

TESTOSTERONE

The Future?

Martin M. Miner MD

Co-Director Men's Health Center

The Miriam Hospital

Clinical Professor of Family Medicine and Urology

Warren Alpert School of Medicine of Brown University

Providence, RI

Testosterone Prescribing: Different Angles of One Story

In the perfect world
all of these components
are in balance creating the
perfect prescribing
patterns

Shortcomings and/or
excesses in certain
components can create a
suboptimal prescribing
pattern



Current Concerns Regarding Testosterone Therapy

- Are we prescribing appropriately?
 - Right patient
 - Confirmed diagnosis
- Are we following treatment protocol?
 - Are we checking follow-up T levels, HCT?
 - Are we repleting T levels to midrange?
- Monitoring T levels after starting replacement therapy is very important to establish
 - compliance
 - effectiveness
 - adverse events

Labeling, Guidance and Diagnosis

- FDA mandated Label Changes: May 2015

Testosterone is indicated for replacement therapy in conditions associated with a deficiency or absence of endogenous testosterone.

- Testosterone replacement therapy
 - Low testosterone levels due to disorders of the testicles, pituitary gland, or brain that cause hypogonadism (classical hypogonadism).
 - FDA has become aware that testosterone is being used extensively in attempts to relieve symptoms in men who have low testosterone for no apparent reason other than aging. The benefits and safety of this use have not been established.

Labeling, Guidance, and Diagnosis

- Manufacturers of all approved prescription testosterone products must change their labeling to clarify the approved uses of these medications.
- Requires these manufacturers to add information to the labeling about a possible increased risk of heart attacks and strokes in patients taking testosterone.
- Health care professionals should prescribe testosterone therapy only for men with (2) confirmed low testosterone levels caused by certain medical conditions and replicated by laboratory testing.

FDA Advisory Panel Sept 2014

- Between 2010 and 2013, the number of pts receiving TRT increased from 1.3 million to 2.3 with 60% prescribed by PCPs
- In a sample of 250,000 men, only 72% had a claim submitted for testosterone level testing prior to receiving TRT Rx.
 - 21% never had a claim
 - 6% had a claim submitted after the initial TRT Rx
 - No study has documented how many of these levels were low
- TRT was originally intended for men with no endogenous T, and clinical benefit data were not required for regulatory approval, as these were well-accepted. No clinical data are presently required for reg approval

FDA Advisory Panel Sept 2014

- FDA requires pharmacokinetic parameters for T approval:
 - 75% men achieve a T level of 300-1000 ng/dL
- Clinical efficacy endpoints are considered exploratory
 - Implicit is that clinicians would measure both basal and post therapy values. Not testing cannot be justified
- FDA approval process is not indicated for age related T decline
- Panel voted 20-1 in favor of revising current indication by limiting TRT to those with classic hypogonadism and including a potential weak signal for CVS risk.

Labeling, Guidance and Diagnosis

- **Label:** Current Labeling does not include symptoms

There is difficulty in understanding that the current labeling does not support the improvement of any of these symptoms as an indication for treatment.

MORE SPECIFIC SIGNS AND SYMPTOMS

- Decreased sex drive (libido) and activity
- Fewer spontaneous erections
- Enlarged breasts, breast discomfort
- Loss of body hair, less shaving
- Very small or shrinking testes
- Low or zero sperm count, inability to father children
- Height loss, low trauma fracture, low bone mineral density
- Hot flushes, sweats
- Incomplete or delayed sexual development

LESS SPECIFIC SIGNS AND SYMPTOMS

- Decreased energy, motivation, and self-confidence
- Feeling sad or blue
- Poor concentration/memory
- Sleep disturbance, increased sleepiness
- Mild anemia
- Reduced muscle bulk and strength
- Increased body fat, body mass index
- Decline in physical or work performance

TESTOPEL is not indicated to improve the symptoms listed above.

