Hormonal Treatment: Androgens

ISSWSH Annual Meeting 2016
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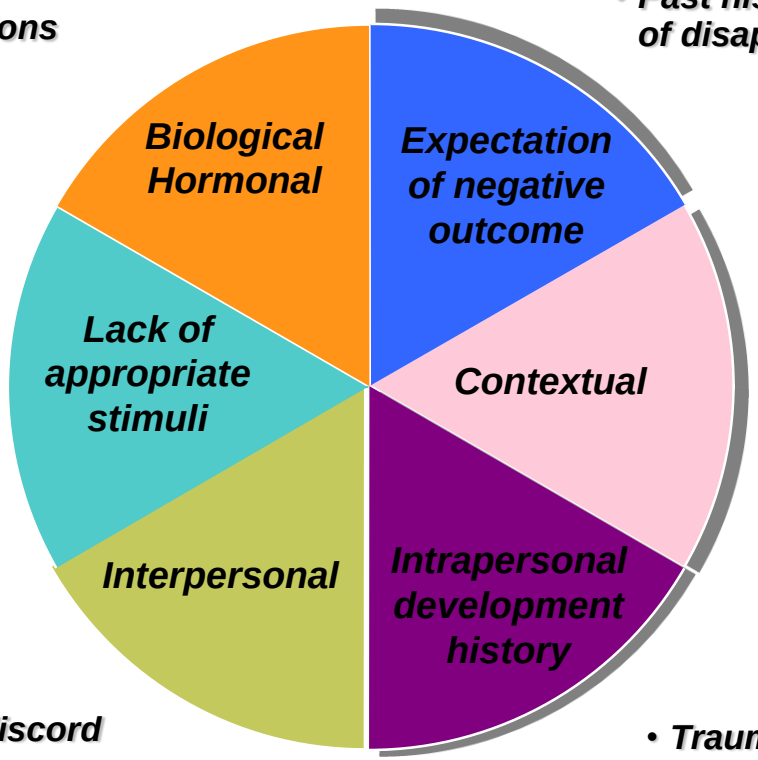
Disclosures

- **Advisory Boards:** Sprout, Pfizer, Emotional Brain

Objectives

- **Discuss the efficacy and safety of testosterone therapy for Hypoactive Sexual Desire Disorder (DSM IV-TR) in women**
- **Review published Clinical Guidelines and Position Statements regarding androgen therapy for women**

