Fate of NE & epinephrine — G3FR_10

A-Reuptake (80%)			B-Metabolism (15%)		C- Excretion in urine unchanged (5%)
Neuronal reuptake **uptake I** (65-70%)	***Vesicular reuptake*** **uptake III**	***Tissue reuptake*** **uptake II** (7-13%)	***MAO*** (mono-amine *oxidase*)	***COMT*** (catechol-ortho-methyl transferase)	
Active reuptake by membrane monoamine transporter (MAT)	Fallow uptake I to protects NE from MAO	NE is taken by the target tissue where it is inactivated by MAO or COMT	**site**		
			Mitochondria of nerve ending and tissues	**Cytoplasm** of extra neuronal tissues only.	
Inhibited by			***MAO-A*** / ***MAO-B***		
cocaine tricyclic antidepressants guandril, guanethidine chlorpromazine phenoxybenzamine	reserpine	Corticosteroids phenoxybenzamine	In peripheral nerves / In CNS		
			metabolizes		
			NE, serotonin dopamine, histamine / dopamine		
			The end result of metabolism is Vanillymandelic Acid (VMA)		

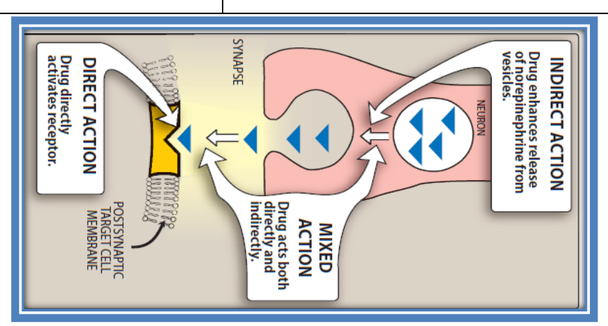
Adrenergic receptor

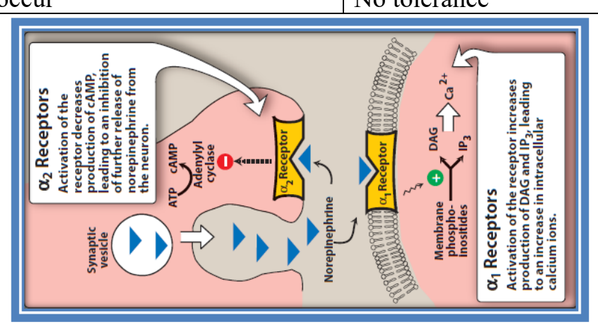
α-receptors				*β-receptors*					Dopaminergic
α_1	α_2			β_1	β_2			β_3	D_1
Mainly post-synaptic smooth muscle	Pre-synaptic	post-synaptic	central	Post-synaptic Mainly cardiac	Pre-synaptic	post-synaptic	central	post-synaptic	post-synaptic
-V.C of Peripheral blood vessels ➡⬆peripheral resistance ➡ hypertension -GIT& UB ➡ contraction of sphincter -D.P.M ➡ Active mydriasis	-⬇NE Release -⬇Ach Release	-⬇ renin release -⬇Insulin release	⬇sympathetic outflow.	-⬆ all cardiac properties -⬆renin release	⬆NE Release	- **V.D** of skeletal muscle & coronary Bl. vessels - relax wall of GIT, UB & uterus -bronchodilatation -facilitate NM transmission ➡ tremors -hypokalemia -⬆ glycogenolysis -⬆ Insulin release	⬆sympathetic outflow	⬆lipolysis	- located on renal vascular smooth muscle are supplied with sympathetic dopaminergic fiber ➡ VD & ⬆RBF.
Gq ➡⬆ intracellular Ca^{++}.	Gi ➡⬇cAMP			Gs ➡⬆cAMP					Gs-coupled receptors.

