DRUGS RELATED TO BALANCE SYSTEM

The overall incidence of dizziness, vertigo & imbalance is 5-10%

It reaches 40% in patients older than 40 years

Accounts for 3% of total visits to emergency department

The incidence of falling is 25% in subjects older than 65 years

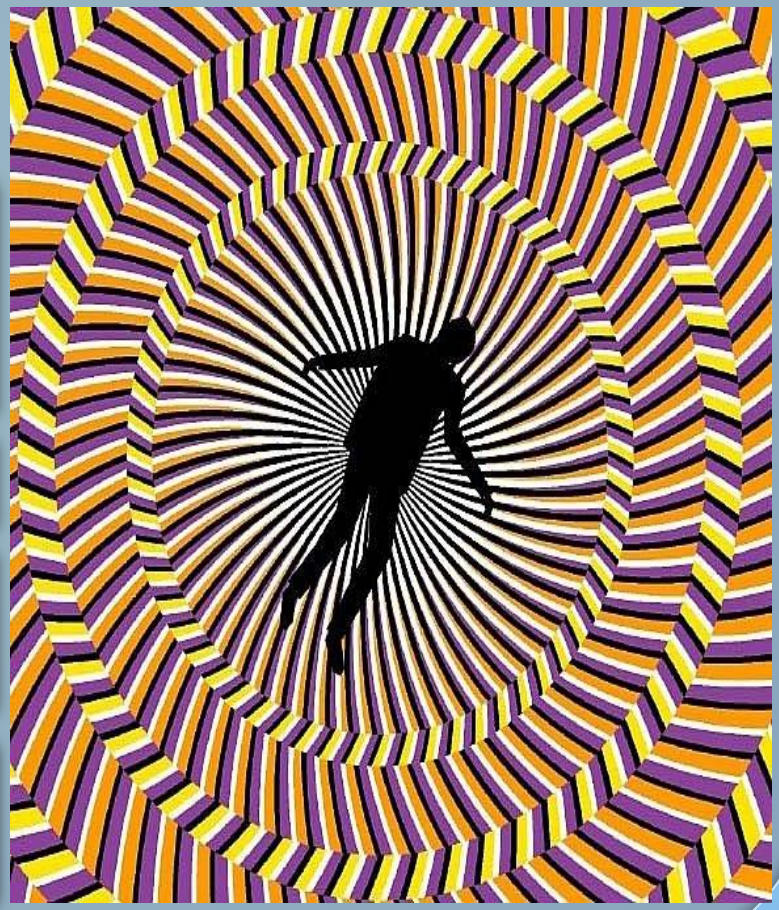
1% of falls results in hip fracture

Roughly 50% of fractured hips will not function normally.

DRUGS RELATED TO BALANCE SYSTEM

ILOS

- To differentiate between classes of drugs used to control or to prevent vertigo
- To hint on some disorders of balance
- To detail on some drugs used to control or to prevent vertigo
- To identify drugs that can precipitate vertigo.



DRUGS RELATED TO BALANCE SYSTEM

Balance Disorders

Definition

Terms

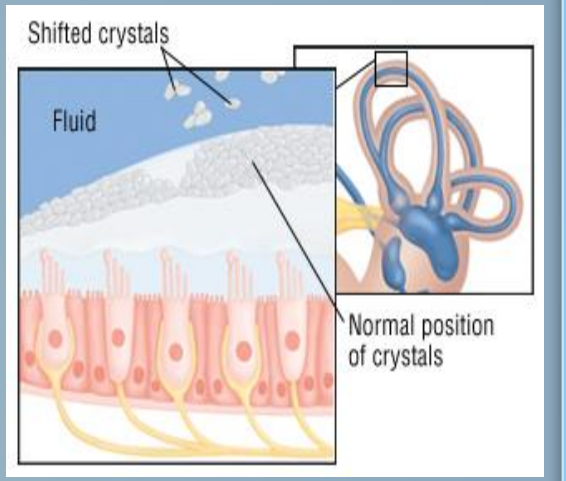
- Dizziness
- Light headedness
- Ménière's disease
- Vertigo

SYMPTOMS

- Spinning (vertigo)
- Confusion or disorientation
- Falling or feeling as if one is going to fall
- Nausea or vomiting
- Sweating
- Abnormal eye movement (nystagmus).

