- **Terminologies:**
  - **Anti-convulsants**: they are used to control convulsions seen in certain types of epilepsy. Convulsions may also occur in other situations/ conditions which are not related to epilepsy (examples include: meningitis and drug overdose).
  - **Anti-epileptic drugs.**
  - **Anti-seizure drugs:**
    - ✓ What is the definition of seizure? → it refers to an abnormal electrical activity of the brain.
    - ✓ Anti-seizure drugs: are medications controlling seizures or convulsions or stop ongoing series of seizures.
- **Approaches to screening anti-seizure drugs in animal models:**
  - **Maximal Electroshock Seizure (MES):** in which an electrical stimulus will be provided to an animal through electrodes so it develops convulsions (these convulsions represent tonic-clonic seizure in which the body of the animal will stiffen first and then jerky movements will start).
  - **Chemical (pentylenetetrazole) induced seizures**: these will represent absence type of seizures.
  - **Genetically susceptible strains of rats and mice.**
- **A focused approach for screening antiseizure drugs in vitro:**
  - **Facilitation of inhibitory (GABAergic) transmission.**
  - **Reduction of excitatory (glutamenergic) transmission (note: another excitatory amino acid neurotransmitter is aspartate).**
  - **Modification of ionic conductance:**
    - ✓ Sodium (Na^+): inactivation of sodium-channels interferes with depolarization.
    - ✓ Chloride (Cl^-): chloride channels are important for hyperpolarization and they are linked with GABA (note: benzodiazapines act through chloride channels).
    - ✓ Calcium (Ca^{++}) channels.
- **Antiepileptics classification (the following drugs are those which you must study and memorize for the exam):**
  - **Hydantoins**: they are on of the earliest developed antiepileptic drugs (Note: the 1st drug which was developed to treat epilepsy is potassium promide). An example of this classification is "phenytoin". Phenytoin is also class 1a sodium channel cardiac antiarrhythmic.
  - **Iminostelbenes**: an example is "carbamazepine".
  - **Succinimides**: an example is "ethosuximide".
  - **Carboxylic acid**: an example is "valproic acid" → it is a broad-spectrum antiepileptic drug with different mechanisms of action but not preferred to be used as the 1st option because it is expensive and producing unpredictable hepatotoxicity. "divalproate" is a prodrug which is converted to valproic acid (the active form) in the body.
  - **Barbiturates: they are used as:**
    - ✓ Anticonvulsants.
    - ✓ General anesthetics.
    - ✓ Sedative hypnotics.

      An example is "phenobarbitone" which is also acting as a long-term anesthetic. "primidone" is the prodrug which is converted to phenobarbitone (the active form) in the body.
  - **Oxazolidinediones**: they are less used nowadays because they cause toxicity.
  - **Benzodiazepines**: these are used to control convulsions. Examples include "diazepam" and "lorazepam" which is likely to produce respiratory depression in postictal period.
  - **Miscellaneous:**

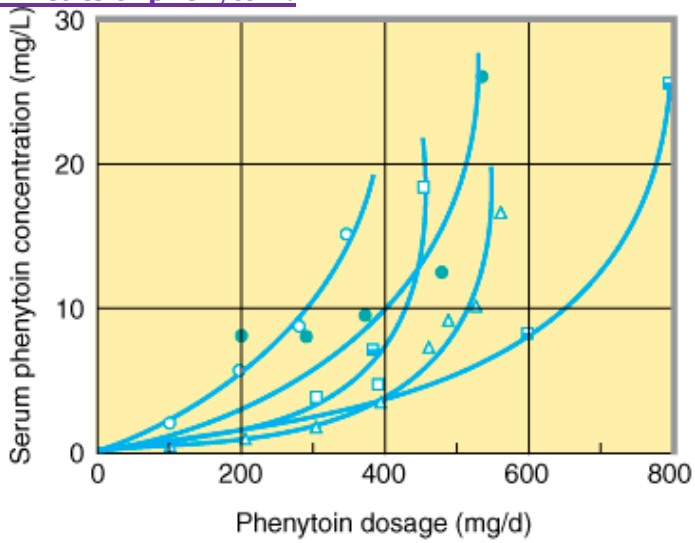
- ✓ ACTH and corticosteroids.
- ✓ Piracetam (used for treatment of age-related memory problems).
- ✓ Acetazolamide (which is a diuretic acting through inhibition of the enzyme carbonic anhydrase and thus affecting the electrolyte environment of neurons).

- **Newer drugs for epilepsy**: they are rarely used as drugs of choice unless the 1st line drug is not controlling the condition. Therefore, you consider adding a second drug which you will select from this category. The most important ones being:
  - Gabapentin.
  - γ-vinyl GABA
  - Pregabalin.

