Practical approach to the patient with menopausal symptoms in 2022

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Conflict of Interest Disclosure

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Learning Objectives

Identify the common symptoms of perimenopausal and menopausal women

Be familiar with current evidence that for many/most women in their 50's or < age 60, the benefits of menopausal hormone therapy (MHT) outweigh the risks.

Utilize nonhormonal strategies and medications to treat hot flashes in women who are not candidates for hormone therapy

2022 Update

- Hormone therapy (HT) is still the most effective therapy for menopause symptoms (hot flashes)
- Up to 20% of women are candidates: moderate-severe symptoms and recently menopausal (in their 50s or <10 years postmenopause)
- Safety well established - Benefits outweigh risks
- Hot flashes last a LONG time; duration of therapy should be individualized
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2022 Update

- The earliest WHI results (2002) continue to have a profound impact on prescribing practices
- Low prescribing rates persist in spite of safety data and availability of newer regimens. (decreased from 25-30% pre-WHI to about 5%. Nearly 20 million untreated women)
- Why?
  - Negative messaging, lack of awareness
  - Generations of trainees have only minimal experience (Manson NEJM 2016; Santen et al 2014; Kling et al Mayo Clin Proc 2019)

Menopause Survey: Internal Medicine + OB/GYN residents

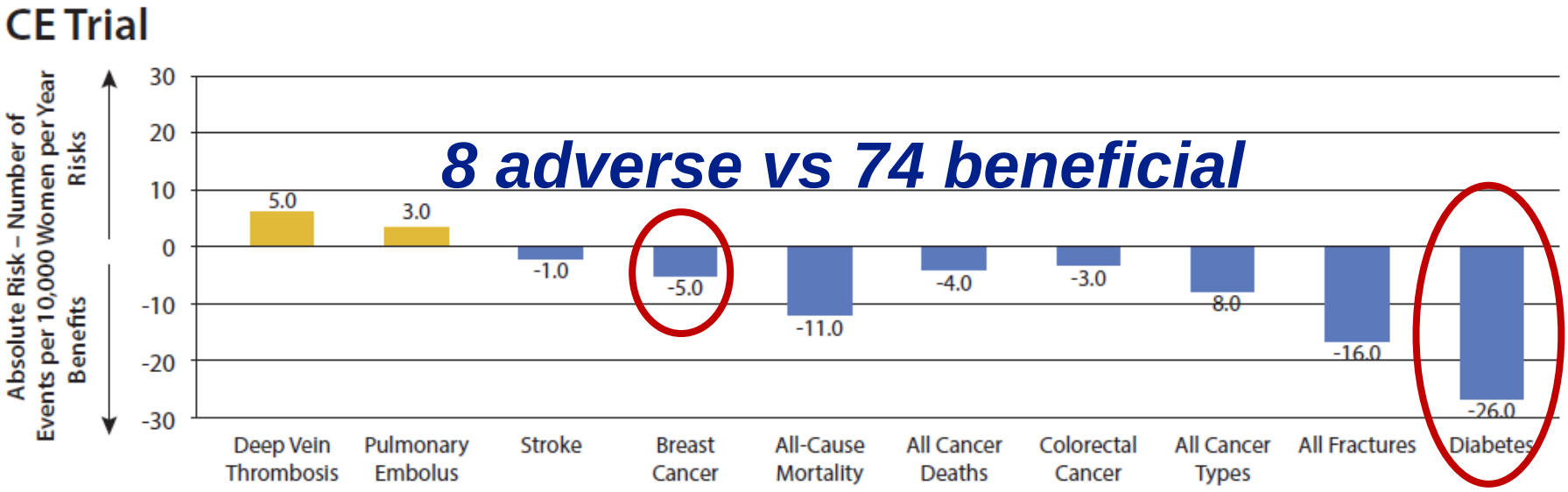
- How prepared are you to manage menopausal women?
  - “Not at all” - IM 50%, OB/GYN 28%
- What is the appropriate mgmt of a 39 year old woman with primary ovarian insufficiency?
  - 60% did not know correct answer (MHT until age 50/51)
- What is the most effective treatment for a healthy 52 yo woman with severe VMS?
  - 40% recommended exercise and/or mind-body interventions rather than MHT *Mayo Clin Proc March 2019)*

