



Reproductive  
System

**PHARMACOLOGY**  
432 TEAM



# DRUGS AFFECTING ERECTILE DYSFUNCTION

## Learning Objectives:

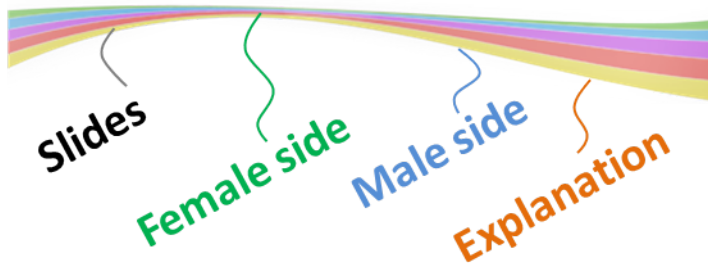
- 1- Revise the haemodynamic changes inducing normal erection
- 2- Interpret its different molecular control mechanisms
- 3- Define erectile dysfunction [ED] and enumerate its varied risks
- 4- List drugs inducing ED and reflect on some underlying mechanisms
- 5- Correlate drugs used in treatment of ED to the etiopathogenesis
- 6- Classify oral 1st line therapy relevant to; Mechanism / Utility / ADRs
- 7- Compare the pharmacological difference of PDE5 inhibitors
- 8- Study the transurethral, intracavernous or topical 2nd line therapies; Mechanism / Utility / ADRs
- 9- Enumerate lines of treatment of priapism

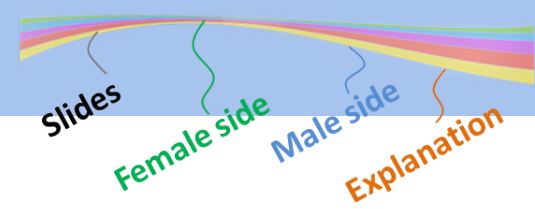
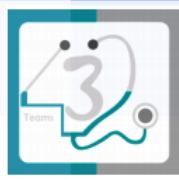
This lecture was done by:

Shroog Al-Harbi &  
Raghad Al-mutlaq

And reviewed by:

Hossam alshehri





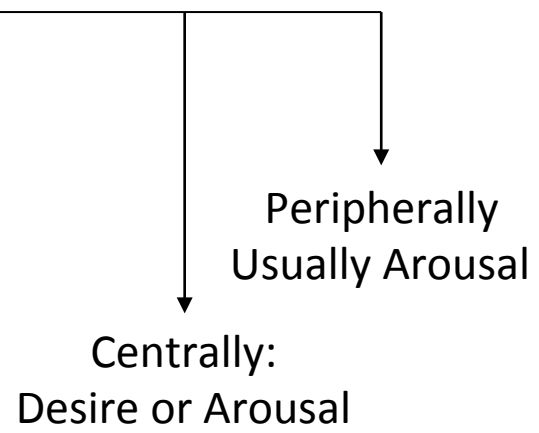
Physiological states of penis.

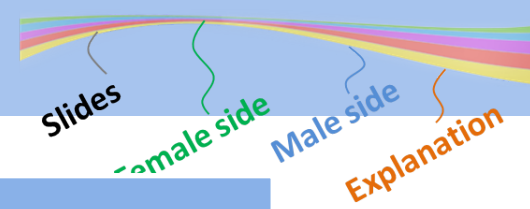
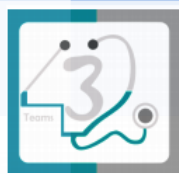
Physiology of sexual act.

Drugs induce Erectile dysfunction (Impotence).

Drugs treat Erectile dysfunction.

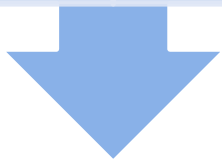
**Terms:**  
Flaccidity: Detumescence  
Erection: Tumescence





# Physiological states of penis

Erect stage (vasodilatation)      Flaccid stage (vasoconstriction)



# Drug induce Erectile dysfunction

ADDs      antipsychotic      antiepileptic      antihypertensive      antiandrogens      Habituating agent



# Drug treating Erectile dysfunction

centrally      Peripherally

- 1- desire
- 2- arousal (cause erection)
- 3- ejaculation
- 4- resolution (back to flaccid state)

