Antiseizure medications (ASMs)
Selection, Initiation & Discontinuation

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Antiseizure medications (ASMs)

"Selection"

Development of ASMs: Organized by generation

FIRST-GENERATION

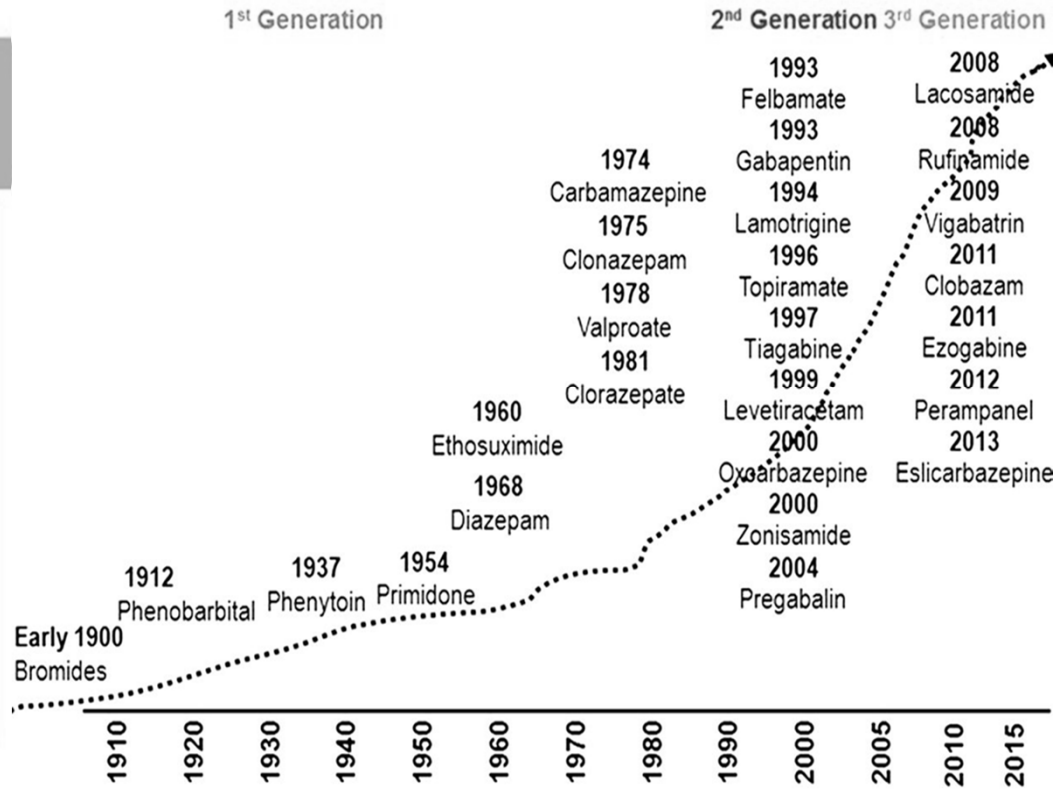
- Carbamazepine
- Phenytoin
- Piracetam
- Valproate

SECOND-GENERATION

- Fosphenytoin
- Gabapentin
- Lacosamide
- Lamotrigine
- Levetiracetam
- Oxcarbazepine
- Pregabalin
- Rufinamide
- Tiagabine
- Topiramate
- Vigabatrin
- Zonisamide

THIRD-GENERATION

- Brivaracetam
- Clobazam
- Eslicarbazepine acetate
- Perampanel
- Retigabine
- Satinamide
- Stiripentol



How to select 1st monotherapy

- Seizure type, syndromic
- Safety profile
- Drug-drug interaction
- Co-morbidity

- Co-morbidity
  (to be discussed in another topic)
  - Elderly
  - Stroke
  - Child baring potential women
  - Renal dysfunction
  - Hepatic dysfunction
  - Overweight, migraine
  - Neuropathic pain
  - etc.

