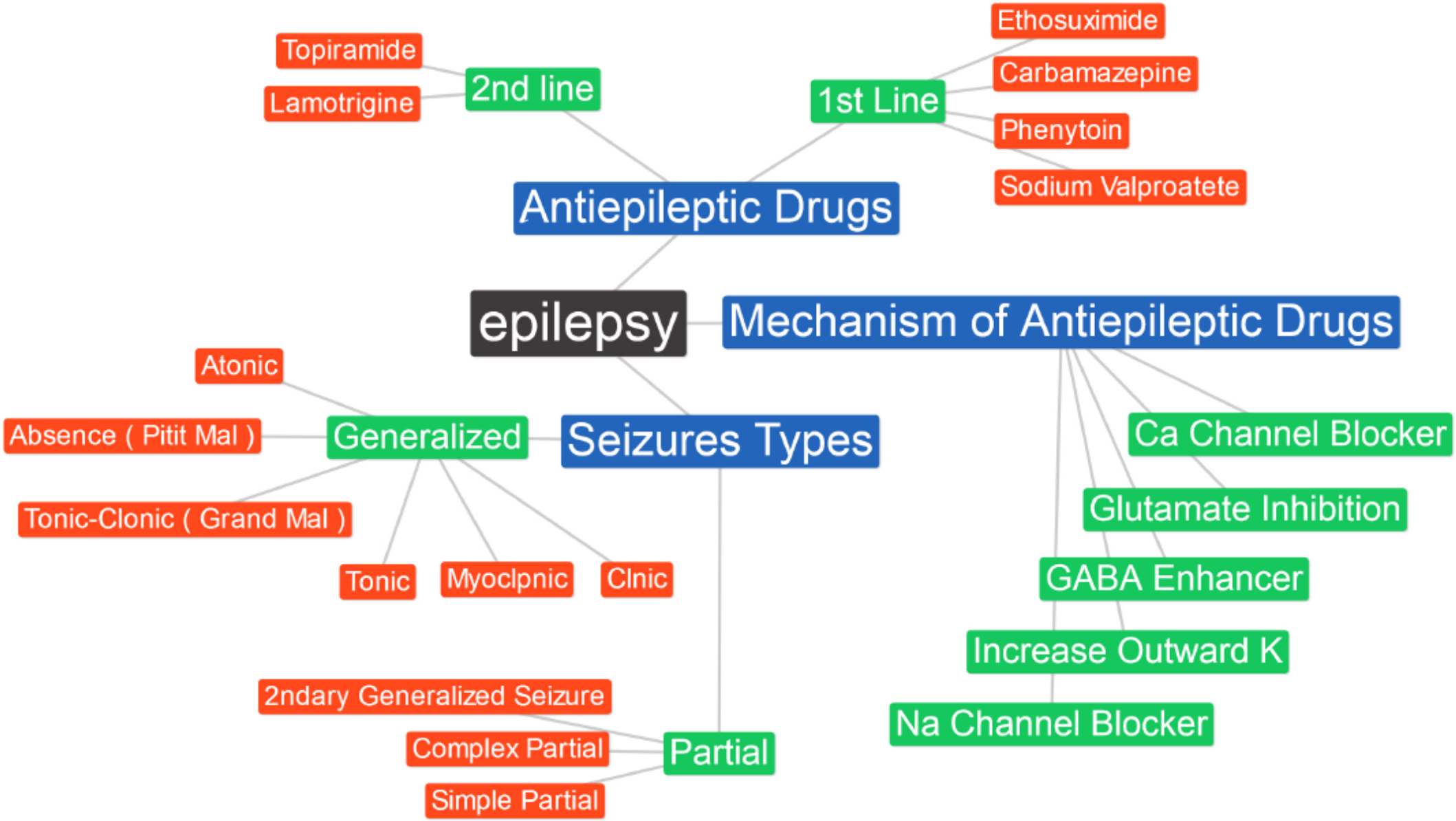
Lecture 13-14

Drugs used in epilepsy

Objectives:

- Describe types of epilepsy
- Classify antiepileptic drugs according to the type of epilepsy treated and generation introduced
- Expand on pharmacokinetic and dynamic patterns of first generation antiepileptic drugs and specify their mechanism of action , therapeutic indications and adverse effects
- Expand on pharmacokinetic & dynamic patterns of 2nd generation of antiepileptic drugs and specify their mechanism of action , therapeutic indications & adverse effects
- Specify management strategies adopted for status epilepticus concentrating on the drugs used.

