

An Evidence-based Review of Clinical Trial Data

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Rationale for Investigating Androgen Administration in Women: Data in Men

- Effects of androgen replacement in men with hypogonadism
 - Brain effects
 - Increases libido
 - Improves quality of life
 - Body composition
 - Increases bone density
 - Decreases body fat, including visceral fat
 - Increases lean body mass
- Will lower doses in women with androgen deficiency result in similar effects?

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Effects of Testosterone in Women: Clinical Endpoints

- Brain effects
 - Libido
 - Most data available for this endpoint
 - Mood
 - Quality of life
- Body composition
 - Bone density
 - Body fat, lean mass, and strength

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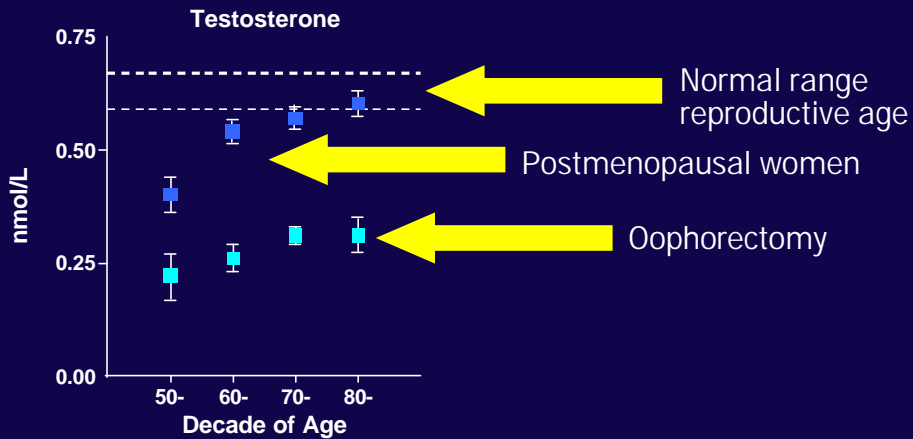
Testosterone Administration in Women: Libido and Quality of Life

- Testosterone transdermal patch in 65 women with oophorectomy led to increase in sexual frequency, pleasure, and mood
 - Severely androgen-deficient population
 - Efficacy seen with higher dose (300 mcg daily) only
 - Resulted in mean free testosterone near upper limit of normal for women

Shifren JL, et al. *N Engl J Med.* 2000;343:682-688.

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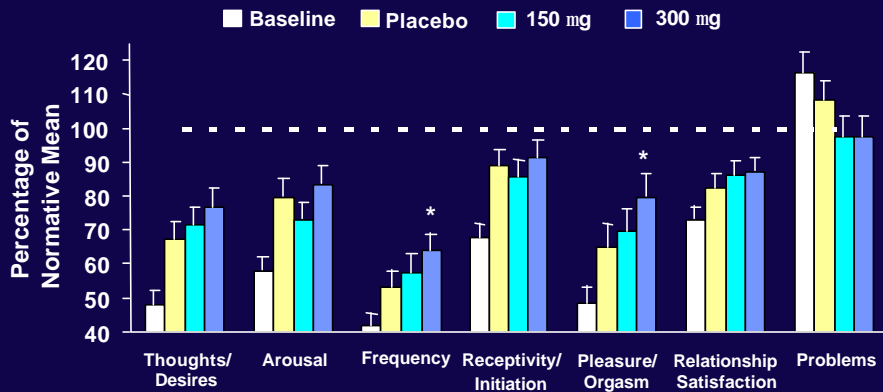
Testosterone Levels in Postmenopausal Women and Salpingo Oophorectomy



Laughlin GA, et al. *J Clin Endocrinol Metab.* 2000;85:648.

