Androgen Treatment Guidelines and Safety Concerns

ISSWSH Fall Course 2014

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Disclosures

- **Advisory Board:** Sprout, Pfizer, SST, Emotional Brain, Apricus

Objective

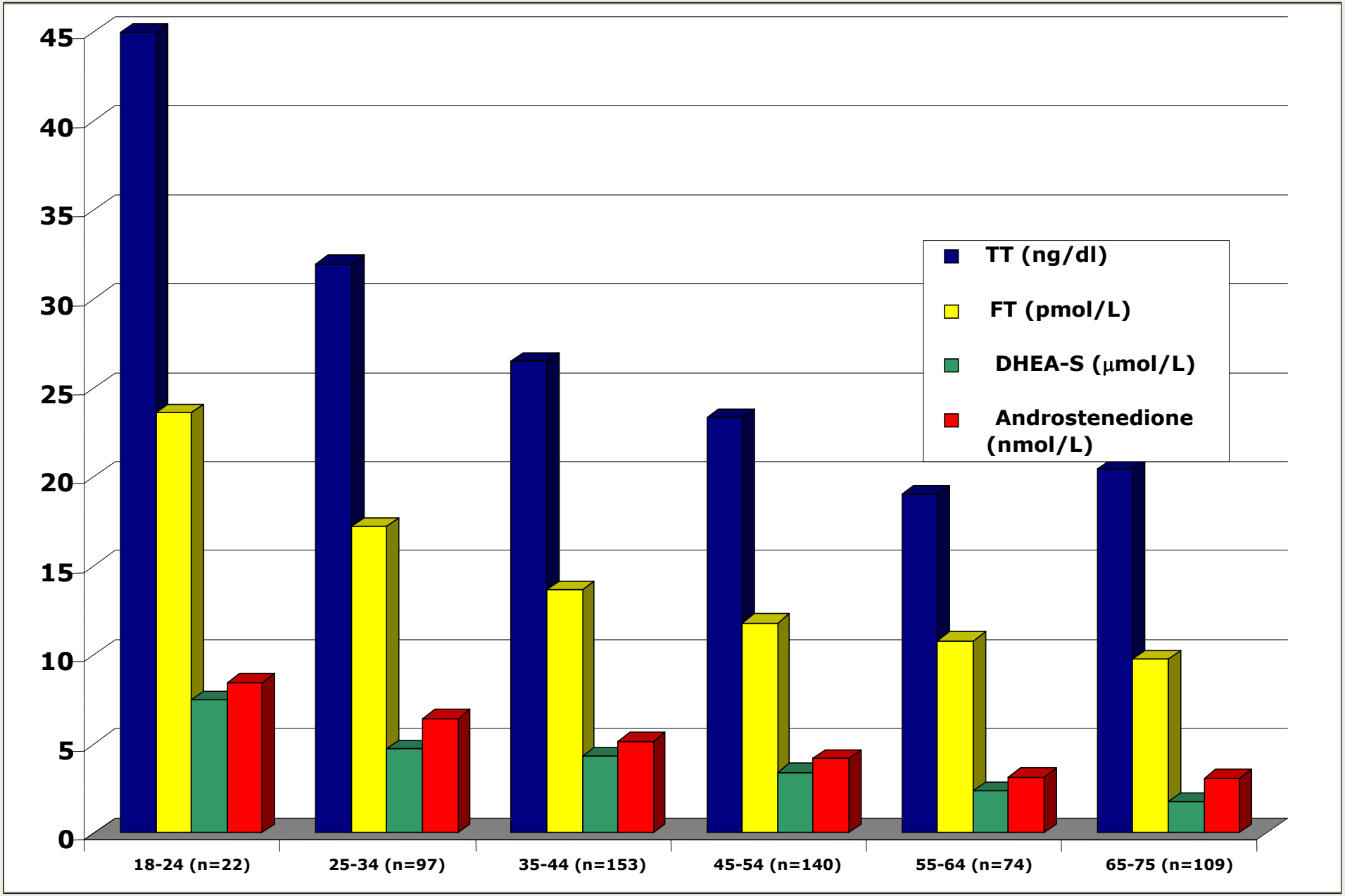
- Discuss the efficacy and safety of testosterone therapy for Hypoactive Sexual Desire Disorder in women

Off-label Testosterone

- Data: IMS Health
- Two million prescriptions written for ♀ 2006-7
- Increased since 2004 (U.S. FDA Intrinsa Advisory Committee Briefing Document)
- 21% of prescriptions for branded male testosterone products written for ♀
- Figures do not include substantial number of prescriptions for compounded T
- Compounded products have no systematic trials to support safety concerns and no black box warnings

