Nuts & Bolts of Sex Hormone Therapy

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

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Disclosure

- The presenter has no conflicts of interest to disclose.
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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.

- Endocrinology
- Cardiology
- Emergency Medicine
- Women's Health
- Oncology, etc.

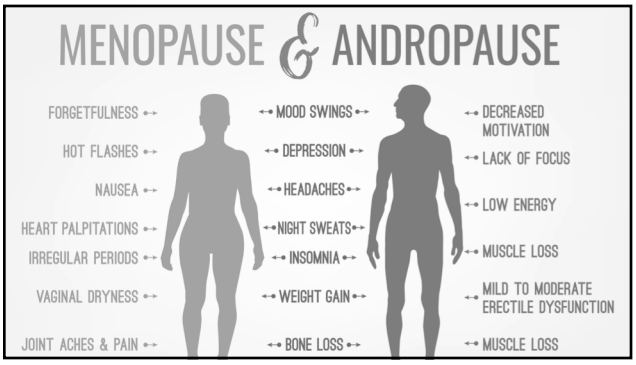
To avoid confirmation bias, we must be committed to lifelong learning, be open to new perspectives and be ready to defend our decision making with the evidence.

Pines, J. M. (2006). Profiles in patient safety: confirmation bias in emergency medicine. *Academic Emergency Medicine*, *13*(1), 90-94.

Tschan, F., Semmer, N. K., Gurtner, A., Bizzari, L., Spychiger, M., Breuer, M., & Marsch, S. U. (2009). Explicit reasoning, confirmation bias, and illusory transactive memory: A simulation study of group medical decision making. *Small Group Research*, *40*(3), 271-300.

Zwaan, L., Monteiro, S., Sherbino, J., Ilgen, J., Howey, B., & Norman, G. (2017). Is bias in the eye of the beholder? A vignette study to assess recognition of cognitive biases in clinical case workups. *BMJ Qual Saf*, *26*(2), 104-110.

My Journey

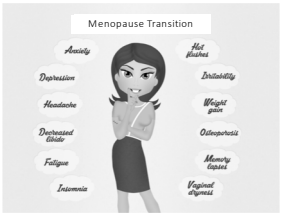


Stages of Menopause:

*Based on Stages of Reproductive Aging Workshop (STRAW)**

Peri-Menopause- lasts 2-8 years

- Early menopause transition
  - Variable duration and menstrual cycles
  - Frequent mood disturbances
  - Women report they feel "crazy"
  - ***Androgen decline peaks during this time***
- Late menopause transition
  - Amenorrhea greater than 60 days
  - Possible vasomotor symptoms
  - ***Hormone related depression and anxiety at worst during this time secondary to major hormone fluctuations***
  - ***Relationship strife in all areas of life reported***



*Harlow SD, Gass M, Hall JE, et al. Executive Summary of the Stages of Reproductive Aging Workshop + 10: Addressing the Unfinished Agenda of Staging Reproductive Aging. *J Clin Endocrinol Metab* 2012

Stages of Menopause:

*Based on Stages of Reproductive Aging Workshop (STRAW)**

Menopause

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

Post Menopause

- Early post menopause
  - Lasts on average 2 years
  - Vasomotor symptoms, urogenital symptoms and psychosomatic complaints exacerbated
  - Bone loss rate increases rapidly*
- Late post menopause
  - Left untreated, symptoms persist throughout the lifespan
  - Vasomotor symptoms decline or cease
  - Urogenital symptoms, vaginal atrophy, at its worst
  - Depression and anxiety continues to have a profound impact

*Finkelstein JS, Brockwell SE, Mehta V, et al. Bone mineral density changes during the menopause transition in a multiethnic cohort of women. *J Clin Endocrinol Metab.* 2008 Mar; 93(3):861-8.

The Women's Health Initiative (WHI) *Why talk about it?*

- The largest research trial to date focused on women's health.
  - What was the focus? Outcomes?
- Because your colleagues & your patients will ask you about it.
- There is a great deal of confusion regarding the trial in the general medical and lay communities. Why?:
  - *Post WHI, the notion was promoted that all hormone therapy products have a* ***single class effect.***
  - *After WHI trial results were published, when people talked about hormone therapy,* ***they were typically referring to conjugated equine estrogen and progestins to mean every kind of estrogen and progesterone****.*
  - *We continue to unravel from this* ***misuse of the terminology****, study intention and results to this day, nearly 2 decades later.*

Hormone Therapy Trial Research Goals

The WHI focused overall on strategies for preventing disease in postmenopausal women:

- Heart disease
- Breast + colorectal cancer
- Osteoporotic fractures

Primary Outcomes

- *Efficacy:* Coronary heart disease (CHD), defined as:
  - Non-fatal myocardial infarction
  - Death consistent with CHD etiology
- *Safety:* Invasive breast cancer

Secondary Outcomes

- Osteoporosis hip + other fractures
- Stroke
- Pulmonary embolism (PE)
- Venous thromboembolism (VTE)
- Colorectal cancer (CRC)
- Endometrial cancer (EC)
- Mortality

Prentice R, et al. *Control Clin Trials* 1989;10:61-109

WHI Reporting Impact

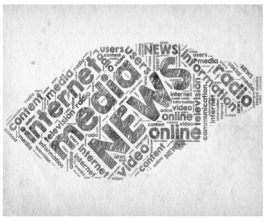
Results not reported in a way that focused on the original question[1]

High participant age not correlating with usual time women are prescribed MHT[2]

- 2/3 enrolled were 60+ y/o
- 21% above age 70 at randomization

Findings publicized as pertaining to women of all ages and not stratified by age and health risks[2]

- Frequency of obesity was above population averages (30% morbid obesity)
- 36% of enrolled participants were treated for HTN or had BP > 140/90



1. Brown S. *Climacteric.* 2012;15(3):275-280.
2. Pedersen B, Ottesen. *Hum. Reprod.* 2003; 18(1):2241-2246.

Clinical Practice Impact

Extrapolated to all hormone therapy formulations + administration routes rather than specifically to oral CEE+MPA or CEE alone. ***THIS IS KEY!!!!***

Prescriptions for the study therapies declined[1-2]

- ↓ 66% for CEE+MPA
- ↓ 33% for CEE alone

- Providers hesitant to treat symptomatic women transitioning into menopause with MHT **resulting in many patients going untreated.**

1. Hersh AL, *et al. JAMA.* 2(62):47-52.
2. 2. Sprague BL, et al. *Obstet Gynecol.* 2012;120(3):591-603.

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 usage.

(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".

Utian, W. H. (2012). A decade post WHI, menopausal hormone therapy comes full circle–need for independent commission. *Climacteric*, *15*(4), 320-325.

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 > 13 years post menopause.*
- There is no evidence to support routine discontinuation of hormone therapy after age 65.

JoAnn V. Pinkerton (2017) Changing the conversation about hormone therapy, Climacteric, 20:4, 293-295, DOI: 10.1080/13697137.2017.1346280
To link to this article: https://doi.org/10.1080/13697137.2017.1346280

Current Treatment Guidelines
Females

NAMS Position (2017):
- 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 progesterone to those investigated in WHI for vasomotor symptom relief:
- May be associated with different risk and stroke/VTE profile than CEE and CEE+MPA

JoAnn V. Pinkerton (2017) Changing the conversation about hormone therapy, Climacteric, 20:4, 293-295, DOI: 10.1080/13697137.2017.1346280
To link to this article: https://doi.org/10.1080/13697137.2017.1346280

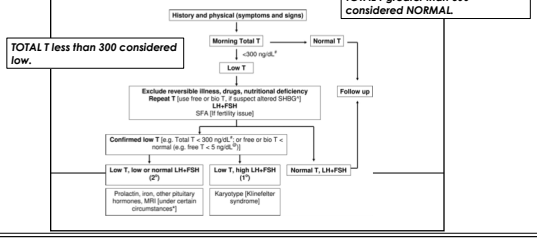
What's missing from the conversation?
Androgen insufficiency in women and the impact on HRQOL.

From Testosterone Replacement Therapy (TRT) to Andropausal Hormone Therapy

Available Clinical Guideline for Male HRT

TOTAL T greater than 300 considered NORMAL

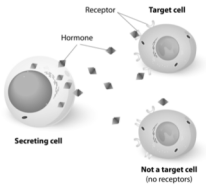
TOTAL T less than 300 considered low.



From: Testosterone Therapy in Adult Men with Androgen Deficiency Syndromes: An Endocrine Society Clinical Practice Guideline

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*.



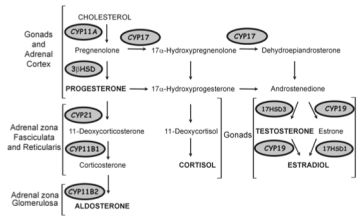
Understand the Nomenclature

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

19

Steroid Pathway

Payne, A. H., & Hales, D. B. (2004). Overview of steroidogenic enzymes in the pathway from cholesterol to active steroid hormones. *Endocrine reviews*, *25*(6), 947-970.



20

Sources of Sex Hormones

Endogenous Production:

- Estrogen & Testosterone
  - Ovaries (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
- Progesterone:
  - Only produced by ovaries
  - Post-menopause = no progesterone

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:

Its not just about hot flashes!

Estradiol's pivotal role in all major organ systems:

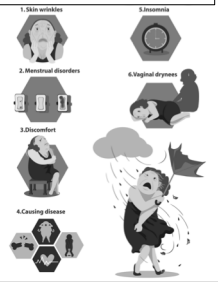
Key hormone of reproduction

Heart health (anti-inflammatory)

Bone density
- Osteoporosis prevention (bone builder, along with testosterone)

Colon cancer
- Low estradiol levels linked to increased rates of colon cancer

Vital to brain health
- Alzheimer's disease prevention (inflammation- beta amyloid deposition)
- Mood alterations & depression
- Mental clarity, memory, cognition



22

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.

Petrone, A. B., Simpkins, J. W., & Ran, Y. L. (2014). 17β-estradiol and inflammation: implications for ischemic stroke. *Aging and disease*, *5*(3), 240.

