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Hormone Science to Health

Treatment of Symptoms of the Menopause:

An Endocrine Society Clinical Practice Guideline

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Task Force Members

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Agenda

I. Overview of *Treatment of Menopausal Symptoms: An Endocrine Society Clinical Practice Guideline*

II. Case Discussion

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I. Overview of *Treatment of Menopausal Symptoms: An Endocrine Society Clinical Practice Guideline*

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Endocrine Society Publications Related to Treatment of Symptoms of the Menopause

- Postmenopausal Hormone Therapy: An Endocrine Society Scientific Statement (2010)
- Androgen Therapy in Women: A Reappraisal: An Endocrine Society Clinical Practice Guideline (2014)
- Compounded Bioidentical Hormones in Endocrinology Practice: An Endocrine Society Scientific Statement
  (in preparation)
- The Endocrine Society Position Statement on Bioidentical Hormones (2006; re-issued, 2009)

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Goals of Recommendations

- Focus on treatment of symptoms of menopause
- Emphasize individualized clinical approach
  - Patient symptoms
  - Personal preferences
  - Overall health status
- Suggest baseline risk assessments
  - Contraindications to medical therapies
  - Cardiovascular risks
  - Breast cancer risks

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Goals of Recommendations (cont.)

- Review treatment options for symptom relief
  - Consider MHT in carefully selected women following benefit /risk assessment
  - Present full spectrum of choices
    - Hormonal, non-hormonal prescription, OTC
- Establish fundamental recommendations while acknowledging global differences in:
  - Populations
  - Practice
  - Prescriptive therapies

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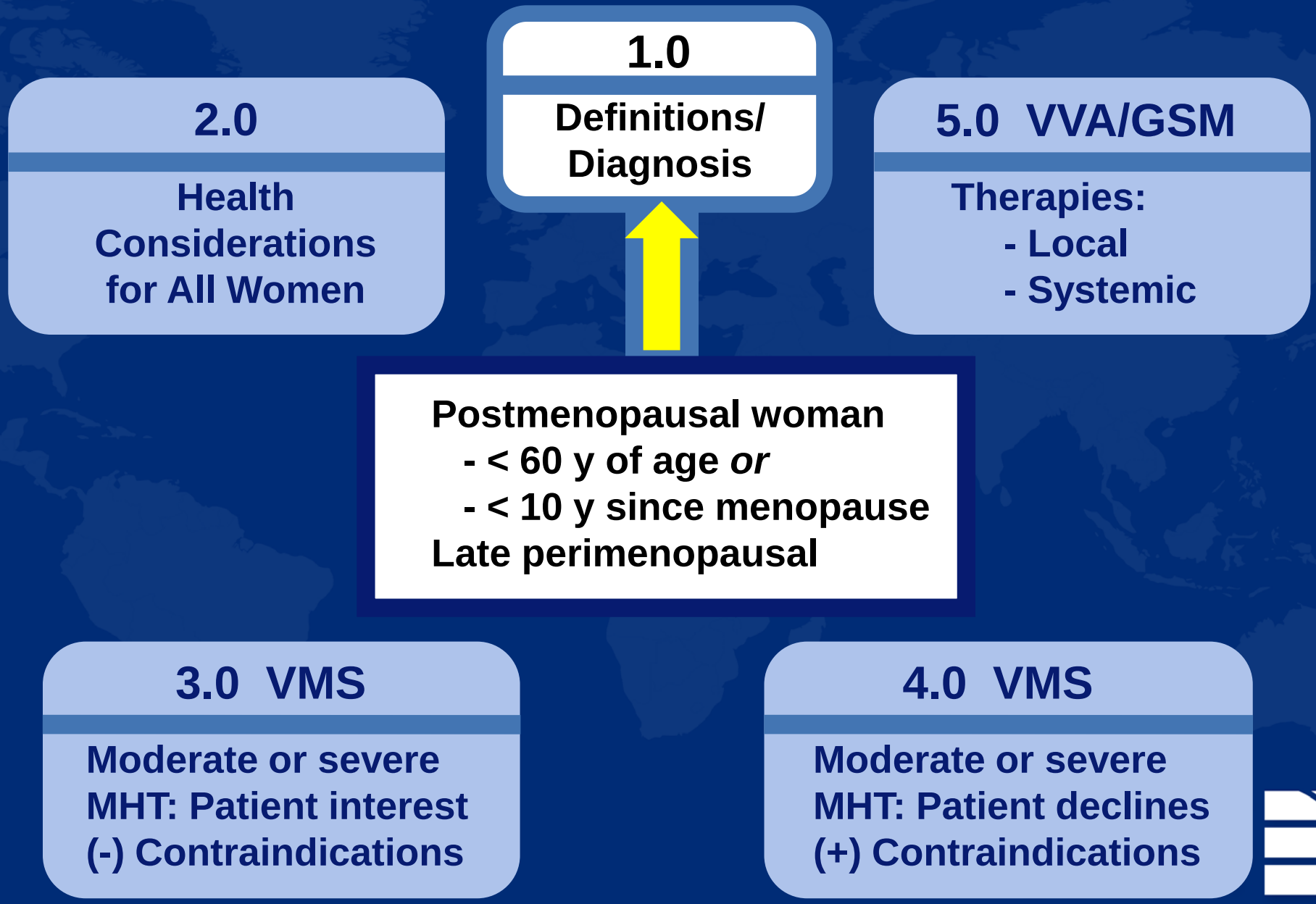
Approach to Menopause Recommendations



