Case 1

53-year-old man referred for evaluation of erectile dysfunction

2-year history of difficulty achieving erections sufficient for intercourse

Normal libido

Weaker spontaneous morning erections

7-year history of Type-2 diabetes—on metformin

Hypertension well-controlled on amlodipine

No genital trauma, penile curvature or fibrosis

Married with 3 children

Smokes 1/2 pack of cigarettes daily

He takes aspirin 81 mg/d (in addition to metformin and amlodipine)

Physical Examination:

- Blood pressure=122/68 mmHg, BMI=31.9 kg/m2
- No Cushingoid features
- Acanthosis nigricans present on the neck
- Phallus normal without curvature or palpable plaque
- Both testes 25 ml

Laboratory Data:

- Total Testosterone=310 ng/dl (mass spectrometry) (8 AM)
- Fasting glucose=109 mg/dl, Hba1c=7.4%, Fasting Lipids normal
- CBC and Chemistry normal

How would you proceed?
Erectile Dysfunction

“Inability of the male to attain and maintain erection of the penis sufficient to permit satisfactory sexual intercourse.”

NIH Consensus Development Panel on Impotence, 1993

“The persistent or repeated inability, for at least 3 months’ duration, to attain and/or maintain an erection sufficient for satisfactory sexual performance (in the absence of an ejaculatory disorder, such as premature ejaculation).”

Process of Care Consensus Panel, 1998

“The consistent or recurrent inability to attain and/or maintain a penile erection sufficient for sexual performance.”

WHO-ISH 1st International Consultation on ED, 1999

Misperceptions About ED

**Old Concepts**
- Most ED is due to psychological problems
- Most ED is due to androgen deficiency

**Facts**
- Most ED is due to organic causes (e.g., diabetes, atherosclerosis)
- ED and androgen deficiency are two distinct clinical disorders (which sometimes coexist)

Mechanism of Penile Erection


Molecular Mechanism of Penile Smooth-Muscle Relaxation

Diabetes: Dominant Risk Factor of ED

<table>
<thead>
<tr>
<th>Chronic Disease</th>
<th>~ED Risk (age-adjusted OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>4.1</td>
</tr>
<tr>
<td>Prostate disease</td>
<td>2.9</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2.6</td>
</tr>
<tr>
<td>Cardiac problems</td>
<td>1.8</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>1.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.6</td>
</tr>
</tbody>
</table>

Diabetes: Highly Prevalent in Patients with ED

- Vascular: 40%
- Diabetes: 30%
- Other: 1%
- Endocrine problems: 3%
- Neurological causes: 5%
- Pelvic surgery, radiation, or trauma: 6%
- Medication: 15%

Diabetes: Highly Prevalent in Patients with ED

Erectile Dysfunction in Diabetes

- ED occurs in 32% of type-1 and 46% of type-2 diabetics
- Diabetics have 3-fold greater incidence of ED than no-diabetics
- After 10 years of diabetes, 50% develop ED
- ED initial presentation in 12% of diabetics

Mechanisms of ED in Diabetes

- Impaired NO Synthesis
- Vascular Disease
- Neurpathy
- AGE Accumulation
- Corporal Fibrosis
- Oz Free Radicals

Drugs Associated with Erectile Dysfunction

- Diuretics
- Antihypertensive drugs: Calcium-channel blockers, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers
- Cardiac or cholesterol drugs
- Statins, fibrinolytics, clopidogrel
- Antidepressants: Selective serotonin-reuptake inhibitors, tricyclic antidepressants, lithium, monoamine oxidase inhibitors
- Transplantation: Cyclosporine, prednisolone
- H2 antagonists: Ranitidine, cimetidine
- Hormones: Pregnenolone, estra
genin, testosterone, dihydrotestosterone, transdermal testosterone
- Cylindrical agents: Minoxidil
- Nitric oxide donors: Intracavernosal, intracorporeal
- Angiotensin II blockers: Losartan, valsartan
- Nitric oxide donors: Alcohol, cocaine

Prevalence of ED in Diabetics

- Prevalence of ED increases with age in diabetics.
- In type-1 diabetics, ED prevalence is 32%.
- In type-2 diabetics, ED prevalence is 46%.
- After 10 years of diabetes, 50% of patients develop ED.
- ED is an initial presentation in 12% of diabetic patients.

