بسم الله الرحمن الرحيم

DOPAMINE SCIENTIFIC TEAM

Antiepileptic drugs

FINAL | Lecture 7

﴿إِنِّي تَوَكَّلْتُ عَلَى اللَّهِ رَبِّي وَرَبِّكُمْ ۚ مَا مِن دَابَّةٍ إِلَّا هُوَ آخِذٌ بِنَاصِيَتِهَا ۚ إِنَّ رَبِّي عَلَىٰ صِرَاطٍ مُّسْتَقِيمٍ﴾

Done by: Hala Swiedan
Sadeel Al-hawawsheh

PHARMACOLOGY

رحلة اليقين مع سورة يس

بِسْمِ ٱللَّهِ ٱلرَّحْمَٰنِ ٱلرَّحِيمِ

وَمَا عَلَّمْنَٰهُ ٱلشِّعْرَ وَمَا يَنۢبَغِي لَهُۥٓ إِنْ هُوَ إِلَّا ذِكْرٌ وَقُرْءَانٌ مُّبِينٌ (٦٩) لِّيُنذِرَ مَن كَانَ حَيًّا وَيَحِقَّ ٱلْقَوْلُ عَلَى ٱلْكَٰفِرِينَ (٧٠)

{وَمَا عَلَّمْنَاهُ الشِّعْرَ وَمَا يَنْبَغِي لَهُ إِنْ هُوَ إِلَّا ذِكْرٌ وَقُرْءَانٌ مُبِينٌ } وما علَّمنا رسولنا محمدًا الشعر، وما ينبغي له أن يكون شاعرًا، ما هذا الذي جاء به إلا ذكر يتذكر به أولو الألباب، وقرآن بيِّن الدلالة على الحق والباطل، واضحة أحكامه وحِكَمه ومواعظه; لينذر مَن كان حيَّ القلب مستنير البصيرة، ويحق العذاب على الكافرين بالله; لأنهم قامت عليهم بالقرآن حجة الله البالغة.

{ لِيُنْذِرَ مَنْ كَانَ حَيًّا } أي: حي القلب واعيه، فهو الذي يزكو على هذا القرآن، وهو الذي يزداد من العلم منه والعمل، ويكون لأنهم قامت عليهم به حجة الله، وانقطع احتجاجهم، القرآن لقلبه بمنزلة المطر للأرض الطيبة الزاكية. { وَيَحِقَّ الْقَوْلُ عَلَى الْكَافِرِينَ } فلم يبق لهم أدنى عذر وشبهة يُدْلُونَ بها.

Introduction

- 1 person in 20 will have an epileptic seizure at some time in their life
- Epilepsy is diagnosed on the basis of two or more epileptic seizures.
- Around 450,000 people in the UK have epilepsy (40 million people worldwide)
- A seizure is triggered by a sudden interruption in the brain's highly complex electro-chemical activity

- In this condition, there is an imbalance between two important types of neurotransmission in the brain: excitatory and inhibitory. Normally, these two systems are balanced. Excitatory neurotransmitters like glutamate stimulate neurons, while inhibitory neurotransmitters like GABA reduce neuronal activity.
- However, in this case, the balance is disturbed. The excitatory system becomes stronger, mainly due to increased activity of glutamate and aspartate on NMDA receptors. At the same time, the inhibitory system becomes weaker because GABA activity is reduced. As a result, the brain becomes more excited and less controlled. This leads to increased **neuronal firing.**

- One of the consequences of this excessive excitation, especially in conditions like serotonin syndrome, is the occurrence of seizures. If these seizures happen repeatedly, the condition is called epilepsy.

Pathological Basis

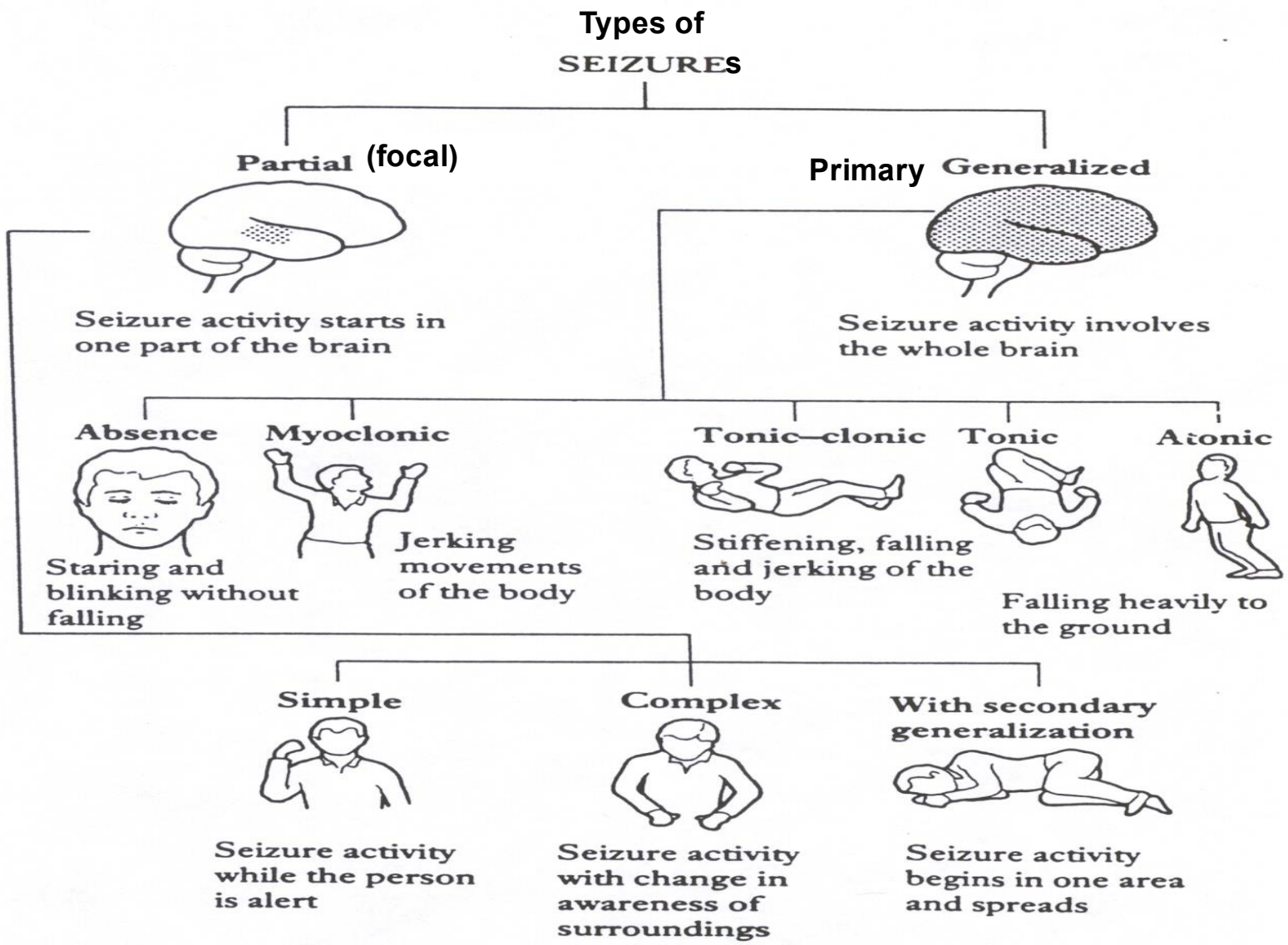
- Abnormal electrical discharge in the brain
- Coordinated activity among neurons depends on a controlled balance between excitation and inhibition
- Any local imbalance will lead to a seizure
- Imbalances occur between glutamate-mediated excitatory neurotransmission and gamma-aminobutyric acid (GABA) mediated inhibitory neurotransmission

