PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

α-Adrenergic Antagonists

Objectives:

- Outline the mechanisms of action of adrenergic neuron blockers.
- Classify α-receptor blockers into selective & non -selective.
- Know the pharmacokinetic aspects & pharmacodynamic effects of a adrenergic blockers.
- Identify the specific uses of non-selective & selective α-adrenergic blockers.

Important

In male and female slides

Only in male slides

Only in female slides

Extra information

helpful video

Editing file

If you memorize this very well, you will be able to guess the pharmacological actions just by knowing the receptor of the drug.

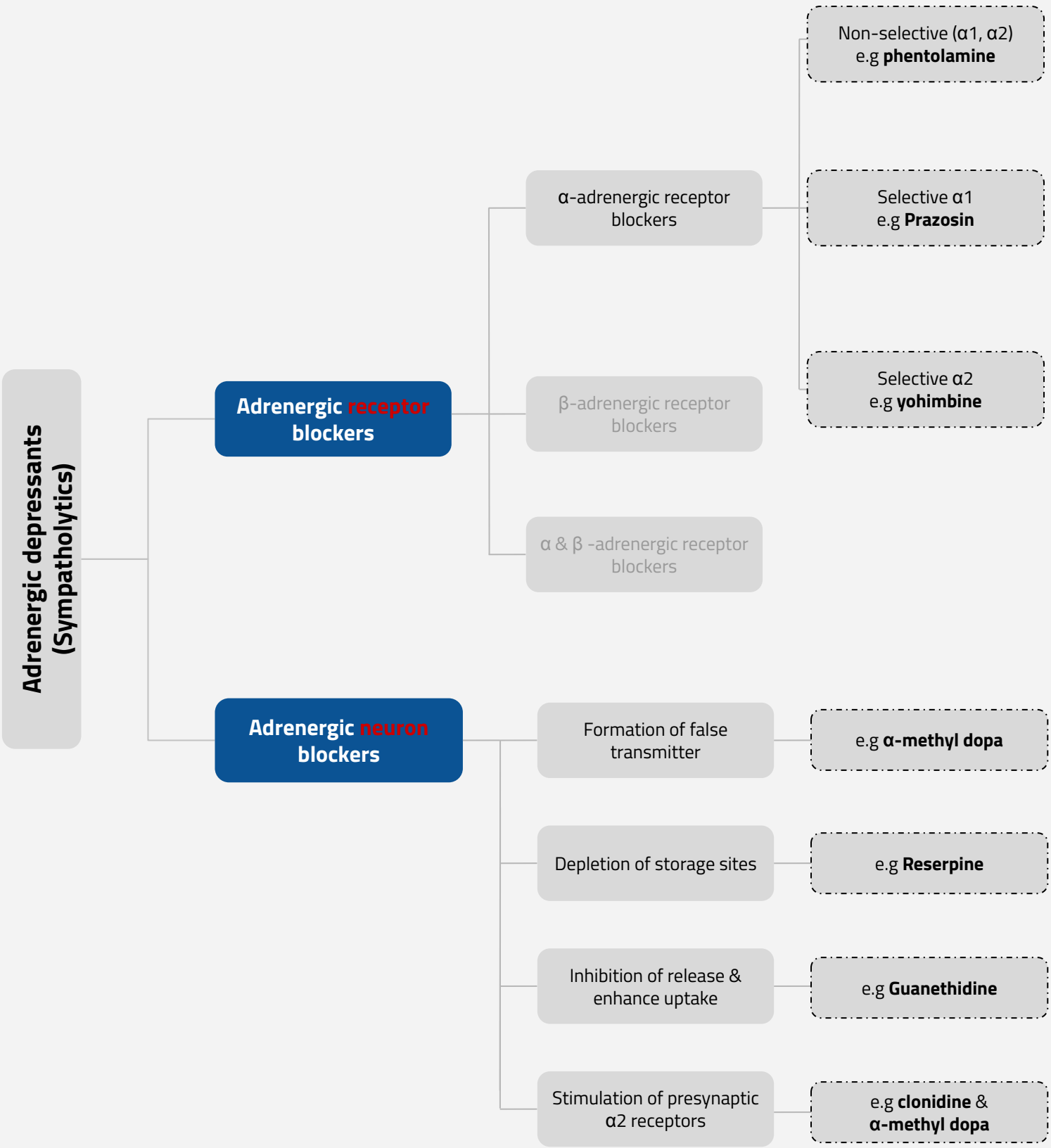
Post-synaptic
(located in the tissue)

