Pharmacology 439

MED439

pharmacology Team 438

Revised & Approved

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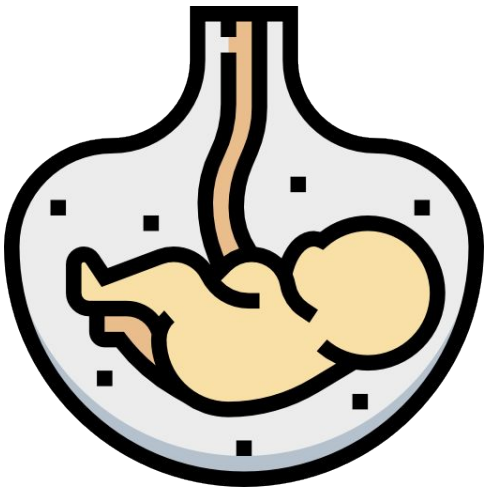
Editing file



Reproduction Block

Pharmacology team 439

Medications Affecting Erectile Dysfunction

Objectives:

By the end of the lecture , you should know:

- 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

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Yellow: Dr. notes (439)
Green: Dr. notes (438)

Mechanism of Erection

01 An erection occurs when **the amount of blood rushing to the penis is greater than the amount of blood flowing from it**[1]

02 A **massive influx of blood accumulates** in the sinusoidal spaces due to **relaxation of smooth muscle & dilatation of arteries** → Corpora cavernosa to swell (tumescence/erection)

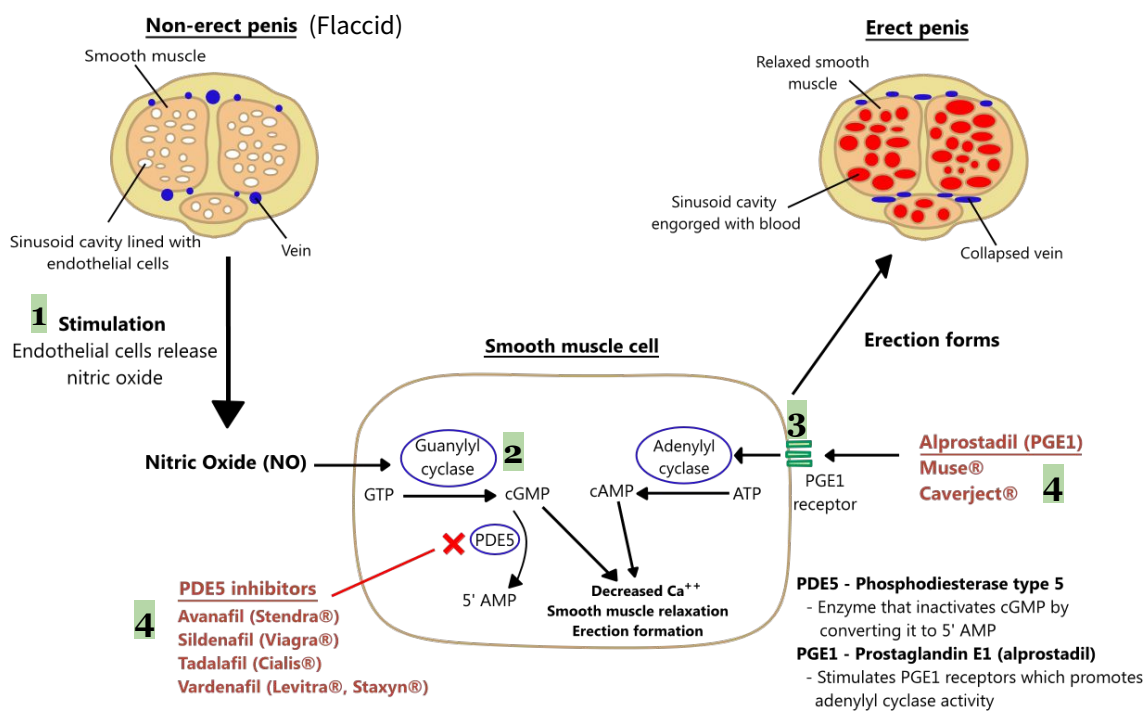
03 Tumescence compresses the veins that normally drain the penis → **reduces venous outflow** & maintains penile rigidity