Benefits of Estrogen

- Decreases LDL/Increase 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 dysfunction
  - Colorectal cancer
  - Glaucoma, cataracts & macular degeneration
  - Memory & cognitive decline
  - Osteoporosis
  - Tooth loss/gingival atrophy

The Cost of Estradiol (ET) Avoidance

TABLE 1—Mortality Estimates for All Women Aged 50–59 Years Using 2 Different Rates of Hysterectomy: United States, 2002–2011

Hysterectomy Rate,[a] %	Population Size[b]	Decline in Estrogen Use,[c] %	Excess Mortality Estimate, No. (95% CI)
39			
2002	17 307 862	28	2115 (976, 3254)
2003	17 851 925	45	3399 (1569, 5229)
2004	18 413 377	53	4219 (1947, 6490)
2005	19 094 469	58	4738 (2188, 7291)
2006	19 769 666	58	4907 (2265, 7548)
2007	20 671 964	63	5442 (2512, 8372)
2008	20 472 322	63	5390 (2942, 8539)
2009	20 853 904	63	5654 (2610, 8698)
2010	21 506 008	70	6467 (2984, 9950)
2011	21 933 149	70	6616 (3054, 10 178)
Cumulative total			49 128 (22 677, 75 580)
40			
2002	17 307 862	28	2564 (1184, 3944)
2003	17 851 925	45	4120 (1902, 6338)
2004	18 413 377	53	5114 (2360, 7867)
2005	19 094 469	58	5744 (2652, 8837)
2006	19 769 666	58	5948 (2745, 9150)
2007	20 671 964	63	6596 (3045, 10 147)
2008	20 472 322	63	6737 (3109, 10 366)
2009	20 853 904	63	6855 (3165, 10 545)
2010	21 506 008	70	7863 (3593, 12 097)
2011	21 933 149	70	8030 (3638, 12 337)
Cumulative total			59 549 (27 486, 91 610)

Note. CI = confidence interval; 95% CIs are derived from the 95% CI around the excess death rate. The excess death[a] rate is 0.0013.

Applying the lower estimate for hysterectomy rate in the population, the best point estimate for excess mortality over 10 years is **49 128 excess deaths**, and the extreme low estimate is **22 677** excess deaths.

Applying a higher estimated rate of hysterectomy in the population, the best point estimate for excess mortality over 10 years is **59 549 excess deaths**, and the extreme high estimate is **91 610.**

Sarrel, P. M., Njike, V. Y., Vinante, V., & Katz, D. L. (2013). The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *American journal of public health*, *103*(7), 1363–1368.

The Cost of HT (ET) Discontinuation

- Discontinuation of postmenopausal HT (estrogen) may be associated with increased risk of cardiac and stroke death in the first posttreatment year.
- Increased cardiovascular death risks 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 (estrogen withdrawal) results in the loss of the beneficial effects of HT on organ systems and tissues across the human body, such as the cardiovascular and skeletal systems.

1. Vemelkoski, M., Sovalainen-Pelttonen, H., Rahkola-Soisalo, P., Hoti, F., Vahlstrand, P., Gissler, M., ... & Mikkola, T. S. (2018). Increased cardiac and stroke death risk in the first year after discontinuation of postmenopausal hormone therapy. *Menopause*, *25*(4), 370-379.
2. Salpeter, S. R., Cheng, J., Thabane, L., Buckley, N. S., & Salpeter, E. E. (2009). Bayesian meta-analysis of hormone therapy and mortality in younger postmenopausal women. *The American journal of medicine*, *122*(11), 1016-1022.
3. Sarrel, P. M., Njike, V. Y., Vinante, V., & Katz, D. L. (2013). The mortality toll of estrogen avoidance: an analysis of excess deaths among hysterectomized women aged 50 to 59 years. *American journal of public health*, *103*(7), 1363-1368.
4. Mikkola, T. S., Tuomikoski, P., Lyytinen, H., Korhonen, P., Hoti, F., Vahlstrand, P., ... & Ylikorkala, O. (2005). Increased cardiovascular mortality risk in women discontinuing postmenopausal hormone therapy. *The Journal of Clinical Endocrinology & Metabolism*, *150*(12), 4288-4294.
5. Hodis, H. N., & Mack, W. J. (2018). Cardiovascular risk after withdrawal of hormone therapy. *Menopause*, *25*(4), 365-367.

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.

Cersosimo, M. G., & Benarroch, E. E. (2015). Estrogen actions in the nervous system: Complexity and clinical implications. *Neurology*, 10-1212.

Symptoms & Impact: *Females*

Employment

Relationships

Informal caregiving: *children, spouses, parents*

Home life/responsibilities

Menopausal 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 conversation – especially during peri-menopause, which can last 2-8 years.

Many women think they are going "crazy"

Only 10% of women with symptoms seek medical advice.

Woods NF et al. *Am J Med.* 2005;118 Suppl 12B:14. DiBonaventura MD et al. *The Primary Care Companion to CNS Disorders.* 2012; 14(6)

Diagnosing Estrogen Insufficiency in Females

Menstrual cycles

- Pre-menopause
- Peri-menopause
- Post-menopause

FSH Labs

- Greater than 23 indicates estrogen fluctuations/insufficiency

Estradiol labs

- 70-100

Progesterone

- Synthetics
  - Progestins
  - Progestogens
  - Gestagens
- 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.

Progesterone

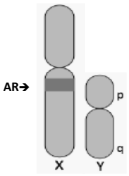
- There are progesterone receptor sites in the uterus, breast, vagina, blood , bone and brain.
- Reduces symptoms of PMS.
- Reduces symptoms of menopause & perimenopause.
- Studies show protects against breast cancer, osteoporosis, heart disease (PEPI) whereas MPA increases these risks.
- All pre/peri and post- menopausal women need adequate progesterone to oppose stimulation of breast and uterine tissue by estrogen.

Testosterone
Its not just for men!

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

Testosterone is the most abundant active hormone in men AND women:

- Derived from ovaries, testicles and adrenals
- Acts at cellular level with direct effect at the androgen receptor (AR)
- Precursor for DHT and Estradiol (ER)



- Longcope C. Adrenal and gonadal androgen secretion in normal female. J Clin Endocrinol Metab. 1986;15:213-228.
- Burger HG. Androgen production in women. Fertility and sterility. 2002;77:3-5.

Androgen Receptors are EVERYWHERE

Hair follicle, skin, scalp

Brain, spinal cord, nerves
Eyes, ears

Thyroid, endocrine glands

Cardiovascular

< Breast >

Pulmonary (Lungs, bronchi)

GI tract, liver, pancreas kidneys, adrenals

Uterus, vagina, bladder

Sexual organs

Muscle (smooth/striated)

Bone, bone marrow, joints

Fat

1. Kimura NORIKO, Misakami ATSUSHI, Oonuma TETSUTAROU, Sasano HIRONOBU, Nagura HIROSHI. Immunocytochemical localization of androgen receptor with polyclonal antibody in paraffin-embedded human tissues. Journal of Histochemistry & Cytochemistry. 1991;41:671-678.
2. Takeda H. Immunohistochemical localization of androgen receptors with mono-and polyclonal antibodies to androgen receptor. 1990
3. Wilson CM, McPhaul MJ. A and B forms of the androgen receptor are expressed in a variety of human tissues. Molecular and cellular endocrinology. 1994;120:51-57.
4. Quigley CA, Bellis AD, Marschke KB, El-Awady MK, Wilson EM, French FS. Androgen Receptor Defects: Historical, Clinical, and Molecular Perspectives*. Endocrine reviews. 1995;16:271-321.
5. Richards M. Hidden in Plain Sight: A Real Solution to the Diseases of Aging and the Imploding Medicare System.

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**
- **Moodiness**
- **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

- Prevention of:
  - CAD
  - Diabetes/insulin resistance
  - Prostate cancer
  - Alzheimer's (beta amyloid production prevention)
  - Depression and mood disorders
  - Sexual dysfunction
  - Sleep dysfunction
  - Memory & cognitive decline
  - Osteoporosis

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 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.

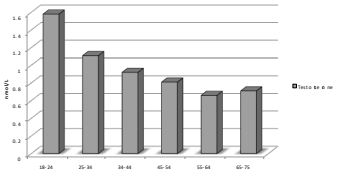
Despite the complexities involved with defining FAIS, the symptoms have been reported to respond well to testosterone replacement.

Rivera-Woll, L. M., Papaleo, M., Davis, S. R., & Burger, H. G. (2004). Androgen insufficiency in women: diagnostic and therapeutic implications. *Human reproduction update*, *10*(3), 421-432.

Androgen deficiency in Women

Androgens peak in women in their twenties

Symptoms may occur across the lifespan



Davis, S. R., Davison, S. L., Donath, S., & Bell, R. J. (2005). Circulating androgen levels and self-reported sexual function in women. *Jama*, *294*(1), 91-96.
Davison, S. L., Bell, R., Donath, S., Montalto, J. G., & Davis, S. R. (2005). Androgen levels in adult females: changes with age, menopause, and oophorectomy. *The Journal of Clinical Endocrinology*

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.

Abandoning myths, misconceptions and unfounded concerns about T and T therapy in women will enable health-practitioners to provide evidenced based recommendations and appropriate therapy.

Testosterone therapy in women: Myths and misconceptions
Rebecca Glaser, Constantine Dimitrakakis. Maturitas. 2012.

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 binds free T

GRAY, A., FELDMAN, H. A., McKINLAY, J. B., & LONGCOPE, C. (1991). Age, disease, and changing sex hormone levels in middle-aged men: results of the Massachusetts Male Aging Study. *The Journal of Clinical Endocrinology & Metabolism*, *73*(5), 1016-1025.

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*

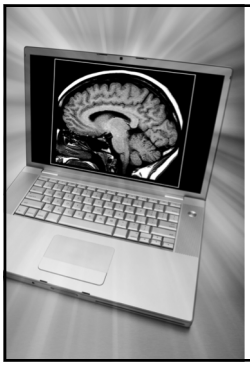
No established "normal" blood levels/ranges in women

Rachmann, G., Bancroft, J., Braunstein, G., Burger, H., Davis, S., Dennerstein, L., ... & Notelovitz, M. (2002). Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertility and sterility*, *77*(4), 660-665.

