# The Swinging Pendulum in Menopause Management

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# Objectives

- Hormone Therapy (HT) is safe and effective
- Studies that prove efficacy and safety
- Understand importance of the timing of Hormone Therapy
- Treatment options for symptoms

# Relevance

- QOL
  - Vasomotor symptoms (VMS)/Genitourinary Syndrome of Menopause (GSM)
  - Sleep disturbances besides night sweats
  - Cognitive concerns (memory, concentration)
  - Psychological symptoms (depression, anxiety, moodiness)
  - General health decline.
- Financial
  - Income lost from days off work
  - Indirect/direct increase in health care cost
- Lives lost from estrogen avoidance

# Common patient experiences

- Hot flashes
- Insomnia
- Dyspareunia
- Palpitations
- Weight gain
- Joint pains/myalgia
- Urinary tract infections

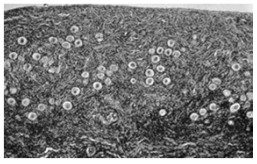
## Likelihood of prescribing hormone therapy

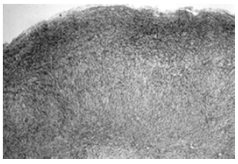
- US OB/GYNs & PCPs: 15 – 20 minute Internet based Survey.[1]
- Assessed knowledge via 9 true-false statements about HT and 6 clinical vignettes
- Primary analysis -> correlation between HT trial knowledge and likelihood of prescribing HT.
- N = 501 Physicians.
  - Mean score of OB/GYNs was 4.5/9.
  - **Mean score of PCP was 2.1/9**
  - Overall mean was 3.8.
- Physicians more knowledgeable about large, published HT trials more likely to prescribe HT.

1. Taylor S Hugh, Kagan R, Altomare, C. Knowledge of clinical trials regarding hormone therapy and likelihood of prescribing hormone therapy. Menopause. Vol 24. No 1. pp27-34.

## Menopause

- Menopause is a normal, natural event, defined as the final menstrual period, confirmed after 1 year of no menstrual bleeding.
- loss of ovarian follicular function.
- Prematurely from medical intervention. (bilateral oophorectomy, chemotherapy, autoimmune)





## Clinical Importance:

- By 2020 - 50 million postmenopausal women in the US.
  - Will spend 1/3rd of their lives in menopause.
- Vasomotor symptoms (VMS)/Genitourinary Syndrome of Menopause (GSM) are most debilitating symptoms
  - 60 – 90% of women.
- Hot flashes can last on average for up to 7.4 years or more
  - Interfering with daily activity and sleep.
- ¼ women find these symptoms unbearable.

1.Utian Wulf, Holly Yu, Joel Bobula, Sebastian Mirkin, Sophie Olivier, james H Pickar. Bazedoxifene/conjugated estrogens and quality of life in postmenopausal women. Maturitas 63(2009)329-335.

**1. Hormone therapy is safe and effective**

## Back to the future

- 1980s- Observational studies and meta-analyses suggested that HT after menopause was beneficial in preventing osteoporosis, cardiovascular disease, dementia and decreased all-cause mortality.
  - American College of Physicians – advocated use in 1992.
- Late 1990s/early 2000s - randomized trials.
- 2002 - Almost immediately after the Women's Health Initiative, HT stopped being prescribed.

Image Author: MsSaraKelly - (CC BY 2.0)

# Women's Health Initiative (WHI)

## WHI Background

- Two arms –
  - Intact Uterus
    - 16, 608 women in 0.625 mg conjugated equine estrogen (CEE) + 2.5 medroxyprogesterone acetate (MPA)
  - s/p hysterectomy
    - 11,739 in 0.625 CEE arm.
- Planned duration of 8.5 years, stopped after 5.3 years in CEE+ MPA arm.

1.Writing Group for the Women's Health Initiative Investigators . Risks and Benefits of Estrogen Plus Progestin in Healthy Postmenopausal Women Principal Results From the Women's Health Initiative Randomized Controlled Trial. *JAMA.* 2002

2. The Women's Health Initiative Steering Committee*. Effects of Conjugated Equine Estrogen in Postmenopausal Women With Hysterectomy. The Women's Health Initiative Randomized Controlled Trial. *JAMA.* 2004;

# WHI Objectives

- Randomized controlled primary prevention trial:
  - Coronary heart disease
  - Nonfatal MI
  - Coronary heart disease death.
- The WHI trials were <u>not designed to study the control of menopausal symptoms</u> and only a fraction of the women enrolled in the WHI were symptomatic.

