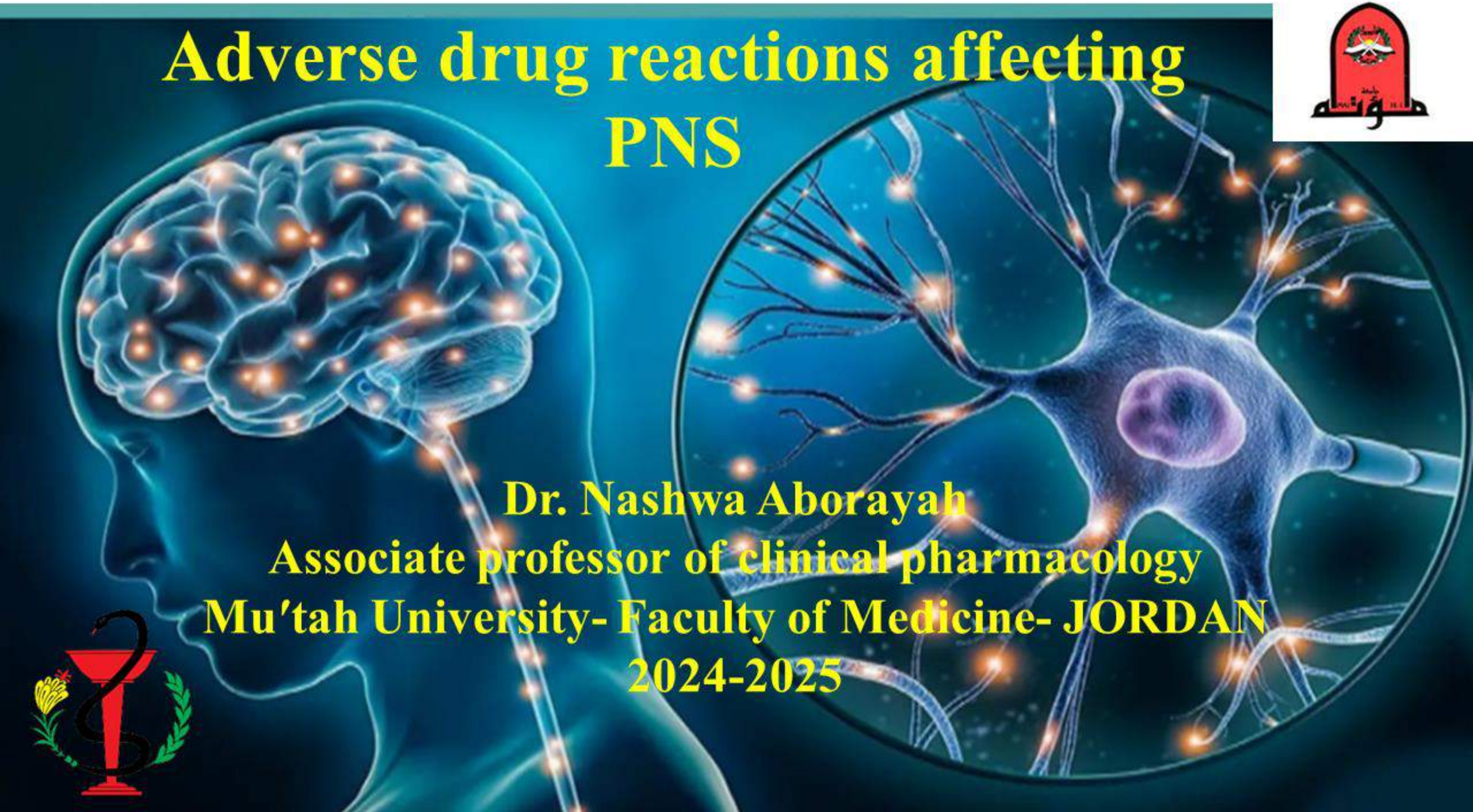
Adverse drug reactions affecting PNS



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Objectives

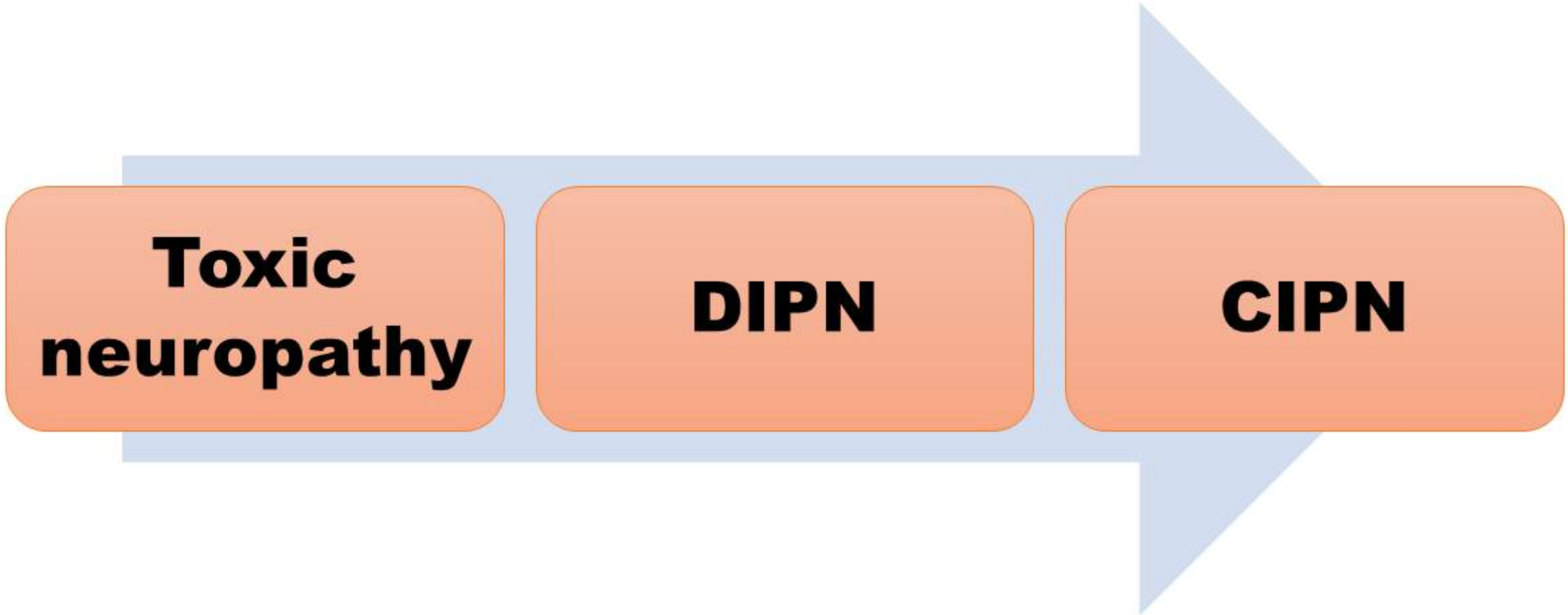
- Classification of adverse drug reactions affecting PNS
- Drug-induced peripheral neuropathy (DIPN): definition, causes, management
- Ototoxicity
- Optic neuropathy
- Neuroleptic malignant syndrome