Evaluation of Erectile Dysfunction

History
* Evaluate psychosexual factors and relationship issues
* Ascertain risk factors
  - Diabetes: Assess for complications, glycemic control
  - Cardiovascular Disease: CAD, PVD, hypertension
  - Prostate disease: Prostate surgery, LUTS
  - Medications
  - Risk factors that might affect choice of therapy (nitrates, α-blockers)

Physical Examination
* BP, peripheral pulses, evidence of hypogonadism, neuro deficit, penile exam

Lab Tests
* Blood counts and chemistry
* Fasting glucose, HbA1c
* Fasting lipids
* Testosterone

Effect of Lifestyle Changes on ED

Androgen Deficiency and Erectile Dysfunction

Independently Distributed Conditions

Androgen Deficiency
Erectile Dysfunction

Penile Revascularization Surgery

Anastomosis of the inferior epigastric artery to the dorsal penile artery

Good success rates in young, non-smoking healthy men with focal arterial occlusion

Only 7% of men with vascular ED are candidates for revascularization surgery

A Few Key Points

17                vs 3

Signs and Symptoms of Androgen Deficiency

<table>
<thead>
<tr>
<th>More Specific Symptoms</th>
<th>Less Specific Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>* Incomplete sexual development</td>
<td>* Decreased energy and motivation</td>
</tr>
<tr>
<td>* Eunuchoidism</td>
<td>* Decreased initiative and confidence</td>
</tr>
<tr>
<td>* Reduced libido (sexual desire)</td>
<td>* Feeling sad, depressed mood</td>
</tr>
<tr>
<td>* Decreased spontaneous erections</td>
<td>* Poor concentration and memory</td>
</tr>
<tr>
<td>* Gynecomastia</td>
<td>* Sleep disturbance, hypersomnolence</td>
</tr>
<tr>
<td>* Loss of body hair (pubes, axilla)</td>
<td>* Mild anemia (normocytic, normochromic)</td>
</tr>
<tr>
<td>* Very small testes (&lt;5 cc)</td>
<td>* Reduced muscle bulk and strength</td>
</tr>
<tr>
<td>* Infertility (low sperm count)</td>
<td>* Increased body fat and BMI</td>
</tr>
<tr>
<td>* Minimal trauma fracture, low bone density</td>
<td>* Diminished work performance</td>
</tr>
<tr>
<td>* Hot flashes</td>
<td></td>
</tr>
</tbody>
</table>

Bhasin et al. JCEM 2010;95:2536
Treatment of erectile Dysfunction in Men with Coronary Artery Disease
Princeton Guidelines

Case 1
How would you proceed?

Mechanism of Action: PDE5 Inhibitors

Oral Pharmacotherapy: PDE-5 Inhibitors

**Mechanism of Action**

- "Augments" corporal smooth muscle relaxant effects

**Dosage/Administration**

- Lead time for gastrointestinal absorption
- Presence of sexual stimulation

**Efficacy**

- 70% successful sexual intercourse rates

**Side Effects**

- Headaches, flushing, dyspepsia, nasal congestion, visual disturbances ("blue haze", NAION)

**Contraindications**

- Nitrate therapy in any form
- Alpha-blocker considerations

**Properties of PDE5 Inhibitors**

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil</th>
<th>Avanafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial name</td>
<td>Viagra</td>
<td>Levitra</td>
<td>Cialis</td>
<td>Spedra</td>
</tr>
<tr>
<td>Onset of Action</td>
<td>60 min</td>
<td>60 min</td>
<td>60 min</td>
<td>30 min</td>
</tr>
<tr>
<td>Duration of Action</td>
<td>4-5 hrs</td>
<td>4-5 hrs</td>
<td>36 hrs</td>
<td>4-5 hrs</td>
</tr>
<tr>
<td>High Fat Meals</td>
<td>Delay Absorption</td>
<td>Delay Absorption</td>
<td>No Effect</td>
<td>No Effect</td>
</tr>
<tr>
<td>Alcohol</td>
<td>Delay Absorption</td>
<td>Delay Absorption</td>
<td>No Effect</td>
<td>No Effect</td>
</tr>
<tr>
<td>Take Empty Stomach (if possible)</td>
<td>Yes</td>
<td>Yes</td>
<td>Not Necessary</td>
<td>Not Necessary</td>
</tr>
<tr>
<td>Starting Dose</td>
<td>50 mg</td>
<td>10 mg</td>
<td>10 mg</td>
<td>50 mg</td>
</tr>
<tr>
<td>Blue Vision</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Contraindicated with Nitrate</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

**Efficacy of Sildenafil in Diabetes**

Rendell et al. JAMA. 1999;281:281-282
Efficacy of Vardenafil in Diabetes

Goldstein et al. Diabetes Care. 2003;26:777

Efficacy of Tadalafil in Diabetes

Fonseca et al. Diabetologia. 2004;47:1914

Efficacy of Tadalafil: Diabetics vs Non-Diabetics

Fonseca et al. Diabetologia. 2004;47:1914

Case 1

Case Summary:

- Erectile dysfunction with a normal libido
- Patient has diabetes, is obese and smokes
- Normal phallus without any curvature or fibrosis
- On metformin and amlodipine
- No cardiovascular history / no use of nitrates

Treatment:

- Good candidate for PDE-5 inhibitors
- The patient was started on a PDE-5 inhibitor with satisfactory results

