Epilepsy

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Pharmacology

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Epilepsy

- Ongoing liability to recurrent epileptic seizures
- Epileptic seizure- Sudden synchronous discharge of cerebral neurons causing symptoms & signs that are apparent either to a patient or to an observer
- Abnormal depolarization of neurons, either excitatory or inhibitory

Management of epilepsy

Clinical Diagnosis, investigated to find a cause

•EEG – To categorize epilepsy and to understand the cause
(False negative rate >20%, False positive rate1%)

•CT/MRI brain- (Focal onset, elderly)

- ECG- Rhythm, conduction anomalies, QT prolongation)

- Blood tests- Glucose/ Electrolytes(Na^{+}, $Ca^{2+)}$

Liver & renal functions

Anti-epileptics

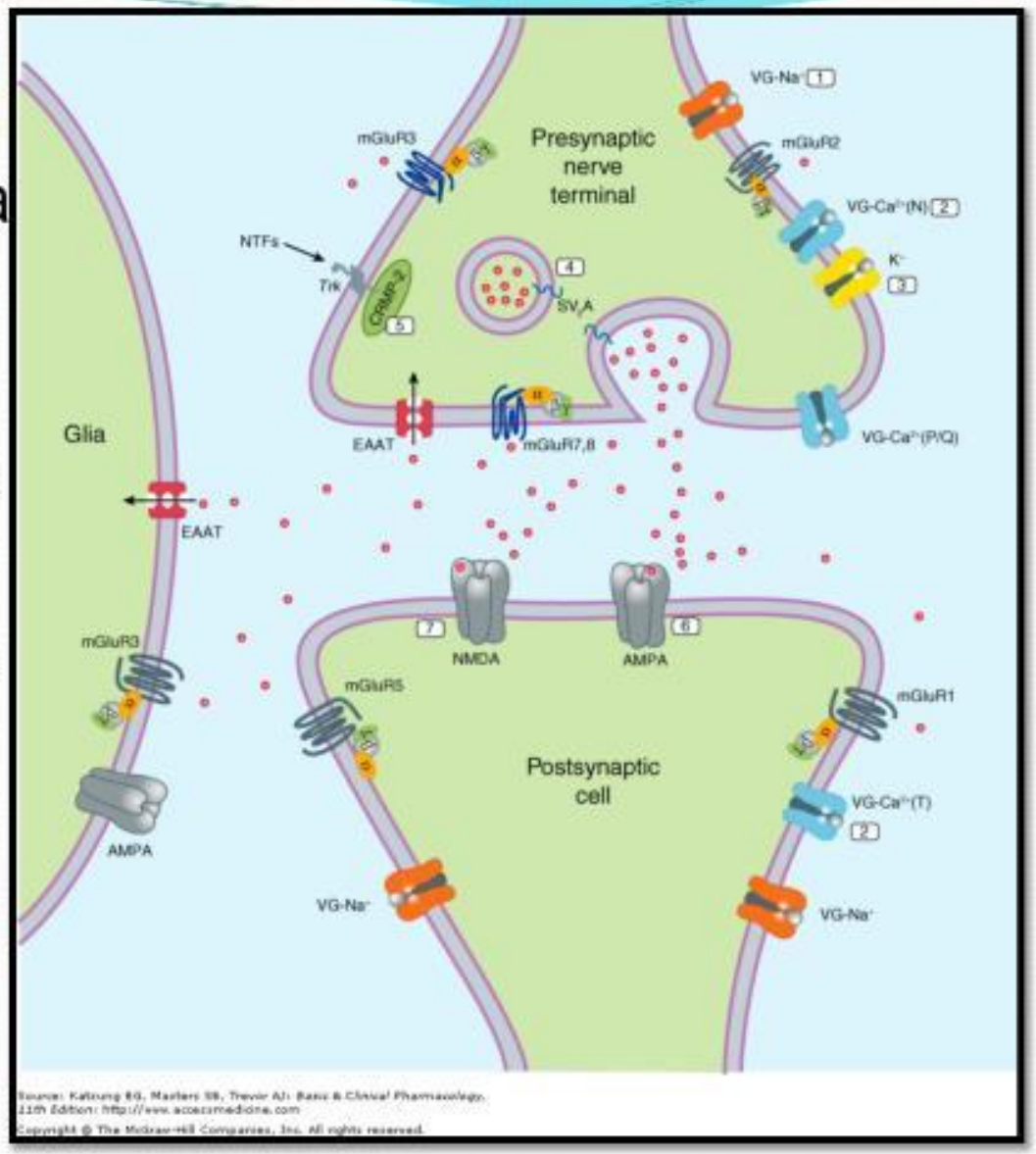
- Drugs that control fits/ seizures

How Drugs Act?