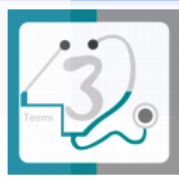
**Desire:**  
androgens

**Arousal:**  
apomorphine

**Orally:**  
PDE5 inhibitor

**Transurethral:**

**Intracavernosal injection**



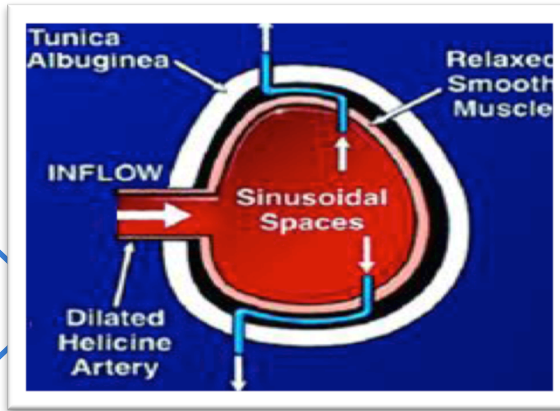
1. Desire

2. Arousal

Cavernous n.

PNS

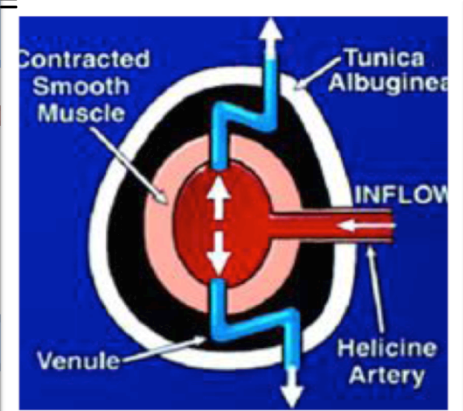
SNS



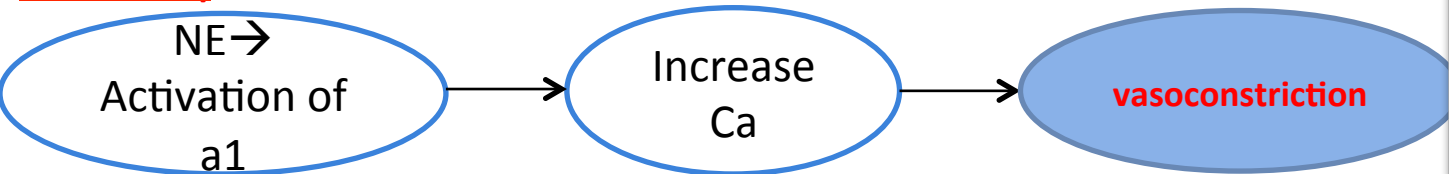
- Ach(work on endothelium) → eNO  
- NANC → nNO → **cGMP**  
- **prostaglandin(PE1,PI2)**  
→ **cAMP**

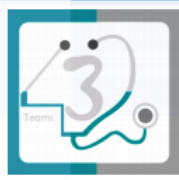
**B2 << NE**  
**TXA2**  
**PF2a**

**Vasodilatation** of vascular SM & endothelium = rigidity = erection (Relaxation Tumescence) (>flow in)



**:B) MOLECULAR CONTROL of FLACCIDIT Contraction Detumescen (blodd flow in = flow out)**





**For reading  
Please  
understand it**

**A MALE SEX ORGAN** In most of the time exists in a Flaccid State .  
However, during a **Sexual Act** the following events occur;

