Depression and Altered Mood States in Peri and Post Menopausal Women:
Understanding the Role of Sex Hormones.

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TEXAS NURSE PRACTITIONERS ANNUAL CONFERENCE 2018

Objectives

Investigate the global issue of depression and anxiety in women.

Overview of the production and role female sex hormones.

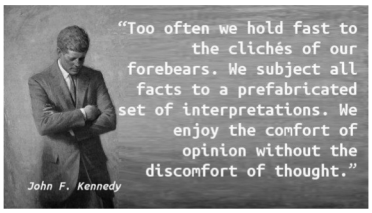
Understand the neurological, psychological and physiologic impact of androgens in the female patient.

Interpretation of sub-optimal serum androgen levels in the female patient.

Explore treatment options for sub-optimal androgen levels as well as understand the risks and benefits of androgen replacement therapy for the female patient.

Glean insights from evidence based treatment outcomes utilizing case studies of androgen therapy in women.

Thought of the Day



Defining Depression

The definition of non-major clinical depression holds a great deal of ambiguity.

Depressive symptoms can be present that do not meet the diagnostic criteria of major depressive disorder (MDD), yet still have profound life altering consequences when they persist.

Mild to moderate depression has been shown to be more prevalent in the general population than MDD and is often overlooked or ignored.

Gyllstrom, et.al, 2007

Depression in Women:
A Global issue

A widespread, worldwide phenomenon, crossing cultural and ethnic lines with a lifetime prevalence of up to 23%.

Twice as likely to occur in women as in men.

A leading cause of dysfunction, decreased productivity and disability in women.

The susceptibility of women over the course of a lifetime to major depression is substantial.

Noted in several studies to be a key component of decreased quality of life and sense of well being.

Documented sex differences have led to the observation that hormone fluctuations are a major contributor to female rates of depression, anxiety and other altered mood states.

Bromberger, et.al., 2011; Davis & Tran, 2001; Gyllstrom, et.al., 2007; McHenry, et.al., 2014; Rohr, 2002; Woods & Mitchell, 2005

Why is this important?

Women are multi-functional, multi-relational and multi-role oriented!

Hormone decline in the 3-5th decades of life can have a profound negative impact of quality of life (QOL) and sense of well-being.

Health Related Quality of Life (HRQOL) is paramount to overall sense of well being and productivity.

- Presenteeism vs Absenteeism

Symptom Impact

The relationship between psychological symptoms of depression, anxiety and altered mood states and hormone deficiency in females plays a key role in HRQOL.

A woman's response to symptoms can have deleterious effects ranging from physiological, psychological, biosocial and behavioral outcomes.

Only about 10% of women will report these symptoms to their primary care provider.

Dodd, et al., 2001
Woods & Mitchell, 2005

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Dazed and Confused:
Many healthcare Providers Lack Understanding

Many practitioners misunderstand and underestimate the encumbering effects of these symptoms.

There is little consensus across National Guidelines regarding hormone replacement therapies.

Confusion around the results of the WHI have left many providers with more questions than answers.

There is confusion in the general medical and lay communities around the role of androgens in women.

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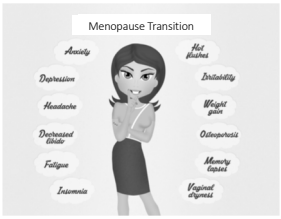
The Women's Health Initiative (WHI)
Why talk about it?

- 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.*

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

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

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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.

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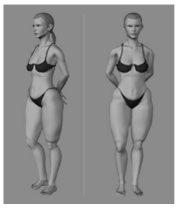
What about before the Menopause Transition (MT)?
Estrogen Dominance = Androgen & Progesterone deficiency = Hormone imbalance



- Sources exogenous estrogens
  - Oral Contraceptive Pills (OCP's)
  - Xynoestrogens
  - Phytoestrogens
- Consequences of exogenous estrogens/estrogen dominance:
  - The body shuts down production of other hormones
    - Low Testosterone
    - Low Progesterone (heavy, painful menstrual cycles)
    - Low Natural production of Estrogen
  - Early Female Puberty
  - PMS Disorders
  - Increase risk of estrogen related cancers secondary to inability to metabolize and excrete estrogen correctly.

