Ian Eardley
Department of Urology, Leeds Teaching Hospital Trust

2016 Update on the Management of Erectile Dysfunction
Outline

- Assessment of the man with ED
- Medical therapy for man with ED
- What to do when pills fail
Normal Male Sexual Response

Normal Male Sexual Response

- Sexual stimulus
- Neural pathways
- Neurotransmitter release
- Smooth muscle relaxation
- Arterial inflow and Veno-occlusion
ED and CAD: The Deadly Quartet

Diabetes  Obesity  Hypertension  Dyslipidemia
BMI and Waist Circumference

189 cm, 93 kg = BMI 26

Waist circumference

> 190 cm, 94 kg = BMI 26

Waist circumference
Atherosclerosis in Coronary Vessels

Atherosclerosis in Penile Arteries
A significant proportion of men with erectile dysfunction (ED) exhibit early signs of coronary artery disease (CAD), and this group may develop more severe CAD than men without ED (Level 1, Grade A) [1]

1400 men 40-75, with no known CAD 10yr follow up [2]

<table>
<thead>
<tr>
<th>Age Group</th>
<th>CAD events per 1000 pt years with CI interval</th>
<th>ED at baseline</th>
<th>No baseline ED</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-49</td>
<td>48.52 (1.23-269.26)</td>
<td>0.94 (0.02-5.21)</td>
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<tr>
<td>50-59</td>
<td>27.15 (7.40-69.56)</td>
<td>5.09 (3.38-7.38)</td>
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<tr>
<td>60-69</td>
<td>23.97 (11.49-44.10)</td>
<td>10.72 (7.62-14.66)</td>
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<tr>
<td>70+</td>
<td>29.63 (19.37-43.75)</td>
<td>23.30 (17.18-30.89)</td>
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</table>

Assessment of Man with ED
Case 1 - Michael

- A 54 yr old fit insurance salesman mentions sexual difficulties
- What would you like to know?
Patient with ED (self-reported)

Medical and psychosexual history (use of validated instruments, e.g. 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 indicated, bio-available or free testosterone
Clarify exactly what the patient’s symptoms are

Some men confuse ED with disorders of ejaculation, orgasm or desire

The basic elements of the sexual history are as follows:
- Nature of the problem
- Psycho-social context of the problem
- Chronology of the problem
- Severity of the problem
- Success with prior treatment
- Definition of patient’s needs and expectations
Psychogenic versus Organic ED

- **Organic ED usually**
  - Has gradual onset
  - Is constant
  - Affects non-coital erections
  - Occurs under all circumstances

- **Psychogenic ED usually**
  - Is sudden in onset
  - Situational with varying degrees of ED under different circumstances
  - Is associated with the presence of nocturnal or early morning erections
**Medical History**

- Ageing
- Hypertension
- Arteriosclerosis
- Diabetes mellitus
- Smoking
- Depression

- Dyslipidaemia
- Pelvic / Perineal / penile trauma or surgery
- Neurological illness
- Endocrine disease
- Prescription and recreational drugs
<table>
<thead>
<tr>
<th>Drug type</th>
<th>Drug or class of drug</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihypertensive drugs</td>
<td>Diuretics</td>
<td>ED</td>
</tr>
<tr>
<td></td>
<td>Beta blockers</td>
<td>ED</td>
</tr>
<tr>
<td></td>
<td>Centrally acting anti-hypertensive agents eg clonidine, methyl DOPA</td>
<td>ED</td>
</tr>
<tr>
<td>Centrally acting agents</td>
<td>Phenothiazines</td>
<td>ED, Reduced libido, Ejaculatory dysfunction</td>
</tr>
<tr>
<td></td>
<td>Butyrophenones</td>
<td>ED</td>
</tr>
<tr>
<td></td>
<td>Serotonin reuptake inhibitors</td>
<td>ED, Ejaculatory dysfunction</td>
</tr>
<tr>
<td></td>
<td>Tricyclic antidepressants</td>
<td>ED, Reduced libido</td>
</tr>
<tr>
<td></td>
<td>Phenytoin</td>
<td>ED, Reduced libido</td>
</tr>
<tr>
<td>Endocrine drugs</td>
<td>LHRH analogues</td>
<td>ED, Reduced libido</td>
</tr>
<tr>
<td></td>
<td>Antiandrogens</td>
<td>ED, Reduced libido</td>
</tr>
<tr>
<td></td>
<td>Oestrogens</td>
<td>ED, Reduced libido</td>
</tr>
<tr>
<td>Recreational drugs</td>
<td>Alcohol</td>
<td>ED, Reduced libido, Ejaculatory dysfunction</td>
</tr>
<tr>
<td></td>
<td>Marijuana</td>
<td>ED</td>
</tr>
<tr>
<td></td>
<td>Cocaine</td>
<td>ED</td>
</tr>
<tr>
<td></td>
<td>Opiates</td>
<td>ED, Reduced libido</td>
</tr>
<tr>
<td></td>
<td>Amphetamines</td>
<td>Reduced libido, Ejaculatory dysfunction</td>
</tr>
<tr>
<td></td>
<td>Anabolic steroids</td>
<td>ED, Reduced libido</td>
</tr>
<tr>
<td>Other drugs</td>
<td>Cimetidine</td>
<td>ED, Reduced libido</td>
</tr>
<tr>
<td></td>
<td>Metoclopramide</td>
<td>ED, Reduced libido</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
<td>ED</td>
</tr>
</tbody>
</table>
Case 1 - Michael