Contributors to Desire Problems™



- *Androgens*
- *Estrogens*
- *Medications*
- *Illness*
- *Fatigue*

- *Past history of disappointing sex*

- *Stimulation*
- *Partner dysfunction*

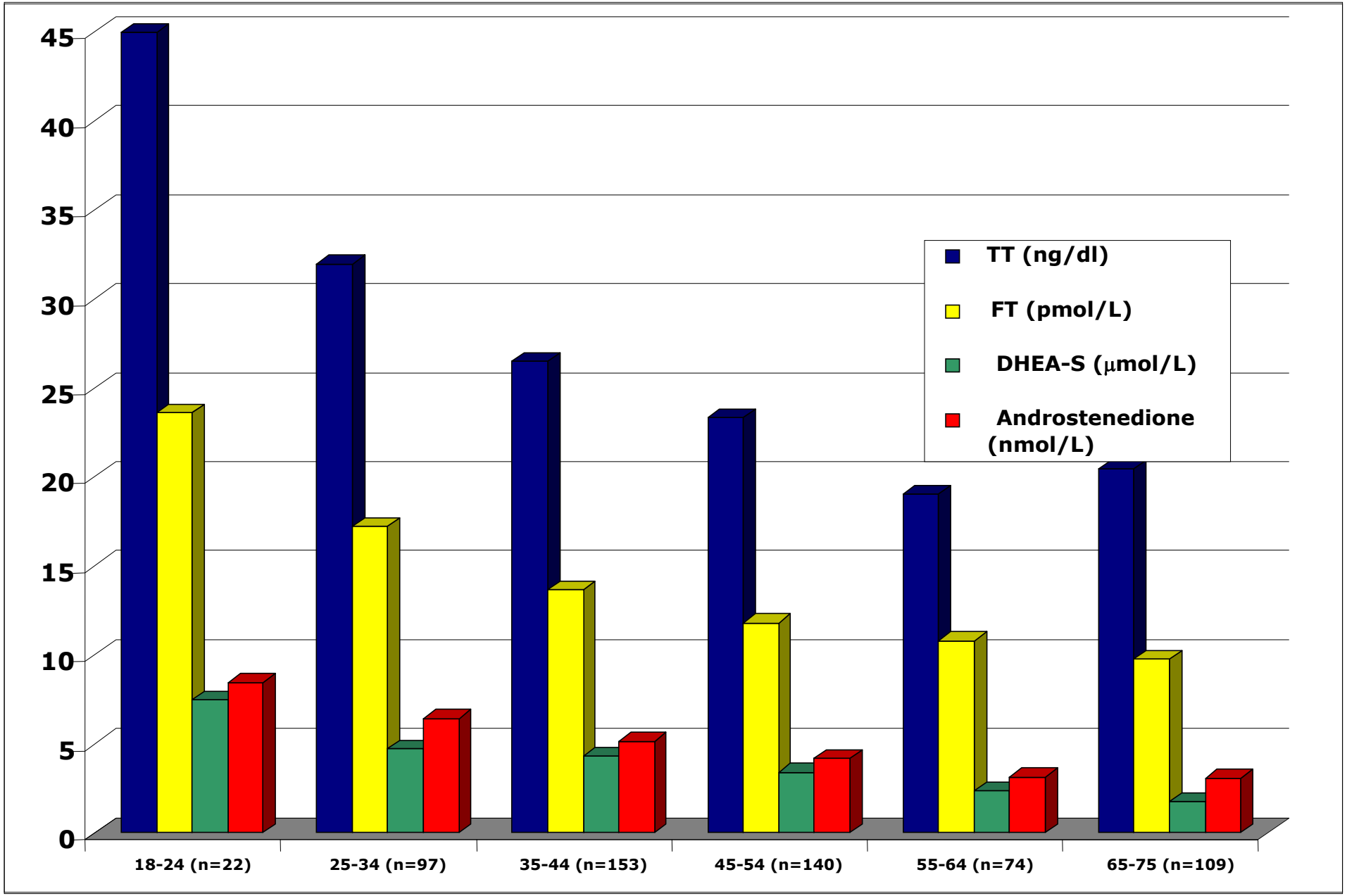
- *Lack of privacy*
- *Safety*
- *Emotional rapport*

- *Relationship discord*
- *Absence of emotional intimacy*

- *Trauma (sexual, physical, medical)*
- *Negative emotions (anxiety, fear, shame, guilt)*

