NEURO-ONCOLOGY GUIDELINES

Nervous System Complications Among children cancer patients include:

- Seizures as Complications in Cancer
- Movement Disorders
- Peripheral Nerve Disease

➢ Seizures as Complications in Cancer

If patient has first attack of seizures before starting Antiepileptic :

- Must to decide if this seizure is

- **Provoked seizure (Acute symptomatic seizures)**
- Occurs due to a particular trigger

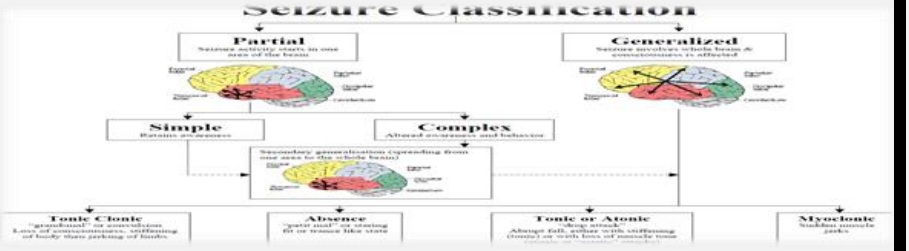
  such as (fever, toxins, head trauma metabolic or electrolyte disturbance)
- Have a low risk of seizure recurrence
- Treatment by correction of particular trigger provoking seizures

- **Unprovoked seizure= Epilepsy**
- Chronic seizure due to abnormal brain function arise from brain lesion or CNS disorder . (genetic, structural, metabolic, immune)
- Have a high risk of seizure recurrence
- Treatment focused on treating chemical neurotransmitters by Anti Epleptic Drug

- Get an accurate description of the seizure from witness involves semiologies of attack with ictal and postictal state. Ask about events may leading up to the seizure to decide if it was provoked or not ,aslo get informations about past antiepileptic compliance, birth history, and any history of CNS infections.
- Order laboratory testing including CBC, glucose, electrolytes, metabolic, renal, liver function, and urinalysis EEG , MRI if needed

l-Asparaginase	Chlorambucil	Interferon-a
Bevacuzimab	Cyclosporin A	Lomustine
Carmustine	Etoposide	Methotrexate
Cisplatin	5-Fluorouracil	Procarbazine
Busulphan	Ifosfamide	Vincristine

Seizure Semiology



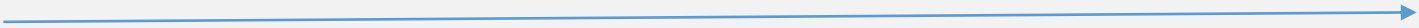
- ❖ **Focal (partial) seizures**: are a type of seizure that affects only one hemisphere of your brain and one side of body

- Focal Onset Aware Seizures (simple partial seizure)
- Patient may be aware during a seizure, remember what happened after the seizure passes.
- Focal Onset Impaired Awareness (complex partial seizure)
  - ❖ Patient may lose consciousness attack , won't remember what happened.
  - ❖ **Generalized Seizures**: affect both hemispheres of brain, causing symptoms affect and similar both sides of body.
- Absence seizures (petit mal) sudden staring, eye blinking and lip smacking and impaired consciousness occurs during childhood, last between 5 and 10 seconds. Repeated dozens or hundreds of times a day.
- Clonic seizures cause rhythmic jerking muscle contractions in arms, neck, and face.
- Myoclonic seizures consist of sudden, brief muscle contractions, occur singly or in clusters, can affect any group of muscles (Arms), fully Consciousness.
- Tonic seizures: muscle stiffening, often associated with impaired consciousness and falling to the ground.
- Atonic seizures (drop seizures) sudden unconsciousness loss of control of the muscles (legs) falling

Factor of **Tumor type &location& mechanism induce seizure**

- All these factors influences the incidence of epilepsy.
- Malignant brain tumors increased metabolic rates and rapid cell growth leading to hypoxia and acidosis within and around the tumor mass leading to neuronal excitability and seizures.
- Frontal, temporal, insular, and parietal lobe tumors are more commonly associated with more Epilepsy than occipital and midline tumours.
- Seizures are common with supratentorial than with infratentorial tumor in the temporal lobe, frontal lobe

Meningioma / HighGrade Glioma (HGG) / Low grade glioma (LGG) / Glionural tumors (DNET & Ganglioma)



