Erectile Dysfunction and Testosterone Therapy

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Objectives

• To define and recognize erectile dysfunction
• How to approach and test
• Overview to initiate treatment
• To understand the role of the Urology ED Clinic
• Other aspects of hypogonadism: the role of bioavailable testosterone
Definition of Erectile Dysfunction (ED)

- ED is the persistent inability to attain and/or maintain an erection sufficient to permit satisfactory sexual intercourse.

- More accurate estimates of the prevalence of ED have become possible due to the development of the International Index of Erectile Function (IIEF) in 1998.

- It is recognized that desire, orgasmic capacity and ejaculatory capacity may be intact in the presence of ED or may be deficient to some extent and contribute to the sense of inadequate sexual function.

References:
What are the risk factors contributing to ED
Anatomy and mechanism of penile erection

The erection pathway can be triggered by direct genital stimulation and by auditory and visual stimulation, which act in concert to increase penile blood flow.

The penis has a highly specialized anatomical structure that allows a massive increase in blood flow to be trapped within the inelastic layers surrounding the penis (the tunica albuginea), which causes rigidity and expansion of the cavernous smooth muscle.
Penile Anatomy and Circulation

Circumferential vein
Deep dorsal vein
Dorsal nerve
**Dorsal artery**
Cavernosal artery
Emissary vein
**Bulbourethral artery**
Corpora cavernosa
Tunica albuginea
Communicating vein
Urethra
Corpus spongiosum
The signal (nitric oxide) is released from nerve endings or from endothelial cells and activates a cascade reaction, which ultimately leads to an increased cellular concentration of cGMP (cyclic guanosine monophosphate). This second messenger molecule induces a series of events that lead to smooth-muscle relaxation through a reduction in the intracellular calcium ion concentration. The enzyme PDE-5 (phosphodiesterase type 5) reverses this effect by metabolizing the cGMP to GMP rapidly. The clinically important inhibitors of this enzyme (sildenafil/Viagra, vardenafil/Lavitra and tadalafil/Cialis) all act to promote smooth-muscle relaxation by their ability to allow cGMP to accumulate when nitric oxide is released, as is the case when sexual stimulation is present.
Physiology of Penile Erection

Adapted from Krane et al, 1989.

Adapted from Kramer et al, 1989.
Erectile Dysfunction:

- Erectile dysfunction is estimated to affect as many as 100 million men worldwide.
- Prevalence of erectile dysfunction increases with age, but erectile dysfunction is not a necessary consequence of aging.
- Social impact of erectile dysfunction can be significant.
- Erectile dysfunction is underdiagnosed due to a reluctance of patients and healthcare providers to discuss sexual function.
- Erectile dysfunction is an important public health problem.
Data for Responses - the ED Question by Age:
†The exact question asked was as follows: “How would you describe your ability to get and keep an erection adequate for satisfactory intercourse?”

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Always or Almost Always Able</th>
<th>Usually Able</th>
<th>Sometimes Able</th>
<th>Never Able</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>65.0</td>
<td>16.5</td>
<td>12.3</td>
<td>6.2</td>
</tr>
<tr>
<td>20-29</td>
<td>81.0</td>
<td>12.5</td>
<td>4.7</td>
<td>1.8</td>
</tr>
<tr>
<td>30-39</td>
<td>88.4</td>
<td>7.8</td>
<td>3.4</td>
<td>0.4</td>
</tr>
<tr>
<td>40-49</td>
<td>71.7</td>
<td>20.0</td>
<td>7.0</td>
<td>1.2</td>
</tr>
<tr>
<td>50-59</td>
<td>56.5</td>
<td>19.6</td>
<td>19.9</td>
<td>4.0</td>
</tr>
<tr>
<td>60-69</td>
<td>28.7</td>
<td>27.5</td>
<td>27.0</td>
<td>16.7</td>
</tr>
<tr>
<td>70-74</td>
<td>18.8</td>
<td>21.0</td>
<td>38.7</td>
<td>21.5</td>
</tr>
<tr>
<td>≥75</td>
<td>5.7</td>
<td>16.8</td>
<td>30.1</td>
<td>47.5</td>
</tr>
</tbody>
</table>

Saigal CS. Arch Int Med 2006;166; 2097-112
High Prevalence of ED

Prevalence

Normal erectile function: 48%
Minimal: 17%
Moderate: 25%
Complete: 10%

Age and prevalence

Prevalence in population (%)
Degree of ED
- Minimal
- Moderate
- Complete

Age (mid point)

Incidence of Erectile Dysfunction

- One-third (34%) of men over 40 suffer from ED.
- Levels are similar across the country, although are slightly higher in Quebec and P.E.I and slightly lower in Manitoba, Alberta and Nova Scotia.

