

Current Concepts in Hormone Replacement; What's New ?

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Menopause Objectives

- Update on the menopause condition
- Explanation of the Women's Health Study and its limitations
- Review of hormone treatment options and alternatives

Financial Disclosures: None

Menopause Manifesting

- **Perimenopause**
 - Can last 1-8 years
- **Menopause**
 - Average age 51 years
- **Postmenopause**

The Menopause Journey

Postmenopause
is a permanent
state that lasts for
the rest of a
woman's life,
beginning 12 months
after her final period.



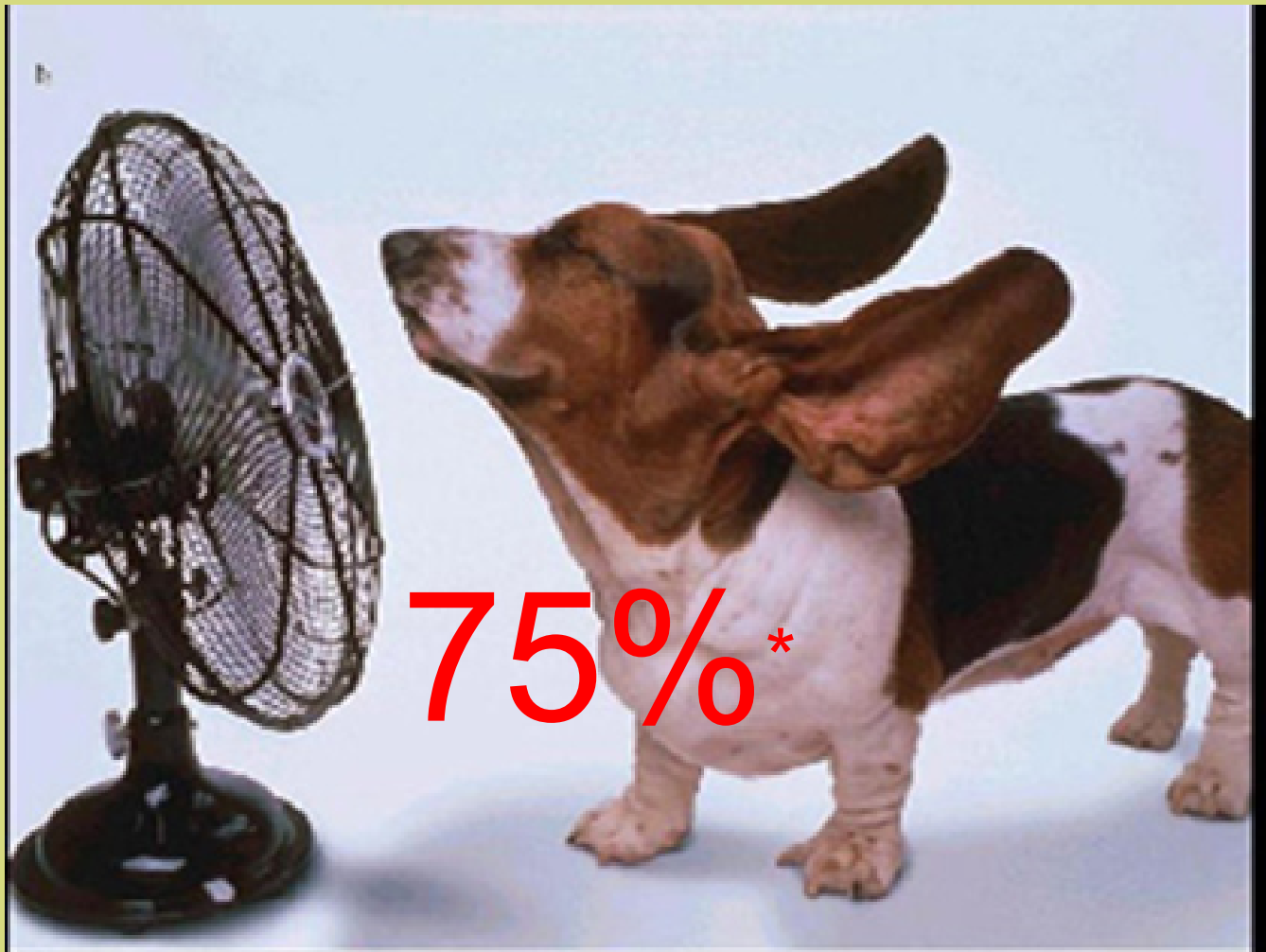
Menopause Predictors

A new stage in life

Predictor of menopause onset

- **Genetics**
- **Family History**
- **Ethnicity (earlier in Latino later in Japanese Americans)**
- **Smokers (2 yrs sooner)**
- **Reproductive history**

Changes of Menopause

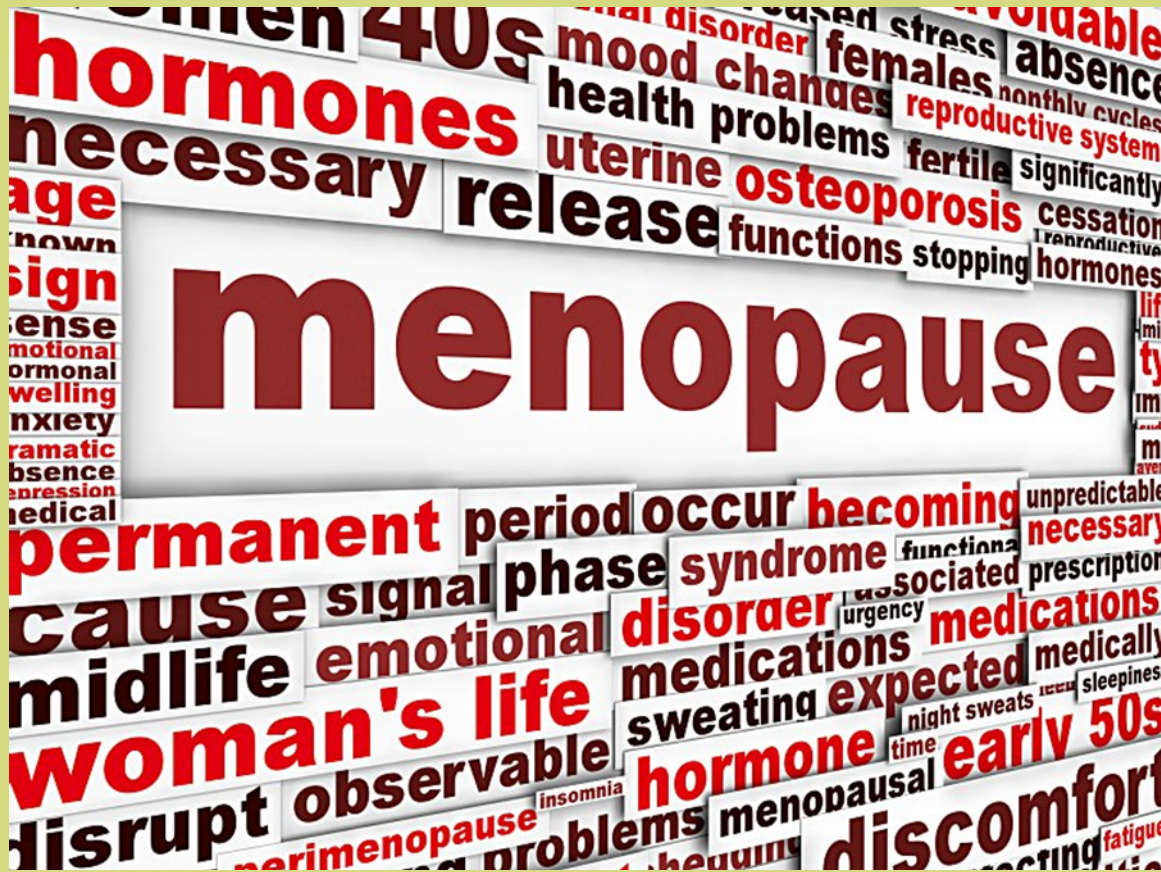


* Umland EM Treatment Strategies for reducing the burden of menopause associated vasomotor symptoms. *J Manag Care Pharm* 2008;14 S14-19