04 A normal erection relies on the coordination:

- Vascular
- Neurological
- Hormonal [2]
- 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

Peripheral haemodynamic changes inducing erection



Explanation of the picture:

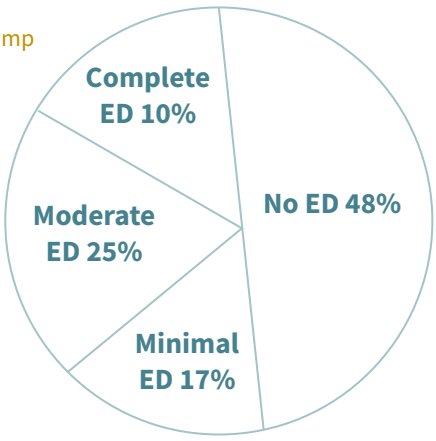
- Erection is maintain by increased level of of cyclic nucleotides **cGMP and cAMP**

1. Sexual stimulation -direct, visual ..etc- causes the releasing of **nitric oxide** from the endothelial cells lining the cavernosal arteries → diffuse into the smooth muscle cells of corpora cavernosa
2. Nitric oxide activate guanylyl cyclase system to release **cGMP** as a second messenger to produce the muscle relaxation action by decreasing the level of Ca+ ; PDE5 degrade cGMP to stop its action
3. PGE1 receptor activated by various stimuli leads to activation of adenylyl cyclase system to release cAMP as a second messenger to help in muscle relaxation
4. Some drugs used in treating ED aim to ↑ cGMP as PDE5 inhibitors , or ↑ cAMP as Alprostadil

1: due to smooth muscle relaxation.
2: e.g.: thyroid hormone (negatively affect erection) and Testosterone

Erectile Dysfunction "ED" Not imp

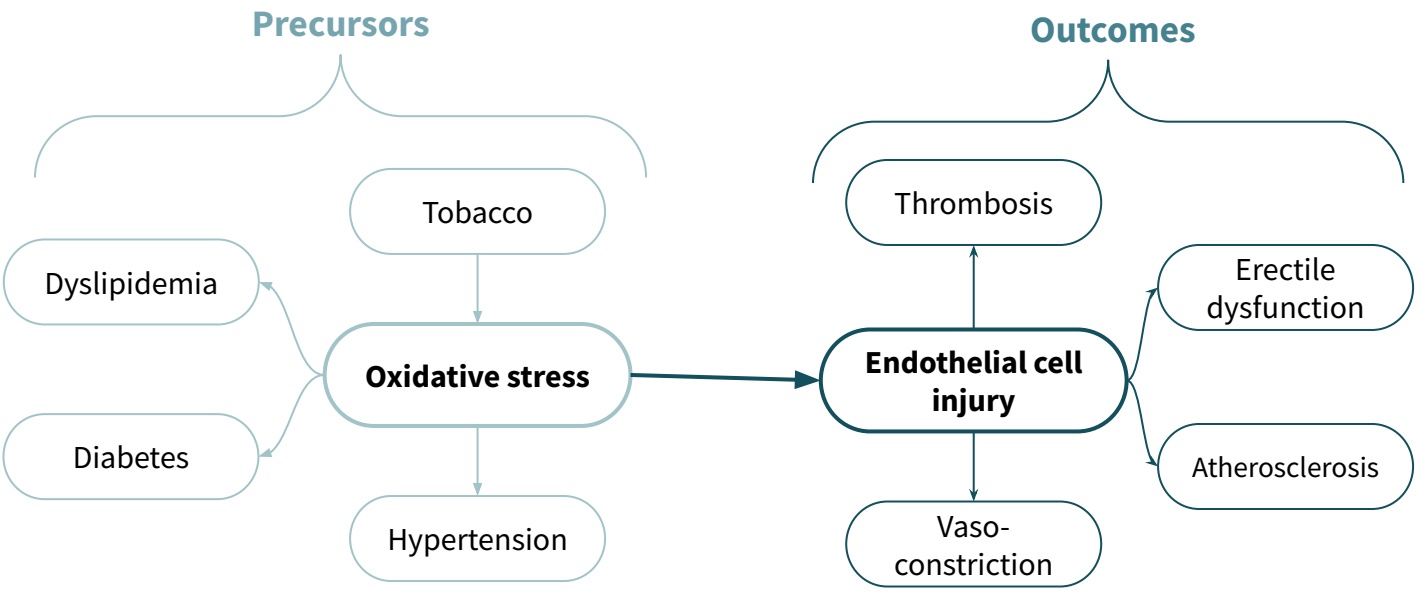
- Persistent or recurrent inability to attain (acquire)& maintain (sustain) an erection (rigidity) sufficient for satisfactory sexual performance.
- **Impotent:** is reserved for those men who experience erectile failure during attempted intercourse more than 75 % of the time