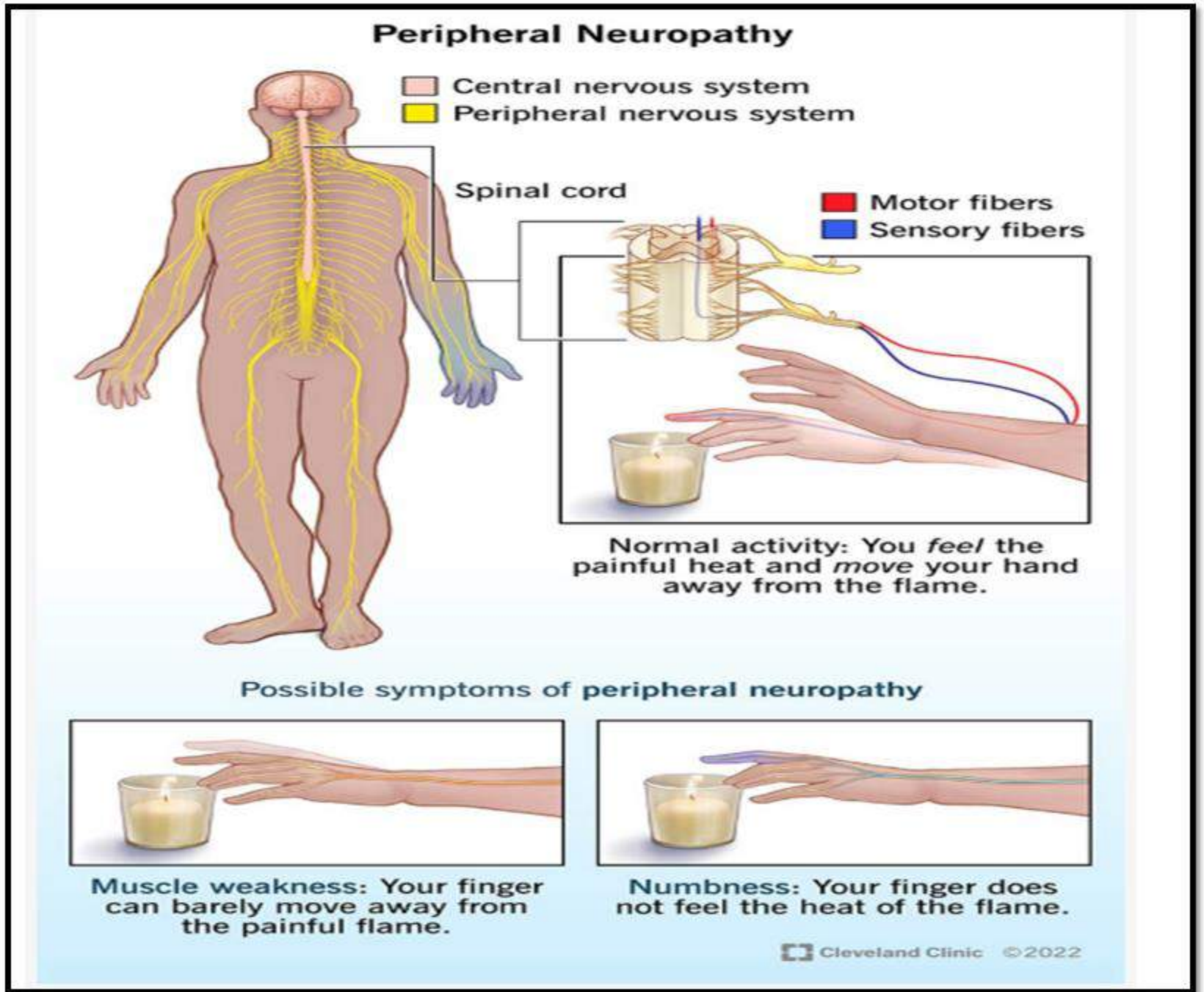
Adverse drug reaction affecting PNS

- 1- Drug-induced peripheral neuropathy DIPN
- 2- Ototoxicity
- 3- Optic neuropathy
- 4- Neuroleptic malignant syndrome

Drug-induced peripheral neuropathy (DIPN)

- **Toxic neuropathy** occurs when **a chemical substance (drug) causes damage to the peripheral nervous system**
- The most common cause of **toxic neuropathy** is **drug toxicity**, particularly associated with **chemotherapy treatments**.
- **Manifestations of Toxic neuropathies are primarily characterized as:**
- length-dependent, symmetric, sensory polyneuropathies with possible motor or autonomic involvement.
- **Length-dependent PN:**
- The longest nerves in the body, those reaching the feet—are affected first.
- Symptoms typically begin in the toes with numbness, (tingling : paresthesia) , or burning gradually progressing upward to the legs and hands as the condition worsens.
- The **longest axons** are most vulnerable to toxic injury, causing them to degenerate from the furthest tip backward toward the cell body.


