Menopause & Manopause
assisting our patients through the hormonal changes of midlife

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- Robert Gobbo, MD; Director, Providence Oregon Family Medicine Hood River Rural Program
Disclosures

Erica Didier, MD; Core Faculty, Providence Oregon Family Medicine Hood River Rural Program
- Nothing to disclose

Robert Gobbo, MD; Director, Providence Oregon Family Medicine Hood River Rural Program
- Merck Pharmaceutical – Nexplanon Trainer
Mr and Mrs. Midlife present to clinic with fatigue

1. Understand the changes in hormone levels at midlife that lead to symptoms
2. Comfortably counsel patients about the risks and benefits of hormone replacement therapy (HRT)
3. Effectively and safely prescribe and monitor HRT in appropriate patients
CC: difficulty sleeping

- Wilma is a 52 y.o. G3P3 woman with sleep interrupted by sweating, palpitations, flushing
- She also reports daytime fatigue and irritability
What percentage of women will continue to experience frequent hot flashes throughout their postmenopausal life?

1. 1%
2. 10%
3. 15%
4. 30%
Bochornos

- 75% of women
- 3-10 minutes each, occur day and night
- Can start at any age
- worst ~12 mos after LMP
- ~15% of women will continue to have throughout life
- Suggestion correlates with reduced BC risk#
What is Wilma’s diagnosis?
Diagnosis

- 12 mos amenorrhea
- Presumptive diagnosis based on vasomotor symptoms
- Laboratory testing only when bleeding history unreliable (hyst)
- Estradiol < 20 pg/mL, elev FSH

No laboratory values define the difference between symptomatic and asymptomatic women.
Husband, Fred: is a 45 year old overweight man. Wilma shows this video of him from last year.

He now presents with the following symptoms:
- Decreased sex drive,
- Loss of body hair
- Developing gynecomastia
- Fatigue, and some depression
- Can’t seem to drive the ball that far anymore……
What might be some additional signs and symptoms you might want to know about.....

- Any additional history that can either point to a cause or help your workup for Fred?
Symptoms and signs suggestive of androgen deficiency include:

- low libido
- decreased morning erections,
- loss of body hair
- low bone mineral density (BMD),
- gynecomastia,
- small testes.

Less specific: fatigue, depression, anemia, reduced muscle strength, and increased fat mass are less specific.
Some clues and causes of hypogonadism,

Gynecomastia, small firm testes, and behavioral/learning abnormalities
- Klinefelter syndrome.

Drugs:
- Chemotherapy (e.g., alkylating agents such as cyclophosphamide),
- Radiation therapy (to the pelvis or as part of total body protocols),
- Medications that cause primary or secondary hypogonadism
  - Ketoconazole
  - Sustained-release opioid preparations

Excessive alcohol consumption

Bilateral torsion, trauma, or a history of painful testicular swelling

Anosmia or hyposmia
- Kallmann syndrome.

Peripheral vision abnormalities or pituitary target gland hormone deficiencies
- Mass lesion in the pituitary gland or hypothalamus.
Consider screening conditions where high prevalence hypogonadism

- Diseases of the sellar region
- Medications that affect testosterone production, such as high-dose glucocorticoids for a prolonged period and sustained-release opioids
- Human immunodeficiency virus (HIV)-associated weight loss
- End-stage renal disease and maintenance hemodialysis
- Moderate-to-severe chronic obstructive lung disease
- Infertility
- Osteoporosis or low-trauma fracture, especially in a young man
- Type 2 diabetes mellitus
You decide to order a serum testosterone on Fred.

Which of the following is false:

1. If three levels of A.M. serum Testosterone are below 300 ng/ml, this is suggestive of Primary or Secondary Hypogonadism

2. One Serum Testosterone level less than 200 ng/ml and symptoms is enough to warrant initiating treatment with prescribed testosterone.

3. Serum Free Testosterone analysis are usually unreliable.

4. If the Testosterone is normal, he does not have hypogonadism

5. Cannot detect if it is Primary or Secondary Hypogonadism by Testosterone results.
Testosterone Assay

- 8 AM – 10 AM: Morning total testosterone level by a reliable assay as the initial test for the diagnosis of androgen deficiency in men
  - 30% of such patients have a normal testosterone level on repeat measurement.
  - 15% of healthy young men have a testosterone level below the normal range in a 24-h period

- Repeat morning testosterone 1-2 times
  - some patients by measurement of free or bioavailable testosterone level, using an appropriate assay system

- Consider case detection by measurement of total testosterone levels in men with certain clinical disorders
Measurement of Serum Testosterone Levels

Circulation Variation in Serum Testosterone in Normal Males

Why at 8 – 10 am and why more than once…..

- Take into consideration its diurnal fluctuation
  - maximum at about 8 AM ~ 70 % the maximum, at about 8 PM
  - It is easier to distinguish subnormal from normal when normal is higher,
  - Measurements should always be made in the morning, ideally between 8 to 10 AM.
- Fasting!
  - Food, especially glucose ingestion decreases the serum testosterone concentration, so the blood should also be drawn fasting.
Divergent gonadotropin-gonadal dose-responsive coupling

Daniel M. Keenan, Johannes D. Veldhuis
American Journal of Physiology - Regulatory, Integrative and Comparative Physiology Published 1 February 2004 Vol. 286 no. 2, R381-R389 DOI: 10.1152/ajpregu.00376.2003
The serum testosterone concentration fluctuates

- If a single 8 to 10 AM value is well within the normal range, testosterone production can be assumed to be normal.

