

A black stethoscope is laid out on a dark wooden surface. A green apple with a single green leaf is placed in the center of the stethoscope's chest piece. The background is a dark, textured wood. A white paper corner is visible in the top left. A teal bar is at the bottom right.

# Clinical Application of Physiologic BHRT

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# Objectives

- Discuss methods and clinical considerations in obtaining physiologic hormone restoration and balance.
- Explain basic dosing principles.
- Provide basic dosage guidelines for BHRT.
- Discuss considerations in changing approaches in hormone therapy to achieve improved outcomes.
- Explore estrogen production, metabolism and choices for therapy.

# Conclusion from Evidence

- If you prescribe hormone therapy and you are going to practice evidence based medicine, then you must prescribe bioidentical hormones.

# Physiologic Bioidentical Hormone Restoration Therapy

- The Objective of physiologic BHRT is to restore hormone levels to the normal physiological level of a younger individual to provide the benefits of the hormones to the entire system.

# Goals of Physiologic BHRT

- **Treat the symptoms** caused by hormone imbalances.
- **Provide the protective benefits** obtained from the hormones:
  - Cardiovascular protection
  - Brain and CNS protection
  - Bone remodeling
  - And many more...

# Physiologic Restoration Therapy

- **First: establish the need**
  - Correlate patient assessment with testing results
  - Include lifestyle factors that may affect symptoms and/or influence the outcome of restoration therapy
- **Be conservative: dose low and go slow on changes**
  - The goal should be to *use the lowest amount of hormone* required to achieve physiological level and control symptoms

# Physiologic Restoration Therapy

- **Consider delivery:** route and timing of dose when assessing lack of symptom control and/or side effects.
  - Efficacy can be increased by altering timing, method of application, or dosage route.
    - May not require more hormone.

# Symptom Evaluation

- **Dose to the patients' symptoms, not the labs – but know all the possible causes of the symptoms.**
- **Look at groups of symptoms and correlate with levels.**

# Dosing Principles

- **Different hormone imbalances often have symptoms that overlap.**
  - Judging needs by symptoms alone is guessing.
- **Tachyphylaxis occurs in hormone receptors with too much hormone.**
  - Symptoms of *too much hormone* can closely mimic symptoms of too little hormone.
- **Too much progesterone down-regulates estrogen receptors.**
  - When receptors are down-regulated, the symptoms reflect those of estrogen deficiency.

# Basic Dosing Principles

- **Base on the individual patient's evaluation of needs, goals, symptoms and levels.**
- **Use dosage guidelines as a starting point.**
- **Start at a low dose and make adjustments slowly:**
  - Use lowest dose that is effective for symptoms and desired benefits.
  - “Current medical advice is that hormones should be used at the lowest dosage (to alleviate symptoms)”  
--National Institute of Health 2004
  - It may take months to fully achieve desired results.

# Dosing Principles

- **Symptoms of different hormone imbalances can overlap:**
  - Symptoms of excess estrogen or excess progesterone, or high cortisol can mimic symptoms we refer to as “estrogen deficiency”
  - Low thyroid and/or poor nutrition look similar to low testosterone
  - High cortisol symptoms can mimic low testosterone, high estrogen, low progesterone

