Pharmacology
Team 437

Drugs Affecting Erectile Dysfunction

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;
9. Mechanism / Utility / ADRs
10. Enumerate lines of treatment of priapism

Color index:
Important Note Extra

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Introduction

Mechanism of an erection

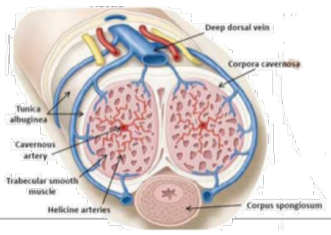
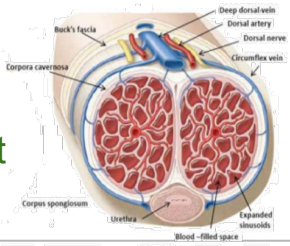
An erection occurs when the **amount of blood rushing to the penis is greater than the amount of blood flowing from it**

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

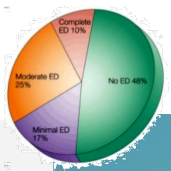
Tumescence(engorgement with blood) compresses the veins that normally drain the penis → reduces **venous outflow** & maintains penile rigidity

- A normal erection relies on the coordination:
  - Vascular
  - Neurological (parasympathetic)
  - 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

Peripheral haemodynamic changes inducing erection

FLACCID State	ERECT State
	Blood in more than blood out 

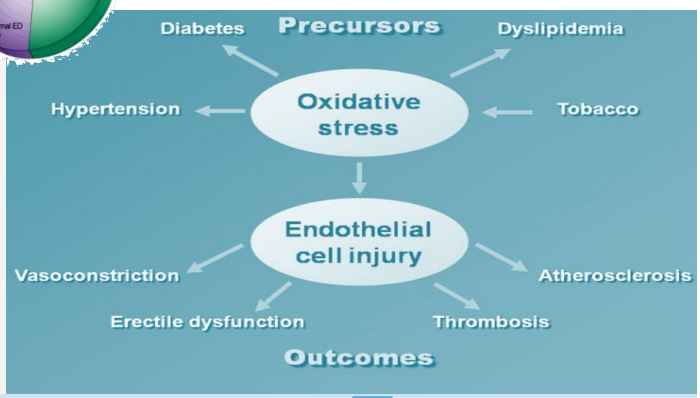
Erectile dysfunction



Prevalence

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.



Endothelial Dysfunction ➡️ Commonest Cause

The ones in red are the only important ones

Causes of Impotence

Inflammatory	Prostatitis, urethritis
Mechanical	Peronei's disease, chordee
Psychological	Depression, performance anxiety, stress, relationship difficulties
Occlusive vascular	Arterial: hypertension, smoking, hyperlipidemia hyperlipidemia (lead to atherosclerosis), DM, peripheral vascular disease (Oxidative stress endothelium damage lose the vasodilator) Venous: venous occlusion due to anatomical or degenerative changes
Trauma	Pelvic fracture, SC injection, penile truma
Endocrine	Hypogonadism, hyperprolactinemia, hypothyroidism, hyperthyroidism
Neurologic	Parkinsons, multiple sclerosis, spina bifida, pelvic surgery, peripheral neuropathy
Chemical	Anti-HTN, anti-arrhythmics, antidepressant, anxiolytics, anti-androgens, anticonvulsants, alcohol, marijuana, anti-parkoson drugs, LHRH analogues
Extra factors	Prostatectomy (may damage the nerve), old age (hormonal imbalance) , CRF, cirrhosis

Drugs Adversely Causing ED

Not important. The dr only emphasized that antidepressants can cause ED (related to 5HT)

Table 1

Commonly used drugs associated with erectile dysfunction

Drug Class	Specific drug 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
Selective serotonin reuptake inhibitors Tricyclic antidepressants Other antidepressants	fluoxetine, sertraline, paroxetine, citalopram amitriptyline, desipramine, nortiptyline 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

Formulary/Source: Mark A. Douglass, Pharm D

Keep in your mind before studying the drugs:

- a1 receptors are postsynaptic and cause vasoconstriction
- a2 receptors are presynaptic and cause -ve feedback → inhibition of neurotransmitter release
- B2 receptors are postsynaptic and cause vasodilation