Toxic neuropathy
DIPN
CIPN


Peripheral Neuropathy
Central nervous system
Peripheral nervous system
Spinal cord
Motor fibers
Sensory fibers
Normal activity: You *feel* the painful heat and *move* your hand away from the flame.
Possible symptoms of peripheral neuropathy
Muscle weakness: Your finger can barely move away from the painful flame.
Numbness: Your finger does not feel the heat of the flame.
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Classification of DIPN

- **Drugs associated with peripheral neuropathies**
- 1- **Chemotherapeutic agents** – cisplatin, paclitaxel, vincristine, bortezomib
- **2- TNF-alpha inhibitors** (infliximab, etanercept)
- 3- **Antiretroviral agents** (stavudine)
- 4- **Cardiac drugs** (amiodarone, statins)
- 5- **Thalidomide**
- 6- **Antimicrobials** (metronidazole, fluoroquinolones, isoniazid)
- 7- **Disulfiram**
- **8- Pyridoxine high doses**
- **9- Colchicine**
- **10- Phenytoin, Lithium**
- **11- Chloroquine, hydroxychloroquine**

Chemotherapy-induced peripheral neuropathy (CIPN)

- A common, often long-lasting, dose-dependent adverse effect of many cancer treatments
- Affecting 30–85% of patients
- **Symptoms of CIPN :**
- Sensory-predominant, often described as a "**glove and stocking**" distribution (starting in feet/hands and moving upward)
- **Sensory changes**: Tingling: "pins and needles," , numbness, or cold/burning pain.
- **Allodynia**: Sensitivity to light touch or temperature changes: unpleasant abnormal sensation of touch: dysesthesia (nerve damage)
- **Motor/Autonomic symptoms**: Muscle weakness, difficulty with fine motor tasks (e.g., buttoning clothes), and potential balance problems (ataxia).
- **"Coasting" effect:** Symptoms may progress or worsen for months after treatment ends.

Common Chemotherapy Agents Causing CIPN

- Platinum agents: Cisplatin, Carboplatin, Oxaliplatin.
- Taxanes: Paclitaxel (Taxol).
- Vinca alkaloids: Vincristine.
- Proteasome inhibitors: Bortezomib.

Pathomechanisms of CIPN

- **Chemotherapeutics damage the nervous system structures and cause CIPN via:**
- Microtubule disruption
- DNA damage
- Oxidative stress and mitochondrial damage
- Altered ion channel activity
- Myelin sheath damage
- Immunological processes and neuro-inflammation

