Lecture 1

Medication affecting the balance system

Objectives:

- To differentiate between classes of drugs used to control or to prevent vertigo.
- To identify drugs that can precipitate vertigo

- Additional Notes
- Important

How does vertigo happen ?

- Movement of the fluid in the semi-circular canal
- Impulses from eyes
- Touch and position sensors in the neck, spine & limbs

All of these → stimulating nerve endings → firing impulses along the vestibular nerve → To vestibular nuclei → relay stations

The processed output goes Conscious brain interpreted as

I. Sense of position in space.
II. Eye muscles to stabilize.
III. Neck spine & limbs to control posture and movement.

Transmitters Involved In Vestibular Firing

- **Main Transmitters**
  - Glutamates (+)
  - Acetylcholine (+)
  - GABA (-)
  - Glycine (-)
- **Modulatory Transmitters**
  - Histamine
  - Noradrenaline

The difference between vertigo and dizziness

DIZZINESS	VERTIGO
- Painless head discomfort - Lighted headedness (decreased blood flow to the brain)	▪ A type of dizziness that creates the sense that you or your environment is SPINNING. ▪ BALANCE DISORDER (The individual will feel unsteady when standing or walking). ▪ Associated with spinning you might feel: 1/Nausea 2/Vomiting 3/Sweating 4/Nystagmus (Abnormal vertical eye movements)

To Understand

Causes of vertigo	
CNS	Impact on vestibular nuclei , afferent inputs or efferent outputs
Inner ear (Meniere's)	Vestibular hair cell stimulation unrelated to head and body motions
Others	Motion sickness, electrolyte disturbances: e.g.↑ BP, ↑ cholesterol, diabetes etc... Or ↓ equalization of air pressure in middle ear

Meniere's Disease

Is a disorder of the inner ear (Effects inner ear fluid homeostasis)

