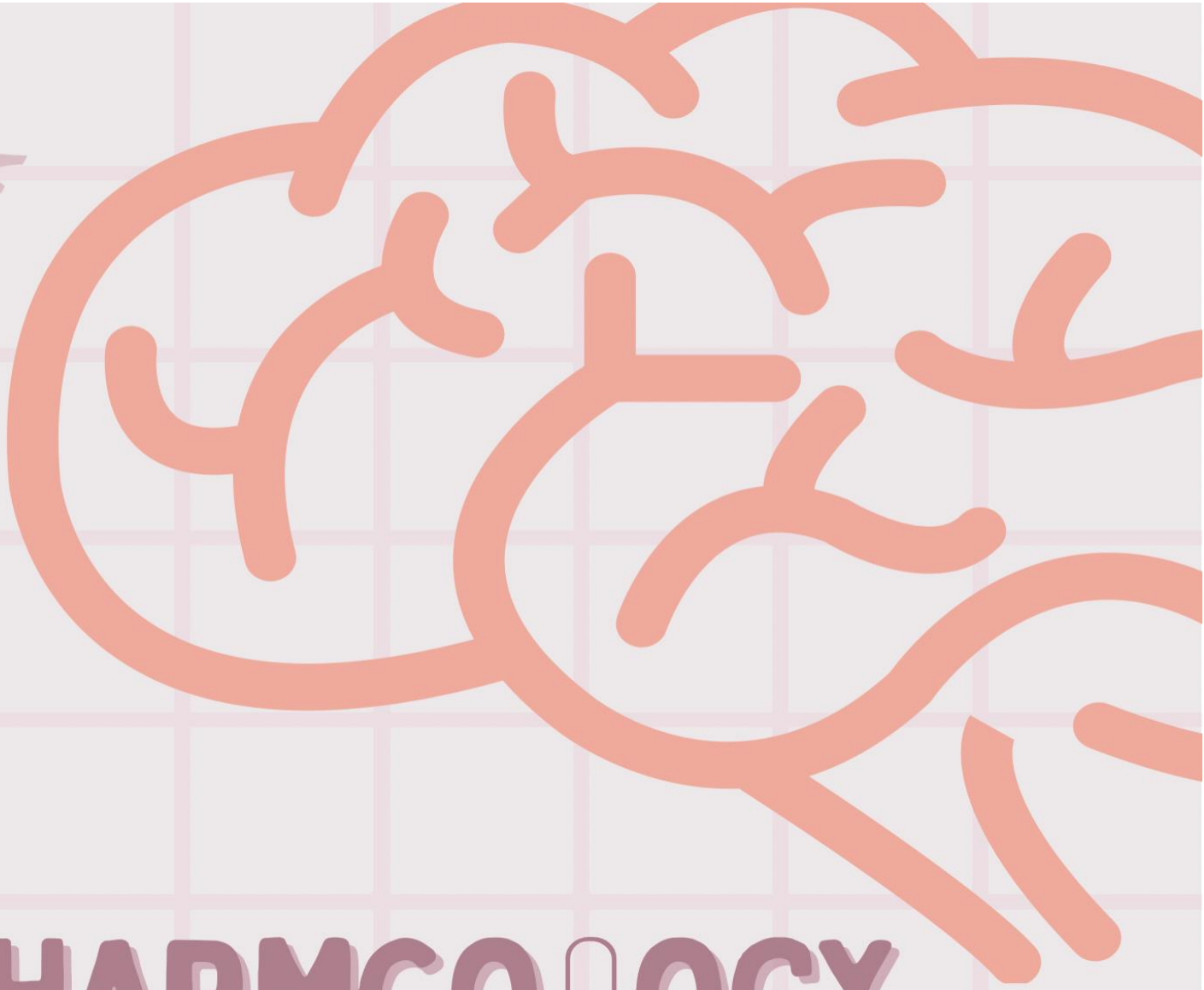

PHARMCOLOGY

SHEET NO. 9

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كلام الدكتور بالبنفسجي الفاتح،
واللي حكا مهم نعرفه بالأصفر

Ethosuximide:

• Ethosuximide is a first-line drug for the treatment of generalized absence (petit mal epilepsy) seizures, only. هاد المطلوب تعرفوه
• It can be used as **monotherapy** unless generalized **tonic-clonic seizures** are also present, in which case **valproate** is preferred.

Mechanism of Action:

• It **inhibits** low-voltage activated **T-type calcium channels** in thalamocortical neurons that underlie the 3-Hz spike-wave مش مهم حاليا discharges of generalized absence seizures.
• Thus, It has narrow spectrum of activity.
• Other ion channels affected include voltage-gated sodium channels, calcium-activated potassium channels, and inward rectifier potassium channels. These actions may contribute to the efficacy of ethosuximide in absence epilepsy.

