

Testosterone Replacement Therapy: The Good, The Bad, and the Ragey.

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Disclosures

- None of the authors have any financial disclosures, investment in, or personal relationship with any of the substances or products described herein neither currently nor in any previous capacity. There will be no off-label endorsement of any pharmaceutical product.
- (Including, Dr. Carrol who reminded me that while excessive testosterone replacement can be associated with aggressive irritability sometimes people are just "ornery.")



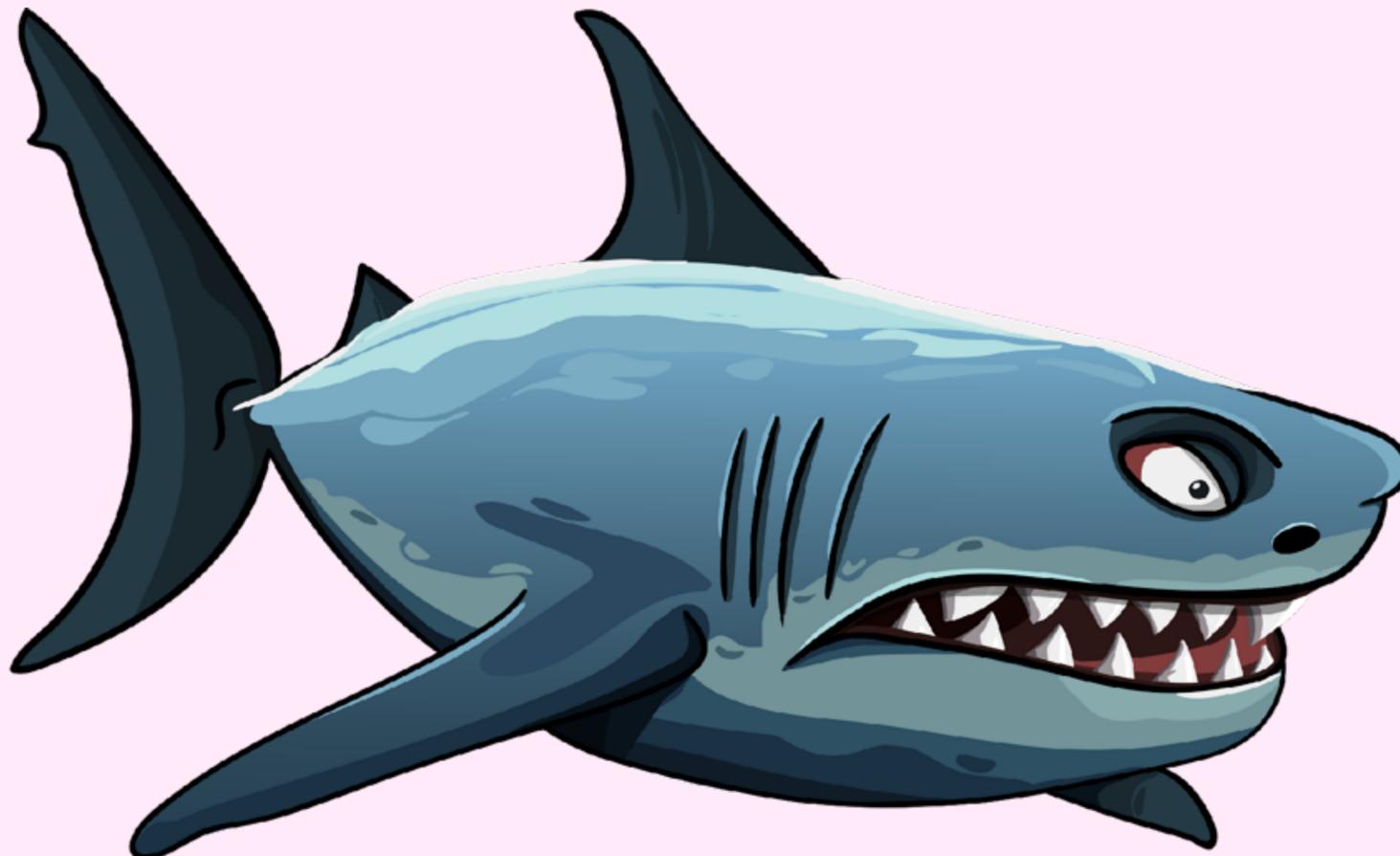
Veteran Presented with "Irritability" on Testosterone Replacement Therapy

- Testosterone level : 1500!



Some Levels For Reference

- Human (Average) ~300 – 600 ng/dL
- Raccoon ~1,316 ng/dL
- Asian Elephant 1,900 – 4,000 ng/dL
- Bull (Bovine)~2,300 – 3,600 ng/dL
- Body Builder Rich Piana around 3000.
- Bull Shark **35,800 ng/dL**



Irritable Veteran

...My role.

- Me: "You remember why I told you that I wouldn't be the one to write for your testosterone replacement therapy?"
- Patient: "Yeah...you said that it was your job to tell me when I was becoming an a-hole."
- Me: "Exactly...you've arrived."

Objectives: You will...

- Know when to diagnose hypogonadism (and when not to)
- Navigate criteria without losing your will to live
- Avoid “tired” into “testosterone”
- Avoid turning every fatigued 63-year-old into a Marvel character.



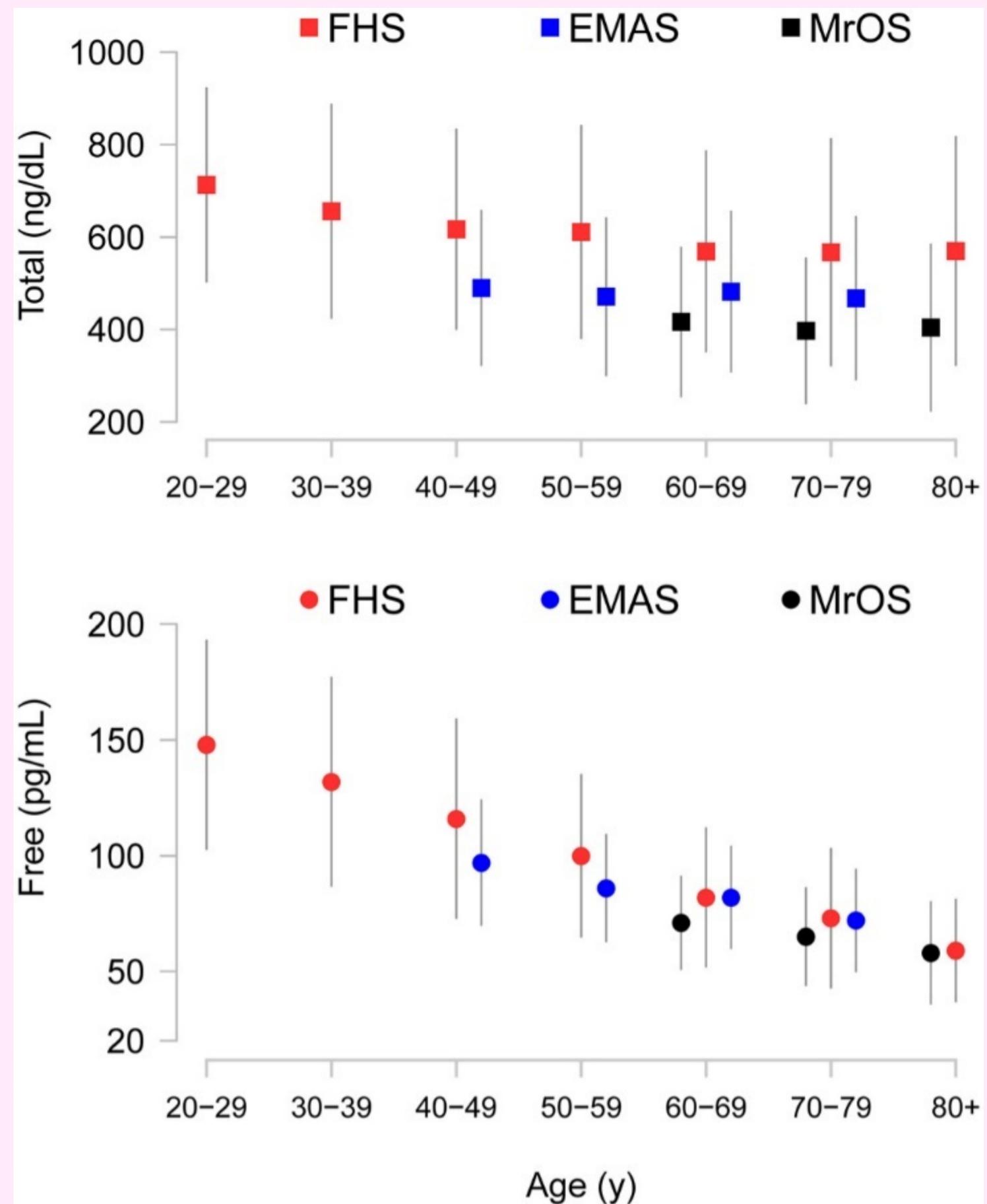
OUTLINE

- Miss Grace will discuss the natural course and variation of testosterone in biologic males from a variety of environmental and health factors.
- I will discuss diagnosis and role of mental health professional in hypogonadal males.
- And show you why the mental health professional is probably the most important factor in determining appropriateness of testosterone therapy.