Labeling, Guidance and Diagnosis

- Label
 - Intended population for TRT products: hypogonadal men with **specific disease conditions** associated with absent or deficient testosterone (e.g., Klinefelter's disease, pituitary injury, etc)
 - Product use data, however, shows a different real-world population: **middle-aged men with “low T” - “age-related hypogonadism” 40-60 yrs.**
 - **“Age-Related” often is consistent with “co-morbid related”**

Labeling, Guidance, and Diagnosis

- Current product labeling does not include “age-related hypogonadism” or “aging”
- However, current labeling did *unintentionally* imply such use by including: “idiopathic gonadotropin or LHRH deficiency” - a physiologic condition that occurs in older men. This may still exist as the FDA replaced idiopathic with “acquired” hypogonadism, yet definitively stated T is not indicated for aging-related clinical issues in men. Co-morbid low T ?= Quagmire

Labeling, Guidance and Diagnosis

- **Guidance:** Endocrine Society recommendation is in contrast to FDA approved label and promotion:

“We recommend making a diagnosis of androgen deficiency only in men with consistent symptoms and signs and unequivocally low serum testosterone levels.”

“We recommend testosterone therapy for symptomatic men with classical androgen deficiency syndromes aimed at inducing and maintaining secondary sex characteristics and at improving their sexual function, sense of well-being, and bone mineral density.”

The FDA now requires 2 levels.

Endocrine Guidelines 2010

Labeling, Guidance and Diagnosis

- Diagnosis: Endocrine Society
 - Normative ranges for total and free testosterone levels in healthy young men vary among laboratories and assays.
 - In some labs, the lower limit of the normal range for total testosterone level in healthy young men is 280–300 ng/dl (9.8–10.4 nmol/liter).
 - Clinicians should use the lower limit of normal range for healthy young men established in their laboratory. Wide variance exists

Awareness and Education

- **Physician:** information regarding **diagnosis of hypogonadism conflicts with the clinical guidelines** creating an environment open to individual **interpretation of the clinician** who is confronted with a middle-aged male patient whose complaints are non-specific yet consistent with the clinical picture of hypogonadism, has low T levels, and one or two comorbidities. Clinicians continue to treat off-label
- **Patients:** are made **aware of “low T” through prior DTC ads and are eager to obtain information** and possible treatment. Despite the absence of DTC, patients remain highly motivated in this aim.



Research and New Paradigms

- Current drug development is not capable of providing data that would support use for “age-related hypogonadism”
- Current indication is not meant to support testosterone replacement for “age-related hypogonadism”
- The two main obstacles to including such use in labeling:
 - It is unclear whether signs and symptoms in aging men purported to reflect hypogonadism (e.g., fatigue, diminished sexual desire, muscular weakness) are a direct result of “low T”
 - The clinical benefit and safety of testosterone replacement for “age-related hypogonadism” has not been demonstrated by substantial evidence from adequate and well-controlled clinical studies. Most data is cross-sectional study

Research and New Paradigms

- Evidence is needed to demonstrate that signs and symptoms in aging males purported to reflect hypogonadism (e.g., fatigue, diminished sexual desire, muscular weakness) are a result of “low T”
- Evidence from adequate and well-controlled clinical trials is needed to show that TRT provides **clinical benefit** (improvement in signs and symptoms) and T repletion is **safe** in an aging male population
- The indication for TRT needs to be clarified. Populations where efficacy and safety data are lacking (e.g., aging males) need to be studied (only one part of remedy)

Promotion and Marketing

- U.S. annual testosterone sales approach \$3B
- Sales of T products 2009-13 has plateaued
- Anti-aging medicine and clinics have flourished while including T in their menus
- DTC promotion increased patient awareness of certain non-specific symptoms associated with hypogonadism.
- Common marketing messages include testosterone for treatment of sexual dysfunction, increase in athletic performance and feeling of well being.
- Marketing of testosterone products has come under the purview of the FTC and not the FDA

Conclusions

- Clinicians must learn to manage expectations derived from subliminal advertising directed to middle aged men.
- Focusing on the increase in sales as an indicator of prescribing patterns does not help in addressing the true challenges of managing hypogonadism in men.
- We eagerly await the results of the T trial which is a RCT of 800 men > 65 yrs of age. There are no safety issues re CVD noted in this trial to be published in the NEJM shortly.
- FDA is requiring manufacturers of approved testosterone products to conduct a well-designed clinical trial to more clearly address the question of whether an increased risk of heart attack or stroke exists among users of these products.