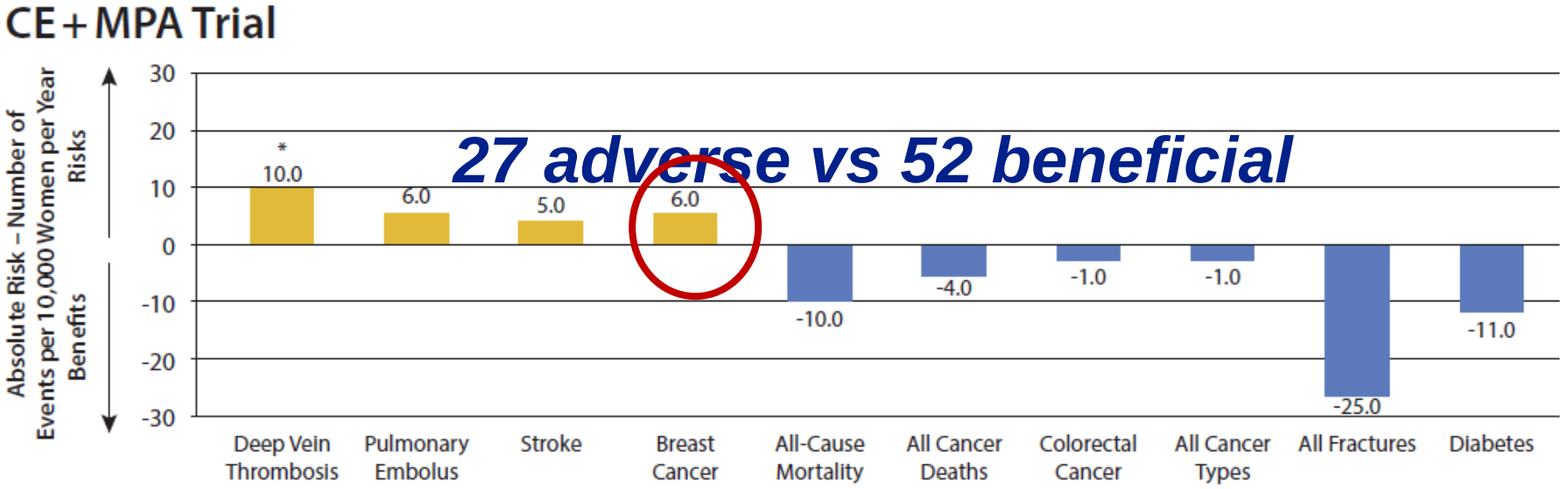
Consequences of not treating PMW

Untreated hot flashes:

- Quality of life
- Sleep disturbances
- Economic impact
  - Lost productivity
  - Increased healthcare costs (Sarrel Menopause 2015)
- Steep rise in osteoporosis-related fractures
- Increase in use of *custom-compounded "bioidentical hormones" (Manson)*

Benefits outweigh risks. Analysis based on WHI: Number of events per 1000 women (ages 50-59) per 5 years use





Most important lessons: WHI and CVD

- Age at initiation of hormone therapy is important (WHI mean age 63)
- Don’t start MHT in older women – possible underlying atherosclerosis
- In younger PMW (ages 50-59, <10 years postmenopausal) safety is *well established*
  - WHI follow-up data
  - Cochrane meta-analysis 2017
  - 2 RCTs [KEEPS, ELITE] in young women)

Breast Cancer: Evidence from WHI

Calculated 5-year risks for women 50-59 (based upon WHI data)

- E + MPA = + 4-5/1000
- E alone = -3.5 cases/1000

The risk attributable to MHT is small and the risk decreases after stopping (Manson JAMA 2013)

Calculate patient's breast cancer risk!

Regimens that may be associated with lower risk

- Micronized progesterone vs MPA
- Low dose versus standard dose estrogen
- Cyclic vs continuous administration of progestin
- Transdermal vs oral estrogen
  - No increase breast cell proliferation (biopsy) or mammographic density (Gynecol Endocrinol 2012;28 suppl2:12)

(Manson 2013, Mehta and Manson, Frontiers Endo 2021)

Evaluate CVD risk before MHT

10-year CVD risk	MHT recommendation if <10 years since menopause
Low (<5%)	MHT ok
Moderate (5-10%)	MHT ok, but use transdermal
High (>10%)	Avoid MHT

Calculated using ACC/AHA risk calculator

Stuenkel et al, JCEM 2015;
Adapted from Manson, Fertil Steril 2014

Breast Cancer Risk Cutoffs for MHT

Risk category	5-y NCI or IBIS Breast cancer risk assessment, %	Suggested approach
Low	<1.67	MHT ok
Intermediate	1.67-3	Caution
High	>3	Avoid
		Stuenkel et al, JCEM 2015