- Blockade of voltage –ga channels (Na^+ or Ca^+)
- Enhancement of GABA

Or interference with

- Glutamate transmission



Types

Older	Newer
Phenobarbitone	Lamotrigine
Phenytoin	**Levetiracetam**
Carbamazepine	Topiramate
Sodium valproate	Vigabatrin
Benzodiazepines	Gabapentine

Cytochrome P450

Enzyme inducers
Bull**S**hit **CRAP GPS**
induces my rage

Barbiturates
St Johns wart
Carbamazepine
Rifampicin
Alcohol(chronic)
Phenytoin
Griseofulvin
Phenobarbitone
Sulphonylurea
Smoking

- **Enzyme Inhibitors**

- **VICK'S FACE All Over GQ**

- **Sodium Valproate**
- **Isoniazid**
- **Cimetidine**
- **Ketoconazole**
- **Sulfonamide**
- **Fluconazole/Fluoxetine**
- **Alcohol(acute)**
- **Chloramphenicol**
- **Erythromycin**
- **Amiodarone**
- **Omeprazole**
- **Grape fruit**
- **Quinidine**

Enzyme inducers

- Induce the metabolism of drugs such as
- Corticosteroids
- OCP
- Warfarin
- Theophylline
- Phenytoin
- Carbamazepine

- Induce the metabolism of
- Dietary and endogenous

-Vitamin D

-Folate

Phenobarbitone

Mechanism of Action

- Enhances GABA function

Indications

- Used in all forms of epilepsy except for absence
- Used in status epilepticus
- 50% albumin bound
- T1/2 50-140 hours
- Enzyme inducer- P450 (OCP, Warfarin, TCA)

Phenobarbitone

Adverse Effects

- Sedation
- Impairment of cognition
- Megaloblastic anaemia
- Mild hypersensitivity
- Osteomalacia
- Not for patients with porphyria (Induces enzymes responsible for porphyrin synthesis and worsen the disease)
- In overdose- coma, respiratory failure
- Behavioural disturbances and hyperkinesia in children

Phenytoin

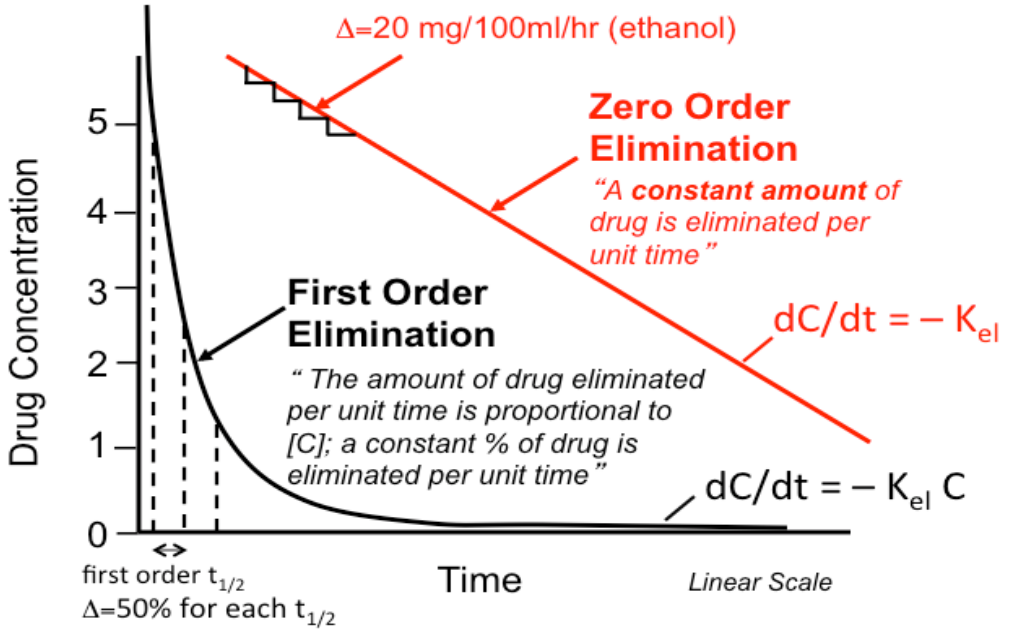
Mechanism of action

- Membrane stabilizer
- Inhibits voltage gated sodium channels
- Prevents the initiation and the spread of repetitive neuronal discharges

