#1

Medication affecting the balance system

Objectives:

- 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.

Color index:

- Drugs names
- Doctors notes
- Important
- Extra

To Understand Better

Vertigo Vs Dizziness

Dizziness	Vertigo
- General term used to express subjective patient complaints related to changes in sensation, movement, perception, or consciousness. - **Lighted headedness**.	- 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)
	Symptoms
	- Confusion or disorientation. - Falling or feeling as if one is going to fall. - **Nausea or vomiting**. - Sweating. - **Nystagmus** (Abnormal eye movement).

Pathophysiology of vertigo (Extra):

21:33 min

As we know that **vestibular system** is used to maintain the balance

↓

by detecting angular and linear acceleration of the head.

↓

Sensory information from the vestibular system is then used to provide a **stable visual image** of the retina (while the head moves) & make adjustment in **posture** that are necessary to maintain balance.

→ **Vertigo** happens if there is abnormality in the vestibular system or CNS structures that process signals from the semicircular canals.

Transmitters involved in vestibular firing (Extra):

	Main transmitters		Modulatory transmitters	
+	Glutamates	Acetylcholine	Histamine	Noradrenaline
-	Glycine	GABA		

To Understand Better

Balance disorders:

BPPV

Benign paroxysmal positional vertigo → a change in head position causes a sudden sensation of spinning.

Meniere's Disease

2:43 min

Acute labyrinthitis

→ Inflammation of the balance apparatus of the inner ear, probably caused by a **viral** infection.

Meniere's Disease

Disorder of the inner ear (Affects inner ear **fluid homeostasis**)

Cause repeat episodes of dizziness, usually with ringing in the ear → Result in progressive **low frequency hearing loss** & **Balance** disorder.

characterized by episodes of (extra)

Vertigo, tinnitus (طنين الأذن), progressive hearing loss.

Pathophysiology (extra)

Inner ear chamber is normally filled with perilymph & endolymph separated from each other by vestibular membrane.

↑ endolymphatic pressure (hydrolymphatic hydrops) → microscopic **breaks** of separating membrane (Vestibular membrane) often with vestibular hair loss → **depolarization** and **functional loss**.

Mind Map

Drugs related to balance disorders

Specific treatment

Involves targeting the **underlying cause** of the Vertigo (e.g. ear infection, use Antibiotics, or inflammation with anti-inflammatory drugs)

Symptomatic treatment

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

Vestibular suppressants

Reduce the intensity of **vertigo** and **nystagmus** evoked by a vestibular imbalance.

1- Anti-cholinergics.
→ **hyoscine**

2- Benzodiazepines.
→ **Lorazepam**, **Clonzepam**, **Diazepam**

3- Betahistine.

Antiemetics

used to control **vomiting** & **nausea**

1- Antihistamines.
→ **dimenhydrinate**

2- Phenothiazines.
→ **prochlorperazine**

3- Dopamine antagonists.
→ **metoclopramide**
→ domperidone → Do not cross BBB.

Prophylactic treatment

Aims to **reduce the recurrence** of specific vertiginous conditions.

1- Diuretics[1]: **Except** Loop diuretics.[2]

2- Corticosteroids[3].

3- L- type Ca^{2+} Channel Blockers[4]
→ **Cinnarizine**
→ Verapamile

1- Loss of Na & H_2O → ↓ H_2O in the endolymph.
2- Because they are **ototoxic** → ↑ incidence of vertigo.
3- To ↓ inflammation.
4- ↑ Vasodilatation.

