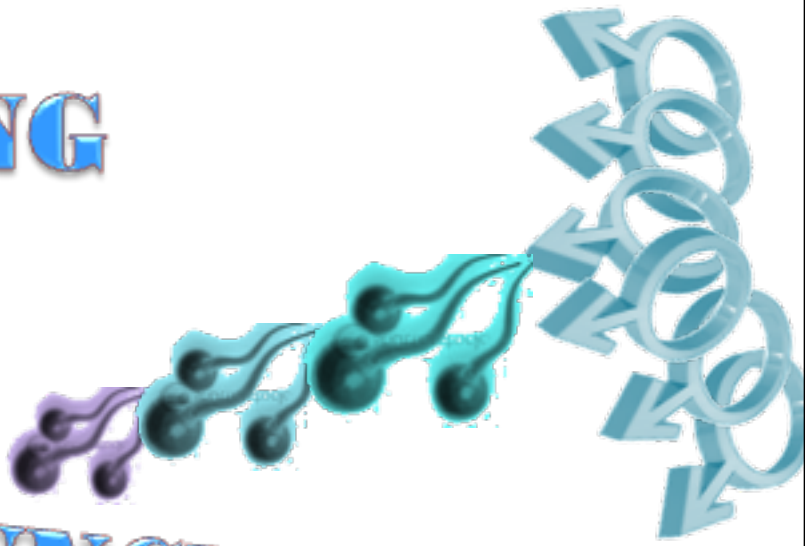
DRUGS AFFECTING



ERECTILE DYSFUNCTION

DRUGS AFFECTING ERECTILE DYSFUNCTION

ILOs

By the end of this lecture you will be able to:

- Revise the haemodynamic changes inducing normal erection
- Interpret its different molecular control mechanisms
- Define erectile dysfunction [ED] and enumerate its varied risks
- List drugs inducing ED and reflect on some underlying mechanisms
- Correlate drugs used in treatment of ED to the etiopathogenesis
- Classify oral 1st line therapy relevent to; Mechanism / Utility / ADRs
- Compare the pharmacological difference of PDE_5 inhibitors
- Study the transurethral, intracavernous or topical 2nd line therapies; Mechanism / Utility / ADRs
- Enumerate lines of treatment of priapism

Pathophysiology:

Mechanism of an erection

- A normal erection relies on the coordination:

Vascular –

Neurological –

Hormonal –

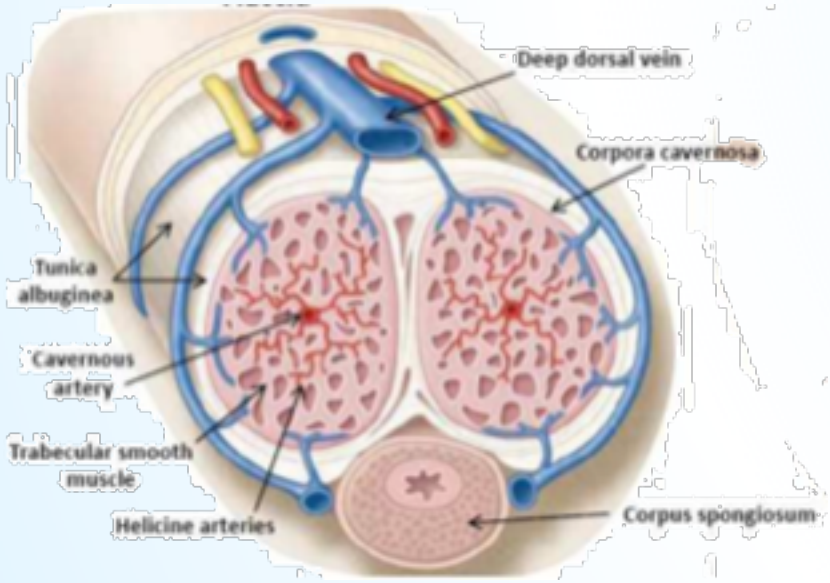
Psychological –

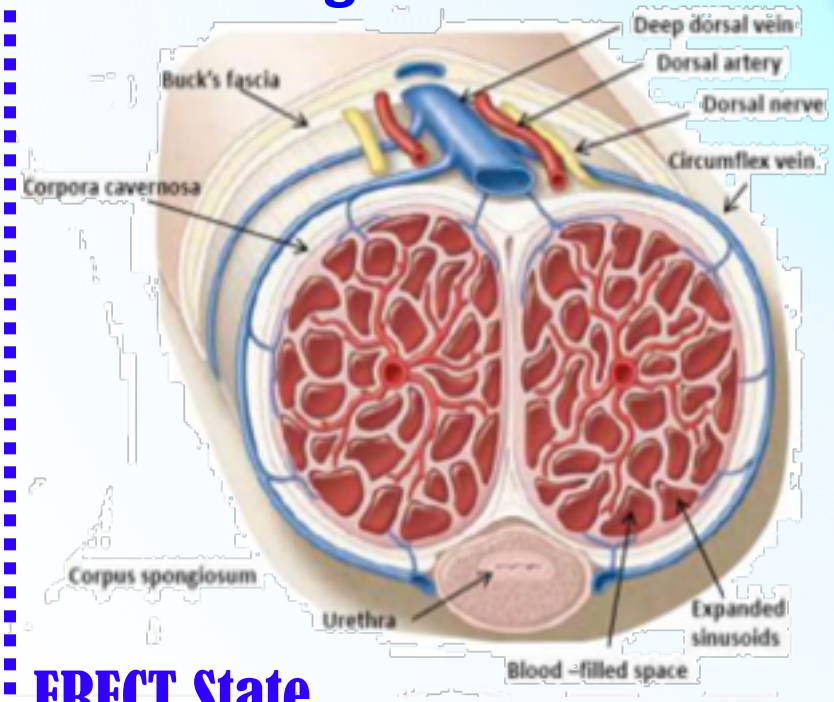
- An erection can occur following direct genital stimulation or auditory or visual stimulation, aspects that contribute to the influx of blood to the penis

Pathophysiology: Mechanism of an erection

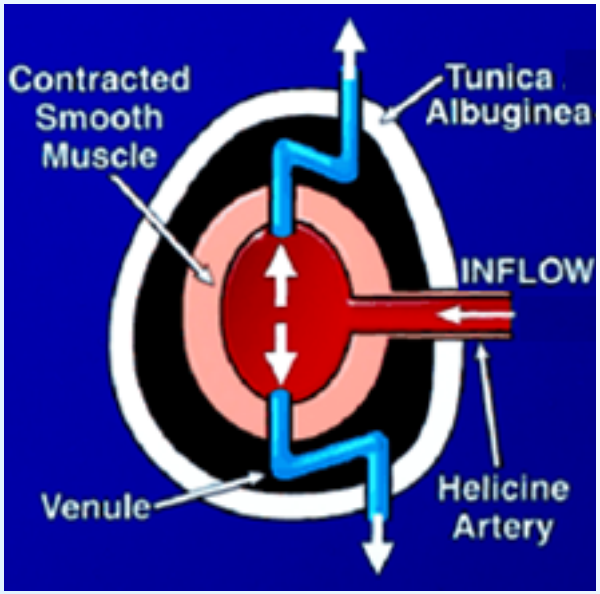
- An erection occurs when the amount of blood rushing to the penis is greater than the amount of blood flowing from it
- A massive influx of blood accumulates in the sinusoidal spaces due to relaxation of smooth muscle & dilatation of arteries → corpora cavernosa to swell (tumescence)
- Tumescence compresses the veins that normally drain the penis → prevents blood outflow & maintains penile rigidity