# Hot Flashes are NOT a Symptom of Estrogen Deficiency

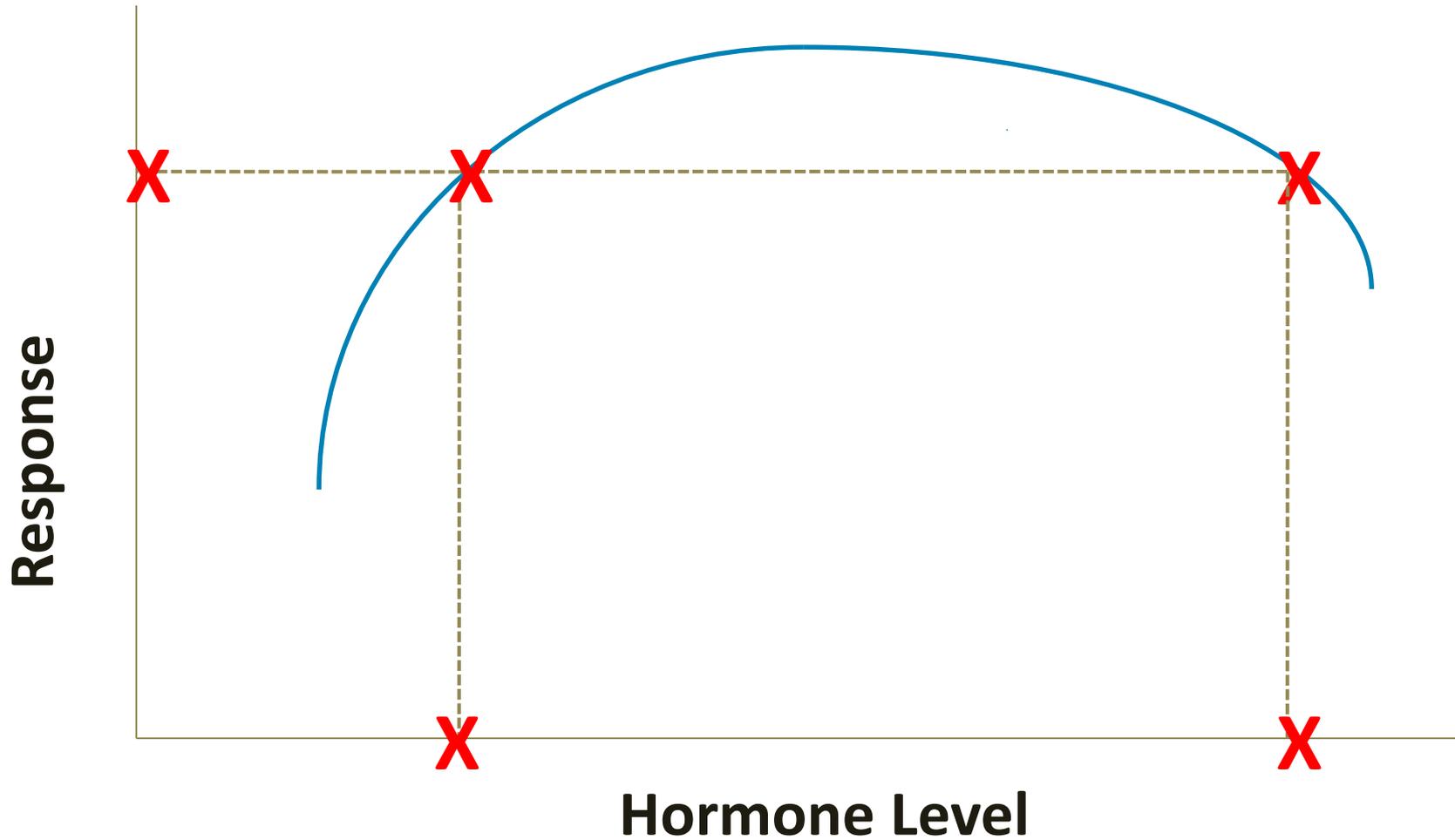
**Other causes of hot flashes, especially in early-to-mid perimenopause include:**

- Low or excessive progesterone
- High or low cortisol - Insulin resistance - Low thyroid function
- Excessive estrogen:
  - Endogenous level not balanced by progesterone
  - Excessive exogenous ERT and/or environmental exposure to pseudo-estrogens and xenoestrogens
  - Poor estrogen elimination

# Important Dosing Principle

- **Symptoms of excess hormone may mirror symptoms of deficiency.**
  - The symptoms of too much of a hormone can closely mimic the symptoms of too little.
  - May indicate the receptor response to hormone level.
  - Delayed response to excessive hormone.

