ERECTILE DYSFUNCTION (ED)

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Wilberforce Health Centre, Hull
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Summary of Presentation

- Prevalence and Etiology of ED
- HIV and ED
- The Importance of Diagnosing ED
- Management of Erectile Dysfunction
- Management of Non Responders
Definition of Erectile Dysfunction

“The persistant inability to achieve or maintain an erection sufficient for satisfactory sexual performance.”

NIH Consensus Development Conference on Impotence Dec 1992
Prevalence and Etiology of Erectile Dysfunction
Predicted Increase in Prevalence of ED by 2025

Worldwide prevalence will increase from 152 million men in 1995 to 322 million men by 2025.

- North America: ↑ 9.1 million
- South/Central America and Caribbean: ↑ 15.6 million
- Europe: ↑ 11.9 million
- Africa: ↑ 19.3 million
- Asia: ↑ 113 million
- Oceania: ↑ 0.9 million

Men aged 40 to 70 years (N=1290)

No ED 48%

ED 52%

Minimal ED, “usually able to get or keep an erection.”

Moderate ED, “sometimes able to get and maintain an erection.”

Complete ED, “unable to get and keep an erection.”

Prevalence of ED increases with age

Data from 34 studies with a Prins score ≥12 and published in peer-reviewed literature showing median and range of ED prevalence in different age groups of men.

Eardley Sex Med Rev 2013
Massachusetts Male Aging Study (US): Under-treatment of ED

n=639 (≥45 years of age)

- 90% Never seek care
- 10% Seek or receive treatment

Organic Causes of ED

Organic

Vascular
Neurogenic
Hormonal
Penile injury/disease
Medications

Major Causes of Erectile Dysfunction

- Spinal Cord Injury: 8%
- Diabetes Mellitus: 40%
- Vascular Disease: 30%
- Radical Surgery: 13%
- Endocrine disorders: 6%
- Multiple sclerosis: 3%
- Multiple sclerosis: 3%

Prescribing Information appears on the last slide.
Psychogenic Causes of ED

Depression
Performance anxiety
Relationship problems
Psychosocial problems
Psychological distress

**Etiology of ED: Psychogenic and Organic**

- ED commonly involves a combination of psychogenic and organic factors.

Importance of diagnosing Erectile Dysfunction
Why Diagnosing ED Is Important

- **ED screening may:**
  - Identify underlying coronary artery disease\(^1\)
  - Uncover diabetes (as ED may be the first symptom in up to 20\%)\(^1\)
  - Detect dyslipidaemia\(^1\)
  - Reveal the presence of hypogonadism\(^1\)

**ED occurs sooner than cardiovascular disease**

- On average, in patients with ED and cardiovascular disease, ED occurs three to five years earlier than any subsequent cardiovascular event

<table>
<thead>
<tr>
<th>Artery</th>
<th>Diameter (mm)</th>
<th>Critical events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penile</td>
<td>1–2</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Coronary</td>
<td>3–4</td>
<td>Angina/myocardial infarction</td>
</tr>
<tr>
<td>Carotid</td>
<td>5–7</td>
<td>Transient ischaemic attack/stroke</td>
</tr>
</tbody>
</table>

ED and Hypogonadism

Androgen deficiency in adult male.

More common with increasing age deficiency leads to:

- Sexual Dysfunction
- Osteoporosis
- Dyslipidaemia
- Type 2 diabetes
- Metabolic syndrome &
- Depression
Components of the Metabolic Syndrome

- Abdominal obesity
- Insulin resistance
- Dyslipidaemia
- Hypertension
ED Strongly Associated with Age and LUTS Severity (MSAM-7)

Erection problems were significantly more common in men with LUTS and were strongly related to the severity of urinary symptoms, independent of age and other comorbidities.

