



BIOIDENTICAL HORMONE REPLACEMENT THERAPY

GARY DONOVITZ MD, FACOG
NASEM COMMITTEE NOVEMBER 12, 2019



OVERVIEW

1. Women's Health Initiative: *Establishing the need for HRT*
2. The Hormone Challenge: *Our hormone levels will decline, putting us at risk for disease*
3. Hormone Replacement Therapy: *Treating the decline in hormone levels*
4. 30 Years of Clinical Experience: *What I have seen in my career*



KEY CONCEPTS

I hope to convey 4 main points to the committee:

1. **Safe and Effective.** Research and clinical experience show that bioidentical hormones are safe and effective, and the adverse effects that have been seen in the past from hormone replacement therapy (HRT) stem from the use of synthetic hormones.
2. **Compounds are Necessary.** Hormones are inherently idiosyncratic, which means bioidentical HRT (BHRT) is a form of personalized medicine that requires practitioners to evaluate each case individually. As such, practitioners need the flexibility that compounded (as opposed to commercial) bioidentical hormone products can offer.



KEY CONCEPTS

- 3. Practitioner Discretion and Education.** Because of the idiosyncratic nature of hormones, patients necessarily rely upon the judgment and analysis of practitioners. We need to continue to empower practitioners to work with their patients to proactively address their individual healthcare needs and desires, and part of that process includes educating practitioners on BHRT.
- 4. Regulatory Oversight Welcomed.** BHRT is making its way to the forefront of medicine as it gets adopted by an increasing number of practitioners who come from a wide array of specialties. We BHRT practitioners want to make sure that the compounded products we use are made pursuant to the heightened specifications we require (i.e., standards that are more stringent than those of commercial products) and are of the highest quality. We therefore welcome FDA oversight of BHRT compounders and appreciate this committee's deep dive into the industry.

I'm providing you with this slide deck as a resource and invite any questions from the committee or any of its members either during this session or after. I have included my contact information on the final slide. I look forward to being part of this process.



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- Board Certified Obstetrician-Gynecologist
- Tulane University – Chief Resident
 - Isadore Dyer Award Best Teaching Resident
- Fellow of The American Congress of Obstetricians and Gynecologists
- Institute For Hormonal Balance – Medical Director
- BioTE Medical – Founder and Chairman
- International Consensus Committee on Testosterone Use in Women – Chairman
- Post-graduate training and 30+ years of experience in advanced HRT and bioidentical hormone optimization
- Treated over 20,000 patients using advanced HRT and bioidentical hormone optimization therapies
- International lecturer on BHRT for 10+ years





WOMEN'S HEALTH INITIATIVE

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WOMEN'S HEALTH INITIATIVE: OVERVIEW & CONSEQUENCES

- In 2002, a WHI study found that taking estrogen plus progestin hormone replacement therapy increased a woman's risk of heart disease and breast cancer. Then, 2 years later, a second WHI study concluded that taking estrogen alone also increased the risk of stroke, dementia, and other conditions. Overall, the WHI studies concluded that HRT caused a:
 - 41% increase in strokes
 - 29% increase in heart attacks
 - 26% increase in breast cancer
 - 76% increase in Alzheimer's Dementia
 - 200% increase in the rate of blood clots





WOMEN'S HEALTH INITIATIVE: OVERVIEW & CONSEQUENCE

- The number of women using HRT dropped considerably after the initial WHI study in 2002. This decline had notable consequences. For example, during the during the 10-year period immediately following that study, **mortality rates in women increased** as 18,000 to 91,000 women were determined to have died prematurely as a result of estrogen avoidance. In addition, there was a notable increase in female mortality from acute myocardial infarctions and breast cancer.
- Despite the WHI studies, there was still a clinical need to have some form of HRT, and as a result, serious practitioners have turned to BHRT and experienced overwhelmingly positive results.