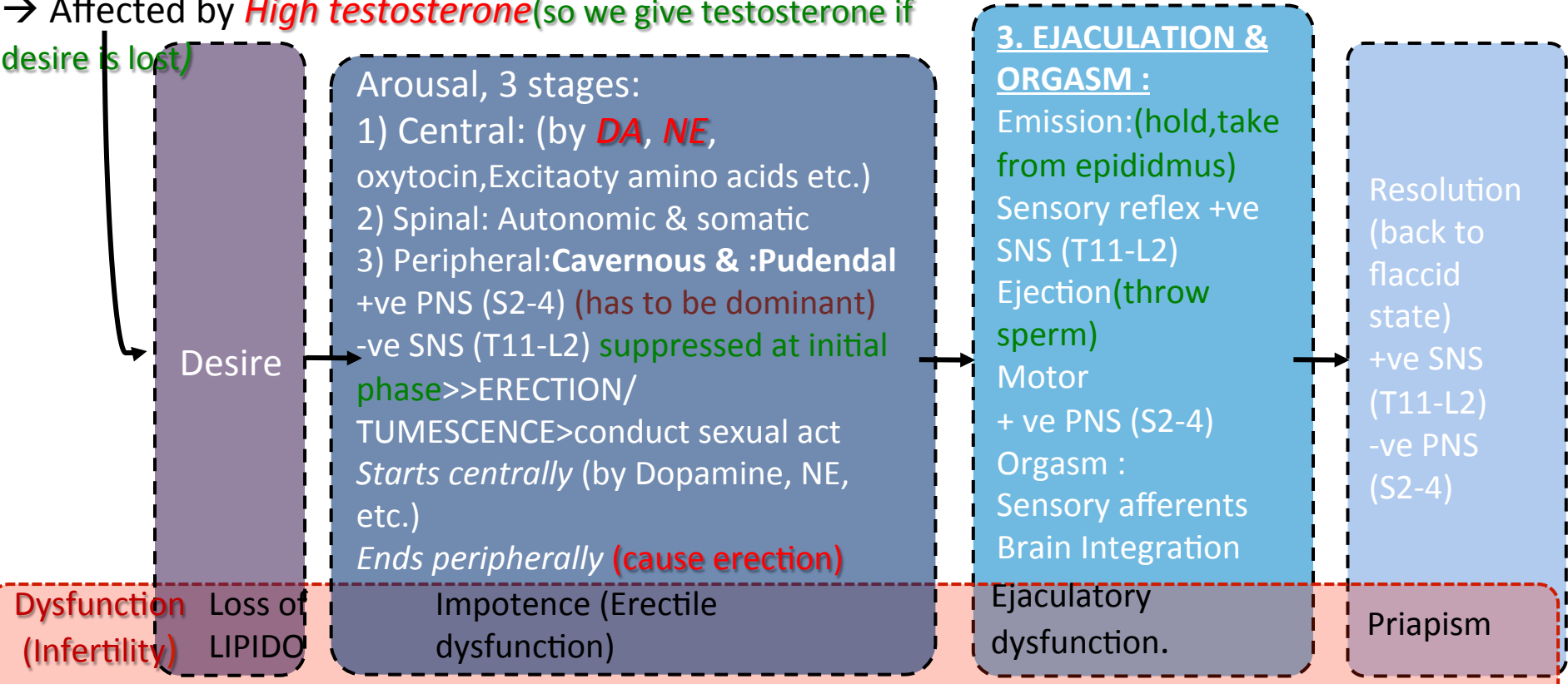
*Male normally has erection during night*  
**Stimulations:**

Visual (occipital) , Tactile (Thalamus), Imaginary (limbic) or Olfactory (rhiencephalon)

→ Affected by **High testosterone**(so we give testosterone if desire is lost)

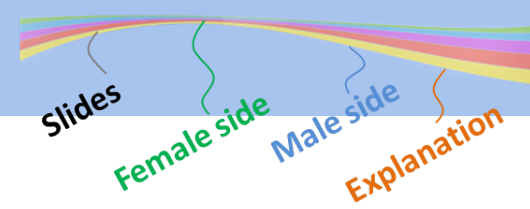
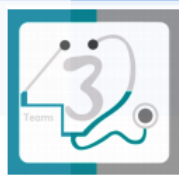
**Physiological states of penis**

Erect stage (vasodilatation)	Flaccid stage (vasoconstriction)
---------------------------------	-------------------------------------



*Arousal is initiated centrally by neurotransmitters (after desire) and then it continues by reflexes*





**Erectile Dysfunction:**

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

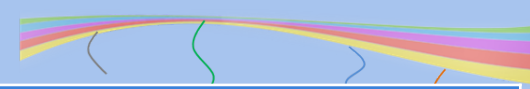
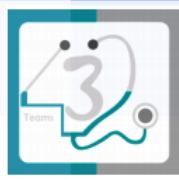
“Impotent” is reserved for those men who experience erectile **failure** (function very limited) during attempted intercourse more than **75 % of the time**.

