

# **Master Journal Club: Testosterone Rx for Female Sexual Dysfunction**

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**Grants/Research:** In the last year he has received or is currently receiving grant/research support from: AbbVie, Inc. (North Chicago, IL), Actavis, PLC. (Dublin, Ireland), Agile Therapeutics (Princeton, NJ), Bayer Healthcare LLC., (Tarrytown, NY), New England Research Institute, Inc. (Watertown, MA), Novo Nordisk (Bagsværd, Denmark), Palatin Technologies (Cranbury, NJ), Symbio Research, Inc. (Port Jefferson, NY), TherapeuticsMD (Boca Raton, FL).

**Patent and Trademark Holder:** U.S. Patent: 4,816,257, March 28, 1989: "Method for Producing an In Vivo Environment Suitable for Human Embryo Transplant.", U.S. Trademark: Reg. No. 3,446,895, Registered June 10, 2008: "You talk...I'll Listen. We'll Plan Together", U.S. Trademark: Reg. No. 3,676,269, Registered September 1, 2009: U.S. Trademark: Reg. No. 3,760,080, Registered March 16, 2010: "Women's Health & Research Consultants & Design", U.S. Trademark Serial No.:86-714,153. "DR. SIMON SAYS" Registered February 2, 2016.

**Stock Shareholder and/or other Financial Support:** Dr. Simon is a stockholder (direct purchase) in Sermonix Pharmaceuticals (Columbus, OH).

Davis SR, Wahlin-Jacobsen S. Testosterone in women—the clinical significance. *Lancet Diabetes Endocrinol.* 2015 Dec;3(12):980-92. doi: 10.1016/S2213-8587(15)00284-3. Epub 2015 Sep 7. Review.

Review

## Testosterone in women—the clinical significance



Susan R Davis, Sarah Wahlin-Jacobsen

Testosterone is an essential hormone for women, with physiological actions mediated directly or via aromatisation to oestradiol throughout the body. Despite the crucial role of testosterone and the high circulating concentrations of this hormone relative to oestradiol in women, studies of its action and the effects of testosterone deficiency and replacement in women are scarce. The primary indication for the prescription of testosterone for women is loss of sexual desire, which causes affected women substantial concern. That no formulation has been approved for this purpose has not impeded the widespread use of testosterone by women—either off-label or as compounded therapy. Observational studies indicate that testosterone has favourable cardiovascular effects measured by surrogate outcomes; however, associations between endogenous testosterone and the risk of cardiovascular disease and total mortality, particularly in older women, are yet to be established. Adverse cardiovascular effects have not been seen in studies of transdermal testosterone therapy in women. Clinical trials suggest that exogenous testosterone enhances cognitive performance and improves musculoskeletal health in postmenopausal women. Unmet needs include the availability of approved testosterone formulations for women and studies to elucidate the contribution of testosterone to cardiovascular, cognitive, and musculoskeletal health and the risk of cancer.

*Lancet Diabetes Endocrinol* 2015

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Women's Health Research Program, School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia (Prof S R Davis MBBS); and Department of Sexological Research, Sexological Clinic, Psychiatric Center Copenhagen, Copenhagen, Denmark (S Wahlin-Jacobsen MD)

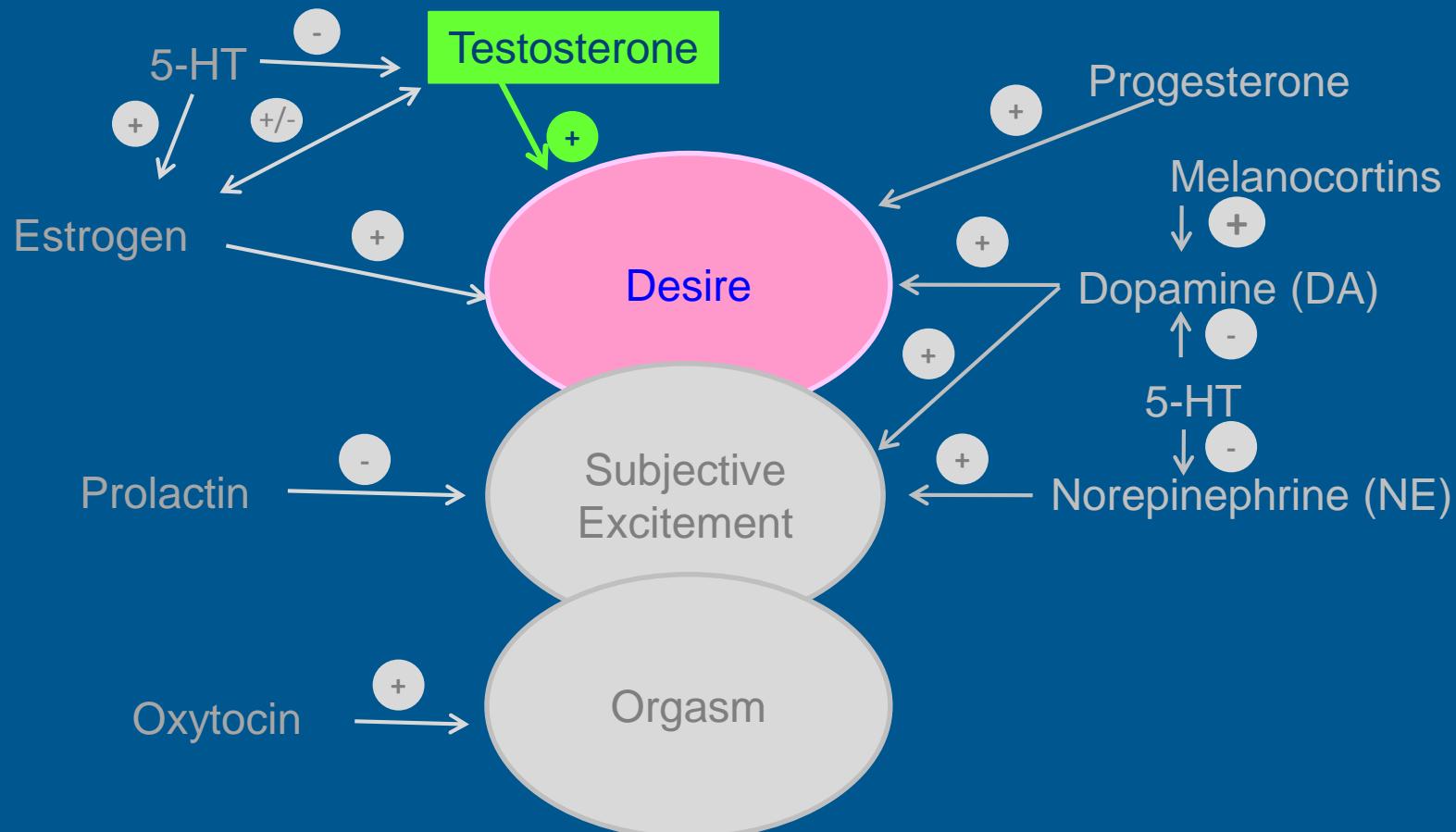
- ❖ Female Androgen Physiology
- ❖ Testosterone and Female Sexual Function
- ❖ Testosterone and Vaginal Health
- ❖ Testosterone and Cardiometabolic Disease
- ❖ Testosterone and Cognition
- ❖ Musculoskeletal Effects of Testosterone
- ❖ Testosterone and Gynecological Cancer (Breast, Ovarian, Endometrial)

# Testosterone in Women: Can the Challenges be Met?

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- **Testosterone for treatment of women with loss of sexual desire or arousal is an active component of clinical practice for which guidelines are inadequate.**
- To pave the way for appropriate treatment of female sexual dysfunction, recognition is needed that women are innately sexual and that female sexual dysfunction is a disorder that merits treatment.
- A well characterized testosterone formulation needs to be approved to protect women from inappropriate dosing when treated with testosterone formulated for men or in compounded form —which is nothing short of an **unregulated human experiment**.