Vestibular suppressants

Drug	Anti-Cholinergics	Benzodiazepines	Betahistine
	Hyoscine	Lorazepam, Clonzepam, Diazepam	
Mech. of action	1- **Inhibit** firing in vestibular nucleus neurons. 2- Reduce the velocity of **vestibular nystagmus**. - Acts by interfering with the transmission of nerve impulses by ACh in the parasympathetic nervous system (specifically the **vomiting center**)	- Minimize **anxiety** and **panic** associated with vertigo by binding adjacent to $GABA_A$ receptors → enhance the effects of GABA by increasing GABA affinity for the GABA receptor → open **Cl^-** ion channel → **hyperpolarize** cell membrane.	- It is a structural analog of **histamine** with: **1- Weak histamine H1 receptor agonist** → By stimulating **H_1** receptors located on BV in the inner ear→ local vasodilation and ↑ permeability → helps to reverse the underlying problem of endolymphatic hydrops. (accumulation of endolymph) → Reduce pressure in endolymph. **2- More potent histamine H3 receptor antagonist properties** → By blocking **H3** receptors in presynaptic nerve end → prevent reuptake of Histamine by H3 R → ↑ the local concentration of histamine in the inner ear → ↑ the direct **H1-agonist** activity. - increases the level of **serotonin** in the brainstem → ↓ the activity of vestibular nuclei.
P.K	———	———	- Tablet or **oral** solution. - Rapidly and completely absorbed (**Lipid soluble**) - t½= 3-4 h. excreted in urine within 24h. - Low protein binding.
Indications	- Management of **vertigo**, sedation & **motion sickness**.	- In **small dosages** useful for the management of **acute** vertigo.	- **Meniere's Disease**
ADRs	- Dry mouth. - Blurred vision. - **sedation**. (تعتبر جانب مضر لسائق السيارة مثلًا، وتعتبر نافعة للخائف من Vertigo) - Urinary retention.	- **Dependence** → for a long time → addiction. - Impaired memory. - **Drowsiness & Confusion** → increased risk of falling. → bc it inhibits the coordination of skeletal muscle.	- Headache → by vasodilation. - Nausea. - GIT side effects. → H1 R is found in smooth muscles of GIT → ↑ contractility by the effect of histamine. - **Hypersensitivity reactions.**
C.I			- **Pheochromocytoma** Histamine is used for **dx** of pheochromocytoma → Epinephrine & NE يطلع كمية كبيرة من ال → precipitating a **hypertensive crisis.** - Bronchial asthma. - History of **peptic ulcer**.

Anti-emetics (مضادة للتقيؤ)

Drug	Anti-histamines	Phenothiazines	Dopamine antagonists
	Dimenhydrinate	**Prochlorperazine** (The most popular)	**Metoclopramide**
Mech. of action	- Competitive antagonist at the histamine H1 receptor, which is widely distributed in the human **brain**. - Block **H1** receptors in **CRTZ** "chemoreceptor trigger zoon " - Has a sedative effects. - Has a weak **anticholinergic** effects. - ↓ Excitability in the labyrinth & blocking conduction in vestibular-cerebellar pathways → **vestibular suppressant**	- Very potent antiemetic drug. - Blocks **dopamine receptors** (D2 receptor) at CRTZ. - **Antipsychotic**, some **sedation** & antiemetic. - has some **vestibular suppressant**.	- A **potent** central antiemetic acting on CRTZ. - Dopamine D2 receptor antagonist. → It raises the threshold of activity in the chemoreceptor trigger zone and decreases the input from afferent visceral nerves. - Has some sedative action. - Potent **gastroprokinetic** effect. → It **inhibits** gastric smooth muscle relaxation produced by dopamine → increasing cholinergic response of the gastrointestinal smooth muscle → GIT smooth muscle contraction → gastric empty → prevent vomiting. * This occurs in some pts, especially in diabetes pts.
Indications	- Vertigo. - Motion sickness.	- One of the Best antiemetics in **vertigo**. - Nausea, Schizophrenia.	
ADRs	- Sedation. - Dizziness. - Anticholinergic side effects (e.g. dry mouth)		- Restless & drowsiness. (movement disoeder) - Extrapyramidal manifestations on prolonged use. → are drug-induced **movement disorders** that include acute and tardive symptoms, some of the symptoms are related to **Parkinsonism**, such as **rigidity and tremors**.
C.I	- **Glaucoma** → bc of the anticholinergic effect → ↑ IOP. - Prostatic enlargement → bc anticholinergics cause urinary retention.		