HIV and Erectile Dysfunction

- Erectile dysfunction is more common in HIV positive men than those uninfected
- Reported prevalence ED in HIV positive men varies between 31-62% \(^2-^5\)
- Aetiology multi-factorial and usually combination of organic and psychogenic factors
- Traditional risk factors for ED are enhanced by the effects of HIV and its treatment
- Hypogonadism probably due to reduced free testosterone and increased SHBG
Chemsex

- Intentional sex under the influence of psychoactive drugs, mostly among MSM.
- The drugs GHB, GBL, and crystal meth often used in combination to facilitate sexual sessions lasting several hours or days with multiple sexual partners.
Chemsex and Sexual dysfunction

- Erectile dysfunction
- Sexual Unhappiness and lack of intimacy
- All chemsex drugs paradoxically make it harder to achieve and maintain an erection leading to use of PDE5i (genuine or counterfeit) online or over the counter leading to subsequent dependence
- Impairs erectile function when sober.
- Difficult to sustain intimate relationship.
Drugs associated with ED in HIV

- **Antiretrovirals (ARV)**
  - Role of ARV is controversial and evidence is conflicting
  - Darunavir and Raltegravir may cause ED as a less common side effect.
  - First report linking protease inhibitors to ED in 14 men emerged in 1999\(^{14}\)
  - Some subsequent studies support the role of ARVs \(^{2,15-17}\) and others do not \(^{5,18,19}\)
  - Causative link remains uncertain

- **Other drugs used to treat complications e.g.**
  - Antidepressants
  - Anti hypertensives
  - Analgesics e.g. opioids
Management of Erectile Dysfunction
Sexual Health Inventory for Men (SHIM)

This questionnaire can help you and your doctor determine if you have symptoms of erectile dysfunction (ED). For each question, circle the number next to the response that best describes your experience. Then add these numbers together and refer to the table below to see what your score may mean. Remember, only your doctor can decide if you have ED.

In the past 6 months:

1. How do you rate your confidence that you could get and keep an erection?
   - 1. Very low
   - 2. Low
   - 3. Moderate
   - 4. High
   - 5. Very high

2. When you had erections with sexual stimulation, how often were your erections hard enough for penetration (entering your partner)?
   - 0. No sexual activity
   - 1. Almost never or never
   - 2. A few times (much less than half the time)
   - 3. Sometimes (about half the time)
   - 4. Most times (much more than half the time)
   - 5. Almost always or always

3. During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
   - 0. Did not attempt intercourse
   - 1. Almost never or never
   - 2. A few times (much less than half the time)
   - 3. Sometimes (about half the time)
   - 4. Most times (much more than half the time)
   - 5. Almost always or always

4. During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
   - 0. Did not attempt intercourse
   - 1. Extremely difficult
   - 2. Very difficult
   - 3. Difficult
   - 4. Slightly difficult
   - 5. Not difficult

5. When you attempted sexual intercourse, how often was it satisfactory for you?
   - 0. Did not attempt intercourse
   - 1. Almost never or never
   - 2. A few times (much less than half the time)
   - 3. Sometimes (about half the time)
   - 4. Most times (much more than half the time)
   - 5. Almost always or always

<table>
<thead>
<tr>
<th>Score</th>
<th>You may have signs of</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-7</td>
<td>Severe ED</td>
</tr>
<tr>
<td>8-11</td>
<td>Moderate ED</td>
</tr>
<tr>
<td>12-16</td>
<td>Mild to moderate ED</td>
</tr>
<tr>
<td>17-21</td>
<td>Mild ED</td>
</tr>
<tr>
<td>22-25</td>
<td>No signs of ED</td>
</tr>
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</table>
The essentials in treating ED

- A detailed medical, psychosexual history and a focused physical examination\(^1\)

- Patient and if possible partner education about their ED medication\(^1,2\)

- Patient follow up and adequate exposure to the drug therapy\(^2\)

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2. Hatzimouratidis K *et al.* Eur Urol. 2007;51:75-89
The Comprehensive Case history continued

- Concurrent medical, psychiatric and surgical history
- Current relationship status and a history of previous sexual partners and relationships.
- Issues of sexual orientation and gender identity should also be noted.
- Alcohol, smoking and illicit drug misuse

Examinations

- All patients should have a focused physical examination.