Guidelines

Seizure type	ILAE (2013)[1] (Level of efficacy and effectiveness evidence)	NICE (2016)[2]		AAN & AES for new-onset epilepsy (2018)[3] (Level of evidence)
		1st LINE	2nd LINE	
Adults with partial-onset seizures	Level A: CBZ, PHT, LEV, ZNS Level B: VPA Level C: GBP, LTG, OXC, PB, TPM, VGB Level D: CZP, PRM	CBZ LTG LEV OXC VPA	CBZ CLB GBP LEV LTG OXC VPA TPM	Level A: None Level B: LTG Level C: LEV, ZNS Level D: None
Children with partial-onset seizures	Level A: OXC Level B: None Level C: CBZ, PB, PHT, TPM, VPA, VGB Level D: CLB, CZP, LTG, ZNS			Insufficient evidence
Elderly adults with partial-onset seizures	Level A: GBP, LTG Level B: None Level C: CBZ Level D: TPM, VPA			Level A: None Level B: LTG Level C: GBP Level D: None

1. Glauser A. et al. Epilepsia 2013;25:320-326. 2. NICE guideline (Update 2018), Accessed date 30th Dec 2018, 3. Kanner AM, et al. Neurology 2018;91:74-81.

Efficacy of main AEDs in seizure type

AED	Focal simple or complex seizures	Secondarily GTCS	Primarily GTCS	Myoclonic jerks	Absence seizures
Carbamazepine	*Effective*	*Effective*	*Effective*		
	Effective	Effective	Effective ?	Effective ?	Effective?
Clonazepam	Effective?	Effective?		Effective	Effective
Ethosuximide				Effective	Effective
Gabapentin	*Effective*	*Effective*			
Lamotrigine	Effective	Effective	Effective		Effective
	Effective	Effective	Effective	Effective	Effective
Oxcarbazepine	*Effective*	*Effective*	*Effective*		
Phenobarbitone	Effective	Effective	Effective	Effective	
Phenytoin	*Effective*	*Effective*	*Effective*		
Tiagabine	*Effective*	*Effective*			
	Effective	Effective	Effective	Effective	Effective?
	Effective	Effective	Effective	Effective	Effective
Vigabatrin	*Effective*	*Effective*			
	Effective	Effective	Effective	Effective	Effective?