Ca^{2+} channel blockers (prophylactic)

Drug	Cinnarizine
Mech. of action	- Selective K^+ channel blocker. - Selective Ca^{2+} channel blocker → L-type & T-type voltage gated calcium channels. - Anti-Histamine, Anti-Serotonin and Anti-Dopamine (D2 receptor) - As physiological condition, ↑ hydrostatic pressure on hair cells activates K^+ currents, Cinnarizine **inhibits K^+ currents** → lessen **vertigo** and motion-induced **nausea** by dampening the over-reactivity of the vestibular hair cells. - It promotes **cerebral blood flow** (by the effect of ↓ viscosity) → **Improve memory** especially in elderly pts.
P.K	- 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.
Indications	- **Nausea** and **vomiting** associated with motion sickness, **vertigo** and Meniere's disease.
ADRs	- Sweating. - Headache. - Drowsiness. - Muscle rigidity and tremor → due to **D2** blocking effect.
C.I	- Parkinsonism → bc they suffer from shortage of dopamine. - **Car drivers**. → bc of anti-histaminic effect → sedation.

Drugs inducing vertigo

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

A- Vestibular toxins

Alter **function**

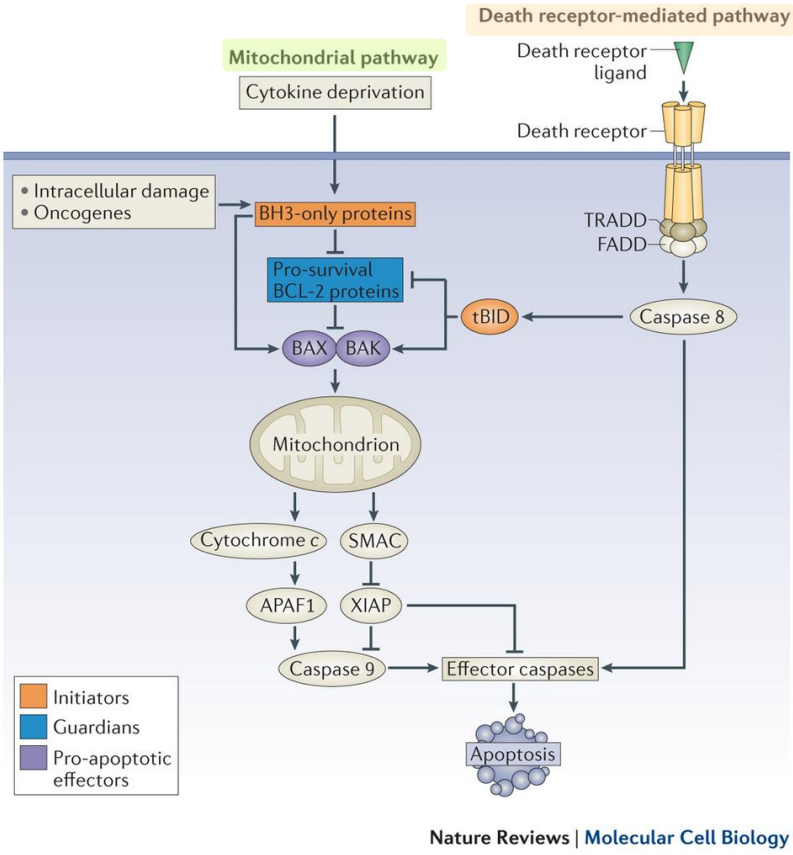
- Affect the **balance**.
- 1- Drugs altering **fluid** & **electrolyte balance**.
  → Diuretics.
- 2- Drugs altering (Inhibit) **vestibular firing**.
  → Anticonvulsants, Antidepressants, Sedative hypnotics
  Alcohol, Cocaine. → They are either CNS depressants, or local anesthetic(e.g. Cocaine)

B- Mixed ototoxins

- Affect **hearing** & balance.

B- Mixed ototoxins → Affect balance & hearing

Altering **Structure**	Altering **Function**
Aminoglycoside antibiotics; - **Gentamycin**, - **Neomycin**, - **Kanamycin**, - **Streptomycin**.	- **Quinine**, **chloroquine**, **quinidine** → Anti-malarial drugs. - Nitrogen mustard → Anti-cancer drug. - Loop diuretics - NSAIDs - Tobacco
GentaMicin Induce apoptosis by evoking free radicals → **Mitochondrial Pathway**.	**- How functional derangement is induced by these drugs?** ↓ Local blood flow → **biochemical changes** → ↓ electrochemical transduction → ↓ **firing of impulse**
NEomycin Induce apoptosis by activating caspases → **DEath Receptor Pathway**.	N.B. Functional damage **recover after stopping the drugs**, but Structural damage **doesn't** recover.



