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Chulalongkorn Comprehensive Epilepsy Centre

How to choose/use anti-epileptic drugs wisely ?

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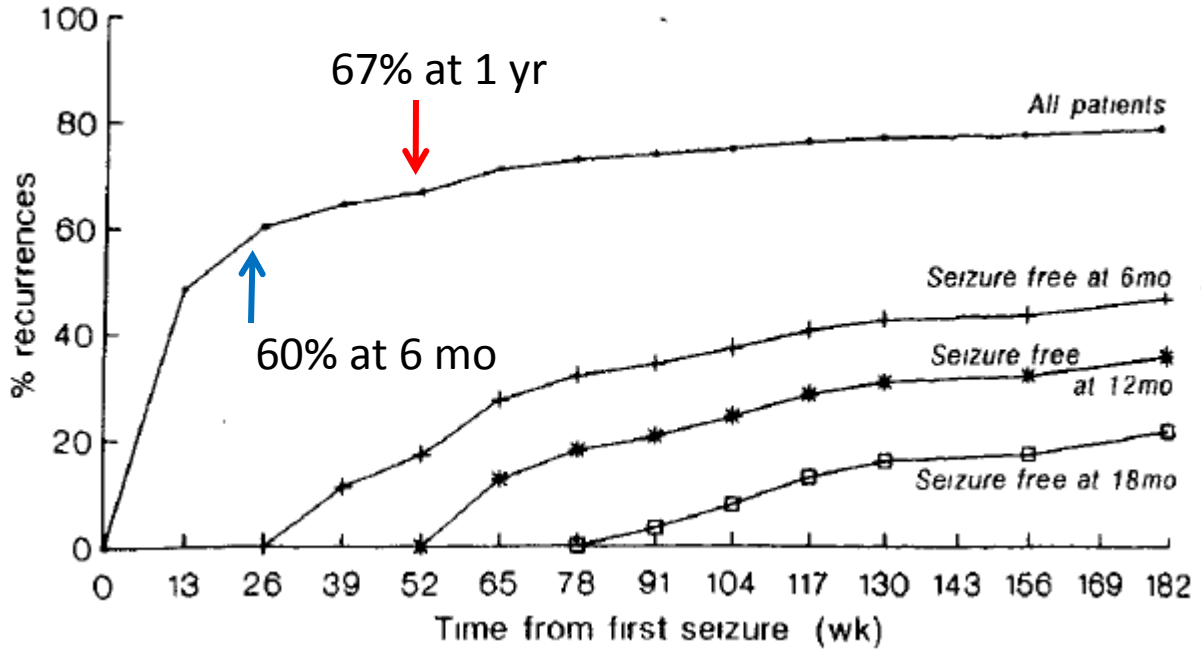
Talk overview

- When to start treatment ?
- Which drug ?
- Monotherapy
- Combining AEDs (Rational polytherapy)
- Old AEDs versus new AEDs
- Drug level monitoring
- When to discontinue AEDs ?

When to start treatment ?

- Correct diagnosis
- Generally start after **the second unprovoked seizure**
  - **First unprovoked seizure:** A seizure or flurry of seizures or occurring within 24 hrs in the person > 1 month old of age with prior history of unprovoked seizure
  - **Epilepsy**: 2 or more epileptic seizures occur unprovoked by any immediately identifiable cause

