Modern Management of Menopause

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No commercial disclosures for this lecture

Topics To Be Discussed

- New information from the WHI
- The expanding range of treatments for managing menopausal symptoms
  - *Which treatments are available to your patient?*
- Practice Recommendations
  - *How can your patient use these treatments safely, effectively, and conveniently?*

Key Points: NAMS 2007, 2008, 2010 Position Statement on Hormone Therapy

The North American Menopause Society. Estrogen and progestogen use in postmenopausal women. 2010 position statement of The North American Menopause Society. *Menopause* 2010; 17 (2): 242-255

Available at: menopause.org

NAMS Definitions

ET	Estrogen (E) therapy
EPT	Combined E+P therapy
HT	Hormone therapy (ET, EPT)
MHT	Menopausal hormone therapy (ET, EPT)
Progestogen	Progesterone or progestin (P)
CC-EPT	Continuous-combined E+P therapy - E+P given every day
CS-EPT	Continuous-sequential E+P therapy - E daily with sequenced P

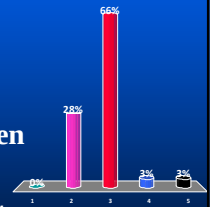
NAMS position statement. *Menopause* 2007.

Case Study

- Ms S is a 52 year old woman with moderate-severe hot flashes and difficulty getting to sleep
- Her menses were regular until one year ago, became irregular, and then stopped 6 months ago
- She has tried a number of herbal remedies, each of which helped for only a few months
- Her medical history, BP, physical exam are normal
- The hot flashes affect her work productivity and she wants to try something else

Would you recommend that she…..

1. Try a different over-the-counter supplement
2. Prescribe a SSRI or SNRI anti-depressant medication
3. Prescribe the lowest dose estrogen and progestin
4. Prescribe a "mid-range" dose of estrogen and progestin
5. Receive a consultation with an ObGyn to discuss this subject and have a treatment plan developed



Explaining HT Risk and Benefit

Criteria	Comment
Current age	Safer if younger
Time since menopause	Safer if shorter time since LMP
Age at menopause	Worse symptoms if early menopause
Cause of menopause	Worse symptoms if surgical menopause
HT types, route, doses used	Choice of product or delivery system
Prior use of any hormone	Hormone vs non-hormonal treatment
Baseline disease risks	Hormone vs non-hormonal treatment
Emerging conditions during treatment	Hormone vs non-hormonal treatment

NAMS position statement. *Menopause* 2008.

SWAN Study

Study of Women Across the Nation

- Longitudinal community sample >16,000 women
  - Non-Hispanic white, African American, Hispanic, Japanese American, and Chinese American
- Reported racial and cultural differences in risk factors, symptoms, physiology, and attitudes re: menopause
- Reference
  - Avis NE, Assmann SF, et al. Quality of life in diverse groups of midlife women: assessing the influence of menopause, health status and psychosocial and demographic factors. Qual Life Res. 2004;13(5):933–946

Observations from the SWAN Study

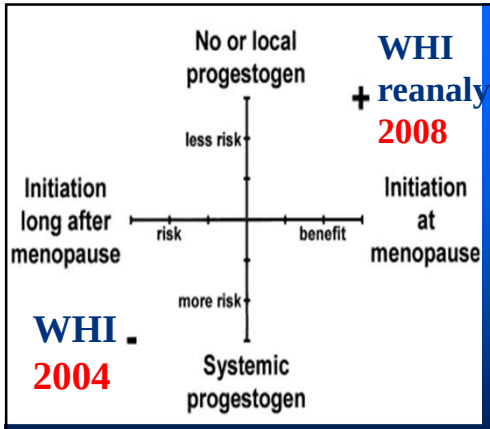
	White	Af-Am	Hispanic	Chinese	Japanese
Vasomotor symptoms, %	31	46	35	21	18
Attitude toward menopause	+	+++	+	--	-
Comp/altern med use, %	60	40	20	46	60
Body mass index, kg/mg^2	27.8	31.5	29.2	23.3	22.9
Genistein intake daily, µg	834	271	310	6398	11,165
Depressive symptoms, %	22.7	27.2	43.3	14	14.6

Act 1

Let's Get This Out of the Way….