Approach to Menopause Recommendations

1.0
Definitions/ Diagnosis

2.0
Health Considerations for All Women

5.0 VVA/GSM
Therapies:
- Local
- Systemic

Postmenopausal woman
- < 60 y of age *or*
- < 10 y since menopause

Late perimenopausal

3.0 VMS
Moderate or severe
MHT: Patient interest
(-) Contraindications

4.0 VMS
Moderate or severe
MHT: Patient declines
(+) Contraindications

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GRADE Classification of Guideline Recommendations

QUALITY OF EVIDENCE		High Quality	Moderate Quality	Low Quality	Very Low Quality
Description of Evidence		• *Well-performed RCTs* • *Very strong evidence from unbiased observational studies*	• *RCTs with some limitations* • *Strong evidence from unbiased observational studies*	• *RCTs with serious flaws* • *Some evidence from observational studies*	• *Unsystematic clinical observations* • *Very indirect evidence observational studies*
STRENGTH OF RECOMMENDATION	**Strong (1):** **"We recommend…"** *Benefits clearly outweigh harms and burdens, or vice versa*	1|⊕⊕⊕⊕	1|⊕⊕⊕O	1|⊕⊕OO	1|⊕OOO
	Conditional (2): **"We suggest…"** *Benefits closely balanced with harms and burdens*	2|⊕⊕⊕⊕	2|⊕⊕⊕O	2|⊕⊕OO	2|⊕OOO

3.0 Hormone Therapy for Menopausal Symptom Relief

3.1 Estrogen and Progestogen Therapy

3.1a. For menopausal women:

- With bothersome VMS ± additional climacteric symptoms
- Who are < 60 years of age or <10 years past menopause
- Without contraindications
- Without cardiovascular or breast cancer risks
- Who are willing to take MHT

We suggest initiating estrogen therapy (ET) for those without a uterus, and estrogen plus progestogen therapy (EPT) for those with a uterus (Grade 2|⊕⊕◯◯)

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Approach to Patient with VMS Considering MHT

Assess Patient Criteria

- Symptomatic woman?
  - – Age < 60 y *or*
  - – < 10 y since menopause
- Interested in MHT?

If age > 60 y or > 10 y since menopause

CONSIDER OTHER OPTIONS

YES

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Approach to Patient with VMS Considering MHT (cont.)

Consider circumstances where MHT should not be used:

- Contraindications
- Cautions

PRESENT

CONSIDER OTHER OPTIONS

ABSENT

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Approach to Patient with VMS Considering MHT (cont.)

EVALUATE CARDIOVASCULAR RISK

HIGH *

CONSIDER OTHER OPTIONS

* Includes known CHD, CVD, PAD, etc.

ACCEPTABLE

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Approach to Patient with VMS Considering MHT (cont.)

EVALUATE BREAST CANCER RISK

HIGH to MODERATE *

CONSIDER OTHER OPTIONS

* Includes calculated level of risk that would qualify for risk-reducing medications

ACCEPTABLE

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Approach to Patient with VMS Considering MHT (cont.)

UTERUS PRESENT?

NO → **ESTROGEN ALONE**

YES

- **ESTROGEN *plus* PROGESTOGEN *or***
- **ESTROGEN *combined with* BAZEDOXIFENE**
- **TIBOLONE *where available***

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One additional caveat …

"As the impact of severe menopausal symptoms on quality of life may be substantial, however, there are instances in which a woman with a history of coronary heart disease or breast cancer, for example, will choose to accept a degree of risk that might be considered to outweigh the benefits of MHT.

