



Cleansing &
Detoxification
for balanced health



BIODIDENTICAL HORMONES :

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St. Michael's Hospital

University of Toronto



BIOIDENTICAL HORMONES :

What Oprah didn't tell you !

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BIOIDENTICAL HORMONES : Objectives

To define Bioidentical Hormone Therapy (BHT) and gain an understanding of both BHT and compounded BHT by

- ◆ Looking at the reasons women seek BHT
- ◆ Considering the claims being made for BHT and their validity
- ◆ Discussing the role & reliability of hormone testing (including salivary hormone testing) in the management of menopausal women

To formulate a practical approach to the woman seeking BHT for treatment of her menopausal symptoms

Case Report: Patient History



54-yo woman presents complaining of recurrent menopausal symptoms after discontinuing HT 1 year ago

8 hot flashes/day

Can't sleep

Exhausted at work

“Believes HT causes CA”

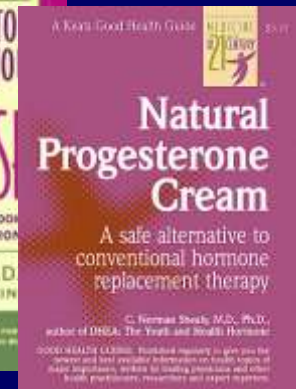
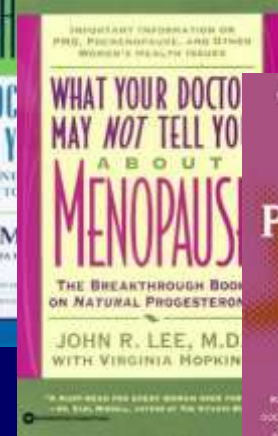
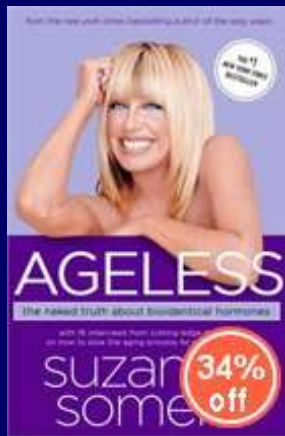
After seeing Suzanne Somers on ‘Oprah’ she realized that bioidenticals are what she needs!

Case Report: Patient History

- ◆ She took standard-dose E+P oral therapy for 4 years without problems but stopped HT after reading about the WHI
- ◆ She has read extensively on menopause Rx and has researched alternatives on the Internet
- ◆ What she now wants is salivary testing and bioidentical HT “because it works better and is safer”

Case Report: Patient History

- ◆ She has been inspired by Suzanne Somers' books and has also read Dr. John Lee's books & was really excited to see Suzanne Somers on Oprah!



- ◆ (She's brought copies along to show you, --- as well as some recent articles on 'natural menopausal therapies')



No way I can compete with this 64 yo woman
--- unfortunately !!

What Is The Status of ET/HT After the WHI?

Controversy

Confusion

Concern About Standard Postmenopausal Drug Therapies

A Search for Alternative Therapies :

Bioidentical Hormones

What is traditional hormone therapy?

Estrogens and progestins prescribed to treat symptoms of menopause (e.g. hot flashes, vaginal dryness) –NOT replace hormones

Also recommended for first-line prevention of osteoporosis in women with menopausal symptoms

Significant body of evidence supporting the efficacy of traditional HT for treating symptoms of menopause.

e.g. progestins, prospective trials have demonstrated low rate of endometrial hyperplasia (<1% when administered for one year with estrogen)



REASONS WOMEN SEEK BHT AT MENOPAUSE FOR SYMPTOM Rx

- Menopause is not a disease –but women are symptomatic
- Response to 2002 WHI : ‘Negative results’ have led to a suspicion of traditional medicine
- ET/HT side effects (mastalgia, bleeding)
- Perception that “natural” products (including BHT) are safer
-fear of cancer (especially of breast ca with traditional HT)
- Patient comfort with alternative medicines
- Wider advertising and broad availability (e.g. internet)
& of course, *celebrity endorsement !*

