YU - MEDICINE
PASSION ACADEMIC TEAM

Central Nervous System

Sheet# 7 - Pharmacology

Lec. Title : Antiepileptic Drugs

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Anticonvulsants

Dr. Romany H Thabet, Ph.D.

Definitions

- **Convulsion**: Sudden attack of involuntary muscular contractions and relaxations.

- **Seizure**: Abnormal central nervous system electrical activity.

- **Epilepsy**: A group of recurrent disorders of cerebral function characterized by both seizures and convulsions.

Sheet #1

- ضروري نفرق بين ال Convulsion وبين ال Seizure.

-Seizure: Abnormal central nervous system electrical activity.(cerebral hemisphere)

- لما نحكي عنده هاد الانسان عنده كهربا زايدة بالجسم ف بيكون عنده مجموعة خلايا معينة بيكون فيها high electrical.

-Seizure attack: there is abnormal electric activity.

- In general, lepsy means a disease in which an attack and recurrent occurs, and the treatment will continue for a long time.

- The length of time that medication will be taken depends on the EEG and the patient's clinical states.

-It may be the EEG NORAML but the clinical states ABNORMAL, and vice versa.

Sheet #2

- It is possible that a person has had an epileptic seizure, but its period is very small, and the period between the first and the second seizures is far away, so it is clinical states NORMAL, but EEG ABNORAML.

- طب متى اعرف انه لازم ابطل اعطي المريض العلاج؟

في حالتين : ١- انه لازم يكون رسم او صورة المخ عنده سليم

٢- انه لازم يكون اقل شي سنيتن ماصابته نوبات صرع اطلاقا

- بس طبعا لازم نبدأ نخفف من جرعة الدوا بشكل تدريجي مو مرة وحدة لانه ممكن يصيرعنا مرة ثانية RELABS THE ATTACK.

Partial (focal) Seizures

- Excessive electrical activity in one cerebral hemisphere.
  -Affects only part of the body.

- **Simple Partial:** Person may experience a range of strange or unusual sensations.
  - Motor
  - Sensory
  - Autonomic
  - **Key feature**: preservation of consciousness.

Sheet #3

Sensory: Abnormal sensation in a specific area - Because of its presence in the sense area.

- Motor : Because of its presence in the motor area it may be (tonic or clonic)or tonic then clonic.

-Tonic : The extensors and flexors are contracted at the same time.

-Clonic: Intermittent contraction and relaxation alternating between extensor and flexor(A flexor contract and an extensor relaxed and vice versa).

- The patient may begin with tonic in extensor and flexor muscles in the same time then transport to clonic.

-The most common condition we encounter is motor.

-Generalized :affected four limbs.

Sheet #4

- Autonomic : For example, a sudden increase in heart rate or increased sweating somewhere because of The dominance of the CNS over the autonomic .

- The most common condition we encounter is motor.

- Partial (focal) Seizures: Affected by part of the limb or in one limb.

- it depends on whether the patient was conscious or unconscious during a seizure.

- There are two types of Partial (focal) Seizures:

simple: If he was conscious during a seizure.

complex: if he was unconscious during a seizure.

Partial (focal) Seizures

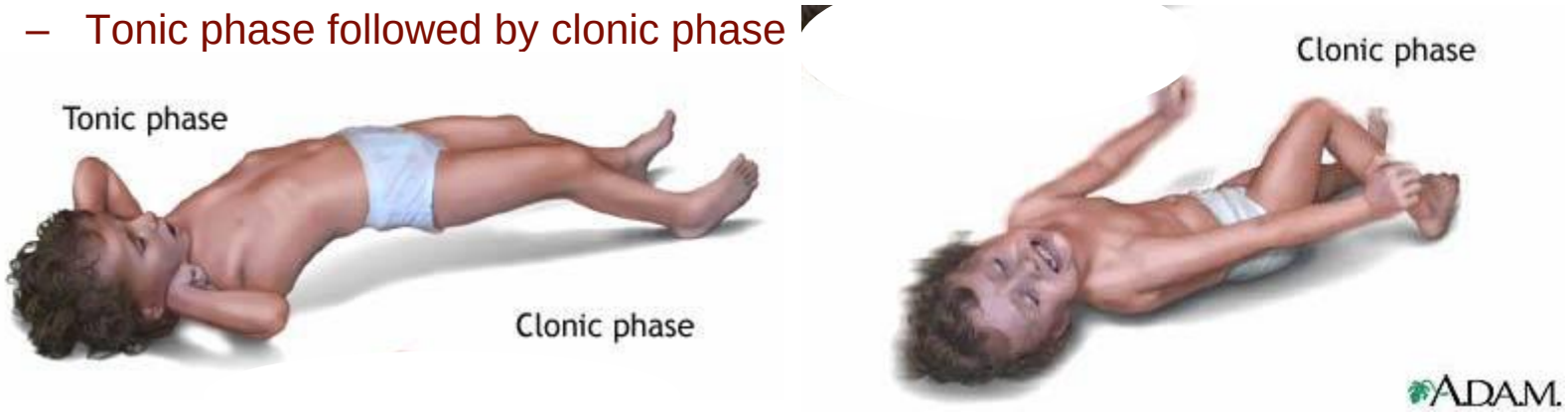
- **Complex Partial**:
  - Loss of awareness at seizure onset. Person seems dazed or confused and exhibits meaningless behaviors.
  - Typically originate in frontal or temporal lobes (e.g. Temporal lobe epilepsy)

Generalized Seizures

- Excessive electrical activity in both cerebral hemispheres.
- Usually originates in the thalamus or brainstem.
- Affects the whole body.
- Loss of consciousness is common.