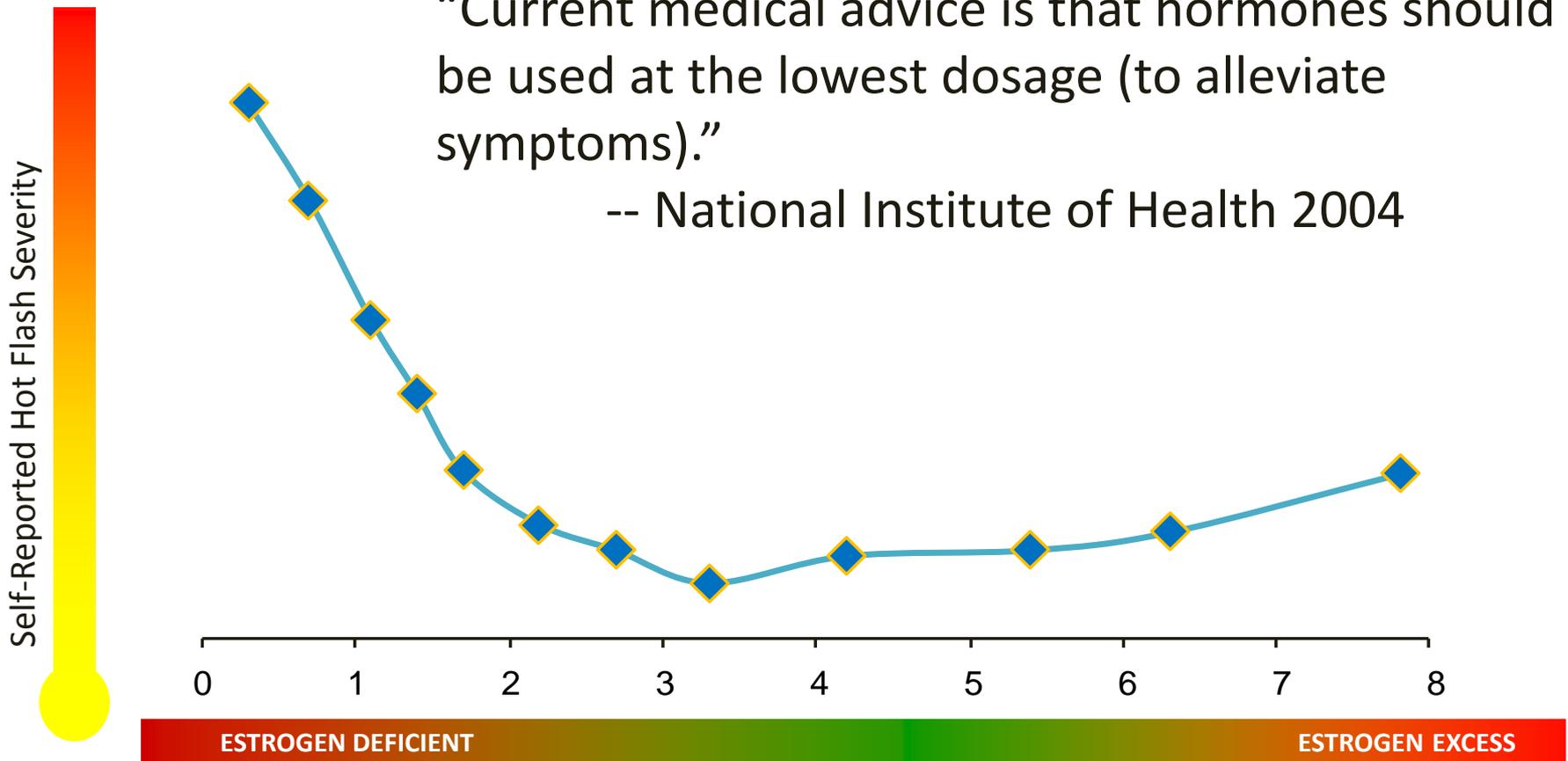
# Optimal Receptor Response



# Salivary Estradiol & Hot Flashes in 49,000 Women

“Current medical advice is that hormones should be used at the lowest dosage (to alleviate symptoms).”