Incidence Of Seizures

ANTIEPILEPTIC DRUG SELECTION

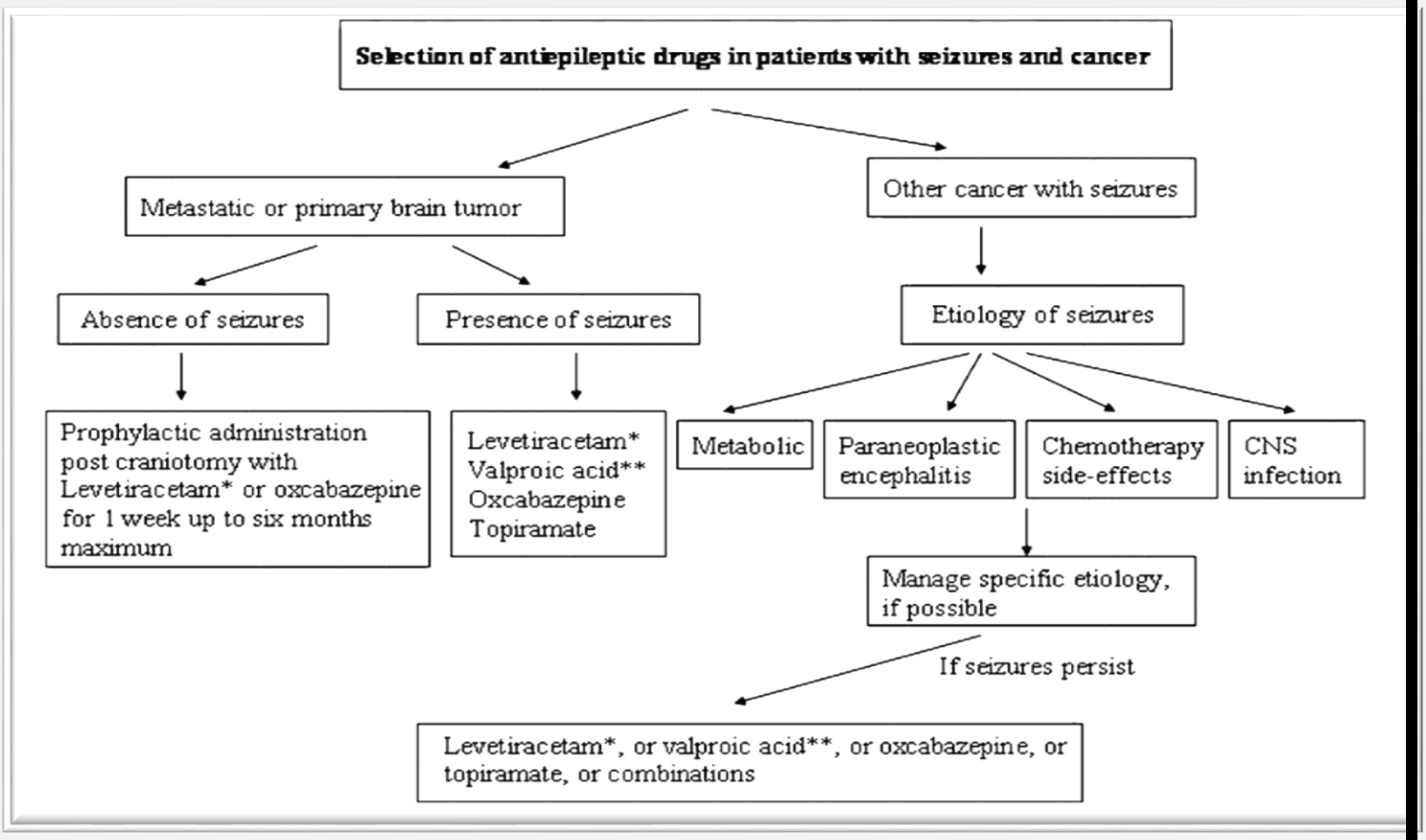
- The choice of a specific antiepileptic drug **(**AED) is primarily based on the type of the epilepsy.

