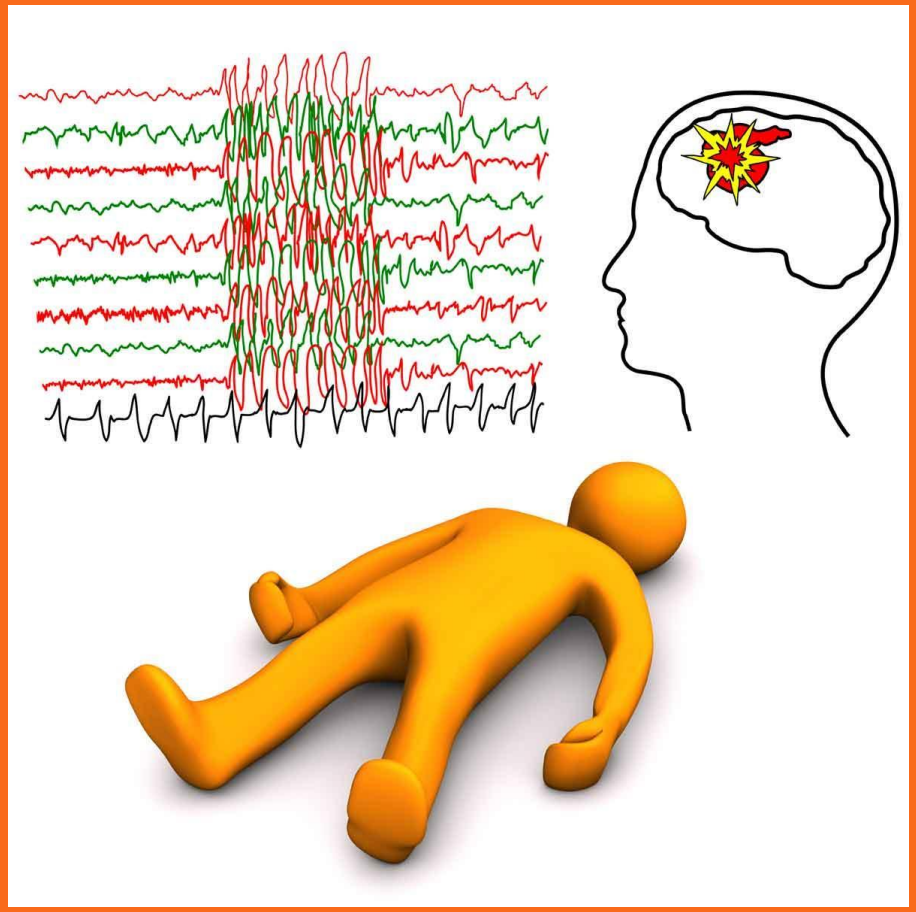
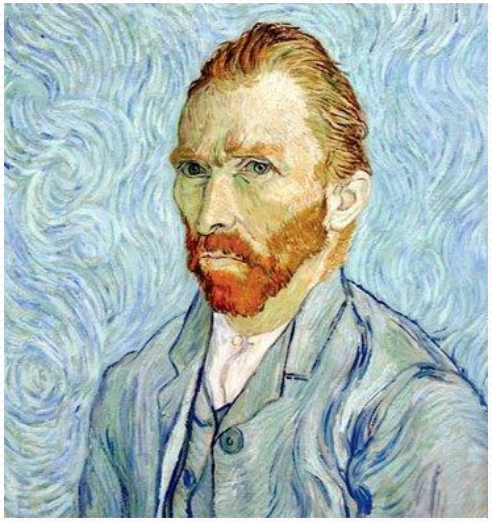
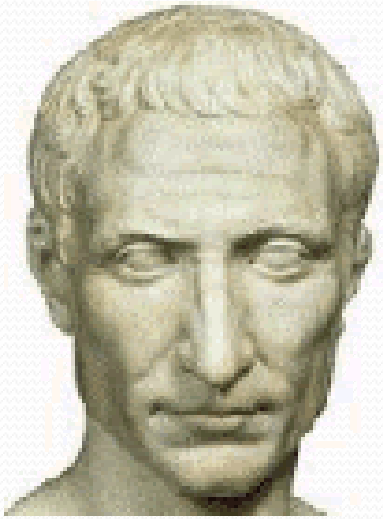
Epilepsy and Treatment

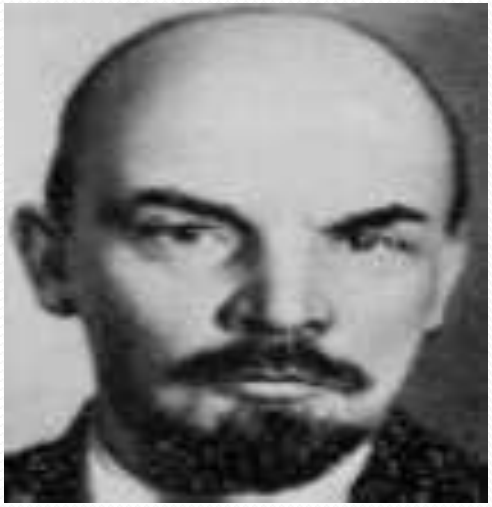


Cathy Lynch
UP 2019

Who am I? - Famous people with epilepsy







Objectives

Learning Outcomes:

- Overview of Epilepsy
- Use cases to:
  - Discuss clinical use of anti-epileptic medicines(AEMs)
  - Consider factors influencing drug selection
  - Identify ADRs and areas of concern for AEMs
  - Identify monitoring required for patients taking AEMs

Epilepsy

- Lifetime prevalence of epilepsy between 2- 5%
- Incidence
  - highest in first 10 years of life
  - declines through to 50 years
  - then increases after 50 years
- Begins before the age of 20 in more than 50% of patients
- Sri Lanka: In a survey in the Kandy district of Sri Lanka, it was observed that 9 out of 1000 people had epilepsy.

Seizures

- Seizure activity arises from the cerebral cortex due to abnormal high frequency discharge of neurone group
- Signs and symptoms of the seizure depend on the area of brain involved
- May involve motor, sensory or behavioural areas of brain

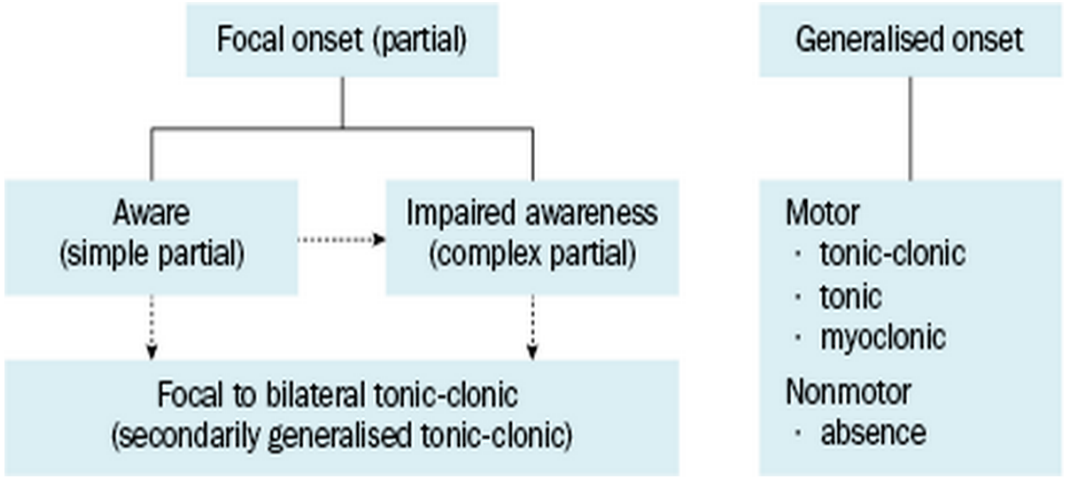
Seizure types

- **Tonic clonic** – stiffening, LOC, fall and jerking lasting 2 minutes- can have cyanosis, tongue biting and urinary incontinence – post ictal confusion and amnesia
- **Absence** – frequent,b rief behavioural arrest without motor features with immediate recovery at end
- **Myoclonic -** single jerks of muscles, usually generalised, occurring during wakefulness- most patients do not recognise these as seizures
- **Focal** - confined to one cerebral hemisphere- motor, somatosensory, autonomic, visual, auditory and experiential/psychic disturbances. Seizures can be with or without impairment of consciousness (simple or complex partial seizures, respectively)

