Bioidentical Hormone Replacement Therapy: What Is It and Is It Effective?

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OBJECTIVES:
1. Define Bio-Identical Hormone Replacement Therapy (BHRT)
2. Understand the history behind BHRT
3. Review the cause and symptoms of menopause
4. Explain blood and saliva testing process
5. List commercially available hormone replacement medications
6. Apply literature to patients in community setting
Background:

- John R. Lee, MD
  - Considered pioneer of BHRT
  - Graduate of University of Minnesota Medical School
  - 30 years as family practice physician
  - Expert in the study and use of the hormone progesterone
  - Used transdermal progesterone in clinical practice
  - Coined term “estrogen dominance”

- Jonathan v. Wright, MD
  - 1969 – graduated from University of Michigan Medical School
  - 1973 – founded Tahoma Clinic in Seattle, WA
  - 1982- 1st to develop and introduce BHRT
  - Has authored/co-authored 14 books

What does “Bio-identical” mean?
- Endocrine Society
  - “compounds that have the exact same chemical and molecular structure as hormones that are produced in the human body”
- American College of Obstetricians and Gynecologists (ACOG)
  - “plant-derived hormones that are biochemically similar or identical to those produced by the ovary or body”
- No defined meaning in any medical or conventional dictionary
- FDA does not recognize the term

Facts and Myths from FDA
- Myth: BHRT are safer and more effective than FDA approved conventional hormone therapy (CHT) drugs.
- Fact: FDA is not aware of any credible scientific evidence to support claims made regarding the safety and effectiveness of compounded “BHRT” drugs
- Myth: BHRT products can prevent or cure heart disease, Alzheimer’s disease, and breast cancer.
- Fact: BHRT have not been shown to prevent or cure any of these diseases. Like FDA approved CHT drugs, they may increase the risk of heart disease, breast cancer, and dementia in some women.
- Myth: BHRT are safer and more effective than FDA approved CHT drugs.
- Fact: FDA is not aware of any credible scientific evidence to support claims made regarding the safety and effectiveness of compounded “BHRT” drugs
- Myth: If BHRT products were unsafe, there would be a lot of reports of bad side effects.
- Fact: Unlike commercial drug manufacturers, compounding pharmacies aren’t required to report adverse events associated with compounded drugs.
- Myth: FDA wants all compounded hormone therapies off the market.
Fact: A woman should be able to get a compounded hormone therapy drug when her physician decides that it will best serve her specific medical needs.

- **Menopause**
  - Most women experience menopause between ages 40 and 58
  - Average age is 51
  - Smoking and genetics can influence timing of menopause

- **Perimenopause**
  - May last 4 to 8 years
  - Begins with changes in the length of time between periods
  - Ends 1 year after the final menstrual period

- **Causes**
  - Woman’s ovaries stop making eggs and produce less estrogen and progesterone
  - Usually confirmed when a woman has missed her period for 12 consecutive months (with no other obvious causes)

- **Symptoms of menopause**
  - Hot flashes
  - Night sweats
  - Skin flushing
  - Vaginal atrophy

- **Other symptoms**
  - Forgetfulness
  - Headaches
  - Mood swings
  - Urine leakage
  - Vaginal dryness and painful intercourse
  - Joint aches and pains
  - Heart palpitations
• Menstrual Cycle

![Diagram of Menstrual Cycle](image)

**Figure 1**

![Changes in Hormone Level Patterns Over Six Months](image)

**Figure 2**
• What's commercially available\textsuperscript{17}

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<thead>
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<th>Brand</th>
<th>Generic</th>
<th>Dosage Form</th>
</tr>
</thead>
<tbody>
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<td>Estradiol, USP</td>
<td>Patch</td>
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<tr>
<td>Estrace®</td>
<td>Estradiol, USP</td>
<td>Cream, Tablet</td>
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<tr>
<td>Estrogel®</td>
<td>Estradiol, USP</td>
<td>Gel</td>
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<tr>
<td>Premarin®</td>
<td>Conjugated Estrogen</td>
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<tr>
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<td>Prometrium®</td>
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<td>Tablets</td>
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<tr>
<td>Femhrt®</td>
<td>Ethinyl estradiol/Norethindrone acetate</td>
<td>Tablets</td>
</tr>
<tr>
<td>Prempro®</td>
<td>Conjugated estrogen/medroxyprogesterone</td>
<td>Tablets</td>
</tr>
</tbody>
</table>

