Hormonal Therapy in Women and Men

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Disclosure: Dr Wierman is CoPI of “Neuroendocrine Dysfunction during rehabilitation after TBI” funded by Colorado Brain Trust – Abbvie provides T gel and placebo for the study
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Case 1:

- 48 yr old woman with stage II breast cancer: s/p surgery, chemotherapy and XRT 1 yr ago presents with intractable hot flashes, anhedonia, sleep disturbance and cognitive issues since she began an aromatase inhibitor

- **What do you advise?**
  a. Prescribe an increase in her Soy intake
  b. Prescribe an Serotonin reuptake inhibitor
  c. Prescribe Gabapentin
  d. Prescribe low dose estrogen progestin therapy
  e. Prescribe tamoxifen
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Mood and Perimenopause

• Lifetime risk of mood disorder: 10-23%, 2-14x increase at menopause

• RISKS: Data are mixed and poor quality
  – *Biologic sensitivity*: hormones, vasomotor sx, sleep disruption
  – *Psychosocial factors*: past hx of mood disorder, attitudes, life events, coping styles, social support, socioeconomic status, education
  – *Lifestyle*: smoking, no exercise, inc BMI

Gibbs et al Ach Womens Ment Health 2012 15:323-332;
Risk for Depression During Transition in SWAN

Adapted from Bromberger et al, 2010.

Note: Referent for early peri, late peri, and post was premenopausal; referent for 1 and 2+ life events was no life events. Adjusted for education, concurrent testosterone, age, smoking status, psychotropic medications, body mass index, and site.

Bromberger JT et al Arch Gen Psych 2010 67: 598-607
HOT FLASHES: MECHANISM STILL UNCLEAR

Perimenopausal/postmenopausal state

- Destabilised thermoregulatory set point
- $\downarrow$5HT, ?imbalance of 5-HT1a/5-HT2 receptors
- Presynaptic neuron

Menopause, antioestrogens, aromatase inhibitors, LHRH agonists

- Adrenal gland
- Ovary
- Testes

Oestrogens

External factors
- Altered thermoregulatory response
- Hot flushes (vasodilatation)
Selective Serotonin Reuptake Inhibitors (SSRIs) or Serotonin Norepinephrine Reuptake Inhibitors (SNRIs) Effects on Hot Flashes

<table>
<thead>
<tr>
<th>Source</th>
<th>Dose</th>
<th>No. of Participants</th>
<th>Duration of Trial</th>
<th>Quality</th>
<th>Mean Difference (95% CI)</th>
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<tr>
<td>Paroxetine Trials</td>
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<tr>
<td>Stearns et al, 2003</td>
<td>12.5 or 25 mg/d*</td>
<td>165</td>
<td>6 wk</td>
<td>Good</td>
<td>-1.52 (-2.36 to -0.69)</td>
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<td>Stearns et al, 2005</td>
<td>10 or 20 mg/d</td>
<td>151</td>
<td>4 wk</td>
<td>Fair</td>
<td>-2.43 (-4.43 to -0.42)</td>
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<td>-1.66 (-2.43 to -0.89)</td>
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<td>Venlafaxine Trials</td>
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<td>Evans et al, 2005</td>
<td>75 mg/d*</td>
<td>80</td>
<td>12 wk</td>
<td>Fair</td>
<td>1.10 (-1.94 to 4.14)</td>
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<td>Loprini et al, 2000</td>
<td>37.5 or 75 mg/d*†</td>
<td>167</td>
<td>4 wk</td>
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<td>-1.09 (-1.99 to -0.18)</td>
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<td>-0.49 (-2.40 to 1.41)</td>
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<td>Fluoxetine Trials</td>
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<td>Loprini et al, 2002</td>
<td>20 mg/d</td>
<td>81</td>
<td>4 wk</td>
<td>Fair</td>
<td>-0.90 (-3.78 to 1.98)</td>
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<tr>
<td>Suvanto-Luukkanen et al, 2005</td>
<td>20 mg/d‡</td>
<td>100</td>
<td>3 mo</td>
<td>Fair</td>
<td>-1.60 (-3.63 to 0.43)</td>
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<tr>
<td>Combined</td>
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<td></td>
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<td>-1.37 (-3.03 to 0.29)</td>
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<td>Citalopram Trials</td>
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<tr>
<td>Suvanto-Luukkanen et al, 2005</td>
<td>20 mg/d‡</td>
<td>100</td>
<td>3 mo</td>
<td>Fair</td>
<td>-0.20 (-1.45 to 1.05)</td>
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<td>Trials With SERM Use Combined§</td>
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<td>-1.40 (-1.97 to -0.82)</td>
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<tr>
<td>Trials Without SERM Use Combined‡</td>
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<td>-0.17 (-1.41 to 1.07)</td>
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<tr>
<td>All Trials Combined</td>
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<td></td>
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<td>-1.13 (-1.70 to -0.57)</td>
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</tbody>
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Case 2

