Erectile Dysfunction: New Paradigms in Treatment

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Disclosures
• I do not have any relevant financial disclosures.

This is a talk about sex, and contains potentially offensive images...
Men’s Health Statistics

With Respect to American Women, Men…

- Die 7 years younger (1 year younger in 1920)
- Die more often from all 15 leading causes of death (except Alzheimer’s)
- Greater risk of serious chronic diseases, and suffer from them at an earlier age
- Are twice as likely to die from heart disease (3 of 4 heart attack deaths under 65 are men)

With Respect to American Women, Men…

- More likely to be drug abusers, pathological gamblers, alcoholics, and smokers…
With Respect to American Women, Men…

- Are responsible for 8 of 10 car accidents!
Men Avoid Doctors

• Twice as many men than women have no regular source of medical care
• Men comprise 70% of those who haven’t seen a doctor in the past 5 years
• 25% of men would wait “as long as possible” to see a doctor

And, yet...

• What universally gets a man’s attention:

Older Men Are Still Sexually Active

Sexual activity = Intercourse, masturbation and any activity that the participant considered “sexual”

Rosen R. Multinational Survey of the Aging Male (MSAM-7). Presented at the Annual Meeting of the AUA; May 26, 2002; Orlando, Fla.
**Epidemiologic Survey:**

**Prevalence of ED**

Men aged 40 to 70 years (N=1290)

- No erectile dysfunction (48%)
- Erectile dysfunction (52%)
  - Complete (10%)
  - Moderate (25%)
  - Minimal (17%)


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**Normal Male Sexual Response**

- Level of excitement
- Time
- Plateau
- Orgasm
- Refractory period
- Resolution


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**Physiology of Normal Erections**

- Erections are a complex event, requiring
  - Intact arterial and venous system
  - Normal innervation
  - Normal hormonal factors
  - Functioning erectile tissue (the penis)

Abnormalities in any or all of these will lead to ED.
Mechanism of Erections: Chemical Pathway

Sexual stimulation

Inflow to corpus cavernosum

Vascular smooth muscle relaxation

cGMP

NO

Breakdown by PDE5

NANC

cGMP = cyclic guanosine monophosphates. NO = nitric oxide. PDE5 = phosphodiesterase type 5.

Mechanism of Erections: Chemical Pathway

Physiology of Normal Erections

Nerve signals

Release of nitric oxide

Smooth muscle relaxation in capillary bed of corporal bodies

Increase in blood flow, filling penis

Draining veins compressed

Normal Erection

Mechanism of Erections: Cross Section

Pathophysiologic Mechanism of ED: The Common Link


The Link Between ED and Other Conditions May Be Endothelial Dysfunction

ED May Be Clinically Evident Prior to CAD Symptoms

Among 300 patients with CAD and angina
- Prevalence of ED among patients was 49%
- Mean time between onset of ED symptoms and onset of CAD is 38.8 months (range 1-168)
- All patients with type 1 diabetes had ED prior to CAD


Relationship of ED to Silent MI in Type 2 Diabetes

- 133 men with type 2 diabetes and documented asymptomatic CAD were compared with 127 men with type 2 diabetes and negative cardiac evaluation
- ED was highly correlated with the presence of asymptomatic silent MI and CAD
- Men with type 2 diabetes who present with ED and no cardiac history need cardiac evaluation


ED as a Predictor of Heart Attack

In a study of >25,000 men
- Men with ED had almost twice the risk of heart attack vs men without ED
- Men aged >40 years with ED had 3 to 4 times the risk of heart attack vs younger (aged 30-39) cohort

ED as Prognostic Indicator in Young Men

- 1,400 community-dwelling men

- Incidence densities of CAD were calculated after adjustment for age and potential confounders

- ED in younger men is associated with a marked increase in the risk of future cardiac events

It doesn’t take much for a man with testosterone to become aroused
The Interpersonal Dilemma