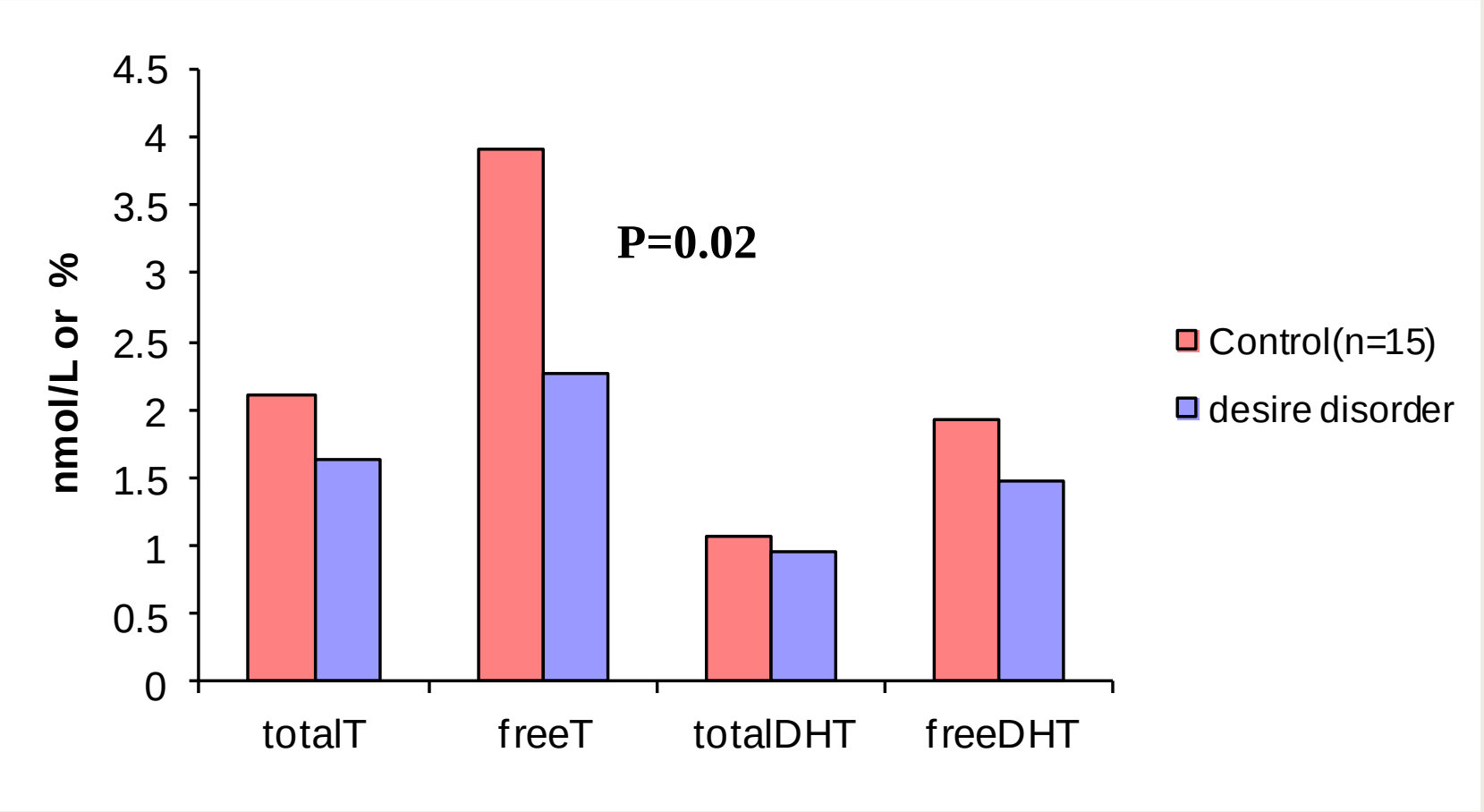
Snabes M , Simes SJ Sex Med 2009;6:1846–1849.

Relationship Between Age and Androgens in Women



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

Free T Significantly Lower in Premenopausal Women with Desire Disorder



Riley and Riley, J Sex Martial Med 2000.

