

Neuropsychiatry Block

Pharmacology Team 439



Helpful video

Color index: Main Text Important Dr's Notes Female Slides Male Slides

We highly recommend studying [pathophysiology of epilepsy] before this lecture

Antiepileptic

drugs

Objectives:

- 1- Describe types of epilepsy
- 2- List the antiepileptic drugs.
- 3- Describe briefly the mechanism of action of antiepileptic drugs.
- 4- Enumerate the clinical uses of each drug.
- 5- Describe the adverse effects of each antiepileptic drug & treatment of status epilepticus.
- 6- Classify antiepileptic drugs according to the type of epilepsy treated and generation introduced

7-Expand on pharmacokinetic and dynamic patterns of first and second generation antiepileptic drugs.

Editing file

Epilepsy

Epilepsy is a chronic medical condition characterized by <u>2 or more unprovoked</u> <u>seizures</u> (within 6-12 months). It is a syndrome.

The Difference Between:

1) Epilepsy & Seizures

1

Epilepsy

A group of related sign and symptoms characterized by a tendency for recurrent seizures

Two or more unprovoked (no trigger) seizures within 6-12 months

Seizures

Brief, sudden, uncontrolled abnormal electrical activity in the brain, are a symptom of epilepsy. A Single episode

2) Syndrome & Disease

1

Syndrome

A set of medical signs and symptoms that occur together and suggest the presence of a certain disease (idiopathic & combination of symptoms).



Disease

The actual diagnosed impairment of health or a condition of abnormal functioning (non- idiopathic & it's a combination of symptoms) distinguished cause, symptoms and treatment

★ Epilepsy results from increased level of Glutamate and decreased level of GABA. (important for MCQs)



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). (Not harmful)
- Hypoglycemia (insulin shock)
- PKU¹ (Phenylketonuria) (Phenylalanine _____Phenylalanine hydroxylase ______ Tyrosine)
- Photo epilepsy (usually due to flashing lights in video games)

 An inherited disorder in which there's an error in the metabolism of phenylalanine caused by the deficiency of the enzyme phenylalanine hydroxylase → the phenylalanine increases in the blood.

Triggers of Epilepsy

Fatigue

Sleep deprivation

Stress

Poor nutrition

Classifications of Epilepsy

Primary Generalized: Both hemispheres + loss of consciousness.



Partial (focal): Arise in one cerebral hemisphere

A) **Tonic-clonic:** Stiffness followed by violent contractions & relaxation (1-2 minute).

B) Tonic: Muscle stiffness

C) Clonic: Spasms of contraction & relaxation

D) **Atonic (loss of tone)**: Patient's legs give under him & drop down

E) Myoclonic: Jerking movement of the body

F) **Absence(Petit mal):**Brief loss of consciousness with minor muscle twitches. Eye blinking (no fall down).

G) **Status epilepticus (Dangerous)**: Recurring/prolonged tonic-clonic seizure (30 min or more) A) **Simple**: consciousness is retained

B) **Complex**: Altered consciousness

C) **Partial with secondary generalization:** Begins as partial (simple or complex) and progress into Generalized seizure (tonic clonic)

General rules for treatment of Epilepsy

- Epilepsy is usually controlled but not cured with medication.
- Up to 80% of patients 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). To avoid ADRs
- 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. Worsens the seizure and higher chances of reoccurrence

Withdrawal considered:



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Treatment of epilepsy



Vagal nerve stimulation

- It is an alternative for patients who have been refractory to multiple drugs
- Who are sensitive to many adverse effects of antiepileptic drugs
- It is expensive procedure, use it as last option



Mechanism of anti-epileptic drugs

They inhibit depolarization of neuron by:



1st Generation

1st	Phenytoin
1st	Carbamazepine
1st	Valproate
1st	Ethosuximide
1st	Phenobarbital and primidone
1st	Benzodiazepines e.g. clonazepam, lorazepam and diazepam

Both gens have the same efficacy, but second gen is safer and more suitable for some people e.g. pregnant

2nd Generation

2nd	Lamotrigine
2nd	Topiramate
2nd	Levetiracetam
2nd	Gabapentin
2nd	Felbamate
2nd	Zonisamide
2nd	Pregabalin

