

# Epilepsy

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# Learning Points

- Definition of epilepsy versus seizure
- Common AED and side effects
- When to check antiepileptic drug concentration?
- Epilepsy and pregnancy
- Epilepsy and bone health.

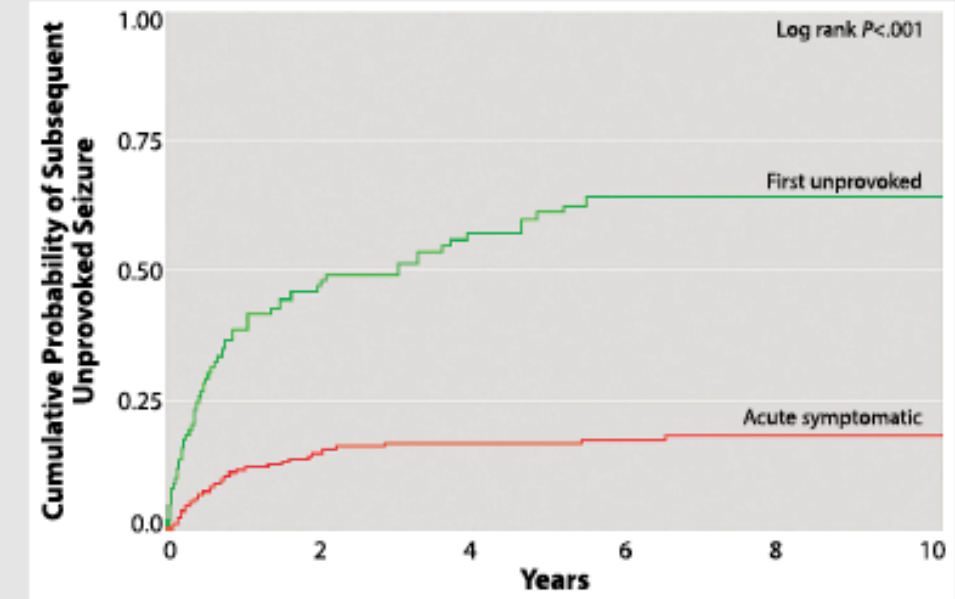
# 1. Definition of epilepsy

## 2014, International League Against Epilepsy definition

1. A disease with recurrent unprovoked seizures (two or more unprovoked seizures occurring >24 hours apart)
  - Hauser prospectively followed 204 Pts after unprovoked seizure. Risk of second seizure was 33%. After second seizure the risk of 3<sup>rd</sup> unprovoked seizure was 76%
2. Heightened tendency towards recurrent unprovoked seizures (a single seizure with electroencephalographic or neuroimaging tests for heightened images of seizure recurrence in next ten years)

# Types of First Seizure

- Provoked seizure (eg seizure caused by toxin, medication, or metabolic factors)- **low risk of recurrence**
- Acute symptomatic seizure (seizure associated with acute brain injury such as stroke, encephalitis) **high short term rate of recurrence**
- Remote symptomatic seizure (seizure caused by preexisting brain injury)- high risk of recurrence
- Seizure associated with epileptic syndrome (eg Juvenile myoclonic epilepsy) **high risk of recurrence**
- Other



**FIGURE 2-2** Risk of subsequent seizure over 10 years after acute symptomatic seizure during acute illness (eg, stroke, central nervous system infection, traumatic brain injury) compared with risk of subsequent seizure in patients with remote symptomatic unprovoked seizure (ie, previous stroke, central nervous system infection, traumatic brain injury).

Reprinted with permission from Hesdorffer DC, et al. *Epilepsia*.<sup>18</sup> [online library: wiley.com/doi/10.1111/j.1528-1167.2008.01945.x/full](https://doi.org/10.1111/j.1528-1167.2008.01945.x/full). © 2009 International League Against Epilepsy.

# When to start

- Not all first seizures require AED started
  - Where they first seizure?
  - Ask for auras
    - Butterflies in stomach
    - Nocturnal bed wetting
    - Jerk-like movement in morning

Common AEDS

## Sodium valproate

- Broad spectrum of efficacy- all focal, generalised and myoclonic seizures.
- Enzyme inhibitor: multiple drug interactions
- Dose related SE- fatigue, drowsiness tremor, weight gain, gait disorder, hyperammonemia
- Idiosyncratic reactions- hepatotoxicity and pancreatitis

# Lamotrigine

- Broad spectrum AED- focal, generalised seizures.
- Low teratogenicity
- Slow titration to avoid a rash (rarely introduced in hospital)
- Dose related side-effects
  - Dizziness, blurred vision, unsteadiness, tremor, rash, diplopia
- Idiosyncratic reactions
  - SJS, toxic-epidermal necrolysis



# Topiramate

- Broad spectrum- active against focal and generalised seizures
- Dose-related side-effects
  - Cognitive slowing, decreased attention and memory, impaired executive function, fatigue, dizziness, ataxia, depression
  - Parathesia (related to carbonic anhydrase inhibition)
  - Weight loss
  - Renal stones

# Levetiracetam

- Broad-spectrum AED: focal, generalised and myoclonic seizures
- No significant PK interactions
- Main side-effects- somnolence, dizziness.
  - Depression and irritability- Use with caution in patients with previous depression and counsel partners to report change in mood.

