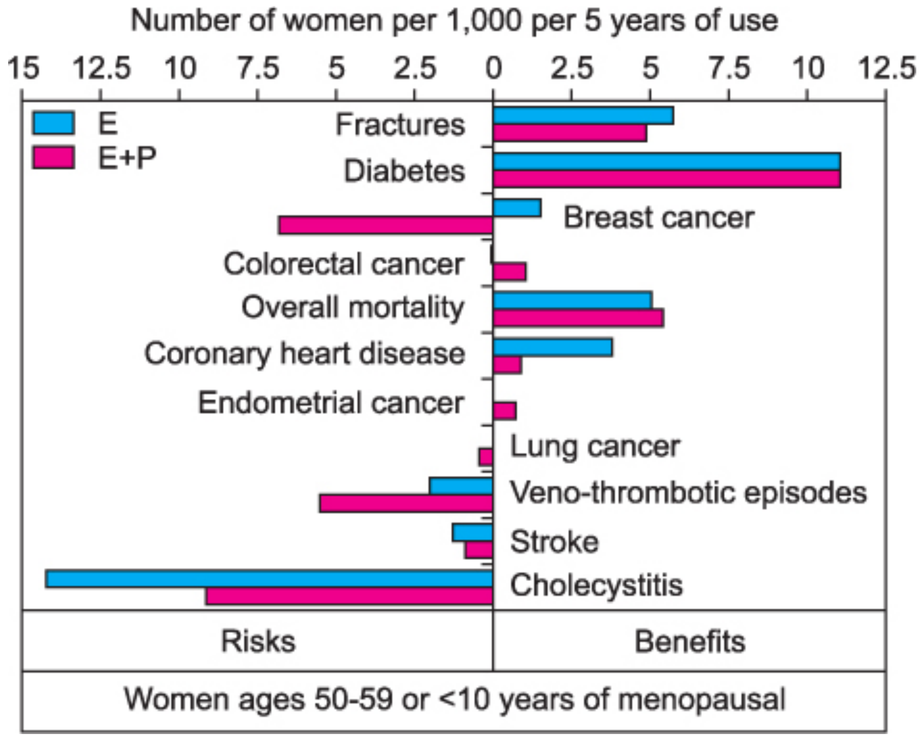
	EPT	ET
Breast Cancer	8	-6
MI	7	-3
CVA	8	12
VTE	18	7
Hip Fracture	-5	-7
COLON CA	-6	1

WHI results for 50-59 age group

(/1000/5 years)

	EPT	ET
Breast Cancer	3	-7
MI	-1	-4
CVA	1	1
VTE	6	2

"Postmenopausal hormone therapy: an Endocrine Society scientific statement", by Santen RJ,et al, 2010, J Clin Endocrinol Metab, 95, pp.s1-66.



Risks and benefits of hormone therapy in women starting between the ages of 50 and 59 year or less than 10 year after the start of menopause.

"Postmenopausal hormone therapy: an Endocrine Society scientific statement", by Santen RJ,et al, 2010, J Clin Endocrinol Metab, 95, pp.s1-66.

Women Have Been Misled About Menopause

Hot flashes, sleeplessness, pain during sex: For some of menopause's worst symptoms, there's an established treatment. Why aren't more women offered it?

