Nuts & Bolts of Sex Hormone Therapy
Diagnoses, Treatment, Ethical & Legal Implications of Sex Hormone Therapy in Women and Men

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Objectives

Overview the role of sex hormones and sex hormone therapy in all body systems: neurological, cardiovascular, psychological, musculoskeletal and reproductive.

Review of the recent hormone therapy clinical guidelines such as NAMS, ACOG, EJOG, European Endocrine Society and the Endocrine Society.

Presentation of various hormone replacement modalities (creams, oral, injections, sublingual, subcutaneous) dosing, prescribing pearls and clinical management.

Ethical and legal implications of hormone therapies including prudent clinical documentation, informed consent and off label prescribing.

Understanding of the importance of this knowledge across disciplines and specialties.

Clinical case studies

Confirmation Bias

Confirmation bias is a phenomenon wherein decision makers have been shown to actively seek out and assign more weight to evidence that confirms their hypothesis, and ignore or under weigh evidence that could disconfirm their hypothesis.

Confirmation bias role in inaccurate medical diagnosis and decision making is well documented.

To avoid confirmation bias, we must be committed to lifelong learning, be open to new perspectives and be ready to defend our decision making with the evidence.

My Journey

MENOPAUSE & ANDROPAUSE

FORGETFULNESS -- MOOD SWINGS --
HOT FLUSHES -- DEPRESSION --
NAUSEA -- LACK OF FOCUS
HEART PALPITATIONS -- INSOMNIA --
IRRREGULAR PERIODS --
VAGINAL DRYNESS -- WEIGHT GAIN --
JINTACHES & PAIN --
-- DECREASED MOTIVATION
-- LOW ENERGY
-- MUSCLE LOSS
-- MILD TO MODERATE ERECTILE DYSFUNCTION
-- BONE LOSS --
-- MUSCLE LOSS
**Stages of Menopause:**
Based on Stages of Reproductive Aging Workshop (STRAW)*

**Perimenopause—lasts 2-8 years**
- Early menopause transition
  - Intense hot flashes
  - Frequent mood fluctuations
  - Women report they feel “crazy”
- Late menopause transition
  - More within a group of 50

- Amenorrhea greater than 60 days
- Relationship decline in all areas of life reported

**Pre-menopause—lasts 1-2 years**
- Late menopause transition
- No change in overall health
- Menopausal symptoms only
- Intense mood fluctuations
- Women report feeling “crazy”

**Menopause**
- A single day in time, defined as 12 months S/P last menstrual cycle

**Post Menopause**
- Early post menopause
  - Lasts on average 5 years
- Vasomotor symptoms, urogenital symptoms and psychosomatic symptoms
- Relationship decline in all areas of life reported

**The Women’s Health Initiative (WHI)**

**Why talk about it?**
- The largest research trial to date focused on women’s health
- Post WHI trial results were published, when people talked about hormone therapy
- The WHI focused overall on strategies for preventing disease in postmenopausal women:
  - Heart disease
  - Breast + colorectal cancer
  - Osteoporosis fractures

**What was the focus? Outcomes?**
- Primary Outcomes
  - Invasive breast cancer
  - Endometrial cancer
- Secondary Outcomes
  - Venous thromboembolism (VTE)
  - Pulmonary embolism (PE)
  - Osteoporosis hip + other fractures

**WHI Reporting Impact**
- Results not reported in a way that focused on the original question
- Findings published in journals that women of all ages and not stratified by age and health risk
- Frequency of obesity was above population average (250% mortality)
- Risk of cardiovascular disease resulting in many patients going untreated

**Clinical Practice Impact**
- Extrapolated to all hormone therapy
- Prescriptions for the study therapies declined
- Prescriptions for conjugated equine estrogen (CEE) dropped
- Providers hesitated to treat symptomatic women transitioning into menopause with MHT resulting in many patients going untreated
Undoing the Damage of the WHI reports

There are two obvious and immediate actions to be called for:

1. The Food and Drug Administration (FDA) needs to revisit the black-box warnings on postmenopausal hormones. Specifically, there needs to be a separation of the advisories for estrogen alone from estrogen and progestogen combined use.

2. Justification is given to call for an independent commission to scrutinize every major WHI paper to determine whether the data justified the conclusions drawn.

"Women progressing through and beyond menopause in the next decade need to be spared the unnecessary harm that may have been inflicted on their sisters of the previous decade."


Current Clinical Practice Impact

The Conversation is FINALLY Changing

- The NAMS Advisory Panel and NAMS Board of Trustees (2017) recognize that the WHI is the largest and longest randomized, blinded trial ever performed, but the findings cannot be translated to women with early (under 63 years) menopause initiating hormone therapy.
- The WHI trial participants were on average older than 63 and >25 years post-menopause.
- There is no evidence to support routine discontinuation of hormone therapy after age 65.


To link to this article: https://doi.org/10.1080/13697137.2017.1346380

Current Treatment Guidelines

Females

- Individualized approach
- No longer “lowest dose for shortest period of time”
- Use evidence-based information to determine the appropriate type, dose, formulation, route, and duration.
- Should be based on the unique health risks of the woman and the goals of therapy.

ACOG guidelines suggest alternative forms of estrogen and progestin to those investigated in the WHI for vasomotor symptom relief:
- May be associated with different risks and stroke/VTE profiles than CEE and CEE+MPA.


To link to this article: https://doi.org/10.1080/13697137.2017.1346380

What’s missing from the conversation?

Androgen insufficiency in women and the impact on HRQOL.

From Testosterone Replacement Therapy (TRT) to Andropausal Hormone Therapy

Available Clinical Guideline for Male HRT

The Sex Hormones

- Estradiol, Progesterone AND Testosterone
- Hormone receptors are present on EVERY cell in the human body.
- Specifically androgen (testosterone) receptors are present in every body system.

TOTAL T less than 300 considered NORMAL.
Understand the Nomenclature

- Estrogen vs. Estradiol
- Progesterone vs. Progestins
- Androgens, testosterone, DHT
- SHBG (sex hormone binding globulin)
- FSH (follicle stimulating hormone)
- Pregnenolone

Sources of Sex Hormones

**Endogenous Production:**
- Estrogen & Testosterone
- Adrenals (majority of hormone production)
- Adrenals produce some estrogen and testosterone via DHEA post-menopause
- Estradiol also produced by fat cells (increased fat cells = increased estrogen)
- Estradiol aromatized from testosterone

**Exogenous Sources:**
- HRT or OCP
- Hormones in our food supply (meat/dairy: estrogens)
- Environmental or Xynoestrogens
  - Food Supply
  - Water Supply
  - Medicines
  - Chemicals
  - Domestic Products
  - Make Up
  - Dryer sheets

Estrogen:

- Synthesized from cholesterol by the ovaries, and to a lesser extent, the adrenal glands.
- Not limited to maintenance of female reproductive function.
- Distributed via the blood to a variety of tissues, including the cardiovascular, immune, and central nervous systems.
- Due to their lipophilic nature, can easily diffuse across cellular membranes, as well as the blood-brain barrier.
- Elicit their actions through interaction with an estrogen receptor (ER).
- 17β-E2 is the most potent estrogen in circulation.

Benefits of Estrogen

- Decreases LDL/increases HDL
- Increases energy and vitality; stamina and motivation
- Prevention of:
  - CAD
  - Alzheimer’s (beta amyloid production prevention)
  - Depression and mood disorders
  - Urogenital atrophy
  - Sexual dysfunction
  - Sleep disturbance
  - Colorectal cancer
  - Vitiligo
  - Age-related macular degeneration
  - Mental clarity, memory, cognition
  - Tooth loss/gingival atrophy
Diagnosing Estrogen Insufficiency in Females

**Menstrual cycles**
- Pre-menopause
- Post-menopause

**FSH Labs**
- Greater than 25 indicates estrogen fluctuations/insufficiency

**Estradiol labs**
- 70-100

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Estrogen & Men

Estrogen in men protective.