Created by: Sandra Leiblum, PhD

Relationship Between Age and Androgens in Women



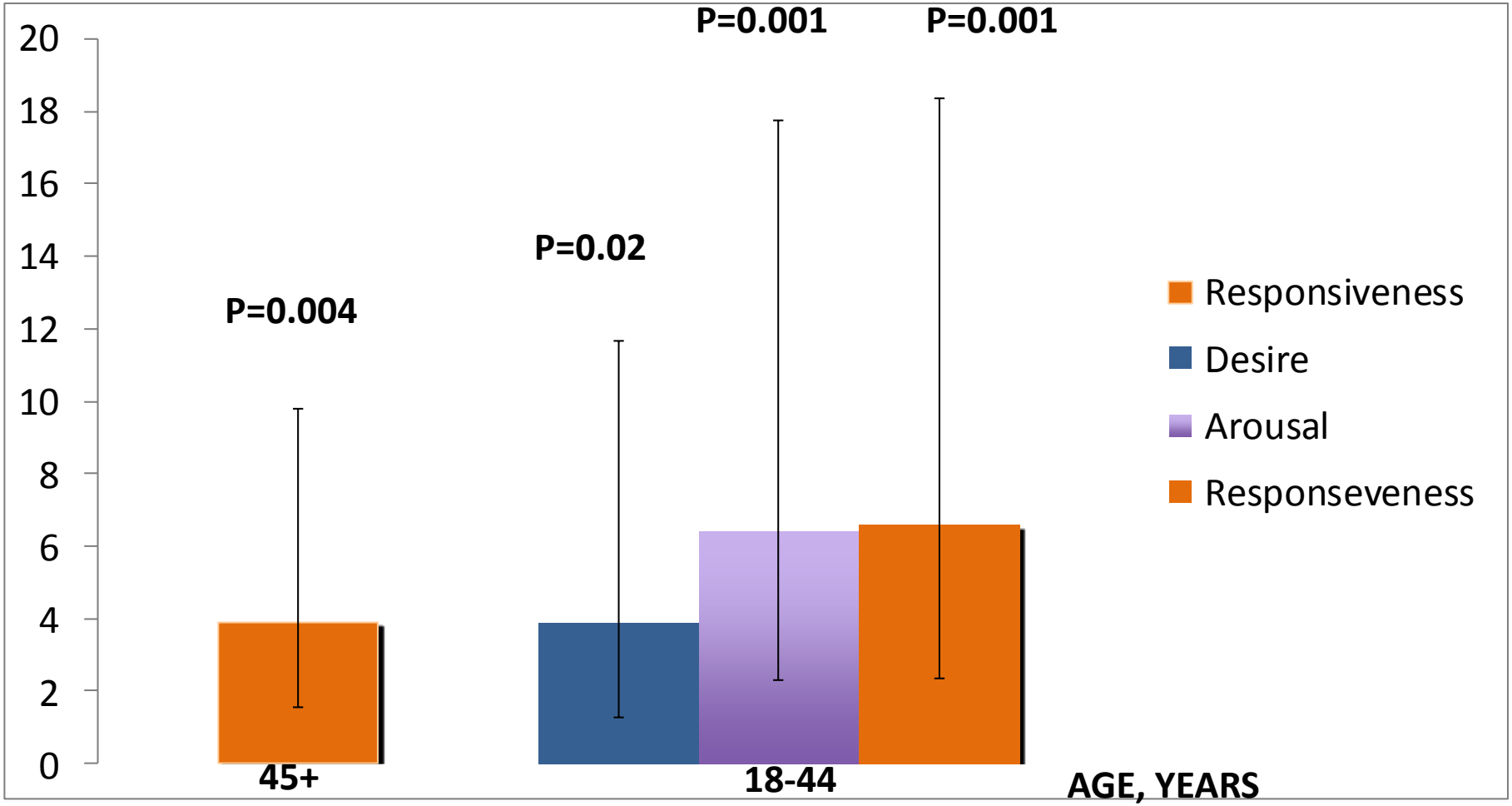
Davison, S. L. et al. J Clin Endocrinol Metab 2005;90:3847-3853

Circulating Androgen Levels and Self-reported Sexual Function in Women

- **Androgenic effects vary according to individual variations in amount and activity of enzymes 5-reductase and aromatase and individual differences in androgen-receptor response.**
- **Substantial androgen production and metabolism - *intracrinology***
- **Measurement of serum testosterone does not provide specific measure of androgen tissue exposure or action.**
- **No serum androgen level defines female androgen insufficiency.**
- **Measurement of serum testosterone, free testosterone, or DHEAS in individuals presenting with low sexual function is not informative and levels should not be used for purpose of diagnosing androgen insufficiency.**

Davis et al. JAMA 2005;294:91-96.