Diagnosing Androgen Deficiency:
Do the lab values matter?

- 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

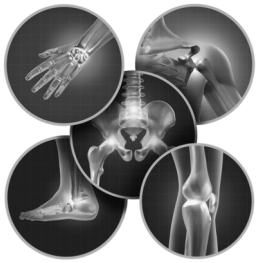
Carruthers, M. (2008). The paradox dividing testosterone deficiency symptoms and androgen assays: a closer look at the cellular and molecular mechanisms of androgen action. *The Journal of sexual medicine, 5*(4), 998-1012.



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 & Bones



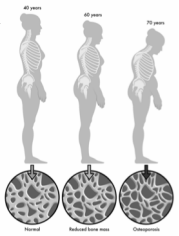
Sex Hormones & Bone

- 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.

Notelovitz, M., Johnston, M, Smith, S, & Kitchens, C. (1987). Metabolic and hormonal effects of 25 mg and 50 mg 17b-estradiol implants in surgically menopausal women. *Obstet Gynecol, 70*, 749-54.

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.



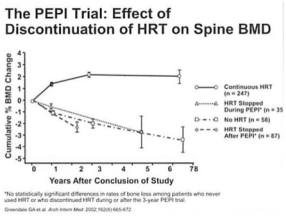
Savvas, M., Studd, J. W. W., Norman, S., Leather, A. T., Garnett, T. J., & Fogelman, I. (1992). Increase in bone mass after one year of percutaneous estradiol and testosterone implants in post-menopausal women who have previously received long-term oral oestrogens. *BJOG: An International Journal of Obstetrics & Gynecology, 99*(9), 757-760.

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.

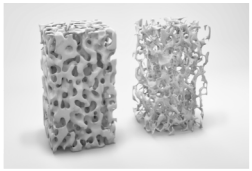
1. Gallagher, J. C., & Levine, J. P. (2011). Preventing osteoporosis in symptomatic postmenopausal women. *Menopause, 18*(1), 109-118.
2. Shea, K. L., Gavin, K. M., Melanson, E. L., Gibbons, E., Stevens, A., Wolfe, P., ... & Kohrt, W. M. (2015). Body composition and bone mineral density after ovarian hormone suppression with or without estradiol treatment. *Menopause (New York, NY), 22*(10), 1045.
3. Chilibeck, P. D., & Candow, D. G. (2007). Effect of estrogenic compounds (estrogen or phytoestrogens) combined with exercise on bone and muscle mass in older individuals. *Applied Physiology, Nutrition, and Metabolism, 32*(1), 208-212.
4. Felson, D. T., Zhang, Y., Hannan, M. T., Kiel, D. P., Wilson, P., & Anderson, J. J. (1993). The effect of postmenopausal estrogen therapy on bone density in elderly women. *New England Journal of Medicine, 329*(16), 1141-1146.

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



Greendale, G. A., Espeland, M., Slone, S., Marcus, R., & Barrett-Connor, E. (2002). Bone mass response to discontinuation of long-term hormone replacement therapy: results from the Postmenopausal Estrogen/Progestin Interventions (PEPI) Safety Follow-up Study. *Archives of Internal medicine, 162*(6), 665-672.

Discontinuation of (estradiol) HRT on Spine BMD



- Long-term HT-use protects from bone loss and wrist fracture, reducing, thus, the incidence of osteopenia and osteoporosis.
- 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 and fear of adverse effects or cancer.

Saarelainen, J., Hassi, S., Honkanen, R., Koivumaa-Honkanen, H., Sirola, J., Kröger, H., ... & Tuppurainen, M. (2016). Bone loss and wrist fractures after withdrawal of hormone therapy: The 15-year follow-up of the OSTPRE cohort. *Maturitas, 85*, 49-55.

Sex Hormones & The Brain

HRT and Neurodegenerative Conditions

- HRT and particularly ERT plays an efficacious role in preventing neurodegenerative conditions.
- E2 (17B 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
  - *Progestin may dampen this affect.*
- Compared to non-users E2 used for avg. 15 years had increased cerebral blood flow.

Henderson, V. W. (2014). Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause. *The Journal of steroid biochemistry and molecular biology, 142*, 99-106.

Sex Hormones & Brain:
Alzheimer's Disease

- 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.

Pike, C. J. (1999). Estrogen Modulates Neuronal Bcl-xl Expression and β-Amyloid-Induced Apoptosis: Relevance to Alzheimer's Disease. *Journal of neurochemistry, 73*(4), 1552-1560.

Alzheimer's Disease- Cache County Utah Study

- 1800 patients
- 30% reduction if MHT started within 5 years of menopause and especially if used for more than 10 years (estradiol).

Shao, H., Breitner, J. C., Whitmer, R. A., Wang, J., Hayden, K., Wengreen, H., ... & Welsh-Bohmer, K. (2012). Hormone therapy and Alzheimer disease dementia: New findings from the Cache County Study. Neurology, 79(18), 1846-1852.

Zandi, P. P., Carlson, M. C., Plassman, B. L., Welsh-Bohmer, K. A., Mayer, L. S., Steffens, D. C., ... & Cache County Memory Study Investigators. (2002). Hormone replacement therapy and incidence of Alzheimer disease in older women: the Cache County Study. Jama, 288(17), 2123-2129.

Estradiol, Inflammation & Stroke

- 17-beta-estradiol (17β-E2), protects the brain from ischemic injury following stroke.
- 17β-E2 activates of several neuroprotective pathways in the brain.
- 17β-E2 mediates the local and systemic immune response to ischemic stroke.
  - Estrogen is an immunomodulator

1. Petrone, A. B., Simpkins, J. W., & Barr, T. L. (2014). 17β-estradiol and inflammation: implications for ischemic stroke. *Aging and disease*, *5*(5), 340.
2. Petrone, A. B., Rudy, C. C., Barr, T. L., Simpkins, J. W., & Reed, M. N. (2015). Neuroprotective effects of estrogen following neural injury. In *Estrogen Effects on Traumatic Brain Injury* (pp. 91-117).

Estradiol, Inflammation & Stroke

- 17β-E2 protects the brain against stroke.
- Multiple ways 17β-E2 is protective from advanced injury post stroke- see reference for deails.
- Following brain insult, 17β-E2 administration increases expression of several proteins involved in cell survival.
- 17β-E2 inhibits expression of pro-apoptotic proteins.
- Following brain injury or ischemia, there is a rapid local production of estrogen, indicating that the hormone may be involved in an immediate physiological response to limit tissue damage.
- The immune response following stroke dictates functional recovery and the extent of brain damage
  - 17β-E2 may be dually protective in stroke by also mediating the immune response.

1. Petrone, A. B., Simpkins, J. W., & Barr, T. L. (2014). 17β-estradiol and inflammation: implications for ischemic stroke. *Aging and disease*, *5*(5), 340.
2. de Tassigny, X. D. A. (2017). Outlook on the neuroprotective effect of estrogen. *Neural regeneration research*, *12*(11), 1798.

Discontinuation of Estradiol & Stroke

- Discontinuation of postmenopausal HT may be associated with increased risk of cardiac and stroke death in the first posttreatment year.
- Rapid withdrawal of estrogen at discontinuation of HT may, however, result in vasoconstriction and potentially adverse arterial changes and cardiovascular events, as the vasodilatory effects of estrogen suddenly cease.
- Declining estrogen may also modulate cardiac rhythm, perhaps via calcium ion channels or by preventing long QT interval
- Acute withdrawal of estrogen may predispose to fatal arrhythmias.
- Study Conclusion:
  - *Discontinuation of postmenopausal HT associated with increased risk of cardiac and stroke death during the first posttreatment year, particularly in women who discontinue HT before the age of 60 years.*

Vanettoski, M., Saukkonen-Petronen, H., Rahola-Soisalo, P., Hott, F., Vattulainen, P., Gissler, M., ... & Mikkola, T. S. **(2018).** Increased cardiac and stroke death risk in the first year after discontinuation of postmenopausal hormone therapy. *Menopause*, *25*(4), 375-379.

Estradiol *Memory & Cognition*

After bilateral common carotid artery occlusion (BCCAO)

- 17β -Estradiol preserves spatial memory.
- 17β -Estradiol prevents axonal damage.
- 17β -Estradiol prevents the loss of hippocampal dendritic spines
- Long-lasting effects of 17β -estradiol on neuronal survival and learning and memory at 6 months post occlusion.
- Long-lasting effects of 17β -estradiol on neuronal survival and learning and memory.
- Study Conclusion:
  - Low dose E2 replacement reverses BCCAO-induced reductions in cognitive impairment.

Zhu, Y., Zhong, Q., Zhong, W., Li, N., Dai, Y., Su, J., ... & Wang, R. (2017). Protective effect of 17β-estradiol upon hippocampal spine density and cognitive function in an animal model of vascular dementia. Scientific reports, 7, 42465.

Androgens & *Myelin repair*

- Testosterone promotes myelin repair.
- The most common demyelinating disease is multiple sclerosis (MS)
- MS involves autoimmune and inflammatory destruction of myelin sheaths and the death of oligodendrocytes, which are the myelin producing cells of the CNS.
- Urgently needed are effective new treatments for promoting the re-myelination of demyelinated axons.
- Testosterone treatment decreased hippocampal pathology by reducing microglial activation, restoring synaptic protein expression and improving synaptic transmission

Said Ghandour, Rhonda Voskuhl & Michael Schumacher (2014) The androgen receptor as a therapeutic target for myelin repair in demyelinating diseases, Expert Review of Endocrinology & Metabolism, 9:1, 5-7, DOI: 10.1586/17446651.2014.861740

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 *EARLY* P.D.

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

Risk of Parkinson's increases after Tamoxifen therapy.

Pavon, J. M., Whitson, H. E., & Okun, M. S. (2006). Parkinson's disease in women: a call for improved clinical studies and for comparative effectiveness research. *Maturitas*, *65*(4), 352–358.