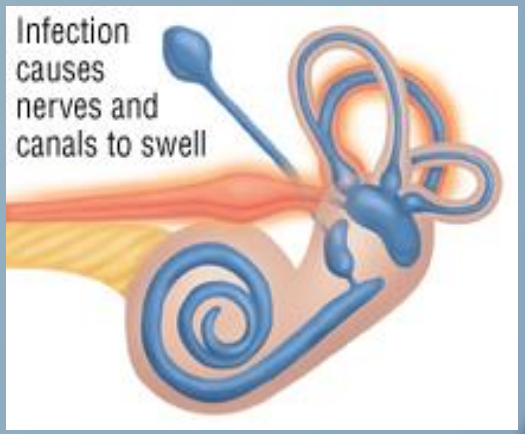
BALANCE DISORDERS

Benign paroxysmal positional vertigo:-A change in head position causes a sudden sensation of spinning

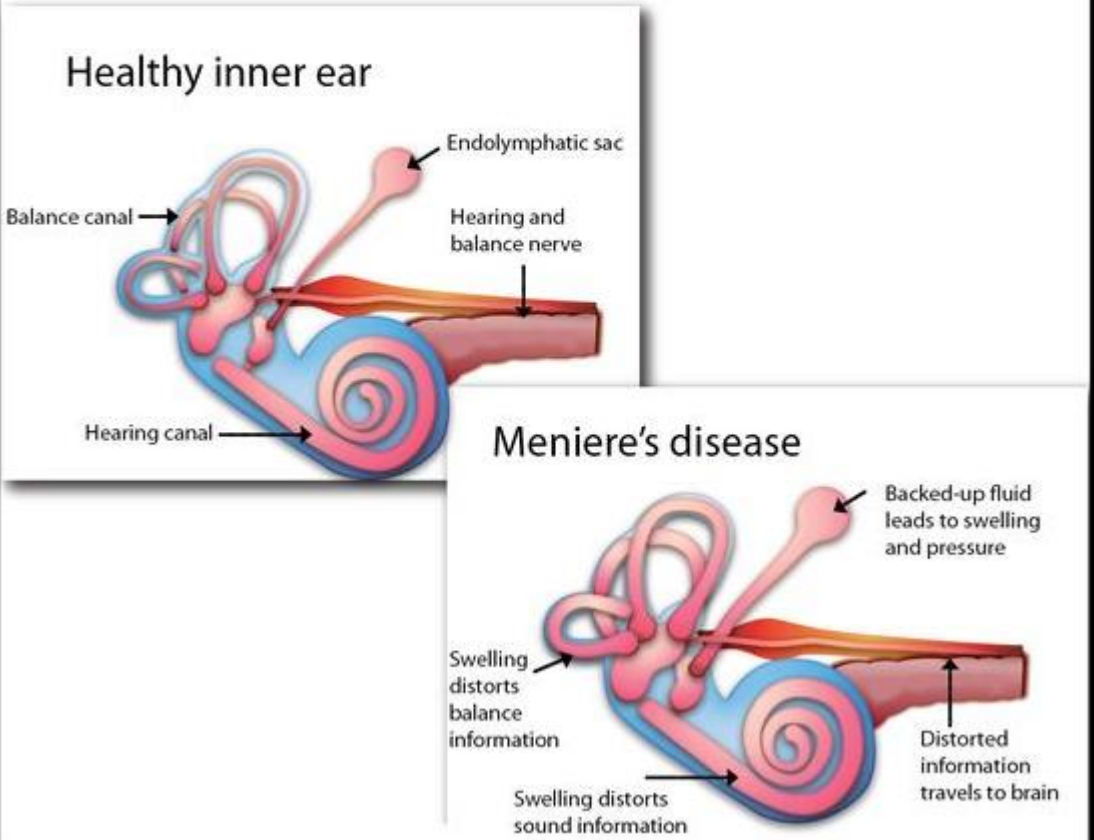


Acute labyrinthitis:-Inflammation of the balance apparatus of the inner ear, probably caused by a viral infection

Ménière's disease:- This causes repeated episodes of dizziness, usually with ringing in the ear & progressive low-frequency hearing loss.



Meniere's disease



PHARMACOLOGIC APPROACH

Specific treatment

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

Symptomatic treatment

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

Prophylactic treatment

Aims to reduce the recurrence of specific vertiginous conditions

- Diuretics (but not loop diuretics)
- Corticosteroids
- Ca & K Channel Blocker & antihistamine e.g. Cinnarizine.

SYMPTOMATIC CONTROL

Antiemetics

Vestibular suppressants are drugs that reduce the intensity of vertigo & nystagmus evoked by a vestibular imbalance, e.g :

1-Anticholinergics

2-Benzodiazepines

3-Betahistine

1-Anticholinergics

Anticholinergics inhibit firing in vestibular nucleus neurons

Reduce the velocity of vestibular nystagmus

e.g. hyoscine, also useful in motion sickness & sedation

ADRs:- dry mouth, blurred vision, sedation.

2-Benzodiazepines

In small dosages useful for the management of acute vertigo

Minimize anxiety & panic associated with vertigo

e.g. Lorazepam, Clonazepam, Diazepam

ADRs:- Dependence, impaired memory, increased risk of falling.