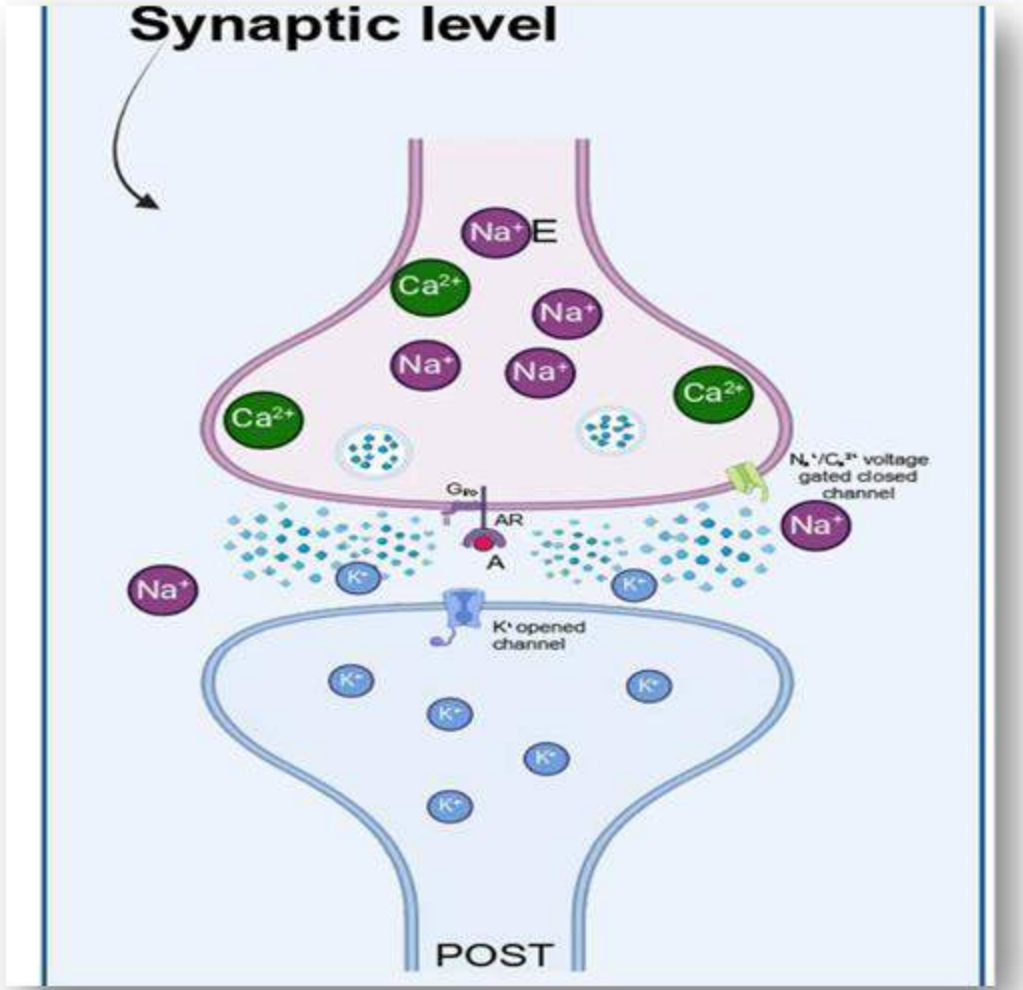
CIPN management

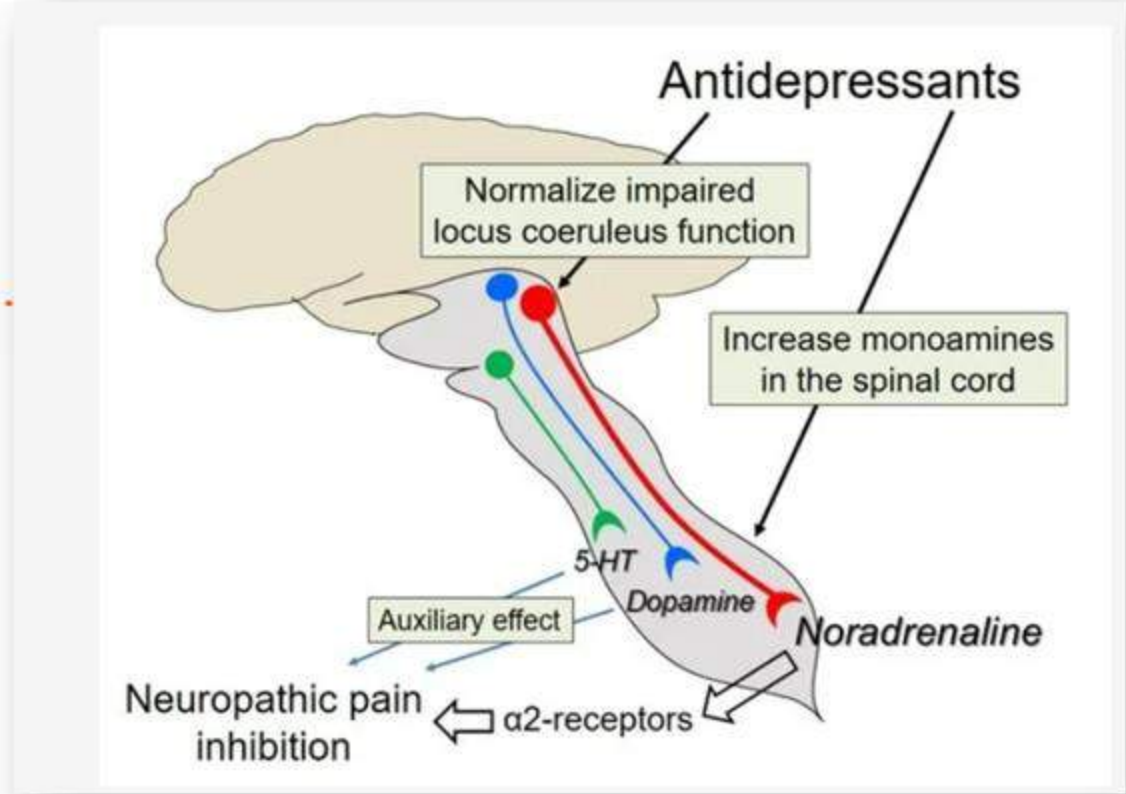
- **Goals:**
- Reducing pain and maintaining quality of life rather than curing the nerve damage
- **The antidepressant duloxetine** is the only agent recommended for treating painful CIPN.
- **Other options include** gabapentin, tricyclic antidepressants, and topical treatments like menthol or capsaicin creams (counter-irritant)
- **Physical Therapy**: Exercise and physical therapy can help with balance and functional issues.
- **Dosage Adjustment**: reducing or stopping chemotherapy doses to prevent further nerve damage

