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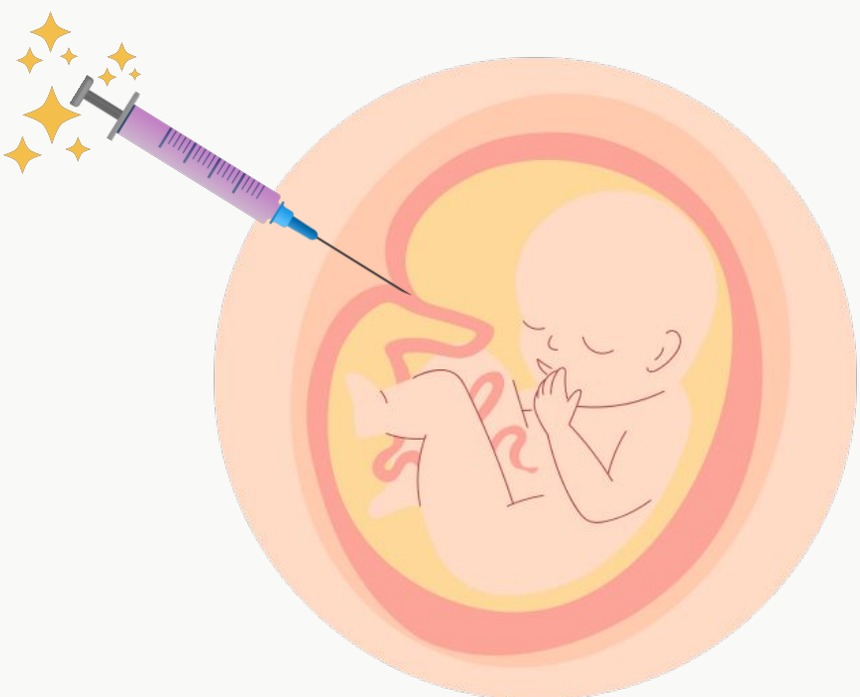
TEAM 443
PHARMACOLOGY

MED 443
King Saud University

Medications affecting erectile dysfunction

Dr. Alaa | Dr. Faris



- Main text
- Male slide
- Female slide
- Important
- Dr, notes
- Extra info

EDITING FILE

Objective

- 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

Introduction

Pathophysiology

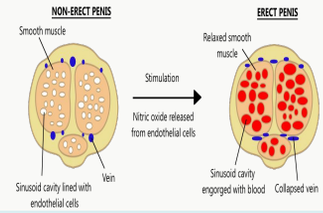
Penile erection is a neurovascular phenomenon (Nerves & Blood vessels)

Normal erection is composed of three processes:

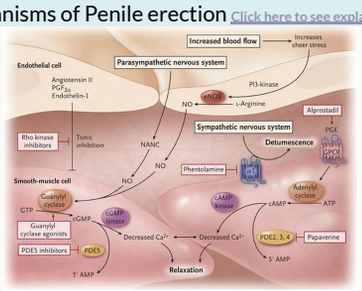
1-Increase in arterial flow into the penis initiated neurologically (2 types of nerves)

2-Relaxation of cavernosal smooth muscle.

3-Restriction of venous outflow from the penis.



Mechanisms of Penile erection Click here to see explanation:



Thus, impairment of neurovascular process or alteration in penile smooth muscle structure and function can result in *Erectile dysfunction*.

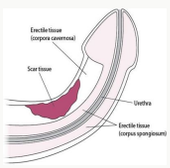
Erectile Dysfunction

Erectile dysfunction (impotence): Persistent or recurrent inability to attain, or to maintain until completion of the sexual activity, an adequate erection

Risk factors

- Increasing age
- Benign prostatic hyperplasia
- Diabetes mellitus
- Depression
- Dyslipidemia
- Lower urinary tract infection symptoms
- Obesity
- Cardiovascular disease & Hypertension

