Adverse drug reactions affecting PNS

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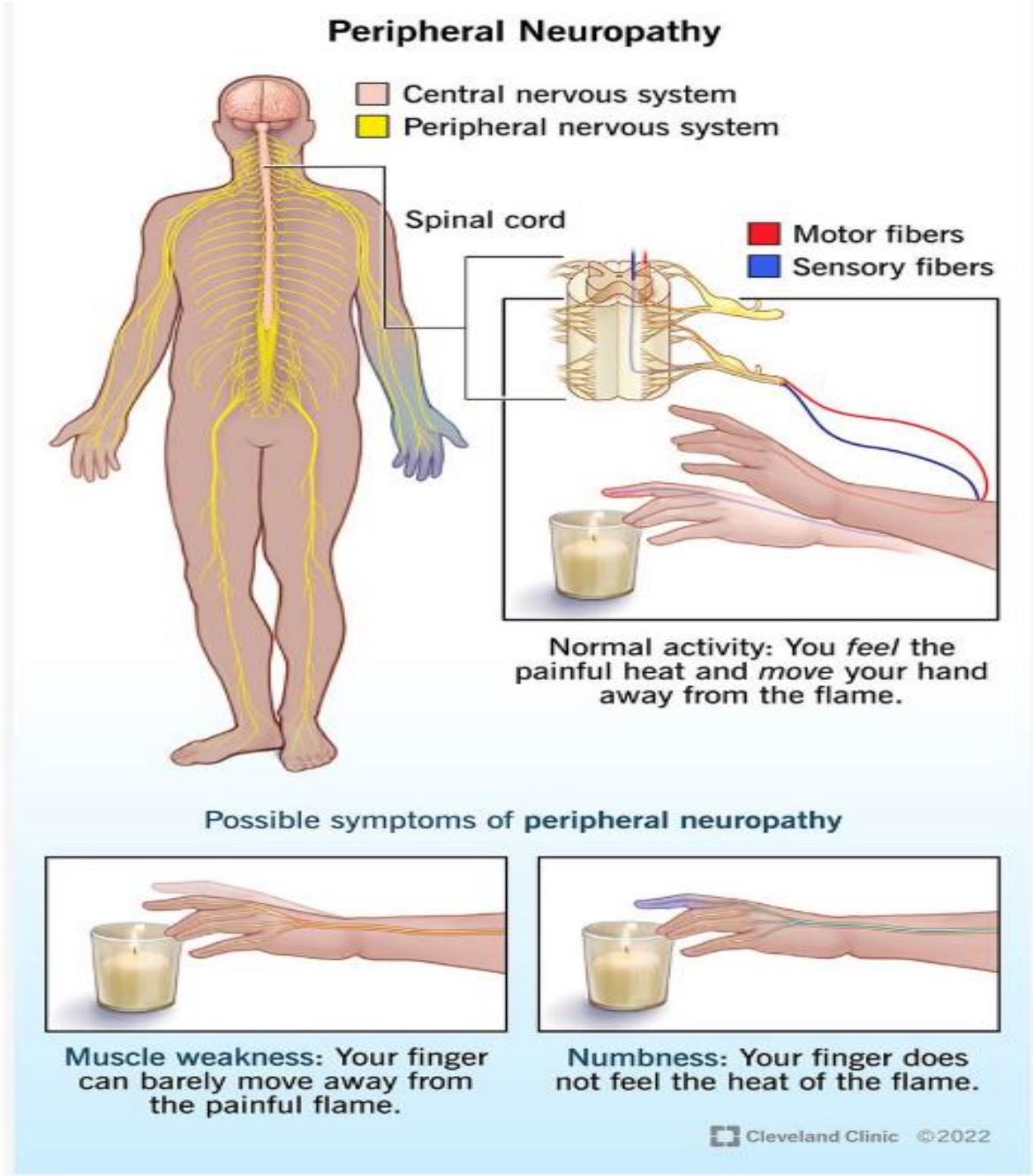
OBJECTIVES

- 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 include:**
- 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.


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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Causes of DIPN (toxic neuropathy)

- There are **more than 200 chemicals** known to be **neurotoxic** to humans.
- There are a number of **prescribed medications**, including **chemotherapeutic agents**, that cause **neurotoxicity**
- **Peripheral neurotoxicity** can be a limiting factor in the use of many chemotherapy agents
- **According to the WHO**, **5.1 % of DIPN** is due to **alcohol**.
- Some **herbal medicine** products commercially available have been shown to contain heavy metals such as **lead, mercury, and arsenic**.
- Using these herbal products may lead to **heavy metal toxicity** and **secondary peripheral neuropathy**.