Don’t over block with AI.
- Important as many T centers put most men on E2 blockers regardless
- E2 also balances “rage” effect of very high T levels.
- Activity of aromatase is critical for E2 biosynthesis; this enzyme is widely expressed in the brain when is located both at presynaptic and postsynaptic sites.

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Symptoms & Impact: Females

**Employment**

**Relationships**

**Informal caregiving: children, spouse, parents**

**Home life/responsibilities**

Menopause transition brings many emotional and cultural implications.

Women don’t necessarily associate their symptoms with hormone changes.

Symptoms can be vague and close down clinical conversations – especially during peri-menopause, which can last 10 years.

Many women think they are going “crazy.”

Only 10% of women with symptoms seek medical advice.

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The Cost of HT (ET) Discontinuation

- Discontinuation of postmenopausal HT (estrogens) may be associated with increased risk of cardiac and stroke death in the first post-treatment year.
- Increased cardiovascular death rate question the safety of annual HT discontinuation practice to evaluate whether a woman could manage without HT.
- Reduction in mortality in postmenopausal women taking hormone therapy compared with no/stopped treatment.
- Discontinuing postmenopausal HT (estrogenswithdrawal) results in the loss of the beneficial effects of HT on organs and tissues across the human body, such as the cardiovascular and skeletal systems.

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Progesterone

- Synthetic
  - Progestins
  - Progestagens
- Natural/Bioidentical
  - Progesterone
  - Prometrium

Unfortunately, the synthetic Progestins are often misnamed “Progesterone” which causes confusion.
**Progesterone**

Natural progesterone (MP)(OMP) protects against uterine and breast carcinoma, osteoporosis, fibrocystic disease, ovarian cysts, ovarian CA, CAD.

Synthetic progestins (MPA) frequently cause bloating, headache, fatigue, weight gain, depression, increased symptoms of PMS by stimulating the estrogen receptor, CAD, CVD, DVT, PE, dementia, CA, DM.

Micronized progesterone (MP) is not associated with any of these complications.

**Testosterone**

Testosterone is not just for men!

Emerging data supports the greater role androgens, primarily testosterone, play in neuropsychology.

**Androgen Insufficiency: Clinical Signs and Symptoms**

- Loss of energy/fatigue
- Loss of mental clarity/focus
- Loss of muscle mass
- Weight gain
- Decreased exercise tolerance
- Increased recovery time from exercise
- Anxiety
- Depression
- Irritability
- Headaches
- Insomnia
- Decreased libido

**Benefits of Testosterone**

- Decreases LDL/Increases HDL
- Increases lean muscle mass, decreases fat mass
- Increases energy and vitality; stamina and motivation
- Improves mood, overall sense of well being
- Breast & Prostate Protective

**Androgens Receptors are EVERYWHERE**

- Hair follicle, scalp
- Brain, spinal cord, nerves
- Eyes, ears
- Thyroid, endocrine glands
- Cardiovascular system
- Pulmonary (lungs, bronchi)
- Gastrointestinal tract, liver, pancreas, kidneys
- Uterus, vagina, bladder
- Sexual organs
- Muscle (smooth/striated)
- Bone, bone marrow, joints

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5. Richards M. Hidden in Plain Sight: A Real Solution to the Diseases of Aging and the Imploding Medicare System.

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Androgen Deficiency: Clinical Signs and Symptoms in Women and Men

- Loss of energy/fatigue
- Loss of mental clarity/focus
- Loss of muscle mass
- Weight gain
- Decreased exercise tolerance
- Increased recovery time from exercise
- Anxiety
- Depression
- Irritability
- Moodiness
- Insomnia
- Decreased libido
- Loss of erectile ability

Female Androgen Insufficiency Syndrome (FAIS)

- Key symptoms:
  - Reduced libido, diminished well being and lowered mood
  - Other vague symptoms also present
  - Diagnosis is made on the basis of these symptoms in the setting of a low serum free testosterone level.
  - Currently no readily available inexpensive assay which reliably measures free testosterone levels in the female range.
  - Further complicated by the lack of data demonstrating a minimum serum free testosterone level which, if below this, correlates with the symptoms.

Despite the complexities involved with defining FAIS, the symptoms have been reported to respond well to testosterone replacement.


Androgen deficiency in Women

Androgens peak in women in their twenties

Symptoms may occur across the lifespan

Myths of T therapy in Women - A Lit review

The study proposed 10 common myths and misconceptions, and provides evidence to support what is physiologically plausible and scientifically evident:

- T is the most abundant biologically active female hormone
- T is essential for physical and mental health in women
- T is not masculinizing
- T does not cause hoarseness
- T increases scalp hair growth
- T is cardiac protective
- Parenteral T does not adversely affect the liver or increase clotting factors
- T is mood stabilizing and does not increase aggression
- T is breast protective
- The safety of T therapy in women is under research and being established.

Testosterone (T) What’s “Normal” Males

What’s “normal”?

- Men age 30-70 will lose 1-10% of total testosterone production per annum.
- More importantly, there is a significant age related change in the balance of albumin and SHBG
- As men age SHBG increases
- SHBG directly affects free T
- High SHBG leads free T

Testosterone (T) What’s “Normal” Females

"Current androgen assays are unsatisfactory primarily because of their lack of (either) sensitivity or reliability at the normal lower ranges of normal"

Consensus statement on female androgen insufficiency*

No established “normal” blood levels/ranges in women
Poor Correlation between symptoms of androgen deficiency and testosterone levels.

Total and free, nor bioavailable testosterone are the definitive measures of androgen deficiency that endocrinologists would like them to be.

There can be both insufficient production and variable degrees of resistance to the action of androgens operating at several levels in the body simultaneously.

These factors becoming progressively worse with aging, adverse lifestyle, other disease processes, and a wide range of medications.

Androgen Deficiency etiology:
- Insufficient production
- Increased androgen binding
- Reduced tissue responsiveness
- Decreased Androgen Receptor activity
- Impaired transcription and translation

Diagnosing Androgen Deficiency:
Do the lab values matter?

The Data
Sex Hormones have been shown in studies to positively many areas

Limitations of studies:
- This is a HIGH LEVEL, limited look at the data.
- Over 10k studies.
- No consistent modality/modalities studied.
- Extrapolations made across modalities based on study of one.
- No comparison studies between different modalities.

Sex Hormones & Bone

- Androgen receptors are found in all three bone cells: osteoclasts, osteoblasts and osteocytes.
- There is an abundance of both AR and estrogen receptors in osteoblasts, indicating the dual role of T and E2 in normal bone physiology.
- Two year study e2 pellets demonstrated marked increase in bone density.
- No adverse effects were noted in the coagulation inhibition and fibrinolysis assays in the (estradiol) pellet patients.
- Systolic and diastolic blood pressure unaffected.

Androgen Therapy and BMD

- Studies show that androgen therapy by subcutaneous pellet implantation or oral methyl testosterone when combined with estrogen therapy, has an additive effect on BMD compared with estrogen alone treatment.
- In the Raisz study women treated with CEE showed decreased serum markers of bone formation.
- In contrast women treated with estrogen/androgen therapy showed significant increases in serum bone formation markers.
- Levels of SHBG increased with CEE, but significantly decreased with estrogen/androgen therapy.
Estradiol & Bone

- Suppression of estradiol results in bone loss
- Estradiol therapy improves bone building.
- Estrogen provides significant protection against osteoporotic fractures.
- Combination exercise and estrogen therapy has greater impact than each alone.

The PEPI Trial: Effect of Discontinuation of (estradiol) HRT on Spine BMD

Discontinuation of (estradiol) HRT on Spine BMD

- Long-term HT use protects from bone loss and vertebral fracture, reducing, thus, the incidence of osteoporosis and osteopenia.
- HT use of less than 5 years does not have long-term bone protection.
- The three main reasons for discontinuation of HT were resolution of menopausal symptoms, disease fear of adverse effects or cancer.