Phenytoin

Pharmacokinetics

- Well absorbed orally
- 90% bound to plasma albumin
- **Shows saturation kinetics**
- **Is a potent hepatic enzyme inducer**
- **Narrow Therapeutic Index**



Phenytoin

Indications

- Grand mal epilepsy
- Partial seizures
- Status epilepticus
- Not for absence seizures

- Cardiac arrhythmias (Class IB antiarrhythmic)
- Trigeminal neuralgia

Phenytoin

Adverse Effects

- At therapeutic doses
  - Vertigo
  - Ataxia
  - Headache
  - Nystagmus

Phenytoin

Adverse Effects (Other)

- Impairment of cognitive function
- sedation
- Cerebellar ataxia
- Peripheral neuropathy
- Gum hyperplasia
- Rashes
- Acne
- Coarsening of facial features
- Hirsutism
- Anaemia
-
- Osteomalacia

Carbamazepine

Mechanism of Action

- Membrane stabilizer
- Inhibits voltage gated sodium channels
- Well absorbed
- Extensively metabolized
- t1/2 36 hrs (On chronic dosage-15hrs)
- Induces its own metabolism
- Starting dose is 100mg daily

Carbamazepine

Indications

- Epilepsy - specially complex partial epilepsy

- Trigeminal neuralgia
- Post herpetic neuralgia
- Mood stabilizer-Bipolar affective disorder (Mania-depression)

Carbamazepine

- Adverse effects
- Drowsiness
- Dizziness
- Ataxia
- Leukopenia
- Osteomalacia
- ⇧ ALP, GGT
- Rashes –

-3% develops an erythematous generalized rash

-Stevens-Johonson syndrome

- Visual disturbances(Blurring,diplopia)
- Less commonly- water retension, GI effects

Sodium valproate

Mechanism of action

- Inhibits voltage gated sodium channels
- Reduce GABA reuptake
- Inhibits GABA transaminase which breaks down GABA
- Well absorbed
- Highly protein bound
- Mostly metabolized in the liver t1/2 12hrs

Sodium valproate

Indications

- Grandmal epilepsy
- Myoclonic epilepsy
- Absence seizures (petit mal)
- Temporal lobe epilepsy
- Post-traumatic epilepsy
- Status epilepticus

- Mood stabilizer- Bipolar affective disorder (Mania-depression)

Sodium valproate

Adverse effects

- Gastrointestinal disturbances
- Thrombocytopenia
- Impaired liver function tests (Rarely-hepatotoxicity)
- Pancreatitis
- Drug interactions- inhibits the metabolism of other antiepileptics
- **Adverse effects particularly seen in women**
- Weight gain
- Polycystic ovarian syndrome
- Teratogenicity-Neural tube defects if prescribed in early pregnancy (By inhibiting metabolism of folic acid)
- Hair loss, thinning and curling- 10%

Benzodiazepines

- Clonazepam and clobazam
- Positive allosteric modulators of $GABA_A$ receptors
- Myoclonic epilepsy and other resistant forms of epilepsies
- Others too sedating for the routine use
- Withdrawal effects-seizures

Ethosuximide

- T-type Calcium channel blocker
- Used in absence seizures

Adverse effects

- Gastrointestinal disturbances
- Eosinophilia
  - Anorexia
  - Lethargy
  - Dizziness
  - Precipitate GTC seizures in susceptible patients
- Rarely hypersensitivity reactions

Lamotrigine

- ?Inhibits voltage gated sodium channels
- Reduce secretion of excitatory amino acids such as Glutamate, Asparate
- Used in grandmal epilepsy and partial epilepsy
- Mood stabilizer
- Commonly causes skin rashes
- Stevens-Johnson syndrome

Levetiracetam

- Exact mechanism by which levetiracetam acts to treat epilepsy is unknown.
- Inhibits presynaptic calcium channels.
- Rapidly & completely absorbed when given orally
- Side effects

-CNS effects such as somnolence, decreased energy, headache, dizziness, mood swings and coordination difficulties.