Sympathomimetics

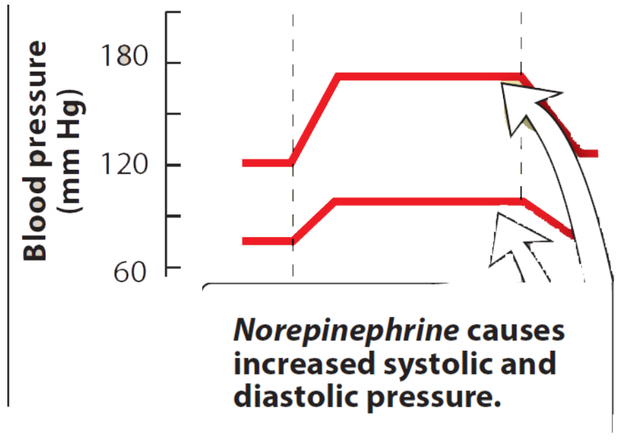
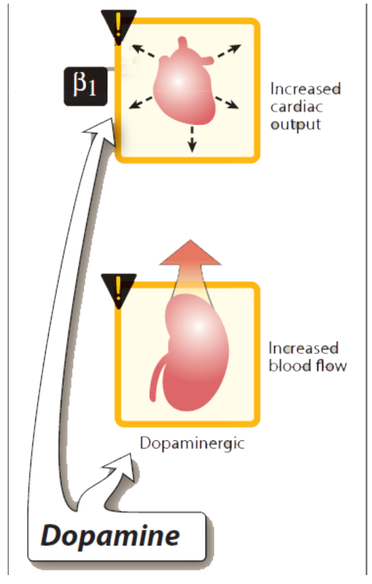
Classification

A- According to mechanism of action			B- According to Chemistry	
1- Direct	**2- Indirect**	**3- Dual (mixed)**	**1-Non-catecholamines**	**2-Catecholamines**
Catecholamines (Sympathectomy ➡⬆ effect. “Supersensitivity”)	- amphetamine & tyramine (by ++ release of (NE) - cocaine & TCA (by -- reuptake). (Sympathectomy ➡⬇ effect) -Tolerance & tachyphylaxis are usually occurs	ephedrine	Not metabolized by MAO&COMT	Rapid metabolism by MAO&COMT
			Slow onset	Rapid onset
			Longer duration	Short duration
			Well absorbed orally	Not absorbed orally
			Pass BBB	Not pass BBB
			Acidification of urine ➡ excretion.	PH changes of urine ➡ Not affect excretion
			Weaker	Potent
			Tolerance can occur	No tolerance