An accepted philosophy is that a fully informed patient should be empowered to make a decision that best balances benefits to that individual when weighed against potential risks."

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Controversies in Treatment of Menopausal Symptoms

- What are the best methods to assess CVD and breast cancer risk prior to MHT?
- **Are some MHT preparations, doses, and routes of administration safer than others?**
- What duration of MHT is safe?
- What are effects of MHT on prevention?
  On mortality?

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Meta-analysis Conducted in Preparation of Clinical Guidelines

- Is transdermal therapy associated with reduced risk of VTE or arterial thromboses when compared with oral estrogen therapies?

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Oral vs. Transdermal Estrogen and the Risk of Venous and Arterial Thrombotic Events: *A Systematic Review and Meta-analysis*

- Mohammed K, Abu Dabrh AM, Khadra KB, Nofal AA, Carranza Leon BG, Prokop LJ, Murad MH

- **Conclusion:** Low quality evidence from 14 observational studies suggests that compared to transdermal estradiol, oral estrogen therapy may be associated with increased risk of VTE, DVT, and possibly stroke, but not MI.

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II. Case Discussion

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Clinical Case

Ms. A is a 55-year-old woman 2 years s/p menopause. She has persistent hot flashes disrupting sleep and daytime effectiveness. Symptoms temporarily improved with increased dietary soy, but this is no longer effective. She is fatigued at work and emotionally labile at home.

She's in good health; takes no meds. No FH of VTE or breast cancer. No vaginal bleeding. BP 120/80; BMI 26 kg/m2; PE unremarkable incl. breast/pelvic. Mammogram negative.

What is your favored recommendation for this patient?

A. No treatment, but reassure that Sx last only 2-3 years
B. Increase soy intake further
C. Menopausal hormone therapy
D. SSRI or SNRI
E. Gabapentin to improve sleep

Ms. A's case (continued)

3 months after starting continuous combined MHT, she now reports that her VMS are improved, but she feels moody, has bothersome breast tenderness, and finds the unpredictable bleeding to be annoying.

What are your options to improve these symptoms?

Ms. A's case (continued)

6 months after finding a regimen that has eliminated unwanted side effects, she comes back to ask about taking compounded bioidentical hormones. Her friends tell her they are safer and work better.

How do you respond to her about "bioidentical" MHT?

Clinical Case:
Relevant Recommendation

3.1i We recommend using MHT preparations approved by the US FDA and comparable regulating bodies outside the United States, and recommend against the use of custom-compounded hormones. (Ungraded Best Practice Statement)

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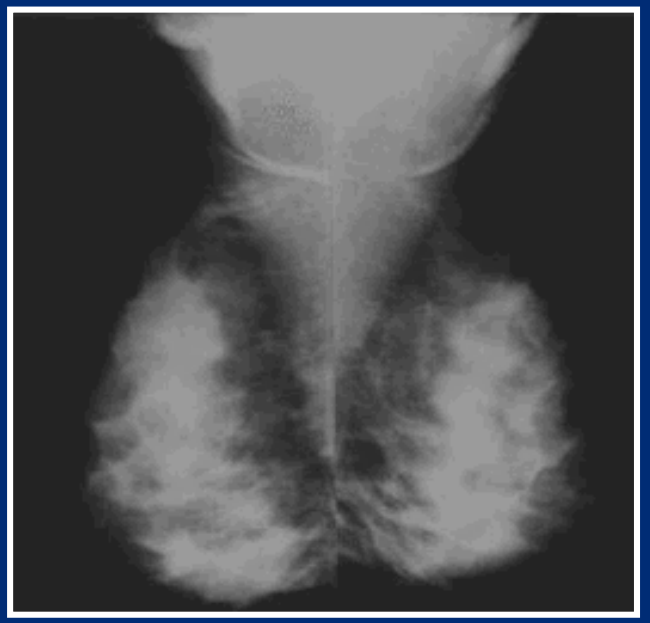
Vignette 1

Mrs. B is a 51 year old woman consulting for severe climacteric symptoms (e.g., hot flashes). She describes irregular menses for 2 years; she has been treated with progesterone (10 days per month) in recent months, but her last menstrual period was 3 months ago.