Times are a'changing, and your testosterone is too

- Gradual decline with a peak in their 20s and 30s
- (Bhasin et al., 2022)



Significant Daily Variation

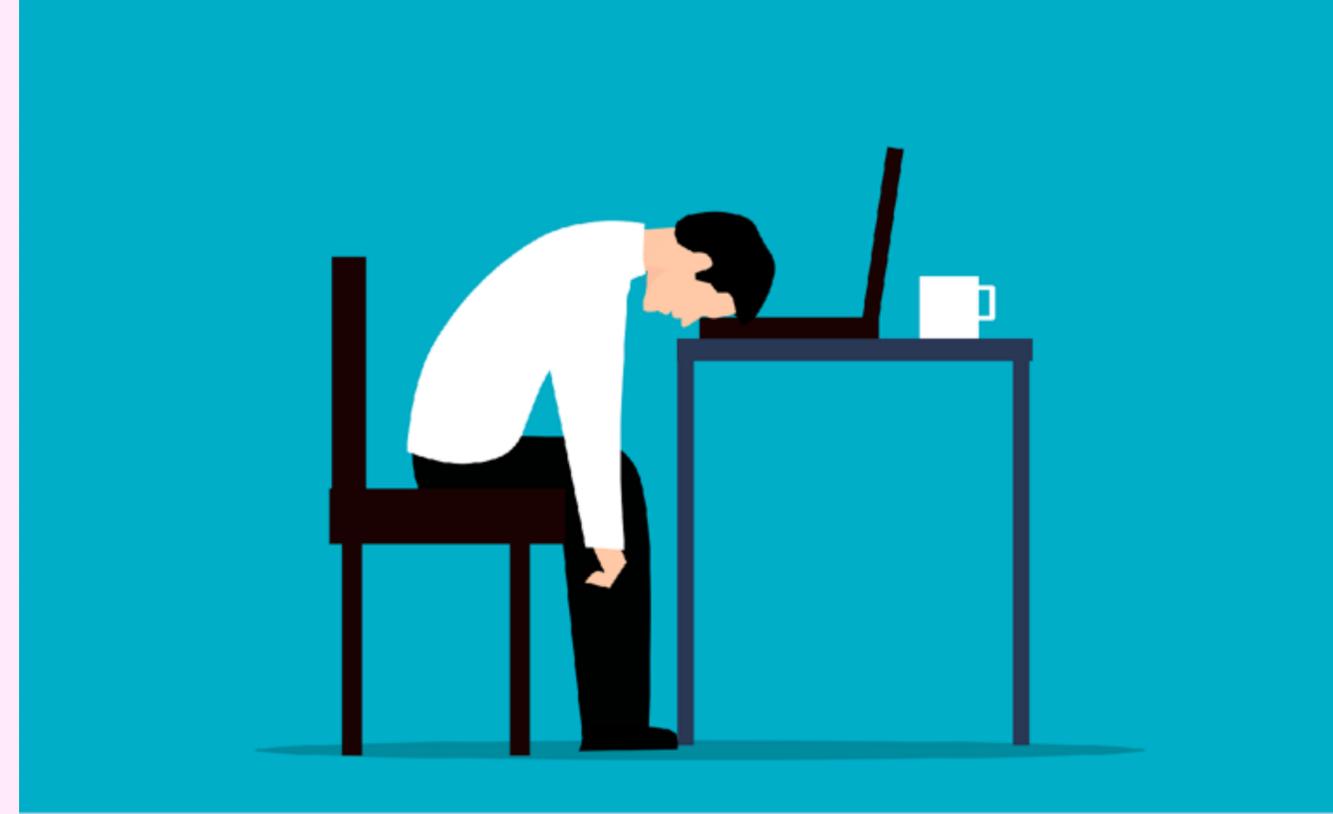
Diurnal Variation (Brambilla et al., 2009)



- 66 men 30-80 yr of age.
- Randomly selected from the Boston Area Community Health Survey who completed at least five visits.
- Blood samples were collected at six separate visits, three morning visits 1-3 d apart and three afternoon visits 1-3 d apart.

Significant Daily Variation

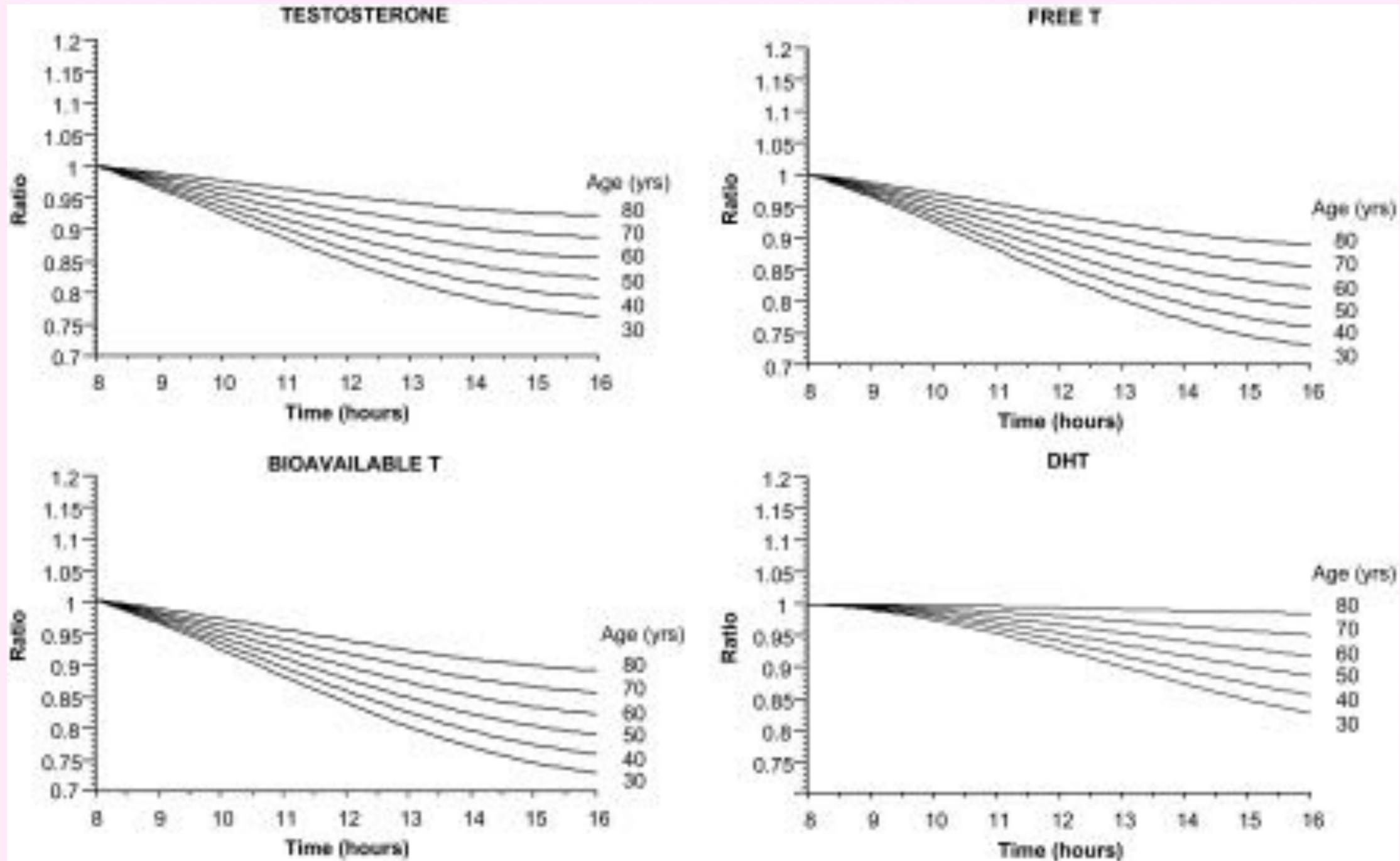
Diurnal Variation(Brambilla et al., 2009)



- Morning peak: Testosterone peaks in the early morning (around 8 a.m.) This is why we test in a.m.
- Afternoon nadir: Levels decline by about **20–25%** by late afternoon 16.
- Older men: The diurnal decline is smaller, about 10%

Significant Daily Variation

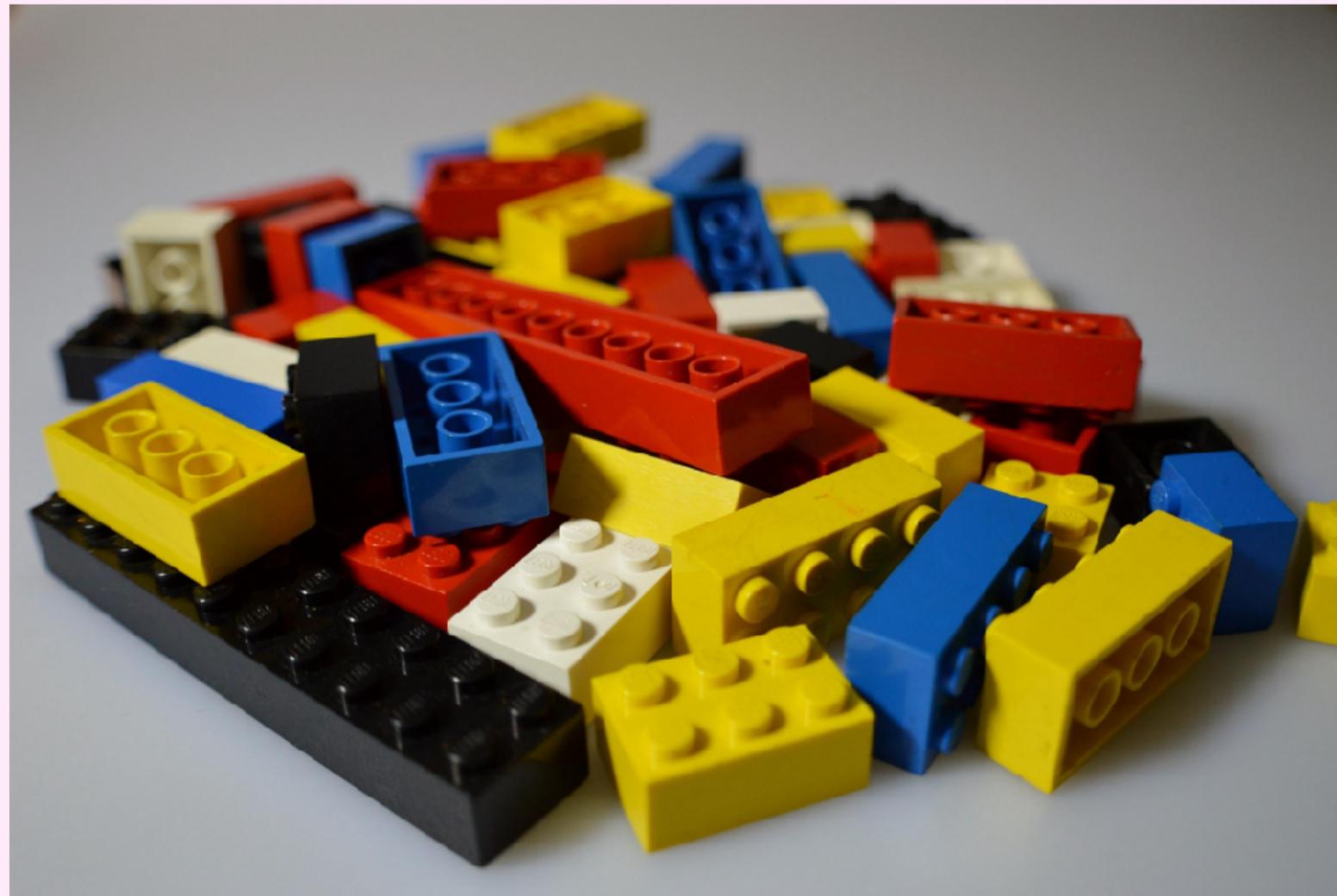
Diurnal Variation (Bhasin et al., 2022)



Other Testosterone Influencers

There's more?...

- We've talked about aging decline
- Talked about daily variation.
- Let's talk about some of the big outside influencers on testosterone levels.



How Much Can Stress Effect Testosterone?

