

Hormonal Agents for HSDD

ISSWSH Precourse 2025

Anita Mikkilineni, MD, FACOG, IF

Assistant Professor of OBGYN

The George Washington University

Disclosures

- Medical Advisory Board of SHE+ Sexual Health Foundation
- I recognize that much of the research I will be discussing refers to “women” but this does not universally describe the genders of all patients that we care for.

Objectives

1. Define the role of testosterone in the sexual function and physiology of people born with ovaries.
2. Review the guidelines for use of testosterone for treatment of hypoactive sexual desire disorder (HSDD)
3. Identify appropriate candidates for testosterone therapy and demonstrate how to safely prescribe testosterone and monitor patients.

Case example

Patient: Mary, a 56-year-old postmenopausal woman.

Chief Complaint: Low libido and decreased sexual satisfaction for the past two years.

History: Mary experienced natural menopause at age 51. Since then, she has noticed a gradual decline in sexual desire, leading to frustration and strain in her relationship. She reports no pain during intercourse but feels less responsive to sexual stimuli. She has no history of hormone-sensitive cancers or cardiovascular disease.

Medical History:

- Hypertension (controlled with medication)
- No history of depression or anxiety
- Estradiol patch 0.1mg/24 hour patch for vasomotor symptoms, Mirena IUD

Case example

Evaluation:

- Normal physical exam and pelvic examination
- Bloodwork: Normal thyroid function and blood glucose; low-normal free testosterone levels. Normal lipid levels and liver function

Management Plan:

1. **Lifestyle Counseling:** Education on the effects of menopause on sexual health and the role of stress and relationship dynamics.
2. **Testosterone Therapy Consideration:** Discussed the option of low-dose transdermal testosterone cream (off-label in some regions) with shared decision-making.
3. **Monitoring Plan:** Initiated a three-month trial of testosterone cream with follow-up to monitor symptom improvement, androgenic side effects (e.g., acne, hair growth), and metabolic markers.

Outcome: After three months, Mary reports a noticeable increase in sexual desire and improved intimacy with no significant side effects. Regular monitoring continues for safety and efficacy.

A reminder of the DSDS

1. In the past, was your level of sexual desire/interest good and satisfying to you?	No <input type="checkbox"/> Yes <input type="checkbox"/>
2. Has there been a decrease in your level of sexual desire/interest?	No <input type="checkbox"/> Yes <input type="checkbox"/>
3. Are you bothered by your decreased level of sexual desire/interest?	No <input type="checkbox"/> Yes <input type="checkbox"/>
4. Would you like your level of sexual desire/interest to increase?	No <input type="checkbox"/> Yes <input type="checkbox"/>
5. Please check all the factors that you feel may be contributing to your current decrease in sexual desire/interest:	
A. An operation, depression, injuries, or other medical condition	No <input type="checkbox"/> Yes <input type="checkbox"/>
B. Medications, drugs or alcohol you are currently taking	No <input type="checkbox"/> Yes <input type="checkbox"/>
C. Pregnancy, recent childbirth, menopausal symptoms	No <input type="checkbox"/> Yes <input type="checkbox"/>
D. Other sexual issues you may have (pain, decreased arousal, orgasm)	No <input type="checkbox"/> Yes <input type="checkbox"/>
E. Your partner's sexual problems	No <input type="checkbox"/> Yes <input type="checkbox"/>
F. Dissatisfaction with your relationship or partner	No <input type="checkbox"/> Yes <input type="checkbox"/>
G. Stress or fatigue	No <input type="checkbox"/> Yes <input type="checkbox"/>

NO to Q1, 2, 3, or 4 = Not generalized acquired HSDD

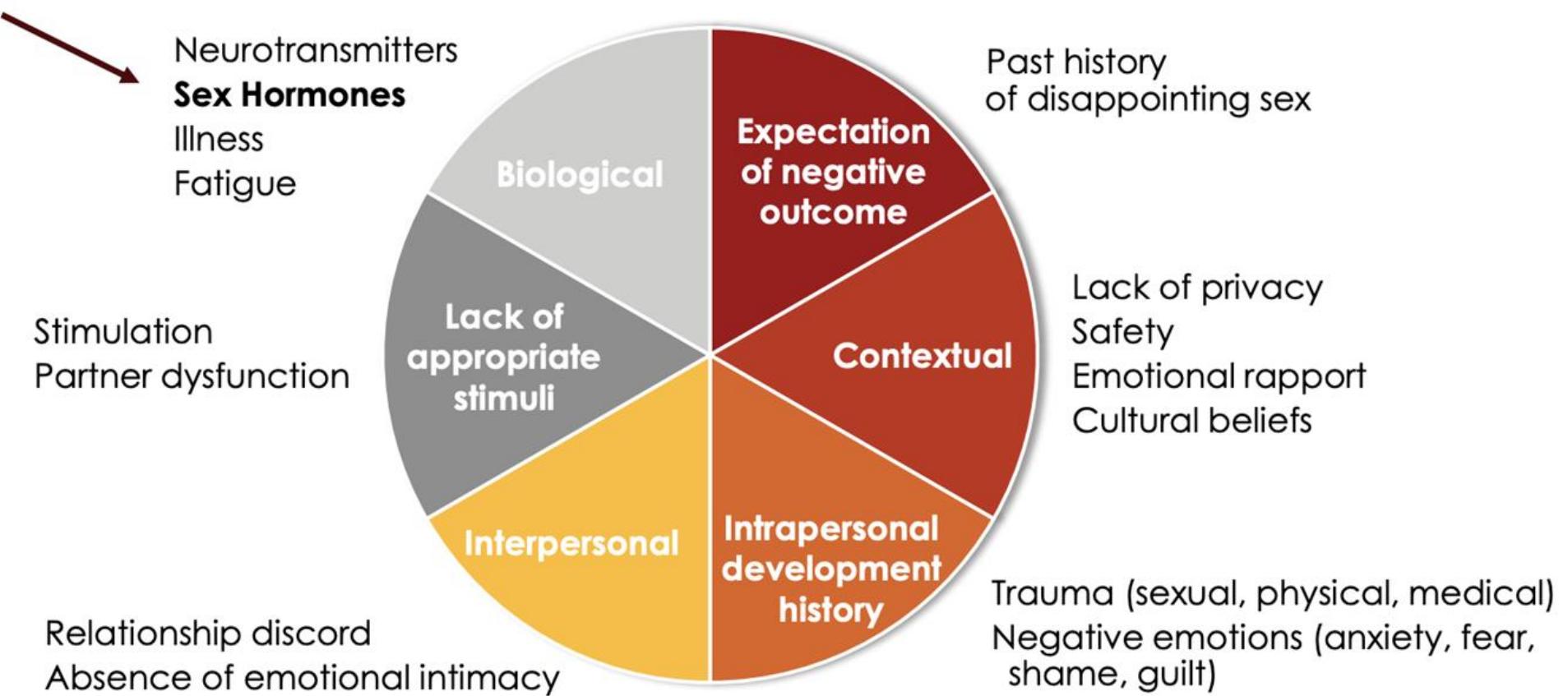
YES to all Q1–4 and clinician-verified NO to all Q5 factors = Generalized acquired HSDD

YES to all Q1–4 and YES to any Q5 factor = clinician to use best judgment to determine diagnosis

Clinical assessment of patient answers is required.

