Pharmacology Team 431

(CNS BLOCK)

Drugs Used In Treatment Of Epilepsy
(lectures 2)

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Drugs Used In Treatment Of Epilepsy

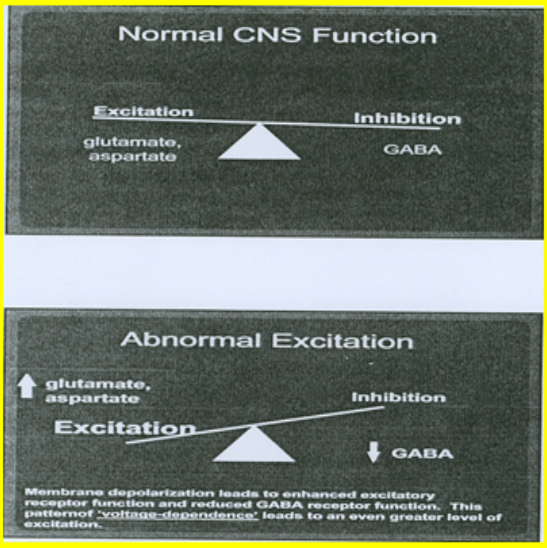
Epilepsy

* the 2nd most common neurological disorder (after stroke)
*epilepsy is a disorder of the brains electrical system.
*Abnormal electrical impulses cause brief changes in movement, behavior, sensation, or awareness.
*These interruptions are known as seizures (=fits).
*The attack may last from a few seconds to a few minutes
*people who have two or more unprovoked seizures "within 6-12 months" are considered to have epilepsy.
*Result in abnormal stimulation, which starts from a certain area and extends into adjacent areas of brain.
*This leads to activation of excitatory neurotransmitters in brain (especially glutamate), as well as suppression to inhibitory neurotransmitters in brain (especially GABA)

In epilepsy:

Increase excitation
Decrease inhibition

MOA of antiepileptic drugs is to (Restore the balance)



Etiology

A) 90% Idiopathic=primary
Before they did not know the cause, but with new technologies, they are saying that the causes are Gene mutations leading to abnormal structures in brain

B) 10%Symptomatic=secondary
There is an underlying cause
Ex1: in brain tumors patients may have epileptic fits. In this case we must treat the underlying cause (=tumor)
Ex2: children with previous multiple head injury may lead to epilepsy in their adulthood

When the patient is already diagnosed with epilepsy. There are some risk factors, which may trigger the onset of epileptic seizures. Even if the patient is under treatment, these triggers may lead to failure of treatment

Triggers: anything that cause brain stress
Fatigue
Stress
Sleep deprivation
Poor nutrition

Classification of epilepsy

Generalized
Involvement of both hemispheres
Loss of consciousness

Partial
Involve one hemisphere
Usually no loss of consciousness

Generalized
Tonic-clonic (Grand-mal)
Absence (Petit mal)

Partial
Simple
Complex
Secondary

Types of epilepsy

**Generalized*

A) Tonic-Clonic
Na+ channels dependent
2phases: stiffness (tonic) then jerky movement, violent contractions and relaxation (clonic)
B) Absence
Ca++ channels dependent
usually in children
blinking of eyes are very characteristic

**Partial*

A) Simple
Na+ channels dependent
usually one area is affected, according to area affected you will have the symptoms
ex: motor area→ jerking or spasms
sensory area→ unusual sensations
visual area→ flashing lights
B) Complex
Na+ channels dependent
altered consciousness
automatism is very characteristic (=repetitive unconscious gestures such as lip smacking, chewing, or swallowing in certain types of epilepsy)
C) Secondary
begins as partial, then progress into generalized

