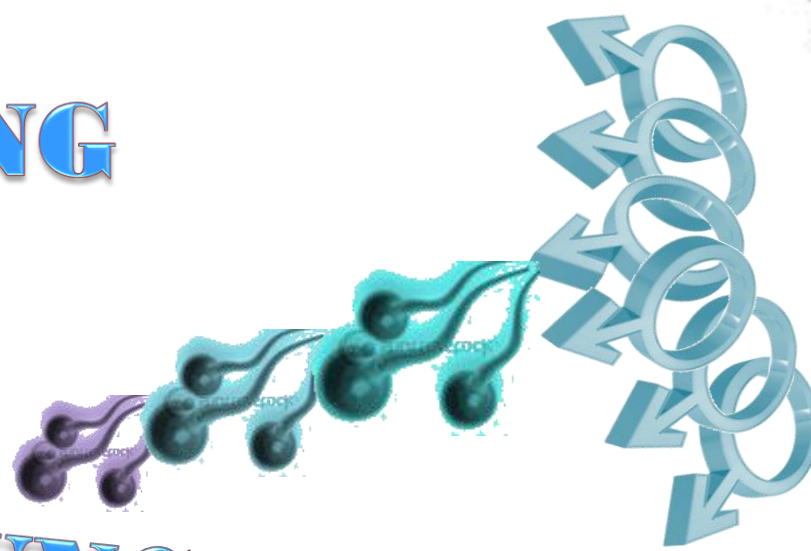


DRUGS AFFECTING

ERECTILE DYSFUNCTION



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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 relevant to; Mechanism / Utility / ADRs
- ✚ Compare the pharmacological difference of PDE₅ 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

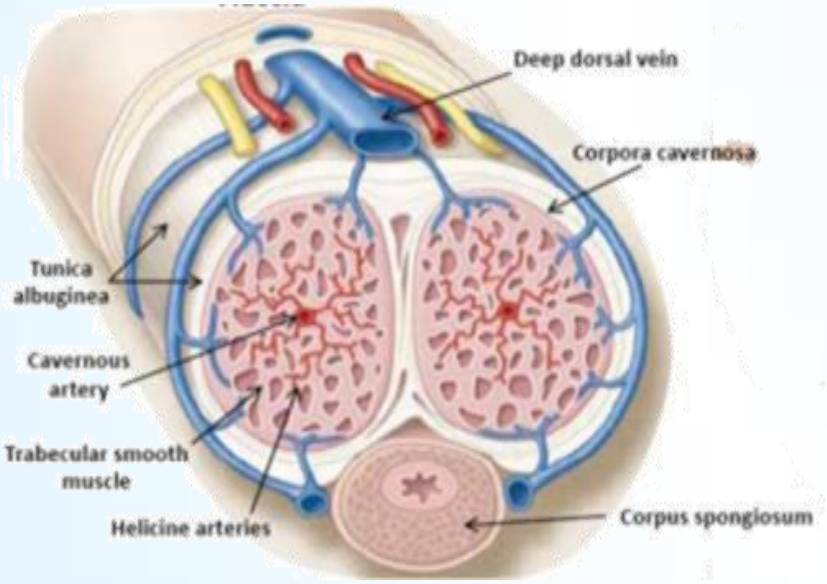
An erection occurs when the amount of blood •
rushing to the penis is greater than the amount of
blood flowing from it

A massive influx of blood accumulates in the •
sinusoidal spaces due to relaxation of smooth
muscle & dilatation of arteries → corpora
cavernosa to swell (tumescence)

