BIOIDENTICAL HORMONES

- Bioidentical Hormone medication containing Estrogen, Progesterone or other hormones that are chemically exact duplicates of hormones produced by women, primarily in the ovary

BIOIDENTICAL HORMONE THERAPY

- Many of these commercially available in several well-tested, FDA approved, brandname prescription drugs.
- List of Government approved products in US and Canada available on the NAMS website

Concerns of “custom compounded” are that these are not FDA approved.
- Individual mixed recipes not tested to prove active ingredients are absorbed appropriately or provide predictable levels in blood and tissue
- No scientific evidence regarding effects - both positive and negative on the body
HORMONE TESTING

• Salivary and blood testing of hormone levels used by compounding pharmacies meaningless for midlife women
• Hormone levels vary throughout the day and from day to day

BIOIDENTICAL HORMONE THERAPY

• Products compounded in the pharmacy account for 1% of all prescriptions in the US or approximately 30 million prescriptions
• Wyeth Pharmaceuticals has filed a petition with the FDA based on concerns about potential risks associated with BHT

FDA APPROVAL REQUIREMENTS

• For estrogen—at least one and usually 2 randomized, prospective, placebo-controlled clinical trials.
• Drug must meet clinical requirements that support the indication. i.e. for hot flashes drug must be statistically superior to placebo in reducing both the frequency and severity of hot flashes

FDA APPROVAL REQUIREMENTS

• To establish superiority, manufacturer must provide 12 weeks of data demonstrating the safety and efficacy of its drug in decreasing the number of moderate to severe hot flashes, defined as 56 or more occurrences per week per patient. The drug must reduce the number of hot flashes per day by at least two
FDA APPROVAL REQUIREMENTS

- Superior efficacy compared with placebo must be evident within 4 weeks after study initiation
- Manufacturer must establish the lowest effective dose to alleviate symptoms
- Other requirements include tracking levels of lipids, lipoproteins, coagulation factors, monitoring serum levels of active and sometimes inactive metabolites

FDA APPROVAL REQUIREMENTS

- For approval of progestogens, manufacturers must conduct an endometrial hyperplasia prevention study of at least 12 months duration and often up to 24 months
- Acceptable rate of hyperplasia is 1% or less with a confidence interval that does not exceed 4% for the population

LABELING STANDARDS

- FDA requires all manufactured HT products to be labeled to include warning language
- Compounded BHT typically not labeled and doesn’t include warnings

LABELING STANDARDS

Warning language-“There is no evidence that the use of natural estrogens results in a different endometrial risk profile than “synthetic estrogens” of equivalent estrogen dose”
Must also mention increased risks of myocardial infarction, stroke, pulmonary embolism, DVT and invasive breast cancer in certain populations
PRODUCT MONITORING
• In 2001, the FDA ordered 29 products from 12 compounding pharmacies for testing
• 34% of these products failed at least one standard quality control test. Additionally 9 with failing analytical results also failed potency testing, with an average range of 59-89% expected potency

PRODUCT MONITORING
• In contrast, FDA monitoring of more than 3000 pharmaceutical products tested since 1996 revealed a failure rate of less than 2% for all tests, with only 4 products failing potency tests
• Whether FDA approved or compounded often suppliers are the same

REGULATION
• FDA has attempted to regulate drug compounding
• One view is that compounded BHT mixtures are unapproved new drugs whose safety and efficacy have not been demonstrated
• Opposite view is that compounding is the practice of pharmacy, which only States can regulate and therefore outside of FDA jurisdiction

HISTORY OF COMPOUNDING REGULATION
• Food, Drug and Cosmetic Act was passed in 1938
• Empowered the FDA to require approval of new drugs made by pharmaceutical manufacturers
HISTORY OF COMPOUNDING REGULATION

- In late 1980’s FDA argued the law was intended to apply to compounded as well as commercially manufactured drugs.
- FDA was angered by bogus health claims promoting compounded prescription products in the 1990’s

HISTORY OF COMPOUNDING PHARMACIES

- In 1997, Bill 127 of the FDA Modernization act (FDAMA) added bill 503A to the original 1938 FDA Act
- FDAMA added conditions for which compounded drugs were exempt from the new drug approval process, but also imposed certain advertising restrictions for compounded drugs.