Other newer antiepileptics

- **Vigabatrin**
- Inhibits GABA transaminase

- **Topiramate**
- ? By interfering with both Sodium and Calcium channels- Enhances GABA activity and inhibits Glutamate activity
- Weak inhibitor of carbonic anhydrase

- **Gabapentine**
- Inhibits L-type Calcium channels

General principles of therapy

- When to initiate therapy- controversial
- (≥2 unprovoked seizures within 1 year)
- Single commonly used relatively non toxic drug- monotherapy is preferred
- If first drug fails to completely control the fits - substitute with another gradually and slowly withdraw the first
- Abrupt withdrawal can precipitate status epilepticus
- If patient is still not seizure free add another drug
- Can tail off only after being seizure free for 3years

Dosage

- start with one third of the maintenance dose
- increase weekly to reach the maintenance dose in 3 to 4 weeks
- If fits continue dose should be adjusted upwards until the fits cease or adverse effects appear
- 2 equal daily doses preferable

❖ **Refractory epilepsy-**

- Re evaluate the diagnosis
- Combine AEDs in maximum tolerated doses
- Consider compliance
- Vagal nerve stimulation
- Ketogenic(High fat) low carbohydrate diet (Simulate starvation)
- Temporal lobectomy (Hippocampal sclerosis)

Pregnancy and epilepsy

- Children born to mothers on therapy show increased rate of malformations at birth
- Withdrawl of antiepileptics is even more dangerous
- Carbamazepine is preferred during pregnancy.
- Folic acid is administered to reduce neural tube defects

Epilepsy in children

- Treated like in adults
- Side effects more problematic
- Febrile convulsions management with prophylactic antiepileptics is not recommended by the WHO anymore

Pharmacological management

	Generalized tonic-clonic seizures (grand mal)	Focal seizures with or without secondary generalization	Myoclonic seizures
First-line	Sodium valproate Levetiracetam Lamotrigine Carbamazepine Oxcarbazepine Topiramate	Carbamazepine Lamotrigine Levetiracetam Sodium valproate Oxcarbazepine Topiramate	Sodium valproate Levetiracetam Topiramate
Second-line and/or add-ons	Phenobarbital Clobazam Clonazepam Phenytoin	Clobazam Gabapentin Pregabalin Zonisamide Lacosamide Tiagabine	Clonazepam Clobazam Lamotrigine Piracetam
May worsen attacks			Carbamazepine Oxcarbazepine

Non pharmacological management

- Patient and the caregivers should be made aware of the nature of the disease, risk of recurrence & importance of adherence to treatment
- Avoid or remove precipitants – Drugs, alcohol, strobe light stimulation, sleep deprivation
- Give advice on safety- Avoid swimming, baths, working at heights
- Safe home environment- Remove unprotected fire places, store sharp equipment properly
- Stop driving
- Pregnancy should be pre planned when patient is on treatment for epilepsy
- Advice on what to do if patient gets a seizure
- Disclose information on being on treatment for epilepsy at any medical encounter

