# Advances in HRT for perimenopausal and postmenopausal patients 18+years after WHI

PRESENTED BY:

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# Objectives

1. Identify the changes in the landscape of HRT since 2002 and the close of the WHI trial.
2. Innumerate the various options for HRT in the perimenopausal and postmenopausal patient.
3. Compare and contrast the benefits of systemic vs transdermal delivery of HRT.
4. Discuss alternative therapies to hormone therapy in patients with contraindications as well as touch on areas of ongoing research in developing areas of concern.
5. Highlight the benefits of complementary treatment with cognitive behavioral therapy, mindfulness training and meditation practice as an adjunct to traditional treatments.
6. Consider the many physiological changes and organ system effects of the menopausal transition and its symptoms on patient satisfaction and quality of life.

# Alphabet Soup

HRT vs MHT – there is a distinction between hormone replacement therapy and “menopausal hormone therapy” with different indications and end points.

WHI- (Women’s Health Initiative) the seminal study first begun in 1991 with initial data published from 2002 to 2006 and referenced continually ad nauseum ever since.

NHS- (Nurses Health Study) Initially begun in 1976 and continues to this day to collect data on the initial cohort of participants and broadened over time to include a more diverse population and even male-identifying members.

SWAN- (Study of Women’s Health Across the Nation) Initially begun in 1994 and recruiting women between 42-52 across a diverse ethnic background this ongoing study has a searchable bank of blood and urine specimens available to researchers all over the world.

NAMS- (North American Menopause Society) Established in 1989 Its multidisciplinary membership of 2,000 leaders in the field – including clinical and basic science experts from medicine, nursing, sociology, psychology, nutrition, anthropology, epidemiology, pharmacy, and education has become the foundational resource for all things related to women’s health in mid-life and beyond.

# Common Estrogen Hormonal Therapy Preparations

| ROUTE | FORMULATION | DOSE | NOTES* |
|---|---|---|---|
| Oral | Conjugated Estrogen (Premarin) | 0.3-1.25mg/day | requires progestin for uterine protection &Daily dosing necessary |
| | Micronized 17B estradiol | 0.25-2mg/day | Bioidentical* |
| | CEE/bazedoxifene (Duavee) | 0.45/20mg | Does not require progestin protection |
| | Ospemifene (Osphena) | 60mg/d | FDA approved for GSM* requires progestin protection |
| Transdermal | 17B estradiol patch | 0.014-0.1 mg/day | patches applied 1x or 2x week |
| | 17B estradiol gel | 0.025-0.1mg/d | Daily dosing necessary |
| | Various compounded formula containing estriol and bi-est an/or tri-est | Doses vary | *not FDA approved or regulated |
| Vaginal | Estradiol rings | 0.05-0.1 mg/day | Replace every 90 days |
| | Estradiol capsule | .004 or .025mg/day | Once daily x 2 weeks then 2x/week |
| | 17B estradiol cream or CEE cream | 0.5-4 g/day | Dosing varies* |

# To add or not to add progestin…

**Any women on systemic (oral) HRT must have progestin protection for risk of endometrial hyperplasia/cancer**

-Provera- 2.5 mg q day or 5 mg 12-14 days of the month

-Prometrium 100mg PO q day or 200 mg 12-14 days of the month

-Levonorgestril containing IUD

-Combined Estrogen/Progesterone therapy whether it is oral or transdermal.

-Compounded progesterone vaginal inserts*

**Patients on low dose vaginal estrogen preparations do NOT require progesterone protection unless bleeding or other symptoms occur**

# “Bio identical Hormone Replacement” myths vs reality

| Myth | Reality |
| --- | --- |
| A more natural and effective treatment for perimenopausal and postmenopausal symptoms | To date there are zero randomized controlled trials comparing the effectiveness and side effect ratios between traditional HRT preparations and compounded “bio-identical” formulations |
| Safer* | Self reported incidence of side effects appear identical and similar risks of thrombotic disease must be assumed although studies are limited |
| All Natural* | Estriol, estradiol and estrone derived from soy and yam products are manufactured and sold predominantly in pill form that is then crushed and blended to make topical creams, oral capsules and hormonal pellets. No preparation is distilled from human serum or urine |
| Individually formulated for maximum benefits | All sex hormones have a wide range of normal values and there is zero research that suggests a specific numerical value is optimal for any patient let alone predictive of effectiveness for symptom relief. |

# The Placebo Effect- how real is it?

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## VERY real!

