Hashemite University
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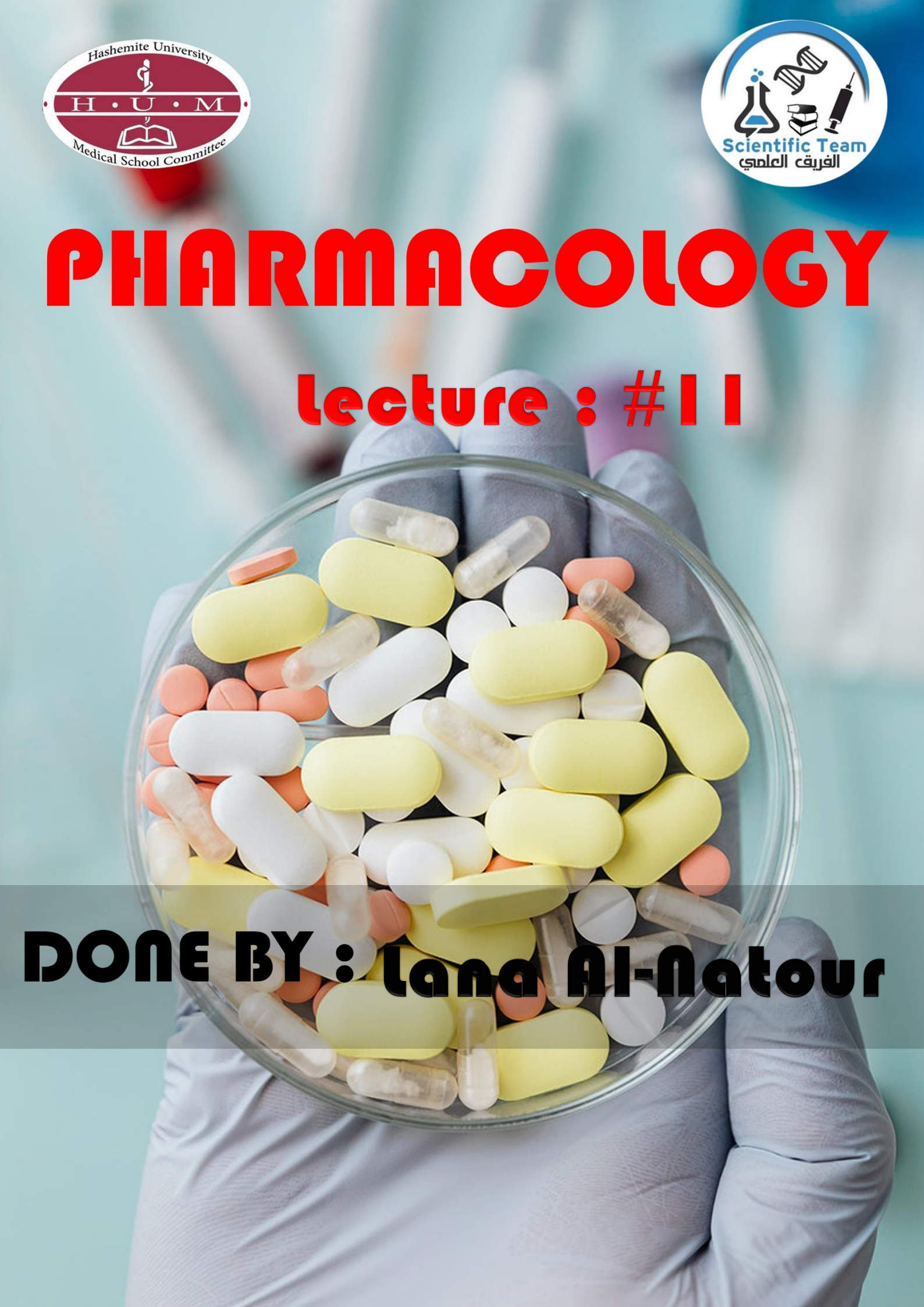
Medical School Committee