α1	β2	β1	β3
Excitatory function (they cause **contraction**) except in GIT (**inhibition**)	**Inhibitory in function** (cause relaxation) نفس مكان α1 لكن عكسها بالوظيفة	**Excitatory in function**	In adipose tissue
Present mainly in **smooth muscles**		Present mainly in heart, **juxtaglomerular cells** of the kidney (discussed later with renin)	↑ lipolysis ↑ free fatty acids
Contraction of uterus (helps with delivery) * راح أجهض طفلي الأول α1	Relaxation of the uterus (Delay premature labor) (The 2nd baby is coming.)*	(قلبي هو بيتك (الأول ↑ Heart rate: Chronotropic effect (Tachycardia) ↑ Force of contraction : inotropic effect (Contraction of ventricles & Increase cardiac output) ↑ Conduction velocity: dromotropic effect Pulse is conducted faster causing tachycardia ↑ Blood pressure ↑ Renin release Enzyme released by the juxtaglomerular cells of the kidneys in response to low blood pressure, causing the transformation of angiotensinogen to angiotensin I which in turn stimulates release of aldosterone **(Which Causes vasoconstriction & increases BP).** This is useful during hemorrhaging to conserve blood	
Vasoconstriction of skin & peripheral blood vessels →increased peripheral resistance (resistance to blood flow due to constriction of blood vessels)→ hypertension.	هذا بيتك الثاني ارتاح = relaxations Relaxation of skeletal & coronary blood vessels (vasodilatation)		
Relaxation Of GIT **muscles** (constipation) & Urinary bladder **muscles**. **Contraction** Of GIT **sphincter** & urinary bladder **sphincter** (urinary retention)			
Contraction of radial muscle of eye causes active *mydriasis* (dilation of pupil, cholinergic agents have no effect on this muscle)	-Relaxation of bronchial smooth muscles (bronchodilation). -Tremor of skeletal muscles		
BOTH Increase blood glucose level (hyperglycemia) either by:			
↑ glycogenolysis So hyperglycemia	↑ glucagon release from pancreas ↑ liver & muscle glycogenolysis		

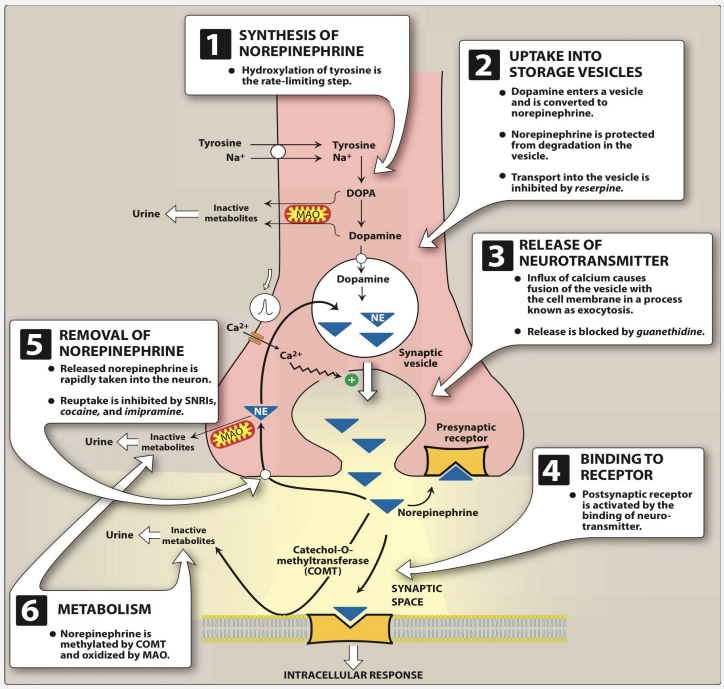
Pre-synaptic
(Regulation of Noradrenaline release)