Management of toxic neuropathy

- **Includes:**
- 1- Prevention
- 2- Rehabilitation of functional impairments
- 3- Dosage reduction or change in the drug
- **Neuropathic pain drug therapy:**
- **1- Serotonin-noradrenalin reuptake inhibitor (SNRI) drugs (duloxetine)**
- **2- Tricyclic antidepressants (amitriptyline):**
- inhibits re-uptake of norepinephrine and serotonin, thereby increasing their concentration at the synaptic clefts of the brain.
- **3- Anticonvulsants/nerve membrane stabilizers** (**gabapentin**, **pregabalin**): block presynaptic Na and Ca voltage-gated channels: block pain signals
- **4- Topical Capsaicin, Topical lidocaine**
- **5- Opiate analgesics and mixed opioids** (**tramadol**).

Neuropathic pain





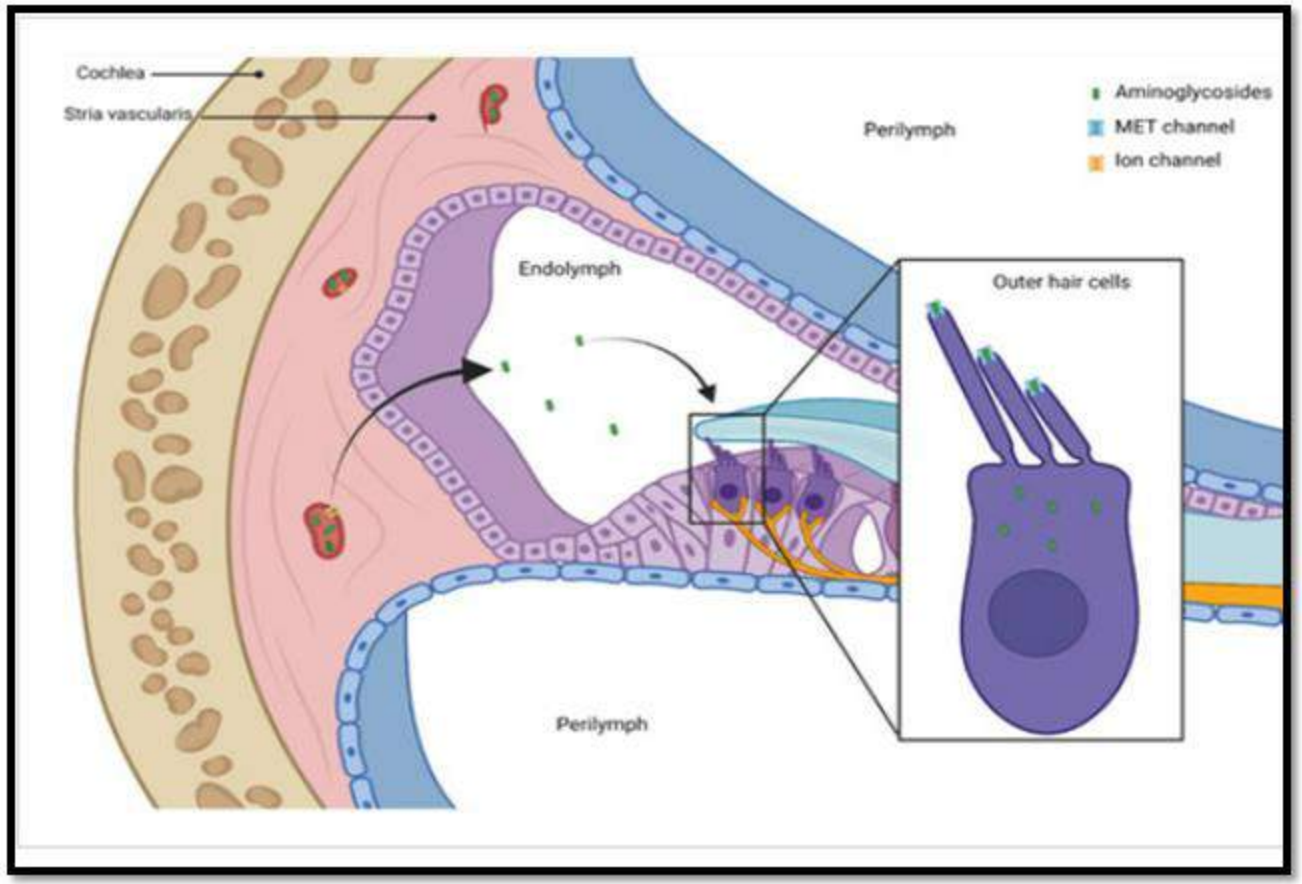