The women's Health Initiative Study Group. Design of the Women's health Initiative clinical trial and observational study. Control Clinic trials 1998.

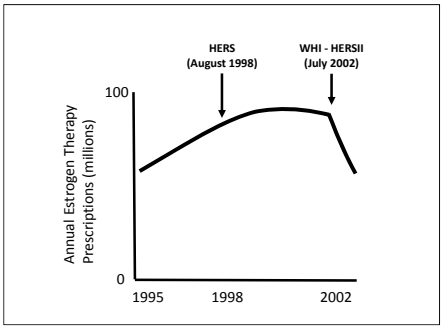
# Women's Health Initiative: CEE+ MPA ENDS EARLY

- 2002 – Ended early due to an apparent increased risk of invasive breast cancer and also an increased risk of VTE or stroke in the treatment estrogen plus medroxyprogesterone acetate (MPA) arm.

# Estrogen Therapy is Dangerous and Harmful

- As a result, an idea became deeply rooted - that estrogen is dangerous and harmful.
- The idea still persists among doctors and the public in spite of the plethora of scientific evidence to the contrary.
- Information and evidence has so far been unable to ward off the idea.

# Annual Number of U.S. Prescriptions for All Forms of Hormone Therapy: 1995-2003




Hersh et al. JAMA 2004;291:47-53

## Consequences of hormone therapy drop-off

- Due to patient and physician confusion over the results- the usage of hormone therapy (HT) dropped off precipitously.
- 60% increase in anti-depressant scripts written during that time.
- Compounded non-FDA approved postmenopausal hormone prescriptions increased.

1. Pinkerton and Constantine et al, "Compounded non-FDA approved menopause hormone therapy prescriptions have increased: Results of a pharmacy survey."

## Women still want treatment

VITA HEALTH
MEDICAL CLINIC

## Compounded non-FDA hormone therapy

- Data estimate the number of prescriptions for compounded non FDA menopause hormone therapy written on an annual basis:
  - 26 to 33 million prescriptions worth over a billion dollars per year.

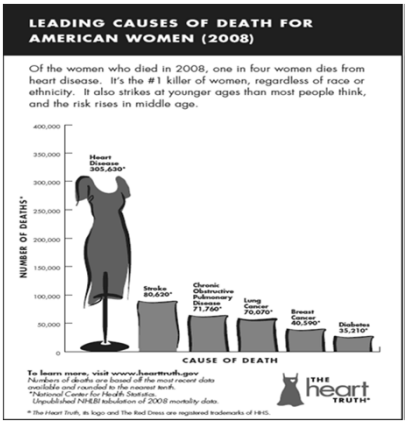
    (Estimating $49 dollars per prescription).

1. Pinkerton and Constantine et al, "Compounded non-FDA approved menopause hormone therapy prescriptions have increased: Results of a pharmacy survey."

## Studies that prove efficacy and safety:

- CARIOVASCULAR DISEASE IN WOMEN
  - Long term WHI data
  - DOPS Trial
  - KEEPS Trial
  - Elite Trial

# Hormone Therapy and Cardiovascular disease




Source – NIH -https://www.nhlbi.nih.gov/health/educational/hearttruth/

## Timing Hypothesis

- Post hoc analysis of the WHI has showed several benefits- especially within ten years of menopause
  - *'timing hypothesis'*
- Long term data from the WHI discloses that women on hormone therapy 50 – 59 or within 10 yrs of menopause:[1,2]
  - Decreased coronary heart disease
  - Decreased all cause mortality
  - Others - reduction in menopausal symptoms, improved quality of life, osteoporosis prevention, & prevention of new onset diabetes mellitus

1. Manson JoAnn E et al. Menopausal hormone therapy and health outcomes during the intervention and extended post stopping phases of the Women's Health initiative Randomized trials. JAMA. 2013;310(13):1353-1368.
2. Bhupathiraju Shilpa N, Manson Joann E. Menopausal Hormone Therapy and chronic disease risk in the women's health initiative; Is timing everything? Endocrine Practice. Vol 20 No11. November 2014.

## Long term WHI data 10/2013

- WHI conjugated equine estrogen only
  - Total mortality HR of 0.73 (0.47-1.13)
- In analysis that combined estrogen/MPA and estrogen therapy
  - Hormone therapy was associated with a significant 30% reduction in mortality among women in their 50s
  - No effect on women in 60s
  - Increased mortality on women in 70s.