Latourelle, J. C., Dybdahl, M., Destefano, A. L., Myers, R. H., & Lash, T. L. (2010). Risk of Parkinson's disease after tamoxifen treatment. *BMC neurology*, *10*(1), 28.

Testosterone & Depression

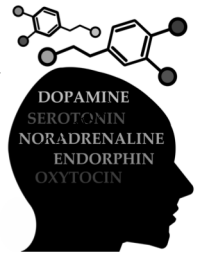
- ***Hundreds of studies support the relationship between androgens and depression in both women and men.***
- Sex hormones influence depression greatly in women, primarily testosterone in the pre menopause years.
- Women journeying through the menopause transition have a higher risk of increased new 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).

Bromberger, J. T., Kravitz, H. M., Youk, A., Schott, L. L., & Joffe, H. (2016). Patterns of depressive disorders across 13 years and their determinants among midlife women: SWAN mental health study. *Journal of affective disorders*, *206*, 31–40.

Bale, H. D. (2005). The impact of testosterone imbalance on depression and women's health. *Maturitas*, *51*, 25–36.

Testosterone & Depression

- The hippocampus and amygdala, critical regions in the brain owing to incidence of depression, are rich with androgen receptors, a key explanation of clinical response with androgen therapy.
- Serotonin plays a key role in the development of depression, and testosterone, as well as estrogen, has been shown to modulate serotonergic transmission.
- Sub-optimal testosterone levels in depressed women compared with women in a control group points to the role testosterone plays in depression.



Kleinger, M., Sievers, C., Ivan, D., Schneider, H. J., & Stalla, G. K. (2008). Is there a neuroendocrinological rationale for testosterone as a therapeutic option in depression? *Journal of Psychopharmacology*, *22*(7), 841–853.

Jovanovic, H., Kocoska-Maras, L., Rådestad, A. F., Hallbäck, C., Borg, J., Hirschberg, A. L., & Nordström, A. L. (2015). Effects of estrogen and testosterone treatment on serotonin transporter binding in the brain of surgically postmenopausal women–a PET study. *Neuroimage*, *106*, 47–54.

Kumar, Ş., Kumcar, N. A., Sağlam, H. S., Kilse, O., Budak, S., & Adsan, Ö. (2014). Testosterone levels and sexual function disorders in depressive female patients: effects of antidepressant treatment. *The journal of sexual medicine*, *11*(2), 529.

Testosterone Therapy & Depression

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

Davis, S. R., & Tran, J. (2001). Testosterone influences libido and well being in women. *Trends in Endocrinology & Metabolism*, *12*(1), 33–37.

Goldstat, R., Briganti, E., Tran, J., Wolfe, R., & Davis, S. R. (2003). Transdermal testosterone therapy improves well-being, mood, and sexual function in premenopausal women. *Menopause*, *12*(3), 290–300.

Zarrouf, F. A., Artz, S., Griffith, J., Sirbu, C., & Kommor, M. (2009). Testosterone and depression: systematic review and meta-analysis. *Journal of Psychiatric Practice®*, *15*(4).

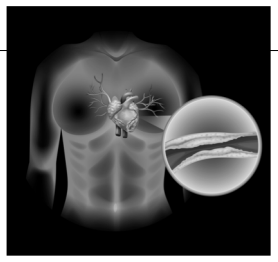
Studd, J., & Panay, N. (2004). Hormones and depression in women. *Climacteric*, *7*(4), 338–345.

MRS- Study of Depression Relief -2017

- 484 charts reviewed for women who received pellet HRT (androgen alone or androgen plus estradiol).
  - 87% 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=0.000).

DeNaul, T., Glider, K. & Michael, J. (2018). *Compliance with Post-Intervention Follow-up in the Depressive Pre. Peri and Post-Menopausal Client: A QI Initiative.* Unpublished Capstone Project. University of Texas of Arlington.

Sex Hormones & The Heart



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 unselected men with coronary disease.

Malkin, C. J., Pugh, P. J., Morris, P. D., Kerry, K. E., Jones, R. D., Jones, T. H., & Channer, K. S. (2004). Testosterone replacement in hypogonadal men with angina improves ischaemic threshold and quality of life. *Heart*, *90*(8), 871-876.

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 those at high risk of cardiovascular disease.

Khaw, K. T., Dowsett, M., Folkerd, E., Bingham, S., Wareham, N., Luben, R., ... & Day, N. (2007). Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation*, *116*(23), 2694-2701.

SEX HORMONES & THE HEART: CARDIOVASCULAR DISEASE

- Low testosterone is an independent predictor of severity of CAD
  - After adjustment for age, BMI, smoking history, hypertension, diabetes mellitus, dyslipidemia and history and treatment of heart disease
- Low serum testosterone are an independent predictor for Gensini 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.

Gururani, K., Jose, J., & George, P. V. (2016). Testosterone as a marker of coronary artery disease severity in middle aged males. *Indian heart journal*, *68*, S15-S20.

SEX HORMONES & THE HEART: CARDIOVASCULAR DISEASE

- Men with low testosterone have a high prevalence of cardiovascular disease and metabolic syndrome
  - Testosterone therapy in these individuals has been associated with reduced obesity, fat mass, waist circumference, decreased mortality, improved glycemic control and overall cardiometabolic status compared with placebo.
- 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 diseases and cancer.
- All-cause mortality is increased in hypogonadal men with Type 2 diabetes and testosterone therapy reduces mortality to 8.4% compared with 19.2% in the untreated group.
- Low testosterone levels are associated with endothelial dysfunction which can be reverted by testosterone therapy.
- Low levels of testosterone are associated with endothelial dysfunction, independent of body mass index, presence of diabetes, hyperlipidemia or hypertension and age.

Lucas-Herald, A. K., Alves-Lopes, R., Montezano, A. C., Ahmed, S. F., & Touyz, R. M. (2017). Genomic and non-genomic effects of androgens in the cardiovascular system: clinical implications. *Clinical Science*, *131*(13), 1405-1418.

SEX HORMONES & THE HEART: CARDIOVASCULAR DISEASE

- Androgenic hormones are beneficial for endothelial cells (ECs) because these hormones induce nitric oxide production, proliferation, motility, and growth of ECs.
- Androgens inhibit inflammatory activation and induction of procoagulant, and adhesive properties in ECs.
- Androgens show anti-thrombotic properties, thereby possessing the cardioprotective function.

Chistiakov, D. A., Myasoedova, V. A., Melnichenko, A. A., Grechko, A. V., & Orekhov, A. N. (2018). Role of androgens in cardiovascular pathology. *Vascular health and risk management*, *14*, 283.

SEX HORMONES & THE HEART: AMI

- 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.

Daka, B., Langer, R. D., Larsson, C. A., Rosén, T., Jansson, P. A., Råstam, L., & Lindblad, U. (2015). Low concentrations of serum testosterone predict acute myocardial infarction in men with type 2 diabetes mellitus. *BMC endocrine disorders*, *15*(1), 35.

SEX HORMONES & THE HEART Hypertension

- Molecular mechanisms linking androgen dysregulation to hypertension seem to be related to increased visceral fat, promoting a chronic inflammatory state through different mechanisms.
- One proposed mechanism may involve the recruitment and over-activation of NF-kB where it may cause the production of inflammatory cytokines and other immune 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.

Moretti, C., Lanzolla, G., Moretti, M., Gnessi, L., & Carmina, E. (2017). Androgens and hypertension in men and women: a unifying view. *Current hypertension reports*, *19*(5), 44.

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.

Debing, E., Peeters, E., Duquet, W., Poppe, K., Velkeniers, B., & Van den Brande, P. (2007). Endogenous sex hormone levels in postmenopausal women undergoing carotid artery endarterectomy. *European journal of endocrinology*, *156*(6), 687-693.

Estradiol & The Heart: *Cardiovascular Disease in Women*

ELITE: Early Versus Late Intervention Trial With Estradiol

- Purpose of the study was to examine the effects of oral 17B-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.

Hodis, H. N., Mack, W. J., Shoupe, D., Azen, S. P., Stanczyk, F. Z., Hwang-Levine, J., ... & Henderson, V. W. (2014). Testing the menopausal hormone therapy timing hypothesis: the Early versus Late Intervention Trial with Estradiol.

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.

Davis, S. R., Walker, K. Z., & Strauss, B. J. (2000). Effects of estradiol with and without testosterone on body composition and relationships with lipids in postmenopausal women. *Menopause*, *7*(6), 395-401.

Estradiol & The Heart: *Cardiovascular Disease*

- 17β -estradiol (E2) and activated Estrogen Receptors (ER) protect the heart from ischemic injury.
- Postmenopausal HT use is accompanied with reduced mortality risk after primary ACS.
- Estrogen should be considered as a preventative strategy for reduction of bone loss, bone fractures, new onset diabetes mellitus, **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.

1. Mahmoodzadeh, S., Leber, J., Zhang, X., Jaisser, F., Messaoudi, S., Morano, I., ... & Regitz-Zagrosek, V. (2014). Cardiomyocyte-specific estrogen receptor alpha increases angiogenesis, lymphangiogenesis and reduces fibrosis in the female mouse heart post-myocardial infarction. *Journal of cell science & therapy*, *5*(1), 153.
2. Tuomikoski, P., Salomaa, V., Havulinna, A., Airaksinen, J., Ketonen, M., Koukkunen, H., ... & Mikkola, T. S. (2016). Decreased mortality risk due to first acute coronary syndrome in women with postmenopausal hormone therapy use. *Maturitas*, *94*, 106-109.
3. Lobo, R. A., Pickar, J. H., Stevenson, J. C., Mack, W. J., & Hodis, H. N. (2016). Back to the future: hormone replacement therapy as part of a prevention strategy for women at the onset of menopause. *Atherosclerosis*, *254*, 282-290.

Estradiol & The Heart: *Cardiovascular Disease*

- 489,105 women who used HT from 1994 to 2009 (3.3 million HT exposure years)
- Risk reductions 19 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.

Mikkola, T. S., Tuomikoski, P., Lyytinen, H., Korhonen, P., Hoti, F., Vattulainen, P., ... & Ylikorkala, O. (2015). Estradiol-based postmenopausal hormone therapy and risk of cardiovascular and all-cause mortality. *Menopause*, *22*(9), 976-983.