Duloxetine

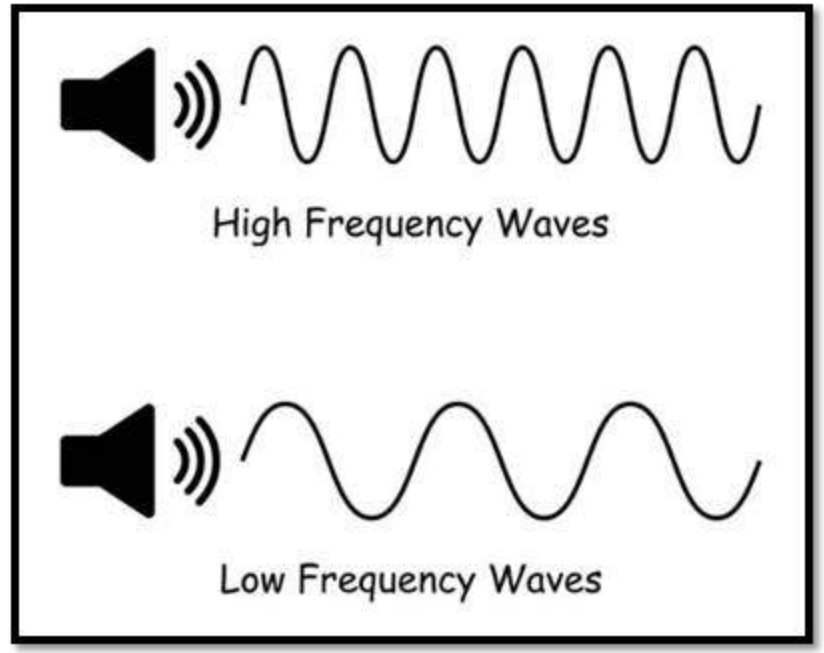
- **Duloxetine** is a balanced serotonin and noradrenaline reuptake inhibitor
- **FAD-approved for the treatment of** major depressive disorders, urinary stress incontinence and the management of neuropathic pain associated with diabetic peripheral neuropathy.
- **Dose**: 60 mg daily dose to effectively treat pain associated with diabetic peripheral neuropathy (DPNP) and fibromyalgia
- Duloxetine: is a recommended **first-line treatment for painful chemotherapy-induced peripheral neuropathy (CIPN)**, particularly for pain associated with taxanes and platinums.
- **Adverse effects**: Common
- Usually mild-to-moderate
- Including: dizziness, sleepiness, fatigue, nausea, constipation, dry mouth, and sweating