Manson, E JoAnn 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.

## Game Changer: DOPS Oct 2012

- 10 year randomized clinical trial of Danish women
- younger symptomatic (age 50)
- Followed for ten years
- Oral EPT (estrogen-progestin therapy) – estradiol + norithindrone
- Significantly reduced:
  - Risk of mortality
  - Heart Failure
  - Myocardial infarction
- Without any apparent increase in risk of:
  - Cancer
  - Venous thromboembolism
  - Stroke

Schierbeck et al. Effect of hormone replacement therapy on cardiovascular events in recently postmenopausal women: randomized trial BMJ 2012; 345x

## Newer Research: KEEPS trial

- Ave age 52.
- 3 arms: Placebo, oCE, tE2 with **cyclic micronized progesterone Days 1-12.**
- Both treatment arms:
  - Improved bone density
  - Improved cardiovascular markers (did NOT include BP)
  - Improved vasomotor symptoms
  - Improved insulin resistance
  - Improved genitourinary syndrome of menopause and lubrication
  - No adverse affect on cognitive function

## Elite Trial: NEJM 2016

- Oral estrogen + vaginal progesterone in women < 6 years or > 10 years after menopause.
- Measure coronary calcium and carotid intimal thickening.
  - Oral E was associated with less progression of subclinical atherosclerosis (measured as carotid intimal media thickness) vs. placebo when started by 6 years of menopause, but not when started 10 years or more after menopause.
- Study confirmed the timing hypothesis -10 year window in which prescribing hormone therapy is beneficial to cardiovascular health, and likely not harmful.

Hodis, H, Mack, W, Henderson V et al. Vascular effects of early verses late postmenopausal treatment with estradiol. NEJM 2016.

## Pathophysiology Continued

- Timing Hypothesis:
  - In earlier stages of atherosclerosis, estrogen may have beneficial effects on lipids and endothelial function.
  - In advanced atherosclerosis, estrogen may trigger acute coronary events through prothrombotic and inflammatory mechanisms.

## Hormone therapy and cardiovascular disease after stopping therapy

- Recently published large observational study from Finland reported increased cardiovascular mortality during the year following discontinuation of HT.[1]
- Post WHI trial analysis showed mortality was increased within the 3 years of cessation of the E+MPA arm relative to those who were assigned to placebo (hazard ratio [HR]=1.15; 95% confidence interval [CI], 0.95-1.39).[2]


1. Mikkola TS, Tuomikoski P, Lyytinen H, et al. Increased cardiovascular mortality risk in women discontinuing postmenopausal hormone therapy [published online ahead of print September 28, 2015]. *J Clin Endocrinol Metab*.
2. 2. Heiss G, Wallace R, Anderson GL, et al; WHI Investigators. Health risks and benefits 3 years after stopping randomized treatment with estrogen and progestin. *JAMA*. 2008;299(9):1036-1045.


## Back to the Future

The Future is Now

- Observation Vs. Randomized Controlled Trials.
- Data show that in primary prevention, HT reduced coronary heart disease and all cause mortality in women who initiate HT before age 60/ten years of menopause.
  - Data are consistent across observational studies, randomized clinical trials and meta-analyses.

## Timing Hypothesis & Coronary Heart Disease

- HT appears to <u>REDUCE</u> coronary heart disease risk when initiated in younger and more recently postmenopausal women.
- Longer HT duration associated with REDUCED coronary heart disease risk and mortality.
- Evidence of lower coronary heart disease risk in women who used HT ≥ 5 yr exists in WHI.

NAMS 2017 position statement

## Hormone therapy & hot flashes, mood and quality of life

## HT & Vasomotor Symptoms

- Treatment of moderate to severe vasomotor symptoms remains primary indication for systemic HT.
- Every systemic product in the US/Canada is approved for this.
- Significant data support its use in women to treat
  - Menopausal symptoms
  - Prevent osteoporosis in women at high risk for fracture.