Likelihood of Low Sexual Function is Greater in Women with LOW DHEAS, n= 1021 women Davis et al JAMA 2005



T levels and Sexual Function: Postmenopausal Women

- **Low T levels closely correlated with reduced coital frequency and loss of sexual desire** *McCoy 1985*

- **Significant positive relationship between free T and ratings of sexual desire by interview questioning, p<0.005** *Bachmann & Leiblum, Maturitas 1991*

- **Decline in libido greater after oophorectomy than after hysterectomy** *Nathorst-Boos et al. 1992*

- **Spectrum of desire and *arousal* disorders, substantial overlap**
  - **Davis SR, Androgen use for low sexual desire in midlife women, *Menopause* 2013;20:795-797.**

T levels and Treatment Decisions

Use of testosterone therapy for treatment of sexual desire/arousal disorders is not based on an established link between symptoms and biochemistry but rather on clinical evidence that exogenous testosterone improves the most commonly reported sexual problems:

sexual desire and arousal, pleasure and overall satisfaction

BUT…after comprehensive clinical assessment testosterone and SHBG should be measured prior to considering treatment

Davis SR. *Menopause* 2013;20:795-797.
Davis SR, Davison SL, Donath S, Bell RJ. JAMA. 2005;294:91-6.

Systemic Testosterone for Treatment of Low Libido

Randomized, placebo controlled trials consistently show benefits of transdermal testosterone vs. placebo for sexual desire and arousal, orgasm, pleasure, satisfaction, and pain.

- **Surgically postmenopausal women on E**
- **Naturally postmenopausal women on E & P**
- **Postmenopausal women on no other HT**
- **Premenopausal women in late reproductive years**
- **No RCT data: Premenopausal women on COCs**

- **Lack of RCT data supporting use of systemic DHEA**

Published Randomized Studies Demonstrating Efficacy of Testosterone (Patch) in Postmenopausal Women

	Doses (mcg/d)	Subjects (n)	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)	+
Liu et al, 2008	300	NM (431)	+
Davis et al, 2008	150/300	NM/SM (814)	-
Panay et al, 2010	300	NM (272)	+/- groups

NM= naturally menopausal
SM= surgically menopausal

Davis: Breast Cancer Risk

- **Observational studies do not support an increased risk of breast cancer among testosterone users or past users.**

- **One large RCT: no effect of exogenous testosterone on mammographic density**

- **No RCT has been of sufficient size or duration to provide adequate evaluable data for impact of testosterone on breast cancer risk**

Davis. Current Opinion in Endocrinology, Diabetes &Obesity 2011, 18:198–203.

Endometrial Safety: Testosterone Patch Studies

- **Shifren et al (2007): "no increases in frequency of vaginal bleeding observed with exposure to testosterone in women with a uterus" (n= 340)**

- **Davis et al (2008): 55% of 815 subjects with a uterus were evaluated at 52 weeks or as indicated.**

Vaginal bleeding 2.6% placebo, 10.6% testosterone 300 mcg/d

  - **2 cases of proliferative and no hyperplasia in testosterone subjects receiving endometrial biopsy**

- **Panay et al (2010): 5% vaginal bleeding in testosterone (n=130) and placebo (n=142) groups at 6 months**

Testosterone: CV Safety

- **Studies of testosterone administered by subcutaneous implant, transdermal patch, spray or gel do not show any adverse effects on lipids, CRP, HbA1C, or insulin sensitivity.**

- **No adverse effects on lipids, insulin resistance, and CRP in postmenopausal women on no concurrent estrogen therapy.**

- **"Available evidence does not support belief that treatment with parenteral testosterone therapy, using doses intended to achieve serum concentrations of total and free testosterone that approximate normal range for premenopausal women, adversely effects CVD risk."**

Davis. Current Opinion in Endocrinology, Diabetes & Obesity 2011, 18:198–203.

Safety Study (Blinded Data)

- **Nearly 5000 women randomized, > 7300 women years of exposure**
- **Rate of adjudicated CV events: 0.72% (53)**
- **Rate of breast cancer: 0.37% (27)**

Snabes et al. J Sex Med 2011;8(suppl 2):62, 17A.
Snabes, NAMS 2011.