- A genital examination is recommended
  - Essential if there is a history of rapid onset of pain, deviation of the penis during tumescence, the symptoms of hypogonadism or other urological symptoms

- A digital rectal examination (DRE) of the prostate is not mandatory in ED
  - Should be conducted in the presence of genito-urinary or protracted secondary ejaculatory symptoms

- Blood pressure, heart rate, weight and waist circumference measurement.

Investigations

- The choice of investigations depends on the individual circumstances of the patient.

- Serum lipids, fasting plasma glucose or HbA1c and S. testosterone (morning sample) should be measured in all patients.

ED and Hypogonadism

Diagnosis:

Clinical Assessment

Blood Testing

Serum testosterone and Sex hormone binding globulin (SHBG)
(Range 8 - 25 nmol/l) varies from lab to lab
samples to be taken between 08.00 to 11.00 and repeat after 2-3 weeks if low.
Check for free Testosterone – It should be more than 0.22 nmol/L or > 2%
on line calculator to calculate the free testosterone.
Men with total serum testosterone that is consistently < 11 mmol/L might benefit from trial of testosterone replacement therapy.
Replacement therapy in men may experience:

  General improvement in sexual dysfunction
  Improved erection
  Restored or enhanced response to PDE5i
Treatment Options

- Alteration of modifiable risk factors
- Oral agents
- Local therapies
- Sexual counselling and education
- Surgical therapy
Alter Modifiable Risk Factors or Causes

- **Lifestyle and psychosocial factors**
  - Smoking, substance abuse, partner conflict, or depression
- **Prescription or nonprescription drug use**
  - Antihypertensives, antidepressants, antipsychotics, antiarrhythmics, antiandrogens, etc.
- **Regular exercise and weight Loss**
- **Pelvic Floor exercises**
- **Hormone replacement therapy**
  (eg, hypogonadism, hyperprolactinemia)
European Association of Urology/BSSM: Treatment algorithm for erectile dysfunction

1st line therapy: PDE5 inhibitor, Vacuum device

Assess response, side effects, patient satisfaction

2nd line therapy: Intracavernous injections, Intraurethral alprostadil

Inadequate treatment outcome

3rd line therapy: Consider penile prosthesis implantation

Inadequate treatment outcome
ED associated with the following medical conditions are deemed to qualify for prescription at NHS expense:

- Diabetes
- Parkinson’s disease
- Prostate cancer
- Multiple sclerosis
- Poliomyelitis
- Prostatectomy
- Radical pelvic surgery
- Severe pelvic injury
- Renal failure treated by dialysis or transplant
- Single gene neurological disease
- Spinal cord injury – spina bifida
- NHS drug treatment before 15th September 1998
- If patient is suffering severe distress on account of their ED
# Therapeutic Options for Erectile Dysfunction

<table>
<thead>
<tr>
<th>Oral</th>
<th>Generic</th>
<th>Brand</th>
<th>Co.</th>
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<tbody>
<tr>
<td></td>
<td>Sildenafil</td>
<td>Viagra&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Pfizer</td>
</tr>
<tr>
<td></td>
<td>Tadalafil</td>
<td>Cialis&lt;sup&gt;®&lt;/sup&gt;</td>
<td>Lilly</td>
</tr>
<tr>
<td></td>
<td>Vardenafil</td>
<td>Levitra&lt;sup&gt;®&lt;/sup&gt;</td>
<td>BSP</td>
</tr>
<tr>
<td></td>
<td>Avanafil</td>
<td>Spedra</td>
<td>Menarini</td>
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<thead>
<tr>
<th>Local</th>
<th>Alprostadil</th>
<th>Vitaros</th>
<th>Takeda</th>
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<thead>
<tr>
<th>Topical</th>
<th>Alprostadil</th>
<th>MUSE&lt;sup&gt;®&lt;/sup&gt;</th>
<th>Meda</th>
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<table>
<thead>
<tr>
<th>Intraurethral</th>
<th>Alprostadil</th>
<th>Caverject&lt;sup&gt;®&lt;/sup&gt;</th>
<th>Pfizer</th>
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Commonly used oral PDE5 inhibitors:
Pharmacological and pharmacokinetic properties