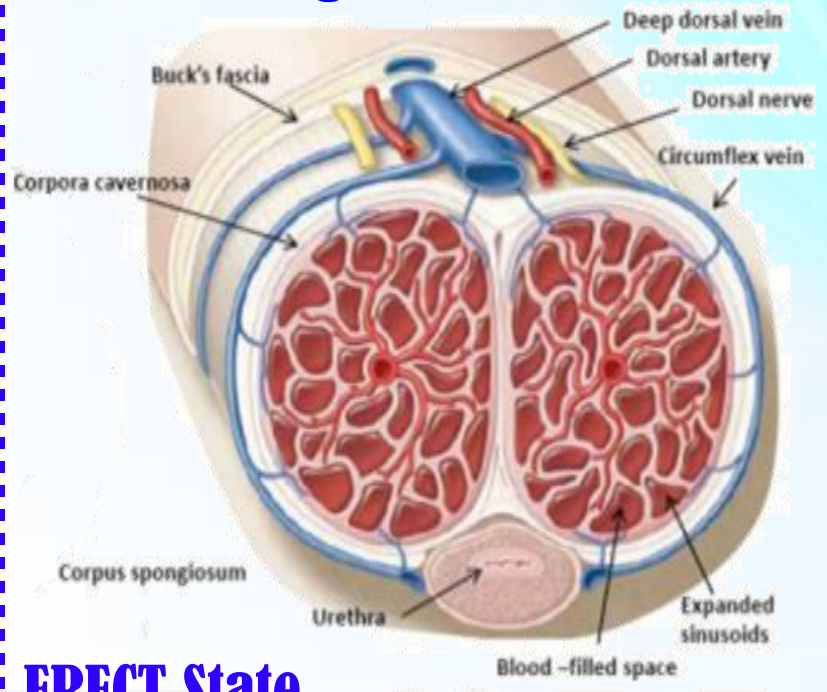
Tumescence compresses the veins that normally •
drain the penis → prevents blood outflow &
maintains penile rigidity



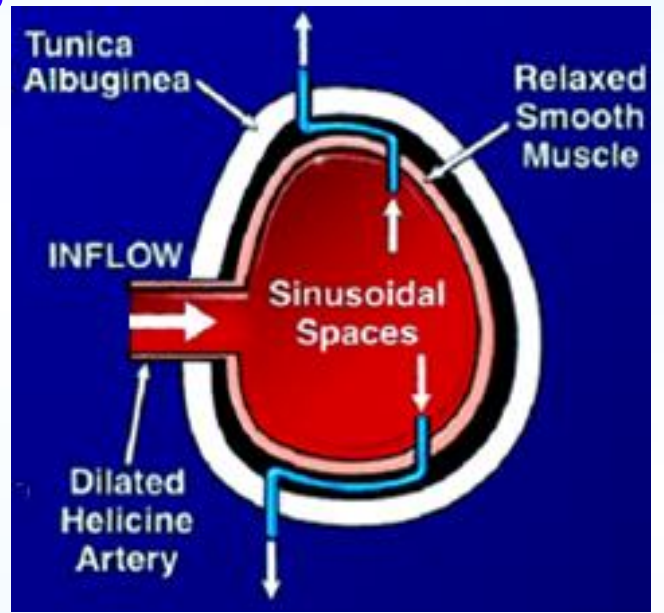
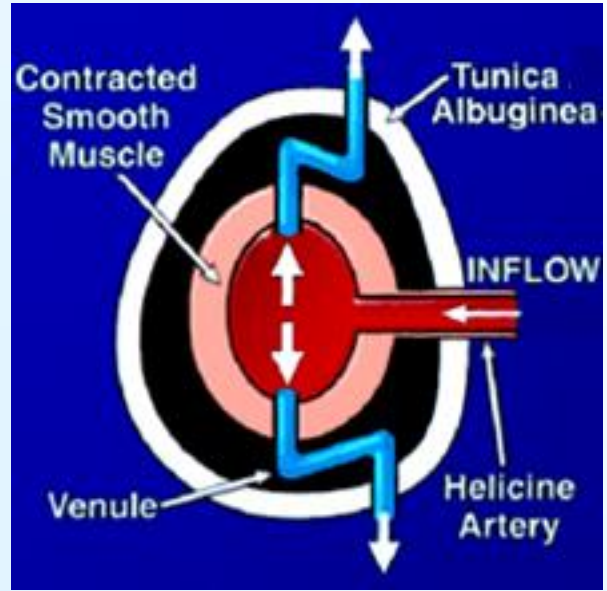
Peripheral HAEMODYNAMIC CHANGES inducing ERECTION