- (Choi et al., 2012) Forty-six healthy male medical students in South Korea were "recruited" for this study. Checked their pain threshold and hormone levels on "resting" days and days they were given "tests" (venipuncture, intubation, local anesthesia)
- Participants sat in a chair, asked to rate their anxiety before pain stimulation applied. Pain was induced experimentally using an electrical stimulation...and increased to "intolerable" levels or 20ma (for reference you can feel 1 ma, and 5 hurts).



How Much Can Stress Effect Testosterone?

Resting vs "Stressed"

- Cortisol: 2.6 / 4.0
- Pain ratings: 25 /40
- Anxiety ratings: 30 /50
- Testosterone: 78.1 / 66.2 (15%)



Other Culprits of Low Testosterone

Obesity (Fernandez et al., 2019)



- Large-scale epidemiological studies, and small population-based surveys suggest prevalence rates as high as 45.0–57.5%
- The resultant increase in oestrogen, leptin, insulin and inflammatory cytokines result in hypothalamo–pituitary–testicular (HPT) axis suppression
- There can be a bidirectional relationship between obesity and hypogonadism

Other Culprits of Low Testosterone

Alcohol and Opioids



- Alcohol lowers testosterone via direct Leydig cell toxicity, chronic use causing 10–20% reductions; some report larger drops with heavy, sustained intake. (Wittert et al., 2022)
- Alcohol lowers testosterone production in men with liver disease AND healthy individuals (Gordon et al., 1976, Southren et al., 1973)
- Opioids inhibit hypothalamic GnRH secretion, disrupting its normal pulsatility and leading to decreased LH levels and therefore testosterone levels decrease (Duca et al., 2019)
 - All opioids tested led to a decrease in testosterone, regardless of type or function (Bawor et al., 2015)

Other Culprits of Low Testosterone

Sleep Disturbance



- Many service members reported sleeping fewer than the recommended 7 h/night: 34.9%, 67.2%, and 77.2% of respondents from New Zealand, Canada, and the United States, respective (Alger et al., 2024)
- One military cohort reports acute 24-hour sleep deprivation lowers testosterone by about 25–30% (Mantua et al., 2020)
- Chronic sleep debt is associated with lower morning, afternoon, and 24-hour testosterone in aging men (Liu et al., 2022)
- Poor sleep habits, as identified by SWSD, may contribute to the more severe hypogonadal symptoms seen in nonstandard shift workers . (Balasubramanian et al., 2020)

How Big and Scary is the Problem?

- Now that we know testosterone can vary dramatically across a lifespan, a day, and life events...how common is low testosterone and how big of a problem is it?



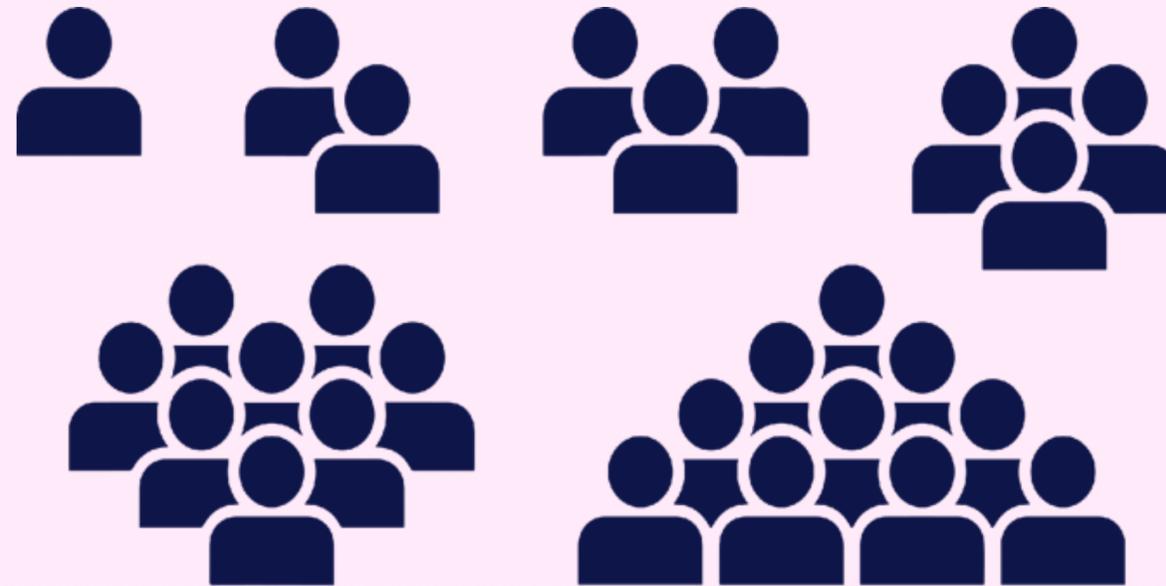
It's BIG...and SCARY



How big of a problem is it?

Definitely a big one.

- Low testosterone (hypogonadism) affects roughly 20% of men by age 50 and up to 50% by age 80 (Harmen et al., 2001)
- (**This study couldn't be more pertinent. It is actually a study of 203 veterans performed in Gainesville VA) (Conover et al., 2017)
 - Even larger possible effect in older male veterans!
 - In the cohort of older male Veterans measured, low total T was present in 34% of men, while low BioT was present in 72% of men.



Should I be scared?

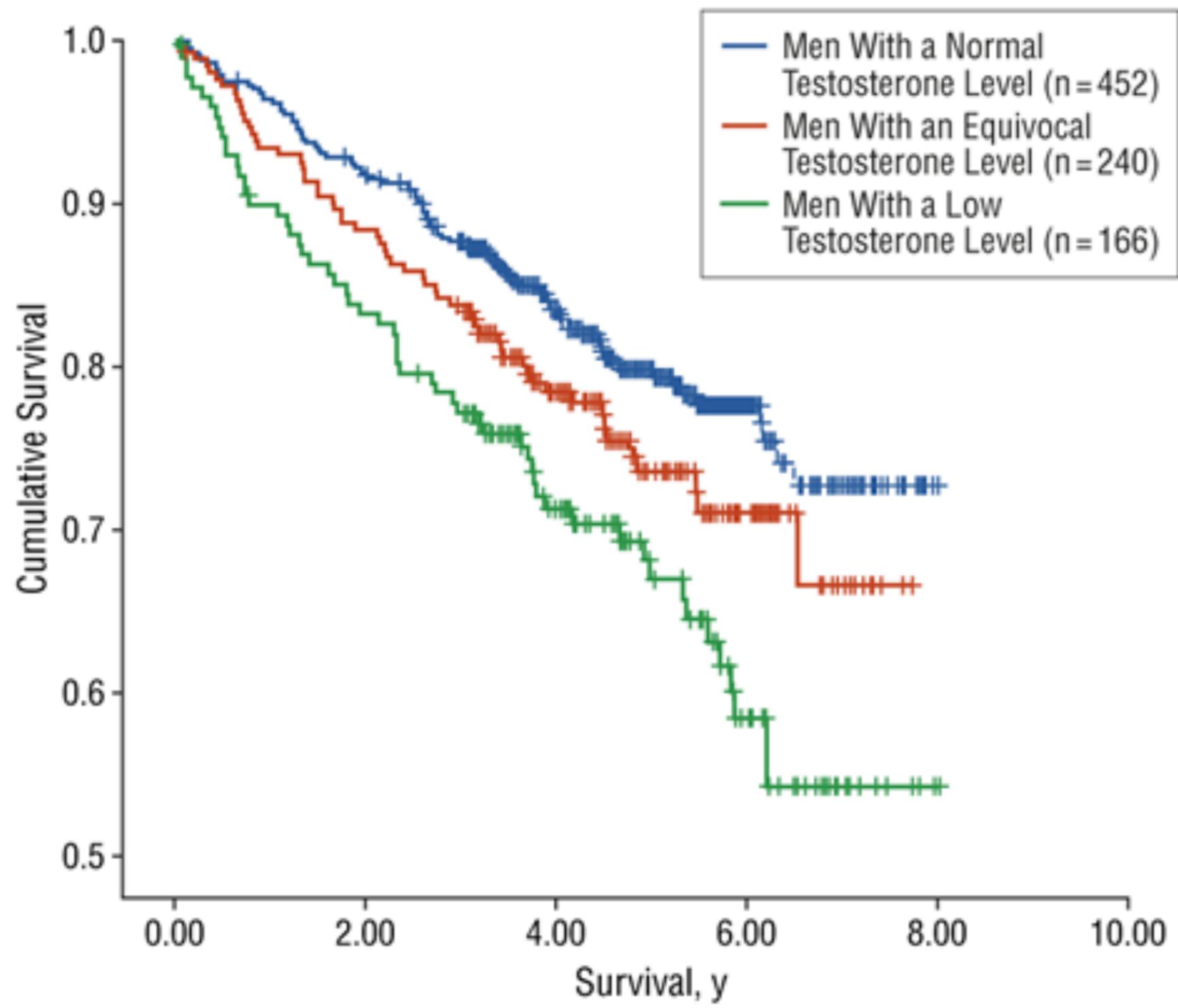
Yes. (Shores et al., 2006)



- (This was another VA study of 858 men in the mid 90's using a clinical database to identify men older than 40 years with repeated testosterone levels without diagnosed prostate cancer. It also had some scary findings.)

Now...for the scary part...mortality data.

- Normal testosterone 20.1%
- Equivocal testosterone levels and 24.6%
- Low testosterone: 34.9%
- Adjusting for age, medical morbidity, and other clinical covariates, low testosterone levels continued to be associated with increased mortality (**hazard ratio, 1.88**; 95% CI, 1.34-2.63; $P < .001$). In a sensitivity analysis, men who died within the first year (50 [5.8%]) were excluded to minimize the effect of acute illness, and low testosterone levels continued to be associated with elevated mortality.
- (Magnitude: The risk is 1.88 times, or nearly double, that of the comparison group. Accounting for medical comorbidities and not counting people who died in first year.)



Million Dollar Question

Does Treatment Make a Difference? Maybe. (Shores et al., 2012)



- 398 treated men out of 1021 male veterans
- Treated men had about half the mortality.
- The mortality in testosterone-treated men was 10.3% compared with 20.7% in untreated men ($P < 0.0001$) with a mortality rate of 3.4 deaths per 100 person-years for testosterone-treated men and 5.7 deaths per 100 person-years in men not treated with testosterone.
- Not randomized but did multivariable adjustment including age, body mass index, testosterone level, medical morbidity, diabetes, and coronary heart disease, testosterone treatment was associated with decreased risk of death (hazard ratio 0.61; 95% confidence interval 0.42–0.88; $P = 0.008$).
- No significant effect modification was found by age, diabetes, or coronary heart disease. (Shores et al., 2012)

Million Dollar Question

Does Treatment Make a Difference...Maybe. (Fallara et al., 2022)



- Meta analysis reviewing 10 studies.
- 179,631 hypogonadal men.
- Hypogonadal men treated with TTh were found to be at lower mortality risk from all causes relative to the control (observation or placebo) arm (HR: 0.70; 95% confidence Interval [CI]: 0.54-0.90; $P < .01$), whilst
- any unfavorable effect of TTh in hypogonadal men in terms of cardiovascular events compared to untreated/observed hypogonadal men was found (HR: 0.98; 95% CI 0.73-1.33; $P = .89$).

