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# Epilepsy and Anticonvulsants


## Epilepsy nuggets

- Recurrent seizures
- Paroxysmal discharge of cerebral neurons

## Types

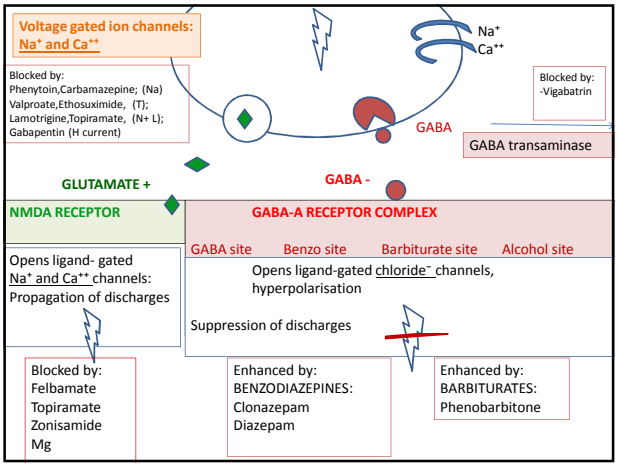
1. Partial (localised)
   1. Simple (no loss of consciousness)
   2. Complex (confusion, impaired consciousness, amnesia)
2. Generalised (involves most of brain)
   1. Tonic clonic (grand mal)
   2. Absence (petit mal)
   3. Myoclonic and akinetic
   4. Infantile spasms (check Vit B6)

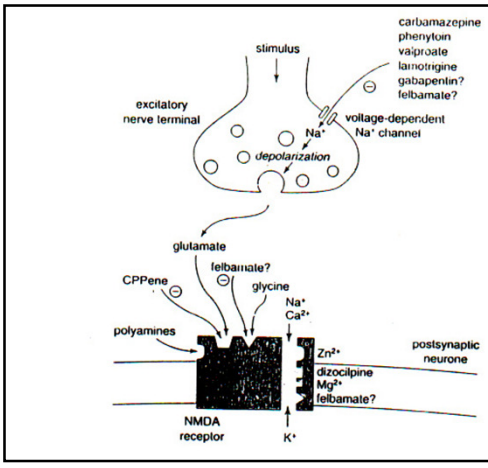
## Mechanism of action of anticonvulsants

- Poorly understood
- Selectively block repetitive discharges by:

1. Prolonging the inactivated state of voltage-gated $Na^+$ and $Ca^{++}$ channels
2. Enhancing the effects of the inhibitory neurotransmitter, GABA (via the GABA-A receptor complex)
3. Inhibiting the effects of the excitatory neurotransmitter, Glutamate (via the NMDA receptor)

Often more than one mechanism of action



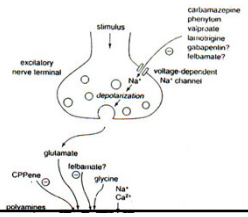
## Prolonging the inactivated state of voltage dependent $Na^+$ and $Ca^{++}$ channels

Reduces the likelihood of repetitive action potentials

Reduces neurotransmitter release

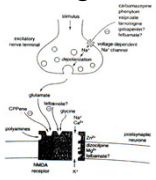
Prevents seizure spread

- Phenytoin
- Carbamazepine
- Oxcarbazepine
- Valproate
- Lamotrigine

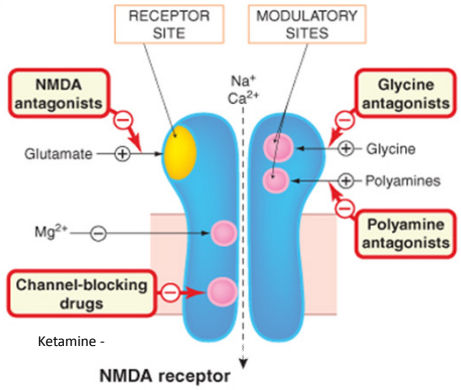



## Inhibiting the effects of the excitatory neurotransmitter, Glutamate, by modulating NMDA (and AMPA) receptors

- Glutamate binds to NMDA receptor
- Opens ligand–gated $Na^+$ and $Ca^{++}$ channels
- Causes genesis and propagation of high frequency discharges
- Felbamate
- Topiramate



