Menopause: Hormones, Hot Flashes, Dryness, Oh My!

G. Wright Bates, M.D.
Professor and Director
Division of Reproductive Endocrinology and Infertility
University of Alabama at Birmingham

Objectives

- Review the pros and cons of hormone replacement therapy.
- Recommend properly administered hormone replacement therapy as a treatment therapy.
- Highlight use of technology for optimizing patient care

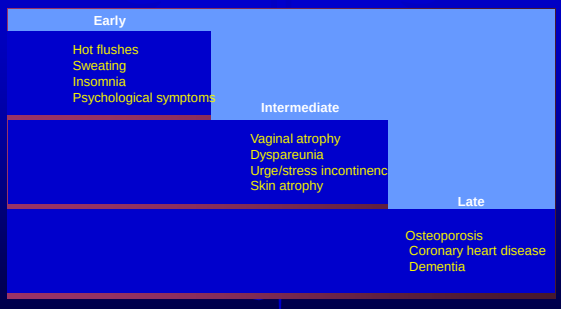
The speaker has no conflict of interest or relevant financial disclosures

By the year 2025, the number of postmenopausal women is expected to rise to 1.1 billion worldwide.

Menopause

- "Permanent cessation of menstruation following decline in ovarian function"
- Mean age: 51.4 years
- Range: 35 - 57 years
- Perimenopause
  - Highly variable
  - can last 2 - 8 years

Possible Results of Menopause



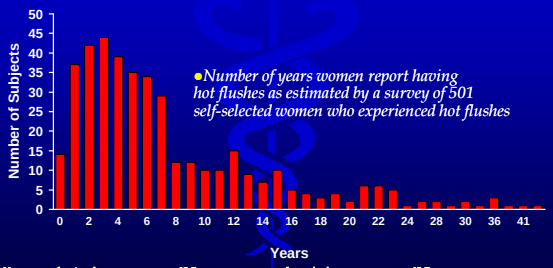
Hot Flushes

- Hot flushes are the most common symptom of perimenopause: 68%[1] to 93%[2] of women
- 84% moderate to severe
- Hot flushes may be characterized by visibly reddened skin, excessive perspiration, dizziness, headaches, palpitations, and may be associated with chills
- 31% experience hot flush prior to menstrual changes
- These symptoms usually last 6 months to 5 years[3]
- Up to 1 in 5 women experience flushing for decades (9% at 72 year old women in Sweden)

[1]Freedman RR. In: Lobo RA, et al, eds. *Menopause: Biology and Pathobiology.* San Diego, Calif: Academic Press; 2000.
[2]Thompson B, et al. *J Biosoc Sci.* 1973;5:71-82.
[3]Kronenberg F. *Ann NY Acad Sci.* 1990;592:52-86.
Samsioe G, et al. *Acta Obstet Gynecol Scand Suppl.* 1985;130:5-7

Hot Flushes May Continue Years After Menopause

Ages 29 to 82 Years



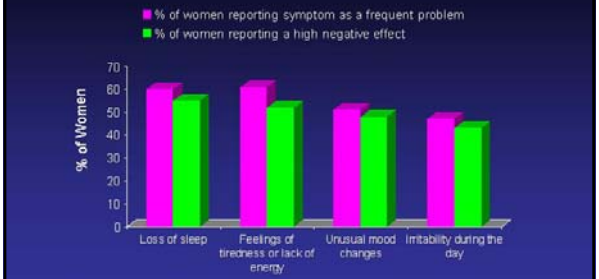
Mean age of natural menopause was 49.5 years; mean age of surgical menopause was 43.7 years.

Kronenberg F. *Ann NY Acad Sci.* 1990;592:52-86.

Hot Flushes

- **Thyroid disease**
- **Epilepsy**
- **Infection**
- **Insulinomas**
- **Pheochromocytomas**
- **Carcinoid Syndrome**
- **Leukemia**
- **Pancreatic Tumors**
- **Autoimmune Disease**

Menopausal Symptoms Have a Negative Impact on Day-to-Day Activities



n=771 postmenopausal women

Data on file, Wyeth Pharmaceuticals (Satisfaction with Hormone Replacement Therapy, Women's Perspectives on Menopausal Symptoms and Treatment. J.D. Power and Associates, 2002).