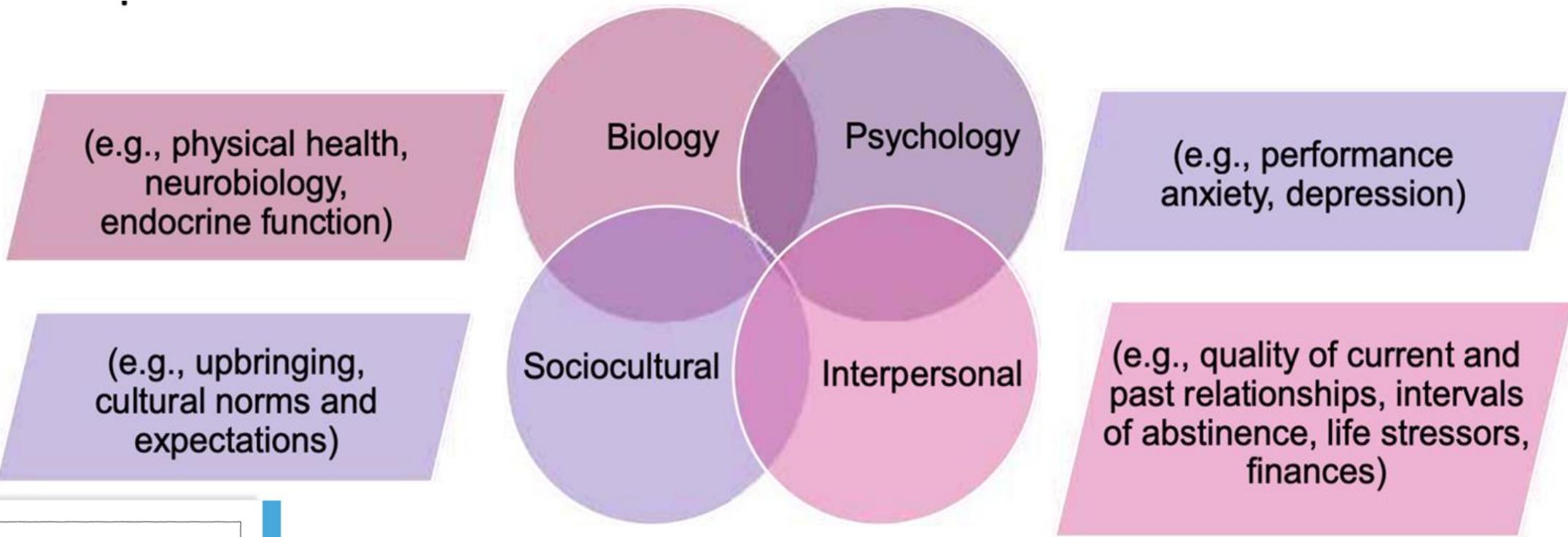
- On average, the DSDS took < 15 minutes to complete in a clinical study (N = 921)
- DSDS had a sensitivity of 0.836 (84%) and a specificity of 0.878 (88%) (N = 263)

Contributors to Sexual Desire



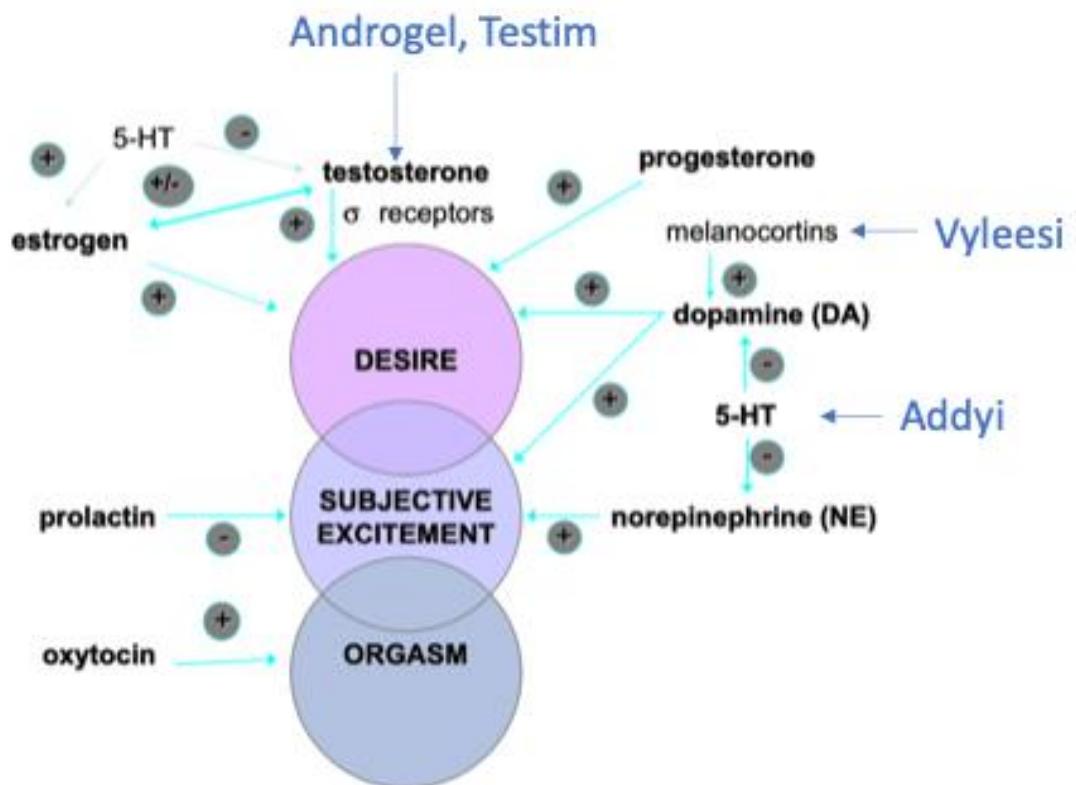
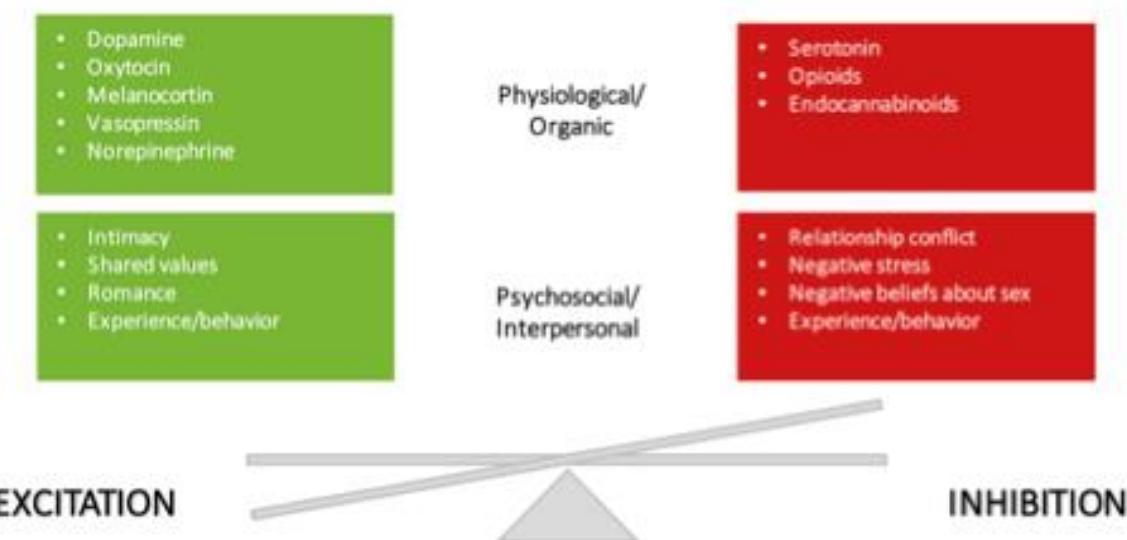
Created by: Sandra Leiblum, PhD.