HRT and Neurodegenerative Conditions

- HRT and particularly ERT plays an efficacious role in preventing neurodegenerative conditions.
- E2 (17β Estradiol) can reduce the risk for Alzheimer’s disease and minimize cognitive decline in otherwise healthy women.
- E2 can protect against B-amyloid induced degeneration
- Progesterone may dampen this effect.
- Compared to non-users E2 used for avg. 15 years had increased cerebral blood flow.

Sex Hormones & The Brain

- Both Estrogen and Testosterone have Neuroprotective role.
- Women have a higher incidence of AD: 8:1 over men.
- Women with lower E2 levels have even greater risk of AD.
- Evidence that E and T helps decrease apoptosis.
- Protective effect of both hormones decreases the beta amyloid deposition.
1. The immune response following stroke dictates functional recovery and the extent of brain damage.

2. Following brain insult, Estradiol (E2) inhibits expression of pro-apoptotic proteins.

3. The estradiol response following stroke dictates functional recovery and the extent of brain damage.

4. Estradiol (E2) may be dually protective in stroke by also modulating the immune response.

5. Discontinuation of estradiol (E2) may be associated with increased risk of cardiac and stroke death in the first posttreatment year.

6. Rapid withdrawal of estrogen at discontinuation of HT may, however, result in vasomotor effects and potentially adverse arterial changes and cardiovascular events, as the vasodilatory effects of estrogen suddenly cease.

7. Declining estrogen may also modulate cardiac rhythm, perhaps via calcium ion channels or by preventing long QT interval recovery.

8. Acute withdrawal of estrogen may predispose to fatal arrhythmias.

9. Estradiol (E2) protects the brain from ischemic injury following stroke.

10. E2 activates several neuroprotective pathways in the brain.

11. E2 mediates the local and systemic immune response to ischemic stroke.

12. Estradiol prevents axonal damage.

13. Estradiol prevents the loss of hippocampal dendritic spines.

14. Estradiol preserves spatial memory.

15. Estradiol prevents spatial damage.

16. Long-term effects of 17β-estradiol on neuronal survival and learning and memory at 6 months post occlusion.

17. Testosterone promotes myelin repair.

18. The most common demyelinating disease is multiple sclerosis (MS).

19. MS involves autoimmune and inflammatory destruction of myelin sheaths and the death of oligodendrocytes, which are the myelin producing cells of the CNS.

20. Testosterone treatment decreased hippocampal pathology by reducing microglial activation, restoring synaptic protein expression and improving synaptic transmission.
Sex Hormones & Brain: Parkinson’s Disease

More common in men raising the suspicion that E2 has a protective role.

Astrocyte and Microglia injury due to MPTP vary according to estrogen status.

It appears that estrogens antioxidant properties has a direct effect on the survival and recovery dopaminergic neurons in MPTP PD.

Estrogen therapy has been shown, however, to be protective against the nearly 30% incidence of dementia in PD patients.

Risk of Parkinson’s increases after Tamoxifen therapy.

Testosterone Therapy & Depression

Testosterone therapy improves well being, mood, and sexual function in pre menopause years.

Testosterone influences libido and well being in women.

Testosterone therapy shows an antidepressant effect depression, libido and energy.

Testosterone therapy improves well being, mood, and sexual function in pre-menopausal women.

Prudent testosterone replacement is effective in relieving both physical and psychological symptoms of androgen insufficiency in clinically affected.

Testosterone supplementation has positive effects for depression, libido and energy.

Testosterone therapy shows an antidepressant effect in depressed patients, the route of delivery may play a role in treatment response.

Testosterone therapy improves well being, mood, and sexual function in pre-menopausal women.

Testosterone Therapy & Depression

Hundreds of studies support the relationship between androgens and depression in both women and men.

Sex hormones influence depression greatly in women, primarily testosterone in the pre menopause years.

Women journeying through the menopause transition have a higher risk of increased new and recurrent depression.

Estrogen fluctuations exacerbate (greatly) these symptoms during peri-menopause.

Androgen decline is at peak in the menopause transition. Androgen levels decline 70% within 24 h when women undergo surgical removal of the ovaries.

Conventional oral contraception or HRT cause a decline in androgens because of higher levels of sex hormone binding globulin (SHBG).

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MRS- Study of Depression Relief -2017

-684 charts reviewed for women who received pellet HRT [androgen alone or androgen plus estradiol]:
  - 97% reported a decreased in depressive symptoms
  - 11% reported an equivocal rating of depressive symptoms
  - 2% reported an increased rating of depressive symptoms

-Analysis of the change in depression scores between pre-intervention MRS and post-intervention MRS showed a statistically significant improvement in depressive symptoms post intervention (p<0.005).

Sex Hormones & The Heart

Risk of Parkinson’s increases after Tamoxifen therapy.

30% incidence of dementia in PD patients.

Estrogen therapy has been shown, however, to be protective against the nearly 30% incidence of dementia in PD patients.

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Risk of Parkinson’s increases after Tamoxifen therapy.
Sex Hormones & The Heart: Cardiovascular Disease

Low serum testosterone is associated with several cardiovascular risk factors including dyslipidemia, adverse clotting profiles, obesity, and insulin resistance.

Testosterone has been reported to improve symptoms of angina and delay time to ischemic threshold in selected men with coronary disease.

In men, endogenous testosterone concentrations are inversely related to mortality due to cardiovascular disease and all causes.

Low testosterone may be a predictive marker for men at high risk of cardiovascular disease.

In this study, a strong and independent association between (low) concentrations of testosterone and AMI was observed in men with type 2 diabetes.

Low concentrations of endogenous androgens were associated with increased artery stiffness in men with type 2 diabetes.

Measuring testosterone in men with type 2 diabetes may help in the assessment of their cardiovascular risk.

Men with low testosterone have a high prevalence of cardiovascular disease and metabolic syndrome.

A prospective study with 11,606 men, aged 40–79 years, found that testosterone baseline levels are inversely related to mortality due to all causes, cardiovascular disease and cancer.

All cause mortality is increased in hypogonadal men with Type 2 diabetes.

Low concentrations of endogenous androgens were associated with increased artery stiffness in men with type 2 diabetes.

Low serum testosterone are an independent predictor for severity of CAD

Low testosterone is an independent predictor of severity of CAD

Sex Hormones & The Heart: Cardiovascular Disease

- Androgens are beneficial for endothelial cells (ECs) because these hormones induce nitric oxide production, proliferation, motility, and growth of ECs.

- Androgens show anti-adhesive properties in ECs.

- Androgens inhibit inflammatory activation and induction of procoagulant, and thrombotic properties, thereby possessing the cardioprotective function.

Molecular mechanisms linking androgen dysregulation to hypertension seem to be related to increased vascular fat, promoting a chronic inflammatory state through different mechanisms.

- One proposed mechanism may involve the recruitment and over-activation of M1-like where it may cause the production of inflammatory cytokines and other relevant factors.

- Chronic inflammation and adipocyte dysfunction may alter endothelial function leading to hypertension.

Both in men and in women, particularly in the postmenopausal period, hypoandrogenism seems to be a major determinant of the increased prevalence of hypertension.

SEX HORMONES & THE HEART: AMI

- Low testosterone is an independent predictor of severity of CAD

- After adjustment for age, BMI, smoking history, hypertension, diabetes mellitus, dyslipidemia and history of treatment of heart disease

- Low serum testosterone are an independent predictor for Geminis score or severity of CAD

- The mechanism of action of T in the cardiovascular system is likely to involve complex interconnected processes including accelerated atherosclerosis, abnormal activation of inflammatory response, impaired vasomotion and endothelial dysfunction.