BIOIDENTICAL HORMONES

“Natural hormones” provide a “risk-free option” for women suffering from symptoms of the climacteric

Patient Handout - ***Bioidentical Hormone Therapy***

Women’s International Pharmacy (Custom Compounded Hormone Therapy for Men and Women
ADVANCE for Nurse Practitioners [www.advancweb.com/NP.2008\(September \)p27](http://www.advancweb.com/NP.2008(September)p27)

What are “bioidenticals”?

Not a scientific term

Molecularly identical to endogenous hormones

Individualized “exact dosages” to replicate homeostatic hormonal levels of estrogen, progesterone, testosterone and DHEA

Dosage is adjusted according to salivary or blood levels

Plant-derived from soybeans, Mexican yams and phytoestrogens

Purported anti-aging, sexual vibrancy and energy effects

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CLAIMS ABOUT BIOIDENTICAL HORMONES (BH) vs STANDARD HT

- BH prevent rather than cause cancer
- No risk of endometrial cancer
- Better side effect profile
- Provide “physiological” estrogens
- Are “natural” not “synthetic”
- Custom blending/compounding addresses individual needs

Bioidentical Hormones : What's available for women in Canada?

Pharmaceutical standardized products

- *17 β -estradiol – oral and transdermal via patch or gel*
- *Micronized progesterone in peanut oil*

Compounded with prescription by physician for pharmacist

"Customized " estrogen mixtures :

- *Bi-Est = 80-90% estriol + 10-20% estradiol
(standard dose is 1.25 or 2.5 mg)*
- *Older Tri-Est = 80% estriol + 10% estradiol + 10% estrone*

Dosing Equivalency of Older Tri-Est

**By weight : 80% estriol, 10% estradiol and
10% estrone**

2.5 mg Tri-Est

2.0 mg estriol

0.25 mg estrone

0.25 mg estradiol

Equivalent to 0.625 mg CEE taken bid

Pharmaceutical Products

Pharmaceutical Products Structurally Identical to Ovarian Hormones

GENERIC	BRAND NAME	ROUTE
<i>17β estradiol</i>	<i>Estrace</i>	<i>Oral</i>
<i>17β estradiol reservoir patch</i>	<i>Estraderm</i>	<i>Transdermal</i>
<i>17β estradiol matrix patch</i>	<i>Climara, Estradot, Oesclim</i>	<i>Transdermal</i>
<i>17β estradiol gel</i>	<i>EstroGel</i>	<i>Transdermal</i>
<i>Progesterone (in peanut oil)</i>	<i>Prometrium</i>	<i>Oral</i>

What is the problem with BHRT?

The Endocrine Society

Position Statement on Bioidentical Hormones,
October 2006.

Available at

www.menopause.org/edumaterials/PG06monograph.pdf

What is the problem with BHRT?

•The Endocrine Society Position Statement on Bioidentical Hormones, October 2006.

Not tested in clinical trials

“Natural” does not equal safe

No clinician or patient inserts documenting safety and efficacy

No uniform manufacturing standards

No formal review of accuracy of advertising claims

- ◆ *In 2001 FDA tested 29 products from 12 compounding pharmacies – 34% failed at least one standard quality control test; 25% failed potency standards; versus 2% of 3,000 pharmaceutical products*

**Food and Drug Administration Report:
Limited FDA Survey of Compounded Drug Products.
At www.fda.gov/cder/pharmcomp.survey.htm**

Claims for BHRT

- Estriol found in greater concentrations in body than E2 or E1-
= *false*
 - ◆ *Single study¹*
 - *Only 26 women with single sample*
 - *Assay modified – not validated*
 - *No peer review*
 - *Other studies don't support ^{2,3}*
- Mimics body's own production of estrogen with 80% estriol, 10% estrone and 10% estradiol
-- *not exactly*
 - ◆ *Estriol is primarily a breakdown product in circulation*

