

“My Hot Flashes Are Killing Me!
Can I Try Hormones?”

How to Answer Your Patients’
Questions about Management of
Their Menopausal Symptoms

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Objectives

- Discuss the impact of both estrogen and combination hormone therapy on the risk of development of breast cancer.
- Differentiate the impact of early start vs. late start hormone therapy on the risk of cardiovascular disease.
- Compare and contrast non-hormonal medications for the treatment of vasomotor symptoms.
- Choose an appropriate treatment for vaginal dryness and dyspareunia.
- Outline a rational and evidence based approach to counseling women with bothersome menopausal symptoms.

Agenda

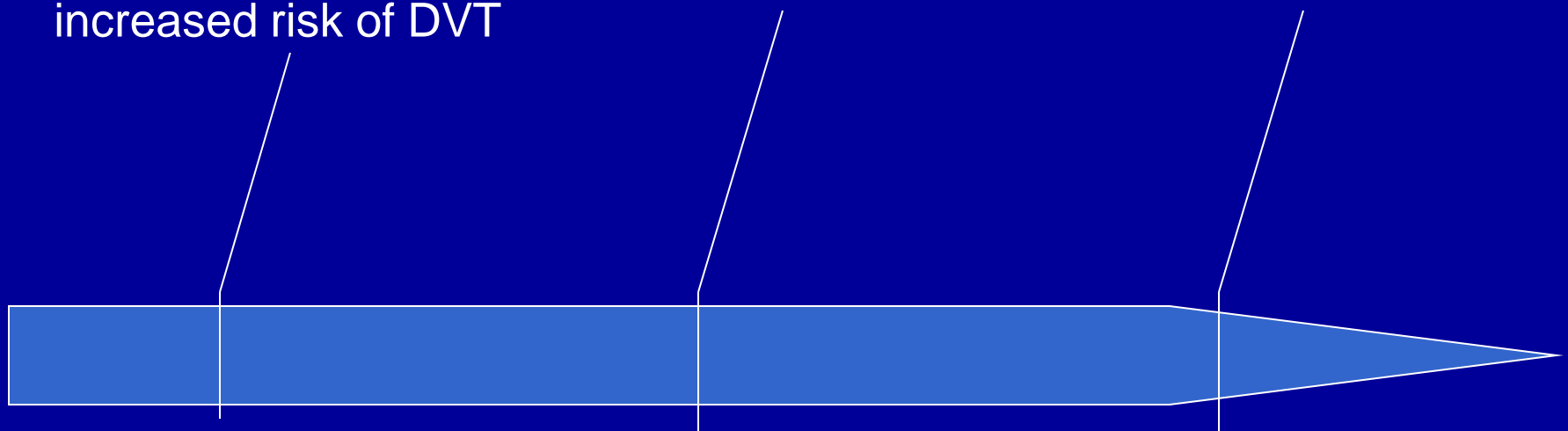
- Overview of Women's Health Initiative results from 2002
- Brief introduction to Team-Based Learning
- Hormone use and breast cancer risk
- Hormone use and CV risk
- Treatment of hot flashes
- Treatment of sexual dysfunction

Hormone use—timeline

HT may prevent CAD/CVA and osteoporosis; reduces hot flashes and sexual dysfunction; may have increased risk of DVT

WHI study stopped early due to breast cancer risk —use of HT drops off drastically

Women wonder how long they can/should take hormones



Up to 2001

2002

after 2002

“Fountain of youth”

“Poison”

?