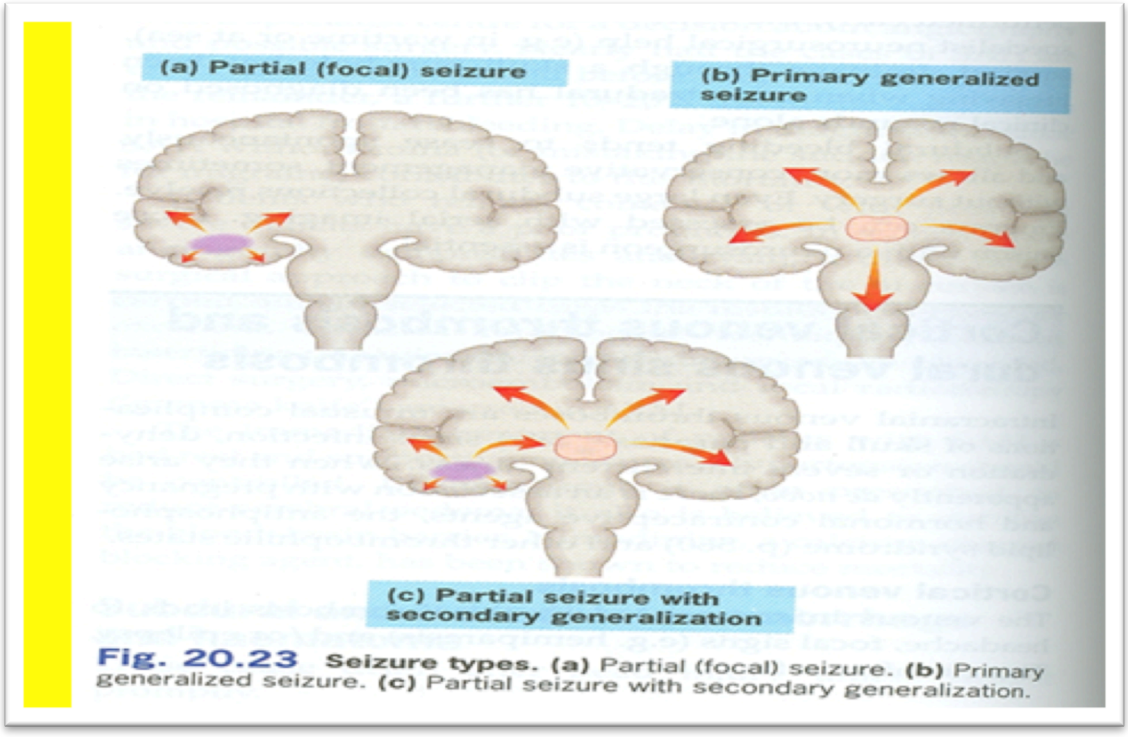
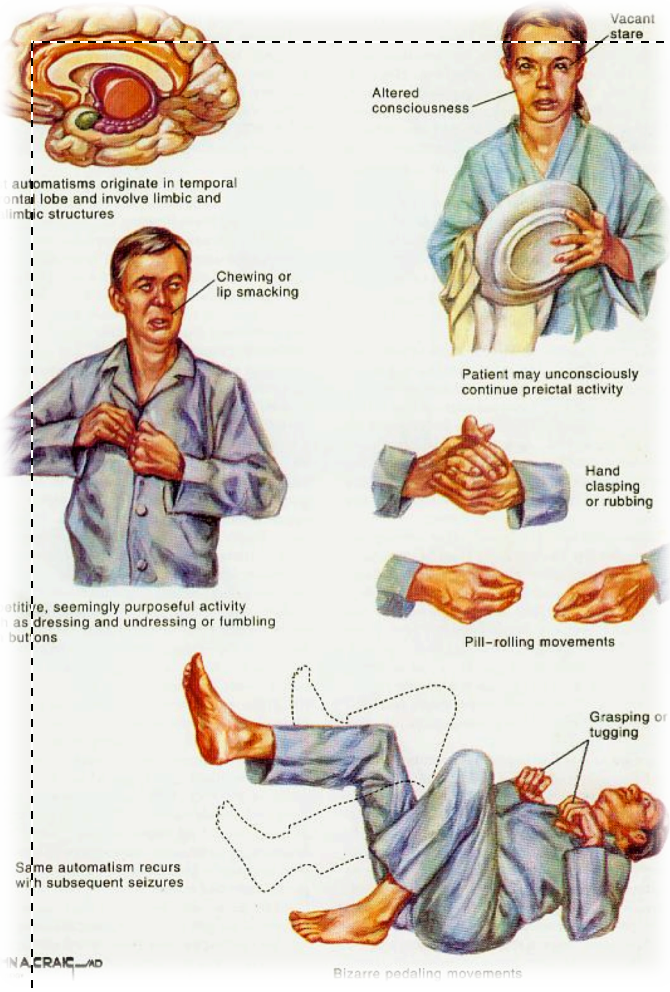