Conclusion

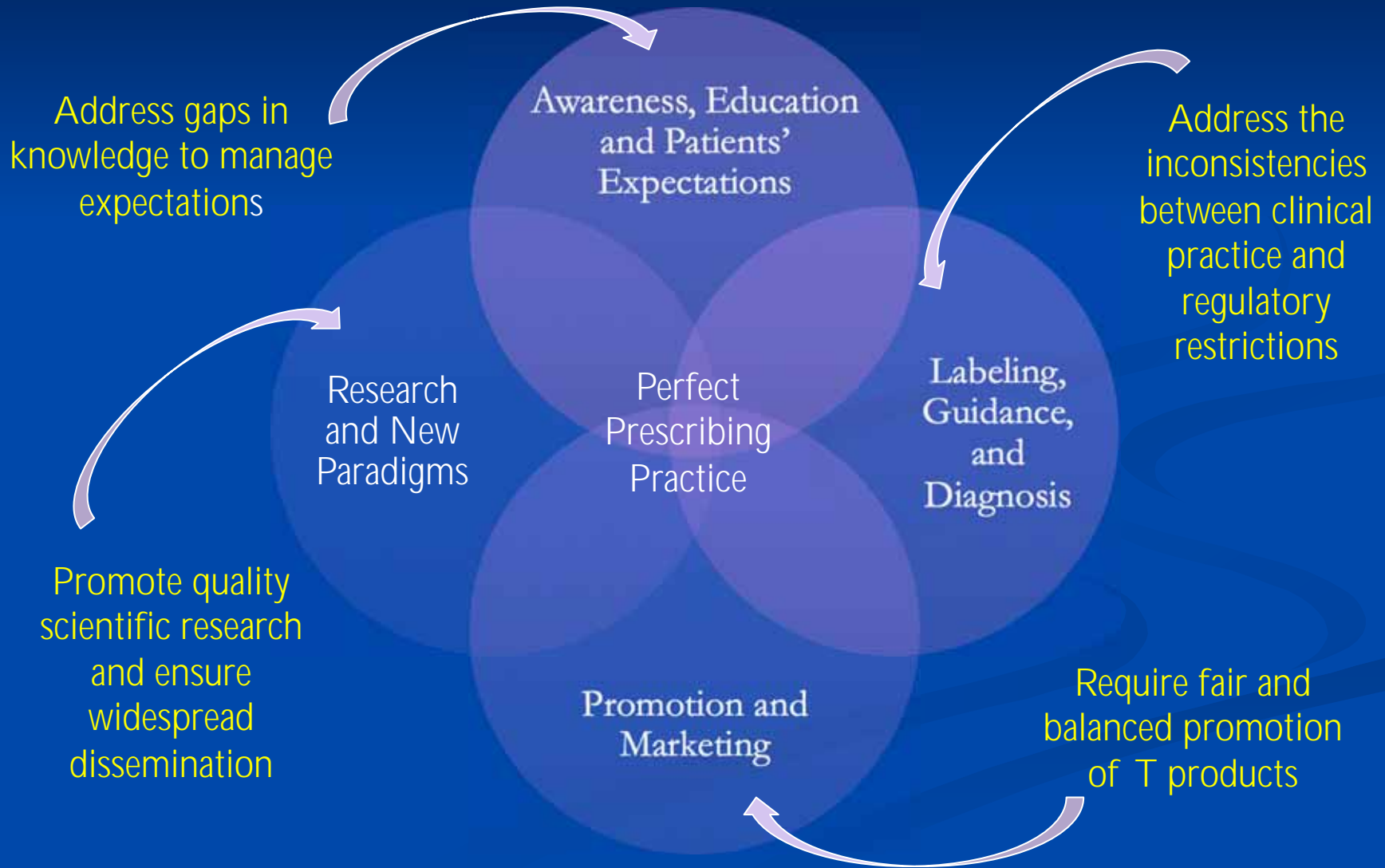
- Prescription practice is consistent with the current understanding of the diagnosis and management of hypogonadism in men.
- We need education rather than a continued quagmire that promotes polarization
- Polarization- “My truth is better than yours”



Conclusion

- ***Hypogonadism*** is the true challenge. The diagnosis and management of this condition remains unclear.
- The current pattern of prescribing is a reflection of a condition that is in need of more collaborative work between medical professionals, patient advocacy, regulatory authorities and industry.

