

TRT Safe & Effective?

You Better Think Twice

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Disclosure of Financial Relationships

Ryan P Terlecki, MD, FACS

Has disclosed relationships with an entity producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients.

Consultant

AMS/Boston Scientific

Honoraria/Advisory Boards

Auxilium

AMS

Research Grants/Contracts

AMS/Boston Scientific

Allergan

Department of Defense

The Holy Grail?



Nothing New



Holy Grail vs Pandora's Box

- First used clinically in 1937, 2 years after its Nobel-Prize-winning discovery
- Now a nearly \$2 billion annual market where the raw drug costs only 1% of the total (higher than most street drugs)
- A 2003 IOM panel concluded there was insufficient evidence of benefit for TRT in older men and recommended a coordinated set of clinical trials

The Cardiovascular Controversy

- Based largely on 4 articles suggesting increased cardiovascular risk with receipt of a Rx for TRT
 - 2 retro reviews with poor methodology
 - 1 meta-analysis with questionable studies and events
 - 1 PCT with few major adverse cardiac events

Cardiovascular Controversy

- After these studies and NYT editorials, many men stopped therapy
- The Endocrine Society warned against using in older men or if hx of CAD
- FDA announced plans to review safety
- Plaintiff attorneys looked for cases of MI/CVA to initiate class action suits

Topical Gel & Injectable

TESTOSTERONE WARNING

A new study shows that prescription testosterone products increase the risk of:

- **STROKES**
- **HEART ATTACKS**
- **BLOOD CLOTS**
- **PULMONARY EMBOLISM**
- **DEEP VEIN THROMBOSIS**



**CALL
RIGHT
NOW!**

Make an informed decision



Seven TTrials

- Physical Function Trial
- Sexual Function Trial
- Vitality Trial (for fatigue)
- Cognitive Function Trial
- Anemia Trial (hemoglobin)
- Bone Trial (bone density)
- Cardiovascular Trial (coronary artery plaque volume)

Seven TTrials

- To enroll, men had to qualify for at least one of the three main trials (The Sexual Function Trial, The Physical Function Trial, or The Vitality Trial).

Seven TTrials: Baseline Evaluation

- Cunningham et al. published cross-sectional study of baseline measures in the TTrials (conducted at 12 sites in US)
- FT and TT were NOT associated with measures of vitality or physical function in symptomatic older men with low T who qualified for the TTrials.

TTrials Data: Vitality, Physical

- TRT had NO significant benefit for vitality
- NO significant improvement in activity from TRT in the Physical Function Trial; but if all three trials pooled, increase in 6 minute walking distance significantly improved
- Four cases of CaP; Three in men with TRT (not powered to assess)

TTrials Data: Sexual

- 790 men; 65 y or older with T < 275 ng/dL and symptoms of HG; T gel or placebo gel for 1 year.
- TRT designed to achieve T levels consistent with mid-normal range for 19-40 y/o men WAS associated with significantly increased sexual activity, sexual desire, and erectile function
- The improvement, however, was MODEST AND LESS than that reported from PDE5Is (2.64 pts on full-length IIEF).

TEAMM Trial (published 8/2015)

- TRT did NOT significantly improve erectile or ejaculatory function, sexual desire, partner intimacy, or HRQOL
- These data are consistent with meta-analyses of older testosterone trials.

TTrials Data: Cognitive

- 788 men; 65 y or older with T < 275 ng/dL and symptoms of HG; T gel or placebo gel for 1 year
- 493 with age-associated memory impairment
- TRT offered NO BENEFIT

TEAMM Trial Update (2016 Data)

- TRT for 36 months (to raise T concentration of older men into a range mid-normal for healthy young men) in this group did NOT improve cognitive function. Absence of effect was evident across all domains of cognition tested.
- Concluded that TRT to improve cognition in older men with age-related decline in T concentrations is NOT justified.

TTrials Data: Bone Health

- 211 men
- Volumetric BMD of spine and hip assessed by CT scan at baseline and at one year
- TRT assoc'd with significant INCREASE in both locations (not tied to any clinical benefit)

TTrials Data: Anemia

- Main outcome measure was % men with unexplained anemia with Hgb rise of 1 gram or more at one year
- TRT was significantly more likely than placebo to result in higher Hgb (No surprise)
- Clinical benefit unclear

TAMRISK

- Finnish study surveyed 670 men > 55 and followed for 28 yrs.
- Compared Hct < 50 to those w/Hct >/= 50
- Men with higher Hct were 2.4x more likely to die from CAD (sig).
- After adjusting for est'd risk factors, risk remained 1.8x (sig).