-- National Institute of Health 2004



# Important Dosing Principle

- **Too much hormone works... for a while**
  - Estrogen given to a woman who has normal or slightly high will control symptoms such as hot flashes, but on a temporary basis:
    - Estrogen up-regulates estrogen receptors and the result is more genomic activity.
    - After a period of a few weeks, tachyphylaxis occurs and symptom return.
    - An increase in dose results in the same sequence of events!
- **Same sequence of events occurs with most hormones**
  - The difference is timing.

Premenopausal women experiencing hot flushes should be screened for thyroid disease and other illnesses. A comprehensive review of all possible causes is available.<sup>183</sup> Clinicians should be sensitive to the possibility of an underlying emotional problem. Looking beyond the presenting symptoms into the patient's life is an important service to the patient and her family that eventually will be appreciated. This is far more difficult than simply prescribing estrogen, but confronting problems is the only way of reaching some resolution. Prescribing estrogen inappropriately (in the presence of normal levels of gonadotropins) only temporarily postpones, by a placebo response, dealing with the underlying issues.

A striking and consistent finding in most studies dealing with menopause and hormonal therapy is a marked placebo response (at least 51% in the first weeks of treatment)<sup>184</sup> in a variety of symptoms, including flushing. In an English randomized, placebo-controlled study of women being treated with estrogen implants and requesting repeat implants, there was no difference in outcome in terms of psychological and physical symptoms comparing the women who received an active implant to those receiving a placebo.<sup>185</sup>

A significant clinical problem encountered in our referral practice is the following scenario: a woman will occasionally undergo an apparently beneficial response to estrogen, only to have the response wear off in several months. This leads to a sequence of periodic visits to the clinician and ever-increas-

# Dosage Adjustment

- **Adjusting dosage for hormone restoration therapy individually requires assessment of therapeutic outcome and levels:**
  - Monitor symptoms.
  - Retest to determine if physiological levels obtained.
- **If symptoms not resolved at normal physiologic levels, other causes should be considered:**
  - *Example*, hot flashes with optimal estrogen levels: consider high cortisol, low thyroid, excessive progesterone, poor diet and exercise.

# Supraphysiologic Doses

- **Higher than normal physiologic level of *estradiol*:**
  - Increases insulin resistance
  - Increases binding globulins
  - Decreases cardiovascular benefits
  - May decrease neuroprotective benefits

# Supraphysiologic Doses

- **Higher than normal physiologic level of *progesterone*:**
  - Inhibits insulin secretion
  - Increases insulin resistance (antagonizes insulin)
  - Leads to hypothyroidism
  - Decreases immune function
  - May lose neuroprotective benefits

# Supraphysiologic Doses

- **Higher than normal physiologic level of *testosterone*:**
  - Lose cardiovascular benefits
  - Lose neuroprotective benefits — becomes excitotoxic
  - Interferes with thyroid (T3) function

HONEY, I SUDDENLY REALIZED  
I DIDN'T NEED HORMONE  
REPLACEMENT... I NEEDED A  
HUSBAND REPLACEMENT!  
MEET DERRICK...



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# Dosing Guidelines (Female)

- **Peri-Menopause**
- **Oral administration of SR capsules**
  - **Progesterone**
    - 25 to 400 mg daily (usual 100 to 200 mg)
    - Dose once or twice a day
    - Give cyclically days 14 through 25
  - **Bi-estrogen 50:50**
    - If estrogen levels confirmed low
    - If progesterone alone doesn't control symptoms
    - 0.1mg to 0.5 mg daily
    - Dose once or twice a day
    - Give cyclically days 1 through 25
    - Continue progesterone as above

# Continuous vs. Cyclic Dosing

- **Continuous dosing:** take a break 2-5 days per month.
- **Hormones do not have to be given in cyclic fashion** to provide benefits of restoration therapy.

