Hormone Replacement Therapy for both Men and Women.

Jim Paoletti, Pharmacist, FAARFM

Disclosure

Jim Paoletti is employed by ZRT Laboratory as a Consultant Pharmacist and Educator

Objectives

• Examine the scientific evidence concerning the use of different types of hormone replacement therapy
• Discuss the basic differences in risks and benefits between various hormone regimens
• Discuss assessment and treatment of hormones imbalances using medical history, patient symptom evaluation, and measured hormone levels
• Examine basic goals and treatment protocols for managing common hormone imbalances
The WHI study demonstrated that when Medroxyprogesterone Acetate was added to Conjugated Equine Estrogens, the following risks increased:

a. Heart attack  
b. Stroke  
c. Blood clots  
d. Breast Cancer  
e. All the above

Which of the following statements is true concerning hormone therapy and the risk of breast cancer?

a. All estrogen replacement therapies increase risk  
b. Progestins decrease the risk when added to estrogen therapy  
c. Synthetic Progestins have been consistently shown to increase risk  
d. Progesterone is associated with an increased risk  
e. All of the above

Medroxyprogesterone provides which of the following actions of progesterone?

a) Works synergistically with estrogen to increase cardiovascular protection  
b) Helps maintain a proper lipid profile  
c) Protects the uterus from over stimulation from estrogen  
d) Decreased estradiol induced breast tissue proliferation  
e) All of the above
Medroxyprogesterone acetate with respect to cardiovascular risks:
  a. Increases both the risks for heart attack and stroke
  b. Negates the positive lipid effects of estrogen and show a consistent reduction in HDL,
  c. Causes increased vasoconstriction and coronary artery spasm
  d. Promotes atherosclerotic plaque formation
  e. Increases the risk of hypertension
  f. All of the above

Weight gain, hot flashes, and fatigue can be caused by
  a. Low estrogen levels
  b. High cortisol levels
  c. Supraphysiologic progesterone levels
  d. Low thyroid function
  e. All of the above

Conflict and Confusion
  • Does “ERT” or “HRT” in addition to eliminating menopausal symptoms improve women’s overall health benefits, decreasing the risk of heart disease, stroke, osteoporosis, and Alzheimer’s disease?
  • When is it appropriate to prescribe “ERT” or “HRT” for a woman?
  • Is there any advantage to BHRT?
Opposition to BHRT

- The FDA, Endocrine Society, ACOG, NAMS, and AMA have all stated there is little or no evidence to support the claim that bioidentical hormones are safer or more effective than synthetic HRT\(^1\)-\(^6\).

- But few if any references cited for the opinion statements, and when there are references they are extremely limited and do not reflect the overall body of literature on the topic.

The FDA

The FDA Subcommittee Report on the FDA

- FDA has reported its own incompetency and inability to keep up with the science\(^7\).
  - "The Agency suffers from serious scientific deficiencies and is not positioned to meet current or emerging regulatory responsibilities”
  - "The FDA cannot fulfill its mission because its scientific base has eroded and its scientific organizational structure is weak.


The FDA Subcommittee Report on the FDA

Implications of declining, the Subcommittee has also analyzed (primarily 3.1.3). The FDA lacks a coherent scientific structure and vision as a result of weak organizational infrastructure (Finding 3.1.4). Strong...

FDA’s inability to keep up with scientific advances means that American lives are at risk. While the world of drug discovery and development has undergone revolutionary change — shifting from cellular to molecular and gene-based approaches — FDA’s evaluation methods have remained largely unchanged over the last half century. Likewise, evaluation methods have not kept pace with major advances in medical devices and use of products in combination.
North American Menopause Society

Adding to the confusion:

• Risks are likely to be smaller in women younger than age 50 who are at low risk for breast cancer, CHD, stroke and osteoporosis.
• Don’t extrapolate to women younger than 50
• For consistency, “hormone therapy” is the preferred term.
• Progestogen is the preferred term for both progesterone and progestins.