Prevalence

Causes

Inflammatory	Prostatitis, urethritis
Mechanical	Peyronie's disease , chordee
Psychological	Depression, performance anxiety, stress, relationship difficulties
Occlusive Vascular	**Arterial**: hypertension, smoking, hyperlipidemia, DM, peripheral vascular disease **Venous**: venous occlusion due to anatomical or degenerative changes
Trauma	Pelvic fracture, Spinal cord injury, penile trauma
Endocrine	Hypogonadism, hyperprolactinemia, hypothyroidism, hyperthyroidism
Neurologic	Parkinsons, multiple sclerosis, spina bifida, pelvic surgery, peripheral neuropathy
Chemical[1]	Anti-hypertension, anti-arrhythmics, antidepressant, anxiolytics, anti-androgens, anticonvulsants, alcohol, marijuana, anti-parkinsonism, LHRH analogues
Extra factors	Prostatectomy, old age[2], CRF, cirrhosis **Endothelial dysfunction is the commonest cause**



1: asking about the patient's drug history is extremely important.
2: due to hypogonadism.

Drugs Adversely Causing ED

#EXTRA, NOT FOUND IN THE ORIGINAL SLIDES

Drug class	Examples
Beta-blockers **Calcium-channel blockers** **Alpha- adrenergic agonists** **Cardiac glycosides**	Propranolol, metoprolol, atenolol Verapamil, nifedipine Clonidine Digoxin
Thiazide diuretics **Aldosterone antagonists**	Hydrochlorothiazide Spironolactone
Fibric acid derivatives	Gemfibrozil , clofibrate
SSRI **Tricyclic antidepressants** **Other antidepressants**	**Fluoxetine, sertraline,paroxetine, citalopram** Amitriptyline , desipramine, nortriptyline Lithium
Benzodiazepines	Lorazepam, alprazolam, diazepam
Histamine (H2) receptor antagonists	Ranitidine, cimetidine
Butyrophenones and phenothiazines	Haloperidol, prochlorperazine, chlorpromazine
Hydantoin anticonvulsant	Phenytoin
Cytotoxic agents	Cyclophosphamide, methotrexate
Recreational drugs	Alcohol, cocaine, marijuana