Biopsychosocial of Female Sexual Response



Rosen et al. 2006

Hypoactive Sexual Desire Disorder (HSDD)



Clayton et al. 2009

Throwback to Biochem

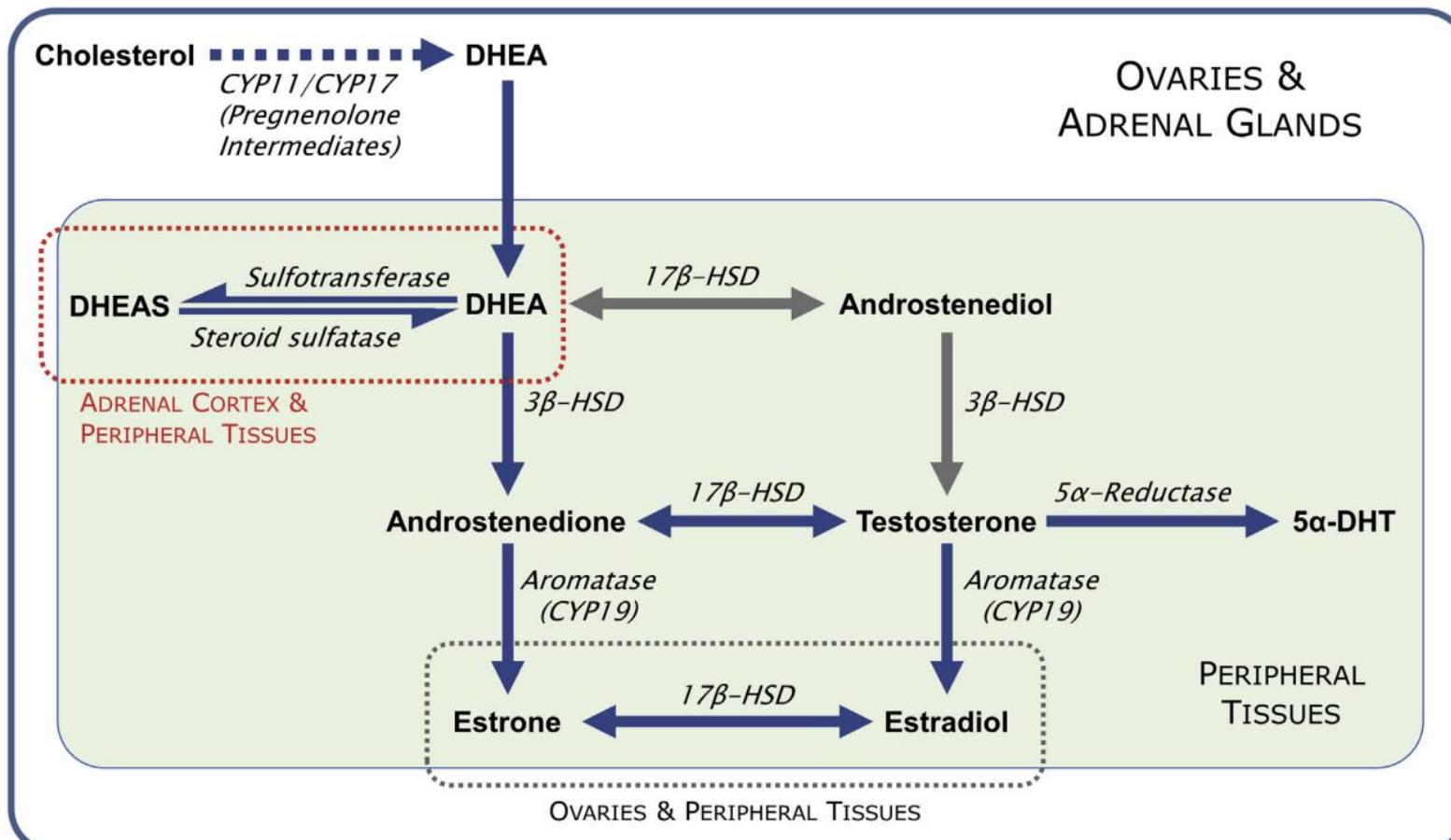


Figure 2. Synthetic pathways of sex steroids. Intermediate steps involved in the conversion of cholesterol to DHEA are not shown. The ovaries and adrenal glands have a full complement of enzymes to produce androgens and estrogens. In addition, circulating DHEA can be converted to testosterone and estradiol in peripheral tissues (green shaded area). The conversion of DHEA to DHEA-S is limited to the adrenal cortex, whereas DHEA-S can be converted back to DHEA in peripheral tissues (red dotted area). Major pathways of synthesis in humans are denoted by blue arrows, and minor pathways are denoted by gray arrows (adapted from Traish et al).⁷⁴ CYP = cytochrome P450; DHEA = dehydroepiandrosterone; DHT = dihydrotestosterone; HSD = hydroxysteroid dehydrogenase.

Androgen

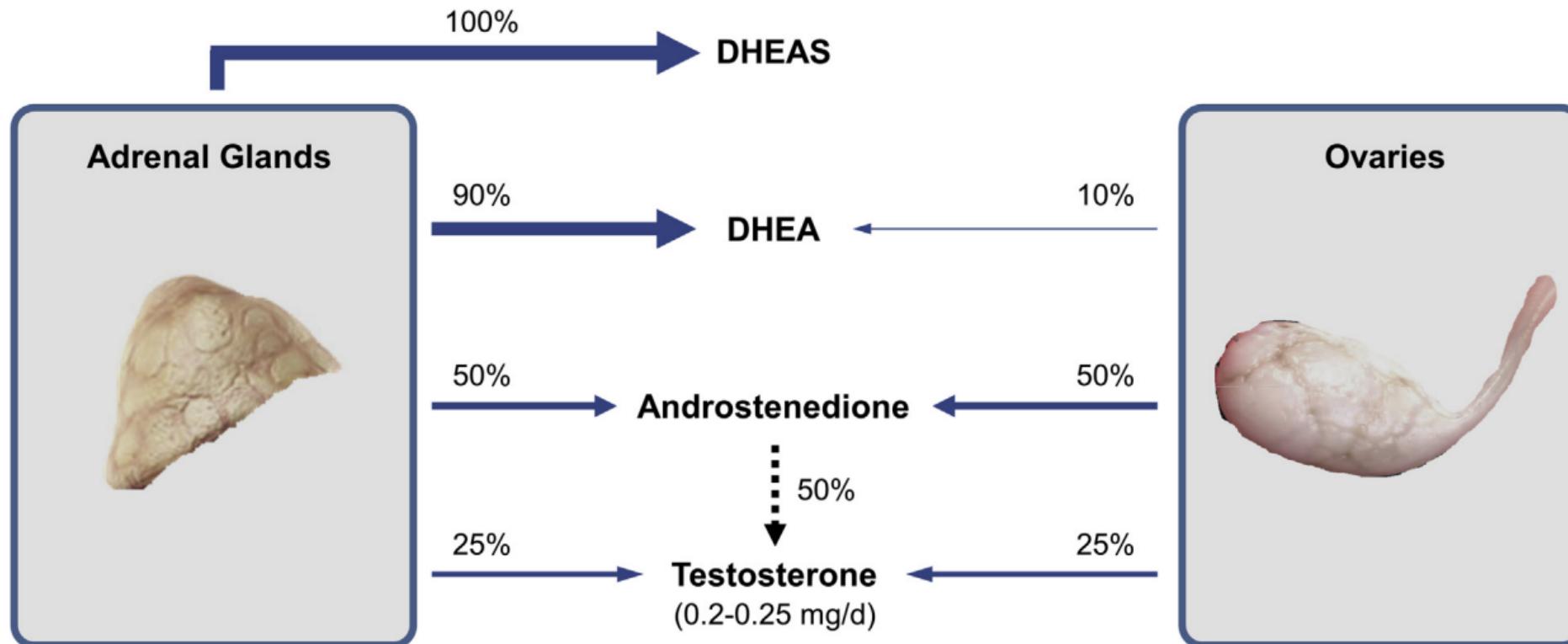
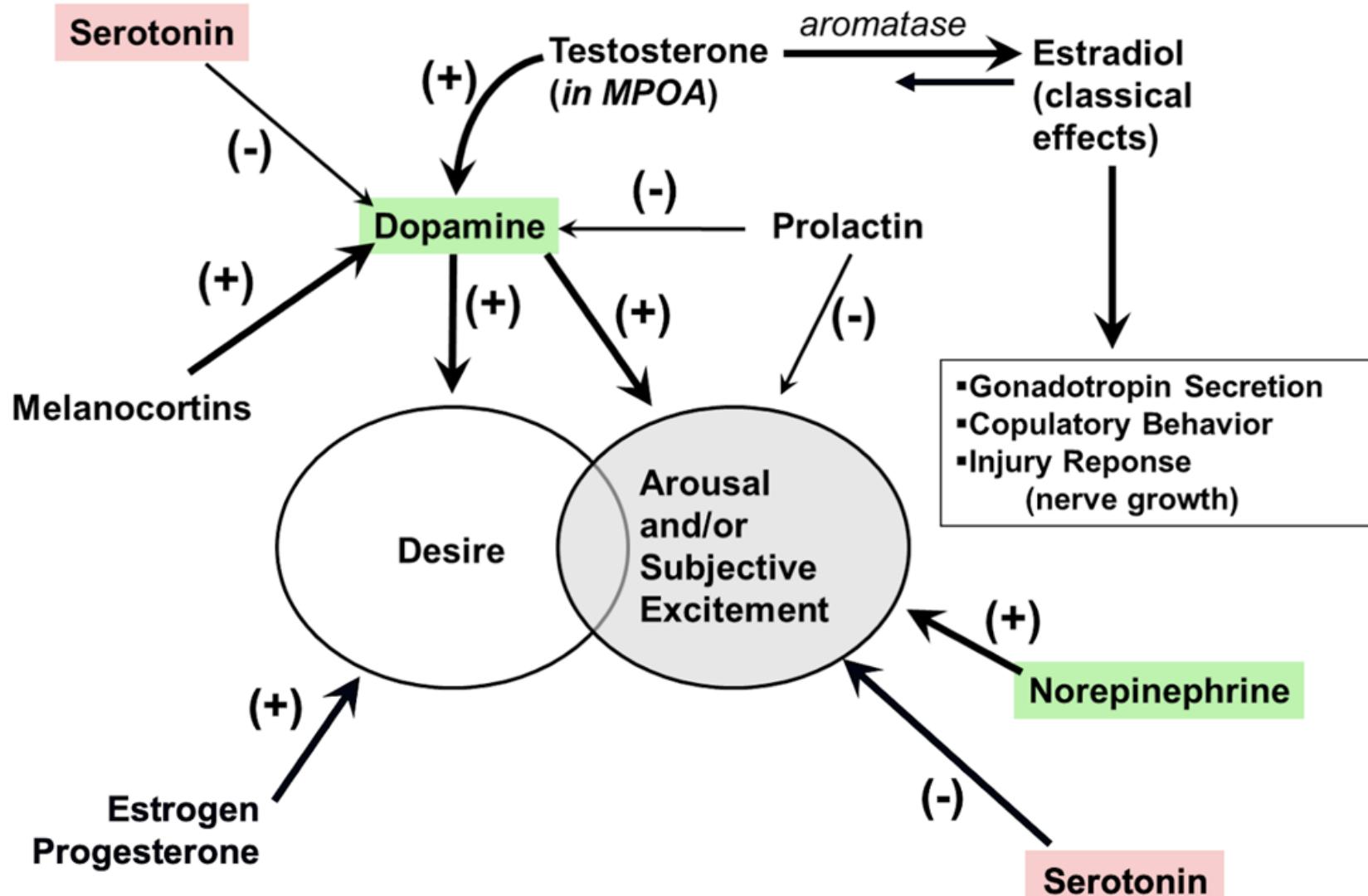