- If a single 8 to 10 AM value is low or borderline low or does not fit with the clinical findings, the measurement should be repeated once or twice before making the diagnosis of hypogonadism.

- If the results are equivocal, measurement of free testosterone can be considered
  
  - Free Testosterone Assays must be done equilibrium dialysis and only in those few laboratories that specialize in endocrine testing.
Back to Wilma
Estrogen

3 major natural estrogens

- **E1 estrone**
  - Most prominent after menopause

- **E2 17-beta-estradiol**
  - Most prevalent premeno, becomes E1

- **E3 estriol** (80x less potent)
  - Peripheral convert

*Generator of Ὠἴστρος (oistros), "verve or inspiration"*
Additional symptoms elicited (A?B)B

**Urogenital atrophy**

- Vulvar/vaginal discomfort at rest
- Pain with intercourse
- Dysuria
- Recurrent infection

**Global**

- difficult concentration/mentation/
- mood
- Skin changes
- Arthralgia
- Disturbed sleep separate from VMS
- Fatigue
- Body composition changes
Quiz

True or False:

Women with active or a history of breast cancer can use vaginal estrogen?

Answer: True*
Menopausal therapy

Identify target symptoms
Replace what’s missing…..?

Hormones remain most effective therapy for all menopausal symptoms
The legacy of the women’s health initiative (UW)

- Estrogen alone (CEE) to prevent chronic disease, \( n = 10k \)

- Minimal significant findings
  - Reduced hip fracture, \( \text{NNT}=1667 \) (ARR of 6/10000 person years)
    - trend decreased breast Ca
  - Increased stroke, \( \text{NNH}=833 \) (ARI 12/10,000) and DVT (but not PE)
WHI, combo study

N = 16,608
Rx = oral conjugated estrogens (CE 0.625 mg) combined with medroxyprogesterone acetate (MPA 2.5 mg)

Decreased
  hip fracture risk (NNT=2000)

Increased
  CAD (NNH=1428)
  CVA (NNH=1250)
  DVT/PE (NNH=1250)
  breast cancer (NNH=1250)
Contraindications to hormone therapy

- Undiagnosed genital bleeding
- Breast cancer
- Endometrial cancer
- DVT/PE
- h/o MI/CVA
- Active liver disease

Relative:
- Gallbladder
- Hypertriglycemia
- Diabetes
- High risk of breast cancer
- High risk of CVD
- Migraine with aura
Silver Lining*

Reminder to review

- Cardiovascular risk factors
  - Smoking
  - Exercise
  - Wt management
  - Alcohol use
  - Bone health

- Cancer prevention and screening
<table>
<thead>
<tr>
<th>Oral</th>
<th>Dosages</th>
<th>Brand Name</th>
<th>OHPTier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conjugated equine estrogens</td>
<td>0.3 mg-1.25/day</td>
<td>Premarin</td>
<td>0, combo</td>
</tr>
<tr>
<td>17β-estradiol (E2)</td>
<td><strong>first pass effect about 90%, aka 0.625mg PO ~ 0.5 mg TD</strong></td>
<td></td>
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</tr>
<tr>
<td>Ethinyl estradiol</td>
<td>0.010-0.05 mg</td>
<td>Femhrt, Jentili</td>
<td>1</td>
</tr>
<tr>
<td>Esterified estrogens</td>
<td>0.3-0.45 mg</td>
<td></td>
<td>2, ST</td>
</tr>
<tr>
<td>Estropipate</td>
<td>0.75mg-3mg</td>
<td>Ogen</td>
<td>1</td>
</tr>
<tr>
<td>Transdermal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol (E2)</td>
<td>0.0375 mg/day TD</td>
<td>Vivelle, Alora, Climara</td>
<td>1 no combo</td>
</tr>
<tr>
<td></td>
<td>0.025 mg/day TD</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.011 mg/day TD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vaginal - high dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol</td>
<td>0.05 mg/day</td>
<td>FemRing</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>PV q90days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intramuscular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Estradiol valerate</td>
<td>10-20 mg IM q4wk</td>
<td>Delestrogen</td>
<td>1</td>
</tr>
</tbody>
</table>
Rx considerations

- Less thrombolic disease (observation data) and lipid elevation (no end point study) with transdermal

- Cyclic vs continuous combination therapy
What % of women on HRT will bleed during first 6 months

- A. 75%
- B. 50%
- C. 40%
- D. 25%
- E. < 10%
Uterine bleeding on HRT - diagnosis

- Continuous: 40% will bleed during first 6 months
  - More common earlier menopause

- Needs work up if >2 cycles or >6mos

- Work up: EMB versus ultrasound (biopsy for endometrial stripe > 4mm)
## Breakthrough bleeding on HRT - management

<table>
<thead>
<tr>
<th>Cyclic HRT</th>
<th>Early “period” - increase progesterone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inter “menstrual” - increase estrogen dose</td>
</tr>
<tr>
<td>Continuous-combined HRT</td>
<td>increase the estrogen dose for 1-3 months may also try increasing the progesterone dose</td>
</tr>
<tr>
<td></td>
<td>consider changing estrogen or to cyclic HRT</td>
</tr>
</tbody>
</table>
A note on shared decision-making*

- Start with open-ended questions
- Elicit concerns, expectations
- Schedule re-evaluation
Genital symptoms of menopause

- Vaginal lubricants
- Low dose vaginal estrogen
  - thought not to confer systemic risks of HRT
- Ospemifene
  - SERM
  - SE of hot flashes!