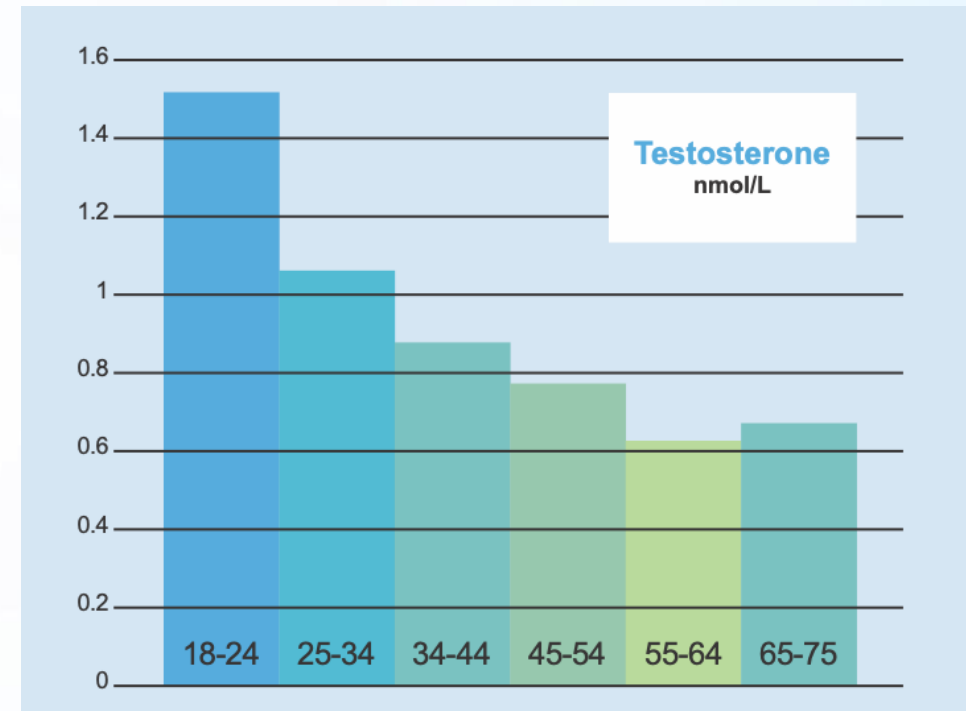
THE HORMONE CHALLENGE

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THE HORMONE CHALLENGE: TESTOSTERONE LOSS

- Androgens peak in women in their twenties.
- Low testosterone in women creates an increased risk for:
 - Alzheimer's Disease
 - Cardiovascular Disease
 - ORF
 - Diabetes Mellitus
 - Possibly Cancer

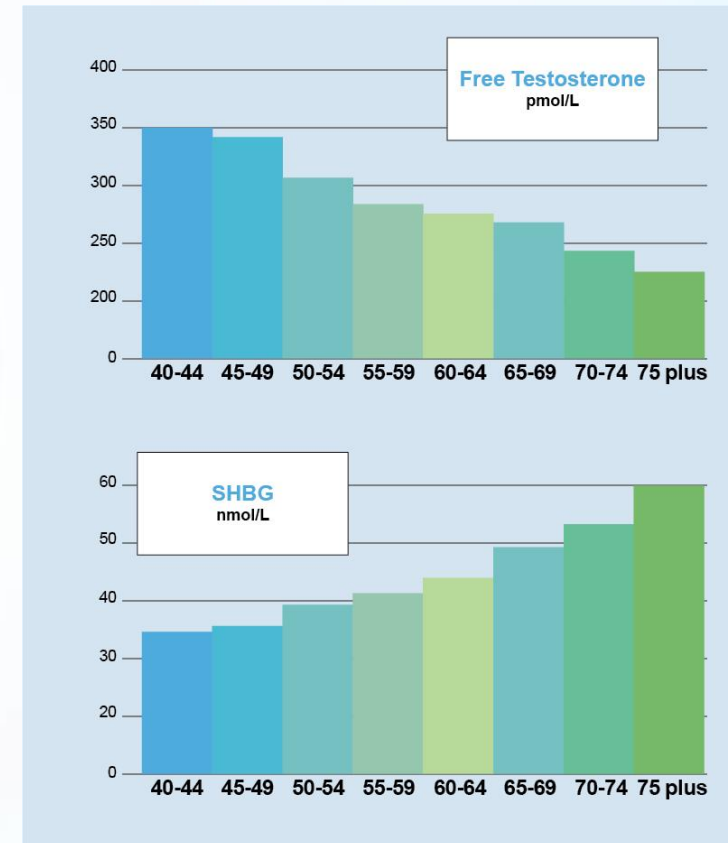


Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab. 2005;90:3847-3853



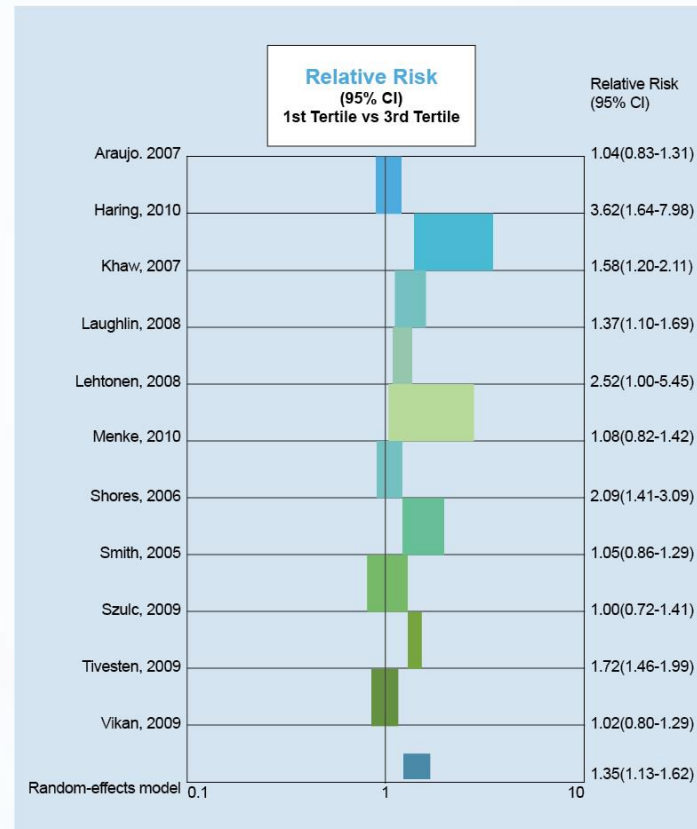
THE HORMONE CHALLENGE: TESTOSTERONE LOSS