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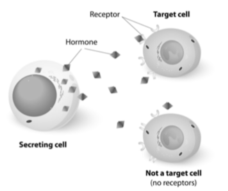
The Sex Hormones

- 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*.



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:

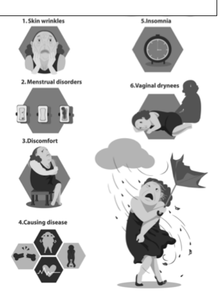
Key hormone of reproduction

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



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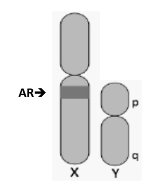
Testosterone
Its not just for men!

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

Testosterone is the most abundant active hormone in men AND women:
- Acts at cellular level with direct effect at the androgen receptor (AR)
- Precursor for DHT and Estradiol (ER)



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- Burger HG. Androgen production in women. Fertility and sterility. 2002;77:3-5.

Testosterone

Androgen receptors are found on virtually every cell in the (female) human body, indicating the role they play in normal tissue homeostasis.

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

Kimura NORIKO, Mizokami ATSUSHI, Oonuma TETSUTAROU, Sasano HIRONOBU, Nagura HIROSHI. Immunocytochemical localization of androgen receptor with polyclonal antibody in paraffin-embedded human tissues. Journal of Histochemistry & Cytochemistry. 1993;41:671-678.
Takeda H. Immunohistochemical localization of androgen receptors with mono-and polyclonal antibodies to androgen receptor. 1990
Wilson CM, McPhaul MJ. A and B forms of the androgen receptor are expressed in a variety of human tissues. Molecular and cellular endocrinology. 1996;120:51-57.
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.
Richards M. Hidden in Plain Sight: A Real Solution to the Diseases of Aging and the Imploding Medicare System.

Testosterone
A Woman's Most Important Hormone?

Androgen replacement has been shown in women to:

- *Improve mood, lift anxiety and depression, and improve sleep patterns.*
- *Prevent osteoporosis, increase muscle mass, increase muscle strength, increase bone density, reduce visceral fat, reduce total cholesterol levels, induce glucose homeostasis, increase metabolism, manage PMS, reduce severity and frequency of migraine headaches, improve cognition and memory, and prevent Alzheimer's disease.*
- *Be protective and preventative for breast cancer, even in breast cancer survivors.*

ALL of the above impact HRQOL!

Bachmann, 1999; Beauchet, 2006; Bialek, et. al., 2004; Boyanov, et. al., 2003; Cherrier, et. al., 2001; Conner, et. al., 2008; Carnahan & Perry, 2004; Davis, et. al., 2001; Davis, 1999; Davis & Tran, 2001; Davison, et. al.,2005; 2011 Ebinger, et. al., 2009; Glaser, et.al., 2011; Glaser, et. al., 2012; Hammond, et. al., 2001; Nappi & Lachowsky, 2009; Okun, 2006; Pike, et. al., 2009; Panay & Fenton, 2009; Sands & Studd, 1995; Studd & Panay, 2004; ; van Geel, 2009; Vanderschue-ren, et. al., 2004.

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Testosterone & Depression

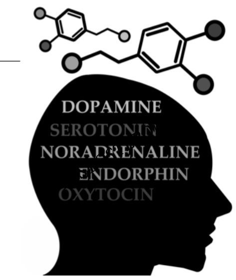
- ***Hundreds of studies support the relationship between androgens and depression in both women and men.***
- Sex hormones influence depression greatly in women, primarily testosterone in the pre menopause years.
- Women journeying through the menopause transition have a higher risk of increased new 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.
Rohr, U. D. (2002). The impact of testosterone imbalance on depression and women's health. *Maturitas*, *41*, 25-46.

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.