Can affect

hearing & balance

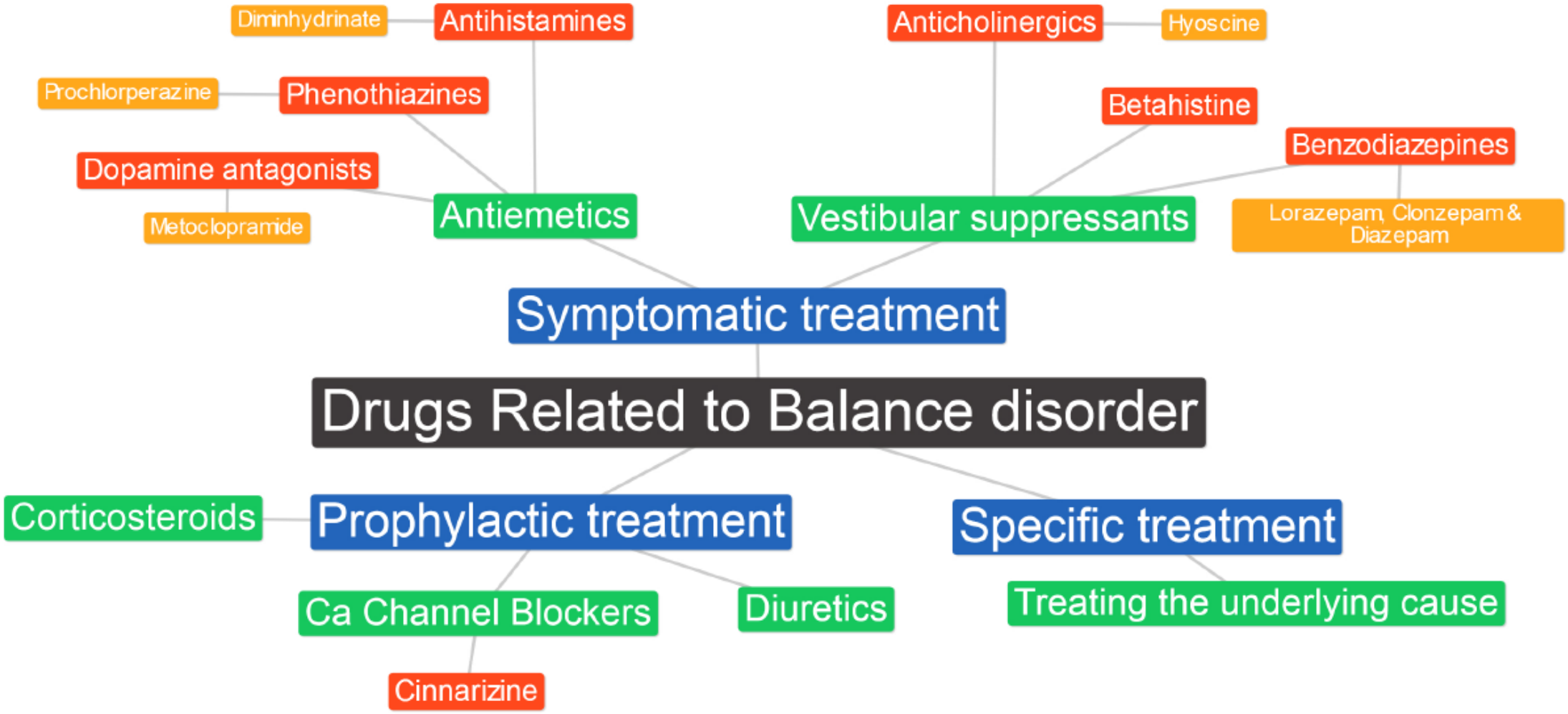
Characterized
by episodes of

1/vertigo
2/tinnitus (Tinnitus is the perception of a ringing, buzzing, roaring, whistling or hissing sound in your ear)
3/ progressive hearing loss

Pathophysiology
(Inner ear chamber is notmally filled with perilymph & endolymph)

↑ Endolymphatic pressure (hydrolymphatic hydrops) → Microscopic breaks of separating membrane often with vestibular hair loss → Depolarization and functional loss

To Understand


Diminhydrinate
Antihistamines
Anticholinergics
Hyoscine
Prochlorperazine
Phenothiazines
Betahistine
Benzodiazepines
Dopamine antagonists
Antiemetics
Vestibular suppressants
Lorazepam, Clonzepam & Diazepam
Metoclopramide
Symptomatic treatment
Drugs Related to Balance disorder
Corticosteroids
Prophylactic treatment
Specific treatment
Ca Channel Blockers
Diuretics
Treating the underlying cause
Cinnarizine

Mind Maps

Pharmacologic approach

Specific treatment

Involves targeting the underlying cause of the vertigo (e.g., ear infection).

Symptomatic treatment

Involves controlling the acute symptoms and autonomic complaints (e.g., vertigo and vomiting)

- Vestibular suppressants
- Antiemetics

Prophylactic treatment

Aims to reduce the recurrence of specific vertiginous conditions

1- Diuretics
(but not loop diuretics)
"↓ fluid retention"

2- Corticosteroids
"↓ inflammation"

3- Ca Channel Blockers
(**Cinnarizine, Verapamil**)
"↑ vasodilation"

Loop diuretics are contraindicated in the case of treating vertiginous conditions because they cause ototoxicity (damage to the ear).

1/ Vestibular suppressants

(Vestibular suppressants are drugs that reduce the intensity of vertigo and nystagmus evoked by a vestibular imbalance)