**Commonest Cause** (endothelial dysfunction) **ex: in old people with heart problem**

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

**Memorize red boxes only**





Decrease Desire	
AntiAndrogenic(Cyproterone acetate)	Peripherally (inhibit synthesis of androgen)
a reductase inhibitor (Finasteride)	irreversible erectile dysfunction
Estrogen-containing medications (if taken by meal)	
Cimetidine (high doses) / Ketoconazole(antifungal) / Spironolactone(diuretics)	hyper-Prolactinemia(decrease testosterone) + gynecomastia

Divided into 3 groups:  
Affecting desire only, Arousal, affecting both

*\* It's a sequential process, so logically when you block it at any level you'll block all next steps. Tow stages affect erection: Desire & Arousal*

*\* High Prolactin or Estrogen → low Testosterone (affect desire)*

**\*You have to memorize the mechanisms**

		Desire	Arousal
Anti-psychotic		DA antagonist → inc. rprolactin → dec. testosterone	DA antagonist
Alcohol	Big amount	Dec. centrally	sedation
	alcoholism	Dec. peripherally: causing hypogonadism + polyneuropathy	-----

Alcohol in small amount promote erection:(no higher central control so inappropriate)

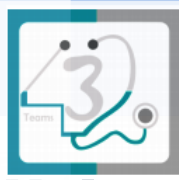
- 1) desire (centrally)+ decrease anxiety
- 2) Vasodilatation ( arousal peripherally)

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

## Arousal

		Centrally	Peripherally
Anti-Dopaminergic drugs (ADD) <b>Anti-depression</b> non-selectively as TCAs ( <b>Tricyclic</b> ) selectively as SSRIs ( <b>selective serotonin reuptake inhibitors</b> )		↓ 5HT uptake → ↑ 5HT in synapse act on <i>*peripherally: delay ejaculation (not erection) treat premature ejaculation</i>	antagonize NO actions ↓ genital sensation > Delay ejaculation ( <b>impede not absolutely</b> )
Central Anti hypertensive	Methyl dopa, Reserpine	-----	Decrease arousal
	Clonidine	Arousal centrally ( <b>a2 antagonists</b> )	Vasoconstriction peripherally
Anti-hypertensive		-----	B2 blockers -ve vasodilating b2 + potentiate a1 effect) Thiazide diuretics (decrease spinal reflex controlling erection)
cigarette smoking		-----	Vasoconstriction + penile venous leakage
Anti-epileptic		↑ GABA effect → ↑ sedation → no arousal (antagonize exc a.a)	-----





# 1- PDE5 inhibitors

You should treat according to the level of dysfunction.

## A- Desire:

Treated by Androgen

## B- Arousal:

- Centrally: Dopamine Agonist (*Apomorphine*)
- Peripherally: **Intracavernosal injection**

1) **Prostaglandin analogues** (if you remember it promotes vasodilatation, if you don't then go revise slide no.4 =P+(transurethral))

2) **Papavarine: has non-selective action**

A- directly: Inc. cAMP through decreasing PDE2,3,4 (**dominant action**)

B- indirectly: decrease PDE5 → ↑cGMP (promote smooth muscle relaxation → vasodilatation)

3) **Phentolamine** : inhibit  $\alpha_1$  effect

4) **Selective PDE5 inhibitors** (more explanation in the next slide):(**oral**)

- Sildenafil •Vardenafil •Tadalafil •Avanafil

PDE5 is an enzyme break down cGMP, but it's not the only one, other types of PDE affect cGMP as well.

**PDE5 present mainly in the erectile tissue & infew amounts in other tissues** (in high dose causing side effects)

In erectile dysfunction don't give testosterone, it causes infertility, most has desire but don't have the act

<b>MOA</b>	Inhibit PDE5 → inhibit break down of cGMP → (high) cGMP (promote smooth muscle relaxation → vasodilatation), (Only in the context of desire) They do not affect the lipido, so sexual stimulation is essential to a successful
<b>Indications</b>	<p>1)Erectile dysfunction. 1st line therapy. All types have similar efficacy</p> <p>2) Pulmonary hypertension (PDE5 presents in the lungs)</p> <p>3) premature ejaculation&amp;BPH</p> <p>4) Congestive heart failure,IBS,Rayanud's disease</p>
<b>Pharmacokinetics</b>	<p><b>Absorption</b>; Fatty food interferes with <b>Sildenafil</b> &amp; <b>Vardenafil</b> absorption so taken on empty stomach / at least 2 hr.s after food Tadalafil &amp; [<b>Avanafil</b>] are not affected by food.</p> <p><b>Metabolism</b>; All by hepatic CYT3A4; <b>Tadalafil</b> &gt; the rest thus;        (increase ADRs with enzyme inhibitors; erythro &amp; clarithromycin, ketoconazole, cimetidine, tacrolimus, fluvoxamine, amiodarone...etc. Decrease efficacy with enzyme inducers; rifampicin, carbamazipine, phenytoin</p>
<b>Administration</b>	<p>Avanafil has the advantage of been given 30 min before intercourse</p> <p>Tadalafil must be given every 72 hrs if used with enzyme inhibitors</p> <p><b>Onset of action: Avanafil is the most rapid.</b></p> <p><b>Duration of action: Tadafil is the longest</b></p>