FLACCID State



ERECT State



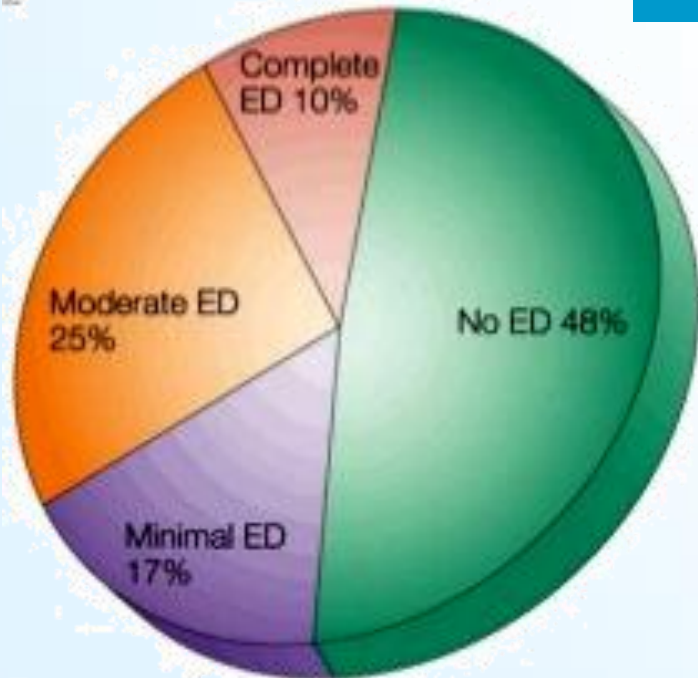
ERECTILE DYSFUNCTION



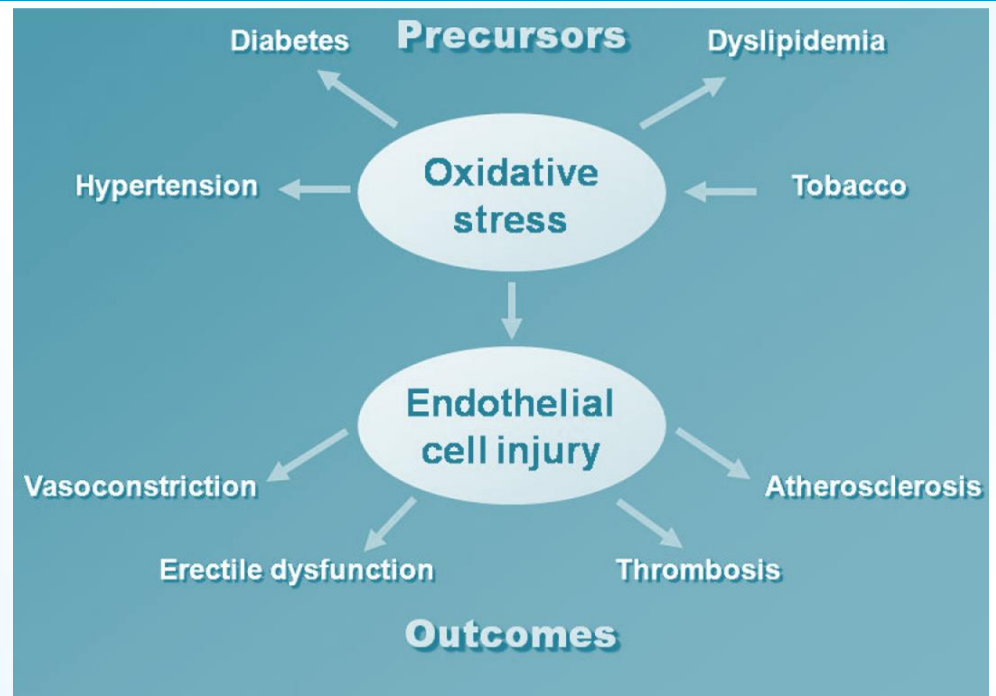
Persistent or recurrent inability to attain (acquire) & maintain (sustain) an erection (rigidity) sufficient for satisfactory sexual performance

