Introduction

- 1 person in 20 will have an epileptic seizure at some time in their life
- Epilepsy is diagnosed on the basis of two or more epileptic seizures.
- Around 450,000 people in the UK have epilepsy (40 million people worldwide)
- A seizure is triggered by a sudden interruption in the brain's highly complex electro-chemical activity

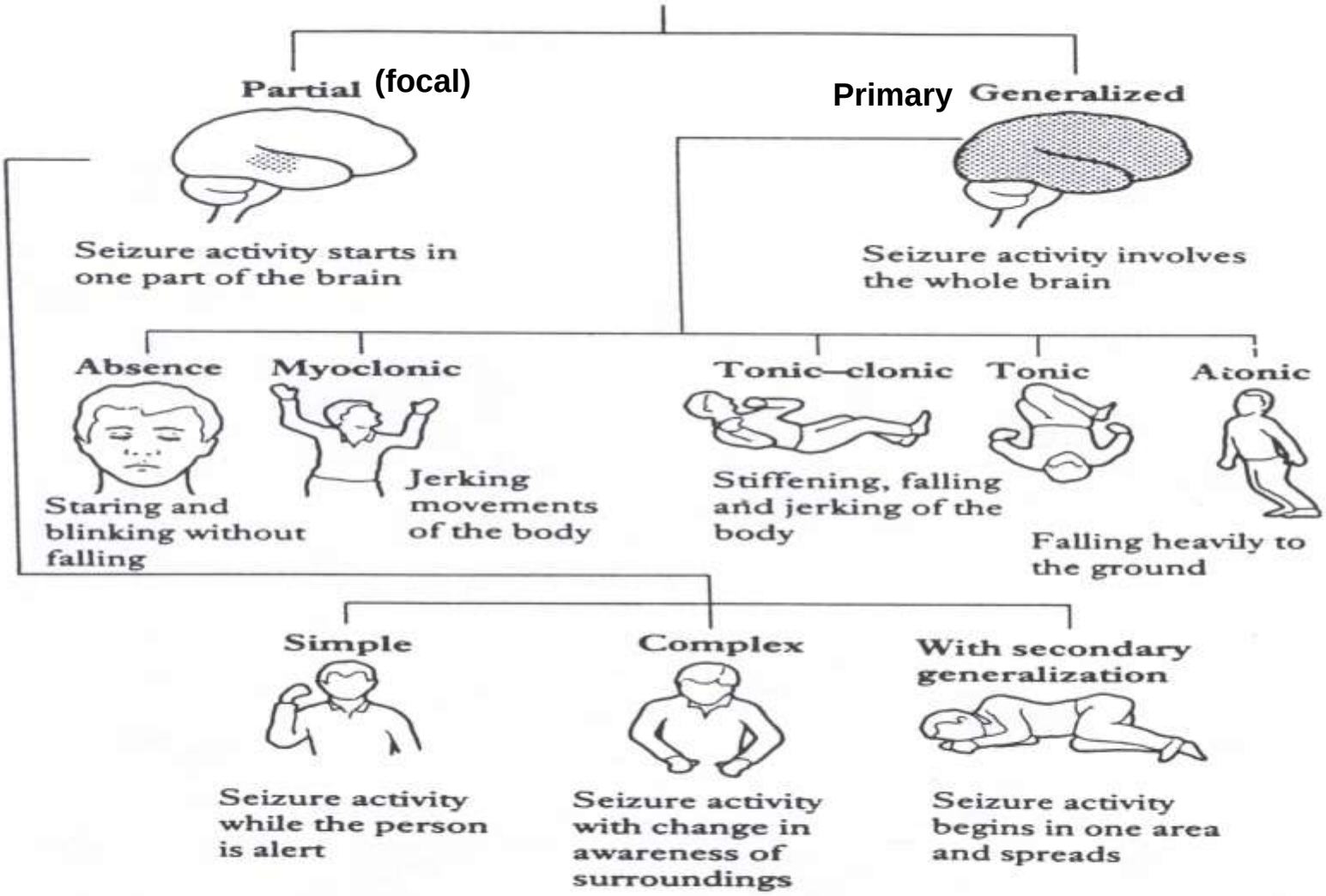
Pathological Basis

- Abnormal electrical discharge in the brain
- Coordinated activity among neurons depends on a controlled balance between excitation and inhibition
- Any local imbalance will lead to a seizure
- Imbalances occur between glutamate-mediated excitatory neurotransmission and gamma-aminobutyric acid (GABA) mediated inhibitory neurotransmission