<table>
<thead>
<tr>
<th>PDE5 inhibitor</th>
<th>Onset of action (minutes after dosing)</th>
<th>Duration (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sildenafil</td>
<td>60</td>
<td>4</td>
</tr>
<tr>
<td>Tadalafil (Cialis)</td>
<td>At least 30</td>
<td>36</td>
</tr>
<tr>
<td>Vardenafil (Levitra)</td>
<td>25-60</td>
<td>4</td>
</tr>
<tr>
<td>Avanafil (Spedra)</td>
<td>15-30</td>
<td>&gt;6 hours</td>
</tr>
</tbody>
</table>

Avanafil SmPC 2013; Sildenafil SmPC June 2013; Vardenafil SmPC April 2013; Tadalafil SmPC April 2013; Kang & Kim Ther Adv Urol 2013
# PDE5 inhibitors: Tolerability

<table>
<thead>
<tr>
<th>AEs</th>
<th>Avanafil</th>
<th>Sildenafil</th>
<th>Vardenafil</th>
<th>Tadalafil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Very common</strong></td>
<td>None reported</td>
<td>Headache</td>
<td>Headache</td>
<td>None reported</td>
</tr>
<tr>
<td><strong>Common</strong></td>
<td>Headache</td>
<td>Flushing</td>
<td>Nasal congestion</td>
<td>Back pain</td>
</tr>
<tr>
<td></td>
<td>Flushing</td>
<td>Dyspepsia</td>
<td>Flushing</td>
<td>Dyspepsia</td>
</tr>
<tr>
<td></td>
<td>Nasal congestion</td>
<td>Visual disorders</td>
<td>Dyspepsia</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Visual colour distortion</td>
<td>GORD</td>
<td>Myalgia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dizziness</td>
<td>Headache</td>
<td>Nasal congestion</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Pain in extremities</td>
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</table>
Patient Education

Optimising success/managing PDE5i "failures"

Sexual stimulation is needed

Absorption affected by food (drugs vary)

Post-dose timing (drugs vary)
Optimising success/managing PDE5i “failures”

Several attempts may be required for optimum effect

Dose optimisation

Consider an alternative PDE5i if first drug is unsatisfactory
Treatment Options for non responders to PDE5i

- Switching to another PDE5 Inhibitors
- Offer second line therapy ie Local therapy
- Combination therapy
- PDE5 Inhibitors with Testosterone replacement therapy in patients with hypogonadism or low testosterone level
A third of Men and Women have no set pattern of sexual timing

Intercourse patterns (%)

- **Night/Evening**
  - Male: 48%
  - Female: 39%

- **Afternoon**
  - Male: 16%
  - Female: 19%

- **Morning**
  - Male: 5%
  - Female: 7%

- **No Set Pattern**
  - Male: 30%
  - Female: 34%

Tadalafil Once a Day Indication

In responder patients to on-demand regimen who anticipate a frequent use of CIALIS (i.e., at least twice weekly)

- A once daily regimen with the lowest doses of CIALIS might be considered suitable, based on patient choice and the physician’s judgement.

- The recommended dose is 5mg taken once a day at approximately the same time of day.