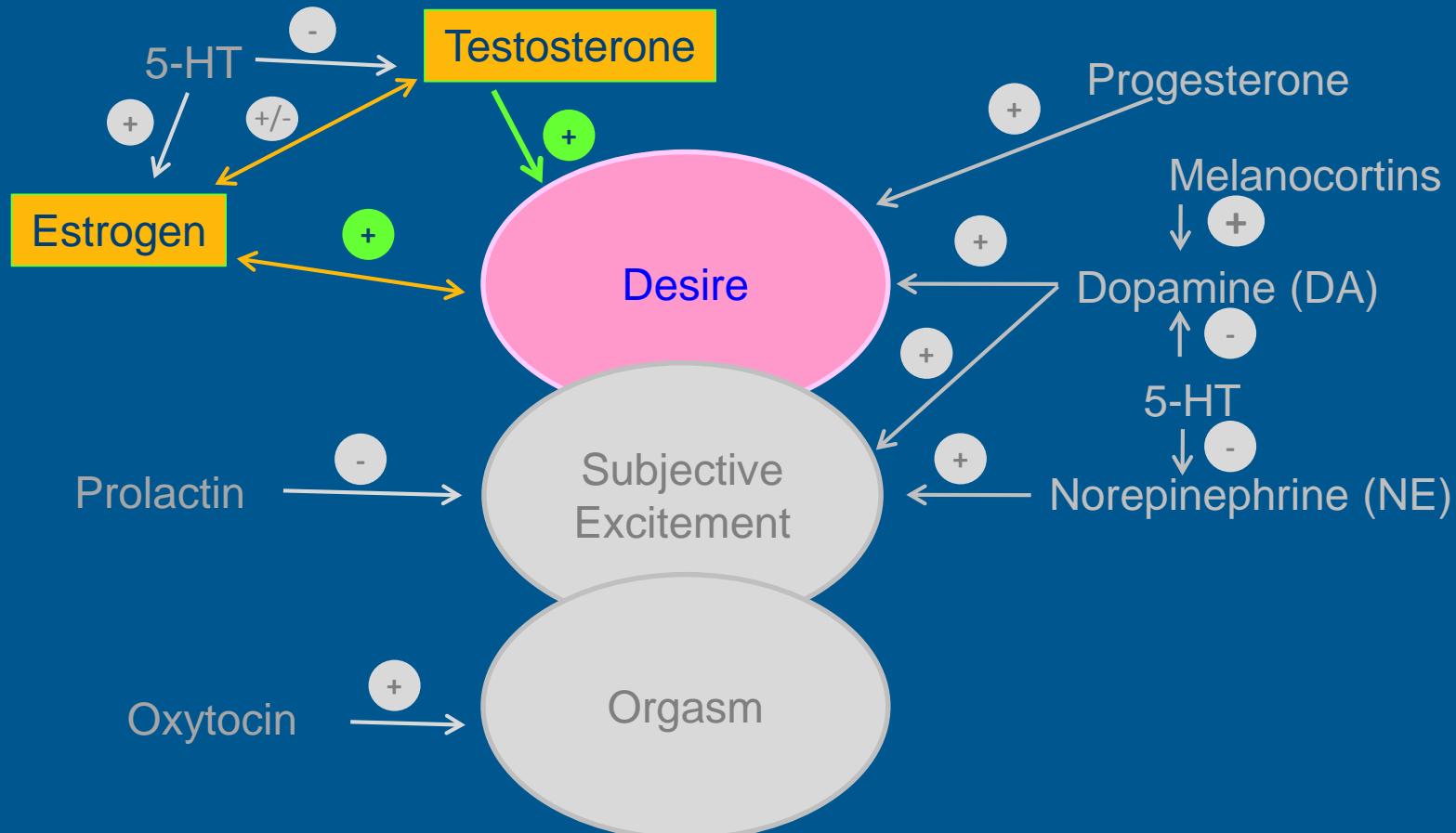
# Testosterone for HSDD



Adapted from Clayton A, Hamilton D. *Psychiatr Clin N Am.* 2010;33:323-338.



# Testosterone for HSDD



Adapted from Clayton A, Hamilton D. *Psychiatr Clin N Am.* 2010;33:323-338.



GOT TESTOSTERONE?



**“Circulating androgens present in women arise solely from the adrenal gland and there is no reason to believe this organ (ovary) is an important source of androgens in normal women...”**

**Dorman and Shipley, 1956**

# *Documented Changes Following Oophorectomy*

## *Greatest Changes >60 Years Olds*

**Clinical Expression of Androgen Deficiency**

*May be subtle*

*Traditionally Accepted as “Aging”*

### **Adrenarche**

Increase in:

- Sexual hair
- Libido
- Bone density
- Stature
- Muscle Mass
- Immune function

### **Menopausal Senescence**

Decrease in:

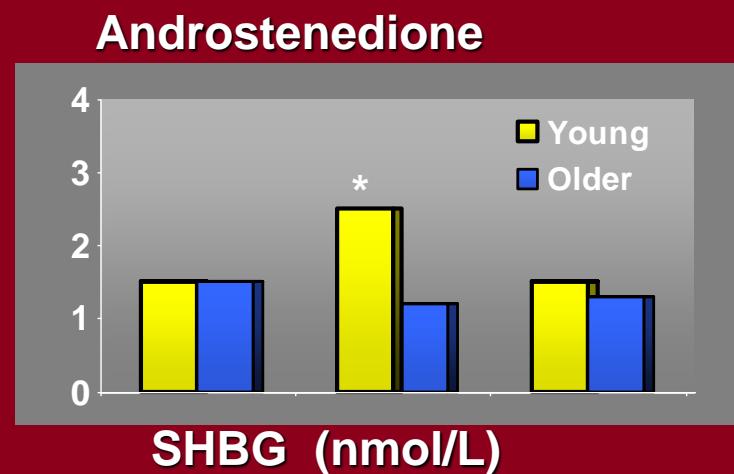
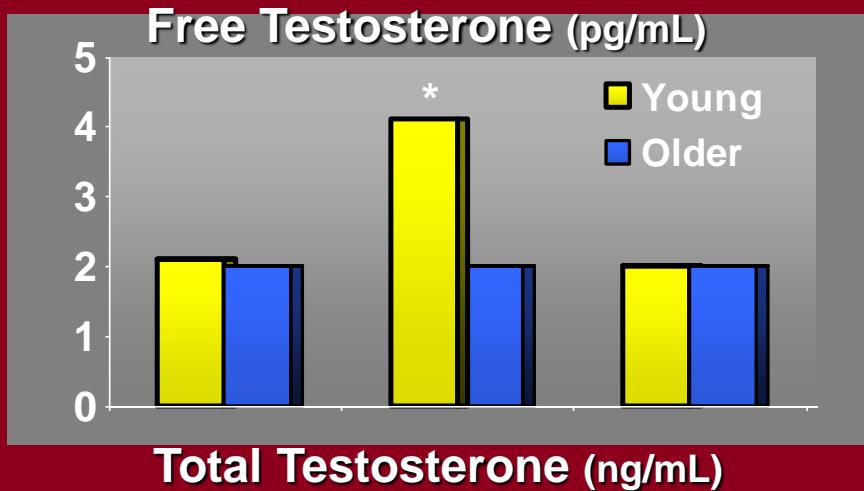
- Sexual hair
- Libido
- Bone density
- Stature
- Muscle Mass
- Immune function

# ***Mean Steroid Levels in Women (pg/ml)***

	<b>Reproductive Age</b>	<b>Natural Menopause</b>	<b>Surgical Menopause</b>
<b>Estradiol</b>	150	10-15	10
<b>Testosterone</b>	400	290	110
<b>Androstenedione</b>	1900	1000	700
<b>DHEA</b>	5000	2000	1800
<b>DHEAS</b>	3,000,000	1,000,000	1,000,000

Buster J. In Lobo R. *Treatment of Postmenopausal Women*. Boston, MA.; Lippocott:1999.  
Judd HL, et. al. J Endocrinol Metab. 1974;39:1020-1024.

# *Sex Steroid Levels in Young and Older Reproductive-Aged Women*



\* $P<0.05$  vs older women.

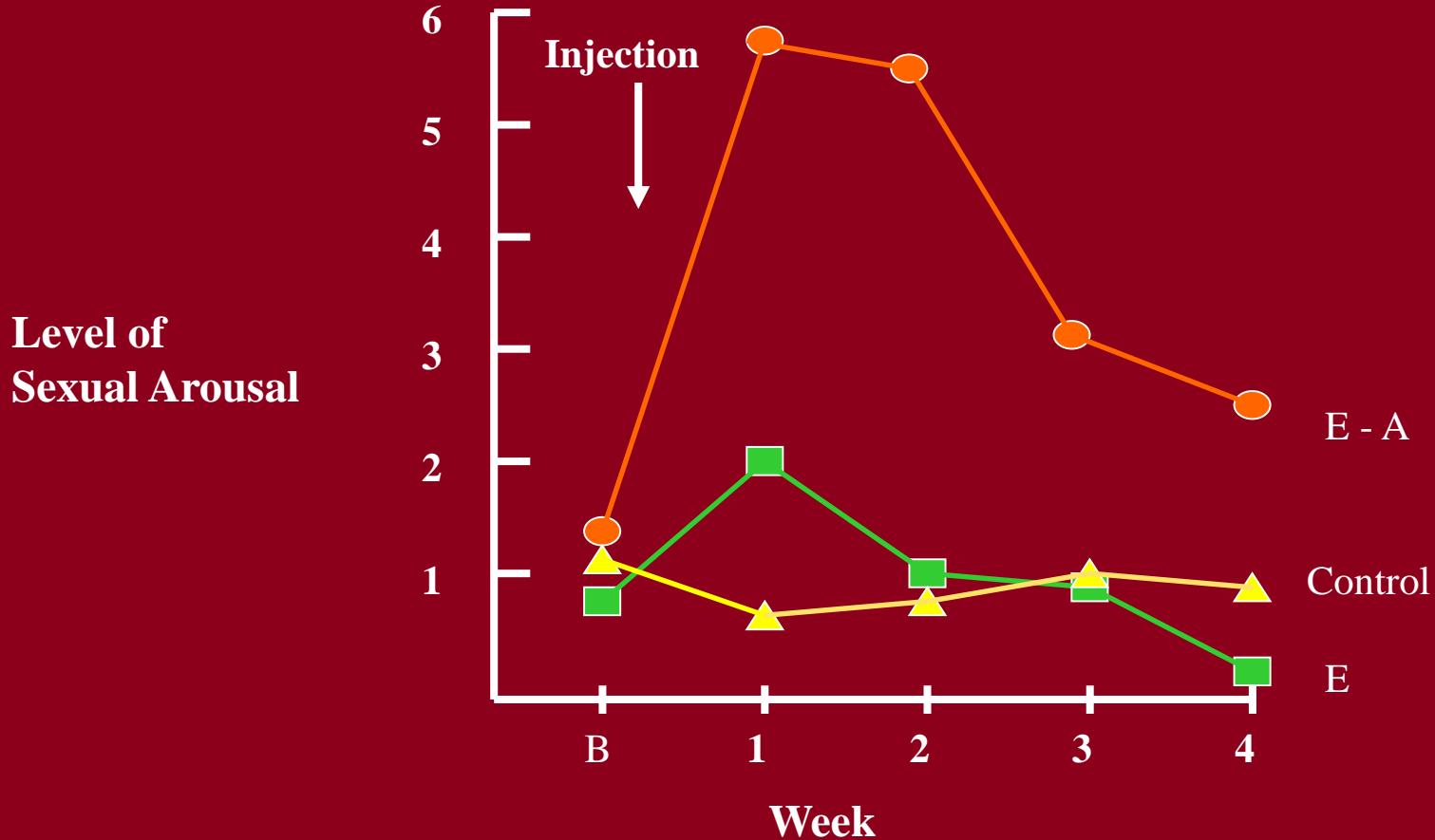
Mushayandebvu T, et al. *Fertil Steril*. 1996;65:721-723.