Endogenous catecholamine G3FR_11

	Epinephrine "Adrenaline"	Norepinephrine "Noradrenaline"	Dopamine
P/K	-Unstable in alkaline solution., it is oxidized by light to adrenochrome (hallucinogenic),so kept in dark bottles with ascorbic acid "reducing agent" -preferred route **I.M** may be given S.C, or by endotracheal tube or inhalation	-Not orally due to its intense V.C So, given only by **I.V infusion**	- **I.V infusion** very short $t_{1/2}$ "2 min" -M: by MAO & COMT➡ Homovalinic a.➡ in urine
P/D	Broad spectrum ($\alpha_1,\alpha_2,\beta_1,\beta_2,\beta_3$)	Directly on ($\alpha_1>\alpha_2>\beta_1$)	Directly on (D_1,β_1,α_1)
systemic actions			
Heart	⬆ **all cardiac properties** (Net result is ⬆COP) -⬆ contractility (COP) ➡+ve inotropic. -⬆ HR (tachycardia) ➡ +ve chronotropic. -⬆A-V conduction ➡ +ve dromotropic. -⬆automaticity & excitability ➡ ⬆risk of arrhythmia. -⬆oxygen demand of myocardium ➡ angina.	- **Reflex bradycardia** due to V.C of blood vessels ➡⬆blood pressure ➡(+) baroceptor ➡ vagal stimulation. "blocked by atropine"	**a) slow rate of infusion: (2-5 µg/kg/min) ➡ (+) D_1** -V.D of cerebral, coronary, renal & splanchnic -V. D of renal vasculature ➡⬆urine output **b) moderate rate of infusion: (5-10 µg/kg/min)➡ (+)β_1** - (+ve) inotropic - (+ve) chronotropic. This leads to ➡⬆COP **c) high rate of infusion: (>10 µg/kg/min) ➡ (+)α_1** -V.C ➡ ⬆blood pressure
Blood vessels	- V.D of skeletal muscle, and coronary blood vessels. (β_2) - V.C of skin, mucous membrane & splanchnic blood vessels. (α_1) - In kidney, ⬆rennin (β_1) ➡⬆ angiotensin ➡V.C.	Severe V.C (α_1) of skin, mucous membrane blood vessels ➡⬆PR	
Blood pressure	-⬆ systolic blood pressure (by⬆ COP) - diastolic bl.pr slight ⬆or⬇ depend on type of receptor stimulated -⬇diastolic Bl.Pr. in **therapeutic dose** & ⬆diastolic Bl.Pr. In **L.D** -hypertensive effect **reversed by** adding α blockers ➡ Hypotension	-⬆ systolic blood pressure -⬆diastolic blood pressure	-Dopamine (+) presynaptic D_2 receptor ➡⬇ NE release
Respiratory system	Bronchodilatation (β_2) & Decongestion of bronchial mucosa (α_1) Inhibits release of allergic mediators e.g. histamine from mast cells		
GIT & UB	- Relax wall (β_2)& Contract sphincters (α_1)		
Uterus	relaxation of the pregnant uterus (β2).		
Sweat gland	⬆ secretion from apocrine glands of palm "non-thermoregulatory"		
Skeletal muscles	facilitates NM transmission & V.D. of BL.V (anti-fatigue).		
Metabolic	a.⬆ glycogenolysis β_2 in liver Hyperglycemia b.⬆lipolysis β_3 ⬆fatty acids in blood. c.⬇K+: hypokalemia (due to ⬆ uptake by skeletal muscle)		
blood	Hypercoagulability of the blood (due to ⬆ factor V)		
Anti-allergic	Physiological antidote to histamine		
eye	decongestion, ⬇IOP & active mydriasis		
local actions			
eye	-No effect on pupil size as it is destroyed by alkalinity of the tears -Mydriasis occurs only with supersensitivity ➡ "STAD" 1- Sympathectomy of the eye. 2- Thyrotoxicosis 3- Acute Hemorrhagic pancreatitis 3- Diabetic ketoacidosis		
skin & mucous membranes Bl. v	V.C. of (skin & mucous membranes) ➡ decongestion & hemostasis. So, it delays absorption of local anesthetics.		
bronchi	Inhalation ➡ bronchodilatation (β2) so, used in bronchial asthma		
Therapeutic uses	**-A**naphylactic shock,allergy (I.M) **- B**ronchial asthma (inhalation) **-C**ardiac arrest (I.V. or intracardiac) **- D**elay absorption of local anesthesia **-E**pistaxis (local nasal pack) **- O**pen angle glaucoma (dipivefrin = prodrug)	**Severe hypotension:**-after sympathectomy. -during spinal anesthesia "spinal shock" -overdose of ganglion blockers.	**Shock:** - cardiogenic Shock - hypovolemic Shock
Side effect α_1	Hypertension ➡ cerebral hemorrhage Gangrene ➡ if injected around finger or toe (end arteries).	-If extravasation ➡ necrosis & gangrene ➡ (ttt: local phentolamine) **-Hypertension**	Hypertension
β_1	Tachycardia, palpitation, arrhythmia & angina	**Bradycardia "reflex"**	arrhythmia
β_2	Skeletal muscle tremors		
CNS	Anxiety, headache & restlessness		Nausea +"See CNS"
Contraindications	1- Hypertension 2-Peripheral vascular disease. 3- Arrhythmia. 4-Thyrotoxicosis ➡ supersensitivity 5- Coronary heart disease (angina). 5- Around finger & toe.	***Precautions***	
Drug interactions	a.With halothane, cyclopropane, thyroxin & digoxin➡ Arrhythmia "supersensitivity b. With cocaine (cocaine ➡# uptake 1) & MAO inhibitors ➡ Severe V.C. c. With non-selective β-blockers ➡ unmask α Severe V.C.	-Frequent measure of blood pressure - gradual stop of NA	I.V infusion with monitoring by Bl.Pr, HR & Urine output.