A. Generalized Seizures: mainly need (Broad spectrum AEDs which work on more than two mechanism on brain)

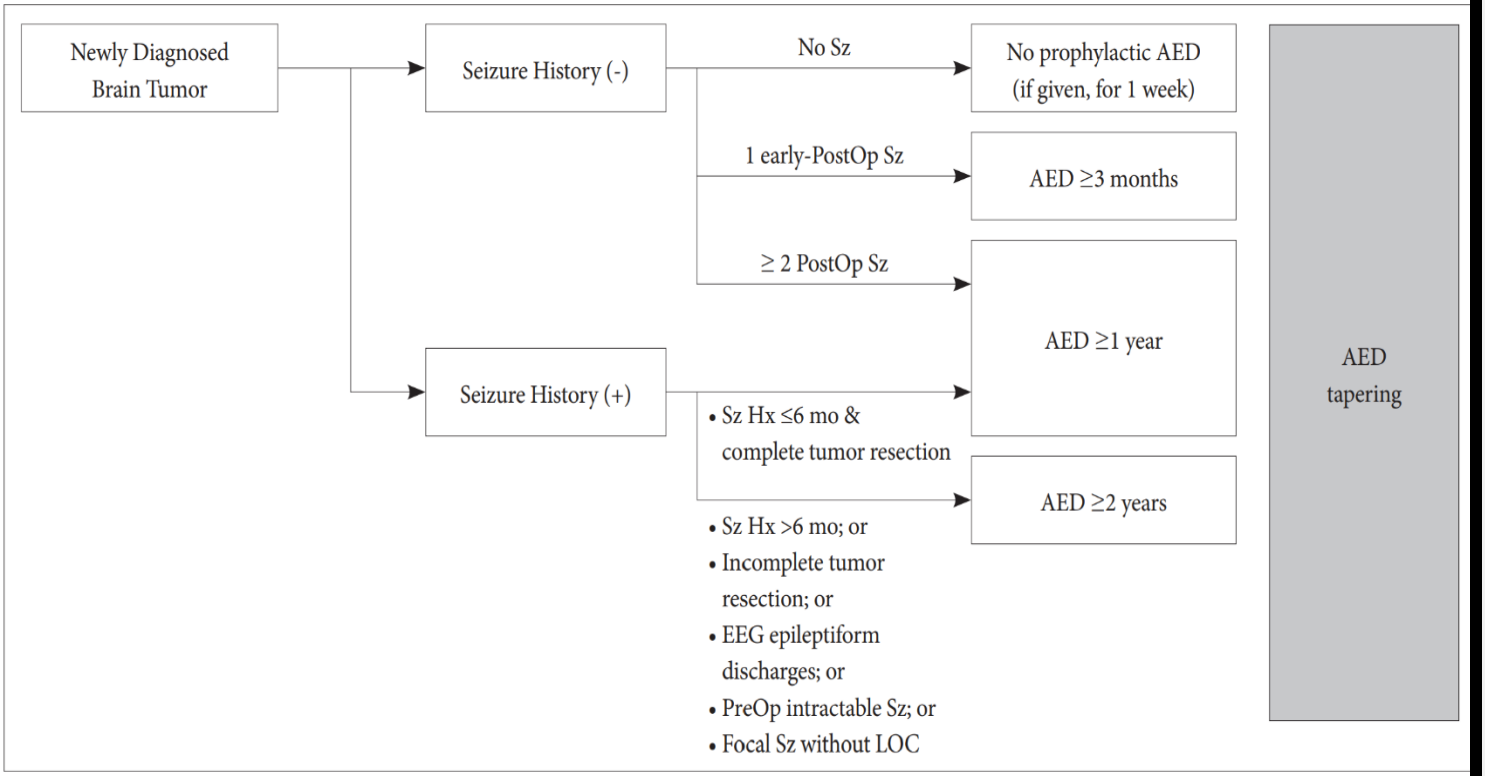
B. Focal (partial) seizures: need (Narrow spectrum which work on two mechanism on brain)

- The basic principles of seizure therapy, administration of **monotherapy AEDs ,** which improve patient compliance, more cost-effective, minimizes drug-drug interactions with other AEDs and chemotherapy

SELECTION OF ANTIEPILEPTIC DRUGS IN CANCER PATIENTS WITH SEIZURES



- ## PRIMARY OR METASTATIC BRAIN TUMOUR



- In patients with newly diagnosed brain tumors who have not had a seizure, clinicians should not prescribe antiepileptic drugs (AEDs) to reduce the risk of seizures (level A).

1. **LEVETIRACETAM (LEV)** is First-line AEDs ,in brain tumours (LGG or brain mets except glioblastoma)
2. **VALPROIC ACID (VPA)** is First-line AED in Glioblastoma
3. **OXCarbazepin** could be monotherapy in brain tumour if produces partial seizures (level A)
4. **Topiramate & zonisamide** not recommended in patients with gliobastoma or HGG, astrocytoma

OTHER CANCER WITH SEIZURES MANAGEMENT

- Provoked seizures may by cytotoxic chemotherapy and Cerebrovascular complications of cancer Stroke, thrombosis, CNS infections, radiation and encephalopathy
- **Firstly; manage specific etiology which may induce seizure if seizures still presistant start**

1. **Levetiracetam** : is 1st line as monotherapy for generalized tonic-clonic seizures myoclonic seizures, partial-onset seizures
2. **Oxcarbazepine** is effective as initial monotherapy for children with partial-onset seizures (level A).
3. **Valproic acid** is FDA approved for the treatment of complex partial seizures and absence seizures