- Androgens peak in men in their mid 30s: 17% drop each decade thereafter.
- Low testosterone in men creates an increased risk for:
 - Alzheimer's Disease
 - Cardiovascular Disease
 - ORF
 - Diabetes Mellitus
 - Possibly increased risk for prostate cancer
 - Sarcopenia





LOWER TESTOSTERONE LEVELS: HIGHER ALL-CAUSE MORTALITY

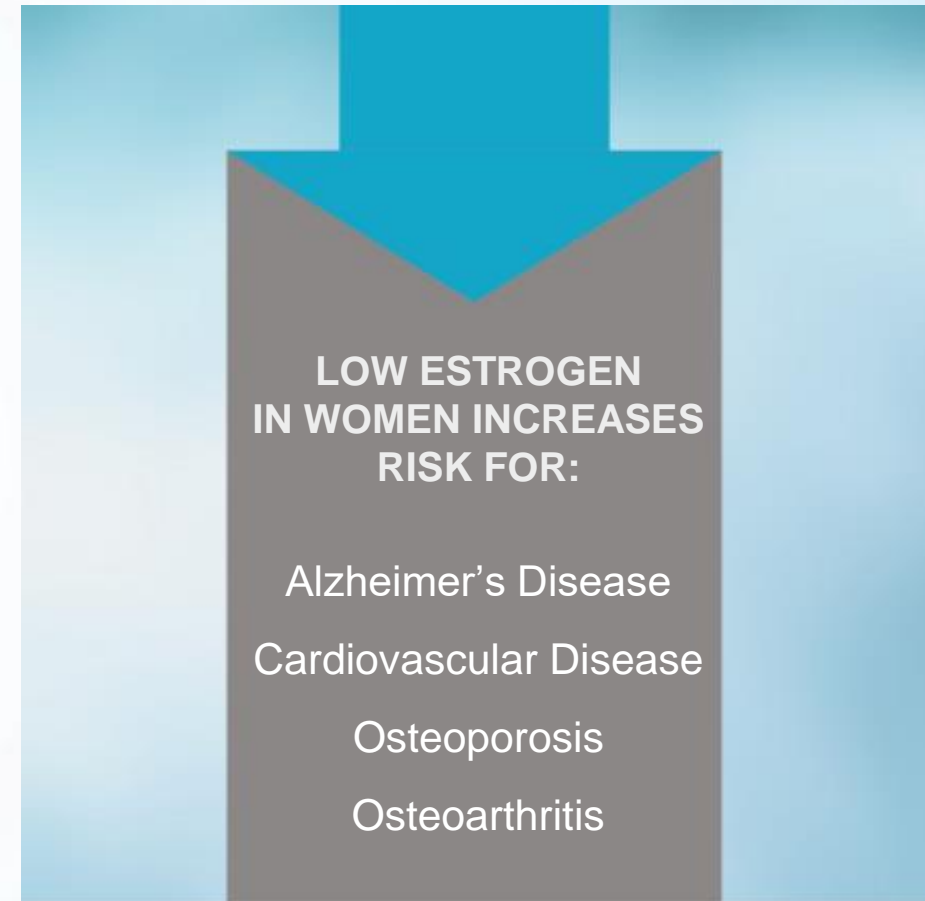


Harman SM, JCEM 2001; 86:724-31



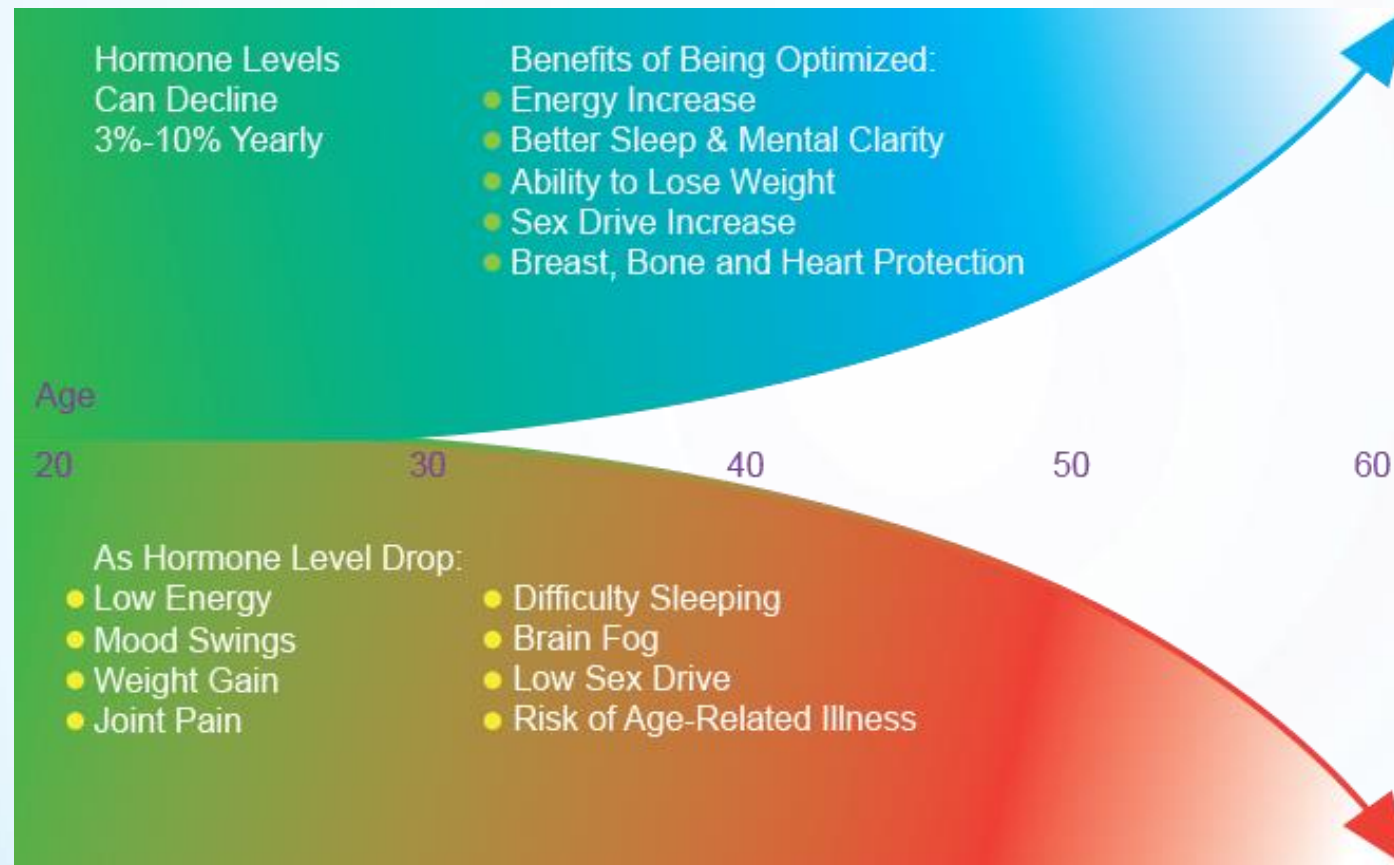
THE HORMONE CHALLENGE: ESTROGEN LOSS

- In 2003, WHI reported that estrogen did not have a “clinically meaningful effect on quality of life.”
- The majority of patients in WHI had non-symptoms and were intentionally selected for their lack of symptoms. Only 13% had significant symptoms.
- ERT has significant improvement in menopausal symptoms, whereas DBRCT using black cohosh, and other alternatives failed to provide a benefit.





HORMONE PRODUCTION LEVELS AND OPTIMIZATION IN MEN AND WOMEN



Davison SL, Bell R, Donath S, Montalto JG, Davis SR. Androgen levels in adult females: changes with age, menopause, and oophorectomy. J Clin Endocrinol Metab. 2005;90:3847-3853



HORMONE REPLACEMENT THERAPY

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HORMONE REPLACEMENT THERAPY: PERSONALIZED PREVENTATIVE MEDICINE

- Hormones are idiosyncratic. HRT is therefore a personalized therapy that requires practitioners to evaluate each patient individually, make case-by-case clinical determinations, and provide unique, customized treatments.
- The North American Menopause Society recognizes that HRT should be individualized for each patient and requires periodic reevaluation for risks and benefits of the selected therapy.
- HRT is *NOT* a one-size-fits-all treatment.



HORMONE REPLACEMENT THERAPY: PERSONALIZED PREVENTATIVE MEDICINE

HRT is fundamentally preventative medicine. In particular, HRT has proven to be helpful in preventing:

- Osteoporosis
- Heart Disease
- Cognitive Decline and Alzheimer's Disease
- Likely Breast Cancer