<table>
<thead>
<tr>
<th>Drug</th>
<th>OHP coverage</th>
</tr>
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<tbody>
<tr>
<td>ESTRing</td>
<td>0</td>
</tr>
<tr>
<td>Vagifem</td>
<td>0</td>
</tr>
<tr>
<td>Ogen</td>
<td>0</td>
</tr>
<tr>
<td>Estrace vag</td>
<td>0</td>
</tr>
</tbody>
</table>
Urethral Caruncle*
Bio-identical and other hormone

- “Bio-identical”
  - Laboratory created from plant sources
    - Progesterone
    - 17 beta-estradiol, estrone, and estriol
    - Usually compounded, not FDA regulated
- DHEA (6.3.2014) Cochrane 28 RCT, n=1273, daily doses 10-1600 mg PO
  - “no evidence that DHEA improves quality of life . . . uncertainty whether DHEA decreases menopausal symptoms . . . may slightly improve sexual function”
Non-Rx Hormone alternatives

- “Lifestyle” and environment changes – stress, obesity, alcohol, spicy foods
- Temperature reduction
- Paced respiration
- Exercise (11/2014 Cochrane review, n=762), no obvious benefit
- Acupuncture (*date* Cochrane review 16 low quality trials, n=1155), sham=acupuncture<HRT
Non-hormonal rx

- SSRI paroxetine (15-70% decrem.), fluoxetine

- SNRI (venlafaxine)

- Gabapentin 30-68% decrem.

- Clonidin 13-30% reduction
  - SE include: fatigue, dry mouth, dizziness
A Woman’s Healing Herbs:

- **Vervain**: Migraine, anxiety, depression, menstrual cramps.
- **Marigold**: Flowers, anti-inflammatory, healing, soothing.
- **Chinese Angelica**: Dried root, anti-inflammatory, healing, delaying periods.
- **Chamomile**: Flowers, anti-inflammatory, calming, soothing, menstrual cramps.

- **Mint**: Tonic, anti-spasmodic, relaxant.
- **Cranesbill**: Antispasmodic, healing, menstrual cramps, painful or missed periods.
- **Scutellaria**: Tonic, anti-spasmodic, healing, menstrual cramps.
- **Chamomile**: Flowers, anti-spasmodic, calming, soothing, menstrual cramps.
Herbal Preparations: The Sad Facts

Top 8 Herbs For Menopause

www.herbs-info.com
Fred’s laboratory reveals the following

- Total Testosterone level of 157 ng/ml
- Repeat levels were 163 and 177

What is next?
1. More Labs
2. Prescribe for “Low T”
3. Tell him to lose weight
4. Have him stop drinking so much beer with Barnie
5. All of the above
Evaluation of the male with possible hypogonadism

Clinical suspicion of hypogonadism*

8-10 AM total T

Normal

Low total T

Repeat 8-10 AM total T x 2, draw LH, FSH

Normal

Low T; LH and FSH not elevated

Secondary hypogonadism

PRL, T4, 8 AM cortisol, Fe, transferrin, imaging: MRI

Eugonadal

Low T; LH and FSH elevated

Primary hypogonadism

Karyotype

---

T: testosterone; LH: luteinizing hormone; FSH: follicle-stimulating hormone; PRL: prolactin; T4: thyroxine; Fe: iron; MRI: magnetic resonance imaging.

* This algorithm applies to the evaluation of outpatients. Men with acute symptoms (e.g., trauma, urethral prolapse, prostate surgery, rectal or pelvic surgery) may require immediate testosterone replacement.
## Total Serum Testosterone Levels

<table>
<thead>
<tr>
<th>Age</th>
<th>Male</th>
<th>T Level (ng/dL):</th>
<th>Female</th>
<th>T Level (ng/dL):</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>0-5 months</strong></td>
<td>75-400</td>
<td></td>
<td>20-80</td>
<td></td>
</tr>
<tr>
<td><strong>6 mos.-9 yrs.</strong></td>
<td>&lt;7-20</td>
<td></td>
<td>&lt;7-20</td>
<td></td>
</tr>
<tr>
<td><strong>10-11 yrs.</strong></td>
<td>&lt;7-130</td>
<td></td>
<td>&lt;7-44</td>
<td></td>
</tr>
<tr>
<td><strong>12-13 yrs.</strong></td>
<td>&lt;7-800</td>
<td></td>
<td>&lt;7-75</td>
<td></td>
</tr>
<tr>
<td><strong>14 yrs.</strong></td>
<td>&lt;7-1,200</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>15-16 yrs.</strong></td>
<td>100-1,200</td>
<td></td>
<td>20-75</td>
<td></td>
</tr>
<tr>
<td><strong>17-18 yrs.</strong></td>
<td>300-1,200</td>
<td></td>
<td>8-60</td>
<td></td>
</tr>
<tr>
<td><strong>19+ yrs.</strong></td>
<td>240-950</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Avg. Adult</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>270-1,070</td>
<td></td>
<td>15-70</td>
<td></td>
</tr>
<tr>
<td>30+ yrs.</td>
<td>-1% per year</td>
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</tbody>
</table>

**30+ yrs.** Total Serum Testosterone Levels: **-1% per year**
LH and FSH – is it Primary (Gonadal) or Secondary (Pituitary)

Testosterone is below normal on two occasions,
- serum LH concentration should be measured to distinguish primary from secondary hypogonadism

Measuring basal serum concentrations of both LH and FSH help to interpret subnormal values for serum testosterone
- If the serum testosterone concentration is subnormal, supranormal serum LH and FSH concentrations (normal range for both about 1 to 8 mIU/mL in most laboratories
  - primary hypogonadism
- Values that are not supra-normal
  - secondary hypogonadism.
- Clearly elevated gonadotropin values are indicative of primary hypogonadism even if the serum testosterone concentration is in the low-normal range.
Why is it important to differentiate between Primary and Secondary hypogonadism?