- A 54 yr old fit insurance salesman mentions sexual difficulties
- He has had difficulty maintaining erection his erections for 12 months but worse last 3 months
- Night-time and early morning erections are absent
- He is happily married
- He is hypertensive and uses Ramipril 5mg
- What would you do?
Patient with ED (self-reported)

Medical and psychosexual history (use of validated instruments, e.g. IIEF)

- Identify other than ED sexual problems
- Identify common causes of ED
- Identify reversible risk factors for ED
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Focused physical examination

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Laboratory tests

- Glucose-lipid profile (if not assessed in the last 12 months)
- Total testosterone (morning sample)
  If indicated, bio-available or free testosterone
Case 1 - Michael

- A 54 yr old fit insurance salesman with 6 month’s hypertension on Ramipril 5mg. Mentions difficulty maintaining erection for 12 months but worse last 3 months.
- Examination shows that he is overweight (BMI 30)
- BP 130/80
- What would you do?
Patient with ED (self-reported)

Medical and psychosexual history (use of validated instruments, e.g. IIEF)

- Identify other than ED sexual problems
- Identify common causes of ED
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Laboratory tests

- Glucose-lipid profile (if not assessed in the last 12 months)
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  - If indicated, bio-available or free testosterone
120 Minute Glucose

Impaired glucose tolerance
Patients: 20 (18%)
Controls: 7 (6%)

New cases diabetes
Patients: 9 (8%)
Controls: 3 (2.5%)

Baldo et al, EAU, 2008
Clinical Physiology of Testosterone

- 2-3% Free (half life 10 minutes)
- 50-80% Bound to SHBG (not Bioavailable)
- 20-50% Bound to Albumin (Bioavailable)
There is no generally accepted lower limit of normal.

There is general agreement that:
- levels above 12nmol/l do not require substitution
- levels below 8nmol/l will usually benefit from substitution

Wang et al, Eur Urol, 55: 121-130, 2009,
Free Testosterone

- If the level is between 8 and 12 nmol/l, then measured or calculated free testosterone may be helpful *(Level 2b, Grade A)*

- Free testosterone levels less than 225 pmol/l can provide supportive evidence for testosterone replacement *(Level 3, Grade C)*

Wang et al, Eur Urol, 55: 121-130, 2009,
Free & Bioavailable Testosterone calculator

These calculated parameters more accurately reflect the level of bioactive testosterone than does the sole measurement of total serum testosterone. Testosterone and dihydrotestosterone (DHT) circulate in plasma unbound (free approximately 2 - 3%), bound to specific plasma proteins (sex hormone-binding globulin SHBG) and weakly bound to nonspecific proteins such as albumin. The SHBG-bound fraction is biologically inactive because of the high binding affinity of SHBG for testosterone. Free testosterone measures the free fraction, bioavailable testosterone includes free plus weakly bound to albumin.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>4.3 g</td>
<td>g/dL</td>
</tr>
<tr>
<td>SHBG</td>
<td>50 nmol</td>
<td>nmol/L</td>
</tr>
<tr>
<td>Testosterone</td>
<td>13.1 nmol</td>
<td>nmol/L</td>
</tr>
</tbody>
</table>

**Calculate**

**Explanation and examples**

- **Free Testosterone**: $0.202 \text{ nmol/L} = 1.54\%$
- **Bioavailable Testosterone**: $4.74 \text{ nmol/L} = 36.2\%$

Disclaimer: Results from this calculator should NOT be solely relied upon in making (or refraining from making) any decision in any case/circumstances without the prior consultation of experts or professional persons. No responsibility whatsoever is assumed for its correctness or suitability for any given purpose.