❖ **Phenytoin** is effective in controlling seizures in brain metastases and is often preferred in the setting of status epilepticus as it can be conveniently loaded intravenously only no need for routine management of seizures in patients with cancer

ANTIEPILEPTIC COMIBINATION (POLYTHERAPY)

1. In Neuro-oncology if the initial anticonvulsant insufficient seizure control, switch to a second agent as monotherapy specific for type of epilepsy.
2. For both low-grade glioma and GBM, if monotherapy is insufficient due to Pharmacoresistance epilepsy
3. Combination therapy should be considered

- **Guidance for combining antiepileptic drug**

A. Maximise dose of first antiepleptic
B. Add drugs with multiple mechanisms and avoid combining similar mechanism of action
C. Titrate new agent slowly then reduce dose of first drug
D. Replace less effective drug if response still poor
E. Try range of different duo therapies, before adding a third drug
F. Add third drug if still sub-optimal control

- Higher numbers of AEDs should be avoided , produce useful seizure reduction without side effects
- polytherapy with more than two anticonvulsant drugs has not been shown to provide additional efficacy

❖ **If pt still has Genarlized seizures…**

1. **Levetiracetam** with **Valproic acid** Suggest synergistic effect (GABAergic or antiglutaminergic).
2. **Levetiracetam** with **Valproic acid + [Oxcarbezpine** or **Lamotrigine]** combination shows supra-additive effects for generalized epilepsy, for its potential of synergistic activity with VPA
3. **Levetiracetam** with **Valproic acid + [Oxcarbezpine** or **Lacosamide] if still not effective finally add Topiramate**
4. **Valproic acid** with **Topiramate** in generalized seizures for children with untreated absence seizures, Myoclonic seizures, is also a broad-spectrum AED that often used as adjuvant avoid **Oxcarbezpine**
5. **Ethosuximide** and **Valproic acid** monotherapy for children with newly diagnosed or untreated absence seizures (level A) and **Lamotrigin** is possibly (level C).

❖ **If pt still has Partial seizures…**

1. **Oxcarbezpine** with **Levetiracetam** for children with untreated partial–onset seizures.
2. **Lacosamide** with **Levetiracetam** shown to be efficacious as an adjunctive agent for focal seizures
3. **If Levetiracetam + [Oxcarbezpine** or **Lacosamide]not effective add (lamotrigine orzonisamide).**
4. **Valproic acid** with **Lamotrigin** Suggest synergistic effect for focal & Atonic seizures
5. **Vigabatrin** is effective in Infantile spasms and Refractory complex partial seizures as adj TTT

❖ **clonazepam** & **Gabapentin used** adjunctive in drug-resistant seizures

➢ SEIZURES CONTROL PERCENTAGE AFTER EACH ADD ON OF AEDS

- There are many reasons to consider reducing polytherapy, including reducing the risk of serious adverse effects, minimizing drug interactions and decreasing costs.
- More than triple drug therapy may did not provide any further improvement of seizures.
- Surgery plays a crucial role in seizure control.

ANTIEPILEPTIC DRUG WITHDRAWAL

- *AEDs withdrawal can be attempted after*

1. **One year of seizure freedom** in non-brain tumour or completely resected patient tumour patient
2. **Two years of seizure freedom** in the presence of any of the following conditions:

a) Still on radiation, Venous sinus thrombosis, CNS infections
b) Incomplete tumour resection In the case of a structural lesion (not completely resected)
c) Preoperative drug-resistant seizures
d) Focal seizure without a loss of consciousness
e) Documented etiology of seizures (mental retardation, perinatal insults, abnormal neurologic exam)

3. Five years of seizure freedom in patients

- Highly malignant progressive tumour, refractory seizures during previous weaning trial after 2 years
- Seizures associated with metabolic or toxic encephalopathies as long as the cause remains present

❖ **In patient with long-term (above one year) good seizure control on polytherapy**

Suitable time try to gradually taper down to monotherapy.