Figure 1. Relative production of circulating androgens in the adrenal glands and ovaries. The substantial contribution of androstenedione to circulating testosterone is shown by a dashed arrow and involves peripheral tissue conversion. DHEA = dehydroepiandrosterone; DHEAS = dehydroepiandrosterone sulfate.

Central Regulation of Desire/Arousal



We need to stop gendering hormones: ratios matter!

Women and people with ovaries make

3-4x MORE TESTOSTERONE

than estradiol over their lifetime.

Sex Steroid Hormones (units matter)

	Cis Female	Cis Male
Estradiol	3-40 ng/dL	1 ng/dL
Progesterone	<100-2000 ng/dL	<100 ng/dL
Testosterone	15–70 ng/dL	270-1070 ng/dL

Age and Changes in Testosterone

Reference ranges of testosterone level in women based on age.

Ages	Reference range of testosterone production by ovaries and adrenal glands (ng/dL)
20–29 years	45.5–57.5 ng/dL
20–39 years	27.6–39.8 ng/dL
40–49 years	27.0–38.6 ng/dL

Uloko, M., Rahman, F., Puri, L.I. et al. The clinical management of testosterone replacement therapy in postmenopausal women with hypoactive sexual desire disorder: a review. *Int J Impot Res* 34, 635–641 (2022)

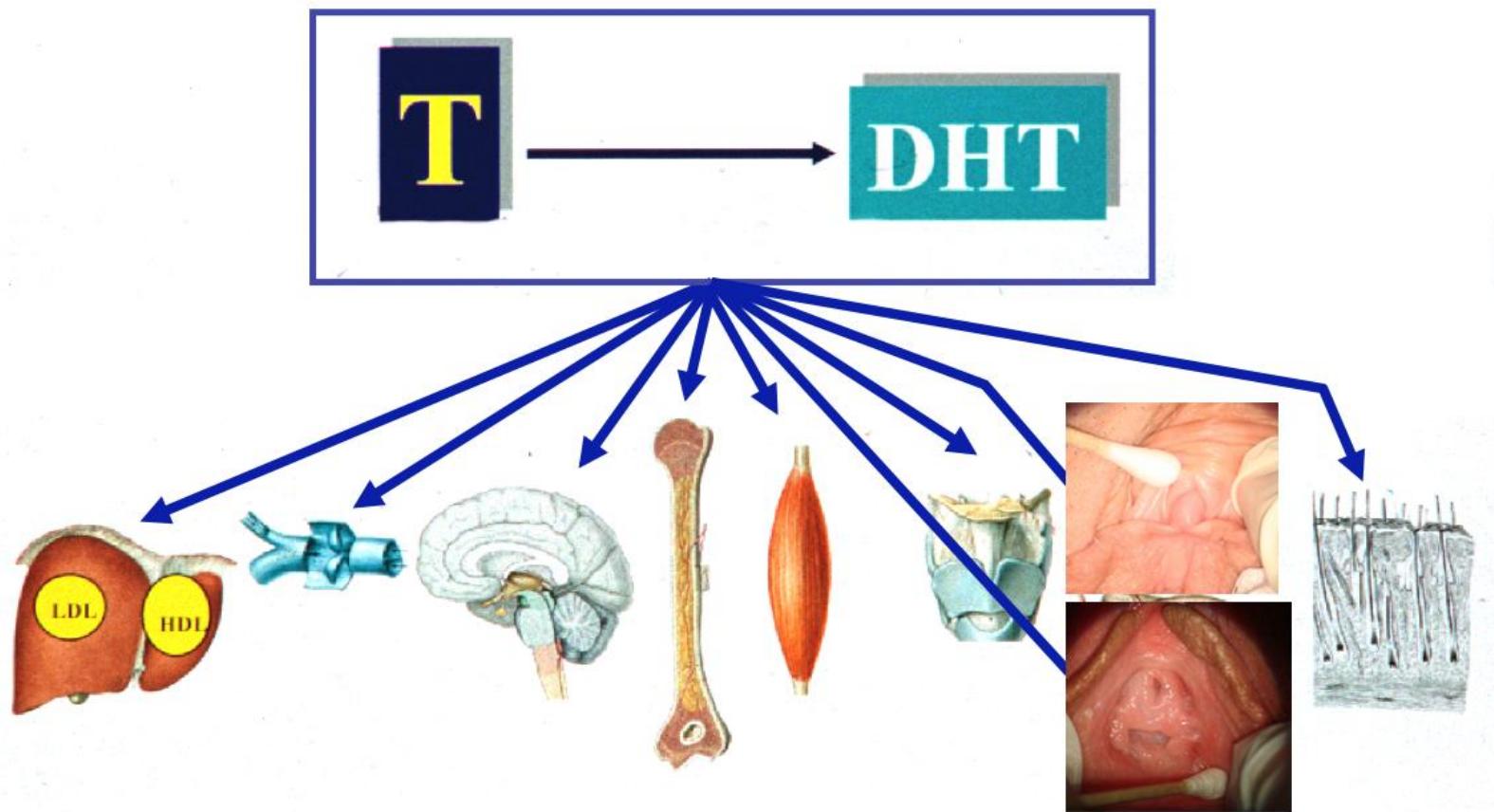
Age and Changes in Androgens

Age Ranges	20 - 29 (n=17)	30 - 39 (n=23)	40 - 49 (n=20)
DHEAS ug/dL <i>Dehydroepiandrosterone Sulfate</i>	176.9 - 214.3	139.0 - 170.8	124.7 - 156.1
SHBG nmol/L <i>Sex Hormone Binding Globulin</i>	43.6 - 58.6	44.6 - 52.4	47.0 - 58.4
Total T ng/dL <i>Total Testosterone</i>	45.5 - 57.5	27.6 - 39.8	27.0 - 38.6
FAI <i>Free Androgen Index</i>	3.72 - 4.96	2.04 - 2.96	1.98 - 2.94
Cal. Free T picomol/L <i>Calculated Free Testosterone</i>	21.5 - 27.2	13.4 - 19.5	12.4 - 17.8
	ng/dL	0.6 - 0.8	

Reprinted with permission from Macmillan Publishers Ltd: International Journal of Impotence Research (Guay A, Munarriz R, Jacobson J et al. Serum androgen levels in healthy premenopausal women with and without sexual dysfunction: Part A. Serum androgen levels in women aged 20-49 years with no complaints of sexual dysfunction. Int J Impot Res 2004;16(2):112-120.), © 2004.