- Androgens show anti-thrombotic properties, thereby possessing the cardioprotective function.

- Low testosterone is an independent predictor of severity of CAD

- After adjustment for age, BMI, smoking history, hypertension, diabetes mellitus, dyslipidemia and history of treatment of heart disease

- Low serum testosterone are an independent predictor for Geminis score or severity of CAD

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- Androgens show anti-thrombotic properties, thereby possessing the cardioprotective function.
Androgens & The Heart: Cardiovascular Disease in Women

- Positive association between low serum androgen levels and severe ICA atherosclerosis in postmenopausal women.
- Higher levels of androgens in postmenopausal women have a protective role in the development of atherosclerosis of ICA.

Sex Hormones & The Heart: Cardiovascular Disease in Women

Both E2 plus testosterone (E & T) were associated with sustained reductions in total cholesterol and low density lipoprotein (LDL) cholesterol.
In women who received E but not E&T, hip and abdominal circumferences and fat mass/fat-free mass (FM/FFM) ratio over the abdomen declined.
E&T but not E alone resulted in increased FFM and a reduced FM/FFM ratio.
For E but not E&T, the decrease in LDL cholesterol was significantly related to changes in total and compartmental body fat and to change in the FM/FFM ratio.

Estradiol & The Heart: Cardiovascular Disease

- 489,105 women who used HT from 1994 to 2009 (3.3 million HT exposure years)
- Risk reductions: 29 fewer CHD deaths and 7 fewer stroke deaths per 1,000 women using any HT (ET) for at least 10 years.
- Risk of CHD death was significantly reduced by 18% to 54% in HT users.
- Risk of stroke death was also reduced by 18% to 39%.
- Risk of all-cause mortality was reduced in HT users by 12% to 38.
- All risk reductions were comparable in women initiating HT before age 60 years and women initiating HT at age 60 years or older.

ELITE: Early Versus Late Intervention Trial With Estradiol

- Purpose of the study was to examine the effects of oral 17β-estradiol (estrogen) on the progression of early (subclinical) atherosclerosis and cognitive decline in 643 healthy postmenopausal women.
- Women who started estrogen early in the ELITE trial (average 3.4 years following menopause) after 6 years of treatment showed a 50% reduction in the rate of progression of atherosclerosis.

Menopausal HT use is accompanied with reduced mortality risk after primary ACS.
- Estrogen has important effects on cardiovascular function including regulation of vascular function, increased fibrinolysis, and anti-inflammatory properties.
- Postmenopausal HT use is associated with a reduced risk of CHD and all-cause mortality.
- Risk of ET use is not statistically significant, particularly when initiated in women <60 years of age and/or <10 years since menopause.

Estrogens and Cardiovascular Disease in the Male

In men with aromatase deficiency low levels of HDL-C have been observed along with high levels of LDL-C and triglycerides. Estrogens act along with testosterone to maintain normal levels of insulin sensitivity.

An association was observed between elevated levels of estradiol and reduced risk of cardiovascular disease for men older than 56 years.


Testosterone, D3 & CAD

- Deficiencies of either free testosterone or 25-hydroxyvitamin D resulted in a 40% increased risk for all-cause mortality (p=0.002)
- Deficiencies of free testosterone and 25-hydroxyvitamin D resulted in a 77% increased risk for cardiovascular mortality (p<0.001)
- Deficiencies of free testosterone and 25-hydroxyvitamin D resulted in a 111% increased risk for all-cause mortality (p<0.001)

Always check D3 levels
Goal: >60

Sex Hormones & Breast Cancer

- Women’s (and providers’) greatest fear when prescribing MHT
- 400,000 deaths annually worldwide
- Androgens highly breast protective
- Data is lacking that supports 17 beta estradiol therapy and increased breast cancer risk theory
- Progestins implicated in B-Ca risk in WHI NOT CEE
- CEE only group showed breast protection
- Focus should be on metabolic theory of cancer and prevention rather than misguided hormone inducing theories

Sex Hormones & Breast Cancer

- Testosterone (T) is the most abundant biologically active hormone in women.
- Androgen receptors (AR) are located throughout the body including the breast where T decreases tissue proliferation.
- Increased aromatase expression and an imbalance in the ratio of stimulatory estrogens to protective androgens impacts breast homeostasis.
- Recent clinical data supports a role for T in BCA prevention.


Androgen & Breast Cancer

- Prominent data from in vitro studies have shown that androgens actually have apoptotic and anti-proliferative effects and not stimulatory effects.
- Animal models have shown similar results finding that androgens inhibit breast cancer growth.
- Efficacy of T + A supports T (therapeutic) effect at the AR.
- The lack of adverse events and cancer recurrence support the safety and tolerability of these doses of T + A in BCA survivors.
- T + A is an option for therapy in symptomatic BCA survivors.
- Efficacy of T + A supports T replacement therapy and risk of breast cancer in a French cohort study of 3175 women. 

Estrogen & Breast Cancer

- Estrogen therapy does not increase risk of recurrence or death in patients with early breast cancer.
- Estrogen therapy safe for women, even breast cancer survivors.
- Estrogen therapy shows no risk in breast cancer survivors.
- Anastrozole (A) alone or with intralymphatic estrogen and prolactin of breast tissue and aromatase.
- Mitogenic activity is higher with estrogen/MPA and lower with estrogen/MP.
- Progesterone could be a promising drug for breast cancer.

Testosterone therapy for Breast Cancer?

- Historically testosterone was the most common line of hormonal therapy for breast cancer, but its use has been virtually abandoned in the past 50 years.
- Anastrozole (A) response in hormone-resistant metastatic BCA (Tamoxifen studied).
- 13 consecutive patients with positive metastatic breast cancer refractory to treatment with other hormones with disease progression treated with testosterone propionate, 250 mg once every two weeks x 2 doses then every four weeks until disease progression, drug toxicity, or death.
- Results: Disease regression in 17%, stabilization in 42%.

Androgen & Breast Cancer - Glaser Study

- 2.4 cm tumor in the left breast.
- Three combination implants each containing 60 mg of testosterone and 4 mg of Anastrozole were placed anterior, superior, and inferior to tumor.
- Three additional testosterone-anastrozole implants were again placed percutaneously 48 days later.
- Day 46, 7-fold reduction in tumor volume, as measured on ultrasound.
- Week 13, 2.2-fold reduction in tumor volume.
- Therapeutic systemic levels of testosterone were achieved without elevation of estradiol.

Sex Hormones & Breast Cancer

- Estrogens (E) stimulate proliferation of breast tissue and cancer cells.
- Progesterone (P) upregulates estrogen receptor alpha, increase breast pain, swelling, thickness and cancer.
- Progesterone (P) alone or with intralymphatic estrogen and prolactin of breast tissue and aromatase.
- Mitogenic activity is higher with estrogen/MPA and lower with estrogen/MP.

Reference:
Sex Hormones & Prostate

- Men with high T are not at risk for prostate cancer.
- Low T offers no protection against prostate cancer.
- 19 studies show no increase cancer risk in men with low T treated with T therapy.
- Multiple studies show men with low T associated with high grade prostate cancer and higher stage at presentation.
- Undetectable or stable PSA levels protect prostate cancer and desire T therapy (2 years out of standard of care).
- Estrogen therapy?

Meta analysis of 197 studies demonstrated that testosterone administration does not increase the risk of prostate cancer or Gleason score.

Blood levels of androgens and other sex hormones are not related to the risk of developing prostate cancer.

Treatment with Testosterone after one year treatment of Prostate cancer and normal PSA - No increase risk of recurrence.

Low levels of testosterone are an independent risk factor for prostate cancer.

Adding testosterone levels to PSA's may improve predictive accuracy.