- ✓ Withdraw one of AEDs by reduction of 25% every 4-7 days up to 2 weeks according to patient history of seizures and if he on another AEDs or has severe side effects from the drug
- ✓ **When seizure occurs during AED withdrawal, AED dose should be increased again and maintained longer**.
- ✓ Patient dis-continuing treatment should be followed for 1 year seizure-free

PROPHYLACTIC ANTIEPILEPTIC

American Academy of Neurology (AAN) , Society of Neuro-Oncology(SNO) European Association of Neuro-Oncology (EANO) *have advised:*

A. There is any role for AED prophylaxis in brain tumour patients without a history of seizures, clinicians should not prescribe antiepileptic drugs (AEDs) to reduce the risk of seizures (level A).
B. There is insufficient evidence to recommend prescribing AEDs for brain tumour patients undergoing surgery to reduce the risk of seizures in the pre or postoperative period (level C).
C. If prophylactic antiepileptic was prescribed should to be discounted during 1–2 weeks after brain tumour surgery in patients who never had a clinical seizures (level A).
D. There is insufficient evidence to support using tumour location, histology, grade, molecular/imaging features when deciding whether or not to prescribe prophylactic AEDs (level U)

AEDs INTERACTION

- Antiepileptic drugs that are known to alter the function of hepatic cytochrome P450 (CYP450)

(e.g., phenytoin, carbamazepine, valproate) should by avoided due to CYP450 enzyme inducing antiepileptic drugs may accelerate metabolism and decrease the efficacy of corticosteroids and chemotherapeutic agent

- Cisplatin and high-dose methotrexate lead to lower plasma levels of phenytoin, VPA, and benzodiazepines
- Patients at particular risk of heart disease should be particularly avoided Carbamazepine, lacosamide, lamotrigine, oxcarbazepine

AED	IV?	CYP inducer	PB (%)	AED effect on chemo	Chemo effect on AED
PHB	Yes	**1A2, 2A6, 2B6, 2C9, 3A4,** 2C19	50	Thi↓ Nit↓ Vbl↓ Vnc↓ Mtx↓ Pac↓ 9AC↓ Ten↓ Pro↑ Prd↓ Dox↓ Tam↓ Ifo↓	Tmz
PHT	Yes	**2B6, 2C9, 2C19, 3A4,** 1A2	**90**	Pro↑ Pac↓ Bus↓ Top↓Vbl↓ Vnc↓ Mtx↓ Iri↓ 9AC↓ Ten↓ Dex↓ SrI↓	Mtx↓ Pro↑ Cis↓ Nit↓ Eto↓ Dox ↓ Dac↓ Vbl↓ Ble↓ Dex ↓↑ Car↓ 5FU↑ Cpc↑ Tam↑ Tmz
CBZ	No	**1A2, 2B6, 2C9, 2C19, 3A4**	**75**	MTX↓ Pac↓ Vbl↓ Vnc↓ Ten↓ 9AC↓ Srl↓ Pro↑	Cis↓ Dox↓ Tmz
OXC	No	3A4	40	–	Tmz
VPA	Yes	2A6 (inhib. 2C9, 2C19, 3A4)	**90**	–	Mtx↓ Dox↓ Cis↓
TPX	No	3A4	30	–	Tmz
ZNS	No	(Inhib. 2E1)	50	–	–
LTG	No	No	50	Mtx	–
GBP	No	No	< 5	–	–
PGB	No	No	< 5	–	–
LVT	Yes	No	<5	–	–
LCS	Yes	No	<5	–	–

AEDs Side-effects

Drug	Systemic side effects	Neurologic side effects
Carbamazepine	Nausea, GIT Disturbance, leukopenia Rash,hepatotoxicity, Hyponatremia,	Drowsiness, Sedation, Lethargy.
Oxcarbazepine	vomiting, rash, hyponatremia	ataxia; diplopia
Lacosamide	Dizziness, headache, nausea, diplopia	Vertigo, Attention and Sleep Disturbance, blurred vision
Lamotrigine	Rash, SJS/TEN, multiorgan hypersensitivity	Dizziness, Tremor, Diplopia
Levetiracetam	Dizziness, somnolence	Agitation, irritability, behavioral problems
Valproate	Weight Gain, Hair Loss, thrombocytopenia, Teratogenicity	Tremor, Dizziness
Perampanel	Weight Gain, Fatigue, Nausea	changes in mood and behavior, aggression, homicidal ideation
Phenytoin	Gingival Hypertrophy, hepatotoxicity, osteomalacia , myelotoxicity	Confusion, nystagmus, myopathy, Ataxia
Pregabalin	Weight Gain, Peripheral Edema, Dry Mouth	Dizziness, Somnolence, Ataxia, Tremor
Topiramate	Weight Loss	Difficulty Concentrating, Confusion, Cognitive impairment
Vigabatrin	Vision Loss	Drowsiness, Fatigue, Dizziness

