

What Is the Low T Syndrome? Is Testosterone Supplementation Safe?

UCSF Osher Mini Medical School
March 7, 2018

*Dolores Shoback, MD
Staff Physician – SF-VAMC
Professor of Medicine, UCSF*

No disclosures or conflicts of interest

QUESTIONS

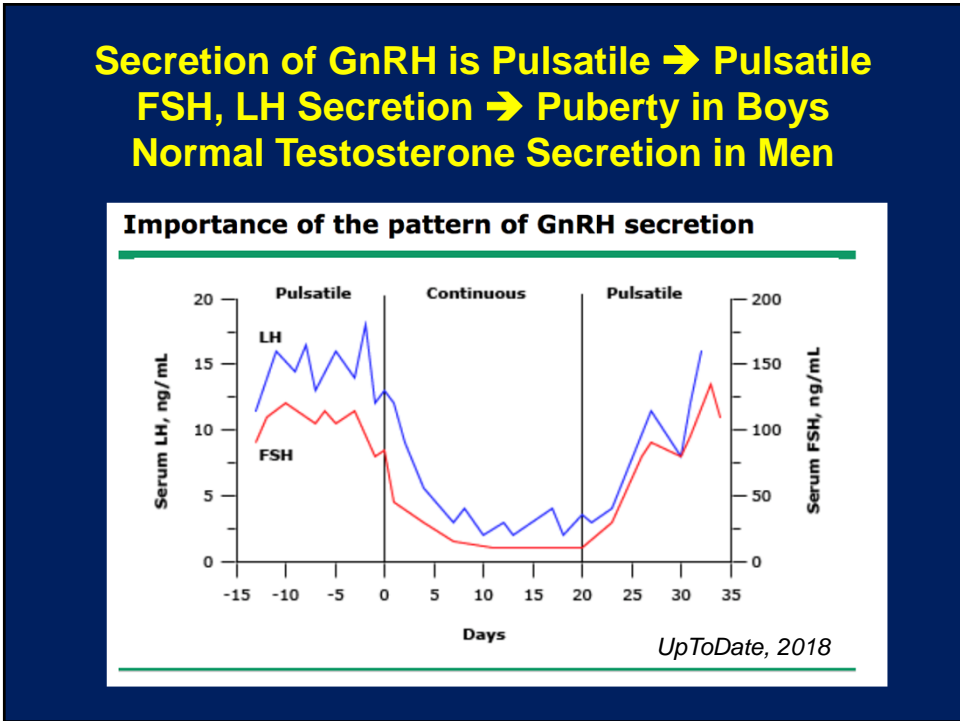
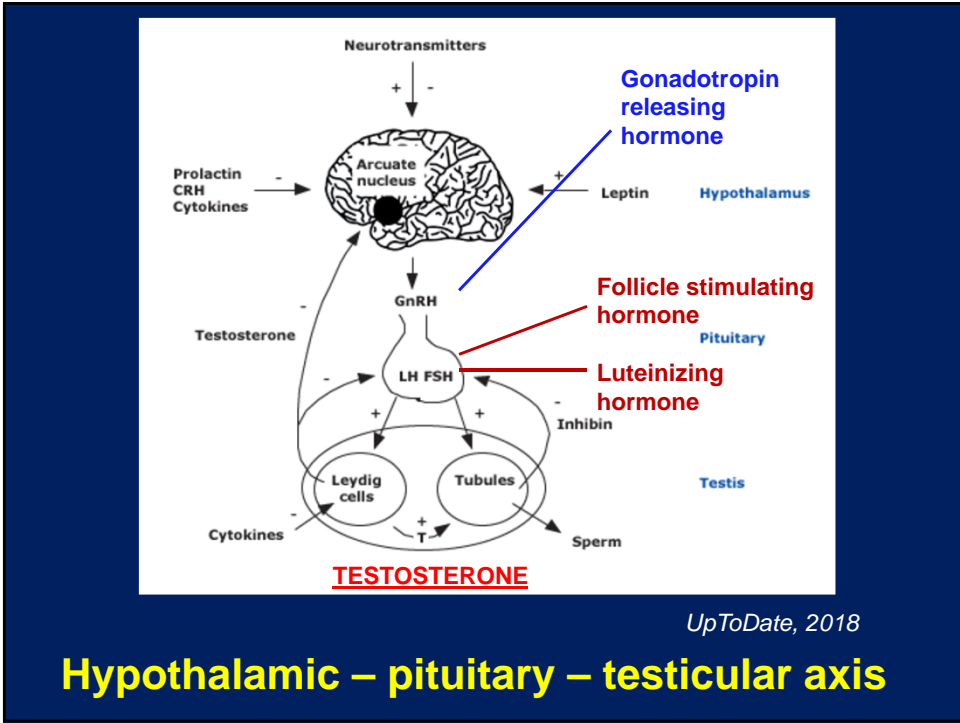
- What is testosterone?
- What does it do in the body?
- What is low T syndrome?
- What is hypogonadism - the real disorder?
- What lab tests are done and what do they mean?
- Testosterone replacement therapy – is it safe?