Generalized Seizures

- **Myoclonic**: Brief shock-like muscle jerks generalized or restricted to part of one extremity. **(لما اكون قاعد مع واحد ومرة وحدة بشكل مفاجئ تصيبه النوبة)**
- **Atonic**: Sudden loss of muscle tone.
- **Tonic Seizures:** sudden stiffening of the body, arms, or legs
- **Clonic Seizures:** rhythmic jerking movements of the arms and legs without a tonic component (**لما اكون قاعد مع واحد وما يرد علي يعني يعطي ايحاء انه رح تصير معه النوبة)**
- **Tonic-clonic (grand mal): (generalized)**
  - Tonic phase followed by clonic phase



http://www.nlm.nih.gov/medlineplus/ency/images/ency/fullsize/19076.jpg

Tonic-Clonic Seizure

Can last from one to several minutes

Therapeutic intervention = lorazepam injection

Generalized Seizures

- **Absence (petit mal):** Person appears to “blank out” - “Daydreaming”
  - Simple Absence (primarily effects consciousness only)
  - Complex Absence
  - Atypical Absence (Includes physical symptoms like eye blinking or lip movements)

- **Lenox-Glastaut Syndrome.**
  - Atypical absence, atonic and myclonic

- **Status Epilepticus:** A seizure lasting longer than 30 min, or 3 seizures without a normal period in between
  - May be fatal
  - Emergency intervention required

Sheet #5

- ركز الدكتور ع Lenox-Glastaut Syndromeونعرف الدوا الي يعالجه.

–Status Epilepticus: the patient is unconscious.

- ممكن يكون في طفل لسا مولود من كم يوم وفجأة نلاقيه رافع اطرافه الاربعة وكانه حدا نغزه او قرصه وهي الحالة بتكون : infantile spasm.

- Adrenocorticotropic hormone (ACTH): treats infantile spasm.

Absence Seizure

Can last from a second to several minutes

Treatment

- Monotherapy with anticonvulsant
  - Increase dose gradually until seizures are controlled or adverse effects become unacceptable.
  - Multiple-drug therapy may be required.
- Achieve steady-state kinetics
- Monitor plasma drug levels
- Avoid sudden withdrawal

Sheet #6

-The first thing we do in the treatment phase: we start with one treatment, even if it does not help us, we start withdrawing it gradually and have to add a second medication.

-We must pay attention to what we administer the treatment, because it is the narrow therapeutic index and it is very dangerous.

-narrow therapeutic index : means that very small dosing changes could have a severe impact on outcomes for the patient.

- Because it is dangerous, hospitals provide a unit to measure the level of drugs in the blood (therapeutic drug monitoring), and it is necessary to check every time.

Mechanisms of Action

- 3 main categories of therapeutics:

  1. Inhibition of voltage-gated Na+ channels to slow neuron firing.

  2. Enhancement of the inhibitory effects of the neurotransmitter GABA.

  3. Inhibition of calcium channels.

- Carbamzepine: It also treats depression.

-The function of this drugs is to stop the increase in electricity in the brain cells.

-These medicines, with time, will change the patient's behavior ,and They prevent sodium absorption and reduce the absorption of folic acid.

There are Many Adverse Effects of Therapeutics!!!!

- **CNS Effects:**
  - Drowsiness, sedation, somnolence
  - Depression
  - Dizziness
  - Slurred speech
  - Ataxia ماشي يترنح بالشارع
  - Nystagmus حركة عينه مو طبيعية
  - Diploplia
  - Vertigo
  - Headache
  - Confusion
  - Tremor
  - Interference with cognitive functions in learning situations