1. Wright et al. Altern Med Rev 1999;4(4):266-70.

2. Longcope C. J Steroid Biochem 1984;20(4B):959-62.

3. Raju U et al. I 1975;6(6):356-64.

Estrogen Receptors in the Body

- 2 estrogen receptors at cellular level: ER- α and ER- β
- Located in different areas of the body
 - ◆ *ER- α in endometrium, breast and reproductive tissue*
 - ◆ *ER- β in kidney, intestine, bone, brain and endothelial cells*
- Different estrogens can therefore have similar effects in one tissue but very different effects in other tissues
 - ◆ *Likewise, the same estrogen can produce additional changes in different tissues*
- Not just blood levels are important



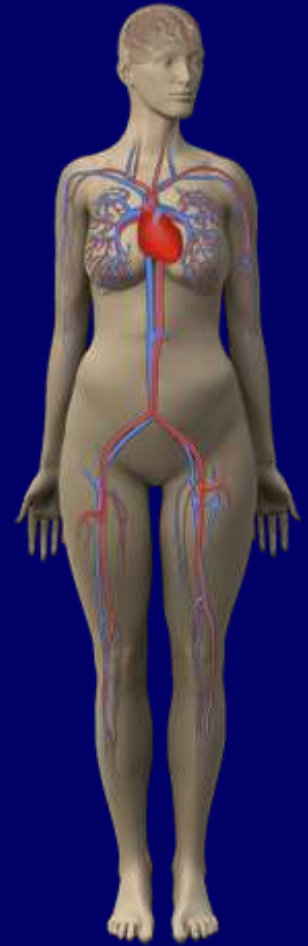
How do estrogens work?

Potency related to activity of specific E and P

- ◆ *Estrone ~1/3 potency of estradiol*
- ◆ *Estriol 1/80 potency of estradiol*

Binding affinity varies widely among the different types of estrogens¹

- ◆ *17 β estradiol - 100% binding for both receptors*
- ◆ *Estrone 10% for ER- α , 2% for ER- β*
- ◆ *Estriol 11% for ER- α , 35% for ER- β*