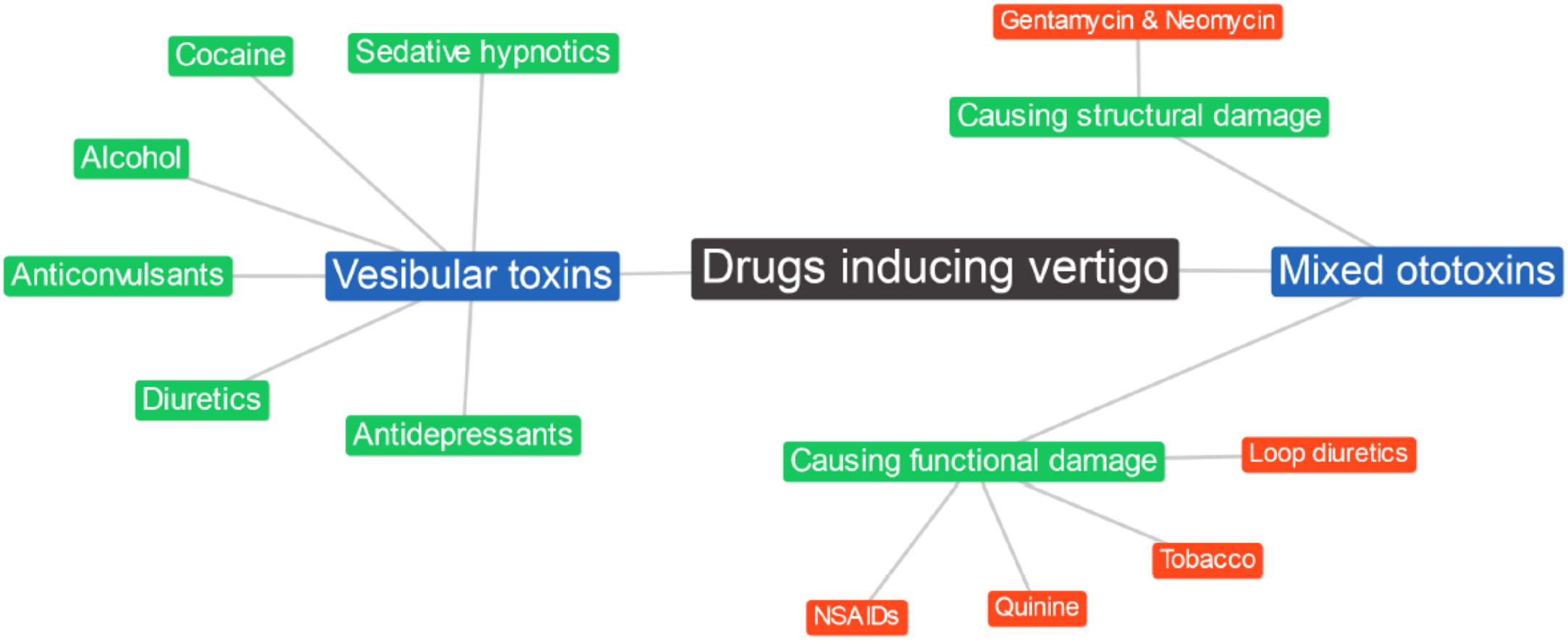
Drug	**Anticholinergics**	**Benzodiazepines 2nd Choice**	**Betahistine 1st Choice**
	Hyoscine (useful in motion sickness, sedation)	Lorazepam, Clonazepam & Diazepam	_____
P.D.	Anticholinergics inhibit firing in vestibular nucleus neurons so it Reduce the velocity of vestibular nystagmus	Act as GABA "suppressant affect" small dosages useful for the management of acute vertigo and Minimize anxiety and panic associated with vertigo	• It is a structural analog of histamine with weak histamine H1 R agonist and more potent histamine H3 R antagonist properties. • By stimulating H_1 R located on B.V in the inner ear → local vasodilation & ↑ permeability, which helps to reverse the underlying problem & By blocking H3 R the concentration of histamine ↑ in the inner ear → vasodilation. • It also increases the level of serotonin in the brainstem → which decreases the activity of vestibular nuclei.
P.K.	_____	_____	• Formulated as tablet or oral solution • Rapidly and completely absorbed (lipid soluble). • ½= 3-4 hours excreted in urine within 24 hours • Low protein binding
ADEs	1/Dry mouth 2/ Blurred vision 3/Sedation 4/Urine retention	1/Dependence impaired memory 2/Increased risk of falling (cause it's a skeletal muscle relaxant)	1/Headache (by vasodilation) 2/Nausea 3/GIT side effects 4/ Hypersensitivity reactions (by Histamine)
C.I	_____	_____	1/Pheochromocytoma (may provoke release of epinephrine and/or norepinephrine from the tumor, precipitating a hypertensive crisis) 2/Bronchial asthma 3/History of peptic ulcer 4/Hypersensitivity reactions

2/Antiemetic (Use to control vomiting & nausea)

Drugs	Antihistamine	Phenothazines (the best antiemetic in vertigo)	Dopamine antagonists
	Diminhydrinate	**Prochlorperazine**	(**Metoclopramide** & domperidone = don't cross BBB)
P.D.	• Block H1 in CRTZ (chemoreceptor trigger zoon) decrease the excitability in the labyrinth & block conduction in vestibular-cerebellar pathways. • Sedation. • Week anticholinergic effect .	• Block dopamine in CRTZ . • Antipsychotic • Sedation.	• Block dopamine in CRTZ • Sedation action • Gatroprkinetic (gastric empty so ↓ vomiting)
Use	I. Motion sickness. II. In vertigo.	I. Vertigo. II. Some vestibular suppressant action.	I. Vertigo. II. Can be effective in prevention motion sickness.
Adrs	I. Sedation. II. Dizziness. III. Anticholinergic side effect.	_____	I. Restless & drowsiness. II. Extrapyramidal manifestation on prolonged use. (parkinsonism like effect)
C.I	I. Glaucoma. II. Prostatic enlargement.	_____	_____

Prophylactic treatment (Ca Channel Blockers)

Drug	Cinnarizine
P.D.	• Ca blockers > Selective. it is block Ca channels so it will inhibit K+ current means inhibit the excitation → Inhibition K+ current reduce the vertigo & Motion induced nausea by decrease the over-reactivity of hair cells. • Antihistamine & Antiserotonine & antidopamine.
P.K.	• Orally. • Rapidly absorbed. • If taken orally it has low bioavailability –due hepatic first pass- . • If taken I.V. we should use lipid emulsion. because it is lipid & cannot absorbed.
Use	I. Nausea & Vomiting. II. Motion sickness. III. Vertigo. IV. Meniere's disease. V. Use for increase memory (by Increase cerebral blood flow).
Adrs	I. Sweating. II. Headache . III. Drowsiness. IV. Muscle rigidity & tremor. (Because of the blockage of Dopamine D2 receptor).
C.I	I. Parkinsonism (because Parkinson's is caused by shortage of Dopamine). II. Car drivers (because of Drowsiness).