3-Betahistine

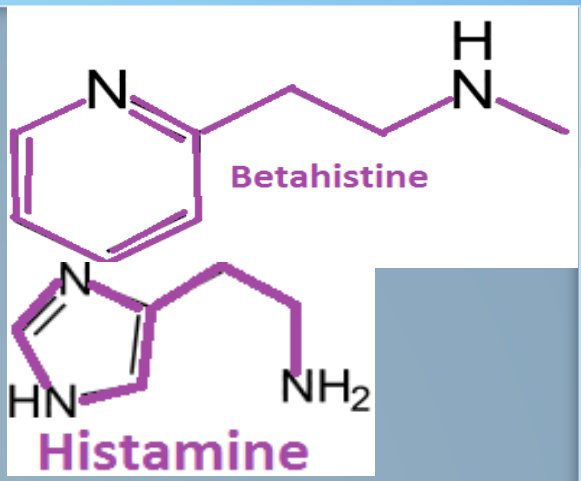
Mechanism of Action:-

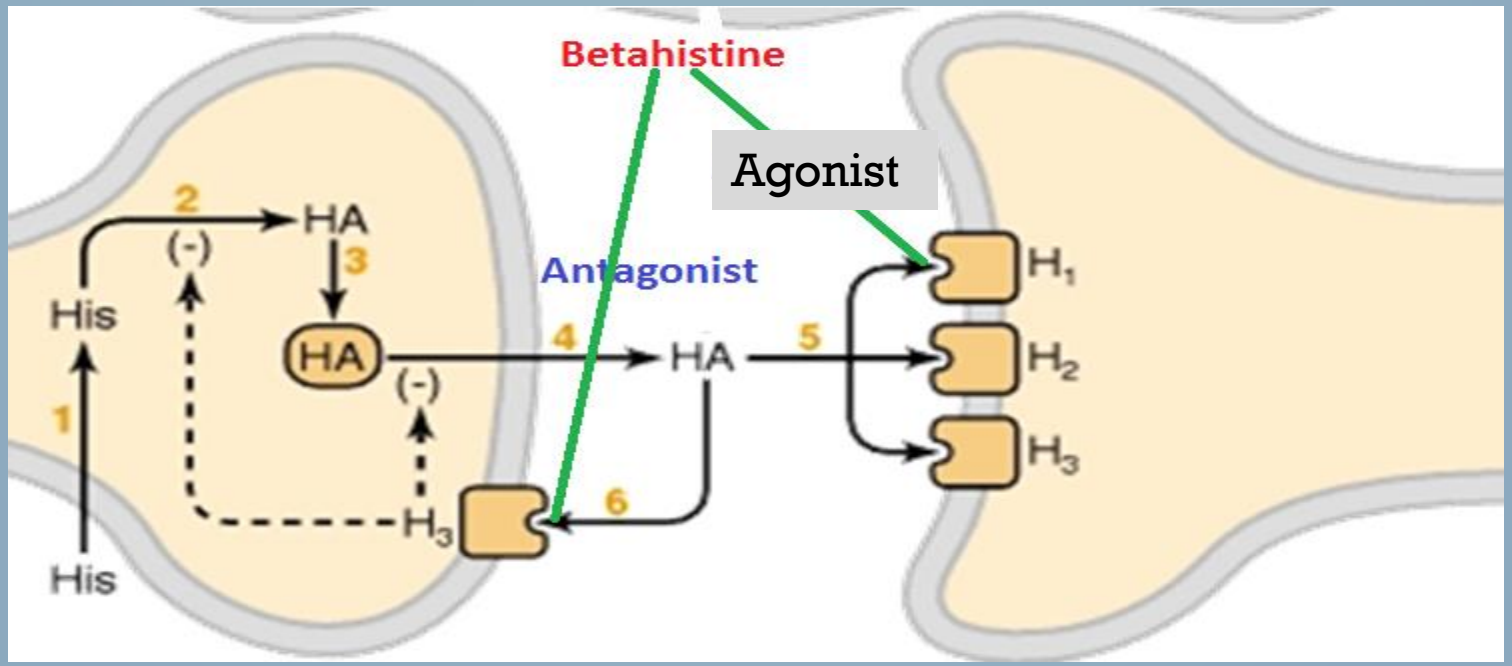
It is a structural analog of histamine with **weak** histamine H1 receptor agonist & more **potent** histamine H3 receptor antagonist properties

By stimulating H_1 receptors located on blood vessels in the inner ear→ local vasodilation & increased permeability, which helps to reverse the underlying problem of endolymphatic hydrops.

By bloking H3 receptors, Betahistine increases the local concentration of histamine in the inner ear.

Betahistine increases the level of serotonin in the brainstem →↓the activity of vestibular nuclei.


N
H
N
Betahistine
N
HN
NH2
Histamine


Betahistine
Agonist
Antagonist
2
(-)
HA
3
His
HA
4
HA
5
1
(-)
H1
H2
H3
6
H3
His

Pharmacokinetics of betahistine

Formulated as tablet or oral solution

Rapidly & completely absorbed

$t_{1/2}$ = 3-4 hours,
excreted in urine within 24 hours

Low protein binding.

ADRs:-

Headache

Nausea

GIT side effects.

Contraindications

- Phaeochromocytoma
- Bronchial asthma
- History of peptic ulcer
- Hypersensitivity reactions.

Clinical indications

Betahistine is indicated for treatment of Ménière's syndrome.