α2	β2
Inhibition of norepinephrine release (Neg**at**ive feedback mechanism) This feedback decreases NE when it's elevated **a2 =(at)wo**	Increase of norepinephrine release (**P**osi**t**ive Feedback mechanism) This feedback increases NE when its levels are low **b2=(PT))wo**

Overview


Adrenergic depressants (Sympatholytics)
Adrenergic receptor blockers
α-adrenergic receptor blockers
Non-selective (α1, α2) e.g phentolamine
Selective α1 e.g Prazosin
Selective α2 e.g yohimbine
β-adrenergic receptor blockers
α & β -adrenergic receptor blockers
Adrenergic neuron blockers
Formation of false transmitter
e.g α-methyl dopa
Depletion of storage sites
e.g Reserpine
Inhibition of release & enhance uptake
e.g Guanethidine
Stimulation of presynaptic α2 receptors
e.g clonidine & α-methyl dopa

Adrenergic neuron blocker drugs



Overview of what goes on inside nerve terminals:

Tyrosine turns into Dopa ⟶ Dopa turns into Dopamine ⟶ Dopamine is stored in vesicles ⟶ inside vesicles dopamine turns into norepinephrine ⟶ release of norepinephrine to the synaptic space is stimulated by an action potential

- Team 439 RESPA block

Adrenergic neuron blockers act by inhibition of

1. **The release of NE**
2. **The storage of NE**
3. **The synthesis of NE**

Reserpine
Interferes with NE

Clonidine
α-methyldopa

False neurotransmitter formation (Synthesis)

Depletion "reduction and decreasing" **it of stores (Storage)**

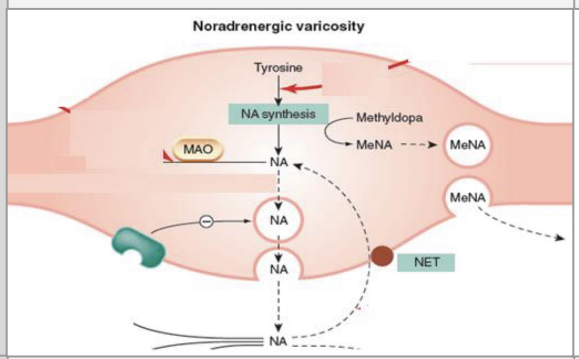
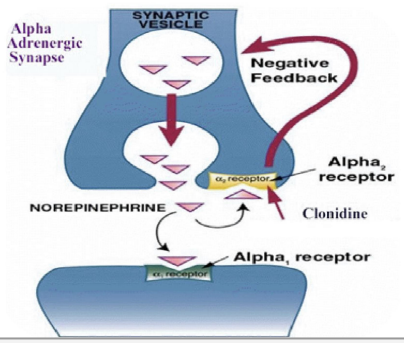
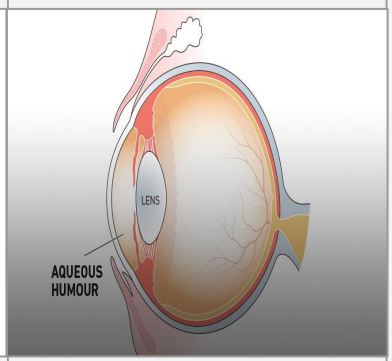
Inhibition of release (Release)