﴿وَأَعِدّوا لَهُم مَا استَطَعتُم مِن قُوَّةٍ وَمِن رِباطِ الخَيلِ تُرهِبونَ بِهِ عَدُوَّ اللَّهِ وَعَدُوَّكُم وَآخَرينَ مِن دونِهِم لا تَعلَمونَهُمُ اللَّهُ يَعلَمُهُم ۚ وَما تُنفِقوا مِن شَيءٍ في سَبيلِ اللَّهِ يُوَفَّ إِلَيكُم وَأَنتُم لا تُظلَمونَ﴾

(سورة الأنفال – الآية 60)

Etiology

- Congenital defects, head injuries, trauma, hypoxia
- Infection e.g. meningitis, brain abscess, viral encephalitis
- Concussion, depressed skull, fractures.
- Brain tumors, vascular occlusion.
- Drug withdrawal, e.g. CNS depressants .
- Fever in children (febrile convulsion).
- Hypoglycemia



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Types of Seizures

❖ Seizures are classified into **two main types:**

1. Focal (partial) Seizures

Start in a **small, localized area of the brain**

Abnormal activity is **limited** and does not spread

May affect **one side of the body** depending on the area involved

2. Generalized Seizures

Involve the **entire brain from the beginning**

Effects are **widespread**

❖ Types of Generalized Seizures:

1. Absence Seizures (Most Common)

Seen mainly in **children < 10 years**

Features:

- **Staring**
- **Blinking**
- **Loss of awareness (loss of contact)**

Mechanism:

- The brain area responsible for **unconsciousness during sleep** becomes active
- There is **increased Ca^{2+} influx**
- This increases **action potential generation**
- Leads to activation of a **sleep-like state**

Treatment :

- Use drugs that **block Ca^{2+} entry**
- Especially **T-type calcium channels in the brain**

Types of Seizures

2. Tonic Seizures

- Cause **sustained muscle contraction**
- Due to activation of **motor areas**

3. Tonic-Clonic Seizures

- Features:
  - **Falling**
  - Followed by **jerking movements of the body**

4. Atonic Seizures

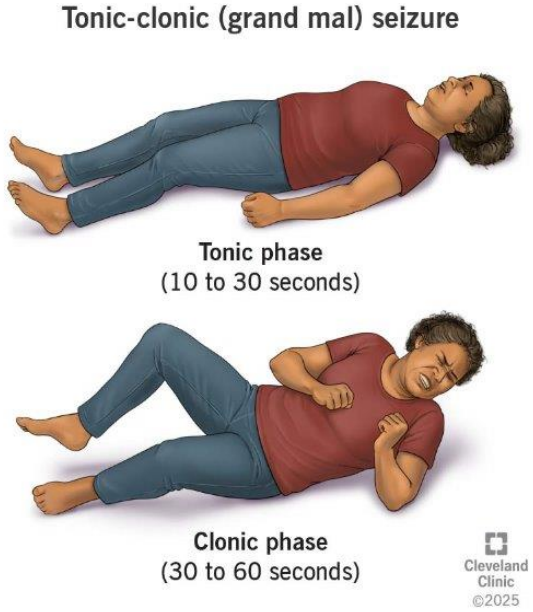
- **Complete loss of muscle contraction**
- Patient suddenly **loses muscle tone**
- Leads to **falling**

5. Myoclonic Seizures

- **Sudden, involuntary muscle movements**
- Occur **without tonic phase**

Important Note

- In some cases, **sensory or motor areas** may be activated
- Patient may:
  - **See or hear unusual things**
  - Develop different seizure types depending on the **most affected area**



A) Focal or partial

*1) **Simple partial(Jacksonian)-** The electrical discharge is confined to the **motor area.***

*2)**Complex partial(psychomotor)-** The electrical discharge is confined in certain parts of the temporal lobe concerned with **mood** as well as **muscle.***

B) Primary generalized

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*1) **Tonic- clonic**. Patient fall in convulsion & may bite his tongue & may lose control of his bladder or bowel.*

*2) **Tonic**. Some pts, after dropping unconscious experience only the tonic or clonic phase of seizure.*

*3) **Atonic (akinetic)**. Starts between the ages 2-5 yrs. The pt's legs simply give under him & drops down.*

*4) **Myoclonic** . Sudden, brief shock like contraction which may involve the entire body or be confined to the face, trunk or extremities.*

*5) **Absence** . Loss of consciousness without involving motor area. Most common in children (4-12 yrs).*

*6) **Status epilepticus (re-occuring seizure).** Continuous seizure without intervening return of consciousness.*

Treatment of Seizures

- Seizures, regardless of the cause, occur due to **abnormal electrical discharge in the brain**, so the main goal of treatment is to **reduce neuronal excitability**.

❖ Sodium (Na^+) Channel Blockers

One way to treat seizures is by **blocking Na^+ channels**. Drugs such as **phenytoin** (which is also a Class 1B antiarrhythmic) and **lidocaine** act by closing Na^+ channels in their active state in the CNS, which decreases repetitive neuronal firing. However, these drugs also affect **Na^+ channels in the heart**, not only in the brain.

❖ Calcium (Ca^{2+}) Channel Effect

Another method of treatment is by affecting **Ca^{2+} channels**. Reducing calcium entry into neurons helps decrease neuronal excitability and therefore reduces seizure activity.

❖ Increasing GABA

Seizures can also be treated by increasing **GABA (gamma-aminobutyric acid)**, which is the main inhibitory neurotransmitter in the brain. Increasing GABA leads to **suppression of neuronal activity**.

❖ Status Epilepticus

This is a serious condition characterized by **continuous or recurrent seizures without regaining consciousness between them**. In this case, the **drug of choice is diazepam or clonazepam**, because they rapidly increase GABA activity and help control the seizures.

❖ Phenobarbital

Phenobarbital is used as an antiepileptic drug because it increases **GABA activity**. It is especially used in **infants instead of thiopental**, because strong activation of GABA is needed, however **diazepam cannot be used in this situation**.