Mechanisms of how these drugs cause ED

Centrally Acting drugs	
Anti-Depressant Drugs E.g non-selective (TCAs) selective (SSRIs)	**Dopamine** [1] **promotes arousal** more than epinephrine which have an opposite effect of 5HT (serotonin) on 5HT2 → ↓ dopamine release → ↓ arousal • anti-depressant drugs (5HT reuptake inhibitors): ↓ 5HT uptake → ↑5HT in synapse act on 5HT2 receptors → ↓ dopamine release → ↓ arousal. • **SSRI**[2] have a peripheral effect: antagonize Nitric Oxide actions →↓ genital sensation→ **delay ejaculation** (use for treatment of premature ejaculation)
Anti-psychotic drugs	• They are DA antagonist, causing hyperprolactinemia
Anti-epileptic drugs E.g phenytoin	• They have GABA effect (inhibitory neurotransmitter) → antagonize excitatory Amino acid → increase sedation → ↓ arousal.
Anti-Hypertension	
Central hypotensive	• Methyldopa, Reserpine[3]: ↓ arousal • Clonidine (presynaptic α_2 agonist): ↓ arousal centrally / Vasoconstriction peripherally
Other hypotensive	• β2 blockers: Inhibit the vasodilating β2 effect → potentiate α1 effect (vasoconstriction) • Thiazide diuretics: ↓ spinal reflex[4] controlling erection + ↓ arousal

1: hormone of sex and desire.
2: out of all anti-depressants, SSRIs causes erectile dysfunction the most.
3: Reserpine is not used as a hypotensive drug anymore due its side effects
4: central effect

Anti-androgen (They ↓ desire [1])	
Finasteride[2]	• α reductase inhibitor (prevent production of active testosterone) → **irreversible** erectile dysfunction (important)
Cyproterone Acetate[3]	• synthetic steroidal antiandrogen
Other drugs	• Cimetidine (high doses), ketoconazole, Spironolactone causes hyperprolactinemia + gynecomastia • Estrogen-containing medications
Habituating agents	
Smoking	• Cigarette smoking cause vasoconstriction + penile venous leakage
Alcohol	• Small amount: ↑ desire + ↓ anxiety + vasodilatation • Large amount: ↑ sedation + ↓ desire • Chronic alcoholism: hypogonadism + polyneuropathy

Drugs Used for the Treatment of ED

According to the route of administration

1) Oral:

-Selective PDE5 inhibitors (1st line)
-Testosterone[4]
- Apomorphine [5]
-Oral Phentolamine
- Yohimbine
-Trazodone
- Korean Ginseng

2) Transurethral:

- Alprostadil [6]

3) Topical:

- **Combinations** of [Papaverine , Minoxidil, Nitroglycerine, Drug absorption enhancer]

4) Intracavernosal:

- Alprostadil
- Papaverine[7]
- Phentolamine [8]

1) Oral Drugs: Selective PDE5 Inhibitors

PDE receptors family and their location

Dr. Ishfaq: the target is PDE5, any effect beyond that is a side effect. this table is not imp, imp ADRs are discussed next slides

Receptor	Location	Receptor	Location
PDE1 (cGMP)	Heart,brain,lung,smooth muscle	PDE7 (cAMP)	Skeletal muscle, heart, kidney, brain, pancreas, T-Lymphocytes
PDE2 (cAMP)	Adrenal gland , heart ,lung ,liver, platelets	PDE8 (cAMP)	Testes, eye, liver, skeletal muscle, heart, kidney, ovary, brain, T-Lymphocyte
PDE3 (cAMP)	Heart, lung, liver, platelets, adipose tissue, inflammatory cells	PDE9 (cGMP)	Kidney, liver, lung, brain, possibly heart
PDE4 (cAMP)	Sertoli cells, kidney, brain, liver, lung, inflammatory cells	PDE10 (cAMP)	Testes, brain
PDE5 (cGMP)	Lung, platelets, vascular smooth muscle, heart	PDE11 (cGMP)	Skeletal muscle, prostate, kidney, liver, pituitary gland, salivary gland, testes
PDE6 (cGMP)	Photoreceptor	-	-