NAMS

No differentiation in therapies available:

• The primary indication is menopause symptoms
• Do not use hormone therapy for primary or secondary prevention of CHD or CVD.
• Don’t use hormone therapy for primary prevention of dementia.
• Use for shortest duration consistent with treatment goals.
• Extended use is acceptable when women feel benefit is worth risk, especially after failed withdrawal attempt.
North American Menopause Society

- 2005 position statement cited study and stated that there was a significant increased risk of breast cancer with synthetic progestins compared to progesterone
  - Reference cited from Menopause

- 2007 position paper states no significant difference in the risks associated with synthetic progestins and progesterone
  - No references cited

NAMS 2010 Position Statement

- NAMS 2010 Position Statement on Postmenopausal Hormone Use
- Diane E. Judge, APN/CNP
- Posted: 06/24/2010; Journal Watch © 2010 Massachusetts Medical Society
- Abstract
  - New evidence as well as recent analyses of benefit-risk ratios shape revisions.
- Introduction
  - The North American Menopause Society (NAMS) has updated its 2008 recommendations (JW Women’s Health Aug 2008, p. 61, and Menopause 2008; 15:584) for use of postmenopausal hormone therapy (HT) based on new evidence and collaboration with other professional societies. As before, the statement addresses only prescription HT products available in the U.S. and Canada. The guidelines newly acknowledge accumulating evidence that various estrogen and progestin products, routes of administration, and timing of therapy confer differing benefit-risk profiles.

ACOG NEWS RELEASE

For Release: October 11, 2010
Contact: ACOG Office of Communications
communications@acog.org

No Scientific Evidence Supporting Effectiveness or Safety of Compounded Bioidentical Hormone Therapy

Washington, D.C.—There is no scientific evidence to support claims of increased efficacy or safety for individualized estrogen or progestin regimens prepared by compounding pharmacies, according to a new Committee Opinion released today by The American College of Obstetricians and Gynecologists (ACOG). "Compounded hormone therapy does not belong in a clinic of care," said an ACOG statement, adding that compounding pharmacies have "no scientific evidence" to support their products and "no guarantee of safety for individualized estrogen or progesterone regimens prepared by compounding pharmacies." ACOG also cited concerns about the "risk of hormone therapy" in patients with "compounded hormone therapy products," "the possibility of hormone therapy being lost," and "the lack of scientific evidence for these products' safety and effectiveness.

ACOG News Release

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The November 2005 ASRM workshop focused on symptomatology in the young, healthy, perimenopausal/menopausal woman. We conclude that young, healthy symptomatic women should be offered the option of hormone therapy. There is clear evidence that hormone therapy improves vasomotor and urogenital symptoms and provides benefits to many women. All hormonal therapy should be individualized in symptomatic women. This involves prescribing the regimen and dosage according to individual needs. All hormonal therapy should be individualized in symptomatic women. This involves prescribing the regimen and dosage according to individual needs.

- Levels of Evidence
  - Ia Evidence obtained from meta-analysis of randomized controlled trials
  - Ib Evidence obtained from at least one randomized controlled trial
  - IIa Evidence obtained from at least one well-designed controlled study without randomization
  - IIb Evidence obtained from at least one other type of well-designed quasi-experimental study
  - III Evidence obtained from well-designed non-experimental descriptive studies, such as comparative studies, correlation studies and case control studies
  - IV Evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities

The Scientific Facts
- The effects and benefits of the sex steroids in the human body have been established and are printed in the biochemistry, endocrinology and physiology reference books that are used to teach health professionals
- Many of these functions of the sex steroids have not been shown to occur with administration of conventional therapy
Research On BHRT

• There are numerous world-wide studies involving bio-identical hormones and the evidence all points to BHRT as an effective and safe therapy option.