CP Panayiotopoulous. THE EPILEPSIES:Seizure, Syndromes and Management 2005:59-82

Antiseizure medications: Spectrum of Action

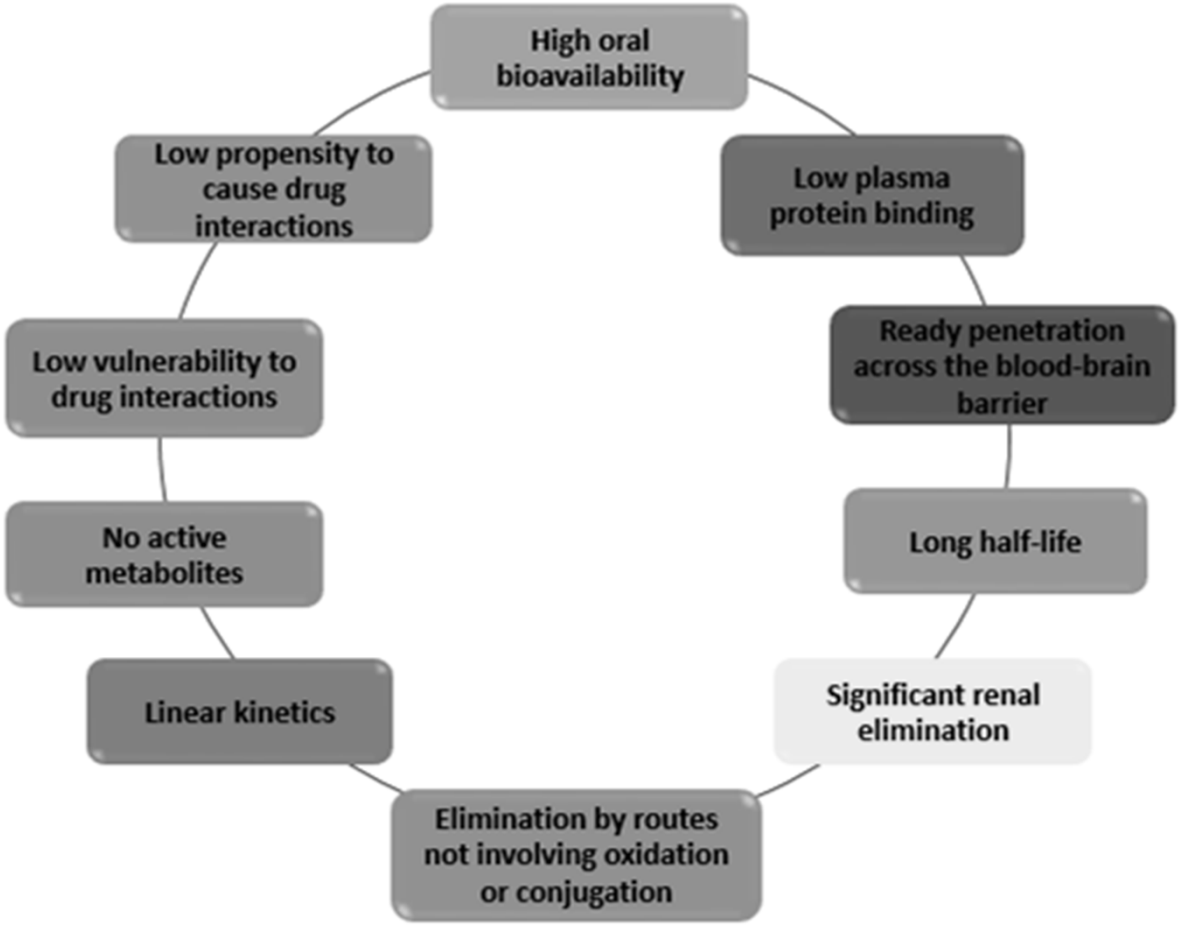
Narrow spectrum

- Carbamazepine
- Ethosuximide
- Gabapentin (pregabalin)
- Oxcarbazepine
- Phenobarbital
- Phenytoin
- Tiagabine
- Vigabatrin

Broad spectrum

- Benzodiazepines
- Valproate
- Lamotrigine
- Levetiracetam
- Topiramate
- Zonisamide

Desirable pharmacokinetic properties of an antiepileptic drug



New generation ASMs
offer equal efficacy
with improved tolerability,
Pk properties, and side effect
profiles compared with
traditional drugs

Emilio Perucca, Svein I. Johannessen. The ideal pharmacokinetic properties of an antiepileptic drug: how close does levetiracetam come? *Epileptic Disord 2003; 5: S17–S26.*

Antiseizure medications (ASMs)

Initiation

ASMs initiation

- General consideration
- When to start?
- How to start
  - Monotherapy or polytherapy
  - Dosage
- Monitoring
  - Seizure diary
  - Side effect profile
  - Blood level
  - EEG

ASMs initiation: general consideration

- Seizure mimics?
- Provoked seizures?, Reflex epilepsies?, Precipitating causes?
- Balance risks between recurrent seizures and adverse events of ASMs
- Expectations should be modest (50%); & ASMs are not DMTs
- Goal: QoLs

ASMs when to start: true first unprovoked seizure

- Generally ***NO*** treatment
  - ??? improve long-term prognosis
  - Unnecessarily expose to side effects
  - Should be deferred until a 2nd seizure occurs.
- Consider to ***TREAT*** if a high risk of recurrence

Berg AT. Neurology 1991.
Musicco M. Neurology 1997.
Hirtz D. Neurology 2003.
Perucca E. Epilepsy Res 2000.
Temkin NR. Epilepsia 2001.
Temkin NR. N Engl J Med 1990.
Foy PM. Neurol Neurosurg Psych 1992.
Temkin NR. Neurosurgery 1999.

First seizure, evaluate high recurrence risk

- A very high risk of recurrence
  - Examples
    - A single seizure occurring at least a month after a stroke
    - A child with a single seizure conjoined with a structural or remote symptomatic etiology and an epileptiform EEG study
    - A patient in whom diagnosis of a specific epilepsy syndrome associated with persistent threshold alteration can be made after the occurrence of a single seizure
    - A first seizure might present present as status epilepticus

ILAE 2014

ASMs when to start: True recurrent unprovoked seizure

- Generally start Rx
- “May” not Rx if
  - Very infrequent seizures
  - Only nocturnal, mild, brief seizure
  - Some benign childhood epilepsies with self-remitting course: BECT (rolandic epilepsy)
  - Predictable precipitating events: Sleep deprivation, photosensitive epilepsy
  - No impact on the patient’s psychological, social/ professional conditions
- The patient could play role in the therapeutic decision. ***

Perucca E. Epilepsy Res 2000.