- A 51 yr old woman with newly dx menopause is symptomatic with hot flashes, dysparunia, sleep and cognitive issues. She is active, has a normal BP, lipids but has a family hx of CAD
- What do you tell her about risk/benefit of HT on cardiovascular disease?
- Would it be different if she was 58 and last period was at 51?
WHI: Patient Characteristics

- Multi-center, double-blind, randomized placebo controlled, US trial
- CEE 0.625 mg+MPA 2.5 mg or placebo
- 16,608 women with intact uterus
- Mean age: 63.3 years
- Average follow-up: 5.2 years

WHI E/P 2002: RESULTS

- **Coronary heart disease:** (1.23, 0.99-1.53)
- **Stroke:** (1.41, 1.07-1.85) constant
- **Pulmonary embolism:** (2.13, 1.39-3.25)
- **Breast cancer:** (1.26, 1.0-1.59)

- Colon cancer: (0.63, .43-.92)
- Hip fracture: (0.66, .45-.98)

WHI E+P: Considerations

- Age at *time* of initiation of HT
- *Dose* of estrogen in older women
- Role of increased BMI: 2/3 >25, 1/3 >30
- Role of *type of progestin*: medroxyprogesterone vs natural progesterone
- Impact of *daily* vs. intermittent progestin
- High unblinded rate (42%) and high dropout rate (38%): effect on detection rate
- *Absolute vs. relative risk*: .7-.8/1000 or 1 event/100 women treated for 5 yrs
- *Primary vs secondary prevention*?
WHI 2004: Estrogen only

- 10,739 surgically menopausal women age 50-79 given placebo or CEE .625mg/d for 6.8yr
- CHD .91 (.75-1.12), stroke 1.39, VTE 1.33
- Breast cancer 0.80 (.62-1.04)
- Colon cancer 1.08
- Hip fracture .61
- **Age 50-59 had benefit** (.56 v 1.0) whereas if >10yr PMP at start of trial had increased risk of CAD

Conjugated Estrogens, Diet and Atherosclerosis in Cynomolgus Monkeys

OVX

1. Healthy diet
   Atherogenic Diet and CEE
   ↓ 70%

2. Atherogenic Diet
   Atherogenic Diet and CEE
   ↓ 50%

3. Healthy Diet
   Atherogenic Diet No CEE
   Healthy Diet and CEE
   ↓ 0%

Premenopausal Years  Postmenopausal Years

Mikkola et al, Cardio Research 53: 2002
WHI CAD: Take Home

- Mechanisms of E and P in vascular system under investigation
- *Importance of primary vs secondary prevention?*
- *Role of lipids, MMPs in destabilizing plaque*

- **KEEPS**: early intervention trial showed no benefit on carotid intimal thickening, but no significant increased risk

Risks of Hormone Therapy

- Gallstones: RR: 1.5-2.0
- Deep venous thrombosis: RR: 1.5-3.0
- *Endometrial cancer*: no, if given with progestin (12d medroxyprogesterone or continuous P)
- *Breast Cancer*: continuous P increases risk
Alternatives and Supplements: Potential Risks