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

Agent	Symptoms and signs	Reversible after discontinuation
Bortezomib	Sensory, painful	Gradually
Paclitaxel (Taxol)	Paresthesias, dysesthesias (weakness), ataxia	Partially
Vincristine	Sensorimotor and autonomic	Yes
Cisplatin	Sensory axonopathy, ataxia (neuronopathy), L'hermitte sign	May worsen after discontinuation

The relationship between the occurrence of neuropathy and the use of cytostatic drugs is usually dose-related.

If axonal or neuronal degeneration has occurred, permanent symptoms and signs remain.

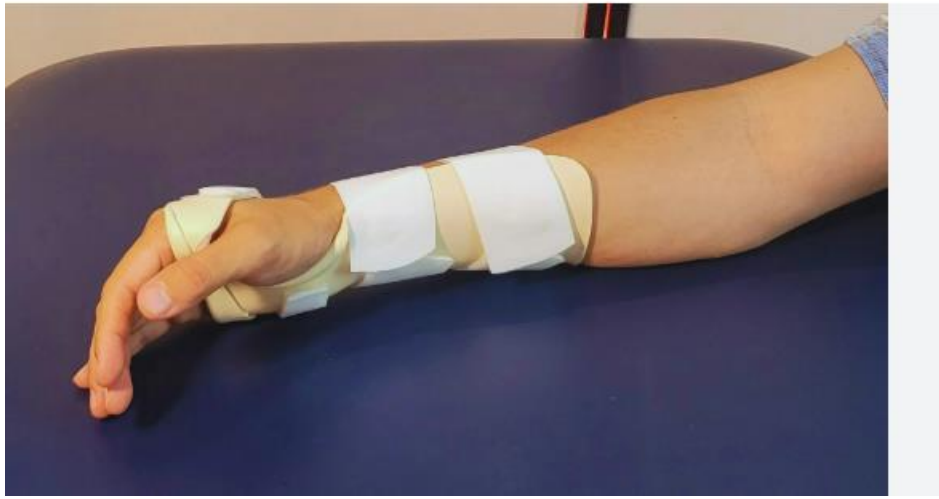
Drug	Mechanism of neuropathy	Drug	Mechanism of neuropathy	Drug	Mechanism of neuropathy
Metronidazole	**Axonal** degeneration, shown to bind to neuronal RNA	**Amiodarone**	Demyelination, loss of large **axons**	**Interferons**	immune mediated **myelin** degradation, **vessel occlusion** leading to nerve ischemia
Linezolid	**Mitochondrial** toxicity	**Thalidomide**	**Mitochondrial** dysfunction in **axons**	**Biologics**	T cell and humoral immune attack on peripheral **myelin** and **vasculitis**
Vincristine	Microtubule-mediated dysfunction	**Statins**	alterations of membrane function, disruption of energy utilization in nerves		

Management of toxic neuropathy

- **Includes:**
- 1- Prevention
- 2- Rehabilitation of functional impairments
- 3- Dosage reduction or change in the drug
- **Neuropathic pain management:**
- **Anticonvulsants/nerve membrane stabilizers** (**gabapentin**, **pregabalin**):
- **Block voltage-gated calcium channels**, to **inhibit the release of excitatory neurotransmitters** (**glutamate and substance P**) in the presynaptic area: block pain by affecting the pain messages travelling through the brain and down the spine.
- **Tricyclic antidepressants** (**amitriptyline**): **inhibits re-uptake of norepinephrine and serotonin**, thereby increasing their concentration at the synaptic clefts of the brain.
- **Serotonin-noradrenalin reuptake inhibitor (SNRI) drugs** (**duloxetine**)
- **Topical Capsaicin; Topical lidocaine**
- **Opiate analgesics and mixed opioids** (**tramadol**).

Management

- **Orthoses and assistive devices:** can aide weakness and impaired balance and sensation.
- **Ankle Foot Orthosis** can serve as a brace to prevent foot drop and also aide in postural instability.
- Assistive devices such as **canes**, **walkers**, **crutches**, etc. can also help with weakness and/or balance impairment.
- **Protective footwear** is of importance for anyone with sensory impairments for peripheral neuropathy to ensure no skin breakdown or wounds occur.
- **Splinting** and **casting** may also be of benefit to prevent or treat joint contractures occurring from weakness and immobilization in peripheral neuropathy.