Etiology

- Congenital defects, head injuries, trauma, hypoxia
- Infection e.g. meningitis, brain abscess, viral encephalitis
- Concussion, depressed skull, fractures.
- Brain tumors, vascular occlusion.
- Drug withdrawal, e.g. CNS depressants .
- Fever in children (febrile convulsion).
- Hypoglycemia

Types of SEIZURES



A) Focal or partial

1) Simple partial(Jacksonian)- *The electrical discharge is confined to the* ***motor area.***

2)Complex partial(psychomotor)- *The electrical discharge is confined in certain parts of the temporal lobe concerned with* ***mood*** *as well as* ***muscle.***

B) Primary generalized

1) ***Tonic- clonic****. Patient fall in convulsion & may bite his tongue & may lose control of his bladder or bowel.*

2) ***Tonic****. Some pts, after dropping unconscious experience only the tonic or clonic phase of seizure.*

3) ***Atonic (akinetic)****. Starts between the ages 2-5 yrs. The pt's legs simply give under him & drops down.*

4) ***Myoclonic*** *. Sudden, brief shock like contraction which may involve the entire body or be confined to the face, trunk or extremities.*

5) ***Absence*** *. Loss of consciousness without involving motor area. Most common in children (4-12 yrs).*

6) ***Status epilepticus (re-occuring seizure).*** *Continuous seizure without intervening return of consciousness.*

Basis of Pharmacological Rx

Most anti-epileptic agents act either by blockade of depolarisation channels (Na+ and Ca++) [increase the threshold of AP, hyperpolarization]

OR

Enhancing the activity of GABA (neurotransmission inhibition)

Current Pharmacotherapy

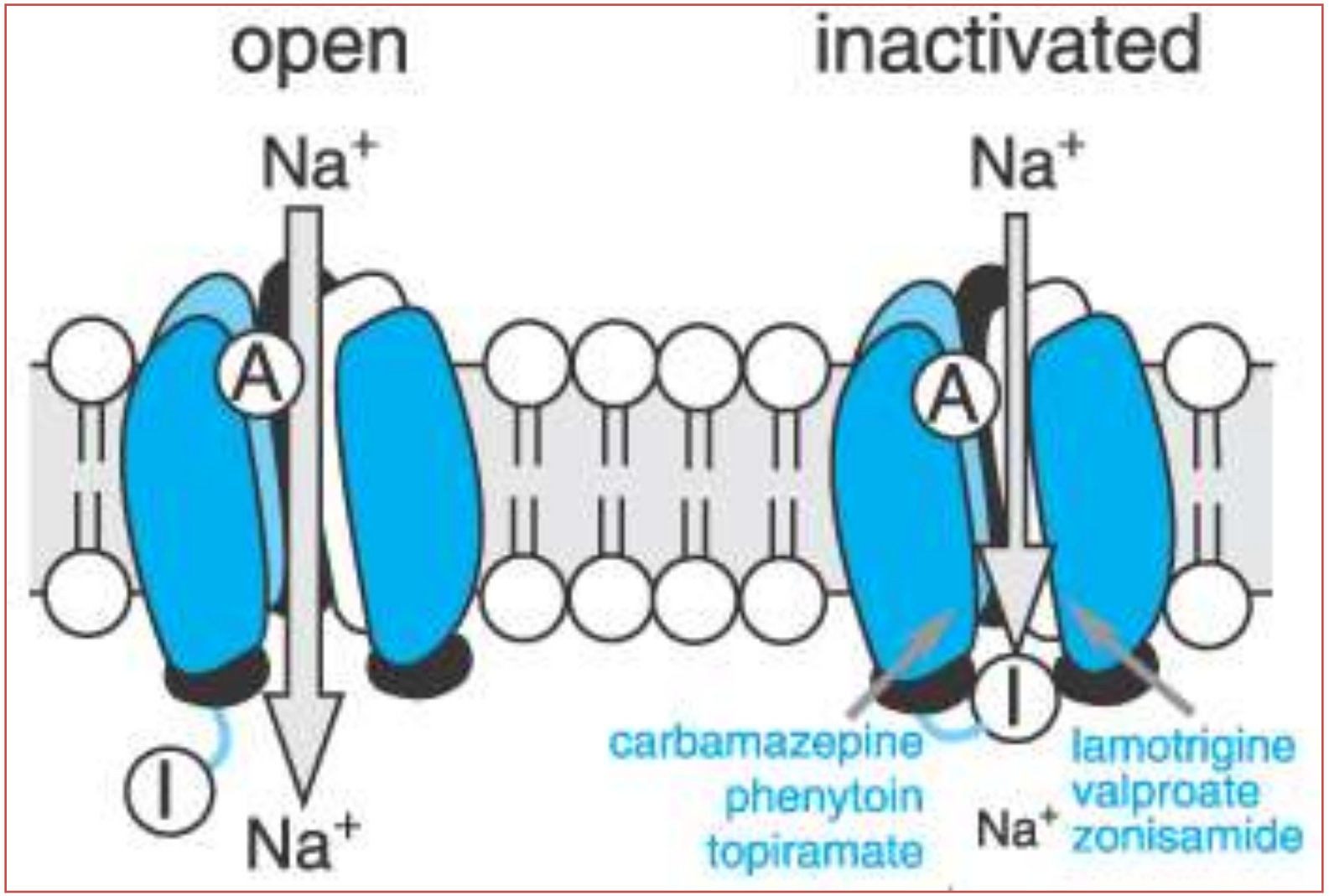
- Just under 60% of all people with epilepsy can become seizure free with **drug therapy**
- In another 20% the seizures can be drastically reduced
- ~ 20% epileptic patients, seizures are refractory to currently available drugs.
- Because of overlapping mechanisms of action, best drug can be chosen based on minimizing side effects in addition to efficacy