Sex Hormones & Pain

- Testosterone deficiency in chronic pain patients has now been recognized by many observers.
- Due to its critical biological functions in pain control, testosterone testing and replacement (TR) should now become a mandatory component in the treatment of chronic pain.
- Numerous studies on both animals and human subjects have also demonstrated the potential effects of gonadal hormones, such as estrogens, on pain transmission.
- These effects most likely involve multiple neuroanatomical circuits as well as diverse neurochemical systems.

Estrogen positively influences pain-processing.

Estrogens, emanating from the systemic circulation or from local synthesis may regulate nociceptive circuitry at spinal and supraspinal levels, thus contributing to pain transmission and modulation.
Sex Hormones & Pain

• Estradiol is known to regulate the activation of astrocytes and microglia after different forms of CNS injury or under conditions of neuroinflammation.
• Protein and mRNA levels of aromatase, as well as the protein and mRNA levels of alpha and beta estrogen receptors, were increased in the dorsal horn of female rats after spinohalamic tract injury, suggesting that the injury increased estradiol synthesis and signaling in the dorsal horn.
• Estradiol decreases pain and inhibitors of aromatase increases pain sensitivity.


Fibromyalgia is a diffuse chronic pain condition that occurs predominantly in women and may be under-reported in men.
• Symptoms include: decreased well-being and generalized widespread flu-like muscle aches and pain that fail to resolve due to central sensitization of nociceptive neurons.
• Fibromyalgia has comorbidities with other chronic pain conditions including PTSD, “Gulf War Syndrome”, and various stress-induced (pain) conditions.
• Deficient testosterone serum levels are linked to a high risk for an inflamed nociceptive nervous system and resultant chronic pain states.
• Testosterone therapy is shown to downmodulates pain signaling.
• The conversion of testosterone to estradiol is thought to be the true moa.


Hormone Replacement Modalities

• Testosterone Pellets
• Injections (Synthetic)
• Creams- Bio identical and synthetic
• Oral – Bio identical and synthetic

Nomenclature confusion
Not all therapies created equal!

Be VERY cautious when researching hormone therapies! Hormone modalities refer to tissue-modulated estradiol or its derivatives. Major differences between mechanisms of action among types of HRT and modalities:
◦ CEE and estradiol
◦ Progesterone and Progestin
◦ Testosterone & methyltestosterone
• Subcutaneous, shot, oral, RDT, transdermal and transvaginal

Estrogens, estrogen/methyltestosterone
Subcutaneous Pellet Implants

- Longest studied modality (1930’s)
- Are plant (soy or yam) based.
- More widely used in states over past decade.
- Dosing may be more individualized than other modalities.
- Levels continuous over 3-5 months.
- Cannot remove once placed.
- Nuisance side effects may be longer lasting than oral or transdermal routes.
- Many nuances with dosing, monitoring and ongoing clinical care.
- Pellet HRT details of prescribing beyond the scope of this lecture

How are Pellets Made and Absorbed

- Pure Estradiol and Testosterone powder.
- Newer formulation infused with triamcinolone
- Primary binder used stearic acid
- Some pharmacies use cholesterol as a lubricant
- Compressed into pellets using thousands of pounds of pressure.
- E-beam or Autoclave (standard) for sterility.
- Third party tested for potency and purity.
- Absorbed based on cardiac output not time released.
- Newer formulations with TCA

Creams

- Less side effect profile than other modalities.
  - Less effect on hair growth at area of application
  - Poor absorption transdermally in typical application areas
  - Skin receptor may become desensitized over time.
  - Structural local application good absorption.
  - Difficult to measure on laboratory assays.
  - Monitor symptom relief.

Injectable Synthetic Testosterone

- Higher side effect profile secondary to higher incidence of DHT conversion (women).
- Higher rates of aromatization than other modalities.
- Absorption is time released.
- Reported higher efficacy than oral or transdermal routes.
- Weekly or bi-monthly dosing
- 200mg/ml
- 1ml q week (standard males)
- 25-50 mg / week (standard females)
- Daily SQ dosing (better)
- 0.15 ml SQ daily (males)
- Rub injection site post injection decreases inflammation from oil

Oral/Sublingual

- Oral bio-identical estradiol
  - Comes in many forms.
  - Dosing 1-2 mg daily
- Oral bio-identical testosterone
  - Micronized
  - Women only, doesn’t work for men
  - 10 mg PO QD

- RDT (rapid dissolve tablets/ sublingual) bio-identical reported better clinical response and lower side effect profile than oral.
  - Testosterone Dose:
    - 3-10 mg 30 or 60 minutes
    - 10-30 mg 60 or 90 minutes

Potential Effects of Oral and CEE / Progestin Therapy

- Breast tenderness
- Increased risk of endometrial cancer and breast cancer
- Vaginal bleeding
- Headaches
- Nausea and vomiting
- Fluid retention
- Blood clots
- Leg cramps
- Gallstones
**Progesterone Dosing Considerations & Potential Side Effects**

**Indications**

- Hysterectomy is never a factor in prescribing progesterone.
- Patient with intact uterus on estrogen a MUST.
  - Giving women unopposed estrogen outside standard of care
- PMS – 14 days or 30 days
- Dysfunctional uterine bleeding – q hs
- Peri & Post-menopause – q hs
  - Do not cycle; do not bleed
- NOT used in men- highly inflammatory

**Dosing Recommendations**

- Formulation of natural progesterone: Oral, SL RDT
  - Dose: QD, BID, QID
    - Capsule: 50-200 mg QHS (best for sleep)
    - Women on postmenopausal doses: E2 x 200 mg qhs
    - Pellets: 50-100 mg QD x 30 days (best for anxiety)
    - Cream: 200 mg/gm – 1 gm QID
    - $$$
    - Poor absorption
    - No good data on uterine protection

**Side Effects**

- With oral only – somnolence.
- Breast or nipple tenderness.
- Switch to sublingual
- Transdermal cream – poor levels, poor compliance, dangerous if not maintaining mid-luteal serum levels.
  - DO NOT USE for uterine protection
- Transdermal cream results in very high saliva levels but very low serum levels.

**Progesterone (MPA) Side Effects:**

- Depression
- Breast swelling & tenderness
- Irregular bleeding
- Weight gain
- Fluid retention
- Breast cancer risk
- Cardiovascular disease risk
- Stimulates estrogen receptors

**Estradiol Labs and Optimal Levels**

- Most accurate lab indicator of estradiol levels is FSH
- Estradiol levels fluctuate throughout the day
- Estradiol converts to other forms in body
- Not good indicator of low levels
- Range of estradiol correlates with symptom relief: 70-100
- FSH secreted by feedback loop like TSH
  - Low E2 – high FSH
  - High E2 – suppressed FSH
  - PSH shows average of what E2 levels been like HOMA
  - Don’t over-suppress
  - Not trying to reach pre-menopausal levels
Testosterone Labs and Optimal Levels

- There are no established “normal” ranges in men or women.
- There are reference ranges, but they are “expected” and differ between labs.
  - No standard assays or methodologies.
- Symptom presentation:
  - Women: 50’s and above mild; 40’s moderate; 30’s severe, <20 extreme.
  - Men: 500’s mild; 400’s moderate; 200-300 severe; <200 extreme.
- Notice the 10% difference between men and women.
- Optimal ranges based on experiential data:
  - Men: 900-1100 (maybe higher).
  - Women: 100-200 (maybe higher).

Diagnosing Androgen Insufficiency in females

Female Androgen Insufficiency Syndrome (FAIS)

Key Symptoms:
- Reduced libido, diminished well being, anxiety, and depression, lowered mood.
- Other vague symptoms also present (brain fog, memory impairment, joint pain, insomnia).
- Diagnosis is made on the basis of these symptoms in the setting of a low (lower quintile of reference range) serum free testosterone level or lower quintile of total testosterone level.
- Currently no readily available inexpensive assay which reliably measures free testosterone levels in the female range.
- Further complicated by the lack of data demonstrating a minimum serum free testosterone level which, if below this, correlates with the symptoms.
- Despite the complications involved with defining FAIS, symptoms have been reported to respond well to testosterone replacement.