Scientific Team
الفريق العلمي

PHARMACOLOGY

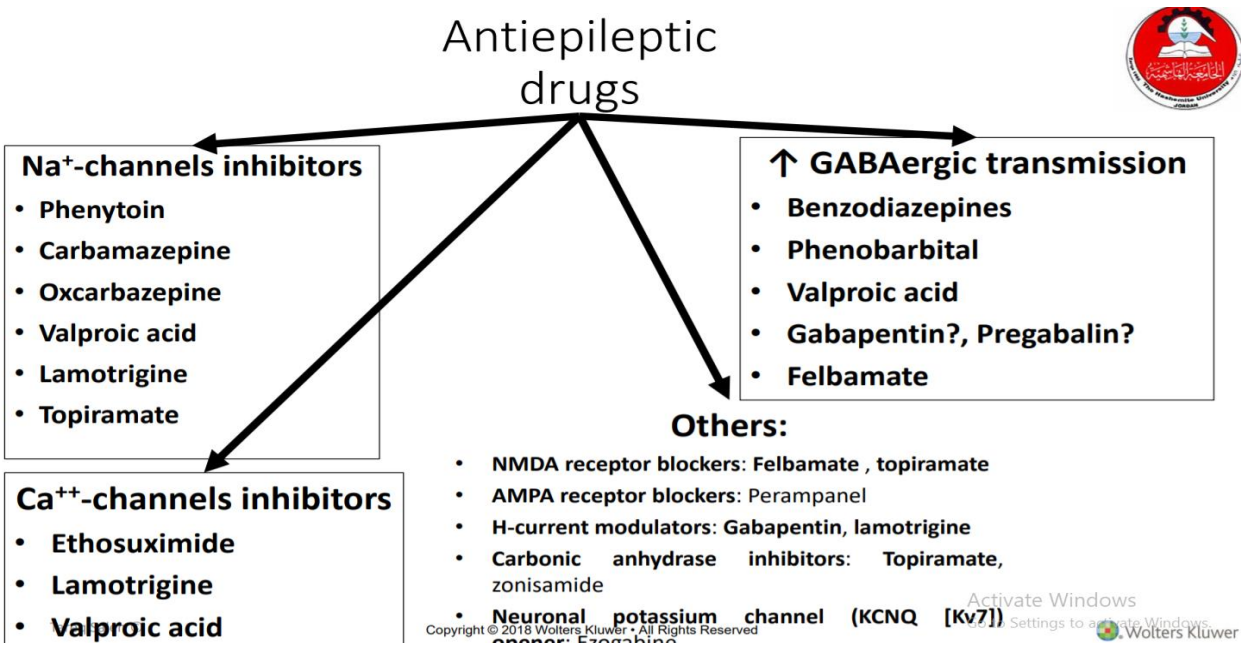
Lecture : #11



DONE BY : Lana Al-Natour

Antiepileptic drugs part -2-

في هاد التلخيص بدنا نكمل على drugs لانه بالمحاضرة السابقة اخذنا عن carbamazepine , phenytoin
بس بداية نرجع نذكر تقسيمتهم حسب mechanism of action :



Sodium channels inhibitors:

3-valproic acid

MOA:

- **Blocks Na+ channels**
- **Blocks GABA transaminase (GABA-T)**

This enzyme is responsible for metabolism of GABA (so to decrease the degradation of such neurotransmitter, increasing GABA effect because it is an inhibitory NT)

- **Blocks T-type Calcium channels**

لانه هدول channels الهم دخل في propagation of action potential وبالتالي لما نعمللهم block بساعدوا انه AP ما يوصل neurons

Indications:

- **Focal seizures • Generalized seizures • Absence seizures • Bipolar disorder**

وهاد الدواء بيفرق عن phenytoin /carbamazepine بحيث منقدر نستخدمه في absence seizures ويعتبر first line treatments in absence seizures(in pediatrics)

Pharmacokinetics:

• **Inhibits CYP2C9, UGT, epoxide hydroxylase**

عكس carbamazepine /phenytoin وبالتالي فيه drug-drug interactions

Adverse effects:

• **Hepatotoxicity**

Used in caution in patients with liver disease

• **Teratogenicity**

Contraindicated in pregnant woman because it results in massive congenital abnormalities and cognitive deficits in new-born

• **CNS-related**

***we have different preparations in valproic acid because there is a problem in absorption in GIT(acidity)**

other preparations like sodium valporate فعشان هيك عنا

efficacy but different pharmacokinetics الهم نفس

Valproic acid vs Sodium valproate vs Divalproex sodium

4-lamotrigine

One of the most important drugs that is used in epilepsy usually in most of the cases is considered as first line drug depending on the factors(type of seizure….)