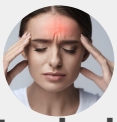
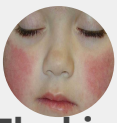
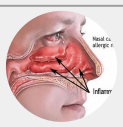
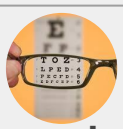
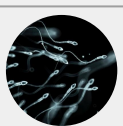
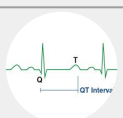
1: Inhibit the conversion of Testosterone → DHT (active form)
2: for treatment of Benign Prostatic Hypertrophy (BPH)
3: Used for acne treatment in females.
4: Act centrally to ↑Sexual Desire
5: Centrally: ↑ Arousal
8: a_1 receptor blocker → vasodilation
6: prostaglandin analogue
7: inhibit PDE2,3,4,5 → increase cAMP, cGMP → vasodilation (not effective clinically used as additive)

<table>
<tr><th>Drugs</th><th>Sildenafil</th><th>Vardenafil</th><th>Tadalafil</th><th>Avanafil</th></tr>
<tr><td>MOA</td><td colspan="4">★ Inhibit PDE5 → prevent breakdown of cGMP → pertain vasodilatation → erection
● They do not affect the libido[1], so sexual stimulation is essential</td></tr>
<tr><td>P.D</td><td colspan="4">Pharmacodynamics action relevant to PDE5 inhibition:
● Vascular smooth muscle cells (VSMCc) of Erectile Tissue of Penis
● Other VSMCs e.g lung[2], brain and heart
● Other non-VSMCs e.g prostate, bladder, seminal vesicle, GIT
● Platelets
● Other tissues; testis, skeletal muscles, liver, kidney, pancreas</td></tr>
<tr><td>Uses</td><td colspan="4">● 1st line therapy in Erectile dysfunction, all types have <u>similar</u> efficacy:
○ Sildenafil: 74-84%
○ Vardenafil: 73-83%
○ Tadalafil: 72-81%
● Pulmonary hypertension
● BPH & premature ejaculation</td></tr>
<tr><td rowspan="2">Selectivity</td><td>10 folds selective on PDE5&6</td><td>16 folds selective on PDE5&6</td><td>>200 fold selective on PDE5&6</td><td>—</td></tr>
<tr><td colspan="4">● Selectivity on PDE5 is not absolute and vary with each drug:
○ Can partially act on PDE targeting cGMP (1,5,6,9,11)
○ In higher doses it can act on PDE targeting cAMP (2,3,4,7,8,10)
○ Stimulation of different types can cause ADRs:
■ PDE1&2 → Ischemic heart diseases , acute myocardial infarction
■ PDE5&6 → Headache, flush, nasal congestion, altered vision
■ PDE11 → Back pain</td></tr>
<tr><td rowspan="2">P.K</td><td colspan="2">● Fatty food interferes with Sildenafil & Vardenafil absorption, so taken on empty stomach or at least 2 hours after food</td><td colspan="2">● Tadalafil & Avanafil absorption doesn't affected by food</td></tr>
<tr><td colspan="4">● Metabolization: All by hepatic CYT3A4; Tadalafil more than the rest, thus:
○ Increase ADRs with enzyme inhibitors; erythromycin & clarithromycin, ketoconazole, cimetidine, tacrolimus, fluvoxamine, amiodarone...etc.
○ Decrease efficacy with enzyme inducers; rifampicin, carbamazepine, phenytoin</td></tr>
<tr><td>Dose</td><td colspan="2">50-100 mg</td><td colspan="2">10-20 mg</td><td>-</td></tr>
<tr><td>Frequency</td><td colspan="3">Once a day</td><td>-</td></tr>
<tr><td>Time of adminis
Not imp</td><td colspan="2">1 hour before intercourse</td><td>- 1-12 hours before intercourse

Must be given every 72 h if used with enzyme inhibitors</td><td>Has the advantage of been given 30 min before (immediate effect) intercourse</td></tr>
<tr><td>Onset</td><td colspan="2">30-60 min</td><td><30-45 min</td><td>-</td></tr>
<tr><td>Duration</td><td>4h</td><td>4-5h</td><td>36h (longest)</td><td>-</td></tr>
</table>

1: don't stimulate desire/ not aphrodisiac
2: therapeutically used in treatment of pulmonary hypertension.