## *Reduction of Hormone Production in Postmenopausal Women*

- Up to 66% of estrogen production is lost after the menopause
- Androgen production decreases up to 50%

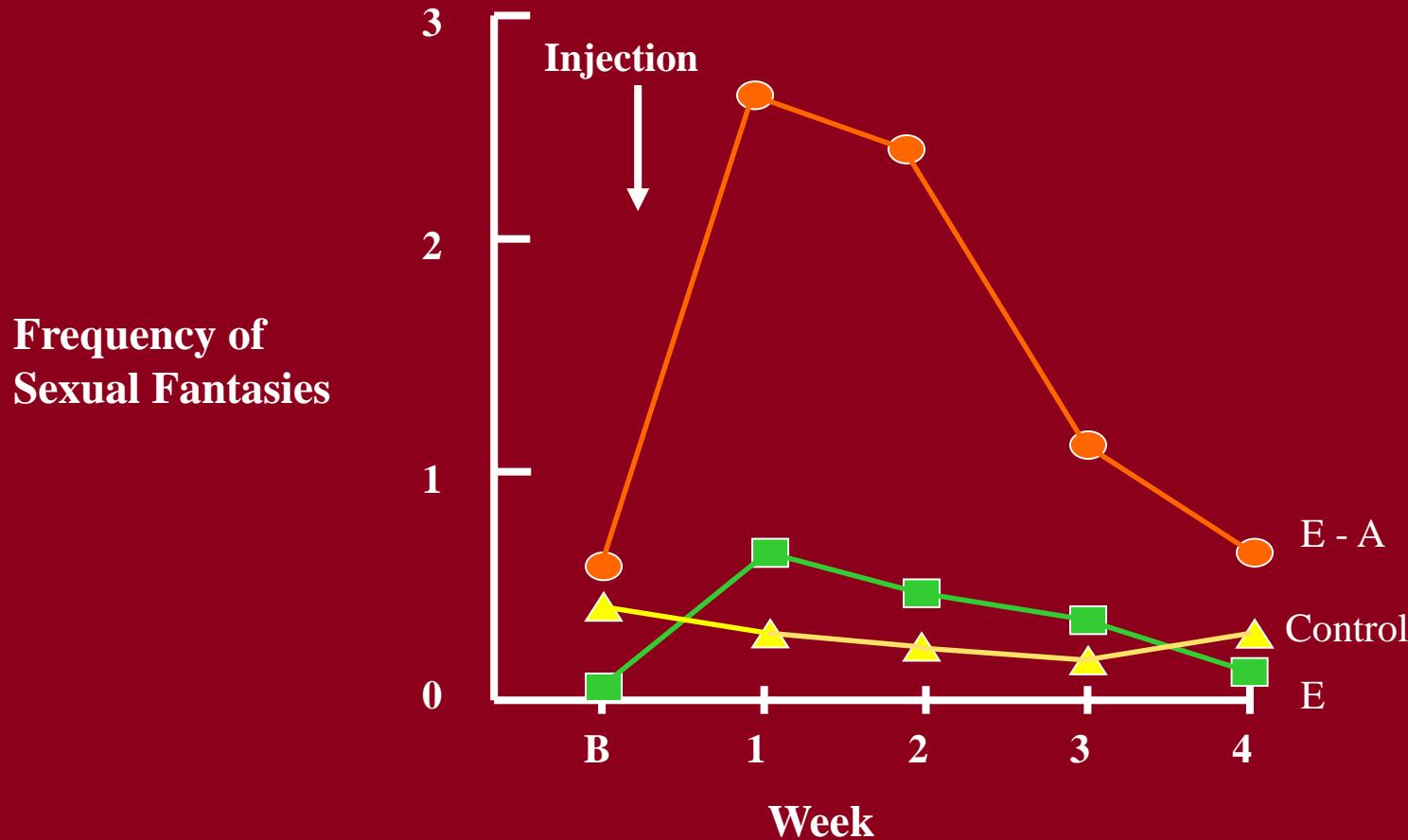
Adapted from Longcope C, et al. *Maturitas*. 1981;3:215-223.

## *Mean Level of Sexual Arousal*



Sherwin & Gelfand, *Psychosomatic Med* 1987;49:397-409.

## *Mean Level of Sexual Fantasies*



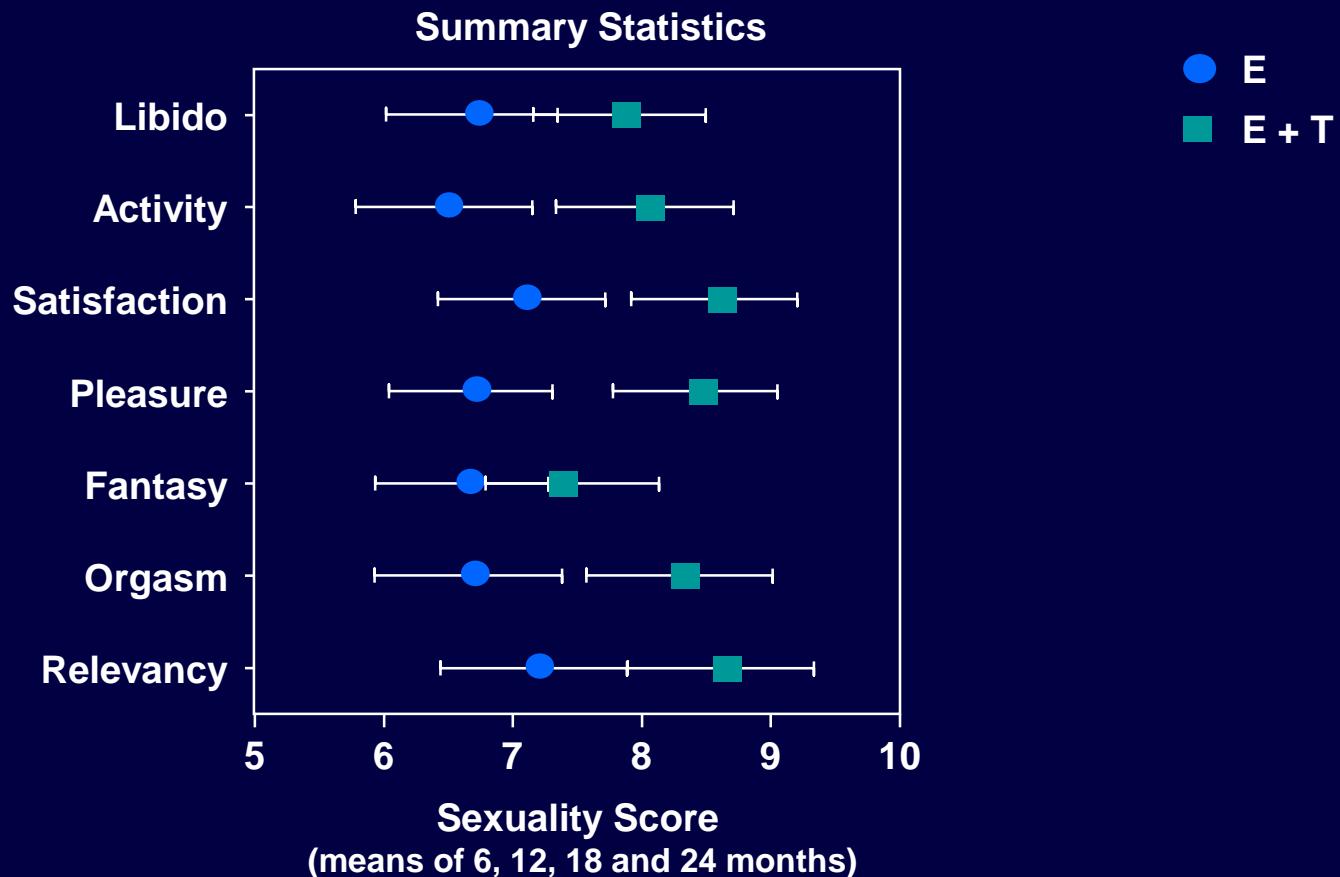
Sherwin & Gelfand, *Psychosomatic Med* 1987;49:397-409.

## *Mean Level of Sexual Desire*



Sherwin & Gelfand, *Psychosomatic Med* 1987;49:397-409.

