Erectile dysfunction
‘the persistent inability to attain and maintain an erection sufficient for satisfactory sexual performance’
Incidence difficult to define
US population 52% of males aged 50-70yrs (Massachusets Male Aging Study; mild, moderate and complete (10%))
In all studies incidence increases with age ? due to decline in smooth muscle concentration and age-related vascular leak
Geographically a/w high incidence of risk factors, namely smoking, obesity, diabetes, hyperlipidaemia and hypertension
Aetiology
Psychogenic
Neurogenic
Central
MS
Stroke
Tumour
Parkinson’s disease
Multi-system atrophy
Spinal cord transection/tumour
Peripheral
MS
Diabetes
Alcoholism
Uraemia
Sacral cord injury
Pelvic or retroperitoneal surgery
Hormonal
Hypogonadism
Hyperprolactinaemia
Hyperthyroidism
Cushings disease
Arterial
Arterial insufficiency due to CVS risk factors [DM, HT, hyperlipidaemia, smoking, obesity]
Post-traumatic arterial insufficiency (obliteration, fistula)
Venous
Peyronie’s
Primary venous leak (rare)
Secondary venous leak
Shunting for priapism
Tunical albuginea injury after penile #
Drug-induced
Anti hypertensives (esp. BB and thiazide diuretics)
Antidepressants
Antipsychotics
Antiandrogens
Antihistamines
Recreational drugs
Investigation (4)
Establish the nature of the problem
Identify any reversible causes of ED
  Psychogenic
  Drug-induced
  Hormonal imbalance
  Post-traumatic arterial insufficiency
Address risk factors
Manage impotence

Schedule
(i) History
  a) Sexual history
     Nature, onset and duration of symptoms
     Libido, quality of erection, orgasm and ejaculation
     Nocturnal, morning erections, non-coital erections, masturbation, relationship problems
     International index for erectile function (IIEF; Rosen 1997) can be used but quite cumbersome
     * psychogenic ED characterised by acute onset, morning and nocturnal erections, rigid non-coital erections and situational ED
  b) Medical history
     Concomitant medical problems
     Previous retroperitoneal or pelvic surgery
     Cardiovascular risk stratification (EAU GL)
     Specific risk factors DM, hyperlipidaemia, hypertension, smoking status, BMI
     No contraindications to sex if:
     Asymptomatic + <3 risk factors
     Post-stenting or mild angina
     Mild CCF (NYHA1)
     Controlled hypertension
  c) Drug history

(ii) Physical examination
     Secondary sexual characteristics
     Groin examination and pedal pulses
     Genital examination
     Size and shape (?chordee)
     Peyronie’s
     Penile sensation
     Bulbocavernosus reflex
     DRE
     Perineal sensation
     Anal reflex and tone
     Prostate examination if over 50 yrs

(iii) Laboratory testing
     Fasting sample
Testosterone (bioavailable or free-T better to diagnose hypogonadism

Lipids
Glucose

Optional
PSA in men > 50 yrs with >10 yr life-expectancy
Prolactin
Hyperprolactinaemia quite rare
Galactorrhoea, gynaecomastia, ED
TFTs in those with clinical features of hypo or hyperthyroidism

In the vast majority of patients the above schedule sufficient. With the exception of patients with psychogenic ED, drug-induced, post-traumatic arterial insufficiency or hormonal imbalance ED cannot be cured. Thus a goal-directed approach is entirely appropriate. Additional tests:

Nocturnal penile tumescence
- Confirm psychogenic ED
- Home testing; 2 rings (base and subcoronal)
- > 60% rigidity at subcoronal for > 10 minutes excludes organic cause

Intracavernous injection +/- stimulation
- Test and teach response to injection therapy
- Alprostadil 10-20ug intracavernosally
- Some patients inhibited by needle – may require additional stimulation

Duplex ultrasonography
- Assessment of vascular flow in penis during erection
- Suspicion of primary venous leak or post-traumatic arterial insufficiency
- PGE1 augmented erections
- Duplex performed 5mins after injection (latent) through to cessation of flow (rigid)
Erectile dysfunction