ASMs How to start?

- Monotherapy vs. Polytherapy
- Administration

Monotherapy is preferable whenever possible

- Minimized toxicity & Better tolerated
- Eliminates the risk of drug interactions
- Facilitates assessment of the effects of individual drugs
- Simple & Possibly better compliance
- Complete seizure control (high efficacy)
  - 60-70% of partial seizure
  - 70-80% of primary GTC
- Less teratogenicity
- Lower cost → Cost effectiveness

Shorvon SD. Brit Med J 1978.
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Mattson RH. N Engl J Med 1992.
Richens A. J Neurol Neurosurg Psychiatr 1994.
Heller AJ. J Neurol Neurosurg Psychiatr 1995.
Verity CM. Dev Med Child Neurol 1995.
De Silva M. Lancet 1996.
Kwan P. N Engl J Med 2000.

Alternative monotherapy

- Avoid abrupt discontinuation of pre-existing medication to minimize the risk of withdrawal seizures.
  - 2-3 months to complete withdrawal
    - Benzodiazepines, barbiturates
    - Carbamazepine, phenytoin and vigabatrin

Polytherapy

- Advantage: in refractory seizures
  - Different mode of actions
  - Rational polytherapy concept (more efficient)
    - Combining drugs with different modes of action (Good combination)
    - VPA + ethosuximide for refractory absence seizures
    - VPA + LTG in a variety of refractory seizure types
      - Seizure reduction 62-78% with lower dosage requirement

- Disadvantages
  - A risk of adverse drug interactions
    - Interaction to other medications (cytochrome P450)
  - Higher chance for adverse events
  - Higher cost

Brodie MJ. Epilepsy Res 1997.
RowanAJ. Arch Neurol 1983.
Panayiotopoulos CP. Lancet 1993.
Pisani F. Epilepsia 1999.

Concepts of polytherapy

Good couple:
• Many AEDs with multiple mechanisms, still have only a primary action
• AEDs with different mechanisms of action are more likely to interact synergistically than AEDs with similar or differing mechanisms
• VPA + LTG: can reduce dosage and frequency of LTG
• LEV or GBP + LTG: no drug interactions

Bad couple:
• AEDs with similar mechanisms may have similar side effect profiles
• An excessive amount of additive side effects
• CBZ + OXC → exacerbate hyponatremia
• BZD + BZD → excessive drowsiness

Administration: dosage

- A loading dose
  - esp. in active seizures, or serial seizures or status epilepticus
- An adequate maintenance dosage
- Increase gradually to a target maintenance level
  - Advantage
    - Adaptation and tolerability to CNS
    - Prevent allergic skin reaction
      - CBZ, PHT, lamotrigine
    - Some patients require at dose below the initial target maintenance dosage.

Besag EMC. CNS Drugs 2000.

Example of suggested initial & maintenance dosages & frequency of administration

Drug	Initial dose (mg/d)	Maintenance dose (mg/d)	Frequency (/day)		Drug	Initial dose (mg/d)	Maintenance dose (mg/d)	Freq. (/day)
CBZ	400-600	400-1,600	2-3 2 for CR		Phenobarbital	50-100	50-200	1
Clobazam	10	10-30	1 or 2		Phenytoin	200-300	200-400	1-2
Ethosuximide	500-750	500-1,500	2-3		Primidone	500-750	500-1,500	2-3
Felbamate	1,800-2,400	1,800-3,600	3-4		Tiagabine	15 30*	15-30 30-50*	2-4
Gabapentin	900-1,800	900-3,600	2-3		Topiramate	100	100-400	2
Lamotrigine	50-100 200-300*	50-200 200-500 *	2 (1 if VPA)		Valproic acid	500-1,000	500-2,500	2-3 1-2 in CR
Levetiracetam	1,000-2,000	1,000-3,000	2		Vigabatrin	1,000	1,000-3,000	1-2
Oxcarbazepine	600-900	600-3,000	2-3		Zonisamide	200	200-500	2