# Estradiol vs. Estradiol + Testosterone Implants Treatment in 32 Postmenopausal Women



# Transdermal Testosterone Patch Development Program: Comprehensive & Robust

- ◆ **9 Pharmacokinetic Studies**

- Range of doses/dosing durations

- ◆ **3 Instrument Validation Studies**

- Followed by a confirmatory validation study

- ◆ **3 Phase II Studies**

- Dose-ranging, different routes of estrogen administration

- ◆ **7 Phase III Studies: well-controlled/comparable**

- 2 in surgically menopausal women (SM)
  - 2 in natural menopausal women (NM)
  - 1 testosterone-only (SM & NM, no estrogen)
  - 1 in natural menopausal women, transdermal estrogen
  - 1 in menopausal women not taking estrogen

- ◆ **Alcohol-free, translucent, matrix patch**

- ◆ **Twice-a-week application to abdomen**

- ◆ **Contains 8.4 mg testosterone**

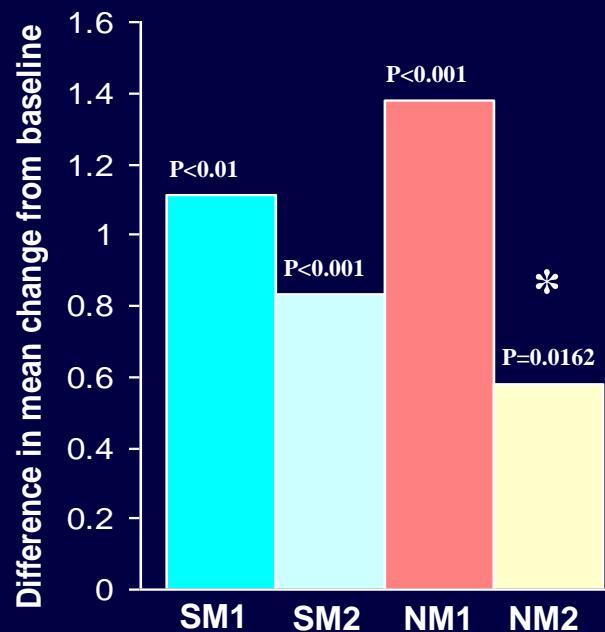
- ◆ **Delivers 300 mcg/day testosterone**



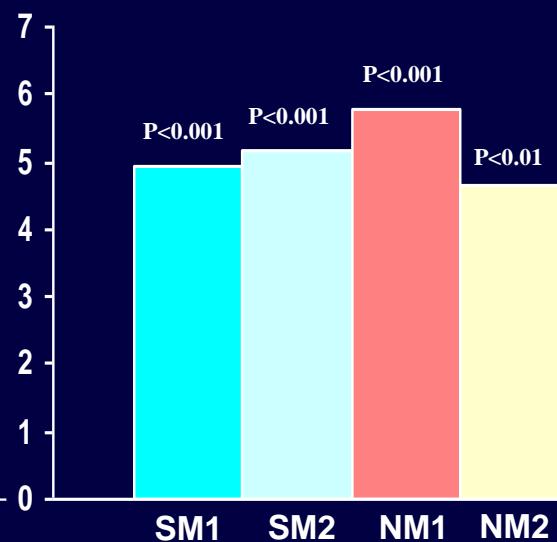
# Consistent Efficacy of Transdermal Testosterone Patches (Intrinsa<sup>TM</sup>) in 4 different Clinical Trials

\* Adjusted & capped data

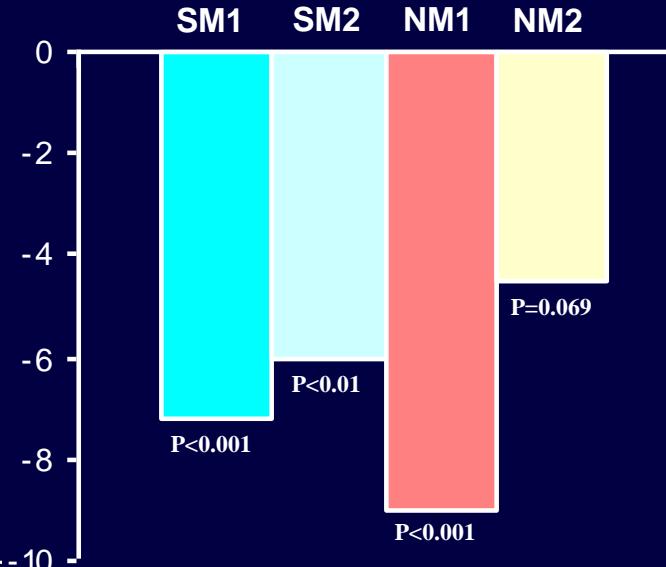
Satisfying Sexual Activity  
(events/4weeks)



Sexual Desire  
(PFSD score)



Personal Distress  
(PDS score)



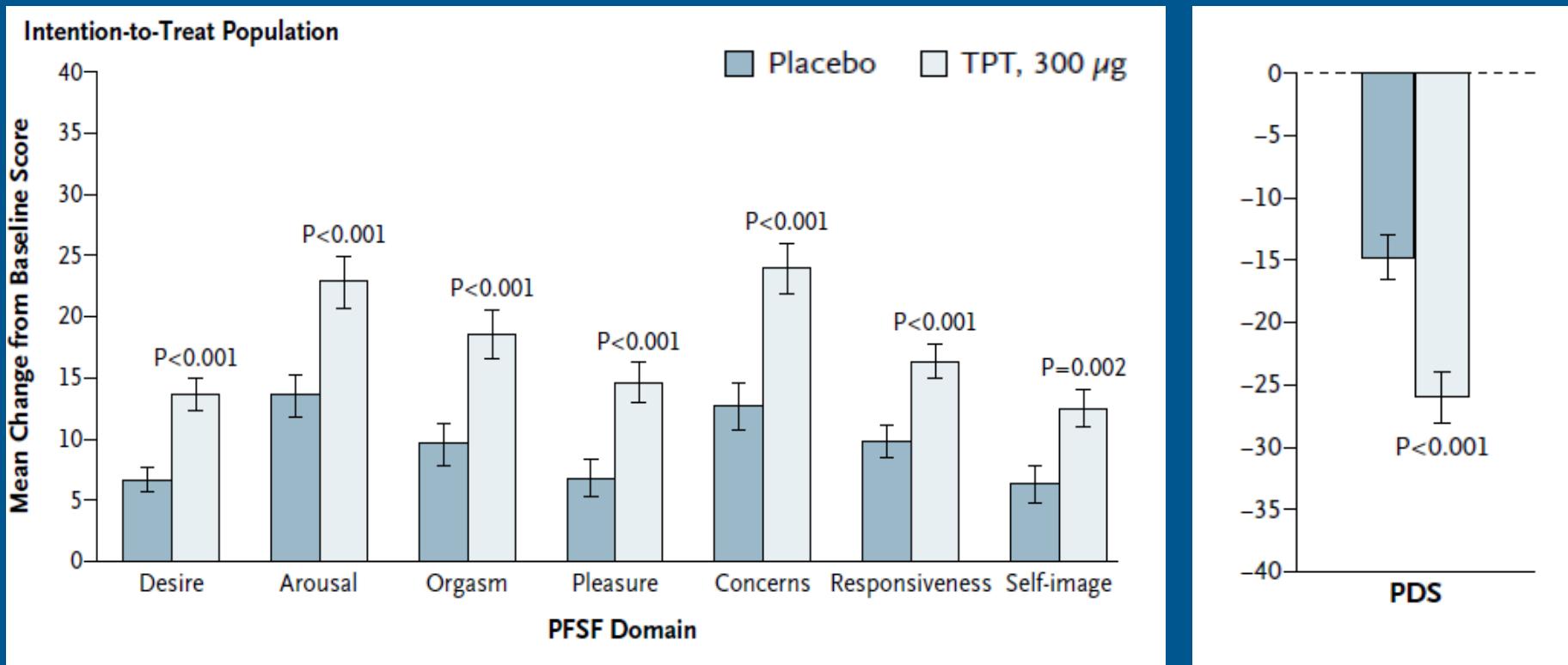
Buster JE, Kingsberg SA, Aguirre O, et. al. Testosterone patch for low sexual desire in surgically menopausal women: a randomized trial. Obstet Gynecol. 2005 May;105(5 Pt 1):944-52.

Simon J, Braunstein G, Nachtigall L, et. al. Testosterone patch increases sexual activity and desire in surgically menopausal women with hypoactive sexual desire disorder. J Clin Endocrinol Metab. 2005 Sep;90(9):5226-33.

Shifren JL, Davis SR, Moreau M, et. al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. Menopause. 2006 Sep-Oct;13(5):770-9. Erratum in: Menopause. 2007 Jan-Feb;14(1):157.

# Transdermal Testosterone for HSDD Postmenopausal Women *Not* Taking Estrogen

## Changes from Baseline Scores at Week 24



TPT: testosterone patch treatment

PFSF: Profile of Female Sexual Function

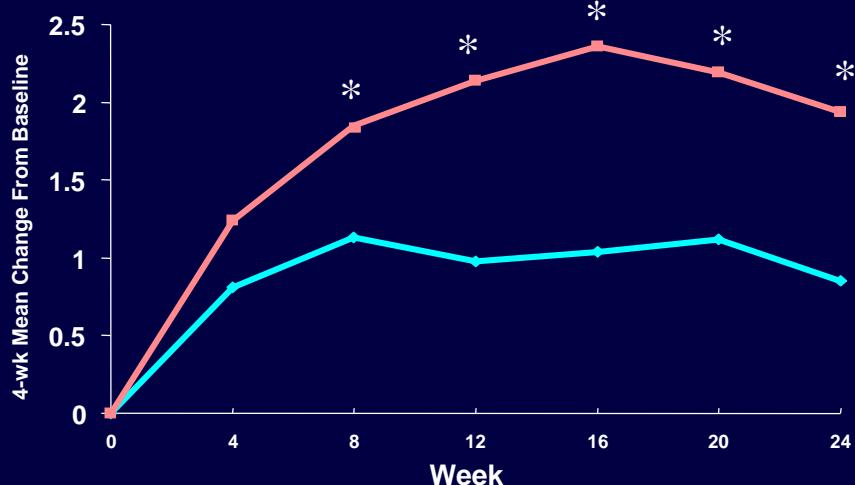
PDS: Personal Distress Scale

Davis S, et al. *N Engl J Med.* 2008;359:2005-2017.

