Evaluation and Treatment of Erectile Dysfunction

General Internal Medicine Conference
March 20, 2013

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Clinical Assistant Professor
Department of Medicine
Case #2

- 34 year old male, no PMH
- HPI:
  - wife made him come in to see you
  - progressive ED x few months
  - no libido
  - no morning erections
  - no substance use
- PE: mild testicular atrophy
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- 56 year old male
- PMH: chronic MSK pain, Hep C w/o cirrhosis.
- SH: EtOH abuse in remission; no tobacco
- Meds: methadone, naproxen
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  - new partner, desires intimacy
  - no morning erections
  - able to masturbate to orgasm, but poor quality erection
- PE: body hair present though not dense; mild gynecomastia; testes normal size but somewhat soft, unremarkable phallus
Case #3

- 53yo male
- PMH: doesn’t doctor much
- SH: 30 pack year smoking history, no exercise.
- HPI: progressive ED x 6-10 years
- PE:
  - Vitals: BP 152/94 HR 87 BMI: 35
  - Gen: central obesity
  - CV: RRR no m/r/g, Lungs CTAB
  - GU: normal circumcised phallus, no testicular atrophy
Case #4

- 62 yo male
- PMH: CAD s/p MI and CABG 7 years ago.
- HPI:
  - Progressive dyspnea = CHF dx 6 months ago
  - New meds: isosorbide mononitrate, hydralazine
  - CHF sx now controlled
  - Hx ED on PDE5i
  - Wants to resume intimacy with his wife
Case #5

- 50 yo male
- PMH: hyperlipidemia, hypertension, depression
- Meds: metoprolol, lisinopril, sertraline
- HPI:
  - Gradual onset ED x few years
  - Tried sildenafil and vardenafil without success.
- PE: obese, otherwise unremarkable
Case #6

- 62 yo male
- PMH: hyperlipidemia, hypertension
- Meds: simvastatin, HCTZ
- HPI:
  - Gradual onset ED x few years
  - Good libido
  - never tried a medication
  - likes spontaneity in his romantic life
- PE: unremarkable
“Once this commercial is over, I’ll have a number of questions on erectile dysfunction.”
Objectives

• Select patients appropriately for hormonal testing
• Compare available therapies for ED
• Select therapies for a variety of patients with ED
• Evaluate treatment effect
• Troubleshoot ED treatment failures
Erectile dysfunction

• NIH Consensus Conference 1993
  – Erectile Dysfunction is the persistent inability to achieve or maintain penile erection sufficient for satisfactory sexual performance.

• ED does not imply:
  – low libido
  – inability to ejaculate
  – inability to achieve orgasm
  – age-related latency
ED: Epidemiology

- Incidence increases with age
- 52% of men aged 40-70*
  - 17.2% “minimal”
  - 25.2% “moderate”
  - 9.6% “complete”
- $2.7 billion (2005)

*Massachusetts Male Aging Study (1994)
ED: Etiology

- ~80% organic
- ~20% psychogenic
ED: Etiology

- **Organic causes:**
  - *Primarily vascular*
  - Endocrine
    - Testosterone deficiency: 12.5-25.3%
    - Hyperprolactinemia: 1.42-14.3%
  - Neurologic
  - Iatrogenic
  - Substances
    - Alcohol
    - Tobacco
  - Anatomical
  - other
**ED: Diagnostic approach**

- **Detailed history**
  - HPI: Libido, morning erections, performance anxiety, age related changes, relationship issues
  - PMH: contributing conditions, substances, or meds
- **Physical exam**
  - Blood pressure, peripheral pulses, habitus, secondary sexual characteristics, gynecomastia, penile abnormalities, testicular exam, +/- prostate exam
- **Diagnostic testing**
Guidelines included

- American Urological Association (AUA): 2005
- Agency for Healthcare Research and Quality (AHRQ): 2009
- American Association of Clinical Endocrinologists (AACE): 2003
- Endocrine Society (ES): 2010
ED: Diagnostic approach

- **AUA:**
  - Labs as needed to exclude non-vascular organic cause
  - OR if failure of first line therapy (no grade)
- **AHRQ:**
  - does not recommend for or against routine hormonal testing (insufficient evidence)
- **AACE:**
  - recommends routine blood tests: glucose, PRL, Free T (no grade)
- **ES:**
When to consider labs

- **Endocrine Society**:  
  - “suggest” testing with “more specific” sx  
  - “suggest… consider” testing with “less specific” sx  
  - (weak recommendation; very low quality evidence)
When to consider labs: signs/symptoms

• “More specific”
  – Incomplete/delayed sexual development
  – Low libido
  – Fewer spontaneous erections
  – Gynecomastia/tenderness
  – Losing body hair (shaving?)
  – Small/shrinking testes (<5ml)
  – Infertility; low/zero sperm
  – Low bone mass signs/sx
  – Hot flushes