- Poor Correlation between symptoms of androgen deficiency and testosterone levels.
- Total and free, nor bioavailable testosterone are the definitive measures of androgen deficiency that endocrinologists would like them to be.
- There can be both insufficient production and variable degrees of resistance to the action of androgens operating at several levels in the body (reversibility).
- These factors becoming progressively worse with aging, adverse lifestyle, other disease processes, and a wide range of medications.

Androgen Deficiency etiology:
- Insufficient production
- Increased androgen binding
- Reduced tissue responsiveness
- Decreased Androgen Receptor activity
- Impaired transcription and translation.

Serum Testosterone Levels in Women

What’s “Normal”?

“Current androgen assays are unsatisfactory primarily because of their lack of (either) sensitivity or reliability at the normal lower ranges of normal.” Consensus statement on female androgen insufficiency.

No established “normal” blood levels/ranges in women.


Testosterone replacement

Clinical Decision vs. Labs

Hormone levels fluctuate and are unreliable.

Standard of care: an individual patient should be treated based on his/her symptoms as well as the benefits and risks of therapy.

An individual’s physical comfort may not be related to their absolute hormone levels.

Am I Normal?

Take home: TREAT PATIENT.
Diagnosis & Treatment of FAIS Take Home:

- There are no established “normal” ranges of testosterone in men or women.
- There are reference ranges, but they are “expected” and differ between labs.
- Experiential levels and symptom presentation:
  - Women: 50’s and above mild; 40’s moderate; 30’s severe, <20 extreme

Serum testosterone optimal ranges based on experiential data:
- Women: 80 - 200 (may be higher!)

PATIENT COMMENT: “I FEEL AMAZING!!!”

Low T in a young man?

- Testosterone below 200 in a male under 30 with no hx of anabolic steroid use, OR any male with total T level in double digits, suspect prolactinoma.
  - Get prolactin level
  - If elevated send for MRI and/or neuro for work up.
  - Depending on level, may start very slow.
    - Consider using HRT to “ease” into therapy
    - Consider lower pellet dose to start with boost in 4 weeks.
  - Depending on levels, may start very slow.
    - Consider oral BHRT to “ease” into therapy
    - Consider lower pellet dose to start with boost in 4 weeks.

T Side Effects Women

- Most are dose dependent and reversible
- Fluid retention
  - May use mild diuretic
  - Common with first round & summer months
- Acne (least common)
  - Dark skin ethnicity worse
  - Hx of acne as teen? Prone to it?
  - Key to change skin care products
  - PCOS??
- Hair loss is extremely rare - look for other sources.
- Hair growth (least common)
  - Everywhere we don’t want it.

T Side Effects Men

- Increased aromatization to estrogen (most common).
  - If symptomatic on DIM 400 - 600 a day, maybe start E2 blocker temporarily
  - Arimidex 1 mg weekly for 4 - 6 weeks
  - Femara 2.5 mg ½ t q 2 weeks for 4 - 6 weeks
- Erythrocytosis (NOT polycythemia)
- Sperm suppression
  - Takes up to 12 months to return to baseline
  - Key conversion with men who still wanting children
  - Clomid helps return to baseline
  - Also a great choice for young men who don’t want pellets
- Decreased effect over 50 years

PCOS is an endocrine problem

- Not an ovarian issue, enlarged ovaries are a symptom only
- Primary defect is hyperinsulinemia.
- Polycystic Ovarian Syndrome or PCOS is the diagnosis
- Easy to mis-diagnose - 50% of PCOS women will be misdiagnosed
- Elevated LH/FSH greater than 2:1 is diagnostic
- Triad of hirsutism, obesity and abnormal menstruation almost always diagnostic
- Insulin abnormalities precede PCOS and elevated androgens
  - Hyperinsulinemia results in hyperandrogenism and decreased SHBG
  - Elevated LH leads to elevated testosterone and high LH/FSH ratio
  - High free testosterone because of low SHBG
  - High free test leads to symptoms of acne, hirsutism and sensitivity of hair follicles

PCOS TREATMENT

- Blocking androgens does not change the etiology as insulin is the culprit
- Fix the insulin and testosterone hypersensitivity resolves
- Metformin, thyroid optimization and progesterone KEY to treatment
  - Lipid lowering
  - Hirsutism tx with spironolactone (takes 6-12 months to work on sx but may help if acne is severe acutely)
  - Metformin can significantly decrease testosterone, hair growth and hirsutism
  - Metformin also helps return to baseline - takes 1-3 years
  - Metformin goal 2000 mg daily
  - Often can taper over 2-3 months
  - Very slow to work up
**HRT in PCOS**

PCOS women even post menopause, even surgical menopause will have side effects because of the insulin issue.

**Excellent History is key**

- Pre-menopausal menstrual history - irregular?
- Fertility issues?
- Acne, hirsutism?

**START LOW GO SLOW**

- VERY low dose testosterone
- MUST optimize thyroid
- Progesterone 100-200 mg q HS
- Metformin protocol
- Spironolactone 100 mg daily
- YAZ if pre-menopause (suppresses androgen production by ovary, raises SHBG)

Important as these women VERY high risk for ovarian and breast cancer and heart disease.

**IF YOUR PCOS PATIENT BECOMES PREGNANT**

DO NOT STOP THE PROGESTERONE

**THIS WILL CAUSE THEM TO MISCARRY**

---

**Estradiol and Androgen (IM injection) Symptom Reduction**

Prospective, double blind, cross over study

**Physical and Psychological Symptoms**
- Estrogen androgen
- Estrogen alone
- Testosterone alone
- Placebo:
  - Testosterone was superior for relief of energy, well being, somatic complaints, and psychological symptoms.
  - Worst was estrogen alone and placebo.

**Testosterone and Estragen implants [100mg/50mg]**

Studied over 4 years
Peri and postmenopausal women

<table>
<thead>
<tr>
<th>Symptom Reduction</th>
<th>Testosterone and Estragen implants (100mg/50mg)</th>
<th>Stratum A: Postmenopausal group</th>
<th>Stratum B: Postmenopausal group</th>
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</thead>
<tbody>
<tr>
<td>Exercise</td>
<td>1.08 ± 0.09</td>
<td>0.39 ± 0.03</td>
<td>0.64 ± 0.07</td>
</tr>
<tr>
<td>Energy</td>
<td>1.09 ± 0.07</td>
<td>0.39 ± 0.03</td>
<td>0.48 ± 0.03</td>
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<tr>
<td>Well being</td>
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<tr>
<td>Somatic symptoms</td>
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<td>0.39 ± 0.03</td>
<td>0.62 ± 0.03</td>
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<tr>
<td>Psychological symptoms</td>
<td>1.10 ± 0.04</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
</tr>
<tr>
<td>Sleep</td>
<td>1.08 ± 0.04</td>
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<td>0.63 ± 0.03</td>
</tr>
<tr>
<td>Appetite</td>
<td>1.07 ± 0.04</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
</tr>
<tr>
<td>Mood</td>
<td>1.09 ± 0.06</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
</tr>
<tr>
<td>Memory</td>
<td>1.08 ± 0.07</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
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<tr>
<td>Fatigue</td>
<td>1.07 ± 0.05</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
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<tr>
<td>Concentration</td>
<td>1.08 ± 0.04</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
</tr>
<tr>
<td>Pain</td>
<td>1.09 ± 0.05</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
</tr>
<tr>
<td>Headache</td>
<td>1.08 ± 0.05</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.08 ± 0.04</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1.07 ± 0.04</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
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<tr>
<td>Diaphoresis</td>
<td>1.08 ± 0.05</td>
<td>0.39 ± 0.03</td>
<td>0.63 ± 0.03</td>
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<tr>
<td>Cognitive function</td>
<td>1.09 ± 0.06</td>
<td>0.39 ± 0.03</td>
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<td>Social function</td>
<td>1.08 ± 0.05</td>
<td>0.39 ± 0.03</td>
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<tr>
<td>Pain</td>
<td>1.08 ± 0.05</td>
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</tbody>
</table>

**Conclusions:**

- Continuous testosterone alone, delivered by subcutaneous implant, was effective for the relief of hormone deficiency symptoms in both peri- and post-menopausal patients.

