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Testosterone Trials: Lessons from Complex Cases

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Disclosures

- I am on the advisory board for Healthy Men, Inc
- I am a consultant for Coloplast for catheters
- I am a consultant for Endo Pharmaceuticals for Men's Health

- All relevant financial relationships have been mitigated.

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Objective

- Analyze complex testosterone cases, differentiate evidence-based indications vs contraindications, and formulate monitoring and referral plans

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Background

- Prevalence of hypogonadism varies widely based on the population studied, and diagnostic criteria used
- Epidemiological studies suggest ~2.1%–5.6% of men under 60 years old experience hypogonadism
  - Rises to about 20% in men over 60
  - Up to 50% in men over 80 years old
- Testosterone levels can be affected by stress, obesity, sleep, general illness, SHBG levels

Background

- Testosterone deficiency
  - Constellation of signs and symptoms
  - Muscle wasting, fatigue, osteoporosis, oligospermia, obesity
  - Sexual dysfunction, erectile dysfunction, decreased libido
  - Loss of sexual drive is considered most genuine symptom of late onset hypogonadism → less affected by age-associated comorbidities
- 100x increase in prescriptions…*despite no new indications*
  - ~18 million in late 1980s
  - 1.8 billion by 2010s
- Predominantly North America: “epidemic-like increase”

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Proposed benefits of testosterone therapy (TT)

- Improved sexual function
- Maintain bone mineral density/strength
- Improve lipid profiles
- Improve anemia
- Improve lean body mass
- +/- improvement to depressive symptoms
- Evaluation and Management of Testosterone Deficiency (2024)
- https://www.auanet.org/guidelines-and-quality/guidelines/testosterone-deficiency-guideline
  - up to 25% of men who receive testosterone therapy do not have testosterone tested prior to initiation of treatment
  - up to 1/3 men placed on TT therapy do not meet diagnostic criteria

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Case 1: JH (NP telehealth visit)

- 48 yo male started TT at a franchise men's health clinic
- c/o some fatigue, mild ED, but "felt like I was losing my edge" "high stress job" and reports many men in his social circle had been starting TT
- Presents to Urology clinic because the clinic pricing program was "getting expensive"
- Seeking testosterone cypionate (TC) refill today, intends no other evaluation/discussion

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Case 1: JH (NP telehealth visit)

- PMH: vasectomy, mild HTN
- FamHx: HTN, paternal hx MI age 54, 2 brothers being managed for HTN/elevated cholesterol
- Declined to provide labs from initial presentation at franchise clinic
- Had been started on 250mg testosterone cypionate (TC) weekly IM
  - Last injection 2 days prior to NP telehealth visit
  - Per his report, the previous interval labs done by the clinic "were fine" but was unclear/unwilling to disclose frequency of lab checks
- Plan: trough labs, to include total T, Hct, estradiol with RV in 2 weeks to discuss/update plan
  - Additional labs were declined

Case 1: JH (RV telehealth visit)

- Since NP visit “they started me on daily Cialis to bring my blood pressure down, but it’s really been boosting my erections”
- Labs: total T 1300, estradiol 85, Hct 56
- Plan?

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Management suggestions

- Routine monitoring may prevent extra cardiovascular risk because of fluid retention
- Fluid retention may increase blood pressure
  - Counsel on dietary sodium restriction
  - Monitoring fluid input
  - BP monitoring
- (More on elevated HCT to come…)

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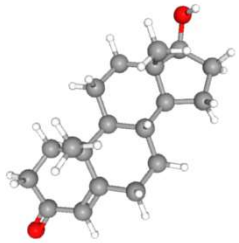
Direct to Consumer advertising is filling a gap

- DTC testosterone campaigns have become a rare entry point for men into the healthcare system
- TC advertising blurs line between medical purpose and non-medical purpose
  - Ultimate form of “doctor shopping”
  - DTC ads reduce perceived stigma by framing care as empowerment
  - “Taking charge” of health rather than “asking for help”



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Direct-to-consumer marketing has redefined testosterone: No longer just a therapy- it’s a promise

- With rising TT prescriptions, many men now seek care influenced more by marketing than by strict clinical indications
- Direct-to-consumer testosterone advertising has significantly amplified men’s expectations about therapy, intertwining notions of identity, aging, and performance with hormone treatment
  - One-click labs, asynchronous chats, and home delivery reduce decisional friction
  - Preference construction is shaped more by interface and copy than by shared decision-making
  - Influenced how men interpret fatigue, sexual changes, mood, and aging—often funneling diffuse concerns into a single, highly branded explanation: “low T”
- Secret-shopper data suggest risk/monitoring discussions are often incomplete