Base: total men with SHIM scores of 21 and below (n=4,539)
<table>
<thead>
<tr>
<th>Comorbid Diagnosis</th>
<th>ED Absent*</th>
<th>ED Present*</th>
<th>Prevalence of ED Among Men With a Comorbid Diagnosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes mellitus</td>
<td>3 675 146</td>
<td>3 572 607</td>
<td>49.3</td>
</tr>
<tr>
<td>Obesity</td>
<td>16 206 023</td>
<td>4 990 098</td>
<td>23.5</td>
</tr>
<tr>
<td>Heart disease</td>
<td>3 055 592</td>
<td>3 344 306</td>
<td>52.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>13 124 111</td>
<td>7 184 282</td>
<td>35.4</td>
</tr>
<tr>
<td>Smoking</td>
<td>20 088 443</td>
<td>3 543 914</td>
<td>15.0</td>
</tr>
</tbody>
</table>

*Data are given as number percentage [95% confidence interval] of subjects for each age group. Percentages may not total 100 because of rounding.

Saigal CS. Arch Int Med 2006;166: 2097-12
Risk Factors Associated with ED

- Erectile Dysfunction
- Coronary Heart Disease
- Diabetes

Endothelial Dysfunction

Risk factors:
- Smoking
- Blood Pressure
- Cholesterol

Endothelial Function is Altered in Ischemic Heart Disease

EDRF: Endothelium derived relaxing factor

Normal Endothelial Cell
- EDRF: Inhibits platelet adhesion, Promotes vasodilatation, Controls shear, Prevents leukocyte adhesion
- Normal t-PA:PAI-1: Promotes fibrinolysis

Dysfunctional Endothelial Cell in Hypercholesterolemia and Atherosclerosis
- Decrease in EDRF: Promotes platelet adhesion, Promotes vasoconstriction, Increases shear
- Decrease in t-PA:PAI-1: Promotes thrombosis
- Increase in adhesion molecules: Promotes monocyte or macrophage retention

tPA: Tissue plasminogen activator
PAI-1: Plasminogen activator inhibitor-1
### Clinical Clues to causes of sexual dysfunction

<table>
<thead>
<tr>
<th>Finding</th>
<th>Cause</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid onset</td>
<td>Psychogenic</td>
</tr>
<tr>
<td></td>
<td>Genitourinary trauma – eg. radical prostatectomy</td>
</tr>
<tr>
<td>Non-sustained erection</td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Vascular steal</td>
</tr>
<tr>
<td>Depression or use of certain drugs</td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Drug-induced</td>
</tr>
<tr>
<td>Complete loss of nocturnal erections</td>
<td>Vascular disease</td>
</tr>
<tr>
<td></td>
<td>Neurologic disease</td>
</tr>
</tbody>
</table>
## Causes of Erectile Dysfunction

<table>
<thead>
<tr>
<th>Classification</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aging</td>
<td>an indirect risk factor as it is associated with direct risk factors</td>
</tr>
<tr>
<td>Vasculogenic</td>
<td>Cardiovascular and ischemic heart disease, atherosclerosis, hypertension, peripheral vascular disease, venous incompetence, cavernosal disorders, major surgery (retroperitoneum), radiotherapy (retroperitoneum)</td>
</tr>
</tbody>
</table>
| Psychological/Psychogenic disorders | • Depression, Anxiety  
• Generalized type (lack of arousability, disorders of sexual intimacy), Situational type (eg, partner-related, performance-related issues, from distress                                                                                                           |
| Neurogenic-central causes       | Multiple sclerosis, multiple atrophy, Parkinson disease, tumors, stroke, disk disease, spinal cord disorders, Pudendal nerve injury                                                                                                                                                                                                                     |
| Neurogenic-peripheral causes    | Diabetes mellitus, alcoholism, uremia, polyneuropathy, surgery (pelvic or retroperitoneal, radical prostatectomy)                                                                                                                                                                                                                                   |
| Anatomic-structural             | Pyronie disease, penile fibrosis (after pelvic radiotherapy or pelvic surgery), penile trauma (penile fracture), congenital curvature of the penis, micropenis, hypospadius, epispadius                                                                                                                                                         |
| Hormonal                       | Primary hypogonadism (eg, late onset gonadism), secondary hypogonadism/hypogonadotropic hypogonadism (eg, hyperprolactinemia), hyper- and hypothyroidism, Cushing disease, Addison disease                                                                                                                                                      |
| Drug- and/or substance-induced  | • Antihypertensives (thiazides and β-blockers are most common), antidepressants, antipsychotics, antiandrogens, antihistamines  
• Marijuana use, alcohol abuse, narcotics, cigarette smoking*                                                                                                                                                              |
| Other disease                   | Diabetes mellitus, hyperlipidemia, renal failure, chronic obstructive lung disease                                                                                                                                                                                                                                                                         |

Smoking has an adverse effect on erectile function as it accentuates the effects of other risk factors, eg vascular disease and hypertension.