5 Categories of Anti-epileptic Drugs

- All classifications are based upon chemistry:
  - Hydantoins
  - Succinimides
  - Benzodiazepines
  - Barbiturates
  - Miscellaneous

Hydantoins - Phenytoin

- **First-line for partial seizures; some use for tonic-clonic seizures**
- Antagonism (blocking) of Na+ channels to reduce excitability and increase the duration of inactivation.
- Highly bound to plasma proteins – displaced by Valproate;
- Induces P450 resulting in increase in its own metabolism,



Antiseizure drugs, enhanced Na^+ channel inactivation

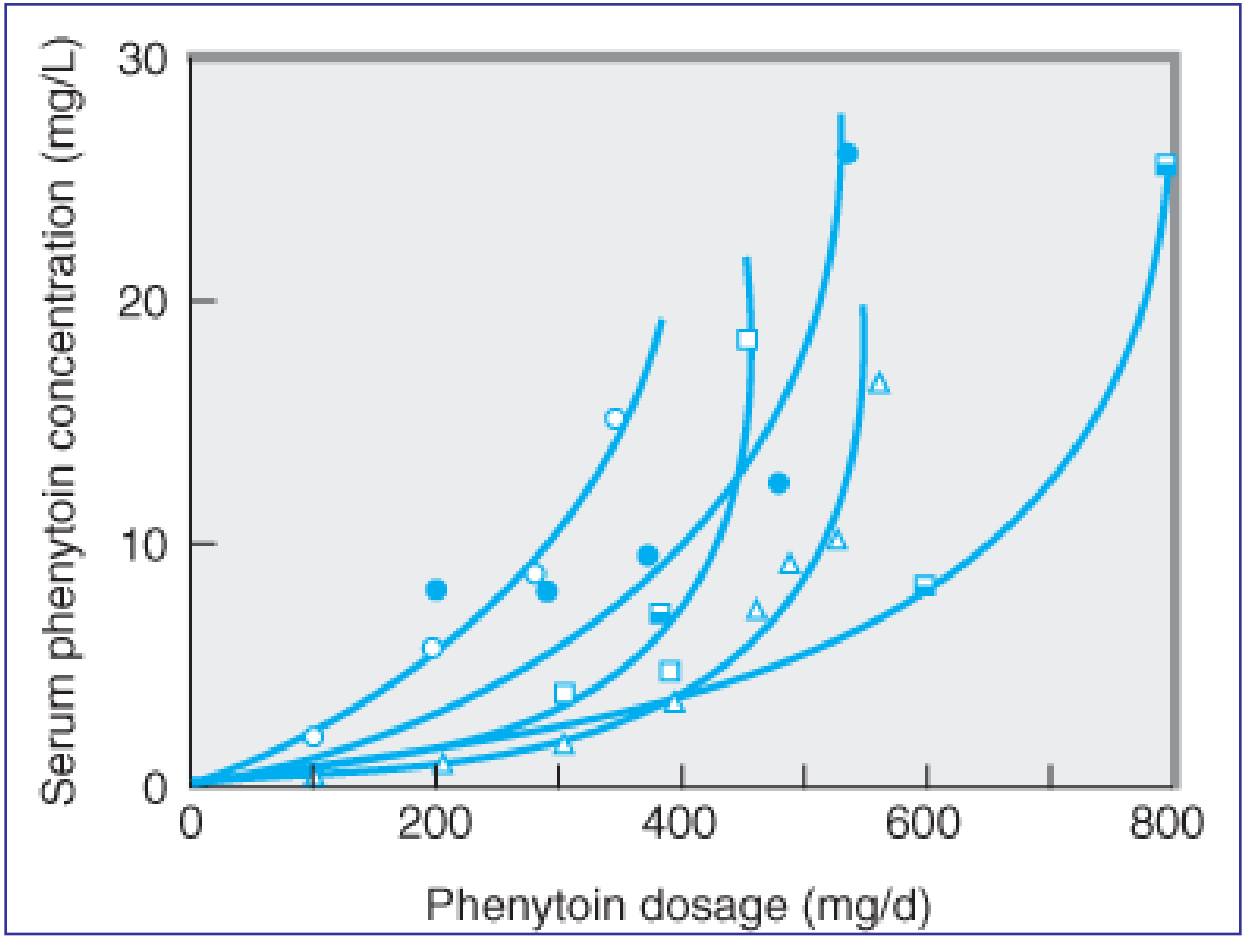
Narrow therapeutic index

- Adverse effects:
  - Nausea & Vomiting
  - Impaired brainstem & cerebellar function (dizziness, tremor, nervousness, blurred vision, **nystagmus**) .
  - Skin rashes
  - Folic acid and Vit. D deficiency

- Interaction: increases metabolism of the contraceptive pill, anti-coagulants, and pethidine

Excretion saturation

- Excretion saturation of these drugs means that when you increase the dose by a certain amount, the conc in the blood increases severely.



Nonlinear relationship of phenytoin dosage and plasma concentrations. Five different patients (identified by different symbols) received increasing dosages of phenytoin by mouth, and the steady-state serum concentration was measured at each dosage. The curves are not linear, since, as the dosage increases, the metabolism is storable. Note also the marked variation among patients in the serum levels achieved at any dosage.

Phenytoin

- Not used in treatment of pure absence seizures due to risk for increasing frequency of seizures.

Gingival hyperplasia is a common problem observed during the first 6 months of phenytoin therapy appearing as gingivitis or gum inflammation.