Menopause Symptoms

- **Hot flushes (> 50)**
- **Night sweats (> 50%)**
- **Sleep disturbances (40-60%)**
- **Vaginal dryness**
- **Loss of libido**
- **Mood swings**
- **Fatigue**
- **Hair loss**
- **Poor concentration**

Menopause Symptoms



#1 Case – Vasomotor RX/HRT

Sarah is a 50 yr old female with debilitating HF's. She is considering hormone therapy although she is concerned about the risk of cardiovascular disease seen in the media



Vasomotor Symptoms

Expected timeframe for Symptoms ?

1. Average duration is 2 years
2. Average duration is 4 years
3. Average duration is 10 years
4. Most likely her symptoms will never go away

Vasomotor Symptoms

Politi MC explored the natural progression of menopause¹

- Sx's increase in the 2 yrs prior to LMP**
- 50% had sx's 4 yrs after LMP**
- 10% has sx's up to 12 yrs after LMP**

¹ Politi MC et al. Revisiting the duration of vasomotor symptoms of menopause: a meta-analysis. JGIM 2008;23;1507-13

Vasomotor Symptoms

Avis NE studied duration of menopause vasomotor sx's¹

- Median duration of VMS – Median 7.4 yrs
- Sx's during perimenopause- Median 11.8 yrs
- Sx's beginning in postmenopause – Median 3.4 yrs

¹Avis NE et al *JAMA Int Med* 2015;175(4)531-539

SWAN: Risk Factors for VMS

- African Americans (OR 1.63)
- Late perimenopause (OR 6.64)
- Anxiety at baseline (OR 3.10)
- Less than college education (OR 1.91)
- Smoking (OR 1.63)
- Age (OR 1.17)
- Increasing BMI (1.03)

Gold et al Am J PH V16, N7 1226-1235 2006

Vasomotor Symptoms

Summary Points

- ✓ Median Duration of VMS – 7+ years
- ✓ Age of onset can impact duration of sx's
- ✓ Psycho-social factors are influential
- ✓ These factors can influence treatment options

#1 Case – Vasomotor RX/HRT

Knowing her symptoms could last what are your recommendations re HRT and whether they are safe for her?
She reports having mild hypertension controlled on HCTZ



Women's Health Initiative (WHI)

- Long term national health study (NIH)
- Strategies for disease prevention:
heart disease, cancer, osteoporosis
- 161,000 women (age 50-79)
- 1992-2005- trial stopped

WHI Limitations

- Women with severe vasomotor sx were excluded
- Only one drug regimen studied
- Results apply to an older population
 - Average age = 63
 - Average years from menopause = 15

Extended WHI: 2005-2010 (ages 50-59)

Women who took E or E+P :

- Neither treatment group had significantly affected all cause mortality
- Decreased coronary artery calcification (CAC) if started therapy within 10 years after menopause
- A small increased risk of VTE
- Stroke risk numbers slightly increased, unlikely to be clinically significant

Manson JE et al JAMA 2013;310(13):1353-1368

Hormone Dilemma

WHI Primary Investigators, Endocrinologist,
JoAnn Manson MD:

“ The WHI findings have been seriously
misunderstood and misinterpreted”
(8/2016)

Vasomotor Symptoms/HRT

Management of Menopause Symptoms, ACOG Practice Bulletin (Jan 2014)

- Systemic HT -most effective therapy
- Low dose -better side effect profile
- Risk of combined systemic HRT -VTE and breast CA
- Individualize care
- ACOG PB #141, Jan 2014 ACOG Ob Gyn 2014

#1 Case – HRT patch vs oral

Sarah wants to use HRT and is considering the patch but she's not sure if there is any benefit over the oral route



Benefit of Transdermal Estrogen

- Avoids first pass effect
- Lower VTE risk
 - Bergendal et al Menopause 2016
- Lower risk stroke
 - Renoux BMJ 2010