Cumulative risk of recurrence after a first unprovoked seizure



78% at 3 yrs

44 % at 3 yrs

32% at 3 yrs

17% at 3 yrs

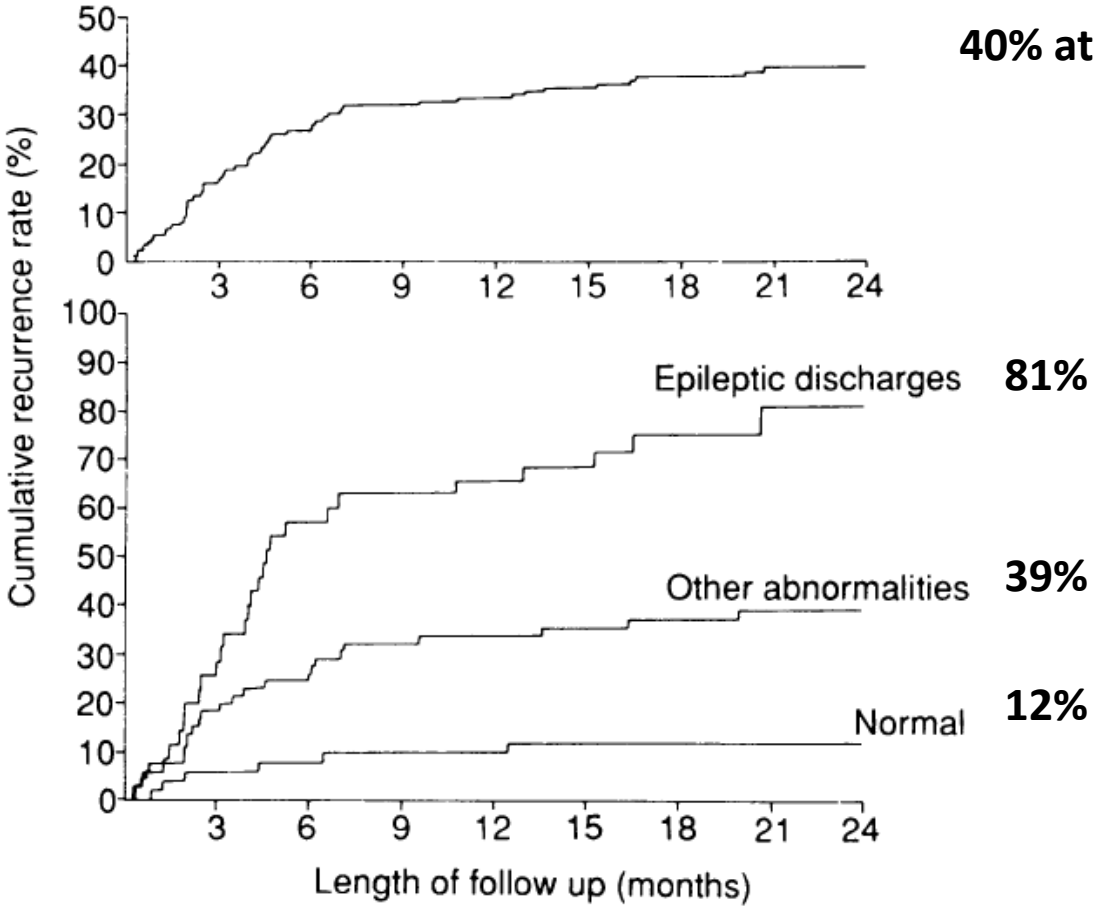
Hart YM et.al; The Lancet 1990

- Treatment after the **first unprovoked seizure**
  1. EEG shows IEDs and/or
  2. lesion on MRI or
  3. physical or psychosocial consequences of a seizure recurrence outweigh the risks associated with drug treatment

Factors associated with increased/lower risk

- **Increased risk**:
  - Adolescence onset
  - associated neurological deficits
  - occurrence while asleep or awakening
  - simple partial seizure/ CPS (> GTC)
- **Lower risk**:
  - seizure occurred within 3 mo after acute insult e.g. head injury, stroke
  - alcohol withdrawal

IEDs and risk of recurrence (idiopathic epilepsy in adults)



40% at 2 years

81%

39%

12%

Van Donselaar CA et.al; BMJ 1991

Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy

Massimo Musicco, MD; Ettore Beghi, MD; Alessandra Solari, MD; and Francesco Viani, MD;
for the First Seizure Trial Group (FIRST Group)*

Patients immediately treated

- 87% had no seizures for 1 year
- 68% had no seizures for 2 years

Patients treated after seizure recurrence

- 83% had no seizures for 1 year
- 60% had no seizures for 2 years

"Same time-dependent probability of achieving 1 and 2 seizure-free years"

Neurology 1997

Which drug ?