- Fazio L & Brock G. CMAJ 2004;170:1429-37
### Frequency of decreased erectile function rigidity and ejaculatory dysfunction by medication class

<table>
<thead>
<tr>
<th>Medication class</th>
<th>Decreased erectile rigidity</th>
<th>Ejaculatory dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>β-adrenergic antagonists</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>Sympatholytics</td>
<td>Expected</td>
<td>Common</td>
</tr>
<tr>
<td>$\alpha_1$ agonists</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>$\alpha_2$ agonists</td>
<td>Common</td>
<td>Less common</td>
</tr>
<tr>
<td>$\alpha_1$ antagonists</td>
<td>Uncommon</td>
<td>Less common*</td>
</tr>
<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>Uncommon</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Diuretics</td>
<td>Less common</td>
<td>Uncommon</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Common†</td>
<td>Uncommon†</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Common</td>
<td>Common</td>
</tr>
<tr>
<td>anticholinergics</td>
<td>Less common</td>
<td>Uncommon</td>
</tr>
</tbody>
</table>

*Patients able to ejaculate, but retrograde ejaculation is seen in 5%-30%.
† Uncommon with serotonin reuptake inhibitors
‡ Delayed or inhibited ejaculation with serotonin reuptake inhibitors.
How to approach and test
# Basic diagnostic work-up in patients with erectile dysfunction

**European Association of Urology Guidelines-Sexual Medicine**

## Recommendations

Clinical use of a validated questionnaire related to ED may help assess all sexual function domains and the effect of a specific treatment modality.

Physical examination is needed in the initial assessment of ED to identify underlying medical conditions associated with ED.

Routine laboratory tests, including glucose-lipid profile and total testosterone, are required to identify and treat any reversible risk factors and modifiable lifestyle factors.

Specific diagnostic tests are indicated by only a few conditions.

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Basic diagnostic work-up in patients with erectile dysfunction
European Association of Urology Guidelines-Sexual Medicine

Patient with erectile dysfunction (self-reported)

Medical and psychosexual history (use valid instruments, eg IIEF)

- Identify other than ED sexual problems
- Identify common causes of ED
- Identify reversible risk factors for ED
- Assess psychosocial status

Focused physical examination

- Penile deformities
- Prostatic disease
- Signs of hypogonadism
- Cardiovascular and neurological status

Laboratory tests

- Glucose-lipid profile (if not assessed in the last 12 months)
- Total testosterone (morning sample)
  If available: bioavailable or free testosterone (instead of total)

### Indications for specific diagnostic tests

<table>
<thead>
<tr>
<th>Indications</th>
<th>Specific diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with primary erectile disorder (not caused by organic disease or psychogenic disorder)</td>
<td>Nocturnal penile tumescence and rigidity using Rigiscan Vascular studies</td>
</tr>
<tr>
<td>Young patients with a history of pelvic or perineal trauma who could benefit from potentially curative vascular surgery</td>
<td>• Intracavernous vasoactive drug injection</td>
</tr>
<tr>
<td>Patients with penile deformities (e.g., Peyronie’s disease, congenital curvature) that might require surgical correction</td>
<td>• Duplex ultrasound of the cavernous arteries</td>
</tr>
<tr>
<td>Patients with complex psychiatric or psychosexual disorders</td>
<td>• Dynamic infusion cavernosometry and cavernosography</td>
</tr>
<tr>
<td>Patients with complex endocrine disorders</td>
<td>• Internal pudendal arteriography</td>
</tr>
<tr>
<td>Specific tests may also be indicated at the request of the patient or his partner</td>
<td>Neurologic studies (e.g., bulbocavernosus reflex latency, nerve-conduction studies)</td>
</tr>
<tr>
<td>For medicolegal reasons (e.g., penile prosthesis implant, sexual abuse)</td>
<td>Endocrinologic studies</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Specialised psychodiagnostic evaluation</th>
</tr>
</thead>
</table>

Overview to initiate treatment
Identify and treat a “curable” cause of ED

• Identify patient needs and expectations
• Shared decision making
• Other conjoint surgical and medical treatment

Assess therapeutic outcomes
• Erectile response
• Side-effects
• Satisfaction with treatment

Inadequate treatment outcomes
• Assess adequate use of treatment options
• Provide new instructions and counselling
• Re-trial
• Consider alternative or combination therapy

Inadequate treatment outcome

Consider penile prosthesis implantation

PDE5 Inhibitors
• Intracavernous injection
• Intraurethral alprostadil
• Vacuum devices