- The validated, MRS(5) questionnaire, Menopause Rating Scale (MRS), proved a reliable tool in the measurement of the beneficial effects of testosterone therapy in both cohorts.
Symptoms of Hormone Insufficiency May Mimic Other Diseases

- Thyroid
- Chronic Fatigue Syndrome & Fibromyalgia (women)
- Metabolic and nutritional deficiencies
- Toxicity
- Gut health/Intestinal permeability
- Psychiatric disorders

The Patient Encounter
Case Study - Bobbie

- 65 year old female, married to retired OB/Gyn
- G4P4, unremarkable gyn history
- Began to feel depressed in late 40’s
- Symptoms exacerbated through 50’s; patient became very moody, anxious and severely depressed
- Began oral estrogen and progesterone combination with some improvement in symptoms in her mid 50’s
- Stopped oral therapy at age 60
- Pre-treatment MRS questionnaire ranked severe in all psychosomatic categories
- Labs reveal low serum testosterone, low estradiol and elevated FSH
  - Testosterone <12, FSH 69, Estradiol 13
- Labs and exam otherwise unremarkable
- Began MHT with estradiol and testosterone pellet implants and oral progesterone for uterine protection
- Follow up in 6 weeks

The Patient Encounter
Case Study - Bobbie

- Post MRS questionnaire all psychosomatic symptoms reported as resolved, score of 0.
- No subjective negative side effects reported
- Follow up hormone labs:
  - Testosterone in above upper range at 112
  - FSH 26, Estradiol 25

Husband states
"You gave me my wife back"
"I wish I would have known about this therapy when..."

The Patient Encounter
Case Study - Nicole

- 67 y/o female
- Menopause x 14 years
- Perimenopause age 47-53
- Hyst 2 years ago due to fibroids
- G2P2
- PMH unremarkable
- Initial symptom presentation late 40’s
- Initial symptom extreme depression refractory to SSRI rx by MD PCP; irregular menses
- NP suggested CEE/MPA combo at age 49
- Depressive sx improved 75% (patient self report); still with occasional “blues” but better
- Vasomotor and somatic complaints resolved
- Transition to pellet MHT in 2009: Estradiol and testosterone pellet with oral progesterone
- Weaned off SSRI
- Depression and mood alterations greatly improved
- Experienced weight loss and increased libido
- Overall HRQOL greatly improved
- Continued pellet MHT for 8 years

The Patient Encounter
Case Study - Nicole

- Travelled/moved to Baja Mexico x 1 year
- Off HRT x 1 year while out of country
- Extreme anxiety and depression returned after 5 months
- Returned to Oregon in July 2018
  - Difficulty breathing, rapid heart rate
  - Extreme depression
  - Full cardiac and pulmonology work up negative
  - PCP recommended psych workup
- Returned to NP who placed patient back on oral MHT: Estradiol, Progesterone and Testosterone.
  - Symptoms began improving after 1 week
  - Symptoms resolved at 2 weeks post initiation of MHT

The Patient Encounter
Case Study - Nicole

- 67 y/o female
- Menopause x 14 years
- Full transparent age 47-53
- 4 y ago due to fibroids
- G2P2
- Menopause unremarkable

- Initial symptom presentation (at 47+)
- Initial symptom extreme depression refractory to SSRI by MD PCP; irregular menses
- NP suggested CEE/MPA combo at age 49
- Depression improved 75% (patient self report); still with occasional “blues” but better
- Vasomotor and somatic complaints resolved
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Thyroid Physiology, Diagnosis and Treatment

HAVE WE BEEN DOING IT WRONG?
Why Thyroid in a Sex Hormone Lecture?

- They go hand in hand.
- Symptoms overlap.
- Imperative you understand the "why" and the evidence to defend your clinical practice.
- The TSH test is not indicative of thyroid hormone function at the cellular level.
  - FT3 is the only ACTIVE thyroid hormone in circulation
  - Must check ALL thyroid hormones: TSH, FT4, FT3
- Understand thyroid evaluation is not about metabolism and hair loss.
- For low FT3 associated with depression, anxiety, chronic fatigue, fibromyalgia, memory, sleep, heart disease, bone loss, cancer, and many others.

Understanding Thyroid Physiology

One of the most important things to understand is that the factors that inhibit the action of deiodinase 1 AND inhibit conversion of T4 to T3, do NOT inhibit deiodinase 2 in the pituitary gland, and therefore do NOT affect the down regulation of TSH.

They also don't inhibit deiodinase 3, which converts T6 to reverse T3.

Now, can you see where this might cause a few problems?

Unraveling the thyroid diagram:
- TSH
- T4
- T3
- rT3
- Energy
- Metabolism
- Cognition
- Weight
- Skin
- Hair
- Depression
- Edema
- Light-headedness
- Inflammatory conditions or diseases on systemic levels
- Chronic fatigue syndrome and fibromyalgia
- Chronic pain
- Chronic illness
- Exposure to toxins and plastic
Physiologic and emotional stress
Depression
Dieting (low calorie/HCG)
Insulin resistance
Inflammation from autoimmune disease or systemic illness
Chronic fatigue syndrome and fibromyalgia
Chronic pain
Exposure to toxins and plastics
LEVOTHYROXINE

SYNTHROID

BUT THE
TSH
IS NORMAL,
SO YOU’RE JUST FINE!

FT3 and Cardiac Mortality

Patients with low T3 at baseline showed a 10-fold increase of the risk of hospital death, required higher inotropic support, and were more prone to develop postoperative low cardiac output syndrome.

*Acute Care!

Patients with the low T3 syndrome undergoing CABG are at increased risk of low CO and death in accordance with several clinical studies.

There is convincing evidence that a low T3 status is associated with reduced survival in the cardiac, noncardiac patient. In a series of 573 patients with heart disease, the overall mortality at 1 year was almost five times higher in patients with low T3 at admission.

*TSH does NOT give any reference to the status of FT3

*TSH should NOT be standard of care for evaluating thyroid status.
FT3 and Heart Failure Mortality

- Thyroid hormones, and in particular, the active form triiodothyronine (T3) regulate the synthesis and action of various cardiac proteins.
- An altered thyroid metabolism characterized by a reduced level of biologically active T3 or FT3/FT4 ratio may contribute to poor prognosis in heart failure or cardiac pathology.
- The probability of death was significantly higher in patients with low T3 syndrome; free (F)T3 resulted also in a powerful independent predictor of cardiac and cumulative death.

- Lack of T3 is a proposed mechanism for heart failure.

*Do you check the FT3 in your cardiac patients?

*Imperative all disciplines understand thyroid physiology and prescribing.

Thyroid Treatment Clinical Guidelines

Although AACE does not recommend combination therapy (T4/T3), you can still prescribe it according to your own guidelines.

American Association of Clinical Endocrinologists: Clinical guidelines for clinical practice are systematically developed statements to assist health care professionals in making decisions about appropriate care for patients, but are in no way a substitute for the medical judgment of the individual practitioner and should not be considered medical advice. Most of the current evidence is based on literature reviews, in cases of uncertainty, professional judgment of the authors was applied.