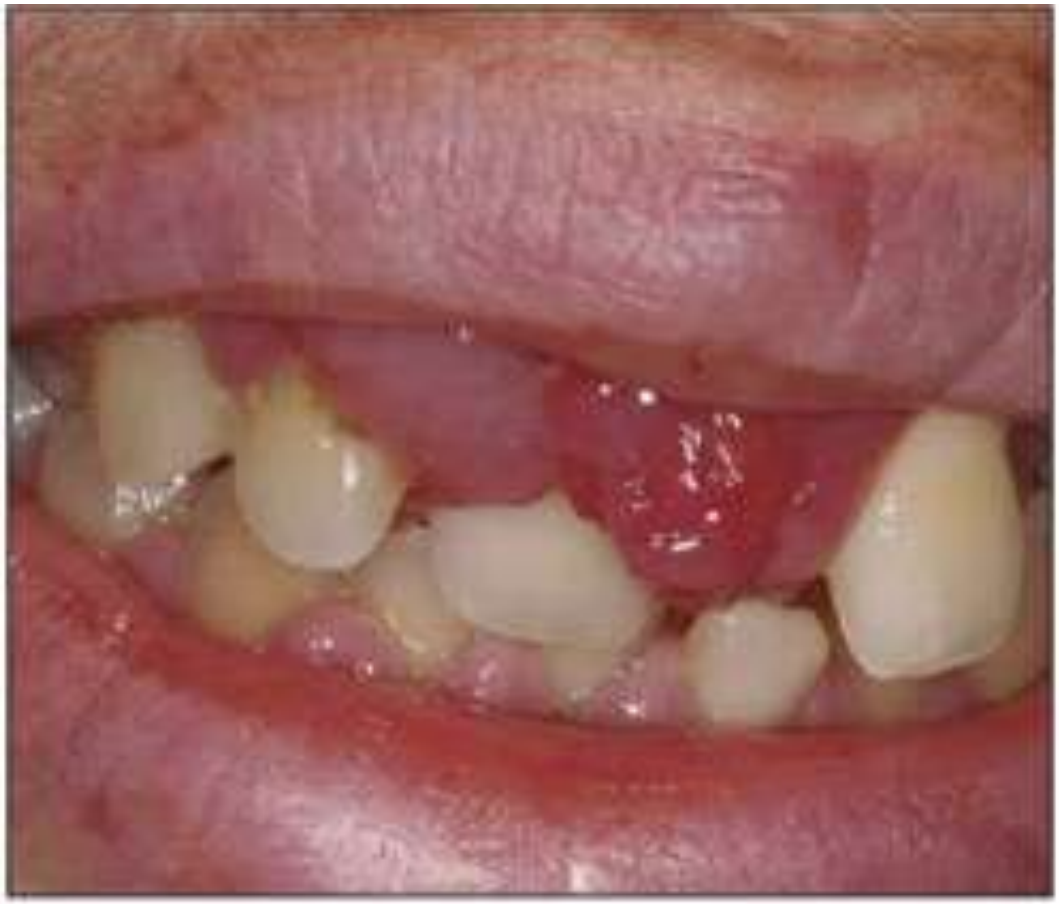


Fig. 1. The enlarged gingiva covers most of the anterior teeth and protrudes from the mouth.

Table 2. Abbreviated table of CYP-450 enzyme substrates, inducers and inhibitors

CYP isoform	Substrates	Inducers	Inhibitors
CYP1A2	**Anti-Alzheimer**: tacrine **Antiasthmatic**: theophylline **Antidepressants**: fluvoxamine, imipramine **Antipsychotics**: clozapine, halperidol	**Antibiotic**: rifampin **Anticonvulsant**: carbamazepine **Foods**: char-grilled meats **Recreational drug**: tobacco	**Antibiotics**: ciprofloxacin, erythromycin, ofloxacin **Antidepressant**: fluvoxamine
CYP2C9	**Angiotensin-2 receptor blockers**: ibresartan, losartan **Anticoagulant**: warfarin **Anticonvulsant**: phenytoin **Hypoglycemics**: glipizide, glyburide, tolbutamide **Non-steroidal anti-inflammatory drugs**: diclofenac, ibuprofen, naproxen	**Antibiotic**: rifampin **Barbiturates**: phenobarbital, secobarbital	**Antibiotic**: metronidazole **Antidepressants**: fluvoxamine, paroxitene, sertraline **Antifungal**: fluconazole
CYP2D6	**Antidepressants**: amitriptyline, desipramine, imipramine, paroxitene **Antipsychotics**: halperidol, risperidone **Beta-blockers**: metoprolol, propranolol, timolol **Narcotic analgesics**: codeine, hydrocodone, tramadol	**Antibiotic**: rifampin **Corticosteroid**: dexamethasone	**Antidepressants**: fluoxetine, paroxitene, sertraline **Antiarrhythmic**: amiodarone **H1 receptor blockers**: hydroxyzine, promethazine