- Tadalafil 5 mgs may also be used in selective patients with both ED and LUTS

ED and HIV

Protease inhibitors

- Potent enzyme inhibitors
- Cause increased plasma levels and enhanced effects of PDE5i$^{25-27}$

- Dosing studies suggest maximum dose of
  - Sildenafil (Viagra®)  25mg in 48 hours
  - Vardenafil (Levitra®)  2.5mg in 72 hours
  - Tadalafil (Cialis®)  10mg in 72 hours
ED and HIV NNRTI

- Mild enzyme inducers
- May require higher doses of PDE5i for desired therapeutic effect
- Doses should be titrated according to response

No dose adjustment necessary with other ARV drug classes inc NRTIs and integrase inhibitors inc Dolutegravir and Raltegravir
ED- PDE5i and Cobicistat

- PDE5i dose adjustment and timing required

- Coadministration has not been studied but expected to substantially increase PDE5i concentrations and may result in an increase in associated adverse events including hypotension, syncope, visual changes and prolonged erection (priapism).
Contraindications for PDE5 Inhibitors in the Management of Erectile Dysfunction

In patients for whom sexual activity is considered inadvisable

- Patients with severe cardiac failure
- Patients with unstable angina
- Hypotension (<90/50 mm of Hg) Due to haemodynamic effect of PDE5 inhibitor
- Recent history of (within prior 6 months)
  - Stroke or myocardial infarction
- Patients receiving Nitric oxide donors (e.g. Nicorandil) or
- Organic nitrate therapy in any form (including sprays/sublingual tablets used on PRN basis)
Local Therapies

- Intraurethral therapy
- Intracavernosal injection therapy
- Vacuum device therapy

Generally Used Second Line

- Failure of oral drug therapy
- Contraindications to specific oral drugs
- Adverse events from oral drugs
- Individual preferences
Intraurethral (IU) therapy - alprostadil

MUSE (Medicated Urethral System for Erection)

Applicator for intraurethral delivery of alprostadil. Depressing the end releases the pellet into the urethra.

Pellet of alprostadil inside the urethra
Vitaros® is licensed for the treatment of men ≥18 years of age with erectile dysfunction

- Vitaros® is applied to the tip of the penis (meatus) where it is rapidly absorbed without invasive delivery
- Vitaros® should be applied 5 to 30 minutes before sexual intercourse

<table>
<thead>
<tr>
<th>Action</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Expose the tip of the penis and widen the opening of the glans of the penis by squeezing gently</td>
</tr>
<tr>
<td>2.</td>
<td>Hold the applicator just above the opening. Slowly push the plunger and let Vitaros® drop into the tip</td>
</tr>
<tr>
<td>3.</td>
<td>The applicator tip should NOT be inserted into the opening</td>
</tr>
<tr>
<td>4.</td>
<td>Hold the penis upright for about 30 seconds to aid absorption. Any excess cream can be rubbed in</td>
</tr>
</tbody>
</table>

**Intracavernosal Injection**
e.g. alprostadil

Drug injected directly into the corpus away from midline

Corpus cavernosum

Cross-section of the shaft of the penis
Penile prosthesis

- Reservoir
- Cylinders
- Pump

Multi-part inflatable prosthesis
New Non Invasive treatment for Erectile Dysfunction

Low intensity Shock Wave therapy (LI-SWT)
Low energy shock waves induce angiogenesis

Shear Stress
↓
Intracellular & Extracellular responses
↓
Stimulates endothelial Nitric Oxide Synthase (eNOS)
↓
Release of Vascular Endothelial Growth Factors (VEGF)
↓
Proliferating Cell Nuclear Antigen (PCNA) production
↓↓↓↓↓
Neovascularization
EEDSWT applied on the penile shaft and crus.

Each treatment includes a 3-minute application of 300 shock waves in 5 different anatomical sites.
The importance of diagnosing ED

Summary

- ED has a significant impact on the quality of life of patients and their partners.
- ED is closely associated with many important physical conditions and may affect psychosocial health.
- ED itself is a cardiovascular risk factor conferring a risk equivalent to a current moderate level of smoking. ED confers a 1.46 increased risk for cardiovascular disease.
- ED may be associated with other causes of cardiovascular disease such as hypertension, dyslipidaemia and endothelial dysfunction.
- ED may be the first presentation of serious medical conditions such as diabetes or hypertension.