Sexual Well Being: 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, Davison SL, Donath S, Bell RJ. *Circulating androgen levels and self-reported sexual function in women. 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 HT**
- **Premenopausal women in late reproductive years**
- **No RCT data: Premenopausal women on COCs**

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

Testosterone Post-Menopausal, No E

- *How much of the above are from estrogen, as well, or in combination with testosterone?*
- **Randomized double-blind placebo-controlled 52-weeks**
- **N=814 HSDD women**
- **Patch (150, 300 ug) vs. placebo**
- **Efficacy: 24 week endpoint, SSE**
- **300 ug: SSE > placebo (2.1 vs. 0.7, p<0.001), NM**
- **Both doses associated with increased desire and decreased distress, NM & SM**

Davis et al. New Engl J Med 2008;359:2005-17

Testosterone Alone Post-Menopause: AEs

- Dose related T level increases, correl. with SSEs
- Mild events, not clearly related to RX
- Withdrawal: application-site reactions
- Androgenic adverse events (300 ug)
  - Hair growth & ↑ facial depilation rates
  - Mild clitoral enlargement (4)
- Breast cancer dx (3) – 2 likely present prior to tx
- ↑ Vaginal bleeding & proliferative endometrium (2)
- No change metabolic parameters

Davis et al. New Engl J Med 2008;359:2005-17.

Exogenous Testosterone: Other Benefits

- **Body composition/ Lean muscle mass**
- **Decreased hip fracture risk**
- **Improvements in:**

- **Visual and verbal memory and concentration**

Shah et al Menopause 2006

Davison et al Maturitas 2011

- **Complex information processing**

Regestein et al J Womens Health Gend Based Med 2001

- **Memory**

Wisniewski et al Horm Res 2002

- **Visuo-spatial task performance**

Aleman et al Psychoneuroendocrinol 2004

Shah et al Menopause 2006

Wisniewski et al Horm Res 2002

RCTs of Systemic DHEA for Female Sexual Dysfunction Do Not Support its Use

Authors	Duration (weeks)	Dose (mg/day)	Participants- postmenopausal n, (age in years)	Sexual function	Instrument to measure sexual function
Mortola and Yen 1990	4	1600	6 (46-61 y)	No change	Self-reported
Morales 1994	24	50	15 (8 on HT) 40-70 y	No change	Visual Analog Scale
Wolf 1997	2	50	15 (69±1.7)	No change	Self reported
Hackbert & Heiman 2002	1	300	16 (51-68y)	Improvement	FES, DSFI, OFQ, self-report, vaginal photoplethysmograph
Schmidt 2005	6	90-450	6	Improvement	Derogatis Sexual Functioning Inventory
Kritz-Silverstein 2008	52	50	115 (55-85y)	No change	Female Sexual Function Index
Panjari 2009	52	50	93 (40-65y)	No change	Sabbatsberg Sexual Self-Rating Scale, sexual event diary, MENQOL

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**

Davis: 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 of women with parenteral testosterone therapy, using doses intended to achieve serum concentrations of total and free testosterone that approximate the 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 receiving estrogens who participated in TTP studies (300 ug)**
- **No increase over time in rate of new occurrences or severity of AEs, serious AEs, or withdrawals due to AEs**
- **AEs: application site reactions and unwanted hair growth**
- **Hematology, lipid profile, carbohydrate metabolism, renal and liver function or coagulation parameters were noted with up to 4 years of therapy**.

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.

Testosterone Therapy: Who to Treat

- **Primary indication for testosterone therapy: treatment of persistent low libido that profoundly impairs quality of life**
- **Women late reproductive years and beyond who have experienced distinct change and are distressed**
- **Women with the following conditions & distressing loss of libido:**
  - **Surgical menopause**
  - **Premature ovarian failure**
  - **Adrenal insufficiency (including glucocorticosteroid)**

Davis SR. Menopause 2013;20(7):795-797.

Endocrine Society Guidelines 2014

- **Many women who had low testosterone levels measured did not exhibit any signs or symptoms of concern.**

  As a result, physicians cannot make a diagnosis of androgen deficiency in women.

- **Hypoactive Sexual Desire Disorder (HSDD): clinical practice guidelines suggests a three- to six-month trial of testosterone to see if the therapy improves sexual function.**
- **No role for DHEA**

Wierman et al. J Clinical Endocrinoloy, 2014

Testosterone Monitoring: ICSM 2009

- Annual breast and pelvic exams
- Annual mammography
- Evaluation of abnormal bleeding
- Evaluation for acne, hirsutism, androgenic alopecia
- Monitor testosterone by mass spectrometry (SHBG, calculated free T)
- Goal: not to exceed normal T values
- Consider: 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.

Clinical Guidelines - UpToDate

Available preparations for Postmenopausal Women not responding to nonpharmacological therapy

- 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, risk to children)
- Oral: methyltestosterone, micronized testosterone (compounded), DHEA
- Intramuscular injections or implants (supraphysiologic dosing)