DPC SUMMIT

Male HRT: All the rage

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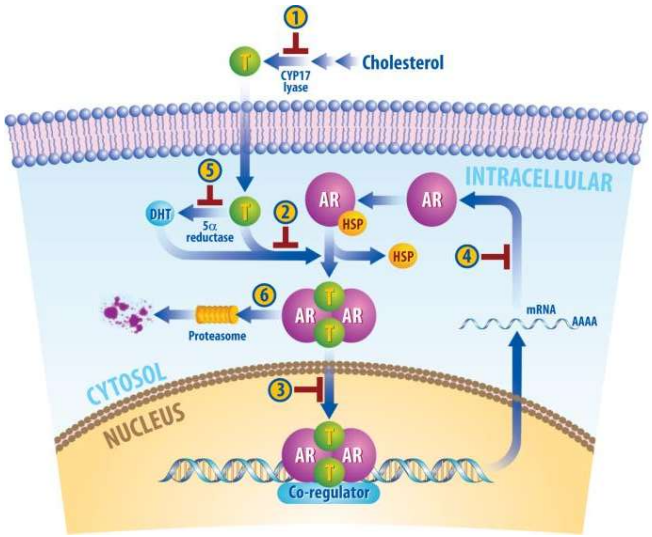
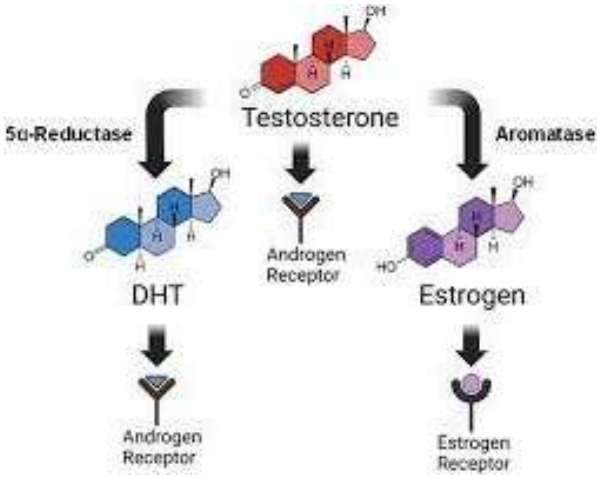
Learning Objectives

1. Identify strategies to optimize endogenous testosterone production and measure their effectiveness.
2. Demonstrate safe testosterone replacement strategies that minimize side effects and improve patient outcomes.
3. Evaluate exogenous molecules that can be used to enhance testosterone production and assess their benefits.

Testosterone Physiology



Testosterone Metabolites



Factors Affecting Testosterone Levels

- Sleep/stress – Hypothalamic production of GnRH
- Pituitary function – LH/FSH
- Testicular function – Ability to produce testosterone
- SHBG
- DHEA
- Androgen Receptor Sensitivity
  - Fewer CAG repeats = inc. Sensitivity to circulating androgens
  - More CAG repeats = dec. Sensitivity to circulating androgens
  - Studies show blacks have fewer repeats than non-Hispanic whites

Lifestyle Interventions

- Exercise – specifically strength training consistently
- Sleep - 7 hours or more of actual sleep per night
- Stress Reduction – Chronic stress, not acute stress, raises cortisol and reduces test production. Massage, acupuncture, meditation, exercise can help to mitigate.

Biomarkers

- **Total Testosterone**
- **Free Testosterone**
- **+/- SHBG**
- **Estradiol**
- LH/FSH
- DHEA

Diagnosis

Monitoring

- Bioavailable Testosterone (Free T + T-Albumin)

What about the cardiovascular risk?

Vigen et al. 2013 - A retrospective analysis of men who had undergone coronary angiography within the Veterans Administration health care system.