Clinical and Behavioral Impacts

- Patients may expect continuation of therapy without proper evaluation
- High prevalence of supratherapeutic dosing and absent baseline data complicate safe care transition
  - Men arriving from DTC platforms often lack baseline labs, prostate screening, cardiovascular risk assessment
  - Supraphysiologic dosing is common
  - Concerns about erythrocytosis, fertility suppression, long-term safety

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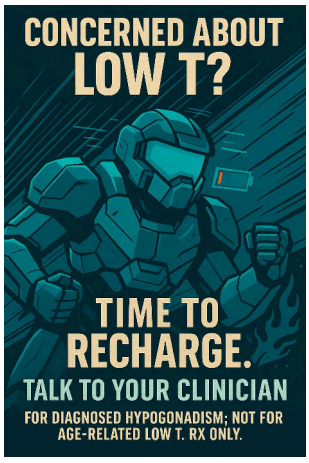
Clinical and Behavioral Impacts

- Provider-patient conflict may arise when clinical guidelines recommend discontinuation or dose reduction
- Clinicians face pressure to continue or escalate therapy to align with patient expectations/previous experience
  - Potential erosion of shared decision-making when patients view therapy as a consumer right rather than a medical intervention
  - Patients treat testosterone more like a product…



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Case 2: RZ (NP telehealth visit 7/2025)

- 55 yo to establish care. Seeking TC refill today, intends no other evaluation/discussion
- Admits little use of CPAP for sleep apnea
- States testosterone has been his only effective method for pain management
- Reports issues with testosterone pellets- bruising; reports allergic reaction to topicals
- Current dose 200mg IM TC weekly
  - Last dose was >3 weeks ago

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Case 2: RZ (NP telehealth visit 7/2025)

- PMH: T2DM, BMI 39, Failed back surgical syndrome; Chronic left-sided low back pain with left-sided sciatica; Lumbar radiculopathy; Sleep apnea; Cervical radiculopathy; OSA; chronic pain syndrome
- No recent safety studies, previous labs ~10 months old
- Plan: update labs

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Case 2: RZ (NP telehealth visit 7/2025)

Component Latest Ref Rng	2/28/2024	3/16/2024	9/19/2024
HCT 40.0 - 50.0 %	57.7 (H)	53.1 (H)	61.1 (HH)

Component Latest Ref Rng	2/28/2024	3/16/2024	9/19/2024
Prostate Specific Antigen <3.5 ng/mL	1.7	1.7	2.0

Component Latest Ref Rng	9/19/2024
Sex Hormone Binding Globulin 10 - 89 nmol/L	18
Bioavailable Testosterone, Males 110.0 - 400.0 ng/dL	271.3
Testosterone Level, Male 250.0 - 950.0 ng/dL	404.1

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Case 2: RZ (NP telehealth visit 7/2025)

- Attempted to explain that his hx previous high Hct placed him at increased risk for clots, heart attack, stoke
- Attempted to explain that we also need to check estradiol, as this also increases risk for clot formation
- He interrupted, very angry that the relationship he had enjoyed with previous provider “was not being honored” and he was not being given a refill

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Case 2: RZ (NP telehealth visit 7/2025)

- He did not feel updated labs were necessary, and as I was offering a plan that was in conflict with what he was accustomed to from previous (male) provider, he stated that my plan must be wrong, and not a plan he intended to follow
- He stated that since he never had chest pain or heart attack, that my evaluation was flawed
- Multiple attempts to explain that I was only declining to refill until safety studies were up to date
- He concluded that I was refusing to provide refills, and that he would seek refills from his PCP "who will give me whatever I want" and disconnected from the visit

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Dose-limiting effect: erythrocytosis

- Erythrocyte mass exceeding 125% predicted based on sex and body mass
- In practice: vary depending on the guideline, ranging from a hematocrit of **48% up to 55%**
  - Across multiple guidelines, polycythemia is grounds for TT cessation/modification, without evidence that this actually increases risk
- Increased blood viscosity→ potential increased risk of thromboembolic events
  - controversial evidence surrounding increased risks of major adverse cardiovascular events (MACE), venous thromboembolic events (VTE) and association with TT
  - meta-analyses do not support an increased risk of MACE
  - BUT these trials not designed to detect MACE as primary outcome, underpowered

Higher risk of developing erythrocytosis after TT

- Type II diabetes mellitus
- Elevated baseline hematocrit (>50%)
- Live in high altitudes
- Smoking
- Obstructive sleep apnea
- Advanced age
- Obesity
- Other hypercoagulable conditions
  - COPD, CHF, prothrombotic conditions such as factor V Leiden, elevated homocysteine, factor VIII

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Dose-limiting effect: erythrocytosis

- Discontinuation of TT results in normalization of erythrocyte mass parameters
  - ~3-12 months
- In many men, the positive effects/perceived benefits of TT make discontinuation challenging
- Altering testosterone formulation or dose may change the risk
  - Phlebotomy vs blood donation

Guidelines….