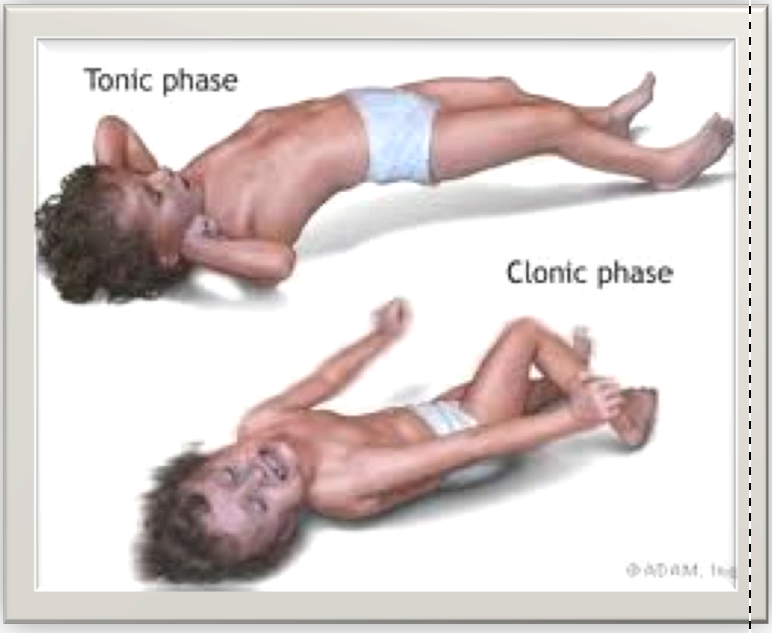