Conclusion



THANK YOU!

From: **Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial**

JAMA. 2015;314(6):570-581. doi:10.1001/jama.2015.8881



Figure Legend:

Flow of Participants Through the Testosterone's Effects on Atherosclerosis Progression in Aging Men (TEAAM) Trial Three hundred eight eligible men were randomized; 2 withdrew consent shortly after being assigned a randomization number and did not receive the study medication. The 306 randomized men who received at least 1 dose of the study medication were included in the primary analysis. BMI indicates body mass index; HbA_{1c}, hemoglobin A_{1c}; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen.

Date of download: 8/12/2015

From: **Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial**

JAMA. 2015;314(6):570-581. doi:10.1001/jama.2015.8881

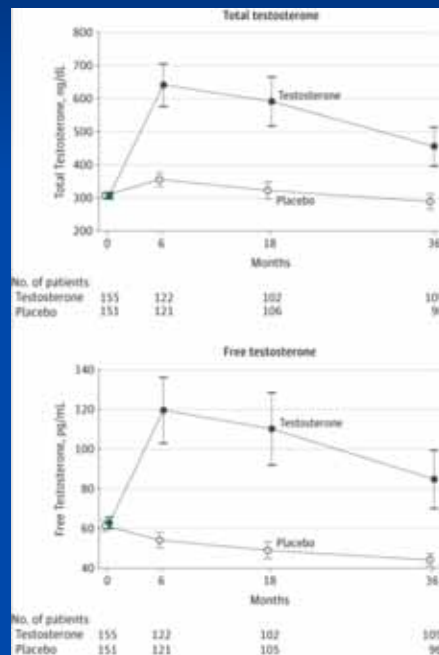


Figure Legend:

Total and Free Testosterone Levels at Baseline and While Taking Study Medication Means and 95% confidence intervals are presented as data markers and error bars.

From: **Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial**

JAMA. 2015;314(6):570-581. doi:10.1001/jama.2015.8881

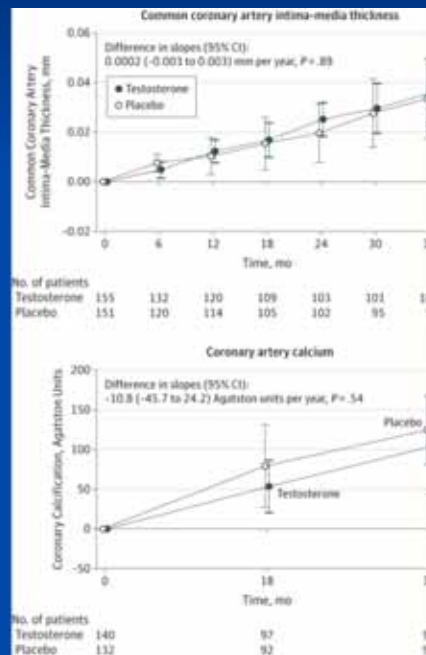


Figure Legend:

Change in Distal Common Carotid Artery Intima-Media Thickness and Coronary Artery Calcium Scores in Participants The trajectory of change in carotid artery intima-media thickness and total coronary artery calcium by time since randomization. The means (data markers) and 95% CIs (error bars), generated from the observed data, are shown. Estimates are derived from mixed-effects regression models supplemented by multiple imputation of missing records (see the Methods section).