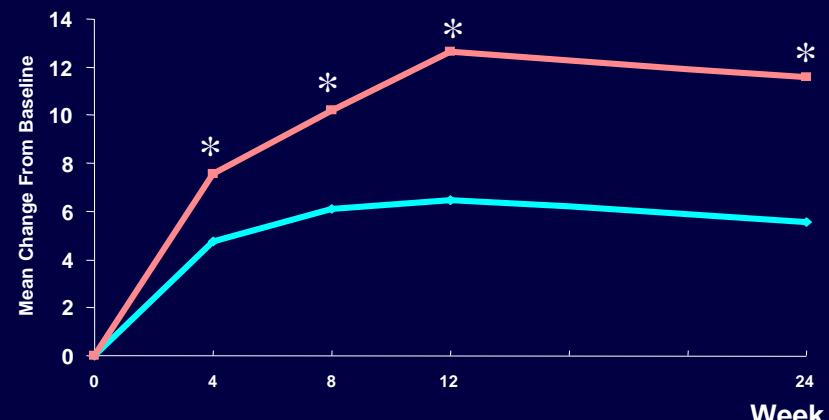


# Timing of Treatment Benefits: Transdermal Testosterone (SM 1 & SM 2)

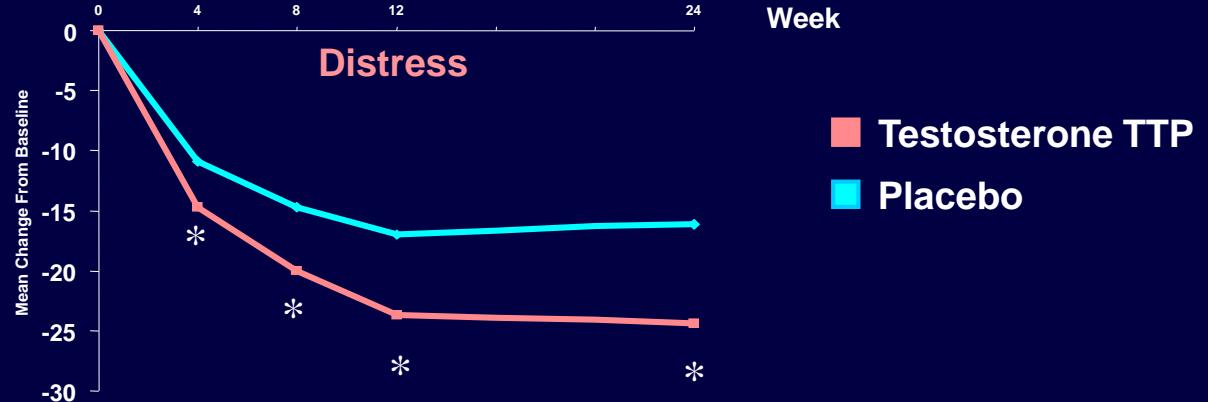
Total Satisfying Activity



Sexual Desire



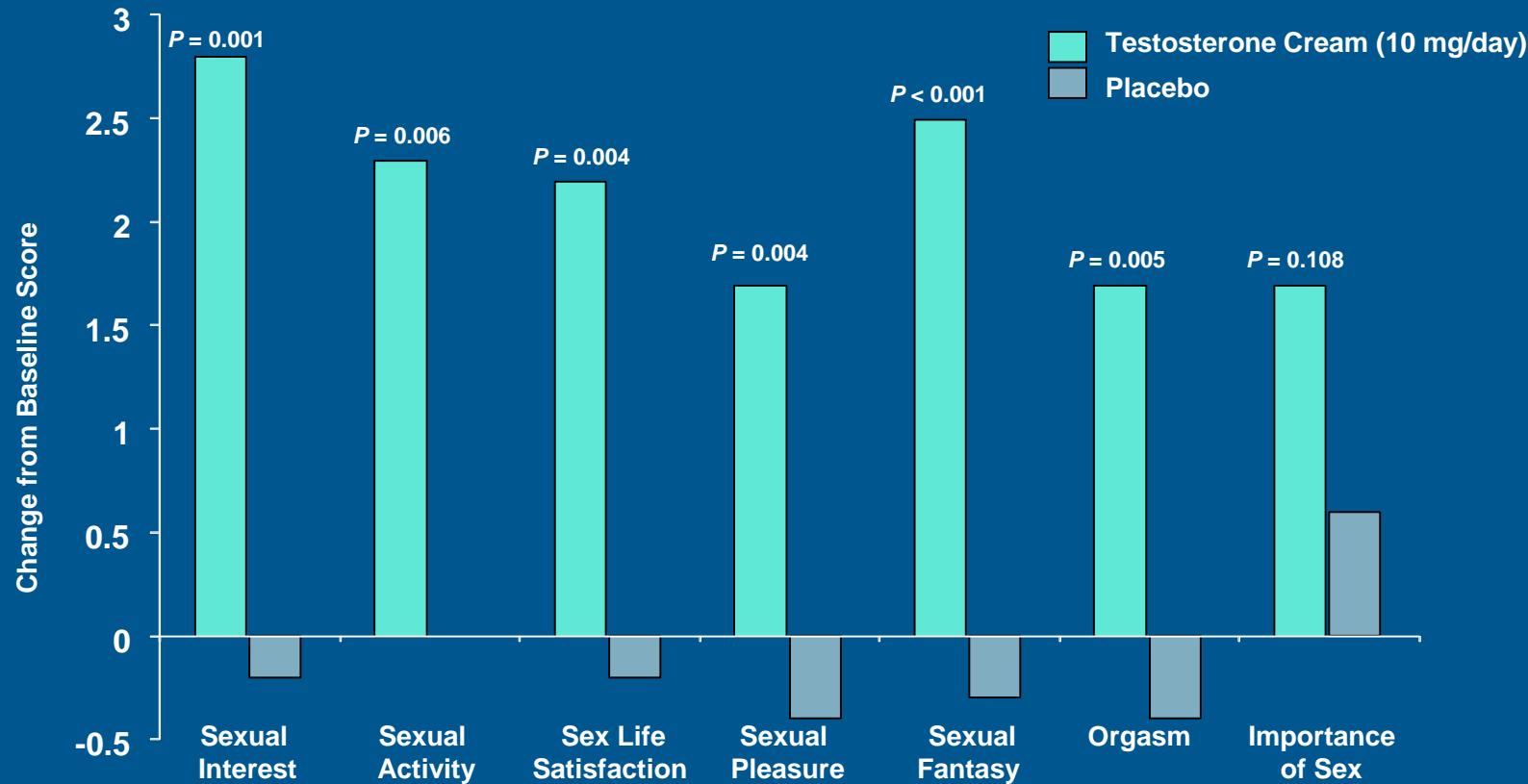
Distress



\* p < 0.05

# Testosterone in Premenopausal Women

## Sabbatsberg Sexual Self-Rating Scale Change from Baseline After 12 Weeks



N = 34 premenopausal women with low libido

Testosterone treatment associated with statistically significant improvement in Psychological General Well-Being Index and SSSRS composite scores vs placebo

Goldstat R, et al. *Menopause*. 2003;10:390-398.



**Fooladi E, Bell RJ, Jane F, Robinson PJ, Kulkarni J, Davis SR. Testosterone improves antidepressant-emergent loss of libido in women: findings from a randomized, double-blind, placebo-controlled trial.**  
***J Sex Med.* 2014 Mar;11(3):831-9. doi: 10.1111/jsm.12426. Epub 2014 Jan 16.**

## ORIGINAL RESEARCH—ENDOCRINOLOGY

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# Testosterone Improves Antidepressant-Emergent Loss of Libido in Women: Findings from a Randomized, Double-Blind, Placebo-Controlled Trial

Ensieh Fooladi, MSc,\* Robin J. Bell, MBBS, PhD,\* Fiona Jane, MBBS,\*  
Penelope J. Robinson, MBiostat,\* Jayashri Kulkarni, MBBS, PhD,<sup>†</sup> and Susan R. Davis, MBBS, PhD\*

\*Women's Health Research Program, School of Public Health and Preventive Medicine, Monash University, Melbourne, Australia; <sup>†</sup>Monash Alfred Psychiatry Research Centre, Alfred Hospital, Melbourne, Australia