Erectile Dysfunction Etiology

Vasculogenic (organic ED):	ED may be an early manifestation of generalized endothelial dysfunction and a predictor of cardiovascular disease. • **Pathophysiology:** Abnormalities of the (NO-cGMP) system (↓cGMP→no relaxation→no blood flow→no erection)→ Vasculogenic ED (organic ED) • **Diseases & Risk factors for vasculogenic ED:** ●Hypertension ●Atherosclerosis and dyslipidemia ●Diabetes mellitus ●Cigarette smoking
Hormonal	●**Primary Hypogonadism**→↓↓testosterone →↓↓ libido **Treatment:** testosterone replacement therapy ●**Hyperprolactinemia** →↑↑ Prolactin →↓↓ testosterone **Treatment:** dopamine agonists (to suppress prolactin release)
Psychogenic	**Performance anxiety and psychosocial factors** ↑Sympathetic → ↑ NE → corporal smooth muscle contraction →↓blood flow
Metabolic	Diabetes mellitus (type II), central obesity and dyslipidemia, HTN.
Neurogenic	**Caused by a deficit in nerve signaling to the corpora cavernosa.** for example: spinal cord injury, multiple sclerosis, Parkinson disease, lumbar disc disease, traumatic brain injury, pelvic surgery
End organ disease	**Peyronie disease** is penis problem caused by scar tissue called plaque that forms inside the penis. It can result in a bent, rather than straight, erect penis. caused by Pelvic or genital radiotherapy treatment. 
Iatrogenic	Drug-Induced Erectile dysfunction (next slide)

Drug-induced erectile dysfunction

1-Centrally acting drugs

A) Antidepressants

Drugs	TCAs	SSRIs
Intro	•DA> NE promote arousal • 5HT action on 5HT2 →↓DA release →↓arousal	
M.O.A.	• **Centrally:** ↓ 5HT uptake → ↑ 5HT in synapse act on $5HT_2$ Centrally→ ↓ DA release → ↓ arousal peripherally. • **Peripherally(especially SSRIs): Antagonize NO actions** → ↓genital sensation →Delay Ejaculation→Treat Premature Ejaculation	
	Non-selectively ↓ 5HT uptake.	Selectively ↓ 5HT uptake.

B) Antipsychotic Drugs (Dopamine Antagonists)

Drugs	Risperidone	Haloperidol
M.O.A.	• Dopamine (DA) antagonist → ↓ arousal → ↓ erection.	
ADRs	• Hyperprolactinemia.(↓ testosterone)	

C) Anti-Epileptic Drugs

Drugs	Phenytoin
M.O.A.	• Have GABA effect → antagonize excitatory amino acid → ↑ sedation → ↓ arousal.

D) Centrally-Acting Antihypertensives

Drugs	Methyldopa	Reserpine	Clonidine
M.O.A.	• ↓ arousal.		• Centrally: ↓ arousal. • Peripherally: vasoconstriction.

2- Peripherally acting drugs

A) Other Antihypertensives

Drug	β2 Blockers	Thiazide diuretics
M.O.A.	• -ve/block vasodilating β_2 → shifting NE to α_1 receptor & potentiate α_1 effect → vasoconstriction.	• ↓ spinal reflex controlling erection + ↓ arousal.

B) Anti-Androgens (↓ Desire)

Drugs	Cyproterone acetate	Cimetidine (high doses), Ketoconazole, Spironolactone	Estrogen-containing medications

3-Habituating factors induced ED

Cigarette smoking	Alcohol
vasoconstriction + penile venous leakage	• **Small amounts:** ↑ desire + ↓ anxiety + vasodilatation. • **Big amounts:** ↑ sedation → ↓ desire. • **Chronic:** hypogonadism + polyneuropathy→ED

Treatment of erectile dysfunction:

Pharmacological treatment	Non-pharmacological interventions: Medical devices & Surgical interventions

Drugs treating erectile dysfunction

Centrally	Androgens	Desire	Oral
	Apomorphine	Arousal	
Peripherally	PDE_5 Inhibitors	Sildenafil, Vardenafil, Tadalafil, Avanafil	
	$PDE_{2,3,4}$ Inhibitors	Papaverine	Intracavernosal Injection
	α1 blocker	Phentolamine	
	Prostaglandin Analogues		Intracavernosal Injection + Transurethral

1- Centrally acting drugs

Testosterone Replacement Therapy

it's not an option if there's damage of nerve that innervate corpora cavernosa

Indication	Hypogonadism(<285ng/dl)
Benefits	• Correct secondary ED • Improve libido • Restore muscle strength and sexual drive
administration	It can be administered Orally, parenterally (effective and less hepatotoxic) or transdermally
ADRs	-Na retention →weight gain and exacerbate HT, CHF(chronic heart failure)& edema. -Gynecomastia -Serum lipoproteins changes. -Polycythemia - Exacerbate BPH and prostate cancer. -Hepatotoxicity (monitor liver enzymes).
#	Patients 40 years and older should be screened for benign hyperplasia and prostate cancer before initiating (it exacerbates BPH)