* With enzyme inducers

Initial target maintenance dosage

- In general
  - The lowest daily dosage to produce seizure control

- Condition with higher dosage and plasma drug levels (the prognosis negatively)

  - High seizure frequency before Rx
  - Symptomatic epilepsy
  - Partial seizures
  - Multiple seizure types
  - Associated neurological handicaps
  - An unfavorable response to previous AED
  - Severe psychological or social impact on the individual's life

Kwan P. N Engl J Med 2000.
Perucca E. CNS Drugs 2001.
Schmidt D. Neurology 1984.
Richens A. J Neurol Neurosurg Psychiatr 1994.

Administration: Concepts of frequency of ASMs use

- 1-2 doses a day → Less likely to obstruct daily routines: a better compliance
- A slow elimination (PB): once daily at bedtime
- PHT: 1. adult: daily, 2. children: more frequent, 3. generic 2-3 time/day, 4. original 1 time/day
- Lamotrigine
  - OD: monotherapy, or on with VPA
  - Bid: on with other enzyme-inducing AED
- VPA, sometimes OK for OD
    - Except in women with childbearing potential → bid
      - Teratogenicity increases by excessive fluctuations in plasma drug levels

Dosage adjustments on patients not responding to the target dosage

- According to pharmacokinetic principles
- 5 x T1/2 = steady state
- Short half-life → steady state = days: VPA, CBZ (instant release)
- Long half-life → weeks: PHT, PB
- If seizures continues even in steady state, increase dosage until maximum tolerated dose

Formulation

- Age>5 years: tablets or capsules ***NOT*** syrup
  - More precise dosing
  - Syrup
    - Tooth damaging from sucrose
    - Excessively rapid absorption

- Enteric-coated tablets
  - Absorbed at intestine, so delayed absorption by ingestion

- Sustained release such as CBZ, VPA, PHT

- Generic drugs
  - ? Identical, ?equivalent bioavailability
  - Drug level should be assessed.

Adjusted medication

- When seizures continue at maximally tolerated dosage
  - Review Dx
    - The cause of inadequate response
      - Poor compliance, sleep deprivation, alcohol abuser, etc.
  - A second monotherapy
    - Better tolerate than combination Rx
  - A trial of combination therapy
    - If 2nd, 3rd monotherapy: failure
  - Considering the feasibility of epileptic surgery

Concepts of treatment

- Start low, go slow: dose dependent properties
- Final dosage, individualized: minimally effective, maximally tolerated
- In urgency/emergency case: fast titrate, intravenous formulation
- NG feeding: liquid formulation
- Fail 1st Mono (1/3 failed)
  - → 2nd mono → polytherapy
  - → rational polytherapy

Outcome assessment

- Complete seizure control
  - An absence of seizures for at least one year
- Definition for seizure freedom by ILAE 2010
  - The absence of seizures for at least the previous year “or”
  - For 3 times the longest pretreatment interval between seizures (rule of 3)
  - whichever was greater

Kwan P, Epilepsia 2010

How to evaluate

- Clinical assessment (seizure diary with simple codes)
- Adverse events
- Blood level: routinely checked?
- Repeat EEG

Example of adverse event

Drug	Dose dependent S/E	Idiosyncrasy
CBZ	Diplopia Dizziness, nausea Headache Drowsiness Neutropenia Hyponatremia	Morbilliform rash Agranulocytosis Aplastic anemia Hepatotoxic effects SJS Teratogenicity
Phenytoin	Nystagmus Ataxia Nausea, vomiting Gum hypertrophy Depression, drowsiness Paradoxical increase in seizures Megaloblastic anemis	Acne, coarse facies Hirsutism Blood dyscrasias Lupus-like syn Rash, SJS Dupuytren's cont Hepatotoxic effects Teratogenicity
Valproic a.	Tremor Weight gain Dyspepsia Nausea, vomiting Alopecia Peripheral edema	Acute pancreatitis Hepatotoxic effects Thrombocytopenia Encephalopathy Teratogenicity
Clonazepam	Fatigue Sedation, drowsiness Dizziness Aggression (children)	Rash thrombocytopenia