- Additional Notes
- Important


Topiramide
Lamotrigine
2nd line
Ethosuximide
Carbamazepine
Phenytoin
Sodium Valproatete
1st Line
Antiepileptic Drugs
epilepsy
Mechanism of Antiepileptic Drugs
Atonic
Absence (Pitit Mal)
Generalized
Seizures Types
Tonic-Clonic (Grand Mal)
Tonic
Myoclpnic
Clnic
Ca Channel Blocker
Glutamate Inhibition
GABA Enhancer
Increase Outward K
Na Channel Blocker
2ndary Generalized Seizure
Complex Partial
Simple Partial
Partial

Mind Map

Epilepsy

Epilepsy is a chronic medical condition characterized by 2 or more unprovoked seizures(within 6-12 months).

Triggers : 1) Fatigue 2) stress 3) sleep deprivation 4) poor nutrition 5) alcohols

Etiology of Epilepsy

- Congenital defects, head injuries, trauma, hypoxia,
- Infection (bacteria or virus) e.g. meningitis, brain abscess, viral encephalitis.
- Concussion, depressed skull, fractures,
- Brain tumors (including tuberculoma), vascular occlusion, stroke.
- Drug withdrawal, e.g. CNS depressants,alcohol or drug abuse or drug overdose,e.g. penicillin.
- A poison, like lead
- Fever in children (febrile convulsion).
- Hypoglycemia
- PKU(phenylalanine → Phenylalanine hydroxylase → tyrosine)
- Photo epilepsy

Classification of Epilepsy

A. Partial(focal): Arise in one cerebral hemisphere
B. Primary Generalized: Both hemispheres + loss of consciousness.

Classification of Epilepsy

A. Partial(focal)

1. Simple: consciousness is retained
2. Complex(psychomotor): Altered consciousness

Partial with secondary generalization:

Begins as partial (simple or complex) and progress into generalized seizure(tonic-clonic seizure).

B. Primary Generalized

1. Tonic-Clonic (grand mal):
   Stiffness (15-30 sec) followed by violent contractions & relaxation (1-2 minute)
2. Tonic: Muscle stiffness
3. Clonic: Spasms of contraction & relaxation
4. Atonic(loss of tone): Pt's legs give under him &drop down
5. Myoclonic: Jerking movement of the body
6. Absence (Petit mal): Brief loss of consciousness with minor muscle twitches eye blinking
7. Status epilepticus: Re-occuring tonic-clonic seizure

Treatment of Epilepsy

1. Drugs
2. surgery
3. Ketogenic diet
4. Vagal nerve stimulation:
    - It is an alternative for patients who have been refractory to multiple drugs .
    - Who are sensitive to the many adverse effects of anti epileptic drugs
    - It is an expensive procedure.

➢ General rules for treatment of epilepsy

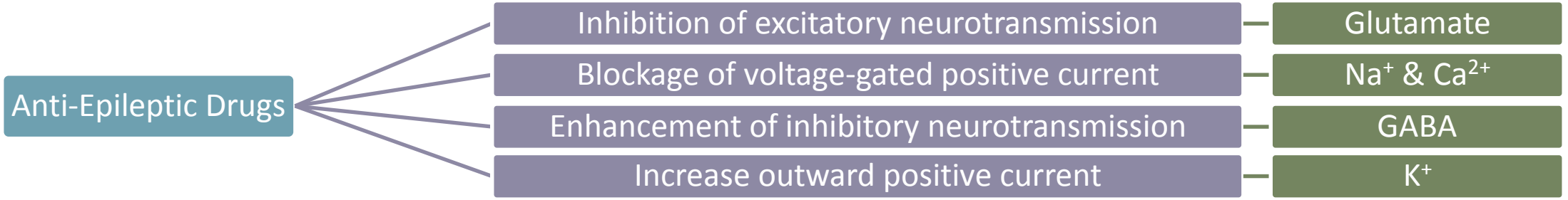
- Epilepsy is usually controlled but not cured with medication.
- Up to 80% of pts can expect partial or complete control of seizures with appropriate treatment.
- Antiepileptic drugs are indicated when there is two or more seizures occurred in short interval (6 m -1y)
- An initial therapeutic aim is to use only one drug (monotherapy).
- Drugs are usually administered orally
- Monitoring plasma drug level is useful
- Triggering factors can affect seizure control by drugs.
- Sudden withdrawal of drugs should be avoided

Withdrawal considered

- Seizure free period of 2-5 yrs or longer, Normal IQ & EEG prior to withdrawal, NO juvenile myoclonic epilepsy
- Relapse rate when anti-epileptics are withdrawn is 20-40%.

