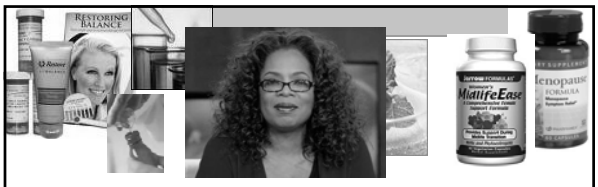

BIOIDENTICAL HORMONES :
What Oprah didn't tell you !

Christine M. Derzko MD, FRCSC
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Obstetrics & Gynecology and Internal Medicine (Endocrinology)
St. Michael's Hospital
University of Toronto

BIOIDENTICAL HORMONES :
What Oprah didn't tell you !

DISCLOSURE STATEMENT

I HAVE NO ACTUAL OR POTENTIAL CONFLICT OF INTEREST IN RELATION TO THIS PROGRAM

BIOIDENTICAL HORMONES : Objectives

- *Define Bioidentical Hormone Therapy(BHT) and compounded BHT (cBHT) & reasons women seek BHT*
- *Discuss the role & reliability of hormone testing (including salivary hormone testing) in menopause management*
- *Consider the stated rationale and supporting evidence for cBHT*
- *Examine the validity of claims for the superior efficacy, tolerance & safety of BHT*
- *Summarize the guiding principles presented in statements from the FDA & academic bodies including the SOGC, NAMS, &The Endocrine Society.*

Case Report: Patient History

54-yo woman presents complaining of recurrence of menopausal symptoms.

She took standard-dose E+P oral therapy for 4 years without problems but stopped HT after reading about the WHI.

Concerned that HT causes cancer

Now….

8 hot flashes/day

Can't sleep

Exhausted at work.

BUT… After seeing Suzanne Somers on 'Oprah' she realized that bioidenticals are the answer for her !

But then she saw the Oprah show with Suzanne Somers…

and the discussion convinced her that bioidenticals were the answer!

She has read extensively on menopause Rx and has researched the alternatives on the Internet

It is clear that what she now needs is salivary testing and then bioidentical HT "because it works better and is safer"

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')**

.....the problem is ……..

--- unfortunately ----
I really can't compete with this 64 yo woman !!

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 HORMONE

"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 Practioners www.advanceweb.com/NP.2008(September)p27

What are "bioidenticals"?

Not a scientific term

Claims:

✓ 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

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

Compounded with prescription by physician for pharmacist

"Customized " estrogen mixtures : ("cBHT")

- *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

Pharmaceutical Products Structurally Identical to Ovarian Hormones

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

What is the problem with cBHT?

The Endocrine Society

Position Statement on Bioidentical Hormones, October 2006.

Available at
www.menopause.org/edumaterials/PG06monograph.pdf

What is the problem with cBHT?

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

Concerns noted in the position paper :

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 cBHRT

- Estriol found in greater concentrations in body than E2 or E1- *= false*
  - *Single study*[1]
    - *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 198420(4B):959-62.
3.Raju U et al. I 1975;6(6):356-64.

What determines the effect of a hormone?

1. ***Dose***
2. ***Potency/strength***
3. ***Distribution of receptors in that specific tissue***
4. ***Affinity of the hormone for the receptor(s)***

Estrogen Receptors in the Body

- 2 estrogen receptors at cellular level: ER-a and ER-b
- 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 estrogens[1]

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

1. Zhu et al. Endocrinol 2006;147(9):4132-50.

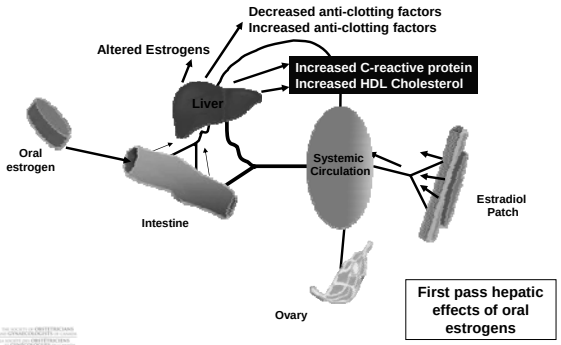
Dosing Equivalency of Estrogens

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

Preparation	Dose
Conjugated equine estrogens (CEE) [1]	0.625-1.25 mg/d
Piperazine estrone sulfate[1]	1.25-2.5 mg/d
Estradiol valerate[1]	1-2 mg/d
Micronized estradiol[1]	1-2 mg/d
Ethinyl estradiol[1]	10-20 µg/d
Estriol[2]	2-4 mg/d

.Felig P. Endocrinology & Metabolism. McGraw-Hill: 2001 (pp. 769)
2.Fugh-Berman et al. J Gen Intern Med 2007;22:1030-4.