1st Generation

Drug	Phenytoin	Fosphenytoin						
M.O.A	 Blockade of Na⁺ & Ca²⁺ influx into neuronal axon. Inhibit the release of excitatory transmitters e.g. glutamate and aspartate Potentiate the action of GABA gamma-Aminobutyric acid (GABA): inhibitory neurotransmitter, Its principal role is reducing neuronal excitability throughout the nervous system. 							
P.k	 Given orally, well absorbed from GIT Also available I.V and I.M (fosphenytoin) Enzyme inducer.; a type of drugs that increase the metabolic activity of the enzyme. They often cause drug-drug interactions → low bioavailability hence should be administered alone Metabolized by the liver to inactive metabolites T¼ approx. 20 hr. Excreted in urine. 	 Parenteral form of phenytoin (IV & IM) A Prodrug rapidly converted to phenytoin in the body. Advantage over phenytoin: Lower local tissue and cardiac toxicity Less pain phlebitis (inflammation of veins) at injection site. 						
Uses	 Partial and generalized tonic-clonic seizures <u>Not</u> in absence seizure. In status epilepticus, given IV. 							
ADRs	 Nausea or vomiting headache, vertigo, ataxia, diplopia, nystagmus Sedation Gum (gingival) hyperplasia¹ (pic on the side) Hirsutism (excessive hair growth, Contraindicated in women) Acne Folic acid deficiency (Megaloblastic anemia) Vit D deficiency (Osteomalacia) Teratogenic effect (Contraindicated in pregnancy)² 							
Extra: Phenytoin ADRs (mnemonic) Pain Hirsutism Enlarged Gum Nystagmus Yellow- brown pigmentation Teratogenic Osteomalacia Interfere with folic acid absorption Neuropathy (peripheral)	(1): blockade of calcium influx → decreased folic acid uptake → decreased collagenase which are enzymes that assist in destroying extracellular structures	(2) generally all antiepileptics are contraindicated in pregnancy and are very harmful in such cases but two drugs are "safer" to use which are Lamotrigine and Levetiracetam						

1st Generation (cont.)

Drug	Carbamazepine (CBZ)
M.O.A Same as before	 Blockade of Na+ & Ca + + influx into neuronal axon Inhibit the release of excitatory transmitters e.g. glutamate and aspartate Potentiate the action of GABA gamma-Aminobutyric acid (GABA): inhibitory neurotransmitter,Its principal role is reducing neuronal excitability throughout the nervous system.
P.k	 Available as capsules & Syrup only orally Well absorbed Strong enzyme inducer including its own metabolism Metabolized by the liver to <u>active & inactive</u> metabolites Half life 18-35 hr Excreted in urine
Uses	 Drug of choice in partial seizures. Tonic-clonic seizures (1ry & 2ry generalized) but Not in absence seizures Other uses: Bipolar depression mood swings Trigeminal neuralgia inflammation of CN5 that results in severe pain sensations in the face Use with patients who have bipolar depression & epilepsy
ADRs	 GIT upset Hypersensitivity reactions Drowsiness , ataxia, headache & diplopia Hyponatremia & water intoxication (hyperosmotic urine) Teratogenicity; contraindicated in pregnancy

Drug	Ethosuximide (ETSM)						
M.O.A	• Inhibits T- type Ca ²⁺ channels in thalamo-cortical neurons (post synaptic)						
P.k	 Absorption is complete Syrup & capsule forms Not bound to plasma proteins or tissues, high volume of distribution Metabolized in liver Half life 52-56 hr 10-20% of a dose is excreted unchanged the urine It's not an enzyme inducer nor bound to plasma proteins → can be used with other antiepileptics (IMPORTANT) 						
Uses	Absence seizures						
ADRs	 Gastric distress: nausea, vomiting Drowsiness, fatigue , hiccups, headaches 						

1st Generation (cont.)