GLUTAMATE binds to NMDA receptor: Excitatory






## Enhancing the effects of the inhibitory neurotransmitter, GABA

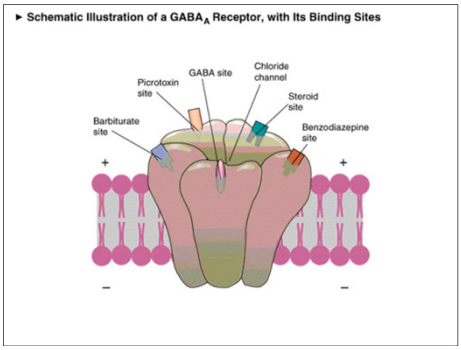
- GABA opens receptor operated Chloride channels
- of the GABA receptor-channel complex:
- Thereby causing hyperpolarisation
- Therefore causing a suppression of discharges

## GABA receptor-channel complex:

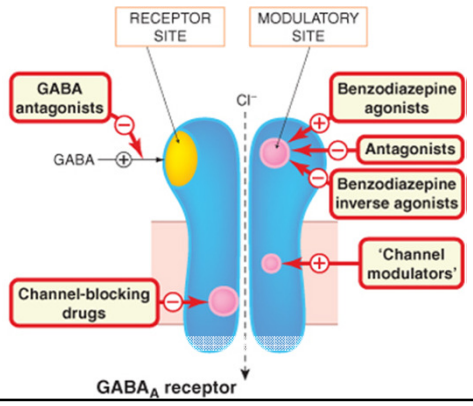
1. **GABA site:**
   Vigabatrin increases GABA by inhibiting GABA transaminase

2. **Benzodiazepine recognition site:**
   Diazepam, Clonazepam

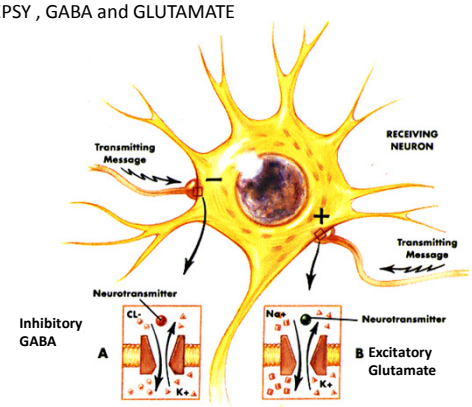
3. **Barbiturate recognition site**
   Phenobarbitone



GABA binds to GABA receptor complex: neuro-inhibitory




EPILEPSY , GABA and GLUTAMATE




## Treatment considerations

1. Type of epilepsy
   - Partial
   - Generalised
2. Age of patient: adult vs child
3. Efficacy of drug
4. Tolerability of drug
5. Side effects
   1. Toxicity
   2. Drug interactions

## Treatment considerations

1. Many older drugs are enzyme inducers which have pharmacokinetic implications in combination therapy as well as hormonal consequences:
   1. Sex steroids hypermetabolised: reproductive dysfunction, OCP failure
   2. Vit D hypermetabolised: osteopaenia
2. Valproic Acid is an enzyme inhibitor
3. Most newer agents have little / no effect on CYP450

## Treatment considerations

- Newly diagnosed epilepsy:
  - Treatment responsive (2/3)
  - Treatment resistant (1/3)
- Attempt single drug: monotherapy highly recommended
- Increase dose until
  - Seizure free
  - Toxicity
    - Clinical
    - Plasma levels

## Treatment considerations

- Discontinue treatment slowly (withdrawal seizures and status epilepticus)
- Introduce 2$^{nd}$ drug while withdrawing the first
- Combination (add-on) Rx in non-responders
  - Increases the likelihood of overall drug toxicity
  - Compounds effects of drug interactions
  - Jeopardises patient compliance

## Traditional Drugs

- Tried and tested
- Broad familiarity
- Lower cost
- Long term experience
- Have complex pharmacokinetics, tolerability issues:

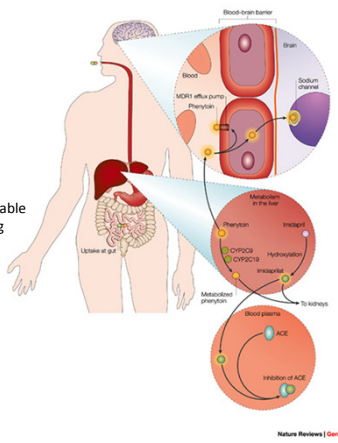
1. Phenytoin
2. Carbamazepine
3. Phenobarbital
4. Primidone (prodrug of phenobarb, rarely used)
5. Valproic Acid (enzyme inhibitor)
6. Ethosuximide (absence seizures)

## Phenytoin

- Indications:
  - Generalised
  - Partial
  - Status epilepticus (iv)
- Complex saturation pharmacokinetics
- Therapeutic Drug monitoring useful
  - Low therapeutic index
- Numerous adverse effects

## Phenytoin pathway

Absorption: variable
Protein binding: 95%
Half life: 7-60 hrs
Liver metabolism: saturable
Entero-hepatic recycling
Excretion: renal




## Phenytoin pharmacokinetics

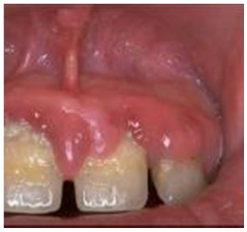
- Enormous inter-individual variation : individualise the dose
- 50 fold variation in steady state [plasma]
  - Age: increased clearance (decreased p binding / decreased p albumin)
  - Reduced protein binding in uraemia, pregnancy, elderly and displacement by Valproate
  - Body weight
  - **Saturable hepatic metabolism** is under polygenic control ; small increase in dose may lead to unpredictable increase in [plasma] with toxicity
- Once daily dosing is used in chronic therapy
- Metabolism is induced by concurrent carbamazepine, and inhibited by cimetidine
- Therapeutic Drug monitoring (10-20mg/L)
  - Start 2 weeks after Rx commences
  - Increase dose by tiny increments (<50mg) every 4-6 weeks

## Phenytoin Adverse effects

- Nervous system:
  1. Cerebellar syndrome (ataxia, nystagmus, dysarthria, tremor)
  2. Involuntary movements
  3. Sedation
  4. Psych. Disturbances
- Allergic effects (with cross sensitivity to Carbamazepine):
  1. Rashes
  2. Drug fever
  3. Hepatitis
- Heart:
  1. Too rapid IV infusion causes arrhythmias, cardiovascular collapse, respiratory arrest (>50mg/min)

## Phenytoin Adverse effects

- Skin and collagen:
  1. Coarse facial features
  2. Gum hypertrophy
  3. Acne
  4. Hirsuitism
- Haematological effects:
  1. Macrocytic anaemia (folate)
  2. Aplastic anaemia
  3. Lymphadenopathy
- Effects on fetus:
  1. Perinatal mortality
  2. Cleft palate
  3. Microcephaly
  4. Congenital heart disease



## Carbamazepine

- Indications:

1. Partial seizures : simple and complex
2. Generalised seizures (excluding absence and atonic)

1. Trigeminal neuralgia and other chronic pain syndromes
2. Prophylaxis of mood swings in B.A.D
3. Intractable hiccups
4. Chronic dystonic disorders
5. Neurohypophyseal Diabetes Insipidus

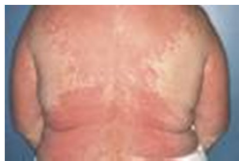
- structurally related to TCAs

## Carbamazepine pharmacokinetics

- Slowly but well absorbed following oral administration
- Plasma levels fluctuate widely during absorption
- Half life
  - After single dose: 25-60hrs
  - After chronic dosing: 10hrs (enzyme induction)
- Controlled release preparations reduce peak plasma concentration (dizziness, drowsiness, diplopia) and fluctuations
- 75% bound to plasma proteins
- Therapeutic Drug monitoring useful (4-12mg/L) to ascertain:
  - Compliance
  - Rapid metabolism
  - Drug failure