Take Home Point from (Shores et al., 2006)



- Hypogonadal men receiving testosterone **clearly** have a better prognosis.
- Selection Bias Probably Plays Some Role
 - Healthier or trying to get there.
 - More aggressively pursuing life (I want to work out, have sex, play rugby, etc.)

Can Quality of life be improved?

Sort of.



- In symptomatic men 65 years of age or older, raising testosterone concentrations through treatment for 1 year from moderately low to the mid-normal range for men 19 to 40 years of age had a moderate benefit with respect to sexual function and some benefit with respect to mood and depressive symptoms (Snyder et al., 2016) and these findings have been agreed with by other studies (Bhasin et al., 2018)
 - The testosterone trials revealed improved sexual function, Hgb and corrects anemia, and slightly improved walking distance, vitality, mood and depressive symptoms and bone density and strength, but did not see improve cognitive function (Matsumoto 2019)
- A meta-analysis was completed in order to develop a guideline to provide clinical recommendations based on the current evidence of the benefits and harms of testosterone treatment in adult men with age-related low testosterone. (Qaseem et al., 2020)

The Testosterone Consult

Chief Complaint: "Hey doc...."

- "I don't have any energy."
- "I just don't have any...you know...desire."
- "My buddy is on it and doing amazing!"
- "I saw a commercial."
- (These are pretty vague complaints that could have a lot medical and non-medical sources.)

What Actually Counts

- Diagnosis requires:
- Symptoms consistent with hypogonadism
- TWO separate morning total testosterone levels under 300 ng/dL
- (our VA 240 over 50 / 221 under 50)
- Calculated free testosterone of about 6–9 ng/dL (3.2/2.6)
- Low levels on both both draws.
- **Exclusion of "REVERSIBLE" CAUSES.**
- One afternoon testosterone level drawn at 3:45 PM after a night shift does not count. That's just circadian rhythm doing its job.



What Actually Counts

- Monitoring requires:
- **Before starting:**
 - Baseline PSA, Hematocrit, Confirmed low T "Secondary"
- **Follow-up:**
 - Testosterone level
 - Hematocrit
 - PSA

What's the biggest predictors of testosterone therapy in VA system?

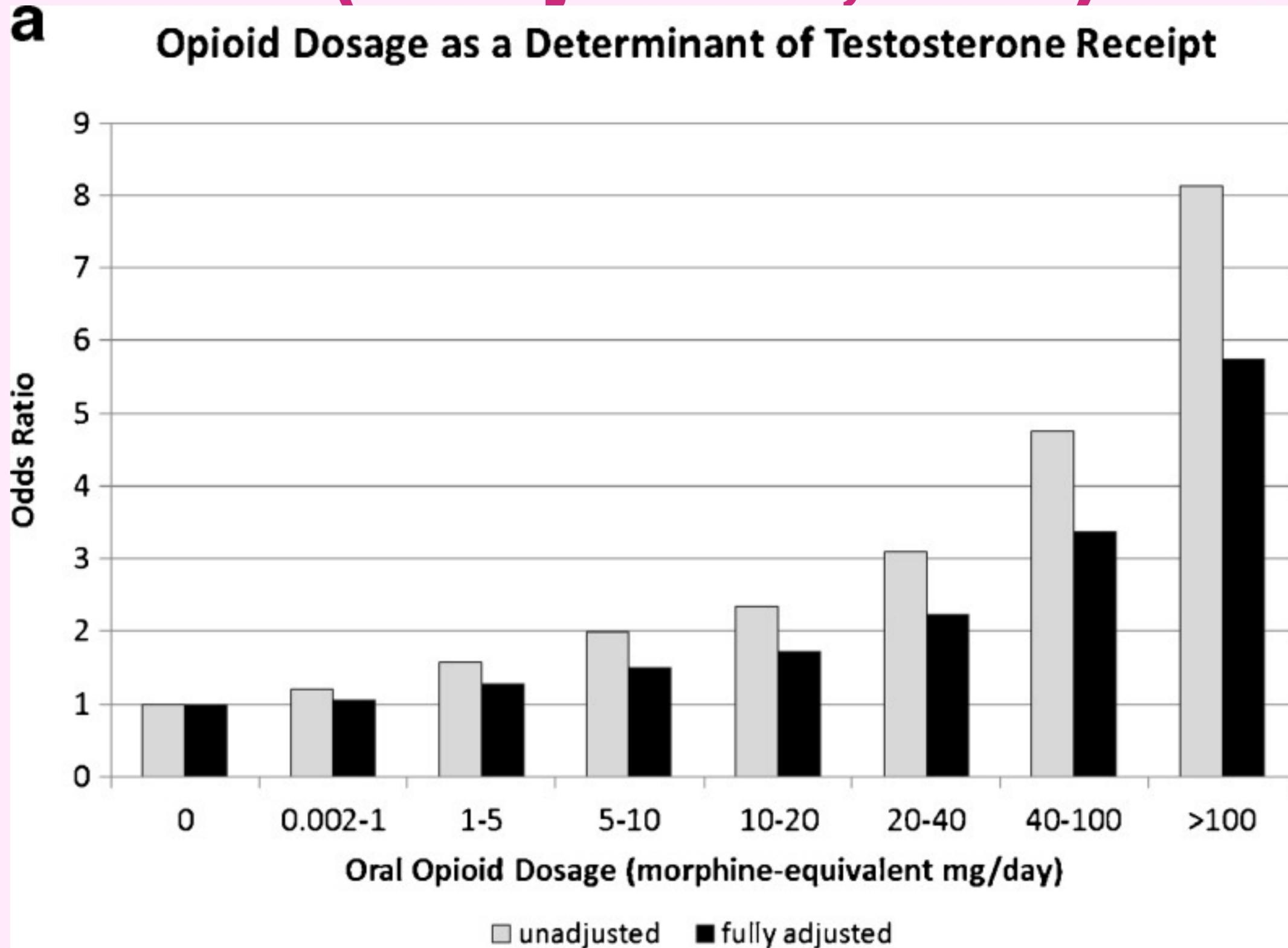


Let's Be Clear(Jasuja et al., 2016)

What is testosterone most prescribed for?

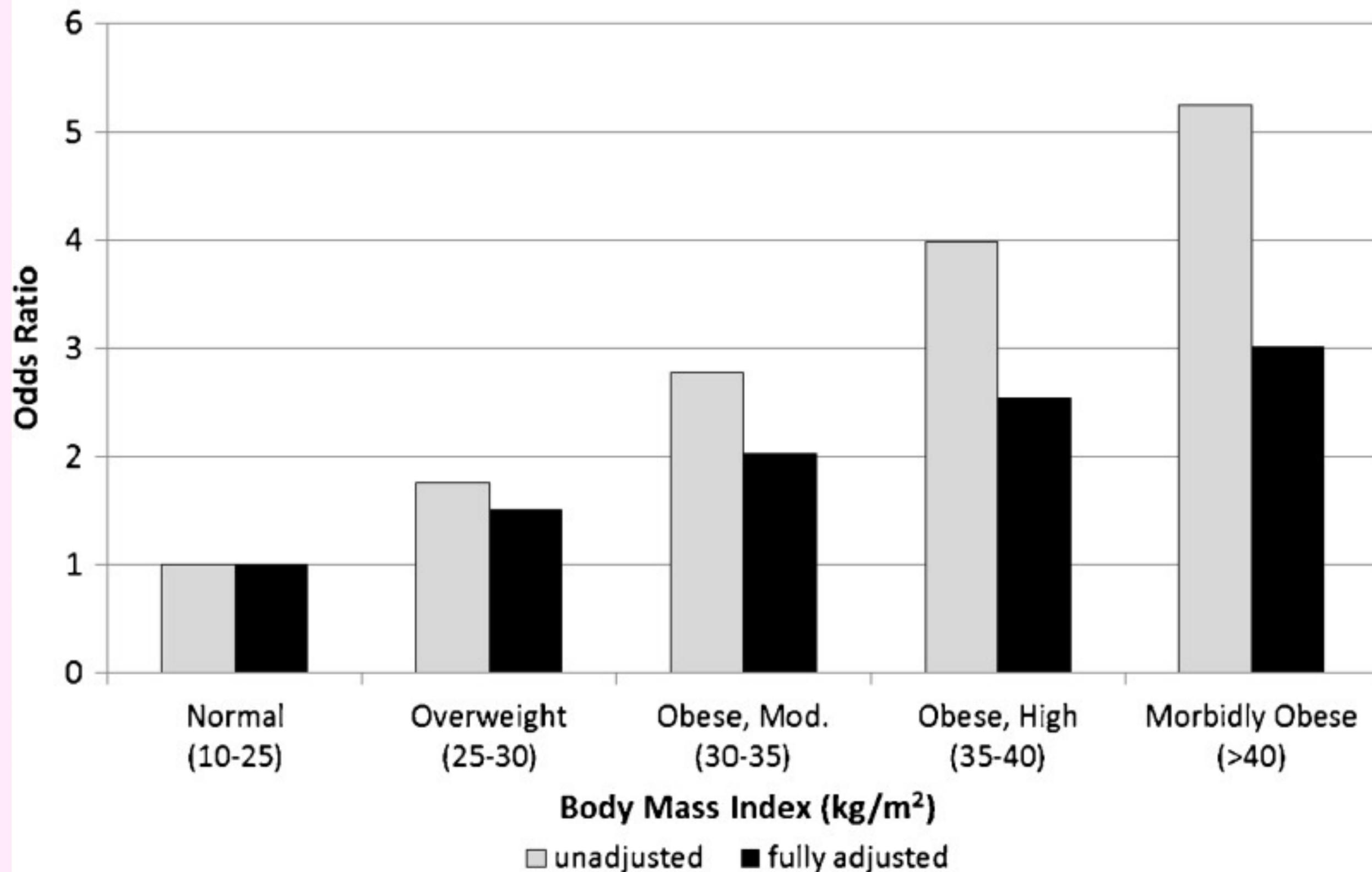
- National cohort of male patients, who had received at least one outpatient prescription within the Veterans Affairs (VA) system during Fiscal Year 2008–Fiscal Year 2012.
- 682,915 non-HIV male patients, of whom 132,764 had received testosterone and a random 10% sample, 550,151, had not
- **WHAT WERE HIGHEST CORRELATION WITH TESTOSTERONE THERAPY?**

Let's Be Clear (Jasuja et al., 2016)



b

Body Mass Index as a Determinant of Testosterone Receipt



Let's Be Clear(Jasuja et al., 2016)

Most testosterone prescribing not for "classic" hypgonadism.

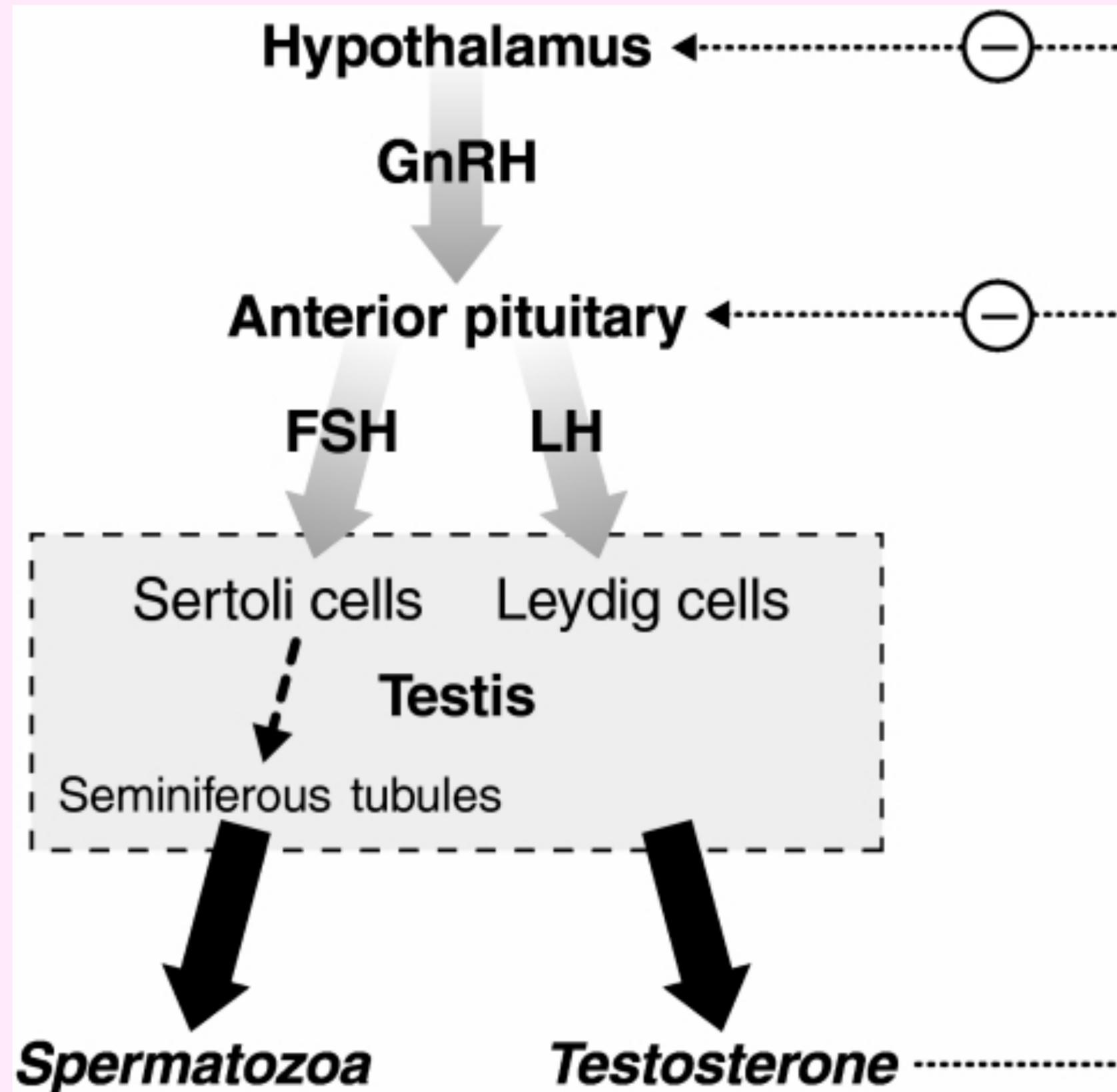
- Certain demographics (age 40–54, White race), comorbid conditions (sleep apnea, depression, and diabetes), and medications (antidepressants, systemic corticosteroids) also predicted a higher likelihood of testosterone receipt, all with an adjusted odds ratio less than 2 ($p < 0.001$).

Let's Be Clear(Jasuja et al., 2016)

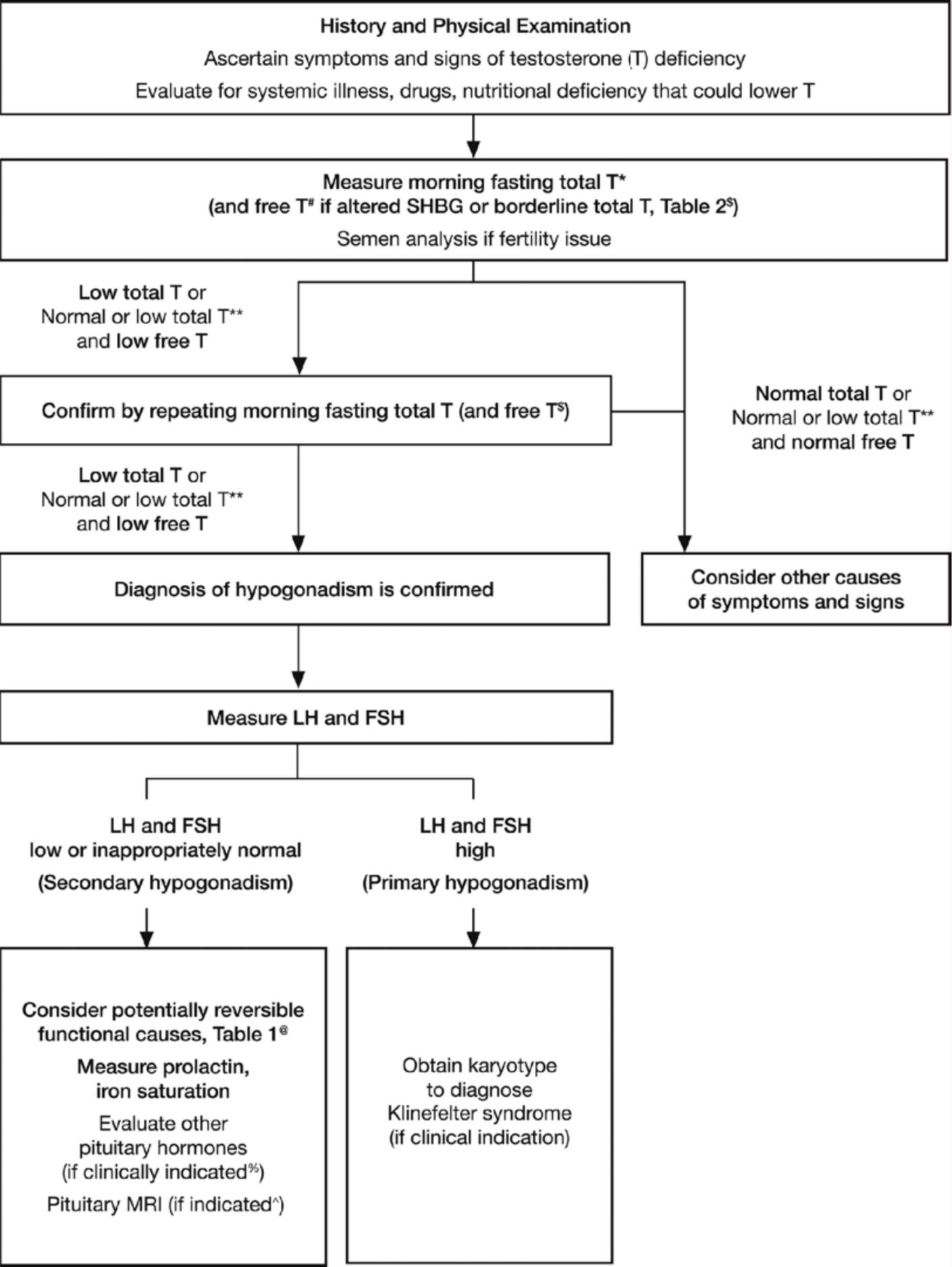
Most testosterone prescribing not for "classic" hypgonadism.

- In the VA, **93.7%** of men receiving testosterone **did not** have a diagnosed condition of the testes, pituitary, or hypothalamus.
- Mumps orchitis, Neoplasm of testis, Klinefelter's syndrome,Orchiectomy
- Undescended testis (cryptorchidism) or retractile, Gonadal dysgenesis
- Any pituitary condition, Neoplasms of pituitary
- Hyperprolactinemia, Hypophysectomy,Pituitary surgery

(Dandora et al., 2010)



Primary Hypogonadism	Secondary Hypogonadism
ORGANIC	
KS	Hypothalamic/pituitary tumor
Cryptorchidism, myotonic dystrophy, anorchia	Iron overload syndromes
Some types of cancer chemotherapy, testicular irradiation/damage, orchidectomy	Infiltrative/destructive disease of hypothalamus/pituitary
Orchitis	Idiopathic hypogonadotropic hypogonadism
Testicular trauma, torsion	
Advanced age	
FUNCTIONAL	
Medications (androgen synthesis inhibitors)	Hyperprolactinemia
End-stage renal disease ^a	Opioids, anabolic steroid use, glucocorticoids
	Alcohol and marijuana abuse^a
	Systemic illness^a
	Nutritional deficiency/excessive exercise
	Severe obesity, some sleep disorders
	Organ failure (liver, heart, and lung) ^a
	Comorbid illness associated with aging ^a



TAKE HOME LESSON

- MOST TESTOSTERONE PRESCRIBED IS CORRELATED WITH REVERSIBLE CAUSES OF DEFICIENCY
- WHEN IS A PATIENT'S REVERSIBLE OBESITY, DIABETES, ALCOHOL, SLEEP APNEA IRREVERSIBLE?

LH FSH AREN'T ALWAYS HIGH

(Dandora et al., 2010)

- Low testosterone can be caused by primary and secondary hypogonadism (also called **mixed hypogonadism**) that reflects defects in the hypothalamus and/or the pituitary as well as the testes.
- (sickle-cell disease, thalassemia, alcoholism, glucocorticoid treatment, and in older men).
- In general, however, the term mixed hypogonadism is not used in clinical practice in the US and is considered part of **secondary hypogonadism.**"

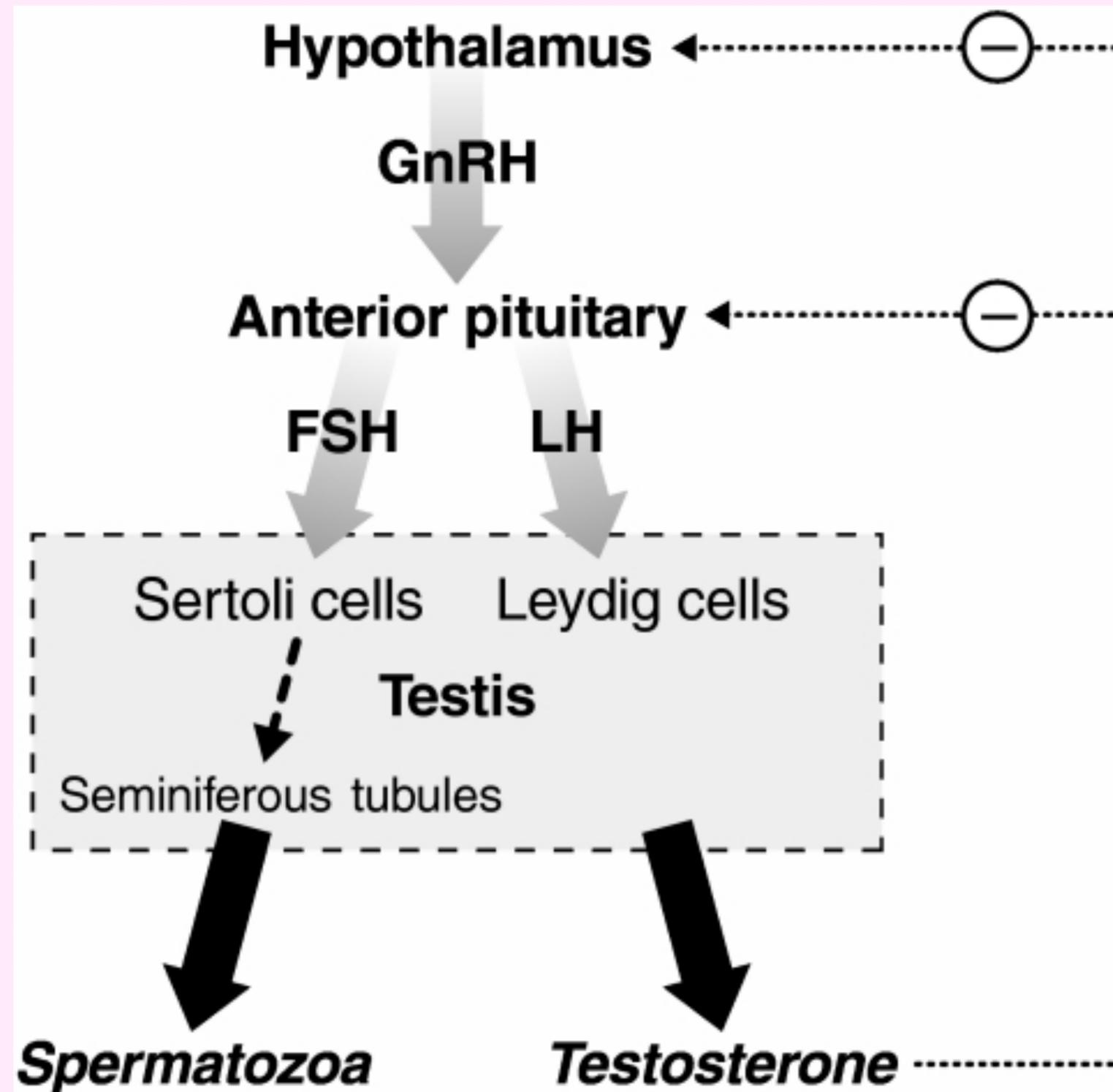
LH FSH AREN'T ALWAYS HIGH

(Tajar et al., 2010)

- Sometimes humans compensate for their testicular deficiencies.
- adult-onset hypogonadism, gonadotropins may be only modestly elevated or even normal, especially in **compensated** states.

LH FSH AREN'T ALWAYS HIGH

(Dandora et al., 2010)



Is testosterone over or under prescribed?



Is testosterone over or under prescribed?



YES!

Let's Be Clear(Jasuja et al., 2016)

Most testosterone prescribing not for "classic" hypgonadism.

- In our study we found that only a small proportion of men with known diseases of the testis, pituitary, and hypothalamus (16%) received testosterone therapy...reinforcing the suspicion that **androgen deficiency is both under- and over-treated.**

We aren't giving ENOUGH testosterone.

(Grossman et al., 2015)

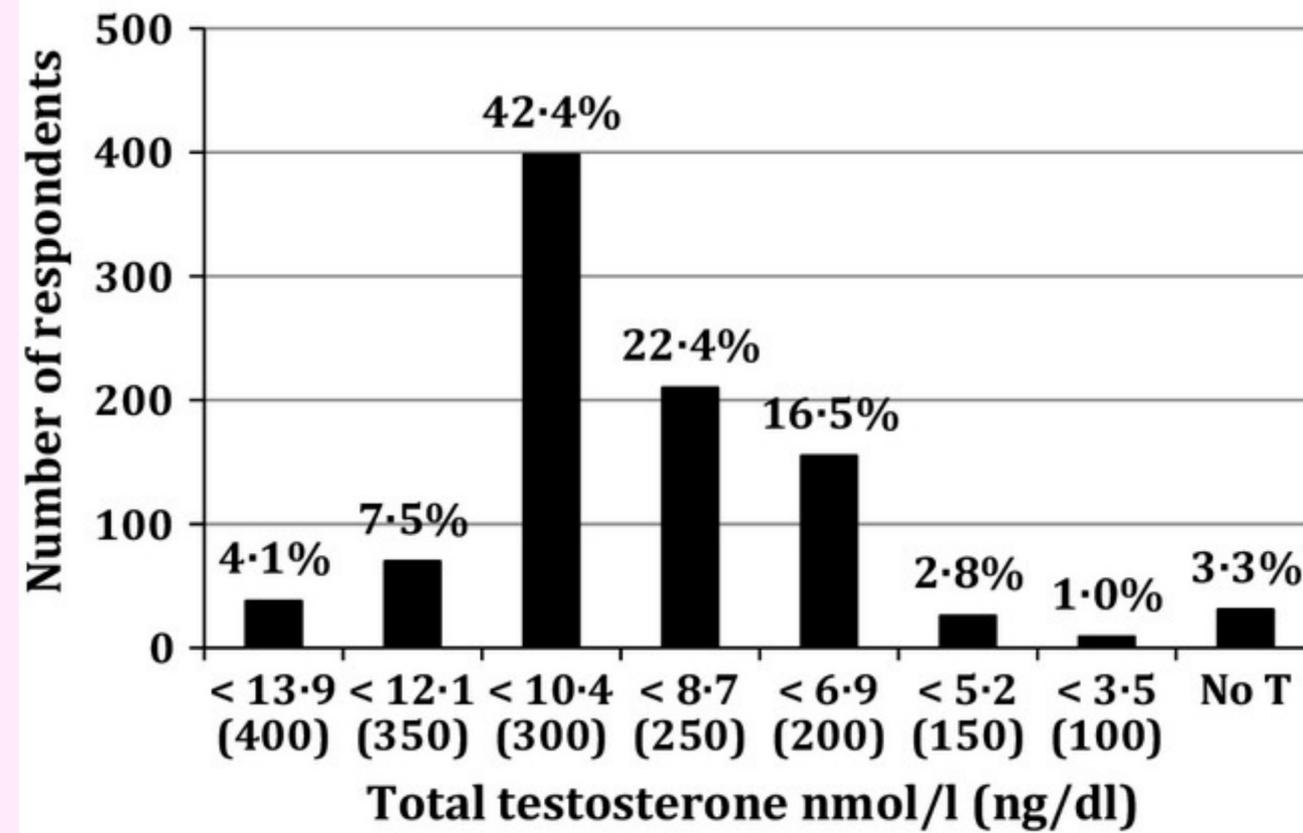
- Members of all major endocrine and andrological societies were invited to participate in a Web-based survey of the diagnostic work-up and management of a hypothetical index case.
- Nine hundred and forty-three respondents (91.2% adult endocrinologists) from Northern America (63.7%), Europe (12.7%), Oceania (8.2%), Latin America and Caribbean (7.6%), and the Middle East, Asia, or Africa (7.8%) completed the survey. Response rates among participating societies ranged from 4.1–20.0%.

We aren't giving ENOUGH testosterone.

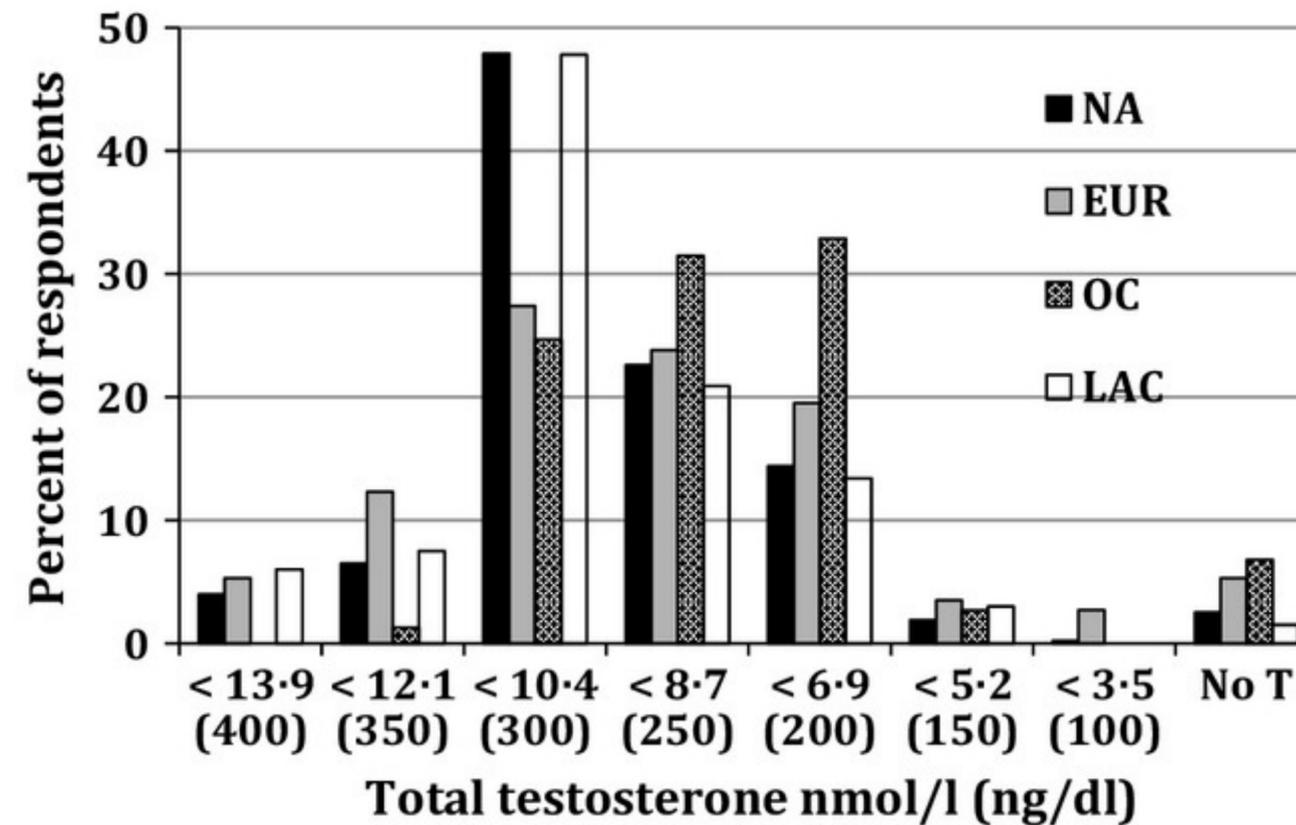
(Grossman et al., 2015)

- A 61-year old man presents with fatigue, low libido, reduced erectile function, and mild irritability. Systems review is otherwise normal. He has well-controlled hypertension and dyslipidaemia treated with an ACE inhibitor and a statin, respectively. There is no other significant past medical history. He does not smoke or consume alcohol. He works in an office and does not exercise. He underwent normal puberty and fathered 3 children in his twenties
- Physical examination reveals a body mass index of 29 kg/m², normal male-pattern body hair, and testes are 18 ml bilaterally. There is no gynecomastia, and no obvious loss of muscle bulk
- He is moderately bothered by his symptoms. While he and his partner seek your advice about testosterone.

(a) All geographic regions



(b) According to major geographical regions



We aren't giving ENOUGH testosterone.

(Grossman et al., 2015)

- "This large-scale international survey shows a wide variability in the management of lowered testosterone in older men, with **deviations from current clinical practice guidelines**, and a temporal **trend towards increasing reluctance** to prescribe testosterone to men without classical hypogonadism."

We aren't giving ENOUGH testosterone.

2/28/25 FDA UPDATE-FDA SAYING SOMETHING IS SAFER

- 2/28/2025 Update

Based on FDA's review of the results from a large clinical trial showing the use of testosterone therapy did not increase the risk of heart attack or stroke compared to an inactive treatment called a placebo, **we are removing information about this risk from the Boxed Warning on all prescription testosterone products.** We are also adding a warning about the risk of increased blood pressure to the prescribing information of testosterone products that currently do not include this information based on the results of separate blood pressure monitoring studies

We aren't giving ENOUGH testosterone.

Cardiovascular Risk Overstated (Lincoff et al., 2023)

- Multicenter, randomized, double-blind, placebo-controlled, noninferiority trial.
- 5246 men age 45 to 80
- Preexisting high risk cardiovascular disease with hypogonadism and had two fasting testosterone levels of less than 300 ng per deciliter. Randomly assigned to receive or placebo.
- End points any component of MI, nonfatal stroke, or coronary revascularization.
- The mean (\pm SD) duration of treatment was 21.7 ± 14.1 months, and the mean follow-up was 33.0 ± 12.1 months. A primary cardiovascular end-point event occurred in 182 patients

We aren't giving ENOUGH testosterone.

Cardiovascular Risk Overstated (Lincoff et al., 2023)

- CHALLENGING POPULATION....KUDOS!
- Cardiovascular **disease** was defined as clinical or angiographic evidence of coronary artery disease, cerebrovascular disease, or peripheral arterial disease.
- Increased cardiovascular **risk** was defined as the presence of 3 or more:
 - hypertension, dyslipidemia, current smoking, stage 3 chronic kidney disease, diabetes, elevated high-sensitivity C-reactive protein level, age of 65 years or older, or an Agatston coronary calcium score that was above the 75th percentile for age and race.

We aren't giving ENOUGH testosterone.

Cardiovascular Risk Overstated (Lincoff et al., 2023)

- Primary cardiovascular end-point event occurred in 182 patients (7.0%) in the testosterone group and in 190 patients (7.3%) in the placebo group (hazard ratio, 0.96; 95% confidence interval, 0.78 to 1.17; $P < 0.001$ for noninferiority).
- **A statistically significant higher incidence of atrial fibrillation, of acute kidney injury, and of pulmonary embolism was observed in the testosterone group but overall no difference in serious adverse events.

We aren't giving ENOUGH testosterone.

Cardiovascular Risk Overstated (Lincoff et al., 2023)

- In hypogonadal men:
 - Controlled testosterone in older men improves sexual function (Brock et al., 2016)
 - Increases volumetric and areal bone mineral density (Snyder et al., 2017)
 - Corrects unexplained anemia (Roy et al., 2016)
 - **Moderately reduces depressive symptoms (Snyder et al., 2017)**
- Because testosterone deficiency is not a life-threatening condition, uncertainty about cardiovascular outcomes has weighed on treatment decisions by clinicians and patients. (Bhasin et al., 2018)
- Testosterone-replacement therapy was noninferior to placebo with respect to the occurrence of major adverse cardiac events during a mean 22-month follow-up, and the overall incidence of **adverse events was low.**

Moderately reduces depressive symptoms

Snyder et al., 2017

- 790 men > 65 years Serum testosterone concentration of less than 275
- Random Testosterone gel or placebo.
- Each man participated in one or more of three trials — the Sexual Function Trial, the Physical Function Trial, and the Vitality Trial.
- Significantly increased sexual activity.
- 6-minute walking distance did improve
- Testosterone had no significant benefit with respect to vitality, as assessed by the Functional Assessment of Chronic Illness Therapy–Fatigue scale, but men who received testosterone reported slightly better mood and lower severity of depressive symptoms than those who received placebo. **(PHQ dropped a significant .72 points)**

Blood Thinners?

- Blood thinners are not routinely used to offset testosterone-related thrombotic risk in men on testosterone therapy. Testosterone can increase hematocrit and blood viscosity, which may modestly elevate **venous thromboembolism (VTE)** risk in some patients, particularly within the first 6 months. (Walker et al., 2020)
- Could this have masked some of the dangers in large study?

I'm sorry...

Did I say we aren't giving enough testosterone?

I apologize.

What I meant to say was....

We're giving too much testosterone!

(Malik et al., 2015)

- Electronic Data Warehouse queried men of ages 18-85 years, who obtained a testing for serum total testosterone level from 2009 to 2012. The frequency of testosterone replacement therapy (TRT), patient demographics, and clinical characteristics were collected.
- 9176 men who underwent testing for low testosterone levels, 3320 (36%) of them were hypogonadal with a mean serum total testosterone level of 194.3 ± 64.9 ng/dL.
- Treatment frequency significantly increased from 8.3% in 2009 to 24% in 2012. A total of 4.8% of men of reproductive ages (age, 18-35 years) were placed on TRTs.
- **Within 180 days of initial testing, only 40% of treated men received follow-up with liver function tests and/or complete blood count, and only 49% had a follow-up serum testosterone level.**

We're giving too much testosterone!

(Baillargeon et al., 2015)

- Retrospective cohort 61,474 men aged ≥ 40 years
- Commercial insurance databases
- One prescription for testosterone therapy from 2001 to 2010.
- **19.5% did not meet Endocrine Society guidelines for low testosterone.**
- **In the 12 months after treatment, 52.4% received a serum testosterone test and 43.3% received a PSA test.**

Let's Be Clear(Jasuja et al., 2016)

Most testosterone prescribing not for "classic" hypgonadism.

- National cohort of male patients, who had received at least one outpatient prescription within the Veterans Affairs (VA) system during Fiscal Year 2008–Fiscal Year 2012.
- 682,915 non-HIV male patients, of whom 132,764 had received testosterone and a random 10% sample, 550,151, had not.
- **Side note: 16.5% of male Veterans Administration Health Care System (VA) patients received this therapy without first undergoing the recommended workup.**

We're giving too much testosterone!

CASE: Does testosterone work like viagra?

- 70+ Y/O WIDOWER WITH DIABETES AND HEART DISEASE ON TESTOSTERONE GEL, GRIEVING FOR LAST YEAR.
- RETURNS AFTER "**A DREAM VACATION**" IN WHICH HE HAD MULTIPLE SEXUAL EXPLOITS THANKS TO HIS "**DREAM COCKTAIL**" BEING VIAGRA, AFTERSHAVE, AND A "**HEALTHY**" DOSE OF GEL PRIOR TO HIS DATE.
- ME: *"I know you've been through a lot and I'm happy you had a good time but I don't think slathering your body with androgel as some sort of pre mating ritual was the safest thing for you or your partner."*

We're giving too much testosterone!

CASE: Does testosterone work like viagra?

- **HOW FAST DOES TESTOSTERONE WORK?**



We're giving too much testosterone!

How fast does testosterone work? (Loizides et, al. 2004)

- 638 men testosterone for 30 days in a multicenter, open-label, single-group study (total testosterone level \leq 300 ng/dL and had not received any testosterone replacement therapy for the prior 6 months.)
- Sexual functioning and mood assessments were based on a validated self-report **daily** diary on:
- **sexual desire, day and nighttime spontaneous erections, intercourse, sexual motivation, sexual enjoyment, satisfaction with duration of erection, and positive and negative mood parameters.**

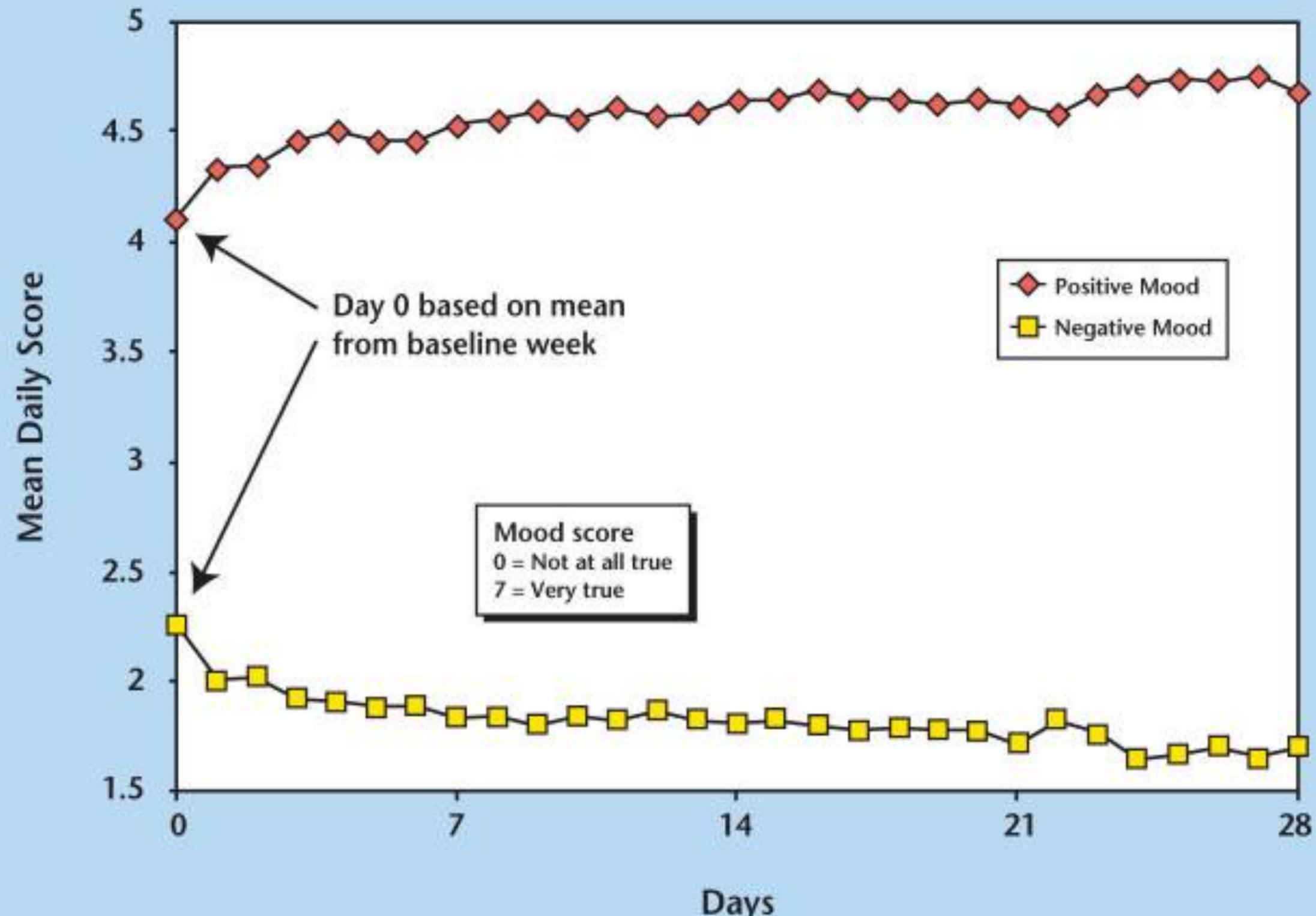
How fast does testosterone work?

(Loizides et, al. 2004)

Baseline	Week 1	Week 2	Week 3	Week 4
Sexual desire (0 = none, 7 = very high)				
2.0 ± 1.4	2.6* ± 1.5	3.0* ± 1.6	3.1* ± 1.6	3.2* ± 1.6
Sexual motivation (# days per week)				
1.6 ± 1.3	1.9* ± 1.5	2.1* ± 1.7	2.2* ± 1.7	2.2* ± 1.7
Spontaneous erections (# days per week)				
0.7 ± 1.1	1.1* ± 1.5	1.3* ± 1.6	1.3* ± 1.7	1.2* ± 1.7
Sexual performance (# days per week)				
0.9 ± 1.1	1.1* ± 1.2	1.3* ± 1.3	1.3* ± 1.3	1.3* ± 1.2
Sexual enjoyment (0 = none, 7 = very high)				
With partner 4.0 ± 1.5	4.4* ± 1.5	4.8* ± 1.4	4.9* ± 1.4	4.9* ± 1.4
Without partner 3.3 ± 1.4	3.6* ± 1.4	4.0* ± 1.5	4.0* ± 1.5	4.1* ± 1.5
Satisfaction with duration of erection (0 = not satisfied, 7 = very satisfied)				
3.1 ± 1.8	3.4* ± 1.8	3.7* ± 1.8	3.8* ± 1.8	4.0* ± 1.8

How fast does testosterone work?

(Loizides et, al. 2004)



Testosterone Gel Prn for women

(Bella et al., 2007)

- Ten patients completed the study. On the five-item self-report Arizona, the item “How easily are you aroused?” was significantly improved on testosterone gel vs. placebo, $P = 0.03$. There were similar trends on the physician-rated SFQ-V1 “arousal–sensation” cluster.
- Sublingual testosterone was reported to cause testosterone levels to peak after 15 minutes and then decline to baseline levels within 90 minutes. Three to 4 hours after reaching testosterone peak, increased genital sensations and sexual lust were reported.

Maybe a role for intermittent use?

(Perrera et al., 2020)

- Androgen deprivation therapy (ADT) is still a mainstay of treatment for advanced prostate cancer. Continuous ADT causes considerable patient morbidity including sexual dysfunction, poor mood and physical capacity, changes in body composition and health-care-related costs. Intermittent ADT has been used as an approach to ADT monotherapy to limit morbidity by enabling cyclical recovery of serum testosterone levels. To date, a number of well-performed randomized controlled trials and meta-analyses have demonstrated statistically **insignificant differences in oncological outcomes between intermittent and continuous ADT monotherapy**

Now...

I couldn't find any studies on prn testosterone in men.

But I'm going to make the argument that might not matter.

Sexual dysfunction is not an area where humanity has a iron-clad track record of rational thought and prioritizing safety.

- Unusual aphrodisiacs listed from around the world:
- Balut: A **boiled fertilized duck embryo**.
- Spanish Fly (*Lytta vesicatoria*): **Beetle secretion**
- Hormigas: **Leafcutter ants** are toasted and eaten for protein-packed passion.
- **Crocodile Dung, Blowfish, Slime Eel, Rhino Horn, Cobra Heart** and others.

Sexual dysfunction is not an area where humanity has a iron-clad track record of rational thought and prioritizing safety.

U.S. Customs Data

- What's the most seized illegal pharmaceutical drug?



Sexual dysfunction is not an area where humanity has a iron-clad track record of rational thought and prioritizing safety.

U.S. Customs Data

- In the 12 months ending September 30, 2021, CBP confiscated \$16.3 million worth of counterfeit erectile dysfunction (ED) drugs. Over one million ED pills were part of a single large seizure in Los Angeles/Long Beach in late 2020.
- 15,000 pills worth over \$1 million seized in Louisville in early 2023, 3,200 pills were seized from a single passenger at Chicago O'Hare in 2021.
- Illicit erectile dysfunction pills, are the most frequent type of pharmaceutical intercepted in international mail facilities, **vastly outnumbering seizures of opioids.**
- A 2012 Pfizer-sponsored study found that 77% of "Viagra" purchased online was counterfeit, often shipped from locations like Hong Kong, the U.S., and the UK, and these pills had inconsistent active ingredients.

"When is the best time of day for an older man with erectile dysfunction to have intercourse?"

Google AI Overview

- "The morning is generally the best time for an older man with erectile dysfunction to have intercourse, as it leverages **higher testosterone levels** and increased energy after rest."

"How quickly does testosterone gel raise your level?"

Google AI Overview

- "Testosterone gel begins raising serum levels within 30 to 60 minutes of application, with peak levels typically occurring 2–5 hours after application. Therapeutic, steady-state levels are usually achieved within 2–4 weeks of daily use, while symptomatic improvements like increased libido may take 3–6 weeks."

I would start asking patients on testosterone if they ever alter their **pattern** of use.

I suspect an epidemic of intermittent and at times megadosing...and little medical research to guide us into how to help.

Take Home Points

- There is evidence of continued testosterone misuse and inappropriate diagnosis and follow-up.
- Patient non-compliance likely plays some role in this.
- This misuse likely contributes to decreased appropriate prescribing of testosterone by cautious physicians.
- Mental health is uniquely situated to educate and empower patients on appropriate use.

Important Problems in Treatment

Difficult to Regain Function

- Long-term TRT can suppress endogenous testosterone production, and recovery after stopping TRT is variable and may be incomplete, especially after prolonged or high-dose use
- Recovery depends on duration, dose, age, and individual factors, and some men require months to years to recover, with a minority never restoring normal production. (Bhasin et al., 2018)

Review: When TRT Is Absolutely Appropriate

Yes, we do treat it. We just don't treat vibes.

- Confirmed primary hypogonadism
- Pituitary disease
- Post-orchietomy
- **Symptomatic and biochemically low**
- **Informed consent and monitoring**

What Testosterone Does Not Do

- Fix a bad marriage
- Cure PTSD
- Replace therapy
- Turn 68 into 28



What Testosterone Does (Realistically)

- Improves libido in true hypogonadism
- Modestly improves energy in some
- May increase lean body mass
- Improves bone density

The Risks (Because We're Still Doctors)

- Hematocrit of 54% is not a badge of honor.
- Erythrocytosis
- Edema
- Acne
- Worsening OSA
- Infertility
- Possible CV risk debate
- Prostate monitoring required

The Role of Mental Health

- **When to say, "No, Go, Woah, and...Maybe So."**

The Art of Saying, "No."

Empathy + data = fewer angry MyHealthVet messages.

- “Your labs don’t support hypogonadism.”
- “Let’s address sleep first.”
- “Testosterone isn’t a treatment for normal aging.”
- “If levels are consistently low, we’ll revisit.”
- **"Are you really ready to possibly be on testosterone for the rest of your life?"**

Case Example

Most “low T” improves with sleep and metabolic control.

- 63-year-old male
BMI 34
OSA untreated
A1c 8.4
Reports fatigue
- Testosterone: 290 (afternoon)
- Plan:
 - Repeat morning labs
 - Address OSA
 - Optimize diabetes

The Art of Saying, "Go!"

Empowering and Encouraging Patients to Have These Discussion

- “We've tested your a.m. testosterone twice. It's low and your having symptoms. Would you like me to message your primary team?”
- “You've tried most of the modifiable things to increase your testosterone. It may be time for another discussion with your primary care physician.”
- “Testosterone at this level **isn't** considered normal aging.”

The Art of Saying, "Whoa."

Empathy + data = fewer angry MyHealthVet messages.

- **Let's make sure we work out and eat right try to keep your bodies own production as healthy as possible.**
- **Take prescribed dose**
- **Get follow up labs**
- **Don't alter your dose...take this like a consistent medication.**
- **Try for the minimum dose that gives you quality of life. We want to preserve as much of your natural functioning as possible.**

The Art of Saying, "Maybe so."

- **51 yo veteran bmi 30 on glp1 lost 45lbs plateaued weight loss.**
- **Hgb A1C 7.2 "Best I've done in years."**
- **Chronic orthopedic shoulder and back pain on low dose intermittent opioids. Multiple surgeries. None scheduled. Limited exercise.**
- **Significant marriage difficulties sexual dysfunction is one of several issues.**
- **A.M. Testosterones: 291, 287**
- **No risk factors**
- **NEXT STEP?**

In Closing

Real VA Superpower Evidence-based care

- Access to labs
- Longitudinal follow-up
- **Integrated mental health**
- Pharmacy oversight
- We practice medicine. Not marketing.
- Diagnose correctly
- Treat underlying causes
- Monitor carefully
- Testosterone is a treatment — not a lifestyle upgrade



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