CYP2E1	**Alcohol**: ethanol **General anesthetics**: enflurane, halothane, isoflurane, sevoflurane **Muscle relaxer**: chlorzoxazone **Non-narcotic analgesic**: acetaminophen	**Antibiotic**: isoniazid **Recreational drugs**: ethanol, tobacco	**Alcoholism rehabilitation agent**: disulfiram
CYP3A4	**Antibiotics**: clarithromycin, erythromycin **Anticoagulant**: warfarin **Anticonvulsant**: carbamazepine **Antipsychotics**: haloperidol, pimozide **Benzodiazepines**: alprazolam, diazepam, midazolam, triazolam **Calcium channel blockers**: amlodipine, diltiazem, felodipine, verapamil **Cholesterol-lowering drugs**: atorvastatin, cerivastatin*, lovastatin, simvastatin **Corticosteroids**: hydrocortisone, methylprednisolone **H1 receptor blockers**: astemizole*, terfenadine* **HIV protease inhibitor**: idinavir, nelfinavir, ritonavir, saquinavir **Hormonal agents**: estrogens, progestins **Immunosuppressants**: cyclosporine, tacrolimus **Local anesthetic**: lidocaine **Prokinetic agent**: cisapride*	**Antibiotic**: rifampin **Anticonvulsants**: carbamazepine, phenytoin **Barbiturates**: phenobarbital, secobarbital **Corticosteroids**: dexamethasone, hydrocortisone, prednisolone, methylprednisolone **Herbal remedy**: St John's wort **HIV reverse transcriptase inhibitors**: efavirenz, nevirapine **Hypoglycemics**: pioglitazone, troglitizone	**Antibiotics**: clarithromycin, erythromycin **Antidepressants**: fluvoxamine, nefazodone **Antifungals**: clotrimazole, fluconazole, itraconazole, ketoconazole **Calcium channel blockers**: diltiazem, verapamil **Foods**: Grapefruit juice, Seville oranges **H2 receptor blocker**: cimetidine **HIV protease inhibitors**: idinavir, nelfinivir, ritonavir, saquinavir