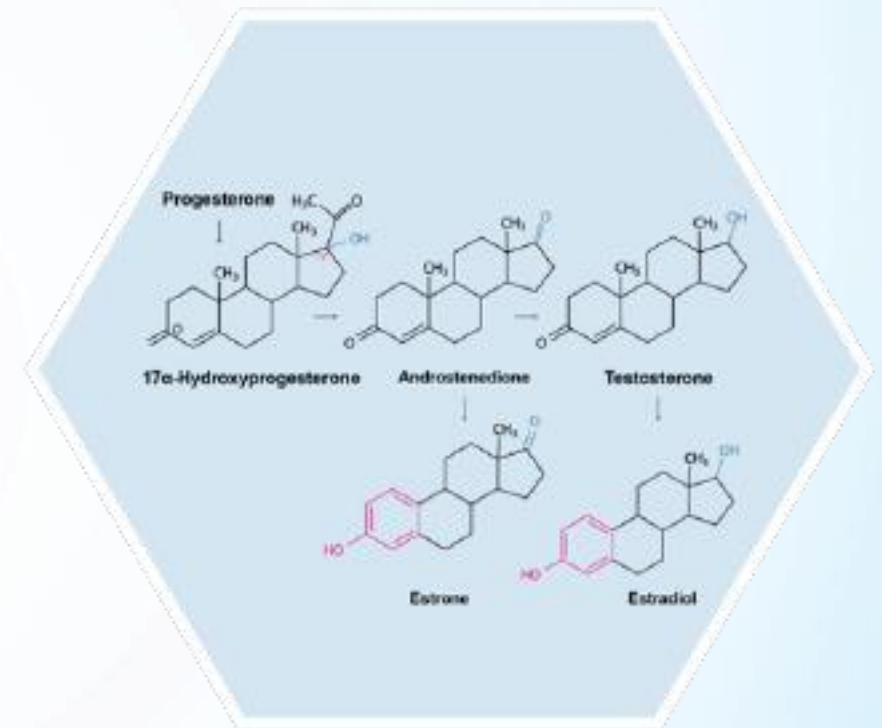


Figure 26.31. Biochemistry, Seventh Edition.
©2012 W.H. Freeman and Company



HORMONE REPLACEMENT THERAPY: BIOIDENTICAL VS. SYNTHETIC HORMONES

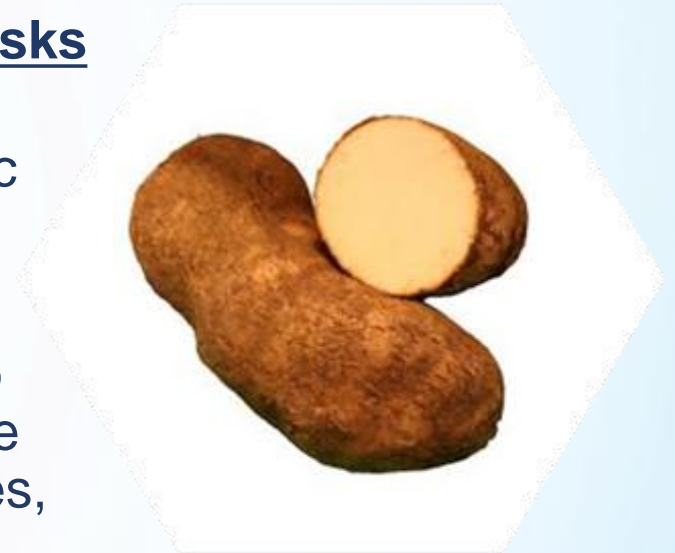
Bioidentical hormones are synthesized by chemically extracting diosgenin from plants such as yams and soy. Plants do not make hormones, but diosgenin, a compound that yams and soy do make, is very similar. Diosgenin is chemically modified to yield the precursor progesterone, which is then used to synthesize bioidentical estrogens and androgens. Bioidentical hormones are, therefore, hormones of a biological origin that are chemically modified to be structurally indistinguishable from the human hormone.





HORMONE REPLACEMENT THERAPY: BIOIDENTICAL VS. SYNTHETIC HORMONES

- Physiological data and clinical outcomes demonstrate that **bioidentical hormones are associated with lower risks** (including the risk of breast cancer and cardiovascular disease) and are **more efficacious** than their synthetic and animal-derived counterparts.
- Because **bioidentical hormones are structurally identical to endogenous hormones**, they are able to bond with human hormone receptors in the exact same manner as endogenous hormones. Synthetic hormones, by contrast, are dissimilar to endogenous hormones except for the portion of their chemical structure that binds to the human body's receptors.



The bioidentical hormone debate: are bioidentical hormones (estradiol, estriol, and progesterone) safer or more efficacious than commonly used synthetic versions in hormone replacement therapy? (www.ncbi.nlm.nih.gov/pubmed/19179815)



HORMONE REPLACEMENT THERAPY: BIOIDENTICAL VS. SYNTHETIC HORMONES

- Because **synthetic hormones have a different chemical structure**, the synthetic hormone molecule may bind to the human hormone receptors in one tissue but not in others, and it might bind to other receptors that the endogenous hormone will not.
- The failure of synthetic hormones to bind with all of the same receptors as endogenous hormones, as well as their binding to other non-endogenous hormone receptors, creates adverse effects (e.g., tumors).