Protective
footwear
must be
worn

Ototoxicity

•**1- All aminoglycosides** are ototoxic due to **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.**

•**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

- **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.
- 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.
- Currently there are three agents available—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

- Optic neuropathy has been associated with the **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.
- **Ethambutol**: This drug, a first-line agent in the treatment and prevention of tuberculosis
- . It has been well documented to cause **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.**

Side Effects of Antipsychotic Medications (neuroleptic drugs)

Neuroleptic Malignant Syndrome (NMS): life-threatening

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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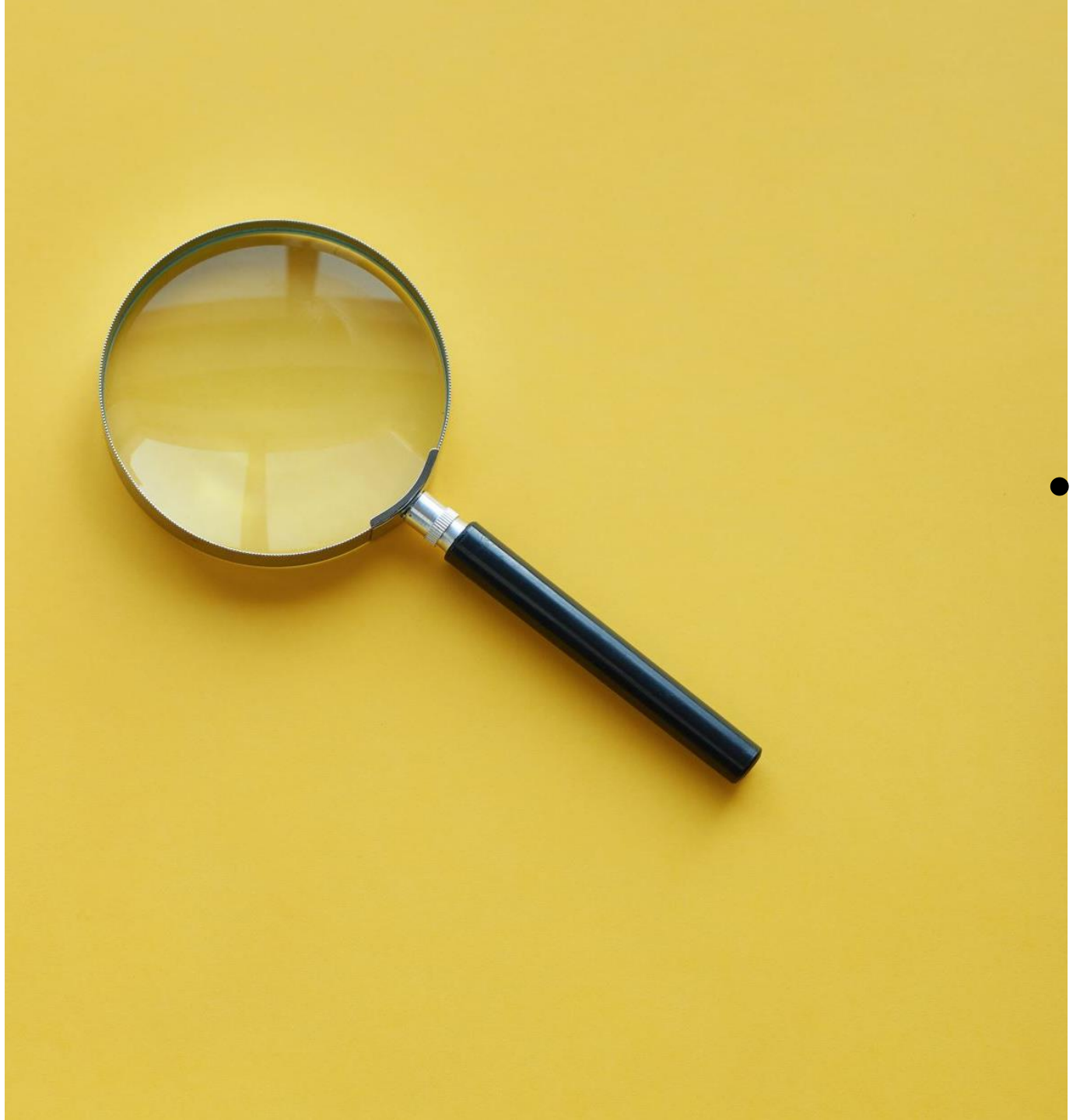

- **Thank you**