MOA:

• **Blocks Na+ channels**

• **Blocks voltage-gated Ca++ channels**

Indications:

• **Focal seizures**

• **Generalized seizures**

• **Absence seizures**

• **Lennox-Gastaut syndrome**

Sever epilepsy syndromes (epilepsy other neurological disorders)

• **Bipolar disorder**

منستخدم هاد الدواء ك mood stabilizer اكثر من valproic acid and carbamazepine عشان كمان هو safe drug

Pharmacokinetics:

• **Metabolized by UGT(in the liver)**

• **What will happen when combined with :**

phenytoin?

الدكتور سأل لو مثلا مريض ما استجاب على lamotrigine لحاله فأنت لازم هيك تعمل combination with other drug فمثلا انت اعطيته مع phenytoin هلا شو ممكن يصير بال lamotrigine levels لما اخذه مع phenytoin ??

رح يقل تركيزه ليش ؟لانه phenytoin بزود هاد enzyme وهو UGT inducer وبالتالي رح يزيد metabolism of lamotrigine

وبالتالي انا لما اعطي lamotrigine مع phenytoin لازم ازود dose تاعت lamotrigine

Valproic acid?

طيب سؤال ثاني لو اعطينا valproic acid مع lamotrigine شو رح يصير بال ? lamotrigine levels

رح يزيد تركيزه لانه valproic acid عبارة عن enzyme inhibitor (UGT)

وبالتالي لازم اقلل dose لما اعطيه مع valproic acid

Adverse effects:

- **CNS-related side effects (headache,dizziness, drowsiness)**

-Severe skin reaction (lifethreatening)(rare)

هون لازم احذر المريض اذا اجا skin rash لازم ييجي على الطوارىء

5- Topiramate

MOA:

- **Blocks Na+ channels**
- **Blocks L-type Calcium channels**
- **Carbonic anhydrase inhibitor**
- **NMDA blocker(glutamate receptor)(because if we want to reduce the activity of the brain we have to antagonize the Glutamate ,to inhibit the signalling)**

Indications:

- **Focal seizures**
- **Generalized seizures**
- **Migraine prevention (prophylactic)**

Pharmacokinetics:

- **Inhibits CYP2C9**

Adverse effects

- **Somnolence(increase sleeping)**
- **Weight loss**
- **Paresthesia**
- **Renal stones**
- **Oligohidrosis (reduced sweating,dry skin)**
- **hyperthermia**

عنده شوية adverse effects ما الها دخل ببعض عشان عنده mechanism of actions مختلفة

6- Zonisamide

MOA:

- **Blocks Na+ channels**
- **Blocks T-type Calcium channels**
- **Limited carbonic anhydrase inhibitor**

In order to inhibit action potential propagation

Indications:

- **Focal seizures**

Not used in generalized seizures

Adverse effects

- **CNS adverse effects**
- **Nephrolithiasis (kidney stones)**
- **Oligohidrosis**
- **Contraindicated in patients with sulfonamide hypersensitivity (because it has sulpha group)**

calcium channel inhibitors:

Ethosuximide:

MOA:

- **Blocks T-type Calcium channels**

Indications:

- **Absence seizure only**

(Drug of choice)

Pharmacokinetics:

Half-life: 30-60 hrs (longer half –life)

To sum up : how many drugs till now are used in absence seizures :

1-ethosuximide
2-valproic acid
3-lamotrigine

Increase in GABA transmission drugs :

-Benzodiazepines
Phenobarbital
MOA:
• Bind to $GABA_A$ receptors and enhance GABA binding → facilitates Cloride entry →inhibitory