• “Less specific”
  – Low energy
  – Depressed mood
  – Poor concentration
  – Sleep changes
  – Mild normocytic anemia
  – Decreased muscle bulk
  – Increasing body fat/BMI
  – Decreasing physical performance
When to consider labs: signs/symptoms

• There are no well validated “case detection” interview or questionnaire tools at this time.
When to consider labs: targeted screening

- Sellar mass, XRT, etc. hx
- Meds: chronic GC/narcotic use
- HIV-associated weight loss
- ESRD on HD
- Moderate to severe COPD
- Infertility
- Male osteoporosis/fragility fx (esp if younger)
- DM2
Evaluation of androgen deficiency

History and physical (symptoms and signs)

Morning Total T → Normal T

Low T #

Exclude reversible illness, drugs, nutritional deficiency

Repeat T [use free or bioavailable T, if suspect altered SHBG^]

LH+FSH

SFA [if fertility issue]

Follow up

Confirmed low T [Low total T #; or free or bioavailable T®])

Low T, low or normal LH+FSH (secondary hypogonadism)

Low T, high LH+FSH (primary hypogonadism)

Normal T, LH+FSH

Prolactin, iron, other pituitary hormones, MRI [under certain circumstances*]

Karyotype [Klinefelter syndrome]

Bhasin S et al. JCEM 2010;95:2536-2559
Evaluation of androgen deficiency

- 8AM total testosterone
- 8AM free or bioavailable testosterone
- SHBG altering conditions:

<table>
<thead>
<tr>
<th>Increases SHBG</th>
<th>Decreases SHBG</th>
</tr>
</thead>
<tbody>
<tr>
<td>obesity</td>
<td>age</td>
</tr>
<tr>
<td>nephrotic syndrome</td>
<td>hepatic dysfunction</td>
</tr>
<tr>
<td>hypothyroid</td>
<td>hyperthyroid</td>
</tr>
<tr>
<td>glucocorticoids</td>
<td>anticonvulsants</td>
</tr>
<tr>
<td>diabetes</td>
<td>HIV</td>
</tr>
</tbody>
</table>
Treatment of Erectile Dysfunction

- Lifestyle modification
  - exercise
  - weight loss
  - SMOKING CESSATION!!!
  - alcohol cessation

- Treat underlying disorders
ED: First line medical therapy

- Phosphodiesterase type 5 inhibitors (PDE5i)
  - sildenafil (Viagra)
  - vardenafil (Levitra)
  - tadalafil (Cialis)

- AHRQ: strong rec; high-quality evidence
- AUA: Standard of care (expert opinion)
- AACE: no grade
PDE5i: patient selection

- Everyone without otherwise treatable organic cause
- Absolute contraindications:
  - Unstable cardiac conditions
  - Use of nitrates (PDE-5i potentiate vasodilation)
PDE5i: mechanism of action

**Endothelial cell**
- L-arginine → NO
- eNOS

**Corpus Cavernosum smooth muscle cell**
- NANC cavernous nerve
  - L-arginine
  - nNOS
  - NO
- Guanylate cyclase
  - NO
- GTP
- cGMP
- GMP
- PDE-5
- NO
- PDE-5i

External sensory stimuli
PDE5i: drug selection

- **AHRQ**: based on patient preferences
  - weak recommendation; low-quality evidence
- **AUA/AACE**: no recs
  - prior to comparative studies
PDE5i: drug selection

- Cost
- Pharmacokinetics
- Patient preferences
- Comorbidities
PDE5i selection: cost

"I'll have someone come in and prep you for the bill."
## PDE5i selection: cost

<table>
<thead>
<tr>
<th></th>
<th>Per dose (mid range) at UW</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Navitus</td>
<td>Cash</td>
</tr>
<tr>
<td>sildenafil (Viagra)</td>
<td>$8.75 (#4/month)</td>
<td>$27.30</td>
</tr>
<tr>
<td>vardenafil (Levitra)</td>
<td>--</td>
<td>$18.98</td>
</tr>
<tr>
<td>tadalafil (Cialis)</td>
<td>--</td>
<td>$33.41</td>
</tr>
<tr>
<td>tadalafil daily (#30)</td>
<td>--</td>
<td>$145.90 (per month)</td>
</tr>
</tbody>
</table>
PDE5i cost tips

- Can split pills
- Target/Wal-Mart cheapest in town
  - store dependent, call ahead
- Walgreens is most expensive
- Revatio will be coming off patent 3-6 mo
PDE5i selection: pharmacokinetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sildenafil(^1,2)</th>
<th>Tadalafil(^3)</th>
<th>Vardenafil(^4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability</td>
<td>40%</td>
<td>nd</td>
<td>15%</td>
</tr>
<tr>
<td>( \Delta C_{\text{max}} ) with food</td>
<td>≤29%</td>
<td>no change</td>
<td>≤20%</td>
</tr>
<tr>
<td>( t_{\text{max}} ) (h)</td>
<td>1*</td>
<td>2*</td>
<td>1*</td>
</tr>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>3-5</td>
<td>17.5</td>
<td>~4</td>
</tr>
</tbody>
</table>