Provide education and counselling to patients and partners

Lifestyle changes and risk factor modification

## Recommendations for the treatment of erectile dysfunction (ED)

### Recommendations

<table>
<thead>
<tr>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lifestyle changes and risk factor modification must precede or accompany ED treatment</td>
</tr>
<tr>
<td>Pro-erectile treatments must be given at the earliest opportunity after radical prostatectomy.</td>
</tr>
<tr>
<td>If a curable cause of ED is found, treat the cause first</td>
</tr>
<tr>
<td>PDE5-Is are first-line therapy.</td>
</tr>
<tr>
<td>Daily administration of PDE5-Is may improve results and restore erectile function</td>
</tr>
<tr>
<td>Inadequate/incorrect prescription and poor patient education are the main causes of a lack of response to PDE5-Is</td>
</tr>
<tr>
<td>Testosterone replacement restores efficacy in hypogonadic nonresponders to PDE5-Is</td>
</tr>
<tr>
<td>A vacuum constriction device can be used in patients with stable relationship</td>
</tr>
<tr>
<td>Intracavernous injection is second-line therapy.</td>
</tr>
<tr>
<td>Penile implant is third-line therapy.</td>
</tr>
</tbody>
</table>

The role of the Urology ED Clinic
SEXUAL HEALTH INVENTORY FOR MEN – (SHIM) IIEF-5
BASED ON THE
INTERNATIONAL INDEX OF ERECTILE FUNCTION

OVER THE PAST 6 MONTHS:

<table>
<thead>
<tr>
<th>Question</th>
<th>Very low</th>
<th>Low</th>
<th>Moderate</th>
<th>High</th>
<th>Very high</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. How do you rate your confidence that you could get and keep and erection?</td>
<td>Very low</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td>Very high</td>
</tr>
<tr>
<td>2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration?</td>
<td>No sexual activity</td>
<td>Almost never/never</td>
<td>A few times (much less than half the time)</td>
<td>Sometimes (about half the time)</td>
<td>Most times (much more than half the time)</td>
</tr>
<tr>
<td>3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?</td>
<td>Did not attempt intercourse</td>
<td>Almost never/never</td>
<td>A few times (much less than half the time)</td>
<td>Sometimes (about half the time)</td>
<td>Most times (much more than half the time)</td>
</tr>
<tr>
<td>4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?</td>
<td>Did not attempt intercourse</td>
<td>Extremely difficult</td>
<td>Very difficult</td>
<td>Difficult</td>
<td>Slightly difficult</td>
</tr>
<tr>
<td>5. When you attempted sexual intercourse, how often was it satisfactory for you?</td>
<td>Did not attempt intercourse</td>
<td>Almost never/never</td>
<td>A few times (much less than half the time)</td>
<td>Sometimes (about half the time)</td>
<td>Most times (much more than half the time)</td>
</tr>
</tbody>
</table>

SCORE______

Add the numbers corresponding to questions 1-5. If your score is 21 or less, you may be showing signs of erectile dysfunction and may want to speak with your doctor.
Male Sexual Health Questionnaire

Date: ___/___/___

Epidemiology

Age: ___  Sexual partner: Yes___  No__  Multiple__  Occasional __
Marital status: Married __  Single __  Divorced__  Widow__  Common-law__

Erections

Duration of ED: _____yrs  ____mo  Onset of ED: Sudden___  Gradual___  Intermittent_____

Erection Quality:  
___Gr. 0 (No erection)  
___Gr. 1 (Increase in size, not rigid)  
___Gr. 2 (Not rigid enough to penetrate)  
___Gr. 3 (Penetrate, not completely rigid)  
___Gr. 4 (Completely rigid)  

Morning:  
___Gr. 0 (No erection)  
___Gr. 1 (Increase in size, not rigid)  
___Gr. 2 (Not rigid enough to penetrate)  
___Gr. 3 (Penetrate, not completely rigid)  
___Gr. 4 (Completely rigid)

Erection with self-stimulation: Yes___  No___  
Morning: Always___  Often___  Rare___  Never___

Duration of erection: _____minutes
Pain with erection: Yes____  No____  
Curve with erection: Yes_____  No_____  

Comments:________________________________________________________________________________________

Treatment to Date

Counseling_____:  Successful: Yes___  No___
PDE-5____:  
Viagra___  Cialis___  Levitra____  MUSE____  Successful: Yes___  No___
Intercavernosal injection____:  
Type____________  Dose:____  Successful: Yes___  No___
Vacuum erection device____:  Successful: Yes___  No___
Penile implant____:  Successful: Yes___  No___

Comments:________________________________________________________________________________________
Intercourse
Ejaculation: Normal____ Premature____ Delayed____ Retrograde____ None____
Orgasm: Normal____ Absent____ Painful____ Unknown____
Libido: Normal____ Low____ Increased____
Number of successful intercourses in the last 3 months: _____
Comments:__________________________________________________________________________