Basis of Pharmacological Rx

Most anti-epileptic agents act either by blockade of depolarisation channels (Na+ and Ca++) [increase the threshold of AP, hyperpolarization]

OR

Enhancing the activity of GABA (neurotransmission inhibition)

Current Pharmacotherapy

- Just under 60% of all people with epilepsy can become seizure free with **drug therapy**
- In another 20% the seizures can be drastically reduced
- ~ 20% epileptic patients, seizures are refractory to currently available drugs.
- Because of overlapping mechanisms of action, best drug can be chosen based on minimizing side effects in addition to efficacy

5 Categories of Anti-epileptic Drugs

- All classifications are based upon chemistry:
  - Hydantoins
  - Succinimides
  - Benzodiazepines
  - Barbiturates
  - Miscellaneous

Phenytoin Overview

- **Phenytoin** is an old drug, but it is **still used** in clinical practice. However, it is associated with **many side effects**, so its use requires careful monitoring.

- Liver Effects : Phenytoin **induces cytochrome P450 enzymes** (unlike most drugs, which inhibit them). This leads to increased metabolism of substances such as **folic acid and vitamin D**, resulting in their deficiency. It can also cause **enlargement of lymph nodes**, especially in the **axillary and cervical regions**.
- Phenytoin can cause **gingival hyperplasia** (gum enlargement). This side effect is also seen with **calcium channel blockers (Amlodipine)** and **cyclosporine**, making these three drugs important causes of this condition.
- Brain Effects: phenytoin decreases neuronal conductivity, which may lead to **dizziness, ataxia, blurred vision, and nystagmus**.
- Phenytoin has significant **drug-drug interactions**, mainly due to its effect on liver enzymes (P450 induction), which alters the metabolism of many other drugs.
- Phenytoin is **teratogenic** and can cause fetal abnormalities, including **neural tube defects and spinal abnormalities**, leading to features such as a **small skull**.
- Phenytoin may cause a **skin rash**, especially in patients with genetic predisposition. However, it does **not progress to Stevens-Johnson syndrome**.
- Phenytoin binds to the Na channels in n the heart and causes **bradycardia** (unlike carbamazepine- to be discussed)
- Phenytoin is usually eliminated by the liver, but at high doses, the liver enzymes that metabolize it become saturated. Once this happens, the body can only remove a fixed amount of the drug per hour, no matter how much more you give. This is called ***zero-order kinetics*** so drug elimination becomes constant and independent of dose once the metabolic enzymes are saturated.
- The problem is that the enzyme capacity differs between people "**interindividual variation**". Some patients reach saturation with a low dose, while others can tolerate more. Because of this unpredictable elimination, giving too much too quickly can cause dangerous drug levels. Therefor , We must check the patient's blood levels and increase the dose slowly to avoid toxicity
- Because of zero-order kinetics, you should **not increase the dose suddenly** if the patient does not respond. Instead, the dose should be increased **gradually**, because it is difficult to predict when the patient will reach the saturation point.
- Phenytoin is **not used in absence seizures** because it increases **CNS depression**. Since absence seizures already involve **loss of awareness for a few seconds**, phenytoin may worsen the condition and can increase **blinking activity**.

Hydantoins - Phenytoin

- **First-line for partial seizures; some use for tonic-clonic seizures and tonic seizures.**

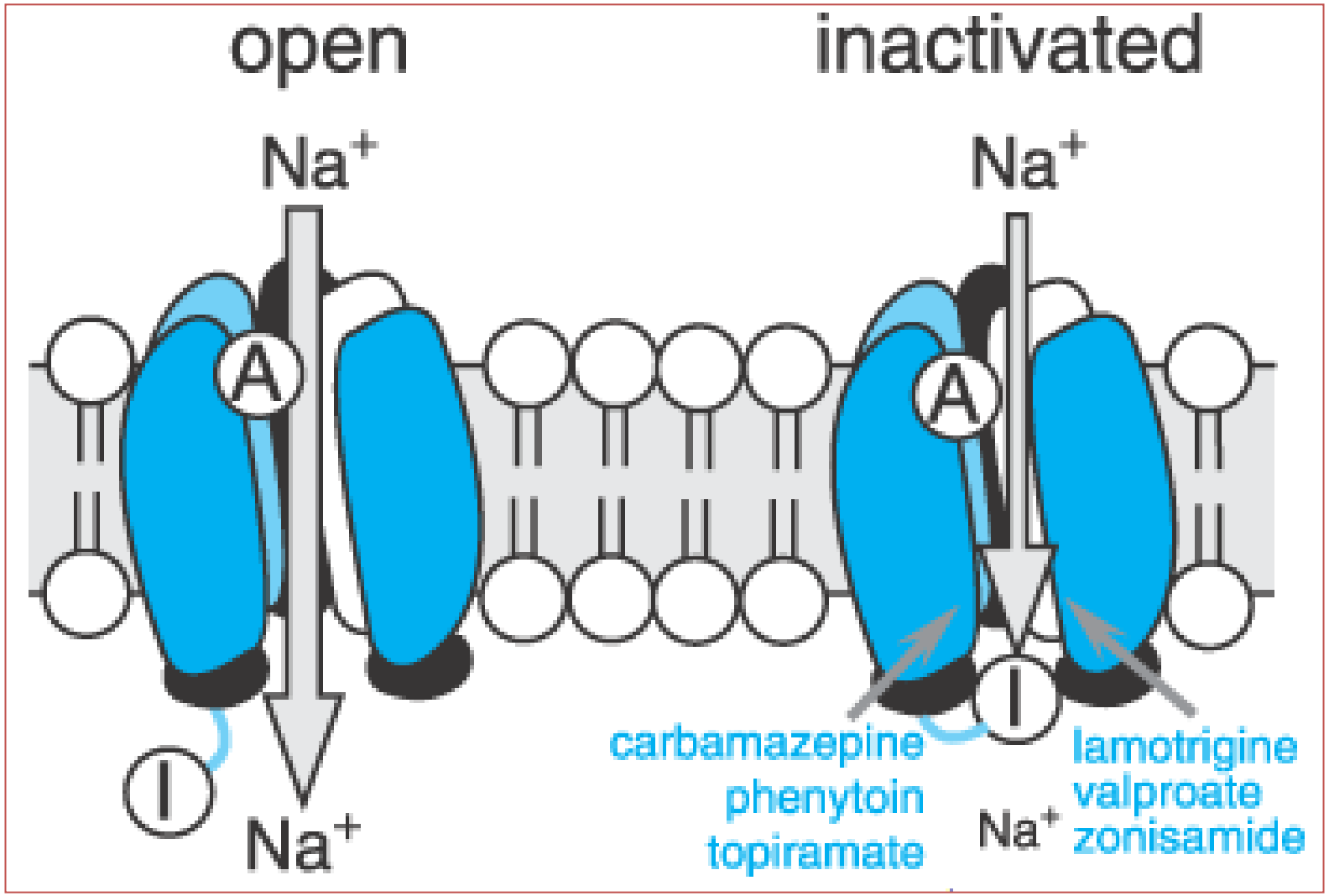
- Antagonism (blocking) of Na+ channels to reduce excitability and increase the duration of inactivation -as local anesthetics effect -

- Highly bound to plasma proteins – displaced by Valproate;

- ***Induces P450*** resulting in increase in its own metabolism,

Mnemonic: "P-G-Z-T-C" → "Please Give Zebras Ten Carrots"