Ethnic Predisposition

- Prevalence: African-American > Hispanic > Caucasian > Chinese > Japanese
- U.S. > Australia > Sweden > China > Mexico
- Symptoms decreased in all postmenopausal women with time

Gold EB, et al. *Am J Epidemiol.* 2000;152:463-73.

Physiology of Vasomotor Symptoms

Decreased Estrogen and Inhibin

Dysfunction of Thermoregulation:
increased core temp
narrowed thermoregulatory zone

-Correlated poorly with Estrogen levels or LH pulses
-Disruption of noradrenergic system
-Increased opiate release (PLACEBO 51%)
-Etc. (substance P, POMC, somatostatin)

Proposed Therapies for Menopausal Symptoms Relief

- **Accupuncture**
- **Muscle Relaxation exercises**
- **Alpha wave EEG biofeedback**
- **Magnetic Therapy**
- **Dietary Modification**
- **Mind Control**

Accupuncture

- Randomized placebo (sham surgery) controlled trial
- Acupuncture was performed on 163 women, and the sham procedure on 164
- 10 treatments for 8 weeks
- Mean HF scores after acupuncture were 15.36 and after sham treatment 15.04
- Mean difference 0.33 (95% confidence interval [CI], −1.87 to 2.52; *P* = .77)

No difference in vasomotor symptoms

Ann Int Med. Published online January 18, 2016

Menopausal Symptoms: Lifestyle Modifications

- Keep Cool
- Lose Weight
- Continue Exercise
- Stop Smoking (especially THC)
- Relaxation Techniques
  - Paced Respirations
    - Meditation
    - Massage
    - Yoga
    - Leisure Baths

Substances Lacking Evidence for Menopausal Symptoms Relief

- **Agrimony**
- **Catnip**
- **Chamomile**
- **Damiana**
- **Dandelion**
- **Vitamin E**
- **Fenugreek**
- **St John's Wort**
- Gotu kola
- Hops
- Licorice root
- Passion flower
- Sage
- Sarsaparilla
- Witch Hazel
- Chasteberry
- Ginkgo Bilbo
- Valerian

Antidepressants

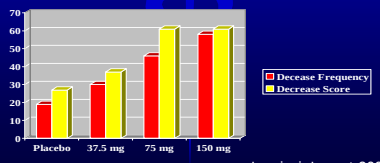
- **Paroxetine (Paxil) 7.5* – 20 mg qD**
  - **67% reported decreased number of events (37%)**
  - **75% reported decreased severity**
  - **7.5 mg dose FDA approved for vasomotor Sx**
- **Fluoxetine (Prozac) 20 mg qD**
  - **Decreased incidence and severity of Hot Flashes (50 vs. 36%) in patients over 4 weeks with h/o breast CA**

Antidepressants

- Venlafaxine (Effexor XR)
  - Combined serotonin AND norepinephrine reuptake inhibitor
  - Effective for Depression and Anxiety (Insomnia, PMDD)
  - Rapid onset of action
  - Good side-effect profile

Antidepressants

- Venlafaxine (Effexor XR)
  - 3 trials demonstrate efficacy
  - RCT (n=155) Patients on 75mg a day experienced over a 60% reduction in hot flashes by 4 weeks (placebo 27%, 37.5mg 37%)
  - Overall improvements in Quality of Life



Loprinzi, Lancet 2000;356:2059

Non-hormonal Drugs

Lacking proven efficacy

- Methyldopa
- Clonidine
- Bellergal (combination ergotamine, belladonna alkaloids, phenobarbitol)