Social
Smoking: Ppd____ # yrs____ Ex-smoker____ Pipe____ Partner____
Alcohol: None____ Social____ Moderate____ Heavy____ Recovering Alcoholic____
Non-prescription drugs: No____ Yes____ (If yes, list in comment section below)
Stressors: Financial____ Employment____ Social____ Other______________
Comments:__________________________________________________________________________

Partner History
Relationship: Stable____ Unstable____ No current____
Discussed erectile difficulties with partner: Yes___ No___ Partner have sexual concerns: Yes___ No___
Partner's attitude: Supportive/Concerned____ Indifferent____ Angry/Resentful____
Comments:______________________________________________________________

Medical History
HTN____ Spinal Cord Injury____ Depression____ Stroke____
IHD____ Multiple Sclerosis____ Prostate cancer____ Diabetes: IDDM or NIDDM
PVD____ Parkinson’s Disease____ Hypothyroid____
Comments:__________________________________________________________________________

Surgical History
CABG____ Pelvic radiation____ Thyroidectomy____ Hernia____
Vascular____ Back/Disc surgery____ A-P repair____ RRP____
Comments:__________________________________________________________________________
Medications

1___________ 3___________ 5___________ 7___________ 9___________
2___________ 4___________ 6___________ 8___________ 10__________
Comments:__________________________________________________________________________

Physical Examination

Vitals: BP: ____mmHg   HR____   RR____   Weight____   Height____
General: Gynecomastia: Yes___  No___     Facial hair: Yes___  No___  Pubic hair: Yes___  No___
Femoral Pulses: Norm bilat/unilat_/___  Dec Bilat/unilat_/___  None bilat/unilat_/___
Penis: Normal___   Abnormal___   Peyronie’s plaque___   Scars___
Testis: Normal___   Abnormal: Number___  Location___  Size___   Consistency___ (see comments)
Scrotal content: Normal___   Abnormal___ (see comments section)
Prostate: Normal___   Abnormal___ (see comments section)   Size____ g
Abdominal: Normal___   Abnormal___ (see comments section)
Neurological: Normal___   Abnormal___ (see comments section)
Comments:__________________________________________________________________________

Investigations to Date

Lab: TT____ BAT____ LH____ FSH____ Prolactin____ PSA____ Other____
Comments:__________________________________________________________________________

Plan/Follow-up

____________________________________________________________________________________
____________________________________________________________________________________
____________________________________________________________________________________
General Considerations before initiating pharmacological treatment for ED

• Before initiating treatment, patients should be informed that sexual stimulation is essential for the efficacy of the drugs.

• Although some may experience limited efficacy after the first trial, patients should be informed that results generally improve with repeated dosing.

• A minimum of six attempts should be made before treatment is considered a failure:
  • Daily tadalafil 2.5-5 mg

• Between 30-50% of non-responders may be converted to responders through:
  • Re-education on proper dosing techniques
  • Dose escalation

Alberson M et al. Med Clin N Am 2011;95:201-12
## Oral treatments for male sexual dysfunction

<table>
<thead>
<tr>
<th>Medication</th>
<th>Mechanism</th>
<th>Pros and Cons</th>
<th>Dosing</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sildenafil</strong></td>
<td>Inhibits phosphodiesterase-5 enzyme, allowing cyclic GMP to accumulate within the penis</td>
<td>100 mg effective in 75% of men</td>
<td>Take one hour before sex and effective up to four hours</td>
<td>$65.96 for 4 x 100 mg tabs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Side effects: headaches dyspepsia, vasodilatation, diarrhea and blue tinge of vision</td>
<td>Stimulation needed for erection</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraindicated if using nitrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dose: 25-100 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vardenafil</strong></td>
<td>Same as Sildenafil</td>
<td>Similar efficacy/side effects to Sildenafil, but no visual effects</td>
<td>Similar onset and duration of action as Sildenafil</td>
<td>$70.82 for 4 x 20 mg tabs</td>
</tr>
<tr>
<td>(Levitra)</td>
<td></td>
<td></td>
<td>Dose: 2.5-20 mg</td>
<td></td>
</tr>
<tr>
<td><strong>Tadalafil</strong></td>
<td>Same as Sildenafil</td>
<td>Similar efficacy/side effects to Sildenafil, but no visual effects</td>
<td>Similar onset of action as Sildenafil</td>
<td>$72.45 for 4 x 20 mg tabs</td>
</tr>
<tr>
<td>(Cialis)</td>
<td></td>
<td></td>
<td>Duration of action is up to 36 hours</td>
<td>$136.31 for 28 x 2.5 mg tabs</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Low-back pain</td>
<td>Dose: 2.5-20 mg (daily 5 mg x 14 d)</td>
<td></td>
</tr>
</tbody>
</table>
The role of the Urology ED Clinic
Second-line therapy
Who should be referred

