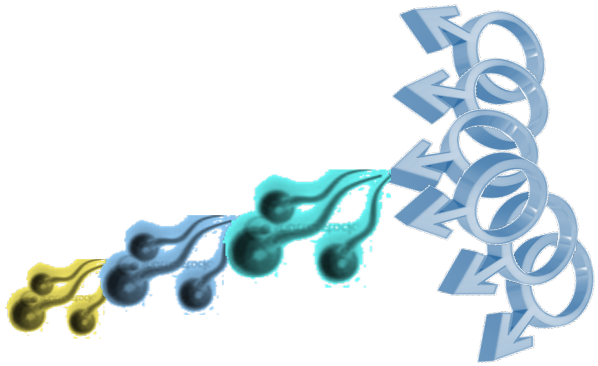


DRUGS AFFECTING ERECTILE DYSFUNCTION

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 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.

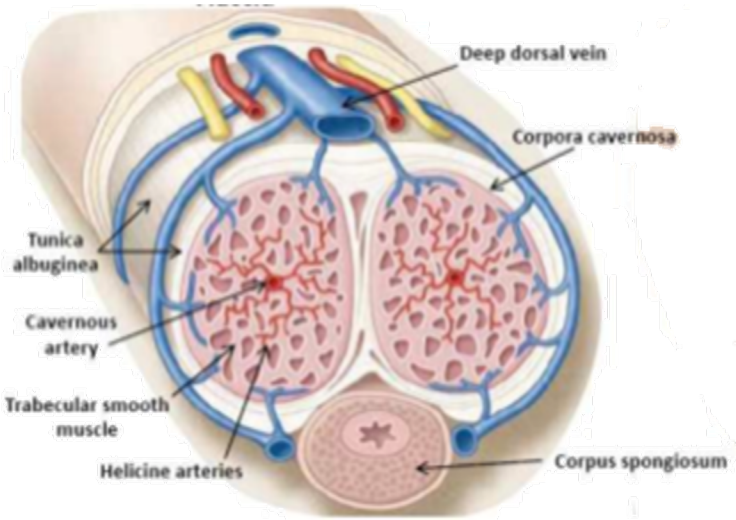
Pathophysiology:
Mechanism of an erection

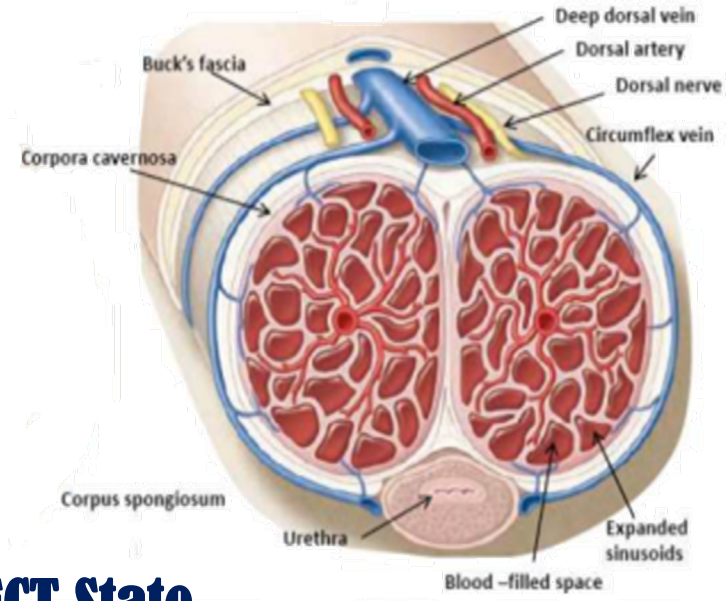
- A normal erection relies on the coordination:
  - Vascular
  - Neurological
  - Hormonal
  - Psychological
- An erection can occur following direct genital stimulation or auditory or visual stimulation, aspects that contribute to the influx of blood to the penis.