# Conversion to BHRT

- **Considerations in conversion from synthetics to bio-identical hormones:**
  - **Length of time on synthetics**
    - Estrogen receptors can lose sensitivity due to exposure to high amounts and/or long exposure of estrogen replacement (any type of estrogen).
  - **Liver detox**

# Conversion to BHRT

- **Taper off high estrogen dose:**
  - Elevated threshold in brain for estrogen.
  - Withdrawal symptoms can be severe and highly individual.
- **Start progesterone immediately:**
  - Discontinue any progestin.
- **Address other hormone imbalances that may be adding to symptoms:**
  - Insulin resistance, adrenals, thyroid and androgens.

# Conversion Considerations - *Progesterone*

- **Progesterone affects estrogen effects:**
  - Regulates estrogen receptors.
  - Has effects on SHBG, thyroid and cortisol actions – all effect “estrogen deficiency” symptoms.
- **Start progesterone prior to switching from synthetic estrogen to bio-identical estrogen:**
  - Discontinue any synthetic progestins.

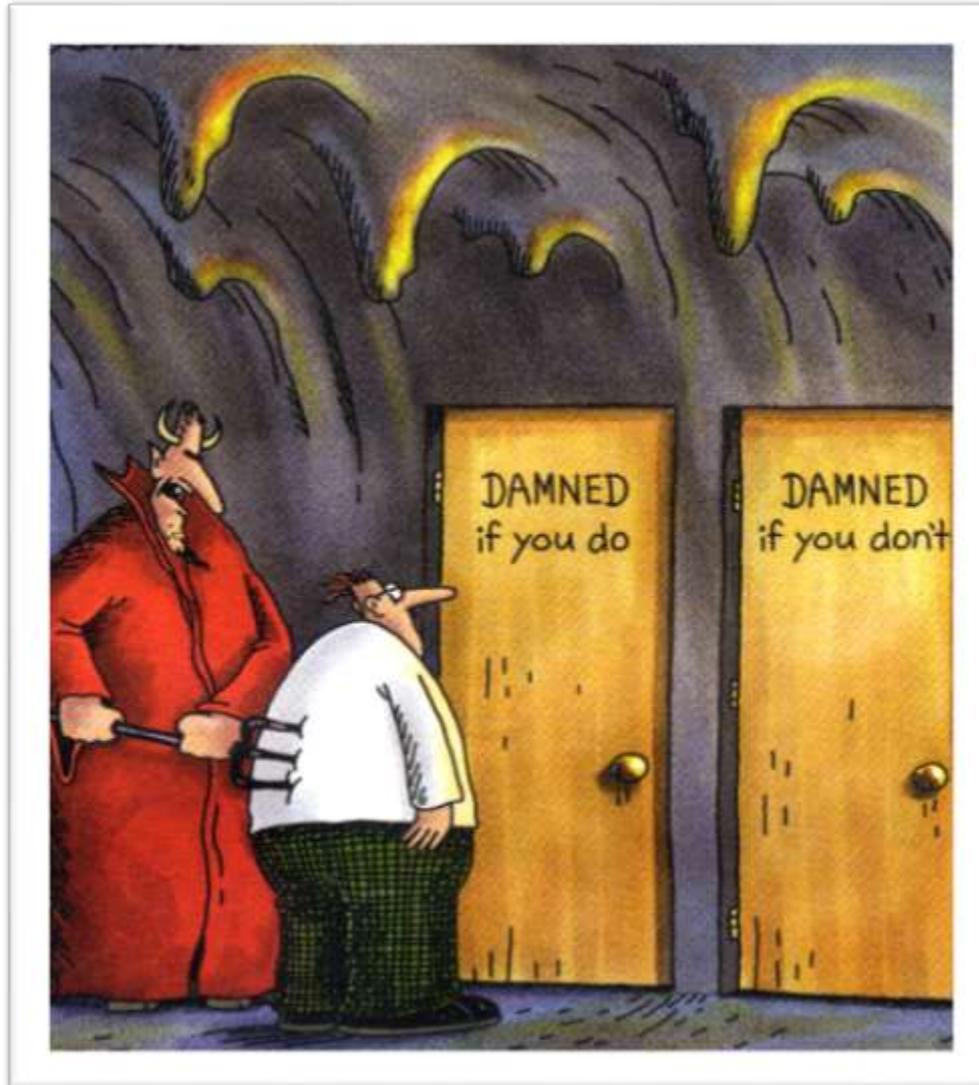
# Conversion Considerations - *Estrogen*