Mechanism of Anti-Epileptic Drugs

Anti-epileptic drugs inhibit depolarization of neurons by following mechanisms:



Classification of antiepileptic drugs	
First-generation	Second- generation
Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Valproate	Levetiracetam
Ethosuximide	Gabapentin
Phenobarbital and Primidone	Vigabatrin
Benzodiazepines (e.g.Clonazepam, lorazepam and diazepam)	Felbamate
	Zonisamide

1st generation

	Phenytoin	Carbamazepine
Drug	Fosphenytoin :- Parenteral form, Progrug , I.V. or I.M. rapidly converted to phenytoin.	_____
P.K.	- Orally, Absorbed in GIT . - Enzyme inducer . - Metabolized by liver (Inactive). - T ½ =20 h, Excreted in urine.	- Orally only, Well absorbed. - Strong enzyme inducer including its own metabolism. - Metabolism in liver to active & inactive. - T ½ = 15-35 h, Excreted in urine.
MoA	Block of Na^+ & Ca^{2+} influx into neuronal axon → inhibit the release of neurotransmitter → action potential of GABA .	Block Na^+ & Ca^{2+} influx into neural axon → inhibit the release of neurotransmitter → potentiate the action of GABA. (like Phenytoin)
Uses	1) Partial & generalized tonic-clonic seizures. 2) Status epilepticus Don't use it in absent seizure	1) Partial seizure (drug of choice). 2) Tonic-clonic seizure (1ry & 2ry generalized). Don't use it in absent seizure
ADRs	Acute :- - Nausea & vomiting . - Neurological (Headache, Vertigo, Ataxia, Diplopia, Nystagmus, Sedation) Chronic :- - Gum hyperplasia. - Hirsutism. (abnormal growth hair) - Acne. - Folic acid deficiency (megaloblastic anemia) - Vit D deficiency (Osteomalacia) - Teratogenic effect.	- GIT upset. - Hypersensitivity reaction. - Neurological (Drowsiness, Ataxia, Headache, Diplopia) - Hyponatremia & water intoxication. - Teratogenicity.

1st Generation

Drugs	Ethosuximide	Sodium Valproate [Broad spectrum antiepileptic]
P.K.	- Complete absorption. - Syrup & capsule form. - Do not bound to plasma proteins or tissues. - Metabolism in liver. - T ½ = 52-56 h (very long). - Excreted unchanged in urine (10-20%)	- Available as Capsules, syrup, I.V. - Metabolism in liver (Inactive). - Enzyme inhibitors. - T ½ = 12-16 h. - Excreted in urine.
MoA	Inhibits T-type Ca^{2+} channels in thalamo-cortical neurons .	- Block activated Na^{+} channels. → enhance GABA synthesis & reduce degradation → suppress glutamate action. - Block T-type Ca^{2+} channels.
Uses	Absence seizures	1) Epilepsy (all form):- Generalized tonic-clonic seizures (1ry & 2ry), Absence seizure, Complex seizure, Myoclonic, Atonic, Photosensitive epilepsy. • Don't use it in Status epilepticus. 2) Other uses :- Bipolar disorder & mania, Prophylaxis of migraine, Lennox-gastaus syndrome (type of epilepsy with multiple type different type of epilepsy).
ADRs	- Gastric distress. (Nausea, Vomiting) - Drowsiness - Fatigue - Hiccups. - Headache.	- Weight gain. (increase appetite). - Hair loss (for short period) with regrowth of curly hair. (type of hair). - Thrombocytopenia. - Hepatotoxicity. - Teratogenicity.

2nd Generation

Drugs	Lamotrigine	Topiramate
P.K.	- Available as oral tablets. - Well absorbed from GIT. - Metabolized by Glucuronidation - Does not inhibit/induce CP450 isozymes. - T ½ =24 h/ 1 day.	- Well absorbed orally (80%). - Food has no effect on the abortion. - No effect on microsomal enzyme. - Minimal protein bound. - T ½ = 18-24 h. - Excreted in the urine unchanged (mostly).
MoA	Block of Na^+ channels → inhibit excitatory amino acid (Glutamate & aspartate).	Block Na^+ channels → potentiate the inhibitory effect of GABA.
Uses	1) Partial seizures (as monotherapy). 2) Lennox-gastaut syndrome.	1) Partial, Generalized (tonic-clonic), absence. (monotherapy) 2) Lennox-gastaut syndrom.
ADRs	- Influenza-like syndrome. - Skin rash. - Somnolence. - Blurred vision. - Ataxia. - Diplopia.	- Psychological or cognitive dysfunction - Sedation. - Dizziness. - Fatigue. - Urolithiasis. (stones) - Paresthesia (abnormal sensation) - Teratogenicity (in animal not in human) - Weight loss. (could be desirable)

Type of seizure	Drug
Partial seizures	1) Phenytoin. 2) Carbamazepine. 3) Valproate. 4) Lamotrigine.
Generalized seizure	
Tonic-clonic (Grand mal)	1) Phenytoin . 2) Carbamazepine. 3) Valproate. 4) Lamotrigine.
Myoclonic	1) Valproate. 2) Clonazepam.
Absence	1) Valproate. 2) Ethosuximide.
Atonic	Valproate

Status Epilepticus

- Most seizure last for 4-5 min, when seizure follow one another without recovery of consciousness it is called "status epilepticus".
- Has high mortality rate.
- Death from cardiorespiratory failure.