One of two sisters was diagnosed with breast cancer at age 62 years. BMI =24 kg/m2; PE (including breast exam) is unremarkable. Her mammogram:

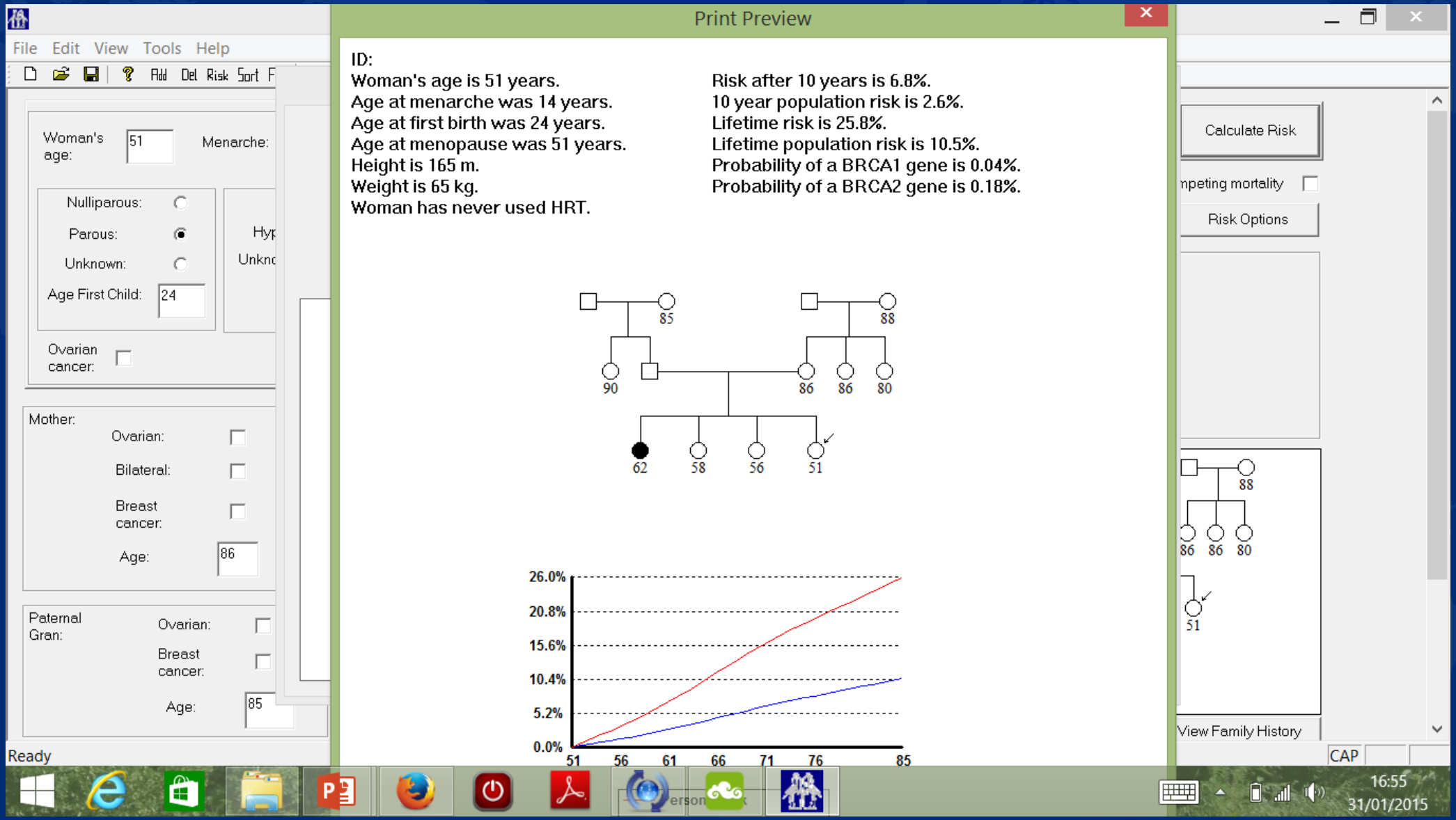
What is her primary risk for MHT, and how can you best quantify and counsel?

Which treatment will you propose for her climacteric symptoms and why?



IBIS

http://www.ems-trials.org/riskevaluator/



Vignette 1:
Relevant Recommendations

3.1f For women considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of breast cancer and taking this risk into consideration when advising for or against MHT and when selecting type, dose, and route of administration. **(Grade 2|⊕⊕◯◯)**

3.1g For women at high or intermediate risk of breast cancer considering MHT for menopausal symptom relief, we suggest non-hormonal therapies over MHT to alleviate bothersome VMS. **(Grade 2|⊕⊕◯◯)**

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Vignette 2

Mrs. C is a 52 y.o. teacher with severe VMS that wake her frequently and compromise her ability to teach effectively.