**Countless studies of multiple medications (not just HRT) and treatment interventions aimed at improving subjective symptom reduction in patients have demonstrated the profound effect of a patient's BELIEF in the strength and effectiveness of the therapy.**

- Antidepressants
- Anxiety medication
- Sleep aids
- Immune boosting agents
- Erectile dysfunction
- Weight loss medications
- Hormone therapy
- CBD/THC
- Psilocybin (set and setting as well)
- Smoking cessation medications
- Etc etc etc

# Problems associated with early menopause and untreated perimenopausal symptoms

## VSM: Vasomotor Symptoms of Menopause

Hot flashes and nightsweats most commonly experienced with up to 80% of perimenopausal and post menopausal patients reporting with an average of 4-5 episodes per day (some report as many as 10-15 per day)

In 2009 the Menopause Epidemiology Study of a cross-section of US women ages 40-65 reported a significant impact of vasomotor symptoms on overall health-related quality of life with additional significant impact on diminished quality of life across multiple factors associated with psychosocial functioning.

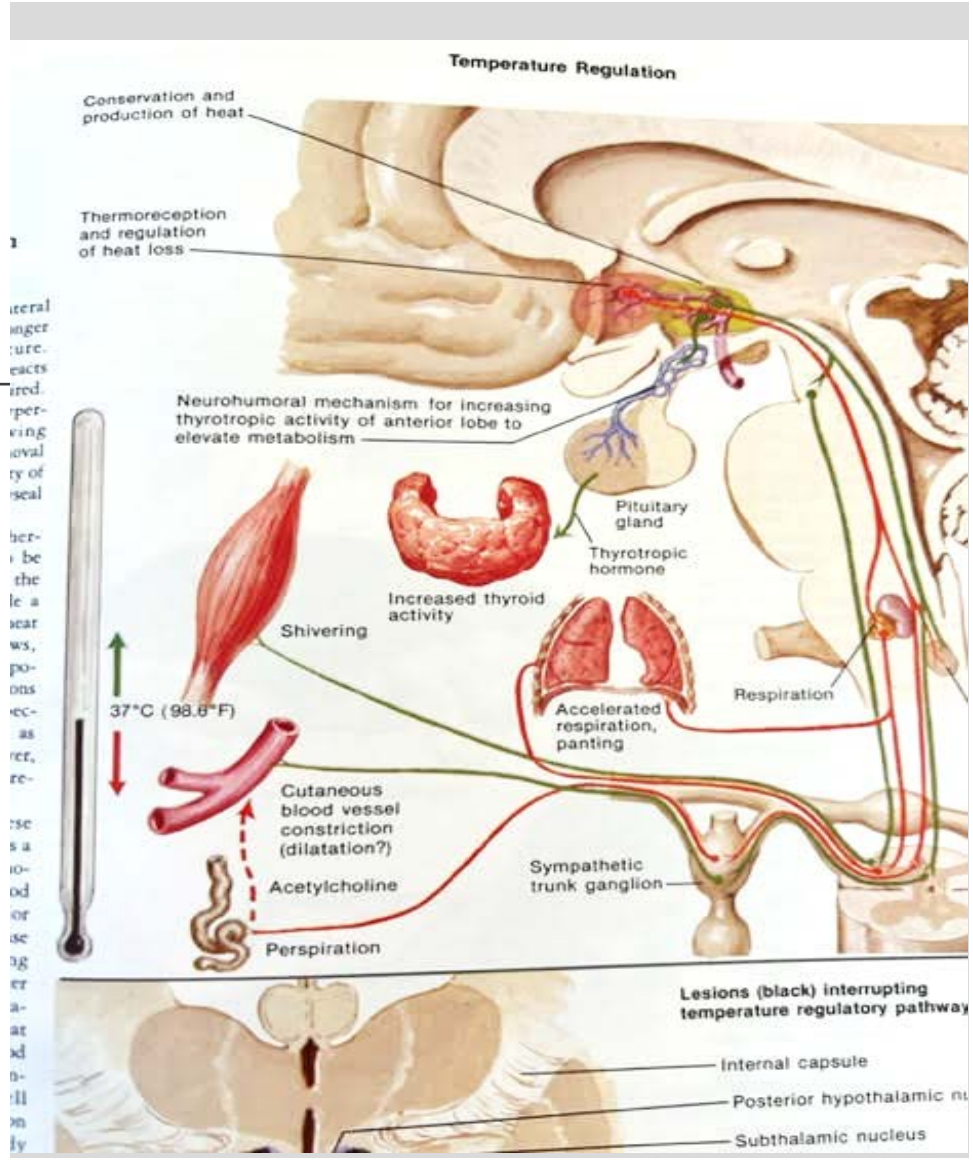
Abrupt surgical menopause in younger women <40 caused even more substantial symptoms and impact to overall quality of life and even ultimately life expectancy and early death for all causes.