So what does testosterone do?

Target organs of androgens



Intracellular MOA

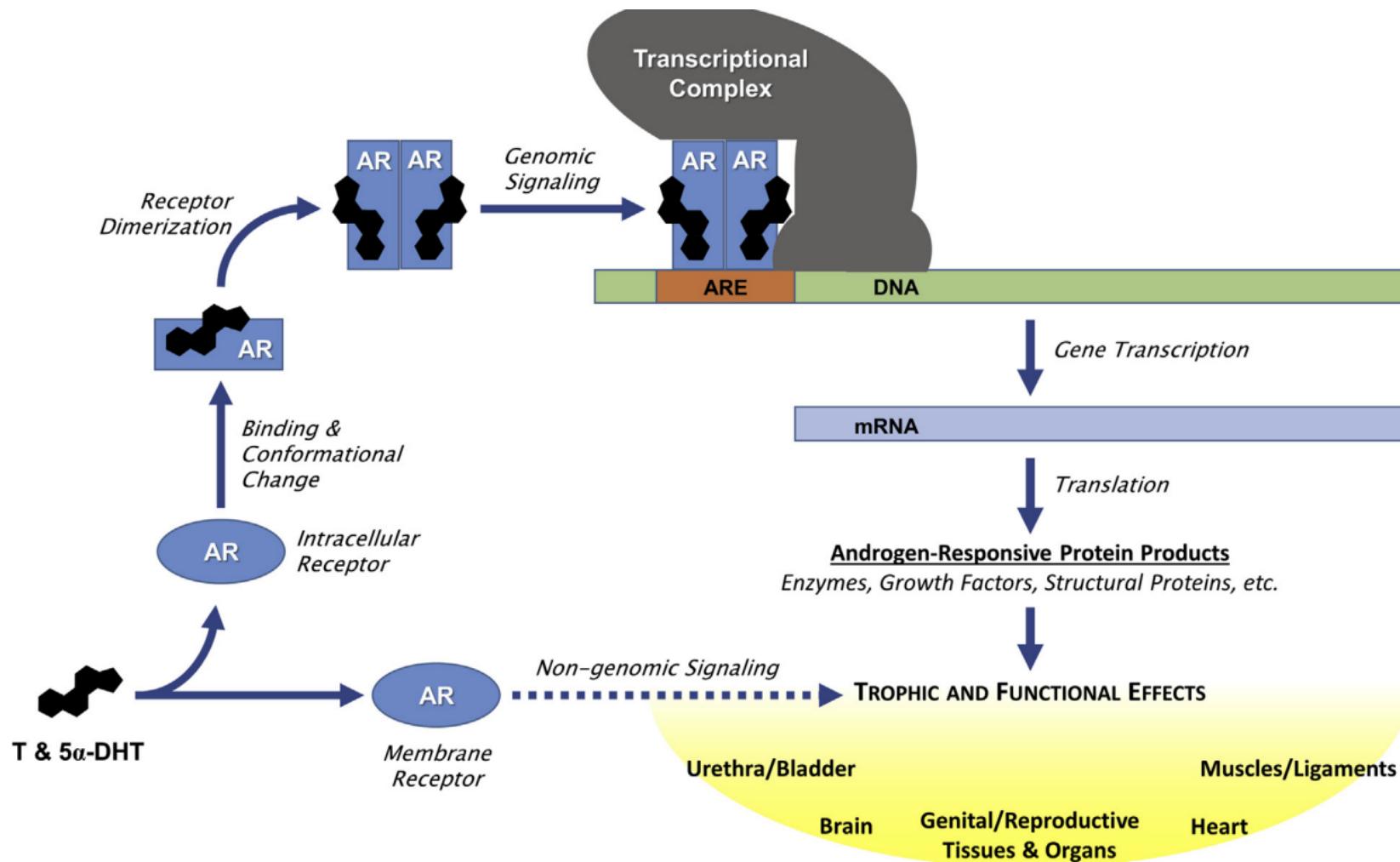


Figure 3. Androgen receptor (AR) mechanism of action (adapted from Traish et al).⁷⁴ ARE = androgen response element; DHT = dihydrotestosterone; T = testosterone.

RCTs demonstrating Efficacy of Testosterone in Postmenopausal women

Research.	DOSSES (mg/d)	SUBJECTS	ESTROGEN
Shifren et al, 2000	150/300	SM (75)	+
Braunstein et al, 2005	150/300/450	SM (447)	+
Buster et al, 2005	300	SM (533)	+
Simon et al, 2005	300	SM (562)	+
Davis et al, 2006	300	SM (61)	+ (patch)
Davis et al, 2006	300	SM (76)	+ (aromatase inhibitors)
Shifren et al, 2006	300	NM (486)	+
Davis et al, 2008	150/300	NM/SM (814)	-
Panay et al, 2010	300	NM (272)	+/- groups