# Phenytoin

- Effective against focal and generalised tonic-clonic seizures
- P450 Enzyme inducer- number of drug interactions. Saturable metabolism
- Dose dependent adverse effects- ataxia, incoordination, dysarthria, nystagmus and diplopia
- Idiosyncratic: SJS, TEN, DRESS
- Long-term effects- acne, hirsutism, cerebellar atrophy, neuropathy

### 3. When to increase AED?

- Depends on a number of factors
  - Treatment goals
  - Prior AED usage
  - Side-effects of treatment
  - Age and comorbidities
  - Polypharmacy
- Not guided by serum drug concentrations\*
- Not necessarily after a seizure
  - Look for precipitants (compliance, alcohol, sleep deprivation etc)

\*Except lamotrigine in pregnancy

Epilepsy in women of child-bearing age

# Significance of epilepsy in pregnancy

- Approximately 1/3 of patients will experience an increase in seizure frequency during pregnancy.
  - Increase in maternal mortality during pregnancy and post-partum period (SUDEP)
- Risk for baby
  - Risk of preterm labour
  - Risk of small for gestational age
- Seizure control prior to contraception: best predictor of seizure control during pregnancy
  - Approximately 90% chance of being seizure free during pregnancy if you were seizure free for the previous nine months.
  - Emphasis on optimizing seizure control prior to contraception- best AED and optimal dose

# Adverse effects of AEDs

- Seizure control versus adverse effects
- Valproate is the most effective agent for generalized epilepsy (Vadja *et al.* 2014) **BUT**
  - Highest rate of major congenital malformations
  - Associated with lower IQ (10 points at 6 years of age) compared to other AEDs
  - Higher risk of autism/autism-spectrum disorder compared to background population.
  - Dose dependent
- 50% of pregnancies unplanned (Davis 2008)
  - Structural abnormalities occur within first eight weeks
  - Importance of reliable contraception and avoiding significant drug interactions

# Teratogenicity of AEDs

- Nine Pregnancy Registries
  - Low malformations rates
    - Lamotrigine
    - Carbamazepine
    - Levetiracetam (Probable)
  - Intermediate malformation rates
    - Phenytoin
    - Phenobarbital
    - Topiramate



# Pregnancy and Lamotrigine

- Oestrogen increases lamotrigine clearance (hepatic)
- Important to check serum concentrations prior to pregnancy to establish target concentration then monthly during pregnancy
  - Increased dose as required.
- Clearance return to normal within 2-3 weeks so plan to reduce dose needs to be established.
  - Do not return to pre-pregnancy dose for 1-2 months due to higher seizure risk with sleep deprivation.

# General

- Folic Acid supplementation important
  - AEDs can be associated with reduced serum folate
  - No direct evidence of benefit
- Encourage Breast-feeding
  - NEAD study (Meador 2014) reported that children exposed to carbamazepine, lamotrigine, phenytoin or valproate had higher IQ and language at 6 years compared to mothers taking AEDs that did not breast-feed
- General Safety
  - Strollers > Baby carriers
  - Avoid sharing bed with baby
  - Caution when bathing baby.
  - Increased risk of post-natal depression

# . Epilepsy and Bone Health

- Increased risk of (Beerhorst 2013)
  - osteopenia (RR 1.3-3.8)
  - osteoporosis (RR 1.7-3.8)
  - Fracture (RR 1.7-6.1)
    - Drug side-effects (ataxia- phenytoin, sedation- phenobarbital)
    - Injury associated from seizure
- Osteoporosis (Multifactorial)
  - Common risk factors
  - Effect of AED on bone health- increased bone turnover (enzyme inducers), reduced Vit D metabolites- (valproate)

# Epilepsy and Osteoporosis

- Recommendations

- Screen for bone disease in patients with high risk AEDs (phenytoin, valproate, carbamazepine).
  - Screening interval not defined.
- General advise
  - Regular aerobic exercise
  - Vit D supplementation +/- Calcium
  - Avoidance of smoking etc.

# References

- The efficacy of the newer antiepileptic drugs in controlling seizures in pregnancy. *Epilepsia*. 2014;55(8):1229-1234
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- Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. *JAMA Paeds*. 2014;168(8):729-736
- Bone disease during chronic antiepileptic drug therapy: general versus specific risk factors. *J Neurol Sci*. 2013;331(1-2):19-25