Seizure classification TG

Topic | Therapeutic Guidelines

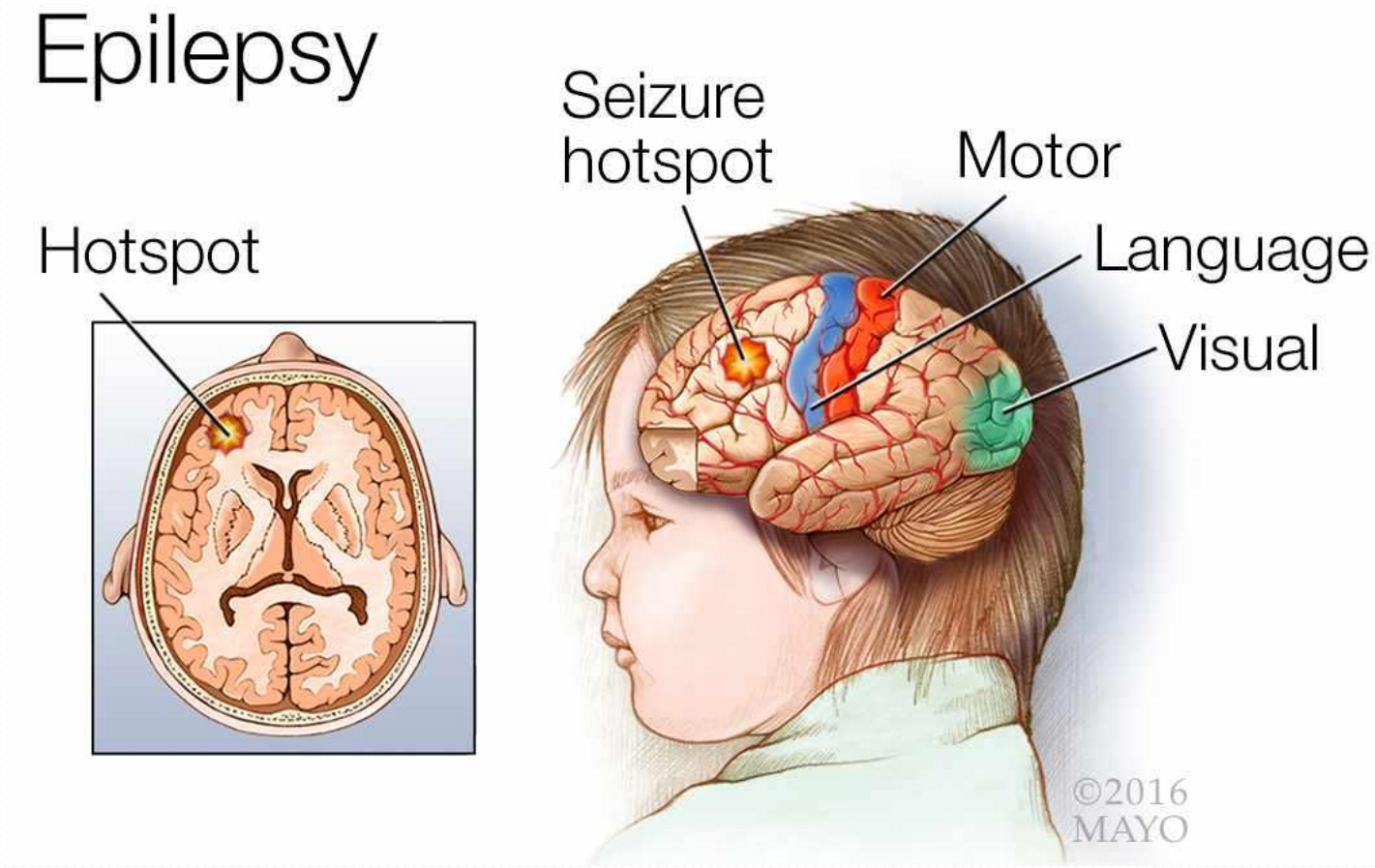
Classification of seizure types (Figure 7.1) [NB1] [NB2]



NB1: Adapted with permission from Fisher RS, Cross JH, D'Souza C, French JA, Haut SR, Higurashi N, et al. Instruction manual for the ILAE 2017 classification of seizure types. Epilepsia 2017; 58(4):531-542. Wiley Periodicals, Inc. © 2017 International League Against Epilepsy [URL]

NB2: Dotted lines with arrows show that a seizure can start as one type, then evolve to another type as it propagates through the brain. Terms in are older terms.

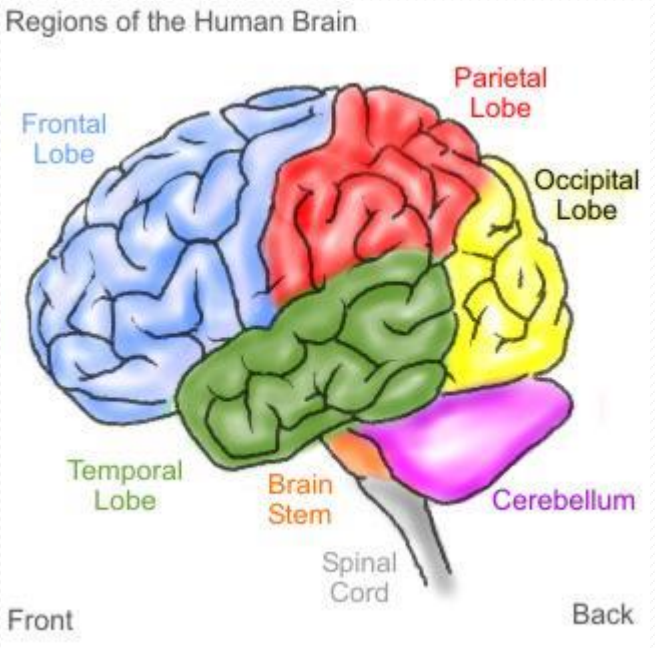
Can you think of any causes of seizures?