- **Taper off of synthetic estrogen:**
  - **Higher than physiological levels reset the threshold for estrogen need within the brain.**
    - Quick reduction in dosage will cause withdrawal symptoms (severe hot flashes).
  - **Various protocols**
    - Example: decrease conventional estrogen therapy by one-half dose every 3 days, then 2 out of three days, then daily, etc.
    - Example: Premarin® — give ½ tab QD x 2 wks then ½ tab QOD x 2 wks.
    - Use ½ dose every 3rd day for 9-12 days, then ½ dose 2 of 3 days for 9-12 days, then ½ dose daily, then ½ dose 2 out of 3 days for 9-12 days, then ½ dose every other day.
  - **When low dose is reached, switch to Bi-est 50:50**
    - Stronger ratio of E2 to E3 than Bi-est 80:20

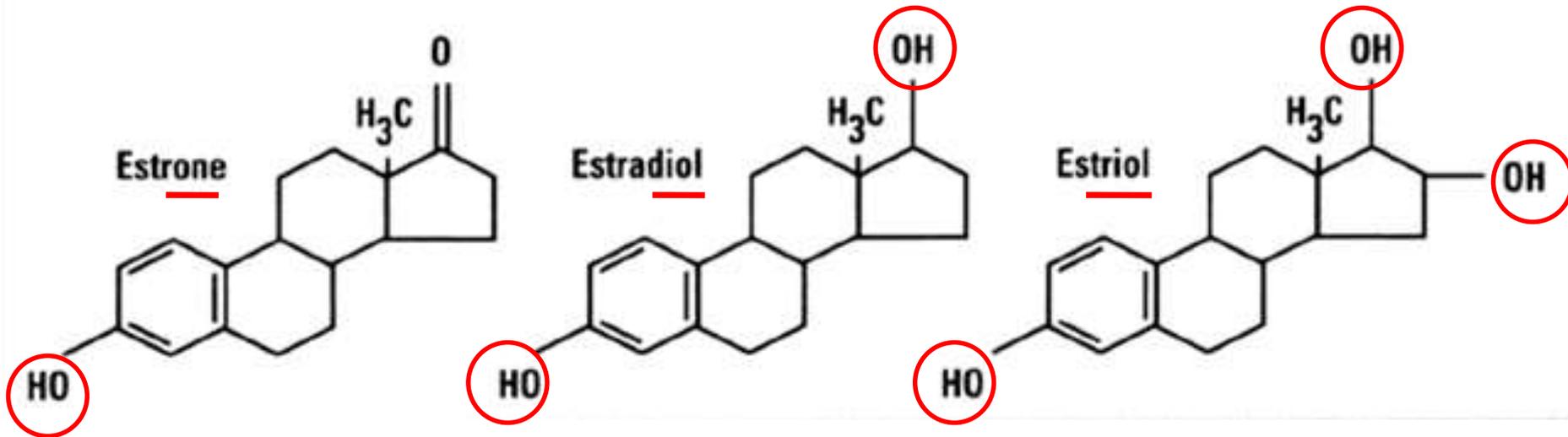
# Conversion Considerations - *Estrogen*

- **Patient compliance:**
  - Let patient determine how quickly then can decrease dose.
  - Patients on synthetics for a long duration may take longer to convert.
- **Dosage considerations:**
  - Start bio-identical estrogen dosage at mid-range.
  - Difficult withdrawal usually requires higher dose of bio-identical.
  - Consider changing the estrogen ratio:
    - Bi-est 40:60, 30:70, 20:80 (E3:E2)

“C’mon, c’mon... it’s either one or the other.”