What is testosterone?

- Hormone
- Chemical made in a tissue (testis)
- Carried through the bloodstream to distant organs and tissues
- Exerts its actions by binding to a receptor
- Nuclear receptor
- Actions result from – DNA binding, altered transcription of key genes (genetic program of tissue)

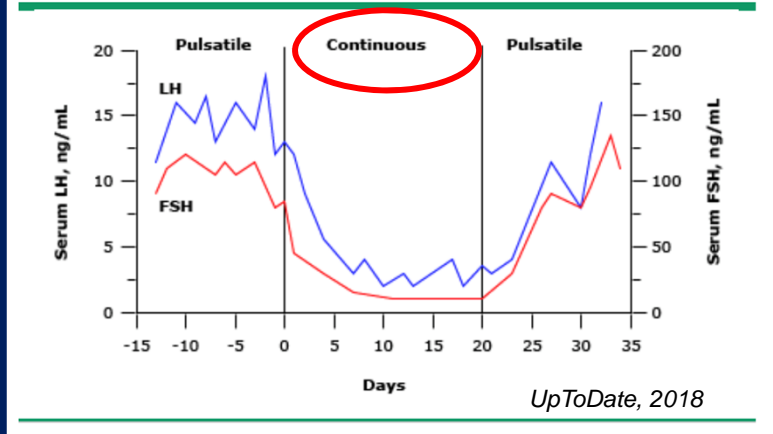


Final effects → “masculinization” of the body, male reproduction, and other processes



**If GnRH (Analogue) Is Given Continuously →
Shuts Off Axis & Testosterone Production
TREATMENT for Prostate Cancer**

Importance of the pattern of GnRH secretion



**Hypothalamic-Pituitary-Testicular AXIS –
Strong Pathway but Sensitive**

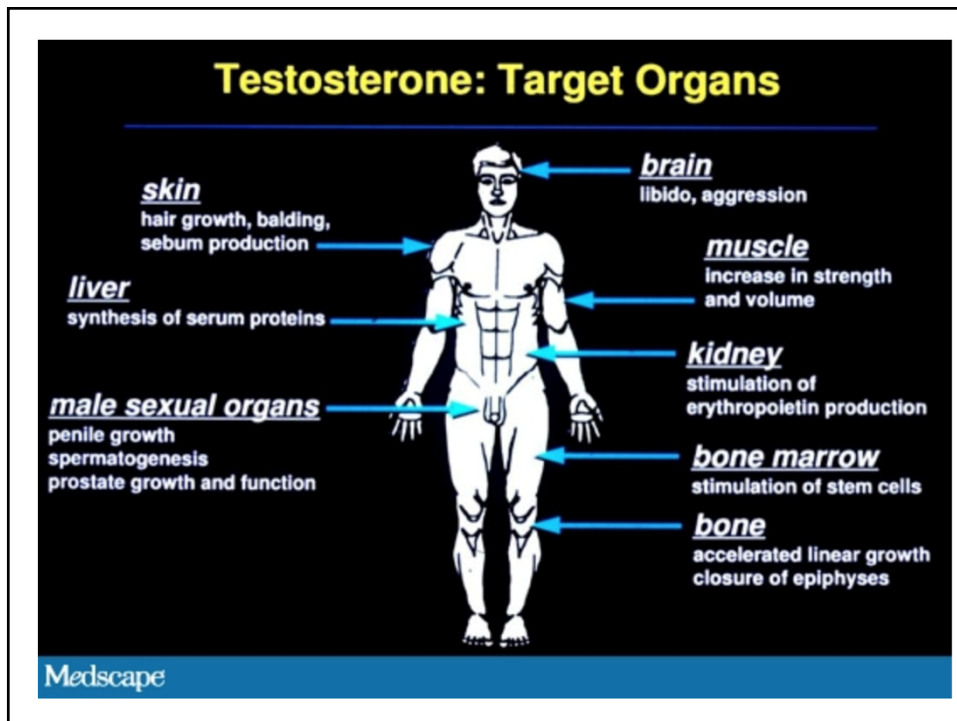
- Highly sensitive to stress
- Stress comes in many forms
- Acute and chronic illness
- Physiologic stress
- Psychologic stress
- Fasting
- Pain – opiates