Drugs treating erectile dysfunction

2-peripherally acting drugs

Oral PDE_5 Inhibitors

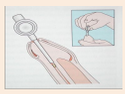
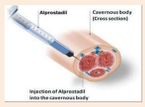
Drug	Sildenafil	Vardenafil	Tadalafil	Avanafil
M.O.A.	• Inhibit PDE_5 → prevent breakdown of cGMP → pertain vasodilation and smooth muscle relaxation → erection • Do not affect libido, so sexual stimulation is essential to a successful erection.			
PK	• Administration: oral. • All the three drugs are metabolized by CYP3A4 • Dose should be **reduced** in patients receiving CYP450-3A4 inhibitors (**cimetidine**, **erythromycin**, clarithromycin, ketoconazole, ritonavir, squinavir) ↑ ADRs with inhibitors			
Efficacy	all types have similar efficacy			
Uses	• **Erectile dysfunction [1st line therapy]** • Pulmonary hypertension. • Benign Prostate Hyperplasia (BPH). • Premature ejaculation. • Overall, 60–65% of men who have ED, including those with hypertension, diabetes, spinal cord injury and other comorbid medical conditions, can successfully response to the PDE5Is			
ADRs	Common: • Headache • Flushing • Nasal congestion • Visual disturbance • Dyspepsia • Back and muscle pain • Priapism (prolonged erection) **unique for Tadalafil:** back pain & muscle pain due to its inhibition to PDE-11 **Rare but serious:** • Sudden loss of vision • Retinitis pigmentosa			
Contra-indications	• Recent cardiovascular event (History of AMI - stroke - fatal arrhythmias in less than 6 months.) • Nitrates (nitroglycerin) Because of ↑ risk of hypotension if combined • Hypotension • Anatomical deformity (Angulation, cavernosal fibrosis,Peyronie's) • Predisposition to prolonged erection (Sickle cell disease , Multiple myeloma ,Leukaemia)			

Drugs treating erectile dysfunction

2-peripherally acting drugs

Prostaglandin Analogues

Alprostadil

M.O.A.	• Prostaglandin E_1 synthetic analogue (vasodilator) • Stimulates AC Adenylyl cyclase to increase production of cAMP and enhance blood flow to corpora cavernosa (cAMP is the 2nd messenger)	
Indications	For patients who did not respond to PDE5Is	
Side effects	• Cavernosa plaques or fibrosis (2-12)% • Penile pain (10-44)% • Priapism (1-15)%, Use with caution in patients at risk of priapism (sickle cell anemia, lymphoproliferative disorders)	
Administr -ation	Intraurethral & intracavernosal injection.	
P.K	**Intraurethral (Muse suppository)** 	**Intracavernosal Injection** 
	Administration: 5-10 mins before intercourse	
	Before administration: Patient should empty his bladder completely.	• Onset: 5-15 mins • Duration: less than one hour
Uses	-	• Effective in 70-90% • Can be combined with vacuum devices or vasoactive agents (papaverine,phentolamine)
ADRs	• pain (24-32)% • Female partner may experience vaginal burning, itching or pain	• Should NOT be combined with PDE5Is →high risk of priapism • priapism treatment→ phenylephrine • Disadvantages: May develop fear of self injury (Needs training)

Other pharmacological treatment vasoactive agents

Drugs	**Papaverine**	**Phentolamine**
MOA	PGE1 synthetic analogue→ Inc cAMP + cGMP PDE2,3,4 Inhibitor	α1 blocker
Administrati on	Intracavernosal Injection	
Uses	Used alone OR combined together OR with Alprostadil	

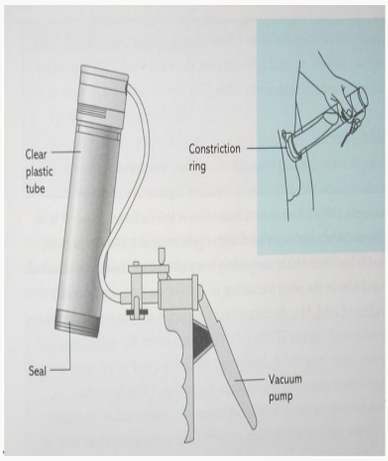
Non-Pharmacological treatment

Lifestyle modifications:

- Smoking cessation
- Reduce fat and cholesterol in diet
- Increase exercise
- Weight loss
- Improve compliance with diabetes and cardiovascular medications
- Reduce stress

Vacuum Constriction Device:

- Penis placed in plastic tube
- Air evacuated from the tube
- Blood trapped in penis with constricting ring
- Duration: 30 minutes
- Results: 80%-90%
- Contraindications: Bleeding disorders



Surgical interventions:

Penile Implants (Reconstructive prosthetic surgery):

- Semi-rigid rod (permanent semi erection)
- Inflatable (hydraulic) prosthesis

Indications:

- Severe penis tissue degeneration
- not respond to pharmacological treatment.

Side effects:

- infection of the prosthesis
- mechanical failure of the device.

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