Synthetic sympathomimetics G3FR_12

Direct acting sympathomimetics

	Catecholamine		Non- Catecholamine	Catecholamine	Non- Catecholamine		
P/D	**Non-Selective beta**	**Selective Beta$_1$**		**Selective Beta$_2$**	**Selective Beta$_3$**	**Selective Alpha$_1$**	**Selective D$_1$**
	Isoprenaline (Isoproterenol)	**Dobutamine** (IVI)	**Prenalterol** (oral)	**Isoetarine**	**salbutamol, terbutaline** "short" **salmeterol, formoterol** "long" **Ritodrine**	**Mirabegron**	**Phenyl**ephrine **Metho**xamine	**Fenoldopam**
Heart	⬆ all cardiac properties (β_1)	-⬆contractility -⬆COP - Minimal⬆ HR - Not ⬆ oxygen demand				-Directly relax detrusor muscle ➡⬆bladder capacity -May increase B.P ➡ Not used in uncontrolled hypertension	**Used as** -mydriatic -decongestant -ttt of hypotension.	V.D of arterioles ➡ ⬇Total peripheral resistance ➡⬇B.P
Bl.v	**V.D** of sk.m, & coronary bl.v (β_2)			- **V.D** of skeletal muscle, bl.v (β_2)				
Blood pressure	-⬆ systolic blood pressure -⬇diastolic blood pressure						**Mido**drine	
Respiratory	Bronchodilatation (β_2).			Bronchodilatation (β_2)			ttt of orthostatic hypotension (due to impaired autonomic function)	
Uterus	Uterine relaxation (β_2).			uterine relaxation (β_2)				
Metabolic	-Hyperglycemia(β_2) -lipolysis β_3			Hyperglycemia (β_2)			**Xylo**metazoline, **Oxy**metazoline	
Therapeutic uses	Bronchial Asthma(Inhalation Heart block (I.V infusion)	- Cardiogenic Shock - Acute heart failure		- Bronchial asthma - preterm labor ➡ Ritodrine		Overactive bladder.	-Used as nasal decongestants -L.D. of oxymetazoline may cause hypotension (clonidine like effect)	**Used in**: hypertensive emergencies. (I.V.I)
S.E β_1	Tachycardia, palpitation, arrhythmia & angina			"in large dose (+)β_1				**S.E**: headache, flushing, tachycardia.
S.E β_2	Skeletal muscle tremors			-Skeletal muscle tremors -hypokalemia				

Mixed acting sympathomimetics

P/D	**Direct on (α_1,β_1,β_2,) & indirect** "mainly"
	Ephedrine
P/K	-Orally & parenteral -pass BBB -Poorly metabolized by MAO&COMT - excreted in urine - Acidification of urine byNH_4Cl⬆excretion
CNS	- (+) **C**ortex ➡ insomnia, anxiety, tremors, convulsion - (+) **C**TZ - (+) VMC - (+) R.C - (+) **S**pinal reflexes - **S**edation in ADHD in children
Heart	⬆ all cardiac properties
Bl.v	- V.C of skin, mucous membrane blood vessels. (α_1)
Blood pressure	-⬆ systolic blood pressure. -⬆diastolic blood pressure - α blockers can **abolish** its effect -***Tachyphylaxis*** (acute tolerance).
Respiratory	Bronchodilatation β_2 & V.C mucous membrane bl.v
GIT & UB	- Relax wall β_2 & Contract sphincters (α_1)
Sk.m	Stimulant more than adrenaline
Local actions	-Skin and mucus membrane ➡ irritant and V.C -Eye ➡ active madrasas -Nose ➡ decongestion of mucosa but, rebound congestion
Therapeutic uses	1-**A**DHD in children. 2-**A**naleptic in toxicity with CNS depressant 3-**B**efore spinal anesthesia" 4-**P**rophylaxis of BA 5.**M**yasthenia gravis (adjuvant). 6.**M**ydriatic eye drop 7-**N**asal decongestant. 8-**N**octurnal enuresis 9-Heart block.
Side effect CNS	- (+) **C**ortex ➡ insomnia, anxiety, tremors, convulsion - (+) **C**TZ ➡ vomiting
Side effect β_1	Tachycardia, palpitation, arrhythmia & angina
Side effect β_2	Skeletal muscle tremors
Side effect α	-Hypertension -Urine retention in old with prostatic enlargement
CI	