Testosterone Patch: Long Term Safety

- **4-year open-label extension safety data from 967 surgically menopausal women on ERT who participated in TTP studies (300 ug)**
- **No increase rate of new occurrences of serious, severe or withdrawal AEs**
- **AEs: application site reactions, unwanted hair growth**
- **Hematology, lipid profile, carbohydrate metabolism, renal and liver function or coagulation parameters unchanged 4 years of therapy**.
- **Expected age related increase rate of breast cancer**

Nachtigall et al. Gynecol Endocrinol 2011;27:39–48.

Summary of Efficacy & Safety

- ***Randomized, double-blind placebo controlled studies have established efficacy of transdermal patch for relieving symptoms of HSDD in naturally and surgically menopausal women with and without concomitant estrogen or estrogen/ progesterone therapy***
- **Main side effects: increased hair growth and acne**
- **Available safety data, although not conclusive, were reassuring with respect to cardiovascular, breast, and endometrial outcomes**
- **Long term safety data demonstrate no significant impact on intermediate metabolic endpoints and a low rate of cardiovascular events and breast cancer in postmenopausal women at increased cardiovascular risk**

Davis SR, Braunstein GD. J Sex Med 2012;9:1134-1148.
Khera M. Sex Med Rev 2015;3:137-144

Testosterone Therapy: 2009-2015

- **ICSM 2009, 2015; ACOG Practice Bulletin 2011**
- **NAMS Recommendation for Clinical Care 2014**
- **Decision to use T individualized, informed consent**
- **Long term safety data lacking to support use > 6 months**
- **Current data do not support T in pre and perimenopausal ♀**
- **Achieving physiological free T levels by transdermal delivery decreases adverse effects**
- **Relative contraindications: androgenic alopecia, seborrhea, acne, hirsuitism**
- **Contraindications: hyperlipidemia, liver dysfunction**
- **Contraindicated with or high risk: breast & endometrial cancer, CVD, veno-thromobotic events pending additional safety data**

Wierman et al. J Sex Med 2010:7:561-585.
Shiffren JL, Gass MLS. Menopause 2014;21:1038-1062.
ICSM, 2015, in press

Testosterone Monitoring: ICSM, NAMS

- **Annual breast and pelvic exams**
- **Annual mammography**
- **Evaluation of abnormal bleeding**
- **Evaluation for acne, hirsutism, androgenic alopecia, voice changes, clitoromegaly**
- **Monitor testosterone by mass spectrometry (SHBG, calculated free T)**
- **Goal: not to exceed normal range for reproductive-aged women**
- **Lipid profile, LFTs, CBC - baseline, 6 mos, annually**
- **Use for > 6 months contingent on clear improvement and absence of adverse events**

Basson et al. J Sex Med 2010:7:314-326.
Shiffren JL, Gass MLS. Menopause 2014;21:1038-1062.

Endocrine Society Guidelines 2014

- ***Recommend against diagnosis of androgen deficiency in healthy women - lack of well-defined syndrome and correlation of data with signs and symptoms***
- **Hypoactive Sexual Desire Disorder (HSDD): 3-6 month trial of high physiological doses of T, monitoring for androgen excess.**
  - **Not male products or compounded, transdermal "if available"**
  - **T levels do not predict response**
  - **Levels 3-6 weeks, then q6 months**
  - **Safety data not available beyond 6 months**
- **Recommend against T therapy**
  - **Surgical menopause, OCs, other sexual dysfunctions, cognitive, cardiovascular, metabolic, bone health, well-being**
- **No role for DHEA**

Wierman et al. J Clinic Metab 2014. 99:3489-3510.

Clinical Guidelines - UpToDate

Available preparations for Postmenopausal Women not responding to nonpharmacological therapy

Not FDA approved

Long term safety data lacking

- Topical compounded 1% testosterone creme, 0.5 grams daily (no regulation)
- Intrinsa 300 mg patch (2x/week) no longer in Europe (consistent blood levels)
- Transdermal patches and gels for men (supraphysiologic dosing, 1/10th dose; arms, legs, abdomen ,risk to children)
- Oral: methyltestosterone, micronized testosterone (compounded), DHEA
- Intramuscular injections or implants (supraphysiologic dosing)