HIV, human immunodeficiency virus; H1, histamine H1; H2, histamine H2.
*Removed from U.S. marketplace.

Carbamazepine (A)

- Used for partial seizures; some use in tonic-clonic seizures.
- Antagonist action of Na+ channels to inhibit repetitive neuronal firing
  - Decreasing the production (or release) of glutamate (excitatory chemical)

- Can also be used in the treatment of neuropathic pain

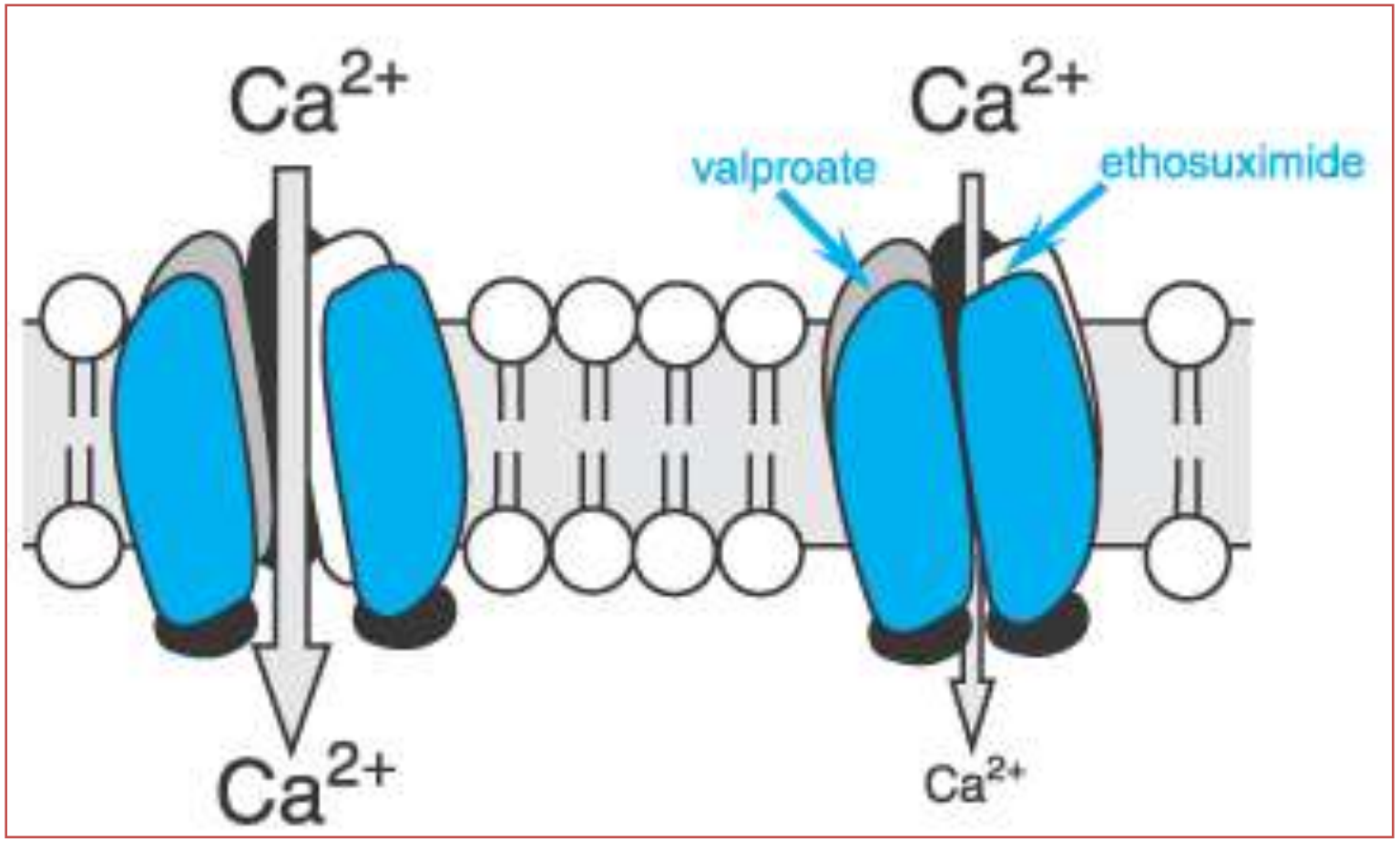
Trigeminal neuralgia. Drug of choice.