Drug	Sodium Valproate (VPA) de Marine (Broad spectrum antiepileptic)						
M.O.A	 Blocks activated Na+ channels. Enhances GABA synthesis & reduces degradation Suppress glutamate action. Blocks T-type Ca²⁺ channels 						
P.k	 Available as capsules, Syrup , I.V Metabolized by the liver (inactive) Enzyme inhibitor → increased bioavailability → potential toxicity Half life 12-16 hr Excreted in urine 						
Uses	It is effective for all forms of epilepsy Generalized tonic-clonic seizures (1ry or 2ry) Absence seizures Complex partial seizures Myoclonic Atonic photosensitive epilepsy Other uses: Bipolar disorder and mania (or Carbamazepine) Bipolar disorder and mania (or Carbamazepine) Drophylaxis of migraine Lennox-Gastaut syndrome: a childhood epileptic encephalopathy which is usually caused by early brain injury or congenital malformations.						
ADRs Extra: Valproate ADRs (mnemonic) Vomiting Appetite † Liver toxicity Pancytopenia Regrowth of curly hair Oedema Aspirin contraindication Teratogenicity Ensume inbiblicer	 GI (nausea, vomiting , heart , burn) Weight gain (↑ appetite) Transient hair loss, with re-growth of curly hair Thrombocytopenia (low platelet count) (not used with aspirin¹ or coumadin² "warfarin") 1) aspirin & valproate are highly bound to plasma proteins → aspirin displaces valproate from its binding site → increase conc of valproate 2) Sodium valproate replace warfarin from protein binding site → Risk of bleeding Transient increase in liver enzymes & hepatotoxicity Teratogenicity (neural tube defect) 						

To wrap things up in first generation, find the appropriate drug

Μ	в	L	С	н	Y	G	Α	Р	κ	Α	G	F
G	в	Ν	A	L	G	G	Q	J	L	F	X	R
Е	Ν	Ι	R	М	Z	н	Х	R	Υ	С	Ζ	Q
D	н	0	в	С	S	Т	н	Т	U	Ν	0	L
	J	Т	A	Р	н	Е	Ν	Y	Т	0	I	Ν
Μ	М	Υ	Μ	E	Т	J	J	М	Μ	в	Μ	Ρ
1	X	Ν	A	0	Т	Ν	J	н	Ν	Μ	L	С
X	S	E	Z	J	L	А	0	S	G	н	V	L
U	М	н	E	Q	Μ	0	R	G	Α	Ρ	J	Ζ
S	к	Р	Р	R	С	Р	Х	0	н	Α	S	F
Ο	L	S	I	V	S	Q	U	Р	Р	0	Μ	S
н	F	0	N	н	L	F	κ	$ \mathbf{w} $	0	L	Α	R
Т	G	F	E	U	J	Α	Ζ	F	R	J	Α	F
F	Т	н	0	н	J	ĸ	7	V	R	U		V

• Hints:

- 1. Inhibits low voltage calcium channels+Used for absence seizures
- 2. Drug of choice in partial seizures+Can cause hyponatremia
- 3. A prodrug+Contraindicated in women
- 4. Enzyme inducer
- 5. Enzyme inhibitor+Reduces degradation of GABA

• Check <u>slide 13</u> for answers

2nd Generation

Drug	Topiramate (Topamax)							
М.О.А	 Blocks Na+ channels (membrane stabilization) Potentiates the inhibitory effect of GABA. 							
P.k	 Well absorbed orally (80%) Food has no effect on absorption T½= 18-24 hrs Has no effect on microsomal enzymes 9-17 % protein bound (minimal) increased volume of distribution Mostly excreted unchanged in urine 							
Uses	 Can be used alone for partial, generalized tonic-clonic, and absence seizures. Lennox- Gastaut syndrome (or lamotrigine, or valproate). Individuals with bipolar disorders that have resisted other forms of treatment (Off-Label). 							
ADRs	 Psychological or cognitive dysfunction Weight loss (can be a <u>desirable</u> effect) unlike Valproate Sedation, Dizziness, Fatigue Urolithiasis (urinary tract stones) Paresthesias (abnormal sensation) Teratogenicity (in animal but not in human) 							

Drug	Lamotrigine
М.О.А	 Blockade of Na+channels Inhibits excitatory amino acid release (glutamate and aspartate)
P.k	 Available as oral tablets Well absorbed from GIT T½ approx. 24 hr Metabolized primarily by glucuronidation. Does not induce or inhibit C.P-450 isozymes can be used as add-on therapy
Uses	 As add-on therapy or as monotherapy in partial seizures. Lennox-Gastaut syndrome (or Topiramate, or valproate) Safe for pregnant
ADRs	 Influenza-like symptoms Skin rashes (may progress to Steven–Johnson Syndrome¹) Somnolence (drowsiness) Blurred vision Diplopia Ataxia 1) Bare but severe rash in the murus membranes
	1) Rare but severe rash in the mucus membranes



Summary (taken from slides)