- **Secondary Hypogonadism** is gonadotropin deficiency or dysfunction as a result of disease or damage to the hypothalamic-pituitary axis. This is known as secondary hypogonadism.
  - Kallmann’s syndrome – absent GnRH
  - Pituitary - tumor, trauma, radiation,
  - Sarcoidosis or Tuberculosis

- **Primary Hypogonadism** is testicular failure.
  - Most are idiopathic or “Manopause”
  - Genetic disorders (e.g., Klinefelter’s syndrome)
  - Orchitis, trauma, radiation, chemotherapy, or
  - Undescended testes
Cardiovascular and All Cause Mortality has been conflicting

- Muraleedharan et al. Population-based prospective cohort 581 men
  - Low T levels predict an increase in all-cause mortality

- Yeap et al. Population-based cohort study 3690 70–89
  - Older men with midrange levels of T and DHT had the lowest death rates from any cause

- Araujo et al. Meta-analysis
  - Low endogenous T levels associated with increased risk of all-cause and CV death

- Laughlin et al.
  - Prospective, population-based study 794 Men with T in the lowest quartile were 40% more likely to die than those with higher levels

- Hyde et al. [76]
  - Population-based cohort study 3.637 70–88 Low T predicts mortality from CVD

- Smith et al. [78]
  - Prospective cohort study 2512 45–59 No association between total T and all-cause mortality
Can his obesity affect the levels?

TRUE
Obesity and SHBG

- Obesity decreases the serum concentration of SHBG
  - How….it’s still unclear

- Decrease serum total T concentration without lowering the free T concentration

- The binding abnormality is proportional to the degree of obesity and is corrected by weight loss.

- Severe obesity (body mass index [BMI] >40) may cause hypothalamic hypogonadism as well as the binding abnormality

Serum Free testosterone

- performed by equilibrium dialysis and only in those few laboratories that specialize in endocrine testing.

- Free testosterone measured by an analog method, (the assay most commonly offered by hospital and commercial laboratories) does not correlate with the results of equilibrium dialysis.
  - This test gives misleading information and should never be ordered.
Principles guiding testosterone therapy:

- Testosterone should be administered **only to a man who is hypogonadal** evidenced by:
  - Clinical symptoms and signs consistent with androgen deficiency
  - A Distinctly subnormal serum testosterone concentration on 2-3 fasting occasions
Testosterone Replacement

Whether primary or secondary hypogonadism.

- Goal of testosterone therapy is to restore the serum testosterone concentration to the normal range.
  - It is not yet known if restoring the normal circadian rhythm of testosterone is important.

- Testosterone therapy is indicated only for testosterone deficiency, not for impaired spermatogenesis.
  - Impairs spermatogenesis further by suppressing pituitary gonadotropin secretion.
Clinical indications for considering testosterone therapy in men with low testosterone levels …..

- **Sexual indications - efficacy data limited and inconsistent**
  - Induction or maintenance of secondary sex characteristics in symptomatic men with classical androgen deficiency syndromes (*Low-quality evidence*)
  - Low or diminished libido (*EAU Grade A, Level 2a*)
  - Erectile dysfunction (*EAU Grade A, Level 2a*)

- **Musculoskeletal indications**
  - Osteoporosis or high risk for fracture due to low bone mineral density, and contraindications to approved drugs for osteoporosis (*Low-quality evidence*); testosterone therapy may increase *bone mineral density* (*level 3 [lacking direct] evidence*)
  - Decreased muscle mass or strength (*level 3 [lacking direct] evidence*)

- **Neuropsychological indications**
  - Impaired cognition, irritability, other mood changes, or declining energy and stamina; intramuscular or transdermal testosterone may improve *quality of life level 2 [mid-level] evidence*
  - To improve sense of well-being (*Endocrine Society Strong recommendation, Low-quality evidence*)

- **HIV infection with weight loss, as short-term adjunctive therapy to promote weight maintenance, and to increase lean body mass and muscle strength** (*Endocrine Society Weak recommendation, Low-quality evidence*)
Clinical Desirable and Undesirable Effects:

- The desirable effects of testosterone administration: **virilization**
  - the development or maintenance of secondary sexual characteristics
  - increases in libido, muscle strength, fat-free mass, and bone density

- Undesirable effects related directly to testosterone include
  - acne,
  - prostate disorders (such as benign prostatic hyperplasia [BPH] symptoms),
  - sleep apnea, and
  - erythrocytosis.
  - Shrinking testicles
  - And........
Virile: definitions, quotes and poetry

**Dictionary:**

- [adj] characteristic of a man; "a deep male voice"; "manly sports"
- [adj] (of a male) able to copulate
- [adj] characterized by energy and vigor; "a virile and ever stronger free society"; "a new and virile leadership"

**Quotes:**

- "It takes a virile man to make a chicken pregnant."
- "What is most beautiful in virile men is something feminine; what is most beautiful in feminine women is something masculine."