Fig. 20.23 **Seizure types.** **(a)** Partial (focal) seizure. **(b)** Primary generalized seizure. **(c)** Partial seizure with secondary generalization.





General rules for treatment of epilepsy:

1) antiepileptic drugs suppress NOT cure epilepsy!
2) Antiepileptic drugs are indicated when there is two or more unprovoked seizures occurred in short interval (within 6months-1year)
3) an initial therapeutic aim is to use one drug only (=monotherapy)
"if failure or resistance of treatment, then we add another drug"
4) monitoring plasma drug level is not essential (only useful)
"only if failure or resistance or refractory or if side effects start to appear"
5) triggering factors can affect seizures control by drugs
6) sudden withdrawal of drugs should be avoided (may cause status epilepticus)
7) drugs are administered orally (chronic disease), but in case of status epilepticus IV (acute emergency)

***status epilepticus (SE)**: most seizures stop within 5 minutes. When seizures follow one another without recovery of consciousness, it is called SE. it has a high mortality rate. And death is from cardiorespiratory failure

When to start withdrawal of drugs?

After seizure-free period of 2-3 up to 5 years from last fit
+
normal neurological examination (normal ECG, normal brain scan "CT, MRI")

Side effects of Antiepileptic drugs:

All may cause….
-Sedation and atxia
-GIT upset (vomit, nausea..)
-Skin rash
-CNS toxicity (Confusion, double vision...)
-Teratogenicity

Lennox Gastaut Syndrome:

severe form of epilepsy
unknown cause
in children between 2-6 years
different degree of mental retardation
congenital anomalies in some organs, especially heart
+different forms of epilepsy in the patient

Many anti seizure drugs act via multiple mechanisms

MOA of antiepileptic drugs:

1)Inhibition of excitatory neurotransmitters(Glutamate)
Decrease synthesis
Decrease release
Increase degradation

2)Enhancement of inhibitory neurotransmitters(GABA)
Increase synthesis
Increase release
Decrease degradation

3)Abort abnormal electrical stimuli
Decrease Na+ influx
Decrease Ca++ influx
Increase K+ enflux

Classification of antiepileptic drugs:

First generation	Second generation
Phenytoin	Lamotrigine
Carbamazepine	Topiramate
Valproic acid	
Ethosuximide	

All Second Generation drugs have…
- Fewer side effects
- Somnolence effect (so better to give before sleep)

***Somnolence** (or "**drowsiness**") is a state of near-sleep, a strong desire for sleep, or sleeping for unusually long periods.

1) Carbamazepine

- Available only orally (so not used in SE "acute emergency")
- Potent enzyme inducer, including its own metabolism (so we must increase the dose to reach effective level)
- MOA: -
*Block Na+ channels
*Attenuates action and release of glutamate
- **Drug of choice in all partial seizures**
- Not used in absence seizures (because no effect on Ca++ channels)
- Side effects: -blood problems (leucopenia, aplastic anemia, agranulocytosis) "so from time to time we should do a complete blood picture
- Hyponatremia + water intoxication

 # Extra information:

Leucopenia :is a decrease in the number of white blood cells (leukocytes) found in the blood

Aplastic anemia: is a condition where bone marrow does not produce sufficient new cells to replenish blood cells.

Agranulocytosis: is an acute condition involving a severe and dangerous leukopenia

2)Phenytoin

- Orally and other forms (IM,IV) , so can be used in SE
- Enzyme inducer (not as potent as Carbamazepine)
- MOA:
*Block Na+ channels
*Affect release of glutamate
*Increase action of GABA
- Used in all epilepsy except absence
- Used in SE
- Used as antiarrhythmic drug
- Side effects:
* Cardiac arrhythmia
- Chronic side effects:
* Gum hyperplasia
* Coursing of facial features, Hirsutism "so not given to young females"
* Folic acid and vitD deficiency (so give supplements)

*Folic acid deficiency causes megaloblastic anemia
*Vitamin D deficiency causes osteomalacia

Extra information:
***IM route:** is not recommended because it may lead to abscess formation
However, there is another preparation "Fas-phenytoin" which can be used IM and not cause abscess formation. → it converts into phenytoin in the body.
***Hirsutism:** is the excessive hairiness on women in those parts of the body where terminal hair does not normally occur or is minimal - for example, a beard or chest hair.

3)Na+ Valproate

- Broad-spectrum antiepileptic (effective in all forms)
- Found orally and in other routes
- Enzyme inhibitor "so prolong action of other drugs"
- MOA:
*Block Na++ channels AND Ca++ channels
*Increase GABA
*Decrease Glutamate
- Drug of choice in patients with 2 types of seizures ex: absence and tonic-clonic. (Multiple epilepsy)→ So used in Lennox-gastaut syndrome

- Side effects:
* Weight gain "increase appetite"
*Transient hair loss "while on treatment"
*Thrombocytopenia
*MOST IMP: hepatitis or severe hepatotoxicity, so we must do liver function test and be cautious.

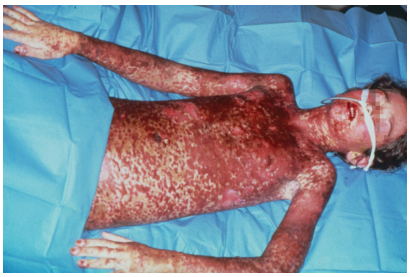
4) Ethosuximide

Inhibits T-type Ca channels in thalamocortical neurons.
Used in Absence epilepsy and has only one side effect "Gastric distress", so it's better than Na-valproate for treatment of Absence.E "less S/E".