Stimulation of presynaptic α2-receptors
negative feedback

α-methyldopa

Guanethidine

Adrenergic neuron blocker drugs

Drug	 **α-methyl dopa** ميثاء دوبا لأنها حامل	**Clonidine**	**Apraclonidine**
M.O.A	-Forms false transmitter that is released instead of **NE**. "α-methylnoradrenaline replaces NE in vesicles" -Centrally acting α2 adrenergic agonist that inhibits **NE** release. Extra info: Instead of forming NE from dopamine, α-methyl dopa will form a false neurotransmitter known as α-methylnoradrenaline which replaces NE in vesicles. This false neurotransmitter will stimulate α2 receptors that will decrease the release of NE **(negative feedback).**	-Central α2 receptor agonist acts on brainstem to inhibit **NE** release. **(negative feedback)** -Suppresses sympathetic outflow activity from the brain. "Decrease of sympathetic outflow to the heart and blood vessels cause decrease in blood pressure"	Acts by decreasing aqueous humor formation. "Aqueous humor maintain intraocular pressure"
			
Uses	-Drug of choice in treatment of **hypertension** in pregnancy (gestational hypertension pre-eclampsia). "disorder of pregnancy characterized by proteinuria and rise in BP" As it has no teratogenic effect "لا يسبب تشوه أجنة"	-**Little** use as an **antihypertensive** drug as sudden discontinuation can cause rebound hypertension due to a rebound in sympathetic outflow.	Open angle glaucoma as eye drops (topical)

Adrenergic receptors blockers
Classification of α-receptor antagonists

Non-Selective α antagonist

e.g.
- Phenoxybenzamine
- Phentolamine

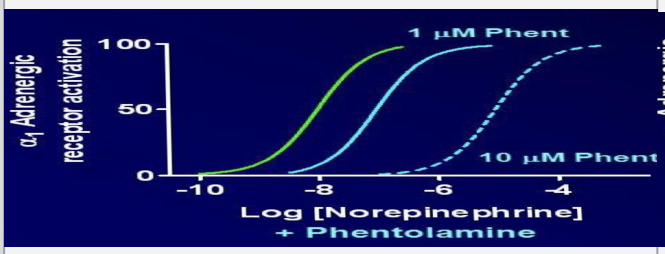
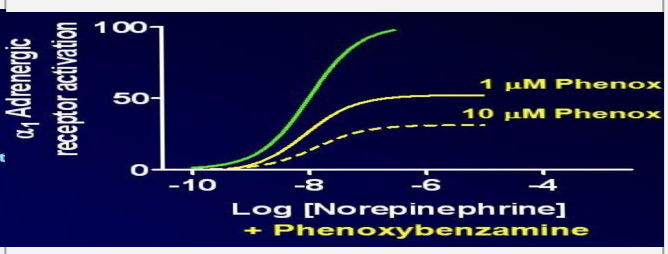
Selective α1 antagonists

e.g.
- Prazosin
- Doxazosin
- Tamsulosin (α1A)
  "more selective α1 antagonist"

Selective α2 adrenoceptor

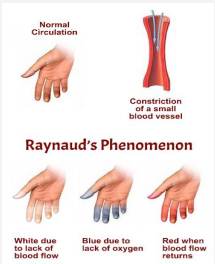
e.g.
- Yohimbine

Non-selective α-receptor blockers

Drug	Phentolamine	Phenoxybenzamine
M.O.A	**Non-selective** antagonists of both α1 and α2 receptors.	
P.K	• **Reversible** block both α1 and α2 receptors.(shift to the right) "Non-covalent bond so less duration of action" • Short acting (4hrs)	• **Irreversible** blocking of α1 and α2 receptors.(No parallel shift) "By covalent bond" • Long acting (24hrs)
		