Women's Health Initiative (WHI): Combination Therapy Results

Summary of Outcome Data:

Over 1 year, in 10,000 women:

- 7 more cardiac events (29% increase)
- 8 more strokes (41% increase)
- 16 more VTE (2X increase)
- 8 more breast cancers (26% increase)
- 6 fewer colon cancers (37% decrease)
- 5 fewer hip fractures (33% decrease)

Many women stopped HT

WHI baseline characteristics: combination therapy

- Average age: 63 yo
- Ethnicity: 84% white
- Previous/current use of hormones: 25.8%
- Study drug: conjugated equine estrogen (CEE), 0.625 mg/d, plus medroxyprogesterone (MPA), 2.5 mg/d (Prempro)
- Average length of follow-up: 5.2 years

WHI results: combination therapy

	Combo HT	Placebo	Hazard Ratio	CI	Adj CI
CHD	164	122	1.29	1.02-1.63	0.85-1.97
Stroke	127	85	1.41	1.07-1.85	0.86-2.31
DVT/PE	151	67	2.11	1.58-2.82	1.26-3.55
Breast cancer	166	124	1.26	1.00-1.59	0.83-1.92
Colon cancer	45	67	0.63	0.43-0.92	0.32-1.24
Hip fracture	44	62	0.66	0.45-0.98	0.33-1.33
Death	231	218	.98	0.82-1.18	0.7-1.3

WHI Writing group, *JAMA*. 2002;288:321-333.

Manson JE et al, *NEJM* 2003;349: 523-534

WHI: Estrogen Alone

- Average age: 63 yo
- Previous hormone use: 48.4%
- No benefit OR risk for CAD events
 - HR 0.91 (CI 0.75-1.12, adj. CI 0.72-1.15)
- Small increase in stroke in older women
- Reduction in hip fracture
- Possible REDUCTION in breast cancer risk
 - HR 0.77 (CI 0.59-1.01, adj. CI 0.57-1.06)
- NO difference in death rates

Unresolved questions

- Does the duration of hormone use matter?
- When is the optimal time to use hormones?
- What is the magnitude of the breast cancer risk?
- Who is at risk of cardiovascular outcomes?
- WHI didn't address symptom management
 - How should we treat hot flashes?
 - What do we do about dyspareunia?

Team-Based Learning

- Usually occurs in semester long course
- Teams: assigned, diverse, heterogeneous, stable over length of course
- Before class: students read pertinent material
- In class:
 - Teams work on solving problems
 - Results simultaneously shared with entire class
 - Instructor fills in gaps in learning

HT and risk of breast cancer

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Case #1

- Marianne: 52yo G3P2 Caucasian woman presenting with complaints of severe hot flashes. She had normal menses her entire life, has not had any for 13 months. She was on oral contraception for most of her life except with her 2 pregnancies. Her first pregnancy was at age 36 and she reports her paternal GM died of breast cancer.
1. How do you counsel Marianne on her risk of breast cancer when considering HT?
 - A. She has received an adequate challenge of hormones throughout her life and is therefore at low risk.
 - B. She has a grandmother with breast cancer and thus her family history puts her at high risk.
 - C. Her Gail score will help quantify her risk for breast cancer.
 - D. She'll need to perform mammograms every 6 months to quantify her risks on HT.



Case #1

2. If Marianne has had a hysterectomy how does that change her risk of breast cancer with HT?
 - A. It doesn't change her risks; risk of breast cancer is the same no matter the type of hormones.
 - B. It decreases her risks as she will be getting only estrogen therapy.
 - C. It increases her risks as she will be getting only estrogen therapy.

Case #2

- Leslie is a 51 year old woman having terrible night sweats and hot flashes where she is “dripping” with sweat. Leslie is otherwise quite healthy. She is single, never had any children (though had one miscarriage in her 20s) and was on various forms of hormonal birth control throughout her life. She lives with her mother who was recently diagnosed with breast cancer.
- What are the important factors in Leslie’s case that will determine her risks?
 - A. Her family history and lifetime history of hormonal birth control effectively “cancel each other” and put her at average risk.
 - B. Her family history and never having children put her at increased risk.
 - C. Her history of miscarriage and lifetime history of hormonal birth control puts her at decreased risk.