- **GI Effects**

–Dry Mouth

–Nausea

–Vomiting

–Anorexia

–Diarrhea

- Rash
- Fetal Abnormalities and birth defects

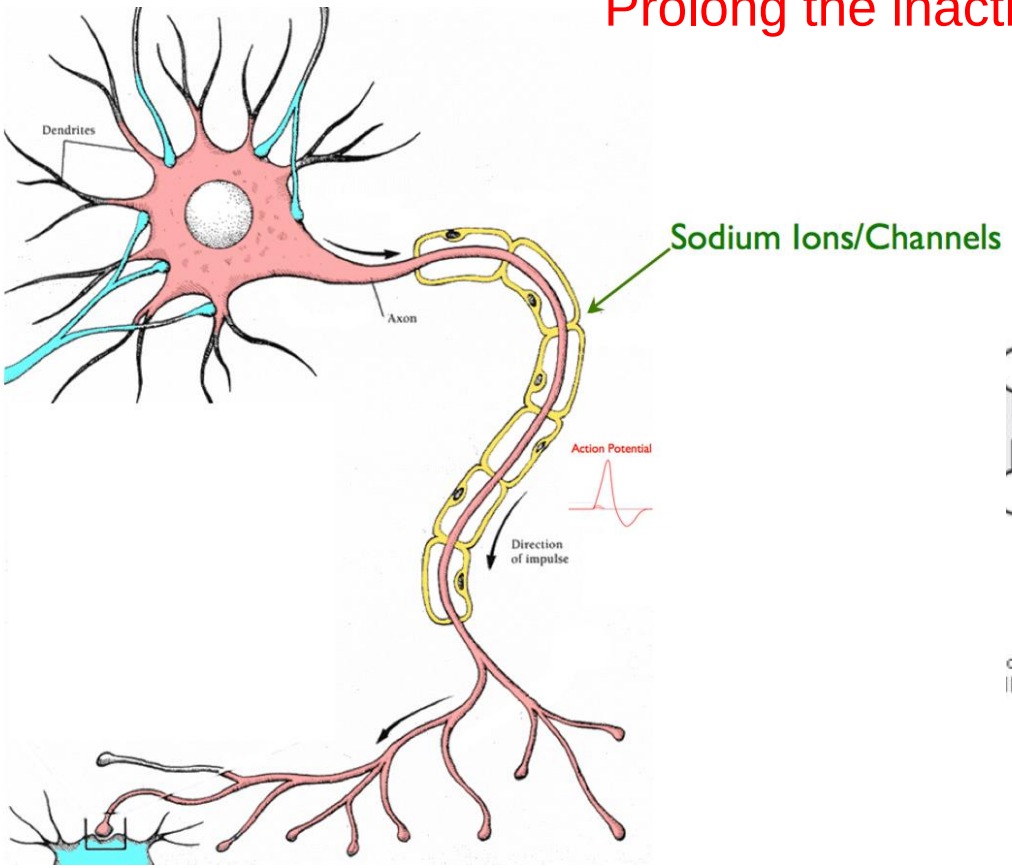
Anti-convulsant Pharmacotherapy

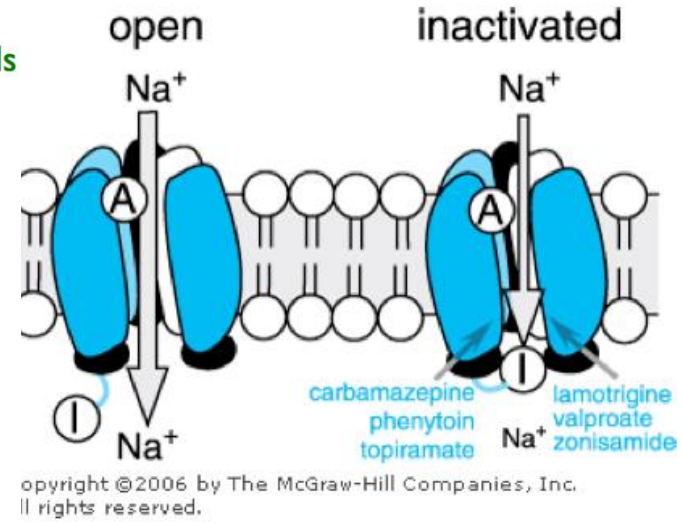
- Medications are listed next with general guidelines for use.
  - good first choice, second choice, etc.

- Actual use will depend more on a combination of your experiences in the clinic and patient individuality and response.

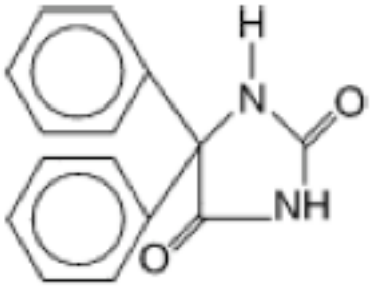
Na+ Channel Inhibitors

Prolong the inactive state of channel





Na+ Channel Inhibitors



- Phenytoin (Dilantin, Phenytek): مطلوبة كلها

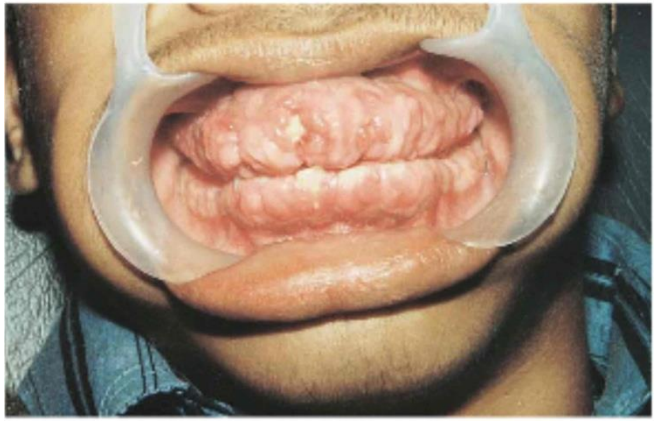
  -inducer of liver metabolism.

  - Indications:
    - First choice for partial and generalized tonic-clonic seizures
    - Some efficacy in clonic, myoclonic, atonic,
    - No effect on infantile spasms or absence seizures
  - Drug Interactions:
    - Decreases blood levels of many medications
    - Increases blood levels of phenobarbital & warfarin

Na+ Channel Inhibitors

- Phenytoin (Dilantin, Phenytek):
  - Adverse Effects:
    - Hirsutism & coarsening of facial features
    - Acne
    - Gingival hyperplasia (20-40%) اللثة متضخمة
      - Brush teeth >8 times per day
        - » A primary reason not to prescribe for children
    - Decreased serum concentrations of folic acid, thyroxine, and vitamin K with long-term use.
    - **Hepatotoxic**

Phenytoin Induced Gingival Hyperplasia



17 year old boy treated with 300mg/day phenytoin for 2 years (unsupervised)

لازم يغسل اسنانه عشان ما يترسب الدوا

Partial recovery at 3 months after discontinuation

Images in Clinical Medicine (Feb 2000) 342:325

Phenytoin

Phenytoin has dose-dependent clearance due to progressive saturation of its hepatic metabolism by cyt P-450 at normal therapeutic plasma levels, and ~10 ug/ml is considered the minimal effective plasma concentration for seizure control.