Efficacy and safety of betahistine treatment in patients with Meniere's disease: primary results of a long term, multicentre, double blind, randomised, placebo controlled, dose defining trial (BEMED trial) *BMJ 2016; 352*

94% of ENT surgeons in Britain prescribe betahistine for Meniere' disease, while in USA they think it is no better than a placebo .

Current evidence is limited as to whether betahistine prevents vertigo attacks caused by Meniere's disease, compared with placebo reactions.

ANTIEMETICS

Antiemetics are drugs used to control vomiting & nausea such as:

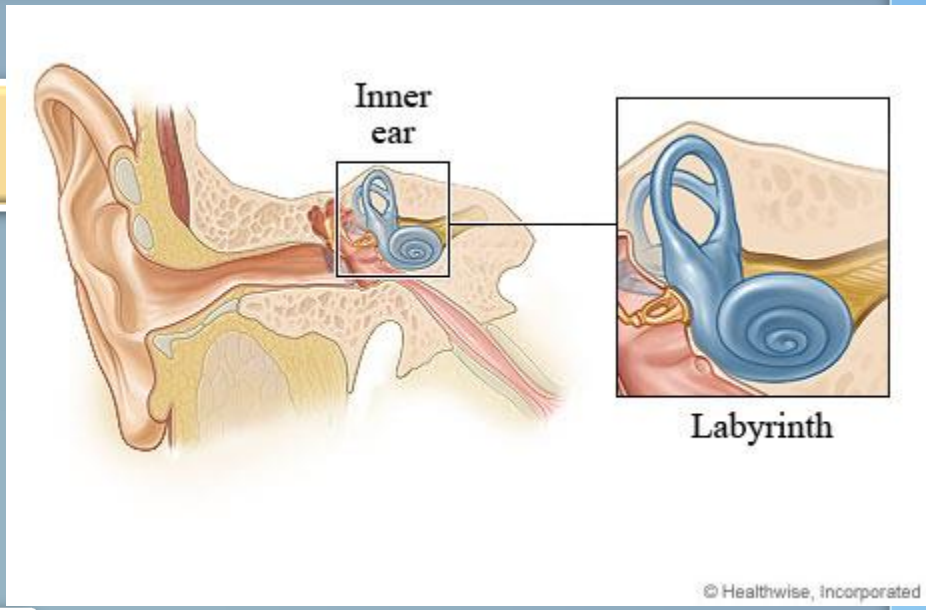
Antihistamines e.g. Dimenhydrinate

Phenothiazines e.g. **prochlorperazine**

Dopamine antagonists e.g. **metoclopramide** & **domperidone**.

DIMINHYDRINATE

- Block H_1 receptors in CRTZ
- Sedative effects
- Weak anticholinergic effects

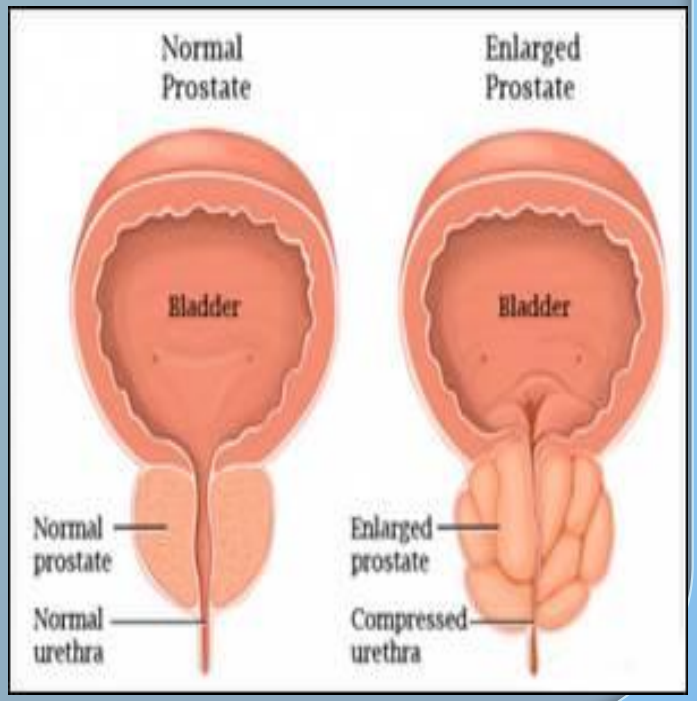


↓ Excitability in the labyrinth & blocking conduction in vestibular-cerebellar pathways