Pharmacokinetics:

• Complete absorption.
• Not protein bound.
• 80% metabolized to inactive products by **CYP3A**.
• t½ ~ 40 (18-72) hours.
• Linear kinetics.
• Therapeutic concentration is ~ 40-100 µg/mL.
• drug interactions: Valproic acid inhibits its metabolism ➡️ decreased clearance.

Adverse Effects:

1. The most common is frequent gastric distress – pain, nausea, & vomiting.
2. Transient lethargy & fatigue. عابرة
3. Headache, dizziness, hiccup (contractions in the diaphragm), & euphoria.

Now we'll move to the newer drugs:

Lamotrigine:

Mechanism of Action:

• The action of lamotrigine on voltage-gated sodium channels is similar to that of carbamazepine.

Pharmacokinetics:

• Almost completely absorbed.
• Linear kinetics.
• Metabolized primarily by glucuronidation.
• Metabolism is inhibited by **valproat, so** its dose should be reduced if given in combination with **valproic acid**.

Therapeutic Uses:

1. **Monotherapy** for focal seizures. مهم
2. Primary generalized tonic-clonic seizures مهم
3. Generalized seizures of the Lennox-Gastaut syndrome. ما تعرفوه حاليا
4. Absence epilepsy (less effective than ethosuximide and valproate).

Adverse Effects:

1. Dizziness, headache, diplopia, nausea, insomnia, somnolence.
2. Hypersensitivity reaction: skin rash.
3. Serious rash occurs in approximately 0.3–0.8% of children age 2–17 years, & in 0.08–0.3% of adults. This rash is increased if given in combination with **valproate**.

Topiramate:

• Topiramate is a broad-spectrum antiseizure drug.
• It a sulfamate-substituted monosaccharide derived from d-fructose.

Pharmacokinetics:

• It is rapidly absorbed, moderate metabolism, primarily excreted in the urine (50–80% is unchanged).

Mechanism of Action:

• It acts through several cellular targets, which may account for its broad-spectrum activity in epilepsy & migraine.
1. Voltage-gated sodium channels.
2. GABAA receptor subtypes.
3. AMPA or kainate receptors.

• It is a weak inhibitor of carbonic anhydrase ➡️ **metabolic acidosis**.

Therapeutic Uses:

1. Treatment of **focal seizures** in adults and children.
2. Primary generalized **tonic-clonic** seizures.
3. Lennox-Gastaut syndrome. مش مهم
4. May be effective in juvenile myoclonic epilepsy, infantile spasms. مش مهم
5. Childhood **absence seizures**.

Adverse Effects:

1.**Cognitive** adverse effects are common and are a frequent reason for drug discontinuation.
• Include: impaired expressive language function (dysnomia (failure to know names) and diminished verbal fluency), impaired verbal memory, and a general slowing of ssssssscognitive processing **without** sedation or mood change.
*You have to know the drugs that cause sedations.
2. Paresthesias, Somnolence, fatigue, dizziness, nervousness and confusion – dose related.
3. Acute myopia & angle closure glaucoma (blindness) may require prompt drug withdrawal.
4. Decreased sweating (**oligohydrosis**) and an elevation in body temperature may occur during exposure to hot weather, mostly in children.
5. Urolithiasis. (kidney stones)
6. Long-term use is associated with significant weight loss, due to fat loss.
7. Teratogenic – oral cleft formation.

Note: most antiepileptic drugs have teratogenic effects.

Drug Interactions:

• Birth control pills may be less effective in the presence of topiramate

Gabapentin & Pregabalin:

• They are amino acid analogs of GABA, but do not act through GABA mechanism.

Mechanism of Action:

• They bind to α2δ, a protein that serves as an auxiliary مساعد subunit of voltage-gated calcium channels but may also have other functions.
• The precise way in which binding of gabapentinoids to α2δ protects against seizures is not known, but may relate to a decrease in glutamate release at excitatory synapses.

Pharmacokinetics:

• These drugs are not metabolized and do **not** induce hepatic enzymes.
• They are eliminated by the kidney unchanged.
• Both drugs are absorbed by the l-amino acid transport system (active transport) in the upper small intestine.
• The oral bioavailability of **gabapentin** decreases with increasing dose because of saturation of this transport system. no benefits from increasing the dose due to saturation.
• Pregabalin exhibits linear absorption within the therapeutic dose range.
• Elimination kinetics are linear.
• **Not** bound to plasma proteins.
• **No significant drug interactions**.

Therapeutic Uses:

1. **Focal seizures** (less effective than other drugs).
2. Non-epilepsy conditions, such as **neuropathic pain** (postherpetic neuralgia and painful diabetic neuropathy).
3. Restless legs syndrome.
4. Anxiety disorders.
5. **Pregabalin** is also approved for the treatment of **fibromyalgia**(a wide spread muscle pain).