HT and Breast Cancer

- HERS– randomized, placebo-controlled
 - 2763 women, mean age 66.7 years

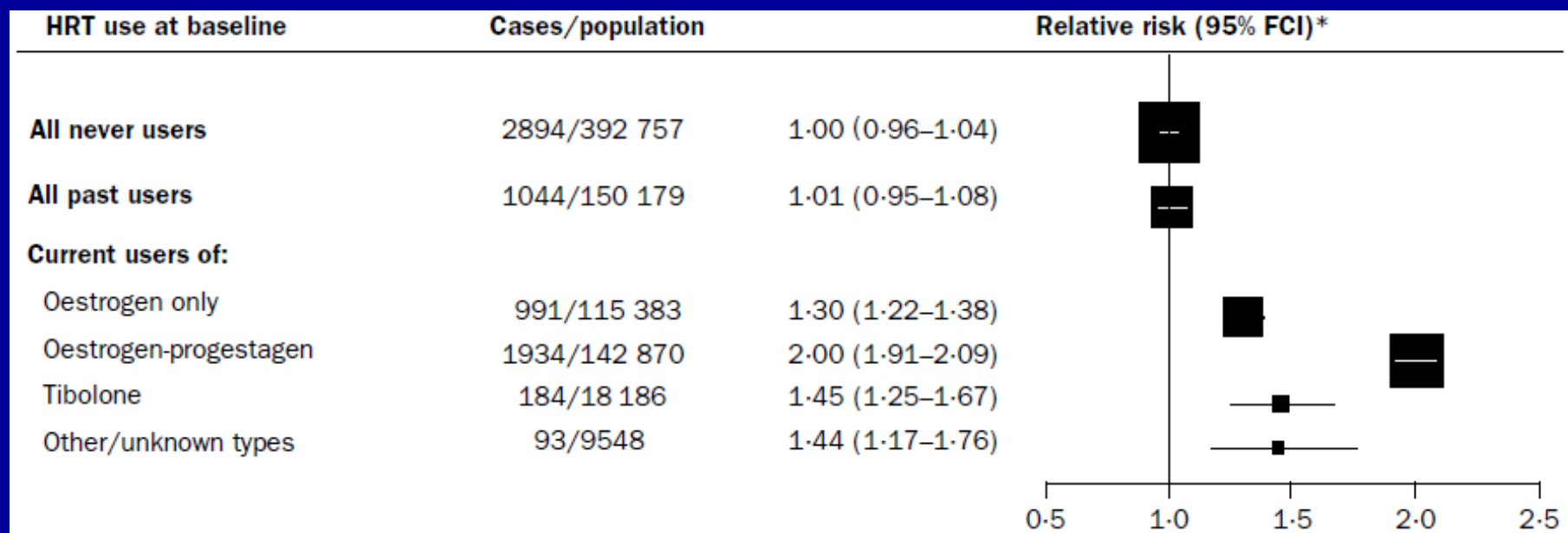
	E+P	Placebo	RH (95% CI)	P value
Breast CA	32	25	1.3 (0.77-2.19)	0.33

- WHI and Combination HRT

	E+P	Placebo	HR	95%CI	Adj 95% CI
Breast CA	166	124	1.26	1.00- 1.59	0.83- 1.92

Million Women Study

- Observational study of >1 million British women ages 50-64 from 1996-2001



Million Women Study

- Criticisms
 - Invited to enroll when presenting for mammography
 - Breast cancer risk seen to increase as early as first year on hormones raising methodologic flaws
 - Failure to record discontinued HT use or crossovers



Delving Further into WHI Breast Cancer Risk

- 16,608 women 50-79 with intact uterus
- Had yearly mammogram and CBE
- Average age, 63
- Average Gail score, 1.5%
 - 33% had Gail score >1.75%

The Gail Model

- Projects the absolute risk of invasive breast cancer over five years for women >35 years
- Factors included in calculating risk:
 - Age
 - Age at menarche
 - Number of first-degree female relatives with breast cancer
 - Number of previous breast biopsies
 - Age at first live birth (or nulliparity)
 - Race
 - Personal history of atypical hyperplasia
- An increased risk of developing breast cancer is defined as a Gail Score of >1.7%

Delving Further into WHI Breast Cancer Risk

Risk of breast cancer according to prior hormone use

Prior use	E+P	Placebo	HR (95% CI)
Never users	141	121	1.09 (0.86-1.39)
<5 years	37	21	1.70 (0.99-2.91)
≥5 years	21	8	2.27 (1.00-5.15)