Medscape Education: PDE5 inhibitor therapy: Overview of Safety and Efficacy
PDE5i: drug interactions

• CYP3A4 inhibitors raise PDE5i blood levels
  – amiodarone
  – some HIV medications
  – some azoles
  – some CCBs
  – fluoxetine
  – GRAPEFRUIT

• Cialis sig if taking CYP3A4: q72hrs
### PDE5i: dosing

<table>
<thead>
<tr>
<th></th>
<th>Range (mg)</th>
<th>&gt;65yo</th>
<th>Hepatic dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>25, 50, 100</td>
<td>25</td>
<td>start 25</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>2.5, 5, 10, 20</td>
<td>5</td>
<td>max 10</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>2.5, 5, 10, 20</td>
<td>-</td>
<td>max 10</td>
</tr>
<tr>
<td>Tadalafil daily</td>
<td>2.5, 5</td>
<td>-</td>
<td>caution</td>
</tr>
</tbody>
</table>
PDE5i: keys to success

- Identify and treat underlying conditions
- Titrate dose
- Manage patient expectations
- Optimize use of medication
  - Food/drug interactions
  - Timing/frequency
  - Lack of adequate sexual stimulation
  - Heavy alcohol use
  - Partner/relationship issues
PDE5i: efficacy

• 68-69% vs 33-35% placebo

"He was unhappy to learn that I had prescribed a placebo but when I told him it was an extra-strength placebo, he was pleased."
PDE5i: side effects

- **Common**
  - Headache
  - Flushing
  - Rhinitis
  - Dyspepsia

- **“Serious”**
  - Equal to placebo
  - Hypotension, AION, vision loss, hearing loss, seizures, syncope, angina, MI

- **Less common**
  - Visual changes
    - Sildenafil
  - Myalgia
  - Nausea
  - Diarrhea
  - Vomiting
  - Dizziness
  - Chest pain
Princeton Consensus Conference

- ED identifies increased CVD risk
- Most low-risk patients can initiate or resume sexual activity and begin ED treatment without further testing or evaluation.
  - Low risk: 4 Mets exercise tolerance
    - NYHA class I, II CHF (>5 Mets)
    - Successfully revascularized CAD
    - Controlled hypertension
Princeton Consensus Conference

- Intermediate risk patients may need further evaluation before pursuing PDE5i
  - past MI 2-8 wks
  - mild/mod, stable angina
  - Hx PAD, CVA, TIA

- High risk patients (unstable cardiac conditions) cannot use PDE5i
Second-line therapies for ED

- Vacuum constriction devices
- Intra-urethral suppositories
- Intracavernous injections

- Side effects: local pain, priapism (inj: fibrosis)
- AUA: panel consensus
Vacuum constriction device

- Available OTC; needs limiter; $140-190
Intracavernous injections

- alprostadil
- papaverine
- phentolamine

Image from Up to Date, “Treatment of Male Sexual Dysfunction”
## IU/injectable treatments: cost

<table>
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<th>Cash</th>
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<tr>
<td>IU alprostadil (Muse)</td>
<td>$56.50</td>
</tr>
<tr>
<td>alprostadil (Caverject)</td>
<td>$68.50</td>
</tr>
<tr>
<td>papaverine*</td>
<td>$0.85-1.70</td>
</tr>
<tr>
<td>custom tri-mix (alprostadil-papaverine-phentolamine)</td>
<td>$8-10</td>
</tr>
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</table>
“Third-line:” Penile Prostheses

- Semirigid rods
- Inflatable prostheses

Image from Harvardprostateknowledge.org
Image from NKUDIC/prostatecancer.org
Evaluating Treatment Response
International Index of Erectile Function (IIEF-15 and IIEF-5)

IIEF-5
Over the past 6 months:
1. How do you rate your confidence that you could get and keep an erection?
2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
5. When you attempted sexual intercourse, how often was it satisfactory for you?
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  – Free testosterone 3.1 pg/mL (12-40)
  – Prolactin 396 ng/mL (<13)
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References


Thanks to: Adam Tierney, MD (Dean Urology); Andy (UW East Clinic Pharmacist)
Princeton Consensus Conference

Sexual inquiry of all men

ED confirmed

Exercise ability$^a$

Low risk

Indeterminate risk

Stress test$^b$

Pass

Low risk

Fail

High risk

High risk

Advice, treat ED

Cardiologist
# Princeton Consensus Conference

## Table 1
Relative Risks for Men With Erectile Dysfunction

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1.48</td>
<td>1.25-1.74</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>1.46</td>
<td>1.31-1.63</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.35</td>
<td>1.19-1.54</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>1.19</td>
<td>1.05-1.34</td>
<td>.005</td>
</tr>
</tbody>
</table>

Adapted from *J Am Coll Cardiol.* 15