Arterial insufficiency  Peak systolic velocity < 25cm/s*
Venous leak  PSV consistently > 25cm/s and end-diastolic velocity > 5cm/s

* if post-traumatic arterial insufficiency suspected and arterial revascularisation considered, DICC should be performed to exclude venous leak. If normal arteriography road map

Dynamic infusion cavernosometry and cavernosography (DICC)

Intracavernous injection of PGE1
Infusion of normal saline and continued pressure measurement
Normal = < 5ml/min required to maintain rigid erection
Pressure drop > 100mmHg after cessation

Rarely performed – Doppler USS more common
Cavernosography occasionally performed to exclude leak prior to revascularisation

Management of erectile dysfunction

3 components
Management of ‘curable’ ED
Address lifestyle factors
Manage impotence

(i) Management of ‘curable’ ED
Hormonal abnormalities referred to endocrinologist
MRI or CT of pituitary fossa in hyperprolactinaemia
Testosterone replacement therapy acceptable in men with LOH and ED in whom DRE and PSA are normal
Psychosexual counselling in patients with severe psychogenic ED
Post-traumatic arterial insufficiency
Staging investigations
Doppler USS, cavernosogram and arteriogram
Donor vessel usually inferior epigastric grafted onto dorsal penile artery. Long-term success rates ~25% at 12-24 months

Penile venous surgery
Venous surgery for venous leak a/w poor outcomes due to persistent leakage
70% success reported (Lue) in patients < 40 yrs with congenital (maldeveloped crura and cavernous leak) and post-traumatic venous leak
Ligation of deep dorsal vein and both crural bases

(ii) Address lifestyle factors
CVS risk factors – refer to cardiologist
Elevated fasting glucose – refer endocrinology/GP
Elevated lipids – refer GP
Smoking cessation self-help groups/new leaf
Promote exercise
Some evidence that modification of CVS risk factors can have significant impact on ED
Atorvastatin in lone hyperlipidaemia  Saltzman 2004
Switch to losartan in hypertension  Caro 2001
However RCT data required and at present most patients receive goal-directed ED therapy in addition to lifestyle modification

A. First-line therapy

(i) PDE5 inhibitors
Inhibition of PDE5 elevates cGMP facilitating smooth muscle relaxation
Not erectogenic – require intact nerve pathways and stimulation
Sildenafil (Viagra, Pfizer), Vardenafil (Levitra, Bayer-GSK), Tadalafil (Cialis, Lilly)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sildenafil 100mg</th>
<th>Tadalafil 20mg</th>
<th>Vardenafil 20mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>30 mins</td>
<td>30 mins</td>
<td>30 mins</td>
</tr>
<tr>
<td>Tmax</td>
<td>1 hr</td>
<td>2 hr</td>
<td>45 mins</td>
</tr>
<tr>
<td>PDE5 inhibition*</td>
<td>+</td>
<td>+++</td>
<td>+++++</td>
</tr>
<tr>
<td>Half-life (T1/2)</td>
<td>3.8</td>
<td>17.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Fatty meal</td>
<td>Impairs action</td>
<td>No effect</td>
<td>Impairs action</td>
</tr>
<tr>
<td>Duration action</td>
<td>12 hrs</td>
<td>36 hrs</td>
<td>12 hrs</td>
</tr>
<tr>
<td>Doses</td>
<td>25,50,100mg</td>
<td>10,20mg</td>
<td>5,10,20mg</td>
</tr>
<tr>
<td>Efficacy @ max**</td>
<td>84%</td>
<td>81%</td>
<td>80%</td>
</tr>
<tr>
<td>Cost (8 tabs)</td>
<td>£47</td>
<td>£54</td>
<td>£47</td>
</tr>
</tbody>
</table>

* All highly potent drugs – no difference in real-world effect
** No direct comparison studies