2nd generation drugs: when first discovered doctors were afraid to use it, so it was used as **add on** therapy in refractory seizures. But now they know how it works and its effect and can be used in Lennox-gastaut syndrome and partial epilepsy

5) Lamotrigine

- MOA:
*Block NA+ channels
*Decrease Glutamate
- Side effects: SEVERE skin rash à Steven Johnson syndrome, influenza like syndrome . . .



6) Topiramate

- MOA:
* Block Na+ channels
* Increase GABA
- Side effects:
*Psycologic and cognitive dysfunction
* Weight loss
* Renal stones “ask patient to drink lots of water”
* Decrease ethinyl estradiol concentration of oral contraceptive preparations à it breaks down oral contraceptive drugs, so there is a chance of pregnancy unless the patient change the type of contraception "not in male slides"

Drugs used for treatment of SE: IV route

Drug of choice → Lorazepam/Diazepam
others:
phenytoin/fosphenytoin
phenobarbital " not recommended in young age because it leads to paradoxical response"

Pregnancy and Epilepsy:

NO antiepileptic drug is safe in pregnancy
but patient has to continue therapy(so what to do?)
Gradually reduce the dose to the lowest effective level
→ lowest teratogenicity → carbamazepine

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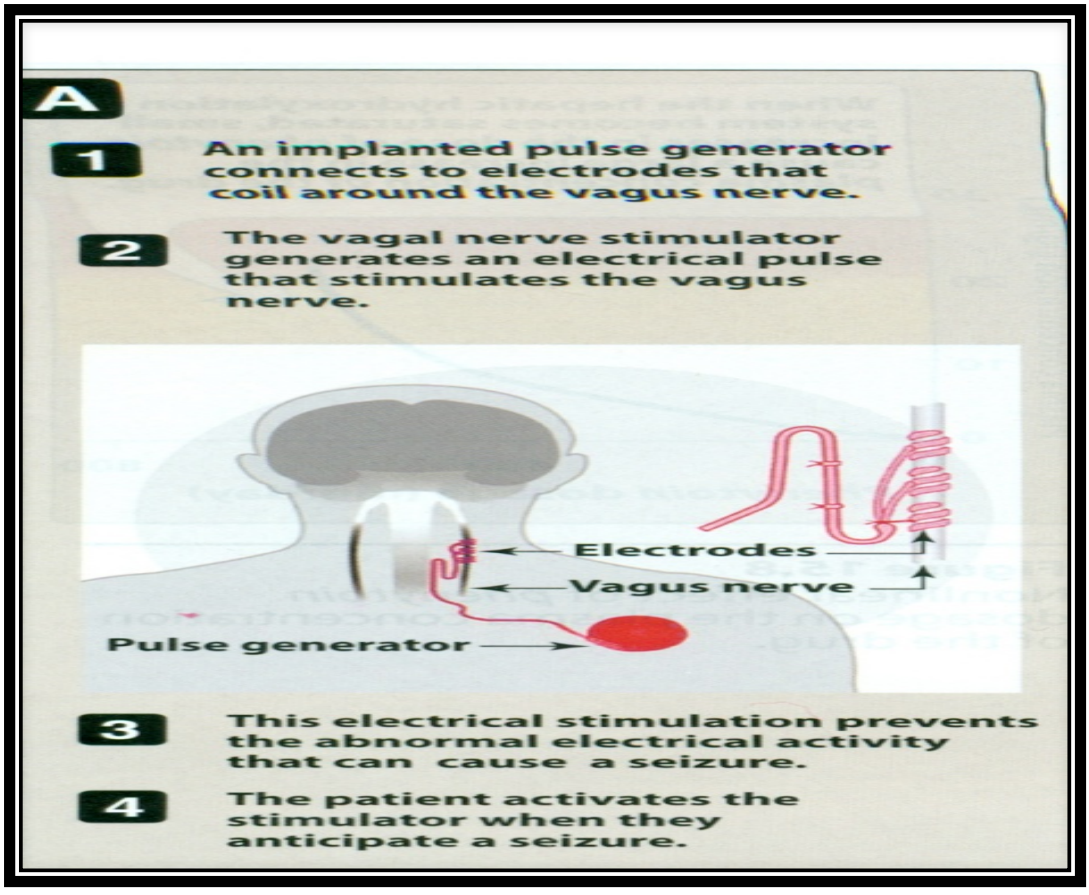
*If very resistant epilepsy and not responding to treatment or patient can not tolerate side effects. We may use **vagal nerve stimulation**, which is very expensive

