TESTOSTERONE
The Future?

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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.

Awareness, Education and Patients’ Expectations

Research and New Paradigms

Perfect Prescription Practice

Labeling, Guidance, and Diagnosis

Promotion and Marketing
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

Bhasin et al J Clin Endo Metab 2010; 95: 2536-2559
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. Baillargeon J JAMA 2013
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.

Gamick M Commentary JAMA 2014
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.

<table>
<thead>
<tr>
<th>MORE SPECIFIC SIGNS AND SYMPTOMS</th>
<th>LESS SPECIFIC SIGNS AND SYMPTOMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Decreased sex drive (libido) and activity</td>
<td>• Decreased energy, motivation, and self-confidence</td>
</tr>
<tr>
<td>• Fewer spontaneous erections</td>
<td>• Feeling sad or blue</td>
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<tr>
<td>• Enlarged breasts, breast discomfort</td>
<td>• Poor concentration/memory</td>
</tr>
<tr>
<td>• Loss of body hair, less shaving</td>
<td>• Sleep disturbance, increased sleepiness</td>
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<tr>
<td>• Very small or shrinking testes</td>
<td>• Mild anemia</td>
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<tr>
<td>• Low or zero sperm count, inability to father children</td>
<td>• Reduced muscle bulk and strength</td>
</tr>
<tr>
<td>• Height loss, low trauma fracture, low bone mineral density</td>
<td>• Increased body fat, body mass index</td>
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<tr>
<td>• Hot flushes, sweats</td>
<td>• Decline in physical or work performance</td>
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<tr>
<td>• Incomplete or delayed sexual development</td>
<td></td>
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</tbody>
</table>

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 wellbeing, and bone mineral density.”

The FDA now requires 2 levels.

Endocrine Guidelines 2010
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 co-morbidities. 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.
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

1. Awareness, Education, and Patients’ Expectations
   - Address gaps in knowledge to manage expectations

2. Perfect Prescribing Practice
   - Address the inconsistencies between clinical practice and regulatory restrictions

3. Promotion and Marketing
   - Require fair and balanced promotion of T products

4. Labeling, Guidance, and Diagnosis
   - Promote quality scientific research and ensure widespread dissemination

- Research and New Paradigms
THANK YOU!
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.

Figure Legend:
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**


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**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


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).
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*


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.