• Reasons for compounding\textsuperscript{16}
  
  o Not commercially available
  o Dosage form
  o Strength
  o Allergies
  o Gluten
  o Peanuts
  o Dyes
  o Sugar

• Process of BHRT Consultation at Dripping Springs Pharmacy
  
  o Assess symptoms
  o Saliva Testing
  o Review results with pharmacist
  o Compound customized medication

• Saliva test or blood test?\textsuperscript{15}
  
  o Saliva: measures level of hormone at the cellular level
    ▪ Active in organs and tissues
• Blood: measures level of hormone circulating in the blood stream
  ▪ “free” and “total” hormone levels

• Saliva Testing

  o Regular Periods - Day 19, 20, or 21 of cycle
  o Irregular Periods - Collect when not bleeding (3 days before expected period)
  o No period – any time of the month

• Saliva collection times

  o Collect the large tube in the morning within 30 minutes of waking, and before eating or drinking anything (except water)
  o Collect a small tube at noon, before lunch
  o Collect a small tube just before dinner
  o Collect the last small tube at bedtime

• Tips for collecting saliva

  o Do not eat, drink (except water), or brush teeth at least 2 hours prior to collection
  o Do not use lip products day of collection
    ▪ Do not want to contaminate the sample
  o Begin collecting saliva by allowing it to first pool in mouth then transfer into tube
  o Fill tube at least ½ full
  o Collection usually takes 5-30 minutes depending on saliva flow

• Progesterone

  o Maintains pregnancy
  o Prepare body for conception
  o Regulate monthly menstrual cycle

• Low Progesterone

  o Lighter sleep
  o Anxiety, panic attacks
  o Water retention
  o Cysts and fibroids
  o Bone loss
  o Worsening PMS
  o Mid-abdominal weight gain
  o Aging skin and hair loss

• Estrogens

  o Estrone (E1)
  o Estradiol (E2)
  o Estriol (E3)
• **Function of Estrogen**\(^{14}\)
  - Stores fat
  - Growth of breasts
  - Decreases thyroid hormone
  - Support vaginal tissue
  - Develop sex characteristics

• **Low estrogen**\(^{14}\)
  - Hot flashes
  - Night sweats
  - Water retention and bloating
  - Weight gain
  - Breast tenderness
  - Depression
  - Fatigue
  - Poor concentration
  - Anxiety
  - Insomnia

• **Low Testosterone**\(^{11}\)
  - Dry and thinning of skin
  - Fatigue
  - Bone loss
  - Incontinence
  - Depression
  - Vaginal dryness
  - Low libido
• **Article to review:**

• **Background of WHI**
  - Long-term national health study that focused on strategies for preventing heart disease, breast and colorectal cancer and osteoporosis in postmenopausal women
  - Between 1993 and 1998, enrolled 161,809 postmenopausal women between 50 and 79 years
  - Clinical Trials
  - Low fat dietary pattern
  - Calcium and vitamin D supplementation
  - Postmenopausal hormone use
  - Sponsored by National Institutes of Health (NIH), National Heart, Lung, and Blood Institute (NHLBI)

• **Objective**
  - To assess the major health benefits and risks of the most commonly used combined hormone preparation in the United States

• **Study population**
  - **Inclusion**
    - 50 to 79 years at initial screening
    - Post menopausal
    - Hysterectomy
    - Used postmenopausal hormones
    - No vaginal bleeding for 6 months
    - 12 months for 50 to 54 year olds
    - Likelihood of residence in the area for 3 years
    - Written informed consent
  - **Exclusions**
    - Competing risks
    - Medical conditions likely to be associated with a predicted survival of < 3 years
    - Safety
    - Prior breast cancer
    - Other prior cancer within the last 1- years except nonmelanoma skin cancer
    - Low hematocrit or platelet counts
    - Adherence and retention concerns
    - Alcoholism
    - Dementia

• **Methods**
  - 16,608 enrolled in trial
3 month washout period was required before baseline evaluation of women using postmenopausal hormones at initial screening.

- Women with intact uterus at initial screening were eligible for the trial of combined postmenopausal hormones.
- Women with a prior hysterectomy were eligible for the trial of unopposed estrogen.