Peripheral HAEMODYNAMIC CHANGES inducing ERECTION

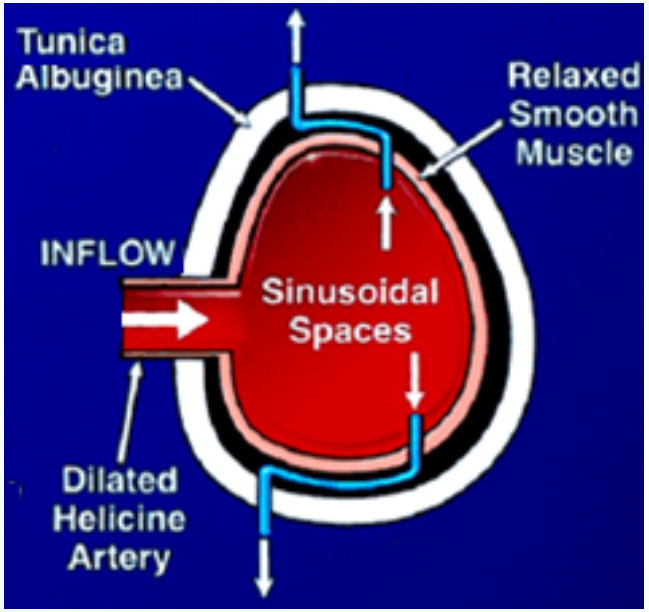




FLACCID State



ERECT State

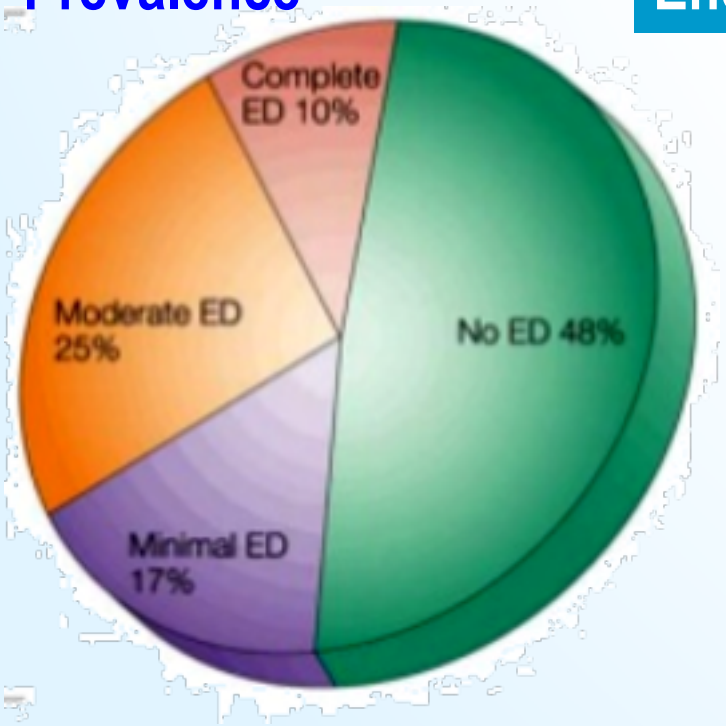


ERECTILE DYSFUNCTION

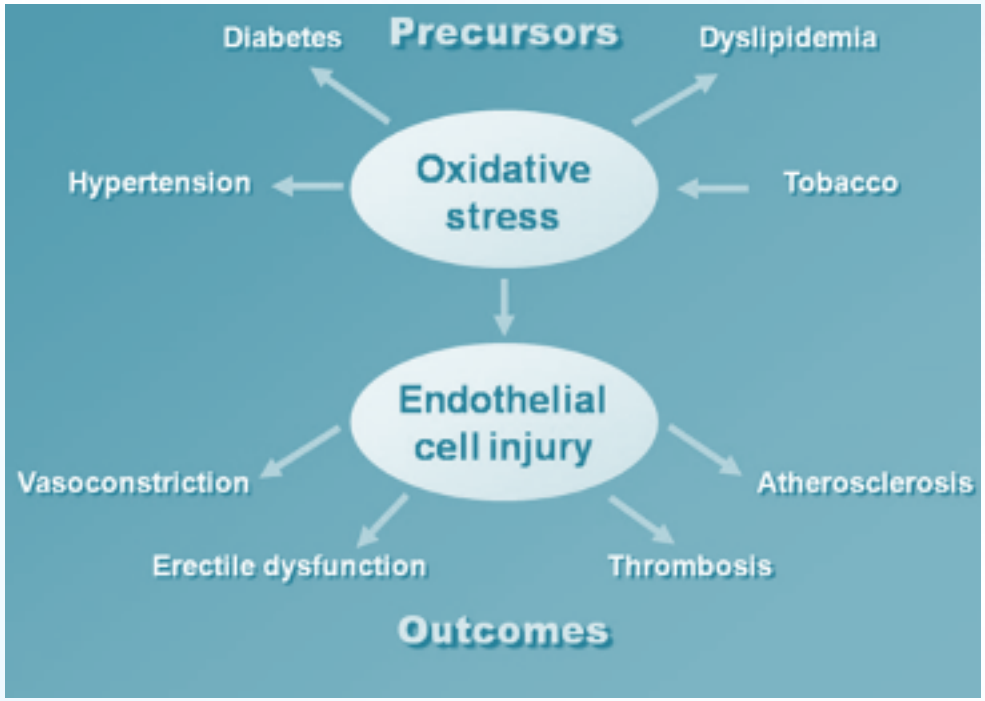
Persistent or recurrent inability to attain (acquire) & maintain (sustain) an erection (rigidity) sufficient for satisfactory sexual performance

"Impotent" is reserved for those men who experience erectile failure during attempted intercourse more than 75 % of the time.