- Seizure type and epileptic syndrome
- Age and sex
- Associated medical conditions
- Potential side effect on QOL
- Medical expertise
- Regulatory aspects and cost

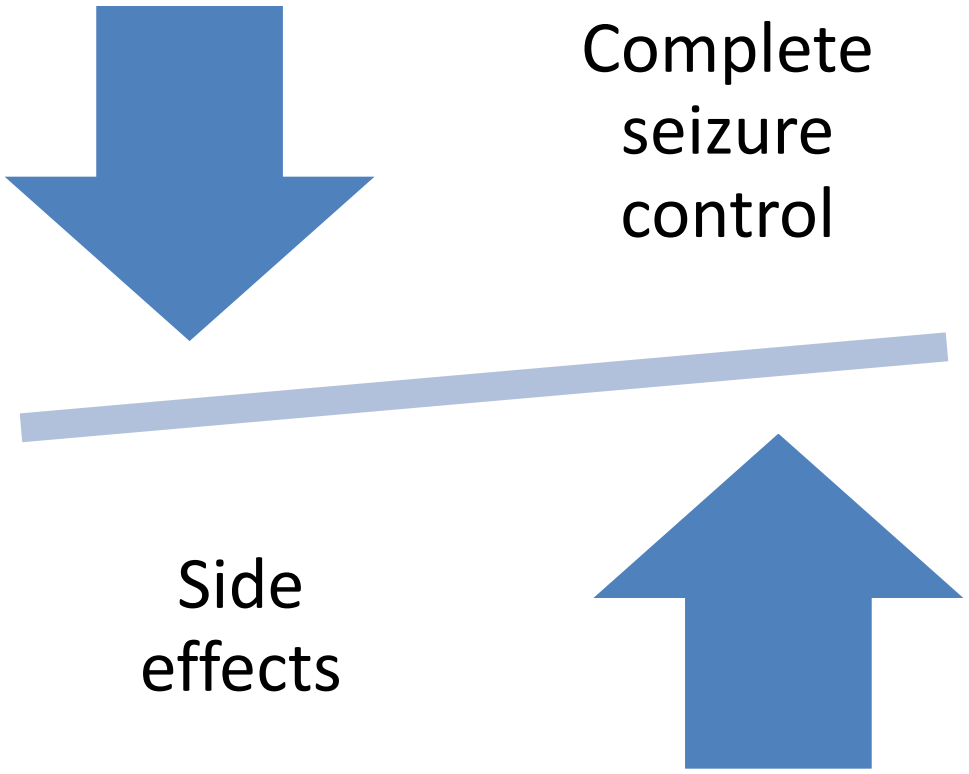
“Case-by-case basis”

At first visit prior to starting AEDs

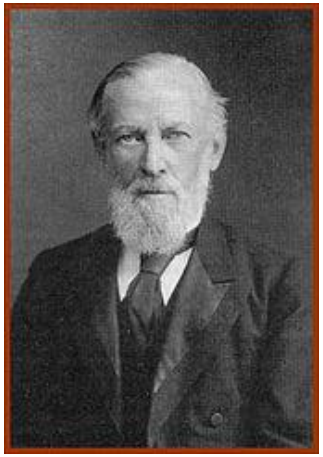
- Nature of disease, its prognostic implications
- Objectives of therapy
- Risks and benefits of treatment
- Alternative therapeutic strategies
- Counseling about marriage, reproduction, driving regulations
- Psychological and social support

Goals of treatment with AEDs

- Complete seizure free without side effects



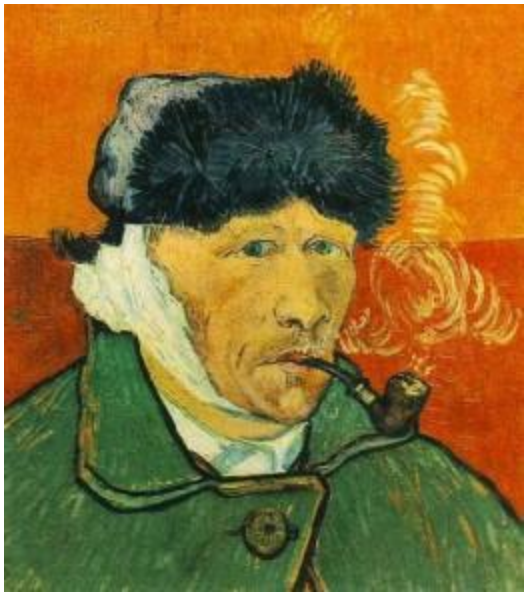
Polytherapy in 19th and early 20th century