Testosterone Improves Sexually Satisfying Events, reduces Distress

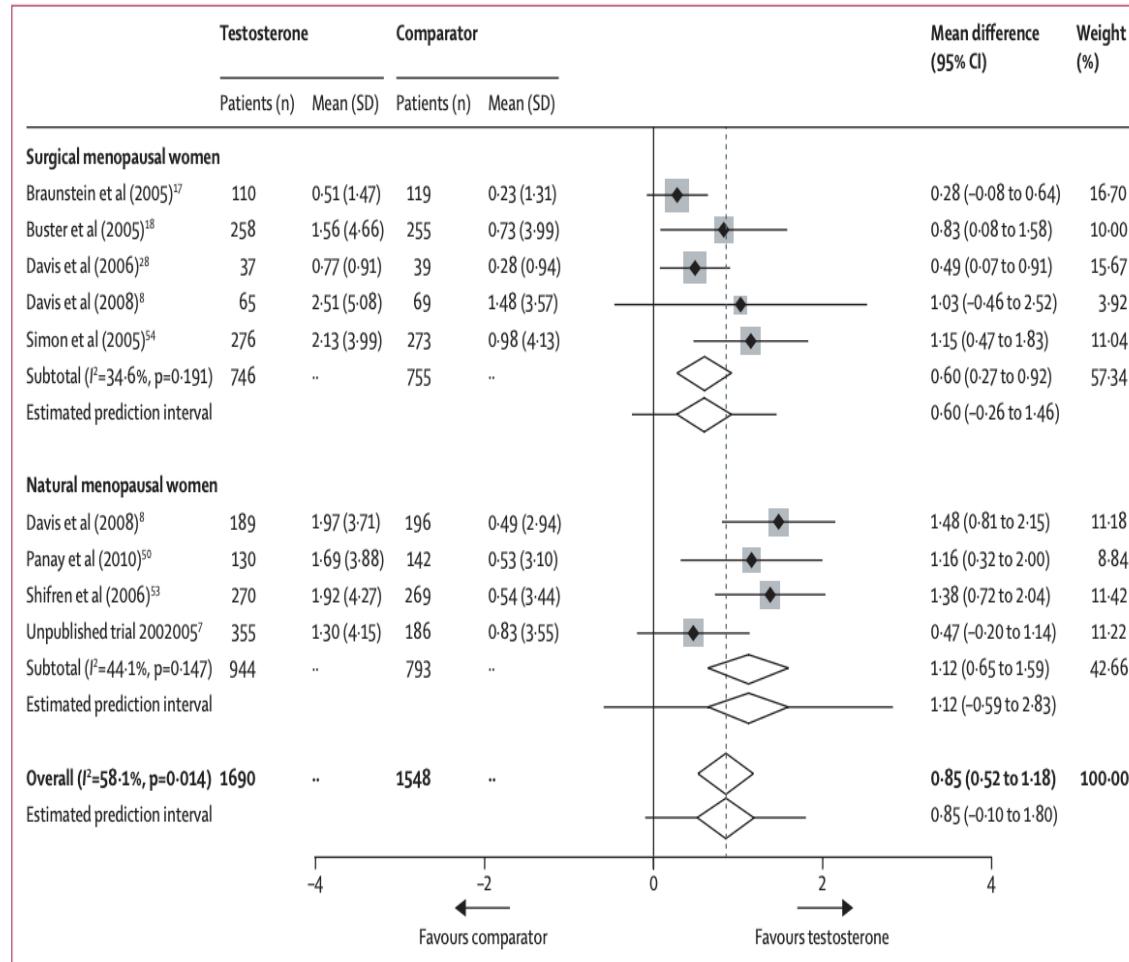


Figure 2: Effect of testosterone versus comparator on satisfying sexual events, by menopausal status

Data are change in number of satisfactory sexual events per month. Grey square indicates the weight of the study. Black diamond represents the mean difference per study and white diamond the mean difference overall. Horizontal lines depict the 95% CI. Vertical dotted line shows overall mean difference.

Sexual Desire Improves with Testosterone in Menopause , metanalysis

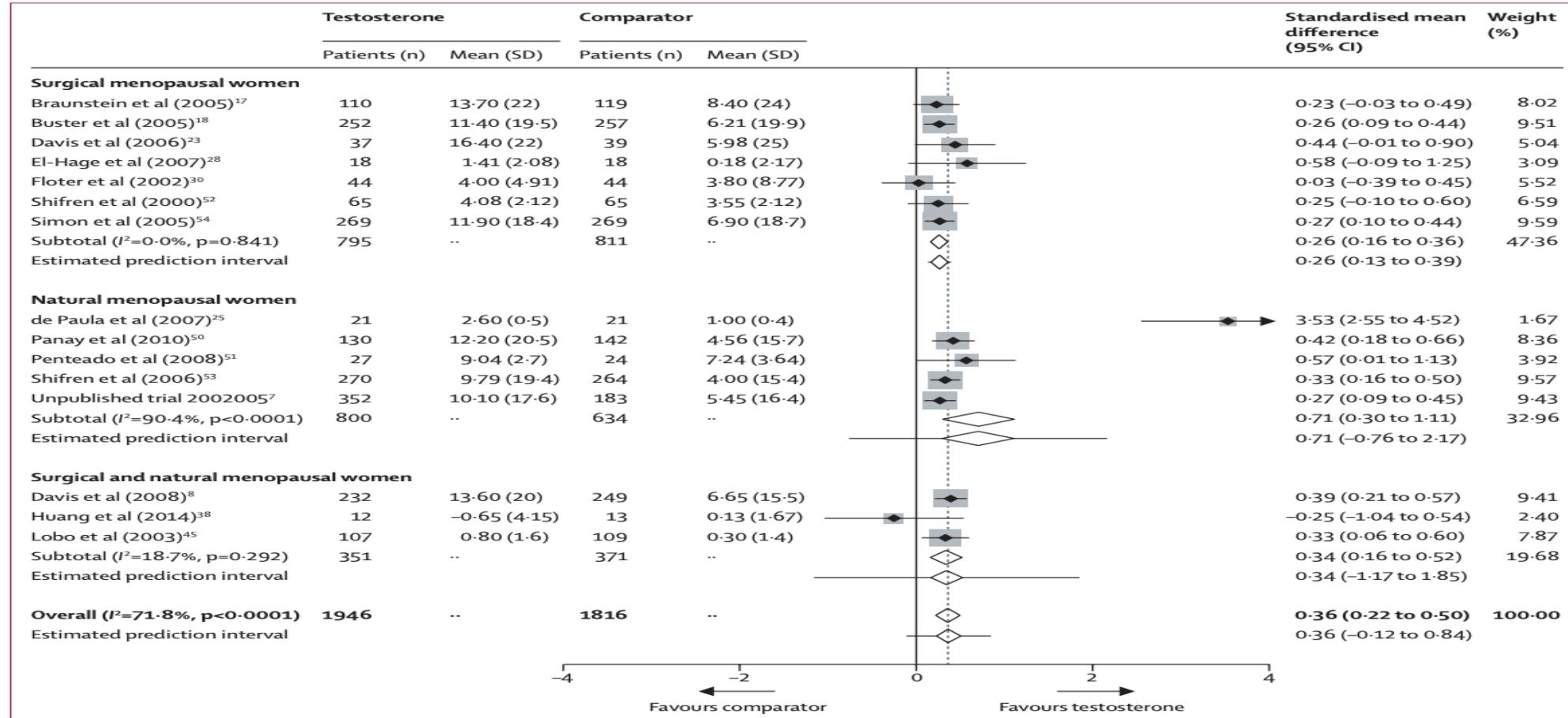


Figure 3: Effect of testosterone versus comparator on sexual desire, by menopausal status

Data are change in sexual desire score per month. Grey square indicates the weight of the study. Black diamond represents the standardised mean difference per study and white diamond represents the overall standardised mean difference. Horizontal lines depict the 95% CI. Vertical dotted line shows overall standardised mean difference.

THE Testosterone Paper

International Society for the Study of Women's Sexual Health Clinical Practice Guideline for the Use of Systemic Testosterone for Hypoactive Sexual Desire Disorder in Women



Sharon J. Parish, MD,¹ James A. Simon, MD,² Susan R. Davis, MBBS, PhD,³ Annamaria Giraldi, MD, PhD,^{4,5} Irwin Goldstein, MD,^{6,7} Sue W. Goldstein, BA, CSE,⁷ Noel N. Kim, PhD,⁸ Sheryl A. Kingsberg, PhD,⁹ Abraham Morgentaler, MD,¹⁰ Rossella E. Nappi, MD, PhD,¹¹ Kwangsung Park, MD, PhD,¹² Cynthia A. Stuenkel, MD,¹³ Abdulkhaled M. Traish, PhD,¹⁴ and Linda Vignozzi, MD^{15,16}

ABSTRACT

Background: The Global Consensus Position Statement on the Use of Testosterone Therapy for Women (Global Position Statement) recommended testosterone therapy for postmenopausal women with hypoactive sexual desire disorder (HSDD).

Aim: To provide a clinical practice guideline for the use of testosterone including identification of patients, laboratory testing, dosing, post-treatment monitoring, and follow-up care in women with HSDD.

Methods: The International Society for the Study of Women's Sexual Health appointed a multidisciplinary panel of experts who performed a literature review of original research, meta-analyses, review papers, and consensus guidelines regarding testosterone use in women. Consensus was reached using a modified Delphi method.

Outcomes: A clinically useful guideline following a biopsychosocial assessment and treatment approach for the safe and efficacious use of testosterone in women with HSDD was developed including measurement, indications, formulations, prescribing, dosing, monitoring, and follow-up.