Drugs Adversely Causing ED

** DOPAMINE = AROUSAL/ TESTOSTERONE= DESIRE

Central acting drugs	
M.O.A	❖ Dopamine more than epinephrine promote arousal. 5HT (serotonin) action on 5HT2 → decrease dopamine release →decrease arousal (there are some neurotransmitters affect the Arousal, one of them is Dopamine, so any agonist of Dopamine will increase Arousal & any antagonist of Dopamine will decrease it).
anti-Depressant Drugs	❖ e.g. non-selectively as TCAs, selectively as SSRIs ADD (anti-Depressant Drugs) decrease 5HT uptake which lead to ↑5HT in synapse act on 5HT2 → decrease dopamine release →decrease arousal Peripheral effect: antagonize NO (NO normally causes vasodilation)actions / decrease genital sensation→ Delay ejaculation (use for Treat of Premature Ejaculation)(SSRI)
Anti-psychotic drugs	❖ DA (dopamine) antagonist + hyperprolactinemia
Anti-epileptic drug	❖ e.g. phenytoin, they have GABA effect (inhibitory neurotransmitter) →. antagonize excitatory Amino acid → increase sedation → decrease arousal.

Anti-hypertensive	
Central hypotensive	❖ Methyl-dopa, Reserpine: they decrease DA by depleting dopamine → decrease arousal Clonidine (α2 agonist): decrease arousal centrally, Vasoconstriction peripherally by anticholinergic action (blocking alpha receptors) → ED
Other hypotensive	❖ β2 blockers: -ve vasodilating β2 + potentiate α1 effect (vasoconstriction) ❖ Thiazide diuretics: decrease spinal reflex controlling erection + decrease arousal

Drugs Adversely Causing ED

Anti-androgen	
Finasteride	❖ (used in Benign prostatic hyperplasia , male androgenic alopecia (during first puberty they have a lot of testosterone lead to acne and hair loss →α reductase prevent production of active testosteroneà →irreversible erectile dysfunction
Cyproterone acetate	❖ synthetic steroidal antiandrogen (this drug is usually given for females with acne)
Drug	❖ Cimetidine (high doses) / Ketoconazole /Spironolactoneàhyper- prolactinemia + gynecomastia
Drug	❖ Estrogen-containing medications
Habituating agent	
Smoking	❖ Cigarette smoking cause vasoconstriction + penile venous leakage (blood flow to penis will not be maintained due to vasoconstriction and wall damaged→ coordination is disrupted blood in <or = out flow)
Alcohol	❖ Small amount: increase desire + decrease anxiety + vasodilatation Big amount: increase sedation + decrease desire Chronic alcoholism: hypogonadism + polyneuropathy

SELECTIVE PDE5 Inhibitors (ORAL)

drugs		Sildenafil	Vardenafil	Tadalafil	Avanafil
M.O.A		Inhibit PDE5 prevent breakdown of cGMP pertain vasodilatation erection. They do not affect the libido, so sexual stimulation is essential. Secxual stimulation → NO release → goes to VSMC in penis → convert GTP into cGMP which decreases intracellular Ca+2 and cause vasodilation. how ever, cGMP can be broken by and enzyme called PDE5, so these drugs inhibit this enzyme → more vasodilation.			
P.D * PDE5 is present in other tissues → side effects or other uses		❖ 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, ... ❖ All types have similar efficacy : Sildenafil: 74-84% , Vardenafil: 73-83% , Tadalafil: 72-81%			
Indications		❖ Erectile dysfunction; **1st line therapy**. ❖ Pulmonary hypertension. They cause vasodilation ❖ BPH & premature ejaculation (not 1st line)			
P.K	Absorption	Fatty food interferes with Sildenafil & Vardenafil absorption so taken on empty stomach (at least 2 hr.s after food)		not affected by food	
	Interactions	All by hepatic CYT3A4; Tadalafil > the rest, thus: ○ Increase ADRs with enzyme inhibitors; erythromycin & clarithromycin, ketoconazole, cimetidine, tacrolimus, fluvoxamine, amiodarone...etc. ○ Decrease efficacy with enzyme inducers; rifampicin, carbamazepine, phenytoin			
	Dose(mg)	50-100	10-20		-
	Time of admin.	1 hour before intercourse		1-12 hours	advantage of been given 30 min
	Onset(min)	30-60		<30-45	-
	Duration (hrs.)	4	4 - 5	36	-

SELECTIVE PDE5 Inhibitors

drugs	Sildenafil	Vardenafil	Tadalafil	Avanafil

Just know the major red side effects without knowing which PDE caused it + know that tadalafil is highly selective

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,...)