Indications:
• Clonazepam → adjunctive antiseizure therapy

first line drugs هما مش

• Diazepam → status Epilepticus ((state of continues seizure)) (drug of choice)

-Gabapentin
Pregabalin
MOA:
• Analog of GABA
• It does NOT act at GABA receptor
• MOA is unknown

Homework :possible mechanism of action of gabapentin: ((google))
mechanism of action as an antiepileptic agent likely involves its inhibition of the alpha 2-delta subunit of voltage-gated calcium channels

Indications:
• Adjunct therapy for focal seizures
• Neuropathic pain, e.g., postherpetic neuralgia, diabetic neuropathy(in diabetes)

Pharmacokinetics:
• Secreted unchanged
• Few drug interactions
• Suitable for elderly
It is not the best choice in renal impairment
Adverse effects
• Sedation
Euphoria (so some people start to abuse such drug)

- Felbamate

MOA:

- **Blocks voltage-gated Na+ channels**
- **Blocks NMDA receptors**
- **Blocks Ca++ channels**
- **Potentiates GABA**

Indications:

- **Reserved for refractory epilepsy**

مثلا في الحالات يلي بكون المريض ياخذ فيها lamotrigine اذا ما استجاب عليها منستخدم فيها بال combinations هاد الدواء

- **Lennox-Gastaut syndrome((sever epilepsy cases))**

Pharmacokinetics:

- **Inhibits CYP2C19**
- **Induces CYP3A4**

بشبه valproic acid

Adverse effects:

- **Aplastic anemia ((sever))**
- **Hepatic failure**

Dangerous drug •

So it is not first line ,so it is not frequently used for example in comparing with lamotrigine in which is important and useful drug

Others :

- Ezogabine

MOA:

- **Open voltage-gated M-type potassium channels → stabilizing resting membrane potential**

It will hyperpolarized the membrane (so in that way the excitability will be reduced)

Pharmacokinetics:

- **No drug interactions at low doses**

Adverse effects

- **Urinary retention**
- **QT interval prolongation**
- **Blue skin discoloration**

Retinal abnormalities ((effect vision))•

- Levetiracetam

Very effective and commonly used ,widely used

MOA:

• unknown

Indications:

• Focal (simple and complex) seizures

• Adjunct therapy for generalized seizures

Adverse effects

• Dizziness

somnolence •

Status Epilepticus

• Continuous or repetitive seizures (> 20 min) with impaired consciousness during the interictal period.

هلا معظم seizures عبارة عن self-limited وبتخلص ولكن لو صار progress of seizures بسرعة لازم يروح على الطوارىء

• Management

1. Diazepam (IV or rectal) → for rapid control.

2. Fosphenytoin (prodrug) or phenytoin→ long-acting, to maintain control.

3. Phenobarbital→2nd choice to phenytoin.

هلا هون افرض انه 3 choices of drugs ما زبطوا بدخل المريض في coma ومنعطي anesthetics

4. Propofol (IV anesthesia)→ in resistant cases.

Antiepileptics during pregnancy

• Monotherapy

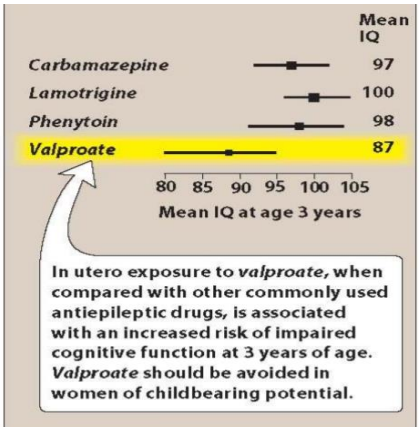
عشان combination رح يكون عنا adverse effects