ALL can suppress production of testosterone

What does testosterone do in the body?

- Initiates and maintains **sperm** production
- Starts and promotes **puberty** and sexual maturation in boys
- Starts development of secondary **sexual characteristics**
- Maintains **lean body mass**, promotes muscle mass and development
- Decreases **body fat**

Many more things



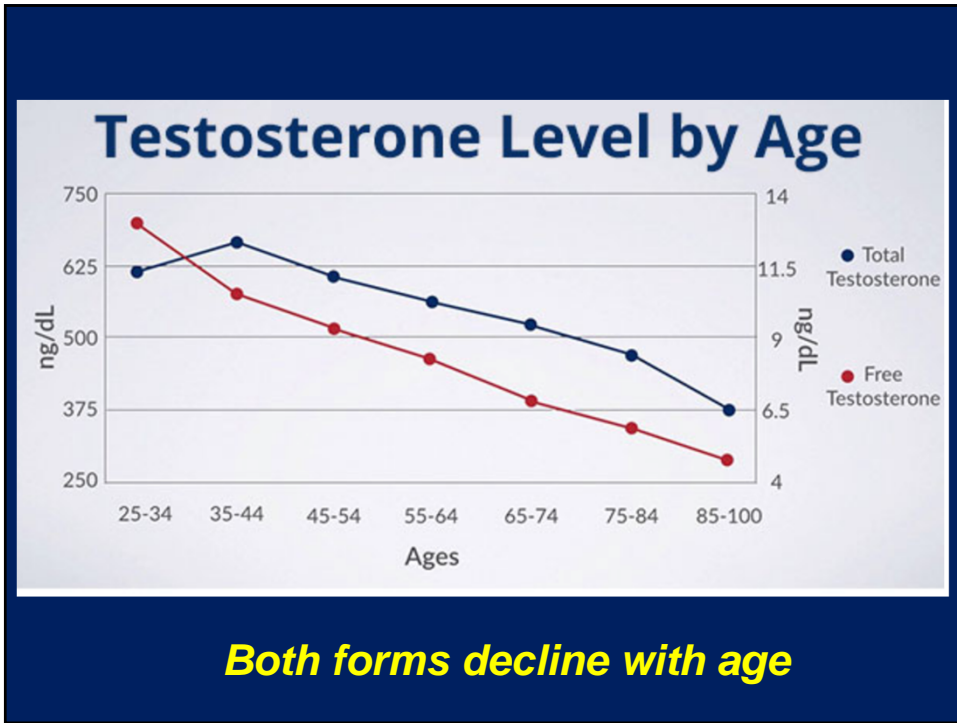
What is “low T” syndrome?

- Low levels of testosterone (T)
- Typically in older men (> age 60 - !)
- Variety of symptoms – (attributed)
 - Poor energy
 - Reduced sense of well-being
 - Low libido (sex drive)
 - Reduced erectile function
 - Declining muscle mass
 - Gaining fat mass

ANDROPAUSE

Physicians Struggle to Define/Diagnose the Low T

- If the levels of testosterone in the morning in a very healthy man who is not sick, stressed, obese, on opiates, drinking alcohol heavily is very LOW – IT IS EASY
- BUT – that is the rare case ! And serum T levels are hard to measure accurately and levels fluctuate
- Almost all the symptoms of low T syndrome overlap with natural (even healthy) aging



We Don't Have Age-Adjusted Normal Ranges for Clinical Use (Quest Labs)