Kent Holtorf, MD Review Article

• The Bioidentical Hormone Debate: Are Bioidentical Hormones (Estradiol, Estriol, and Progesterone) Safer or More Efficacious than Commonly Used Synthetic Versions in Hormone Replacement Therapy?
  – Evaluate the evidence comparing bioidentical hormones, including progesterone, estradiol, and estriol, with the commonly used nonbioidentical versions of HRT for clinical efficacy, physiologic actions on breast tissue, and risks for breast cancer and cardiovascular disease.
  – Published papers were identified from PubMed/MEDLINE, Google Scholar, and Cochrane databases, which included keywords associated with bioidentical hormones, synthetic hormones, and HRT.
  – Postgraduate Medicine, Volume 121, Issue 1, January 2009, ISSN – 0032-5481, e-ISSN – 1941-9260

The Bioidentical Hormone Debate

• Progesterone, compared with MPA, is associated with greater efficacy, patient satisfaction, and quality of life.
• Synthetic progestins shown to consistently increase breast cancer risk, increase cardiovascular risks, and do not improve the quality of life, whereas bioidentical progesterone has demonstrated just the opposite.
The Bioidentical Hormone Debate

- With the exception of estriol only therapy, estrogen only therapy is not based on good science or physiology and increases the risk of breast cancer
- Conjugated equine estrogens carry the greatest risk of breast cancer of all estrogens
  - Increased risk in every patient
- Estriol does not initiate cancer causing DNA adducts and is non-proliferative
  - Does not increase the risk of breast cancer

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Estrogens and Cancer Risk

- Three Stages of Breast Cancer
  - Initiation - DNA Damage
    - Estrogen metabolites involved
  - Promotion - Tumor Growth
  - Progression - Invasion/Metastasis

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Estrogens and Cancer Risk

- ER-α promote breast cell proliferation
- ER-β inhibit proliferation and prevents breast cancer development via G2 cell arrest
  - Estradiol equally activates ER-α and ER-β
  - Estrone selectively activate ER-α at a ratio of 5:1
  - Estriol selectively binds ER-β at a ratio of 3:1
  - Components of CEE selectively bind to ER-α are potent down regulators of ER-β
    - Most carcinogenic potential

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The Debate -Conclusions

- Based on both physiological results and clinical outcomes, current evidence demonstrates that bioidentical hormones are associated with lower risks than their nonbioidentical counterparts.

- The current evidence clearly dictates that bioidentical hormones are the preferred method of HRT.

- A thorough review of the medical literature supports the claim that bioidentical hormones have some distinctly different, often opposite, physiological effects to those of their synthetic counterparts.

- With respect to the risk for breast cancer, heart disease, heart attack, and stroke, substantial scientific and medical evidence demonstrates that bioidentical hormones are safer and more efficacious forms of HRT than commonly used synthetic versions.

Medroxyprogesterone Acetate

- Only mimics the actions of progesterone in the uterus
  - Offsets entirely the lipid profile and cardio protective benefits provided by estrogen
  - WHI showed that MPA significantly increased the risks of heart attacks, stroke, blood clots, and breast cancer
    • Consistent significant increase in risk of breast cancer
  - Increases the estrogen induced proliferation of breast tissue
    • Increases breast cancer risk added to any estrogen

MPA vs. Progesterone

- MPA :Cardiovascular risks
  - Increases the risk of heart attack and stroke
  - Causes a reduction in HDL
  - Increases vasoconstriction and coronary artery spasm
  - Promotes formation of atherosclerotic plaque
  - Increases the risk of hypertension

- Progesterone
  - Exact opposite effects

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Thromboembolism

- Increased by
  - Oral estrogen therapy
  - Synthetic progestins

- Not increased by
  - Transdermal estradiol
  - Oral or transdermal progesterone

Is BHRT Safer?

- Studies have shown that the combination of estradiol and progesterone at physiological levels has a significantly lower risk of breast cancer

- The PEPI study showed a significant difference with progesterone compared to MPA and the writers concluded that we should be giving women natural progesterone

Is BHRT Safer?

- Progesterone acts synergistically with estradiol to provide the best cardiovascular protection

- Progestin side effects (increased seizures, insomnia, nervous disorders, depression) have health risks not seen with progesterone
  - MPA produces the exact opposite action of progesterone everywhere but the uterus.
Summary

Bioidentical vs. Synthetic Hormones

• Synthetic progestins show increased estrogen-induced breast tissue proliferation and a risk for breast cancer, whereas progesterone inhibits breast tissue proliferation and reduces the risk for breast cancer.

• In cardiovascular disease, synthetic progestins, as opposed to progesterone, negate the beneficial lipid and vascular effects of estrogen.

• Transdermal bioidentical estrogen and progesterone are associated with beneficial cardiovascular and metabolic effects compared with the use of oral estrogens (especially CEE) and synthetic progestins.