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

Prevalence



Endothelial Dysfunction → Commonest Cause



I.M.P.O.T.E.N.C.E

Inflammatory	Prostatitis, urethritis
Mechanical	Peyronie's Disease, chordee
Psychological	Depression, performance anxiety, stress, relationship difficulties
Occlusive vascular	Art: Hypertension, smoking, hyperlipidemia, DM., peripheral vascular disease Ven: venous occlusion due to anatomical or degenerative changes
Trauma	Pelvic fracture, SC inj, penile trauma
Endocrine	Hypogonadism, hyperprolactinemia, hypo + hyperthyroidism
Neurologic	Parkinsons, multiple sclerosis, spina bifida, pelvic surgery, peripheral neuropathy
Chemical	Anti-HTN, anti-arrhythmics, antidepressants, anxiolytics, anti-androgens, anticonvulsants, alcohol, marijuana, anti-parkinson drugs, LHRH analogues
Extra factors	Prostatectomy, old age, CRF, cirrhosis



DRUGS ADVERSLY CAUSING ED

Centrally Acting Drugs

DA > NE promote arousal / 5HT action on 5HT₂ → ↓ DA release → ↓ arousal

Most **ADDs** → ↓ 5HT uptake;

non-selectively as TCAs
selectively as **SSRIs**

↑ 5HT in synapse
act on 5HT₂

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 \rightarrow -ve vasodilating β_2 + potentiate α_1 effect
- ✦ **Thiazide diuretics** \rightarrow \downarrow spinal reflex controlling erection + \downarrow arousal