- **SERMS**: Raloxifene appropriate for early bone protection, equivocal for cardiac (in early menopause, worsen hot flashes) limited use
- **Soy**: meta-analysis: *little effects*
- **Herbals**: *none* beneficial in controlled studies to date
- **Drug/drug interactions**: worry with alternatives, pharmacologic dosing, limited data
- **Compounded preparations**: *no quality control of the delivery preparation? Risk vs benefit*
- **Use** lipids and bone biomarkers to assess supplements patients are taking
Case 3

A 48 yr old woman with early symptomatic menopause and sexual dysfunction wants to know about potential therapies. Which of the following is the best option?

- a. Testosterone patch at 300ug/d
- b. DHEAS at 100mg/d
- c. Compounded T, E1, E2 and yam Progesterone
- d. Estrogen patch 0.05mg with cyclic medroxyprogesterone 5mg d 1-12
- e. Raloxifene daily
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Testosterone Therapy for Women

- No evidence of Androgen deficiency syndrome in women
- T patch at high physiologic dosing was effective in Hypoactive Sexual Desire Disorder (one more satisfying sexual relations/mo), BUT denied at FDA because of concerns re breast and cardiovascular risk
- For HSDD, consider short-term trial in selected patients 3-6 mo but d/c if not effective, monitor for overuse or signs of hyperandrogenism
- Longterm risk /benefit unknown
- Normative levels of T in women across the lifespan under investigation with new sensitive MS assays

Menopausal Hormone Therapy in 2015

- **Short term**: Benefits outweigh risks in some symptomatic women; individualize regimen
- **Long term**: Must weigh benefits vs. risks for individual patient
- **New regimens**: Lower doses, transdermal delivery, intermittent or no progestins
- **Alternative therapies**: Do no harm--we need additional research
- **Importance of lifestyle interventions early**

Testosterone Therapy in Men

- What causes real hypogonadism?
- Is there an age related andropause?
- What are the potential cardiovascular risks of T therapy?
Hypogonadism: Definition

“Hypogonadism in men is a clinical syndrome that results from failure of the testes to produce physiological levels of testosterone (androgen deficiency) and the normal number of spermatozoa due to disruption of one or more levels of the hypothalamic-pituitary-gonadal axis”

— The Endocrine Society Clinical Practice Guideline

Bhasin S et al. J Clin Endocrinol Metab. 2006;91:1995-2010

Testosterone products are FDA approved only for use in men who lack or have low testosterone levels in conjunction with an associated medical condition

FDA drug safety communication 9/14
# Clinical Manifestations of Hypogonadism

<table>
<thead>
<tr>
<th>Physical</th>
<th>Psychological</th>
<th>Sexual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased bone mineral density</td>
<td>Depressed mood</td>
<td>Diminished libido</td>
</tr>
<tr>
<td>Decreased muscle mass and strength</td>
<td>Diminished energy, sense of vitality or well-being</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Gynecomastia</td>
<td>Impaired cognition and memory</td>
<td>Difficulty achieving orgasm</td>
</tr>
<tr>
<td>Anemia</td>
<td></td>
<td>Decreased performance</td>
</tr>
<tr>
<td>Frailty</td>
<td></td>
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<tr>
<td>Increased body fat, body mass index</td>
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<tr>
<td>Fatigue</td>
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</tbody>
</table>

Defining Normal: Problems Interpreting Data

• Total Testosterone levels
  – Assay changes over the last 10-20 yrs
  – Total T levels in most hospitals are run on platform assays not sensitive or specific <250 ng/dl
  – Change in T level may reflect altered free T or instead change in Sex Hormone Binding Globulin (SHBG)
  – Impact of aging, adiposity, insulin resistance etc on SHBG levels
  – WHAT is LOW?
Testosterone Levels are Dependent on Sex Hormone Binding Globulin Levels

Testosterone normal range 240-800ng/dl (8.4nmol/l)