These guidelines are a working document that reflects the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. The purpose of this publication is to encourage medical professionals to use this information in conjunction with, and not in replacement for, their best clinical judgment. The presented recommendations represent the consensus of the authors and do not reflect the opinions of all practitioners or the affiliated organizations to apply these guidelines must be made in light of local resources and individual patient circumstances.

https://www.aace.com/publications/guidelines

Thyroid Documentation Pearls

- Understand if they do not have a TSH over 5 they are not hypothyroid.
- Do not code with this diagnosis unless TSH greater than 5.
- All thyroid prescriptions given with TSH below 5 are considered off label; document document document!
- Consider uploading studies into patients chart.
- Do not prescribe thyroid for weight loss.
- HF2020 goal-HR QOL-Thyroid therapies directly impact HRQOL.

Ethical and Legal Considerations in HRT

Objectives:

- Understanding your regulatory boards (TMB/BON)
- Understanding of ANA (TMB) Code of Medical Ethics
- Understanding and documenting the literature
- Understanding off label prescribing
- Consenting for off label and hormone therapies
- Prescriptive Authority Agreements for Alternative/Off label prescribing
- DEA logs for in office controlled substances (testosterone)
- Understand TMB and Pharmacy board rules
PREVENTION STARTS WITH EDUCATION AND ENDS WITH DOCUMENTATION.

- Alternative therapies are considered:
  - Any off-label use of a medication or therapy utilized for something other than its FDA approval.
  - Any off-label use of a therapy (therapeutic medication that is not FDA approved).
- Robust PA agreement that includes prescribing guidelines of alternative therapies.
- Document off-label use in consent forms.
- Document off-label use in patient chart.
- Educate all new patients on off-label prescribing.
- Upload relevant studies into patients chart.

Off Label Prescribing

BE PRECISE WITH DEFINITIONS – EDUCATE THE PATIENT!

- Defined as prescribing medications for indications, or using a dosage or dosage form, that have not been approved by the US Food and Drug Administration.
- This is very common done with many medications.
  - Beta blockers for headaches or stage fright.
  - BCP for dysfunctional uterine bleeding.
  - Trazodone is only approved for use in depression but is most commonly prescribed for sleep.
  - Seroquel is only approved to treat schizophrenia, bipolar disorder and MDD.
  - Testosterone is only approved for use in men with morning T > 300 ng/dl.
- All thyroid medications prescribed with TSH<5 is considered off label.

AMA Code of Medical Ethics

Alternative Therapies

1.2.11 Ethically Sound Innovation in Medical Practice

Innovation in medicine can range from improving an existing intervention, to introducing an innovation in one's own clinical practice for the first time, to using an existing intervention in a novel way, or translating knowledge from one clinical context into another. Innovation shares features with both research and patient care, but is distinct from both.

When physicians participate in developing and disseminating innovative practices, they act in accord with professional responsibilities to advance medical knowledge, improve quality of care, and promote the well-being of individual patients and the larger community. Similarly, these responsibilities are honored when physicians enhance their own practices by expanding the range of techniques and interventions they offer to patients.

TMB Code of Medical Ethics

Alternative Therapies

- Many states include similar language in their Medical Practice Act.
- APRNs in Texas operate under the delegation of prescriptive authority by physicians.

Texas looks like this:

“A licensed physician shall not be found guilty of unprofessional conduct or be found to have committed professional failure to practice medicine in an acceptable manner solely on the basis of employing a health care method of complementary or alternative medicine, unless it can be demonstrated that such method has a safety risk for the patient that is unreasonably greater than the conventional treatment for the patient’s medical condition.”

The Texas Medical Board will use the following guidelines to determine whether a physician’s conduct violates the Medical Practice Act, §164.051-053 in regard to providing complementary and alternative medical treatment.

1. Patient Assessment.
2. Professionalism.
3. Communication.
4. Patient’s Consent.
5. Documentation.
6. Follow-up.
7. Financial.
8. Legal.

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Alternative Therapies Guidelines

1. Patient Assessment. Prior to offering advice about complementary and alternative health care therapies, the physician shall undertake an assessment of the patient. This assessment should include but not be limited to, conventional methods of diagnosis and may include non-conventional methods of diagnosis. Such assessment shall be documented in the patient's medical record and be based on the physician’s evaluation and review of the following:
   (A) the patient’s medical history;
   (B) the patient’s physical examination;
   (C) any prior conventional medical treatments attempted and the outcomes obtained or whether conventional options have been refused by the patient;
   (D) whether the complementary health care therapy could interfere with any other recommended or ongoing treatment.

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(2) Disclosure. Prior to rendering any complementary or alternative treatment, the physician shall provide information to the patient that includes the following with the disclosure documented in the patient’s records:

(A) the objectives, expected outcomes, or goals of the proposed treatment, such as functional improvements, pain relief, or expected pasturgical benefit;

(B) the risks and benefits of the proposed treatment;

(C) the extent the proposed treatment could interfere with any ongoing or recommended medical care;

(D) a description of the underlying therapeutic basis or mechanism of action of the proposed treatment purporting to have a reasonable potential for therapeutic gain that is written in a manner understandable to the patient; and

(E) if applicable, whether a drug, supplement, or remedy employed in the treatment is:

(i) approved for human use by the U.S. Food and Drug Administration (FDA);

(ii) exempt from FDA preapproval under the Dietary Supplement and Health Education Act (DSHEA); or

(iii) a pharmaceutical compound not commercially available and, therefore, is also an investigational article subject to clinical investigation standards as discussed in paragraph (7) of this section.

(3) Treatment Plan.

(A) The physician may offer the patient complementary or alternative treatment pursuant to a documented treatment plan tailored for the individual needs of the patient by which treatment progress or success can be evaluated with stated objectives such as pain relief and/or improved physical and/or psychosocial function, upon a documented treatment plan that includes pertinent medical history, previous medical records and physical examination, as well as the results of further testing, consultations, referrals, or the use of other treatment modalities.

(B) The treatment offered should:

(i) be based upon the reasonable expectation that it will result in a favorable patient outcome, including preventive practices; and

(ii) be based upon the reasonable expectation that it will result in a greater benefit for the same condition than what can be expected with no treatment.

(4) Periodic Review of Treatment. The physician may use the treatment subject to documented periodic review of the patient’s care by the physician at reasonable intervals. The physician shall evaluate the patient’s progress under the treatment prescribed, ordered or administered, as well as any new information about etiology of the complaint in determining whether treatment objectives are being adequately met.

(5) Adequate Medical Records. In addition to those elements addressed in paragraph (1)(A) – (D) of this section, a physician implementing complementary and alternative therapies shall keep accurate and complete medical records to include:

(A) any diagnostic, therapeutic and laboratory results;

(B) the results of evaluations, consultations and referrals;

(C) treatments employed and their progress toward the stated objectives, expected outcomes, and goals of the treatment;

(D) the date, type, dosage, and quantity prescribed of any drug, supplement, or remedy used in the treatment plan;

(E) all patient instructions and agreements;

(F) periodic review;

(G) documentation of any communications with the patient’s concurrent healthcare providers informing them of treatment plans.

(6) Therapeutic Validity. All physicians must be able to demonstrate the medical, scientific, or other theoretical principles connected with any healthcare method offered and provided to patients.

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Alternative Therapies Guidelines

(5) DEA Logs for controlled substances

- Testosterone is a Schedule III controlled substance in Texas.
- In-office use of testosterone must include strict DEA logs and documentation.
- Injections
  - Keep records
  - Electronic
- Can be manual or electronic
  - Electronic easier for researching lot numbers
- Log must include drugs logged in (received) and each time a drug is logged out with patient information and lot/expiration numbers.

Conclusion

Nurse practitioners have a unique opportunity to open the dialogue of sex hormone and thyroid optimization with their patients.

At Imparative, we expand our horizons in the areas of treating hormone insufficiency states and broaden the scope of our education and knowledge in the role of estrogen, androgen, progesterone and thyroid replacement in optimizing the overall health of our clients.
PEOPLE want to LIVE

Not just be alive...