## HT and improvement in mood & quality of life

- KEEPS trial
- Oral - improvement in mood.
  - Improved significantly on measures of depression-dejection and anxiety-tension.
  - Showed a trend in improvement on measures of anger-hostility
  - Improvement in memory recall
- Transdermal-
  - Improved arousal and desire
  - Insulin sensitivity

# Hormone therapy & insulin sensitivity

## HT & Insulin Sensitivity

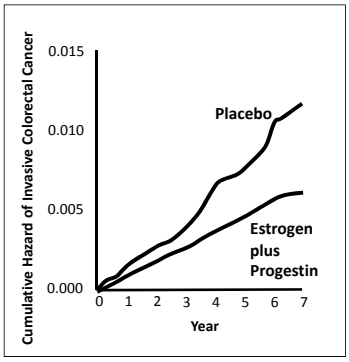
- PM women on HT have higher glucose utilization and improved insulin sensitivity than women not on HT. [1]
- Kaiser data: shows a 30% reduction in risk of diabetes in women on HT.
- WHI Data
- In diabetics - Transdermal ET may have advantages over oral estrogen.
- Inadequate evidence to recommend HT for sole or primary indication for diabetes mellitus prevention.

1. Bitoska, Iskra, Kretevaska, Branka, Milenkovic, tatjana et al. Effects of Hormone Replacement therapy on insulin resistance in postmenopausal diabetic women. J med Sci. 2016 mar 15; 4(1):83-88.

## Hormone therapy & colon cancer

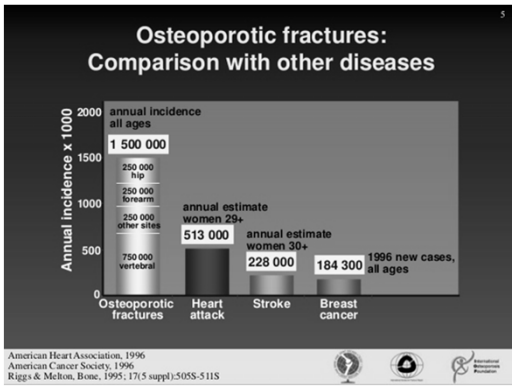
## HT & Colon Cancer

In the E+MPA arm of the of the WHI, there was a statistically significant **decrease** in the incidence of colorectal cancer.[1]



But Wait There's More

# Hormone therapy & Osteoporosis




***16.7 Billion Dollars annual Spent***

## Osteoporosis

- **In the WHI, HT reduced the risk of hip fracture by 50%.**
- **In the conjugated equine estrogen arm fracture reduction was seen at all sites.[1]**
- **In the E +MAP arm, after approximately 5 years there was[2,3]**
  - **33% reduction in hip fractures.**
  - **24% reduction in all fractures.**
- **A meta-analysis of 22 trials of estrogen for the prevention of fractures[4]**
  - **33 % reduction in non-vertebral fractures in women under age 60**
  - **12 % reduction in women over 60.**


1. Anderson GL, Limacher M, Assaf AR et al. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the women's health Initiative randomized controlled trial. JAMA 291:1701-1712,2004.
2. J.A.Cauley et al. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the women's health Initiative randomized controlled trial. JAMA 290 (13) 2891-2897 2003.
3. R.D.Jackson et al. Effects of conjugated equine estrogen on risk of fractures and BMD in postmenopausal women with hysterectomy: results from the women's health initiative randomized trial. J bone Miner Res 21 (5) (2006) 817-828.
4. D.J Torgerson, S.E bell-Syer. Hormone replacement therapy and prevention of nonvertebral fractures: a meta-analysis of randomized trials. JAMA 285. June 22 (2001) 2891-2897


## HT & Osteoporosis

- **HT proven to reduce postmenopausal osteoporotic fractures.**
- **Most systemic HT is approved for the prevention of post-menopausal osteoporosis through long-term treatment.**
- **Extended use of HT is option for women with low bone mass, <u>regardless of menopause symptoms</u>, when alternate therapies not appropriate.**

**NAMS position statement 2017**

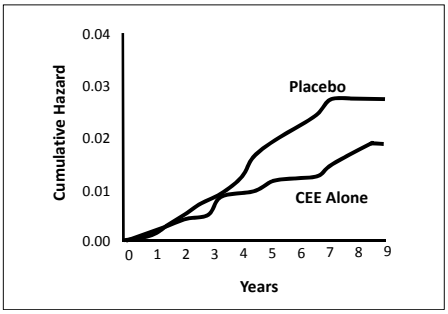
## Hormone therapy & Breast cancer risk

## HT & Breast Cancer: Estrogen Only

- **WHI - At end of intervention of 7.1 years, fewer invasive breast cancers in the estrogen alone group**
  - **HR 0.80, CI 0.62-1.04**
- **After longer follow-up 12 years, statistically significant lower incidence of invasive breast cancer emerged in the estrogen alone arm**
  - **HR 0.77, CI 0.62-0.95**
  - **Effect is seen during and after intervention.**

Stefanick ML e al. Effects of conjugated equine estrogens on breast cancer and mammography screening in postmenopausal women with hysterectomy. JAMA 2006.