**Poetry:**

There was a virile wallpaper hanger called Brunn Who did his best to make every job well done. His fame spread far and near. And clients were heard to cheer "Hire Brunn if you want something well hung."
So what happens with normalization of T concentrations....

- **Virilization or sexual function** —
  - normal virilization in men who are not virilized
  - maintenance of virilization in those who already are.
    - Note a marked improvement in symptoms.
    - Failure of improvement when the serum testosterone concentration has been restored to normal suggests another cause of the symptoms.

- **Muscle strength/fat-free mass** —
  - substantial improvements in muscle strength and fat-free mass in hypogonadal men.

- **Bone Density**
  - 39 percent increase in the first year of testosterone replacement
Less well supported

- **Mood**
  - Inconsistent Data
  - Older Men with “subclinical depression”

- **Cognition**
  - No improvement in older men

- **Cardiovascular**
  - Mixed Data

- Sharma et al European Heart Journal August 2015
  - large observational cohort with extended follow-up, normalization of TT levels after TRT was associated with a significant reduction in all-cause mortality, MI, and stroke
Time course of effects

- Quite variable.
  - Increases in fat-free mass, prostate volume, erythropoiesis, energy, and sexual function occurred within the first three to six months.
  - In contrast, the full effect on bone mineral density (BMD) did not occur until 24 months.
Contraindications to testosterone therapy include:

- Known prostate cancer
- Prostate-specific antigen (PSA) concentration >4.0 mcg/L, or >3.0 mcg/L in high-risk men or breast cancer
- Exception - hypogonadal man who had a radical prostatectomy for cancer confined to the prostate, and has been free of disease and has had an undetectable PSA for at least two years

- Severe lower urinary tract symptoms (LUTS) with an International Prostate Symptom Score [IPSS] >19,
- Hematocrit >50 percent,
- Untreated severe sleep apnea
- Uncontrolled heart failure

If LUTS, erythrocytosis, or sleep apnea is successfully treated, then testosterone treatment may begin.
Fred is excited…What Testosterone Preparation will you advise him to use?

A. Injections
B. Patches
C. Gels
D. Buccal Tablets
E. Implants
F. Nasal Spray
G. None of these…tough it out you Neanderthal
Choice of testosterone regimen

Choosing among the different testosterone preparations requires an understanding of their pharmacokinetics. Native testosterone is absorbed well from the intestine, but it is metabolized so rapidly by the liver that it is virtually impossible to maintain a normal serum testosterone concentration in a hypogonadal man with oral testosterone. Testosterone gels result in normal and relatively stable serum testosterone concentrations, and most patients prefer them to other preparations. However, other factors affect choice of regimen, including patient preference, cost, convenience, and insurance coverage, which varies by plan and regimen. In general, the newest preparations (the gels) cost the most, the patch costs somewhat less, injectable esters cost the least.
Oral preparations

Several 17-alpha alkylated androgens (eg, methyltestosterone) have been available for oral use for many years

- Suggest not using them.
- Oral testosterone undecanoate is available in some countries but not the United States

- Adding an alkyl group in the 17-alpha position of the testosterone molecule retarded its catabolism by the liver

- Not fully effective in producing virilization, although no studies have tested these observations

- Hepatic side effects with these preparations,
  - including cholestatic jaundice, a hepatic cystic disease called peliosis hepatis, and hepatoma

- GI side effects

- Cannot serum testosterone concentration normal in hypogonadal men.
Long-acting injections

- Testosterone enanthate and testosterone cypionate.
  - Esterification of a lipophilic fatty acid to the 17-beta hydroxyl group of testosterone
  - Intramuscular (IM) injection of testosterone esters results in their storage and gradual release from the oil-based vehicle
    - prolonging the presence of testosterone in the blood.
  - Advantages: biologically effective in initiating and maintaining normal virilization in all hypogonadal men and freedom from daily administration
  - Disadvantages:
    - need for deep IM administration of an oily solution every one to three weeks and
    - fluctuations in the serum testosterone concentration - fluctuations in energy, mood, and libido in many patients.
      - These fluctuations are more pronounced as the dosing interval is increased.

- Testosterone enanthate can be administered once every one to two weeks in most men, every three weeks in a few, but not every four weeks
  - Doses of 50 to 100 mg every week or 100 to 200 mg every two weeks.
Extra-long-acting injections

- An IM formulation of another ester of testosterone, testosterone undecanoate, is available in several countries for treatment of hypogonadism.

- United States preparation slightly different:
  - Each dose is 750 mg in 3 mL of oil injected only into the buttocks.
  - The initial dose is followed by a second dose four weeks later and by subsequent doses every 10 weeks.
  - The extra-long-acting preparations have been associated with rare cases of pulmonary oil microembolism (POME) and anaphylaxis (1.5 and 0.4 cases per 10,000 injections, respectively)
  - In the United States, the drug is available only through a restricted program called the AVEED Risk Evaluation and Mitigation Strategy (REMS) Program.
    - All injections must be administered in an office or hospital setting by a trained and registered health care provider and monitored for 30 minutes afterwards for adverse reactions.