Demonstrated Efficacy in some cases

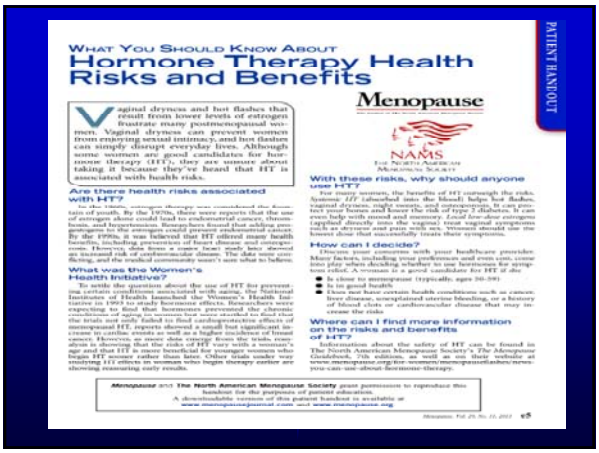
- Gabapentin

WHI Results

Overall Relative and Attributable Risk for Women 50 to 80 Years of Age

Health Event	Overall Hazard Ratio	Confidence Interval Nominal 95%	Confidence Interval Adjusted 95%	Attributable Risk per 10,000 Women/Year	Benefit per 10,000 Women/Year
CHD	1.29	1.02–1.63	0.85–1.97	7	
Breast cancer	1.26	1.00–1.59	0.83–1.92	8	
Stroke	1.41	1.07–1.85	0.86–2.31	8	
VTE	2.11	1.58–2.82	1.26–3.55	18	
DVT	2.07	1.47–2.87	1.14–3.74	13	
PE	2.13	1.39–3.25	0.99–4.56	8	
Colorectal cancer	0.63	0.43–0.92	0.32–1.24		6
Hip fractures	0.66	0.45–0.98	0.33–1.33		5
Total fractures	0.76	0.69–0.85	0.63–0.92		44

DVT = deep vein thrombosis; PE = pulmonary embolism.
Writing Group for the Women's Health Initiative Investigators. *JAMA*. 2002;288:321-33.



WHAT YOU SHOULD KNOW ABOUT

Hormone Therapy Health Risks and Benefits

PATIENT HANDOUT

Menopause

NAMS

Vaginal dryness and hot flashes that result from lower levels of estrogen frustrate many postmenopausal women. Vaginal dryness can prevent women from enjoying sexual intimacy, and hot flashes can simply disrupt everyday lives. Although some women are good candidates for hormone therapy (HT), they are unsure about taking it because they've heard that HT is associated with health risks.

Are there health risks associated with HT?

What was the Women's Health Initiative?

With these risks, why should anyone use HT?

How can I decide?

Where can I find more information on the risks and benefits of HT?

Apps Apps and more Apps

MenoPro / NAMS

- Health Care Provider or Patient
- Age
- Moderate – Severe Hot flashes
- Tried behavior modification for 3 months
- Patient interested in HT
- free of contra-indications

HT Contraindications

- Unexplained vaginal bleeding
- Liver disease
- Clotting disorder
- Untreated hypertension
- History of estrogen dependent cancer
- History of CHD, stroke or TIA
- ≥1 1st degree relatives with breast cancer (Increased risk of breast cancer)

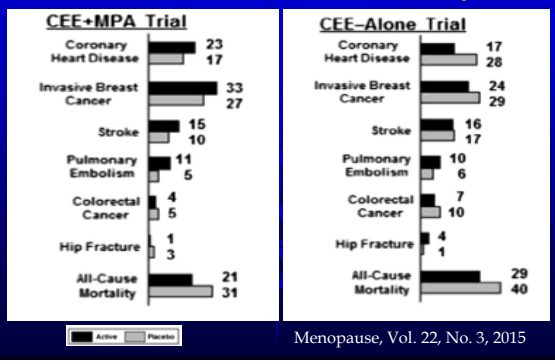
HT Considerations

- **Less than 10 years passed menopause**
- Hysterectomy
- Race
- Smoker
- HTN: Systolic BP
- Diabetes
- Cholesterol medication: Total and HDL

CVD Risk Score over 10 years

Recommendations

NAMS 2015: WHI 50 – 59 yoa



Menopause, Vol. 22, No. 3, 2015

NAMS 2015

Systemic Hormone Therapy after 65:

- Lowest effective dose
- If woman who has persistent bothersome menopausal symptoms
- Benefits of menopause symptom relief outweigh the risks

"Use of HT should be individualized and not discontinued solely based on a woman's age"

Menopause, Vol. 22, No. 7, 2015
Obstet Gynecol 2014;123:202-216.