Drug	Dose dependent S/E	Idiosyncrasy
Primidone	Fatigue Listlessness Depression Psychosis Decreased libido Impotence	Rash Agranulocytosis Thrombocytopenia Lupus-like syndrome teratogenicity
Ethosux.	Nausea, vomiting Anorexia Agitation Drowsiness Headache Lethargy	Rash Erythema multiforme SJS Lupus-like syndrome Agranulocytosis Aplastic anemia
Phenobar.	Fatigue Listlessness Depression Insomnia, irritability (children)	Maculopapular rash Exfoliation Toxic epidermal necrolysis Hepatotoxic effects Arthtitic changes Dupuytren's contracture teratogenicity

Potential adverse event

- Monitors also for potential side effect
- Informs patients or family about AE and early signs of serious toxicity
- CBC, blood chemistry
  - Before Rx, once in between and whenever another Rx is added.
  - BM suppression
  - Hepato-toxicity
- Visual field defect
  - Vigabatrin

Harden CL. Epilepsia 2000

Blood level: routinely checked?

- Pharmacokinetics: inter-individual variation
- The primary aim of Rx: A patient's clinical response ***NOT*** a lab value
- Dose adjustments should be based primarily on clinical response.
  - Seizure free at suboptimal concentrations
  - Tolerability above the upper limit of the optimal range

Glauser TA. Epilepsia 2000.

When should drug concentrations be measured?

1. Failure to achieve an adequate therapeutic response despite an apparently adequate dosage	
2. Conditions associated with pharmacokinetic changes	• Pediatric, pregnancy, old age, Liver, kidney and GI tract diseases • Drug binding to plasma proteins
3. ? Drug toxicity	• Exacerbation of seizure frequency • In-coordination or mental symptoms
4. To minimize the difficulties in dosage adjustments, particularly with phenytoin	
5. Multiple drug Rx	• To identify & to minimize adverse drug interactions
6. ? Poor compliance	• Unusually low and variable concentrations • Increase level following supervision of drug intake

When should blood samples be taken?

- At steady-state
  - At least 5 x T1/2 since the last dose change
- Long T1/2 drug such as phenobarbital
  - Little daily fluctuation in plasma concentration
    - No meaning of the exact time of sampling
- Other medications
  - Preferable to collect the morning before the first daily dose
    - ***"Trough level"***
- Short T1/2 such as VPA, CBZ
  - Another ***"peak level"*** to estimate
    - The degree of fluctuation
    - Potential causes of intermittent side-effects

Example: Half-life and steady state: in adults

Drug	T ½ (hr)	SDS (d)		Drug	T ½ (hr)	SDS (d)
Clobazam	10-30	2-6		**Phenobarbital**	50-170	8-30
Clonazepam	20-60	2-10		**Phenytoin**	10-80	3-15
Carbamazepine	15-25	2-7		**Primidone**	10-20	2-4
Ethosuximide	40-60	4-10		**Tiagabine**	4-13	2
Felbamate	14-23	2-4		**Topiramate**	20-30	2-5
Gabapentin	5-7	2		**Valproic acid**	12-18	2-4
Lamotrigine	15-35	2-6		**Vigabatrin**	5-8	2
Levetiracetam	6-8	2		**Zonisamide**	50-70	5-12
Oxcarbazepine	8-15	2-4				

NB: T ½ in patients not talking enzyme inducers

The concept of “Therapeutic range”

- The ranges of the plasma concentration at which most patient respond

- Clinical variation from therapeutic level
  - Pharmacokinetics: inter-individual variation
  - Type of seizures variable response to Rx
  - Adaptation (Tolerance): esp. benzodiazepine & barbiturate
  - The degree of drug binding to plasma proteins
  - Drug interaction with concomitant medications

- Toxicity even in therapeutic level
  - Protein binding
  - Active metabolites
  - Additive AE from concomitant medications

Glauser TA. Epilepsia 2000.