- After the 3rd injection, the average peak serum testosterone value occurs about one week after an injection,
  - Followed by a gradual decline until the next injection.
  - The serum testosterone concentration at about five weeks would provide an approximate average for the interdosing period.
Transdermal/topical delivery

- Transdermal delivery of testosterone first became available in 1994 with the introduction of a scrotal patch - but the scrotal patch is no longer available.

- Body patches and gels

- The major advantage - relatively stable serum testosterone concentrations, resulting in maintenance of relatively stable energy, mood, and libido.

- Androderm patch
  - is available in some countries but not in the United Kingdom.
  - Androderm relies upon chemical means to increase the absorption of testosterone across nongenital skin, such as the arm or torso.
  - Delivers approximately 2 or 4 mg of testosterone per 24 hours and results in normal serum testosterone concentrations in the majority of hypogonadal men.
  - Anecdotal reports suggest that as many as one-third of men who try this preparation cannot continue it because of severe skin rash. A matrix transdermal testosterone patch is available in countries outside of the United States.
Gels

- Four testosterone gels are available:
  - AndroGel, Testim, Fortesta, and Axiron.
AndroGel

- Supplied in both 1% and 1.62% concentrations and in 2.5 and 5.0 g packets, and in 20.25 and 40.5 mg packets.
- Packets contain 25 and 50 mg of testosterone, respectively
- 1 pump of 1% - contains 12.5 mg of testosterone
- 1 pump of 1.62% - contains 20.25 mg of testosterone.
- Doses delivering 50 to 100 mg of testosterone the serum testosterone concentrations usually reach the normal male range within a month and remain steady throughout 24 hours.
- The serum concentrations of testosterone throughout the 24 hours from one application to the next are similar at one, three, and six months.
- Occasional local skin irritation occurs but usually does not necessitate discontinuation of therapy.
Other Testosterone Preps

- Testim (1% testosterone gel - tubes containing doses of 5 and 10 g, which contain 50 and 100 mg of testosterone,. Anecdotal reports suggest that this preparation gives a musk-like odor.

- Fortesta (2% testosterone gel) is also supplied in a metered-dose pump, with each pump depression delivering 0.5 g of gel (containing 10 mg of testosterone)
  - The recommended starting dose is 40 mg, applied to the front and inner thighs, and adjusted to a minimum of 10 mg and a maximum of 70 mg, as determined by the serum testosterone concentration.

- Axiron (2% testosterone solution) is a solution of testosterone that also comes in a metered-dose pump with applicator. Each depression yields 30 mg (1.5 mL) of testosterone.
  - The package insert suggests a starting dose of 30 mg applied to each axilla (total of 60 mg) once a day and adjustment of the dose as low as 30 mg and as high as 120 mg once a day
Other preparations

- A buccal tablet (Striant SR), 30 mg, is applied twice a day and adheres to a depression in the gum above the upper incisors.
  - Releases testosterone across the buccal mucosa into the systemic circulation.

- A subcutaneous testosterone pellet (Testopel)
  - The manufacturer recommends three to six 75 mg testosterone pellets every three to six months.
  - Implanted into the subdermal fat of the buttocks, lower abdominal wall, or thigh with a trocar under sterile conditions using a local anesthetic.
  - Adverse events include pellet extrusion, infection, and fibrosis.
  - Not routinely recommend this preparation.

- A nasal testosterone gel (Natesto)
  - The gel is administered into the nostrils via a metered-dose pump applicator.
  - One pump actuation delivers 5.5 mg of testosterone; the recommended dose is 11 mg (two pump actuations, one in each nostril), three times daily (total 33 mg/day).
  - An advantage over other formulations is the minimal risk of gel transfer to a partner or child.

- Human chorionic gonadotropin (hCG),
  - While not an androgen, stimulates the testes to make testosterone and is especially useful in stimulating both testosterone and sperm production. It is given by subcutaneous or IM injections two to three times weekly.
https://www.youtube.com/watch?v=yqPuRelnfR0
Fred’s buddy - Barney Comes in the Next Day

- Amazed with Fred’s Improvement
- Wants some of the juice
- He and Betty are having their issues
- How about it Doc?
Manopause?! Aging, Insecurity and the $2 Billion Testosterone Industry

David Von Drehle  July 31, 2014

The sign over the clinic door says Low T Center, as in low testosterone, as in not enough man juice in the tank. Inside, the place is musky with masculinity. The spacious suite is situated in a handsome office building in the prosperous North Texas suburb of Southlake, staffed by attractive female receptionists who welcome patients into the “man cave.” ESPN plays on the flat-screen near a bar stocked with drinks and snacks. The rooms are decorated with autographed football jerseys and other sports memorabilia. A he-man with a firm handshake named Mike Sisk is the proprietor, but he’s no doctor. Instead, Sisk is enough of a businessman to realize that America’s beer bellies could be worth their weight in ...
What about those with symptoms but not consistent lab evidence:

- Inappropriate use of testosterone in healthy middle-aged men
- Dramatic increase in inappropriate use of testosterone therapy
- Direct-to-consumer advertising encouraging use of testosterone products for nonspecific symptoms
- It is important for clinicians to understand that the diagnosis of testosterone deficiency should be made only on the basis of clinical symptoms and signs consistent with androgen deficiency and consistently subnormal serum testosterone concentrations at 8 to 10 AM on three occasions.
- Vague symptoms that could be the result of low testosterone (e.g., fatigue), and a single but not repeatedly subnormal serum testosterone concentration, recommend strongly against testosterone use.
- Once men have started treatment, they may find cessation difficult because of the prolonged period of hypogonadism during recovery of the pituitary-testicular axis
Less Clear

- In men who have a low testosterone for no apparent reason other than age, the benefits of testosterone treatment have not been established.