## HT & Breast Cancer: Estrogen Only




**Stefanick et al. JAMA 2006**

## Estrogen Only

- Women receiving ET who did develop breast cancer, had a 63% reduction in deaths from the disease (6 deaths) versus those in the placebo group (16 deaths)
- Use of estrogen alone did not substantially interfere with breast cancer detection by mammography.

## Combined Estrogen + MPA

- WHI - Associated with a 24% increased risk of invasive breast cancer.
- The RR of 1.26 with E/MPA translates to an excess risk of 4 per 1,000 women taking hormone replacement therapy for a 5 year time period.
- Epidemiologic data have linked alcohol consumption to risk of breast cancer
  - An approximate 11-50% increase in breast cancer risk from 15-30 grams/day of alcohol consumption.

## Combined Estrogen + Progestin

- Post-menopausal primate model using estradiol + MPA versus estradiol + micronized progesterone
  - MPA significantly increased breast cancer cell proliferation whereas micronized progesterone did not
- Analysis from French prospective cohort study
  - No increased risk of invasive breast cancer in users of synthetic progesterone
  - Increased risk in estrogen + compounded progestin's (MPA, cyproterone, promesgestone, nomesgestrol, medrogestone)

1. Fournier A, Berrino F, Clavel-Chapelon F. Unequal risks for breast cancer associated with different hormone replacement therapies: results from the E3N cohort study. Breast Cancer Res Treat 2008; 107: 103-111.

## Hormone therapy and cognitive function

## Women's Health Initiative Memory Study (WHIMS)

- HT not recommended at any age for the sole or primary indication of preventing cognitive aging or dementia.[1,2]
- HT seems to increase dementia incidence when initiated at ≥ 65
  - Increase stroke risk.
- WHIMS did not look at women < age 65

1. Stefanick ML et al. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women. JAMA 2003.
2. Shumaker SA et al conjugated equine estrogens and incidence o probable dementia and mild cognitive impairment in postmenopausal women. JAMA 2004

## Hormone therapy and venous thromboembolism risk

## HT & Venous Thromboembolism

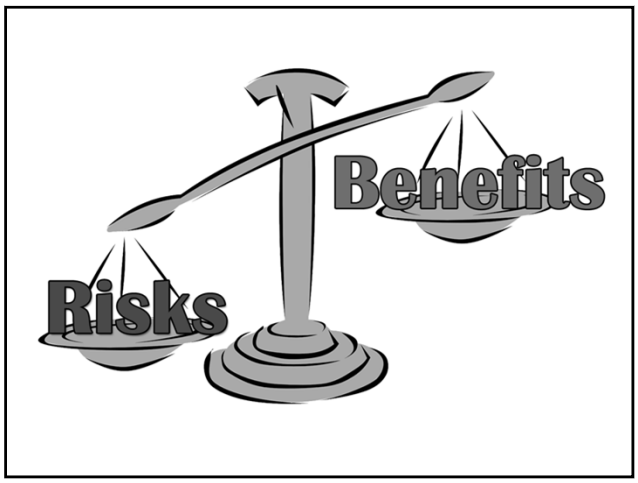
- Oral HT increases venous thromboembolism risk in postmenopausal women
  - Similar deep venous thrombosis risk with SERMs
- Venous thromboembolism risk emerges soon after HT initiation
  - Peaks at 6 months
  - Decreases over time.
- Lower venous thromboembolism risk with in women <60 yrs
- Lower venous thromboembolism risk risk with transdermal than with oral (ET-ESTER study)
- Lower HT doses may be safer than higher doses

Scarabin PY et al. Lancet 2003.