# Bio-identical Estrogens

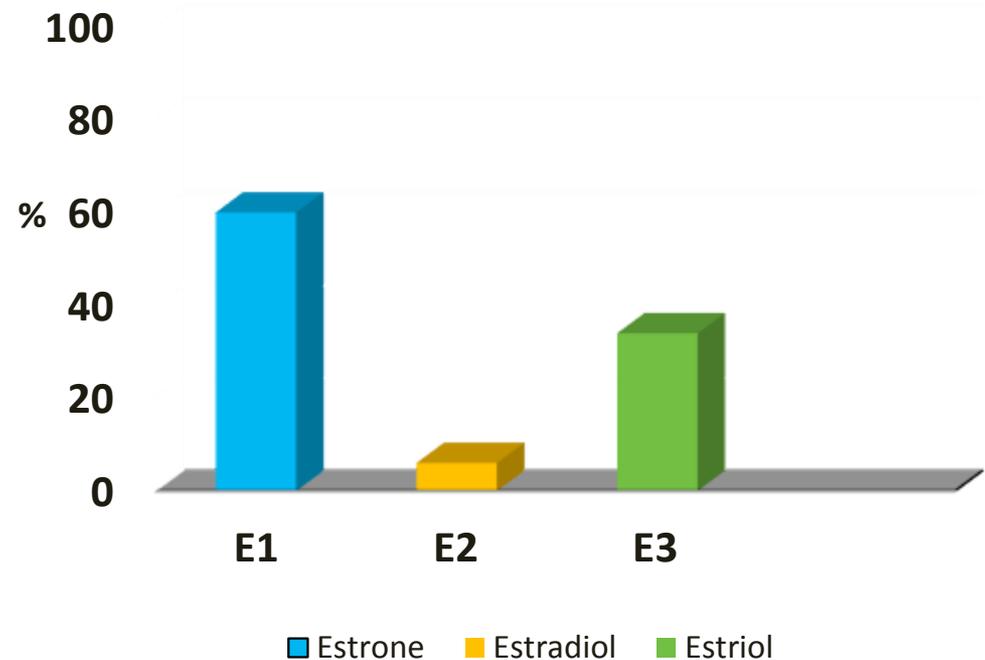


# Relative Potency of Estrogens

- **Estradiol (E2) is:**
  - 12x more potent than estrone (E1)
  - 80x more potent than estriol (E3)
  - ...as measured by action on the uterine tissue.
- **Vaginal/Urogenital tissue responds better to estriol.**
- **Estradiol estimated by some to be 1000x more potent** in regards to proliferative effect.

# The Three Major Estrogens Produced by Our Bodies:

- Estrone (E1)
- Estradiol (E2)
- Estriol (E3)



**Wright, Jonathan V. Altern Med Rev 1999;4(4):266-270**

Xu X, Duncan AM, Merz-Demlow BE, Phipps W, Kurzer MS. *Menstrual Cycle Effects on Urinary Estrogen Metabolites* J Clin Endocrin Metab Nov 1999;84(11)

# Bio-identical Estrogens

## Original Formulations (80% Estriol)

### Human Estrogen

Estradiol 10%

Estrone 10%

Estriol 80%

### Tri-Est (original) 1.0 mg

Estradiol 0.1 mg (10%)

Estrone 0.1 mg (10%)

Estriol 0.8 mg (80%)

### Bi-est (original) 1.0mg

Estradiol 0.2 mg (20%)

Estriol 0.8 mg (80%)