Table 2. Testosterone Reference Ranges in Adults

Age (years)	Total Testosterone ^a (ng/dL)	Free Testosterone ^b (pg/mL)	Free and Bioavailable Testosterone ^c	
			Free (pg/mL)	Bioavailable (ng/dL) *
Females				
≥18	2-45			
18-69		0.1-6.4	0.2-5.0	0.5-8.5
70-89		0.2-3.7	0.3-5.0	0.5-8.8
18-89				
Males				
≥18	250-1100			
18-69		35-155	46-224	110-575
70-89		30-135	6.0-73	15-150

* Includes albumin-bound, weakly bound

Left to make adjustment yourself

What Is “Low T” Syndrome? (non-regulated ads, websites)

- 1) Decrease in sex drive
- 2) Orgasm less strong
- 3) Lack of energy
- 4) Decrease in strength or endurance
- 5) Lost height
- 6) Decreased 'enjoyment of life'
- 7) Sad and/or grumpy
- 8) Deterioration in sports ability
- 9) Falling asleep after dinner
- 10) Decreased work performance

SF Low T Clinic ...



We Are Your Solution

As a specialty clinic focusing on men's health, our staff of California-licensed physicians approach your sexual health from a total health perspective.

Are you currently experiencing:

- Fatigue?*
- Loss of sex drive?*
- Difficulty concentrating?*
- Depression or low mood?*
- Loss of muscle mass and gain of fat mass?*
- Low sense of overall wellness?*
- Erectile dysfunction?*

All consultations are discreet and confidential. Your comfort and privacy is our priority.

Low T

1 in 4 men have low testosterone levels, causing weight gain and decreased energy. We analyze your current levels and administer prescribed testosterone treatments to restore them to optimal.

Erectile Dysfunction

Viagra, Cialis and Levitra are ineffective solutions for almost 70% of men. The physicians at Low T 99 understand that one of the primary symptoms of low testosterone is Erectile Dysfunction.

Premature Ejaculation

Diagnosing the cause is our expertise and putting our proven improvement plan in place will increase your stamina.

TriMix Shot

A nearly painless procedure which combines three medications specifically compounded to effectively treat you.



Webpages – Low T

Dear *Health eTalk* Reader,

If you're a man in your mid-60s, you'll want to pay close attention to what I'm about to tell you...

At this very moment, a hormonal shift could be taking place in your body that – for all intents and purposes – could be destroying your manhood. But before I go any further, let me ask you:

Does this sound like you?

- Do you have flabby thighs, a "spare tire" or extra belly fat?
- Do you feel zapped of energy, tired... going to bed exhausted... and waking up worn out?
- Do you find it hard to answer questions, focus, or recall recent conversations?
- Does a low sex drive leave you struggling to satisfy your partner?

If you answered YES to any of the above, the real cause of your symptoms may be a low testosterone level.



The epidemic of *low testosterone*

The 7 Enemies of Your Manhood...

You don't need to put up with the draining effects of a declining testosterone level one day longer

**It's time to take back your manhood and your life.
Don't let low testosterone steal it!**

“Don’t worry ! I’m not going to ask you to take a testosterone shot that will mess with your hormones”

Don't worry! I'm not going to ask you to take a testosterone shot that will mess with your hormones. I'm going to tell you about a scientific breakthrough that can boost your testosterone levels naturally and make you like the man you once were, or even the man you always wanted to be. The big side effect of this natural breakthrough could be that women much younger than you will feel very attracted to you.



*. . . Natural breakthrough → herbal remedies
“The big side effect . . . could be that women much younger than you will feel very attracted to you.”*

Next page

Could you feel 10, 20 or even 25 years younger?

For many men, supporting their testosterone levels is the secret to restoring their youthful vigour, their energy and excitement for life.

I see men who complain that they can hardly get out of bed become transformed. Instead of planning their afternoon naps, they're planning trips, new projects or an extra nine holes of golf.