TTrials: Cardiovascular Trial

- Hypothesis was TRT would SLOW progression of noncalcified coronary plaque volume
- CT angiogram at baseline and at 12 months
- There was actually a significant INCREASE in those on Androgel relative to placebo (no major events)
- This degree of coronary luminal narrowing in 12 months is an “UNPRECEDENTED” drug effect and appears ominous

BUT...

- “Those were older men and the testosterone group was worse at baseline” (SMSNA 2017)
- Remember the levels of evidence
- Let me take you back to my childhood, as a kid born in the late 70s, growing up largely in the 80s

Macho Man Randy Savage

- Died at age 58
- Had MI while driving
- Long-term steroid use



James Brian Hellwig

- The Ultimate Warrior
- Admitted to testosterone use and claimed it was rampant in field
- Died age 54 of MI due to atherosclerosis per autopsy report



Chris Benoit

- Died at age 40
- Killed his wife and 7 y/o son before hanging himself
- 10x nml T level



Eddie Guerrero

- Best friends with Benoit
- Died age 38 from atherosclerotic cardiovascular disease
- Steroid user as per a SI investigative report



David 'Davey Boy Smith'

- British Bulldog
- Died May 2002 at the age of 39
- Died from MI and autopsy report stated anabolic steroids were causative



'Flying' Brian Pilman

- One of the Four Horsemen
- Found dead from MI at age 35, secondary to atherosclerotic heard disease

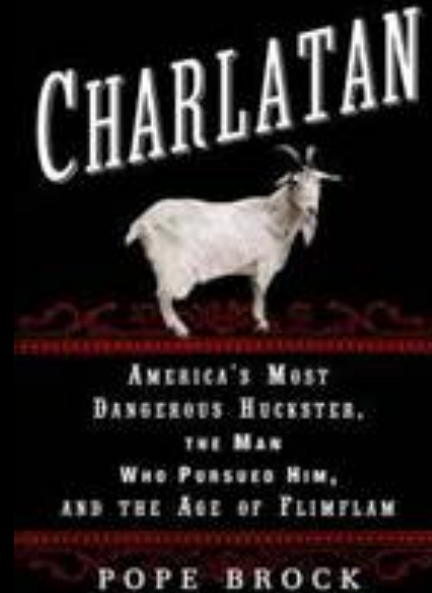


But the 'experts' say...

- Some high volume providers continue to adamantly support TRT and skirt the evidence
- Pay attention to the COI
- What if testosterone is one of the contributing factors to why men don't live as long?
- Think about the WHI and the potential parallels as Estrogen increased risk of CVA, PE
 - Rowdy Roddy Piper died a cardiac death with a massive PE
 - Bret 'the hitman' hart suffered a CVA and was also diagnosed with prostate cancer
 - In the words of my kids, 'just sayin'



John Romulus Brinkley



John Romulus Brinkley

- Born in 1885 in impoverished North Carolina
- Has been called a ‘quack’ and a ‘Snake-oil salesman’
- Ads read “Are you a Manly Man Full of Vigor”
- Injections of colored distilled water
- Faked medical degree, bailed out of jail (fraud/unpaid debt) and took job as a house medic at meat-packing firm where he observed mating habits of goats

John Romulus Brinkley

- George Lydston (Chicago) and Sergey Voronoff (France) famous for implanting human testicular tissue or monkey glands into elderly men to improve virility
- JB implanted goat testicles into a farmer who claimed sex drive was full speed afterward
- Went to LA in 1922 on Wilshire Blvd to advertise (named for magnetic belt charlatan Gaylord Wilshire)

John Romulus Brinkley

- JB built a radio station KFKB (Kansas First Kansas Best) and could be heard from Canada to Mexico.
- Eventually exposed and retreated to Mexico and created the world's most powerful radio station
- Introduced country music and blues and paved the way for rock and roll
- By the end of 1939 he amassed \$12 million

Shay



- AKA kid #3
- You know what he wants?