# Physiology of the “Hot Flush” or “Heat Bloom”

Temperature regulation in the body is primarily controlled by the hypothalamus and mediated through the sympathetic system

In normally ovulating pre-menopausal females falling estrogen levels in the luteal phase allow receptors in the hypothalamus to slightly increase the core body temperature for an optimal microclimate in the reproductive system to aid ovum and sperm lifespan and transit time.  This increase basal body temp at ovulation is still reliably used for natural family planning

In perimenopausal females with fluctuating levels of circulating estrogens from cycle to cycle and in active menopause with low estrogen levels this system becomes dysregulated and chaotic.



When estrogen suppression of these thermoregulatory receptors is removed a cascade effect to rid the body of the excess heat that the brain is creating causes vasodilation of the blood vessels and an increase in heart rate to move the blood more quickly to the skin surface and thus release it.

# But for every action there is an equal and opposite reaction…

Once the self generated excess heat reaches the surface of the body the sweat glands are activated to cool the skin surface.

The vasomotor flushing can occur at any time of the day and can be triggered by intense emotional responses or stress, as well as spicy foods and alcohol consumption.

While intense sweating can occur at any time of the day, the soaking monsoon effects at night that many patients experience is due to the core body temperature fluctuations during different phases of the sleep cycle.

Which is also conveniently regulated by our friend the hypothalamus and his buddies in the rest of the limbic system.

# Other Actions and Reactions to Hypothalamic Dysruptions

Paradoxically- stimulation as well as lesions or damage in the ventromedial nuclei of the hypothalamus cause food cravings, voracious eating and rage.

# Problems associated with early menopause and untreated perimenopausal symptoms

## GSM: The genitourinary syndrome of menopause

vaginal dryness

dyspareunia

increased susceptibility to BV, Candidiasis and STIs

worsening of urinary incontinence

increased susceptibility to UTIs

decreased libido*

increased risk of developing lichen sclerosis

exacerbate or even cause new onset vulvodynia

# Major Metabolic Disruptions of other body systems linked to long term and premature onset of hypoestrogenism

## CARDIOVASCULAR HEALTH

increase in total cholesterol and inversion of the LDL/HDL ratio

Increased risk of metabolic syndrome

Increased waist to hip ratio and abdominal adiposity

Impaired vascular endothelial function

Acceleration of atherosclerosis and plaque deposits

***ALL OF WHICH SIGNIFICANTLY INCREASE THE RISK OF CVD AND DEATH**

## BONE/CONNECTIVE TISSUE AND MUSCULOSKELETAL

Accelerated skin aging from loss of collagen and reduced elasticity

Increased symptoms of arthralgias and worsening or new onset of arthritis, fibromyalgia, osteoarthritis and rheumatoid arthritis

Profound effects on bone remodeling with an increase in bone resorption and a decrease in new formation leading to a significant net loss that continues indefinitely.

Bone density changes are greatest in the vertebral bodies and the hip but affect every area of the skeletal system.

# “Cognitive Functions and Neurologic Effects”

*Mood Disorders of all kinds are affected as well as:*

Major Depression

Anxiety Disorders

PMDD

Bipolar Disorder

Schizophrenia

**Prevalence of major depression in American women is 10-12% and the incidence of reported depressive episodes without a formal diagnosis of major depression is as much as 28-30%**

- more than ½ of all women already diagnosed with depression demonstrate an increased frequency and severity of episodes during the perimenopausal transition and this increase persists into menopause as well.
- Women with pre-existing bipolar disorder reported as much as 20-77% increase in depressive symptoms and hypomania during early perimenopause as well as late menopause with or without hormone replacement.
- Women with PMDD report a significant increase in all related symptoms during the perimenopausal transition as well and are at an increased risk to develop major depression and anxiety disorders.
- Younger women undergoing surgical menopause after BSO have a profoundly increased risk of developing new onset depression and anxiety as well as reporting a decrease in overall emotional health that persisted at least 2 years after surgery and was not affected by HRT.