It is an alternative for patients who:
-Have been refractory to multiple drugs
-Are sensitive to the adverse effects



Questions:

Q: Drug of choice in partial seizures is
Phenytoin
Carbamazepine
Topiramate
Valproic acid

Q: a very potent enzyme inducer is
Phenytoin
Lamotrigine
Carbamazepine
Ethosuximide

Q: a drug found only orally is
Lamotrigine
Carbamazepine
Topiramate
Valproic acid

Q: chronic use of …. May lead to gum hyperplasia is
Phenytoin
Lamotrigine
Valproic acid
Ethosuximide

Q: vitD and folic acid supplements should be given with
Phenytoin
Lamotrigine
Carbamazepine
Valproic acid

Q: a drug that is not recommended to be given to young females
Lamotrigine
Carbamazepine
Phenytoin
Ethosuximide

Q: used in multiple epilepsy (Lennox gastaut syndrome)
Phenytoin
Lamotrigine
Carbamazepine
Topiramate

Q: Liver function test must be done in patients taking …
Carbamazepine
Topiramate
Valproic acid
Ethosuximide

Q: drug of choice in absence seizures:
Carbamazepine
Topiramate
Valproic acid
Ethosuximide

Q: vary severe abdominal pain and nausea is very characteristic in patients taking
Phenytoin
Lamotrigine
Carbamazepine
Topiramate
Valproic acid
Ethosuximide

Q: Somnolence is a side effect of ..... And ..... (2 answers)
Lamotrigine
Carbamazepine
Topiramate
Ethosuximide

Q: a drug which mainly works on Ca++ channels **(important Q)**
Phenytoin
Lamotrigine
Carbamazepine
Topiramate
Valproic acid
Ethosuximide

Q: Stevens Johnson syndrome is a side effect of
Phenytoin
Lamotrigine
Topiramate
Ethosuximide

Q:Drug of choice in treatment of SE is:
Phenytoin
Carbamazepine
Topiramate
Lorazepam/Diazepam

Q: lowest teratogenic drug is:
Phenytoin
Lamotrigine
Carbamazepine
Topiramate
Valproic acid
Ethosuximide

Q: a patient with epilepsy and takes valproic acid is now pregnant. What should the doctor do?
-Stop valproic acid immediately and give carbamazepine instead
-Increase the dose of the drug
-Decrease the dose of drug
-Stop giving any medication

Q: a patient is diagnosed with epilepsy:
-When there are 2 or more seizures occurred in 7 months
-From first seizure
-When ECG findings are abnormal

Q: sudden withdrawal of antiepileptic drugs may lead to:
-Lennox gastaut syndrome
-Steven Johnson syndrome
-Status epilepticus

Q: MOA of antiepileptic drugs include all of the following except:
Block Na+ channels
Block Ca++ channels
Increase glutamate release
Decrease GABA degradation
Increase GABA synthesis

Q: main MOA of drugs used in treatment of absence epilepsy is:
Block Na+ channels
Block Ca++ channels
Increase glutamate release
Decrease GABA degradation
Increase GABA synthesis

Thanks & Good Luck