HORMONE REPLACEMENT: COMPOUNDED BHRT PRODUCTS THERAPY

- Compounded Products allow HRT practitioners to:
 - Accurately dose patients
 - Customize medication based on patients' individual, specific needs
 - Use medications with higher quality standards than are offered by (or required of) commercial manufacturers (e.g., lower potency variations)
 - Have significantly greater access to medications required by their therapies





HORMONE REPLACEMENT THERAPY: COMPOUNDED BHRT PRODUCTS

- Commercially available products are best suited for conditions that consistently present across the majority of the population within a narrowly defined range of symptoms.
- There are relatively few commercially available BHRT medications currently available on the market, presumably because BHRT treatments are highly personalized and therefore pharmaceutical companies do not perceive it as a space suitable for FDA approval.





HORMONE REPLACEMENT THERAPY: COMPOUNDED BHRT PRODUCTS

- Given the preventative nature of HRT and the lack of a standardized patient condition that requires HRT, **compounded products are the natural fit.**
- BHRT is personalized medicine and compounded medications provide practitioners with the **flexibility** necessary to provide treatment that, in their clinical opinions, is optimal for the health of each of their patients.





30 YEARS OF CLINICAL EXPERIENCE

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NASEM COMMITTEE NOVEMBER 12, 2019



30 YEARS OF HRT EXPERIENCE: LITERATURE

- BHRT is improving overall health as it combats diseases such as osteoporosis, heart disease, cognitive diseases, and breast cancer.
 - **Osteoporosis**. Of women over the age of 50, approximately 1 in 7 has osteoporosis, and about 1 in 2 can expect to suffer an osteoporosis-related fracture in their lifetime. After a hip or vertebral fracture, direct and indirect mortality rates can be as high as 25% to 30%.⁽¹⁾
A 1990 study on the bone density and the impact of subcutaneous estradiol and testosterone hormone implants established that testosterone works as a “bone builder” as it helped to increase bone density in subjects. That same study demonstrated showed that subcutaneous testosterone pellets increased bone density by 8.3% per year compared to just 1-2% for oral estrogen.⁽²⁾



(1) A.B.O.G 2014 MOC

(2) STUDD, J WW, ET AL (1990), *AM JOURNAL OB/GYN* 163, 1474-1479



30 YEARS OF HRT EXPERIENCE: LITERATURE

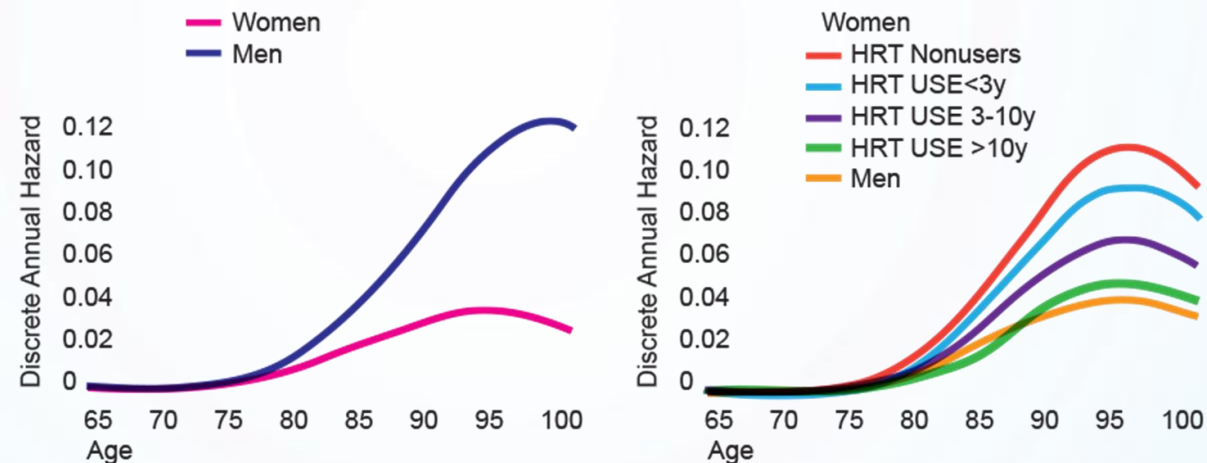
- **Cardiovascular**. It has been established that not only does transdermal HRT not increase the risk of venous thromboembolism or stroke, but is, in fact, cardioprotective as it significantly reduces the incidence of myocardial infarction.⁽⁶⁾