# Bio-identical Estrogens

## 50% Estriol Formulas

### Human Estrogen

Estradiol	6%
Estrone	60%
Estriol	34%

### Tri-Est 0.2 mg

Estradiol	0.05 mg (25%)
Estrone	0.05 mg (25%)
Estriol	0.1 mg (50%)

### Bi-est 0.2mg

Estradiol	0.1 mg (50%)
Estriol	0.1 mg (50%)

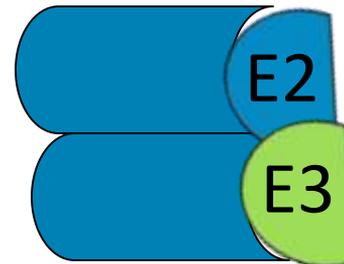
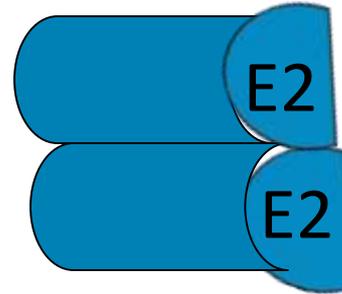
# Bi-est Formulas

- **There is NO standard ratio.**
- **Prescribe/label in a manner that clearly indicates your intention or preparation:**
  - Ex: Bi-est: E2 0.1 mg/E3 0.1 mg or
  - Ex: Bi-est 0.2 mg (E2 0.1/E3 0.1)
- **Prescribe/label individual amounts:**
  - Avoid percentages!

# The Influence of Estriol



# The Influence of Estriol



# The Influence of Estriol

E3:E2

- 1.0 mg Bi-est 80:20 ? 0.2 mg
- 0.4mg Bi-est 50:50 ? 0.2 mg

# Inappropriate Approach with “HRT”

- **Estrogen given to women who did not need estrogen and in excessive amounts:**
  - Excessive estrogen temporarily controls hot flashes and other symptoms thought to be caused by lack of estrogen.
  - Estradiol levels in perimenopausal women are high or high normal until the last 6 to 12 months of perimenopause.
  - CEE 0.625 mg elevates overall estrogen burden well beyond normal physiological amount.

# Inappropriate Approach with “HRT”

- **FSH measurement used to verify need for estrogen:**
  - Increase in FSH is correlated with decreased Inhibin levels, not with free estrogen.
  - Inhibin B decreases with decreasing follicles not menopause.
  - Inhibin A decreases with anovulation, not menopause.
  - FSH correlates with progesterone production, not estrogen.

# Inappropriate Approach with “HRT”

- **Oral estrogen therapy not appropriate in women:**
  - Significantly increased risk of stroke and VTEs compared to sublingual or topical administration.
  - Increased binding proteins SHBG, TBG, CBG.
  - Improper ratio of E1 to E2 created by oral route:
    - When oral estrogen creates a normal level of estradiol, estrone is significantly higher than it should be.

# Estradiol (E2), Estrone (E1) and Oral Estrogen Supplementation

	<u>Serum E2</u> <u>(pg/ml)</u>	<u>Serum E1 (pg/ml)</u>	<u>E2/E1</u>
<b>Premenopause</b>	60	60	1
<b>Postmenopause</b>	20	60	0.33
<b>Oral Estradiol</b>	60	<b>300</b>	0.2

# Considerations in Estrogen Replacement Therapy

- **Establish need:**
  - Measure Estrogen, not FSH.
  - Correct cortisol, thyroid and progesterone first.
- **Never give unopposed estrogen.**
- **Start at low dose and use lowest dose necessary:**
  - Monitor levels and outcomes.
- **Bi-est instead of tri-est.**
- **Always balance with progesterone:**
  - Estrogen only therapy is not supported anywhere in the literature.

# Would you pass this car?



A black stethoscope is laid out on a dark wooden surface. A green apple with a single green leaf is positioned in the center-left. The text is overlaid on the right side of the image.

# Thank You

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