Pathophysiology:
Mechanism of an erection

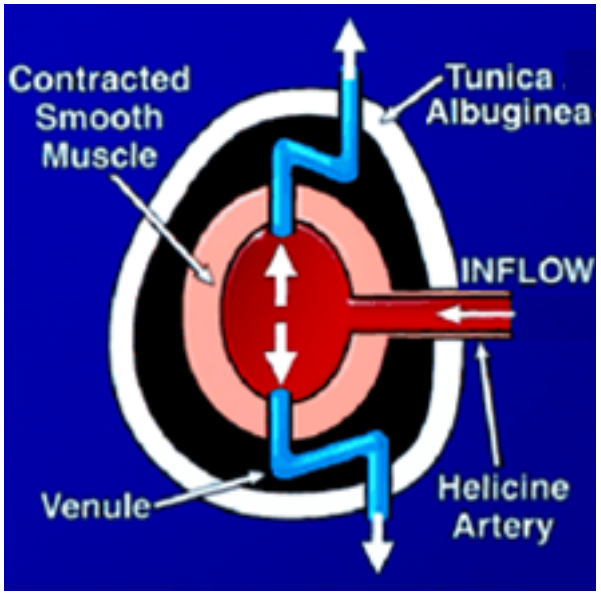
- An erection occurs when the amount of blood rushing to the penis is greater than the amount of blood flowing from it.
- A massive influx of blood accumulates in the sinusoidal spaces due to relaxation of smooth muscle & dilatation of arteries→ corpora cavernosa to swell (tumescence).
- Tumescence compresses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