WARNING! The calculated free and bioavailable testosterone are reliable in most clinical situations, but should not be relied upon in situations with potential massive interference by steroids binding to SHBG; e.g. in women during pregnancy, in men during treatment inducing high levels of DHT (e.g. transdermal DHT, oral testosterone) or mesteron.

This calculator was developed at the Hormonology department, University Hospital of Ghent, Belgium. If you have suggestions to improve this calculator, or for further questions or help contact us **Dr. Tom Fiers** or **Prof. Dr. J.M. Kaufman**.
A 54 yr old fit insurance salesman (BMI 30) with 6 month’s hypertension on Ramipril 5mg. Mentions difficulty maintaining erection for 12 months but worse last 3 months.

Examination NAD. BP 130/80

Bloods
- FBG; 5.2
- TC; 6.0, LDL; 3.7,
- TT; 14.2nmol/l, PSA 0.7

What would you do?
Psychogenic
Traumatic
Endocrine

Treatment of erectile dysfunction

Identify and treat ‘curable’ causes of erectile dysfunction
Lifestyle changes and risk factor modification
Provide education and counselling to patients and partners

Identify patient needs and expectations
Shared decision-making
Offer conjoint psychosocial and medical treatment

PDE5 inhibitors
Intracavernous injections
Vacuum devices
Intraurethral/topical alprostadil

Assess therapeutic outcome:
• Erectile response
• Side-effects
• Treatment satisfaction
Case 1 - Michael

- Ramipril changed to Losartan 150mg
- Commenced on simvastatin 40mg
- Exercise and life style advice
- Erections returned to normal within 4 weeks with complete spontaneity in relationship.

**Learning points**: Early detection of ED can be treated with risk and lifestyle management without the need for ED specific medication.
## Risk Factors

<table>
<thead>
<tr>
<th></th>
<th>Effect</th>
<th>Cause</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hypertension</strong></td>
<td>The risk of ED is twice that of a normotensive man of the same age</td>
<td>Endothelial dysfunction</td>
<td>Antihypertensives</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atherosclerosis</td>
<td></td>
</tr>
<tr>
<td><strong>Diabetes</strong></td>
<td>The risk of ED is twice that of a non diabetic man of the same age</td>
<td>Endothelial dysfunction</td>
<td>Diabetic treatment</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Atherosclerosis</td>
<td>Weight loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neuropathy</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>hypogonadism</td>
<td></td>
</tr>
<tr>
<td><strong>Dyslipidaemia</strong></td>
<td>For men under 55 yrs there is no effect</td>
<td>Endothelial dysfunction</td>
<td>Statins</td>
</tr>
<tr>
<td></td>
<td>For men over 55 the risk of ED is almost doubled</td>
<td>Atherosclerosis</td>
<td></td>
</tr>
</tbody>
</table>
### Risk Factor Modification

#### Hypertension
- Most antihypertensive agents increase risk of ED (by around 20%)
  - Certainly beta blockers and thiazides
- Angiotensin II inhibitors (ARBs) probably improve erectile function [2-4]
  - Mechanism probably improved penile SM relaxation due to Ang II

<table>
<thead>
<tr>
<th>Antihypertensive drugs</th>
<th>Effect on erectile function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central acting</td>
<td>- - -</td>
</tr>
<tr>
<td>Diuretics</td>
<td>- -</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>-</td>
</tr>
<tr>
<td>Calcium antagonists</td>
<td>±</td>
</tr>
<tr>
<td>ACE-inhibitors</td>
<td>±</td>
</tr>
<tr>
<td>Alpha-blockers</td>
<td>+</td>
</tr>
<tr>
<td>Angiotensin receptor blockers</td>
<td>+ +</td>
</tr>
</tbody>
</table>

Figure 3. Forest plot shows the standardized difference in means of International Index of Erectile Dysfunction (IIEF-5) score after lifestyle intervention only and pharmacotherapy for cardiovascular (CV) risk factors.