SHGB

Free Testosterone

Young Man
Total T 550ng/dl
MORE SHBG makes a higher total T level

Older Man
Total T 240ng/dl
LESS SHGB makes a lower total T level

Lower SHGB due to insulin resistance MetS Diabetes

BOTH ARE NORMAL ie SAME FREE TESTOSTERONE LEVEL
Central Hypogonadism
(low LH, FSH, T)

• Acquired:
  – *GnRH pulse generator defect* due to stress, severe illness, abnormal weight loss
  – *Narcotics*: opioids and other pain medications, synthetic marijauna etc
  – *Glucocorticoids*: usually steroid injections in joints
  – *Obstructive sleep apnea*: snoring, erectile dysfunction, insulin resistance, metabolic syndrome (often T is not really low)
Pituitary Hypogonadism

(low LH & FSH, low T)

• Prolactinoma or meds increasing Prl
• Infiltrative disorders: hemochromatosis
• Tumors/Mass effects:
  – Craniopharyngioma, Rathke’s cleft cyst
  – Pituitary tumor (GH, ACTH, some gonadotrope)
  – Metastasis
  – Inflammatory (new T cell targeted therapies ie IPI for melanoma)
Hypergonadotrophic Hypogonadism:
High FSH +/- LH, low T

- **Congenital: Klinefelter’s Syndrome**
  - XXY: 1/400-1/1000 live births
  - Delayed puberty, eunuchoid body habitus, gynecomastia
  - Low inhibin B levels
  - Progressive tubular fibrosis, no sperm
  - Eventual need for T replacement, mammograms
Hypergonadotropic Hypogonadism: Acquired

- Trauma or torsion
- Mumps orchitis
- Alcohol: direct testicular toxin
- Diabetes
- Radiation/chemotherapy
- Autoimmune testicular failure: check for other autoimmune diseases (TSH, glucose, B12, vit D)
- Gonadotrope (nonfunctioning) pituitary tumors: hi FSH>LH
Real Hypogonadism

• SYMPTOMS and Low T and you can identify the cause
  – Mechanical or Hormonal
  – Congenital or Acquired
Is there a Andropause or Late-Onset Hypogonadism?

• A symptom complex in the presence of low levels of testosterone

• Age-related changes in physiologic function affected by testosterone levels:
  – Body fat/lean ratio
  – Bone mineral density
  – Cognition, memory, and mood
  – Sexual desire and function
  – Strength and energy
Prevalence of Hypogonadism: 20-30%?

Based on only T levels

**Baltimore Longitudinal Study on Aging**

Men in Hypogonadal Range (%)

- **Age (years)**
  - 40-49
  - 50-59
  - 60-69
  - 70-79

- **Total testosterone** <325 ng/dL
- **Free testosterone index** <0.153 nmol/nmol

Hartman SM et al. *J Clin Endocrinol Metab.*
2001;86:724-731

40y study: 890 men 87% white, T q 2 yr
Late Onset Hypogonadism

- 3369 men 40-79 at 8 European centers surveyed using questionnaires and T by mass spectrometry

- Poor morning erection, low sexual desire, ED, decreased vigorous activity, depression and fatigue correlated with T level
- 3 sexual symptoms and T level < 230-320ng/dL (8-13nmol/l) or free T <46-81pg/ml (160-280 nmol/l)

- More symptoms higher correlation BUT……
- **FOUND:** many men had low T and *NO Symptoms*
- **SIMILARLY:** men had symptoms and *NORMAL T*

F Wu et al NEJM 363:123,2010
T levels of < 230-370 ng/dl (8-11 nmol/l) correlated with symptoms

F Wu et al NEJM 363:123, 2010
Late Onset Hypogonadism: as defined by >=3 sexual symptoms (ED, dec morning erections and dec sexual thoughts) and low T <320ng/dL

INCIDENCE MUCH LOWER !!! Max 3-5%

F Wu et al NEJM 363:123,2010
Weight Loss Increases Testosterone and SHBG Levels

T levels increase with WEIGHT LOSS

Even free T levels increase when you lose 15% weight!