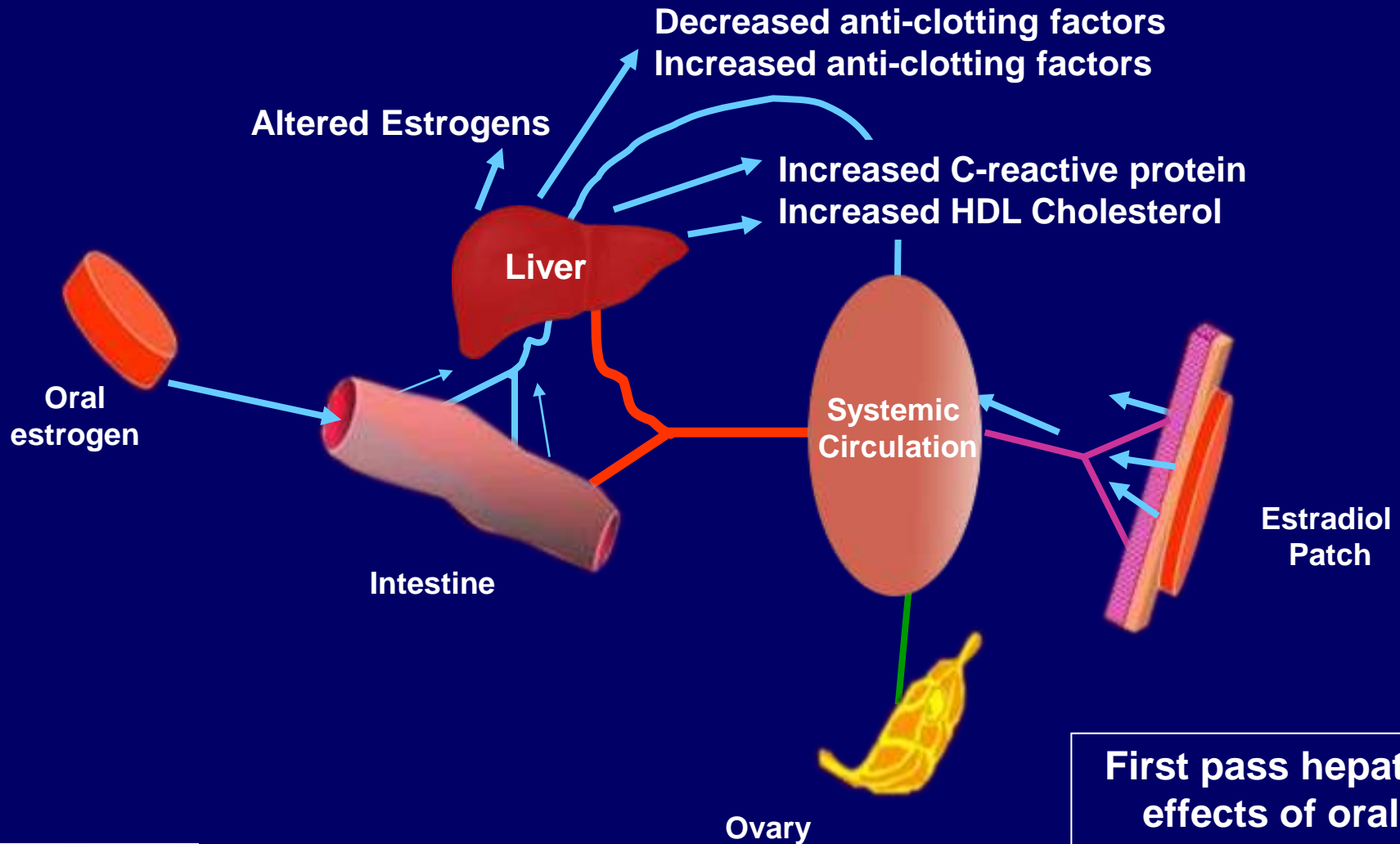


Dosing Equivalency of Estrogens

***** NOTE :** *All dosing is approximate equivalency of estrogens*

Preparation	Dose
<i>Conjugated equine estrogens (CEE) ¹</i>	<i>0.625-1.25 mg/d</i>
<i>Piperazine estrone sulfate¹</i>	<i>1.25-2.5 mg/d</i>
<i>Estradiol valerate¹</i>	<i>1-2 mg/d</i>
<i>Micronized estradiol¹</i>	<i>1-2 mg/d</i>
<i>Ethinyl estradiol¹</i>	<i>10-20 µg/d</i>
<i>Estriol²</i>	<i>2-4 mg/d</i>

First Pass Hepatic Effects



First pass hepatic effects of oral estrogens

Estrone (E1)

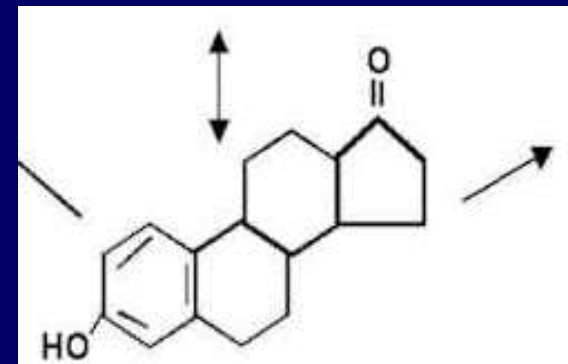
Metabolized to estriol after oxidation

Metabolized to or from E2 in liver and from androstenedione and DHEA in fat cells