AED Monograph

COMMON MECHANISMS OF ANTISEIZURE DRUG ACTION

Drug	Na+ channels	Ca+ channels	K+ channels	Inhibitory transmission	Excitatory transmission	SV2A binding
Levetiracetam		+	+	+	+	+++
Valproate	+	+		++	+	
Topiramate	++	++		++	++	
Phenytoin	+++	+				
Oxcarbazepine	+++	+	+			
Lamotrigine	+++	+				
Zonisamide	++	++				
Carbamazepine	+++	+				
Lacosamide	+++					
Ethosuximide		+++				
Perampanel					+++	
Vigabatrin				+++		

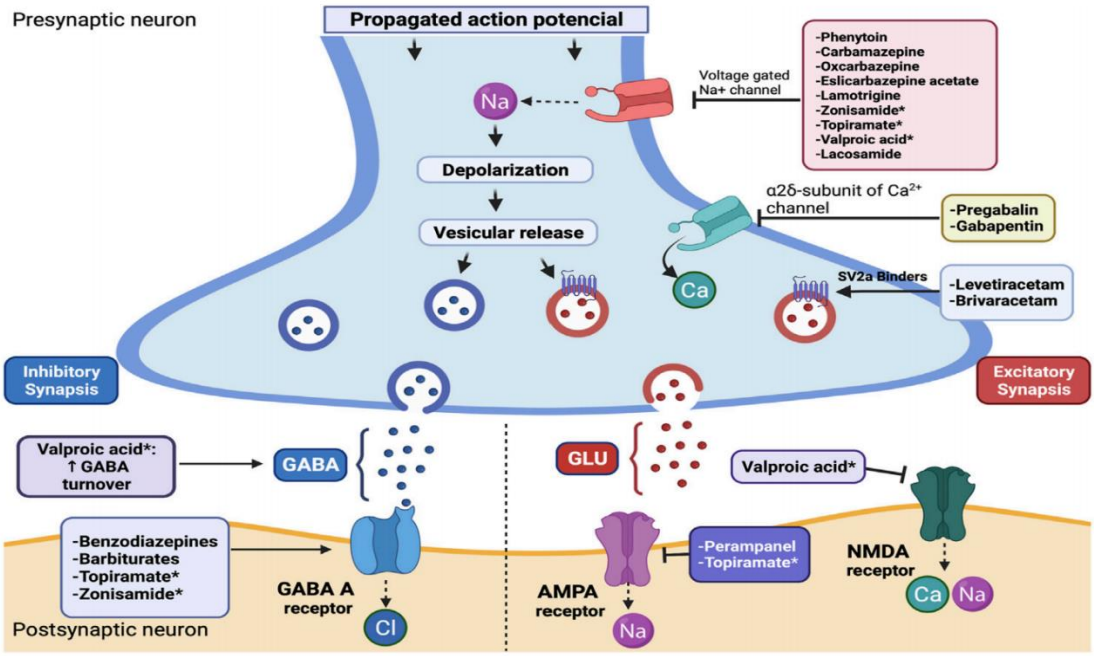
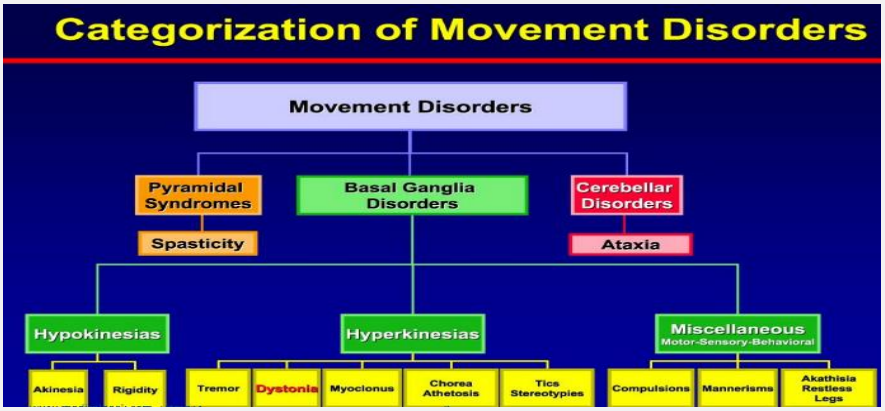


FIGURE 1
Scheme of the mechanism of action of antiseizure medications. *ASM with more than one proposed mechanism of action. Modified from (Löscher and Klein, 2021). Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, gamma-aminobutyric acid; GLU, glutamate; NMDA, N-methyl-D-aspartate.