- For women with no prior menopausal hormone use, breast cancer rates were \leq placebo until year 4

WHI: Hormones without a Uterus

- Estrogen-only arm of WHI
 - Average age: 63 years
 - Previous hormone use: 48.4%
- Discontinued after 7 years as no evidence on risk of heart disease, increased risk of stroke

WHI: Hormones without a Uterus

Risk of breast cancer in women using estrogen after hysterectomy

	CEE	Placebo	HR	95% CI	Adj. 95% CI
Breast CA	94	124	0.77	0.59-1.01	0.57-1.06

WHI Follow Up Data

- After release of WHI data in 2002, use of HT decreased substantially
- 15,387 participants in WHI not previously diagnosed with breast CA
- Rates of mammography remained the same between HT and placebo groups

WHI Follow Up Data

- Number of breast cancer diagnoses in HT group decreased by 28% in the 1st year after trial stopped
 - 48 cases to 34 cases
- Continued to decline each year after

WHI Summary: HT and Breast CA

- EPT: 8 additional breast cancers per 10,000 women per year
- ET alone: no increased risk
- The increase in breast cancer risk appears related to postmenopausal HT prior to enrollment in WHI and length of time on HT

HT and Breast CA: Take Home Points

- Degree of association remains controversial
- Diagnosis of breast cancer increases with EPT use beyond 3-5 years
- Available evidence suggests ET for fewer than 5 years has little impact on risk
- Would avoid HT use in women already at higher risk for breast CA (i.e. Gail >1.7%)

Cardiovascular Risk and Hormone Therapy

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Case - Linda

- 50 yo G2P2, asking for symptom relief
- Two months s/p hysterectomy for fibroids
- Very bothersome hot flashes, night sweats
- PMH - hyperlipidemia
 - Total cholesterol 240, HDL 30
- FM - parents alive and no issues
- VS/PE - WNL
- Best friend recently had a myocardial infarction so worried about CV risk in general

Questions

4. How do you determine Linda's CV risk?
 1. Check CRP level
 2. Electron Beam CT
 3. NHLBI Framingham risk score
 4. Cardiac MRI
 5. Stress Test

Questions

5. What do you tell Linda about her CV risk after starting HT?

- 1.It will improve
- 2.It will get worse
- 3.It will be unchanged
- 4.It depends...

What is Linda's CV Risk?

Risk Assessment Tool for Estimating 10-year Risk of Developing Hard CHD (Myocardial Infarction and Coronary Death)

The [risk assessment tool](#) below uses recent data from the Framingham Heart Study to estimate 10-year risk for "hard" coronary heart disease outcomes (myocardial infarction and coronary death). This tool is designed to estimate risk in adults aged 20 and older who do not have heart disease or diabetes. Use the calculator below to estimate 10-year risk.

Age:

years

Gender:

Female Male

[Total Cholesterol:](#)

mg/dL

[HDL Cholesterol:](#)

mg/dL

[Smoker:](#)

No Yes

[Systolic Blood Pressure:](#)

mm/Hg

Currently on any medication to treat high blood pressure.

No Yes



Calculate 10-Year Risk

What do you tell Linda?

5. What do you tell Linda about her CV risk after starting HT?
 1. It will improve
 2. It will get worse
 3. It will be unchanged
 4. It depends...



What we *thought* we knew

- Estrogen therapy seemed logical based on the **hypothesis**:
 - Menopause is associated with:
 - Decrease in estrogen
 - Accelerated cardiovascular disease
 - If estrogen is replaced, this would have a cardio protective effect.
- For many years, HT prescribed based on this hypothesis and observational trials

The Different Studies

- Nurses Health Study (NHS)
- Heart and Estrogen/Progestin Replacement Study (HERS)
- Women's Health Initiative (WHI)
- WHI Aftermath: "The Timing Hypothesis"

NHS Conclusions

- Postmenopausal hormone use appears to decrease risk for major coronary events in women without previous heart disease
 - No statistically significant difference in cardiovascular outcome in type of estrogen used or the dose of estrogen used.
 - Stroke: 45% higher risk estrogen + progestin