When excreted as 2-hydroxyestrone – may be a marker for a lower breast cancer risk

- ◆ *Women with higher 16-hydroxyestrone excretion ratio had higher risk of breast cancer in one study*

Different metabolites between women



Estradiol (E2)

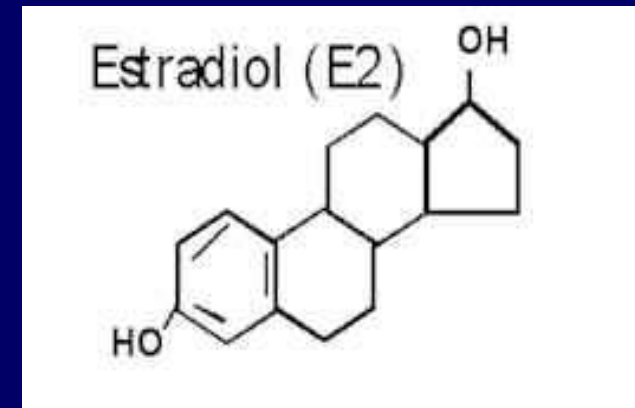
Attaches 100% to both ER- α and ER- β receptors

Half-life 2-60 minutes

Absorbed orally and converted to estrone sulphate in GI tract

Absorbed well transdermally

Major sources: ovaries, adrenals



Estriol (E3)

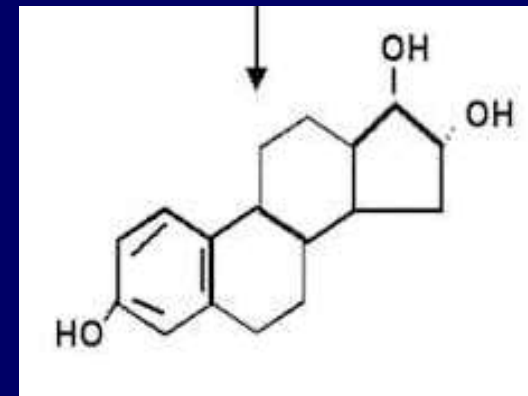
Estriol has 1/80 potency of estradiol

Still has estrogen risk including endometrial hyperplasia and stimulation of MCF breast cancer cell line

No bone protection

Primary urinary metabolite

MCF is a cell line derived from a human mammary adenocarcinoma



Efficacy of BHRT

- Many new pharmaceutical formulations are “bioidentical”
 - shown to reduce symptoms in RCTs
- Efficacy for compounded not well characterized
 - ◆ *Small numbers*
 - ◆ *Not placebo controlled*
 - ◆ *No endometrial safety data*
- Exception is low-dose intravaginal estriol for urogenital symptoms
 - ◆ *88 women in RCT received 1 mg (1 ovule) daily for 2 weeks followed by 2 mg weekly for 6 months versus control*
 - ◆ *Measured clinical and urodynamic effects*

Clinical and urodynamic effects of low-dose intravaginal estriol on urogenital symptoms

	<i>Treatment n=44</i>		<i>Control n=44</i>		
<u><i>Variables</i></u>	<u><i>Before Rx</i></u>	<u><i>After Rx</i></u>	<u><i>Before Rx</i></u>	<u><i>After Rx</i></u>	<u><i>P value</i></u>
<i>Vaginal dryness</i>	100	20.5	100	90.9	<0.001
<i>Dyspareunia %</i>	86.4	20.5	84.1	86.4	<0.001
<i>Urogenital atrophy</i>	100	27.3	100	93.2	<0.001
<i>MUP (cm H2O)</i>	50.82+6.15	62.15+8.64	52.35+6.30	49.40+6.54	<0.05
<i>MCUP (cm H2O)</i>	45.25+7.20	56.87+9.23	44.77+6.86	43.32+6.32	<0.05

MUP: maximal urethral pressure; MCUP: maximal urethral closure pressure.