Case 2

58-year-old man presents with erectile dysfunction

- 6-year history of difficulty achieving erections
- Decreased libido as a result of ED
- No morning erections
- 11-year history of Type-2 diabetes—on metformin, lispro and glargine
- Hypertension and hyperlipidemia / smokes 1 pack daily
- No response to maximum doses of two different PDE-5 inhibitors

Laboratory Data:

- Fasting glucose=179 mg/dl
- HbA1c=11.4%

Second-Line Therapies for Management of ED
**Vacuum-Assisted Erection Devices**

**Mechanism:**
- Negative pressure ↑ arterial inflow
- Occlusive ring ↓ venous egress

**Use:**
- Manual dexterity required

**Efficacy:**
- Successful erections: 60-70% / Satisfaction rates: 25-50%

**Side Effects:**
- Genital ecchymosis, penile coldness

**Contraindications:**
- Sickle cell disease

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**Intraurethral Alprostadil: MUSE**

**Mechanism of Action:**
- Relaxes corporal smooth muscles

**Dose/Administration:**
- 125, 250, 500, 1000 ug / Manual dexterity

**Efficacy:**
- Responder rate: ~60-70%

**Side Effects:**
- Local pain, urethral bleeding, urethral burning

**Contraindications:**
- Sickle cell anemia, leukemia, myeloma, Peyronie’s disease

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**The Applicator for the Transurethral Administration of Alprostadil**

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**Intercourse after Treatment with Alprostadil or Placebo**

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Intracavernous Pharmacotherapy

**Mechanism of Action**
Corporal smooth muscle relaxation

**Dosage/Administration**
Technical requirements
Proper dose titration

**Side Effects**
Penile pain, penile fibrosis, priapism

**Contraindications**
History of priapism, coagulopathy, sickle cell anemia

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**Trade Name Drug Dosages Efficacy**

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Drug</th>
<th>Dosages</th>
<th>Efficacy (Intercourse)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caverject</td>
<td>Alprostadil (Prostin VR)</td>
<td>5-40 ug/ml</td>
<td>~70%</td>
</tr>
<tr>
<td>Edex</td>
<td>Alprostadil (Prostin VR)</td>
<td>5-40 ug/ml</td>
<td>~70%</td>
</tr>
<tr>
<td>Bi-mix</td>
<td>Alprostadil + Phentolamine</td>
<td>20 ug/ml + 0.5 mg/ml</td>
<td>~90%</td>
</tr>
<tr>
<td>Bimix Androskat (EU)</td>
<td>Papaverine + Phentolamine</td>
<td>30 mg/ml + 0.5 mg/ml</td>
<td>~90%</td>
</tr>
<tr>
<td>Tri-mix</td>
<td>Alprostadil + Papaverine + Phentolamine</td>
<td>10 ug/ml + 30 mg/ml + 1.0 mg/ml</td>
<td>~90%</td>
</tr>
<tr>
<td>Invicorp</td>
<td>VIP + Phentolamine</td>
<td>NA</td>
<td>~80%</td>
</tr>
<tr>
<td>Thymoxamine</td>
<td>Moxisylyte</td>
<td>NA</td>
<td>~70%</td>
</tr>
</tbody>
</table>

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**Case 3**

58-year-old man presents with erectile dysfunction

- 6-year history of difficulty achieving erections
- Decreased libido as a result of ED
- No morning erections
- 11-year history of type-2 diabetes—on metformin, lispro and glargine
- Hypertension and hyperlipidemia / smokes 1 pack daily

- No response to maximum doses of PDE-5 inhibitors
- Could not tolerate vacuum pump device
- Progressive failure to respond to cavernosal injections
Third-Line Therapies for Management of ED

**Penile Prosthesis Surgery**

**Indications**
- Major penile injury or deformity
- When medical therapy is contraindicated, unsuccessful or undesirable

**Mechanism of Action**
- "Splint" within the penis produces rigidity

**Technique**
- Hand dexterity

**Side Effects**
- Risk of infection (higher incidence in diabetes) or device malfunction

**Contraindications**
- Surgical candidacy considerations

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**Malleable Penile Prosthesis**

- Semi-rigid
- Permanent erection
- <10% of prostheses

**Inflatable Penile Prosthesis**

- 2-piece model
- Intracavernosal cylinders + scrotal saline pump
- Achieves rigidity and flaccidity
- >90% satisfaction

- 3-piece model
- Intracavernosal cylinders + scrotal saline pump + retropubic reservoir
- Achieves rigidity and flaccidity
Inflatable 3-Piece Penile Prosthesis

Key Points

- Sexual dysfunction is highly prevalent in men with diabetes
- Penile erection is a neurovascular event, both vascular and neurological components are affected in diabetes
- Androgen deficiency and ED are two independently distributed clinical disorders (with some overlap). Testosterone replacement predominantly influences libido
- PDE5 inhibitors form the first line treatment of ED
- Vacuum/MUSE/cavernosal injections form the 2nd line treatment
- Penile prosthesis reserved for non-responders to medical therapy (greater risk of infection in diabetics)