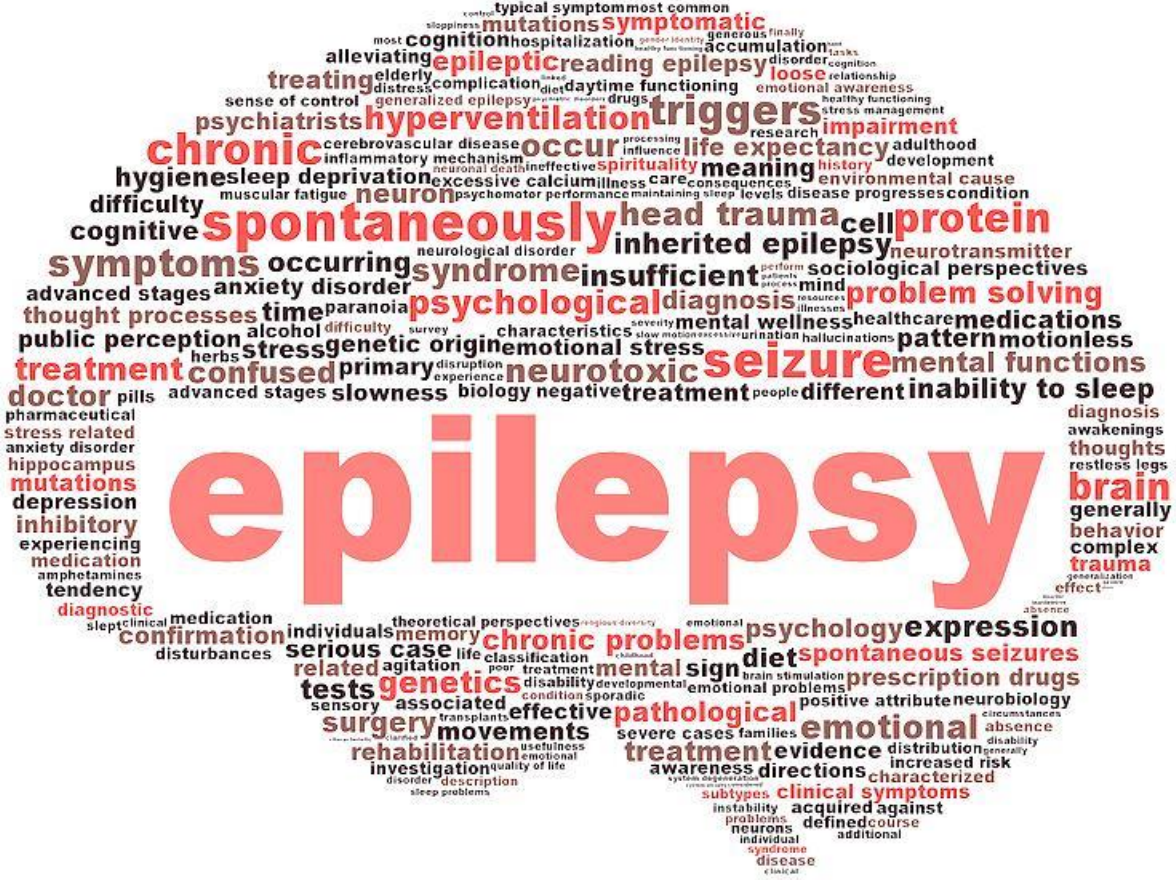
Management of status epilepticus

- Home work

- Reference:
- Oxford emergency Medicine Handbook

Anti-epileptics ; Summary

- Reduce abnormal excitation of neurons
- Different drugs for different types of seizures
  - **GTC seizures – Na valproate/ Levetiracetam/ Lamotrigine/ Carbamazepine/**
  - **Partial seizures –Carbamazepine/ Levetiracetam/ Lamotrigine/ Na valproate**
  - **Myoclonic seizures – Na valproate/ Levetiracetam/ Benzodiazepines**
  - **Absence seizures – Na valproate/ Ethosuximide**
- Idiosyncratic side effects are common
- Seizure control with minimum dose monotherapy is the goal


epilepsy
typical symptom
most common
mutations
symptomatic
cognition
hospitalization
accumulation
alleviating
epileptic
reading epilepsy
disorder
loose
treating
elderly
distress
complication
daytime functioning
emotional awareness
sense of control
generalized epilepsy
drugs
triggers
psychiatrists
hyperventilation
impairment
chronic
cerebrovascular disease
occur
life expectancy
adulthood
inflammatory mechanism
spirituality
meaning
development
hygiene
sleep deprivation
excessive calcium
illness
care
consequences
environmental cause
muscular fatigue
neuron
levels
disease progresses
condition
difficulty
spontaneously
head trauma
cell
protein
cognitive
inherited epilepsy
neurotransmitter
neurological disorder
symptoms
occurring
syndrome
insufficient
sociological perspectives
advanced stages
anxiety disorder
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problem solving
thought processes
time
paranoia
psychological
diagnosis
public perception
alcohol
difficulty
characteristics
mental wellness
healthcare
medications
stress
genetic origin
emotional stress
pattern
motionless
herbs
seizure
mental functions
treatment
confused
primary
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doctor
pills
advanced stages
slowness
biology
negative
treatment
people
different
inability to sleep
pharmaceutical
stress related
anxiety disorder
hippocampus
mutations
depression
inhibitory
experiencing
medication
amphetamines
tendency
diagnostic
diagnosis
awakenings
thoughts
restless legs
brain
generally
behavior
complex
trauma
effect
medication
confirmation
individuals
theoretical perspectives
memory
chronic problems
psychology
expression
disturbances
serious case
diet
spontaneous seizures
related
agitation
mental
sign
prescription drugs
tests
genetics
disability
emotional problems
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positive attribute
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families
absence
rehabilitation
treatment
evidence
distribution
investigation
increased risk
awareness
directions
characterized
clinical symptoms
acquired
against
defined
course
neurons
individual
syndrome
disease

Thank you