Indications

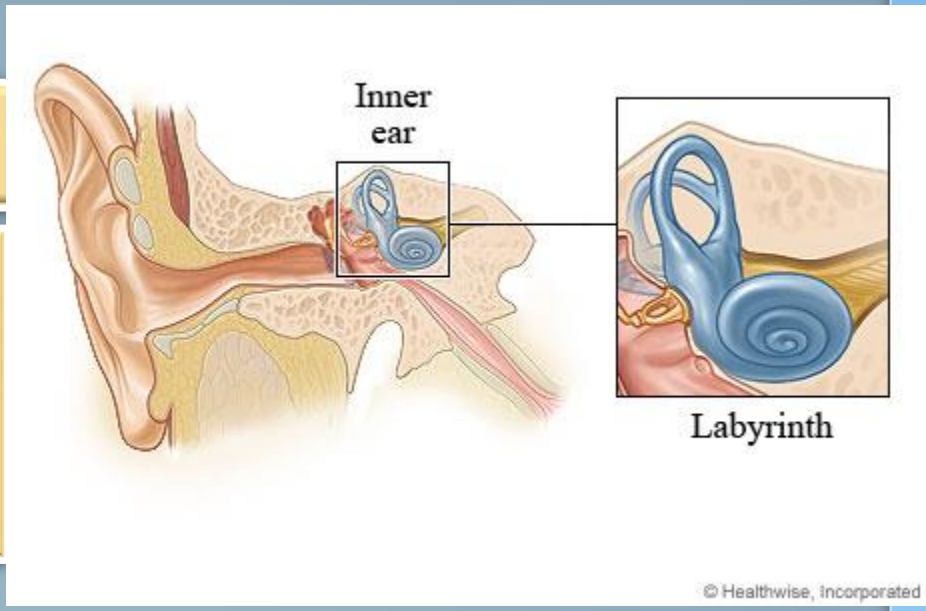
In vertigo

Prevent nausea & vomiting associated with motion sickness.

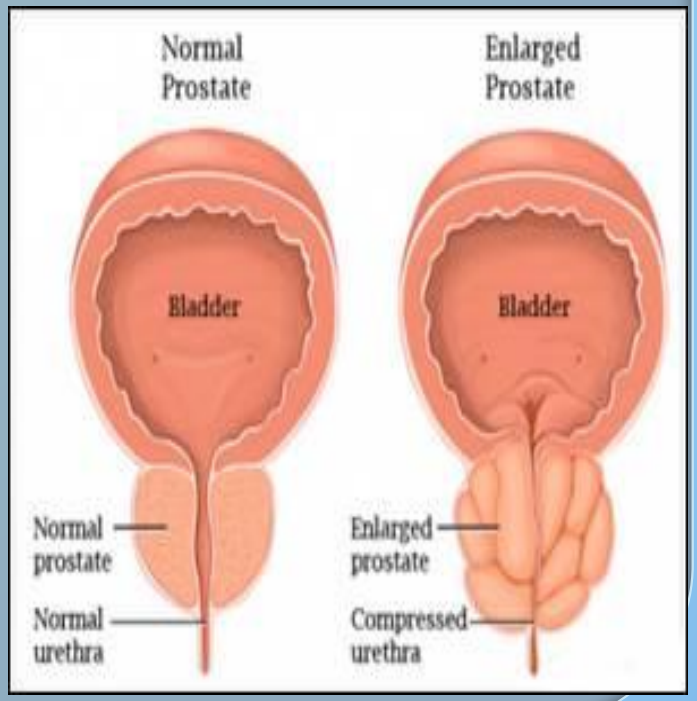


DIMINHYDRINATE

ADRs:-
Sedation
Dizziness
Anticholinergic side effects.



Contraindications:-
Glaucoma
Prostatic enlargement



PROCHLORPERAZINE

Antipsychotic, some sedation + antiemetic

Mechanism of action:
Blocks DOPAMINE receptors at CRTZ

Indications:

One of the best antiemetics in vertigo,
has some vestibular suppressant action.

Metoclopramide & DOMPERIDONE

block DOPAMINE D2 receptors in the CRTZ of the medulla, resulting in potent **central** antinausea & antiemetic action

Has some sedative action

Has potent **gastroprokinetic** effect

ADRS:-

Restlessness or drowsiness

Extrapyramidal manifestations on prolonged use.

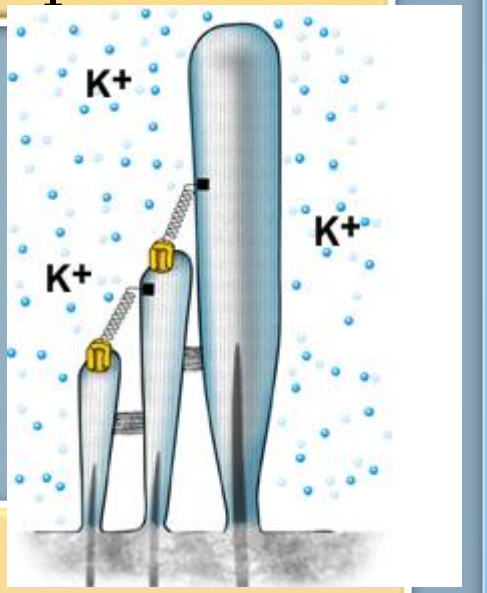
CINNARIZINE

Mechanism of action

Selective Ca^{2+}channel blocker (vascular smooth muscle relaxation), antihistamine, antiserotonin, antidopamine

It promotes cerebral blood flow

Increased hydrostatic pressure on hair cells activates K+ currents



Cinnarizine inhibits K^+ currents.
Inhibition of K^+ currents lessen the vertigo & motion-induced nausea by dampening the over-reactivity of the vestibular hair cells.