Estradiol & The Heart: *Cardiovascular Disease*

- Coronary arteries, expressing estrogen receptors, are a target for estrogen action.
- Prior to the Women's Health Initiative (WHI) study, postmenopausal hormone therapy (HT) was widely advocated for primary prevention of CAD, but such use was criticized after the WHI publication.
- New data accumulated in the USA and in Europe indicate that the use of estradiol-based HT regimens does not endanger the heart, but rather, it significantly reduces the incidence of CAD events and mortality.
- Discontinuation is not recommended as new data shows acute withdrawals of estradiol from the circulation may predispose to potentially fatal CAD events.
- Estrogen has important effects on cardiovascular function including regulation of vascular function, blood pressure, endothelial relaxation, the development of hypertrophy and cardio-protection.

1. Mikkola, T. S., Savolainen-Peltonen, H., Venetkoski, M., & Ylikorkala, O. (2017). New evidence for cardiac benefit of postmenopausal hormone therapy. *Climacteric*, *20*(1), 5-10.
2. Menazza, S., & Murphy, E. (2016). The expanding complexity of estrogen receptor signaling in the cardiovascular system. *Circulation research*, *118*(6), 994-1007.

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 TG.
- In healthy men, estradiol level is positively associated with levels of apolipoprotein A and regulation of systolic and diastolic blood pressure.
- E2 acts along with testosterone to maintain normal levels of insulin sensitivity.
- The effects of estrogens can also be explained by their action as regulators of nitric oxide.
- An association was observed between elevated levels of estradiol and reduced risk of cardiovascular disease for men older then 56 years.

Fiete-Asín, B. (2007). Estrogens and cardiovascular disease in the male. *Revista espanola de cardiologia*, *60*(04), 447-448.

Testosterone, D3 & CAD

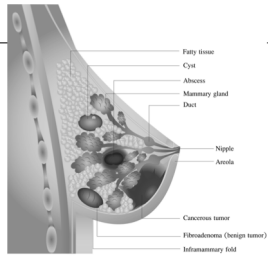
- Deficiencies of *either* free testosterone or 25-hydroxyvitamin D resulted in a 40% increased risk for all-cause mortality (p=0.002)
- Deficiencies of free testosterone *and* 25-hydroxyvitamin D resulted in a 77% increased risk for cardiovascular mortality (p<0.001)
- Deficiencies of free testosterone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

Always check D3 levels

Goal: >60

Nimptsch, K., Platz, E. A., Willett, W. C., & Giovannucci, E. (2012). Association between plasma 25-OH vitamin D and testosterone levels in men. *Clinical endocrinology*, *77*(1), 106-112.

Sex Hormones & Breast Cancer



Sex Hormones & *Breast Cancer*

- Woman'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.

Glaser, R. L., & Dimitrakakis, C. (2014). Rapid response of breast cancer to neoadjuvant intramammary testosterone-anastrozole therapy: neoadjuvant hormone therapy in breast cancer. *Menopause (New York, NY)*, *21*(6), 673.

Glaser, R., & Dimitrakakis, C. (2015). Testosterone and breast cancer prevention. *Maturitas*, *82*(3), 291-295.

Sex Hormones & *Breast Cancer*

- Women with symptoms of hormone deficiency treated with pharmacological doses of T alone or in combination with anastrozole (A), delivered by subcutaneous implants, had a reduced incidence of BCA.
- T combined with A effectively treated symptoms of hormone deficiency in BCA survivors and was not associated with recurrent disease.
- Clinical and non human primate studies suggest androgens inhibit mammary epithelial proliferation and breast growth.

Glaser, R. L., & Dimitrakakis, C. (2014). Rapid response of breast cancer to neoadjuvant intramammary testosterone-anastrozole therapy: neoadjuvant hormone therapy in breast cancer. *Menopause (New York, NY)*, *21*(6), 673.

Glaser, R., & Dimitrakakis, C. (2015). Testosterone and breast cancer prevention. *Maturitas*, *82*(3), 291-295.

Dimitrakakis, C., & Bondy, C. (2009). Androgens and the breast. *Breast cancer research*, *11*(5), 212.

Sex Hormones & *Breast Cancer*

- Predominant 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 direct (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.
- ERT does not increase either recurrence of breast cancer or mortality rates.

P. Natrajan and Gambrell et al Am. Journal of OB/GYN. Volume 187, No. 2, Aug 2002 Estrogen Replacement Therapy In Women with Previous Breast Cancer Menopause International 2008; 14: 117-122.

Sex Hormones & *Breast Cancer*

- Progestins (MPA) stimulate proliferation of breast tissue and cancer cells.
- Progestins (MPA) upregulates estrogen receptor sites- increase breast pain, swelling, thickness and cancer.
- **Progesterone (MP)** alone or with estradiol decreased stimulation and proliferation of breast tissue and cancer cells.
- Mitogenic activity is higher with estrogen/MPA and LOWER with estrogen / MP
- Progesterone could be a promising drug for breast cancer

Gizard F, Robillard R, Gervois P, et al. Progesterone inhibits human breast cancer cell growth through transcriptional upregulation of the cyclin-dependent kinase inhibitor p27Kip1 gene. FEBS Lett. 2005 Oct 24;579(26):5835-41.
Campagnoli C, Abba C, Ambroggio S, Perlo C. Pregnancy, progesterone and progestins in relation to breast cancer risk. J of Steroid Biochemb Molecular Biol. 2005;97:431-435.
Foidart JM, Colin C, Denoo X, et al. Estradiol and progesterone regulate the proliferation of human breast epithelial cells. Fertil Steril. 1998 May;69(5):963-9.
Wood CE, Register TC, Lees CJ, et al. Effects of estradiol with micronized progesterone or medroxyprogesterone acetate on risk markers for breast cancer in postmenopausal monkeys. Breast Cancer Res Treat. 2007 Jan;101(2):125-34.

Estrogen & *Breast Cancer*

- Estrogen therapy shows no risk in breast ca survivors
- Estrogen therapy does not increase breast cancer recurrence or mortality
- Estrogen therapy safe for women, even breast cancer survivors
- Estrogen therapy does not increase risk of recurrence or death in patients with early breast cancer
- There is not evidence to support universal withholding of estrogen in women who have survived low stage breast cancer
- No increased risk of breast caner in estrogen plus progesterone users

Decker DA, Pettinga JG, VanderVelde N, et al. Estrogen replacement therapy in breast cancer survivors: a matched-controlled series. Menopause. 2003 Jul-Aug;10(4):277-85.
de Lignieres B, de Vathaire F, Fournier S, et al. Combined hormone replacement therapy and risk of breast cancer in a French cohort study of 3175 women. Climacteric. 2002;5:332-340.
Jancin B. HRT Safe for Survivors of Early-Stage Breast Ca. Family Practice News. 2001 Jun 1.
Natrajan PK, Gambrell RD. Estrogen replacement therapy in patients with early breast cancer. Am J Obstet Gynecol. 2002 Aug;187(2):289-94.
Natrajan PK, Soumakis K, Gambrell RD Jr. Estrogen replacement therapy in women with previous breast cancer. Am J Obstet Gynecol. 1999 Aug;181(2):288-95.
Lesgar M. Hormone therapy for women after breast cancer. J of Reprod Med. 2004 Jul;49(7):510-26.
Peters GN, Fodera T, Saboil J, et al. Estrogen replacement therapy after breast cancer: a 12-year follow-up. Ann Surg Oncol. 2001 Dec;8(10):828-32.

Testosterone therapy for Breast Cancer?

Historically testosterone was the most common line of hormonal therapy for breast cancer, but its use has been almost completely abandoned in the past 50 + years.

- Late 1940's-1950's 58.5% response in hormone resistant metastatic BCA (Test cypionate studied)
- 53 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%

- Bonl C, Pagano M, Panebianco M et al. Therapeutic Activity of Testosterone in Metastatic Breast Cancer. Anticancer research. 2014;34:1287-1290.
- Goldenberg, I.S. (1964). Testosterone Propionate Therapy in Breast Cancer. JAMA, 188(12), 117-120.
- Kouth, H.D. & DeNicosapo, N. (1960). Report to the Council: Androgens and estrogens in the treatment of disseminated mammary carcinoma. JAMA, 172(12), 135-172.

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 peritumorally 48 days later.
  - *Day 46, 7-fold reduction in tumor volume, as measured on ultrasound.*
  - *Week 13,12-fold reduction in tumor volume.*
- Therapeutic systemic levels of testosterone were achieved without elevation of estradiol.

Glaser, R. L. & Dimitrakakis, C. (2013). Reduced breast cancer incidence in women treated with subcutaneous testosterone, or testosterone with anastrozole: a prospective, observational study. Maturitas, 76(4), 342-349.

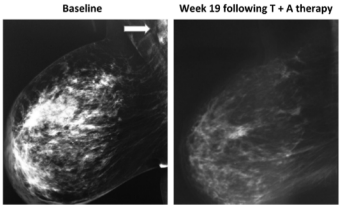


Fig. 3. Comparison mammography, right medial lateral oblique view at baseline (left) and at follow up (right), week 19 following neoadjuvant, intramammary T + A therapy of infiltrating lobular, hormone receptor positive BCA (ER+, PR+, AR+). Note the significant reduction in tumor size and absence of previously palpable axillary lymph nodes. (Previously unpublished images, Glaser, Dimitrakakis).

Courtesy of Rebecca Glaser MD

Sex Hormones & Prostate

Sex Hormones & *Prostate*

- Men with high T ***not*** at risk for prostate cancer
- Low T affords ***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 level if post prostate cancer and desires T therapy (2 years out standard of care)
  - *Estrogen therapy?*

Khera, M., Crawford, D., Morales, A., Salonia, A., & Morgentaler, A. (2014). A new era of testosterone and prostate cancer: from physiology to clinical implications. *European urology, 65*(1), 115-123.