Type of seizure	Choice among drugs				
Partial seizures	Carbamazepine, phenytoin, valproate lamotrigine.				
Generalize	ed seizures				
Tonic-clonic (grand mal)	Valproate, carbamazepine, phenytoin, Lamotrigine				
Myoclonic	Valproate, clonazepam				
Absence	Valproate, ethosuximide, Topiramate				
Atonic	Valproate				
Lennox–Gastaut syndrome (LGS)	Valproate, Lamotrigine, Topiramate				

Enzyme Inducers? Phenytoin, Carbamazepine Enzyme Inhibitors? Valproate

No enzyme activity? Ethosuximide, Topiramate, Lamotrigine What causes weight gain/loss? Gain: Valproate, Loss: Topiramate What blocks T-type Ca²⁺ channels? Ethosuximide, Valproate

Drugs Used for Treatment of Status Epilepticus (IV)

- Most seizures last from few seconds to few minutes. When seizures follow one another without recovery of consciousness, it is called "status epilepticus"
- It has a high mortality rate
- Death is from cardiorespiratory failure.



Summary (taken from slides)

- ★ Epilepsy is classified into partial or generalized according to the site of lesion
- ★ The exact mechanism of action of antiepileptics is not known
- ★ Phenytoin is mainly used for treatment of generalized tonic-clonic seizures
- ★ Carbamazepine is mainly used for treatment of partial seizures
- ★ Sodium valproate is a broad spectrum antiepileptic drug
- ★ Lamotrigine & levetiracetam are used as monotherapy or adjunctive therapy in refractory cases
- ★ Lorazepam , diazepam , phenytoin are used intravenously for treatment of status epilepticus

		Site	of action					
Drug	Sodium channel	GABA _A receptor	Calcium channel	Other	Main uses	Main unwanted effect(s)	Pharmacokinetics	
Carbamazepine®	+	_	_	_	All types except absence seizures Especially focal seizures such as temporal lobe epilepsy Also trigeminal neuralgia	Sedation, ataxia, blurred vision, water retention, hypersensitivity reactions, leukopenia, liver failure (rare)	Half-life 12–18 h (longer initially) Strong induction of liver enzymes, so risk of drug interactions	
Phenytoin ^b	+	_	_	-	All types except absence seizures	Ataxia, vertigo, gum hypertrophy, hirsutism, megaloblastic anaemia, fetal malformation hypersensitivity reactions	Half-life ~24 h Saturation kinetics, therefore unpredictable plasma levels Plasma monitoring often required	
Valproate	+	?+	+	GABA transaminase inhibition	Most types, including absence seizures	Generally less than with other drugs Nausea, hair loss, weight gain, fetal malformations	Half-life 12–15 h	
Ethosuximide	—	—	+	_	Absence seizures May exacerbate tonic–clonic seizures	Nausea, anorexia, mood changes, headache	Long plasma half-life (~60 h)	
Phenobarbital ^d	?+	+	_	_	All types except absence seizures	Sedation, depression	Long plasma half-life (>60 h) Strong induction of liver enzymes, so risk of drug interactions (e.g. with phenytoin)	
Benzodiazepines (e.g clonazepam, clobazam, lorazepam, diazepam)	_	+	_	_	Lorazepam used intravenously to control status epilepticus		See Ch. 45	
Lamotrigine +		?+	Inhik gluta relea	oits amate ase These	All types fest drug during pregnancy	Dizziness, sedation, rashes	Plasma half-life 24–36 h	
Topiramate +	?+	?+	AMF	PA-receptor k	Partial and Sedation generalised Fewer onic-clonic pharmacokinetic seizures. interactions than ennox-Gastaut phenytoin syndrome Fetal malformation		Plasma half-l fe ~20 h Excreted unchanged	

Extra Summary







Check out <u>these</u> great mind maps made by Sultan Alqahtani!