Due to saturation of its metabolism, even small increases in maintenance dosage can cause large, unpredictable increases in plasma drug concentrations, which increases the risk of adverse effects such as ataxia, nystagmus, confusion, gingival hyperplasia, hirsuitism (and the list goes on). In addition, other drugs that either inhibit or induce P-450 can produce marked changes in phenytoin plasma levels.

Images in Clinical Medicine (Feb 2000) 342:325

Sheet #7

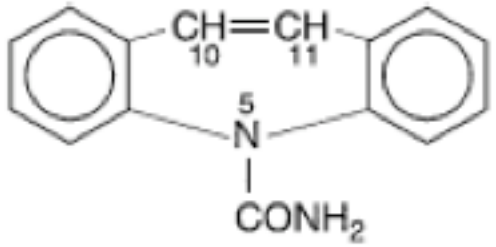
-important question: What happens when we increase the dose?

ANS: unpredictable increases in plasma drug concentrations.

- Meaning: if you increase the dose twice, the plasma will increase more than twice, and the reason is that it will transport from the first order elimination to zero order elimination.

Na+ Channel Inhibitors

- Carbamzepine (Tegretol, Carbatrol):



  - Indications:
    - First choice for complex partial and generalized tonic-clonic seizures.
  - Contraindications:
    - May exacerbate absence or myoclonic seizures. مهم جدا
    - Blood disorders
    - Liver disorders

- Carbamazepine :is a drug from the group of anticonvulsants, similar in chemical structure to tricyclic antidepressants.
-causes Bone marrow depression.
- auto inducer.

Na+ Channel Inhibitors

- Carbamazepine (Tegretol, Carbatrol):

  - Drug Interactions:
    - CBZ metabolism is affected by many drugs, and CBZ affects the metabolism of many drugs.
  - Adverse Effects:
    - Mild leukopenia or hyponatremia
    - Circulating concentrations of thyroid hormones may be depressed; TSH remains normal.

-المطلوب فقط:

- CBZ metabolism is affected by many drugs, and CBZ affects the metabolism of many drugs.

–inducer of liver metabolism.

? Exam question: the patient who takes this medication,

-what should he do tests

١-therapeutic drug monitoring

٢-Complete blood count (cbc)

Na+ Channel Inhibitors

- Oxcarbazepine (Trileptal):
  - FDA approved in 2000 for partial seizures
    - Complex partial seizures
    - Primary & secondarily generalized tonic-clonic seizures
    - No effect on absence or myoclonic seizures
  - Fewer adverse effects than CBZ, phenytoin

- بنسميه ابن بديل عشان ما بيعمل عنا auto inducer

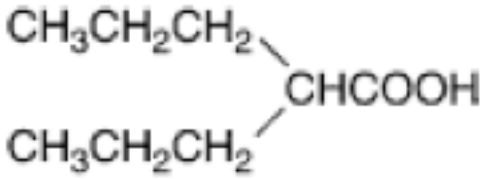
ومشاكله اقل بكتير من Carbamazepine and Phenytoin.

Na+ Channel Inhibitors

- Valproic Acid (Valproate; Depakene, Depakote):

  - كان دوا مذيب وقوي وبيعالج كل انواع الصرع ما عدا Status epilepticus.

  – Other Mechanisms of Action:
    - 1) Some inhibition of T-type Ca2+ channels.
    - 2) Increases GABA production and decreases GABA metabolism.
  – Indications:
    - Simple or complex partial, & primary generalized tonic-clonic
    - Also used for absence, myoclonic, and atonic seizures.
    - Highly effective for photosensitive epilepsy and juvenile myoclonic epilepsy.
  – Contraindications:
    - Liver disease



Na+ Channel Inhibitors

- Valproic Acid (Valproate; Depakene, Depakote):

  - Drug Interactions:
    - Affects metabolism of many drugs through liver enzyme inhibition
      - Phenobarbital
        - » “Drunkenness”
      - Clorazepam
        - » Prolonged absence seizures

-المطلوب فقط:

-not inducer of liver metabolism.

-Affects metabolism of many drugs through liver enzyme inhibition.

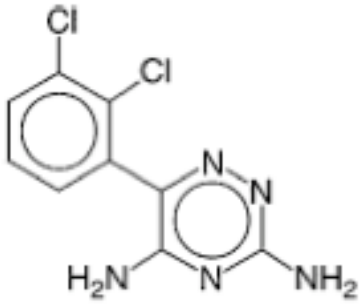
Na+ Channel Inhibitors

- Valproic Acid (Valproate; Depakene, Depakote):

  - Adverse Effects:
    - Weight gain (30-50%)
    - Dose-related tremor
    - Transient hair loss
    - Polycystic ovary syndrome and menstrual disturbances
    - Bone loss
    - Ankle swelling
    - **Spina bifida**(pregnant women)
    - **Acute pancreatitis**

- Side effect: fulminant hepatitis and pancreatitis.
-treats bipolar affective disorder.
-Weight gain (30-50%)