Anti-epileptics used in status epilepticus. (Intravenous injection)				
Lorazepam (drug of choice)	Diazepam	Phenytoin	Fosphenytoin	Phenobarbital

Pregnancy & Antiepileptic

- No antiepileptic drug is safe in pregnancy.
- Monotherapy is usually better than drug in combination.
- Patient has to continue therapy.
- Valproate & Phenytoin are contraindication during pregnancy
  (use carbamazepine has the least teratogenic effect) → from 433

Summary

1st Generation

Drug	Mechanism	Indications	ADR	Extra Info.
Phenytoin	• Blocks Na+ & Ca++ channels • Inhibits release of excitatory NT • Potentiates GABA action	• Partial Seizures • Generalized tonic-clonic seizures	• Folic acid deficiency • Vitamin D deficiency • Teratogenicity	Parenteral form (Fosphenytoin) is given IV to treat Status epilepticus
Carbamazepine	• Blocks Na+ & Ca++ channels • Inhibits release of excitatory NT • Potentiates GABA action	• Partial Seizures (drug of choice) • Generalized tonic-clonic seizures	• GIT upset • Hyponatremia • -Teratogenicity	Strong Enzyme inducer
Sodium Valporate	• Blocks Na+ and T-type Ca++ channels • Enhances GABA synthesis and reduces its degradation • Supresses Glutamate action	• Generalized tonic-clonic seizures • Absence seizures • Complex partial seizures • Myoclonic • Atonic • Photosensitive	• Weight gain • Hepatotoxicity • Thrombocytopenia	Other uses: • Bipolar disorder and mania • Prophylaxis of migraine • Lennox-Gastaut syndrome
Ethosuximide	Blocks T-type Ca++ channels	Absence Seizures	Gastric distress Drowsiness, Hiccups	

2nd Generation

Lamotrigine	• Blocks Na+ Channels • Inhibits Glutamate and aspartate release	Lennox-Gastaut syndrome	Influenza-like syndrome. Skin rash.	Metabolized primarily by Glucuronidation
Topiramate	• Blocks Na+ Channels • Potentiates GABA action		Psychological or cognitive dysfunction, Weight loss, Urolithiasis	

MCQs

1. **Which of the following is a prodrug and is used IV for partial and generalized seizures?**
   A. Phenytoin
   B. Fosphenytoin
   C. Benzodiazepines
   D. Carbamazepine

2. **Which of the following can be used in absence seizures ?**
   A. Sodium vaporate
   B. Carbamazipine
   C. Phenytoin
   D. Topiramate

3. **Which of these drug can cause Thrombocytopenia?**
   A. Lamotrigine
   B. Phenytoin
   C. Sodium vaporate
   D. Carbamazipine

4. **Which of the following can be used only in absence seizures?**
   A. Ethosuximide
   B. Lamotrigine
   C. Carbamazipine
   D. Sodium vaporate

5. **Certain drug was given to a patient with seizures and he developed some side effects such as Gum hyperplasia. What other side effects could this patient has?**
   A. Hyponatremia , Thrombocytopenia
   B. GIT upset
   C. Hirsutism , megaloblastic anemia
   D. Drowsiness, Fatigue

Answers: 1. B 2. A 3. C 4. A 5. C

6. **Certain drug X is metabolized by P450 enzyme in the liver is added to the phenytoin in a patient with seizures, What is effect on concentration of the X drug?**
   A. Increase
   B. Decrease
   C. No effect
   D. It depends on which type is the X drug.

7. **Patient is diagnosed with partial seizures, what is the drug of choice in this case of seizure?**
   A. Phenytoin
   B. Ethosuximide
   C. Lamotrigine
   D. Carbamazepine

8. **Patient with seizures treated lamotrigne + phenytoin, what is the side effect can be seen to this patient if he continue on these medication?**
   A. Psychological or cognitive dysfunction
   B. Urolithiasis
   C. Steven –Johnson syndrome
   D. Hepatotoxicity

Answers: 6. B 7. D 8. C

1. What is the drug of choice in status epilepticus?
    - Lorazepam
    - Diazepam

2. What is the effect of Carbamazipine on liver enzymes?
    - Enzyme inducer

3. Which of antiepileptic drugs are the main drugs contraindicated during pregnancy?
    - Valproate
    - phenytoin

SAQs

Good luck!

Done by Pharmacology Team 434

- Mishari Alsalem
- Qasem Alsultan
- Moath AlEisa
- Abdulaziz Alsaud
- Abdullah Alammari
- Mashhoor Alzarie
- Khalid Alduraibi

For any correction, suggestion or any useful information do not hesitate to contact us: Pharmacology434@gmail.com