MCQs

Q1: A 25-year-old woman with generalized seizures is well controlled on valproate. She indicates that she is interested in becoming pregnant in the next year. With respect to her antiseizure medication, which of the following should be considered?											
A- Leave her on therapy.	her current	B- C Iamo	onsider swi otrigine.	tching to	C- Co antis	C- Consider adding a second antiseizure medication.			D- Decrease her valproate dose.		
Q2: A 27-year-old woman has a history of epilepsy. She finds that sodium valproate is causing her to put on weight and she is kee to switch to an alternative medication. Which one of the following would be the most appropriate medication for her?											
A- Carbamazepi	ne	B-Cl	onazepam		C- To	opiramate		D-	Phenytoin		
Q3: A 16-year-old female is brought to the emergency department (ED) because of increasing drowsiness and inattentiveness. Her family tells you that she takes medication for epilepsy and may have taken an extra dose that day. On examination, she has an ataxic gait, nystagmus, and gingival hypertrophy. What medication does she take?											
A- Phenytoin		B- C	arbamazepi	ne	C- E	thosuximide	2	D-	Valproic acid		
Q4: The preferre	ed treatmer	it of status	epilepticus	is intravend	ous admini	stration of					
A- Chlorpromaz	ine	B- D	iazepam		C- S	uccinylcholi	ne	D-	Tranylcypromine		
Q5: A 32-year-o stated that his v Which of the fol	ld woman v vife had bee lowing pairs	vas brough en suffering s of neurot	t to the em g from epile ransmitters	ergency der psy since ch are though	partment b hildhood, b t to be mos	ecause of a ut the seizu st involved i	generalized res were only n seizure dis	tonic-cl y partial orders?	onic seizure. Her husband Iy controlled by medication.		
A- GABA and se	rotonin	B- G	B- GABA and glutamate			C- GABA and acetylcholine			D- Serotonin and glutamate		
Q6: Which drug administered co	used in mar ncomitantly	nagement (?	of seizure di	sorders is n	nost likely	to elevate t	he plasma co	ncentra	tion of other drugs		
A- Carbamazepine	2	B- Cl	B- Clonazepam			C- Phenobarbital			Valproic acid		
Q7: A child is exp following therap	periencing a vies would b	bsence sei e most apj	zures that i propriate fo	nterrupt his r this patien	ability to p t?	bay attentio	n during scho	ool and	activities. Which of the		
A- Ethosuximide	2	B-Ca	B-Carbamazepine			C-Diazepam			D-Carbamazepine plus primidone		
Q8:A 9-year-old boy is sent for neurologic evaluation because of episodes of apparent inattention. Over the past year, the child has experienced episodes during which he develops a blank look on his face and his eyes blink for 15 seconds. He immediately resumes his previous activity. Which best describes seizures in this patient?											
A- Focal	B- To	onic–clonic		C- A	C- Absence			Myoclonic			
		I			I						
	1	2	3	4	5	6	7	8			
	B C A B B D A						С				



Answers 1-Ethosuximide. 2-Carbamazepine . 3-Fosphenytoin. 4-Phenytoin. 5-Valproate.

SAO

Q1) 51-year-old woman with a history of type-2 diabetes and bipolar disorder is admitted for review because of low sodium (118 mmol/l). On examination her blood pressure is 139/72 mmHg, her pulse is 70 bpm, regular, and she is not in cardiac failure.

- a) what drug is most likely to be responsible?
- b) List 2 ADRs

Q2) 37-year-old woman was at a routine neurology clinic visit. The woman had a long history of refractory grand mal epilepsy. She was being treated with several drugs, but with poor results. The neurologist decided to prescribe phenytoin.

a) Blockade of what type of ion channels is most likely to mediate the therapeutic efficacy of the drug in the patient's disease?

b) list 2 ADRs

Q3) young male patient suffers from a seizure disorder characterised by tonic rigidity of the extremities followed in 15–30 s of tremor progressing to massive jerking of the body. This clonic phase lasts for 1 or 2 min, leaving the patient in a stuporous state.,

- a) what is the type of epilepsy the patient has?
- b) What is the most suitable drug for long term management of this patient? (2)
- c) Mention the MOA of each drug

Q4) 9 years old boy was playing and suddenly he stopped and started staring and blinking and then he got back to normal.

- A) What is the type of seizure that he had?
- B) Which drug would be most appropriate for this patient?

Answers

A1) a) Carbamazepine; As well as being used for the management of epilepsy, carbamazepine is used in the

management of bipolar disorder and is a recognised cause of hyponatremia. b) Water intoxication, Teratogenicity

A2) a) Blockade of Na⁺ & Ca²⁺ influx into neuronal axon. b) Folic acid deficiency, Vit D deficiency

- A3) a) This patient is suffering from generalized tonic-clonic seizures.
 - b) carbamazepine or phenytoin
 - c) Blockade of Na+ & Ca²⁺ influx into neuronal axon
- A4) a) Absence seizure, b)Ethosuximide







Neuropsychiatry Block

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