Sex Hormones & *Prostate*

- 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 PS- *No increase risk of recurrence.*
- **Low** levels of **testosterone** an *independent risk factor* for **prostate cancer.**
- Adding testosterone levels to PSA's may improve predictive accuracy.

Morgentaler, A., Lipshultz, L. I., Bennett, R., Sweeney, M., Avila, D., & Khera, M. (2011). Testosterone therapy in men with untreated prostate cancer. *The Journal of urology, 185*(4), 1256-1261.

Pastuszak, A. W., Pearlman, A. M., Lai, W. S., Godoy, G., Sathyamoorthy, K., Liu, J. S., ... & Khera, M. (2013). Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *The Journal of urology, 190*(2), 639-644.

Sex Hormones & Pain

Sex Hormones & *Pain*

- Testosterone deficiency in chronic pain patients has now been recognized by many observers.
- Due to its critical biologic 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.

Tennant, F., & Uchoko, L. (2010). Testosterone replacement in chronic pain patients. *Pract Pain Manag, 10*, 12-15.

Margarete Melchior, Yannick Poisbeau, Isabelle Gaumond, Serge Marchand: Insights into the mechanisms and the emergence of sex-differences in pain. Neuroscience, Volume 338, 2016, pp. 53-80

Sex Hormones & *Pain*

- 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.

Amandusson, Å., & Blomqvist, A. (2013). Estrogenic influences in pain processing. *Frontiers in neuroendocrinology, 34*(4), 329-349.

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 spinothalamic 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.**

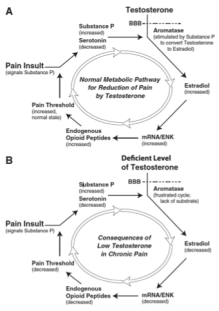
Ghorbanpoor, S., García-Segura, L. M., Naeni-Rohani, A., Khodaygholi, F., & Jorjani, M. (2014). Aromatase inhibition exacerbates pain and reactive gliosis in the dorsal horn of the spinal cord of female rats caused by spinothalamic tract injury. *Endocrinology*, *155*(11), 4341–4355.

Sex Hormones & *Pain*

- 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 commonalities 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.

White, H. D., & Robinson, T. D. (2015). A novel use for testosterone to treat central sensitization of chronic pain in fibromyalgia patients. *International Immunopharmacology*, *27*(2), 244-248.

Sex Hormones & *Pain Signaling*



White, H. D., & Robinson, T. D. (2015). A novel use for testosterone to treat central sensitization of chronic pain in fibromyalgia patients. *International Immunopharmacology*, *27*(2), 244-248.

Hormone Replacement Modalities

HRT Delivery Methods

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

Nomenclature confusion

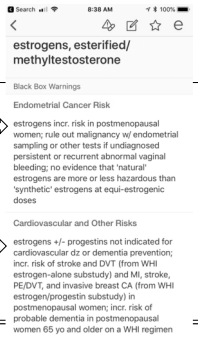
Not all therapies created equal!

Be VERY cautious when researching hormone therapies!

Literature and resources erroneously refer to ALL modalities of estrogen as "estrogens".

Major differences between mechanisms of action among types of HRT and modalities:

- CEE and estradiol
- Progesterone and Progestin
- Testosterone & methyltestosterone
- Sub-cutaneous, shots, oral, RDT, transdermal and transvaginal



102

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.
  - No spikes/roller coaster effect
- 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.
  - Side effect of hair growth at area of application.
- Poor absorption transdermally in typical application areas
  - Skin receptor may become de-sensitized over time.
  - Scrotal and labial application good absorption.
- Difficult to measure on laboratory assays.
  - Monitor symptom relief.
- Lipoderm base 10% (or 20%)
  - Males: 100-200mg/gm
  - ½-1 gm scrotal BID
  - Females: 20-40mg/gm
  - ¼-1/2 gm labial BID

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
  - 30 mg PO QD
- RDT (rapid dissolve tablets/ sublingual) bio-identical reported better clinical response and lower side effect profile than oral.
  - Direct to blood stream, no first pass metabolism
  - Testosterone Dose:
    - 2-10 mg QD or BID females
    - 200-400 mg QD or BID males

107

Potential Effects of **Oral** CE 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

Progesterone 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- rec 200 mg qhs
  - Pre/peri-menopause- rec 100 mg qhs
- *RDT:* 50-100 mg QD x 30 days (best for anxiety)
- *Pellets?*
- *Cream:* 200 mg/gm – 1 gm QID
  - $$$
  - Poor absorption
  - No good data on uterine protection

Progesterone 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.

Progest**in** (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 o 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
  - FSH shows average of what E2 levels been like HGA1C
  - 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 depressed, lowered mood.
- Other vague symptoms also present (brain fog, memory impairment, joint pain, insomnia).

- Diagnosis is 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 complexities involved with defining FAIS, symptoms have been reported to respond well to testosterone replacement.

Rivera-Woll, L. M., Pagalia, M., Davis, S. R., & Burger, H. G. (2006). Androgen insufficiency in women: diagnostic and therapeutic implications. *Human reproduction update*, *3*(5), 421-432.

Diagnosing Androgen Insufficiency
Do the lab values matter?

- 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

Carruthers, M. (2008). The paradox dividing testosterone deficiency symptoms and androgen assays: a closer look at the cellular and molecular mechanisms of androgen action. *The journal of sexual medicine*, *5*(6), 998-1012.

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.

COMMENTS: FASTING:NO

Test Name	In Range	Out Of Range
TESTOSTERONE, TOTAL AND FREE AND SEX HORMONE BINDING GLOBULIN		
TESTOSTERONE,FR(DIALYSIS) AND TOTAL(LC/MS/MS)		
TESTOSTERONE, TOTAL, LC/MS/MS		<1 L
This test was developed and its analytical performance characteristics have been determined by Quest Diagnostics Institute Valencia. It has not been cleared or approved b Food and Drug Administration. This assay has been validat pursuant to the CLIA regulations and is used for clinical purposes.		
FREE TESTOSTERONE		0.1 L
SEX HORMONE BINDING GLOBULIN		93 H

Tanner Stages (7-17 Years)	Male (nmol/L)	Female (nmol/L)
Tanner I	47-166	47-166
Tanner II	23-168	25-129
Tanner III	23-168	25-129
Tanner IV	21-79	35-86
Tanner V	9-49	15-130

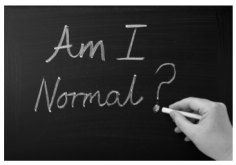
Bachmann, G., Bancroft, J., Braunstein, G., Burger, H., Davis, S., Dennerstein, L., & Notelovitz, M. (2002). Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertility and sterility*, *77*(4), 660-665.

Testosterone replacement
Clinical Decision vs. Labs

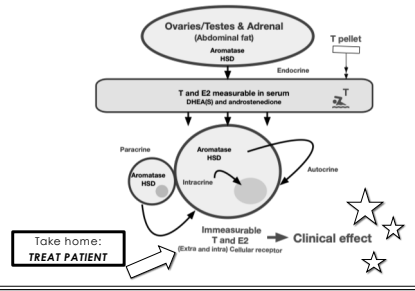
Hormone levels fluctuate and are unreliable.

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

An individuals physical comfort may not be related to their absolute hormone levels.



Sherif K, Sherif K. Medical Association Guidelines, Post-2002/Women's Health Initiative Findings. Hormone Therapy: A Clinical Handbook. 2010;23-3



Courtesy of Dr. Rebecca Glaser

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.
  - No standard assays or methodologies
- 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!!!"***

FOLLICLE STIM HORMONE	13.5	IU/L	SEE BELOW	MAIN
******* EXPECTED VALUES FOR FSH FOR FEMALES >17 YEARS *******				
FOLLICULAR . . . . . .IU/L		3.5-12.5		
MID-CYCLE PEAK . . . . . .IU/L		4.7-21.5		
LUTEAL . . . . . .IU/L		1.7-7.7		
POSTMENOPAUSAL . . . . . .IU/L		25.8-134.8		
TESTOSTERONE	179 H	NG/DL	<=55	MAIN
NOTE: TOTAL TESTOSTERONE ASSAY SENSITIVITY IS 12 NG/DL. TO DETERMINE NORMAL VS. SUBNORMAL TESTOSTERONE IN CHILDREN AND WOMEN, CONSIDER TESTING WITH ULTRASENSITIVE TESTOSTERONE.				
SEX HORM BIND GLOBULIN	87.5	NMOL/L	17.3-125.0	MAIN

UNLESS OTHERWISE INDICATED, ALL TESTING PERFORMED AT
CLINICAL PATHOLOGY LABORATORIES, INC. 9200 WALL ST AUSTIN, TX 78754
LABORATORY DIRECTOR: MARK A. HILSENBECK, M.D.
CLIA NUMBER 4505095003 CAP ACCREDITATION NO. 21525-01

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 nuero for work up.
- If normal OK to pellet after w/u.
- Depending on levels, may start very slow.
  - Consider oral BHRT to "ease" into therapy
  - Consider lower pellet dose to start with boost in 8 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 (most 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*
    - Arimadex 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 conversation 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

Polycystic Ovarian Syndrome *PCOS*

PCOS is an endocrine problem

- Not an ovarian issue, enlarged ovaries are a symptom only
- Primary defect is hyperinsulinemia.

Most common endocrine disorder in pre-menopausal women (10%)

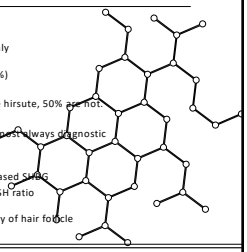
Easy to miss- 90% of PCOS women will be misdiagnosed

- Difficult to diagnose as 50% are overfat, 50% not; 50% are hirsute, 50% are NOT.
- Elevated LH/FSH greater than 2:1 is diagnostic
- Triad of hirsutism, obesity and abnormal menstruation almost always diagnostic

Difficult to manage (because we miss it and don't understand it)

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 so s/s of acne, hirsutism and sensitivity of hair follicle

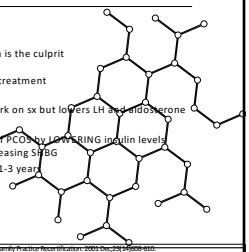


Hunter MH, Sterrett J. Polycystic ovary syndrome: it's not just infertility. American Family Physician. 2000 Sept 1;62(5):1079-1087.
Jancin B. Hyperinsulinemia, Not Ovaries, at Core of PCOS. Family Practice News. 2001 Jan 15:26.