Peripheral HAEMODYNAMIC CHANGES inducing ERECTION

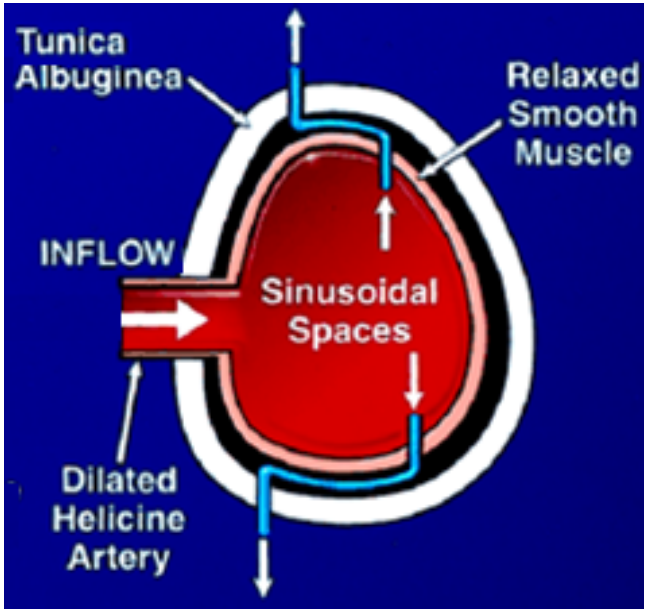




FLACCID State



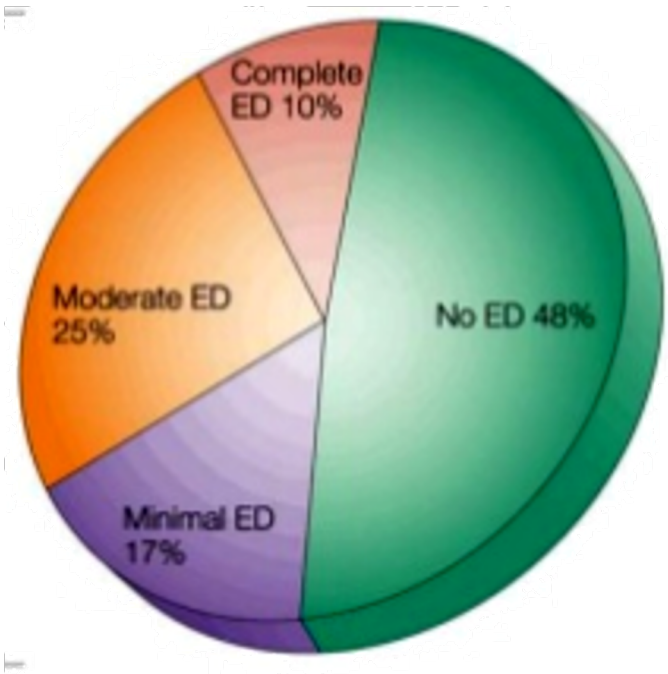
ERECT State



ERECTILE DYSFUNCTION

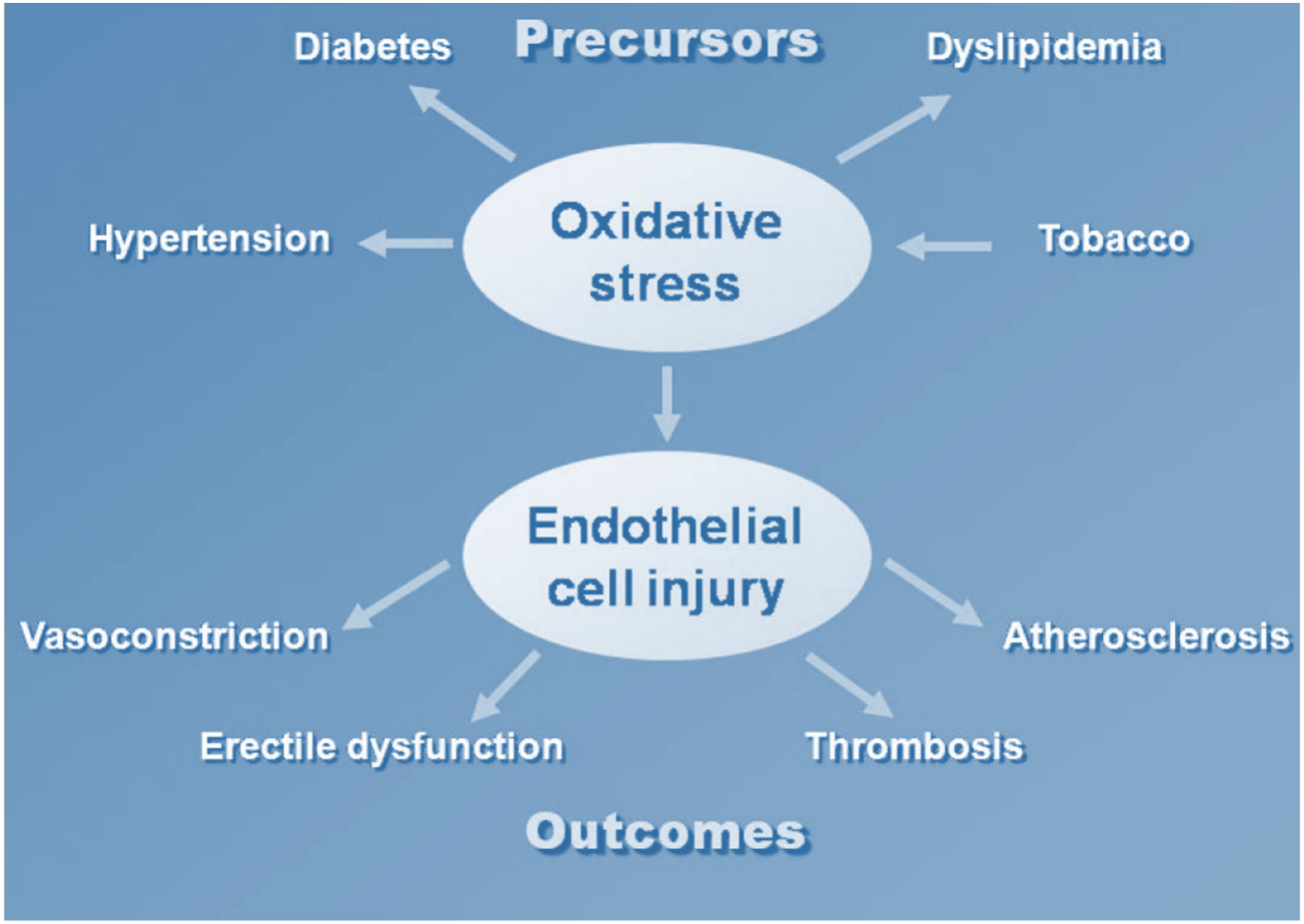
- Persistent or recurrent inability to attain (acquire) & maintain (sustain) an erection (rigidity) sufficient for satisfactory sexual performance.
- “Impotent" is reserved for those men who experience erectile failure during attempted intercourse more than 75 % of the time.