Ototoxicity

- **1- All aminoglycosides** are ototoxic
- **The toxicity on the inner ear** can manifest as cochleotoxicity or vestibulotoxicity..
- **Cochleotoxicity: destruction of the hair cell in organ of Corti.**
- **Manifestations**: Affection of **cochlear part** causes **tinnitus and hearing loss** (high-pitched sound is affected first), affection of **vestibular part** causes **nausea, vertigo and disturbance in gait.**
- The effect may does not appear until several days after stoppage of drug administration and may progress to **complete** and **permanent hearing loss (as no regeneration in the hair cell).**
- **Streptomycin and gentamicin are more toxic to the vestibular division**.
- **Neomycin, kanamycin and amikacin are more toxic to the cochlear division**.
- **Tobramycin is toxic to both divisions**.
- **They can cross placenta causing damage to eighth cranial nerve of fetus.**

Ototoxicity of aminoglycosides





Ototoxicity

- Factors enhance the ototoxicity of aminoglycosides: (also enhance nephrotoxicity):
- a) Use of high doses for long duration as ototoxicity is a dose-dependent.
- b) Renal failure as there is failure of drug excretion.
- c) Elder patients as more susceptible to toxicity.
- d) Use of loop diuretics especially ethacrynic acid (less with furosemide) as they potentiate the ototoxicity of aminoglycosides

Ototoxicity

- **2- Loop diuretics:** can cause **dose-related hearing loss** that is usually **reversible.**
- It is most common in patients who have **reduced renal function** or who are also **receiving other ototoxic agents** such as aminoglycoside antibiotics.
- **Mechanism:**
- Inhibiting active ion transport (specifically the Na-K-2Cl cotransporter) in the stria vascularis of the cochlea, which leads to a rapid decrease in the endolymph and damage to the hair cells.
- It can also disrupt the integrity of the blood-labyrinth barrier BLB, making the inner ear more vulnerable to damage.
- Ototoxicity occurs most frequently with **rapid intravenous administration.**
- **Ethacrynic acid** appears to induce ototoxicity more than do other loop diuretics

Optic neuropathy

- **Phosphodiesterase type 5 (PDE-5) inhibitors**, **amiodarone**, **linezolid**, **isoniazid**, **ethambutol**.
- **PDE-5 Inhibitors**: **treatment of erectile dysfunction** (ED) in males.
- Example: sildenafil (Viagra).
- **Mechanism**: Inhibitory effects on **PDE 6**, an isoenzyme expressed in the rods and cones of the eye.
- **Amiodarone**: This drug, a **class III antiarrhythmic agent**: exact mechanism of optic neuropathy is unknown.
- The condition is typically **insidious in onset**, **takes months to resolve**, and presents **bilaterally**

Optic neuropathy

- **Linezolid:** long-term use of linezolid, with reported duration of treatment ranging from 5 to 11 months in doses of 600 to 1,200 mg/day.
- **Mechanism**: inhibition of mitochondrial protein synthesis in the optic nerve
- **Ethambutol**: treatment and prevention of tuberculosis
- It causes **optic neuropathy in up to 5% of patients taking the drug.**
- The **mechanism** is related to **related to chelation of copper in retinal cells**.
- **Isoniazid-induced optic neuropathy** is thought to be **less frequent** and **reversible.**
- **Mechanism:** pyridoxine depletion and disruption of neurotransmitter synthesis (specifically GABA)

Neuroleptic Malignant Syndrome (NMS)

- **Neuroleptic Malignant Syndrome (NMS): life-threatening:**
- **Induced by typical antipsychotics:** Haloperidol, Chlorpromazine, Fluphenazine

Due to autonomic disturbances

•Hyperthermia, muscular rigidity, rhabdomyolysis, tachycardia, hyper or hypotension, confusion

•**Complications**: Coma and death

•**Treatment:**

•Stop drug

•Supportive management and

•Sever cases: ICU

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- **Thank you**