Purported Cancer-protective Properties of Estriol

“Estriol Hypothesis”

*A high urinary ratio of E3 : E1 + E2
has cancer protective effects*

Purported Cancer-protective Properties of Estriol

*Lemon et al case-control study*¹

- ◆ Using rodent data hypothesized that women with BreastCa excrete lower levels of E3 : E2 and E1
- ◆ No differences in hormone profiles between control and Breast Ca groups
- ◆ Significant methodological flaws

*Zumoff cohort studies*²

- ◆ No support of protective role for estriol

Most recent research concerned about safety of estriol – converted to 16-hydroxyestrone – implicated in carcinogenesis

Progestins

Includes synthetic progestins and “natural progesterone”

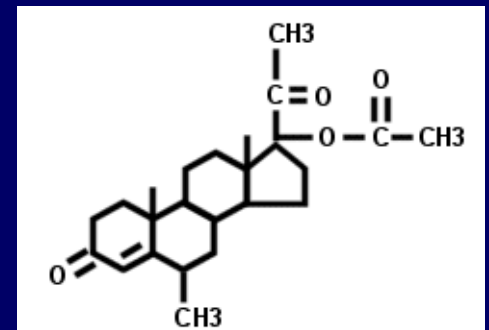
Early oral progesterone pdts were broken down in GI tract

Therefore progestins were derived from progesterone or testosterone (19-nortestosterone) precursors

After micronization was discovered, progesterone could be given orally

Prescribed in HT for women with uterus to protect against uterine cancer

May have sleep and weight benefits



Progesterin 1700000

Progesterone Metabolism

Metabolized primarily by the liver

Metabolites act at non-sex-steroid receptor sites

Beneficial effects of metabolites

- ◆ *Sedation** with higher doses of oral progesterone –
**utilized therapeutically for sleep*

Adverse effects of metabolites

- ◆ *11-deoxycorticosterone has aldosterone properties*
 - *May cause fluid retention – some have edema, breast tenderness and mood changes*
- ◆ *Other metabolites may cause dysphoria and confusion*

Topical Progesterone

Often sold in health food stores

Not yam cream

Typical dose: 20-40 mg/d

- ◆ *Delivered by 2-4 g of 1% compounded progesterone cream*

Present clinical data inadequate to support use in combination with estrogen for endometrial safety

One study showed benefit for hot flashes¹



Topical Progesterone

ENDOMETRIUM : No evidence for protection at prescribed dosages.

VASOMOTOR : Resolution of vasomotor symptoms

BONE : No bone protection

Although adverse effects have not been reported with topical progesterones, safety concerns should be the same as for other progesterone preparations.

*****NAMS does not endorse the use of topical progesterone creams for symptomatic relief of hot flashes.***

Topical Progesterone

Endometrial Effects (Wren et al)

*Endometrial response after continuous micronized transdermal P 14 days
– plasma levels low <3.2 nmol/L*

No endometrial secretory changes

Vasomotor Symptoms / Bone Loss (Leonetti et al)

*Resolution of vasomotor symptoms by 83% using transdermal P (20 mg) and
19% for placebo (P<0.001)*

No bone protection

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What about testosterone?

No approved products for women in Canada

Decreased libido frequent complaint

Sometimes male products are prescribed in conjunction with HT for women (off-label use)

- ◆ **Andriol 40 mg qd or every other day**
- ◆ **Androgel 1% pump or ¼ of sachet, Testim 1% gel**
- ◆ **Need to measure T levels after 3 months**
- ◆ **Apply to posterior calf**

Compounded preparations

- ◆ **T gel or cream in dosage of 0.25-1 mg**
- ◆ **Micronized T 1-5 mg in capsules or tablets**

XXX – T patch 300 µg ---approved in UK & EU – not in US or Canada

FDA-Approved Indications for HT

OK.