Candy



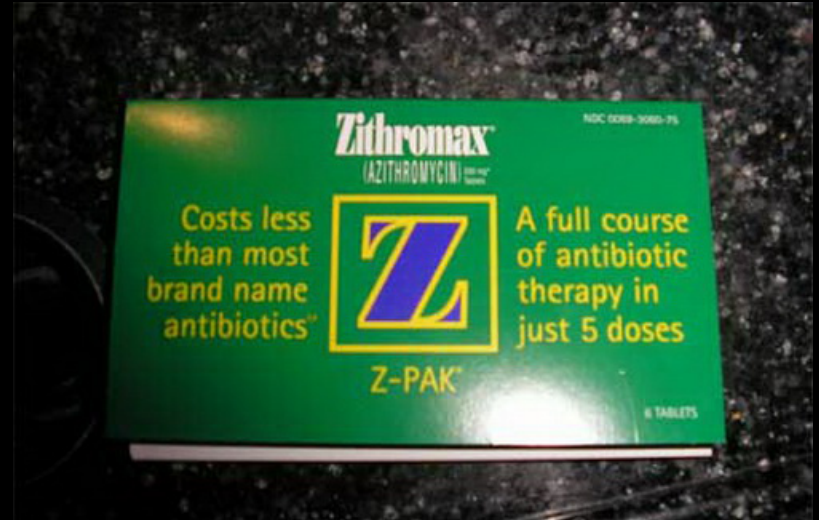
- Makes him feel good
- He seems to have more energy
- When it wears off, he crashes, and then he craves more
- Long-term, presumably a risk of weight gain, cavities, etc...

But...PATIENTS WANT IT!!!

- You have Press Ganey scores and online satisfaction to think about.
- Giving them a Rx makes them feel that you 'did something' for them, and what's the harm?
- Does this sound similar to something else on the primary care side?

The infamous Z-Pak

- The ultimate placebo for the viral URI
- Sales of \$464 million in 2011
- The following year, FDA warned of assoc'd risk of CV death
- Implicated in aggravation of 'superbugs'



Well, they're well informed, right?

- “It’s ok if they have informed consent.”
- I’m sure their lawyer will agree after their cardiac stent
- When they get the IM injections in your office, they don’t see the FDA labeling they’d see if they were using a commercial topical at home

Setting the scene

- Clinic full of 45-50 y/o guys missing the glory days...and needing prior auth forms filled out
- Jesse Ventura workout pants, huge arms covered in acne
- Hairline running for the hills and testicles that look like raisins
- Touting their witch-doctor provided regimen of testosterone, hcg, arimidex, DHEA, and a garbage back full of GNC products, asking you to hurry so they can get to their chiropractor

The new normal

- In practical reality, many of these men are really hoping for a less stigmatic solution to their ED
- Often, they may see minimal clinical benefit (possibly placebo effect based on no vitality benefit in trial), but that doesn't mean they won't suffer in withdrawal

Creating Drug Dependency?



“What have you done for me LATELY?” – Janet Jackson



“I used to do a little, but a little wasn't doin, so a little got more and more.” --GNR

What are you chasing?

- A symptom?
- A questionnaire score?
- Some arbitrary magic number on a blood test so you can convince a patient that they're better and it's worth getting the metal trocar in the rear every few months to slide in some pellets that, in case you've never looked closely, have small glass shards attached from imperfect breakage of ampules

AUA Resources

- 2014/2015:AUA Position Statement on Testosterone Therapy
 - Treatment AFTER FULL DISCUSSION of potential adverse effects (tell them it causes heart disease)
 - Per the AUA, “Only FDA-approved medications should be used”. (But this is off label)
 - Should NOT be offered to those with normal T levels (who knows what those are???)

Conclusions

- NO BENEFIT for physical function
- NO BENEFIT for vitality
- NO BENEFIT for improved cognition
- MODEST increase in sexual function (early)
- IMPROVED bone density/anemia (potential risk)
- POTENTIALLY DANGEROUS increase in coronary plaque volume (NEVER a good thing)
- Given LIMITED EFFICACY from T trials, public funding does NOT appear warranted to support long-term powered RCT for CV risk

Conclusions

- Remember how to be a doctor and give some sound advice:
 - Weight loss
 - Moderate/high intensity exercise
 - Sleep hygiene
 - Reduce stress (cortisol increases SHBG)
 - Optimize Vitamin D, B12
 - High protein (? Organic), Lower carbs, healthy fats

Have you chosen wisely??

