Extended Use of Systemic Hormone Therapy

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Case: 63 year old woman

- Prior hysterectomy, age 42 for uterine fibroids
  - Due to bothersome VMS, began oral estrogen therapy in her early 50s
  - Maternal history of hip fracture (age 76 years)
  - BMI 21
- Recently took a 3-week trip, leaving estrogen tablets at home
  - Noted no hot flashes off estrogen

She asks: should she continue ET?

Extended Use of HT: Overview and Objective

- Providing guidance to patients regarding duration of HT use is controversial
  - However, clinicians commonly encounter this issue in practice
- Objective: Provide guidance to clinicians regarding extended duration HT use, based on available evidence as well as personal clinical experience

Conventional Wisdom re Duration HT Use

- Many experts have opined:
  - “…it remains prudent to keep the… duration of treatment short”
  - “…may serve a useful role in short-term symptom management…”

VMS: most common indication for systemic HT...
How Long do VMS Persist? (I)

- Penn Ovarian Aging study, population-based prospective cohort designed to assess duration of VMS:
  - Median duration of bothersome VMS: 10.2 years
  - Symptoms beginning during perimenopausal transition: > 11.25 years


How Long do VMS Persist? (II)

- Prospective cohort study of women with osteoporosis:
  - Mean age 67 years; mean years since menopause 19
  - 11.8% of women reported ‘clinically significant’ hot flushes at baseline; more than half of these symptomatic women continued to report bothersome symptoms 3 years subsequently


In many women, short-term HT will not be sufficient to control bothersome VMS

Standard dose ET prevents osteoporosis

- Most estrogen formulations/doses approved for prevention of osteoporosis
- Standard doses:
  - Oral estradiol (E2) 1 mg
  - Oral conjugated equine estrogen (CEE) 0.625 mg
  - Transdermal (TD) E2 0.05 mg

NAMS. Menopause 2011.


Lower dose ET also prevents osteoporosis

- Weekly ultra-low 0.14 mg patch (TDET): serum E2 levels remain in menopausal range;
- BMD maintained/enhanced in two year trial of women (mean age 66; intact uterus)
  - Impact of ultra-low dose E2 patch on osteoporotic fractures: no data available
  - No endometrial hyperplasia noted; however, proliferative changes observed
  - In women using unopposed ultra-low dose ET, periodic endometrial monitoring likely appropriate


WHI EPT Trial Outcomes @13 Years Cumulative f/u in Participants OVERALL (all ages at randomization)

- EPT Hazard Ratios (HRs):
  - All-cause mortality: 0.99 (NS)
  - Global index: 1.06 (P=.05)
  - Significant ↑ risk breast cancer: 1.28

  Putting this elevated relative risk in context:
  - <1 additional case per 1,000 EPT users annually
  - HR with EPT slightly higher than that seen with one daily glass of wine, less than HR with 2 daily glasses

- ET Hazard Ratios:
  - All-cause mortality: 0.99 (NS)
  - Global index: 1.02 (NS)
  - Significant ↓ risk breast cancer: 0.79


All-cause Mortality Hazard Ratios* at 13 Years Cumulative f/u by Age at Randomization

- 50-59 years
  - ET: 0.78
  - EPT: 0.88
- 60-69 years
  - ET: 1.02
  - EPT: 0.99
- 70-79 years
  - ET: 1.06
  - EPT: 1.04

* All p-values>0.05

[Sources: J.E. Manson, et al. JAMA October 2, 2013]

Conclusions: WHI EPT+ET Trial- 13 Years of Follow-Up

- HT Risk:Benefit ratio most favorable when initiated in younger women
- Overall, R:B ratio more favorable for ET than EPT

RCT data assessing benefits and risks of long-term HT initiated during early menopause not available

[Sources: J.E. Manson, et al. JAMA October 2, 2013]
**Use of HT to Prevent Osteoporosis: Clinical Considerations**

- Use of HT for this indication more appropriate in higher-risk women (e.g. low BMI, +FH)
- If osteoporosis prevention the only indication for use, lower than standard dose HT appropriate
- Unlike bisphosphonates, rapid loss of BMD after stopping HT
  - consider BMD assessment several years after stopping HT
- Given EPT’s less favorable safety profile, long-term use of ET to prevent osteoporosis more appropriate than EPT
  - Post hysterectomy: ET
  - Uterus present, consider low/ultra-low dose ET without P (with appropriate endometrial surveillance)

**Duration of HT Use:**

*NAMS 2012 HT Position Statement*

“...extending EPT use with the lowest effective dose is acceptable under some circumstances, including (1) for the woman who has determined that the benefits of menopause symptom relief outweigh risks, notably after failing an attempt to stop EPT, and (2) for the woman at high risk of fracture for whom alternate therapies are not appropriate or cause unacceptable adverse effects.”