Drug	Starting	Maintenance	Frequency	Blood level	Laboratory[¶]
Levetiracetam	10- 20 mg/kg/day (maximum: 1000 mg/day)	40 to 60 mg/kg/day (maximum: 3000 mg/day)	Q12 (IR) or Q 24 (for ER)	Not useful	non
lamotrigine	Monotherapy: 0.3 mg/kg/day	4.5 to 7.5 mg/kg/day (maximum: 300 mg/day)	Q12 (IR) or Q 24 (for ER)	1.5 to 10 mcg/mL	CBC/platelets every three months
	Added to VPA: 0.15 mg/kg/day	1 to 5 mg/kg/day (maximum: 200 mg/day)			
	Added to inducer (PB, CBZ, PHT): 0.6 mg/kg/day	5 to 15 mg/kg/day (maximum: 400 mg/day)			
Topiramate	1 to 3 mg/kg/day (maximum 25 mg/day)	5 to 9 mg/kg/day (usual maximum 500 mg/day;	Q12 (IR) or Q 24 (for ER)	5-20 mcg/mL	electrolytes, CBC/plts, on maximum dose at 3-6 months
Valproate	10 to 15 mg/kg/day	30 to 60 mg/kg/day	Q 8,12 (IR) or Q 24 (for ER)	50-150 mcg/mL	VPA level 1-2 weeks after initial dose; Hepatic transaminases every 1-2 months.
Zonisamide	1 to 2 mg/kg/day (maximum 100 mg/day)	5 to 8 mg/kg/day (maximum 500 mg/day)	Q 12 or Q 24	10-20 mcg/mL	electrolytes, CBC/plts, on max dose at(3-6 months
Phenytoin	5 mg/kg/day (maximum 300 mg/day)	4 to 8 mg/kg/day (300 mg/day children, adolescents; maximum 600 mg/day)	Dosed Q8 (for IR) or Q 12 , 24 (for ER)	10-20	CBC & Plts & hepatic function Phenytoin level 1-2 weeks after initial dose
Oxcarbazepine	8 to 10 mg/kg/day (maximum 600 mg/day)	30 to 40 mg/kg/day (maximum 2400 mg/day as monotherapy)	Q 8 (for children <5 years) or Q12 (school-children) Q24 (for ER)	8-35 mcg/mL	CBC/plts every 3 months risk for hyponatremia.
Carbamazepine (CBZ)	10 to 20 mg/kg/day	10 to 35 mg/kg/day (maximum in children ≤15 years: Lower of 35 mg/kg or 1000 mg/day; maximum in >15 years: 1200 mg/day)	Q 6, 8 (for IR) Q12 or Q 24 (for ER)	4 to 12 mcg/mL	CBC WBC low (particularly ANC), repeat as needed. hyponatremia. Tegretol level
Ethosuximide	15 mg/kg/day (maximum: 500 mg/day)	15 to 40 mg/kg/day (maximum: 1500 mg/day)	Q 8,12 or Q 24	40 to 100 mcg/mL	CBC/plts ethosuximide level every 3 monthst .
Lacosamide	Child 11 to 29 kg: 2 mg/kg/day	6 to 12 mg/kg/day (titrate in 2 mg/kg/7day)	Dosed twice daily	1.8 to 7.2 mcg/mL	lab tests not recommended.
	Child 30 to 49 kg: 2 mg/kg/day	4 to 8 mg/kg/day (titrate in 2 mg/kg/7day)			
	Child ≥50 kg: 50 mg Q12	Monotherapy: 300 to 400 mg/day (increments 100mg/7days) Adjunctive therapy: 200 to 400 mg/day (increments 100mg/7days)			
Eslicarbazepine		titrate in 300 mg increments at every week	Dosed once daily	Not well established	Serum sodium prior to initiation, at maintenance risk for hyponatremia.
	Child 22 to 31 kg: 300 mg/day	Range 500 to 800 mg/day			
	Child 32 to 38 kg: 300 mg/day	Range 600 to 900 mg/day			
	Child >38 kg: 400 mg/day	Range 800 to 1200mg/day			
Ethosuximide	15 mg/kg/day (maximum: 500 mg/day)	15 to 40 mg/kg/day (maximum: 1500 mg/day)	Dosed once or twice daily	40 to 100 mcg/mL	CBC/platelets]ethosuximide level at one to three weeks.
Clonazepam	0.01 to 0.03 mg/kg/day (maximum: Lower of 0.05 mg/kg/day or 1 mg/day)	0.05 to 0.2 mg/kg/day (maximum: Lower of 0.2 mg/kg/day or 20 mg/day)	Dosed two or three times daily	Not useful	Routine lab tests not recommended.
Gabapentin	10 to 15 mg/kg/day; may titrate to initial dose over three days (maximum: 900 mg/day)	40 to 50 mg/kg/day (maximum: Lower of 70 mg/kg/day or 4800 mg/day)	Dosed three times daily (for IR)	Not useful	CBC/platelets every three months

➢ Movement Disorders



Hypokinetic Movements

• Parkinsonism (2nd most common) • Rigidity

Hyperkinetic Movements

• Tremor • Chorea/Athetosis • Dystonia • Ballism • Myoclonus • Tics • Ataxia •Akathesia

All due to excessive dopaminergic activity in the basal ganglia, imbalance of activity in the complex basal ganglia circuits.