- **P → P450 inducer** → ↓ folic acid & vitamin D
- **G → Gingival hyperplasia**
- **Z → Zero-order kinetics** → monitor blood levels carefully
- **T → Toxic CNS effects** → dizziness, ataxia, nystagmus
- **C → Caution in absence seizures** → do not use



Antiseizure drugs, enhanced Na^+ channel inactivation

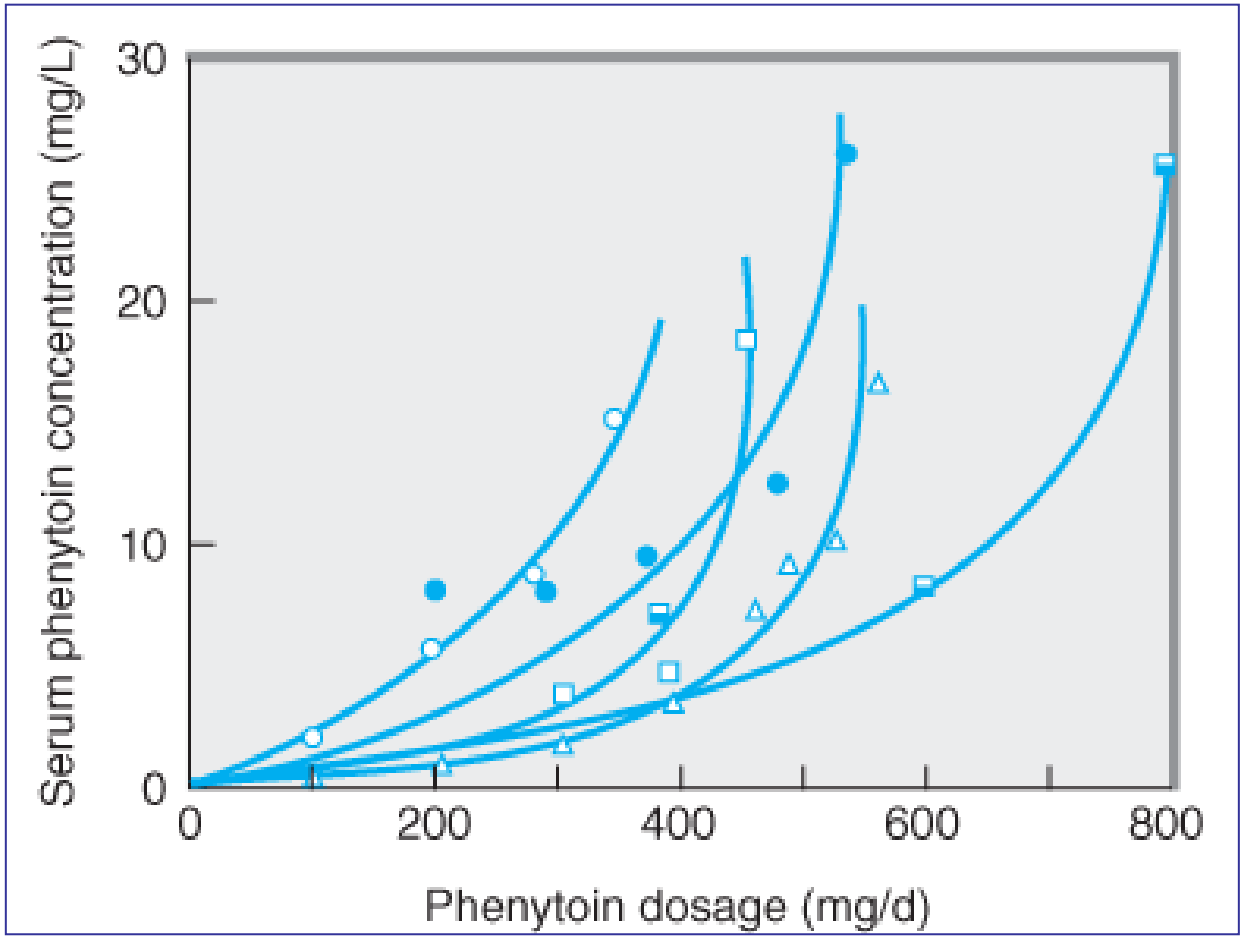
Narrow therapeutic index

- Adverse effects:
  - Nausea & Vomiting
  - Impaired brainstem & cerebellar function (dizziness, tremor, nervousness, blurred vision, **nystagmus**) .
  - Skin rashes
  - Folic acid- cause megaloblastic anemia- and Vit. D deficiency -cause osteoporosis -
- **Bradycardia** →because it binds to Na^+ channels in the heart

- Interaction: increases metabolism of the contraceptive pill, anti-coagulants, and pethidine .

Excretion saturation

- Excretion saturation of these drugs means that when you increase the dose by a certain amount, the conc in the blood increases severely.



Nonlinear relationship of phenytoin dosage and plasma concentrations. Five different patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases, the metabolism is storable. Note also the marked variation among patients in the serum levels achieved at any dosage.

Phenytoin

- Not used in treatment of pure absence seizures due to risk for increasing frequency of seizures.

دعيت الهم ؟

Gingival hyperplasia is a common problem observed during the first 6 months of phenytoin therapy appearing as gingivitis or gum inflammation.