Indirect acting sympathomimetics

P/D	**Drugs that⬆ release of stored catecholamine**		**Reuptake inhibitors**
	Amphetamine	***Tyramine***	***Atomoxetine***
P/K	- excreted in urine - Acidification of urine byNH$_4$Cl⬆excretion	-Normal byproduct of tyrosine metabolism -Found in fermented food as cheese, beer, red wine, chocolate & smoked fish - metabolized by MAO in liver & intestine during first pass metabolism (So normally inactivated if taken orally). -it ⬆release of stored catecholamine ***Cheese reaction:*** Tyramine containing food with MAOIs ➡ ⬆NE Release ➡ V.C. ➡ sever hypertension	selective inhibitor for NE reuptake transporter .Used in **ADHD**.
CNS	- (+) Cortex, - (+) RAS ➡ euphoria ⬆mental activity, alertness & anti-fatigue - (+) R.C ➡ **A**naleptic - (+) spinal cord ➡ facilitates mono & polysynaptic transmission. - (+) satiety center ➡ Anorexigenic "⬇**A**ppetite"		***Duloxetine***
	The same as ephedrine in local & systemic actions (but less on bronchi).		-Inhibit serotonin & NE reuptake. -Used as: **anti-depressant**
			Cocaine
			-Local anesthetic drug -⬇NE reuptake "uptake1" - (-) MAO -It passes CNS ➡ amphetamine like action
Therapeutic uses	- ADHD "Attention Deficit Hyperkinetic Disorder" - Narcolepsy (hypersomnia). - Obesity	***Amphetamine Derivative***	
		1)**Phen**metrazine, **Diphen**metrazine Used in obesity	
		2)**Fen**fluramine, **Dexfen**fluramine ***Anorexigenic drugs*** (+) 5-HT receptors in CNS -in L.D. ➡ arrhythmia	
		3-Modafinil -(+) 5-HT & glutamate receptors - It used in **narcolepsy** & **ADHD**.	
		4- Methamphetamine - More CNS effects -less peripheral actions	
		5- Methylphenidate Used in **ADHD**	
Side effect CNS	- insomnia, anxiety, convulsion, coma, - hallucination, psychosis -**Tolerance**: occurs to anorexigenic & psychic effects. -**Addiction** with prolonged use		
Side effect β_1	Tachycardia, palpitation, arrhythmia & angina		
Side effect β_2			
Side effect α	Hypertension, Mydriasis		
CI	Like epinephrine + -insomnia -Prostatic hypertrophy -with MAOIs		

Sympathetic depressant "1st table" G3FR_13

		Adrenergic neurone blockers			Centrally acting Sympatholytic Drugs		
		Guanethidine	**Reserpine**	**α-methyl tyrosine (Metyrosine)**	**α-Methyl dope (Aldomet)**		**Clonidine Guanfacine Guanabenz**
Mechanism		-Guanethidine enter the peripheral adrenergic nerve via uptake I ➡ stored in granules to be released instead of NE ➡Depletes stores of NE	- Inhibits irreversibly vesicular reuptake Ill of monoamines - Expose NE, dopamine & 5-HT to MAO enzyme ➡ Depletes their stores centrally & peripherally.	1) Competitive inhibitor to tyrosine hydroxylase (rate limiting step in biosynthesis of catecholamines) 2) Depletes NE, dopamine in CNS, adrenal medulla & peripheral nerves	$\alpha\,Methyl\ dope \xrightarrow{dopa\ decarboxylase} \alpha\,methyl\ dopamine \xrightarrow{dopamine\ hydroxylase} \alpha\,methyl\ NE$ -***α-methyl NE*** stored in adrenergic vesicle and released instead of normal NE. SO, the effect is delayed for 5-8 hrs (even if given i.v.) - ***α-methyl NE*** is α_2 agonist ➡ a. Central α_2 agonist (main action) ➡⬇ sympathetic outflow. b. Presynaptic α_2 agonist ➡⬇release of NE. - Also ⬇ synthesis of dopamine & serotonin in CNS.		Selective α_2 agonist: 1) Central α_2 agonist ➡ ⬇sympathetic outflow 2) presynaptic α_2 agonist ➡ ⬇ release of NE. Both effect ➡ ⬇BP & ⬇HR
action	**CNS**	Not pass BBB, No CNS actions.	⬇(NE, 5-HT, dopamine) ➡ Sedation, depression, ⬇dopamine ➡ extrapyramidal symptoms "parkinsonism"				Sedation
	CVS	-bradycardia -orthostatic Hypotension	Hypotension, bradycardia				
	GIT	⬆motility (diarrhea) & ⬆secretion (peptic ulcer). Due to unopposed parasympathetic tone			⬇motility(constipation) & ⬇secretions (dry mouth) Due to (+) presynaptic α_2 in cholinergic nerves ➡⬇A.Ch. release		
Uses		1) hypertension Moderate to Severe degree 2) Hypertensive crisis	Hypertension (Mild to moderate degree)	inhibits synthesis of catecholamines in ***pheochromocytoma***: 1- Preoperative Preparation of surgical resection of the tumor (1 week before operation) 2- Patients with inoperable or metastatic pheochromocytoma. 3- Hypertensive crises of pheochromocytoma (in combination with α & β blockers)	1- **hypertension with pregnancy**. "DOC" 2- Renal hypertension as does not impair renal blood flow. 3- Moderate to severe hypertension (in combination with other drugs		1) Hypertensive urgency. 2) Migraine prophylaxis in postmenopausal flushing 3) Alleviating opiates (morphine) & Alcohol withdrawal symptoms.
Side effects		- orthostatic Hypotension - bradycardia - nasal stuffiness. - Salt & water retention,	- hypotension - bradycardia - nasal stuffiness. - Sedation, depression, ‘ - extrapyramidal symptoms (must be stop suddenly at first sign of depression)	- Sedation, depression, ‘ - extrapyramidal symptoms - Crystalluria due to deposition of drug crystals in kidney (avoided by ⬆ water intake)	**I- Type-A** - hypotension -bradycardia - Sedation, depression - extrapyramidal symptoms - nasal stuffiness - salt and water retention	**II- Type-B** Interaction with patient's immune system ➡ auto-antibodies ➡ - haemolytic anemia - aplastic anemia - leukopenia - thrombocytopenic purpura - hepatitis	-Sedation - Sudden withdrawal ➡ Rebound severe Hypertensive overshoot **ttt by**: - re-using of clonidine or α+β blockers
GIT S.E		Diarrhea & peptic ulcer.			dry mouth & constipation.		
DI		Anti-hypertensive effect of guanethidine antagonized by: 1- Cocaine & TCA 2- amphetamine, ephedrine					