• The lowest possible dose

• Lamotrigine; gabapentin = safe

• Valproic acid; phenobarbital; phenytoin, others = contraindicated

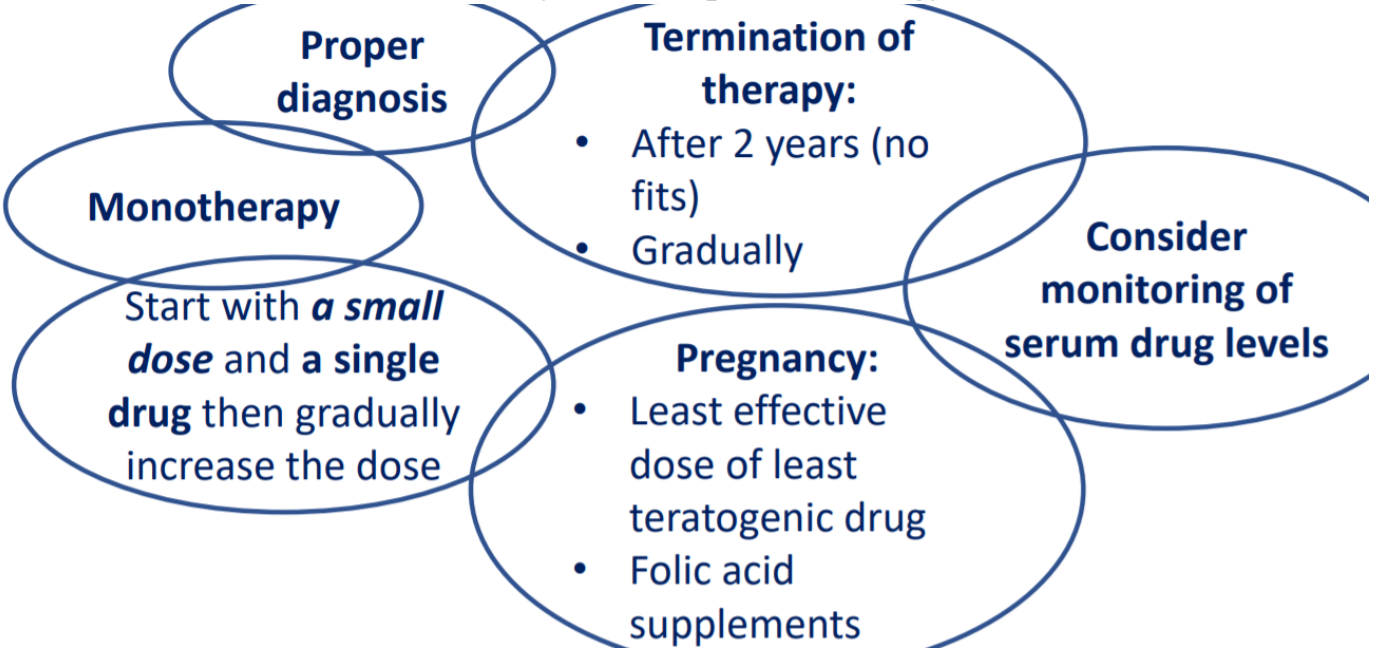
• Cleft lip, neural tube defect (patients considering pregnancy while on antiepileptics should receive folic acid supplements)



مثلا مريضة كان معها epilepsy واخذت ادوية زي valproic acid وكانت control وبعدها طلعت حامل ؟شو الاجراء يلي لازم ينعمل؟

انه نسوي switch ونعطيها safe drugs

Summary of Therapeutic Strategy



لازم نعمل proper diagnose وبناء عليه نعطي monotherapy وlowest dose واذا patient صارله لمدة سنيتين control على single therapy ومنبلش نسوي termination gradually

AAN Guidelines for Epilepsy Treatment

Level	Recommendation
Level B	LTG use should be considered to decrease seizure frequency.
Levels B and Level C	LTG use should be considered (**Level B**) and GBP use may be considered (**Level C**) to decrease seizure frequency in patients aged ≥60 years.
Level C	LEV use may be considered to decrease seizure frequency.
Level C	ZNS use may be considered to decrease seizure frequency.
Level C	VGB use appears to be less efficacious than immediate-release carbamazepine (CBZ) use and may not be offered; furthermore, toxicity profile precludes VGB use as first-line therapy.
Level C	PGB use at 150 mg/d is possibly less efficacious than LTG use at 100 mg/d.
Level U	Evidence is insufficient to consider GBP, OXC, or TPM instead of CBZ.
Level U	Evidence is insufficient to consider TPM instead of phenytoin in urgent treatment of new-onset or recurrent focal epilepsy, unclassified generalized tonic-clonic (GTC) seizures, or generalized epilepsy (GE) presenting with GTC seizures.
Level U	Data are lacking to support or refute use of third-generation AEDs, CLB, FBM, or VGB in treating new-onset epilepsy.
Level U	Data are lacking to support or refute use of newer AEDs in treating unclassified GTC seizures.