SHBG levels increase when you lose weight

Paired T levels available over time in subset of pts


© 2013 European Society of Endocrinology
So, WHAT SHOULD we recommend to pts with low normal T levels?

- DIET
- LIFESTYLE
- Successful weight loss will
  - Increase testosterone levels
  - Improve obstructive sleep apnea
  - Improve cardiovascular and metabolic fitness
  - Sometimes, improve erectile dysfunction
• 2010-2013: Testosterone prescriptions increased from 1.3 to 2.3 million (76%)
• Men aged 40-64>65-74: 70% of scripts
• Only 50% documented hypogonadism
• 25% no first T measured and 21% never had level checked
• 57% also prescribed cardiac med
• Median fill 3 mo, mean duration T Rx: 6 mo
Does Testosterone Therapy impact Cardiovascular Disease events?
TOM Trial: Adverse CAD Events with T Therapy

- 209 men >65 yrs old (74) with limitations in mobility
- T 100-350ng/dl were randomized to placebo or T gel 10g
- High baseline prevalence of DM, HTN, hyperlipidemia
- Outcome measures: leg and chest press, stair climbing with a load

- Study stopped at 24wks due to increase in cardiac, respiratory and dermatological SAEs
- 23 vs 5 cardiac events: 1 death, ACS, MI, syncope, HTN, arrhythmia, edema, CHF

- Risk of event correlated with HIGHER T levels; HR 2.4 P=0.05, some >1000ng/dl

Basaria et al NEJM 2010 363:109
T Therapy increased cardiac events in elderly men

Events happened early, within a month and persisted within a 3 mo f/u

Basaria et al
NEJM 2010
363:109
Cardiac Risk increased with T Level and Hct on therapy

But...Baselines not equivalent: increase in hyperlipidemia and on statin and HTN in T group

Basaria et al
NEJM 2010
363:109
## Recent T and Cardiovascular Risk Epidemiology Studies

<table>
<thead>
<tr>
<th>Study, first author</th>
<th>N of men with low T/T-treatment</th>
<th>Mean duration testosterone treatment (months)</th>
<th>Outcome</th>
<th>HR (95% CI)</th>
<th>T threshold</th>
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<tbody>
<tr>
<td>Shores et al. [69]</td>
<td>1031/398</td>
<td>20 months</td>
<td>Total mortality</td>
<td>Treated vs. not 0.61 (0.42–0.88)</td>
<td>TT 9.7 nmol/l</td>
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<tr>
<td>Muraleedharan et al. [5]</td>
<td>238/64 treated(^a)</td>
<td>42 months</td>
<td>Total mortality</td>
<td>Untreated vs. treated 2.3 (1.3–3.9)</td>
<td>TT 10.4 nmol/l</td>
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<tr>
<td>Vigen et al. [70(^**)]</td>
<td>8709/1223</td>
<td>12.5 months(^b)</td>
<td>Composite of MI, stroke, total mortality</td>
<td>Treated vs. not 1.29 (1.04–1.58)</td>
<td>TT &lt; 10.4 nmol/l</td>
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<tr>
<td>Finkel et al. [71(^*)]</td>
<td>55,593 prescribed testosterone level unknown</td>
<td>Mean treatment NR followed for 90 days after first prescription</td>
<td>Nonfatal MI</td>
<td>Post-T vs. Pre-T prescription 1.36 (1.03, 1.81) overall 2.19 (1.27, 3.77) &gt;65 years 2.90 (1.49, 5.62) &lt; 65, w/CAD</td>
<td>T level NR</td>
</tr>
</tbody>
</table>

CAD, coronary artery disease; CI, confidence interval; HR, hazard ratio; N, number; NR/-, not reported; T, testosterone.

\(^a\)Required testosterone treatment > 1 year, excluded shorter testosterone treatment.