HERS Trial

(Randomized double-blinded, placebo-controlled trial)

Outcomes	E+P	Placebo	RH (95% CI)	P value
Primary CHD events	172	176	0.99 (0.80-1.22)	.91
CHD death	71	58	1.24 (0.87-1.75)	.23
Non-fatal MI	116	129	0.91 (0.71-1.17)	.46



HERS: Summary

- E+P did not reduce rate of CHD events in women with established disease
- Rate of CHD events 52% higher during the first year of therapy but lower thereafter
- Increasing duration of hormone use: marked and statistically significant trend toward decreasing risk of CHD events
- Higher risk of DVT in HT group

Women's Health Initiative

(Randomized double blind placebo-controlled trial)

Outcomes	E+P	Placebo	Hazard Ratio	Nominal 95% CI	Adjusted CI
CHD	164	122	1.29	1.02-1.63	0.85-1.97
CHD death	33	26	1.18	0.7-1.97	0.47-2.98
Nonfatal MI	133	96	1.32	1.02-1.72	0.82-2.13
CABG/PTCA	183	171	1.04	0.84-1.28	0.71-1.51
Stroke	127	85	1.41	1.07-1.85	0.86-2.31
Fatal	16	13	1.20	0.58-2.50	0.32-4.49
Nonfatal	94	59	1.50	1.08-2.08	0.83-2.70

WHI Conclusions

- E+P: rate of CHD events increased by 29%
 - Most were nonfatal MI (nominally statistically significant, but adjusted CI not significant)
 - No significant differences between E+P and placebo with respect to CHD death or revascularization procedures
- Estrogen + Progestin should not be used in the primary prevention of CHD
 - No clear benefit, may cause harm

WHI: Estrogen Only Arm

Both groups: mean age 63.6 years

Outcomes	CEE	Placebo	Hazard ratio	Nominal 95% CI	Adjusted 95% CI
CHD	177	199	0.91	0.75-1.12	0.72-1.15
CHD death	54	59	0.94	0.65-1.36	0.54-1.63
Nonfatal MI	132	153	0.89	0.70-1.12	0.63-1.26
Stroke	158	118	1.39	1.10-1.77	0.97-1.99
Fatal	15	14	1.13	0.54-2.34	0.38-3.36
Nonfatal	114	85	1.39	1.05-1.84	0.91-2.12

Estrogen Only Arm

- No significant effect from estrogen on incidence of CHD
- Younger women who use estrogen may be at a decreased risk of CHD, but not statistically significant
- Small non-significant increase in the risk of CHD in the first year of using estrogen



“Timing Hypothesis”

- Initiation of HT closer to menopause tended to reduce CHD risk compared with the increase in CHD risk for HT users more distant from menopause
 - Not statistically significant in the WHI trial secondary analyses

WHI Revisited in 2010: Conclusions

- Increased CHD risk in the first 2 years in women who started HT within 10 years after menopause
- Possible cardioprotective effect in women who initiated HT close to menopause who used their hormones continuously for >6 years
 - Not statistically significant

Conclusions

- NHS, HERS Trial, and WHI: some cardioprotective effect of long-term use of HT (varying levels of statistical significance)
- WHI not powered to see effect of hormone therapy on 50-59 age group
- If used for vasomotor symptoms, usually do not use HT continuously for >6 years to see cardioprotective effect

Conclusions

- HT is not a good strategy for primary or secondary prevention of CHD
 - Increased risk of stroke, DVT
 - Increased risk of CHD in early year(s) of hormone use
 - Possible cardioprotective effect if used continuously long term (6 years)
- Hormones should not be started if > 10 years from menopause
- If use HT for symptomatic relief:
 - Starting HT early in the menopause does not cause a statistically significant increase in the risk of coronary heart disease

Treatment of hot flashes

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VA Pittsburgh Center for Health Equity
Research and Promotion