Recommendation for childhood absence epilepsy

Level	Recommendation
Level B	Unless there are compelling reasons based on adverse events (AEs) profile, ethosuximide (ETS) or VPA use should be considered before LTG use to decrease seizure frequency in treating absence seizures in childhood absence epilepsy.

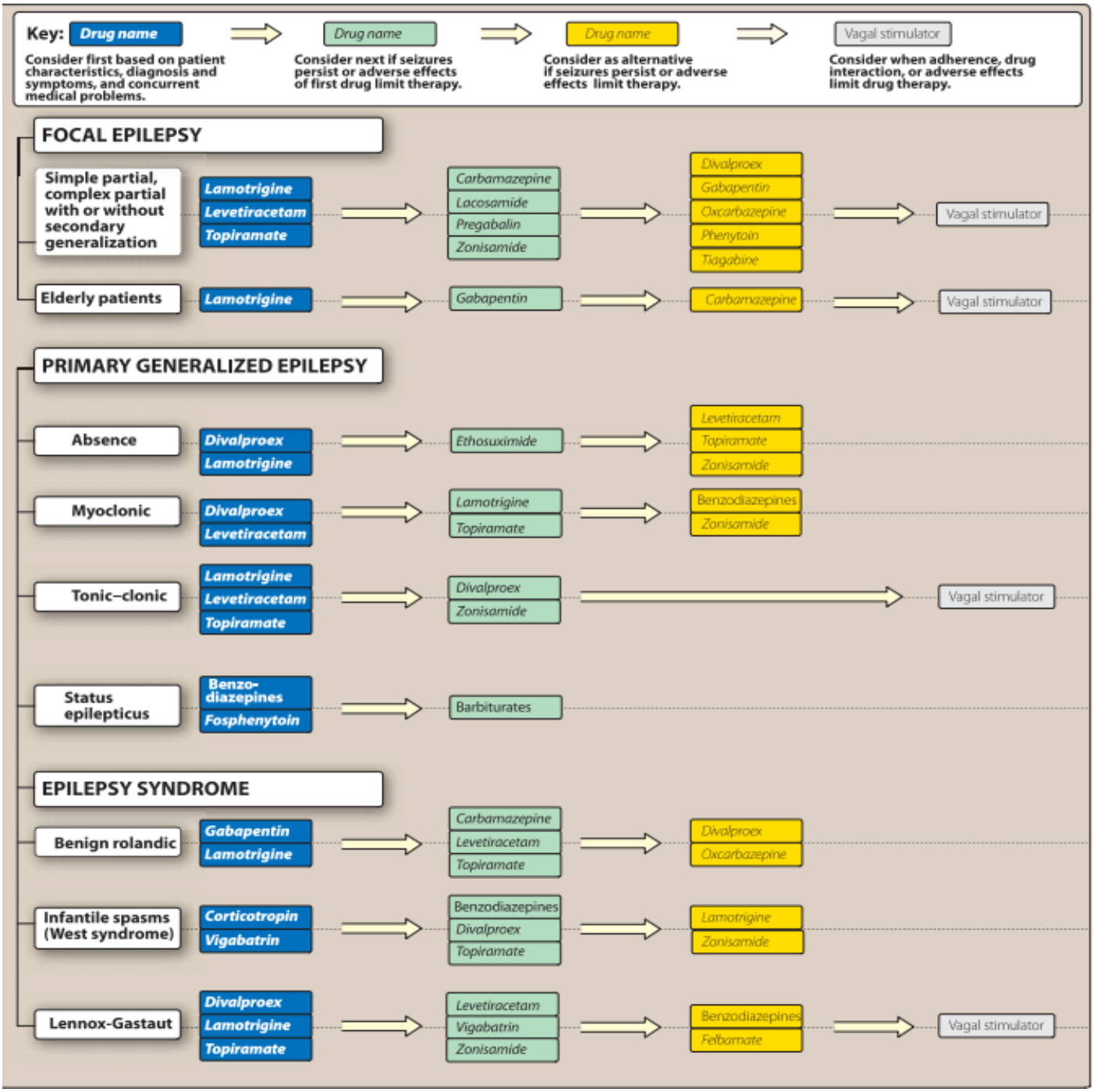
LTG:lamotrigine

هدول levels لكل antiepileptic drugs

**الدكتور ركز على تاع level B (absence seizure) فممكن يجيب case عليها ☺

فيه جدول مهم حكا عنه الدكتور من الكتاب ويسأل عنه ب cases :

كل type of seizure كيف منبلش نعالجها بأي antiepileptic drugs



Summary of the drugs :

DRUG	MECHANISM OF ACTION	ADVERSE EFFECTS AND COMMENTS
Carbamazepine	Blocks Na^+ channels	Hyponatremia, drowsiness, fatigue, dizziness, and blurred vision. Drug use has also been associated with Stevens-Johnson syndrome. Blood dyscrasias: neutropenia, leukopenia, thrombocytopenia, pancytopenia, and anemias.
Divalproex	Multiple mechanisms of action	Weight gain, easy bruising, nausea, tremor, hair loss, GI upset, liver damage, alopecia, and sedation. Hepatic failure, pancreatitis, and teratogenic effects have been observed. Broad spectrum of antiseizure activity.
Eslicarbazepine acetate	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Ethosuximide	Blocks Ca^{2+} channels	Drowsiness, hyperactivity, nausea, sedation, GI upset, weight gain, lethargy, SLE, and rash. Blood dyscrasias can occur; periodic CBCs should be done. Abrupt discontinuance of drug may cause seizures.
Ezogabine	Enhances K^+ channels	Urinary retention, neuropsychiatric symptoms, dizziness, somnolence, QT prolongation, reports of blue skin discoloration, and retina changes.
Felbamate	Multiple mechanisms of action	Insomnia, dizziness, headache, ataxia, weight gain, and irritability. Aplastic anemia and hepatic failure. Broad spectrum of antiseizure activity. Requires patient to sign informed consent at dispensing.
Gabapentin	Unknown	Mild drowsiness, dizziness, ataxia, weight gain, and diarrhea. Few drug interactions. One hundred percent renal elimination.
