



Lecture 1

Drugs Affecting Erectile Dysfunction

Objectives:

- ★ 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

- Additional Notes
- Important
- Explanation –Extra-

before starting, please check our [Reproductive block correction](#)

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com

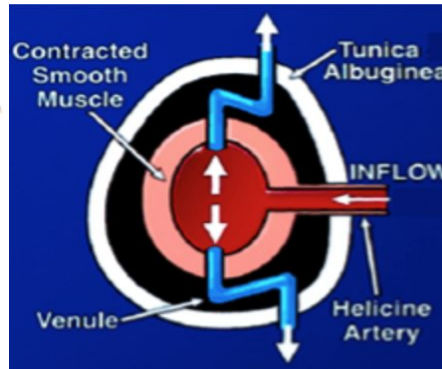
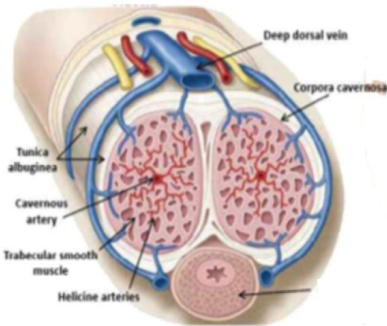
ERECTION

- **A normal erection relies on the coordination of** vascular, neurological, hormonal and psychological.
- An erection can occur following direct genital stimulation or auditory or visual stimulation or any aspects that contribute with the influx of blood into the penis

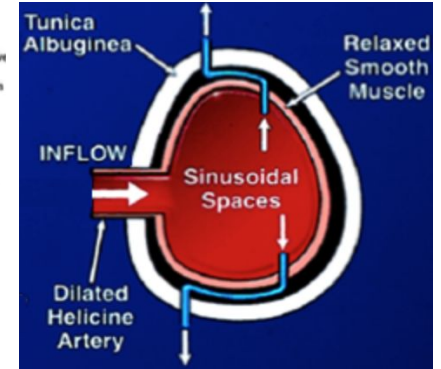
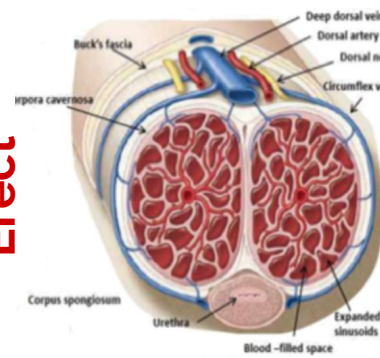
★ Mechanism of Erection:

- 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

Flaccid



Erect



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.

→ The **most common** cause of erectile dysfunction is **endothelial dysfunction**.

Other causes of ED including :

- Old age
- Hypertension, smoking, hyperlipidemia, DM and peripheral vascular disease
- Hypogonadism
- some drugs like; Anti-HTN, Anti-Arrhythmia, antidepressant, Anticonvulsant, Alcohol, Anxiolytic, Anti-androgens, Marijuana, Antiparkinson drugs

Drugs Adversely causing ED

Drug Class	Specific drug examples
Beta-blockers	propranolol, metoprolol, atenolol
Calcium-channel blockers	verapamil, nifedipine
Alpha-adrenergic agonists	clonidine
Cardiac glycosides	digoxin
Thiazide diuretics	hydrochlorothiazide
Aldosterone antagonists	spironolactone
Fibric acid derivatives	gemfibrozil, clofibrate
Selective serotonin reuptake inhibitors	fluoxetine, sertraline, paroxetine, citalopram
Tricyclic antidepressants	amitriptyline, desipramine, nortriptyline
Other antidepressants	lithium
Benzodiazepines	lorazepam, alprazolam, diazepam
Histamine (H ₂) receptor antagonists	ranitidine, cimetidine
Butyrophenones and phenothiazines	haloperidol, prochlorperazine, chlorpromazine
Hydantoin anticonvulsants	phenytoin
Cytotoxic agents	cyclophosphamide, methotrexate
Recreational drugs	alcohol, cocaine, marijuana

The doctor said this table is not really important, you just have to memorize the drugs in the next slides

Drugs adversely causing ED:

centrally acting drugs

DA > NE promote arousal, so whenever 5HT act on 5HT₂ → ↓ DA release → ↓ arousal

1- Most **ADDs (Antidepressant drugs)** leads to ↓ **5HT uptake** → ↑ 5HT in synapse and act on 5HT₂ → ↓ DA release → ↓ arousal
Like non-selectively as **TCA**s and selectively as **SSRIs**

NOTE: SSRIs also work Peripherally and antagonize NO actions → decrease genital sensation → Delay ejaculation → it can be used to Treat Premature Ejaculation.