- Hematocrit > 54%: testosterone-independent but weak associated rise in CV events/mortality
  - *Lower threshold for erythrocytosis in transgender males- higher hazard ratio for increased Hct compared to cisgender men*
- Endocrine Society uses a hematocrit threshold of >50% as relative contraindication to initiating TT
  - Stop tx at Hct 54%
- Hct level at or above 54%, both EAU/AUA recommend intervening
  - Stopping or reducing dose
- Canadian guidelines: 55% as the safe upper limit
- Therapeutic phlebotomy
  - no absolute contraindications

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Formulation-based risk

- Intramuscular injections: ~40%
  - Increase 4.0%
- Subcutaneous pellets: 35%
- Transdermal: 15%
- Topical: 3%
- Intranasal: 0.2%
- Oral: 0.03%
  - oral testosterone undecanoate 4.3%

Ohlander SJ et al Erythrocytosis following testosterone therapy. Sex Med Rev. 2018;6(Jan):77–85.
Rogol A et al, A novel testosterone nasal gel, normalizes androgen levels in hypogonadal men. Andrology. 2016;4:46–54.
Best JC et al. A cross-sectional comparison of secondary polycythemia in testosterone-deficient men treated with nasal testosterone gel vs. intramuscular testosterone cypionate. Can Urol Assoc J 2021;15:E118.

Dose-limiting effect: erythrocytosis

- "no TT formulation had a pooled mean HCt increase over 4.3%, suggesting that the risks of testosterone-induced erythropoiesis may be mitigated through close clinical monitoring and careful patient selection."
- Existing evidence does not support causal role between TT and adverse CV events when hypogonadism appropriately diagnosed and treated
  - Discuss risks in a shared-decision making approach

Ory J, Ramasamy R. Secondary Polycythemia in Men Receiving Testosterone Therapy Increases Risk of Major Adverse Cardiovascular Events and Venous Thromboembolism in the First Year of Therapy. Reply. J Urol. 2022;208:567. doi: 10.1097/JU.0000000000002791.
Nackeeeran, S et al The Effect of Route of Testosterone on Changes in Hematocrit: A Systematic Review and Bayesian Network Meta-Analysis of Randomized Trials 2022 J Uro, 207, 44-51.

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When to intervene?

- No evidence-based guidelines which outline the frequency or volume of phlebotomy protocols in patients receiving TT
  - temporizing measure to allow dose/formulation alterations
- Elevated hematocrit without comorbidities, acute CV or venous thromboembolism events: management
  - reducing testosterone dose
  - switching to different formulation
  - phlebotomy, blood donation
- In most cases, discontinuation of testosterone therapy is not required

Dose-limiting effect: erythrocytosis

- Estradiol, a breakdown product of testosterone via aromatase, may also play a role in polycythemia
  - increase in estradiol via increased aromatization may increase telomerase activity, resulting in increased hematopoietic stem cell proliferation and survival
- Relationship between obstructive sleep apnea (OSA) and TT leading to erythrocytosis is not yet completely understood
  - OSA believed to cause erythrocytosis via hypoxemia
  - physiological response from inappropriate stimulation of erythropoiesis, decreased oxygenation

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Management

- Dose adjustment has to be made based on hematocrit
- Marked erythrocytosis has to be avoided
- Reduction in dose + increase in frequency of administration should help manage hematocrit
  - reduce risk of MACE
  - splitting 100 mg weekly dose into 2-3 three smaller doses throughout the week may effectively maintain testosterone levels while minimizing potential for elevated hematocrit

Case 3: MM (NP in person)

- 41 yo Presents to establish care. c/o much fatigue, low libido, some sexual dysfunction
- Has randomly given himself TT injections at several points in the past, vague about how he has obtained, vague about dose
- Noted some improvement to symptoms
- Never took for more than 4-8 weeks at any given time

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Case 3: MM (NP in person)