Sympathetic depressant "2nd table" G3FR_14

α-Adrenoceptor Antagonists

Nonselective α-blocker

Irreversible

Phenoxybenzamine

Action

- # α_1 ➡ sever V.D ➡ ⬇ Peripheral resistance ➡ reflex tachycardia
- # Presynaptic α_2 ➡ ⬆ NE release ➡ tachycardia due to (+) β_1 in heart
- # muscarinic receptor
- # serotonin receptor
- # histamine receptor

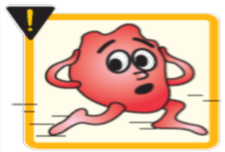
uses

pheochromocytoma:
1- Preoperative Preparation
2- Life-long management of the disease in inoperable patients
3- Hypertensive emergency of pheochromocytoma

Side effect

1) Postural hypotension ➡ reflex tachycardia & arrhythmia.
2) Nasal stuffiness.
3) Failure of ejaculation (inhibits α_1 in vas deferens & ejaculatory duct

Orthostatic hypotension


Tachycardia


Sexual dysfunction

Contraindication

Competitive

Phentolamine

uses

1) Control hypertensive crises in:
- Pheochromocytoma.
- sudden stop of clonidine.
- cheese reaction

2) Inhibits tissue necrosis caused by extravasation of α-agonists "NE"

Side effect

1- Hypotension.
2- ⬆ HR, arrhythmia, ischemic as MI
3- GIT: abdominal pain, nausea, peptic ulcer.

Contraindication

Phentolamine used cautiously in
-Coronary artery disease
-History of peptic ulcer.

Tolazoline

uses

1) Pulmonary hypertension in newborn.
2) arteriography to Visualize distal peripheral vessels

Ergot Alkaloids

Action

1- Direct vasoconstrictor "partial agonist on α & 5-HT "
2-α-blocking.
3- Uterine stimulant (oxytocic)
4- Dopaminergic stimulant:
- CTZ ➡ nausea & vomiting
- Basal ganglia ➡ anti-parkinsonian
- Hypothalamus ➡ ⬇ prolactin & ⬇ GH

Ergotamine | **Dihydroergotamine**

Vasoconstrictor (oral)
moderate ➡ α-blocking & oxytocic

Vasoconstrictor (i.v& i.m)
minimal ➡ α-blocking & dopaminergic

Used in Acute attack of Migraine better taken during the aura alone or combined with caffeine

Ergotoxine | **Dihydroergotoxine**

Marked α-blocking
moderate ➡ VC & oxytocic

Very potent α-blocking

Used in Senile dementia (as it ⬆ cerebral blood flow)

Ergometrine | **Methylergometrine**

Potent oxytocic
moderate ➡ VC & α-blocking

more potent oxytocic
- NO dopaminergic effect

Used in Post-partum haemorrhage.