2- **Anti-psychotic drugs** they are **DA antagonist** + hyperprolactinemia that leads to ↓ arousal that leads to Erectile Dysfunction

3- **Anti-epileptic drugs (phenytoin)** have **GABA** effect that leads to antagonize Exc. amino acid, causes ↑ sedation and ↓ arousal

Centrally acting antihypertensives

1- **Methyl dopa, Reserpine** ↓ arousal

2- **Clonidine** leads to ↓ arousal centrally / Vasoconstriction peripherally

Other antihypertensives :

1- **β 2 blockers** leads to -ve vasodilating on β 2 + potentiate α 1 effect

2- **Thiazide diuretics** leads to \downarrow spinal reflex controlling erection + \downarrow arousal

Anti-androgens leads to \downarrow desire :

1-**Finasteride**: leads to α reductase inhibitor (prevent production of active testosterone \rightarrow irreversible erectile dysfunction

2-**Cyproterone acetate**: it is synthetic steroidal antiandrogen

3-**Cimetidine** (high doses) / **Ketoconazole** / **Spirolactone** leads to hyperprolactinemia + gynecomastia

4-**Estrogen-containing medications**

Habituating Agents:

1-**Cigarette smoking** leads to vasoconstriction + penile venous leakage

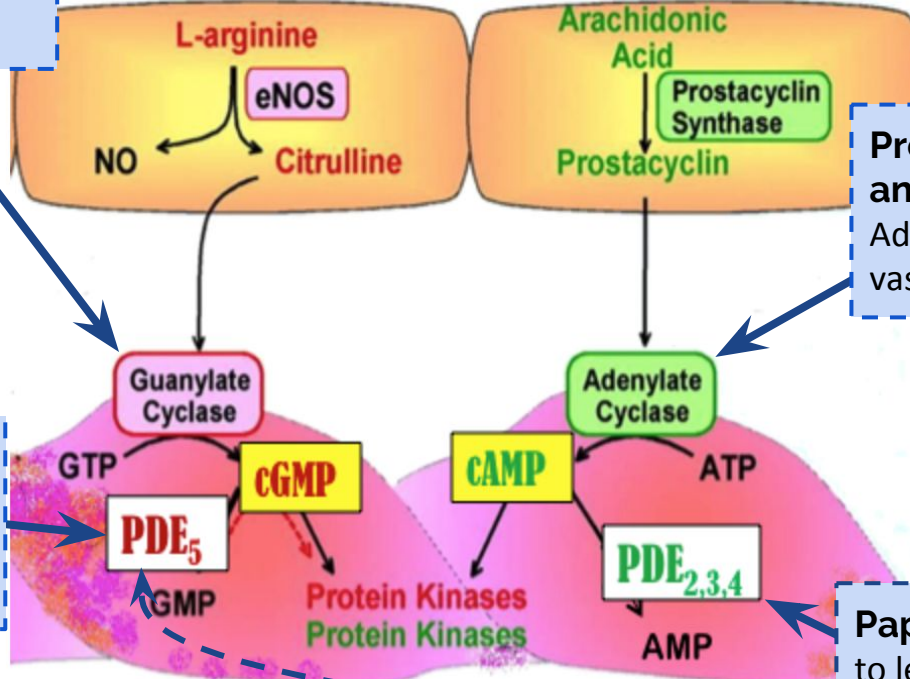
2-**Alcohol** [small amounts] leads to \uparrow desire + \downarrow anxiety + vasodilatation

3-**Alcohol** [big amounts] leads to \uparrow sedation + \downarrow desire

4-**Chronic alcoholism** leads to hypogonadism + polyneuropathy

Drugs treating erectile dysfunction

Nitrates activate Guanylate Cyclase → vasodilatation



Prostaglandin analogues and Salbutamol activate Adenylate Cyclase → vasodilatation

PDE₅ Is (Sildenafil) inhibit the conversion of cGMP to GMP → vasodilatation

Papaverine inhibit PDE_{2,3,4} and to lesser extent PDE₅ to cause vasodilatation

NOTE: both **Nitrates** and **Salbutamol** are not used nowadays because of their weak efficacy.