Current MHT guidelines*

Strong recommendations

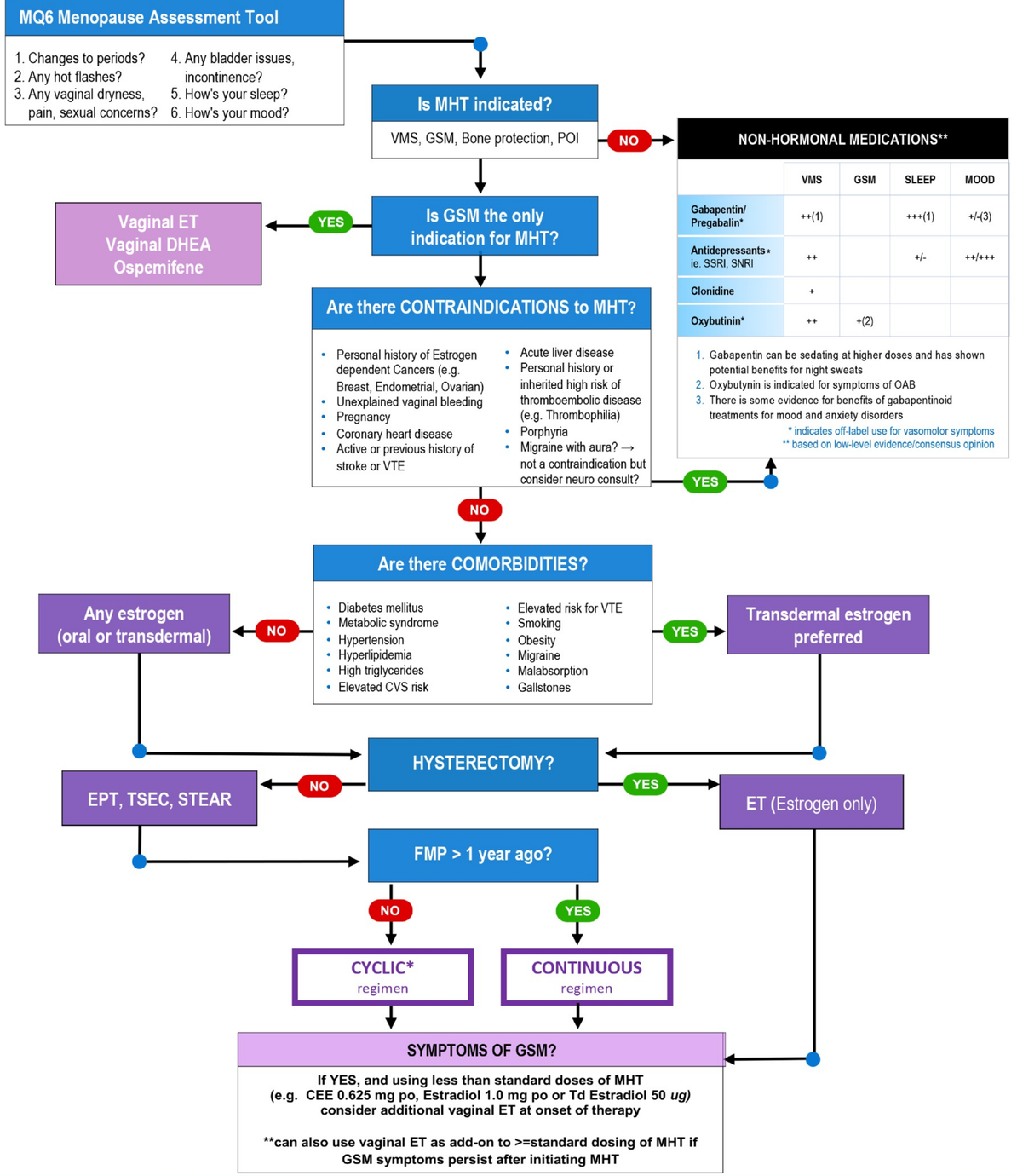
- MHT is approved for the first-line treatment of moderate to severe VMS in eligible females.
- Local vaginal ETs recommended for moderate to severe vaginal dryness and symptoms of GUSM. Can be given at any age and do not require added progesterone.
- Treat symptoms within the 10 years from the FMP or under the age of 60 yrs, for short term (2-5 years)*, at the lowest effective dose.

**Society of Obstetrics and Gynaecology Canada (SOGC) Clinical Practice Guidelines on Managing Menopause, August 2021.*

MHT considerations

- Estrogen +/- Progestogen, Tissue Selective Estrogen Complex (TSEC) Selective Tissue Estrogenic Activity Regulator
- If uterus is present, must add a progestogen to systemic estrogen to prevent endometrial hyperplasia and ca (not
- Transdermal ET if there is an increase risk of CVD, liver, gallstones, DM, Obesity, HTN, or smoker.
- Common AEs: unexpected vaginal bleeding, breast tenderness, mood changes, headache.
- Perimenopause? consider contraception options
- Benefits of MHT: No hot flashes, no vaginal dryness, bone protection!!

Bottom Line: Individualized approach with discussion of benefits vs risks and patient preferences.



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

Estrogen therapy

Formulations

Oral :

Conjugated estrogen (0.3, 0.625, 1.25 mg)

17B-estradiol (0.5, 1, 2 mg)

Transdermal :

17b-estradiol Patch 25-100 mcg. (1-2x weekly)

17b-estradiol Gel 0.75 per 1.25 g metered dose (daily)

V*aginal:*

CEE cream 0.625mg/g, 0.5-1mg pv hs

Estrone 1 mg/g

17b-estradiol 10mcg tab

17b-estradiol ring

- Oral - daily dose, cheaper, but VTE/Stroke risk, first pass at liver.
- Transdermal best for smokers, or migraines, high TGs, HTN, because by-passes liver
- Gel: need to apply to same area daily and let gel dry for 2 mins
- Matrix patch: can have irritation at patch site but can cut it when wanting to wean off.