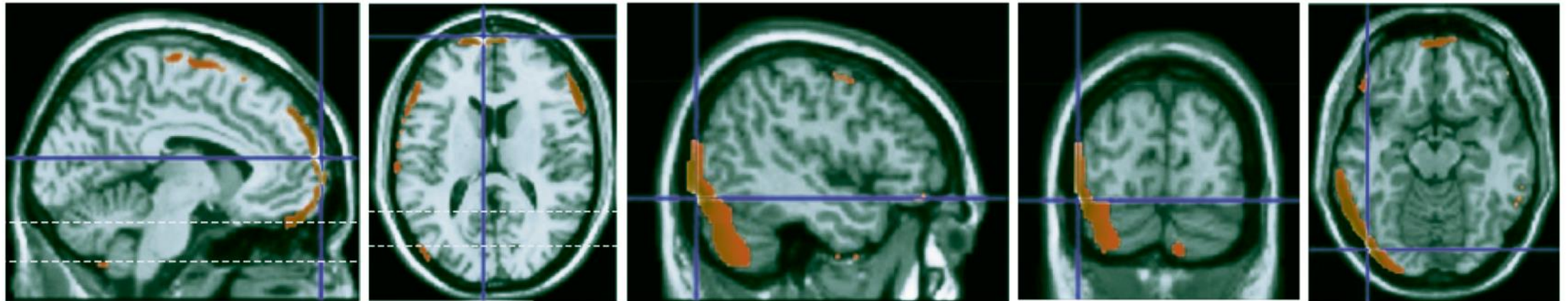
30 YEARS OF HRT EXPERIENCE: LITERATURE

- **Neurodegenerative Conditions.** Silverman et al looked at 17B Estradiol vs C.E.E. vs C.E.E. plus progestin on cerebral metabolic activity. Their conclusion was that verbal memory in patients receiving BHRT treatments was 3 standard deviations better than those who were not on it. The deterioration of verbal memory is an early predictor of Alzheimer's disease.





30 YEARS OF HRT EXPERIENCE: LITERATURE



Bilateral medial metabolism (pictures 1 and 2) and left temporo-occipital metabolism (pictures 3,4 and 5) were significantly preserved in HT+ women who were ApoE-e4 negative compared to HT- women who were ApoE-e4 negative.

Color voxels shown have significance of $p < 0.001$.



30 YEARS OF HRT EXPERIENCE: LITERATURE

Below is a table that shows the effect of hormones on biochemical reactions associated with Alzheimer's Disease:

	Alzheimer's Disease	Testosterone	Estradiol	Progesterone 10 days every 30 Days
Beta Amyloid	↑ Increases	↓ Decreases	↓ Decreases	↓ Decreases
42/40 Ratio	↑ Increases	↓ Decreases	?	?
Alpha Secretase	↓ Decreases	↑ Increases	↑ Increases	?
Beta Secretase	↑ Increases	↓ Decreases	↓ Decreases	?
Gamma Secretase	↑ Increases	?	?	?
Nepriylsin	↓ Decreases	↑ Increases	↑ Increases	?
Hyperphosphorylated Tau Protein	↑ Increases	↓ Decreases	No Effect	↓ Decreases
Brain Cell Glucose Metabolism	↓ Decreases	↑ Increases	↑ Increases	?
Blood Flow to the Brain	↓ Decreases	↑ Increases	↑ Increases	?



30 YEARS OF HRT EXPERIENCE: MY PRACTICE

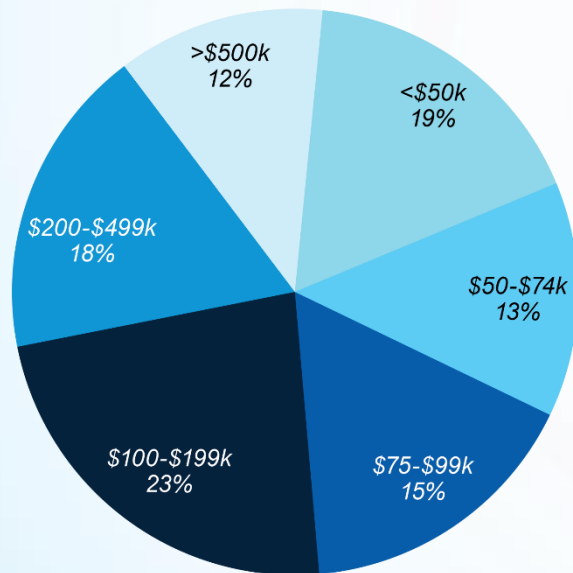
- Since 2006, I have performed over 66,000 subcutaneous bioidentical hormone pellet procedures on more than 20,000 patients.
 - 95% of my patients having their hormones optimized after their first round of therapy.
 - < 1% complications
- My patients include:
 - Premenopausal women with TI
 - Menopausal women with TI
 - Males with TI
 - Breast cancer survivors
 - Patients whose symptoms were not effectively treated with commercially available products
 - Patients seeking to reduce their risks for disease, most notably cardiovascular disease