\(^b\)After excluding men who had only one prescription fill (17.6% of treated men).
PLOS 1: Health Care Database Study

- Risk of *acute nonfatal MI w/in* 90d after T or PDE5 Rx vs the 1 yr before  \( N=55,593 \)
- **Results**: PreRx RR 1.36 (1.03, 1.81)
- **Post T Rx >65**: T Rx RR 2.19 (1.27, 3.77) versus 1.15 (0.83, 1.59) for PDE5 inhibitor fill
- RR increased with age: 0.95 (0.54, 1.67) <55 to 3.43 (1.54, 7.56) for >75
- Risk <65 associated only those with preexisting CAD: RR T Rx 2.9 (1.49, 5.62)
- **RISK declined to baseline in 90-180 after d/c fill**

WD Finkel et al PLOS one 2014 9:1-5.
Epidemiologic studies: Limitations

• Data was observational, cannot measure all potential confounders
• Lack of information on clinical decision making in prescribing T
• Dose or type of T prescription
• No equal comparator groups
• NIA T trial 800 men T or placebo started in 2009 will report next year, STAY TUNED
Testosterone in Men:
Who to treat? How to treat?

- Treat for signs sx and low T levels after confirming etiology

- **T gels**: 2.5, 5, 10 g daily (different concentrations, different application sites)

- **T patch**: 2, 4 mg daily

- DepoT: 200mg IM q 2-3wks (trough at 150-200 ng/dl), nonphysiologic highs and lows

- CBC, **PSA watch for rise >1.5 ng/dl**

- Reassess risk benefit
Testosterone TAKE HOME

• Too little is bad
• Too much is bad
• Just right is good

• Treat men with hypogonadism with sx and low T due to known disorder and target physiologic levels
Case 1

- A 22 yr old man presents with fatigue, sexual dysfunction after returning from active military duty. His provider checks a testosterone and it is 100ng/dl, with LH 0.1mIU/ml, FSH 0.2mIU/ml. He has an anxious, somewhat depressed affect.

His exam is significant for a muscular build, well virilized and testes are 20ml (nl >10ml) but soft.

What is the most likely diagnosis?
- a. Idiopathic hypogonadotrophic hypogonadism
- b. A pituitary prolactinoma
- c. Ingestion of exogenous anabolic steroids
- d. Klinefelter’s syndrome
- e. Delayed puberty
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Case 2

- A 55 yr old man with obesity (BMI 32), high blood pressure and metabolic syndrome presents with fatigue and erectile dysfunction. He snores and his wife thinks he stops breathing in the middle of the night. His **Testosterone level is 280ng/dl, LH 5miU/ml, FSH 6miU/ml.**

**What do you advise?**

- a. Order a nocturnal pulse oximetry
- b. Order an MRI of the pituitary
- c. Order a testicular ultrasound
- d. Order a Karyotype
- e. Order a Cat scan of the adrenals
A 55 yr old man with obesity (BMI 32), high blood pressure and metabolic syndrome presents with fatigue and erectile dysfunction. He snores and his wife thinks he stops breathing in the middle of the night. His Testosterone level is 280ng/dl (nl240-800), LH 5miU/ml, FSH 6miU/ml.

What do you advise?

- **a. Order a nocturnal pulse oximetry**
- b. Order an MRI of the pituitary
- c. Order a testicular ultrasound
- d. Order a Karyotype
- e. Order a Cat scan of the adrenals
Case 3

• A 67 yr old man presents with sexual dysfunction, fatigue and decreased libido. He had a triple vessel coronary artery bypass in 2012. His hypertension, and hyperlipidemia are at goal on medications. He exercises once weekly. He can walk a ¼ mile without significant dyspnea on exertion. His testosterone level is 280ng/dl (nl 240-800), LH 7miU/ml, FSH 8miU/ml, PSA is 3.5ng/ml.

What is the best treatment option?

• a. Depotestosterone 300mg IM q 2 wks.
• b. Type 5a phosphodiesterase inhibitor one hour before sexual relations
• c. Testosterone gel at 10gm/d
• d. Continuous positive airway pressure ventilation
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