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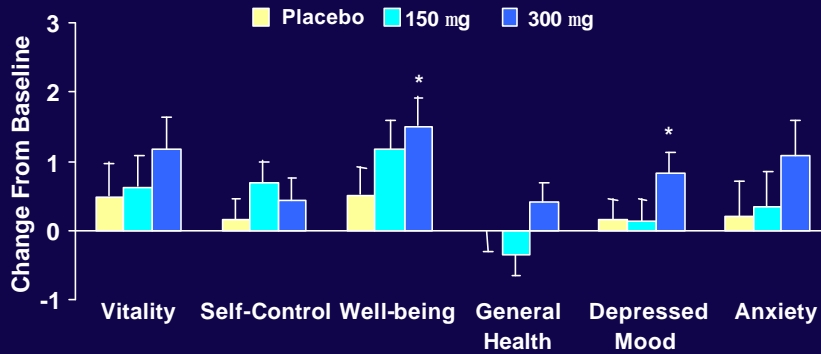
Frequency and Pleasure Scores Increased



* $P < 0.05$ for comparison with placebo
 Shifren JL, et al. *N Engl J Med.* 2000;343:682-688.

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Well-being and Depressed Mood Subscales Increased



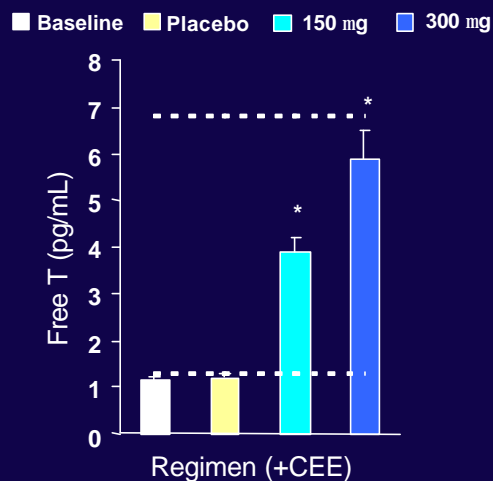
Higher scores indicate improved mood

* $P < 0.05$ for comparison with placebo

Shifren JL, et al. *N Engl J Med.* 2000;343:682-688.

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Free Testosterone Increased Into Normal Range



* $P < 0.001$ for comparison with placebo

--- Endocrine Sciences normal range for cycling women

Shifren JL, et al. *N Engl J Med.* 2000;343:682-688.

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Testosterone Patches for the Treatment of Surgically Menopausal Women: Unpublished Phase 2B and 3 Studies Confirmatory with regard to Libido

- Double-blind, placebo-controlled, randomized trial
- 447 surgically menopausal women with HSDD on oral estrogen
- Testosterone patch 150, 300, 450 mcg/d vs. placebo x 24 weeks

Braunstein GD, et al. Abstract Presented at: *NAMS Annual Meeting 2003*.

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HSDD: Hypo-sexual Desire Disorder

Testosterone Patches for the Treatment of Low Sexual Desire in Surgically Menopausal Women: Results

- 150 mcg—no difference as compared to placebo
- 300 mcg—increase in total satisfying sexual activity and sexual desire as compared to placebo
- 450 mcg similar to 300 mcg
- No significant adverse events

Braunstein GD, et al. Abstract Presented at: *NAMS Annual Meeting 2003*.

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Other Populations: Adrenal Insufficiency (DHEA) Improvements in Libido, Mood and Well-being

Arlt *et al.*, *N Engl J Med*, 1999

- Androgen- and DHEAS-deficient population
- Double-blind, randomized, placebo controlled
- DHEA 50 mg daily x 4 months
- Free T raised into low-normal female range
- 24 women: 1° and 2° adrenal insufficiency
- ↑ in frequency of sexual thoughts, interest and satisfaction c/w placebo
- ↑ improvement in well-being, depression and anxiety

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Other Populations: Adrenal Insufficiency and Hypopituitarism (DHEA)

Improvements in Libido, Mood and Well-being

- Subsequent studies: results less dramatic
 - Lower doses?
 - Men and women combined?
 - Lack of efficacy?