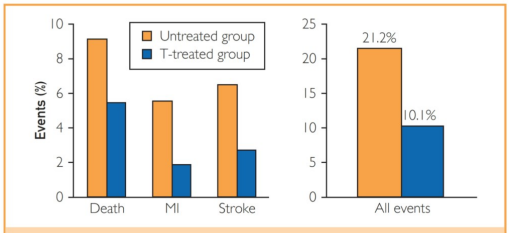


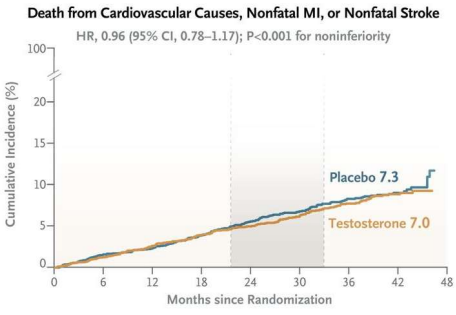
FIGURE. Actual percentage of individuals who experienced an adverse cardiovascular event in the testosterone (T)-treated and untreated groups in the study by Vigen et al.[1] The authors reported a higher rate of adverse events in the T-treated group using inverse stabilized propensity weighting in which an event was counted as more than 1 event in the T-treated group and less than 1 event in the untreated group. MI = myocardial infarction. From *J Sex Med*,[77] with permission. ©2014 International Society for Sexual Medicine.

10% of those in the study were actually women

Finkel et al. 2014

- Incidence of non-fatal MI in the 90-day period following initiation of TRT
- Compared this to the incidence of non-fatal MI in the SAME patients in the previous 12mo
- No control group, not randomized, selection bias
- Someone is very unlikely to get an Rx for T if they had an MI <12mo ago

TRAVERSE TRIAL



CONCLUSIONS

In middle-aged and older men with hypogonadism and preexisting cardiovascular disease or an increased cardiovascular risk, daily treatment with transdermal testosterone for approximately 2 years was noninferior to placebo with respect to the incidence of major adverse cardiac events.

- Avg inc. 148 ng/dL (interquartile range: 34 to 312 ng/dL) 60% dropout rate at 5 years
  - If it increased linearly with total T, Free T would have bumped 3-4 ng/dL
- Does not look at avg. risk population
- The conclusion was attainable using meta-analyses of the prior studies that were more reliable than Finkel and Vigen et al.

Side Effects

Potential Risk	Comments
Cardiovascular disease	Existing evidence suggests a neutral or possible beneficial effect
Lipid alterations	Most studies show no change with physiologic replacement doses
Erythrocytosis	Wide range of risk, depending on mode of administration: 3–18% with transdermal administration, up to 44% with injection; requires monitoring
Fluid retention	Rarely of clinical significance
Benign prostatic hyperplasia	Rarely of clinical significance
Prostate cancer	Controversial; unknown level of risk; requires long-term monitoring
Hepatotoxicity	Limited to oral agents, which are infrequently used in the United States
Sleep apnea	Infrequent
Gynecomastia	Rare, usually reversible
Skin reactions	High incidence with patch (up to 66%), low incidence with gel (5%), rare with injections
Acne or oily skin	Infrequent
Testicular atrophy or infertility	Common, especially in young men; usually reversible with cessation of treatment

Contraindications

- MI within the past year
  - Stimulates EPO in the kidney → inc. risk of clots → MI is a clot
- Men with breast CA that is ER+ or AR+
  - No actual trials done in this population
- Men with prostate CA(though this is evolving)
  - Many urologists are now Rx'ing TRT to men with low grade (Gleason 3+3 and lower) prostate CA
  - Most studies validate we need to r/o metatstatic prostate CA before starting TRT

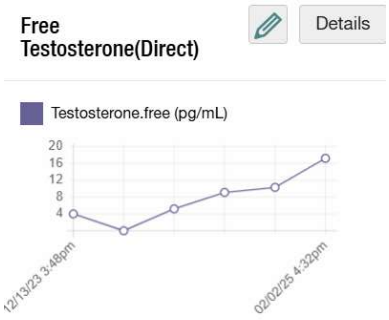
Increasing Endogenous Production

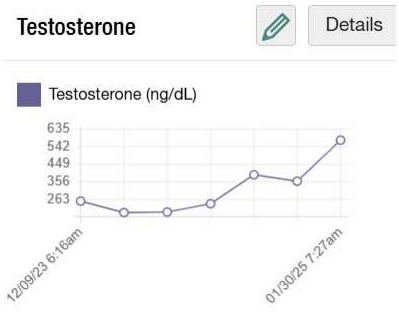
- Clomiphene or enclomiphene
  - Estrogen R antagonist – tricks the brain into thinking you have no estrogen around
  - 50mg qOD or 25mg qD
  - Preserves testicular function
  - Common fertility treatment for men and women
  - Made popular when hCG compounding was shut down
  - Raises lipids significantly and decreases libido
  - 60% of men see inc. in testosterone
- hCG
  - LH mimetic
  - Preserves testicular fx and fertility
  - Common dose is 1mL 2x/week after reconstituting to 10,000u
  - Must be refrigerated
  - $225 per vial of FDA-approved Pregnyl
  - Order from compounding pharmacy
  - Commonly taken with testosterone in those looking to preserve testicular volume/fx
- Anastrazole
  - Aromatase inhibitor