Contraindications to PDE5i
Nitrates  All PDE5is absolutely contraindicated in patients taking nitrate preparations (including poppers)
a-blockers  Vardenafil and alpha-blockers banned in US
Sildenafil not within 4 hrs of an alpha-blocker

Drug interactions
PDE5i effect increased  erythromycin, ketoconazole, itraconazole, HIV meds (CYP3A4 enzyme pathway)
PDE5i effect decreases  rifampcin, phenytoin, carbamazepine

NB.  Sildenafil a/w blurred vision, blue vision, hypersensitivity (PDE6 cross-inhibition)
Erectile dysfunction

NHS PDE5i (mark prescription SLS)
Neurogenic ED
MS, DM, Parkinson’s disease, polio, spina bifida, spinal cord injury
Dialysis or renal transplant
Prostate cancer/TURP/radical pelvic surgery
Rx prior to September 1998
Severe mental stress

(ii) Other oral agents

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
<th>Efficacy</th>
<th>Tolerability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apomorphine</td>
<td>Centrally acting dopamine agonist</td>
<td>30-50%</td>
<td>Well tolerated (N+V) no BP drop</td>
</tr>
<tr>
<td></td>
<td>D1 and D2 receptor specific</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Efficacy originally thought to be 30-50%</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Well tolerated (N+V) no BP drop</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>? first-line in those with nitrates</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Withdrawn from UK in 2006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phentolamine</td>
<td>Centrally acting alpha blocker</td>
<td>~50% efficacy</td>
<td>Not licensed</td>
</tr>
<tr>
<td>L-arginine</td>
<td>NO donor. Not licensed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yohimbine</td>
<td>Centrally acting alpha-2 adrenoceptor blocker</td>
<td></td>
<td>No improvement vs. placebo</td>
</tr>
<tr>
<td>Trazodone</td>
<td>Serotonergic and alpha blocker</td>
<td></td>
<td>No improvement</td>
</tr>
</tbody>
</table>

All of above except apomorphine not recommended. Apomorphine withdrawn. PDE5i therefore first and only oral option. New agents with potential activity comprise guanylate cyclase activators, potassium channel activators and Rho-kinase inhibitors.

(iii) Topical therapy

Nitroglycerine, alprostadil and papaverine gels all used
Absorption thro’ tunica albuginea poor
Even with enhancers results poor (33% responders) and skin irritation common

(iv) Vacuum constriction device

Highly effective > 90% erections sufficient for intercourse
Drop-out rates high ~50% usage at 2 yrs
Complications pain, bruising, no ejaculation, cool paraesthetic penis impaired spontaneity, pivoting of soft penis below constriction ring, occasionally skin necrosis

B. Second-line therapy

(i) PDE5i salvage

Consider failure if 4 attempts with maximum dose have not worked
Daily dosing of PDE5i may improve benefit, but most studies have shown only a modest benefit (IIEF score reported rather than absolute success rates)
Erectile dysfunction

Similar reports for adjuvant T in hypogonad PDE5 non-responders (<10% of patients with ED hypogonad)

(ii) Intracavernous injection
Alprostadil, papaverine and phentolamine, or combinations
Alprostadil is a synthetic prostaglandin E1 analogue which acts on adenylate cyclase-cAMP pathway
Papaverine is a non-selective PDE inhibitor which prevents cAMP and cGMP breakdown
Phentolamine alpha-adrenoceptor agonist which reduces cytosolic IP3

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Papaverine</th>
<th>Pap&amp;Phent</th>
<th>Alprostadil</th>
<th>Trimix</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose</td>
<td>7.5 – 60mg</td>
<td>0.1-1ml</td>
<td>1- 60ug</td>
<td>0.1-1ml</td>
</tr>
<tr>
<td>Efficacy</td>
<td>50%</td>
<td>70%</td>
<td>85%</td>
<td>92%</td>
</tr>
<tr>
<td>Pain</td>
<td>-</td>
<td>-</td>
<td>15-30%</td>
<td>2-20%</td>
</tr>
<tr>
<td>Priapism</td>
<td>5%</td>
<td>8%</td>
<td>1%</td>
<td>2%</td>
</tr>
<tr>
<td>Fibrosis</td>
<td>7%</td>
<td>7%</td>
<td>3%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Only Alprostadil (PGE1) licensed in UK. If pain is a particular problem, Trimix could be considered on a named patient basis
Overall failure of injection therapy 5-10%: 30% of these may be salvaged with combination PGE1 and PDE5i
Sickle cell disease but not anticoagulants contraindicated with ICI