Ebinger, 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*. *23*(7), 841-853.
Jovanovic, H., Kocoska-Maras, L., Rådestad, A. F., Halldin, 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.
Kumsar, Ş., Kumsar, N. A., Sağlam, H. S., Köse, 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

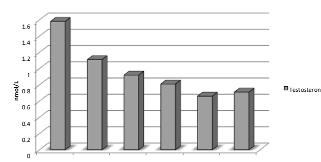
- Prudent testosterone replacement is effective in relieving both physical and psychological symptoms of androgen insufficiency in clinically affected women.
- Testosterone supplementation has positive effects for depression, libido and energy.
- Testosterone therapy shows an antidepressant effect in 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
Studd, J., & Panay, N. (2004). Hormones and depression in women. *Climacteric*, *7*(4), 338-346.
Zarrouf, F. A., Artz, S., Griffith, J., Sirbu, C., & Kommor, M. (2009). Testosterone and depression: systematic review and meta-

Androgen Insufficiency in Women

Androgens peak in women in their twenties.

Symptoms of insufficiency 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 & Metabolism*, *90*(7), 3847-3853.

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

How do we diagnose?

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., Papalia, M., Davis, S. R., & Burger, H. G. (2004). Androgen insufficiency in women: diagnostic and therapeutic implications. *Human reproduction update*, *10*(5), 421-432.

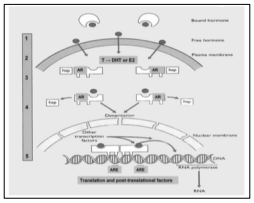
Diagnosing Androgen Insufficiency
Do the lab values matter?

- 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.

Why symptoms of androgen deficiency persist/exist with total testosterone levels "in range"?

1. Impaired androgen synthesis and regulation
   - *Aging, infections, trauma, stress, diet, xenoestrogens, medications*
2. Androgen binding
   - *Only 1-3% available/free*
3. Reduced tissue responsiveness
   - *Aging, endothelial damage, DM, metabolic changes*
4. Androgen receptor (AR) activity
   - *Aging, number of AR decreases, genetics, xenoestrogens, zinc deficiency*
5. Transcription and translation
   - *Anti-androgens, new area of study as relates to disease*



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	30-86
Tanner V	9-49	15-130

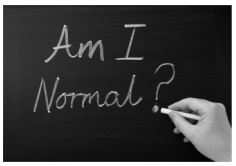
Bachmann, G., Bancroft, J., Braunstein, G., Burger, H., Davis, S., Dennerstein, L., & Notelovitz, M. (2002). Female androgen insufficiency: the Princeton consensus statement on definition, classification, and assessment. *Fertility and sterility*, *77*(4), 660-665.

Testosterone replacement
Clinical Decision vs. Labs

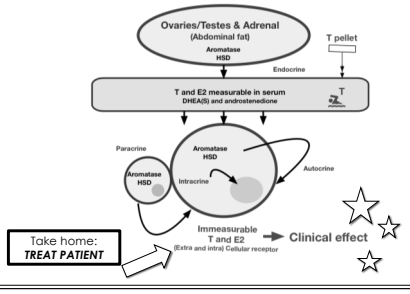
Hormone levels fluctuate and are unreliable.

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. 2012;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	3.5-12.5
MID-CYCLE PEAK	4.7-21.5
LUTEAL	1.7-7.7
POSTMENOPAUSAL	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 MALL ST AUSTIN, TX 78754
LABORATORY DIRECTOR: MARK A. KILLENBERG, M.D.
CLIA NUMBER 45D0565803 CAP ACCREDITATION NO. 21525-01

Restoring Androgen Homeostasis

Despite the plethora of data to support androgen replacement in women globally, and the fact that it has been used safely in women for almost a century there are no testosterone only products licensed by the FDA for use in women in the U.S.

As there are no FDA approved testosterone products for women on the market, many practitioners are not educated about the role of this vital hormone in women.

Many practitioners have reported they were unaware women even made testosterone, much less needed it for optimal functioning.

Glaser & Dimitrakakis, 2013; Maclaran & Panay, 2012

Female Androgen Insufficiency
Treatment Options

All testosterone replacement modalities prescribed for women in the US are considered "off label" use.

Testosterone is a controlled substance and is highly FDA regulated, no matter the modality.