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

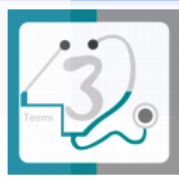
Depend on desire duration

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	5
Myalgia & Back pain %	-	-	5
Sperm functions	-	-	↓?
Q-T prolongation	-	↑	-

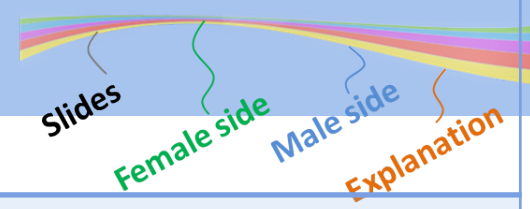
**Side effect**  
 Less common: **1. IHD & AMI** > patients on big dose or on nirates 2. Hypotension > patients on a-blockers than other antihypertensives 3. Bleeding; epistaxis.....etc. 4. Priapism; if erection lasts longer than 4 hours ' emergency situation Rare: 1. Ischemic Optic Neuropathy; can cause sudden loss of vision 2. Hearing loss

**Contraindication**  
 Hypersensitivity to drug  
 Patients with history of AMI/stroke / fatal arrhythmias <6 month (has to be >6 months AMI & arrhythmias) >> Tendency to hypotension and decrease coronary filling cuz sexual act has severe burden on heart and he already has heart problems  
 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 Pyronie's disease deformity in male sex organ due to presence of fibrous tissue  
 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 abnormality in the fields of vision



**ORAL**  
**2- Testosterone**



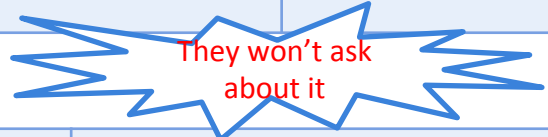
Uses:

Given to those with **hypogonadism** or **hyperprolactenemia** and promotion of desire.

**3- Apomorphine**

<u>:Mechanism</u>	<u>:action</u>	<u>Pharmacokinetic</u>	<u>Uses:</u>	<u>ADRs:</u>
A dopamine agonist on D2 receptors. (n. paraventricularis)	Activates arousal centrally; <b>Erectogenic+ Little promotion of desire</b>	Given sublingual Acts quickly Weaker than PDE5	Given in mild-moderate cases / <b>psychogenic</b> (those who are depressed +anxious have fear from sexual act)	nausea, headache, and dizziness but <b>safe with nitrate</b>

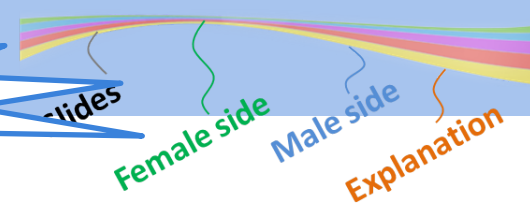
**4- Oral phentolamine** = a1 blocker / debatable efficacy



<u>Yohimbine</u>	Central and peripheral a2 agonist	<b>Aphrodetic</b> = Erectogenic but low efficacy many CV side effects
<u>Trazodone</u>	Antidepressant, a 5HT reuptake inhibitor(antagonize NO cuz it has a role in depression)	priapism
<u>Korean Ginseng</u>	Questionable / may be a NO donor	