Prevalence



Endothelial Dysfunction → Commonest Cause



DRUGS ADVERSLY CAUSING ED

Centrally Acting Drugs

DA>NE promote arousal / 5HT action on $5HT_2$ →↓DA release →↓ arousal

Most ADDs→ ↓ 5HT uptake;

non-selectively as TCAs

selectively as SSRIs

↑ 5HT in synapse

act on $5HT_2$

Peripherally; ↓ genital sensation→

Delay ejaculation

Treat Premature Ejaculation

- Anti-psychotic drugs → DA antagonist + hyperprolactenemia
- Anti-epileptic drugs (phenytoin) → have GABA effect
  →antagonize Exc. Amino acid. → ↑ sedation → ↓ arousal.

Centrally acting anti-hypertensives

- Methyl dopa, Reserpine !!! → ↓ arousal
- Clonidine → ↓ arousal centrally / Vasoconstriction peripherally !!!

Other anti-hypertensives

- β_2 blockers → -ve vasodilating β_2 + potentiate α_1 effect
- **Thiazide diuretics** → ↓ spinal reflex controlling erection + ↓ arousal

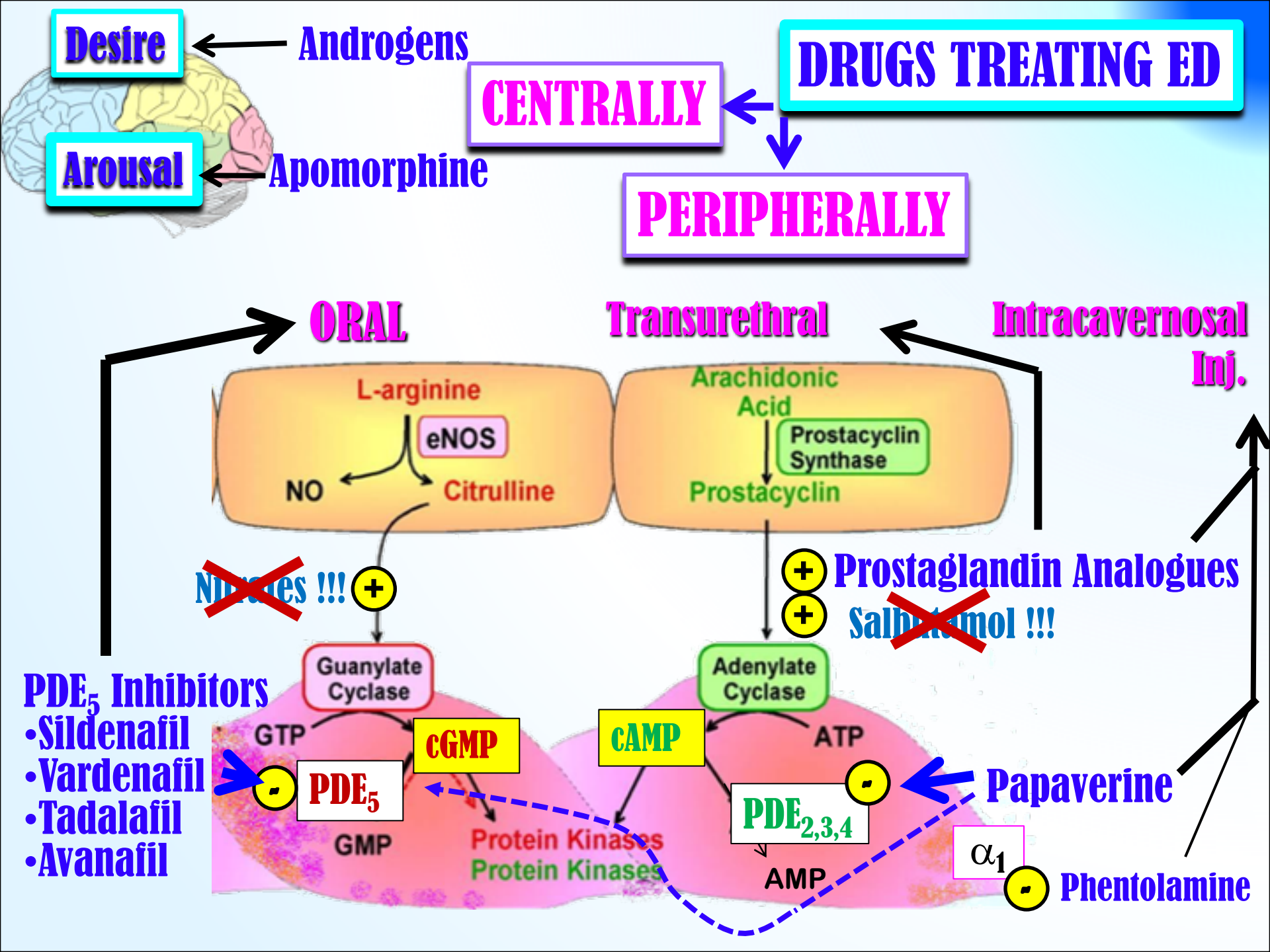
↓ Desire

Anti-androgens

- **Finasteride** → α reductase inhibitor (prevent production of active testosterone → **irreversible erectile dysfunction**
- **Cyproterone acetate** → synthetic steroidal antiandrogen
- **Cimetidine** (high doses) / **Ketoconazole** /**Spironolactone** → hyper-prolactinemia + gynecomastia
- **Estrogen-containing medications**

Habituating Agents

- **Cigarette smoking** → vasoconstriction + penile venous leakage
- **Alcohol** [small amounts]→↑ desire +↓ anxiety + vasodilatation
- Alcohol [big amounts]→↑ sedation+ ↓ desire
- Chronic alcoholism→ hypogonadism + polyneuropathy


Desire
Androgens
Arousal
Apomorphine
DRUGS TREATING ED
CENTRALLY
PERIPHERALLY
ORAL
Transurethral
Intracavernosal Inj.
L-arginine
eNOS
NO
Citrulline