Benefit of Transdermal Estrogen

ACOG Committee Opinion, April 2013

- Prothombotic effect of Estrogen possibly related to high concentrations in the liver
- Transdermal Estrogen has little/no impact in elevating prothrombogenic substances

VMS – HRT Summary

- ✓ **Estrogen is highly effective treatment for VMS**
- ✓ **Generally early menopause it can be taken for a few years and stopped**
- ✓ **A progestin necessary for those with an intact uterus**
- ✓ **Therapy can be modified based upon preference**

Personalized dosing, appropriate duration

Vasomotor Symptoms- Hormones

Estrogen Hormone dosing – Rx that treats 80% of women

- 1mg micronized 17 beta estradiol (Estradiol)
- 50mcg transdermal 17 beta- estradiol (Climara)
- 0.625mg conjugated equine estrogen (Premarin)

Vasomotor Symptoms- Progestins

Progestin dosing

Medroxyprogesterone acetate

- 2.5mg daily

Micronized progesterone (bio-equivalent)

- 200mg for 12 days/ 100mg daily

Levonorgestrel containing IUD- unclear efficacy/safety

Cyclic vs continuous – preexisting cycle can determine this

Case #2 – HRT discontinuation

Jean is 65 years old and has been on hormones for years and considering stopping what is the best way to do so?



#2 Case – HRT discontinuation

- Symptoms will recur up to 25% of cases
- Unclear whether tapering or more gradual course is better
- Taper by daily dose or number of days/ week or strength of HRT
- Taper until symptoms are mild maintain that dose until symptoms resolve

#2 Case – HRT discontinuation

Newton et al evaluated factors in successful discontinuation

Factors associated with success

- **MD advice**
- **Lack of symptom relief w HRT**
- **Vaginal bleeding w HRT**
- **Coping with symptoms**

Factors associated with failed weaning

- **Depression/mood swings**
- **Insomnia**

#2 Case – Compounded HRT

Pinkerton et al estimate 2.5 Million US women using non FDA approved therapies¹

- 75% of women unaware these are not FDA approved**
- Contesting celebrity endorsement**
- Perception of the relative safety of “ natural hormones”²**

Pinkerton et al Compounded bioidentical hormone therapy: identifying use trends and knowledge gaps among US women *Menopause* 2015Sep22(9)926-36

²Kaunitz et al Compounded bioidentical hormone therapy: time for a reality check ? *Menopause*. 2015;22(9):919-920

Policy Statement – Compounded HRT

ACOG 2014

FDA approved HRT is the preferred agent for management of VMS

NAMS 2012

Does not recommend the use of compounded HRT for treatment of menopausal sx's unless a patient is allergic to ingredients in FDA approved meds

Alternative Choices

- **SSRI**
- **Clonidine**
- **Gabapentin**
- **Efficacy**
 - **50-67% ↓ in HF**



Options- Antidepressants

Paroxetine reduces HF (vs 38% in placebo)

62% reduction in 12.5mg group

65% reduction in 25mg group

Venlafaxine reduced HR (vs 27% in placebo)

61% reduction in HF

150mg no more effective then 75 mg

Alternative Options

Clonidine

- Start with 0.1mg/day transdermal patch
- 40% reduction in HF
- Side effects can be limiting

Gabapentin

- 45% reduction in HF vs placebo(29%)
- 900mg /day
- 300-600mg qHS may help w HF at night

#2 Case– Vasomotor Rx/ Herbs +

Herbal options:

- Black cohosh
- Evening primrose
- Ginseng
- Dietary Soy
- Wild yam



Position Statement – HRT Alternatives

Position statement of NAMS (Menopause 2015)

Objective to update and expand the NAMS evidence based position on non-hormonal management of VMS

- Recommend
- Recommend with caution
- Do not recommend

Herbs etc ..

Recommend:

- CBT and hypnosis
- Paroxetine (only non hormonal agent FDA approved)

Recommend w caution:

- Weight loss
- Mindfulness
- Soy isoflavin
- Stellate ganglion block

Herbs etc ..