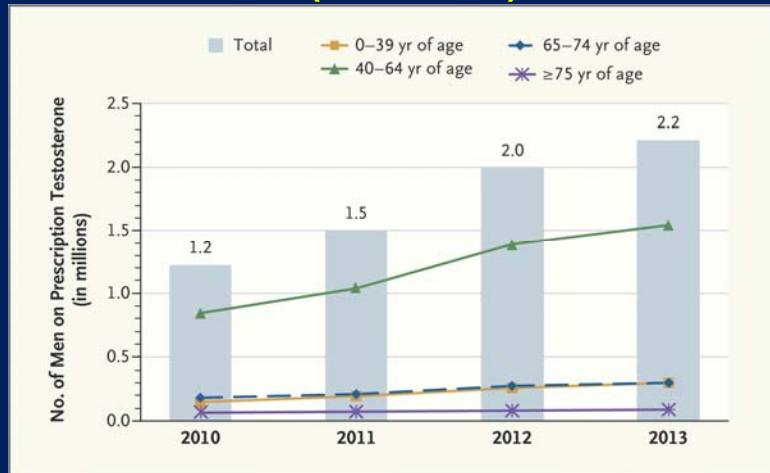
Let me give you an example from some clinical studies that were conducted using the same ingredients used in the research...



Continues...

Marketing “Low T Syndrome” Has Been Successful

Men with Claims for Testosterone: US Outpatient Pharmacies, Stratified by Age (2010–2013)



Nguyen CP et al. N Engl J Med 2015;373:689-691.

\$18 M (1988) → \$1.6 B (2011)



100-FOLD

*

What is hypogonadism - the real disorder?

- Host of conditions → low testosterone (in the context of man's age and overall health)
- **Pituitary disease** – tumors, infections, inflammation
- **Hypothalamic disease** – same things
- **Problems with the testes** – drugs (chemo), radiation, trauma, mumps (both sides), cancer, genetic disorders (Klinefelter's syndrome)
- Alcoholism
- Androgen deprivation therapy for prostate cancer

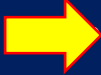
What do the lab tests mean?

- Serum total testosterone 
- (sometimes get) free testosterone 
- Test in the a.m. - 800 – 1000, ideally fasting
- At least 2 (or 3) values
- Unstressed state
- If T is low → gonadotropins (FSH, LH – pituitary gland) – next step - (normal, low or high) – helps to figure things out

Testosterone replacement therapy – is it safe?

- Options:
 - Testosterone injections – given into muscle every 1, 2, 3 or 4 weeks
 - Testosterone gel (1 or 1.62%) (1 or 2 pumps applied daily to skin)
 - Testosterone transdermal patch daily
 - Buccal bioadhesive tablets (adhesive controlled release tablets twice daily)

Large Number of Studies: Safety and Effectiveness

- Retrospective series
- Data base studies
- Cohort studies
-  Randomized, placebo-controlled clinical trials

Benefits Seen with Testosterone

Randomized controlled trials in men less than 50 yrs with hypogonadism:

- 2° sex characteristics induced and maintained
- Improved sexual function, libido, mood and well-being
- Increased muscle mass and strength
- Increased bone mineral density (DXA)
- Reduced body fat

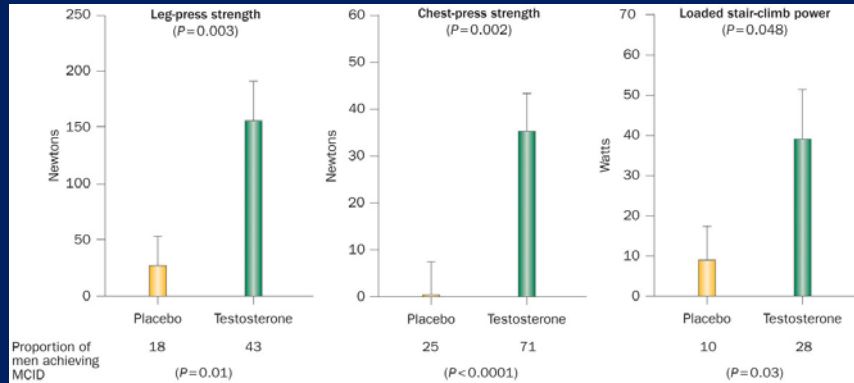
What about older men?