WOMEN'S HEALTH INITIATIVE

The WHI Re-analyzed



WHI 2004

WHI reanalysis 2008

HT and CVD: The Unified Hypothesis

Phillips LS, Langer RD, Postmenopausal hormone therapy: critical reappraisal and a unified hypothesis. Fertility and Sterility 2005; 83:558-66

Clinical Implications: Unified Hypothesis

- Mild cardioprotection
  - Women in their early-mid 50s, who
  - Initiate HT soon after menopause, with
  - Few or no heart disease or stroke risk factors
  - And who use estrogen-only regimens
- Increased heart disease risk
  - Women in their mid-60s or later, who
  - Initiate HT long after menopause, who have
  - Heart disease or stroke risk factors
  - And who use estrogen *and* progestin regimens

HT & Coronary Heart Disease (CHD)

- HT may reduce CHD risk when initiated in younger and more recently postmenopausal women
- Longer HT duration associated with reduced CHD risk and mortality
  - Long-term HT associated with less accumulation of coronary artery calcium
  - Some evidence of lower CHD risk in women who used HT ≥ 5 years

NAMS position statement. *Menopause* 2008.

HT & Coronary Heart Disease (cont'd)

- Short-term HT may increase CHD risk in women farther from menopause at time of initiation
- HT currently not recommended as sole or primary indication for coronary protection in women of any age

NAMS position statement. *Menopause* 2008.

HT & Venous Thromboembolism

- Oral HT increases VTE risk in menopausal women
- VTE risk emerges early (1-2 y); decreases over time
- Lower VTE risk with EPT or ET in women <60 y.o.
- Lower HT doses may be safer than higher doses
- Likely lower risk with transdermal vs. oral ET
- VTE risk fall into the "rare" category

NAMS position statement. *Menopause* 2008.

HT and Stroke

- In the WHI EPT + ET trials
  - Increased ischemic stroke risk
  - No effect on hemorrhagic stroke risk
  - In women 50-59 at study entry, HT had no effect on risk of stroke (RR 1.13; 95% [CI], 0.73-1.76)

    NAMS position statement. *Menopause* 2008
- Transdermal estrogen not associated with increased stroke risk (Renoux C. BMJ 2010; 340: c2519)

HT & Breast Cancer

- **EPT use >3-5 years increased breast cancer risk**
  - **Increased absolute risk of EPT in WHI: "rare"**
  - **4-6 additional cases/10,000/yr of EPT for ≥ 5 yrs**
- **Estrogen only regimens**
  - **WHI ET trial showed no increased risk after 7.1 yrs**
    - **6 fewer cases/10,000 women/yr of ET use (not SS)**
  - **Other studies showed that ET for < 5 yrs has little or no impact on breast cancer risk**

NAMS position statement. *Menopause* 2008.

HT & Total Mortality

- **HT may reduce total mortality when initiated soon after menopause**
  - **Both ET and EPT reduce total mortality by 30% when initiated in women <60 years old**
  - **HT not associated with mortality reduction among women who initiate HT at ≥60 years old**

NAMS position statement. *Menopause* 2008.

Hot Flashes: Lifestyle Changes

- **Exercise routinely, at least 3-4 days/week**
- **Cool room temperature, especially at night**
- **Dress in layers (remove outer layers if warm)**
- **Avoid hot and spicy foods**
- **Relaxing activities**
- **Avoid cigarettes**
- **Minimize alcohol**

Botanicals and PhytoSERMs

***Probably* better than placebo**

- **Black cohosh**

No evidence of efficacy

Soy isoflavones	**No better than pbo**
Red clover isoflavones	**No better than pbo**
Evening primrose oil	**No better than pbo**
Dong quai	**No better (as monotx)**
Ginseng	**No better than pbo**
Vitamin E	**No better than pbo**
Chasteberry (Vitex)	**No studies**

Botanicals: Black Cohosh

- **Total of 14 trials reported, including 4 randomized trials using placebo and/or estrogen treatment arm**
  - **3 of 4 RCTs found black cohosh to be beneficial**
  - **12 of 14 trials reported *some* benefit**
  - **Currently, longest trial is 6 months**
- **NIH-funded, large, randomized, prospective, 2-year trial ongoing**
  - **Preliminary data fail to show binding to E receptors**
  - **Binding to serotonin receptor noted**