HISTORY OF COMPOUNDING REGULATION

- In response 8 pharmacies from 7 states sued the FDA in Federal Court in 1998, contending advertising restrictions violated their 1st amendment rights
- Case (Western States) heard in 9th Circuit Court-FDA position unconstitutional

HISTORY OF COMPOUNDING REGULATION

- Result was FDA no longer had regulatory authority over compounded drugs
- Decision upheld by Supreme Court in 2002
COMPOUNDING VS MANUFACTURING

• Current FDA position is that it has authority to regulate some compounding activities
• FDA and American Pharmacy Association differ on definitions of compounding and manufacturing
• United States code allows pharmacies to be exempt from FDA requirements

SOLUTIONS

• In addition to requesting more state oversight of compounding practices, ACOG, Endocrine Society and NAMS have issued position statements in regard to manufactured vs compounded hormone products
• Currently, no national standard of regulation applying uniformly to compounding pharmacies

OVERSIGHT OF COMPOUNDING

• Drug Enforcement Agency (DEA)
• Occupational Safety and Health Administration (OSHA)
• Environmental Protection Agency (EPA)
• Nuclear Regulatory Commission (NEC)

US Pharmacopeia

• USP is official public standard-setting authority for all prescription and over the counter medicines, dietary supplements and other healthcare products manufactured and sold in US
• Independent, nonprofit, public health organization
USP REFERENCE STANDARDS

• United States Pharmacopeia-National Formulary (USP-NF) is reference standard for medicines, dosage forms, drug substances, excipients, medical devices and dietary supplements

QUALITY STANDARDS

• In addition to USP, several other quality standards and organizations guide the compounding industry
• Current Good Compounding Practices (CGCP)-described in Chapter 1075 of USP-NF
• Compliance Policy Guidelines (CPG) of the FDA

CONTROVERSIES IN COMPOUNDING

• Federal vs State jurisdiction
• Authority for setting compounding standards
• Definitions of a “new” drug, off label use, and
• Who generates requests, the clinician or patient?

DEFINING BHT

• Two known estrogen receptor-ER-alpha and ER-beta
• 17 beta estradiol has 100% binding affinity for both receptors, but estrone, estrone sulphate, and estriol have lower and varied binding affinity profiles
• Estrogen binding affinity does not predict biologic activity
• 17 beta estradiol has highest potency
DEFINING BHT

- ER-alpha receptors found in endometrium, breast ca cells and ovary
- ER-beta receptors found in kidney, intestinal mucosa, lung, bone and bone marrow, brain and endothelial cells

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DEFINING BHT

- Estriol is commonly used in compounded products
- Has 1/80 potency of estradiol
- Carries risks of estrogen including endometrial hyperplasia and stimulation of MCF breast cancer cell lines
- No bone protective effects
- Topical use can reverse vaginal atrophy

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DEFINING BHT

- Biest- commonly used custom mixture with 80-90 estradiol, 10-20% estriol
- Estriol not commercially available in US
- Proponents claim superior safety for estriol

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DEFINING BHT

- Essential claims about estriol include fact that it circulates in much greater concentration than estradiol or estrone in non pregnant women
- Tri-est mimics body’s own production because 80% estriol, 10% estradiol, 10% estrone
- Estriol has cancer preventive properties
DEFINING BHT

• Data to support view of estriol come from a single study-26 recipients, non peer reviewed and commercial RIA platform was not validated
• Cancer protective properties -1966 study by Lemon-significant methodological flaws and failed to show predicted differences in hormone profiles between controls and breast cancer patients

• Most studies did not support protective role for estriol
• Recent research raises concerns about estriol which is formed through 16-hydroxyestrone
• This metabolite has been implicated in carcinogenesis. Estriol also converts to this metabolite

TOPICAL PROGESTERONE STUDIES

• Australian study-evaluated endometrial response after continuous micronized transdermal P4 16-64 mg/day for 14 days. Plasma P4 very low (<3.2nmol/L) and no endometrial secretory change

• Transdermal progesterone cream for vasomotor symptom relief and prevention of postmenopausal bone loss. Placebo-controlled double blind study included menopausal women within 5 years of menopause. Used cream with 20 mgm.P4. Resolution of vasomotor symptoms in 83% of treated and 19% of controls. No bone protection
**SALIVARY HORMONES**

- Recommended by some compounding pharmacies to determine baseline levels of hormones including estradiol, progesterone and testosterone.
- Claims by some that comparing hormone levels to normal range for woman’s age can help in selecting and evaluating BHT.

**SALIVARY TESTING**

- NAMS states that saliva testing has not been proven accurate or reliable and desired levels of hormones in postmenopausal women have not been established.
- NAMS also questions relationship of physical symptoms to absolute hormone levels.

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**SALIVARY TESTING**

- Mean salivary estradiol patterns obtained from studies of large numbers of women look similar to serum estradiol and P4 during the menstrual cycle.
- Individual serum hormone levels vary substantially.

**SALIVARY TESTING**

- Studies of salivary E2 and P4 showed individual patterns varied significantly, however for a group of women relatively consistent pattern.
- Estrogen along with progesterone, cortisol, testosterone and other steroid hormones secreted in pulses.
**SALIVARY TESTING**

- Fairly good correlation between serum and salivary estrogen for within-subject analysis but poor correlation between subjects.
- As a result, no standard concentration of hormone levels that can be used to set values.

**SALIVARY TESTING**

- Clinical results suggest that salivary assays are useful for assessing individual hormone status if measurements are based on at least 5 daily saliva samples.
- Salivary and serum patterns correlate within individuals.
- Ratio of saliva to serum is variable between individuals.