- PMH: Class 3 severe obesity and body mass index (BMI) of 40.0 to 44.9 in adult; Essential hypertension; Testosterone insufficiency; Umbilical hernia; Erectile dysfunction; Obstructive sleep apnea syndrome; Polycythemia
  - Intermittent CPAP use
  - Considering bariatric surgery/other weight mgmt options
- Exam demonstrated normal testicular volume, Tanner stage age appropriate
- BMI 42.3
- Review of current labs:

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Case 3: MM (NP in person)

- TT 176 [250-950]
- Estradiol 67 [<40]
- Hct 52.7
- LH normal
- FSH normal
- SHBG low normal
- Prl low normal

Component Latest Ref Rng	1/4/2025	6/7/2025	6/20/2025	6/28/2025
HCT 40.0 - 50.0 %	55.3 (H)	62.5 (HH)	60.0 (H)	56.0 (H)

Plan?

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"Functional Hypogonadism"

- Low testosterone concentration alone does not establish hypogonadism in men with obesity
- Obesity-related SHBG suppression is reason total testosterone can be misleading
  - NOT structural hypothalamic-pituitary-testicular disease
- Expert literature argues that many obese men with nonspecific symptoms, low total testosterone, normal gonadotropins represent functional or reversible state
- Reduced testosterone & SHBG concentrations accompanied by normal serum LH/FSH concentrations confirm eugonadal state, best descried as the pseudo-hypogonadism of obesity

Muir, et al. 2025 Approach to the Patient: Low Testosterone Concentrations in Men With Obesity, *J Clin Endocrinology & Metabolism*, Volume 110, Issue 9, September 2025, Pages e3125–e3130, https://doi.org/10.1210/clinem/dgaf137

"Functional Hypogonadism"

- Extreme obesity (BMI> 40) may have modest impact on hypothalamic-pituitary-testicular (HPT) axis function
  - Changes are responsive to weight loss
  - Do not constitute pathological hypogonadism
- Free T: insufficient quality controls required to form reference ranges
  - Flawed- unbound T equally accessible to sites of degradation as it is to target tissues

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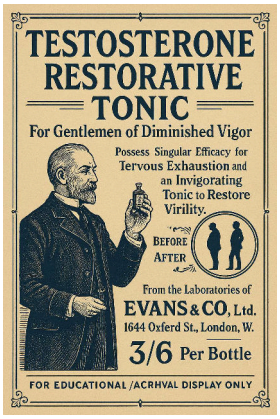
"Functional Hypogonadism"

- Mainly represented by overweight or obese men
- Changes in lifestyle, including physical exercise and dieting could improve symptomatology besides favoring a rise in T
- Available data show each 5 kilogram of weight reduction, whatever obtained result in one nmol/L of T level increase



Corona G, et al Treatment of functional hypogonadism besides pharmacological substitution. World J Mens Health 2020;38:256–270.

Management with hx of testosterone use

- Treatment with hCG, SERMs, and Aromatase inhibitors (AIs)
  - hCG stimulates intratesticular testosterone production by mimicking LH activity
  - SERMs (tamoxifen and clomiphene citrate) inhibit estrogen receptor-mediated suppression of HPG axis and induce LH/FSH secretion
  - AIs (anastrozole) block estrogenic feedback inhibition and facilitate gonadotropin release
- Combination therapy of hCG 3000 IU on alternate days with clomiphene citrate 25 to 50 mg daily

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Management Pearls

- Controversial whether successful treatment of OSA restores serum testosterone to normal
  - some studies demonstrating benefit but most showing no effect
- Rx commercially manufactured testosterone products should be prescribed rather than compounded testosterone, when possible (AUA guideline #28)
- Enclomiphene citrate (SERM)
  - Not FDA approved- Rx via compounding
  - short-acting isomer of clomiphene citrate
  - found to increase FSH and LH and preserve or increase sperm count
  - increases estradiol, with increases to T/E ratio
  - increased gonadotropin secretion, subsequent stimulation of T production
  - limited current literature for EC: small sample sizes, paucity of comparisons between EC & other SERMs

Conclusions

- Disparities in guideline awareness and implementation, which may reflect differences in specialty care, provider knowledge, or institutional practices
  - Community expectations?
- Ideal goal of TT is to focus on the recovery of serum testosterone levels
  - Safety studies
- AUA defines range of 450 -600 ng/dL (middle tertile of the reference range for most labs) accompanied by symptom/sign improvement/resolution
  - T cypionate/enanthate 50-200mg every 7-14 days