Patients with a low CVD Risk Score appear to be candidates for either oral or transdermal estrogen therapy. Women with hysterectomy are candidates for estrogen-alone therapy.

Estrogen Therapy options and dosages

Duration of treatment

Recommendation if patient has metabolic syndrome

Handout on risks/benefits of HT

Email summary and handout to patient and/or yourself

Oral estrogen products

Active Ingredient(s)	Product Name(s)	Dosages (mg/d)
17β-estradiol*	Estrace Various generics	0.5, 1.0, 2.0
Conjugated estrogens	Premarin	0.3, 0.45†, 0.625, 0.9‡, 1.25
Synthetic conjugated estrogens, A	Cenestin†	0.3. 0.45, 0.625, 0.9, 1.25
Synthetic conjugated estrogens, B	Enjuvia†	0.3, 0.45, 0.625, 0.9, 1.25
Conjugated estrogens, CSD (synthetic)	Pr'C.E.S.‡ Pr'pms-Conjugated estrogens, CSD‡	0.3, 0.625, 0.9, 1.25
Esterified estrogens	Menest† Estragyn‡	0.3, 0.625, 1.25, 2.5 0.3, 0.625
Estropipate	Ogen† Various generics†	0.625 (0.75 estropipate), 1.25 (1.5), 2.5 (3.0) 0.625 (0.75), 1.5 (3.0), 5.0 (6.0)

Menopause, Vol. 22, No. 3, 2015

Oral Estrogens

Pros

- Familiar, easy
- Beneficial effect on HDL-C, LDL-C, and total cholesterol
- Relatively low cost
- Large amount of data
- Can measure estradiol levels with some preparations

Cons

- Risk of thrombosis, stroke
- Decreased libido
- Increased triglycerides, CRP, hepatic proteins

When to consider transdermal?

- First Line??
- Obesity
- Diabetes
- Metabolic Syndrome (3 or more)
  - Waist circumference >35 inches
  - Triglycerides >150 mg/dL
  - HDL < 40 mg/dL
  - BP > 130/95
  - FBS > 110 mg/dL

(ATP III National Cholesterol Ed Program 2010)

Menopause, Vol. 22, No. 3, 2015

Transdermal estrogen products

Active Ingredient(s)	Product Name	Dosage (mg E_2/day)
Patch		
17β-estradiol*	Alora†	0.025, 0.05, 0.075, 0.1 twice/wk
	Climara	0.025, 0.0375, † 0.05, 0.075, 0.1 once/wk
	Estradot‡	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Estraderm†	0.06, 0.1 twice/wk
	Minivelle*	0.0375, 0.05, 0.075, 0.1 twice/wk
	Oesclim‡	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Vivelle†	0.025, 0.0375, 0.05, 0.075, 0.1 twice/wk
	Vivelle-Dot†	0.05, 0.06, 0.025, 0.0375, 0.75, 0.1 once or twice/wk
	Various generics	
Transdermal gel		
17β-estradiol*	Divigel	0.25, 0.5, 1.0
	EstroGel	0.75 (use lowest effective)
	Elestrin†	0.52 (use lowest effective)
Topical emulsion		
17β-estradiol*	Estrasorb†	0.05 (2 packets) (use lowest effective)
Transdermal spray		
17β-estradiol*	Evamist†	1.53 (1/d initially, adjust dosage by response)

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Transdermal

Pros

- Avoids hepatic first-pass effect
- Less increase of triglycerides than oral ET
- Less effect on C-reactive protein than oral ET
- Less risk of reducing libido than oral ET
- Fewer GI AEs than oral ET
- Topical emulsion is moisturizing
- Perhaps less risk of thrombosis than oral ET

Cons

- Patch-adhesive sensitivity/residue
- Patch is less private
- Usually relatively higher cost
- Gels, creams can possible transfer to others