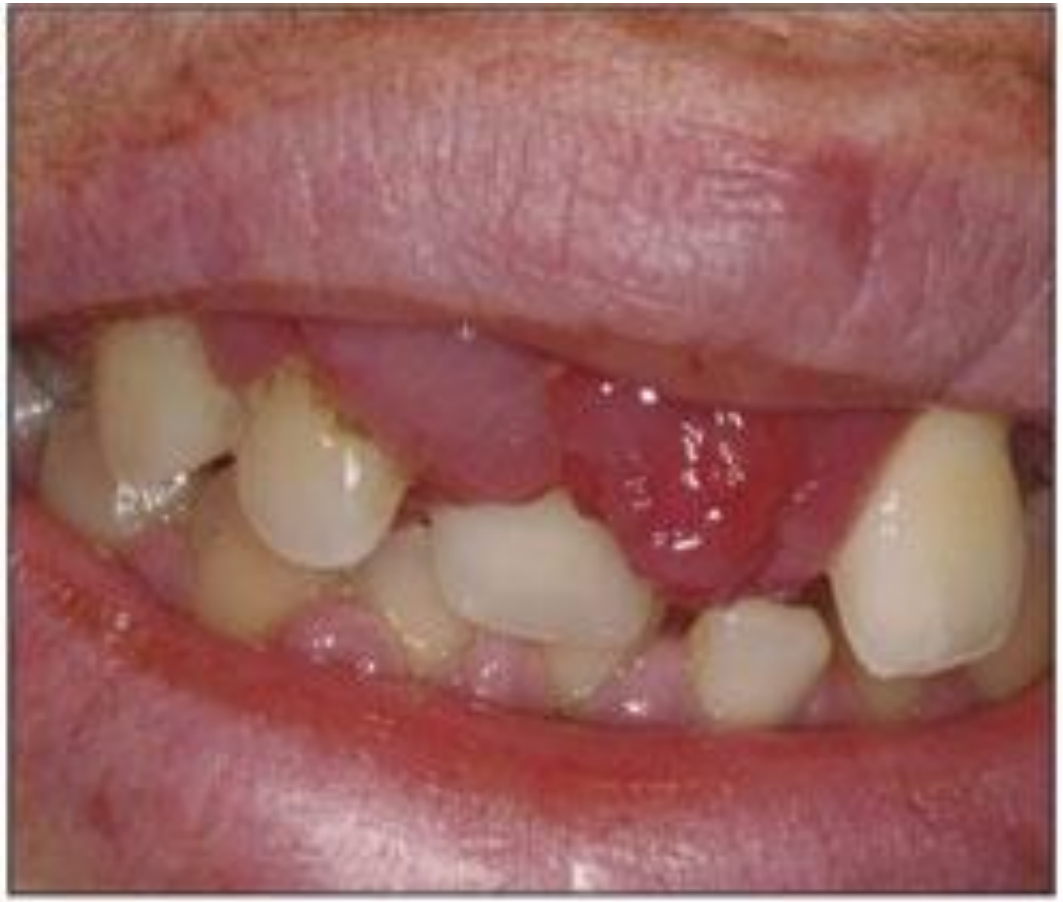


Fig. 1. The enlarged gingiva covers most of the anterior teeth and protrudes from the mouth.

Table 2. Abbreviated table of CYP-450 enzyme substrates, inducers and inhibitors

CYP isoform	Substrates	Inducers	Inhibitors
CYP1A2	**Anti-Alzheimer**: tacrine **Antiasthmatic**: theophylline **Antidepressants**: fluvoxamine, imipramine **Antipsychotics**: clozapine, halperidol	**Antibiotic**: rifampin **Anticonvulsant**: carbamazepine **Foods**: char-grilled meats **Recreational drug**: tobacco	**Antibiotics**: ciprofloxacin, erythromycin, ofloxacin **Antidepressant**: fluvoxamine
CYP2C9	**Angiotensin-2 receptor blockers**: ibresartan, losartan **Anticoagulant**: warfarin **Anticonvulsant**: phenytoin **Hypoglycemics**: glipizide, glyburide, tolbutamide **Non-steroidal anti-inflammatory drugs**: diclofenac, ibuprofen, naproxen	**Antibiotic**: rifampin **Barbiturates**: phenobarbital, secobarbital	**Antibiotic**: metronidazole **Antidepressants**: fluvoxamine, paroxitene, sertraline **Antifungal**: fluconazole
CYP2D6	**Antidepressants**: amitriptyline, desipramine, imipramine, paroxitene **Antipsychotics**: halperidol, risperidone **Beta-blockers**: metoprolol, propranolol, timolol **Narcotic analgesics**: codeine, hydrocodone, tramadol	**Antibiotic**: rifampin **Corticosteroid**: dexamethasone	**Antidepressants**: fluoxetine, paroxitene, sertraline **Antiarrhythmic**: amiodarone **H1 receptor blockers**: hydroxyzine, promethazine
CYP2E1	**Alcohol**: ethanol **General anesthetics**: enflurane, halothane, isoflurane, sevoflurane **Muscle relaxer**: chlorzoxazone **Non-narcotic analgesic**: acetaminophen	**Antibiotic**: isoniazid **Recreational drugs**: ethanol, tobacco	**Alcoholism rehabilitation agent**: disulfiram
CYP3A4	**Antibiotics**: clarithromycin, erythromycin **Anticoagulant**: warfarin **Anticonvulsant**: carbamazepine **Antipsychotics**: haloperidol, pimozide **Benzodiazepines**: alprazolam, diazepam, midazolam, triazolam **Calcium channel blockers**: amlodipine, diltiazem, felodipine, verapamil **Cholesterol-lowering drugs**: atorvastatin, cerivastatin*, lovastatin, simvastatin **Corticosteroids**: hydrocortisone, methylprednisolone **H1 receptor blockers**: astemizole*, terfenadine* **HIV protease inhibitor**: idinavir, nelfinavir, ritonavir, saquinavir **Hormonal agents**: estrogens, progestins **Immunosuppressants**: cyclosporine, tacrolimus **Local anesthetic**: lidocaine **Prokinetic agent**: cisapride*	**Antibiotic**: rifampin **Anticonvulsants**: carbamazepine, phenytoin **Barbiturates**: phenobarbital, secobarbital **Corticosteroids**: dexamethasone, hydrocortisone, prednisolone, methylprednisolone **Herbal remedy**: St John's wort **HIV reverse transcriptase inhibitors**: efavirenz, nevirapine **Hypoglycemics**: pioglitazone, troglitizone	**Antibiotics**: clarithromycin, erythromycin **Antidepressants**: fluvoxamine, nefazodone **Antifungals**: clotrimazole, fluconazole, itraconazole, ketoconazole **Calcium channel blockers**: diltiazem, verapamil **Foods**: Grapefruit juice, Seville oranges **H2 receptor blocker**: cimetidine **HIV protease inhibitors**: idinavir, nelfinivir, ritonavir, saquinavir

HIV, human immunodeficiency virus; H1, histamine H1; H2, histamine H2.
*Removed from U.S. marketplace.

Not required for exam purposes; just know that a huge drug-drug interactions occurs with these drugs due to their effect on cytochrome enzymes.

Carbamazepine Overview

- **Carbamazepine** is similar to phenytoin in its mechanism, but unlike phenytoin, it primarily **acts on the brain and does not affect the heart**, so it **does not cause bradycardia**. Because it acts more directly on the brain, it can cause **greater CNS toxicity than phenytoin**, including **sedation, dizziness, drowsiness, and confusion**.
- In China, the **carbamazepine leaflet recommends genetic testing for HLA-B*15:02 subtypes**, as these genes are found only in the Chinese population and **increase the risk of Stevens-Johnson syndrome**. To minimize this risk, the **dose is escalated slowly** (e.g., 5 mg → 10 mg → 15 mg) to monitor for skin rash, which is common, but only patients with genetic predisposition may develop Stevens-Johnson syndrome.
- Carbamazepine is the **drug of choice for trigeminal neuralgia**, and it is usually given **together with corticosteroids**.
- The drug is a **CYP1A1 inducer** and induces several other liver enzymes, including the enzyme that metabolizes carbamazepine itself. This process, called **autoinduction**, increases its metabolism over time. There is also **interindividual variation in enzyme activity**, so different patients metabolize the drug at different rates. The cause of **interindividual variation** differs: in phenytoin it is due to **zero-order kinetics**, while in carbamazepine it is due to **autoinduction.**Drug leads to **drug-drug interactions.**


Stevens-Johnson syndrome

Carbamazepine (A)

- Used for partial seizures; some use in tonic-clonic seizures.
- Antagonist action of Na+ channels to inhibit repetitive neuronal firing
  - Decreasing the production (or release) of glutamate (excitatory chemical)

- Can also be used in the treatment of neuropathic pain

Trigeminal neuralgia. Drug of choice.