First Pass Hepatic Effects



Estrone (E1)

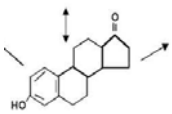
Metabolized to estriol after oxidation

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

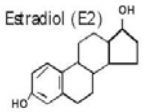
- *Women with higher 16-hydroxyestrone excretion ratio had higher risk of breast cancer in one study*

Different metabolites between women



Estradiol (E2)

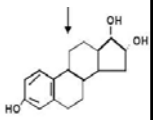
Attaches 100% to both ER-α and ER-β receptors
Half-life 2-60 minutes
Absorbed orally and converted to estrone sulphate in GI tract
Absorbed well transdermally
Major sources: ovaries, adrenals
Like E1 metabolized by hydroxylation
@ C2, C4 or C16 pathway



Estriol (E3)

Estriol has 1/80 potency of estradiol
Concerns re potential cancer risks
a)estrogen induced endometrial hyperplasia
b)known stimulation of *MCF breast cancer cell line and consequences of its hydroxylation by C2, C4 or C16 pathway
No bone protection
Primary urinary metabolite

*MCF is a cell line derived from a human mammary adenocarcinoma



Efficacy of Bioidentical HT

•Many pharmaceutical formulations are "bioidentical" & in RCTs have been shown to reduce symptoms

- Efficacy for compounded (cBHTs) not well characterized
  - *Small numbers*
  - *Studies 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*

Dessole et al. Menopause 2004;11(1):49-56.

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

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

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

Dessole et al. Menopause 2004;11(1):49-56.

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

1.Lemon et al. JAMA 1966;196(13):1128-36.
2.Zumoff et al. Cancer Res 1975;35(11 Pt 2):3365-73.

Progestins

Includes synthetic progestins and "natural progesterone"

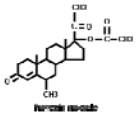
Early oral progesterone pdts were broken down in GI tract

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



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 flashes[1]

1. Leonetti HB et al. *Obstet Gynecol* 1999;94(2):225-8.

Topical Progesterone

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

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

1. Leonetti HG et al. Obstet Gynecol 1999;94(2):225-8
2 .Wren BG et al. Lancet 1999;354:1447-8. .
2..

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.***

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

The FDA-Approved HT Option

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?

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

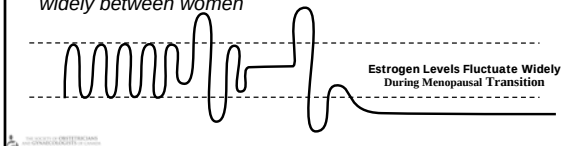


Table 2. Criteria for ordering hormone testing

	Patient groups	
	Surgical menopause Premature ovarian failure	Peri- and postmenopausal
Estradiol	To approximate physiology, when it is an appropriate goal	When treatment failures occ When unusual side effects occur
Progesterone	No clinical application	No clinical application
Testosterone	To assess baseline status To ensure replacement doses are not excessive To evaluate treatment failures	

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***

Saliva and Hair Tests for Hormones

- No reference standards available
- Lack of correlation with serum estradiol levels
- Data from saliva does not tell you what is going on in the target tissue
- No way to determine appropriate dosing through these tests
- Inter- and intrapatient variability
- In reality, dosage adjustments based only on symptomology
- No evidence to suggest that "individualized estrogen or progesterone regimens" based on these tests increase efficacy or improve safety

Wren BG, et al. *Climacteric*. 2000;3:155-60; Boothby LA, et al. *Menopause*. 2004;11:356-67; Lewis JG, et al. *Maturitas*. 2002;41:1-6.

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**

Boothby LA, et al. Menopause. 2004;11:356-67.

SOGC & Traditional Postmenopausal HT

Standard 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

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

✓ = Proven; X = Unfounded.
*Based on E_2 dosing
†May have benefit with mild symptoms.
‡2 hot flushes per day/14 per week.

Position of Medical Societies

THE SOCIETY OF OBSTETRICIANS AND GYNAECOLOGISTS OF CANADA — LA SOCIÉTÉ DES OBSTÉTRICIENS ET GYNÉCOLOGUES DU CANADA

- 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

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 !

THANK YOU !

Back-up Slides

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**

Boothby LA, et al. *Menopause.* 2004;11:356-67.

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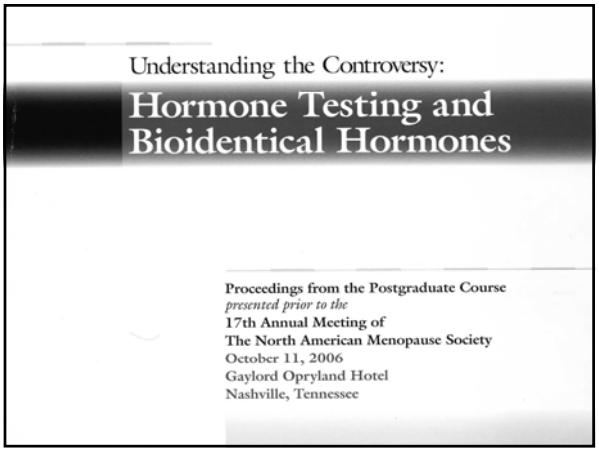

The Endocrine Society <societyservices@endo-society.org> 01/09/08 4:45 PM >>>

"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…."