Testosterone in Older Men (TOM) Trial

(Basaria S et al, NEJM, 2010)

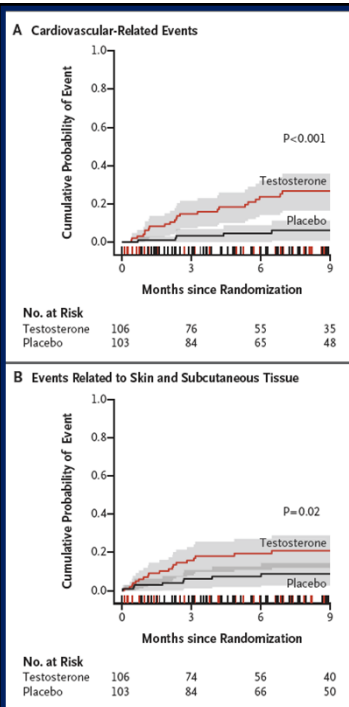
- 209 men with limited mobility (age 74 yr)
- Many with diabetes, high blood pressure, lipids, obesity
- Total T: 100 to 350 ng/dL
- Randomized to T vs placebo gel
- Testosterone - treated men - **improved muscle strength**
- Greater rate of cardiac, respiratory, skin events vs PBO group
- Trial stopped early → cardiovascular safety

Effects of Testosterone on Maximal Voluntary Strength in Older Men: TOM Trial



Muscle testing – NOT PROOF of improved physical function or fewer falls, fractures or disability

(Spitzer M et al, Nat Rev Endo, 2013)



Cardiovascular and Skin Events: TOM Trial

- Cardiac events (23 vs 5; included all cardiac procedures, events, symptoms)

Odds ratio: CV-related

Unadj: 5.4 (2.0-14.9)

Adjusted: 5.8 (2.0-16.8)

- Dermatologic events

Odds ratio:

Unadj: 2.6 (1.1-6.2)

Adjusted: 4.9 (1.7-14.6)

(Basaria S et al, NEJM, 2010)

Adverse Events in Older Men – 1.

(Spitzer M et al, Nat Rev Endo, 2013)

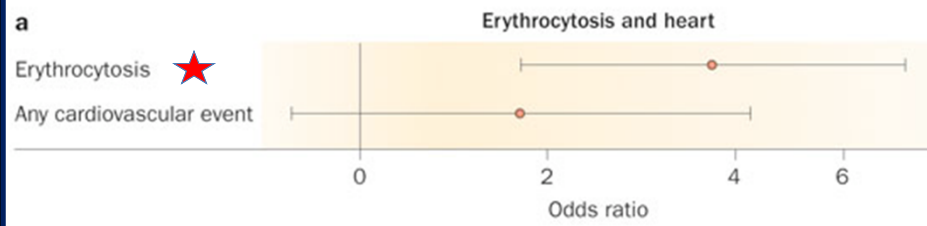
➤ Elevated red blood cell counts

Most common adverse event (men 60-75 yrs)

Role in cardiac events and strokes

High RBC may change viscosity of blood.

Older (vs younger) men → having more RBCs does not = greater O₂ carrying capacity.



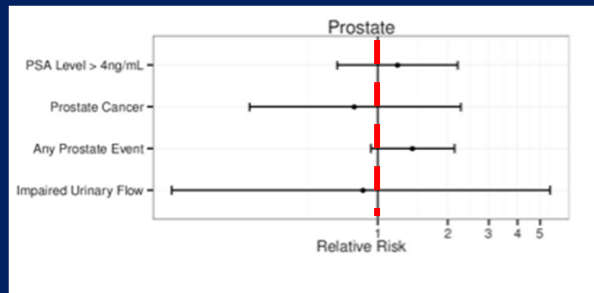
We monitor with treatment

Adverse Events in Older Men – 2.

(Spitzer M et al, Nat Rev Endo, 2013)

➤ Prostate issues – controversial

Does not cause prostate cancer or worsen lower urinary tract symptoms (trials in men ≥ 45 yrs)



- Men on testo – more PSA monitoring, more biopsies
- Change of **1.4 ng/ml** – needs to be evaluated

Adverse Events in Older Men – 3.

(Spitzer M et al, Nat Rev Endo, 2013)

- Changes in lipid profile → modest decreases in HDL
- Salt and water retention
- Obstructive sleep apnea – may be exacerbated – if it is not being treated