Progesterone Therapy

Formulas

Oral :

Medroxyprogesterone (2.5 mg continuous, 5-10 mg po od X 10-14 days cyclical)

Micronized progesterone (100-200 mg od or 200-300 mg cyclical)

Intrauterine system:

Levonorgestrel (52 mg)

- Oral - MPA is cheaper, not appropriate for women with breast cancer risk.
- Cyclical oral PT and IUD best during *perimenopause*
- Sedating - best to take hs
- If oral formula is not tolerated, evidence supporting IUS.
- Risks of IUD insertion

Combination products

Oral :

17b Estradiol/norethindrone acetate (1 mg/0.5 mg)

17b Estradiol/drospirenone (1 mg/1 mg)

NEW: Estradiol 1 mg/micronized progesterone (1 mg /100mg)

Transdermal patch:

17b Estradiol/norenthindrone acetate (50 mcg/140mcg)

17b Estradiol/levonorgestrel

Trade ($40-100):

Activelle

Angeliq

Bijuva

Estalis

Climara

Other agents

$$$$

Oral :

1. CEE + Bazedoxifene (0.45/20 mg)
2. Tibolone 2.5 mg od
3. Ospemiphene 60 mg po od (GSM)

Vaginal:

Prasterone* (DHEA) 6.5 mg ovule daily

Other

Testosterone** 1% gel (1/10 of std dose)

- TSEC - progestin-free MHT
- Evidence showing no increase in breast density/cancers (RR: 1.1)*
- Good option for women concerned about breast cancer risk.
- Tibolone - STEAR, active on brain, vagina and bone, not breast or endometrium. AEs: acne, hair growth.
- SERM: Effect on vagina but anti-estrogenic on breast, no effect of endometrium.
- Testosterone - off-label, used for Hypoactive Sexual Desire Disorder (HSDD)

*Lee, D. J. Menopausal Med. 2020 Aug 26 (2): 99-103

**

“Bioidentical” Hormone Therapy

- Bioidentical hormone definition: “identical to molecular structure to human hormones”
- Not a scientific medical term but used primarily for marketing purposes.
- Same hormone (e.g. 17-b estradiol) used in commercial prescription formulas is used in compounded preparation
- Bioidentical is not to be confused with custom compounded bioidentical hormone therapy (cBHT)
- cBHT lack safety data, have unknown additives, variable absorption.
- Health Canada, SOGC, Menopause Societies do not recommend cBHT.
- cBHT like swimming at an unguarded beach ———>

Summary

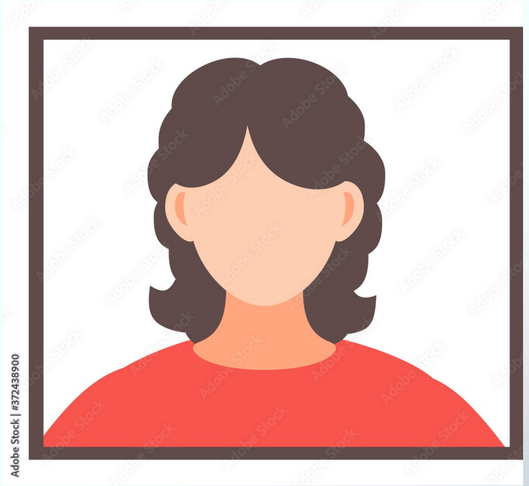
- A gap in knowledge and care exists for women navigating the menopause transition.
- The FD is in the best position to screen and help women navigate this life stage that can present with multiple symptoms.
- Validated tools exist to help FDs recognize and treat menopausal symptoms.
- There are many effective prescription therapies - non-hormonal and hormonal for menopausal symptoms.
- MHT is a first-line, evidence-based treatment option with proven safety for VMS symptoms.
- Transdermal estrogen formulas+/- micronized progesterone is a good first option.
- MHT is not a panacea or a cure for aging.
- Referral to an OB/GYN may be necessary in complex cases.

Case

- 45 yo female, previously well, complaining of:
  - > 6 month hx of menstrual changes
  - new onset joint pain (> 2 weeks)
  - palpitations, and acne.
- PAPs, Mammograms - up to date and normal
- Fam hx of arthritis, and breast cancer on both sides (2nd degree relatives)
- Non-smoker, occasional alcohol use (1-2 drinks our week).
- Works full-time, likes to exercise. Lives with a supportive partner and teenage children. She supports her elderly parents.
- Most bothersome symptoms? Palpitations and joint pain but they don’t stop her from doing anything.