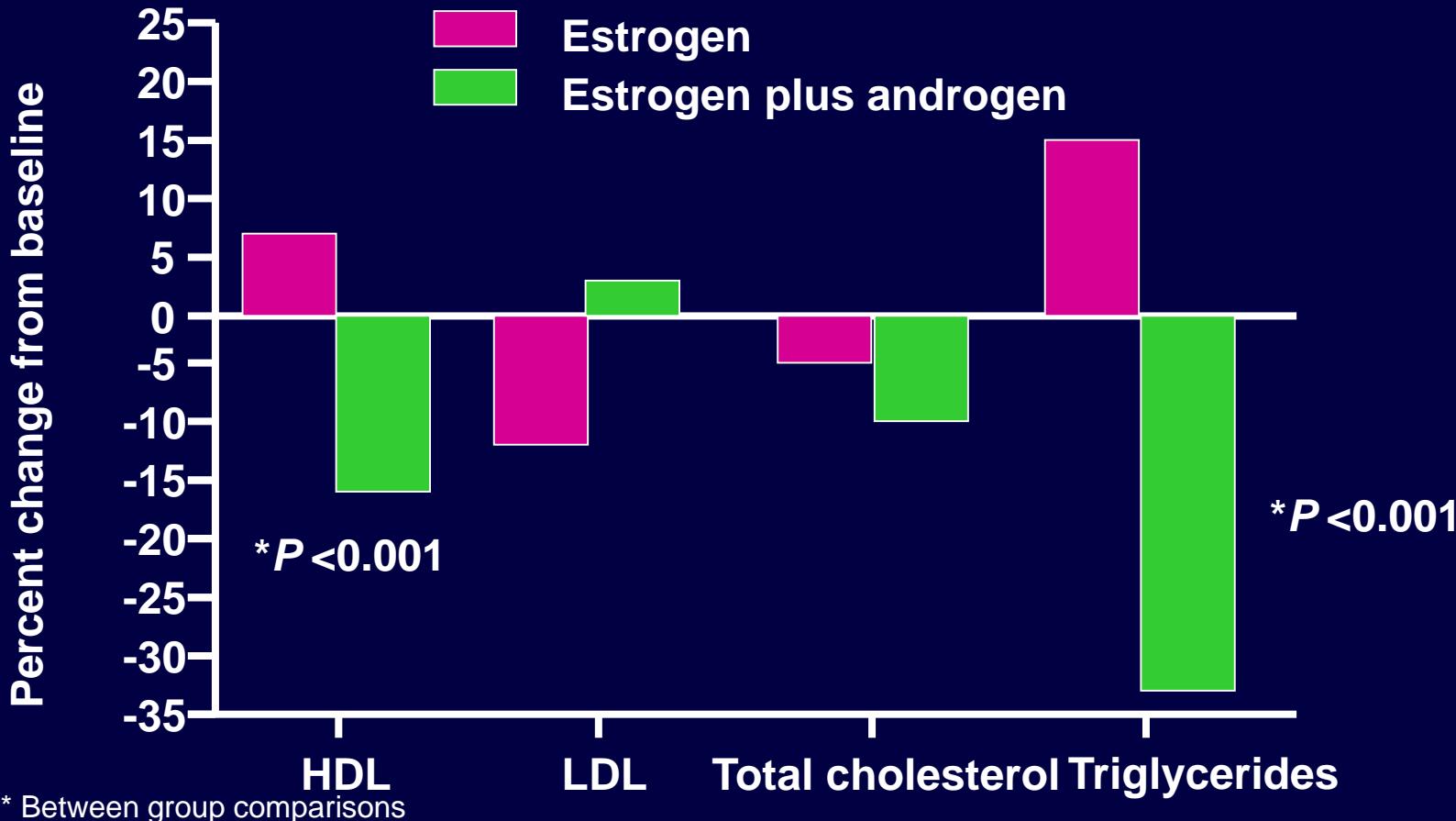
# *Testosterone Safety*

# **Outline of Safety Concerns (FDA): Testosterone Administration to Women**

- ◆ Androgenic effects
- ◆ Cardiovascular
  - Lipids
  - Vascular
  - Glucose tolerance
  - Hematopoietic
- ◆ Endometrial and breast effects
- ◆ Recommendations

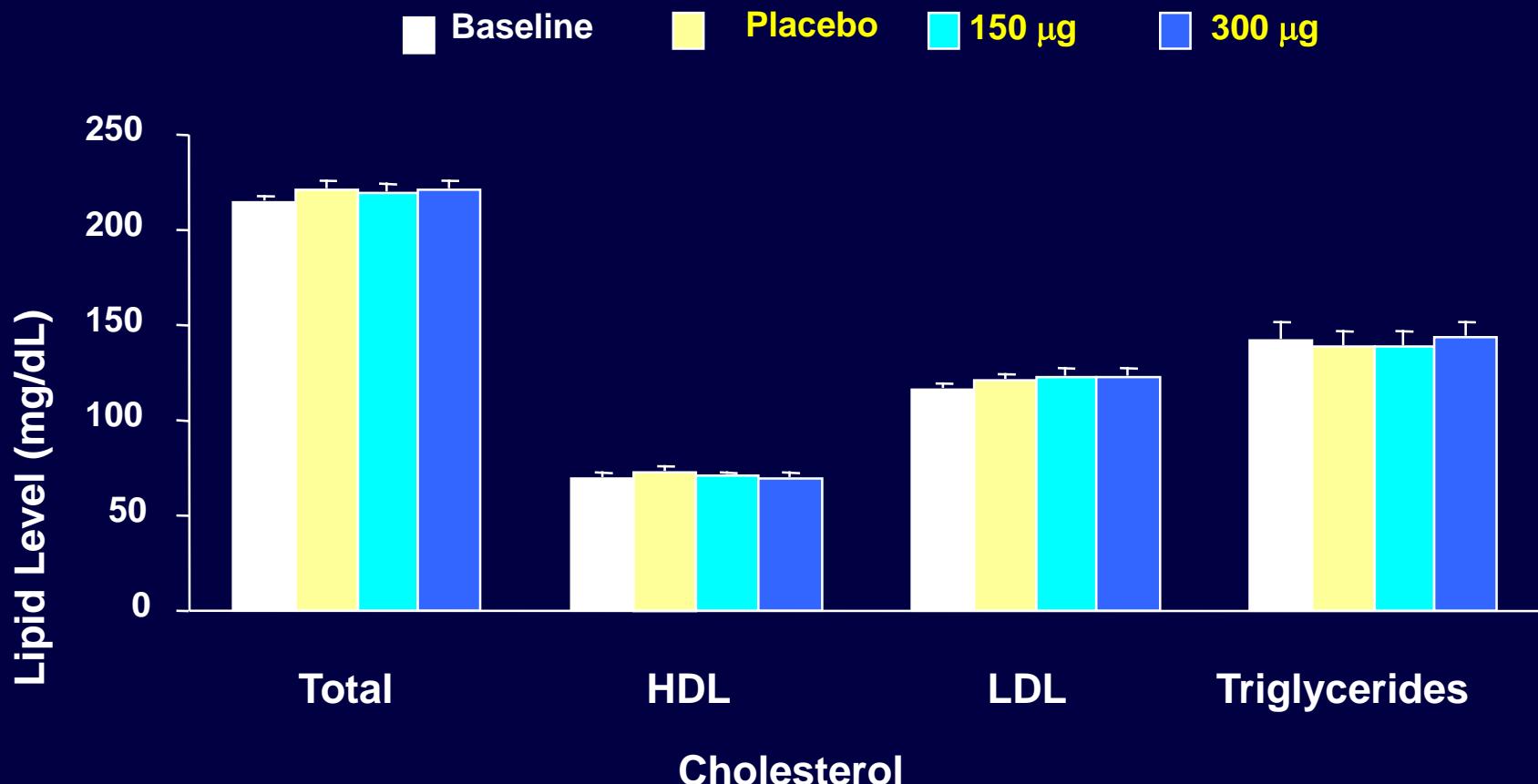
Dobs A. Presented at FDA Advisory Board Meeting, December 2004. Available at  
<http://www.fda.gov/ohrms/dockets/AC/04/transcripts/2004-4082T1.htm> Androgenic effects

# Lipid Profiles Following 2 Years of Estrogen or Estrogen Plus Androgen Therapy in Postmenopausal Women



Adapted from Watts NB, et al. Comparison of oral estrogens and estrogens plus androgens on bone mineral density, menopausal symptoms, and lipid-lipoprotein profiles in surgical menopause. *Obstet Gynecol.* 1995;85:529-537.

# Lipid Parameters Did Not Change with Transdermal Testosterone Administration



Shifren JL, Davis SR, Moreau M, et. al. Testosterone patch for the treatment of hypoactive sexual desire disorder in naturally menopausal women: results from the INTIMATE NM1 Study. Menopause. 2006 Sep-Oct;13(5):770-9.  
Erratum in: Menopause. 2007 Jan-Feb;14(1):157.

# **Safety of Transdermal Testosterone Over 48 Months (1092 patient-years exposure)\***

- ❖ **No clinically relevant changes in:**
  - Lipids
  - Liver function
  - Hematology
  - Carbohydrate metabolism
- ❖ **Small weight gain of 1.7 kg (p<0.05)**
- ❖ **Small increase in blood pressure (<2mmHg) (p>0.05)**
- ❖ **Rate of invasive breast cancer consistent with age appropriate expected rates (SEER)**

\*Open Label Extension

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.