- Reluctance to discuss ED because of embarrassment, shame, or ignorance about normal sexual functioning
- Cultural beliefs about discussing sexuality
- Discomfort
- Fear of offending patient or causing discomfort
- Lack of confidence in diagnosing and treating ED
- Interpersonal differences with patient (cultural, religious, ethnic)
- Concern with appearing “overly interested” in patient’s sex life


Barriers to Identifying Erectile Dysfunction (ED)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Physician</th>
</tr>
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<tbody>
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<td>• Reluctance to discuss ED because of embarrassment, shame, or ignorance about normal sexual functioning</td>
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ED Treatment-Seeking Behavior in Urology Offices

- Prevalence of previously unreported ED among 500 men (aged ≥50) visiting for non-ED complaint

Diagnosing ED

- Basic evaluation of sexual dysfunction
  - Sexual, medical, and psychosocial history
- Focused physical examination
- Recommended diagnostic tests including
  - Glucose, lipids, serum chemistries, testosterone, prostate-specific antigen (PSA), and complete blood count

Empiric trials of therapy are discouraged without this basic evaluation.


Classification of ED:
Psychogenic or Organic?

<table>
<thead>
<tr>
<th>Psychogenic</th>
<th>Organic</th>
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<tbody>
<tr>
<td>Sudden onset</td>
<td>Gradual onset</td>
</tr>
<tr>
<td>Complete immediate loss</td>
<td>Incremental progression</td>
</tr>
<tr>
<td>AM erections present</td>
<td>Lack of AM erections</td>
</tr>
<tr>
<td>Varies with partner and circumstance</td>
<td>Lack of erections under most sexually stimulating circumstances</td>
</tr>
</tbody>
</table>


Why Use Patient Questionnaires?

- Facilitate dialogue and diagnosis
- Evaluate treatment changes
- Examples of self-administered, standardized questionnaires
  - Sexual Health Inventory for Men (SHIM)\(^1\)
  - International Index of Erectile Function (IIEF)\(^2\)

SHIM

- Valid, reliable, 5-question inventory (IIEF-5) to assess a patient’s ability to
  - Obtain and maintain an erection
  - Complete intercourse
- Questions answered on scale of 1 to 5
  - Score ≤21 may suggest a diagnosis of ED
- May be useful to administer to all male patients aged >50 years


Erectile Dysfunction: Management

Interventions

- Lifestyle/drug therapy modification
- Psychosocial counseling and education
- Androgen replacement therapy
- Oral therapy

First-Line Intervention: Drug Therapy Modifications

- Modify drug regimens associated with ED
  - Antihypertensives/diuretics
  - Selective serotonin reuptake inhibitors
  - Hormonal agents (eg, antiandrogens)
  - Histamine-2-receptor antagonists


Evaluating for hypogonadism: ED and Testosterone

- The chemical mechanism for normal erections seems to be testosterone dependent
- Men with low testosterone have a diminished response to PDE5i
- Improvement of other health problems, including low testosterone, → improved response rates with PDE5i

Diagnostic Testosterone Testing: Initial Tests

- Serum Total Testosterone (free plus protein-bound)
  Morning sample recommended in young men
  Reasonable screening tool
- Serum Free Testosterone (nonprotein-bound)
  Better in older/obese men
- Serum Bioavailable T (free plus albumin-bound)
  Measures albumin-bound and free testosterone
  Best test, most expensive

DM: Hypogonadism and ED

- Both ED and Hypogonadism (low T) are increased in the diabetic patient
- There does not appear to be a common pathophysiology
  - ED $\rightarrow$ peripheral neuropathy, small vessel angiopathy and endothelial dysfunction
  - HypoT $\rightarrow$ obesity, metabolic syndrome or dysfunctional adipocytes
- Each abnormal state needs to be diagnosed and treated as with any other patient