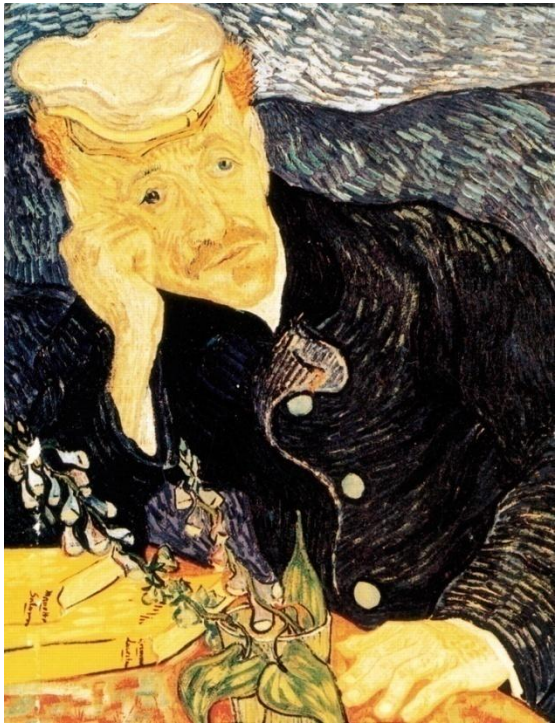


William Gowers (1881):
"The combinations of bromide with other drugs are of much value in the treatment of epilepsy"
- Other drugs included digitalis, belladonna, cannabis, opium, borax

- Pervasive belief that polytherapy was more efficacious than monotherapy
- Most of the treatments offered at the time were of doubtful antiepileptic efficacy