• **Gabapentin** may aggravate absence seizures and myoclonic seizures.

Adverse Effects:

• Somnolence, dizziness, ataxia, headache tremor, weight gain, & peripheral edema.

Levetiracetam:

• Levetiracetam is a broad-spectrum antiseizure agent.
• Commonly prescribed because:

1. Favorable adverse effect profile (??). not surely :) they have bad effects too.
2. Broad therapeutic window.
3. Favorable pharmacokinetic properties.
4. Lack of drug-drug interactions.

Mechanism of Action:

• It binds selectively to SV2A, a synaptic vesicle integral membrane protein, which may facilitate synaptic vesicle exocytosis. go back to the figures above.
• The drug accesses the luminal side of recycling synaptic vesicles by vesicular endocytosis.
• The result is **reduction of the release of** the excitatory neurotransmitter **glutamate**.

Therapeutic Uses:

1. **Focal seizures** in adults and children.
2. Primary generalized **tonic-clonic seizures**
3. **Myoclonic seizures** of juvenile myoclonic epilepsy.

• Oral absorption is complete, rapid & **unaffected** by food.

Adverse Effects:

1.Somnolence, asthenia, ataxia, infection (colds), and dizziness.

2. Less common but more serious are behavioral & mood changes (irritability, aggression, agitation, anger, anxiety, apathy, depression, & emotional lability متأرجح).

Pharmacokinetics:

• Oral absorption is rapid & nearly complete.
• Food slows absorption rate but does not affect the amount absorbed.
• Kinetics are linear. t½ ~ 6-8 hours.
• Protein binding is low.
• 2/3 excreted unchanged, the rest is metabolized in the blood.

Vigabatrin:

• Is gama-vinyl-GABA (analog of GABA).
• It is an irreversible inhibitor of GABA transaminase, the enzyme responsible for the degradation of GABA ➡️ an increase in the amount of GABA at synapse.

Therapeutic uses:

1. Infantile spasms, especially when associated with tuberous sclerosis.
2. Focal seizures.

Adverse effects:

1. The most important adverse effect is irreversible retinal dysfunction.
• Patients may develop permanent bilateral concentric visual field constriction.
• It can damage the central retina.
• The onset of vision loss weeks months of starting treatment.
• Therefore, it is used only in patients refractory to other drugs. الباقي اقرؤوه لحالكم
2. Somnolence, headache, dizziness, and weight gain.
3. Agitation, confusion, & psychosis.
• Preexisting mental illness is a relative contraindication.

Lacosamide:

• An amino acid-related compound.

Mechanism of action:

• It binds selectively to the fast inactivated state of sodium channels.

Therapeutic Uses:

• Focal onset seizures in patients age 17 years and older.

Adverse effects:

• Dizziness, headache, nausea, & diplopia.
• Negligible drug interactions.

Zonisamide:

• Zonisamide is a broad-spectrum antiseizure drug that is effective for:
1. Focal & generalized tonic-clonic seizures in adults & children.
2. May be effective in some myoclonic epilepsies and in infantile spasms.
3. May improve generalized onset tonic-clonic seizures & atypical absence seizures.

Mechanism of Action:

• There is little information on its mechanism of action.
• It does block voltage-gated sodium channels, but other actions may also contribute to its

antiseizure activity.
• Carbonic anhydrase inhibition.
Adverse effects:
• Drowsiness, cognitive impairment, **renal stones**, and potentially serious skin rashes.
• Weight loss • Kidney stones • **Oligohydrosis.**
Drug Interactions:
• **Carbamazepine, phenytoin, & phenobarbital** increase its clearance.

Benzodiazepines:

• First-line acute treatment for seizures, either in **status epilepticus** or **acute repetitive seizures**.
• Two prominent aspects of benzodiazepines limit their usefulness in the chronic therapy of epilepsy: **sedation & tolerance**.

1) Diazepam:

• Given IV is a first-line treatment for status epilepticus.
• Used in a **rectal gel** formulation for the treatment of **acute repetitive seizures**.

2) Lorazepam:

• It is more commonly used in the treatment of status epilepticus because it has a more prolonged duration of action after bolus IV injection.
• Lorazepam is more effective and longer-acting, because it binds more tightly to GABA receptors and has a longer distribution half-life (2-3 hours vs 15 min for diazepam which is much more lipid soluble).

3) Clonazepam:

• Long-acting, with documented activity against absence, atonic, & myoclonic seizure.

4) Nitrazepam:

• Used for **infantile spasms** & **myoclonic seizures**.

5) Clorazepate dipottasium:

• Adjunct treatment of focal seizures.
- Drowsiness and lethargy are common.

دعواتكم -