Bio-identical Hormones

• The term “bio-identical” indicates that the chemical (molecular) structure of the replacement hormone is identical to that of the hormone that exists intrinsically in the human body.

Physiologic Bio-identical Hormone Restoration Therapy

• The goal of BHRT is to restore hormone levels to the normal physiological level of a younger individual to provide the protective benefits of the hormones to the entire system.
Objectives of Balanced Hormone Restoration

• #1: Treat the symptoms of Menopause or Andropause
• #2: Protection of various body systems
  – Cardiovascular
  – Lipid Profile
  – Blood Pressure
  – Nervous system
  – Immune system
  – Bones and muscles
  – Eyes, skin, hair, etc.

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
• Goal should be to use the lowest amount of hormone required to achieve physiological level and control symptoms
  – Be conservative: dose low and go slow on changes
• Follow up: monitor symptoms and levels

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

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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
- Symptoms of different imbalances often overlap
- Symptoms of excess of any hormone reflect symptoms of deficiency of that hormone

Menopausal Signs & Symptoms

- Hot flashes
- Hair loss
- Dry skin
- Sleep disruption
- Night sweats
- Anxiety
- Vaginal dryness
- Vaginal atrophy
- Foggy Thinking
- Weight Gain
- Irritability
- Memory loss
- Depression
- Nervousness
- Diminished sex drive
- Painful intercourse
- Urinary incontinence
- Heart palpitations
- Loss of scalp hair
- Unwanted hair growth

Andropause Sign & Symptoms

Apathetic, burned out
Loss of muscle mass
Erectile Dysfunction
Weight gain in waist
Low Stamina
Sleep disturbances
- Decreased urine flow
- Depression
- Mental fatigue
- Night sweats
- Low libido
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, especially in early to mid perimenopause include:
  Low Progesterone  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 of any hormone reflect symptoms of deficiency of that hormone
  – The symptoms of too much of a hormone can closely mimic the symptoms of too little
  – Function of receptor response to hormone level
  – Delayed response to excessive hormone
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 symptoms return
    - An increase in dose results in the same sequence of events
- Same sequence of events occurs with most hormones
  - Difference is timing

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
• Higher than normal physiologic level of progesterone:
  • Inhibits insulin secretion
  – Increases insulin resistance (antagonizes insulin)
  – Leads to hypothyroidism
  – Decreases immune function
• Other “reversals” of normal function??

Thanks for Listening!

Jim Paoletti, RPh, FAARFM

ejpaoletti@zrtlab.com
503-597-1865

Which of the following statements is true concerning hormone therapy and the risk of breast cancer?
a. Conjugated Equine Estrogens increase risk in all woman
b. Progestins increase the risk when added to estrogen therapy
c. Synthetic Progestins have been consistently shown to increase risk
d. Progesterone in associated with a decreased risk
e. All of the above

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Which of the following statements is true concerning hormone therapy and the risk of breast cancer?

a. Conjugated Equine Estrogens selectively bind the proliferative ER
b. Conjugated Equine Estrogens downregulate anti-proliferative ER
c. Synthetic Progestins have been consistently shown to increase risk
d. Progesterone is associated with a decreased risk
e. Answers (a) and (c)
f. All of the above

Down regulation of hormone receptors:

a. Occurs relatively rapidly for most hormone
b. Is caused most commonly be a deficiency of hormone
c. Is caused by supraphysiologic levels of hormone
d. Is independent of hormone dosage
e. All of the above

The risk of venous thromboembolism has been shown to be increased by

a. Oral estrogens
b. Transdermal estradiol
c. Oral Progesterone
d. Synthetic progestins
e. Answers (a) and (d)
f. All of the above
Basic dosing principles to consider with hormone restoration therapy include

a. Use of symptoms alone to determine hormone requirements will result in optimal therapeutic response
b. If hormone restoration therapy does not resolve the symptoms first, then lifestyle changes should be considered.
c. The symptoms of excess of a hormone reflect the symptoms of deficiency of that hormone
d. Levels of hormone indicate when and how much hormone should be dosed
e. Answers (a) and (c)