Case studies – hCG Dose Escalation

Fatigue and libido issues in a 46yoM

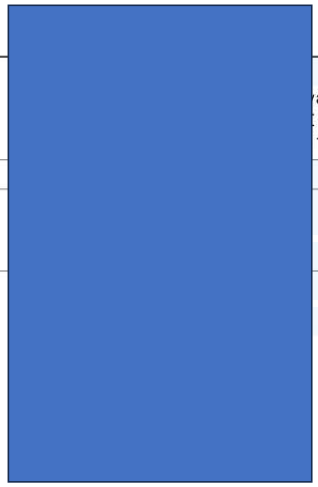
Went from hCG 0.75mL BiWeek to 1mL, then 1.5mL (750u → 1000u → 1500u)





Case Study – hCG in TBI

38yoM with recent TBI



Test	Previous Result and Date		Units	Reference Interval
Testosterone [01]	347	05/06/2025	ng/dL	264-916
	val is based on a population of <30) between 19 and 39 years old. 102;1161-1173. PMID: 28324103.			
Free Testosterone(Direct) [02]	11.4	05/06/2025	pg/mL	8.7-25.1
Sex Horm Binding Glob, Serum [01]	26.4	05/06/2025	nmol/L	16.5-55.9
▼ **LH** [01]	3.8	05/06/2025	mIU/mL	1.7-8.6
▼ **FSH** [01]	4.6	05/06/2025	mIU/mL	1.5-12.4
Estradiol [01]	**<5.0**	05/06/2025	pg/mL	7.6-42.6

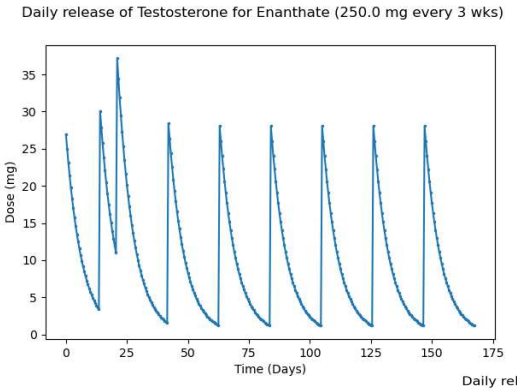
FDA approved forms of Testosterone

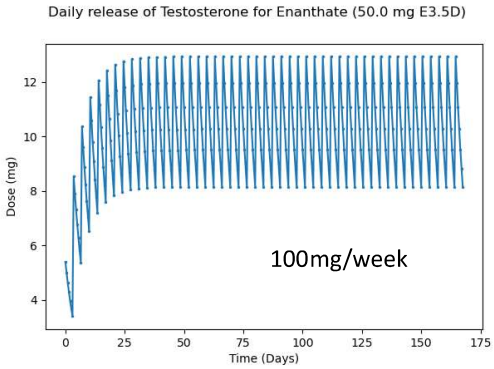
Generic Name	Brand Name(s)	Form
Testosterone	**Gel:** Androgel, Fortesta, Testim, Vogelxo **Nasal Gel:** Natesto **Patch:** Androderm **Pellet:** Testopel	Gel, Nasal gel, patch, pellets
Testosterone enanthate	Xyosted	Subcutaneous Injection
Testosterone cypionate	Depo-Testosterone	Intramuscular injection
Testosterone undecanoate	**Injection:** Aveed **Pill:** Jatenzo, Kyzatex, Tlando	Intramuscular injection Pill

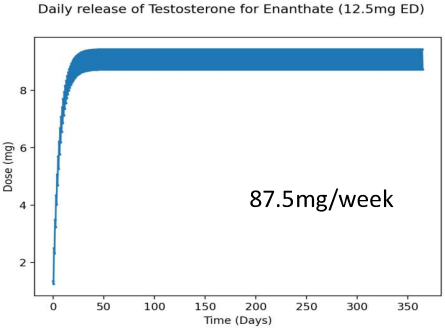
How Physiology Informs Treatment

- AACE recommends 100-200mg q2 weeks
- This results in huge peaks and very low troughs
- A large portion is wasted in the conversion to DHT & E2

- At a minimum we perform biweekly dosing, typically starting around 50mg per injection, which puts us at 0.25mL for the 200mg/mL Testosterone Cypionate or Enanthate formulations.