- Patients in whom PDE5 pathway is disturbed/diminished NO availability will benefit far less from PDE5Is:
  - Degeneration of erectile tissue after radical prostatectomy
  - Severe diabetes
  - Atherosclerosis
  - Metabolic syndrome
  - Aging
  - Hypogonadism

Alberson M et al. Med Clin N Am 2011;95:201-12
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effect</th>
<th>Pros and Cons</th>
<th>Usage pattern</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Suppository</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MUSE</td>
<td>Alprostadil (prostaglandin E₁) in gel form delivered by applicator into meatus of penis</td>
<td>Can be used twice daily. Not recommended with pregnant partners.</td>
<td>Inserted 5-10 minutes before sex. Effects last one hour.</td>
<td></td>
</tr>
<tr>
<td><strong>Penile injection</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TriMix</td>
<td>Combines papaverine 18-25 mg, phentolamine 1-2 mg, and alprostadil 10-25 µg/mL</td>
<td>Effective in 92% of 116 patients in original study Prolonged erection, bleeding, fibrosis (?)</td>
<td>1-2 times/week</td>
<td>$≈60</td>
</tr>
<tr>
<td><strong>Device</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vacuum pump</td>
<td>Removes air from chamber over penis, creating a vacuum and drawing blood into penile cavernosae. Elastic tourniquet at base holds blood in penis.</td>
<td>One time expense. Safe if erection not maintained more that one hour (30 minutes). May not be acceptable to partner. Penis is hinged at base. May interfere with ejaculation.</td>
<td>Inflated just before sexual activity. Erection lasts until elastic ring removed</td>
<td>$70-700</td>
</tr>
</tbody>
</table>
Education: Vacuum pump for erectile dysfunction

- Using a pump may be a good option if erectile dysfunction medications don't work and penile implant surgery isn't a good choice and may also help regain sexual function following prostate surgery:
  - Less risk of side effects or complications
  - Cost: initial only
  - Non-invasive
  - Can be used with other treatments
  - Benefits following surgery
Treatments for Erectile Dysfunction

Vacuum and Constriction Device
Intracavernosal injection

Vasoactive substance is injected into the corpus cavernosum

Dorsolateral location of injection site
To be fully effective, the medication must be injected directly into one of the penile erectile bodies, the corpus cavernosum.

The medication will diffuse to the other side of the penis so that symmetrical erection is achieved.
Intraurethral (IU) Therapy: 

**Alprostadil** *(MUSE®)*

- **Efficacy**
  - Moderately effective; clinical experience suggests 1 in 3 patients respond at home
  - Improved with constriction band *(Actis®)*

- **Adverse Effects**
  - Local: Penile pain
  - Systemic: Dizziness/hypotension, syncope
Invasive Treatment Options

• Penile prosthesis implantation

• Venous/arterial surgery
Third-line therapy

Surgery

- Implantation of penile prosthesis in whom pharmacologic therapy is ineffective:
  - Inflatable
  - Malleable

- Patients should be made aware that surgery is irreversible

- Reported satisfaction rates are 70%-90%

- Adverse events:
  - Mechanical failure: 50% after a 10-year interval
  - Infection: 1-3%
  - Erosion: rare
Sexual activity/dysfunction and cardiac risk: the Princeton II algorithm

Sexual Inquiry

Clinical Evaluation

Low Risk
Initiate or resume sexual activity or Treat for sexual dysfunction*

Intermediate Risk
Cardiovascular Assessment and Restratification

High Risk
Sexual activity deferred until cardiac condition is stabilized

Risk Factors and CHD Evaluation, Treatment and Follow up for all patients with ED

• Kostis JB. Am J Cardiol 2005;96:313-321
• Alberson M et al. Med Clin N Am 2011;95:201-12
Other aspects of hypogonadism
the role of testosterone and bioavailable testosterone
Testosterone Deficiency Syndrome (TDS)

- Characterized by:
  - Deficiency in serum testosterone (T) levels
  - ± changes in receptor sensitivity to androgens

- Also known as:
  - Hypogonadism
  - Late-onset hypogonadism (LOH)

- Formerly termed: Andropause
Clinical Manifestations$^{1,2}$

- Decreased libido
- Decreased vitality
- Fatigue
- Mood changes
- Insomnia
- Anemia
- Delayed ejaculation
- Flushes
- Erectile dysfunction
- Decreased muscle mass
- Increased visceral body fat
- Testicular atrophy
- Weakness
- Osteopenia/osteoporosis
- Loss of facial, axillary and pubic hair

Manifestations may present alone or in combination

Prevalence

• Crude prevalence rate in Canada:
  o 25% of men aged 40 to 82 years are biochemically testosterone deficient
  1

• Prevalence rates expected to rise with life expectancy (LE)
  o Over the next 40 years LE in North America will increase by 4.8 years
  2