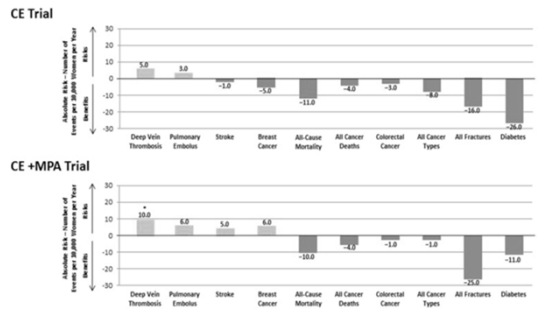
## HT vs hormone contraceptives

- Venous thromboembolism major issue with both:
  - 2-4 fold increase with HT
  - 3-6 fold increase for hormone contraceptives
- Transdermal hormone contraceptives
  - Higher venous thromboembolism risk compared to transdermal HT.

Gomes, Marcelo, Deitcher, Steven. Arch Intern med 2004.




## Absolute benefits / Risks 13+ years




Absolute benefits and risks from the 13 year follow up study from the hormone trials of WHI: Conjugated Estrogens (CEE) alone trial and the trial with CEE combined with medroxyprogesterone acetate (MPA.) Data on the initiation of HRT in women 50–59 years of age or < 10 years from the onset of menopause: number of events per 10,000 women per year.* The only statistically significant adverse outcome. Adapted from Manson JE et al. N Engl J Med 2016; 803–806

## The Morbidity & Mortality Toll of Estrogen Avoidance

- Over a 10-year span, starting in 2002, a minimum of 18,601 and as many as 91,610 PM women died prematurely because of the avoidance of estrogen therapy (ET). [1,2]
- Substantial increase in hip fractures due to HT discontinuation rates.

1.Sarrel PM, Njike VY, Vinante V, Katz DL. The Mortality Toll of Estrogen Avoidance: An Analysis of Excess Deaths Among Hysterectomized Women Aged 50 to 59 Years. *American Journal of Public Health*. 2013
2. RA Lobo et al. Atherosclerosis 2016.

*NAMS position statement 2017*

## Incremental Direct and Indirect Costs of Untreated Vasomotor Symptoms

- Employer-based Insurance Records
- U.S Fortune 500 companies.
- Case Cohorts: Untreated vasomotor symptoms vs. vasomotor symptoms (control).
  - N=252,273; mean age = 56
- Number of health care visits & cost of lost work for 12 months.
  - 1.5 million more outpatient visits (per year) by women with untreated vasomotor symptoms .
  - (PerPtPerYr) = $2,000.00 more for women with untreated vasomotor symptoms .
  - Total cohort cost (252,273 women in each group): Nearly $400,000,000 more for women with untreated vasomotor symptoms .

Philip Sarrel et al. Menopause. March 2015.

## Length of treatment

- The American College of Obstetricians and Gynecologists and NAMS have expanded their treatment definition to state that women on HT do not need to stop treatment at the age of 65.
- Often, symptoms return.
- Consider lower doses with aging due to decreased metabolism.

*NAMS position statement 2017*

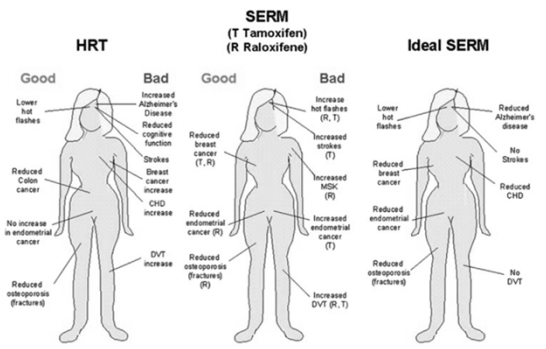
## New Paradigm

## "Designer" Estrogens

## SERMs/ERAAs

## Estrogen Agonists/Estrogen Antagonists

## The ideal SERM/ ERAA




NIH - National Library of Medicine (CC BY 2.5)

## ERAA: Bazedoxifene/conjugated equine estrogen: Duavee

- SERM/ERAA
- 20 mg Bazedoxifene with 0.45 conjugated equine estrogen
- SMART Trials:
  - Effective and safe treatment for menopausal symptoms in women with intact uterus.
  - FDA Approved to treat vasomotor symptoms.
  - FDA approved to prevent osteoporosis.
  - No increase in uterine cancer.
    - Bazedoxifene competitively inhibits binding of 17-B estradiol – antagonist at uterus.
- Carries similar risk of deep venous thrombosis as HT

Pinkerton JV et al, SMART-5 Investigators. Effects of BZD/CE on the endometrium and bone. J Clin Endo Metab. 2014