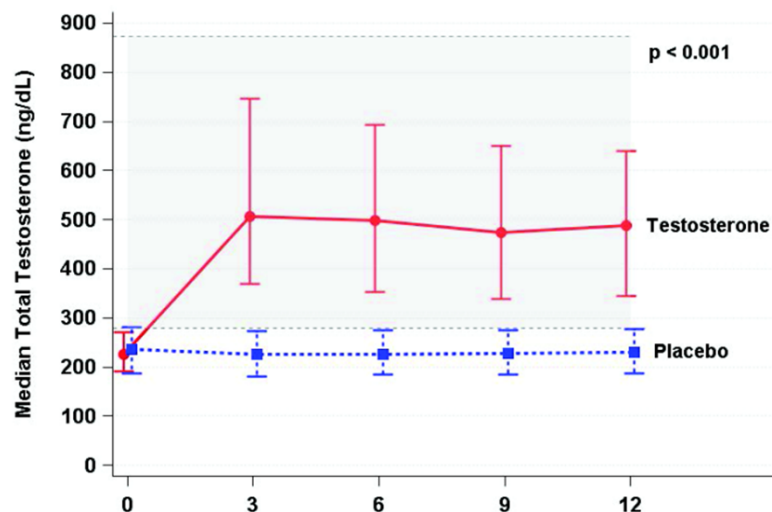
“Testosterone Trials” – (NIH-sponsored, multicenter)

***Is Testosterone Effective and Safe
in Older Men?***

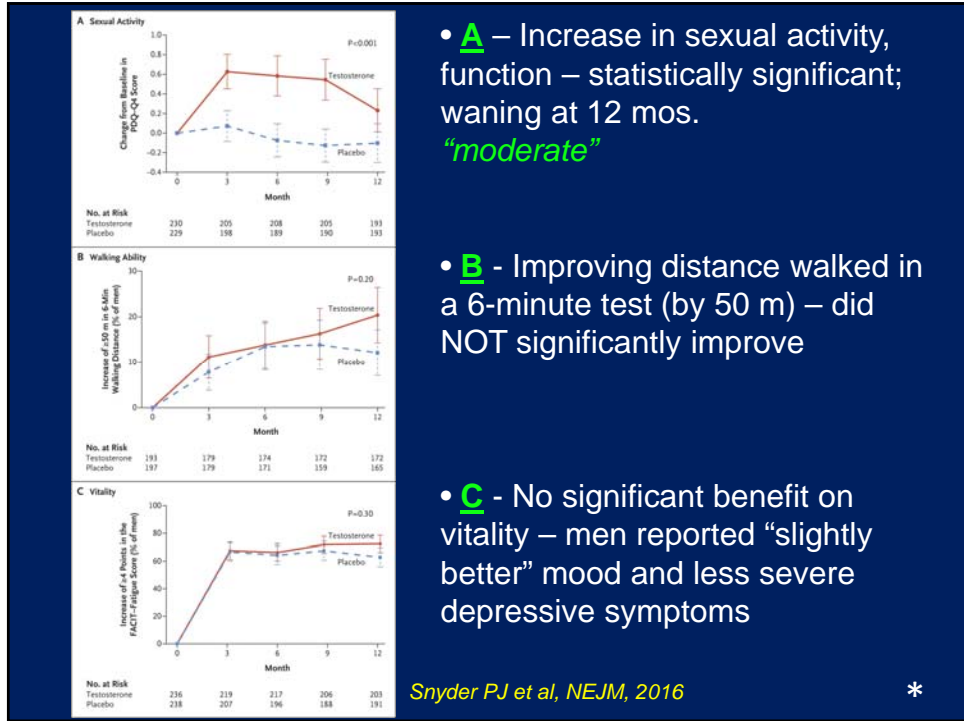
'Testosterone Trials'

(Snyder PJ et al, NEJM, 2016)

- 7 independent randomized trials
- **Sexual function, vitality, physical function, cognition, anemia, bone, heart status**
- 790 men, ≥ 65 yrs, serum T < 275 ng/dL with symptoms
- Testosterone gel or placebo X 1 year
- Levels treated into mid-normal range (men 19-40 years)
- Data: surveys, questionnaires, functional testing (heart attack not an outcome)



Snyder PJ et al, NEJM, 2016



- **A** – Increase in sexual activity, function – statistically significant; waning at 12 mos.