Carbamazepine

- Adverse effects:
  - Nausea & vomiting (especially early Rx), constipation, diarrhoea and anorexia
  - Skin irritation (Rash)
  - **CNS toxcity –** Sedating, **dizzy, drowsy, confusion**
  - Bone marrow depression (rare)
- It is teratogenic.

اللَّهمَّ إِنِّي ظَلَمْتُ نَفْسِي ظُلْمًا كثِيرًا، وَلا يَغْفِر الذُّنوبَ إِلاَّ أَنْتَ، فَاغْفِر لي مغْفِرَةً مِن عِنْدِكَ، وَارحَمْني، إِنَّكَ أَنْتَ الْغَفور الرَّحِيم :قُلْ :عَلِّمني دُعَاءً أَدعُو بِهِ في صَلاتي، قَالَ :ﷺقَالَ لِرَسولِ الله

Succinimides – ***Ethosuximide***

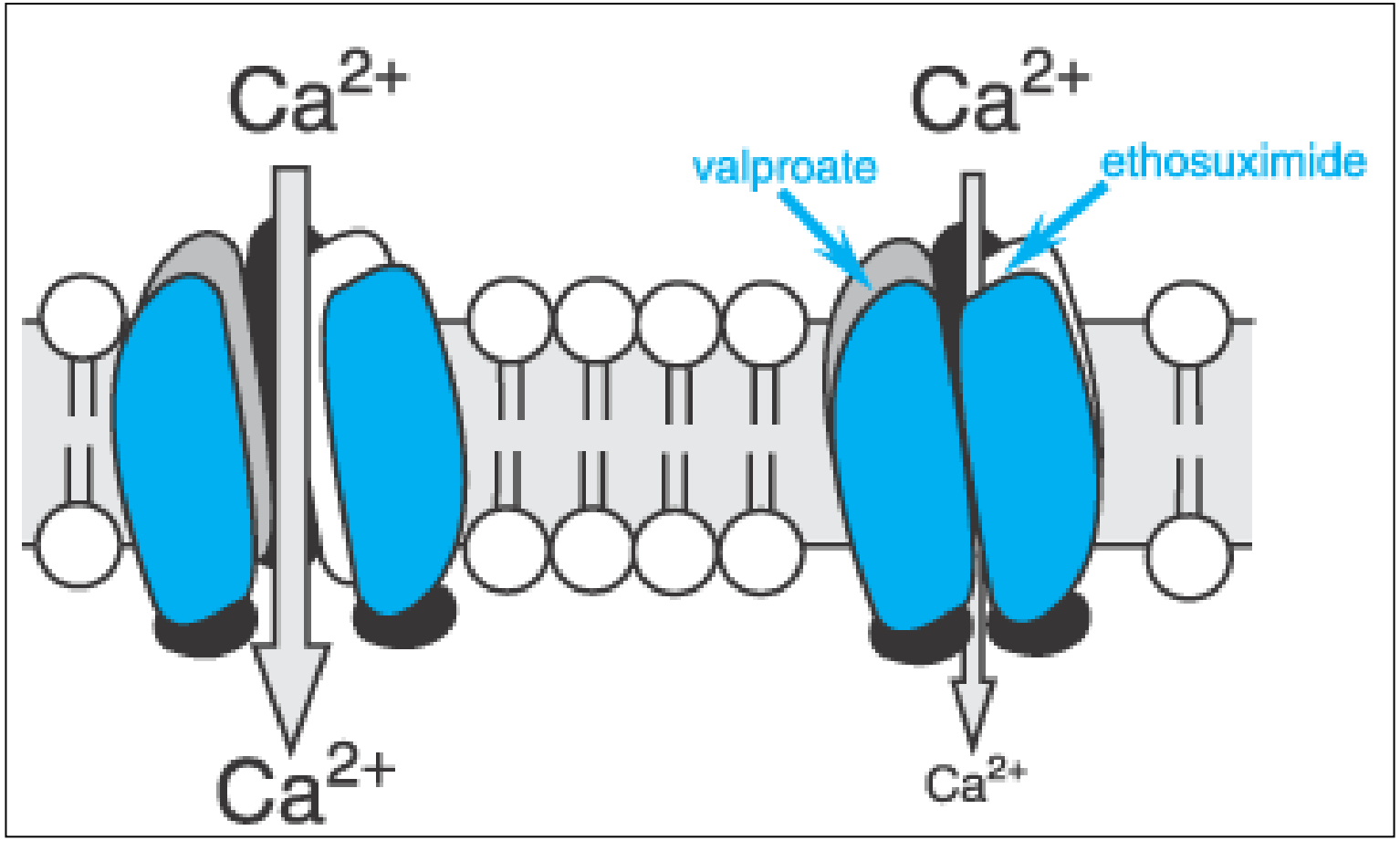
- **First choice** Use for patients with **Absence seizures** and is the **ONLY** medication specifically recommended for this condition. It has **very mild adverse effects** and it is one of the **oldest** and most **well-established** drugs used for this purpose.

- Carbamezipine and Phenytoin are contraindicated.

- Acts specifically on **T-type** channels in thalamus, and is very effective **against absence seizures**. By inhibiting this **calcium** entry, **ethosuximide** helps **prevent** the induction of sleep and un**consciousness** associated with absence seizures.

- Absence seizures are caused by oscillations between thalamus and cortex that are generated in thalamus by T-type (transient) Ca^{2+} currents

Succinimides – Ethosuximide



Antiseizure drugs, induced reduction of current through T-type Ca^{2+} channels.

The prof skipped this slide

Ethosuximide

- Adverse effects: Slightly wider therapeutic index
  - Nausea, vomiting and anorexia
  - Cerebellar disturbance (drowsiness, dizziness, photophobia, headache, depression)
  - Skin irritation
  - Not to be used when pregnant (teratogencity)

Sodium Valproate (valproic acid)

- Use in all forms of epilepsy, as it suppresses the initial seizure discharge and its spread.
- First-line for generalized seizures, also used for partial seizures
- K+ channels have important inhibitory control over neuronal firing in CNS—repolarizes membrane to end action potentials
- K+ channel agonists would decrease hyperexcitability in brain
- So far, the only Antiepileptic drug with known actions on K+ channels is valproate
- Also blocks Na+ channels and enhances GABAergic transmission (highly pleiotropic*)

Sodium Valproate (valproic acid)

Valproic acid is a widely used drug in the management of **bipolar disorder** and **epilepsy**. Interestingly, its discovery was somewhat **accidental**. During early pharmacological experiments on rats, researchers used **valproic acid** as a **solvent**, similar to how **bicarbonate** is used in **local anesthesia** to **adjust pH** in cases of **inflammation** (Lecture 6). They noticed that the rats **responded** to the **solvent** itself, which led to the **recognition** of **valproic acid's pharmacological effects.**

Valproic acid has **multiple mechanisms of action**, which is why it is considered a "magical" drug in neuropsychiatry. It works as a **mood stabilizer in bipolar disorder**, helping to **balance the swings between mania and depression** (Lecture 9).