Arachidonic Acid
Prostacyclin Synthase
Prostacyclin
Nitrates !!!
Prostaglandin Analogues
Salbutamol !!!
Guanylate Cyclase
Adenylate Cyclase
GTP
cGMP
cAMP
ATP
PDE5 Inhibitors
•Sildenafil
•Vardenafil
•Tadalafil
•Avanafil
PDE5
PDE2,3,4
Papaverine
GMP
AMP
Protein Kinases
Protein Kinases
α1
Phentolamine

SELECTIVE PDE_5 Inhibitors

Mechanism

ORAL

- Sildenafil
- Vardenafil
- Tadalafil
- Avanafil

Inhibit PDE_5 ➜ prevent breakdown of cGMP ➜ pertain vasodilatation ➜ erection.

They do not affect the libido, so sexual stimulation is essential to a successful

Indications

- Erectile dysfunction; 1st line therapy. All types have similar efficacy

	Sildenafil	Vardenafil	Tadalafil
% Efficacy	74-84	73-83	72-81

- Pulmonary hypertension
- BPH & premature ejaculation

Selectivity on PDE_5 is not absolute and vary with each drug

- Can partially act on PDE targeting cGMP (6, 11, 9, 1) ★
- In higher doses it can act on PDE targeting cAMP (2,3,4, 10,…) ★

PDE 1 ★	Heart, brain, lung, smooth muscle	IHD / AMI
PDE 2 ★	Adrenal gland, heart, lung, liver, platelets	
PDE 3 ★	Heart, lung, liver, platelets, adipose tissue, inflammatory cells	
PDE 4 ★	Sertoli cells, kidney, brain, liver, lung, inflammatory cells	
PDE 5 ★	Lung, platelets, vascular smooth muscle, heart	Headache/Flush nasal congestion
PDE 6 ★	Photoreceptor	Altered VISION
PDE 7 ★	Skeletal muscle, heart, kidney, brain, pancreas, T lymphocytes	
PDE 8 ★	Testes, eye, liver, skeletal muscle, heart, kidney, ovary, brain, T lymphocyte	
PDE 9 ★	Kidney, liver, lung, brain, possibly heart	
PDE 10 ★	Testes, brain	
PDE 11 ★	Skeletal muscle, prostate, kidney, liver, pituitary and salivary glands, testes	Back Pain