Optimal range

Drug	µg/mL	µmol/L	Relationship b/w level & effect
Phenytoin	10-20	40-80	Relatively consistent
Carbamazepine	4-11	17-46	Relatively good
Ethosuximide	40-100	284-710	Relatively good
Phenobarbital	10-40	43-172	Tolerance
Primidone	4-12	18-55	Measure the levels of metabolically derived phenobarbital (not unchanged primidone)
Valproic acid	50-100	350-700	Variable response & little value
Vigabatrin	N/A	N/A	No relationship
Zonisamide	7-30	33-140	N/A

Monitoring total or unbound drug concentrations?

- Pharmacologic effects
  - Only the free, non-protein bound fraction
- Routine measurement
  - Total concentration: may mislead the clinicians
- Highly protein-bound drugs: PHT, VPA
  - Hypoalbuminemia: increased un-bound fraction
    - Found in neonatal age, advanced pregnancy, old age, chronic liver disease, nephrotic syndrome
  - Uremia: accumulation of endogenous displacing agents
  - Drug interaction: VPA displacing PHT molecules from protein binding sites

Perucca E. Epilepsy-A Comprehensive Textbook. 1997.

Repeat EEG?

- EEG
  - Diagnostic & prognostic considerations
  - Guide for medication
- **<u>Generally of little or no value in assessing therapeutic response</u>**
  - Some cases with marked clinical improvement
    - EEG: unchanged or even deteriorates EEG
- Useful to repeat in treatment of status epilepticus
- Paroxysmal EEG activity may predict of the risk of seizure recurrence when treatment is discontinued.

Prognostic groups

1) Spontaneous remission (20-30%)
- Benign epilepsy of childhood with centrotemporal spikes (BECT)
- Childhood absence epilepsy (CAE)

2) Remission on AEDs (20-30%)
- Most focal epilepsy
- Juvenile myoclonic epilepsy (JME)**

3) Persistent seizure with AEDs (30-40%)
- Refractory patients
  - An increase risk of psychosocial and medical morbidities and mortality

Kwan P, J Neurol Neurosurg Psych 2004, Schuele SU, Lancet Neurol 2008

Antiseizure medications (ASMs)

Discontinuation

-- debate –

On ASMs → may still have seizures, risk of AEs, teratogenic

Not on ASMs → may be seizure free

Decision – individualized

Prognosis

- A study, 2,200 patients: 1-year remission rates after drug treatment

Idiopathic generalized epilepsy	82%
Cryptogenic partial epilepsy	45%
Symptomatic partial epilepsy	35%
Partial epilepsy associated with hippocampal sclerosis	11%
Hippocampal sclerosis & another lesion	3%

Semah F. Neurology 1998.

How long to treat with AED? & Can AED be discontinued?

- Many epilepsies: spontaneous remission
- Relapse rate in 2 years : range 0-90%, average 30%
- Predictors
  - Increasing age
  - Symptomatic epilepsy, an abnormal EEG
  - A longer duration of active disease prior to seizure control
- Relapse: epilepsy syndrome

BECTs (Rolandic epilepsy)	**very rare**
Childhood absence epilepsy	**rare (5-25%)**
Cryptogenic or symptomatic partial epilepsy	**intermediate (25-75%)**
Juvenile myoclonic epilepsy	**high (85-95%)**

Consider

- Social aspects
  - Job
  - Adverse effects
  - Drug interactions
  - Driving license
  - Leisure activities
  - Emotional and personal factors
  - Patients' decision ***

How to discontinue medication?

- Avoid stopping antiepileptic drugs abruptly
  - Withdrawal seizures: even status epilepticus
  - Gradual discontinuation of medications
- Discuss with patient & family
  - The probability of relapse
  - Side-effects of treatment
  - Patient's attitude to continuation of treatment
  - Legal implications with driving regulations

Berg AT. Neurology 1994.
Beghi E. Drugs 1995.

Summary

- The most important is to diagnose correctly
- Plans of initial management both pharmacological and non-pharmacological approaches are essential
- Evaluation and prompt treatments including using either standard or new AEDs should be done on a case-by-case basis
- Identify refractory epilepsy case and consider refer to Epilepsy centers at the proper time

Thank you