PCOS TREATMENT

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 lowers LH and aldosterone acutely)
- Metformin cuts insulin, LH and test levels and reduces sx of PCOS by LOWERING insulin levels
- Metformin decreases testosterone hypersensitivity by increasing SHBG
- Metformin restores menstrual cycles and ovulation- takes 1-3 years
- Metformin goal 2000 mg daily
  - Often cant tolerate GI side effects
  - VERY slow titrate up



Sarraj O. How should I manage the young woman with menstrual abnormalities and hirsutism? Family Practice Recertification. 2003 Dec;25(4):609-610.

HRT in PCOS

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

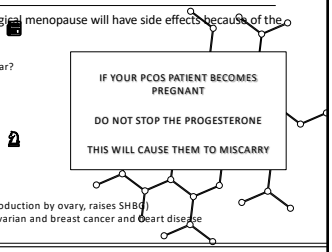
Excellent History is key

- 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



Hormone Insufficiency
Treatment Impact

128

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.

Sherwin, B. B., & Gelfand, M. M. (1985). Differential symptom response to parenteral estrogen and/or androgen administration in the surgical menopause. American Journal of Obstetrics and Gynecology, 151(2), 153–160.

Testosterone and Estrogen implants (100mg/50mg)
Studied over 4 years
Peri and postmenopausal women

TABLE I
SYMPTOM RELIEF.

Symptoms	Present (% of patients)		Complete relief (% of patients with symptom)		No relief (% of patients with symptom)	
	Group A	Group B	Group A	Group B	Group A	Group B
Hot flushes/sweats	71.7	89.6	97.4	86.7	0.0	0.0
Headaches	83.0	73.1	65.9	67.3	9.1	4.1
Insomnia	71.7	74.6	63.2	58.0	13.1	10.0
Palpitations	50.9	40.3	55.6	63.0	14.8	7.4
Bone pains	54.7	64.2	55.2	53.5	6.9	11.6
Dyspareunia	45.3	53.7	62.5	77.8	16.7	2.8
Loss of libido	84.9	82.1	66.7	67.3	6.7	10.9
Irritability	90.6	79.1	68.8	77.4	6.3	1.9
Poor memory/concentration	79.2	62.7	59.5	66.7	9.5	7.1
Depression	81.1	77.6	79.1	73.1	2.3	0.0
Lethargy	79.2	73.1	61.9	69.4	4.8	0.0
Urethral syndrome	13.2	26.9	28.6	50.0	28.6	16.7

Group A: peri-menopause **Group B: post-menopause**

Cardozo, L., Gibb, D. M., Turk, S. M., Thorn, M. H., Studd, J. W., & Cooper, D. J. (1984). The effects of subcutaneous hormone implants during the climacteric. Maturitas, 6(3), 177–184.

Androgen only therapy study

- 300 pre- and post-menopausal women with symptoms of relative androgen deficiency.
- Completed self-administered 11-item MRS (validated tool) at baseline and 3 months after their first insertion of the subcutaneous testosterone implant.
- Baseline hormone measurements, menopausal status and BMI, were assessed to determine correlation with symptoms and clinical outcome.

Menopause Rating Scale (MRS)

Which of the following symptoms apply to you at this time?
(X ONE Box For EACH Symptom) For Symptoms That Do Not Apply, Please Mark "None").

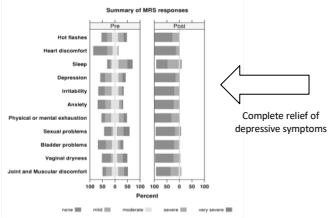
Symptoms:	none	mild	moderate	severe	extremely severe
Score =	0	1	2	3	4
1. Hot flashes, sweating (episodes of sweating)	☐	☐	☐	☐	☐
2. Heart discomfort (unusual awareness of heart beat, heart skipping, heart racing, tightness)	☐	☐	☐	☐	☐
3. Sleep problems (difficulty in falling asleep, difficulty in sleeping through the night, waking up early)	☐	☐	☐	☐	☐
4. Depressive mood (feeling down, sad, on the verge of tears, lack of drive, mood swings)	☐	☐	☐	☐	☐
5. Irritability (feeling nervous, inner tension, feeling aggressive)	☐	☐	☐	☐	☐
6. Anxiety (inner restlessness, feeling panicky)	☐	☐	☐	☐	☐
7. Physical and mental exhaustion (general decrease in performance, impaired memory, decrease in concentration, forgetfulness)	☐	☐	☐	☐	☐
8. Sexual problems (change in sexual desire, in sexual activity and satisfaction)	☐	☐	☐	☐	☐
9. Bladder problems (difficulty in urinating, increased need to urinate, bladder incontinence)	☐	☐	☐	☐	☐
10. Dryness of vagina (sensation of dryness or burning in the vagina, difficulty with sexual intercourse)	☐	☐	☐	☐	☐
11. Joint and muscular discomfort (pain in the joints, rheumatoid complaints)	☐	☐	☐	☐	☐

Glaser, R., York, A.E., & Dimitrakakis, C. (2010). Beneficial effects of testosterone therapy in women measured by the validated Menopause Rating Scale (MRS). Maturitas, doi:10.1016/j.maturitas.2010.12.001.

131

Conclusions:

- Continuous testosterone alone, delivered by subcutaneous implant, was effective for the relief of hormone deficiency symptoms in both pre- and post-menopausal patients.
- The validated, HRQOL questionnaire, Menopause Rating Scale (MRS), proved a valuable tool in the measurement of the beneficial effects of testosterone therapy in both cohorts.



Complete relief of depressive symptoms

Glaser, R., York, A.E., & Dimitrakakis, C. (2010). Beneficial effects of testosterone therapy in women measured by the validated Menopause Rating Scale (MRS). Maturitas, doi:10.1016/j.maturitas.2010.12.001.

132

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

A 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 35

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

The Patient Encounter

Case Study-Nicole

- 67 y/o female
  - Menopause x 14 years
  - Peri-menopause 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 HRT 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 recommend 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 re-initiation of HRT*

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
  - Maybe TPO Ab, RT3
- Understand thyroid evaluation is not about metabolism and hair loss.
  - Low FT3 associated with extreme depression, sleep disorders, chronic fatigue, fibromyalgia, memory, lipids, heart disease, heart failure, cancer, and many others.

139

Understanding Thyroid Physiology

- 20% OF T3 IS DIRECTLY EXCRETED BY THE THYROID GLAND
- LEVOTHYROXINE MONOTHERAPY DOESN'T REPLACE THIS LOST T3
- 80% OF T3 COMES FROM PERIPHERAL CONVERSION FROM T4
- T4 TO T3 CONVERSION IS REGULATED BY DEIODINASE 1 ENZYME
- DEIODINASE 1 IS INHIBITED BY:
  - Physiologic and emotional stress
  - Depression
  - Dieting
  - Insulin resistance
  - Inflammation from autoimmune disease or systemic illness
  - Chronic fatigue syndrome and fibromyalgia
  - Chronic pain
  - Chronic Stress
  - Exposure to toxins and plastics
  - LEVOTHYROXINE

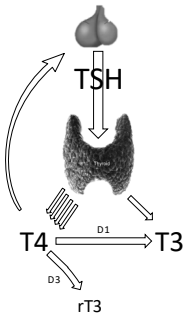
140

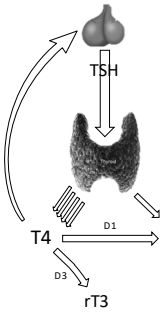
Understanding Thyroid Physiology

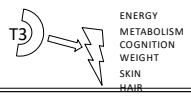
ONE OF THE MOST IMPORTANT THINGS TO UNDERSTAND IS THAT THE FACTORS THAT INHIBIT THE ACTION OF DEIODINASE 1, AND INHIBIT CONVERSION OF T4 TO T3, DO NOT INHIBIT DEIODINASE 2 IN THE PITUITARY GLAND, AND THEREFORE DO NOT AFFECT THE DOWN REGULATION OF TSH!

THEY ALSO DON'T INHIBIT DEIODINASE 3, WHICH CONVERTS T4 TO REVERSE T3!

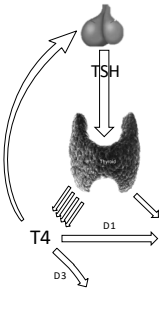
NOW, CAN YOU SEE WHERE THIS MIGHT CAUSE A FEW PROBLEMS?