**Intervention**
- One daily tablet
  - Prempro® (Conjugated equine estrogen 0.625mg/medroxyprogesterone acetate 2.5mg)

**Primary outcome**
- Coronary heart disease (CHD)
- Nonfatal myocardial infarction
- CHD death

**Follow Up**
- Contacted by telephone 6 weeks after randomization to assess symptoms and reinforce adherence.
- Follow up for clinical events occurred every 6 months.
- Self administered questionnaire.
- Adherence assessed.
- Required annual in-clinic visits.
- Electrocardiograms were collected at baseline and at follow-up years 3 and 6.
- Annual mammograms and clinical breast examinations.
- Medications were withheld.

**Conclusions**
- Overall health risks exceeded benefits from use of combined estrogen plus progestin.
- Average of 5.2 year follow up.
- Should not be initiated or continued for primary prevention of CHD.
• **Article to review:**

• **Patients**
  - 189 menopausal women
  - Ages 45 – 60 at beginning of therapy
  - Received natural estrogen, progesterone, testosterone, and DHEA
  - Patients treated for symptoms of menopause in a private clinic
  - 90 out of 189 had pre-existing risk factors for a cardio-vascular event, including high CRP, hypertension, hyperlipidemia, and diabetes
  - 4 out of 189 had history of atrial fibrillation

• **Methods**
  - Only 189 who had completed at least 12 months of therapy are included
  - Average follow-up is 30 months
  - Base-line blood levels for estradiol, progesterone, testosterone, DHEA
  - Rechecked at 3 and 6 months
  - All patients asked to have yearly mammograms

• **Protocol**
  - All received estrogen + progesterone
    - Biest cream (estradiol 1mg + estriol 4mg)
    - Progesterone 50-100mg sublingually
  - Patients were asked to use ½ gram twice daily and to adjust the starting dose, gradually increasing if needed to control hot flashes and decreasing if there was any breast tenderness
  - Testosterone administered to 125 women who were troubled with diminished libido and had low or low normal levels
  - DHEA given to 146 women with low levels

• **Results**
  - Common symptoms:
    - Hot flashes
    - Night sweats
    - Insomnia
    - Lack of energy
    - Low libido
    - Minor stiffness or achy joints
  - 97% showed improvement
    - Most improved in 49
    - Improved in 122
    - Some improved in 13
    - Questionable/minimal improvement - 5

• **Results**
  - Weight loss - 63 (60%)
  - Mental Clarity - 119/131 (90%)
    - 80 completely, 39 partially
• Complications
  o No complications
  o One patient with family history of breast cancer developed cancer after being in the program for 28 months
  o Tumor negative for both estrogen and progesterone receptors
  o One patient on Premarin for 10 years then switched to protocol found to have an ER+ and PR+ after 6 months
  o No abnormalities with mammograms
  o 3 patient with suspicious baseline findings had normal follow-up mammograms

• Discussion
  o Significant improvement of common menopausal symptoms
  o Most patients used emphatic terms to describe improvement in quality of life
  o Cognitive improvement experience by most patient on the protocol was an unexpected finding
  o 60% of participants experienced weight loss
  o Absence of myocardial infarctions and strokes

• Presenter's conclusions
  o Positive outcomes
  o Limitations
  o Symptoms not separated
  o Number of participants
  o No statistics reported

• Article to review:

• Objective
  o Evaluate the effectiveness of compounded BHRT provided in the community pharmacies

• Methods
  o Oakdell Pharmacy, Inc
  o Six independent community pharmacies located throughout San Antonio, TX
  o Observational cohort study
  o Data included patient demographics, comorbidities, therapeutic outcomes, and hormone therapies
  o Women self rated menopausal symptoms

• Patient eligibility
  o Inclusion
    ▪ Female
- > 18 years of age receiving compounded BHRT at Oakdell Pharmacy Inc.
- January 1, 2003 to April 30, 2012
  - Exclusion
    - Received compounded BHRT from Oakdell Pharmacy, but managed through outside offices
    - No follow-up evaluation form
- BHRT Consultation services
  - Referred through physicians, family members, and friends for BHRT service
  - Extensive initial evaluation, hormone replacement education, and follow up
  - Prior to initial visit – evaluation form and lab hormone panel
  - Questions about medical history, menopausal symptoms, treatment goals
  - During visit – education about hormones
  - Monitor symptom resolution and adverse effects
  - Decide on an individualized treatment
  - Prescription recommendation to physician for modification, signature, and/or approval
  - OTC product
  - 3 to 6 months and annually – hormone panels
- Common BHRT compounds
  - Bi-est (estriol/estradiol)
    - 80%/20%
    - 70%/30%
    - 50%/50%
  - Tri-est (estriol/estradiol/estrone)
    - 80%/10%/10%
  - Progesterone
  - Testosterone
  - Dehydroepiandosterone (DHEA)
- Common Compounded Bioidentical Hormones Dose Classifications
  - Topical Estrogen – Table 4