Common causes of seizures

Primary or acquired neurological causes

- Febrile seizures of childhood
- Genetic or developmental disorders
- Idiopathic epilepsies
- Head trauma
- Cerebrovascular disease
- Brain tumour
- CNS infection
- Neurodegenerative disease e.g. Alzheimer's

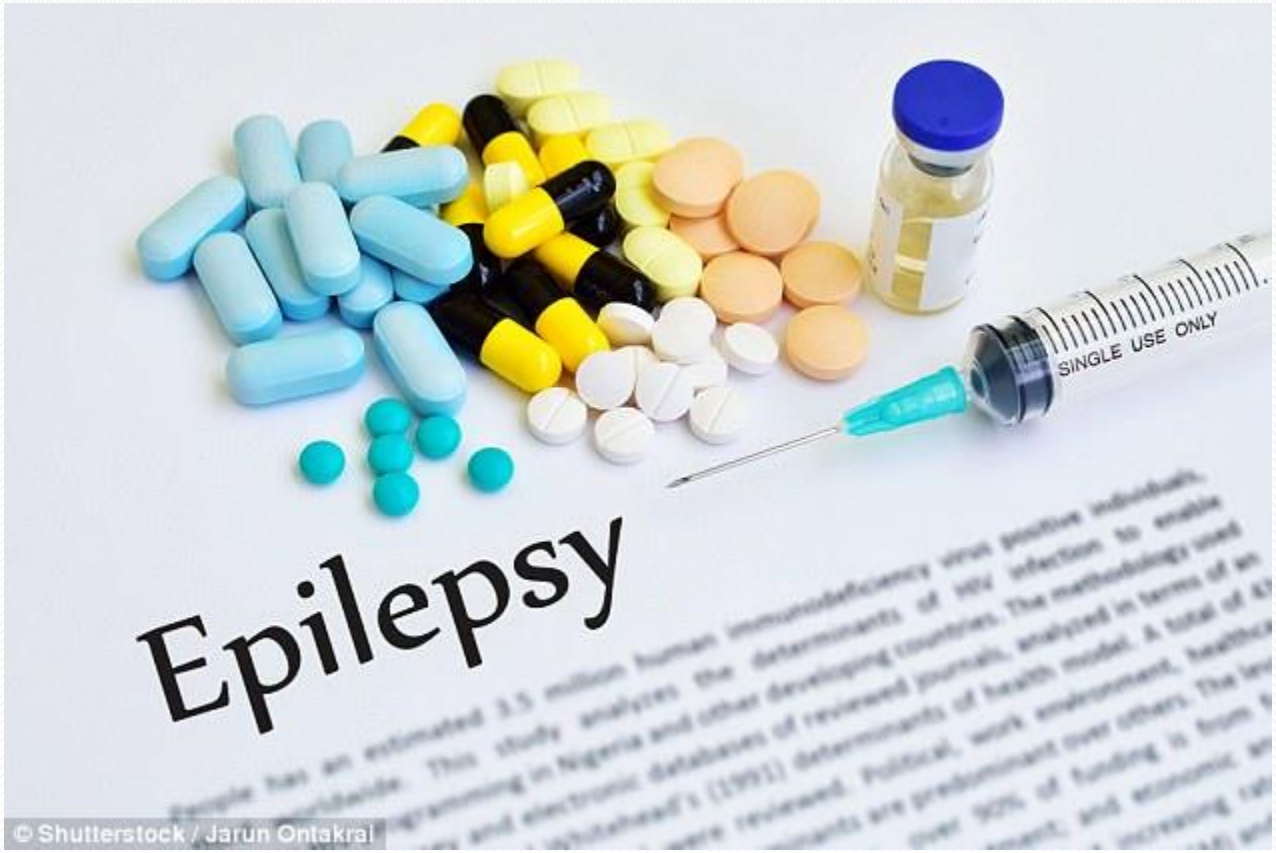


Common causes of seizures

Systemic or metabolic disorder

- Electrolyte disorders
- Liver failure
- Renal failure
- Alcohol abuse/withdrawal
- Eclampsia
- Porphyria
- Anoxia or ischaemia
- Drug overdose or drug toxicity

Can you think of any DRUG causes of seizures?