Common ADRs:

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

Major less common ADRs:

1. **Ischemic heart diseases & Acute myocardial infarction:** patients on large dose or on **nitrates**[1]
2. Hypotension "due to vasodilation": 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. Sudden Hearing loss (unknown cause)

C.I:

1. **Nitrates: total C.I,**PDEIs in small dose + spacing at least 24hrs (48 hrs with *Tadalafil*) for fear of developing IHD/AMI due to **severe hypotension**
2. Hypersensitivity to drug
3. Patients with history of acute MI, stroke, fatal arrhythmias <6 month

Precautions:

1. With α blockers (except tamsulosin[2]) → orthostatic hypotension
2. With hepato/renal insufficiency [3]
3. With **bleeding tendencies**[4] (leukemia, hemophilia, Vit K deficiency, antiphospholipid syndrome,...etc)
4. Vardenafil: With quinidine, procainamide, amiodarone (class 1 & 3 antiarrhythmic)[5]
5. Dose adjustment; when using drugs that have interaction on hepatic liver microsomal enzymes i.e. inhibitors or inducers.
6. Retinitis pigmentosa[6]

1: due to sudden drop in BP.
2: selective blocker to α1A receptors in the prostate and urinary bladder → facilitate urine passage, used in the treatment of BPH.
3: decrease drug clearance = prone to side effects
4: Congestion (dilated vessels) + Bleeding tendency → increased risk of epistaxis
5: due to QR prolongation induced by vardenafil.
6: potentiate retinal deposition →visual abnormality

Other Oral Drugs to Treat ED

Testosterone (Androgens)	• Given to those with hypogonadism or hyperprolactinemia. • Given for promotion of desire (centrally acting)
Apomorphine	• A **dopamine agonist on D_2 receptors.** • Activates arousal **centrally**; Erectogenic + Little promotion of desire • Given sublingual, so Acts quickly. • Not FDA approved, **Weaker** than PDE5 inhibitors • Given in mild-moderate cases, psychogenic, **if PDE5 Is C.I** • ADRs: nausea, headache, and dizziness **but safe with nitrate** (doesn't cause vasodilation)
Oral Phentolamine	• An α1 blocker, has debatable efficacy (vasodilator)
Yohimbine [1]	• Central(desire) and peripheral presynaptic α2 agonist (**Aphroditic** [2] + Erectogenic) but low efficacy and many CV side effects [3]
Trazodone [4]	• Antidepressant, a 5HT reuptake inhibitor (**priapism**) treated with phenylephrine (α_1 Agonist) • Atypical antidepressant, has no effect on dopamine transmission, thus causes priapism not ED

2) Topical Drugs to Treat ED

- 20% Papaverine:
increase cAMP + cGMP

- 2% Minoxidil:
NO donner + K channel opener

- 2% Nitroglycerine

-a drug absorption enhancers

Combinations[6]

Disadvantages

- Low efficacy and not FDA approval

- Female Partner can develop hypotension and headache due to vaginal absorption

3) Transurethral Drugs to Treat ED

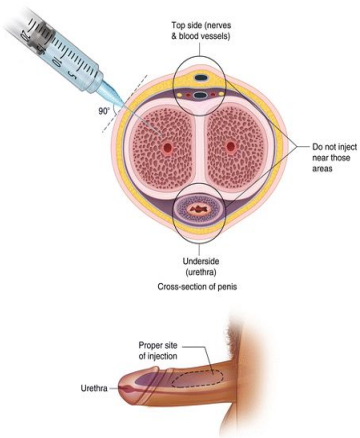
Drug	Alprostadil
MOA	• Synthetic PG analogues: Stimulates PGE1 →increase cAMP[5]
P.K	• Synthetic + more stable • Applied by a special applicator into penile urethra & acts on corpora cavernosa which lead to erection • Low - Intermediate Efficacy • **Minimal systemic effects and rarity of drug interactions.**
ADR	• Variable penile pain • Urethral bleeding, urethral tract infection • Vasovagal reflex, Hypotension • Priapism or Fibrosis (rare)