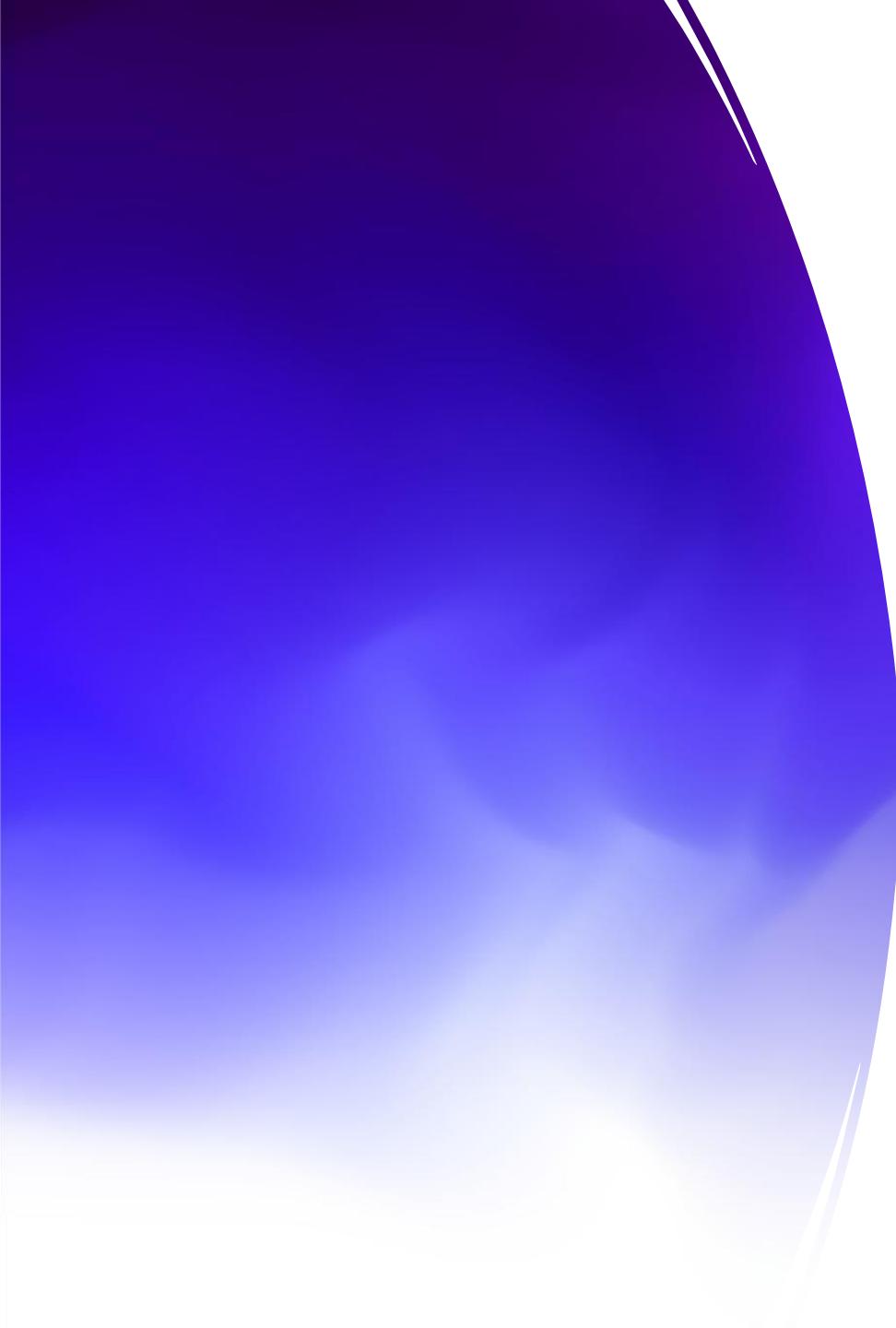
Results: Although the Global Position Statement endorses testosterone therapy for only postmenopausal women, limited data also support the use in late reproductive age premenopausal women, consistent with the International Society for the Study of Women's Sexual Health Process of Care for the Management of HSDD. Systemic transdermal testosterone is recommended for women with HSDD not primarily related to modifiable factors or comorbidities such as relationship or mental health problems. Current available research supports a moderate therapeutic benefit. Safety data show no serious adverse events with physiologic testosterone use, but long-term safety has not been established. Before initiation of therapy, clinicians should provide an informed

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¹Department of Psychiatry & Department of Medicine, Weill Cornell Medical College, New York, NY, USA;

Obstetrics and Gynecology Unit, IRCCS S. Matteo Foundation, University of Pavia, Pavia, Italy;

¹²Department of Urology, Chonnam National University Medical School, Gwangju, Korea



The position statement Globally supported by

- The International Society for the Study of Women's Sexual Health
- International Society for Sexual Medicine
- The Menopause Society (formerly the North American Medical Society)
- The Endocrine Society
- The International Menopause Society
- The European Menopause and Andropause Society
- The Royal College of Obstetricians and Gynaecologists
- Federación Latinoamericana de Sociedades de Climaterio y Menopausia (FLASCYM)
- The International Society of Endocrinology
- The Endocrine Society of Australia
- The Royal Australian and New Zealand Royal College of Obstetricians and Gynaecologists

Global Consensus Position Statement on the Use of Testosterone Therapy for Women

Davis SR, Baber R, Panay N, Bitzer J, Cerdas Perez S, Islam RM, Kaunitz AM, Kingsberg SA, Lambrinoudaki I, Liu J, Parish SJ, Pinkerton J, Rymer J, Simon JA, Vignozzi L & Wierman ME. **Global consensus position statement on the use of testosterone therapy for women.** *Climacteric*, 22:5, 429-434, DOI: 10.1080/13697137.2019.1637079, September 2, 2019. (FREE)

Davis SR et al. *Journal of Clinical Endocrinology and Metabolism*, 104(10): 1-7, DOI:10.1210/jc.2019-01603, September 2019.

Davis SR et al. *Journal of Sexual Medicine*, 2019 Sep;16(9):1331-1337. doi: 10.1016/j.jsxm.2019.07.012.

Davis SR et al. *Maturitas*, 2019 Jul 17. pii: S0378-5122(19)30628-0. doi: 10.1016/j.maturitas.2019.07.001.

Global Statement: Summary and Key Messages

- International panel concluded only evidence-based indication for testosterone therapy for women is for **treatment of HSDD**.
- Data supports **moderate therapeutic effect in postmenopausal women**.
- Meta-analyses shows **no severe adverse events** during physiological testosterone use, with caveat that women at high cardiometabolic risk were excluded from study populations.
- **Safety of long-term testosterone therapy** has not been established.
- Diagnosis of HSDD involves full clinical assessment and that other factors contributing to FSD must be identified and addressed before testosterone therapy is initiated...guided by available diagnostic criteria (**ISSWSH or ICD 11**).
- A blood total testosterone level should not be used to diagnose HSDD (**NO CUTOFF**).

Global Statement: Summary and Key Messages

- Treatment should only be with formulations that achieve blood concentrations of testosterone that approximate **premenopausal physiological concentrations**.
- As **no approved female product** is approved by a national regulatory body, **male formulations** can be judiciously used in female doses and blood testosterone concentrations must be monitored regularly.
- The panel recommended **against use of compounded testosterone** (no pellets, no injectables!!!!)

--The panel highlighted the pressing need for more research into testosterone therapy for women and the development and licensing of products indicated specifically for women.

Global Consensus Statement on the Use of Testosterone in Women—Key Messages

- Proper dosing should attain and maintain testosterone levels in the premenopausal physiological range.
- If an approved female formulation is not available, **one-tenth of a standard male dose** of 1% transdermal testosterone or about 300 mcg/day can usually achieve the normal premenopausal physiological range.
- Additional testing and alternative strategies may be required to assess failure to respond to typical testosterone treatment, particularly when testosterone or SHBG levels are high.

Global Consensus Statement on the Use of Testosterone in Women—Key Messages

- *Compounded testosterone, pellets, IM injections, and oral formulations are not recommended!!!!!!*



How many government approved therapies are available for men in the US

Formulation	Brand Names	Administration Method	Dosing Frequency	Notes
Injectable (Intramuscular or Subcutaneous)	Depo-Testosterone, Delatestryl, Aveed, Xyosted	Injection (IM or SubQ)	Every 1-4 weeks (depending on type)	Common, cost-effective; requires regular injections.
Transdermal Gel	AndroGel, Testim, Fortesta, Vogelxo	Applied to skin (shoulders, upper arms)	Daily	Easy to apply but requires skin contact precautions.
Transdermal Patch	Androderm	Applied to skin (back, thigh, upper arm)	Nightly	Can cause skin irritation at application site.
Buccal (Oral Patch)	Striant	Applied to the gum (buccal mucosa)	Twice daily	Adheres to gum; avoids liver metabolism.
Implantable Pellets	Testopel	Subcutaneous implant	Every 3-6 months	Long-lasting; requires minor surgical procedure.
Nasal Gel	Natesto	Applied to nostrils	Three times daily	Convenient but requires frequent dosing.
Oral (Capsules)	Jatenzo, Tlando	Oral capsules	Twice daily	Easier to take but may have liver-related risks.