- Experts disagree as to what level should be considered unequivocally low in these men;
  - some favor <300 ng/dL,
  - but others <200 ng/dL.

- Discuss with these men the uncertainty of the benefits of testosterone treatment and the possible risks:
  - Erythrocytosis, exacerbation of prostate cancer, benign prostatic hyperplasia (BPH), and cardiovascular disease
Fred has been applying the topical gel now for some months

- What type of monitoring is needed?
- How many testosterone levels before making any adjustments?
- Does it matter what T replacement he is on as to when the T is checked?
- Are there some specific things you need to inquire about that are preparation specific?
Monitoring- Is the testosterone dose therapeutic?

- Serum testosterone concentration — Patients who are treated with testosterone should be monitored to determine that normal serum testosterone concentrations are being achieved.
  - 2-3 months after initiation of treatment and after changing a dose.
  - When the dose stable, monitoring over 6 to 12 months should suffice.
Preparation Specific Timing of Serum testosterone measurements

- **IM Testosterone** - measured midway between injections
  - mid-normal, eg, 500 to 600 ng/dL (20.8 to 24.3 nmol/L)

- **Transdermal** – anytime
  - Peak values occur six to eight hours after application of the patch.

- **Gel** - vary substantially when a gel is used, but not in a predictable way.
  - Two serum testosterone measurements before making dose adjustments
  - The therapeutic goal should be a testosterone value well within the normal range (400 to 700 ng/dL [13.9 to 27.7 nmol/L]).
Formulation-specific adverse events at each visit

- Buccal testosterone tablets:
  - alterations in taste and examine gums and oral mucosa for irritation.

- Injectable testosterone esters:
  - fluctuations in mood or libido
  - evaluate hematocrit to detect excessive erythrocytosis, especially in older patients.

- Testosterone patch:
  - signs of skin reaction at the application site.

- Testosterone gels:
  - advise patients to cover the application site with clothing and wash the skin before having skin-to-skin contact,
## Monitoring testosterone therapy: What the consensus guidelines say

q, every; BMD, bone mineral density; DRE, digital rectal exam; PSA, prostate-specific antigen

<table>
<thead>
<tr>
<th>Organization</th>
<th>First follow-up</th>
<th>Digital Rectal Exam (DRE)</th>
<th>PSA test</th>
<th>Testosterone levels</th>
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<th>Lipids</th>
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<tr>
<td>American Association of Clinical Endocrinologist</td>
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<td>q 6-12 mo</td>
<td>Annually</td>
<td>q 6 mo x 3, then annually</td>
<td>q 1-2 y, then annually</td>
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<td></td>
</tr>
<tr>
<td>American Society for Reproductive Medicines</td>
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<td>At 3 and 6 mo, then annually</td>
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<td></td>
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<tr>
<td>The Endocrine Society</td>
<td>At 3 mo, then annually</td>
<td>At 3 mo, then per routine guidelines</td>
<td>At 3 mo, then per routine guidelines</td>
<td>At 3 mo, then annually</td>
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<td>At 1-2 y</td>
<td></td>
</tr>
<tr>
<td>European Association of Urology</td>
<td>At 3 mo</td>
<td>At 3 and 6 mo, then annually</td>
<td>At 3 and 6 mo, then annually</td>
<td>At 3 mo, then annually</td>
<td>At 3 mo, then annually</td>
<td>q 1-2 y</td>
<td></td>
</tr>
</tbody>
</table>

From: VOL 59, NO 12 | DECEMBER 2010 | THE JOURNAL OF FAMILY PRACTICE
Prostate Exam every 3 months???

https://www.youtube.com/watch?v=beqdxDlNnVs
Wilma returns to clinic

- 6 months out
- On CEE/MPA 1.25mg/5mg qd and fluoxetine 20 mg a day
- Sleep improved, mood improved, fewer hot flashes
- She wonders … what is the next step?
  - Dose reduction
  - Duration of therapy
  - Endometrial monitoring
Summary: Menopause

- Laboratory testing unnecessary
- Identify target symptoms
- Patient-centered treatment plans
- Anticipate bleeding on HRT
Summary:

- **Diagnosis of androgen deficiency**
  - consistent symptoms and signs
  - unequivocally low serum testosterone levels.
    - morning total testosterone level by a reliable assay as the initial diagnostic test. (EAU Grade A, Level 2a)
    - repeating the measurement of morning total testosterone and in some patients by measurement of free or bioavailable testosterone level, using accurate assays. (EAU Grade C, Level 3)

- **Testosterone therapy only for**
  - Symptomatic men with androgen deficiency,
  - Low testosterone levels, [Endocrine Society Strong recommendation, Very low-quality evidence](#)
  - For:
    - induce and maintain secondary sex characteristics
    - improve their sexual function,
    - sense of well-being,
    - muscle mass and strength
    - bone mineral density.
Monitoring Men on Testosterone

- measure testosterone level and hematocrit at baseline, at 3-6 months, then annually (Endocrine Society Strong recommendation, Very low-quality evidence)

- Measure prostate-specific antigen (PSA) and perform digital rectal exam at baseline,
  - at 3-6 months, then according to age- and race-specific prostate cancer screening guidelines in men ≥ 40 years old with baseline PSA > 0.6 ng/mL (Endocrine Society Strong recommendation, Very low-quality evidence)

- Assess symptoms, response to treatment, adverse effects, and patient compliance at 3-6 months, then annually (Endocrine Society Strong recommendation, Very low-quality evidence)

- in men with osteoporosis or low-trauma fracture, repeat lumbar spine, femoral neck, and hip bone mineral density after 1-2 years of testosterone therapy (Endocrine Society Weak recommendation, Very low-quality evidence)
Thanks…..and Yabba-Dabba-Do!