• Yet <10% of affected men receive T therapy
  3

Barriers to Proper Diagnosis & Management

• Lack of physician awareness on associated diseases
  o Metabolic Syndrome (MetS)$^1$
  o Diabetes$^1$
  o Cardiovascular disease$^2$-$^4$

• Lack of physician awareness on the ability of testosterone replacement therapy (TRT) to reduce disease symptoms

• Controversy regarding prostate health$^5$

• Lack of Canadian guidelines for distribution

Clinical Disorders or Conditions Associated with a High Prevalence of Low T

- Type II diabetes mellitus
- Metabolic syndrome
- HIV-associated weight loss
- Treatment with opioids, glucocorticoids or ketoconazole
- Osteoporosis or low trauma fracture at a young age
- End-stage renal disease and maintenance hemodialysis
- Chronic obstructive pulmonary disease
- Infertility
- Sellar region mass, disease, radiation or trauma
- Use of street drugs
- Liver disease

*** Patients with these clinical disorders/conditions are considered “high risk” and should be screened for testosterone deficiency

Diabetic Men Are at High Risk

- 33% of men with diabetes have hypogonadism
- 34%-45% of men with diabetes have ED
- Men with higher levels of T (15.6-21.0 nmol/L) have a 42% lower risk of Type II diabetes

*** Men with Type II diabetes should be screened for testosterone deficiency

Measurement Tests for T
Forms of T

Bioavailable (BT: 40%)

Albumin-bound (38%)

Free (FT: 2%)

SHBG-bound (60%)

Total (TT: 100%)
Measurement Tests for T

• Measured BT is the gold standard
  - Ammonium sulphate precipitation correlates well with symptoms of TDS\(^1\)

• If measured BT is unavailable or unaffordable, acceptable alternatives are\(^2,3\):
  - TT or
  - Calculated free T (cFT) or
  - Calculated bioavailable T (cBT)
  - Free calculator for cFT and cBT\(^4\):
    - [http://www.issam.ch/freetesto.htm](http://www.issam.ch/freetesto.htm)

Calculated Bioavailable Testosterone at Capital Health to Hospitals In Common Laboratory-Toronto

\[ y = 0.9591x + 0.2061 \]

\[ R^2 = 0.9812 \]

\[ r = 0.99 \]
Low levels of bioavailable testosterone can be present within normal total testosterone levels

Low/Borderline T Requires Confirmation

- Repeat T
- **Plus**, measures of:
  - SHBG
  - Luteinizing hormone (LH)
  - Follicle-stimulating hormone (FSH)
  - Prolactin
- **Other tests/serum markers that may be included:**
  - Complete blood count (CBC)
  - Ferritin
  - Thyroid-stimulating hormone (TSH)
  - Prostate-specific antigen (PSA)
  - Digital rectal exam (DRE)
Hypogonadism and Testosterone Replacement Therapy
British Society for Sexual Medicine Guidelines on the Management of Sexual Dysfunction

• Androgen deficiency increases with age but its management remains controversial
• As well as sexual dysfunction, it is also associated with Osteoporosis, Dyslipidemia, NIDDM, Metabolic syndrome, Depression

• Diagnosis of androgen deficiency:
  • Non-specific clinical features
  • Blood testing for testosterone:
    • Should be drawn in the morning: 08:00-11:00
    • Repeated after 2-3 weeks as a single assay may be misleading (pulsatile release)
    • Men with total serum testosterone < 11 nmol/L might benefit from a trial of testosterone replacement therapy for ED and should be managed according to the BSSM Guidelines.
  • There is no evidence that giving testosterone to men with ED and normal androgen levels restores or improves their erectile function
  • Hypogonadal men restored to the eugonadal state with testosterone replacement may experience:
    • A general improvement in sexual function
    • Improved erection
    • Restored or enhanced responsiveness to PDE5 inhibitors
Male with ED, First time presentation

Screen all ED patients for T

T normal

ED therapies (e.g. PDE5I)

Unsatisfactory response

Alternative ED therapies, e.g., injections, prosthesis

T low

T therapy

Satisfactory response

Unsatisfactory response

Continue T therapy

Male with ED, Failure of PDE5I. No previous T testing

Screen all ED patients for T

T low

Combination therapy; e.g., T + PDE5I

Unsatisfactory response

Alternative ED therapies, e.g., injections, prosthesis

Satisfactory response

Continue Combination therapy

T normal

Testosterone Therapies
# Intramuscular (IM) Injectables

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone cypionate(^1)</td>
<td>200 mg every 2 weeks (Max. dose 400 mg per month)</td>
</tr>
<tr>
<td><em>(Depo-Testosterone)</em></td>
<td></td>
</tr>
<tr>
<td>Testosterone enanthate(^2)</td>
<td>100-400 mg every 1-4 weeks</td>
</tr>
<tr>
<td><em>(Delatestryl)</em></td>
<td></td>
</tr>
</tbody>
</table>

1. Prescribing Information: Depo-Testosterone (testosterone cypionate injection USP, Sterile Solution) 100 mg/mL. Kirkland, Québec: Pfizer Canada Inc.; 2007.
# Oral Medication

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone undecanoate(^1,2) (Andriol)</td>
<td>120-160 mg daily divided in 2 doses(^a)</td>
</tr>
</tbody>
</table>

This dose should be taken for 2-3 weeks. Subsequent dosages may be reduced to 40-120 mg daily.