Case

6. Karen, a 51-year-old woman, presents to your office with the complaint of severe and frequent hot flashes. Her last period was 14 months ago. What can you tell her about hormonal management of hot flashes?
 - a. Hormone therapy offers significant relief for 80-90% of women
 - b. Oral estrogen therapy is superior to transdermal therapy
 - c. SERMS such as tamoxifen and raloxifene can offer both relief from hot flashes and provide bone protection
 - d. Progestin-only hormone therapy is not effective

Case

7. Karen agrees to a trial of oral hormone therapy. Of the following regimens, which would you use to initiate treatment?
 - a. Low-dose combined oral contraceptive: 20 mcg ethinyl estradiol + 0.1 mg levonorgestrel
 - b. Continuous standard-dose EPT: 0.625 mg conjugated equine estrogen (CEE) + 2.5 mg medroxyprogesterone acetate (MPA)
 - c. Continuous low-dose EPT: 0.3 mg CEE + 1.5 MPA
 - d. Continuous low-dose ET alone: 0.3 mg CEE

Case

8. Two years later Karen returns and reports that she self-tapered her hormone therapy over the course of 6 months and is now experiencing moderate to severe hot flashes. She does not want to try hormonal therapy again. All of the following medications have been shown to improve vasomotor symptoms EXCEPT:
- a. Gabapentin
 - b. Clonidine
 - c. Venlafaxine
 - d. Amitriptyline

Incidence and natural history

- 75% of women will report hot flashes
- Symptoms usually start in the perimenopausal period, peak within 2-3 years after menopause and then subside for most women
 - Majority of women experience hot flashes for <7 years
 - 15% of women report severe hot flashes for >15 years
- Prevalence varies by ethnicity
- Risk factors include surgical menopause, increased BMI, and cigarette smoking

Estrogen therapy

- The most effective treatment for moderate-severe hot flashes and associated problems (diminished sleep quality and reduced QOL)
- Multiple trials have established the efficacy of estrogen supplementation in reducing hot flashes as anywhere between 80 and 100%

Estrogen therapy

- Dosing and administration:
 - All routes of systemic therapy are equally effective
 - By avoiding first-pass metabolism, non-oral routes may reduce risk of VTE, gallbladder disease, and have less effect on testosterone levels
 - Use lowest effective dose
 - Continuous regimens of estrogen associated with fewer hot flashes during estrogen-free period and also eventually induce amenorrhea in most women
 - Women with a uterus should be given a progestin as well
 - Although not yet approved for the indication, some use intrauterine systems for progestin delivery

Estrogen therapy

- Dosing and administration continued:
 - Low-dose OCPs in peri-menopausal women offer both symptomatic relief and contraception; can switch to traditional EPT or discontinue at age 50-51
- Discontinuation:
 - Experts disagree on optimal approach: immediate cessation versus taper
 - Can try prolonged 6-12 month taper if patient had symptom recurrence after an abrupt stop
 - NAMS suggests that extended use of HRT is reasonable in women who feel that the benefits of symptom relief outweigh the risks

Bioidentical hormones

- Term may refer to hormones similar in chemical composition to those made endogenously
 - There are FDA-approved bioidentical products containing estradiol and progesterone
- More commonly, term refers to custom-made HT formulations compounded for an individual often in conjunction with salivary testing
- Bioidentical products have not undergone rigorous RCTs of safety and efficacy

Alternatives to estrogen therapy

	Drug vs Placebo	Evidence
Progestin methods		
MPA 400mg	80% vs 25%	Single RCT
Megace 20 – 80mg	85% vs 21%	Single RCT
Venlafaxine 75 & 150 mg	57% vs 24%	Single RCT
Desvenlafaxine 100 & 150mg	66% vs 51%	Single RCT
Fluoxetine 20 mg	37% vs 24%	Single RCT
Paroxetine 10- 25 mg	37-65% vs 24%	2 RCTs
Gabapentin 900 -2,400 mg	59-62% vs 24%	3 RCTs
Clonidine 0.1- 0.2mg	30-55%	4 RCTs