From: **Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial**

JAMA. 2015;314(6):570-581. doi:10.1001/jama.2015.8881

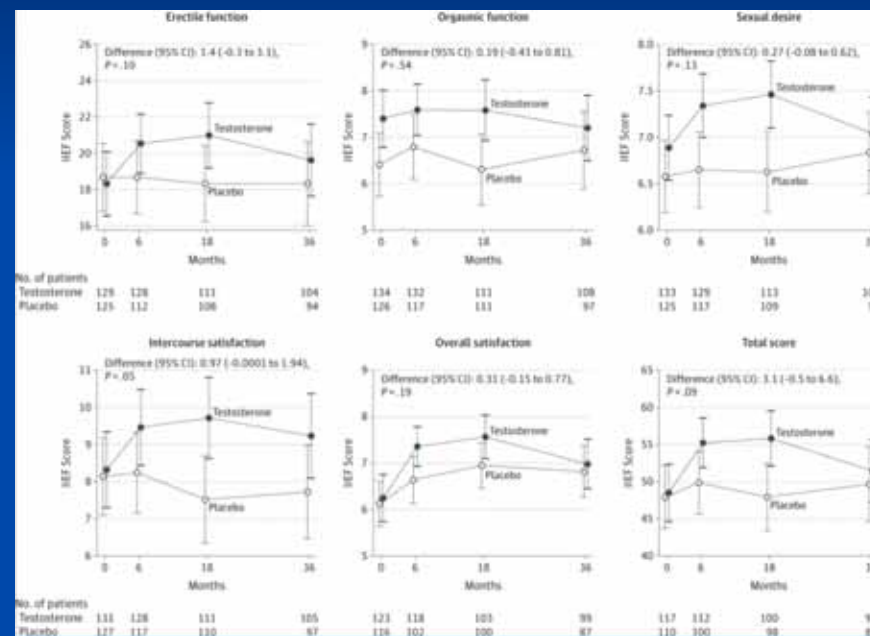


Figure Legend:

Sexual Function at Baseline and While Taking Study Medication Each panel represents 1 of the 5 domains of the International Index of Erectile Function (IIEF). Means and 95% confidence intervals are presented as data markers and error bars. The mean estimated difference were derived while participants were taking the study medications (testosterone minus placebo); estimates were derived from a mixed-effects regression model after adjusting for age group and study center, supported by multiple imputation of missing records (see the Methods section).

Date of download: 8/12/2015

From: **Effects of Testosterone Administration for 3 Years on Subclinical Atherosclerosis Progression in Older Men With Low or Low-Normal Testosterone Levels: A Randomized Clinical Trial**

JAMA. 2015;314(6):570-581. doi:10.1001/jama.2015.8881

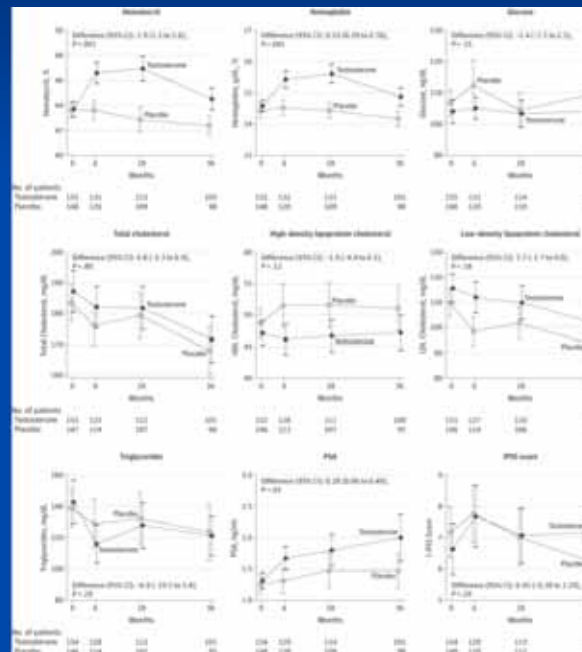


Figure Legend:

Safety and Laboratory Assessments: Baseline and On-treatment Analytes and International Prostate Symptom Score Means and 95% confidence intervals are presented as data markers and error bars. The mean estimated difference (testosterone minus placebo) were derived while participants were taking the study medication; estimates were derived from a mixed-effects regression model after controlling for age and study center, supported by multiple imputation of missing records (see the Methods section). PSA indicates prostate-specific antigen; IPSS, International Prostate Symptom Score.

Date of download: 8/12/2015