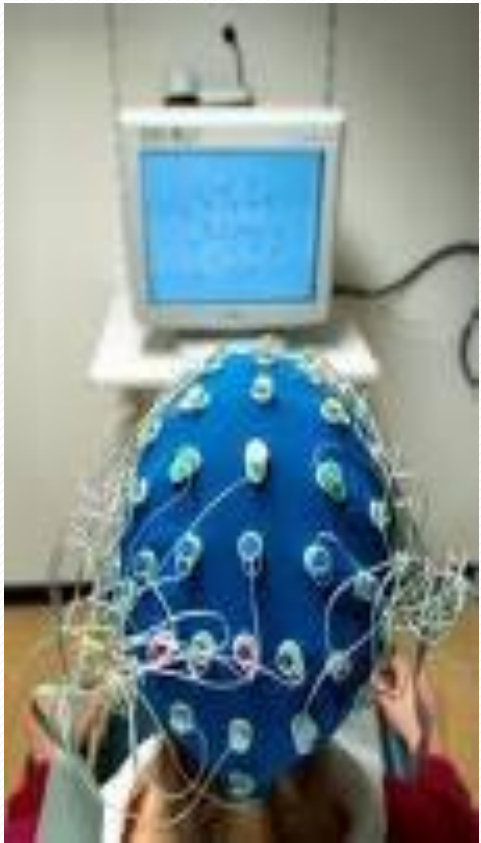


Drugs that may cause seizures

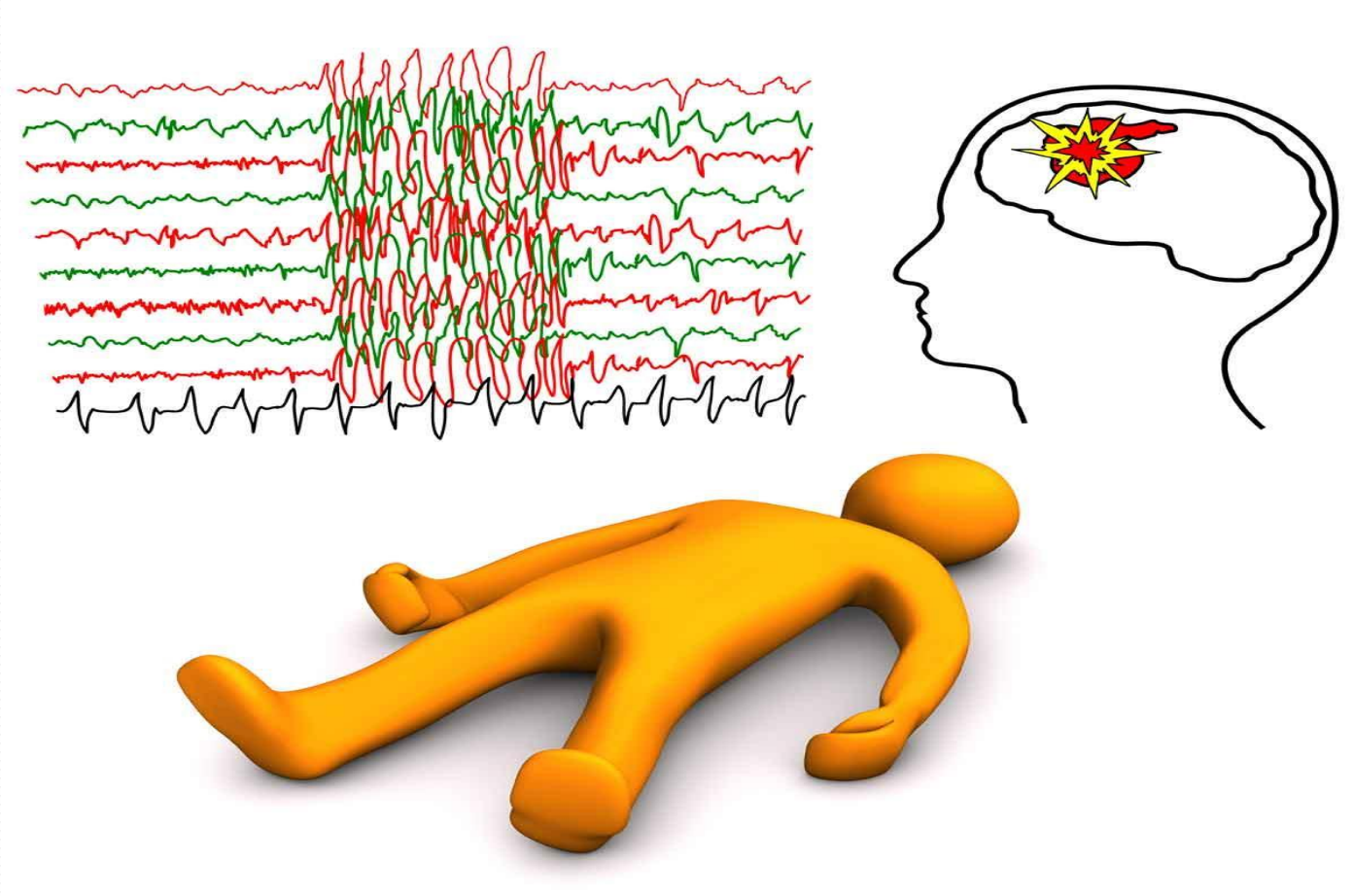
- **Antiarrhythmics**
  Lignocaine, mexiletine
- **Antihistamines**
- **Antimicrobials**
  Penicillins, quinolones
- **Antivirals**
  Aciclovir, ganciclovir
- **Antidepressants**
- **Antipsychotics**
- **Bronchodilators**
  Theophylline
- **Stimulant**
  Dexamphetamine, cocaine
- **Drug withdrawal**
  Alcohol Benzodiazepines
- **Others**
  Hormonal preparations
  Narcotic analgesics e.g. tramadol, pethidine

Diagnosis and Investigation of Epilepsy

- Clinical features – description of seizure
- Past and family history
- EEG (electroencephalogram)
- ECG
- Neurological examinations
- Blood count and plasma biochemistry
- Neuroimaging



Do you know any triggers for seizures in patients with epilepsy?