SELECTIVE phosphodiesterase 5 Inhibitors (PDE5)

Drugs

(Sildenafil ,Vardenafil ,Tadalafil , Avanafil)

MOA

- They **inhibit PDE5** (which is **convert cGMP into GMP**) so they will prevent breakdown of cGMP in corpus cavernosum which will **increase** the flow of blood into corpus cavernosum at any given level of of sexual stimulation.
- PDE5 inhibitors have **NO** effect in the absence of sexual stimulation.They do not affect the libido, so sexual stimulation is essential to a successful.

Pharmacodynamic

Inhibition of :

- 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.

Indication

- 1- erectile dysfunction , **first line therapy** , they have the same efficacy .
- 2- pulmonary hypertension
- 3- BPH and premature ejaculation.

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

ACTS ON PDE5 & PDE6 :

★ **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)**

- **PDE1 & PED 2 cause :** AMI, IHD
- **PDE5 cause :** Headache/Flush nasal congestion
- **PDE6 cause :** altered vision
- **PDE11 cause :** back pain

SELECTIVE phosphodiesterase 5 Inhibitors (PDE5)

Adverse Effects

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	-	-	decrease
Q-T prolongation	-	prolonged	-

★ **Major less common ADRs:**

1. IHD & AMI > patients on big dose or on nitrates
2. Hypotension > patients on a-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

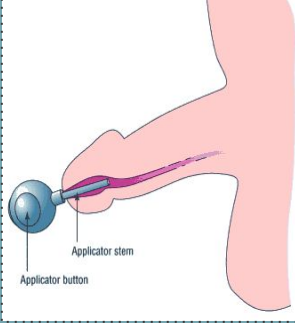
SELECTIVE phosphodiesterase 5 Inhibitors (PDE5)

Pharmacokinetic	Absorption	<ul style="list-style-type: none"> ★ 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 ★ Avanafil has the advantage of been given 30 min before intercourse ★ Tadalafil must be given every 72 hrs if used with enzyme inhibitors
	Metabolism	<p>All by hepatic CYT3A4; Tadalafil > the rest thus;</p> <ul style="list-style-type: none"> - increase ADRs with enzyme inhibitors; erythro & clarithromycin, ketoconazole, cimetidine, tacrolimus, fluvoxamine, amiodarone...etc. - decrease efficacy with enzyme inducers; rifampicin, carbamazepine, phenytoin
Contraindications		<p>1-Hypersensitivity to drug</p> <p>2-Patients with history of AMI / stroke / fatal arrhythmias <6 month</p> <p>3-Nitrates , <u>total contraindication</u> what should we do? PDEIs in small dose + spacing at least 24hrs (48 hrs with <i>Tadalafil</i>) for fear of developing IHD/AMI due to severe hypotension.</p>
Precautions		<ul style="list-style-type: none"> - With α blockers [except tamsulosin] cause orthostatic hypotension - With hepato/renal insufficiency - With bleeding tendencies [leukemia, hemophilia, Vit K deficiency, antiphospholipid syndrome,...etc] - With <i>quinidine, procainamide, amiodarone</i> (class I & III antiarhtmics) (Mainly Vardenafil) - Dose adjustment; <i>when using drugs that have interaction on hepatic liver microsomal enzymes i.e inhibitors or inducers.</i> - Retinitis pigmentosa