*I know they're effective :
they worked for me in the
past.*

BUT

*the (WHI) study proved they
were NOT SAFE.*

*On the other hand
according to the authorities
in the field, the bioidentical
hormones specifically
tailored to a woman's needs
clearly IS a safe option.*



**Will you be testing my hormones
or do I test my saliva myself and
then bring the results to you?**



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Custom-Compounded HT?

- ◆ **Lack of controlled clinical trials of safety and efficacy**
 - **No evidence that they are safer**
 - **Clinical trials unlikely to be performed because of high cost and lack of patent protection**
- ◆ **Compounding is allowable for individual patients unable to tolerate FDA-approved products**
 - **Mass production and marketing beyond state lines does not meet federal guidelines**
- ◆ **Prescribers are responsible for risk/benefit education**

Salivary Testing

E2, P, cortisol and T secreted in pulses – fluctuations

Salivary assays are not recommended for clinical use because of variable concentrations

Individual cycles show variability from day to day and have limited use

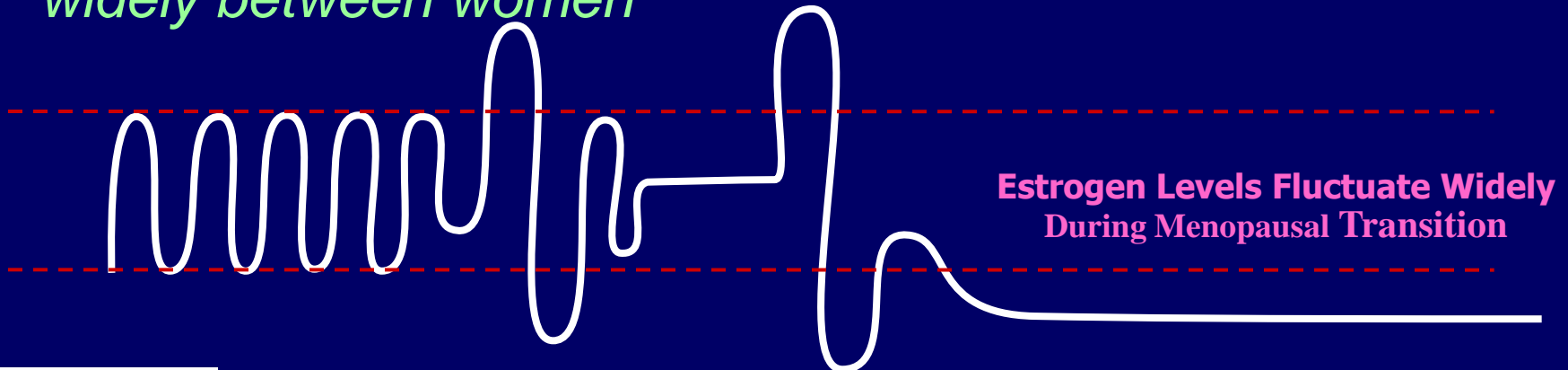
******HT should be adjusted according to clinical response***

When to measure estrogen levels?

Sometimes perimenopausally if unsure if patient is estrogen deficient or anovulatory

Patients unresponsive to standard estrogen therapy

Sometimes with transdermal approach as levels vary widely between women



SOGC & Traditional Postmenopausal HT

- ◆ Proven efficacy to treat menopausal symptoms
- ◆ Not meant to replace endogenous hormones
- ◆ Approved for symptomatic relief of hot flashes, vaginal dryness and prevention of osteoporosis

If patient desires 'bioidentical' HT, prescribe pharmaceutical with standardized dosages

The Decision : Treatment Options



Treatment Option Summary

	<i>VMS</i>	<i>Bone</i>	<i>Vaginal Atrophy</i>
<i>HT</i>	✓	✓	✓
<i>Bioidentical therapy</i>	Probable*	Unknown	Unknown
<i>Alternative</i>			
<i>Non-Rx</i>	Possible†	X	X
<i>Rx*</i>	✓‡	X	X

✓ = Proven; X = Unfounded.