Triggers of seizures

- Stress
- Exercise
- Alcohol
- Caffeine consumption
- Missed meals
- Sleep deprivation
- Metabolic disturbances
- Allergies
- Infections (fever)
- Menstruation
- Flickering lights, (sunlight, TV, computers etc)
- Missed doses of antiepileptic drugs

Epilepsy - psychosocial issues

- Anxiety
- Impaired sense of independence
- Driving restrictions
- Insurance and employment
- Need to avoid certain activities when alone e.g. swimming
- Social stigma
- Embarrassment

Clinical Use of Anti Epiletic Medicines (AEMs)

Rationale for drug treatment with anti-epileptic medicines

Prevention

- prevent seizures –ideally with monotherapy
- prevent injury, brain damage
- prevent psychosocial consequences of recurrent seizures
- maximise the patient's quality of life

Acute Treatment

- Status epilepticus
- Febrile convulsions

Epilepsy – drug treatment

- Therapy is symptomatic – medicines inhibit seizures but **a cure for epilepsy not available**
- Optimum AEMs abolish seizures in up to 70% of patients with epilepsy
- Significant adverse events associated with AEDs contribute to initial treatment failure in >40% of patients

Factors affecting drug selection - ANY IDEAS?

When to start AEDs

Start AEDs when impact of further seizures outweighs risks of treatment.

? After first seizure

- Only 30–50% of people will have a recurrence
- Factors to consider when deciding to treat include:
  - **symptomatology** (previous seizures may have been unrecognised, eg in complex partial seizures)
  - **signs** (an abnormal EEG or neurological abnormalities may indicate an increased risk of recurrence)
  - **seizure type** (certain syndromes are more likely to be recurrent, eg juvenile myoclonic epilepsy, partial seizures)
  - **age** (elderly people are at higher risk of recurrence)
  - **patient's wishes**
  - **lowest recurrence rates** are associated with a normal EEG and no identifiable cause for seizures or when there is a clear avoidable precipitant (eg sleep deprivation, drugs).

When to start

After second seizure

- treatment is usually indicated when 2 or more seizures have occurred within 6–12 months

- about 80% of people will have recurrent seizures after 2 seizures, except when there is a clear avoidable precipitant or with some types of seizures (eg benign childhood epilepsy with centrotemporal spikes).

Which drug treatment?

- Establish type of seizure
- Exclude non-epileptic causes
- Consider side effects
- Interactions with patient's other drugs
- Patient wishes
- If patient is female, likelihood of pregnancy?
- Age of patient
- Compliance – need regimen that is manageable for patient

Epilepsy – drug treatment

Monotherapy is preferred

- Begin with 1st line agent, increase dose gradually to maximal with minimum adverse effects
- Check compliance (non-compliance is most common cause of treatment failure)
- Consider therapeutic drug range
- If treatment failure occurs, add another 1st line agent, increase to optimal dose and gradually withdraw 1st drug
- Consider 2nd line agent if patient resistant
- Add 2nd agent only if monotherapy options have failed
- Attempt to withdraw drug(s) slowly if no seizures within 2 to 3 years (over several weeks to months) **DO NOT STOP ABRUPTLY**

Dosing

- Commence at low dose
- Increase dose to therapeutic doses as tolerated
- Plasma levels are a poor guide to determining therapeutic dose
- Some patients can have adequate control at low plasma levels
- Review for adverse events

Treatment choices

Seizure type	1st line drug choice	2nd line drug choice
Focal (partial)	Carbamazepine	Phenytoin, valproate gabapentin, lamotrigine, levetiracetam,clobazam phenobarbitone, lacosamide, regabalin, topirmate
Generalised tonic-clonic	Sodium Valproate	Phenytoin, lamotrigine, levetiracetam, clobazam phenobarbitone,
Absence	Sodium Valproate Ethosuximide	Clonazepam, lamotrigine, clobazam
Myoclonic	Sodium Valproate Levetiracetam,	Clonazepam, phenobarbitone, topiramate, clobazam

Treatment choices

	Carbamazepine	Valproate	Phenytoin	Levetiracetam
Initial dose (adults)	100mg bd	300mg bd	4-5mg/kg	250 mg bd
Dose schedule	bd	Daily to bd	daily	bd
Bioavailability(%)	75 to 85	100	85 to 95	100
Time to peak (hr)	4 to 8	2 to 8	4 to 8	1
Volume of distribution (L/kg)	0.8 to 1.6	0.09 to 0.17	0.5 to 0.7	0.7 L
Protein binding	75 to 78	88 to 92	90 to 93	<10
Half life (hr)	8 to 24	6 to 16	9 to 40	7
Plasma levels mg/L	4 to 12	50 to 150	10 to 20	

Activity

- The neurologist has decided to start his adult patient on AED for tonic-clonic seizures.
  - What drug could he use and what would be starting dose?

Sodium valproate 300mg bd

- The neurologist has decided to start his adult patient on AED for focal (partial) seizures.
  - What drug could he use and what would be starting dose?