	Boy's slides	Boy's slides
Pharmacological actions	• Increase cardiac output (α2 block) • Decrease peripheral vascular resistance. • Postural (orthostatic) hypotension. "Due to baroreceptor reflex, pull of gravity and reduced BP contribute to low venous return which causes hypotension when standing" • Reflex tachycardia due to fall in B.P, mediated by **baroreceptor reflex** and due to block α2 in heart. "**Baroreceptors** are sensors in the aortic arch that sense blood pressure and relay this information to the brain. When baroreceptors sense sudden drop in BP, reflex tachycardia is stimulated."	
Indication	In **Pheochromocytoma** : Should be given before surgical removal to protect against hypertensive crisis. "pheochromocytoma is a tumor of the adrenal medulla that causes an excessive release of **Adrenaline** + NA (synthesized in the medulla), resulting in an **overstimulation of α1** receptors, resulting in hypertension" **Phentolamine**: • Dermal necrosis following extravasation of NA. • Reversal of local anesthesia. • Hypertensive crisis following abrupt withdrawal of clonidine or ingestion of tyramine in patients MAO inhibitors. Phenoxybenzamine: Raynaud disease & frostbite PHEochromocytoma symptoms: • Palpitations • Headache • Episodic sweating (diaphoresis)	
ADRs	• Postural hypotension. • Tachycardia • Headache • Nasal stuffiness or congestion • Vertigo & drowsiness " caused by the hypotension" • Male sexual dysfunction (Inhibits ejaculation) "caused by hypotension"	
Contradiction	Patients with decreased coronary perfusion, because both drugs can precipitate arrhythmias and angina.	

adrenoceptors = adrenergic receptors

Selective α1-receptor Antagonists

Drug	Prazosin	Doxazosin	Terazosin
M.O.A	Selective α1- adrenoceptor antagonist		
P.K.	Short half life	Long half life	
Pharmacological effects	- Vasodilation due to relaxation of arterial and venous smooth muscles. - Fall in arterial pressure. - Less reflex tachycardia than with non-selective α-blockers. - First dose may produce an orthostatic (standing position) hypotensive response that can result in syncope and fainting. 		
Uses	- Treatment of **essential hypertension** (prior to any disease) with prostate enlargement.(Hypertrophy) - Urinary obstruction associated with benign prostatic hyperplasia (BPH). - Raynaud's disease (rare disorder of the blood vessels, vasospasm) causes some areas of your body such as your fingers and toes to feel numb and cold **in response** to cold temperatures or stress. When this happens, blood can't get to the surface of the skin and the affected areas turn white and blue. 		

Remember, α receptors stimulate the following:
- Vasoconstriction of skin and peripheral blood vessels.
- Relaxation of muscles in urinary bladder and contraction of sphincter (urinary retention).

And therefore the antagonist drugs will stimulate the opposite effects.
1) Vasodilation
2) Constriction of muscles of bladder and relaxation of urinary sphincter