Tremors Myoclonus Tics Chorea Dystonia Ataxia

→

Movements become - Less violent / explosive / jerky, Smoother and more flowing- More sustained

Tremor	Involuntary, rhythmic, oscillatory movements affecting the hands, head or voice	•First line-(propranolol 100-40 mg/d) •Second line-(Clonazepam /01-5mg). Gaptin (100 – 400 mg/day) • Third line- (Pk-Merz 4 - 9 mg/kg/day)
Chorea	Involuntary, arrhythmic , jerky, brief movements flow from one part to another	AntiPsychotic (Risperdone/Olanzapine/Haloperidol) •GABAergic (clonazepam, gaptin, valproat) •Coenzyme Q10 Q24
Dystonia	Sustained muscle contraction, causing twisting, abnormal postures	• First line - Anticholinergics (benzatropine 1-2mg/day) • Second line- ((Levodopa, Carpidopa) add 12.5 mg/25mg q12 up by 0.5 – 1 tab every 3days, Max 20mg/day • Third line- muscle relax (Baclofen 5-10-20 mg/day tizanidine 0.5 -4mg/day) •clonazepam.0,1mg/kg/day •Finally if all else fails- try Botox
Akathitia	Feeling of inner, general restlessness Unable to sit still" relieved by moving	•First line-(propranolol 100-40 mg/d) •Second line-(benzatropine 1-2mg/day) •Third line- (Clonazepam /01-5mg)
Tourette's Syndrome (Tics)	Brief recurrent jerky stereotyped purposeless movement (motor tic) or sound (vocal tic) Worsen under stress, ability of the patient to suppress their occurrence, for a short time.	•First line- (Risperdone 0.5/3mg/day) •Second line-(Clonazepam.0,1mg/kg/day) •Baclofen (5-10-20 mg/day)
Myoclonus	Sudden, abrupt, arrhythmic, rapid, involuntary, jerky. Differs from tics by interfering with normal movement & not suppressible.	•Valproic acid / Levetracetam •Benzodiazepines-clonazepam •Piracetam •Intravenous immune globulin IVIG

➢ Peripheral Nerve Disease

1) Involve sensory nerves, motor nerves, or both
2) May affect one nerve (mononeuropathy), or several nerves afficted (polyneuropathy)
3) Includes : Cancer-related neuropathy - Central neuropathic pain- Phantom limb pain

❖ **Motor Symptoms:** Weakness, Atrophy, Hypotonia,Walking Difficulty, Gait imbalance, Footdrop
❖ **Sensory Symptoms:** numbness and tingling to proximal body parts Hyporeflexia ↓ Pain↓ Temperature
❖ **Autonomic Symptoms:** ↓ Sweating autonomic nerves & Hypotension, Urinary retention, impotence

Causes

- Carcinoma & infections leprosy
- VIT B12 deficiency
- Cytotoxic drugs: CISPLATIN , VINCRISTINE, VINPLASTIN, PACLITAXEL, Nitrous oxide

Diagnosis by

- NERVE CONDUCTION STUDY
- EMG-muscle denervation changes
- Sensory threshold
- Urea, electrolytes, LFTCSF ANALYSIS

Management of neuropathies

- Treat causative factors, offending drugs should be holded & metabolic abnormalities should be corrected
- VIT B12 (500-1000mg/day)
- Alpha Lipoic Acid (300 to 900 mg/day)
- Levocarnitine (10 to 20 mg/kg/day)
- Piracetam (400-1200 mg /day)
- Amitriptyline(10-50 mg/day)
- Gabapentin (100-900 mg/day)
- Duloxetine (20-60 mg /day) and venlafaxine (75-150 mg/day)
- Physiotherapy & occupational therapy
- Finally if Neuropathy is severe and all medecations fails try:
- IVIG: 400-600 mg/kg/day for 5 days or a more rapid course of 1–2 g/kg given over 1–2 days.
- Anti Epleptics: Carabmezbine (200-1200 mg/day)
- Atypical neuroleptics: [Olanzapine (5-15mg/day) – Quetiapine (25-200mg/day)]

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