Modalities prescribed in women include:

- Sub-cutaneous pellet implants
- IM injections
- Creams
- Oral / Sublingual

Androgen Insufficiency Treatment Options
Pellet implants

- Longest studied modality
  - Developed in 1939 for women who had radical hysterectomies.
  - 1940's studies discussed the use of estradiol and testosterone pellets for the symptoms of menopause.
- Are plant (soy or yam) based.
- More widely used in states over past decade.
- Dosing may be more individualized than other modalities.
- Levels continuous over 3-5 months.
- Cannot remove once placed.
- Nuisance side effects may be longer lasting than oral or transdermal routes.

Greenblatt, R. (1949). American Journal of OB/GYN 57, 244-301.

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Androgen Insufficiency Treatment Options
Injections

- Not widely used in women.
- Not widely researched in women.
- Higher side effect profile secondary to higher incidence of DHT conversion.
- Higher rates of aromatization than other modalities.
- Absorption is time released.
- Reported higher efficacy than oral or transdermal routes.
- Weekly or bi-monthly dosing

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Androgen Insufficiency Treatment Options
Transdermal Creams

- Less side effect profile than other modalities.
  - Side effect of hair growth at area of application.
- Little data to support sustained symptom relief.
- Poor absorption transdermally
  - Skin receptor de-sensitivity over time.
- Difficult to measure on laboratory assays.
- Daily dosing.

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Androgen Insufficiency Treatment Options
Oral / Sublingual

- Combination *Methyl-testosterone/Conjugated equine estrogen*.
  - First pass metabolism of methyl-testosterone through liver may increase estrogen metabolites and side effects.
- Little data to support sustained symptom relief of oral delivery.
- Difficult to measure and monitor.
- RDT (rapid dissolve tablets/ sublingual) reported better clinical response and lower side effect profile than oral.
  - Direct to blood stream, no first pass metabolism

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Female Androgen Insufficiency
Treatment Impact

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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., Tuck, S. M., Thom, M. H., Studd, J. W., & Cooper, D. J. (1984). The effects of subcutaneous hormone implants during the climacteric. Maturitas, 6(3), 177-184.

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

TABLE II
SIDE EFFECTS OF HORMONE IMPLANTS.

Side effect	Incidence (%)	
	Group A	Group B
Breast discomfort	28.3	17.9
Increased facial hair	22.6	19.4
Acne	5.7	1.5
Abnormal bleeding	16.3	16.4

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

Cardozo, L., Gibb, D. M., Tuck, S. M., Thom, 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.

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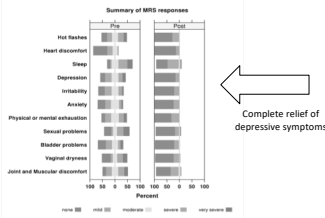
Conclusions:

- 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.

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MRS- Study of Depression Relief -2017

484 charts reviewed for women who received pellet HRT (androgen alone or androgen plus estradiol).

Design: Retrospective chart review of pre- and post- andropause hormone therapy treatment (pretest-intervention-posttest) using the validated, open access Health related Quality of Life Menopausal Rating Scale (HRQOL MRS) Questionnaire.

Population: Pre- and postmenopausal females; 35-70 years with androgen deficiency who received androgen therapy and completed the pre- and post-intervention MRS survey (and met other inclusion criteria).

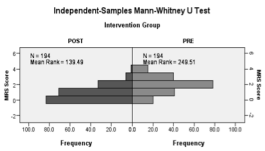
Setting: Primary care, hormone/endocrine specialty practice.

Measurement: HRQOL MRS Questionnaire at baseline and 6-12 weeks post therapy.

DeNeui, T., Gilder, R., & 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 at Arlington.

Conclusions

- 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).



DeNeui, T., Gilder, R., & 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 at Arlington.

Myths of Testosterone 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.

Glaser, R., Dimitrakakis, C. (2013). Testosterone therapy in women: Myths and misconceptions. *Maturitas.*

The Patient Encounter

Case Study

- 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

- 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"

Conclusion

Nurse practitioners have a unique opportunity to open the dialogue of altered mood states in their female patients.

It is imperative we expand our horizons in the areas of treating hormone related depression, anxiety and altered mood states and broaden the scope of our education and knowledge in the role of androgen replacement in optimizing women's health.

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Thank you for your attention!

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