Na+ Channel Inhibitors



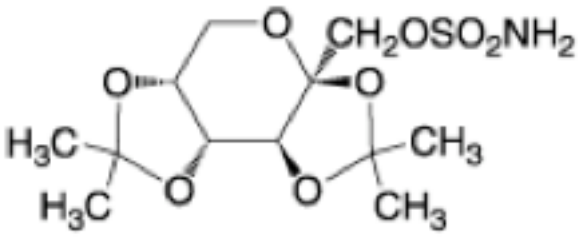
- Lamotrigine (Lamictal):
  - كله مطلوب بس اهم النقاط : ←
  - Other Mechanism of Action:
    - May inhibit synaptic release of glutamate. ←
  - Indications:
    - Adjunct therapy (ages 2 & up):
      - Simple & complex partial seizures
      - Generalized seizures of Lennox-Gastaut Syndrome ←
    - Monotherapy (adults):
      - Simple & complex partial seizures
  - Contraindications:
    - May make myoclonic seizures worse. ←

Na+ Channel Inhibitors

- Lamotrigine (Lamictal):
  - Adverse Effects:
    - Rash (10%)
      - Rare progression to serious systemic illness
    - Increased alertness

Na+ Channel Inhibitors

- Topiramate (Topamax):



- كله مطلوب بس اهم النقاط :
  - Other Mechanism of Action:
    - Enhances post-synaptic $GABA_A$ receptor currents.
    - Kainate receptor antagonist (blocks a certain type of glutamate channel)
  - Indications:
    - Adjunct therapy for partial and primary generalized tonic-clonic seizures in adults and children over 2.
    - Decreases tonic and atonic seizures in children with Lennox-Gastaut syndrome.
  - Contraindications:
    - History of kidney stones

- the glutamate is excitatory.

-الدوا خطير

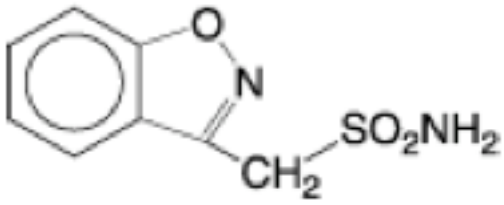
ما حكى شي عنه

Na+ Channel Inhibitors

- Topiramate (Topamax):
  - Drug Interactions:
    - CBZ, phenytoin, phenobarbital, & primidone decrease blood levels
  - Adverse Effects:
    - Nervousness & paresthesias
    - Psychomotor slowing, word-finding difficulty, impaired concentration, interference with memory
    - **Weight loss** & anorexia (مهم)
    - Metabolic acidosis

Na+ Channel Inhibitors

- Zonisamide (Zonegran):



  - Other Mechanism of Action:
    - Inhibits T-type Ca2+ currents.
    - Binds to GABA receptors.
    - Facilitates dopaminergic and serotonergic neurotransmission.

-In Thalamus, it will have electricity, and it has a kind of channel named (t ca + channel), completely different from the one responsible for the muscles.

-The time it is excreted and goes to the cells, it increases the electricity and leads to a loss of consciousness for a short period.

- وهاد الدوا بيعالج Generalized و Partial +Absence.

-Inhibits T-type Ca2+ currents.

-Binds to GABA receptors.

-Na+ Channel Inhibitors.

Na+ Channel Inhibitors

- Zonisamide (Zonegran):
  - Indications:
    - Approved for adjunct treatment of partial seizures in adults.
    - Appears to have a broad spectrum:
      - Myoclonic seizures
      - Infantile spasms
      - Generalized & atypical absence seizures
      - Lennox-Gastaut Syndrome
  - Drug Interactions:
    - Phenytoin and carbamazepine decrease its half-life by half.