Carbamazepine

- Adverse effects:
  - Nausea & vomiting (especially early Rx), constipation, diarrhoea and anorexia
  - Skin irritation
  - **CNS toxcity –** Sedating, **dizzy, drowsy, confusion**
  - Bone marrow depression (rare)

Succinimides – Ethosuximide

- **First choice** Use for patients with **Absence** seizures
- Carbamezipine and Phenytoin are contraindicated.
- Acts specifically on T-type channels in thalamus, and is very effective against absence seizures.
- Absence seizures are caused by oscillations between thalamus and cortex that are generated in thalamus by T-type (transient) Ca^{2+} currents



Antiseizure drugs, induced reduction of current through T-type Ca^{2+} channels.

Ethosuximide

- Adverse effects: Slightly wider therapeutic index
  - Nausea, vomiting and anorexia
  - Cerebellar disturbance (drowsiness, dizziness, photophobia, headache, depression)
  - Skin irritation
  - Not to be used when pregnant (teratogencity)

Sodium Valproate (valproic acid)

- Use in all forms of epilepsy, as it suppresses the initial seizure discharge and its spread.

- First-line for generalized seizures, also used for partial seizures

- K+ channels have important inhibitory control over neuronal firing in CNS—repolarizes membrane to end action potentials

K+ channel agonists would decrease hyperexcitability in brain

- So far, the only Antiepileptic drug with known actions on K+ channels is valproate

- Also blocks Na+ channels and enhances GABAergic transmission (highly pleiotropic*)

Narrow therapeutic index

- Adverse effects:
  - GI upset (Nausea, vomiting, anorexia, abdominal pain and diarrhoea)
  - **Weight gain (appetite stimulation)**
  - Transient hair loss
  - Tremor
  - Coma (rare)
  - Thrombocyptopenia (platelets)
  - Oedema
  - **Severe hepatotoxicity (liver damage)**

- Contraindications: People with liver damage or a history hepatic dysfunction

LAMOTRIGINE (much wider therapeutic window)

- Act Primarily on Na+ Channels also nhibits excitory neurotransmitter glutamate.

- Lamotrigine is effective for the treatment of partial and secondarily generalized tonic-clonic seizure.

- It is generally well tolerated but may cause serious **ARs** of the skin,

- Including Stevens–Johnson syndrome (severe rash).

Gabapentin (Neuronitin)

- Used for partial seizures in adults
- Designed to be a structural analogue of GABA but it does not mimic GABA in the brain.
- Acts via:
  - **Increased synthesis and release of GABA**
  - Decrease degradation of GABA
  - Inhibition of Ca++ channels