Lacosamide	Multiple mechanisms of action	Dizziness, fatigue, and headache. Few drug interactions; Schedule V.
Lamotrigine	Multiple mechanisms of action	Nausea, drowsiness, dizziness, headache, and diplopia. Rash (Stevens-Johnson syndrome—potentially life threatening). Broad spectrum of antiseizure activity.
Levetiracetam	Multiple mechanisms of action	Sedation, dizziness, headache, anorexia, fatigue, infections, and behavioral symptoms. Few drug interactions. Broad spectrum of antiseizure activity.
Oxcarbazepine	Blocks Na^+ channels	Nausea, rash, hyponatremia, headache, sedation, dizziness, vertigo, ataxia, and diplopia.
Perampanel	Blocks AMPA glutamate receptors	Serious psychiatric and behavioral reactions, dizziness, somnolence, fatigue, gait disturbance, and falls, long half-life.
Phenytoin	Blocks Na^+ channels	Gingival hyperplasia, confusion, slurred speech, double vision, ataxia, sedation, dizziness, and hirsutism. Stevens-Johnson syndrome—potentially life threatening. Not recommended for chronic use. Primary treatment for status epilepticus (*fosphenytoin*).
Pregabalin	Multiple mechanisms of action	Weight gain, somnolence, dizziness, headache, diplopia, and ataxia. One hundred percent renal elimination.
Rufinamide	Unknown	Shortened QT interval. Multiple drug interactions.
Tiagabine	Blocks GABA uptake	Sedation, weight gain, fatigue, headache, tremor, dizziness, and anorexia. Multiple drug interactions.
Topiramate	Multiple mechanisms of action	Paresthesia, weight loss, nervousness, depression, anorexia, anxiety, tremor, cognitive complaints, headache, and oligohidrosis. Few drug interactions. Broad spectrum of antiseizure activity.
Vigabatrin	Irreversible binding of GABA-T	Vision loss, anemia, somnolence, fatigue, peripheral neuropathy, weight gain. Available only through SHARE pharmacies.
Zonisamide	Multiple mechanisms of action	Nausea, anorexia, ataxia, confusion, difficulty concentrating, sedation, paresthesia, and oligohidrosis. Broad spectrum of antiseizure activity.