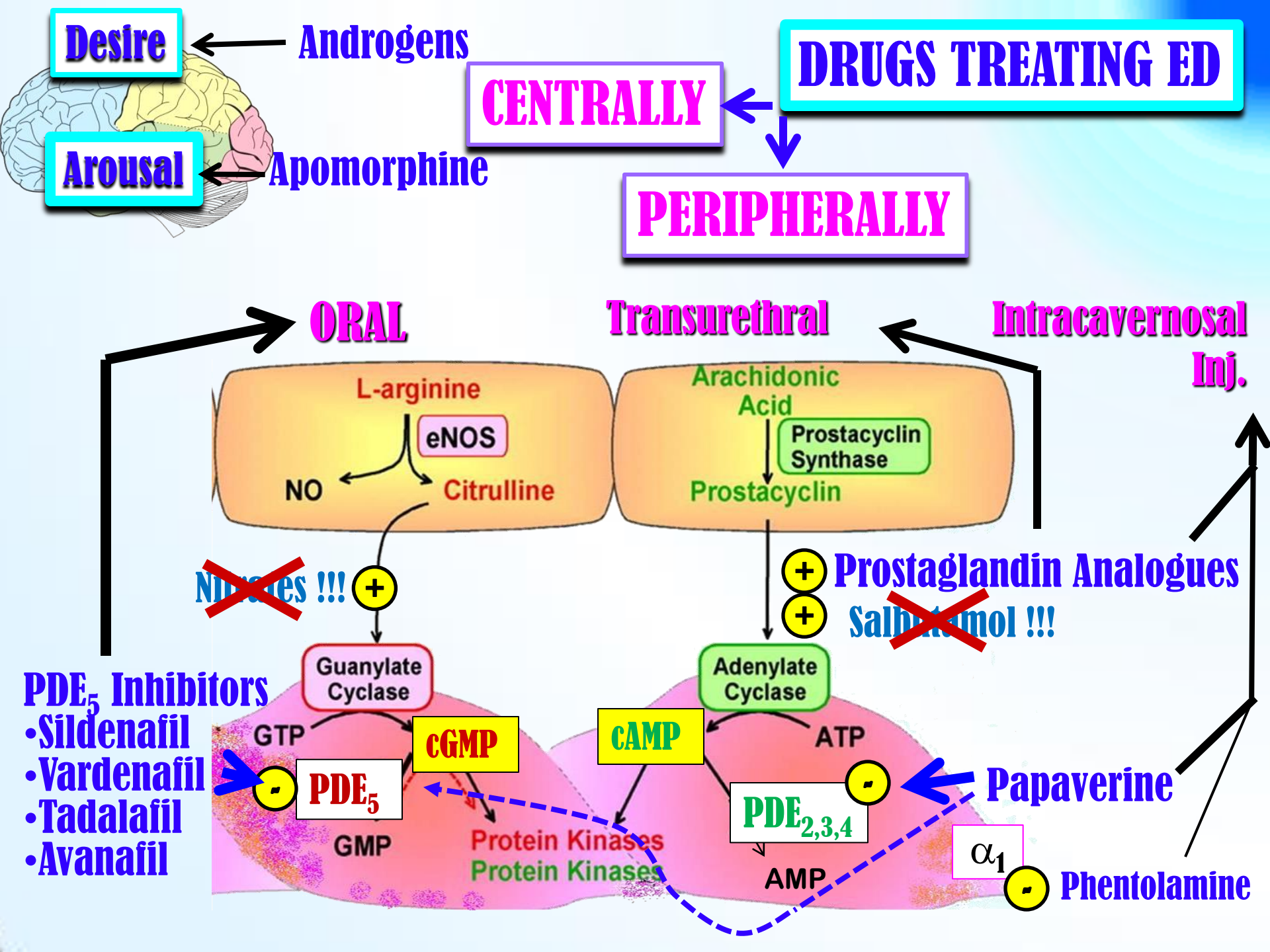
\downarrow Desire

Anti-androgens

- ✦ **Finasteride** \rightarrow α reductase inhibitor (prevent production of active testosterone \rightarrow irreversible erectile dysfunction)
- ✦ **Cyproterone acetate** \rightarrow synthetic steroidal antiandrogen
- ✦ **Cimetidine** (high doses) / **Ketoconazole** / **Spirolactone** \rightarrow hyperprolactinemia + gynecomastia
- ✦ **Estrogen-containing medications**

Habituating Agents

- ✦ **Cigarette smoking** \rightarrow vasoconstriction + penile venous leakage
- ✦ **Alcohol** [small amounts] \rightarrow \uparrow desire + \downarrow anxiety + vasodilatation
- ✦ **Alcohol** [big amounts] \rightarrow \uparrow sedation + \downarrow desire
- ✦ **Chronic alcoholism** \rightarrow hypogonadism + polyneuropathy



SELECTIVE PDE₅ Inhibitors

Mechanism

- Sildenafil
- Vardenafil
- Tadalafil
- Avanafil

Inhibit PDE₅ → prevent breakdown of cGMP → **pertain vasodilatation → erection.**

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

Pharmacodynamic action relevant to PDE₅ inhibition ►

- ✚ VSMCs of **Erectile Tissue of Penis** (vascular smooth muscle cells (VSMCs))
- ✚ Other VSMCs (lung, brain....) / heart
- ✚ Other non-VSMCs (prostate, bladder, seminal vesicle, GIT....)
- ✚ Platelets
- ✚ Other tissues; testis, sk. muscles, liver, kidney, pancreas,

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 PDE₅ 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
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
PDE 6 ★	Photoreceptor
PDE 7 ★	Skeletal muscle, heart, kidney, brain, pancreas, T lymphocytes
PDE 8 ★	Testes, eye, liver, skeletal muscle, heart, kidney, ovarv, 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

IHD / AMI

Headache/Flush
nasal congestion
Altered VISION

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; epistaxis.....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 hrs 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, carbamazepine, 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, antiphospholipid syndrome,...etc]
- ✚ 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

Testosterone

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

Apomorphine

- + A dopamine agonist on D₂ receptors.
 - + Activates arousal centrally; Erectogenic + Little promotion of desire
 - + Given sublingual / Acts quickly.
 - + Not FDA approved / Weaker than PDE₅ Is
 - + Given in mild-moderate cases / psychogenic / PDE₅ Is contraindication
 - + ADRs: nausea, headache, and dizziness but safe with nitrate
-

Oral phentolamine → α_1 blocker / debatable efficacy

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

Trazodone → Antidepressant, a 5HT reuptake inhibitor → priapism

Korean Ginseng → Questionable / may be a NO donor.