  Note: these drugs are mainly used for treatment of neuropathic pain.
- **The following drugs in the table are very important (these are what you must memorize for the exam):**

Drug	Effective Level (mcg/mL)	High Effective Level[1] (mcg/mL)	Toxic Level (mcg/mL)
Carbamazepine	4–12	7	> 8
Primidone	5–15	10	< 12
Phenytoin	10–20	18	> 20
Phenobarbital	10–40	35	> 40
Ethosuximide	50–100	80	> 100
Valproate	50–100	80	> 100

  - As you can notice from the table above, the high effective dose is near the toxic levels. Therefore, you cannot administer a very low dose to the patient because there will be no therapeutic effect. On the other hand, if you increase the dose administered to the patient → you might cause unwanted adverse effects (there must be a balance and you must be very careful).
- **Dose-dependent kinetics of phenytoin:**



  - The normal range of dose of phenytoin is 300-400 mg/d. as you increase the dosage there is proportionate increase in plasma concentration of the drug, but when you increase the dosage beyond 400 mg/d there will be disproportionate increase in plasma concentration of the drug (which means that the drug shifted from 1st order kinetics to zero order kinetics).
- **Mode of action of antiepileptic drugs:**
  - Suppression of seizure discharge or spread of seizure in the brain (you don't need to memorize other points which are mentioned in the slide).

- **Electrophysiologic effects of antiepileptics:**

Effect	Mechanism	Drugs
Inhibit neuronal depolarization	Prolongation of sodium channel inactivation	Carbamazepine-phenytoin-topiramate
Reduce thalamic pacemaker current	Blockade of t-type calcium channels	Ethosuximide-valproate
Produce neuronal hyperpolarization	Opening of chloride channels by activation of GABA receptors	Vigabartin-valproate-benzodiazapines-barbiturates

- **Characteristics of antiepileptic drugs:**
  - **Carbamazepine**: it is the drug of choice for treating partial epilepsy. Adverse effects include: GI disturbances and sedation (Note: these adverse effects occur in the first weeks but then disappear due to tolerance).
  - **Phenytoin**: adverse effects of this drug include:
    - ✓ Ataxia and nystagmus (due to cerebellar toxicity which is occurring in association with long-term therapy).
    - ✓ Sedation.
    - ✓ Hirsutism.
    - ✓ Gum hyperplasia.
    - ✓ Osteomalacia and megaloblastic anemia.

    This drug is characterized by enzyme induction and high protein binding → therefore, leading to many drug-drug interactions.
  - **Valproic acid**: it is a broad-spectrum antiepileptic. Adverse effects of this drug include fine tremor, weight gain and hepatotoxicity (being the most important).
  - **Ethosuximide**: adverse effects of this drug include: GI disturbances (which will disappear later due to tolerance).
  - **Phenobarbitone**: this drug is used to treat febrile convulsions occurring in children but it is not preferred because it produces behavioral disturbances (school performance declines) and addiction.
- **Kinetic parameters of major antiepileptic drugs:**

Drug	% Oral Absorption	t ½ (hrs)	Dosage Schedule	% Protein Binding	Time to Steady state (days)
Carbamazepine	90 - 100	10 – 20	BID - TID	75	2 – 4
Phenytoin	90 - 100	6- 24 Dose-dependent Time-dependent	BID	95	5 – 10
Valproate	100	10 – 16	BID	90 +	2 – 3
Ethosuximide	90 - 100	30 – 60	BID	0	5 – 10
Phenobarbitone	100	80 - 100 (variable)	OD	50	2-3 wks
Topiramate	80	6-8	BID	15	2-3
Gabapentin	40-60	5-9	TID-QID	0	1-2
Pregabalin	90	6-8	BID-TID	0	1-2

  - All antiepileptic drugs used as a long-term treatment are given orally (they are given parentally only in emergency situations).
  - Phenobarbitone has a very long half life so it is given once daily while the majority of other antiepileptic drugs are given twice daily.
  - Notice that gabapentin has the least percentage of oral absorption.

- One week is required (on average) for drugs to reach steady-state levels (equal to 5 half lives).

- **Drugs of choice in epilepsy:**
  - **Partial seizure**: carbamazepine (DOC) or valproic acid (an alternative).
  - **Absence seizure**: ethosuximide (DOC) or valproic acid (alternative).
  - **Myoclonic seizure**: valproic acid.
  - **Tonic-clonic seizure**: carbamazepine or valproic acid or phenytoin.
- **Principles of antiepileptic drug therapy:**
  - **If the first onset of seizure occurs suddenly during adult-life** → investigation must be done (because usually a lesion is suspected).
  - **When treating epilepsy** → always start with one drug at moderate-dosage and the titrate it upward until you reach the maximum therapeutic dose.
  - **Choose the drug according to age: a child female must not be treated with phenytoin because it causes:**
    - ✓ Hirsutism.
    - ✓ Gingival hyperplasia.
    - ✓ Facial coarsening.
  - **Valproic acid is not used in treating a pregnant female** → because it leads to spina bifida in the fetus. **Phenytoin is also teratogenic** → producing midline deformities (cleft palate).
  - **Health education is relevant (you must counsel the patient).**
  - **When to consider termination of antiepileptic drug therapy?** → when there is 2-3 years period which is free of attacks.
- **Management of status epilepticus:**
  - Admit the patient and secure his airway.
  - Give oxygen and make the patient in semi-prone position.
  - Load the patient with IV benzodiazepine and then continue administering it with slow infusion.
  - If the patient is still not controlled → administer fosphenytoin.
  - If still not controlled → administer phenobarbitone or valproic acid
  - If still not controlled → general anesthesia would be your last option (either by producing barbiturate coma through sodium thiopental or giving propofol).