Botanicals and PhytoSERMs

- **Evidence supports positive effect of black cohosh vs placebo**
  - **Improvement is less than with HT**
- **Some of the impact is due to placebo effect, which is none-the-less therapeutic**
- **Relatively little risk of adverse effects**
- **Reasonable first-line choice for women**
  - **With mild menopausal symptoms**
  - **Who feel strongly about avoiding hormones**
  - **Who are willing to use medications that are not "proven" effective by EBM or regulated by FDA**

Non-Hormonal Hot Flash Therapies

Drug	% of women with >50% HF Reduction
Antidepressants	
•Paroxetine	62-65%
•Venlafaxine	38-60%
•Fluoxetine	20%
Anticonvulsants	
•Gabapentin	45%
Antihypertensives	
•Methyldopa	65%
•Clonidine	38%

Recent study supports hot flash reduction with escitalopram (Lexapro)

% women with >50% ↓ HF

- **Escitalopram: 55%**
- **Placebo: 36%**

Freeman EW, JAMA 2011

Menopause 2004; 11(1): 11-33
ACOG Task Force on HT. Obstet Gynecol 2004; 104:106s-17s.

Gabapentin (GBP) and Hot Flashes (HF)

Author	Dose	% HF ↓ GBP	% HF↓ Placebo	% HF↓ Estrogen
Butt DA 2008	300 mg TID	51%	26%	NA
Guttuso TJ 2003	900 → 2700 mg	54%	31%	NA
Pandya KG 2005	300 mg TID	46%	18%	NA
Reddy SY 2006	Up to 2400 mg	71%	54%	72%

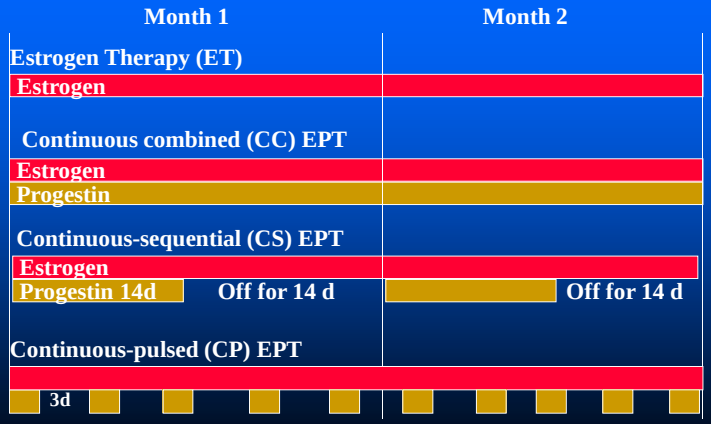
Conclusion: gabapentin equal to, or more effective, than SSRIs

Prescription HT Options: ET and EPT

	Oral	Transdermal	Intravaginal
ET	• Micronized estradiol • Conjugated equine estrogens (CEE) • Synthetic conjugated estrogens • Esterified estrogens • Estropipate • Estradiol acetate	• Patches • Gels • Emulsion • Spray	• Creams • Intravaginal tablet • Rings
EPT	• CC-EPT • CS-EPT	• E+P (combination) patches	

Med Lett Drugs Ther 2004; 46:98.

Hormone Therapy Regimens



Choice of HT Regimen

- If no uterus: estrogen only
- If uterus present
  - Goal is to avoid vaginal bleeding entirely, or, at least, to make it predictable
- Endometrial activity predicts bleeding pattern
  - Recent spontaneous or induced bleeding
    - » Use continuous sequential
  - No bleeding for >2-3 cycles
    - » Use continuous combined

HT Dosages

- Therapeutic goal is lowest effective estrogen dose (plus low progestogen dose for women with a uterus) consistent with individual treatment goals, benefits, and risks
- Lower doses better tolerated, may have more favorable benefit-risk ratio than standard doses
- Additional local ET may be needed for persistent vaginal symptoms

NAMS position statement. *Menopause* 2008.

HT Starting Dosages

- Lower daily doses typically used with systemic ET
  - 0.3 mg oral CE
  - 0.5 mg oral micronized 17ß-estradiol
  - 0.014-0.025 mg transdermal 17ß-estradiol patch
- Typical lowest doses of progestogen
  - 1.5 mg oral MPA
  - 0.1 mg oral norethindrone acetate
  - 0.5 mg oral drospirenone
  - 50-100 mg oral micronized progesterone

NAMS position statement. *Menopause* 2008.