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Other Populations: Premenopausal Women Improved Libido and Sexual Function in Premenopausal Women : Testosterone Cream vs. Placebo for 12 Weeks

	Treatment Effect	
	Mean (95% CI)	P
Sabbatsberg Sexuality Scale	+15.7 (+6.5 to +25.0)	0.001
Sexual interest	+3.0 (+1.3 to +4.6)	0.001
Sexual activity	+2.3 (0.7 to +3.8)	0.006
Satisfaction of sexual life	+2.4 (+0.8 to +4.0)	0.004
Sexual pleasure	+2.2 (+0.7 to +3.7)	0.004
Sexual fantasy	+2.7(+1.3 to +4.1)	0.000
Orgasm	+2.1 (+0.7 to 3.5)	0.005
Importance of sex	+1.1 -(0.3 to +2.5)	0.108

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

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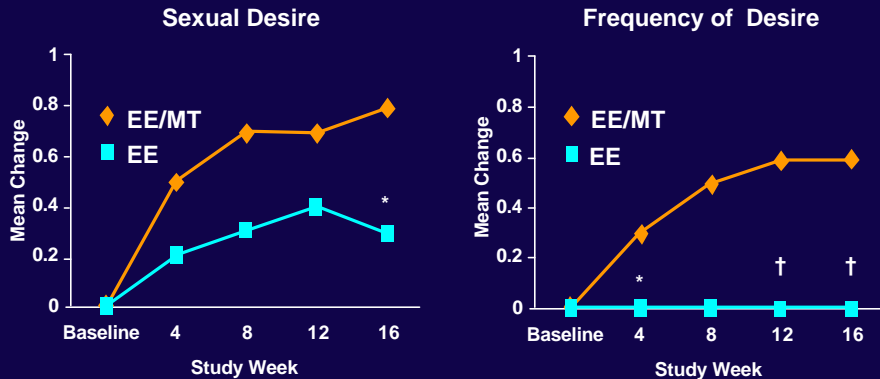
Other Populations: Premenopausal Women Improved Quality of Life in Premenopausal Women: Testosterone Cream vs. Placebo for 12 Weeks

	Treatment Effect	
	Mean (95% CI)	P
Psychological general well-being	+12.9 (+4.6 to 21.2)	0.003
Anxiety	+3.2 (+0.8 to +5.6)	0.009
Depressed mood	+1.3 (0.0 to +2.5)	0.053
Positive well being	+2.4 (+0.6 to +4.2)	0.009
Self - confidence	+1.5 (+0.2 to +2.7)	0.024
General health	+1.3 (+0.3 to +2.3)	0.014
Vitality	+3.1 (+0.8 to +5.4)	0.010

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

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Other Populations: Natural Menopause Increase in Sexual Desire and Frequency with Methyltestosterone plus Esterified Estrogen in 218 Postmenopausal Women

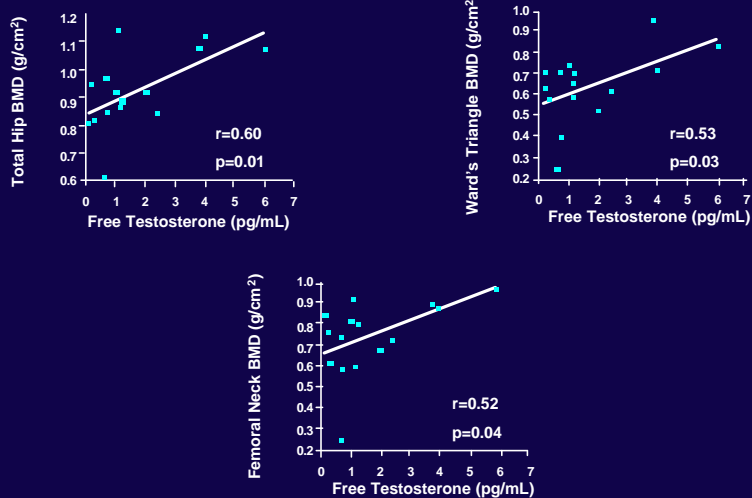


* $P < 0.05$; † $P < 0.01$

EE=Esterified estrogen; MT=methyltestosterone
Lobo RA, et al. *Fertil Steril.* 2003;79:1341-1352.