Mother had a stroke (age 72); father died of MI (age 60). She is a non-smoker and eats a reasonable diet, but does not exercise. BMI = 30 kg/m2, waist circ. = 87cm, BP 150/90. T. chol. 251 mg/dl (6.5 mmol/l); HDL-C 50 mg/dl (1.3 mmol/l); LDL-C 165 mg/dl (4.3 mmol/l); TG 177 mg/dl (2.0 mmol/l).

A population-relevant CVD risk assessment tool suggests that she is at moderate risk for a CVD event over the next 10 years. Her GP prescribed atenolol (HTN) and a statin, but refused treatment for VMS.

What do you recommend for this patient?

Can MHT be considered? If so, what type?

What if she had a personal history of MI or stroke?

Vignette 2: Relevant Recommendations

3.1b For women < age 60 or < 10 years past menopause onset considering MHT for menopausal symptom relief, we suggest evaluating the baseline risk of cardiovascular disease (CVD) and taking this risk into consideration when advising for or against MHT and selecting type, dose, and route of administration. **(Grade 2|⊕⊕◯◯)**

3.1c For women at high risk of CVD, we suggest initiating non-hormonal therapies to alleviate bothersome VMS ± climacteric symptoms over MHT. **(Grade 2|⊕⊕◯◯)**

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Vignette 2:
Relevant Recommendations (cont.)

3.1d For women with moderate risk of CVD, we suggest transdermal estradiol as first-line treatment, alone for women without a uterus, or combined with micronized progesterone (or another progestogen that does not adversely modify metabolic parameters) for women with a uterus, because these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism. **(Grade 2|⊕⊕◯◯)**

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Vignette 3

Ms. D is 62 years old. She has been on MHT continually for 13 years (since age 49) — currently oral estradiol 1.0 mg/d + norethindrone acetate 0.5 mg/d.

Attempts at stopping have been unsuccessful (severe hot flushes, nocturnal sweats → sleep deprivation/fatigue). She has tried SSRIs/gabapentin to no avail.

No worrisome personal or family medical history. BMI = 24 kg/m^2; PE otherwise unremarkable. Estimated 10-y CVD risk <5%. Mammogram unremarkable. DXA: femoral neck T-score –2.3.

What do you recommend to Ms. D regarding MHT (discontinue vs. continue vs. change dose/prep/route)?

If MHT is continued, for how long?

Would management be different if her age was 72 yrs?

Vignette 3:
Relevant Recommendations

3.4b We recommend informing women about the possible increased risk of breast cancer during and after discontinuing EPT and emphasizing the importance of adhering to age-appropriate breast cancer screening. **(Grade 1|⊕⊕⊕◯)**

3.4c We suggest that the decision to continue MHT be revisited at least annually, targeting the shortest total duration of MHT consistent with the treatment goals and evolving risk assessment of the individual woman. (Ungraded Best Practice Statement)

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Vignette 4

Mrs. E is a 55 year old G0 patient had treatment for DCIS 6 years ago. She is taking a combination of low dose paroxetine and gabapentin for frequent, severe hot flashes. This approach has worked acceptably.

She now comes to you complaining of vaginal dryness and itching in addition to painful intercourse. She has tried OTC vaginal moisturizers and lubricants without significant improvement.

What are the most appropriate treatment options to consider?

Vignette 4: Relevant Recommendations

5.2a For women without a history of hormone- (estrogen) dependent cancers who are seeking relief from symptoms of genitourinary syndrome of menopause (GSM) [including vulvovaginal atrophy (VVA)], that persist despite using vaginal lubricants and moisturizers, we recommend low-dose vaginal estrogen therapy. **(Grade 1|⊕⊕⊕◯)**

5.2b In women with a history of breast or endometrial cancer, who present with symptomatic GSM (including VVA), that does not respond to non-hormonal therapies, we suggest a shared decision-making approach that includes the treating oncologist to discuss using low-dose vaginal ET. (Ungraded Best Practice Statement)

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Key Take Home Points: Treatment of Menopausal Symptoms

- MHT is suggested therapy for relief of menopausal symptoms for appropriately selected patients
- Effective relief of vasomotor symptoms can be achieved with non-hormonal prescription therapies
- Vaginal and urinary symptoms are undertreated; local estrogen and a systemic SERM therapy are effective
- Transdermal estrogen therapy is not associated with VTE
- Individualize approach to initiation and continuation of MHT

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