Carbamazepine 100mg bd

Therapeutic drug monitoring

- An appropriate dose of AED is that which controls seizures without causing significant adverse effects.
- Standard assays report total drug levels rather than the more clinically relevant free fraction, and this is subject to variable plasma-protein-binding, especially for valproate
- TDM may be useful in selected cases when patient adherence is questioned or when altered pharmacokinetics is expected, (eg. due to pregnancy, drug–drug interactions (including polytherapy) or hepatic or renal impairment)
- TDM is readily available for carbamazepine, phenytoin, phenobarbitone, valproate and lamotrigine.

Identify ADRs

Identify ADRs

Phenytoin

- drowsiness, dysarthria, tremor, ataxia, diplopia, cognitive difficulties
- gum hypertrophy
- acne
- hirsutism
- facial coarsening

Carbamazepine

- sedation
- headache
- ataxia
- dizziness
- nausea
- diplopia
- mild leucopenia

Identify ADRs

Sodium Valproate

- tremor
- hair loss
- sedation
- appetite stimulation
- anorexia, nausea and vomiting
- thrombocytopenia
- hepatotoxicity and pancreatitis

Levetiracetam

- dizziness
- somnolence
- emotional lability
- nervousness
- aggression
- irritability and agitation

FDA Alert

Carbamazepine, Gabapentin, Lamotrigine, Levetiracetam

Now all have FDA Alert :

Suicidal Behaviour and Ideation and Antiepileptic Drugs

The association is controversial and the benefits will often outweigh the risks in epilepsy; the risk–benefit may be less certain in other conditions

www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.

Other risks

Fracture risk

- patients with epilepsy are at increased risk of fractures as a result of:
  - falls due to seizures
  - adverse effects of antiepileptics, eg reduced BMD (particularly with barbiturates, carbamazepine, phenytoin and valproate) and CNS effects that increase risk of falling

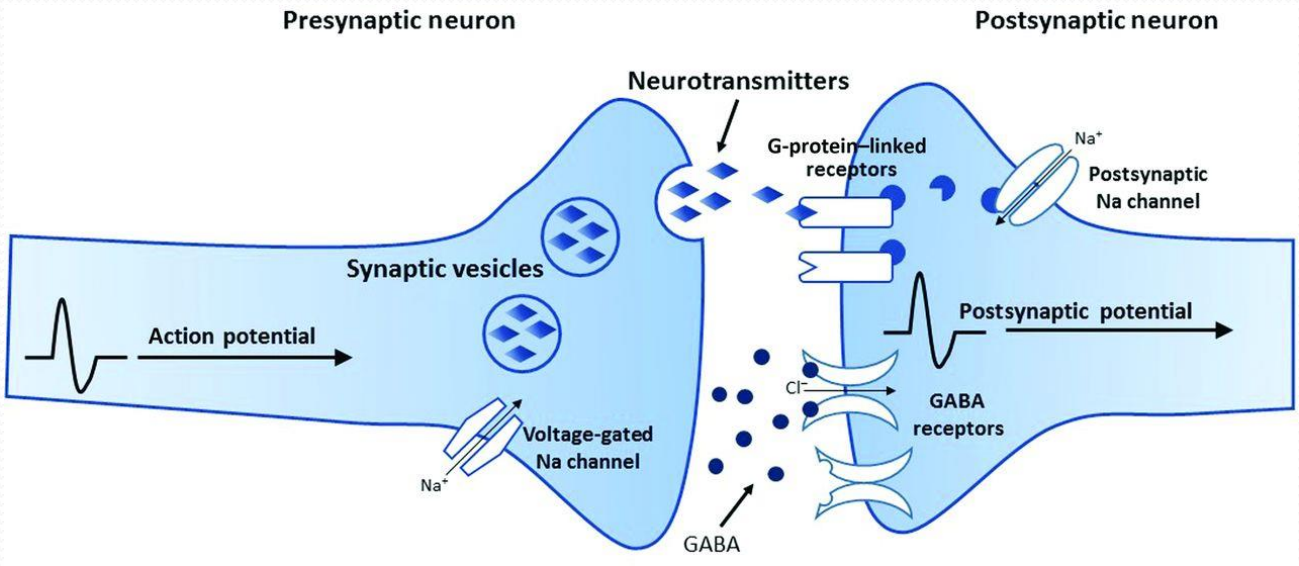
- consider fall prevention strategies and BMD monitoring during long-term treatment; ensure adequate vitamin D and calcium intake

Activity

- How would you counsel a patient when he first starts carbamazepine?
- What extra information would you provide if the patient was female?
- What lifestyle issues would you discuss?

Drug Interactions

- Consider drug interactions (Cytochrome P450)
  - **Carbamazepine** induces CYP3A4 and increases metabolism of many drugs including itself
  - **Phenytoin** induces CYP3A4 and increases metabolism of many drugs



Activity (hint AMH)

- Can you name some drugs that may increase levels of carbamazepine?
  - CYP3A4 inhibitors eg diltiazem, erythromycin fluconazole

- Can you name some drugs that may decrease levels of carbamazepine?
  - CYP3A4 inducers eg phenytoin, St Johns's Wort, rifampicin

Areas of concern for AEMs

Special areas for considerations for AEMs

- Status epilepticus
- Epilepsy in women

Case study Mr SE

Mr S.E.