Add-on drug not suitable as a single agent

Now used as an analgesic (inhibits neuronal pain) in Migraine

Topiramate

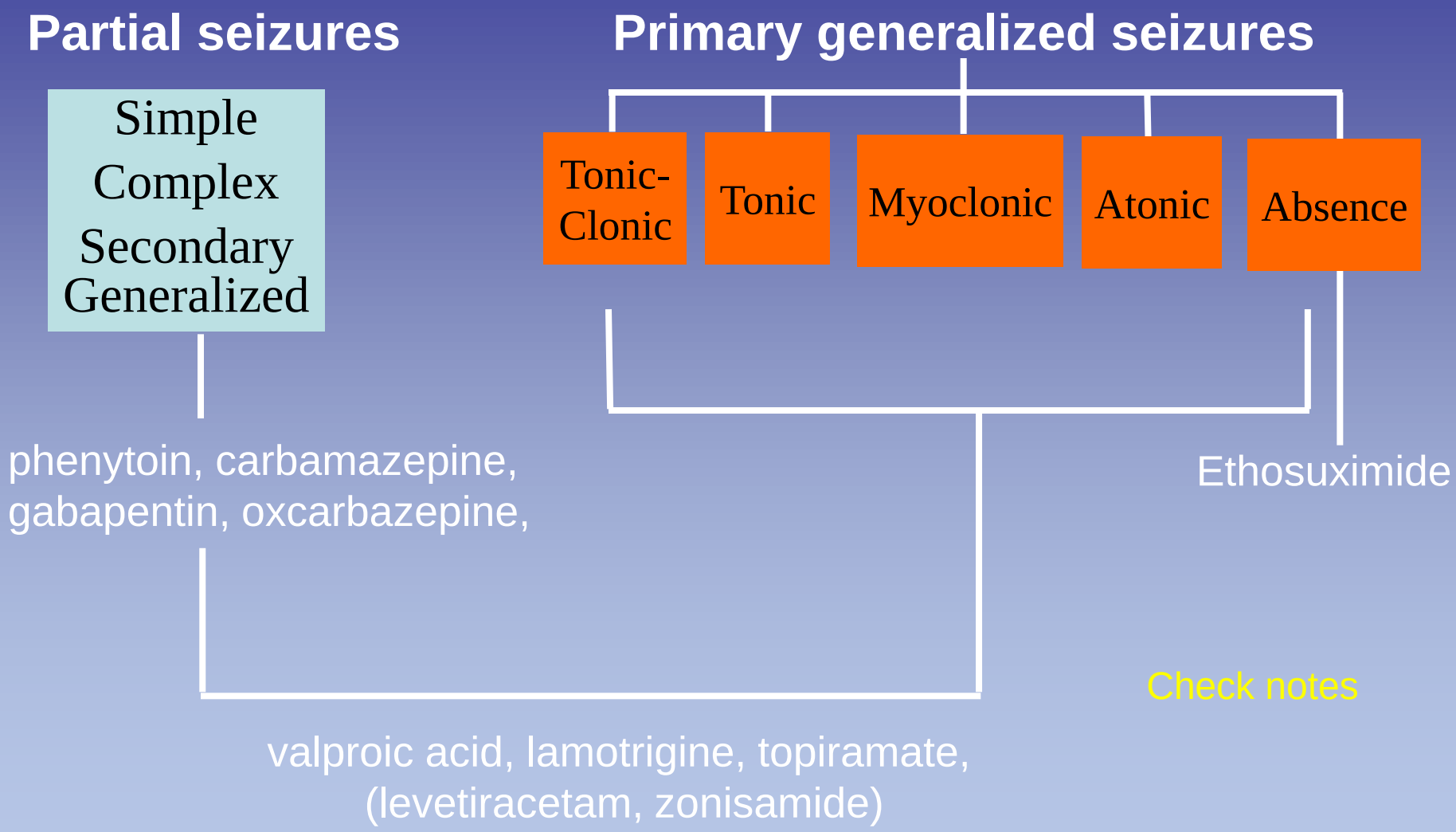
- Acts on AMPA receptors, blocking the glutamate binding site, *but* also blocks kainate receptors and Na+ channels, and enhances GABA currents (highly pleiotropic*)

- Used for partial seizures, as an adjunct for absence and tonic-clonic seizures (add-on or alternative to phenytoin)

- Very long half-life (20h)

Drugs	Grand mal	Status epilepticus	Petit mal (absence seizure)	Partial seizure
Carbamazepine (p.o.)	++		contraindicated	+++
Clonazepam (p.o./i.v.)	+	+	++	
Diazepam (p.o./i.v.)		+		
Ethosuximide (p.o.)			+++	+
Lamotrigine (p.o.)	+++		+++	++
Lorazepam (i.v.)		+		
Midazolam (i.v.)		++		
Oxacarbazepine (p.o.)	++			+++
Phenobarbital (p.o./i.m.)	+	+++	contraindicated	
Phenytoin (p.o./i.v.)	+	+++	contraindicated	++
Topiramate (p/o.)	+			++
Valproic acid (p.o.)	+++		+++	++

AED Treatment Options



Treatment:

- *Up to 80% of pts can expect partial or complete control of seizures with appropriate treatment.*
- *Antiepileptic drugs suppress but do not cure seizures*
- *Antiepileptics are indicated when there is two or more seizures occurred in short interval (6m -1 y)*
- *An initial therapeutic aim is to use only one drug (monotherapy).*

Addition of a second drug is likely to result in significant improvement in only approx. 10 % of patients.

- *The sudden withdrawal of drugs should be avoided*

withdrawal may be considered after seizure- free period of 2-3 or more years

- *Relapse rate when antiepileptics are withdrawn is 20 - 40 %/*

When to Withdraw Antiepileptic Drugs?

Normal neurological examination

Seizure- free for 2-5 yrs or longer