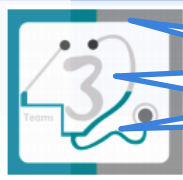


**TRANSURETHRAL**

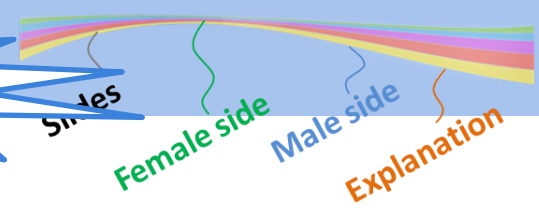


## Alprostadil

<u>Mechanism of action</u>	<u>Pharmacokinetic</u>	<u>ADRs</u>
<p><b>Prostaglandin</b>                      ↑ <b>cAMP</b>                      Synthetic + more stable                      Applied by a special applicator into penile urethra &amp; acts on corpora cavernosa=&gt; Erection</p>	<p>Low - Intermediate Efficacy                      Minimal systemic effects                      Rarity of drug interactions</p>	<p>1- Variable penile <b>pain</b>                      2- Urethral <b>bleeding</b>                      3- Urethral tract <b>infection</b>                      4- Vasovagal reflex                      5-<b>Hypotension</b>                      6-<b>Priapism or Fibrosis (rare)</b></p> <p><b>Priapism : painful medical condition in which the penis does not return to its flaccid state</b></p>



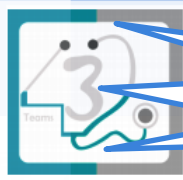
**TOPICAL**



Cream has no efficacy( very mild)

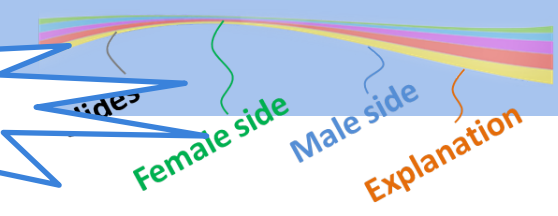
<u>Drug:</u>	<u>Mechanism:</u>	<u>Disadvantage :</u>	<u>ADRs :</u>
20% Papaverine	↑ cAMP + cGMP	Low efficacy No FDA approval	<b>Female Partner can develop:</b> 1- <b>hypotension</b> , 2- headache 3- vaginal absorption
2% Minoxidil	NO donor + K channel opener		
2% Nitroglycerine	-----		
+ a drug absorption enhancers			





**INTRACAVERNOSAL**

**Inj.**



**1- Alprostadil**

<u>Mechanism:</u>	<u>Disadvantage:</u>	<u>ADRs:</u>
Prostaglandin => cAMP  ↑	1- Needs training 2- Erection => after 5-15 min lasts according to dose injected 3- May develop fear of self injury / Discontinuation	1- <b>Pain or bleeding</b> at injection site 2- <b>Cavernosal fibrosis</b> 3- <b>Priapism serious condition</b> painful medical condition in which the penis does not return to its flaccid state

**2- Papaverine**

<u>Mechanism:</u>
Prostaglandin=> ↑ cAMP+ cGMP

**3 combined in severe cases**

**3- Phentolamine**

<u>Mechanism:</u>
α1 blocker

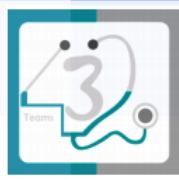
**Treatment of Priapism** :A medical emergency

1- **Aspirate blood** to **decrease intracavernous pressure.**

Or 2- **Intracavernous injection of Phenylephrine** → α1 agonist

15 → **detumescence**





**1. A patient came to the clinic suffering from infertility. Investigations proved that he has a normal erection and ejaculation. His testosterone level is lower than normal. What's the most appropriate treatment?**

- A. Dopamine agonist
- B. Oral PDE5 Inhibitors
- C. ADD
- D. Testosterone

**2. 45 year old impotent male had suffered from AMI 2 months ago is requesting a treatment for his impotency, which one of the following drugs the doctor should avoid to treat him?**

- A. Anti-epileptic
- B. Thiazide diuretics
- C. Sildenafil
- D. Testosterone

**3. Which of the following drugs cause erectile dysfunction by increasing 5HT in the synapse?**

- A. Tadalafil
- B. SSRI
- C. Central antihypertensive
- D. Alprostadil



Reproductive  
System



**PHARMACOLOGY**  
**432 TEAM**



**Pharmacology Leaders**  
**Tuqa Al-Kaff & Abdullah Al-Anzi**

[Pharmacologyteam1@gmail.com](mailto:Pharmacologyteam1@gmail.com)