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Other considerations

- Cognitive function and dementia – transition versus postmenopause. Younger vs older menopausal women
- Ovarian cancer – excess risk unlikely
- Gallbladder disease – increased risk with oral estrogens
- Lung cancer – excess risk unlikely
- Meningiomas (growth)

Benefits of estrogen

- Hot flashes
- Sleep
- Perimenopausal depression and anxiety *Menopause 2018;25:1069*
- Prevention of depression *Gordon et al JAMA Psych 2018*
- Joint pain *Watt Post Reproductive Health 2018*

STRAW: Stages of Reproductive Aging Workshop

Menopausal transition | **Postmenopause**

Early | **Late**

Perimenopause → **Early postmeno**

>7 day diff in length of consecutive cycles; FSH variable	*Intervals of amenorrhea ≥ 60 days* *FSH >25 IU/L*	*Final menstrual period. Variably high FSH, then stabilizes*

Low AMH and inhibin B →

Harlow Menopause 2012

Menopausal symptoms

Hot flashes

- Peak in late menopausal transition/ early postmenopause (longitudinal cohort studies about 85%)
- Risk factors: obesity, PMS, genetic variants *tachykinin receptor 3* (*TACR3)*

Duration

- For many/most women: 7 to 10 years
- Long duration of symptoms has important implications for duration of therapy
- Patterns/trajectories

Trajectories – hot flashes

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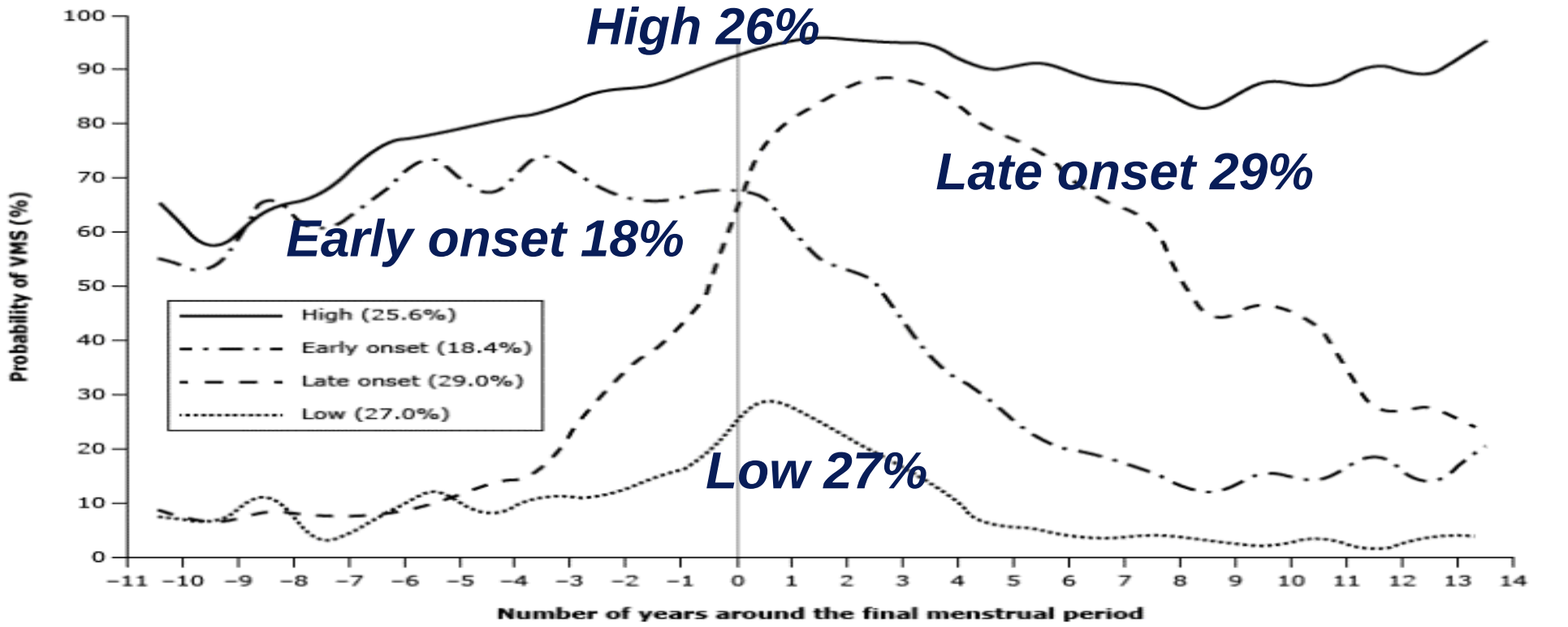
Trajectories of vasomotor symptoms over the menopause transition



Probability of VMS represents the average observed probability of VMS at each time point within each trajectory subgroup. No factors were included in the model.