# FDA Approved Testosterone Products

<u>Drug Name</u>	<u>Active Ingredients</u>
<u>ANDRODERM</u>	TESTOSTERONE
<u>ANDROGEL</u>	TESTOSTERONE
<u>ANDROID 10</u>	METHYLTESTOSTERONE
<u>ANDROID 25</u>	METHYLTESTOSTERONE
<u>ANDROID 5</u>	METHYLTESTOSTERONE
<u>AVEED</u>	TESTOSTERONE UNDECANOATE
<u>AXIRON</u>	TESTOSTERONE
<u>DELAESTRYL</u>	TESTOSTERONE ENANTHATE
<u>DEPO-TESTADIOL</u>	ESTRADIOL CYPIONATE; TESTOSTERONE CYPIONATE
<u>DEPO-TESTOSTERONE</u>	TESTOSTERONE CYPIONATE
<u>DITATE-DS</u>	ESTRADIOL VALERATE; TESTOSTERONE ENANTHATE
<u>FORTESTA</u>	TESTOSTERONE
<u>METANDREN</u>	METHYLTESTOSTERONE
<u>METHYLTESTOSTERONE</u>	METHYLTESTOSTERONE
<u>NATESTO</u>	TESTOSTERONE
<u>ORETON</u>	METHYLTESTOSTERONE
<u>ORETON METHYL</u>	METHYLTESTOSTERONE
<u>STRIANT</u>	TESTOSTERONE
<u>TESTIM</u>	TESTOSTERONE
<u>TESTODERM</u>	TESTOSTERONE
<u>TESTODERM TTS</u>	TESTOSTERONE
<u>TESTOPEL</u>	TESTOSTERONE
<u>TESTOSTERONE</u>	TESTOSTERONE
<u>TESTOSTERONE CYPIONATE</u>	TESTOSTERONE CYPIONATE
<u>TESTOSTERONE CYPIONATE-ESTRADIOL CYPIONATE</u>	ESTRADIOL CYPIONATE; TESTOSTERONE CYPIONATE
<u>TESTOSTERONE ENANTHATE</u>	TESTOSTERONE ENANTHATE
<u>TESTOSTERONE ENANTHATE AND ESTRADIOL VALERATE</u>	ESTRADIOL VALERATE; TESTOSTERONE ENANTHATE
<u>TESTOSTERONE PROPIONATE</u>	TESTOSTERONE PROPIONATE
<u>TESTRED</u>	METHYLTESTOSTERONE
<u>VIRILON</u>	METHYLTESTOSTERONE

# FDA Approved Testosterone Products

Drug Name

ANDRODERM

ANDROGEL

ANDROID 10

ANDROID 25

ANDROID 5

AVEED

AXIRON

DELATESTRYL

DEPO-TESTADIOL

DEPO-TESTOSTERONE

DITATE-DS

FORTESTA

METANDREN

METHYLTESTOSTERONE

NATESTO

ORETON

ORETON METHYLDENE

STRARIANT

TESTIM

TESTODERM

TESTODERM TTS

TESTOPEL

TESTOSTERONE

TESTOSTERONE CYPIONATE

TESTOSTERONE CYPIONATE

TESTOSTERONE ENANTHATE

TESTOSTERONE ENANTHATE AND ESTRADIOL

TESTOSTERONE PROPIONATE

TESTRED

VIRILON

# Is there a double standard at FDA RE: Testosterone Approvals?

## Male Testo Approval

1. Requires restoration of normal testosterone blood levels
2. Requires short term safety (typically 6 months)

## Female Testo Approval

1. Requires amelioration of HSDD
2. Requires restoration of normal testosterone blood levels
3. Requires longterm breast and cardiovascular safety (typically 5 years)

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## Male Testo Approval

1. Requires restoration of normal testosterone blood levels
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Estimated total development cost:

\$10-20 million

## Female Testo Approval

1. Requires restoration of normal testosterone blood levels
2. Requires amelioration of HSDD
3. Requires longterm breast and cardiovascular safety (typically 5 years)

Estimated total development cost:

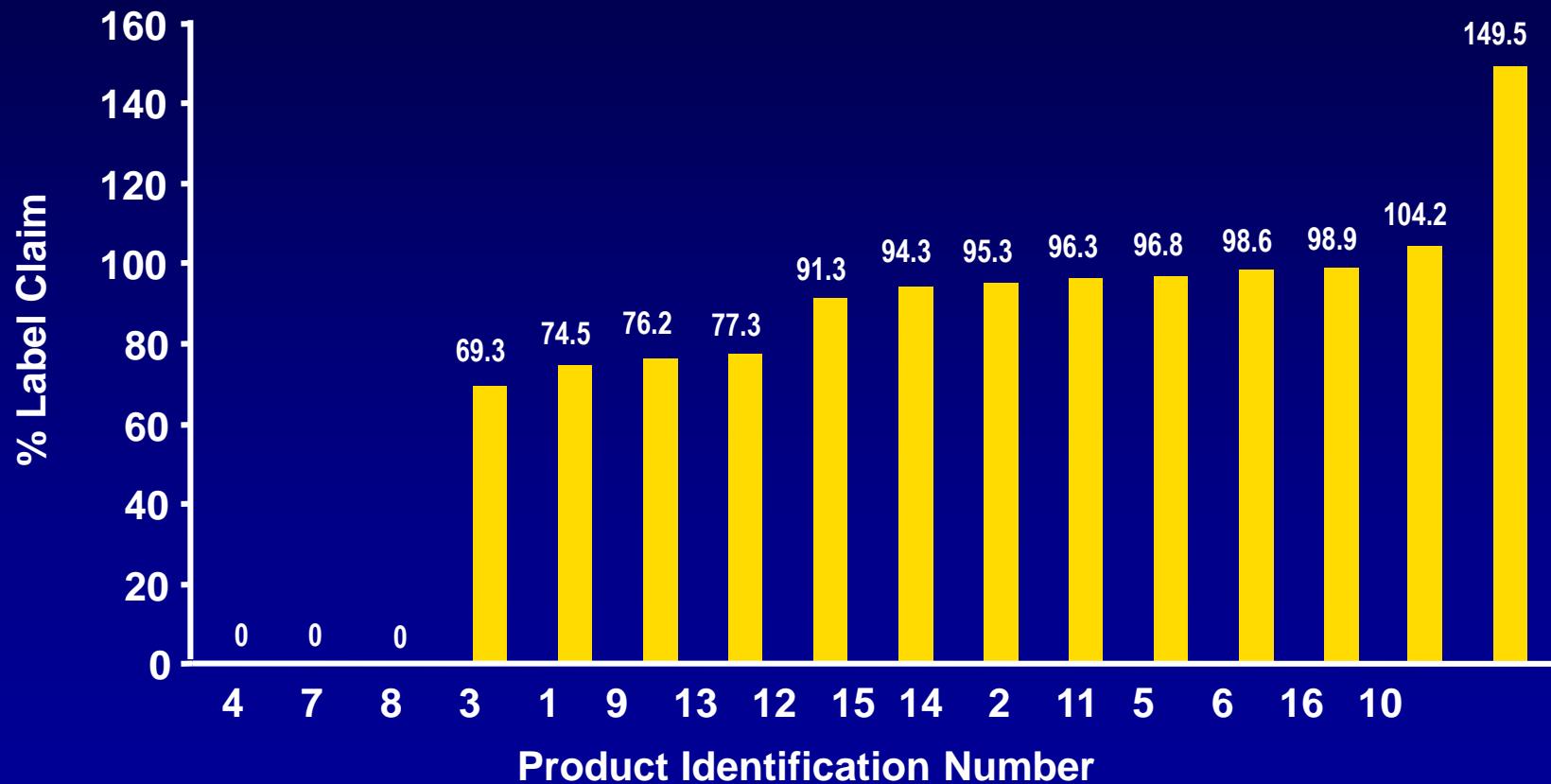
\$1 billion

# ***So...What Exactly Do I Do?***

***(Has she tried an “Estratest” generic?)***

- If good clinical response, determine which form of ongoing therapy is most acceptable/appropriate for the patient
  - Local, local/systemic or systemic
- Local therapy: 1-2% testosterone in aquaphor, light petrolatum, Alboline, cocoa butter or other oily base (patient’s preferences and compounding pharmacist’s recommendation) pea size application to clitoris and labia minora 2-3x/w
- Systemic: DHEA 25-75 mg/day (always check freshness date, know the source)
  - Androgel® (pump) 1% (**generic; NOT 1.62%**): 1 actuation (1.25gm), 2-3x/w (depending on route of estrogen administration) apply to thigh and lower leg (hair)
  - Testim® (**generic**): 5-6 drops to thigh or leg daily
- For All Therapies: Check total and free testosterone in 4-6 weeks (to be done at least 2 hrs after application, and again in 3 months once on stable dose). Must be assayed by GCMS, not a direct method (blood draw from non-dominant arm).
  - Goal: Total testosterone at upper limit of premenopausal normal range and free testosterone in the upper half of premenopausal normal range.

# DHEA Content in Dietary Supplements



Parasrampuria J, et al. *JAMA*. 1998;280:1565

NDC 60887-001-05

# Testim® 1%

(testosterone Gel)

Contains 50 mg testosterone per 5 g tube

Rx Only

CIII

Lawley Pharmaceuticals Pty Ltd  
Unit 2/ 15A Harrogate Street, West Leederville, 6007  
Western Australia, AUSTRALIA

## AndroFeme® 1

Cream containing 1% w/v (10mg/mL) Testosterone B.P (17- $\beta$ - Hydroxyandrost-4-en-3-one)



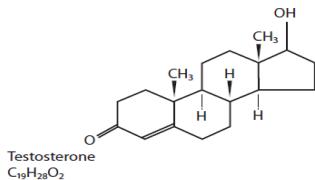
### PRODUCT INFORMATION

**Composition Active:** Testosterone B.P.

**Chemical Structure:** 17- $\beta$ -Hydroxyandrost- 4 - en-3-one

**Molecular Weight:** 288.4

**CAS:** 58-22-0.



### Contraindications

Testosterone is contraindicated in females with known or suspected carcinoma of the breast, known or suspected androgen-dependent neoplasia, nephrotic syndrome, history of thromboembolism or hypercalcaemia.

Known sensitivity to testosterone, ANDROFEME® or any of its components.

ANDROFEME® contains almond oil.