ANTIEPILEPSY MEDICATION	PROTEIN BINDING*	HALF-LIFE	ACTIVE METABOLITE	MAJOR ORGAN OF ELIMINATION	DRUG INTERACTIONS
Carbamazepine	Moderate	6–15	CBZ-10,11-epoxide	Liver	✔
Eslicarbazepine acetate **^	Low	8–24	Eslicarbazepine (S-licarbazepine)	Kidney	✔
Ethosuximide	Low	25–26		Liver	✔
Ezogabine	Moderate	7–11	monoacetylated metabolite	Liver	✔
Felbamate	Low	20–23		Kidney/Liver	✔
*Fosphenytoin***	High	12–60	phenytoin	Liver	✔
Gabapentin	Low	5–9		Kidney	
Lacosamide	Low	13		Various	
Lamotrigine	Low	25–32		Liver	✔
Levetiracetam	Low	6–8		Hydrolysis	
*Oxcarbazepine***	Low	5–13	Monohydroxy metabolite (MHD)	Liver	✔
Phenobarbital	Low	72–124		Liver	✔
Phenytoin	High	12–60		Liver	✔
Primidone	High	72–124	Phenobarbital, PEMA	Liver	✔
Perampanel^	High	105		Liver	✔
Pregabalin	Low	5–6.5		Kidney	
Rufinamide	Low	6–10		Liver	✔
Tiagabine	High	7–9		Liver	✔
Topiramate	Low	21		Various	✔
Vigabatrin	Low	7.5		Kidney	✔
Valproic Acid (Divalproex)	Moderate/ High	6–18	Various	Liver	✔
Zonisamide	Low	63		Liver	✔

Questions :

Several classes of antiepileptic drugs (AEDs) interfere with the propagation of action potentials in hyperactive epileptic foci by inhibiting the activation of voltage-gated Na+ channels. All of the following medications share this mechanism of action, EXCEPT:

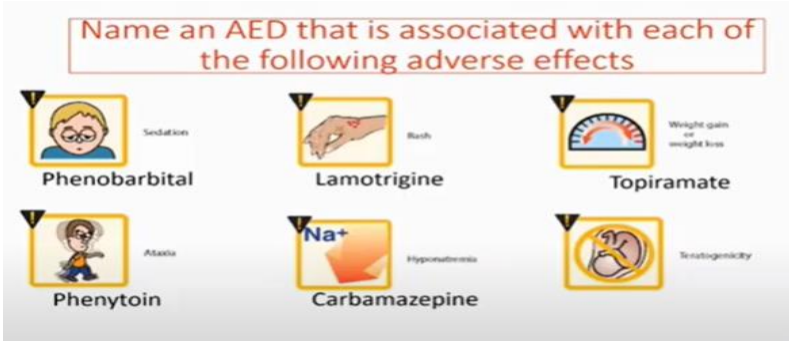
A) Zonisamide
B) Carbamazepine
C) Conazepam
D) Valproic acid
E) Phenytoin

answer:C

All of the following mechanisms of action account for the antiepileptic effects of the drug topiramate, EXCEPT:

a) Voltage-gated Na+ channel blockade
b) L-type Ca++ channel blockade
c) Carbonic anhydrase inhibition
d) Glutamate NMDA receptor antagonist
e) Facilitation of Cl- influx at GABA receptor

answer :e



Good luck ☺