<table>
<thead>
<tr>
<th>Dose Classifications</th>
<th>Dose Range</th>
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<td>Low Dose</td>
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<td>Moderate Dose</td>
<td>0.51 – 1mg</td>
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<tr>
<td>High Dose</td>
<td>&gt; 1mg</td>
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</table>
- Oral Estrogen – Table 5

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<tr>
<td>Low Dose</td>
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<tr>
<td>Moderate Dose</td>
<td>1.1 - 2mg</td>
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<tr>
<td>High Dose</td>
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- Topical Progesterone – Table 6

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<td>Low Dose</td>
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<td>Moderate Dose</td>
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<td>High Dose</td>
<td>&gt;50mg</td>
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- Oral Progesterone – Table 7

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<td>Moderate Dose</td>
<td>101 – 200mg</td>
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<td>High Dose</td>
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- Data collection
  - Patient demographics, comorbidities, laboratory values, medications, adverse effects of hormone therapy
  - Used Last-observation-carried-forward (LOCF) method
    - Determine BHRT effectiveness at 3 and 6 months follow up
  - Dependent variable
    - Vasomotor and mood symptoms, myocardial infarction, breast cancer
  - Independent variables
    - BHRT regimen and BHRT dosage form
  - Length of therapy (LOT) obtained from pharmacy records and patient charts

- Results
  - 296 out of 431 met criteria
  - Mean age: 52 years old
  - Women included in the study
    - Hysterectomy (p=0.02), previous BHRT use (p<0.01), previous CHT use (p<0.01) baseline
Table 2 Baseline Characteristics

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<tr>
<th>Demographic</th>
<th>Estrogen + P4 (N = 170)</th>
<th>P4 (N = 126)</th>
<th>P-value (Estrogen + P4 vs. P4)</th>
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<tr>
<td>Age (yrs); mean (SD)</td>
<td>33 (7)</td>
<td>50 (10)</td>
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<td>Weight (lbs); mean (SD)</td>
<td>152 (32)</td>
<td>155 (32)</td>
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<td>Comorbid Conditions %</td>
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<tr>
<td>Heart disease</td>
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<td>Caffeine use; %</td>
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<td>0.51</td>
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<td>Baseline Chf; %</td>
<td>8</td>
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<td>Baseline BHRT; %</td>
<td>15</td>
<td>10</td>
<td>0.17</td>
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Table 8

Figure 5

Proportion of Dosage Forms

- Topical (n=212) 72%
- Oral (n=128) 43%
- Vaginal (n=66) 22%
- Sublingual (n=13) 4%

Figure 6

Proportion initiated on various BHRT doses

- Progesterone (n=199) Low Dose: 65%, Moderate Dose: 31%, High Dose: 5%
- Estrogen Combination (n=97) Low Dose: 63%, Moderate Dose: 21%, High Dose: 17%
Figure 7: Proportion initiated on various BHRT Doses.

Figure 8: Proportion with moderate to severe symptoms.

Figure 9: Proportion with moderate to severe symptoms.
• Limitations
  o Located in one geographical region
  o Sample size
  o Subjective reporting
  o Did not evaluate changes in regimens
  o More generalized to hysterectomized women

• Conclusions
  o Clear evidence that compounded BHRT is effective for reducing menopausal mood symptoms
  o Larger studies are needed to examine the impact of BHRT

• Presenter’s conclusion
  o Provides positive results for BHRT
  o Larger population
  o Broaden region

• Current clinical trials\(^9,10\)
  o Objective: Aim to find the dose of Bioidentical compounded hormone therapy that is equivalent to conventional hormone therapy.
    ▪ A Pharmacokinetic Evaluation of Bioidentical Compounded Estrogen Cream and Natural Progesterone (HRT)
    ▪ Mayo Clinic
    ▪ Rochester, Minnesota
    ▪ Richa Sood, MD – Principal Investigator
  o Purpose: Gather early information about safety when “natural” or bioidentical hormones are used during early menopause
    ▪ Bioidentical “Natural” Hormone Evaluation in Early Menopause
    ▪ University of Kansas
    ▪ Jeanne Drisko, MD, CNS, FACN

• Presenter’s recommendations
  o Patients consistently be monitored
  o Lack of long term safety profile
  o Customized dosage and dosage form for your needs
References:


