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Declarations

- No relevant conflict of interests to declare.

OAT and the long-term effects of opioid therapy

Objectives: At the end of this session, participants will be able to:

1. Describe the physiologic impact of long-term opioids on the immune and endocrine systems
2. Consider the impact of long-term opioids use on pain sensitization and pain management
- 3. Offer testosterone therapy when appropriate, including discussion of risks and benefits, monitoring, formulations and frequency**

- “The opium addicts in Assam are more effeminate than women”
 - Charles Bruce (1839)
- “Opium ate out the virility of the individual”
 - Reverend RH Graves (1895)
- “Opium makes a man effeminate”
 - Surgeon General HS Cumming (1925)



Pathophysiology

- Exogenous and endogenous opioids exert an effect on the same receptors
- They interfere with GnRH synthesis, release, pulsatile nature, and response to negative feedback from sex steroids.
 - Naloxone: increased GnRH levels -> increased LH concentration and pulse frequency. LH more affected than FSH.
- Decrease in adrenal androgens
- Possibly also direct action of opioids on hypothalamic receptors that affect sexual function.

Hypogonadism Guidelines (2018)

- Hypogonadotropic hypogonadism is **common** in men receiving chronic enteral, parenteral, or intrathecal opioid medications for pain management.
- **Longer acting** opioids induce **greater and more sustained suppression** of T concentrations
- Men receiving **methadone maintenance therapy** are at **high risk of developing opioid-induced hypogonadism**, whereas the prevalence of opioid-induced hypogonadism is substantially lower with buprenorphine.
- Opioid-induced suppression of the endogenous hypothalamic–pituitary–testicular axis is associated with sexual dysfunction, low mood, osteoporosis, and increased risk of fracture.
- Only limited clinical trials data are available on the benefits of T therapy in men with opioid-induced hypogonadism. In one RCT in men with opioid-induced T deficiency, T administration improved pain sensitivity, sexual desire, body composition, and some aspects of quality of life¹. **Clinicians should consider T-replacement therapy in men with opioid-induced hypogonadism who are experiencing sexual symptoms and in whom discontinuation of opioid medication seems unlikely.**

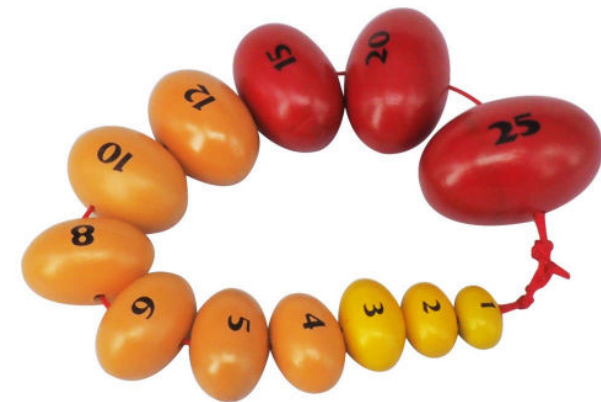
¹Basaria S, Travison TG, Alford D, Knapp PE, Teeter K, Cahalan C, Eder R, Lakshman K, Bachman E, Mensing G, Martel MO, Le D, Stroh H, Bhasin S, Wasan AD, Edwards RR. Effects of testosterone replacement in men with opioid-induced androgen deficiency: a randomized controlled trial. *Pain*. 2015;156(2):280–288.

What is male hypogonadism?

- An adult male with:
 - Symptoms and signs of testosterone deficiency, *and*
 - Unequivocally and consistently low serum testosterone concentration

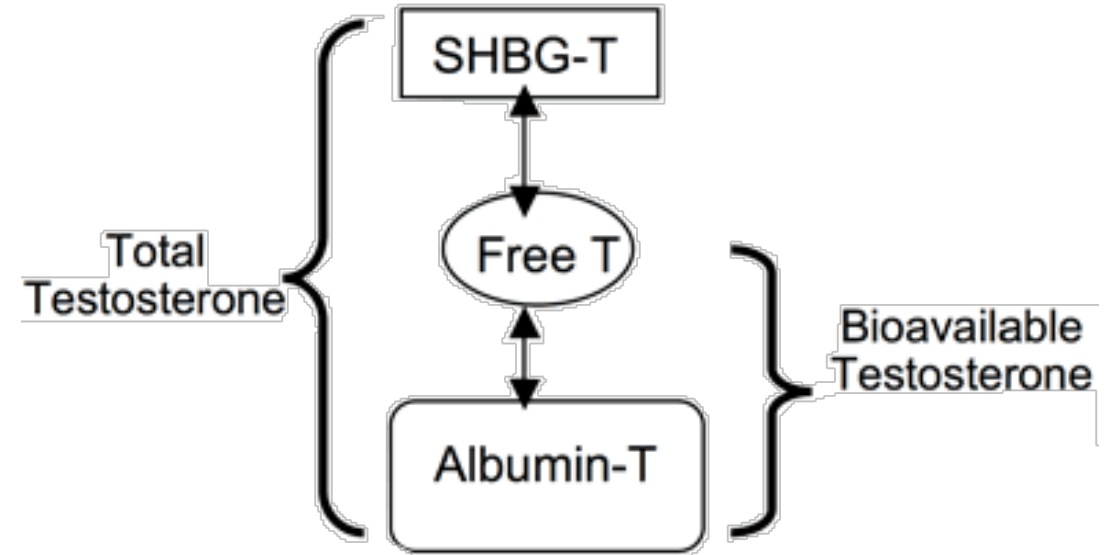
Symptoms and Signs

- Specific for hypogonadism:
 - Delayed puberty and sexual development
 - Loss of facial / axillary / body / pubic hair
 - Testicular atrophy (<15 cc)
- Suggestive of hypogonadism:
 - Reduced sexual desire (libido)
 - Decreased spontaneous erections
 - Erectile dysfunction
 - Breast discomfort / gynecomastia
 - Infertility / oligospermia / azoospermia
 - Osteoporotic fracture / low BMD
- Non-specific associated symptoms of hypogonadism:
 - Decreased energy / motivation / initiative
 - Low mood
 - Poor concentration / memory
 - Decreased muscle-to-fat ratio
 - Anemia

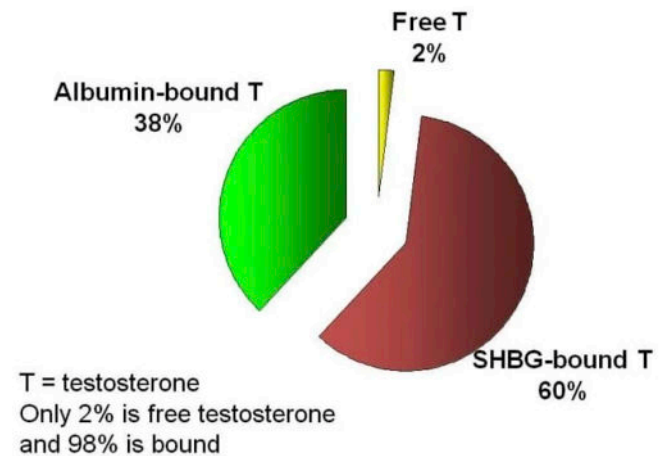


Labs

- Total testosterone <9.2 nmol/L (Endocrine Society)
 - Dynacare <7.6 nmol/L
 - LifeLabs <8.4 nmol/L
 - Mount Sinai Hospital <10.0 nmol/L
 - UHN <7.7 nmol/L
- Bioavailable testosterone



Testosterone Fractions in the Blood



*****Low Total T can be low because of low SHBG, while BioT remains normal*****

Labs

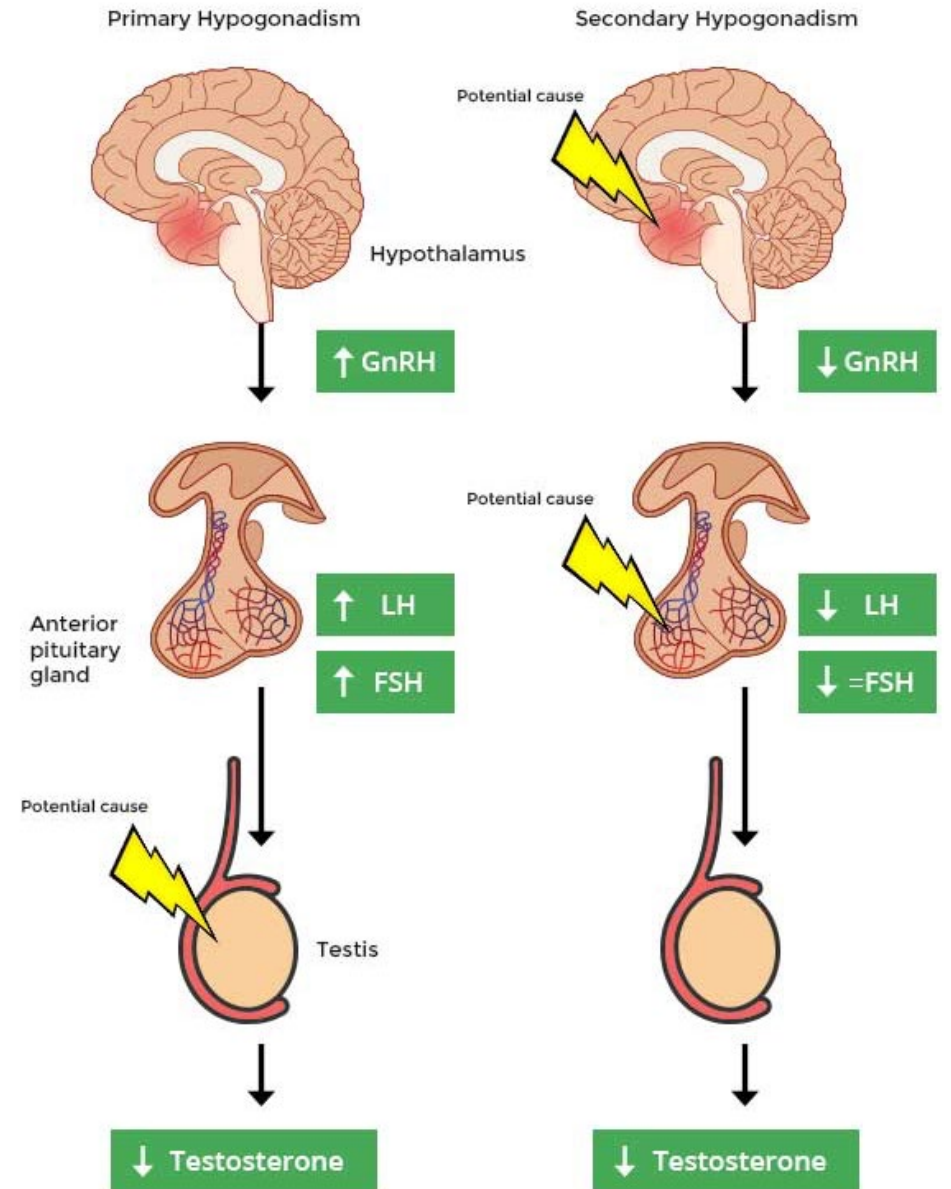
- Testosterone has significant diurnal and day-to-day variations
 - Peaks at 8 AM
- Suppressed by food intake or glucose

In summary, check testosterone:

- Fasting
- 8 AM
- On ≥ 2 occasions
- With an SHBG level or bioavailable testosterone level if uncertain



General Review of Endocrine Pathway



Reasons for Low Testosterone Levels

1) Primary Hypogonadism (high LH, high FSH)

- Klinefelter Syndrome
- Cryptorchidism / Anorchia
- Orchitis (e.g. mumps)
- Testicular damage (trauma, torsion, radiation)
- Advanced age
- ESRD

2) Secondary Hypogonadism

- Hypopituitarism
 - Pituitary tumour
 - Infiltrative / destructive disease of the pituitary
 - Hyperprolactinemia
- GnRH deficiency (Kallman Syndrome / NIHH)
- Idiopathic hypogonadotropic hypogonadism

Physiologic Reasons for Low Testosterone

Normal (*NOT HYPOGONADISM*)

- Time of day
- Non-fasting
- Low SHBG

“Functional” hypogonadism

(potentially reversible central suppression)

- Obesity
- Underweight
 - Nutritional deficiency
 - Excess exercise
- Systemic illness
- Medications
 - **Opioids**
 - Glucocorticoids
- Drugs
 - Alcohol
 - Marijuana

The symptoms are **non-specific**

Hypogonadism can only be diagnosed
with consistent, repeated, frankly
abnormally **low testosterone levels**

Ddx: Low Libido

- **Testosterone deficiency**
- Systemic illness
- Medications
- Alcohol
- Depression / psychological
- Fatigue
- Partner interactions / relationship problems
- Infertility difficulty
- ED/premature ejaculation / other sexual dysfunction (e.g. fear of humiliation)

Ddx: Erectile Dysfunction

- Pre-existing cardiovascular disease
 - Atherosclerosis
 - Hyperlipidemia
 - Hypertension
 - Diabetes mellitus
 - Smoking
- Anatomical
 - Penile fibrosis
 - Peyronie's disease
 - Micropenis
- Neurological—central
 - Traumatic brain injury
 - Parkinson's disease
 - Cerebrovascular disease
 - Multiple sclerosis
 - Brain tumours
 - Spinal cord disease/injury
 - Intervertebral disc disease
- Neurological—peripheral
 - Peripheral neuropathy (e.g. diabetic)
 - Uremia
 - Alcoholism
 - Pelvic surgery
- Hormonal
 - **Hypogonadism**
 - Thyroid disease
 - Cushing's disease
 - Hyperprolactinemia
- Drugs
 - Beta blockers
 - LHRH analogues
 - Antidepressants (SSRIs/tricyclics)
 - Histamine H₂-receptor antagonists (cimetidine/ranitidine)
 - Recreational drugs

****First-line medical treatment for ED is a PDE5-I****



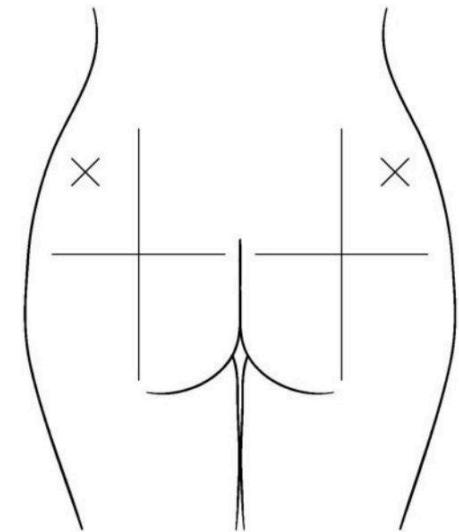
Treatment



Injections

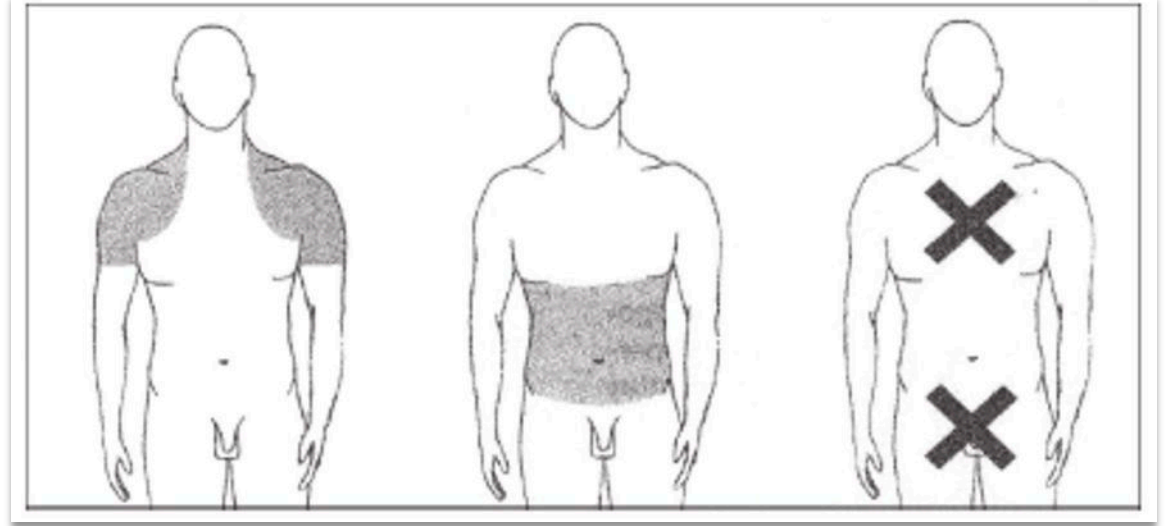
- IM injections
 - Vastus lateralis (thigh)
 - Gluteus maximums (buttock)
- 50-100 mg weekly *or* 100-200 mg q14d
- Testosterone cypionate (Depo-Testosterone)
 - 100 mg / mL (one 10 mL vial = 1 g total)
- Testosterone enanthate (Delatestryl)
 - 200 mg / mL (one 5 mL vial = 1g total)

Cost: ~\$40-50 per cypionate vial
~\$65 per enanthate vial
Monthly cost: ~\$25-35



Gel

- Dosing: 2.5 g – 10 g per day (= 25g-100g T)
- Sachets
 - 2.5g and 5.0g options
- Metered-dose pump
 - 1 pump = 1.25 g = 12.5 g T
 - 60 actuations per pump
 - 2.5g -> 30d, 5.0g -> 15d, 10g ->7.5d
- Apply to dry skin
- No showering / swimming for 5 hrs after
- Careful who touches the skin for hrs



Cost: \$3-4 per 5 g sachet

Monthly Cost: ~\$110 for 30 x 5g sachets, ~\$175 for two pumps

Pills

- 40 mg capsules of testosterone undecanoate
- Dosing up to 80 mg BID
- Best absorbed with fatty foods

- Least potent

Cost: 50¢ / capsule

Monthly Cost: \$60 if 4 capsules per day



hCG

- Homologous to LH
- Stimulates testicular production of testosterone and sperm
- Only helpful in secondary hypogonadism
- Main use is fertility
- Typical dose is 1500 IU 2x/w SC or IM



Adverse Effects

- Skin changes: acne, oily skin
- Worsening androgenic alopecia
- Gynecomastia
- Mood changes
- Prostate enlargement / growth
- Polycythemia
- Worsening of OSA
- Dyslipidemia / CV disease
- (Testicular atrophy)
- (Infertility)

**These are issues
if the dose is excessive**



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiovascular Safety of Testosterone- Replacement Therapy

A.M. Lincoff, S. Bhasin, P. Flevaris, L.M. Mitchell, S. Basaria, W.E. Boden, G.R. Cunningham, C.B. Granger, M. Khera, I.M. Thompson, Jr., Q. Wang, K. Wolski, D. Davey, V. Kalahasti, N. Khan, M.G. Miller, M.C. Snabes, A. Chan, E. Dubcenco, X. Li, T. Yi, B. Huang, K.M. Pencina, T.G. Trivison, and S.E. Nissen, for the TRAVERSE Study Investigators*

Monitoring

- Testosterone level
 - Mid-way between injections
 - 2-6 hours after applying the gel
- Hg and Hct
 - Don't start if Hct ≥ 0.48 .
 - Hold if Hct ≥ 0.54 .
- Liver enzymes annually
- Lipids annually
- Prostate
 - Assess for BPH and LUTS
 - Prostate cancer screening annually, if age >40



Contraindications

- Active (or suspected / potential) prostate cancer
- Hct >0.54, or thrombophilia
- Breast cancer
- Uncontrolled heart failure

Recommend avoiding in:

- Severe LUTS
- Untreated, severe OSA
- MI or stroke within the last six months

Illicit Testosterone Use

- Typically used at much higher doses
 - Risk of complications is much higher
 - Dependency increased and recovery time lengthened
- Typically combined with multiple other drugs
- Often cycled
- Not regulated

Summary

1. Does the patient actually have low testosterone?
 - Fasting, 8 AM, normal SHBG, no confounders / reversible causes
2. Is it primary or secondary hypogonadism? (check LH + FSH)
3. Is there another potential etiology aside from opiates?
4. Any contraindications to T? (Hct, PSA, OSA)
5. Injectable vs. gel vs. oral
6. Safe if monitored, and given physiologic doses
7. Monitor Hct and T (mid-way between injections)

Thank you
and
Discussion