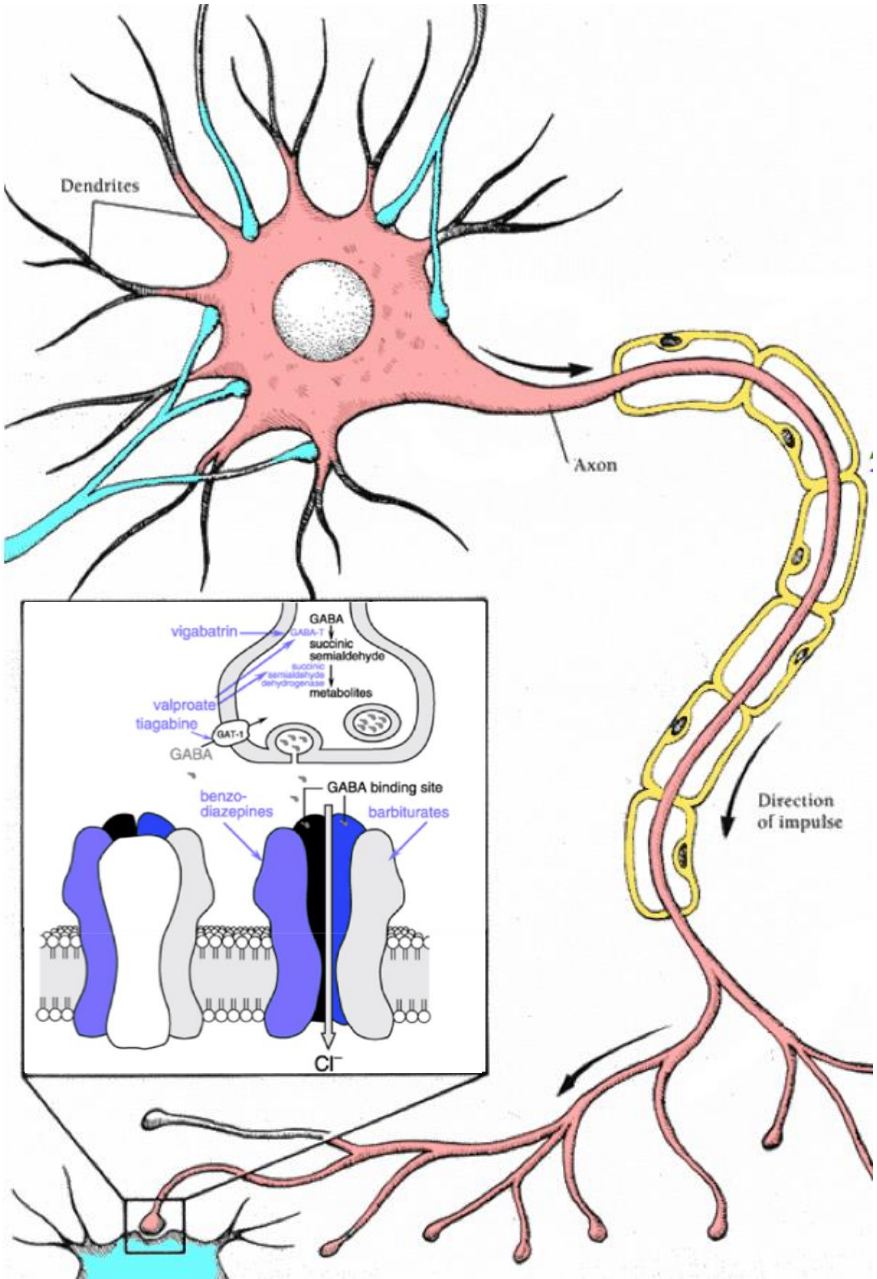
Na+ Channel Inhibitors

- Zomisamide (Zonegran):
  - Adverse Effects:
    - Weight loss (ركز عليه)
    - Abnormal thinking
    - Nervousness
    - Agitation/irritability
    - Usually well tolerated

Na+ Channel Inhibitors

- Lidocaine: Only when other drugs are refractory for status epilepticus.

Enhancement of GABA Inhibition



Enhancement of GABA Inhibition

- **Barbiturate drugs:** Phenobarbital (Luminal) & Primidone (Mysoline):
  - Mechanism of Action:
    - Increases the duration of $GABA_A$-activated Cl- channel opening.

Enhancement of GABA Inhibition

- Phenobarbital (Luminal):
  - Indications:
    - Second choice for partial and generalized tonic-clonic seizures.
    - Rapid absorption has made it a common choice for seizures in infants, but adverse cognitive effects cause it to be used less in older children and adults.
    - Status epilepticus
  - Contraindications:
    - Absence Seizures

Sheet #8

-Phenobarbital: long acting (دوا ينيم الفيل).

-It is not recommended to be given to a child who is learning. (طفل بدرس بالمدرسة)

-drugs used to treat Status epilepticus:(بالترتيب)

1-Diazepam

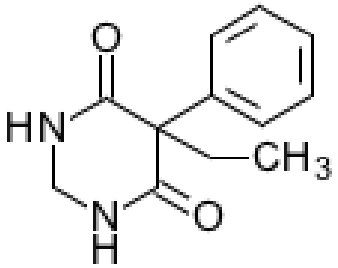
2-Phenytoin

3-Phenobarbital

4- A muscle relaxant by placing it in a ventilator because the attack affects the respiration.

Enhancement of GABA Inhibition

- Primidone (Mysoline):



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  - Indications:
    - Adjuvant or monotherapy for partial and generalized tonic-clonic seizures
    - May control refractory generalized tonic-clonic seizures
  - Contraindications:
    - History of porphyria

-Primidone precursor to Phenobarbital.

Enhancement of GABA Inhibition

- Phenobarbital (Luminal) & Primidone (Mysoline):
  - Drug Interactions:
    - Other CNS depressants
    - Increased metabolism of vitamin D and K
    - Phenytoin increases the conversion of primidone to phenobarbital.

المطلوب فقط:

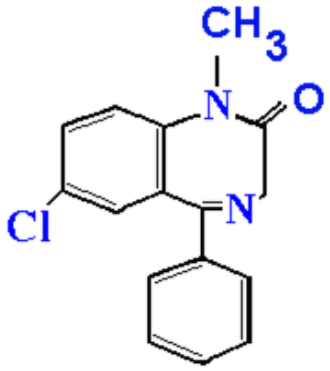
- من اشهر الادوية الي بتعمل inducer of liver enzymes.

-Inducer metabo of vitamin D and K.

Enhancement of GABA Inhibition

- Phenobarbital (Luminal) & Primidone (Mysoline):
  - Adverse Effects:
    - Agitation and confusion in the elderly.
    - Worsening of pre-existing hyperactivity and aggressiveness in children
    - Sexual side effects
    - Physical dependence

Enhancement of GABA Inhibition



- Benzodiazepine drugs:
  - Diazepam (Valium), lorazepam (Ativan), clonazepam (Klonopin), clorazepate (Transxene-SD)
  - Mechanism of Action:
    - Increases the frequency of $GABA_A$-activated Cl- channel opening.