PHARMACOKINETICS

- Taken orally in tablet form
- Rapidly absorbed
- Low oral bioavailability due to hepatic first pass metabolism
- If administered IV in lipid emulsion, it has better bioavailability.

Clinical uses:-

Used to treat nausea & vomiting associated with motion sickness, vertigo & Meniere's disease.

ADRS:-

Sweating
Drowsiness & Headache
Muscle rigidity & tremor

Contraindications

Parkinsonism
Car drivers.

DRUGS INDUCING VERTIGO

Drugs producing damaging effects on structure or function of labyrinthine hair cells &/ or their neuronal connections

Vestibular toxins

Mixed ototoxins

Drugs altering fluid & electrolyte balance: Diuretics

Drugs altering vestibular firing (neuronal depressants):
- Anticonvulsants
- Antidepressants
- Sedative hypnotics
- Alcohol
- Cocaine

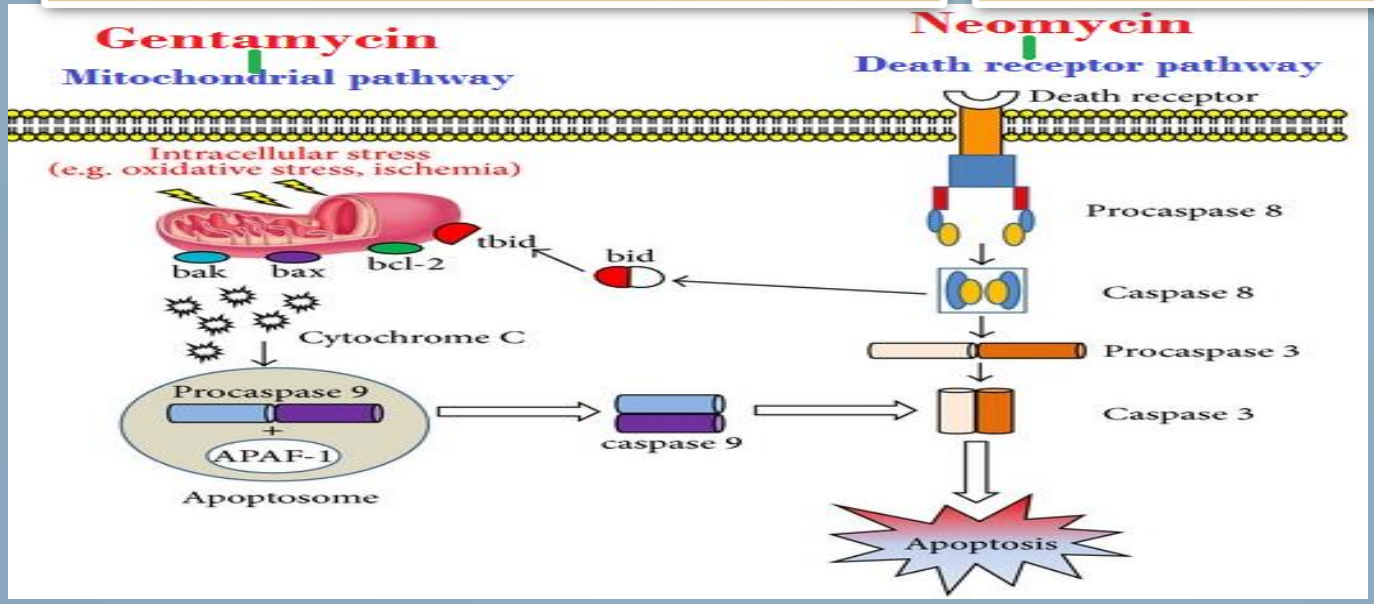
Alter function

MIXED OTOTOXINS

Aminoglycoside antibiotics;
e.g. *gentamycin, kanamycin, neomycin, streptomycin*

Gentamycin → Induce apoptosis by evoking free radicals → Mitochondrial Pathway

Neomycin →Induce apoptosis by activating caspases → Death Receptor Pathway



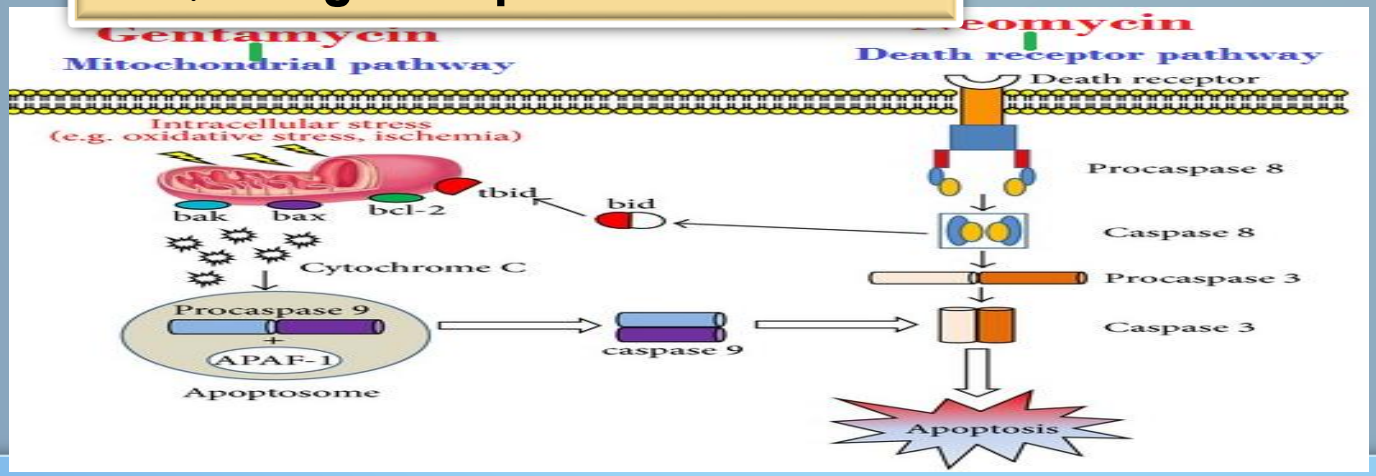
MIXED OTOTOXINS

- Quinine, chloroquine, quinidine
- Nitrogen mustard
- Loop diuretics
- NSAIDs
- Tobacco

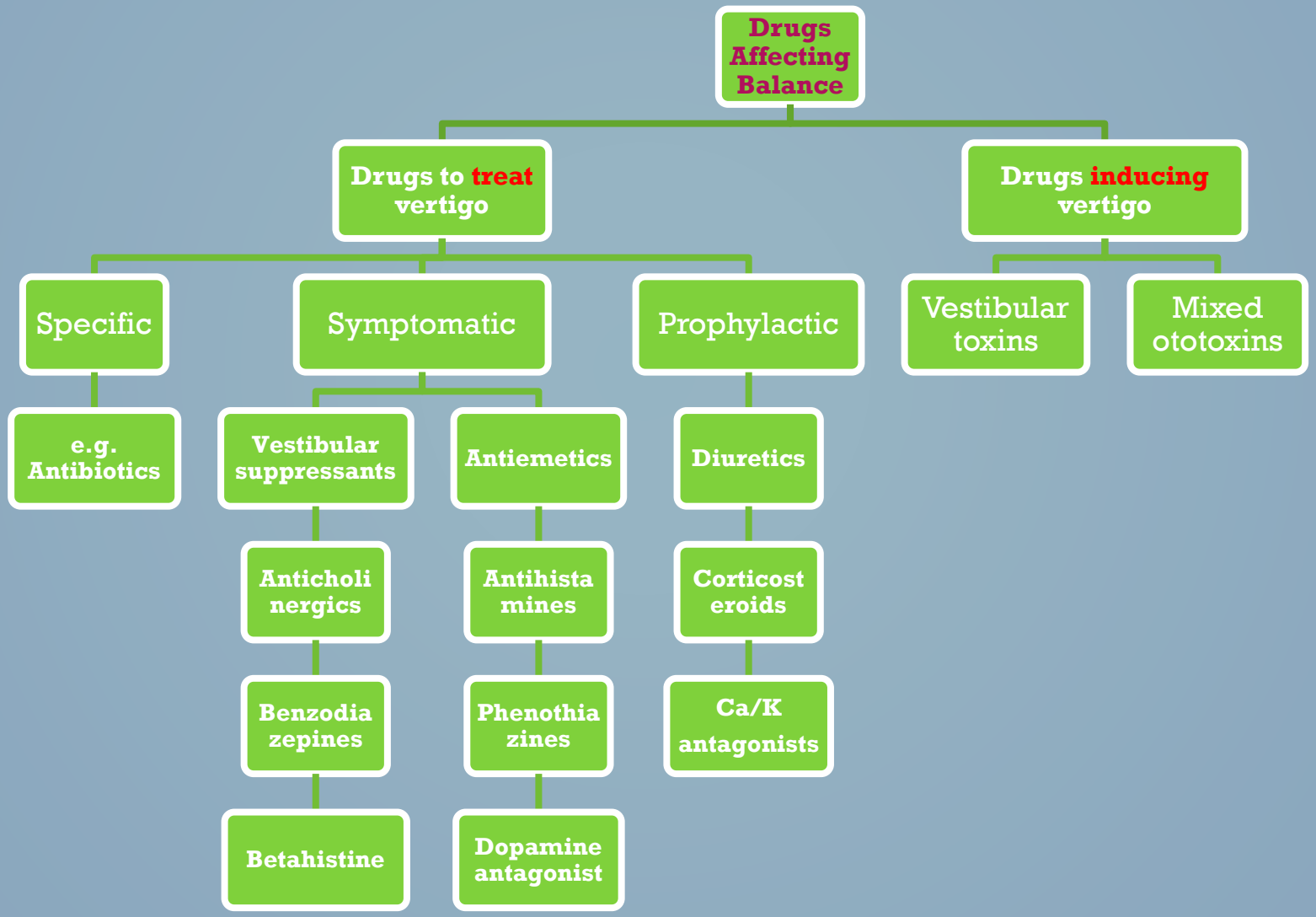
↓Local blood flow → biochemical changes → ↓ electromechanical transduction → ↓firing of impulse

