# When to start and How to select AEDs

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## When to start AED

- True epileptic seizure
- First unprovoked seizure ??
- Diagnosis of epilepsy
  →AED should be offered as soon as epilepsy has been established

# Epilepsy: definition

1. At least 2 unprovoked seizures occurring at least 24 hours apart
2. One unprovoked seizure with probability of further sz (>60%) over the next 10 yr eg. Remote structural lesion
3. Epileptic syndrome

Fisher et al. A practical clinical definition of epilepsy, Epilepsia 2014

# First unprovoked seizure

- Risk of second unprovoked sz = 33%
- Risk of third sz = 73%
- Risk of fourth sz = 76%

Hauser et al. NEJM 1998

- Overall risk of recurrent seizure = 40-50% within 2 years

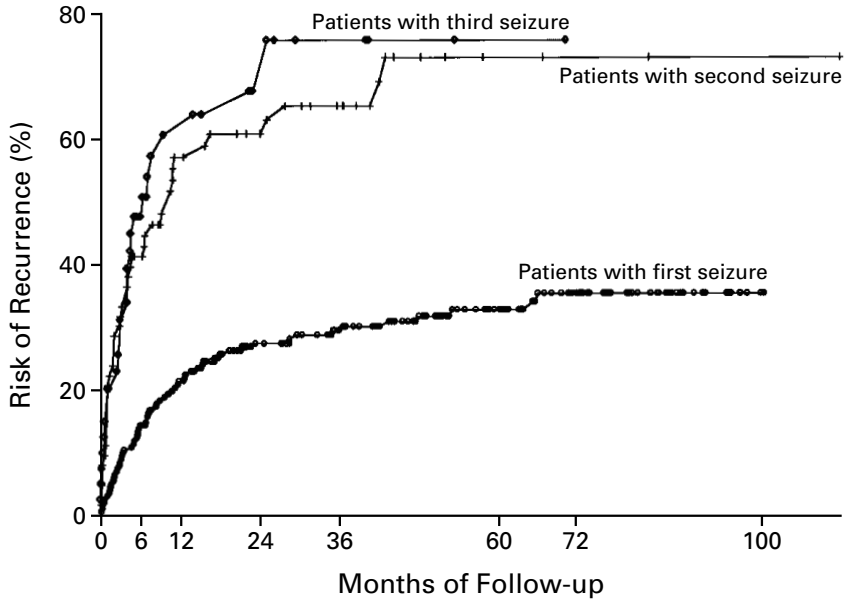
Berg AT. Epilepsia 2008

The New England Journal of Medicine

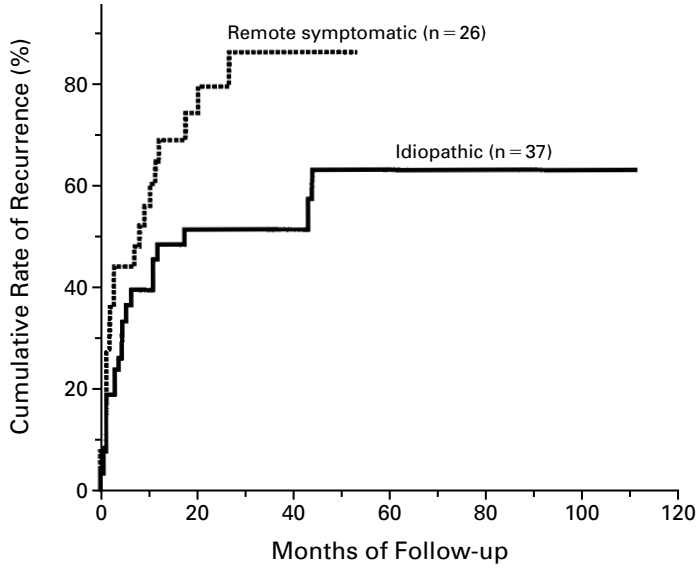
**TABLE 2.** RECURRENCE OF SEIZURES AT VARIOUS TIMES AFTER THE INDEX SEIZURE AND ACCORDING TO THE SEIZURE-FREE INTERVAL.*

| VARIABLE | FIRST SEIZURE | SECOND SEIZURE | THIRD SEIZURE |
|---|---|---|---|
| No. of patients | 204 | 63 | 41 |
| | percent with recurrence (95% confidence interval) | | |
| Within 12 mo | 21 (16–27) | 57 (45–70) | 61 (44–77) |
| Within 24 mo | 27 (21–34) | 61 (48–73) | 67 (51–84) |
| Within 36 mo | 29 (23–36) | 65 (53–78) | 76 (60–91) |
| Within 48 mo | 32 (25–38) | 73 (59–87) | 76 (60–91) |
| Within 60 mo | 33 (26–40) | 73 (59–87) | 76 (60–91) |