“moderate”

- **B** - Improving distance walked in a 6-minute test (by 50 m) – did NOT significantly improve

- **C** - No significant benefit on vitality – men reported “slightly better” mood and less severe depressive symptoms

Adverse Events

(Snyder PJ et al, NEJM, 2016)

- Testosterone vs placebo - imbalances
 - PSA increased by 1 ng/ml (23 vs 8)
 - No major risk of cancer of prostate
 - Red blood cell count up in 7 (vs 0)
 - Major cardiovascular events – 7 in each group (MI, stroke, death) in year 1; in next year → 2 in testo group, 9 in placebo group
 - Deaths (3 vs 7)
 - Hospitalizations (68 vs 78)



“Safety ok”

'T Trials' – Sexual Function

(Cunningham G et al, JCEM, 2016)

- 470 men, \geq 65 yrs, serum TT < 275 ng/dL
- Low libido, randomized T gel or PBO X 1 year with levels in mid-normal range (men 19-40 years)
- Sexual function assessed by 3 instruments:
Psychosexual Daily Questionnaire, Derogatis Interview for Sexual Function, International Index of Erectile Function

'T Trials' – Sexual Function

(Cunningham G et al, JCEM, 2016)

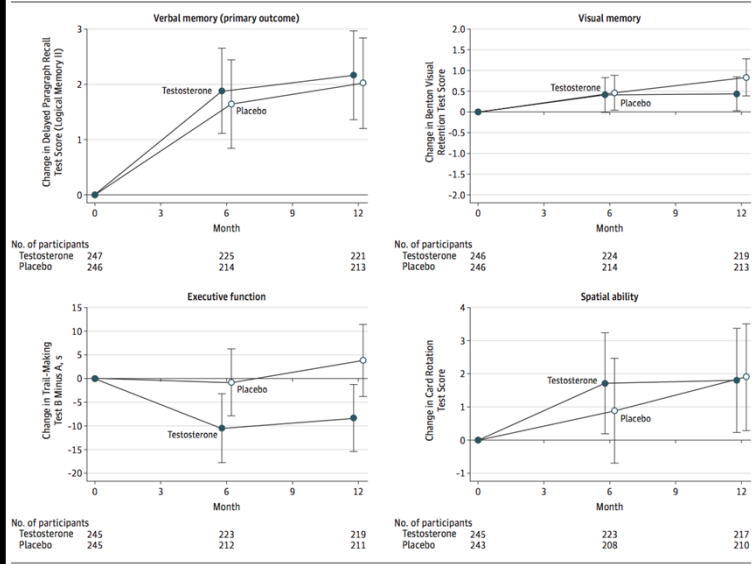
- Findings: Taking testosterone improved 10/12 aspects of sexual activity/desire (by survey), but did not change erectile function; general correlation with T levels achieved

'T Trials' – Cognition

(Resnick SM et al, JAMA, 2017)

- Men \geq 65 yrs, serum TT < 275 ng/dL
- 493 met criteria for age-associated memory impairment (AAMI)
- Randomized T gel or PBO X 1 year with levels in mid-normal range (men 19-40 years)
- Memory thoroughly assessed →

Figure 2. Adjusted Mean Change From Baseline to 6 Months and 12 Months for Men With AAMI by Treatment Group (Testosterone vs Placebo) for Verbal Memory (Delayed Paragraph Recall), Visual Memory, Executive Function, and Spatial Ability



Bottom Line: T vs PBO → NO significant differences

Resnick SM et al, JAMA, 2017

'T Trials' – Bone Mass & Strength

(Snyder PJ et al, JAMA Int Med, 2017)

- 211 men, \geq 65 yrs, serum TT < 275 ng/dL
- At baseline, average BMD by DXA - normal
- Assessments: Bone density and strength estimates (DXA and CT)
- **Findings: positive (mass improved and calculated strength got better)**

'T Trials' – Cardiovascular

(Budoff MJ et al, JAMA, 2017)

- **170** of 788 men in T Trials participated
- Mean age: 71 yrs, baseline ~51% had coronary artery calcium scores >300 (heart disease)
- Randomized T gel or PBO X 1 year
- 1^o outcome: noncalcified coronary artery plaque volume (coronary artery CT angio)
- 2^o outcome: total coronary artery plaque volume and coronary artery Ca score

'T Trials' – Cardiovascular

(Budoff MJ et al, JAMA, 2017)

- *Non-calcified plaque volume (coronaries) increased with 1 year of testosterone (vs placebo)*
- *Total plaque volume increased*
- Coronary artery Ca score – did not change
- Study too small to count events

Treating Older Men with Low T

- T TRIALS –
 - best we have
 - helpful, but short
 - *don't speak to clinical cardiac endpoints that are biggest concerns in older men;*
 - *don't establish safety*
- Testosterone is not a panacea for aging
- Beware of marketing, exercise caution with supplements