Prevalence



ERECTILE DYSFUNCTION

Endothelial Dysfunction → Commonest Cause



DRUGS ADVERSLY CAUSING ED

1.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

DRUGS ADVERSLY CAUSING ED

Centrally Acting Drugs

- **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 !!!

DRUGS ADVERSLY CAUSING ED

2. Other anti-hypertensives

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

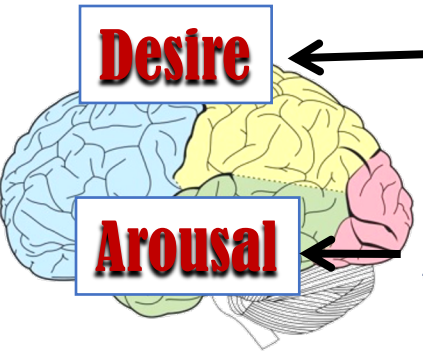
3. Anti-androgens > ↓ Desire

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

DRUGS ADVERSLY CAUSING ED

4. Habituating factors

- **Cigarette smoking → Vasoconstriction + Penile venous leakage.**
- **Alcohol [small amounts]→↑ Desire +↓ Anxiety + Vasodilatation.**
- **Alcohol [big amounts]→↑ Sedation+ ↓ Desire**
- **Chronic Alcoholism→ Hypogonadism + Polyneuropathy.**



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

GTP

cGMP

PDE$_5$

GMP

Protein Kinases

Protein Kinases

Adenylate Cyclase

cAMP

ATP

PDE$_{2,3,4}$

AMP

Papaverine

α_1

Phentolamine

PDE$_5$ Inhibitors

- Sildenafil
- Vardenafil
- Tadalafil
- Avanafil

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**
- **Pulmonary hypertension**
- **BPH (benign prostatic hyperplasia) & premature ejaculation**

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

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, 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 a 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

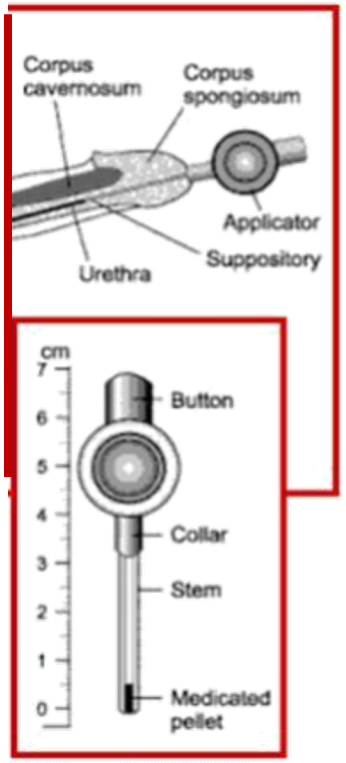
Trazodone → Antidepressant, a 5HT reuptake inhibitor → priapism (treateted with phenylephrine)

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

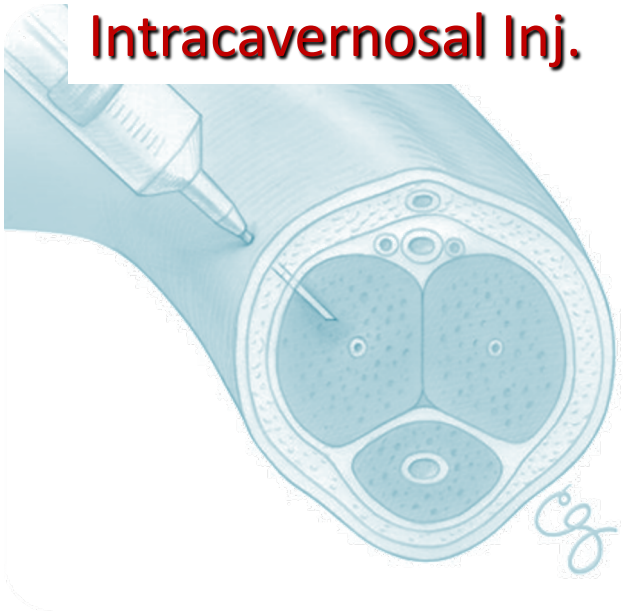
May develop fear of self injury / Discontinuation

ADRs

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

2. Papaverine; PG E1 → ↑cAMP + cGMP

3. Phentolamine; a_1 blocker



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

Thanks