Enhancement of GABA Inhibition

- Benzodiazepine drugs:

* ملحوظة :الانتقال للسلايد ٥٠

  - Indications:
    - Only clonazepam & clorazepate approved for long-term treatment.
    - Clorazepate
      - In combination for partial seizures
    - Clonazepam
      - Lennox-Gastaut Syndrome, myoclonic, atonic, and absence seizures
      - Tolerance develops after about 6 months

Enhancement of GABA Inhibition

- Benzodiazepine drugs:

* ملحوظة :الانتقال للسلايد ٥٠

  - Indications:
    - Diazepam and lorazepam are used in treatment of status epileticus.
      - Diazepam is painful to inject; lorazepam is more commonly used in acute treatment.
    - Diazepam
      - Intermittent use for control of seizure clusters
      - Diazepam frequently combined with phenytoin.

Sheet #9

المطلوب فقط:

-Diazepam and lorazepam for Status epilepticus.

- Clorazepate for partial seizures.

- Clonazepam for absence seizures.

Enhancement of GABA Inhibition

- Benzodiazepine drugs:

- ما حكا شي عن السلايد .

  - Contraindications:
    - Diazepam in children under 9
    - Narrow angle glaucoma
  - Adverse Effects:
    - Hypotonia, Dysarthria
    - Muscle in-coordination (clonazepam)
    - Behavioral disturbances (especially in children)
      - Aggression, Hyperactivity, Irritability and Difficulty concentrating

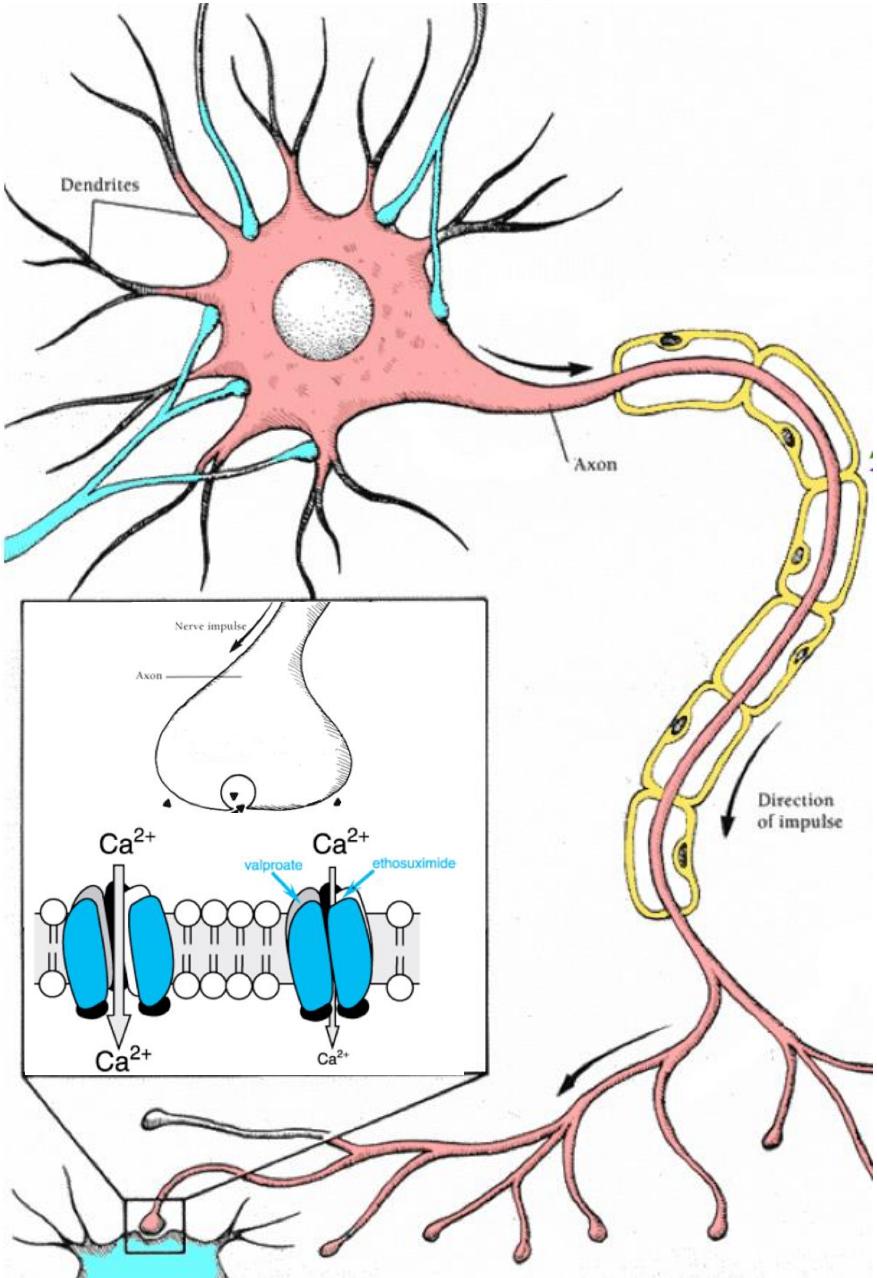
Enhancement of GABA Inhibition

- Tiagabine (Gabitril):
  - Mechanism of Action:
    - Inhibition of GABA transporter (GAT-1) – reduces reuptake of GABA by neurons and glial cells.
  - Indications:
    - Approved in 1998 as an adjunct therapy for partial seizures in patients at least 12 years old.
  - Contraindications:
    - Absence seizures