Other Oral DRUGS

Testosterone	<ul style="list-style-type: none"> Given to those with hypogonadism or hyperprolactinemia Given for promotion of <u>desire</u>.
Apomorphine	<p>characteristics</p> <ul style="list-style-type: none"> D₂ agonist Activates arousal centrally; Erectogenic + Little promotion of desire given sublingual → Acts quickly Not FDA approved
	<p>Indication</p> <p>Given in mild-moderate cases / psychogenic</p>
	<p>ADRs & Contraindications</p> <ul style="list-style-type: none"> Nausea, headache, and dizziness but safe with nitrate PDE₅ Is contraindication
Oral Phentolamine	<ul style="list-style-type: none"> α₁ blocker / debatable efficacy
Yohimbine	<ul style="list-style-type: none"> Central and peripheral α₂ agonist → Aphroditic + Erectogenic but low efficacy and many CV side effects
Trazodone	<ul style="list-style-type: none"> Antidepressant, a 5HT reuptake inhibitor → can cause priapism
Korean Ginseng	<ul style="list-style-type: none"> Questionable / may be a NO donor.

Other DRUGS

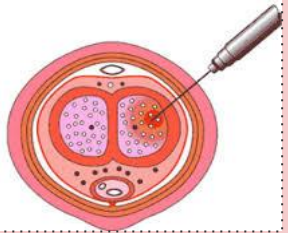
<p>Alprostadil (Transurethral)</p> 	<p>Mechanism</p>	<p>Prostaglandin E1 analogue → ↑ cAMP</p>	
	<p>Route of administration</p>	<p>Applied by a special applicator into penile urethra & acts on corpora cavernosa → Erection (low/intermediate efficacy)</p>	
	<p>ADRs</p>	<p>Minimal systemic effects / Rarity of drug interactions:</p> <ul style="list-style-type: none"> • variable penile pain • Urethral bleeding / Urethral tract infection • Vasovagal reflex / Hypotension • Priapism or Fibrosis (rare) 	
<p>Topical drugs</p>	<p>20% Papaverine</p>	<p>↑ cAMP + cGMP</p>	<p>We use these three drugs a Drug Absorption enhancer</p>
	<p>2% Minoxidil</p>	<p>NO donor + K channel opener</p>	
	<p>2% Nitroglycerine</p>	<p>-</p>	
	<p>Their Efficacy:</p> <ul style="list-style-type: none"> • Low efficacy / No FDA approval • Female Partner can develop → hypotension, headache → due <u>vaginal absorption</u>. 		

Other DRUGS

Alprostadil	Mechanism	Prostaglandin E1 analogue → ↑ cAMP Erection → is after 5-15 min
	ADRs	<ul style="list-style-type: none">● Pain or bleeding at injection site● Cavernosal fibrosis● Priapism
Papaverine	Mechanism	Prostaglandin E1 analogue → ↑ cAMP
Phentolamine	Mechanism	α1 blocker

Those three drugs are combined in severe cases.

And they are used **intracavernosal injection (Need training)**



The diagram shows a cross-section of the penis with a needle inserted into the cavernous body to administer an injection. The cavernous body is shown as a chamber containing blood, and the needle is positioned to inject a substance into this chamber.

Treatment of Priapism:

it is **MEDICAL EMERGENCY**

1- Aspirate blood to decrease incavernous pressure

2- Intracavernous **Phenylephrine** injection (**α1 agonist**, detumescence)

MCQs

Q1/ Which one of the following drugs can cause urethral tract infection as an adverse effect for using it :

- A. Testosterone
- B. Alprostadil
- C. minoxidil
- D. Sildenafil

Q2/ Which of the following is one of the mechanism that can cause impotence :

- A. Activation of PE1
- B. Increase the ACH
- C. Increase in B2 activity
- D. Decrease dopamine

Q3/ 45 year old impotent male had suffered from AMI, months ago is requesting a treatment for his impotency, which one of the following drugs the doctor should avoid to treat :

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

Q4/ Which one of the following anti-depressing drugs doesn't affect the dopamine release :

- A. TCAs
- B. Serotonin antagonist
- C. Norepinephrine reuptake inhibitors
- D. Norepinephrine dopamine reuptake inhibitors

Good luck!

Done by Pharmacology team

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For any correction, suggestion or any useful information do not
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