(iii) Intraurethral therapy
125ug-1mg alprostadil via MUSE applicator
Efficacy ~50% only with higher doses (start at 500ug)
Pain (33%) dizziness (10%) urethral bleeding (5%) common Ses

C. Third-line therapy
Penile implants
Malleable
Mechanical
Inflatable (two-piece or three-piece)
AMS 700CX/CXM and Mentor alpha I most commonly inserted (both three-piece inflatable). Typically inserted via infrapubic or penoscrotal incisions. Subcoronal only for malleable prostheses. Traditional bougie sizing of corpora cavernosa oversizes by ~2cm. Reservoir best placed in retropubic place to avoid autoinflation.
Counselling
Partner and wife ideal
‘Erect’ penile length shorter than natural erection (glans soft)
Mechanical failure requires re-operation or removal
Infection & erosion mandate removal
Re-implantation often smaller due to scarring
Overall satisfaction rates 80% (best for three-piece)
Mechanical failure and cost
3-piece > 2-piece > malleable
AMS 700CX/CXM failure rates 7-16% at 5 yrs follow-up
Erectile dysfunction

Best paper Wilson et al 2007 – revision-free survival 60% at 15 years (infection rate 9%; therefore mechanical failure rate ~30% at 15 years)

Infection
  Early infection GNB, late infection GPB
  <5% for two most popular implants
  2-3% for broad-spectrum antibiotics (gentamicin and vancomycin 1 hr pre-op)
  1% for antibiotic impregnated implants
  9% infection rate in spinal cord injury
  No increased infection rate in diabetics

Infected graft
  Removal, antibiotics and re-implant after 3-6 months, but significant scarring and fibrosis
  Single stage removal, antibiotic lavage and re-implant a/w infection rates of ~20% (Mulcahy 2000)
Appendix

**EAU cardiac risk stratification**

<table>
<thead>
<tr>
<th>Low-risk category</th>
<th>Intermediate-risk category</th>
<th>High-risk category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asymptomatic, &lt; 3 risk factors for CAD (excluding gender)</td>
<td>Moderate, stable angina</td>
<td>High-risk arrhythmias</td>
</tr>
<tr>
<td>Recent M (≤ 2, &lt; 6 weeks)</td>
<td>Recent MI (≤ 2 weeks)</td>
<td></td>
</tr>
<tr>
<td>LV/D/CHF (NYHA class III)</td>
<td>LV/D/CHF (NYHA class III)</td>
<td>LV/D/CHF (NYHA class III)</td>
</tr>
<tr>
<td>Post-successful coronary revascularization</td>
<td>Non-cardiac sequelae of atherosclerotic disease (e.g., stroke, peripheral vascular disease)</td>
<td>Hypertrophic obstructive and other cardiomyopathies</td>
</tr>
</tbody>
</table>

**New York Heart Association classification of CCF**

Class I: patients with no limitation of activities; they suffer no symptoms from ordinary activities.

Class II: patients with slight, mild limitation of activity; they are comfortable with rest or with mild exertion.

Class III: patients with marked limitation of activity; they are comfortable only at rest.

Class IV: patients who should be at complete rest, confined to bed or chair; any physical activity brings on discomfort and symptoms occur at rest

**IIEF Questionnaire**

International index of erectile function
Typically short-form 5 used (IIEF-5)
5 domains/questions covering erection/sexual performance: Achievement Adequacy Maintenance after penetration Maintenance to orgasm/ejaculation Satisfaction
Points given in range 0-5 (5 = best outcome)

0-7  Severe ED
22-25  No ED