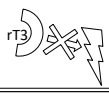






ENERGY
METABOLISM
COGNITION
WEIGHT
SKIN
HAIR





ENERGY
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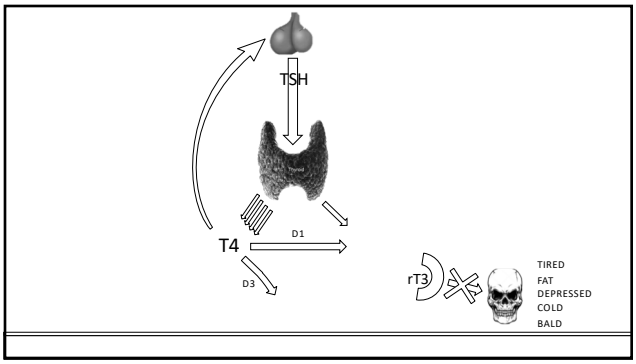

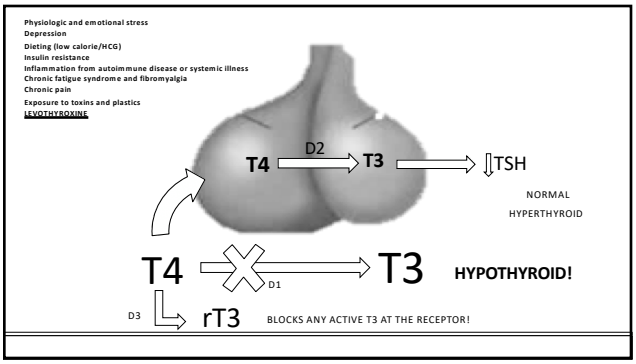

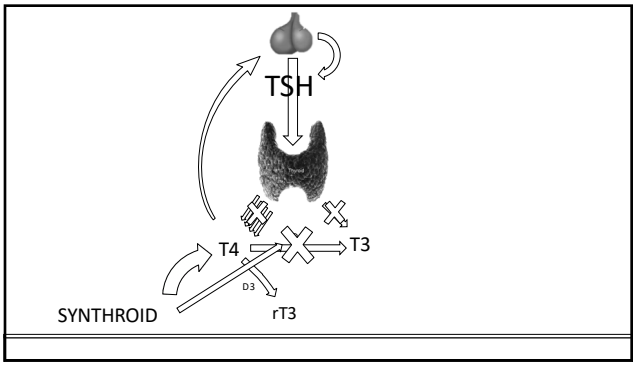

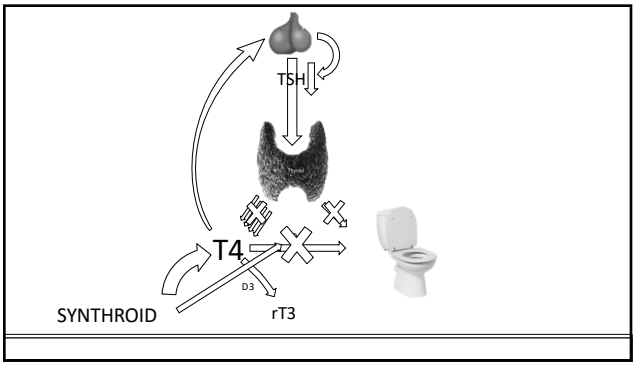

BUT THE

TSH

IS NORMAL,

SO YOU'RE JUST FINE!

Courtesy of Dr. Kenneth Wilgers

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 is in accordance with several clinical studies.

There is convincing evidence that a low T3 status is associated with reduced survival in the cardiac, nonsurgical 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.

Cerillo, A. G., Storti, S., Kallushi, E., Hashiademi, D., Micell, A., Murzi, M., ... & Iervasi, G. (2014). The low triiodothyronine syndrome: a strong predictor of low cardiac output and death in patients undergoing coronary artery bypass grafting. *The Annals of thoracic surgery*, *97*(6), 2089-2095. *Emphasis author's

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.***

Pingitore, A., & Iervasi, G. (2005). Thyroid (dys) function in heart failure: is it a potential target for medical treatment?. *Vascular health and risk management*, *1*(2), 97.

*Emphasis author's

151

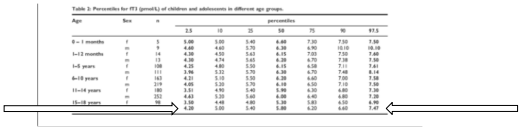

Table 3: Percentiles for fT3 (pmol/L) of children and adolescents in different age groups.

Age	Sex	n	percentiles						
			2.5	10	25	50	75	90	97.5
0 – 1 months	f	5	5.00	5.00	5.40	6.60	7.30	7.50	7.50
	m	9	4.60	4.60	5.70	6.20	6.90	10.10	10.10
1–12 months	f	14	4.30	4.50	5.63	6.15	7.02	7.50	7.60
	m	13	4.30	4.74	5.65	6.20	6.70	7.20	7.50
1–5 years	f	108	4.25	4.80	5.50	6.15	6.58	7.11	7.41
	m	111	3.96	5.12	5.70	6.30	6.70	7.40	8.14
6–10 years	f	163	4.21	5.10	5.50	6.20	6.60	7.00	7.58
	m	219	4.00	5.20	5.70	6.10	6.50	7.10	7.50
11–14 years	f	180	3.61	4.50	5.40	6.00	6.30	6.80	7.20
	m	183	3.61	4.70	5.40	5.90	6.30	6.80	7.30
15–18 years	f	98	3.30	4.48	4.80	5.30	5.83	6.50	6.90
			4.30	5.00	5.40	5.80	6.20	6.60	7.47

OD onFT3?

Kapelari, K., Kirchlechner, C., Högler, W., Schweitzer, K., Virgolini, I., & Moncayo, R. (2008). Pediatric reference intervals for thyroid hormone levels from birth to adulthood: a retrospective study. *BMC endocrine disorders*, *8*(1), 15.

152

Thyroid Treatment Clinical Guidelines

ALTHOUGH AACE DOES NOT RECOMMEND COMBINATION THERAPY (T4/T3), YOU CAN STILL PRESCRIBE IT ACCORDING TO THEIR OWN GUIDELINE:

American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice are systematically developed statements to assist health care professionals in medical decision making for specific clinical conditions, ***but are in no way a substitute for a medical professional's independent judgment and should not be considered medical advice.*** *Most of the content herein is based on literature reviews. In areas 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. ***We encourage medical professionals to use this information in conjunction with, and not a replacement for, their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made in light of local resources and individual patient circumstances.***

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

153

Thyroid Treatment Synthetic *(monotherapy)* VS. Desiccated *(combo-therapy)*

- Before levothyroxine in 50's, only used desiccated
- Desiccated is T4, T3, (T1 and T2)
  - Dosed in grains (1/2, 1, 1.5, 2, etc.)
- Studies report many patents on monotherapy dissatisfied with results.
- Recent retrospective study comparing outcomes between desiccated users vs synthetic users for over 2 years reported:

"the symptoms of hypothyroidism improved significantly as reported on follow-up encounters with subsequent improvement in laboratory thyroid function studies and questionnaires, and furthermore, not resulting in hyperthyroidism that caused hospitalizations for medication adverse effects, arrhythmias, or cardiac death".

Tariq, A., Wert, Y., Cheriyath, P., & Joshi, R. (2018). Effects of long-term combination LT4 and LT3 therapy for improving hypothyroidism and overall quality of life. *Southern medical journal*, *111*(6), 363.

154

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 up[loading studies into patients chart.
- Do not prescribe thyroid for weight loss.
- HP2020 goal- HR QOL- Thyroid therapies directly impact HRQOL

155

Ethical and Legal Considerations in HRT

Objectives:

- Understanding your regulatory boards (TMB/BON)
- Understanding of AMA (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

156

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 (BHRT)
- 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.
  - *Why?*

157

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 commonly 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.
    - Commonly used to treat dementia, generalized anxiety disorder, OCD.
- All thyroid medications prescribed with TSH<5 is considered off label
- Recent study: 80-90% of all testosterone prescriptions are for off-label indications.
  - Testosterone for men with morning T > 300 ng/dl is considered Off-Label
  - All testosterone for women prescribed as off-label

158

EVEXCEL

Informed Consent for Off-Label Medication

The off-label use of a medication is defined as the use of a medication that is currently approved for use by the FDA in a manner that is different than its approved use. An example of this would be using quinine, a medication approved to treat malaria, for leg cramps. This is a very effective medication for this condition and is safe. Although the FDA has not approved this use, it is very common for doctors to prescribe this medication for this reason. Many, many medications are commonly used off-label. Sometimes, the off-label use of a medication will lead to further studies being done and for the FDA to allow additional indications and uses for the medication. An example of this is Topamax, a medication that was originally approved to treat seizures. It was later used for bipolar disorder. It wasn't a very effective medication for these conditions. It was commonly used off-label to treat migraines. It now has FDA approval for this and is also approved for weight loss. Off-label use of medication is a common, almost daily practice for physicians.

The American Medical Association and the Texas Medical Board have put forth guidelines for the off-label use of medications. It is the policy of this clinic to follow these guidelines.

Because off-label use of medication usually begins with individual ideas or experiences of individual physicians, often there are other physicians who are not familiar with certain off-label uses of medications. This can be confusing to the patient and can affect treatment with these medications.

You are being prescribed a medication for off-label use. In addition to this general information on off-label prescribing, you will receive specific instructions about the medication you will be receiving. You may talk with other physicians about this medication before beginning treatment. If you receive any conflicting information about this treatment, you are free to discontinue the treatment or have further discussions about it. We would also be willing to provide your other physicians with additional information regarding your treatment if needed.

Name_____ Date_____

I have received and understand the above information. I consent to off-label treatment.

Signature_____

159

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.

160

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.

161

TMB Code of Medical Ethics

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 performance and review of the following listed in subparagraphs (A) - (D) of this paragraph:

(A) an appropriate medical history and physician examination of the patient;

(B) the conventional medical treatment options to be discussed with the patient and referral input, if necessary;

(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.

162

TMB Code of Medical Ethics
Alternative Therapies Guidelines

(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 improvement, pain relief, or expected psychosocial 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 investigation article subject to clinical investigation standards as discussed in paragraph (7) of this section.

163

TMB Code of Medical Ethics
Alternative Therapies Guidelines

(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. Such a documented treatment plan shall consider pertinent medical history, previous medical records and physical examination, as well as the need for further testing, consultations, referrals, or the use of other treatment modalities.

(B) The treatment offered should:

(i) have a favorable risk/benefit ratio compared to other treatments for the same condition;

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

(iii) be based upon the expectation that a greater benefit for the same condition will be achieved 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.

164

TMB Code of Medical Ethics
Alternative Therapies Guidelines

(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 reviews;

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

165

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Alternative Therapies Guidelines

(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.

KNOW THE LITERATURE!

166

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
  - Pellets
- 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.
- Great resource:
  https://www.deadiversion.usdoj.gov/pubs/manuals/pract/pract_manual012508.pdf

167

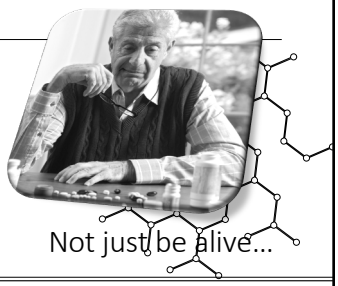
Conclusion

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

It is imperative 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.

168

PEOPLE want to LIVE



Not just be alive…