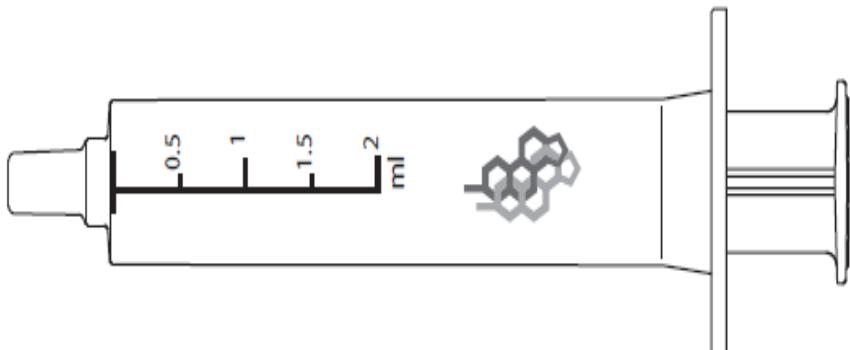
ANDROFEME® is contraindicated in pregnancy and while lactating.

High level athletes need to be aware of the rules governing androgen use if prescribed ANDROFEME® cream.

Close skin contact with the area of application within an hour of application by a partner or child should be avoided. This may result in the partner or child absorbing some testosterone through the skin contact.

### Precautions

The applicator is marked with 0.5mL graduations for dosing accuracy.



Lower Torso

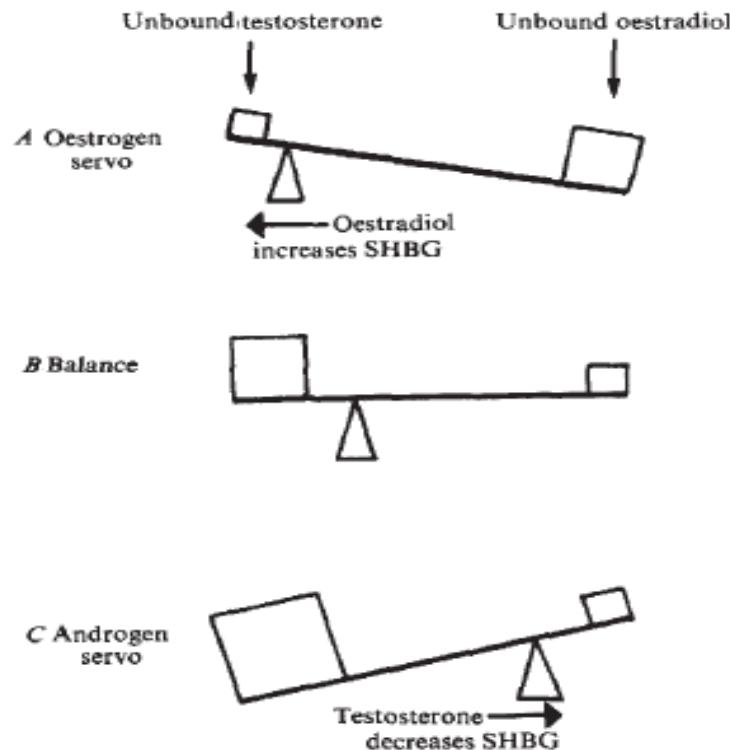
Outer Thigh

# GTOPI-CCLICK®



# Sex-Hormone-Binding Globulin is an Oestrogen Amplifier

NATURE VOL. 240 NOVEMBER 3 1972



**Fig. 3** Testosterone-oestradiol balance and SHBG concentration. SHBG is denoted by the fulcrum, which moves in response to oestradiol or testosterone; the movement of the fulcrum increases the tendency of the balance to tip in the direction of unbound oestradiol or testosterone, as the case may be.

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Raghunandan C, Agrawal S, Dubey P, Choudhury M, Jain A. A comparative study of the effects of local estrogen with or without local testosterone on vulvovaginal and sexual dysfunction in postmenopausal women. *J Sex Med.* 2010 Mar;7(3):1284-90. doi:10.1111/j.17436109.2009.01667.x. Epub 2010 Jan 19.

## ORIGINAL RESEARCH—ENDOCRINOLOGY

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### A Comparative Study of the Effects of Local Estrogen With or Without Local Testosterone on Vulvovaginal and Sexual Dysfunction in Postmenopausal Women

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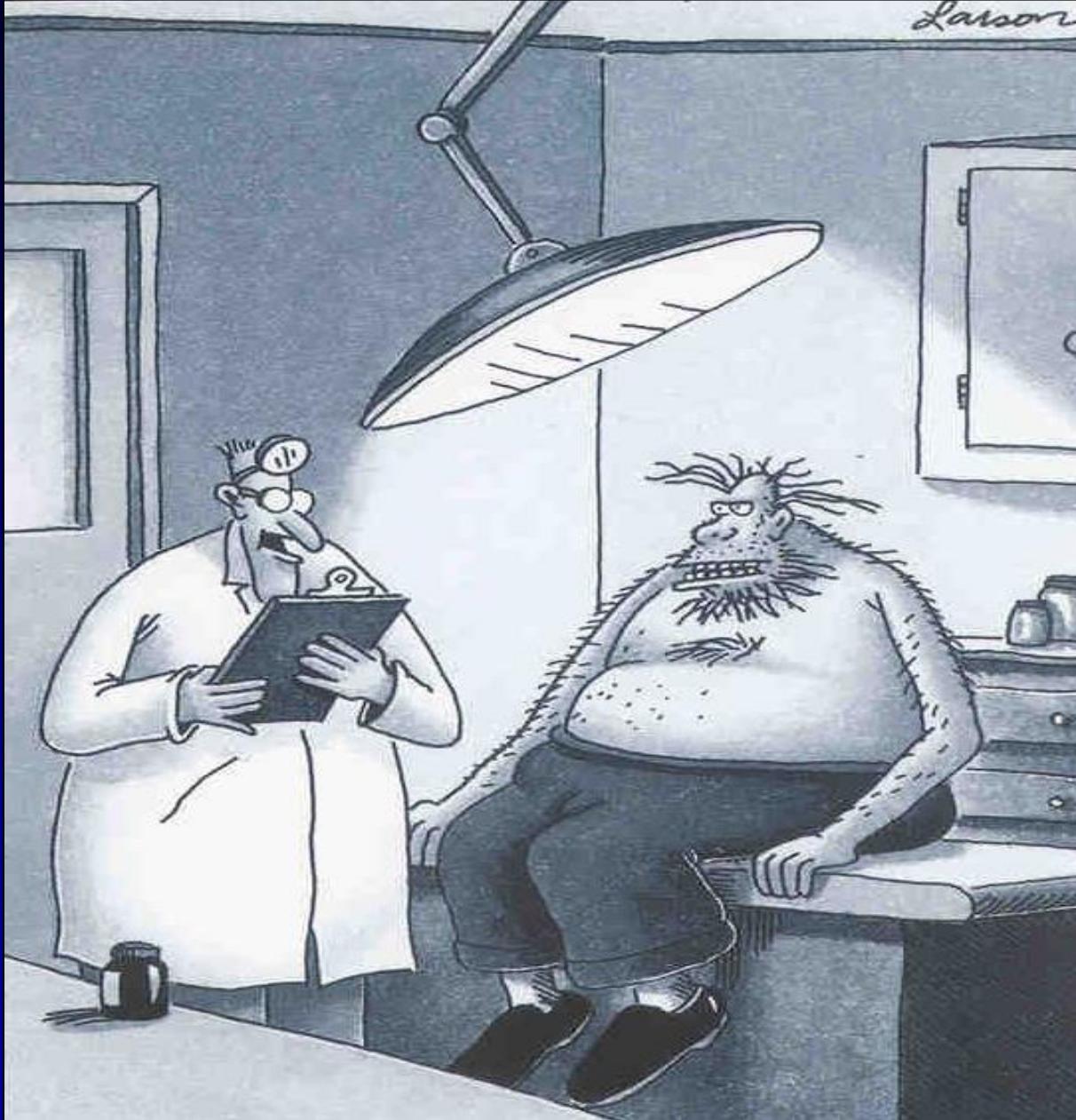
# Differential Effects of Estrogen-Androgen and Estrogen-Only Therapy on Vasomotor Symptoms, Gonadotropin Secretion, and Endogenous Androgen Bioavailability in Postmenopausal Women

James Simon, MD,<sup>1</sup> Edward Klaiber, MD,<sup>2</sup> Brinda Wiita, PhD,<sup>3</sup> Angela Bowen, MD,<sup>4</sup> and Hwa-Ming Yang, PhD<sup>3</sup>

1. Primary effect of oral Esterified Estrogens + Methyltestosterone (EEMT) was to decrease SHBG and increase bioavailable estrogen and testosterone.
- 2) Higher doses of Methyltestosterone (2.5mg/day) were not more effective than 1.25mg/day in this effect.

# Testosterone Therapies “In Development” for Female FSD

Drug Name	Drug Category	Pharma Sponsor	Current Developmental Status
Transdermal testosterone patch (Intrinsa®)	testosterone	Warner Chilcott	EMA –Approved for HSDD (surgical menopause) FDA NDA withdrawn US; off the market EU
Lybrido (on demand oral tablet)	sildenafil + testosterone	Emotional Brain	Phase III for HSDD
Lybridos (on demand oral tablet)	buspirone + testosterone	Emotional Brain	Phase III for HSDD
Topical testosterone gel (Libigel)	testosterone	BioSante Pharmaceuticals	Phase III efficacy (failed) Phase III safety (stopped early)
Intranasal testosterone gel (Tefina™)	testosterone	Trimel Pharmaceuticals	Phase II complete for anorgasmia



"Well, Mrs. Rosenberg, your lab results look pretty good ...  
although I might suggest your testosterone level is a tad high."