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
  - Antihypertensives (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
    - * pyschogenic 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

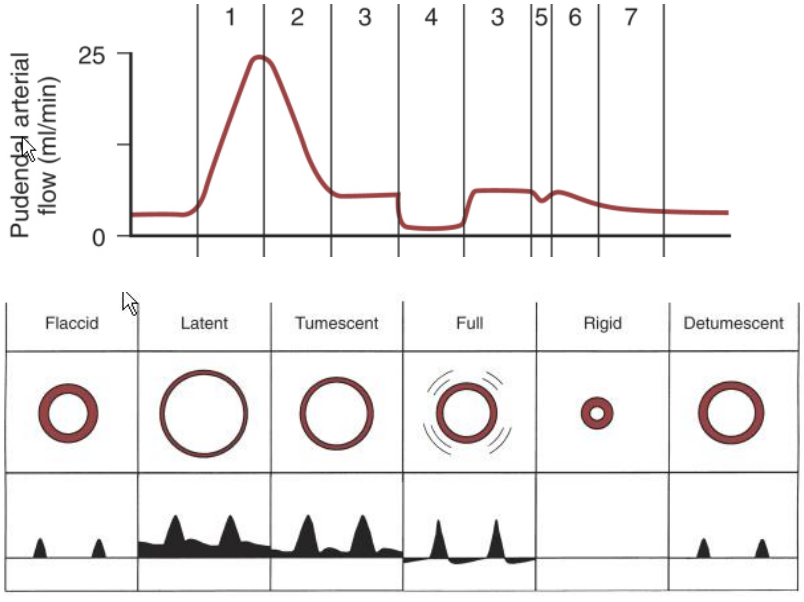
Optional
PSA in men > 50 yrs with >10 yr life-expectancy
Prolactin
Hyperprolactinaemia quite rare
Galactorrhoea, gynaecomastia, ED
TFTs in those with clinical features of hypo or hyperthyroidism

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 inbalance 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

Intracavenous 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 insufficency
PGE1 augmented erections
Duplex performed 5mins after injection (latent) through to cessation of flow (rigid)



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 re-vascularisation 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 pychogenic 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)

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

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

Adverse event	Sildenafil	Tadalafil	Vardenafil
Headache	12.8%	14.5%	16%
Flushing	10.4%	4.1%	12%
Dyspepsia	4.6%	12.3%	4%
Nasal congestion	1.1%	4.3%	10%
Dizziness	1.2%	2.3%	2%
Abnormal vision	1.9%		<2%
Back pain		6.5%	
Myalgia		5.7%	

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

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	erythromicin, ketoconazole, itraconozole, HIV meds (CYP3A4 enzyme pathway)
PDE5i effect	decreases	rifampcin, phenytoin, carbamazepine

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

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 first-line in those with nitrates Withdrawn from UK in 2006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

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

(iii) Topical therapy

Nitoglycerine, 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 spontanaeity, pivoting of soft penis below constrction ring,occasionally skin necrosis

B. <u>Second-line therapy</u>

(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)

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

Parameter	Papaverine	Pap&Phent	Alprostadil	Trimix
Dose	7.5 – 60mg	0.1-1ml	1- 60ug	0.1-1ml
Efficacy	50%	70%	85%	92%
Pain	-	-	15-30%	2-20%
Priapism	5%	8%	1%	2%
Fibrosis	7%	7%	3%	2%

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. <u>Third-line therapy</u>

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

- 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

Low-risk	Sexual activity OK
Intermediate-risk	Cardiac investigation first
High-risk	Sexual activity not recommended

Low-risk category	Intermediate-risk category	High-risk category
Asymptomatic, < 3 risk factors for CAD (excluding gender)	≥ 3 risk factors for CAD (excluding gender)	High-risk arrhythmias
Mild, stable angina (evaluated and/or being treated)	Moderate, stable angina	Unstable or refractory angina
Uncomplicated past MI	Recent MI (> 2, < 6 weeks)	Recent MI (< 2 weeks)
LVD/CHF (NYHA class I)	LVD/CHF (NYHA class II)	LVD/CHF (NYHA class III/IV)
Post-successful coronary revascularization	Non-cardiac sequelae of atherosclerotic disease (e.g. stroke, peripheral vascular disease)	Hypertrophic obstructive and other cardiomyopathies
Controlled hypertension		Uncontrolled hypertension
Mild valvular disease		Moderate-to-severe valvular disease

CAD, coronary artery disease; CHF, congestive heart failure; LVD, left ventricular dysfunction; MI, myocardial infarction; NYHA, New York Heart Association.

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:
- Acheivement
- 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