*Based on E₂ dosing

†May have benefit with mild symptoms.

‡2 hot flashes per day/14 per week.

Position of Medical Societies



No scientific evidence to support claim of increased efficacy or safety of BHRT

Concern about purity, potency and quality of compounded products

Product inserts – no data for endometrial safety

SOGC Guidelines: Canadian Consensus on Menopause, JOGC, No 171, February 2006

Position of Medical Societies

The Endocrine Society

- Need regulatory activity for purity and dosage accuracy, adverse events and uniform information for patients

Endocrine Society Position Statement: Bioidentical hormones.
Available online at www.endo-society.org, October 2006

The Endocrine Society <societyservices@endo-society.org>

01/09/08 4:45 PM >>>

“In a significant victory for physicians and patients, the U.S. Food and Drug Administration (FDA) today announced that it has begun enforcement action against seven compounding pharmacies making false and misleading claims about the safety and efficacy of "bioidentical hormones."

The announcement was made by teleconference, during which Agency representatives also stated that the FDA considers the term "bioidentical" to be a marketing term and not one of scientific or medical merit.

FDA officials repeatedly stated that the claims being made about safety and efficacy of compounded "bioidentical hormones" are false and misleading, with no credible scientific evidence to support them....”

Official Position

Food and Drug Administration

- **Warning letters sent to pharmacies**
- **BHRT claims are unsupported by medical evidence and mislead women and HCPs**

Food and Drug Administration: FDA News, January 9, 2008.

WHI : FDA PRONOUNCEMENT ON THE SAFETY OF POSTMENOPAUSAL HT

“Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar”

WHI : FDA PRONOUNCEMENT ON THE SAFETY OF POSTMENOPAUSAL HT

“a class effect”

“Other doses of conjugated estrogens and medroxyprogesterone acetate, and other combinations and dosage forms of estrogens and progestins were not studied in the WHI clinical trials and, in the absence of comparable data, these risks should be assumed to be similar”

FDA Approval Process for HT

- ◆ **Benefits must be proven/approved for each product**
- ◆ **Risks are considered as a class effect unless specific evidence to the contrary**

SOGC's Clinical Pearls



- ***Media and popular books pressure physicians to write prescriptions for compounded therapies***
- ***Don't confuse science and marketing***
- ***Prescription implies endorsement***
- ***Advise patient regarding lack of standardization, efficacy and safety data***
- ***Offer prescriptions available based on evidence-based medicine***

PRIMUM NON NOCERE !

Class Labeling

- ◆ FDA required class labeling that addresses the results of the WHI for all estrogen therapies
- ◆ Exemptions only if controlled clinical trials demonstrate a different risk profile
- ◆ Custom-compounded products have no official labeling and therefore no contraindications or warnings

References

Moskowitz D. A comprehensive review of the safety and efficacy of bioidentical hormones for the management of menopause and related health risks. *Altern Med Rev* 2006;11:208-21.

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Speroff. Council on Hormone Education 2004;2(4). Available at www.cme.wisc.edu/hormonecme/newsletters2/newslettervol2no4.pdf

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Vanderhaeghe L, Pettle A. *Sexy Hormones. Unlocking the Secrets to Vitality* 2007.

Warren M, Stanczyk F. Custom-compounded Hormone therapy: Is there science to support the claims? Council on Hormone Education 2004;2(4). Available at www.cme.wisc.edu/hormonecme/newsletters2/newslettervol2no4.pdf

Understanding the Controversy:

Hormone Testing and Bioidentical Hormones

Proceedings from the Postgraduate Course
presented prior to the
17th Annual Meeting of
The North American Menopause Society
October 11, 2006
Gaylord Opryland Hotel
Nashville, Tennessee