Bromocriptine

used in 1- Parkinsonism
2- ⬇ (prolactin (suppress lactation) & GH secretions)

Contraindication

- During pregnancy (except bromocriptine)
- Hypertension
- coronary artery disease
- PVD

Selective α_1

Prazosin
($t_{½}$ = 3 h)

Action

- # α_1 ➡ V.D ➡ ⬇ BP ➡ reflex tachycardia
-(+) presynaptic α_2 ➡ ⬇ sympathetic ➡ no tachycardia
result ➡ no tachycardia
-Inhibition phosphodiesterase ➡
⬆ cAMP ➡ V.D. + tachycardia
⬆ cGMP ➡ V.D. + bradycardia
result ➡ V.D. without tachycardia

uses

1. Essential Hypertension (especially with BPH).
2. Hypertensive urgency

Side effect

1) 1st dose phenomenon:
- postural hypotension 30-90min
- ***To avoid***:
-start with small dose (1mg) at bed time then ⬆ dose gradually
-Use other anti-hypertensive drugs cautiously
2) Nonspecific adverse effects: headache, dizziness & drowsiness

Terazosin ($t_{½}$ 9-12h).

used in ttt of HTN & relieves urinary symptoms of BPH

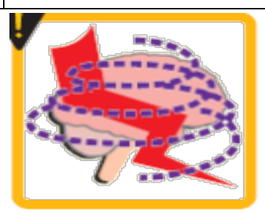
Doxazosin ($t_{½}$ 22h).

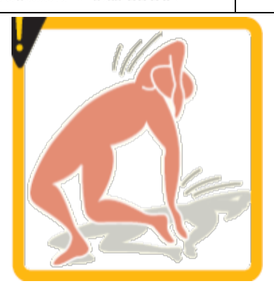
used in ttt of HTN with BPH
longest $t_{½}$.

Tamsulosin

- Selective α_{1A} blocker ➡ relax sphincter of bladder & prostatic tissue
- no effect on Bl.v ➡ α_{1B}.

used in BPH if not associated with HTN


headache, dizziness


1st dose phenomenon

Selective α_2

Competitive

Yohimbine

Action

- CNS ➡ ⬆ sympathetic outflow to the periphery.

uses

- sexual stimulant
- erectile dysfunction.

However, it's not recommended

Sympathetic depressant "3rd table" G3FR_15

Beta-adrenoceptor blockers (BBs)

	First generation (Non-selective BBs)	Second generation (Selective β_1 blockers)	Third generation (β blockers + V.D)	BBs + I.S.A	BBs + M.S.A	Lipophilic BBs	Hydrophilic BBs
Classification	-**P**ropranolol - **P**indolol "ISA" -Timolol - Nadolol "تامر وندى" -Sotalol	-**A**tenolol -**A**cebutolol"ISA" -**B**isoprolol -**B**etaxolol -Metoprolo -Esmolol "متولي وأسماء"	- **#α_1 receptor: C**arvedilol, Labetalol - **#Ca Channel: C**arvedilol, Betaxolol - **Anti-oxidant: C**arvedilol. -**(+)β_2 receptor: C**eliprolol -⬆**Nitric oxide C**arteolol, Nebivolol - **K^+ channel opener**: Tilisolol	-**Acebutolol** "اسيبلوا قلمين" -**Pin**dolol -**Pen**butolol -Oxprenolol -Labetalol ISA ➡ intrinsic sympathetic activity = partial agonist effect (Initial stimulation then inhibition)	Propranolol Sotalol M.S.A ➡membrane stabilizing activity #Na Channel (Anti-arrhythmic)	Well abs GIT & IV Pass BBB Metabolized in liver by $CYP_{450}2D6$ Not preferred in liver disease	Poor from GIT Not pass BBB Excreted unchanged in urine Not preferred in renal failure
p/k	**Absorption** ➡ ALL BBs are well absorbed orally except Esmolol "I. V.I" **elimination.**➡ Most BBs have t½= 3-10 hrs. **except** Esmolol which has ultrashort (due to rapid metabolism by RBC esterase, t½ = 10 min ➡ So used by I. V.I)					Propranolol Metoprolol	Atenolol Nadolol (long t½= 24h)