Men with DM are 2X as likely to have low T levels than they are to have normal T levels
DM independently predicts low levels of testosterone
Patients with DM had even greater declines in Testosterone than those with Metabolic Syndrome (MetS)


Hypogonadism and ED: Intervention

- Intervention with TRT in hypogonadal men has shown improvement in:
  - Individual body weight
  - Waist circumference
  - Lipid profiles
  - MetS $\rightarrow$ complete reversal
- Randomized, double blind trial intramuscular TU for 12 months improved MetS parameters, waist circumference and fat mass

Guidelines on Testosterone and ED

• AUA Recs: Testosterone therapy is not indicated for the treatment of erectile dysfunction in the patient with a normal serum testosterone level.

• EUA Recs: Laboratory testing must be tailored to the patient’s complaints and risk factors. Hormonal tests include a morning sample of total testosterone.

Testosterone level and ED

- In erectile dysfunction hard to tease out contribution of metabolic risk factors, smoking, etc
- Concentrations below 8 nmol/liter (230ng/dl) consistently contributed to ED

Androgen Replacement

- Oral Tablets
- Intramuscular Injections
- Transdermal Patches
- Transdermal Gels
- Pellet Implants
## TRT Formulation-Specific Adverse Effects

<table>
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<th>Formulation</th>
<th>Effects</th>
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<tr>
<td>Oral tablets</td>
<td>– Effects on liver and cholesterol (methyltestosterone)</td>
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<tr>
<td>Intramuscular injections of</td>
<td></td>
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<tr>
<td>testosterone enanthate or cypionate</td>
<td>– Fluctuation in mood or libido</td>
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<td></td>
<td>– Pain at injection site</td>
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<td></td>
<td>– Excessive erythrocytosis (especially in older patients)</td>
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<tr>
<td>Transdermal patches</td>
<td>– Skin reactions at application site</td>
</tr>
<tr>
<td>Transdermal gel</td>
<td>– Potential risk for testosterone transference to partner</td>
</tr>
<tr>
<td>Pellet implants</td>
<td>– Infection, expulsion of pellet</td>
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## First-Line Therapy: Oral Agents

- US Food and Drug Administration (FDA)-approved phosphodiesterase type 5 (PDE5) inhibitors
  - Sildenafil citrate – 1998
  - Vardenafil – 2003
  - Tadalafil – 2003
  - Avanafil – 2012
- Investigational oral agents
  - Yohimbine and L-arginine

Role of NO and cGMP in Erections

- Sexual stimulation
- NO from NANC neurons
- Conversion of GTP to cGMP
- Relaxation of smooth muscle
- Erection

NO=cyclic guanosine monophosphate. GTP=guanosine triphosphate. NANC=nonadrenergic, noncholinergic neurons. NO=nitric oxide. PDE5=phosphodiesterase type 5.

Management of Psychogenic ED

- Daily Cialis 5mg for 3 months → taper to every other day for next 3 months → then stop
- If Cialis alone not sufficient, add Viagra 100mg on demand

Distribution of PDE Isoenzymes

- PDE1: Testes, heart, olfactory cilia, central nervous system (CNS)¹
- PDE2: CNS, adrenal cortex¹
- PDE3: Adipose tissue, cardiac muscle, vascular smooth muscle, liver, platelets²
- PDE4: Neural and endocrine tissues¹
- PDE5: Vascular smooth muscle, corpus cavernosum, lung, kidney, platelets¹²
- PDE6: Retina (rods and cones)¹²
- PDE7: Skeletal and cardiac muscle, lymphoid tissue¹

**Distribution of PDE Isoenzymes (cont’d)**

- **PDE8**: Testes, ovary, colon, small intestine
- **PDE9**: Spleen, intestine, kidney, heart, brain
- **PDE10**: Not reported
- **PDE11** (*): Penile smooth muscle, corpus cavernosum, testes, prostate, pituitary, heart

*Physiologic role and clinical relevance are not yet known.