Complementary modalities

	Efficacy	Comment
Herbal/vitamin therapies Vitamin E Black cohosh Evening primrose oil Ginseng Wild yam Phytoestrogens (isoflavones)	No effect Mixed results No effect No effect No effect Mixed results	Sources: soy and red clover
Mind-body therapies Paced respiration Acupuncture Yoga Exercise Homeopathy/ magnet therapy	May be effective Mixed results May be effective Mixed results No effect	Small RCTs Small pilots + 1 RCT

Summary

- ET is the gold standard treatment for moderate-severe hot flashes
 - Use lowest effective dose in continuous regimen
 - FDA-approved products are recommended over compounded bioidentical hormones
 - Non-oral approach may be safer, but no RCT evidence available
- Nonhormonal options:
 - Venlafaxine, gabapentin, paroxetine, and clonidine appear to be most effective
- Paced respiration and yoga also appear to be promising, larger studies needed

Treatment of sexual dysfunction

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Center for Research on Health Care

9. Ms. D is a 55 year old woman w/ a h/o mild HTN.

Social Hx: Married x 30 years, 2 grown children, no Tob, moderate alcohol

Menopause History:

- Prior hot flashes, now resolved, no tx
- Decreased interest in sex, when it happens it is cursory
- Does have fantasies, is able to orgasm
- Intercourse uncomfortable b/c of decreased lubrication

Which treatment option(s) are appropriate for Ms. D?

- A. She should just have more sex, it will get better.
- B. An over the counter moisturizer; because she is not having hot flashes, it is not appropriate to use estrogen
- C. Oral estrogen with progesterone
- D. Local, vaginal estrogen

More Sex?

- Data from Leiblum et. al. 1983 that women who are more sexually active have less vaginal atrophy
- This may be an option

Vaginal Moisturizer

- Prospective randomized trials of HT vs. Replens vaginal moisturizer
 - Equivalent improvements in vaginal maturation index, vaginal moisture and vaginal fluid
 - Equivalent improvement of vaginal itching, irritation and dysparunia
- Superior to vaginal lubricants

Moisturizer vs. Lubricant

- Vaginal Moisturizers
 - Bioadhesive delivery of vaginal moisturizer
 - Improves vaginal epithelium
- Vaginal Lubricant
 - Make intercourse more comfortable
 - No long term benefit to vaginal epithelium

Systemic Estrogen Data

- Relieves vaginal atrophy
- May improve sexual function
- Low dose (e.g., CEE=0.3 mg) is effective
- Both transdermal and oral routes are effective

Women's HOPE study

- Multisite RCT of oral CEE .625, .45, and .3 w/ or w/ out varying doses of progesterone
- All groups had improvement in vaginal atrophy

Systemic Estrogen

- Advantages
 - Benefit to multiple symptoms
 - Benefit to bone health
- Disadvantages
 - Need for progesterone to protect uterus
 - Increase in SHBG can decrease free T
 - Transdermal estrogen may have less of an effect on SHBG

Local Estrogen

- Relieves vaginal atrophy
- May improve sexual dysfunction
- Low dose is effective
- Not necessary to oppose with progesterone

Vaginal Estrogen Comparison

	Cream	Ring	Tablet
Dose	0.3 mg CEE 0.5mg E2	5-10 micrograms daily	25 micrograms/ tablet
Frequency	Daily for 2 wks, then 3 times a wk	Replace ring every 3 months	Daily for 2 wks, then 3 times a wk
Safety	No reports of endometrial CA	No endometrial proliferation at 1 yr	No reports of endometrial CA
Comments	Can achieve systemic estrogen levels	No rise in serum estrogen	Lack of systemic or endometrial absorption

Back to our patient

Multi-modal recommendations:

1. Topical lubrication for intercourse
 - Likely not forever
2. Local estrogen or vaginal moisturizer for long-term relief of vaginal atrophy
3. Increased frequency of sexual intercourse

What if Ms. D reported decreased libido?

- Linear vs. circular theory of women's sexual response
- Other medications
 - SSRIs inhibit libido
 - bupropion can improve libido

Thank you!

- Please fill out evaluation forms