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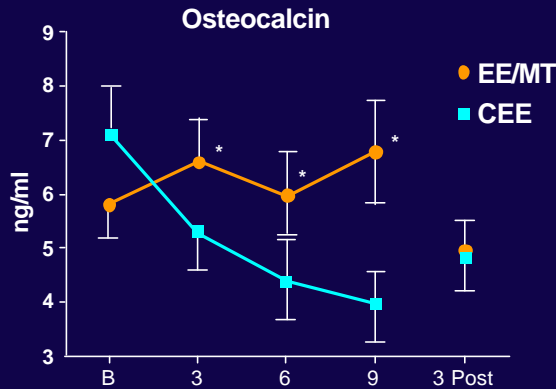
Correlations Between Free Testosterone and Bone Density



Miller KK, et al. *J Clin Endocrinol Metab.* 2002;87:2770-2776.

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Methyltestosterone Plus Estrogen (E) Increases Bone Formation Compared With E Alone in Postmenopausal Women

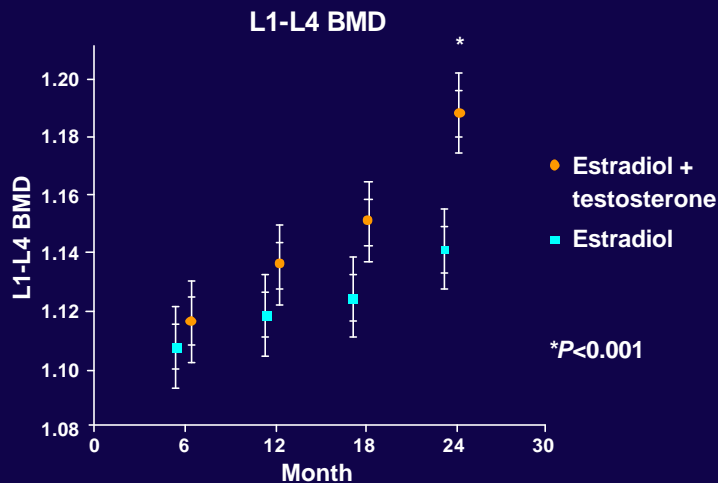


* $P < 0.05$

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Raisz LG, et al. *J Clin Endocrinol Metab.* 1996;81:37-43.

Bone Density Increases With Testosterone Administration: 34 Women with Natural Menopause



* $P < 0.001$

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Davis SR, et al. *Maturitas.* 1995;21:227-236.

Supraphysiologic hormone levels achieved

Effects of Testosterone Administration on Bone

- 311 women with salpingo oophorectomy
 - An increase in bone density was seen among women on the highest dose of oral estrogen plus methyltestosterone, as compared with women on estrogen alone
 - No increase in bone mass was seen among women on lower doses

Barrett-Connor E, et al. *J Reprod Med.* 1999;44:1012-1020.

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Effects of Testosterone in Women: Summary

- **Preliminary** data suggest that testosterone administration at doses that increase serum free testosterone to the upper limits of normal in a subset of women may
 - Increase libido
 - Most data available for this endpoint
 - Most data in surgically menopausal women
 - Improve mood
 - Improve quality of life
 - Increase bone density
- **However, further study is needed to confirm these findings**

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Effects of Testosterone in Women: Future Directions

- Effects on body composition, strength?
 - Lean and fat mass
 - Bone density/fracture risk
- Neuropsychiatric effects
 - Mood and cognitive function
- Physiologic replacement vs. pharmacologic therapy
- Relative efficacy and safety of preparations, optimal dosing, and short- and long-term safety
 - Dr. Braunstein