While other drugs like **carbamazepine** and **phenytoin** provide ONLY **partial effects**, **valproic acid** stabilizes brain activity through several pathways, including **modulation of sodium (Na^+)** channels, **potassium (K^+)** channels, and enhancement of **GABAergic** activity. **Lithium**, similarly, functions as a mood stabilizer with antipsychotic, antidepressant, and antiepileptic properties (Lecture 9).

Because of its **broad** and **multi-targeted mechanisms**, **valproic acid** is also the **drug of choice** for patients with **generalized seizures**.

Narrow therapeutic index

- **Valproic acid** has a **narrow therapeutic index**
- Adverse effects:
  - GI upset (Nausea, vomiting, anorexia, abdominal pain and diarrhoea)
  - **Weight gain (appetite stimulation)**
  - Transient hair loss
  - Tremor
  - Coma (rare)
  - Thrombocyptopenia (platelets)
  - **Oedema** which occurs because **valproic acid** can **increase** the **release of antidiuretic hormone (ADH)**. This effect involves the **hypothalamus** and the **endocrine system**, leading to **fluid retention** in the body and sometimes relative **hyponatremia**. (IMPORTANT)
  - **Severe hepatotoxicity (liver damage)** along with the risk of **pancreatitis**.

- Contraindications: People with liver damage or a history hepatic dysfunction it is also **teratogenic**, so it is **contraindicated** in **pregnancy**.
- **Drug-drug interactions:** it acts as a **CYP2C9 inhibitor (unlike phenytoin and carbamazepine)**

LAMOTRIGINE (much wider therapeutic window)

- **First-generation antiepilptic** drugs include **phenobarbital**, **benzodiazepines**, **phenytoin**, **carbamazepine**, and **valproic acid**. In contrast, **second-generation** drugs have been developed. Let's discuss them.

- **Lamotrigine** is considered a **strong competitor to valproic acid**, especially because it is **NOT teratogenic**, making it **the drug of choice during pregnancy.** **(IMPORTANT)**

- It has **2 mechanisms of action**, which allows it to be effective in **generalized seizures**, similar to valproic acid. Act Primarily on **Na+ Channels and also inhibits excitory neurotransmitter glutamate.**

- **Lamotrigine** is effective for the treatment of partial and secondarily generalized tonic-clonic seizure.

- Unlike many antiepileptic drugs that act as **central nervous system (CNS) depressants** and and cause **sedation, ataxia, blurred vision or nystagmus**, **lamotrigine has the opposite effect in some patients and may lead to insomnia**, although this is not very common.

- It is generally well tolerated but may cause serious **ARs** of the skin, Including **Stevens–Johnson syndrome** (severe rash).

- **Lamotrigine** must be started at a **low dose and increased gradually (dose escalation)** to minimize the risk of adverse effects and improve tolerability.

Gabapentin (Neuronitin)

- **Gabapentin and pregabalin (Lyrica)** were initially developed as **antiepileptic drugs**, but they showed **limited** effectiveness. Instead, they became widely used for their **analgesic properties**, particularly in **neuropathic pain** and conditions like **migraine**. Their main role is in **reducing neuronal inflammation.**
- Used for partial seizures in adults
- Designed to be a structural analogue of GABA but it does not mimic GABA in the brain.
- Acts via:
  - **Increased synthesis and release of GABA**
  - Decrease degradation of GABA
  - Inhibition of Ca++ channels
- **Add-on drug not suitable as a single agent**
- **Now used as an analgesic (inhibits neuronal pain) in Migraine** (IMPORTANT)
- Their common **adverse effects** include **ataxia**, **CNS depression, fatigue, and drowsiness.**
- Like other antiepileptic drugs, they also carry a **black box warning** for increased risk of **suicidal thoughts** and behaviors, likely due to their effects on **brain neurotransmitter balance.**

The prof skipped this slide

Topiramate

- Acts on AMPA receptors, blocking the glutamate binding site, *but* also blocks kainate receptors and Na+ channels, and enhances GABA currents (highly pleiotropic*)

- Used for partial seizures, as an adjunct for absence and tonic-clonic seizures (add-on or alternative to phenytoin)

- Very long half-life (20h)

Levetiracetam

the drug binds to SV2A, a synaptic vesicle glycoprotein, and inhibits presynaptic calcium channels, reducing neurotransmitter release and acting as a neuromodulator. This is believed to impede impulse conduction across synapses

- **Levetiracetam** is different from many other antiepileptic drugs because it has a **unique mechanism of action** and does **not cause general CNS depression** like other drugs.
- Levetiracetam acts on **excitatory synaptic vesicles** that contain **glutamate and aspartate**. It stabilizes these vesicles by **binding to SV2A**, a protein responsible for releasing glutamate and aspartate into the synapse. It also **inhibits presynaptic Ca^{2+} channels** and **modulates Na^{+} channels**, which reduces the release of excitatory neurotransmitters.
- Since epilepsy is caused by **excessive excitatory activity**, reducing glutamate release helps **stop abnormal neuronal firing**. Levetiracetam is effective in **all types of seizures**, including **absence seizures and best effect appear in generalize seizures.**It **does not cause teratogenic effects**
- This drug affect excitatory activity in the brain which can increase the risk of psychiatric problems and suicidal thoughts.
- All of these side effects (IN NEXT SLIDE)may appear during the **first month of treatment**, so patients require **close monitoring at the beginning**. However, **levetiracetam is considered the best among the antiepileptic drugs we have studied**.

  – Contraindications: Renal dysfunction

Adverse Effects:

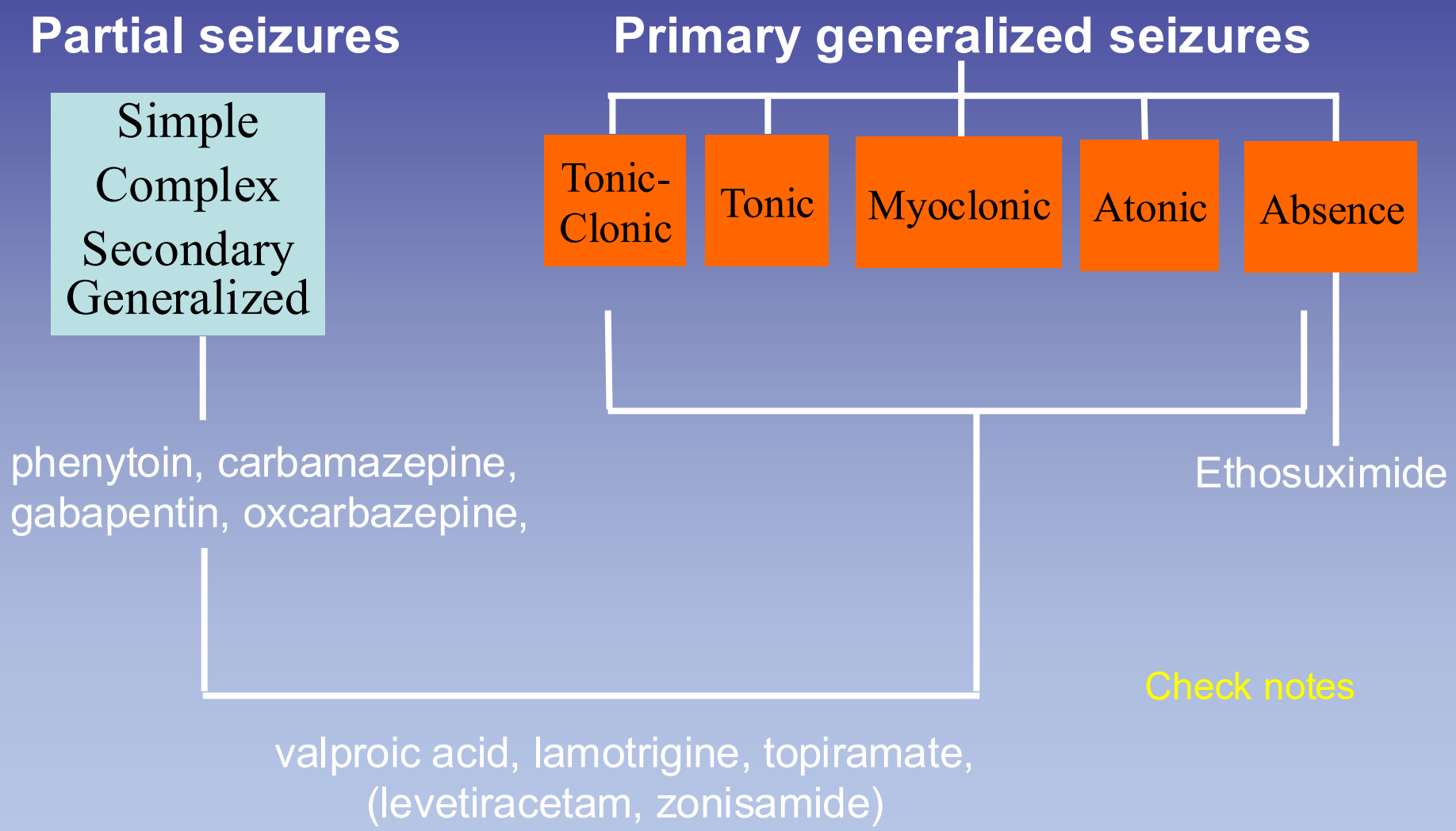
somnolence, decreased energy, headache, dizziness, mood swings and coordination difficulties. These adverse effects are most pronounced in the first month of therapy.

- About 13% of people taking levetiracetam experience adverse neuropsychiatric symptoms, which are usually mild. These include agitation, hostility, apathy, anxiety, emotional lability, and depression. Serious psychiatric adverse side effects that are reversed by drug discontinuation occur in about 1%.

Drugs	Grand mal	Status epilepticus	Petit mal (absence seizure)	Partial seizure
Carbamazepine (p.o.)	++		contraindicated	+++
Clonazepam (p.o./i.v.)	+	+	++	
Diazepam (p.o./i.v.)		+		
Ethosuximide (p.o.)			+++	+
Lamotrigine (p.o.)	+++		+++	++
Lorazepam (i.v.)		+		
Midazolam (i.v.)		++		
Oxacarbazepine (p.o.)	++			+++
Phenobarbital (p.o./i.m.)	+	+++	contraindicated	
Phenytoin (p.o./i.v.)	+	+++	contraindicated	++
Topiramate (p/o.)	+			++
Valproic acid (p.o.)	+++		+++	++

Barbiturates are used in **neonatal epilepsy**, and among them, **phenobarbital is considered the drug of choice**.

AED Treatment Options



Treatment:

- *Up to 80% of pts can expect partial or complete control of seizures with appropriate treatment.*
- *Antiepileptic drugs suppress but do not cure seizures*
- *Antiepileptics are indicated when there is two or more seizures occurred in short interval (6m -1 y)*
- *An initial therapeutic aim is to use only one drug (monotherapy).*

Addition of a second drug is likely to result in significant improvement in only approx. 10 % of patients.

Important: Never stop antiepileptic drugs abruptly. Before considering withdrawal, the patient should have been **seizure-free for at least one year**

- *The sudden withdrawal of drugs should be avoided*

withdrawal may be considered after seizure- free period of 2-3 or more years

- *Relapse rate when antiepileptics are withdrawn is 20 - 40 %/*

When to Withdraw Antiepileptic Drugs?

Normal neurological examination

Seizure- free for 2-5 yrs or longer

رسالة من الفريق العلمي

اللهم يا ودود، يا ذا العرش المجيد، يا فعال لما يريد، نسألك باسمك الأعظم الذي إذا دعيت به أجبت وإذا سُئلت به أعطيت، أن تكتب لنا في هذا اليوم المبارك عتقاً من النيران، وأن تغفر لنا الذنوب والآثام، وأن تفرج عن أمتنا همومها، وأن تلهم جراحها، وتجمع شتات أبنائها في ظل راية ترضيك، وأن تجمع شملنا على كل خير، يا رب نسألك أن تفرج هم المهمومين، وتكرب المكروبين، وأن ترفع البلاء عن إخواننا في غزة، وأن ترفع الظلم عنهم، وأن تسكن في قلوبهم طمأنينة وسكينة، وانصرهم على أعدائهم، اللهم إنك تعلم ما حلّ بهم من كربٍ وضيق، فكن لهم ولياً ونصيراً، اللهم اجعل لهم من كل ضيقٍ مخرجاً، ومن كل همٍ فرجاً، ومن كل بلاءٍ عافية، اللهم ارفع عنهم البلاء واشفِ جرحاهم، وارحم شهداءهم، وانصرهم نصراً عزيزاً مؤزراً، اللهم كن لإخواننا في السودان ناصراً ومعيناً، وادفع عنهم الفتن ما ظهر منها وما بطن، واجعل بلدهم آمناً مستقراً، اللهم احفظ بلاد المسلمين من كل سوء، واجعلها دار أمنٍ وأمان، اللهم إنا نسألك أن تنصر المستضعفين في كل مكان، وأن ترفع الظلم عنهم، وأن تجعل لهم من لدنك ولياً ونصيراً.

اللهم أنت نور السماوات والأرض، ومن كل ظلمةٍ أخرجتنا، ومن كل همٍ فرجتنا، ومن كل ضيقٍ نجيتنا، ومن كل بلاءٍ عافيتنا، اللهم اجعل لنا في هذا اليوم نصيباً من رحمتك، وفضلاً من كرمك، وبركةً في أعمالنا، وسعةً في أرزاقنا، وطمأنينةً في قلوبنا، اللهم ارزقنا الإخلاص في القول والعمل، واجعل أعمالنا خالصةً لوجهك الكريم، اللهم اجعل لنا من كل همٍ فرجاً، ومن كل ضيقٍ مخرجاً، ومن كل بلاءٍ عافية، اللهم إنا نسألك العفو والعافية في الدنيا والآخرة، اللهم احفظنا بحفظك، واكلأنا برعايتك، ووفقنا لما تحب وترضى، اللهم اجعل هذا البلد آمناً مطمئناً، وسائر بلاد المسلمين، اللهم دم علينا نعمة الأمن والإيمان، والسلامة والإسلام.

Highly recommended , click here :)

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Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			