## Carbamazepine adverse effects

- Common, but seldom severe , occur when levels > 8.5mg/L:
  - Sedation
  - Ataxia
  - Dizziness
  - Nystagmus, blurred vision
  - Slurred speech
- Rash
- Rare blood dyscrasias
- Cholestatic jaundice
- Renal impairment
- Lymphadenopathy
- Hyponatraemia and water intoxication (AD action)



## Carbamazepine
### Drug interactions

- Should not be combined with MAOI
- Potent enzyme inducer
  - Warfarin
  - Theophylline
  - Oral contraceptive
  - Other anticonvulsants
- Contra-indicated in
  - AV abnormalities,
  - porphyria,
  - pregnancy (neural tube defects, hypospadias)

## Phenobarbitone (barbiturate)

- Indications:
  - Generalised
  - Partial seizures
- Used as second line because
  - Adults: too sedative
  - Children: behavioural disturbances
- Tolerance occurs
- relationship between plasma levels and therapeutic / adverse effects less predictable
  - Monitoring plasma levels not as useful as in phenytoin

## Phenobarbitone
## Other adverse effects:

- Rashes
- Anaphylaxis
- Folate deficiency
- Aplastic anaemia
- Rickets and osteomalacia
- Congenital abnormalities

## Sodium Valproate

- Indications:
  - Partial
  - Generalised epilepsy
- Pharmacokinetics:
  - Well absorbed 95-100% bioavailability
  - Slow onset of action (2-3 days)
  - Highly (p)protein bound (it is a fatty acid)
  - Inter-individual variation of free drug
  - Half life 7-10hrs
  - Active metabolites account for long course of action
  - Brain: plasma ratio is low. Large doses needed
  - [plasma] do not correlate with efficacy
  - Enzyme inhibition

## Sodium valproate adverse effects

- Nausea, vomiting, abdo pain
- Enhancement of sedatives
- Thrombocytopaenia
- Hair loss
- Teratogen
- Rare hepatic necrosis, acute pancreatitis

## Ethosuximide

- One of the succinimides
- Drug of choice in absence seizures
- (not effective in tonic-clonic)
- Continued into adolescence, then gradually withdrawn over a period of months
- Adverse effects:
  - Dizziness
  - Nausea
  - Abdominal pain
  - Blocks T-type voltage gated Ca channels

## Ethosuximide pharmacokinetics

- Oral
- Well absorbed
- Given o.d
- (p) half life:
  - 70hrs adults
  - 30hrs children
- Steady state: 7 days
- Extensive hepatic metabolism
  - 2 inactive metabolites
- Protein binding not significant
- [CSF]=[plasma]

## Newer anticonvulsants

- Equal efficacy
- Better tolerability
- Lack of clinical data
- Lack of experience

1. Gabapentin
2. Lamotrigine (+ absence)
3. Topiramate
4. Vigabatrin
5. (Oxcarbazepine)
6. (Levetiracetam)

## Gabapentin

- Licensed for ‘add on’ therapy for partial seizures
- But effective monotherapy for treatment of newly diagnosed partial and generalised epilepsy
- GABA analogue, but thought to act on ligand gated Ca channels!
- Well tolerated
- Adverse effects include somnolence, weight gain, peripheral oedema

## Gabapentin

- Well absorbed
- Average half life = 4-6 hours
- No interference with protein binding / metabolism of other anticonvulsants
- Renal elimination 100%

## Lamotrigine

- Prolongs inactivated state of Na channels and inhibits glutamate release
- Can be used as monotherapy or adjunctive therapy in
  - Partial
  - Generalised
  - Absence seizures
- Contra-indicated in hepatic / renal impairment

## Lamotrigine pharmacokinetics

- Oral absorption
- 55% protein bound
- Metabolised in liver by glucuronidation (90%)
- Inactive metabolites

## Lamotrigine adverse effects

Well tolerated BUT occasionally:

- Hypersensitivity rashes: (Black box warning)
  - Stevens-Johnson
  - Toxic Epidermal Necrolysis
  - Angioedema
- Flu-like symptoms
- Dizziness
- Insomnia
- GIT disturbances
- DIC
- Aggression

## Topiramate

Attenuates neuronal excitation, rather than elevating seizure thresh-hold:

- Blocks Na channels
- Enhances GABA mediated inhibition
- Glutamate receptor antagonism

- Effective in
  - Generalised
  - Partial

- Modest dose dependent Induction of CYP3A4
  May reduce effectiveness of OCP
- Inhibition of CYP 3C19 may result in increase in [phenytoin ]
- Carbamazepine and phenytoin induce its metabolism

## Topiramate adverse effects

- Poor [ ] and memory
- Impaired speech
- Mood disorders
- Ataxia
- Somnolence
- Anorexia, taste perversion
- Weight loss
- Syndrome of acute myopia associated with 2ndary closed –angle glaucoma

## Vigabatrin

Increases brain [GABA]

- By irreversibly inhibiting GABA transaminase
- Reserved for resistant epilepsy because of significant irreversible visual defects
- Lower doses required
  - Elderly
  - Diminished renal function
- Avoid in those with psych. hx

## Vigabatrin pharmacokinetics

- Absorption not influenced by food
- [peak plasma] within 2hrs of oral dose
- NOT metabolised in liver
- Excreted unchanged via kidney
- Half life=5hrs
- Efficacy not proportional to [plasma]
- Action prolonged due to irreversible binding to transaminase

## Vigabatrin adverse effects

- Drowsiness 30%
- Fatigue, Irritability, Dizziness, Confusion
- Weight gain
- Behavioural changes
- Psychosis
- Nystagmus, ataxia, tremor
- Paraesthesias

- Ocular
  - Retinal changes
  - Visual defects (test)
  - Photophobia

## Oxcarbazepine

- Derivative of carbamazepine
- Fewer adverse effects and drug interactions
- But greater propensity to cause Na loss
- Has replaced carbamazepine as first line agent in some countries
- Effective as monotherapy in newly diagnosed
  - partial
  - Generalised
- As add on in partial

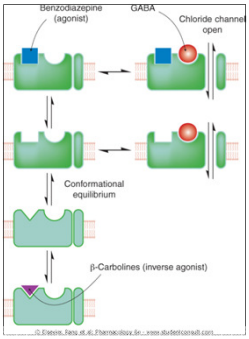
## Benzodiazepines

- Anxiolytic
- Hypnotic
- Muscle relaxant
- Anticonvulsant (not for long term use: tolerance. except clonazepam)

- Clonazepam indicated long term for:
  - Motor seizures of childhood
  - Absence
  - Infantile spasms
  - Complex partial seizures
  - Myoclonic epilepsy as add on Rx

- Status epilepticus: first line agents
  - Diazepam iv or rectal
  - Clobazepam iv
  - Lorazepam iv
  - Clonazepam (Long half life) ivi

**BENZODIAZEPINE / GABA –A RECEPTOR INTERACTION**



## Status Epilepticus
## Medical Emergency – mortality 10%

- Rapid suppression of seizure activity essential

1. IV benzo (diazepam 10mg over 5 mins, clonazepam, lorazepam) (rectal in kids)
   Remove dentures, establish airway, oxygen
2. Repeat benzo if fitting continues
   (transient resp. depression / hypotension)
3. IV phenytoin loading dose to prevent relapse
4. Identify precipitants
   hypoglycaemia,/ OH / drug OD / low [plasma]
5. ICU with anaesthetist
6. IV thiopentone /chlormethiazole / propofol
   Monitor EEG and resp. function
7. Paraldehyde rectally if no facilities

## Withdrawal of anticonvulsant drugs

- 70% pts eventually enter prolonged remission
- Gradually withdraw drugs over 6 months
- Patients should refrain from driving for 6 months thereafter

## Febrile convulsions

- Most common seizures of childhood (3%)
- Age 3 months -5 years
- 3% develop epilepsy
- Rx:
- Reduce temperature
  - Tepid bathing, fan, paracetamol, etc
- Rectal diazepam occasionally