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Bob Gobbo  
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Well.....what about Mr. Slate

- Fred’s Boss at Bedrock Industry’s
- Wants to be tested for low T
- Claims he can’t remember where he puts his money
- Is feeling a bit blue and tired.....not even Trump gets him excited
- Thinks he is shrinking
- Heard about Fred’s Low T and wants some of the same
- Used to have his eye on Wilma
AGE RELATED DECLINE IN TESTOSTERONE LEVELS

Free Test (nmol/T)

Total Test (nmol/T)

Free Test

Total Test

YEARS: 18-29 30-49 50-59 60-69 70-79 80-89 90-100 >100

0.775 0.5 0.375 0.25

25 20 15 10
IS THERE A SYNDROME OF HYPOGONADISM IN OLDER MEN?

- Supported by:
  - The combination of low serum testosterone (<317 ng/dL [11 nmol/L]) and three sexual symptoms was significantly associated with
    - lower hemoglobin, estimated heel bone mineral density (BMD), mid-upper arm circumference, and physical performance.
    - More severe hypogonadism (serum testosterone concentration <230 ng/dL [8 nmol/L]) was also associated with insulin resistance.
    - The associations were stronger when the serum testosterone concentration was <230 ng/dL (8 nmol/L) than when it was in the 230 to 317 ng/dL range (8 to 11 nmol/L).

- These data support the concept of a low testosterone syndrome in middle aged and older men,
  - but only in a small percentage
“Andropause” or “Late-onset hypogonadism”

- As men age, their serum concentrations of testosterone and, to a greater extent, free testosterone,”

- Unlike menopause, where complete estrogen deficiency with known clinical consequences occurs,

- The decline in testosterone in aging men is modest and the possible clinical consequences have not been well-established

- The question of whether or not testosterone should be administered to older men is difficult to.
Decline with Age

- Relatively small.
  - In one study, testosterone declined about 100 ng/dL (3.5 nmol/L) from age 20 to age 80 years [11].
  - Young men exhibit a diurnal variation, with highest values at about 8 AM and lowest about 8 PM, but older men have little variation (figure 1) [6].
  - Serum testosterone decreases at a fairly constant rate, independent of other clinical variables.

- As a result of this fall, a greater percentage of older men have testosterone values sufficiently low to be considered hypogonadal in young men.

- Serum total testosterone concentration falls 0.4% a year and the free testosterone concentration fell 1.3% a year.

- 2.8 percent per year.

- The percentage of subjects with total testosterone concentrations in the hypogonadal range (defined in this study as total testosterone <325 ng/dL [11.3 nmol/L]) was 20, 30, and 50 percent for men in their 60s, 70s, and 80s, respectively (figure 3).
Consequences of the decline in serum testosterone with age

- None known with certainty

- Sexual function, measured by frequency of orgasm or intercourse or by sexual satisfaction, is less in older men than in young men

- In 3369 men ages 40 to 79 years who were participating in the European Male Aging Study (EMAS), the only symptoms that were significantly associated with a serum testosterone concentration less than 320 ng/dL (11.1 nmol/L) were three sexual symptoms:
  - poor morning erection,
  - low sexual desire
  - erectile dysfunction
Bone mineral density and fractures

In a prospective cohort study of men over age 65 years, the risk of nonvertebral fractures was increased in those who had low serum concentrations of bioavailable estradiol or high sex hormone-binding concentration (SHBG) but not in those who had only a low bioavailable testosterone.

- Risk was greatest (hazard ratio [HR] 3.4 [2.2 to 5.3]) in men with low bioavailable estradiol and testosterone and high SHBG.
Recent NEJM Article Feb 18th 2016

- Effects of Testosterone on Older Men

- 790 Men 65 and older
  - Serum T < 275 ng/dl and symptoms
  - Randomized to Testosterone or Placebo Gel for 1 year

- Results:
  - Testosterone group had serum T in 19-40 Mid-Normal Range
    - Increased Sexual Activity, Desire and Erectile Function p < .001
  - No change in walking distance
  - No effective on vitality
  - Slightly better mood and less depressive symptoms
  - Adverse events similar
Testosterone replacement in older men?

- Impact of treatment in older men remains unclear in the absence of known pituitary or testicular disease,

- Testosterone therapy only for men with low serum testosterone concentrations on more than one occasion and symptoms of testosterone deficiency

- The target serum testosterone concentration in older men should be lower than that for younger men, for example, 300 to 400 ng/dL

- Do not offer testosterone therapy to older men with low testosterone levels without clinically significant symptoms of androgen deficiency (Endocrine Society Strong recommendation, Very low-quality evidence)
That’s all we got......

YABBA DABBA DOO!