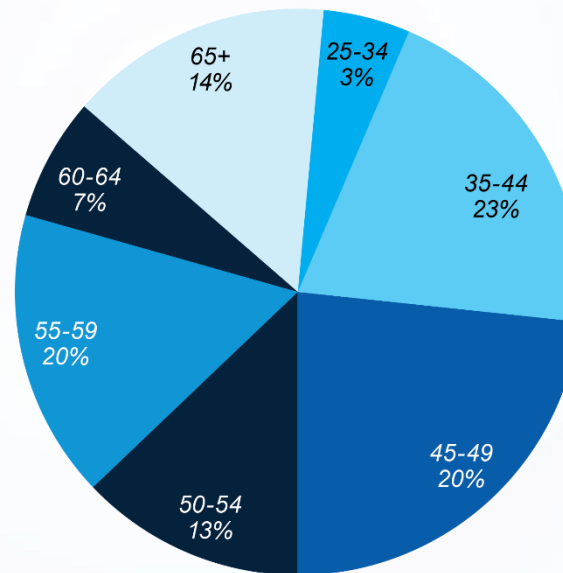
30 YEARS OF HRT EXPERIENCE: MY PRACTICE

Patient demographics:

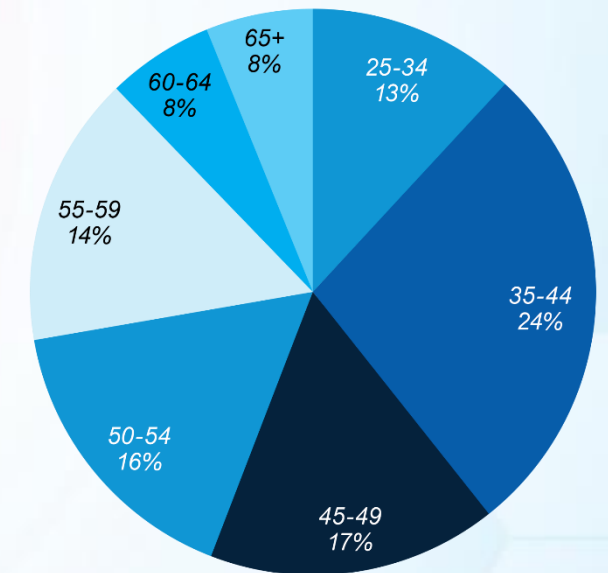
Patient Annual Household Income Levels



Male Patients by Age



Female Patients by Age





30 YEARS OF HRT EXPERIENCE: RESEARCH

- IRB approved retrospective study of 1.2 million pellet procedures using Testosterone in men and women and Estradiol in women to examine complications and secondary responses.
- Prospective 10-year study on Breast Cancer Incidence following testosterone with and without estradiol therapy using sub-cutaneous hormone pellet implants.
 - 41,000 insertions – 20% males; 80% females
 - Total females = 32,800 insertions; avg frequency = 4 months
 - 8,111 female patients – total 18 breast cancers; 0 mortality
- Prospective validation of a Male Health Assessment and Female Health Assessment to evaluate Hormone deficiency symptoms and to validate that testosterone is an insulin sensitizer in females as it is in males.



30 YEARS OF HRT EXPERIENCE: RESEARCH

- Female Consensus Committee Resolutions:
 - RESOLUTION 1: Testosterone is not a male-exclusive hormone. It is the most abundant gonadal hormone throughout a woman's life.
 - RESOLUTION 4: Testosterone therapy may be breast protective.
 - RESOLUTION 5: Testosterone insufficiency in women negatively affects sexuality, general health, and quality of life. Testosterone supplementation may positively influence sexuality, general health, and quality of life.
 - RESOLUTION 6: Testosterone insufficiency may be associated with an increased risk of CVD in women.



30 YEARS OF HRT EXPERIENCE: RESEARCH

- Male Consensus Committee Resolutions:
 - RESOLUTION 1: TD is a well established, significant medical condition that negatively affects male sexuality, reproduction, general health, and quality of life.
 - RESOLUTION 7: The evidence does not support increased risks of CV events with T therapy.
 - RESOLUTION 8: The evidence does not support increased risk of PCA with T therapy.



KEY TAKEAWAYS & CONTACT INFORMATION

GARY DONOVITZ MD, FACOG
NASEM COMMITTEE NOVEMBER 12, 2019



KEY TAKEAWAYS

My hope is that my comments today have helped show that:

1. Research and clinical experience alike have established that bioidentical hormones are **safe and effective**.
2. With hormones being highly idiosyncratic, and with BHRT therefore being rooted in personalized medicine, **compounded bioidentical hormones are essential** to the continued safe and effective use of BHRT treatments.
3. We need practitioners to be proactive about their patients' health, which means **allowing educated practitioners to rely on their case-by-case clinical judgments** to treat patients.
4. Practitioners want BHRT to be a safe, well-respected industry, and to that end, **outsourcing facilities have been instrumental** in ensuring that we can receive compounds that are made under the highest-quality standards and pursuant to FDA regulations.



BIOIDENTICAL
HORMONE
REPLACEMENT
THERAPY

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CONTACT INFORMATION

I'd like to thank each of you individually and the committee as a whole for hearing my comments today. I support your evaluation of BHRT and its compounded products and look forward to further assisting you however I can. If I can be of any assistance to this committee after today's hearing, please do not hesitate to reach out to me.

Gary S. Donovanitz M.D., FACOG

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THANK YOU

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