	Pharmacological actions	Therapeutic uses	Side effect	Individual BBs
Heart	#β_1➡⬇ **all cardiac properties** -⬇ contractility➡ -ve inotropic. -⬇ HR (bradycardia) ➡ -ve chronotropic. -⬇A-V conduction ➡ -ve dromotropic. -⬇automaticity & ⬇ excitability ➡ Anti-arrhythmic -⬇oxygen demand & ⬇cardiac work ➡ anti-anginal	-**Hypertension** ➡ Alone in mild & combined with other drugs in moderate and sever HTN **-Angina pectoris** (prophylaxis of angina of atherosclerosis) But, BBs worsen vasospastic angina. - **Acute myocardial infraction** ➡ prevent recurrence - **Supraventricular Arrhythmia** **-Chronic Heart failure**: (small dose Metoprolol, Bisoprolol & Carvedilol) ➡ Prevent myocardial remodeling ➡⬇ risk of death. - **HOCM** "Hypertrophic obstructive cardiomyopathy" ➡ BBs slow ventricular ejection &⬇ outflow resistance **-Acute Dissecting aortic aneurysm** ➡ (⬇systolic blood pressure) **-Esophageal varices** ➡ prevent bleeding from varices in portal HTN.	- Heart failure - Bradycardia & heart block. - Worsen symptoms of P.V.D. - Sudden stop ➡Rebound tachycardia, angina, arrhythmia Due to Upregulation of receptors) avoided by tapering the dose over several weeks before discontinuation	**Esmolol used in ttt of:** -Supraventricular Arrhythmia - arrhythmia of thyrotoxicosis - perioperative HTN -hypertensive emergency -myocardial ischemia in acutely ill patients, **-Carvedilol,Labetalol ➡#(α&β)** ➡ peripheral V.D ➡ used in hypertensive patients with PVD **- Labetalol** used in Hypertension with pregnancy instead of α-methyldopa **-Carvedilol** ➡ ⬇lipid peroxidation & vascular wall thickening ➡ benefit in heart failure
Blood vessels	-# β2 ➡ V.D. ➡ unmask α_1 ➡ V.C.➡ ⬇blood supply to **periphery** and **liver** -with prolonged use peripheral resistance returns to normal			
Blood pressure	-BBs have anti-hypertensive effect but not ⬇ BP **Mechanism of anti-hypertensive action: "written"** 1. # β_1 in heart ➡⬇ COP. 2. # β_1 in kidney ➡⬇ renin secretion. 3. # β_2 in CNS ➡⬇ sympathetic outflow. 4. # presynaptic β_2 ➡⬇ NE release. 5. Reset Baroreceptor. 6.⬆Prostaglandins (PGI_2) ➡ V.D.			
Resp	-Non-selective BBs ➡ -little effect on normal individual -bronchospasm in susceptible patients (asthma & COPD) ➡ life threating	Selective B_1 blockers & BBs with ISA used in (asthma & COPD) with caution.	bronchospasm in COPD & asthmatic patients.	***Atenolol, Metoprolol*** (# β1)➡ -Safer in patients with bronchospasm in respond to propranolol -better in diabetes & PVD
Metabolic	1. # β_2 in liver ➡⬇ glycogenolysis ➡ hypoglycemia. 3. # β_2 in skeletal muscle ➡ inhibit K^+ influx ➡⬆ hyperkalemia 2. # β_3 ➡⬇lipolysis ➡⬇FFA,⬇HDL & ⬆TGs.	**Hyperthyroidism** ➡ -#β1 in heart ➡ "protect heart in thyroid storm" - propranolol ⬇peripheral conversion of T_4 ➡ more potent T_3 inhibit deiodinase	- Hypoglycemia and mask its symptom ➡coma - Atherosclerosis ➡ ⬇HDL & ⬆TGs	
Eye	-⬇IOP in glaucomatous patient due to ⬇ aqueous formation -BBs have no effect on size (pupil or ciliary muscle)	Glaucoma(topical)		**Timolol, levobunolol, Betaxolol** ➡ttt of open angle glaucoma
CNS	-⬇anxiety (# sympathetic outflow) -⬇tremors (# β_2 in NMJ). -**P**rophylaxis of migraine	-**A**nxiety -**T**remors -**P**rophylaxis of migraine headache (not useful in acute attack)	lipophilic BBs ➡ Depression, fatigue & sleep disturbances (insomnia, nightmares).	

DRUG INTERACTION	Pharmacokinetic interactions	Pharmacodynamic interactions
	1- Aluminum salts, cholestyramine, and colestipol ➡ decrease absorption 2- enzyme inducers (phenytoin, rifampicin, phenobarbital) ➡⬆rate of metabolism (⬇plasma conc) 3-enzyme inhibitors (Cimetidine and hydralazine) ➡⬇rate of metabolism (⬆plasma conc) 4- β-blockers decrease the portal blood flow ➡ impair the clearance of lidocaine.	1-β-blockers + Ca^{2+} channel blockers (e.g. verapamil) ➡heart failure and heart block 2- β-blockers + anti-hypertensive agent ➡ Sever hypotension 3- NSAIDs "indomethacin" ➡⬇(PGI_2) ➡ Antagonize The hypotensive effects of BBs
Over dose	Hypotension, bradycardia and seizures may occur. **Treatment by** : 1- atropine antagonize Bradycardia 2- Glucagon ➡ +ve chronotropic & +ve inotropic	

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