Summary

Drugs related to balance disorders

1- Specific treatment	2- Symptomatic treatment	3- Prophylactic treatment
Targeting the cause.	Control the acute **symptoms** & autonomic compliants.	↓ **recurrence** of specific vertiginous conditions.

2- Symptomatic treatment

A- Vestibular suppressants	B- Antiemetics
To ↓ intensity of **vertigo** & Nystagmus evoked by **vestibular imbalance**.	To control **vomiting** & **nausea**.

A- Vestibular suppressants

Drug	Anti-cholinergic → Hyoscine	Benzodiazepines → Lorazepam, Clonzepam, Diazepam	Betahistine
MOA	1- ⊗ firing of **vestibular nucleus** neurons. 2- ↓ velocity of vestibular **nystagmus**.	Enhance the effect of GABA receptors.	It has: 1- Weak **H1** R agonist → **Vasodilation**. 2- Potent **H3** R antagonist on presynaptic n→ ↑ Histamine. 3- ↑ Serotonin → ↓ activity of vestibular nuclei.
Uses	Management of vertigo & **motion sickness**.	Small doses useful for management of acute vertigo	
ADRs	Dry mouth, **Sedation**, Blurred vision.	**Dependence**, **impaired memory**, ↑ risk of falling.	**Hypersensitivity reaction**, GIT side effects, headache, nausea.
C.I	–	–	**Pheochromocytoma**.

B- Antiemetics

Drug	Anti-Histamine	Phenothiazines	Dopamine antagonist
	DimenHydrinate	Prochlorperazine	Metoclopramide
MOA	Block **H1** R in CRTZ. Weak **anticholinergic** effects	Block **D2** R in CRTZ. Anti-psychotic.	**D2** R antagonist. (central, potent) Potent **gastroprokinetic** effect.
Uses	Vertigo, Motion sickness	**Best** antiemetics in vertigo.	–
ADRs	Dizziness & **anticholinergic** side effects	—	**Extrapyramidal maniefestations**
C.I	**Glaucoma** & prostatic enlargement.		

Summary

3- Prophylactic treatment

A- Diuretics. **Except** Loop diuretics!	B- Corticosteroid	C- Ca^{2+} blockers

C- Ca^{2+} blockers

Drug	**Cinnarizine**
MOA	1- Selective Ca^{2+} channel blocker. 2- **Anti- histamine**, **Anti-serotonine**, **Anti-dopamine**. 3- ⊗ K^+ current → K^+ channel blocker.
Uses	- Nausea. - Vomiting associated with Meniere's disease and **vertigo**.
ADRs	- **Muscle rigidity** & tremor. - Sweating.
C.I	- **Parkonism.** - Car drivers

Drugs induced vertigo

1- Vestibular toxins

Alter **function**	1- Drugs altering **fluid** & **electrolyte balance**. → Diuretics. 2- Drugs altering **vestibular firing**. → Anticonvulsants, Antidepressants, Sedative hypnotics, Alcohol, Cocaine.

2- Mixed ototoxins

Altering **Structure**	Altering **Function**
Aminoglycoside antibiotics; - **Gentamycin**. - **Kanamycin**, - **Neomycin**. - **Streptomycin**.	- **Quinine**, **chloroquine**, **quinidine** - Nitrogen mustard - Loop diuretics - NSAIDs - Tobacco
GenTamicin Induce apoptosis by evoking free radicals → **MiTochondrial Pathway**.	**- How functional derangement is induced by these drugs?** ↓ Local blood flow → biochemical changes → ↓ electrochemical transduction → ↓ **firing of impulse**
NEomycin Induce apoptosis by activating caspases → **DEath Receptor Pathway**.	

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Thank you for checking our team!

Pharmacology 435

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دلال الحزيمي
رغدة قاسم
ريم العقيل
سارا الحسين
ساره الخليفة
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محمد ابونيان
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