# ERAA Ospemifene: Osphena

- **Approved for the treatment of genitourinary syndrome of menopause.**
  - **Agonistic estrogen effects in vagina.**
- **Agonistic effects on the bone.**
  - **Similar efficacy to raloxifene, -> yet it does not carry an FDA approval for treating osteoporosis (Komi et al)**
- **In rat models there appears to be a dose dependent reduction in breast cancer development. (Wurz GT et al)**
- **Shows antagonistic effects on uterine tissue (Cui, Yuanshan et al).**
- **However, carries similar risk of deep venous thrombosis as HT.**

# ERAAs and their respective benefits

| ERAA | + VMS | + GSM | + Bone effects seen clinically | FDA Approval | +Breast Cancer Reduction |
|---|---|---|---|---|---|
| Tamoxifen | | | + | + for treatment of metastatic breast cancer, DCIS, and reduction of incidence of breast cancer in high risk women. | + |
| Raloxifene | | | + | + for prevention and treatment of osteoporosis | + |
| Ospemifene | | + | + | + for GSM | |
| Bazedoxifene/CE | + | + | + | + for prevention of osteoporosis + Tx of VMS of menopause in women with uterus. | |

# Non- Hormonal Options for vasomotor symptoms

# Non-Hormonal Option for Menopause Symptoms

- FDA Approved:
  - Brisdelle 7.5 mg at night (Paroxetine)
  - **7.5 mg low dose not associated with weight gain or sexual dysfunction**
- Several off label options for vasomotor symptoms:
  - Desvenlafaxine
  - Venlafaxine
  - Gabapentin
- Insomnia:
  - sleeping agents

## NAMS 2015: Lifestyle Symptom Management

- Recommended:
  - CBT
  - Hypnosis (to lesser extent)
- Recommend with caution:
  - Weight loss
  - Mindful stress reduction
  - Soy isoflavones
- Not Recommended
  - Exercise, yoga
  - OTC supplements and herbals
  - Acupuncture
  - Chiropractic interventions.

## Genitourinary Syndrome of Menopause

## GSM

- Symptoms:
  - Vaginal dryness
  - Vulvo-vaginal irritation/itching
  - Dyspareunia
  - Frequent bladder infections
  - Urinary incontinence, dysuria, urethral symptoms
  - Experienced in most postmenopausal women, yet only 25% of these women seek treatment.
- Unlike vasomotor symptoms, vaginal atrophy is progressive and unlikely to resolve on its own

## Genitourinary Syndrome of Menopause Treatment

- NAMS position statement:
  - non-hormonal lubricants
  - moisturizers in combination
  - regular sexual activity considered first line.
- <u>This is often, if not usually, inadequate</u>
- Local vaginal ET more effective
- Systemic HT may be needed to treat genitourinary syndrome of menopause.

## Vaginal Estrogen

- Creams

- Vaginal Rings

- Vaginal tablet

## Prasterone

- FDA - Approved Prasterone for Dyspareunia in Postmenopausal Women.
- Once-daily vaginal insert
- The first FDA-approved product containing the active ingredient prasterone, -> dehydroepiandrosterone (DHEA)
- Efficacy establish in 2 - 12 week clinical trials of 406 women with dyspareunia.
  - Reduced pain with intercourse
- Safety established in 52 week trial

## Summary: Explaining HT Risk

- Potential absolute risks with the use of HT are very low
  - Especially for ET in hysterectomized women
  - Especially for younger women closer to menopause
- GOLD standard for vasomotor symptoms, genitourinary syndrome of menopause, and osteoporosis prevention
- Greatest risk of HT related to venous thromboembolism (same for ERAA/SERMs and hormone contraceptives)

## Summary: Benefits >> Risks

- Benefits outweigh risks
- Each regimen, route, and timing of therapy has distinct beneficial and adverse effects.
- Each woman must be informed of her known risks/benefits and alternatives.
  - Acceptance of HT risk balanced with understanding risks in not treating
  - And compared to risks similar to other agents commonly used (eg Statins, ERAAs/SERMS, diabetic agents, aspirin others)

## Lastly: Individualized Treatment Needed

- An individual risk profile is essential when contemplating HT.
- Late HT initiation in older women-with no indication is less favorable
- Women with premature menopause have increased symptoms and risks-TREAT or REFER
- Recommendations are DIFFERENT for first users versus previous users in their 60s - REFER


## Thanks!

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