Hauser et al. NEJM 1998




Hauser et al. NEJM 1998




Hauser et al. NEJM 1998

# First unprovoked seizure

Two large randomized trial

- FIR.S.T (First Seizure Trial Group, Italy 1993)
  193 untreated pts. vs. 204 treated pts.
- MESS (Multicenter Epilepsy and Single Seizure study, European-wide 2005) including first ever seizure and newly diagnosed epilepsy
  408 untreated pts. vs. 404 treated pts.

Berg AT. Epilepsia 2008

## FIR.S.T: risk of recurrent sz

| | Deferred gr. | Treatment gr. |
|---|---|---|
| 3 months | 18% | 7% |
| 6 months | 28% | 8% |
| 12 months | 41% | 17% |
| 24 months | 51% | 25% |

60% reduction in the rate of relapse for immediate versus delayed treatment

## MESS study: risk of recurrent sz

| | Deferred gr. | Treatment gr. |
|---|---|---|
| 6 months | 26% | 18% |
| 2 years | 39% | 32% |
| 5 years | 51% | 42% |
| 8 years | 52% | 46% |

Overall hazards ratio = 1.4 for untreated vs. treated

Reduction in recurrence rate = 30%

## Predictors of recurrent sz

- Abnormal EEG
- Neurological deficit
- Age of onset
- Type of seizure
- Status epilepticus
- Hx of febrile seizure

## Abnormal EEG and neurological sign

MESS study: lower risk if normal EEG and normal neurological status in untreated arm

- 25% recurrence risk at 2 years (overall 39%)
- Hazards ratio for abnormal EEG = 1.54
  symptomatic case = 1.35

Kim et al. Lancet neurol 2006

# Age

Children vs. adult

- FIR.S.T: slightly higher risk of recurrence in children (<16 yr)
- MESS: no significant change

Berg AT. Epilepsia 2008

# Type of seizure

- Focal sz may be associated with higher risk of recurrence
- But focal sz often associated with abnormal EEG and symptomatic cause
- Independent effect of focal sz is weak and variable

Berg AT. Epilepsia 2008

## Status epilepticus

- Adult: multiple seizures within a day or status epilepticus was associated with elevated risk of recurrence within the subgroup of patients with remote symptomatic first seizures

  Hauser et al. neurology 1990

- Higher risk if status epilepticus and in teenager with multiple seizures within a day

  Loiseau et al. epilepsia 1999

## History of febrile seizure

- Increased risk of recurrence sz may be associated with previous febrile seizures in the group with remote symptomatic first unprovoked seizures

  Hauser et al. Neurology 1990
  Shinnar et al. Pediatrics 1996

## First unprovoked seizure

- Overall risk of recurrent seizure = 40-50% within 2 years

Increased risk if

- Abnormal EEG
- Identifiable neurological condition (neuro deficit)
- Remote symptomatic etiology (+ve brain lesion)
- Status epilepticus and a history of febrile seizures in individuals with symptomatic sz

Berg AT. Epilepsia 2008

## First unprovoked seizure in children Common question from parents

1. Will it happen again?
2. How long do I have to wait for a recurrence?
3. Could my child die during a recurrence?
4. Could there be brain damage with a recurrence?
5. If I choose to delay medication treatment will there be any long-term change in the chance of a permanent remission?

Camfield and Camfield. Epilepsia 2008

## Will it happen again?

Risk is increased by

- Focal versus generalized sz
- Presence of spike discharge on EEG
- Presence of concomitant neurological deficits

→ Children with none of these factors have approximately a 20% chance of recurrence