1: alkaloid drug.
2: = stimulate desire and sexual drive.
3: e.g. angina pain.
4: causes vasodilation of blood vessels of corpus cavernosa.
5: by activation of adenylate cyclase.
6: risk of arrhythmia, not commonly used

4) Intracavernosal Drugs to Treat ED

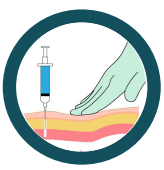
Alprostadil	• PGE1⟶ increase cAMP
	• Needs training: Erection ⟶ after 5-15 min and lasts according to dose injected
	• May develop fear of self injury, so Discontinuation
	• ADRs:
	  ○ Pain or bleeding at injection site
	  ○ Cavernosal fibrosis
	  ○ Priapism

Papaverine [1]	• PG E1 ⟶ ↑ cAMP + cGMP, It is a direct acting smooth, muscle relaxant
Phentolamine [1]	• α1 **blocker**
3 combined in severe cases	

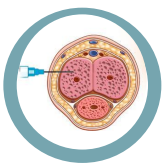


Treatment of Priapism

It is a medical emergency



Aspirate blood to decrease intracavernous pressure.



Intracavernous injection of Phenylephrine (local α1 agonist [2]) ⟶ Detumescence

1: promote vasodilation.
2: promote vasoconstriction.

Quiz

MCQ

Q1- Which of the following is/are contraindications to the use of PDE-5 inhibitors?

A- History of a myocardial infarction more than 6 months ago. B- Mild, stable angina.
C- Nitrate use. D- All of the above are contraindications to the use of PDE-5 inhibitors.

Q2- Sildenafil produces a penile erection by inhibiting what enzyme?

A- Cytochrome 3A4 B- cGMP C- Phosphodiesterase D- Adenyl cyclase E- Nitric oxide synthase.

Q3- Alprostadil produces an erection by

A- increasing tissue levels of GTP. B- increasing tissue levels of cAMP.
C- decreasing tissue levels of nitric oxide. D- decreasing tissue levels of cGMP.
E- increasing tissue levels of cGMP.

Q4- Finasteride causes irreversible erectile dysfunction by blocking:

A- α- reductase enzyme B- α receptors C- androgen receptors D- β receptors

Q5- The following drugs may be used in erectile dysfunction except?

A- Phenylephrine B- Apomorphine C- Alprostadil D- PGE1 analogues (Papaverine)

SAQ

- 66-years-old man complained of difficulty maintaining an erection. He is concerned about the use of drugs to restore sexual function, particularly about the need to time therapy with anticipated sexual activity.

Q1- What is the drug of choice that is indicated for this patient because of its long duration of action?
Q2- What is the M.O.A of that drug?

- 42-years-old patient who is taking a PDE-5 inhibitors for treating ED, later he is diagnosed with angina and be treated with Nitroglycerin.

Q3- Which drug would be the safest to be used with Nitroglycerin in this patient to treat erectile dysfunction?

Q4- Mention 2 ADR of that drug.

Q5- 44-years-old male came to ER with Priapism persist for 6 hours, What is the drug of choice that is indicated in this case ?

Answers:

MCQ

Q1	C
Q2	C
Q3	B
Q4	A
Q5	A

SAQ

Q1	Tadalafil
Q2	Inhibit PDE5 → prevent breakdown of cGMP → pertain vasodilatation→ erection
Q3	Apomorphine
Q4	nausea, headache, and dizziness
Q5	Intracavernous injection of Phenylephrine

Thank you for all the love and support you gave the team in those two years!

Hope we made the context much easier to study.
God bless you, Future doctors.

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