Sildenafil 10-fold selective
Vardenafil 16-fold selective
Tadalafil >200-fold selective

Give variability in ADRs

Common ADRs	Sildenafil	Vardenafil	Tadalafil
Headache %	14	10	15
Flushing %	12	11	3
Nasal	Congestion	Rhinitis	Congestion
Dyspepsia %	7	3	15
Abnormal vision %	> 4	< 2	-
Myalgia & Back pain %	-	-	5
Sperm functions	-	-	↓?
Q-T prolongation	-	↑	-

Major less common ADRs

1. IHD & AMI > patients on big dose or on nirates
2. Hypotension > patients on α-blockers than other antihypertensives
3. Bleeding; epistaxsis…..etc.
4. Priapism; if erection lasts longer than 4 hours ➔ emergency situation

Major rare ADRs

1. Ischemic Optic Neuropathy; can cause sudden loss of vision
2. Hearing loss

Pharmacokinetic profile difference of PDE5 inhibitors

Absorption; Fatty food interferes with **Sildenafil & Vardenafil** absorption
→ so taken on empty stomach / at least 2 hr.s after food
Tadalafil & [Avanafil] are not affected by food

Metabolism; All by hepatic CYT3A4; Tadalafil > the rest thus;
↑ADRs with enzyme inhibitors; erythro & clarithromycin, ketoconazole, cimetidine, tacrolimus, fluvoxamine, amiodarone…etc.
↓ efficacy with enzyme inducers; rifampicin, carbamazipine, phenytoin

Administration

All drugs are given only once a day	Sildenafil	Vardenafil	Tadalafil
Dosage (mg)	50-100	10-20	10-20
Time of administration before intercourse (hrs.)	1	1	1-12
Onset of action (min)	30-60	30-60	<30-45
Duration of action (hrs.)	4	4-5	36

NB. **Avanafil** has the advantage of been given 30 min before intercourse
Tadalafil must be given every 72 hrs if used with enzyme inhibitors

Contraindications

- Hypersensitivity to drug
- Patients with history of AMI / stroke / fatal arrhythmias <6 month
- Nitrates→ total contraindication / ? PDEIs in small dose + spacing at least 24hrs (48 hrs with *Tadalafil*) for fear of developing IHD/AMI due to severe hypotension *(see detailed mechanism in antianginal drugs)*

Precautions

- With α blockers [except tamsulosin] →orthostatic hypotension
- With hepato/renal insufficiency
- With bleeding tendencies [leukemia's, hemophilia, Vit K deficiency,]
- With *quinidine, procainamide, amiodarone* (class I & III antiarhtmics) (Vardenafil)
- Dose adjustment; *when using drugs that have interaction on hepatic liver microsomal enzymes i.e inhibitors or inducers.*
- Retinitis pigmentosa

ORAL

Testosterone

- Given to those with hypogonadism or hyperprolactenemia
- Given for promotion of desire.

Apomorphine

- A dopamine agonist on D_2 receptors.
- Activates arousal centrally; Erectogenic + Little promotion of desire
- Given sublingual / Acts quickly.
- Not FDA approved / Weaker than PDE_5 Is
- Given in mild-moderate cases / psychogenic / or if PDE_5 Is contraindication
- ADRs: nausea, headache, and dizziness but safe with nitrate

Oral phentolamine → α_1 blocker / debatable efficacy

Yohimbine → Central and periphral α_2 agonist → Aphrodetic + Erectogenic but low efficacy and many CV side effects

Trazodone → Antidepressant, a 5HT reuptake inhibitor → priapism (treateted with phenylephrine)