VMS: vasomotor symptoms.

Case 1

- 50-year- old woman on MHT for severe hot flashes and depression presents for further evaluation. Age 49 – TAH/BSO. Otherwise in good health. BMI 29 kg/m2
- Started transdermal E2 0.005 mg (50 mcg) three months ago
- Her hot flashes are much better, but her mood symptoms persist and she is having trouble sleeping.

Case 1-What would you suggest next?

A. Increase estrogen dose

B. Add an SSRI

C. Add progesterone

D. Add zolpidem

Perimenopausal mood disorders

- Depression/mood disorders (35-40% in menopausal transition)
  - More common in women with hot flashes (nighttime)
  - Other risk factors: personal or family history of mood disorders, PMS Freeman EW Arch Gen Psych 2006
- *Screen for mood disorders!*
- Choose initial therapy based upon predominant symptom (depression vs VMS) – often need both E and SSRI (citalopram, escitalopram, duloxetine)
- Usually progestin intolerant
- Prevention

Other menopausal symptoms

- Sleep disturbances
  - 40% even in the absence of HF: contributors are primary sleep disorders, anxiety and depression
- Joint pain – similar to the MS side effects of aromatase inhibitors (AIs), improves with estrogen
- *Vulvovaginal atrophy (VVA)* - Genitourinary syndrome of menopause (GSM)--tends to develop in the years or decades after menopause

- Long-term consequences: bone loss, CVD

Choice of E and P

All estrogens and progestins are not created equal

Estrogen:

- *17- B estradiol* vs conjugated estrogens
- Low dose vs standard doses
- Transdermal vs oral

Progestins:

- *Micronized progesterone* vs medroxyprogesterone
- Cyclic and continuous – depends upon menopausal stage

Route: transdermal vs oral

Transdermal estrogens have less effect on:

- Clotting factors, triglycerides, C-reactive protein
- SHBG

Lower risk of:

- VTE (Canonico et al; Renoux et al J Thromb Haemost 2010)
- Stroke (if dose < 50 mcg) Renoux BMJ 2010)
- Increase in mammographic density

Most important for women with high TG, gallbladder disease, and risks for CVD or VTE

My approach

Late transition/early postmenopause

- Transdermal E2 0.025 mg (25 mcg) and titrate up
- Higher dose (50 – 75 mcg) for severe symptoms
- Cyclic micronized progesterone 200 mg days 1-12 (to minimize bleeding)
- Low dose OC in some women in 40s with symptoms, heavy bleeding who desire contraception (caution if obese)

My approach

Postmenopausal women

- Transdermal E2 0.025 mg (25 mcg)
- Higher dose for severe symptoms
- Continuous MP 100 mg daily

Oral E2 ok for healthy women without DVT risks who prefer oral preps (0.5-1 mg)

Women with primary ovarian insufficiency (POI)

- Menopause before age 40
- Treat with MHT until age 50/51 to prevent bone loss, premature CHD, stroke, and dementia
- Use higher dose of estrogen
  - Transdermal E2 100 mcg
  - Oral E2 2 mg
- Some women prefer taking an OC

Similar principles for early menopause (ages 40 to 45)

Nonhormonal options

Complementary therapies: Black cohosh – no more effective than placebo; Acupuncture, phytoestrogens/isoflavones – data are mixed

SSRIs/SNRIs – Effective. Avoid paroxetine in pts on TAM. Our top choices: citalopram 20mg and escitalopram 10 to 20 mg over venlafaxine (to avoid side effects and withdrawal sx)

Gabapentin – My first choice for those with primarily night sweats (100 to 900 mg at bedtime. Titrate up starting with 100 mg)

Experimental: NK3R antagonist therapy

Key points

- Symptomatic peri-and postmenopausal women are woefully undertreated
- The benefits of MHT outweigh the risks for symptomatic women < age 60 or <10 years postmenopause
- Use an individualized approach: assess baseline CVD and breast cancer risks
- Preferred regimen: transdermal E2 and oral MP
- Extended use (beyond age 60) in some women
- Nonhormonal options – SSRIs and gabapentin
- *Discuss vaginal estrogen*