AndroFeme (Australia)

- **Transdermal 1% Testosterone Cream**
- This cream is applied to the skin, delivering a controlled dose of testosterone
- It is the only TGA-approved female-specific testosterone therapy
- Currently available in Australia
- 50mL tube contains 500mg of 1% testosterone (10mg/mL), and a dose applicator calibrated in 0.5mL graduations for dose delivery.



Which Government approved Testosterone for Women is available



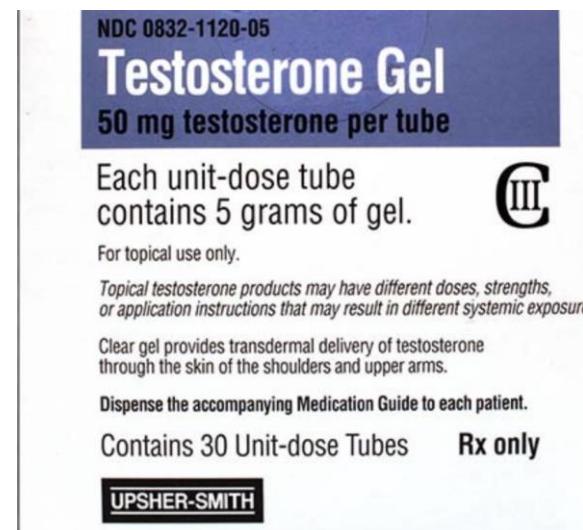
Dosing Recommendations

- Men use 30 tubes or packets per month
- 1/10th – 1/15th of a tube or packet/day; 3 tubes/month
- Resealable tubes, room temp. (4 drops, syringe)
- Apply gel to skin surface, back of calf or thigh, upper outer thigh, or buttock (to avoid transference).
- Patients should be counseled that on average efficacy emerges 6 to 8 weeks after initiation of therapy.
- Many women feel improvement after 4 weeks, including reductions in distress, with maximal efficacy in 12 weeks.
- Generally not covered by commercial insurance
- Cost saving apps may be recommended:
 - GoodRx (www.goodrx.com)
 - SingleCare (www.singlecare.com)



Testosterone Therapy

Here are the absurd ways we have to prescribe FDA approved Men's testosterone to our patients



Testosterone Therapy—Off Label

Testosterone Preparation	Daily Dosing	Mode of Delivery
FDA-approved male products Testosterone 1% gel	1/10 male dose ½ cc / 5 cc syringe (tube) 4 drops (packets)	Transdermal
Testosterone 1 % compounded cream/ointment meter-dosed dispenser	5 mg	Transdermal
Testosterone 1% cream (10 mg per mL), Australia	0.5 mL (5 mg) www.androfeme.com , doctor direct code needed	Transdermal



Testosterone Therapy Follow -up

- Baseline total testosterone should be measured before initiating therapy with **repeat level in 3–6 weeks**.
- Check T levels 6 weeks after dose increase and 2-3 weeks after supraphysiological level and dose decrease.
- **Monitor for clinical response**, assess for signs of androgen excess and decrease dose if side effects occur.
- Check serum **total testosterone level every 4-6 months** to screen for overuse and inherent androgenic consequences.
- If no benefit by 6 months, treatment should be ceased.
- If testosterone therapy results in improvement of HSDD, consider continuing for 6–12 months and then taking a drug holiday to see if further treatment is still required.
- In most cases, ongoing testosterone therapy is needed to maintain the improvement in HSDD.

Testosterone Monitoring and Follow up

- Measurement of SHBG and assessing Free T may contribute to understanding lack of response.
 - Women whose blood levels are in physiologic range and not experiencing improvement of HSDD symptoms
 - Healthy women, high dose oral estrogens, estrogen-containing hormonal contraceptives, untreated hyper- and hypothyroidism, thyroid replacement
- Androgenic side effects may occur despite standard dosing or normal levels of total testosterone or both.
 - May occur with low concentrations of SHBG, associated with type 2 diabetes, metabolic syndrome, and/or obesity

Testosterone Measurements

- Total testosterone measured with high accuracy and reproducibility using liquid/gas chromatography and tandem mass spectrometry assays (LC/GC-MS/MS).
- Direct assays for measurement of total and free testosterone are highly unreliable in the female range.
- Direct assays are appropriate to exclude high baseline concentrations and also to exclude supraphysiological concentrations during treatment.

*Use **TOTAL TESTOSTERONE** – evidence regarding free T as biologically active fraction is lacking.

Other Treatment Considerations

- Compounded ‘bioidentical’ testosterone therapy cannot be recommended due to the lack of evidence for efficacy and safety, unless an authorized equivalent preparation is not available (Expert opinion).
- If a compounded product is needed, the compounding pharmacy should be compliant with purity of Active Pharmaceutical Ingredients (API) and Good Manufacturing Practice (GMP) to meet industry standards for quality and safety.
- Systemic DHEA is not associated with significant improvement in libido or sexual function in postmenopausal women with normal adrenal function and not recommended for women with HSDD (Level IA, Grade A).

Testosterone Clinical and Lab Monitoring

- Annual breast and pelvic exams
- Annual mammography
- Evaluation of abnormal bleeding
- Evaluation for acne, hirsutism, androgenic alopecia, voice changes, clitoromegaly
- Lipid profile, LFTs, CBC - baseline, 6 mos, annually
- Use for > 6 months contingent on clear improvement and absence of adverse events

But is it safe?!

- Short answer, the current data say YES in most cases
- Need long term safety data
- Cardiovascular/breast cancer: No increased risk (Agrawal 2024)
- Androgenic side effects: acne and increased hair growth, generally mild (Al-Imari 2012.)
- Metabolic side effects (Davis 2019)- Decrease HDL

Safety and Efficacy of Testosterone Therapy in Women

- 46 reports of 36 randomized controlled trials of **8,480 participants**
 - Testosterone significantly increased sexual function, including **satisfactory sexual event frequency, desire, arousal, orgasm, and self-image**, and reduced distress in postmenopausal women.
 - Associated with greater likelihood of reporting **acne and hair growth**
 - No serious adverse events (**breast, intermediate CV endpoints, uterus**)
 - Administration via non-oral routes (eg, **transdermal application**) preferred because of **neutral lipid profile**.
-
- Islam. Et al. Safety and Efficacy of Testosterone for women, Lancet D+E , July 2019

Safety of Transdermal Testosterone over 48months

- Safety of 300 µg/day transdermal testosterone patch (TTP) treatment for up to 6 months in 1094 surgically menopausal women with hypoactive sexual desire disorder (HSDD)
- No important changes in the safety or tolerability profile of TTP were revealed with long-term use for up to 4 years in otherwise healthy oophorectomised women with HSDD on concomitant estrogen.
- No clinically significant changes in
 - Lipids
 - Carbohydrate metabolism
 - Hematology
 - Liver Function
- Nachtigall L, Casson P, Lucas J, Schofield V, Melson C, Simon JA. Safety and tolerability of testosterone patch therapy for up to 4 years in surgically menopausal women receiving oral or transdermal oestrogen. *Gynecol Endocrinol*. 2011 Jan;27(1):39-48.

Key Points To Remember

- Testosterone via transdermal route is moderately effective in the treatment of HSDD in peri and postmenopausal women
- Compounded Testosterone , PELLETs, INJECTABLES and ORAL TESTOSTERONE IS NOT RECOMMENDED AND AVOIDED AT ALL COSTS
- If you cannot get the government approved form , you must titrate the dose to 1/10 of government approved 1% transdermal male testosterone (300mcg/day) and monitor to premenopausal physiologic doses . Monitor total testosterone levels to ensure within premenopausal range

Questions



*"It says it will increase my sexual desire but not necessarily
for you."*