The Effect of Food on Absorption of Testosterone Undecanoate

- T undecanoate should be taken with a normal meal or breakfast to achieve proper T levels

Transdermal T Gels

- Dosage: 5-10 g daily, to deliver 50-100 mg of testosterone

Side Effects of T Formulations

<table>
<thead>
<tr>
<th>Reported Side Effects for Testosterone Products&lt;sup&gt;1,2&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>AS Reaction: Irritation, Redness, Rash</td>
</tr>
<tr>
<td>Acne</td>
</tr>
<tr>
<td>Enlarged Prostate</td>
</tr>
<tr>
<td>Change in Mood / Depression</td>
</tr>
<tr>
<td>Sleep Disturbances</td>
</tr>
<tr>
<td>Breast Enlargement</td>
</tr>
<tr>
<td>Hair Loss / Baldness</td>
</tr>
<tr>
<td>Headache</td>
</tr>
</tbody>
</table>

1. Prescribing Information: Depo-Testosterone (testosterone cypionate injection USP, Sterile Solution) 100 mg/mL. Kirkland, Québec: Pfizer Canada Inc.; 2007.
Potential Benefits of TRT

- **Enhanced:**
  - Overall health/survival
  - Strength
  - Sexual desire
  - Energy
  - Emotional well-being
  - May improve some symptoms of MetS

- **Reduced:**
  - Body fat

MetS = Metabolic Syndrome
Contraindications to TRT

- TRT is absolutely contraindicated in patients with:
  - Breast cancer
  - Prostate cancer
  - *** PSA/DRE prior to initiating TRT: refer if abnormal

- TRT may worsen:
  - Erythrocytosis
  - Untreated obstructive sleep apnea
  - Severe congestive heart failure
  - *** Do not initiate TRT until these medical issues have been addressed

- TRT is not suggested during biological fatherhood as it may cause infertility in young men

- TRT can reduce overall body fat content

# Alternative Treatments to TRT

<table>
<thead>
<tr>
<th>Approach</th>
<th>Anticipated Outcome(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diet and exercise</td>
<td>Healthy weight reduction(^1)</td>
</tr>
<tr>
<td></td>
<td>Improved muscle strength(^2)</td>
</tr>
<tr>
<td></td>
<td>Enhanced emotional well-being</td>
</tr>
<tr>
<td>Bisphosphonates</td>
<td>Increased BMD(^3)</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Enhanced emotional well-being</td>
</tr>
<tr>
<td>Continuous Positive Airway Pressure (CPAP)</td>
<td>Treatment of sleep apnea(^4)</td>
</tr>
<tr>
<td>Phosphodiesterase-5 inhibitors</td>
<td>Improved erectile function(^5)</td>
</tr>
<tr>
<td>Discontinuation of opioids</td>
<td>Improvement in multiple symptoms of hypogonadism(^6)</td>
</tr>
</tbody>
</table>
Monitoring

• At each appointment monitor:
  – Symptom response (clinic)
  – Changes in blood parameters
    • T
    • Hemoglobin
    • Hematocrit
  – PSA/DRE
    • Refer if abnormal

Frequency

Every 3–6 months
Year 1
Annually
Timeline of Symptom Improvement

Duration of Treatment (months)

Symptom Improvement

- Enhanced libido
- Improved emotional well-being
- Increased energy
- Reduced ED
- Increased strength
- Enhanced BMD
- Improved cognition
- Enhanced cardiovascular health
- Decreased body fat
- Improvement in some components of MetS

MetS = Metabolic Syndrome

Other endocrine disorders in hypogonadism and ED

Hyperprolactinemia

- Hyperprolactinemia is associated with ED, loss of sexual interest and anorgasmia

- Frequently accompanied by androgen deficiency
  - because high prolactin suppresses LH production leading to hypogonadism

- High prolactin should be excluded in all men with reduced sexual interest, however moderate elevation of prolactin is unlikely to cause ED

- Causes of hyperprolactinemia
  - Medical and physical stress
  - Drugs: major tranquilizers
  - Prolactin secreting pituitary tumor
  - Chronic renal failure
  - big-big prolactin: a complex of prolactin and immunoglobulin

Hyper- and hypothyroidism
Acknowledgement

Thanks to Drs. John Grantmyre and Jerzy Gajewski for the slides and educational material he provided
Thank you