Drugs inducing vertigo
Vesibular toxins
Cocaine
Sedative hypnotics
Alcohol
Anticonvulsants
Diuretics
Antidepressants
Mixed ototoxins
Gentamycin & Neomycin
Causing structural damage
Causing functional damage
Loop diuretics
Tobacco
NSAIDs
Quinine

Drugs (or chemicals) producing destructive damaging effects on structure or function of labyrinthine hair cells &/ or their neuronal Connections.

Vestibulotoxins

Cause functional damage only
(Affecting only the balance)

Drugs altering Fluid & Electrolyte	Drugs altering Vestibular firing
1/Diuretics 2/Antihypertensives	1/Anticonvulsants 2/ Antidepressants 3/Sedative hypnotics 4/Alcohol 5/Cocaine

Mixed Ototoxins

Cause functional &structural damage
(Affecting the balance &hearing)

STRUCTURAL	FUNCTIONAL
- Aminoglycoside antibiotics (Gentamycin, Kanamycin, Neomycin, Streptomycin, Tobramycin, Netlimycin) - Fluroquinolines, Vancomycin, Polymixin	1/Quinine, chloroquine, quinidine 2/Nitrogen mustard (cancer chemotherapy drug) 3/Loop diuretics 4/NSAIDs 5/Tobacco

➢ Mixed Ototoxins

- **How structural derangement is induced by these drugs?**

  1/Neomycin → activate caspases → Death R Pathway → Apoptosis. **2/Gentamycin** → evoke free radicals → Mitochondrial Pathway → Apoptosis.

  Caspase : the enzyme that activate the final stage to produce apoptosis. Neomycin and Gentamycin both will leads to apoptosis → permanent structural damage

- **How functional derangement is induced by these drugs?**

  ↓ local blood flow → biochemical changes → alter electromechanical transduction →Firing of impulses

N.B. Functional damage recover after stopping the drugs, but Structural damage doesn't recover.

Summary

Drugs		P.D.	Uses	ADEs
Vestibular Suppressants	Hyoscine	inhibit firing in vestibular nucleus	motion sickness, sedation	Blurred vision & Sedation
	Benzodiazepines	Act as GABA “suppressant affect”	acute vertigo	Dependence impaired memory
	Betahistine	I. By stimulating H1 R cause → local vasodilation II. By blocking H3 R the cause → ↑ histamine III. ↑ Serotonin → ↓ activity of vestibular nuclei	anti-vertigo Meniere’s Disease	Nausea
Antiemetic	Diminhydrinate	Block H1 in CRTZ	Motion sickness	Anticholinergic side effect
	Prochlorperazine	Block dopamine in CRTZ & Antipsychotic	Vertigo	Extrapyramidal manifestation
	Metoclopramide	Block dopamine in CRTZ & Gatroprkinetic	Vertigo	Extrapyramidal manifestation
Prophylactic	Cinnarizine	Ca blockers > Selective → ↑ vasodilation	Vertigo Use for ↑ memory	Drowsiness

1. **Neomycin induces apoptosis through:**
   A. Death receptor pathway
   B. Biochemical changes
   C. Mitochondrial pathway

2. **Which type of these diuretics is functional ototoxin?**
   A. Thiazide diuretics
   B. K-sparing diuretics
   C. Loop diuretics

3. **Which one of these can't be prescribed in case of bronchial asthma?**
   A. Betahistine
   B. Metoclopramide
   C. Dimenhydrinate

4. **Which one of these is ADEs for Cinnarizine?**
   A. Sedation
   B. Git side effects
   C. Drowsiness

5. **50 years old male. Is traveling from Jeddah to Egypt by ferry and suddenly he feels nauseous and dizzy. Which one of the following can stop his symptoms:**
   A. Betahistine
   B. Dimenhydrinate
   C. Quinine

Answers: 1. A 2. C 3. A 4. C 5. B

MCQs

SAQs

1. Write three symptoms for the balance disorders?
   - Spinning (vertigo)
   - Nausea or vomiting
   - Nystagmus (abnormal eye movement)

2. Write two of Benzodiazepines drugs, and what its used for?
   - Lorazepam & Colnzepam, Minimize anxiety and panic associated with vertigo

3. What are the indications, and the contraindications of Diminhydrinate?
   - Indications: In vertigo & Motion sickness
   - Contraindications: Glaucoma & Prostatic enlargement

4. Drugs inducing vertigo divided into two groups, name it and give an example for each group?
   - Vestibulotoxins: Diuretics
   - Mixed ototoxins: Gentamycin

Good luck!

Done by Pharmacology Team 434

- Mishari Alsalem
- Qasem Alsultan
- Saad Altweurqi
- Abdulaziz Alsaud
- Abdullah Alammari
- Moath walbi
- Khalid Alduraibi

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com