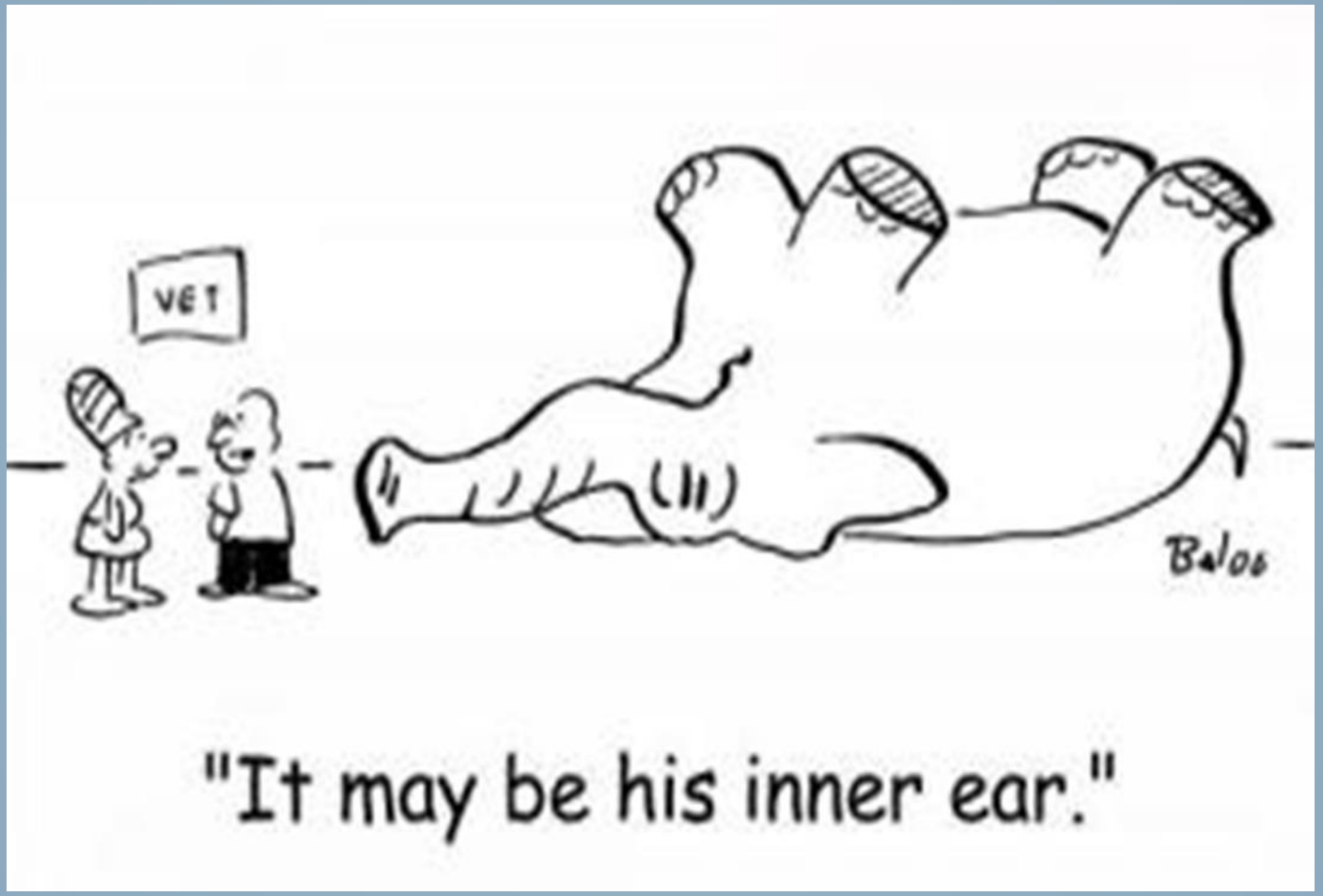
Alter function

Alter structures



SYNOPSIS


Drugs Affecting Balance
Drugs to treat vertigo
Drugs inducing vertigo
Specific
Symptomatic
Prophylactic
Vestibular toxins
Mixed ototoxins
e.g. Antibiotics
Vestibular suppressants
Antiemetics
Diuretics
Anticholinergics
Antihistamines
Corticosteroids
Benzodiazepines
Phenothiazines
Ca/K antagonists
Betahistine
Dopamine antagonist


VET
"It may be his inner ear."