Choice of Estrogens

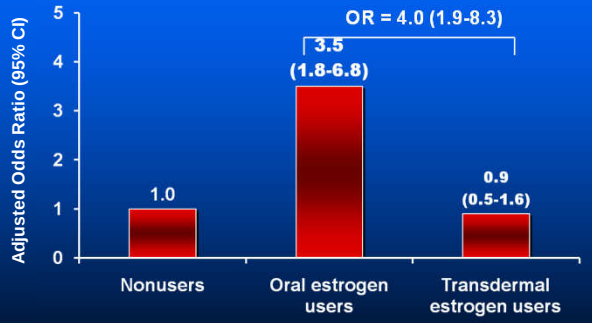
- Start *low dose* transdermal or oral estrogen
- If suboptimal response, modify by
  - Change the estrogen dose (upward)
  - Change the estrogen preparation
  - Change delivery systems (oral ⇄ transdermal)
  - Consider an estrogen-androgen combination
- Injectable estrogen not recommended
  - Dosage equivalencies are not known
  - Estrogen cannot be discontinued easily

HT Routes of Administration

- No clear benefit of one route of administration for systemic ET
- Non-oral routes may offer both advantages and disadvantages compared with oral route
- Transdermal ET may be associated with lower DVT risk than oral (observational data, not RCTs)
- Local ET preferred when solely vaginal symptoms

NAMS position statement. *Menopause* 2008.

Oral vs. TD-E: The Risk of VTE
The ESTHER Study



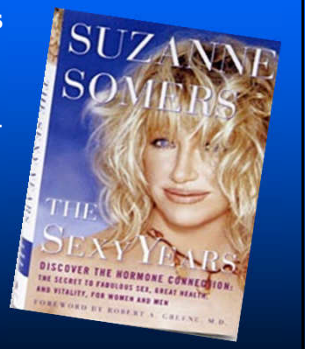
Scarabin P-Y, et al. Lancet. 2003;362:428-432

"First Line" Use: Transdermal Estrogen

- Underlying medical conditions
  - History of DVT or PTE
  - High triglyceride levels
  - Gall bladder disease
- Need for "steady state" drug release
  - Daily mood swings (especially while on oral HT)
  - Migraine headaches
- Inability to use oral tablets
  - Stomach upset due to oral estrogen intake
  - Problems with taking a daily pill

Compounded Bioidentical Hormones

"Then, suddenly, the Seven Dwarfs of Menopause arrived at my door without warning: Bitchy, Sweaty, Sleepy, Bloated, Forgetful, and All-Dried-Up….What was it that sent those wretched dwarfs packing? Natural bioidentical hormones."



Somers S. *The Sexy Years: Discover the Hormone Connection: The Secret to Fabulous Sex, Great Health, and Vitality for Women and Men.* Front Matter. 2004 Random House, Crown Publishing, NY.

Compounded Hormone Therapy

- The ***marketing*** of compounded hormonal therapy
  - Only bioidentical hormones are used
  - Combination of 2 or 3 estrogens is more "natural"
  - Dosage is tailored to the individual
  - More "pure" than commercial products
  - Safer delivery systems (no dyes, etc)
- ***The reality***
  - The ***same*** hormones are used in commercial and compounded 17b-E_2 and progesterone

Sources of Exogenous Hormones

Compounded Hormone Therapy

Compounded hormones will probably work about as well as commercial HT products, but…

- **Value of adding E_1 + E_3 has not been evaluated**
- **Progesterone skin cream is not absorbed**
- **Compounded hormone doses are not standardized**
- **Salivary hormone levels are not useful**
- **FDA-approved HT products will offer**
  - **Bioidentical hormones**
  - **Choice of delivery systems**
  - **Formulary coverage/ lower out-of-pocket costs**

Act 3

Practice Guidelines

How can your patient use these treatments safely, effectively, and conveniently?