"Equivalent" Dosing

Oral	
Conjugated estrogens	0.625 mg
Synthetic conjugated estrogens	0.625 mg
Esterified estrogens	0.625 mg
Estropipate (0.75 mg)	0.625 mg
Ethinyl estradiol	0.005 mg-0.015 mg
17β-estradiol	1.0 mg
Transdermal/Topical	
Estradiol patch	0.05 mg
Estradiol gel	1.5 mg/2 metered doses

Menopause, Vol. 22, No. 3, 2015

Vaginal

Pros

- Vaginal benefit at lower dose
- Low-dose therapy typically avoids adverse systemic effects

Cons

- Increase in vaginal discharge
- Some may consider less convenient to use
- Lack of long-term uterine safety data for low-dose products

Progestogens

Pros

- Reduced AEs of estrogen on endometrium
- Some progestogens reduce AEs of oral estrogen on triglycerides
- Progesterone dosed at night can decrease insomnia, improve sleep

Cons

- Some progestogens increase risk of breast cancer
- Some progestogens reduce beneficial effect of oral estrogen on HDL-C
- AEs such as bloating
- Dysphoric effect for some women

HT Starting Dosages

Lower daily doses 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

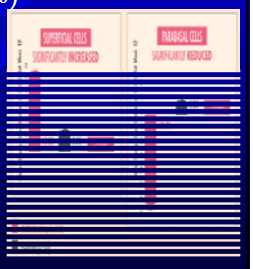
Typical lowest doses of progestogen:

- 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.

Osphena

- SERM indicated for dyspareunia
- 3 out of 4 women reported improved symptoms (72% vs. 54%)
- Improved tissue health
- 60mg po qD with food



Menopause. 2015;22(7):1-11
www.osphenahcp.com 8/23/15

Oh my……Little Pink Pill
Female Viagara

- Flibanserin (Addyi)
- Alters serotonin, dopamine, norepinephrine
- PREMENOPAUSE
- COMPLETE AVOIDANCE of alcohol
- increased coital episodes per month by 0.5
- 10% experienced increase satisfaction
- Prescriber certification required

www.addyirems.com, 1/22/16

"Female Viagra"
Addyi® Flibanserin

- Premenopausal HSDD
- 3rd time the charm
- Risk Evaluation and Mitagation Strategy

Perspective

FDA Approval of Flibanserin — Treating Hypoactive Sexual Desire Disorder

Hylton V. Joffe, M.D., M.M.Sc., Christina Chang, M.D., M.P.H, Catherine Sewell, M.D., M.P.H, Olivia Easley, M.D., Christine Nguyen, M.D., Somya Dunn, M.D., Kimberly Lehrfeld, Pharm.D., LaiMing Lee, Ph.D., Myong-Jin Kim, Pharm.D., Ashley F. Slagle, Ph.D., and Julie Beitz, M.D.

N Engl J Med 2016; 374:101-104 | January 14, 2016 | DOI: 10.1056/NEJMp1513686

Prescriber Certification Confirmation

To: **Gordon Bates**
University of Alabama at Birmingham
Phone: 205-934-1030
Fax: 205-975-5732
Email: gbates@uabmc.edu

From: **Addyi REMS Program**
Phone: 1-844-233-9415
Fax: 1-844-694-3373
Date: 01/19/2016

Dear Gordon Bates,

This correspondence confirms your successful certification in the Addyi REMS Program.

Listed below is your Addyi REMS Program Certification ID.

Certification ID: PRS0963317523

DHEA

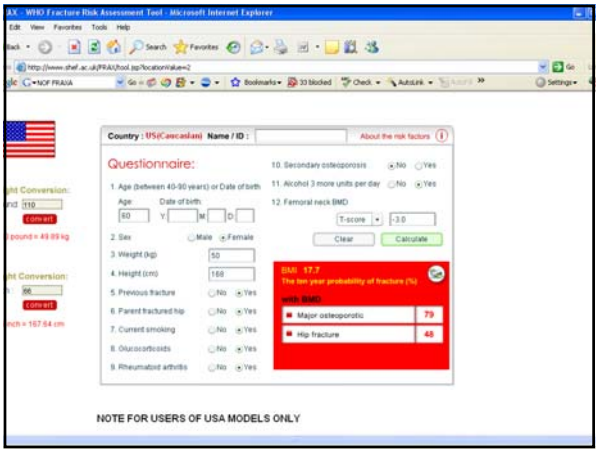
Daily 0.5% DHEA (6.5 mg) vaginal supp (n=325) vs placebo (n=157) for 12 weeks.