22 year old chef

PC: Arrived in ED with status epilepticus

PMH: Epilepsy, depression

PDH: Carbamazepine CR 400mg bd

Sodium valproate 500mg tds

Venlafaxine 150mg d

Cause

Check

- Drug levels
  - carbamazepine 4mg/L (10-20)
  - Sodium valproate 20mg/L (50-100)
- Recent activity

  Weekend drinking binge

  Dehydration

  Sleep deprivation
- Electrolytes
  - GGT 120 units/L (<50)

Cause

- Sub-therapeutic levels of AEM identified. Causes?
  - Non-compliance
  - Alcohol binge
  - Sleep deprivation
  - Missed meals

Status epilepticus

- Frequent and prolonged epileptic seizures
- Generalised convulsions lasting for at least 30 minutes or successive frequent convulsions where patient does not recover consciousness
- Is a medical emergency – can be fatal
- Neurological outcome is age dependent – can lead to persistent epilepsy, motor deficits, behavioural or learning difficulties

Status epilepticus treatment

- Basic life support
- First give benzodiazepine
  - midazolam 5-10mg IV, IM, bucally, intranasally
  - diazepam 10mg slow IV, or rectally if no IV access
  - clonazepam 1mg IV
- If prolonged, give long acting antiepileptic drug (e.g. phenobarbitone, phenytoin, valproate, levetiracetam)
- If status epilepticus persists, ICU for midazolam infusion or anaesthetic doses of thiopentone, midazolam or propofol

Epilepsy in women

Women of child-bearing age

- Discuss possibility of pregnancy before selecting an AEM
- Risks of unplanned treatment withdrawal

Contraception

- Several AEDs (carbamazepine, phenytoin, barbiturates) induce hepatic enzymes and increase metabolism of OCP
- Use high dose combined oral contraceptive or medroxyprogesterone depot but still risk of failure
- Non-hormonal contraception is preferable

Case study - Mrs JW

Mrs JW is a 30 year old lady who is planning to get pregnant

PMHx: Epilespy – well controlled

PDHX: Carbamazepine CR 200mg bd

Last level: 13mg/L

HER QUESTION

Should she continue her medication during her pregnancy?

Pregnancy and epilepsy

- Seizure frequency ↑ in approximately 45%, ↓ in 5% and same in 50% of patients.
- Uncontrolled epilepsy in a pregnant woman is a serious condition for both mother and foetus.
- Incidence of birth defects 2-3 times higher in womenwith epilepsy whether on AEM or not
- Uncontrolled fits cause fetal acidosis, hypoxia and increase risk of cerebral palsy
- All antiepileptic drugs are potentially teratogenic

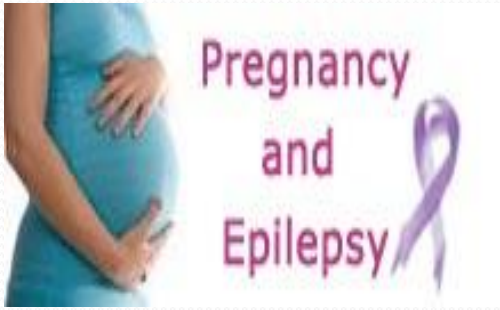
Pregnancy and epilepsy

- Literature reviews indicate that anticonvulsants are associated with an increase in congenital defects. **However** the benefits in preventing maternal seizures with the use of medication are thought to outweigh the risk to the infant
- The use of more than one antiepileptic drug carries a higher risk of birth defects
- Monitoring anticonvulsant therapy throughout the course of the pregnancy will be important, and dose adjustments should be made based on serum concentration, frequency of seizures, and adverse effects/tolerability.

Pregnancy and epilepsy

Treatment aims

- avoid sodium valproate, especially >1200mg/day
- best choice of treatment is the drug that best controls the epilepsy, at the lowest effective dose, in monotherapy if possible
- some AEMs interfere with folic acid metabolism, - need to supplement with folic acid starting at least 1 month before and for 3 months after conception at 5mg daily



Monitoring patients taking AEMs

What should we monitor for:

- Seziure control
- ADRs
- Non-compliance
- TDM if indicated
- Drug interactions

Role of the Pharmacist?

What should we counsel about:

- Importance of compliance. Emphasise that AEDs should not be stopped abruptly - increased seizures and status epilepticus may occur
- When withdrawing treatment, reduce the dosage of antiepileptic drugs over several weeks to months
- Adverse drug reactions
- Monitor outcomes of drug therapy
- Drug interactions
- Monitoring
- Reduce stigmatisation
- Issues with driving
  - Seizure. 1998 Aug;7(4):305-8. **Driving and epilepsy in Sri Lanka.** Seneviratne SL, Gunatilake SB, Adhikari AA, De Silva HJ. Department of Medicine, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka.

What drug would you choose?

- After 1st tonic-clonic seizure

?Watch and wait

- After repeated tonic-clonic seizures

Sodium valproate

- After numerous absence seizures

Sodium valproate