Treatment of Hot Flashes

- **If mild symptoms, try lifestyle, CAM therapy**
- **Indications for hormone therapy**
  - **Moderate or severe symptoms**
  - **Non-hormonal treatments have failed**
  - **No interest in non-hormonal therapy**
- **Titrate estrogen dosage upward *if* needed**
- **When estrogen can't be used, offer**
  - **SSRI or SNRI**
  - **Gabapentin, clonidine, a-methyldopa**
  - **Progestins alone**
- **Attempt discontinuation after 2 years**

Treatment of Sleep/ Irritability Sxs

- If mild symptoms
  - Lifestyle change, CAM therapy
- If severe symptoms or no response to above
  - Low dose HT, then titrate upward
  - If mood swings, transdermal E preferred
- Depression component, or no response to HT
  - SNRI or SSRI

HT and Vaginal Atrophy

- When HT is considered solely for this indication, local (not systemic) vaginal ET is recommended
- Progestogen generally *not indicated* with low-dose, local vaginal ET
- Vaginal lubricants often improve vaginal dryness and painful intercourse

NAMS position statement. *Menopause* 2007.

Vaginal Estrogen Therapies

Product	Brand	Dosage	Dose
Conjugated estrogen cream	Premarin cream	0.625 mg/ gram	Daily, then 1-3 time/wk
Estradiol cream	Estrace	0.01% (0.1 mg/ gm)	Daily, then 1-3 time/wk
Estradiol vaginal tablet	Vagifem	25 micrograms	Daily for 2 wks, BIW
Estradiol ring	Estring	7.5 mcg/ 24 hrs	Every 90 days
Estradiol ring*	Femring	0.05 mg/d 0.1 mg/d	Every 3 months

***Intended for use as *systemic* HT**

HT & Urinary Health

- Local ET may benefit some women with urge incontinence who have vaginal atrophy
- Unclear if ET by any route is effective for overactive bladder
- Controversial if local ET can improve stress incontinence (systemic ET may worsen or provoke it)
- Local vaginal ET may reduce risk of recurrent UTI
- No HT product approved for urinary health in US/Canada

NAMS position statement. *Menopause* 2008.

HT & Sexual Function

- Treatment of moderate to severe vaginal atrophy with systemic ET/EPT or local ET can relieve dyspareunia
- One oral systemic ET product FDA is approved for dyspareunia
- HT is not recommended as sole treatment of other sexual function problems (e.g., diminished libido)

NAMS position statement. *Menopause* 2008.

HT & Cognitive Aging/Decline, Dementia

- HT not recommended at any age for the sole or primary indication of preventing cognitive aging or dementia
- HT seems to increase dementia incidence when initiated at ≥ 65 years old
- Inadequate data if HT started soon after menopause increases or decreases later dementia risk
- Limited data do not support HT for Alzheimer's disease

NAMS position statement. *Menopause* 2008.

HT and Fracture Prevention

Pros

- Good data on fracture prevention (mainly 2º prevention)
- Relatively lower cost than bisphosphonates
- Less concern of adverse effects with ET alone (vs EPT)

Cons

- Requires long term use and surveillance, but
- Increased risk of breast cancer after 3-5 years of use
- Post-menopausal bleeding can be troublesome

Utility

- Fracture prophylaxis *if using HT for another indication*
- Otherwise, consider bisphosphonates as first line

HT and "Quality of Life"

- RCTs and retrospective studies show that HT has no effect on "quality of life" measures
- Many woman who wean from HT state that they "feel worse"…even after 20 years after menopause!
- Conventional wisdom
  - In women who "feel better on/ worse off" of HT, continue low dose HT if few or no risk factors
  - When (& how often) to re-attempt wean uncertain
  - Don't start HT for solely for improving QOL

Act 4

The *Finale*

HT Discontinuance/ Symptom Recurrence

- After 2 years of use, recommend drug vacation to determine whether HT is still needed
- Vasomotor symptom recurrence similar whether tapered or abrupt discontinuance
  - 25-50% chance of symptoms recurring when HT discontinued
- Decision to resume HT must be individualized

NAMS position statement. *Menopause* 2008.

HT Discontinuance

- Extending HT use is acceptable
  - For women well aware of risks and benefits
  - With lowest effective dose
  - For prevention of further osteoporosis-related fracture when alternate therapies not appropriate
  - With clinical supervision

NAMS position statement. *Menopause* 2008.