- pain with sex (0 to 3) decreased 0.36 ($P = .0002$)
- improved vaginal pH-0.66 lower ($P < .0001$).
- Patient with mod – severe dryness at baseline experience greatest benefit
- 86% to 121% improvements in vaginal secretions, lining thickness, tissue color ($P < .0001$)

Menopause December 28, 2015

Osteoporosis

- Identify risk factors
  - AGE
  - Postmenopausal (especially POF)
  - Thin, Caucasian
  - Steroid use
  - Smoking, Alcohol
  - Sedentary
  - Previous fracture
  - Family history
- Screen
  - DEXA (T score, Z score)

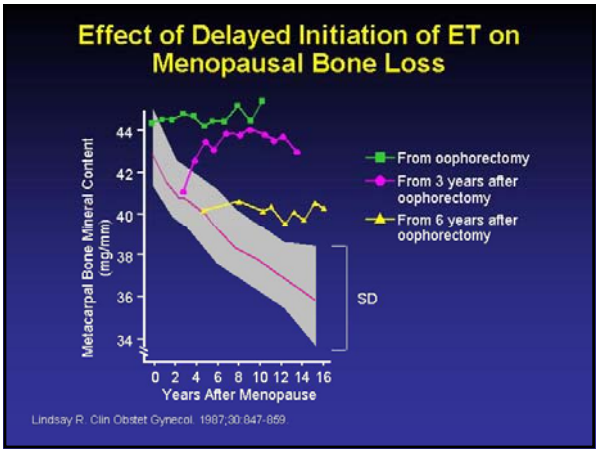


Management of Osteoporosis

- Lifestyle modification – Weight Bearing Exercise
- Calcium (>1200 mg) and Vitamin D (800 mg)
- Hormone therapy
- Bisphosphonates – Antiresorptives
  (alendronate, ibandronate, risedronate, zoledronate)
- SERMs
- PTH therapy
- Calcitonin
- Combinations

SERM and CEE

- Bazedoxifene 20 mg/CEE 0.45-0.625 daily (Duavee)
- Indicated for Post menopausal osteoporosis and hot flashes
- Take with Calcium and Vit D
- Avoids need for progesterone
- Costly ~3 dollars a pill



NAMS

Osteoporosis:

HT reduces the risk of postmenopausal osteoporotic fractures including hip fractures (even in women without osteoporosis)

HT approved for prevention of osteoporosis

Menopause 17(2) 2010

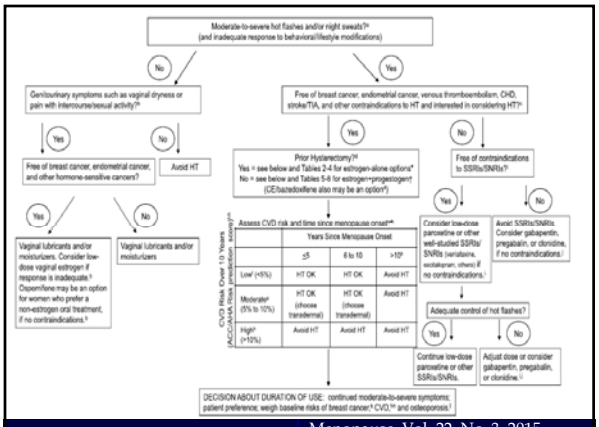
NAMS

Vaginal Symptoms:

HT is the most effective treatment for vulvar and vaginal atrophy

- Less dyspareunia, more coital satisfaction
- Not recommended for decreased libido
- Improved urge incontinence
- ? Effect on stress incontinence or overactive bladder?

Menopause 17(2) 2010



Menopause, Vol. 22, No. 3, 2015

HT: where do we go from here?

- Individualize based on indication
- Inform of risk AND benefits
- Initiate Early