Alprostadil; PG E1 → ↑cAMP

(MUSE)

TRANSURETHRAL

Synthetic + more stable

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

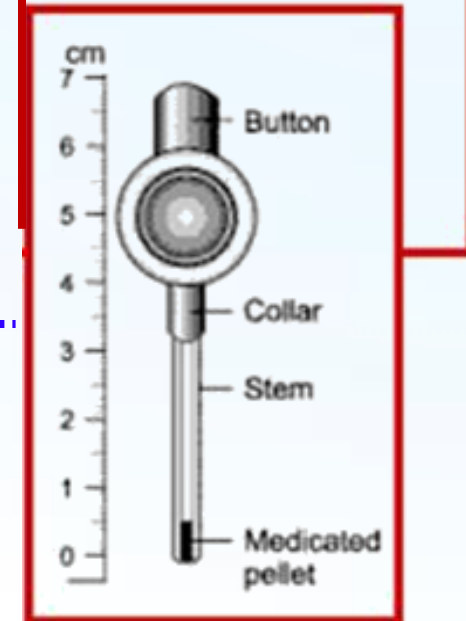
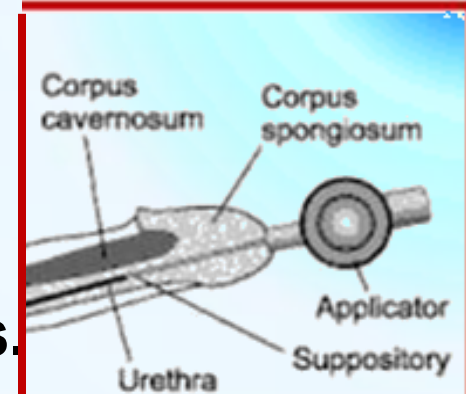
2% Minoxidil; NO donor + K channel opener

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



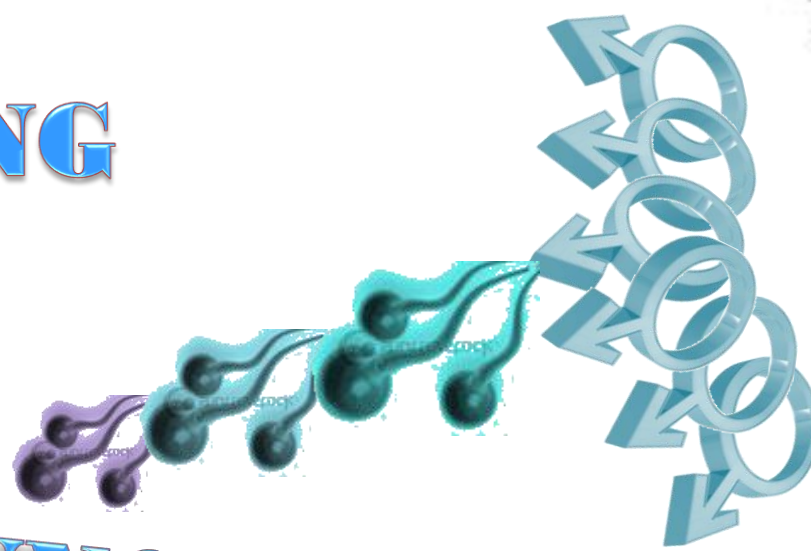
3 combined in severe cases

Treatment of Priapism

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

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ERECTIONAL DYSFUNCTION



GOOD LUCK