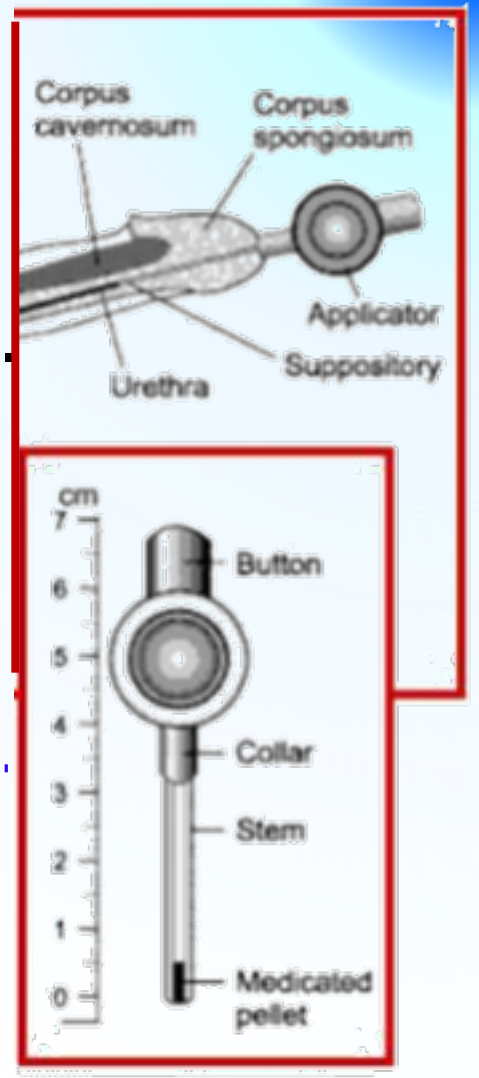
Alprostadil; PG E1 → ↑cAMP (MUSE)

TRANSURETHRALORAL

Synthetic + more stable

Applied by a special applicator into penile urethra & acts on corpora cavernousa →Erection

- Low - Intermediate Efficacy
- Minimal systemic effects / Rarity of drug interactions.



ADRs

- Variable penile pain
- Urethral bleeding / Urethral tract infection
- Hypotension
- Priapism or Fibrosis →rare

Topical

20% Papaverine; ↑cAMP + cGMP
2% Minoxidil; NO donner + K channel opener
2% Nitroglycerine
+ a drug absorption enhancers

Low efficacy / No FDA approval

Female Partner can develop → hypotension, headache → vaginal absorption.

1. Alprostadil; PG E1 → ↑cAMP

Needs training → Erection → after 5-15 min
lasts according to dose injected →
May develop fear of self injury / Discontinuation

ADRs

- Pain or bleeding at injection site
- Cavernosal fibrosis
- Priapism

2. Papaverine; PG E1 → ↑cAMP + cGMP

3. Phentolamine; α_1 blocker

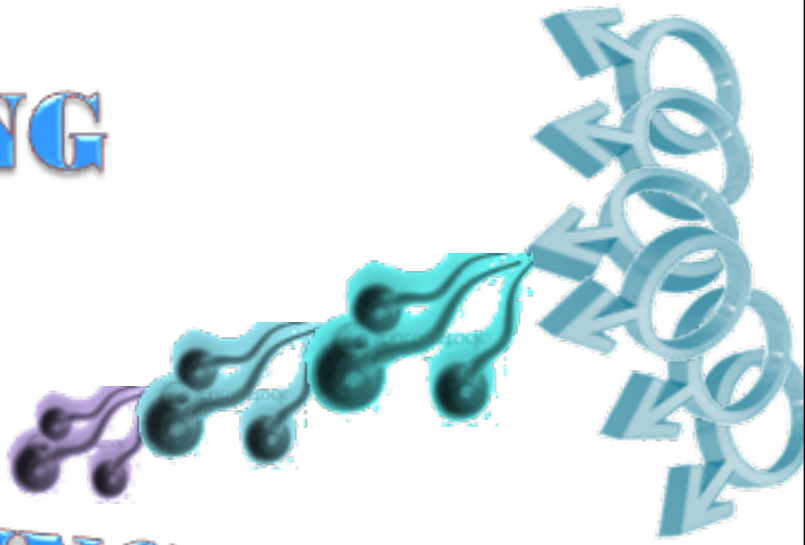
Intracavernosal Inj.

3 combined in severe cases

Treatment of Pripism

- A medical emergency
- Aspirate blood to decrease intracavernous pressure.
- Intracavernous injection of **Phenylephrine** → α_1 agonist
  → detumescence

DRUGS AFFECTING



ERECTILE DYSFUNCTION

GOOD LUCK