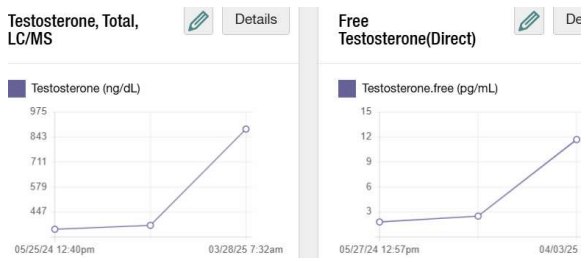
TRT – SubQ injection

- Rx for Test Cypionate or Enanthate 200mg/mL MDV sent to local pharmacy
- 50mg (0.25mL) injection BiWeek (Ex: Thursday & Sunday)
- Supplies:
  - 1 box of 1cc luer lock syringes
  - 1 box of 18g needles (length doesn't matter)
  - 1 box of 25g x 5/8" needles
  - Pt can purchase the alcohol swabs and sharps container
- Downsides: not good if needle-phobic, site infxn, pharmacy issues

TRT SubQ Injection – Case Study

70yoM w/ IDDM, fatigue, low libido, depression

Test	Current Result and Flag	Previous Result and Date	Units	Reference Interval
Testosterone[01]	885	376.2	ng/dL	264-916
	Adult male reference interval is based on a population of healthy nonobese males (BMI <30) between 19 and 39 years old. Travison, et.al. JCEM 2017,102;1161-1173. PMID: 28324103.			
Free Testosterone(Direct)[02]	11.7	**2.5** 08/29/2024	pg/mL	6.6-18.1
Sex Horm Binding Glob, Serum[01]	40.4		nmol/L	19.3-76.4
Estradiol[01]	26.5	18.5 05/20/2024	pg/mL	7.6-42.6



50mg Testosterone Enanthate BIweek

TRT - Topical

- Gel or Cream
  - Drawbacks: Penetrance is variable, can vary throughout the day. Transference issues. Daily application. Has an 80% attrition rate. Varies based on how clean the skin is, where it's applied, if it's been exfoliated or not.
  - Comes in 1%, 1.62%, 2% gel and 2% solution. 1% gel is 12.5mg/pump. Starting dose is 50mg (4 pumps)
- Patch – Androderm
- Nasal – Natesto
  - 11mg 3x/day for 33mg/day
  - Does not suppress spermatogenesis as much
  - "Gooey and gel-like." Men don't like it.
  - Fastest onset – some people take it before sex, or before working out

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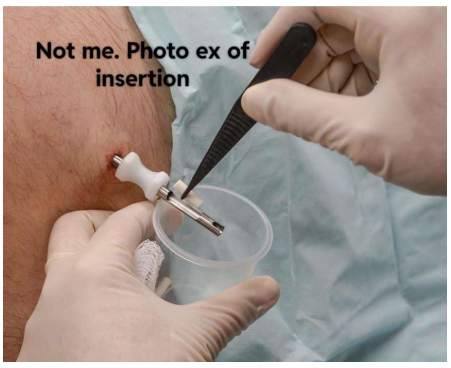
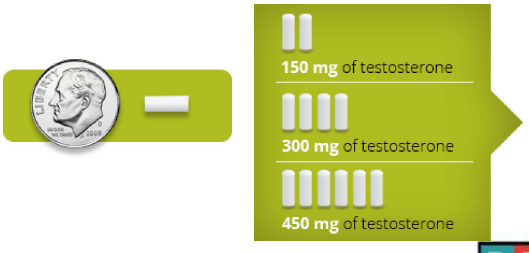
TRT – Pellet