→Children with all of these factors have about an 80% risk of recurrence

Camfield et al. Neurology 1985

## Waiting for recurrence, how long?

- Children
- 88-90% recurrence by 2 years

Camfield et al. Neurology 1985
Shinnar et al. Ann neurol 2000

- Risk is rarely increasing after 5 years

Hauser et al. NEJM 1998

## Could my child die during recurrence?

- Risk of a child dying during a recurrent seizure is very low

Except

- Status epilepticus
- SUDEP

The most frequent cause of death is **not** related to seizures

Camfield and Camfield. Epilepsia 2008

## Any brain damage with a recurrence?

- The National Collaborative Perinatal Project (NCPP)
- 55,000 children from birth to 7 years of age
- Intelligence and academic testing at 7 years of age showed no difference between the siblings with seizures and those without
- 62 children had one or more afebrile seizures between age 4 and 7 years. Comparisons of the cognitive testing before and after seizure showed no change
- Clinically significant brain injury does not result from a few recurrent unprovoked seizures

Camfield and Camfield. Epilepsia 2008

## Any risk of delayed treatment?

FIR.S.T and MESS study:

- early AED treatment reduced early recurrences but over several years the remission rates were identical

Camfield et al. epilepsia 2002 (14 AED VS. 14 without)

- Fewer recurrences in 1-year F/U for AED group
- No difference in the long-term remission rate (20-year) between the two groups

The chance of remission is not altered by delaying AED treatment after a first seizure

Camfield and Camfield. Epilepsia 2008

## AED ? In first unprovoked seizure

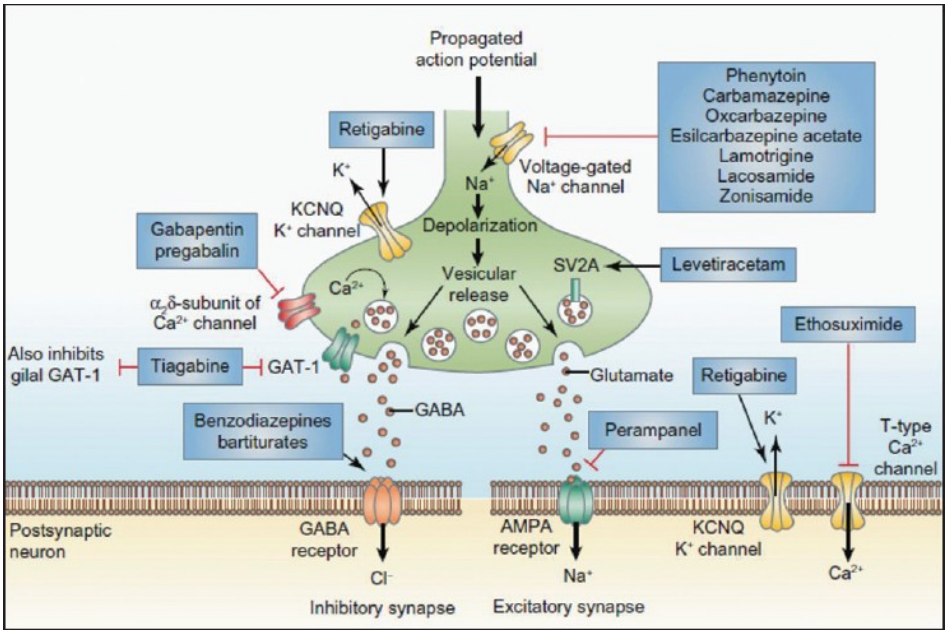
- Risk of recurrence
- Effect of recurrent seizure
- Data from EEG ± MRI
- Risk of AED, adverse drug reaction
- Give all information to patient / parents to decide

# How to choose AEDs for epilepsy?

## Ideal AED

- Fully control seizures
- Well tolerated
- No long-term adverse event (teratogenicity, organ toxicity)
- Once- or twice-daily dosage
- No drug interactions
- No need for serum monitoring

Schmidt et al. Drug treatment of epilepsy in adults. BMJ 2014




Singh. Muller J Med Sci Res 2014

## Old AED

- Phenobarbital (PB)
- Phenytoin (PHT)
- Carbamazepine (CBZ)
- Valproate (VPA)

## Newer AED

- Topiramate (TPM)
- Levetiracetam (LEV)
- Clobazam (CLB)
- Clonazepam (CZP)
- Oxcarbazepine (OXC)
- Lamotrigine (LTG)
- Vigabatrin (VGB)
- Gabapentin (GBP)
- Pregabalin (PGB)
- Zonisamide (ZNS)
- Lacosamide (LCM)
- Perampanel (PER)

## AED in newly diagnosed epilepsy

- 50% of patients with new-onset focal or generalized seizures become seizure-free while taking the first appropriately selected first-line AED