**Oral vs. Transdermal ET (TDE2)**

- Cardiovascular safety profile of HT with TDE2 (particularly 0.05 mg or lower dose) appears more favorable than oral HT (no RCT data)
  - 5 observational studies: lower risk VTE
  - One observational study: lower risk CVA
- TDE2 particularly advisable if baseline CVD risk elevated
  - Older age, obesity, metabolic syndrome, smoking

**Use of HT to Treat Menopausal Symptoms: ACOG Guidance**

“...ACOG recommends against routine discontinuation of systemic estrogen at age 65 years. As with younger women, use of HT and estrogen therapy should be individualized based on each woman’s risk–benefit ratio and clinical presentation.”

*AM Kaunitz. Menopause June 2014.*

Long-term Use of HT: One Clinician’s Approach (I)

- In women initiating HT for bothersome VMS, consider TDE2 for overweight/obese women, smokers and other women with ↑ risk CVD
  - Reasonable starting dose for TDE2 is 0.05 mg
- After VMS have resolved for several years on initial dose of estrogen, encourage patient to try a lower dose
  - Patients should understand that if VMS or loss of sense of wellbeing occur on the lower dose, they can resume prior higher dose without an office visit

AM Kaunitz. Menopause June 2014.

Long-term Use of HT: One Clinician’s Approach (II)

- When patient has been using a low or ultra low dose of HT (0.0375, 0.025 or 0.14 mg TDE2, 0.5 mg oral E2, or 0.3-0.45 mg oral CEE) and reports no recent VMS:
  - If patient not at elevated risk for osteoporosis, encourage discontinuing systemic HT
    - Patient can restart HT if bothersome VMS recur
    - Lowering the dose of systemic HT can result in symptomatic VVA; start vaginal ET if appropriate

AM Kaunitz. NAMS Menopause June 2014.

Follow-up of Case

- At age 63, she chose to continue ET for skeletal health reasons, switching to 0.025 mg estradiol patch
- DXA at age 65:
  - Lumbar Spine: T= -0.8
  - Femoral neck: T= -0.2
- She is now age 71
  - BMI 22

She chooses to continue low dose transdermal ET...
Extended Use of HT: Summary

- Although commonly encountered in clinical practice, this issue remains controversial as clinical trial data have not assessed extended duration use of HT
- Clinicians prescribing extended duration HT should individualize treatment, paying attention to formulation dose, route and informed consent

Shared decision making helps patients make sound choices

Appendix Slides

Use of HT to Prevent Osteoporosis:
FDA Package Labeling: Systemic HT

Treatment and Usage
“Prevention of postmenopausal osteoporosis. When prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and non-estrogen medications should be carefully considered.”

UK RCT of unopposed ET: Two-year f/u

- 1017 women (age range, 50–69) with an intact uterus randomized to 2 mg estradiol valerate (eg ~1.5 mg E2) or placebo daily for 2 years
  - Endometrial biopsy performed in all women reporting bleeding; short course of P therapy administered if hyperplasia:
    - 2 cases of endometrial cancer found in ET arm
    - 3 cases found in placebo arm (RR 0.52; NS)

This RCT suggests short-term endometrial safety of [high dose] ET with appropriate endometrial monitoring

Cherry N et al. BJOG 2014

Notice Received From Insurance Company (65 yo patient on 0.025 mg estradiol patch)

- "Your patient is at least 65 years old and has evidence for either an oral or transdermal estrogen containing preparation. These estrogen containing preparations should be avoided in older women due to the risk of thrombosis and cancer. If your patient fits this clinical profile, and if not already done, consider reassessment of risks/benefits of continuing estrogen."


Beers Criteria for Potentially Inappropriate Medication Use in Older Adults

- In 1991 the late geriatrician Mark Beers catalogued medications that "... cause adverse drug events in older adults due to their pharmacologic properties and the physiologic changes of aging."
- List includes systemic estrogens (oral and transdermal) with or without progestins