Selective

type	locations	main ADRs
PDE1	Heart, brain, lung, smooth muscle	IH3D / AMI
PDE2	Adrenal gland, heart, lung, liver, platelets	
PDE3	Heart, lung, liver, platelets, adipose tissue, inflammatory cells	
PDE4	Sertoli cells, kidney, brain, liver, lung, inflammatory cells	-
PDE5	Lung, platelets, vascular smooth muscle, heart.	Headache/Flush nasal congestion)
PDE6	Photoreceptor	Altered VISION
PDE7	Skeletal muscle, heart, kidney, brain, pancreas, T lymphocytes	-
PDE8	Testes, eye, liver, skeletal muscle, heart, kidney, ovary, brain, T lymphocyte	
PDE9	§Kidney, liver, lung, brain, possibly heart	
PDE10	Testes, brain	
PDE11	Skeletal muscle, prostate, kidney, liver, pituitary gland and salivary glands, testes	Back Pain

PDE5.PDE6 : Sildenafil 10-fold selective - Vardenafil 16-fold selective - Tadalafil >200-fold selective

SELECTIVE PDE5 Inhibitors (ADRs)

drugs			Sildenafil	Vardenafil	Tadalafil	Avanafil
ADRS	Common	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	1.IHD & AMI > patients on big dose or on nirates ** ABSOLUTE CONTRAINDICATION 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	1.Ischemic Optic Neuropathy; can cause sudden loss of vision 2.Hearing loss				

SELECTIVE PDE5 Inhibitors				
drugs	Sildenafil	Vardenafil	Tadalafil	Avanafil
Contraindications	❖ Hypersensitivity to drug ❖ Patients with history of AMI / stroke / fatal arrhythmias <6 month ❖ Nitrates total contraindication			
Precautions	❖ With a blockers [except tamsulosin] àorthostatic 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.			

Oral Drugs to Treat ED

Testosterone	❖ Given to those with hypogonadism or hyperprolactinemia. ❖ Given for promotion of desire.
Apomorphine	❖ A dopamine agonist on D_2 receptors. (increase dopamine → increase arousal) ❖ Activates arousal centrally; Erectogenic + Little promotion of desire. ❖ Given sublingual / Acts quickly. ❖ Not FDA approved / Weaker than PDE_5 . ❖ Given in mild-moderate cases / psychogenic / PDE_5Is contraindication. ❖ ADRs: nausea, headache, and dizziness but safe with nitrate.
Oral Phentolamine	❖ $a_1$blocker, debatable efficacy.
Yohimbine عشبة	❖ Central and peripheral pre-synaptic alpha 2-adrenergic blocking agent → Aphrodetic + Erectogenic but low efficacy and many CV side effects.
Trazodone	❖ Antidepressant, a 5HT reuptake inhibitor → priapism.
Korean Ginseng	❖ Questionable / may be a NO donner.

Topical Drugs to Treat ED

cream

Combination	❖ 20% Papaverine; ↑ cAMP + cGMP ❖ 2% Minoxidil; NO donner + K channel opener ❖ 2% Nitroglycerine ❖ + a drug absorption enhancers
Disadvantages	❖ Low efficacy / No FDA approval ❖ Female Partner can develop → hypotension, headache→ vaginal absorption

Transurethral Drugs to Treat ED

Alprostadil	
M.O.A	❖ PG E1 → ↑ cAMP
P.K	❖ 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 ❖ Vasovagal reflex / Hypotension ❖ Priapism or Fibrosis → rare

There are PGE1 receptors on VSMCs of penis → drug binds to receptor → convert ATP into cAMP → decrease intracellular ca+2 → vasodilation.