# What about DHEA and DHEA-S then?

DHEA  and its sulfated form DHEA are sex steroid precursors formed from cholesterol in the adrenal glands, brain, ovaries and testes and circulating levels in healthy young adults approach 10,000x the levels of estrogen or testosterone in serum studies. (0.1 ng/mL of estrogen vs 1000 ng/mL of DHEA-S)

There are a few small randomized studies of DHEA supplementation dosed at 50100mg that demonstrated an increase in circulating levels of androstenedione testosterone and dihydrotestosterone in treated subjects vs placebo.  An increase in serum IGF-1 was also noted as well as a decrease in SHBG


# But what does it DO??

# The Hype

Proponents claim all sorts of positive effects from DHEA therapy.

Some go so far as to declare its effects to be “the fountain of youth”

# The Reality

There are almost zero rigorous randomized controlled trials of DHEA and DHEA-S.

Intrarosa (the only FDA approved product) was given a single indication based on the research studies and that indication is dyspareunia.

Much like hGH the studies found no significant improvement in physical performance, libido, cognitive function or body fat composition.

A small RCT on infertility patients did show a possible improvement in live birth rates with in vitro fertilization however the mechanism of this is unknown.

# Oral Contracetive Use in Women over 35

## MAJOR/MINOR CONSIDERATIONS

- Symptoms associated with menses
  - PMDD
  - AUB
  - Acne
  - Breast tenderness

- Perimenopausal symptoms
  - Hot flashes
  - Night sweats
  - Mood swings
  - Vaginal dryness
  - Sleep disturbances
  - Cognitive symptoms “foggy brain”

# Oral Contracetive Use in Women over 35

- Many of us were indoctrinated in the dogma of “No birth control pills in women over 35” due to cardiovascular and thrombotic risks
- As in many other areas of medicine the decision of what type of birth control to recommend in this population is much more complicated than a simple yes or no.
- The benefits of avoiding unintended pregnancy and controlling menstrual symptoms in healthy, normal weight patients without other risk factors are **overwhelmingly positive**
- Individualization in patients with obesity, a strong family history of CVD or breast cancer and also smokers is crucial for shared decision making.
- Ultimately our duty is to inform patients of their relative risks and benefits and assist them with making their own decisions

# “What other options besides hormones do I have Dr.?”

# Alternatives to Hormone Therapy

SSRIs and anti-depressants

- Most notably Effexor (venlafaxine) has been shown in several studies to be almost equally effective in treating mild to moderate hot flashes although there is still a significant amount of intractability with a percentage of patients.
- Effexor can be used safely in conjunction with HRT
- Wellbutrin, Zoloft and Prozac also have shown some benefit although mainly in sleep disturbance

Amberen

An herbal supplement containing black cohosh.

Estroven

An herbal supplement containing soy and rhubarb extracts

Other holistic approaches to the management of the symptoms of perimenopause and menopause include cognitive behavioral therapy, yoga, meditation, mindfulness training and counselling. Acknowledgement of the legitimacy of the impact of symptoms and reassuring patients that while it is a “normal” part of life it is still something that can be managed and improved can go a long way.

# Special Instances

Surgical Menopause prior to age 40

- Acceleration of cardiovascular changes associated with aging
- Higher risk of cardiovascular disease overall
- Increased incidence of stroke
- Increased risk of all cause mortality
- Bone density decreases by 6-7% after BSO in premenopausal women and continues to decline by 1-2% annually threrafer

Patients with BRCA mutations and/or Personal History of breast cancer

Ongoing and evolving research is just beginning but even in these populations the benefits to quality of life and improvements in other areas of health and overall satisfaction of the patients is leading many oncologist and gynecologic experts to consider and even recommend limited amounts of hormone replacement.

There are NO protocols to follow and the tasks of education and informed consent as well as shared decision making with each individual patient is CRUCIAL

# Some good resources I have found to give the patients (rather than Facebook ☺)

www.menopause.org ( The North American Menopause Society site

http://drjengunter.com and ANY of her books or podcasts such as:
The Menopause Manifesto
and
The Vagina Bible
also her podcast called “Body Stuff”

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