- Can get pellets compounded or from TestoPel
- Dosing varies: q3mo-q6mo
- 1000mg-1800mg dose
- Highly individualistic in how it is metabolized
- Very stable, but you do end up with a peak at some point





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TRT - Pellet

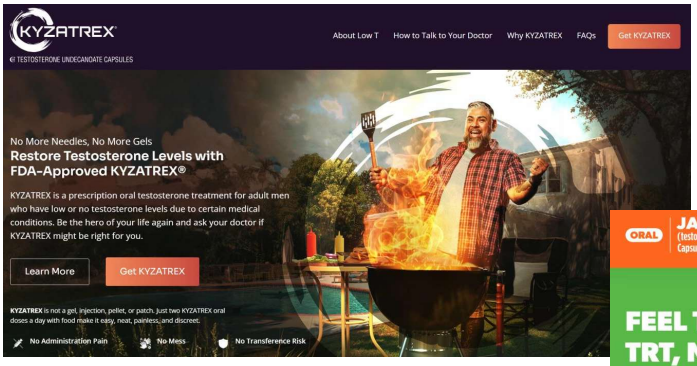
- Downsides: Seroma formation, expulsions, infection at injection site
- Notify physician if there is any thickening or hardening of the skin at the implant site, inflammation, bleeding, bruising, wound drainage, pain, itching, or pellets expulsing.
- Expulsions have increased post-COVID (still <10%)

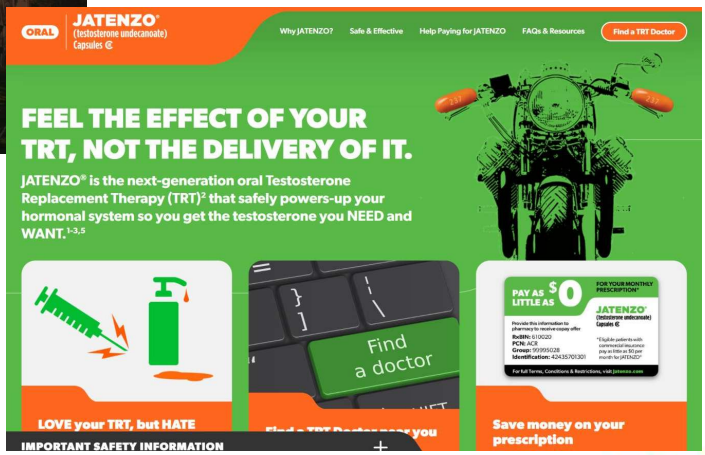
TRT - oral

Testosterone Undecanoate

- All are absorbed via lymphatics.
- First hit the market in 2019 as oral testosterone traditionally caused hepatotoxicity.
- Must give with food, doesn't have to be a fatty meal.
- Best to give at Breakfast & Lunch.

- JATENZO – 158, 198, 237mg tabs are taken BID (two times a day)
  - Primary hypogonadism - recommend 237mg starting dose.
- TLANDO - 225 mg taken BID (Two 112.5mg caps)
  - No titration
- KYZATREX – 100mg qAM → 400mg BID
  - Comes in 100mg, 150mg, & 200mg caps





Monitoring

- After 6 weeks, check:
  - Total/Free T
  - E2
  - PSA, CBC
  - Lipids often improve
  - Can check DHT, very pricey
- Check levels after 6 weeks and adjust accordingly, always using free T as the ultimate biomarker

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Avoiding Erythrocytosis and other SEs

- This study shows the worst thing you can do is give 200 mg IM every 2 weeks
  - That doesn't make a lot of sense since the drug lasts about 10 days, so there's no medication on board for about 4 days
  - But the spiking level of testosterone results in a higher rate of erythrocytosis
  - If you drop the dose down to 50 mg twice a week, the rate of erythrocytosis goes down. It's a more physiologic dose
  - More events around Hb of 18 or 19
- Increased E2 causes fluid retention.
  - Too much T (supratherapeutic)
  - Increased Adiposity
  - Option to use aromatase inh. like anastrazole or letrozole
  - Decrease T dose and increase frequency of injection

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Cultural Application

Drugs people like
- Testosterone
- Adderall
- GLP-1s

Drugs people don't like
- HTN meds
- Statins
- SSRIs
- Antibiotics

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Live Content Slide

When playing as a slideshow, this slide will display live content

Social Q&A for Male HRT: All the Rage