Remember : PDE5 → cGMP

PGE1 → cAMP

Intravenous Inj. Drugs to Treat ED

Alprostadil	❖ 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
Papaverine	❖ It is a direct-acting smooth muscle relaxant
Phentolamine	❖ $a_1$blocker

3 combined in severe cases

Treatment of Priapism

	❖ A medical emergency ❖ Aspirate blood to decrease intracavernous pressure ❖ Intracavernous **injection** of Phenylephrine ○ A_1agonist ○ detumescence

summary

Drugs adversely causing ED	
Centrally Acting Drugs	Antidepressant drugs, SSRI (Treat premature ejaculation.), Anti-psychotic drugs and Anti-epileptic drugs (phenytoin).
antihypertensives	• Centrally acting antihypertensives: Methyldopa, Reserpine, Clonidine • Other antihypertensives: β2 blockers and Thiazide diuretics
Antiandrogens leads to ↓ desire	• Finasteride: α reductase inhibitor (cause irreversible erectile dysfunction) • Cyproterone acetate • Cimetidine / Ketoconazole / Spironolactone: leads to hyperprolactinemia & gynecomastia .
Habituating Agents	E.g. Cigarette smoking and alcohol intake.

Drugs used in treatment of ED

Selective PDE5 Inhibitor.

Sildenafil, Vardenafil, Tadalafil, Avanafil

• Inhibit PDE5 which prevent breakdown of cGMP.
• They don't affect libido (don't produce NO)
• It target multiple tissues in the body
• Used as treatment in Erectile dysfunction, Pulmonary hypertension and BPH

ADRs:
• Headache, flushing, nasal irritation
• Abnormal vision, more with Sildenafil
• Myalgia, back pain and decreased sperm function with Tadalafil
• QT prolongation, prolonged with vardenafil
• IHD and AMI, Bleeding; epistaxis, Priapism.
• Ischemic Optic Neuropathy, hearing loss (both rare)

C.I:
• Patient using nitrate
• Hypersensitivity to drug.
• Patients with history of AMI, stroke or fatal arrhythmias

Precautions:
With alpha blocker, hepato/renal insufficiency. Retinitis pigmentosa. With Quinidine, procainamide, amiodarone Dose adjustment when using drugs that have interaction on hepatic liver microsomal enzymes

Oral drugs

Testosterone: given to those with hypogonadism or hyperprolactinemia for promotio of desire.

Apomorphine: A dopamine agonist on D2 receptors, safe with nitrate. Given if PDE5 is contraindicated.

ADRs: Nausea, headache, and dizziness Oral phentolamine: α1 blocker / debatable efficacy.

- Trans-urethraloral (Alprostadil):
Prostaglandin E1 analogue

ADRs: Variable penile pain Urethral bleeding, infection. Vasovagal reflex, Hypotension and priapism.

- Intra-cavernosal (Alprostadil, Papaverine, Phentolamine)
- Topical (20% Papaverine, 2% Minoxidil, 2% Nitroglycerine)

Female Partner can develop: Hypotension, headache because of vaginal absorption.

Treatment of Priapism:
• Aspirate blood to decrease intracavernous pressure
• Intracavernous injection of Phenylephrine (α1 agonist)

Quiz

Q1: Which of the following drugs causes irreversible erectile dysfunction ?
A. Phenytoin
B. Amitriptyline
C. Clonidine
D. Finasteride

Q2: what is the mechanism of action of sildenafil in the management of erectile dysfunction ?
A. agonist on D2 receptors.
B. Inhibit the reuptake of 5HT.
C. Inhibit alpha-1 receptors.
D. Inhibit phosphodiesterase-5

Q3: which of the following is the most selective phosphodiesterase-5 inhibitor?
A.sildenafil
B. Tadalafil
C. Vardenafil
D. Avanafil

Q4: a patient came to the emergency room complaining of persistent erection for 5 hours. Which of the following drugs is the appropriate management of this patient?
A. Phenylephrine
B. phentolamine
C. Alprostadil
D. papaverine

Q5: Which of the following drugs is an absolute contraindication for the use of Sildenafil?
A. Aspirin
B. warfarin
C. Nitroglycerine
D. phenytoin

Q6: which of the following drugs is a synthetic PGE1 analogue that acts by increasing cAMP?
A. Alprostadil
B. Trazodone
C. Phentolamine
D. Yohimbine

Answers:
1) D
2) D
3) B
4) A
5) C
6) A

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Thanks for those who worked on the lectures :

Khulood Alwehaibi
Rawan Altamimi
Ghada Alqarni
Munira Alhadlg
Noura Alothaim
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References:

✓ Doctors' slides and notes

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