Brodie et al. Neurology 2012

# AEDs and Seizure types

| | Focal sz | GTC sz | Absence sz | Myoclonic sz | Atonic sz | CYP450 | PK & PD | Protein bound |
|---|---|---|---|---|---|---|---|---|
| **PB** | √ | √ | | | | Inducer | | |
| **PHT** | √ | √ | | | | Inducer | Zero order kinetic | High |
| **CBZ** | √ | √ | | | | Inducer | Autoinducer first few wks | |
| **VPA** | √ | √ | √ | √ | √ | Inhibitor | First order kinetic | High |

# ILAE evidence review of AED as initial monotherapy for epileptic sz and syndrome

**Table 3. Relationship between clinical trial ratings, level of evidence, and conclusions**

| Combination(s) of clinical trial ratings | Level of evidence | Conclusions |
|---|---|---|
| ≥ 1 Class I studies or meta-analysis meeting class I criteria sources OR ≥ 2 Class II studies | A | AED established as efficacious or effective as initial monotherapy |
| 1 Class II study or meta-analysis meeting class II criteria | B | AED probably efficacious or effective as initial monotherapy |
| ≥ 2 Class III double-blind or open-label studies | C | AED possibly efficacious or effective as initial monotherapy |
| 1 Class III double-blind or open-label study OR ≥ 1 Class IV clinical studies OR Data from expert committee reports, opinions from experienced clinicians | D | AED potentially efficacious or effective as initial monotherapy |

**Table 2. Rating scale of evidence for potentially relevan studies**

| Class | Criteria |
|---|---|
| I | A prospective, randomized, controlled clinical trial (RCT) or meta-analysis of RCTs, in a representative population that meets all six criteria:<br>Primary outcome variable: efficacy or effectiveness<br>Treatment duration: ≥ 48 weeks<br>Study design: double blind |

Glauser et al. Epilepsia 2013

| Sz type, epileptic syndrome | Level A | Level B | Level C | Level D |
|---|---|---|---|---|
| Adult with focal sz | CBZ, LEV PHT, ZNS | VPA | OXC, TPM, LTG, GBP, PB, VGB | CZP |
| Children with focal sz | OXC | - | CBZ, PB, PHT, VPA, TPM, VGB | CLB, CZP, LTG, ZNS |
| Adult with GTC sz | - | - | CBZ, OXC, LTG, PB, PHT, TPM, VPA | LEV, GBP, VGB |
| Children with GTC sz | - | - | CBZ, PB, PHT, VPA, TPM | OXC |
| Absence epilepsy | VPA, (ESM) | - | LTG | - |
| Benign Rolandic epilepsy | - | - | CBZ, VPA | LEV, OXC, GBP |
| Juvenile myoclonic epilepsy | - | - | - | VPA, TPM |

Glauser et al. Epilepsia 2013

**Table 2**
**Preferred first-line antiepileptic drugs for new-onset and refractory epilepsy in adults**

| New-Onset Partial Epilepsies | Refractory Partial Epilepsies |
|---|---|
| Carbamazepine | Lacosamide |
| Gabapentin | Pregabalin |
| Lamotrigine | Zonisamide |
| Levetiracetam | Perampanel |
| Oxcarbazepine | Clobazam |
| Topiramate | |
| Valproate | |
| **New-Onset Idiopathic Generalized Epilepsies** | **Refractory Idiopathic Generalized Epilepsies** |
| Lamotrigine | Clobazam |
| Topiramate | Levetiracetam |
| Valproate | |

Schmidt D. Neurologic clinics 2016

## Benign epilepsy with centrotemporal spikes (BECTS)

1st line: Carbamazepine (CBZ), Lamotrigine (LTG)

- If not tolerated or unsuitable
- 2nd line: Valproic acid (VPA), Levetiracetam (LEV), Oxcarbazepine (OXC)

- CBZ and OXC may exacerbate continuous spike and wave during slow sleep, which may occur in some children with BECTS

NICE pathways 2016

## Absence epilepsy syndrome

1st line: VPA (be aware of teratogenic risks)

- Offer LTG (if VPA is ineffective or unsuitable)

- Adjunctive: combination VPA + LTG
- Next: clobazam (CLB), clonazepam (CZP), LEV, topiramate (TPM) or zonisamide (ZNS)

## Dravet syndrome

1st line: VPA or TPM

- Adjunctive: CLB, Stiripentol
- Do Not offer: Na ch. blocker

## Idiopathic generalized epilepsy (IGE)

1st line: VPA

- Offer LTG (if VPA is ineffective or unsuitable)
  Be aware of LTG can exacerbate myoclonic sz
- Consider TPM (S/E)
- Adjunctive: LEV, CLB, CZP, ZNS