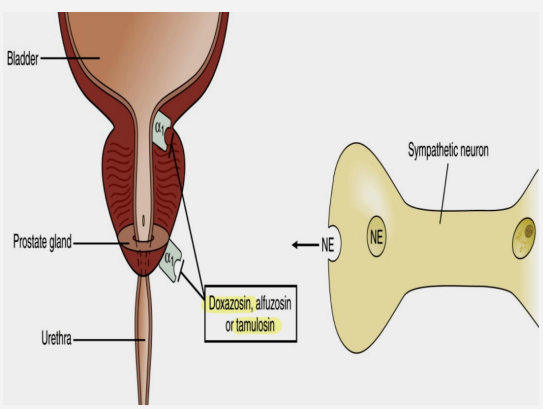
Selective α1A & α2 receptor Antagonists

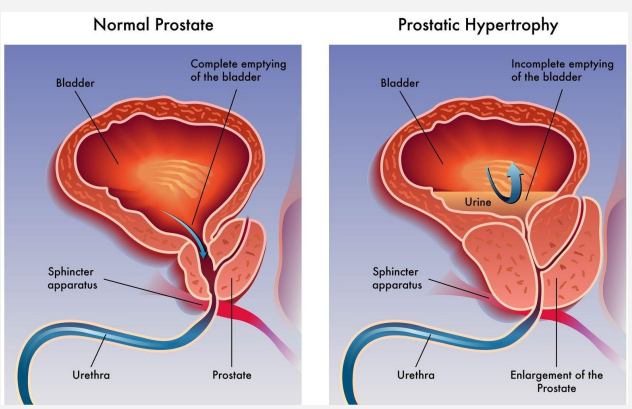
Drug	Tamsulosin تميس ولوزين (Uroselective) Selective α1A	Yohimbine (Yohim)(bine)(α2) يو هم بين اثنين Selective α2
Found in	Receptor α1A is present in prostate and neck of bladder.	———————
M.O.A	- Relaxation of smooth muscles of bladder neck & prostate → improve urine flow. - Has ***minimal*** effect on blood pressure. Why? It's more selective on prostate rather than blood vessels in the rest of the body.	Increase nitric oxide "NO" released in the corpus cavernosum (male anatomy) thus producing vasodilator action and contributing to the erectile process.
Uses	Treatment of benign prostatic hypertrophy (BPH). Symptoms of this could include inability to urinate and weak stream.	Used as aphrodisiac in the treatment of erectile dysfunction. aphrodisiac= stimulates sexual desire.
ADRs	As before with non selective but to a **lesser degree**.	———————

Which is best to treat benign prostatic hypertrophy?

a) Terazosin
b) Phenoxybenzamine
c) Tamsulosin

Tamsulosin is most selective therefore it's our first choice in the case of BPH. Why? It works on a specialized type of α1 receptor (α1A) found in the neck of urinary bladder making it the better choice.





MCQ

1-:Which one of the following Sympatholytic drugs can be used as eye drop for patient who has open angle glaucoma and he did not respond to timolol ?			
A- Reserpine	B- Terazosin	C- Apraclonidine	D- Guanethidine

2-Drug of choice in gestational hypertension?			
A-Clonidine	B- Apraclonidine	C- α-methyl dopa	D- Reserpine

3-A 32 year old man presented to the ER with hypertension and was prescribed treatment. He later returned to the ER complaining of sexual dysfunction. Which of the following was prescribed:			
A- Yohimbine	B- Clonidine	C- α-methyl dopa	D- Phenoxybenzamine

4- Which of the following is selective α antagonist and have short half life ?			
A- Prazosin	B- Terazosin	C- Doxazosin	D- Phenoxybenzamine

5- which of the following is an indication for doxazosin usage?			
A- essential hypertension with prostate enlargement	B- erectile dysfunction	C-pheochromocytoma	D- anti-hypotensive treatment

6- which of the following is an indication for phentolamine?			
A- essential hypertension with prostate enlargement	B- erectile dysfunction	C-pheochromocytoma	D- anti-hypotensive treatment

Answers

1	2	3	4	5	6
C	C	D	A	A	C

SAQ

Q1) A pregnant woman was diagnosed with Gestational Hypertension. What is the drug of choice and its mechanism of action?

Q2) A former alcoholic presented with hypertension caused by abrupt withdrawal of an alpha blocker drug. What is the drug that possibly caused the hypertension and its mechanism of action?

Q3) List three adverse effects of phentolamine.

Q4) What is the mechanism of action for Tamsulosin?

Q5) What are the pharmacological effects of prazosin?

Q6) what are the indications for terazosin?

Answers

A1) α-methyl dopa, It is a centrally acting α2 adrenergic agonist that inhibits the release of NE by forming false transmitters.

A2) Clonidine, Acts as an α-2 receptor agonist to inhibit NE release and suppresses sympathetic outflow activity from the brain.

A3) postural hypotension, tachycardia, headache,

A4) Relaxation of smooth muscles of bladder neck & prostate → improve urine flow.

A5) check table in page 7

A6) essential hypertension with prostate enlargement, Urinary obstruction associated with(BPH), Raynaud's disease

GOOD LUCK!

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