Do Not Recommend:

- **Acupuncture**
- **OTC supplement and herbal remedies**
- **Chiropractic's**
- **Exercise/yoga**
- **Avoidance of triggers**

Lifestyle Changes

- Don't smoke
- Exercise
- Healthy diet
- Manage Stress
- Support systems
- Body image



3 Case- Vaginal Dryness

Denise is a 65-year-old female who has been widowed for over 10 years. She recently got involved in a relationship and is finding it difficult to be sexually active due to the vaginal dryness and pain associated with intercourse- she wants to know what options there are ?

Vaginal Dryness

**Vulvovaginal atrophy (VVA)- GSM
genitourinary syndrome**

- Physical discomfort**
- Reduced quality of life**

Incidence can be 60%

**Primary options – hormones, topical
agents**

Vaginal Dryness – Treatment

**Vaginal moisturizers can be used
several times a week**

Replens, Vagisil

Hyaluronic acid

Lubricants used during intercourse

Astroglide, KY Jelly

Vaginal Dryness – Treatment

Topical Estrogen – most effective treatment

Often given daily then 2-3x/week

Can also improve some sx's of overactive bladder

Vaginal Dryness – Treatment

Cream

Estradiol (1app qd – 7 days, then ¼ app 2x/w)
2-4g/d for 1-2 week, then 1g/1-3 x week

Tablet

Vagifem (10mcg estradiol, 1 tab/d for 2 week
then 1 tab 2x/week)

Ring

Estring 2mg (7.5mcg estrogen daily – 90 d)

Vaginal Dryness - Treatment

Ospemifene¹

- An estrogen selective agonist (SERM)
- FDA approved for PM dyspareunia/GSM
- Improvement in all 6 Female Sexual Function scale
- Hot Flashes are the most common side effect
- Not for use in those w Br CA

¹ CG et al. Climacteric 2015;18:226-32

Vaginal Dryness - Treatment

Prasterone¹

- Local conversion androstenedione/testosterone to Estrone/E2
- Require daily insertions
- No studies in Br Ca patients
- Decrease vaginal pH
- Improve vaginal epithelium maturation index

¹ AD et al Menopause.2015;22(9):950-963.45

Vaginal Dryness - Treatment

Summary

- ✓ Regular sexual activity maintain vaginal health
- ✓ Start with moisturizers/lubricants
- ✓ Vaginal estrogen if first line fails
- ✓ Ospemifene is an option if vaginal products are not preferred

Treating Menopause Symptoms

Summary

- ✓ Average duration of symptoms 4-7+ years
- ✓ Risk and benefit of HRT differ by age
- ✓ Estrogen works best for Sx's
- ✓ Focus on tailored treatment for an appropriate timeframe

Treating Menopause Symptoms

Summary

- ✓ Unclear on the most acceptable way to discontinue HRT
- ✓ Start with lifestyle modification
- ✓ Effective alternatives exist

Teaching Tool

Mobile app- Android/iOS

- ✓ Produced by NAMS (free)
- ✓ Assists in personalizing treatment plans
 - 2 modes – clinician and patient

Additional risk models

- 10yr risk HD/Stroke
- Br CA risk
- Osteoporosis/fracture risk



Laughing, Healthy and Wise



Vaginal Dryness - Treatment

Unique case- Breast Cancer

- Topical estrogen has minimal absorption
- Start with first line non-hormonal options
- Women with low risk of recurrence- likely its safe to use topical estrogen (review risk/benefit)

WHI Estrogen Alone: Breast CA

- No increased risk of breast cancer after 7 years of follow-up, and had a possible decrease in risk.
- 7 fewer cases per 10,000 women per year

WHI: Breast Cancer Risk with EPT

Original report:

- Relative risk = 1.24 (24% increased risk)
Absolute risk = 9 more cancers per 10,000 women per year of EPT use

Further Analysis:

- Breast cancer risk factor differences between treated and placebo groups HR 1.2 (not significant)*

* Anderson GL. Matuirtas 2006;55 103-115