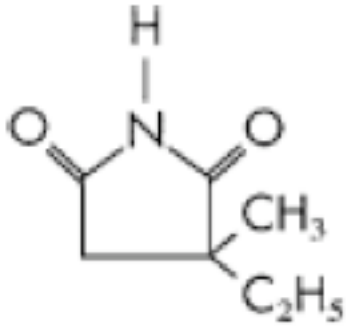
Enhancement of GABA Inhibition

- Tiagabine (Gabitril):
  - Interactions:
    - Blood levels decreased by CBZ, phenytoin, phenobarbital, & primidone
  - Adverse Effects:
    - Asthenia
    - Abdominal pain

Calcium Channel Blockers



Voltage-Gated Ca2+ Channel T Currents



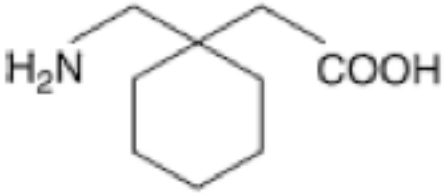
- Ethosuximide (Zarontin):
  - Mechanism of Action:
    - Reduces low threshold Ca2+currents (T currents) in the thalamic neurons.
    - Half-life is ~60 hr in adults; ~30hr in children.
  - Indications:
    - First line for absence seizures
  - Contraindications:
    - May exacerbate partial & tonic-clonic seizures

Voltage-Gated Ca2+ Channel T Currents

- Ethosuximide (Zarontin): مو مهمة كتير
  - Adverse Effects:
    - Psychotic behavior
    - Blood dyscrasias
    - Persistent headaches
    - Anorexia
    - Hiccups
    - Lupus-like syndromes
  - Toxicity:
    - parkinson-like symptoms
    - photophobia

Blockade of Calcium Channels (α2−δ)

- Gabapentin (Neurontin):



  - Mechanism of Action:
    - Originally designed to be a centrally acting GABA agonist.
    - Selective inhibition of v-g Ca2+ channels containing the α2δ1 subunit. (n Ca2+ channels)
  - Indications:
    - adjunct therapy in adults and children with partial & secondarily generalized seizures.
    - Also effective as monotherapy.

Blockade of Calcium Channels (α2−δ)

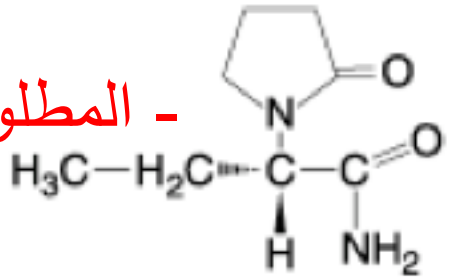
- Gabapentin (Neurontin):
  - Contraindications:
    - Can exacerbate myoclonic & absence seizures.
  - Adverse Effects:
    - **Weight Gain** (5%) with ankle edema (مهمة)
    - Irritability
    - Behavioral problems in children (6%)
    - Has been associated with movement disorders.

Blockade of Calcium Channels (α2−δ)

- Pregabalin (Lyrica):
  - Mechanism of Action:
    - Same as gabapentin مهمة
  - Indications:
    - Approved in 2005
    - Adjunct therapy for partial & secondarily generalized seizures
  - Contraindications:
    - No effect on absence, myoclonic, or primary generalized tonic-clonic seizures
  - Other uses:
    - Prescribed for neuropathic pain, fibromyalgia

Other/Unknown MOA

- Levetiracetam (Keppra):



.Not exactly known+ المطلوب بس الاسم -

  - Mechanism of Action:
    - Not exactly known
    - Binding affinity to Synaptic Vesicle Protein 2A correlates with its anticonvulsant activity.
    - Also blocks calcium channel N-currents, increases intracellular Ca^{2+} levels, modulates GABA channel currents
  - Indications:
    - Approved in 1999 as an adjunct therapy for adults with partial seizures.
    - Some patients have success with monotherapy

Other/Unknown MOA

- Levetiracetam (Keppra):

غير مهم-

  - Contraindications:
    - Renal dysfunction
  - Adverse Effects:
    - Asthenia
    - Infection
    - Behavioral problems in children

Other/Unknown MOA

- Magnesium chloride: Used for magnesium deficiency seizures.
- Paraldehyde: Alcohol withdrawal seizures.

-غير مهم

Primary Generalized Tonic-Clonic (Grand Mal) Seizures

- **Drugs of Choice:**
  - Phenytoin
  - Carbamazepine
  - Oxcarbazepine
  - Valproate
- **Alternatives**
  - Lamotrigine
  - Topiramate
  - Zonisamide
  - Levetiracetam
  - Primidone
  - Phenobarbital
  - Diazepam

Partial, Including Secondarily Generalized Seizures

- **Drugs of Choice:**
  - Phenytoin
  - Carbamazepine
  - Oxcarbazepine
  - Valproate
- **Alternatives**
  - Lamotrigine
  - Topiramate
  - Zonisamide
  - Levetiracetam
  - Primidone
  - Phenobarbital
  - Gabapentin
  - Pregabalin
  - Tiagabine

Absence (Petit Mal)

- **Drugs of Choice:**
  - Ethosuximide
  - Valproate
- **Alternatives**
  - Clonazepam
  - Zonisamide

Atypical Absence, Myoclonic, Atonic Seizures

- **Drug of Choice:**
  - Valproate
- **Alternatives**
  - Clonazepam
  - Topiramate
  - Zonisamide
  - Levetiracetam