## Juvenile myoclonic epilepsy (JME)

1st line: VPA

- Offer LTG, LEV, TPM (if VPA is ineffective or unsuitable)
- Adjunctive: CLB, CZP, ZNS

## Infantile spasm

1st line: Vigabatrin (VGB) in tuberous sclerosis

Prednisolone or VGB in non-TSC

## Lennox-Gastaut syndrome (LGS)

1st line: VPA

- Adjunctive: LTG
- Next: TPM, Rufinamide

## Advantage
## Newer V.S. Older AEDs

- Not affecting hepatic enzyme function (GBP, PGB, LTG, LEV, LCM)
- Rapid onset of action (GBP, OXC, LEV, LCM)
- Intravenous loading (LEV, LCM)
- Broad spectrum efficacy (LTG, TPM, ZNS, LEV)

Unterberger I. Epileptologie 2015

# Adverse reaction & tolerability

- Approximately 50% of patients reported at least one side effect from CBZ or VPA as well as from newer AEDs (LTG, GBP, OXC, TPM)

  from SANAD study. Lancet 2007

- Newer AEDs: better tolerated
- Newer AEDs such as GBP or LEV cause fewer or no dermatologic hypersensitivity reactions and do not cause the drug interactions seen with older AEDs

# Common dose-related AE

| AED | somnolence | dizziness | tremor | ataxia | diplopia | n/v | anorexia | Wt. gain |
|---|---|---|---|---|---|---|---|---|
| PB | + | + | + | + | + | | | |
| PHT | | + | + | + | + | + | | |
| CBZ | + | + | + | + | + | + | | |
| VPA | | | + | + | | + | | + |
| TPM | + | + | | + | | + | + | |
| LEV | + | | | | | + | + | |
| LTG | + | + | + | + | + | + | | |
| OXC | + | + | | + | + | + | | |
| VGB | + | | | | | + | | + |

# Risk of rash from AEDs

| High risk | Moderate risk | Low risk |
|---|---|---|
| PHT (10%)<br>CBZ (8.7%)<br>LTG (6.2%) | PB<br>OXC | VPA<br>TPM<br>LEV<br>GBP<br>VGB |

CBZ and OXC: cross reactivity 30%

Arif et al. Neurology 2007

Aromatic ring AED: cross reactivity 40-80%

Hyson, Sadler. 1997 Krauss. Epilepsy Curr 2006

HLA B*1502 testing before starting CBZ

# VPA: Liver toxicity/failure

- Potentially fatal
- First 3 months of treatment, very rare after 6 m
- Higher risk in
- Age < 2 years, polytherapy with enzyme inducing AEDs, inborn errors of metabolism, previous liver disease, mental retardation
- Risk ~ 1:600 (< 3 yr with polytherapy)
  ~ 1:16,000 (3-10 yr with monotherapy)

Bryant et al. Neurology 1996

# Drug interaction

No drug interaction

- Levetiracetam
- Gabapentin
- Pregabalin
- Clobazam
- Vigabatrin
- Retigabine

Schmidt D. Neurologic clinics 2016

# AED-induced seizure aggravation

| Seizure type | May be aggravated by |
|---|---|
| Absences | CBZ, PHT, ETX, VPA, OCBZ, VGB, TGB |
| Atypical absences | CBZ, OCBZ |
| Myoclonic | CBZ, PHT, OCBZ, VGB, TGB, LTG, LEV, PGB, BZ |
| Negative myoclonus | CBZ, PB, VPA, LTG |
| Generalized | CBZ, PB, ETX, OCBZ, VGB, TPM |

Chaves J and Sander J. Epilepsia 2005

## AED dosing administration

Slow titration
- Carbamazepine (2-5 wk)
- Lamotrigine (8-12 wk)
- Topiramate
- Zonisamide

Rapid titration
- Phenytoin
- Valproate
- Levetiracetam
- Oxcarbazepine (1-2 wk)
- Gabapentin

Ferrendelli J., Epilepsia 2001

## How to choose AEDs for epilepsy ?

- Seizure type / Epileptic syndrome
- Pharmacokinetic profiles
- Mechanism
- Drug interaction
- Side effect
- Co-morbidity
- Familiarity
- Cost