**Figure Legend:**
Figure 3. Forest plot shows the standardized difference in means of International Index of Erectile Dysfunction (IIEF-5) score after lifestyle intervention only and pharmacotherapy for cardiovascular (CV) risk factors.
Treatment of erectile dysfunction

Identify and treat ‘curable’ causes of erectile dysfunction

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PDE5 inhibitors

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Intraurethral/topical alprostadil

Assess therapeutic outcome:
- Erectile response
- Side-effects
- Treatment satisfaction
# PDE5i: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>Efficacy Successful Intercourse (SEP3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Broad population</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>69%</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>68%</td>
</tr>
<tr>
<td>Vardenafil</td>
<td>68%</td>
</tr>
<tr>
<td>Avanafil</td>
<td>57%</td>
</tr>
</tbody>
</table>

- Goldstein et al, NEJM, 1998
- Carson et al, BJUI, 2004
- Boulton et al, Diabet, 2001
- Saenz de Tejada et al, Diabet Care, 2004
- Goldstein et al, Diabet, 2003
- Goldstein et al, JSM, 2012
Pharmacology of the PDE5i’s Pharmacokinetics

<table>
<thead>
<tr>
<th></th>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil</th>
<th>Avanafil</th>
</tr>
</thead>
<tbody>
<tr>
<td>T max (hrs)</td>
<td>1.16</td>
<td>0.66</td>
<td>2.0</td>
<td>0.6</td>
</tr>
<tr>
<td>T½ (hrs)</td>
<td>3.82</td>
<td>3.94</td>
<td>17.5</td>
<td>1.5-5</td>
</tr>
</tbody>
</table>
PDE$_{5i}$: Tolerability

- Headache: 10-15%
- Flushing: 5-10%
- Indigestion: 5-15%
- Nasal congestion: 3-10%
- Blue vision: 0-5% (Sildenafil)
- Back pain: 5-10% (Tadalafil)
Practical Issues

- **Generic issues**
  - Sexual stimulation
  - Delay between taking drug and intercourse
  - Side effects
  - Nitrates and alpha blockers

- **Drug specific issues**
  - Cost
  - Other indications (LUTS)
  - Timing of dosing
  - Duration of action
  - Food interactions
  - Drug interactions
Salvaging the PDE5 Non-Responder

- 20-60% patients fail to respond to PDE5i
- Salvage techniques include:
  - Dose titration – use the top dose
  - Correct timing – initially be conservative
  - Food issues – initially use on empty stomach
  - Risk factor management
  - Testosterone
  - Continuous dosing
  - Alternative therapies
Testosterone and the Treatment of ED
Testosterone: Indications

- Primary and Secondary hypogonadism
- [Late onset hypogonadism]
Testosterone Therapy
Contraindications

- Controversial
- (Established prostate cancer)
- Breast cancer
- Erythrocytosis (PCV > 50%)
- Sleep apnoea
- (Severe LUTS)
Pharmacokinetics of Testosterone

*Testosterone enanthate is not available in the UK. It is a 250mg 3-weekly injection, which is the most widely-used testosterone therapy in Europe.

Monitoring

- Symptoms
- DRE
- Testosterone levels
  - After 1 month with gels (at least 4 hours after application)
  - After 6-9 months with injections

- Safety parameters
  - PSA
  - Lipids
  - FBC
Testosterone: Side Effects

- Erythrocytosis
- Acne / Oily skin
- Reduced sperm production and reduced fertility
- Deterioration of pre-existing sleep apnoea
- [Prostate problems]
Treatment of erectile dysfunction

- Identify and treat ‘curable’ causes of erectile dysfunction
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PDE5 inhibitors

Intracavernous injections
- Vacuum devices
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Assess therapeutic outcome:
- Erectile response
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Intracavernosal Alprostadil

**Pros**
- Effective
- Rigidity
- Reliability

**Cons**
- Lack of spontaneity
- Invasive
- Complications
- Risk of priapism
- High drop out rate
- Expensive
Topical and Urethral Alprostadil

Pros
- Relatively non invasive
- Low complication rates
- Rapidly acting

Cons
- Poor efficacy
- Side effects
  - Flushing, pain, transmission to partner
Vacuum Erection Devices

**Pros**
- Potentially effective for all
- Non-invasive
- Low complication rates
- No restriction of frequency

**Cons**
- Needs manual dexterity
- Quality of erection
- Side effects
- Pivoting, Discolouration, Temperature, Bruising, Blocks ejaculation
- Cost
Penile Implants

Pros
- Efficacy
- Rigidity
- Satisfaction

Cons
- End stage treatment
- Complications
- Cost

Issues
- Expectations
- Needs manual dexterity
- Quality of erection
Penile Implants

**Pros**
- Efficacy
- Rigidity
- Satisfaction

**Cons**
- End stage treatment
- Complications
- Cost

**Issues**
- Expectations
- Needs manual dexterity
- Quality of erection
Conclusion

- ED is a symptom
- Assessment should involve a wider consideration of men’s health
- Treatment is effective and escalating
- Consider partner’s needs