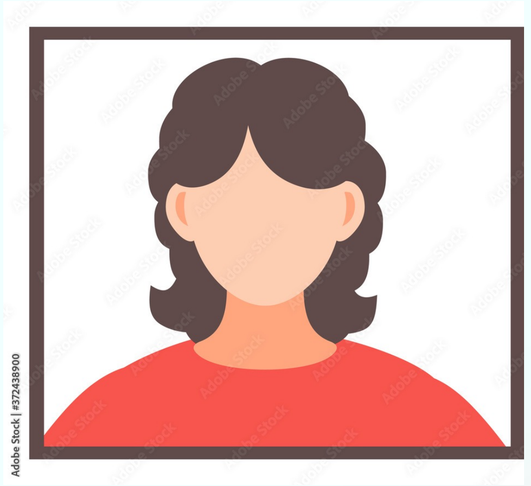
18 months later…

Late Perimenopause



- No period for 6 months.
- Sudden onset sweating
- Memory changes
- 3:00 wake-ups calls, insomnia
- “Interfering with my life” work, relationships
- Wants treatment but *“I’m not interested in hormone therapy.”*

CASE



- Start: Venlafaxine 37.5 mg po od
- Continue with lifestyle modifications.
- Recommend some legitimate websites/resources (e.g. menopauseandu.ca)

Follow up 6 months later…

- No period in 1 year
- Hot flushes have not improved much.
- Sleep is so bad, has to take sick days.
- *“I’m considering MHT but I’m worried about the risks. Should I try it?”*

Case closed

- After discussing risks vs. benefit and no contraindications, agreeable to try MHT.
- 17b Estradiol gel 2 pumps daily + micronized progesterone 100-200 mg po hs (she has a drug plan!)
- Follow-up:
- Within 3 weeks, she has noticeably reduced hot flashes and sleeping through the night,
- Within 3 months, only occasional hot flashes and feels “more herself”.

Resources

- https://menopausefoundationcanada.ca/
- Menopause Foundation of Canada report. The Silence and the Stigma: Menopause in Canada. The Menopause Experience. October 2022.
- https://www.menopauseandu.ca (SOGC site)
- https://www.menopause.org/for-women (NAMS)
- https://www.sigmamenopause.com/professionals
- https://www.sigmamenopause.com/sites/default/files/pdf/publications/Pocket%20Guide%20-%20udpated%202023%20Final.pdf
- https://mq6.ca/mq6-assessment-tool/
- The North American Menopause Society. Menopause Practice - A Clinicians Guide. 6th edition.
- Simon JA et al. *Low-dose paroxetine 7.5 mg for menopausal VMS: two randomized controlled trials*. Menopause 2013: 20(10): 1027-1035.
- https://www.menopause.org/docs/default-source/professional/2023-nonhormone-therapy-position-statement.pdf
- Lega IC, et al. *A pragmatic approach to the management of menopause*. CMAJ. 2023 May 15; 195:E677-82.
- Lega, I and Jacobson, M. *Perimenopause*. CMAJ. 2024 Oct 15;196: E1169.
- Society of Obstetrics and Gynaecology Canada (SOGC) *Clinical Practice Guideline No. 422a: Menopause: Vasomotor Symptoms, Prescription Therapeutic agents, Complementary and Alternative Medicine, Nutrition and Lifestyle.* Aug 2021.
- Goldstein, S. *An efficient tool for the primary care management of menopause*. Can Fam Phys 2017 Apr 63 (4): 295-298.
- Manson JE et al. *Menopausal hormone therapy and health outcomes during the intervention and extended poststopping phases of the Women's Health Initiative randomized trials.* JAMA 2013 Oct; 310 (13): 1353-68.
- Manson JE et al. *Menopausal hormone therapy and long term all cause and cause-specific mortality: the Women's Health Initiative randomized trials*. JAMA. 2017:318 (10): 927-938.
- Virginia Miller et al. *The Kronos Early Estrogen Prevention Study (KEEPS): what have we learned?* Menopause. 2019 Sep; 26 (9):1071-1084.
- Prentice R. et al. *Randomized Trial Evaluation of the Benefits and Risks of Menopausal Hormone Therapy Among Women 50-59 years of Age.* American Journal of Epidemiology. 2021 March 190 (3): 365-375.
- https://whri.org/wp-content/uploads/2024/11/HER_BC_Report_V1.2Hres.pdf
- The Menopause Society Statement on Misinformation Surrounding Hormone Therapy. September 2024.
- Goldstajn, M et al. *Effects of Transdermal versus Oral Hormone Replacement Therapy in Postmenopause: A Systematic Review.* Arch. Gynecol Obstet. 2022Jun17; 307(6) 1727-1745.
- Johnson K et al. *Efficacy and Safety of Fezolinetant in Moderate to Severe Vasomotor Symptoms Associated with Menopause: A Phase 3 RCT.* The Journal of Clinical Endocrinology and Metabolism. 2023 Aug; 108 (8): 1981-1997.

Thank You!

maria.migas@nshealth.ca