Polytherapy
Bromide + Digitalis



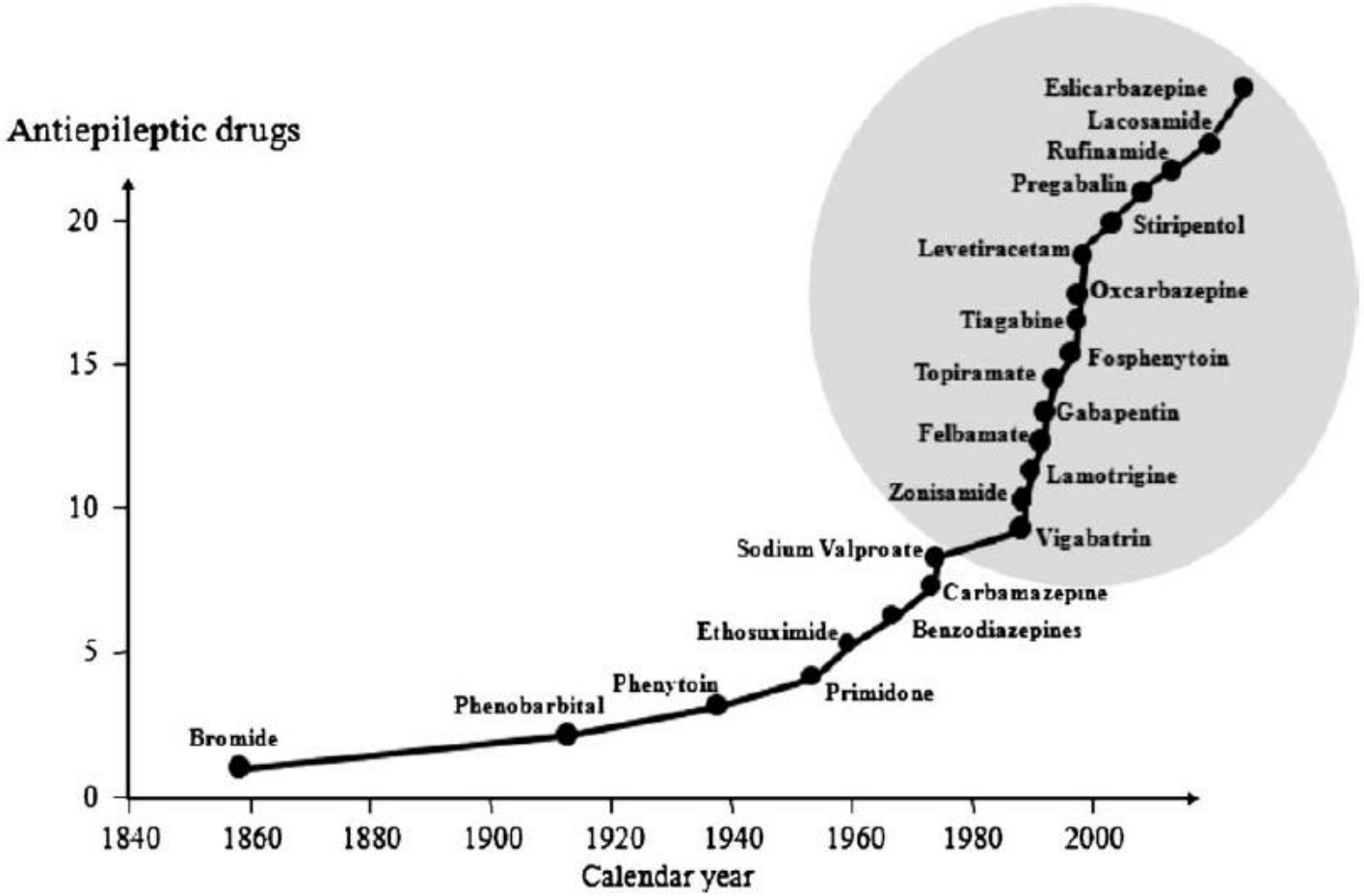


Henri Gastaut (1956);

Identified **van Gogh's** major illness during the last 2 years of his life as **temporal lobe epilepsy** precipitated by the use of **absinthe** in the presence of an early limbic lesion

Since 1980 “ Monotherapy era”

- ✓ equally or higher efficacious than polytherapy
- ✓ better tolerated
- ✓ no drug interaction
- ✓ possibly better compliance
- ✓ better cost effective
- ✓ Particularly desirable in
  - women
  - elderly
  - patients with co-morbid conditions



Brodie MJ and Sills GJ; Seizure 2011

Seizure types

Effective or possibly effective against all seizure types	Effective against all seizure types except absence	Effective against partial and GTCs	Effective against absence seizures
Valproic acid Lamotrigine Benzodiazepines Topiramates Zonisamide Levetiracetam Felbamate	Phenobarbital Primidone	Carbamazepine Phenytoin Oxcarbazepine Gabapentin Pregabalin Tiagabine Vigabatrin	Ethosuximide

Broad spectrum

Narrow spectrum

Epileptic syndromes

- **JME**: initially presented with absence seizure later developed GTCs and myoclonus

  ⇩

  may initially consider starting **VPA** or **LTG** instead of **ETX**

- If a clear diagnosis cannot be made e.g. only GTCs

  ⇩

  wise to choose

  a broad-spectrum AED

Seizure aggravation by AEDs

- Increase in seizure frequency or the appearance of a new seizure type

AEDs	Aggravated seizure types/epileptic syndrome
• CBZ, OXC, PHT , TGB, VGB (drugs for focal epilepsy) • CBZ • GBP • PB • LTG • BZD	• Myoclonus, absence seizure in IGE/SGE •Epileptic negative myoclonus, atonic seizure in BCERS • Myoclonus • Absence seizure • Myoclonus in Dravet's syndrome • Tonic seizure/tonic status epilepticus in LGS

Seizure aggravation by AEDs

- **Alternative explanations**
  - spontaneous fluctuation

(need adequate baseline frequency)

  - known seizure aggravators

(e.g. sleep deprivation, alcohol)

  - drug interactions

(lowering the level of the baseline effective AEDs)

  - noncompliance
  - development of drug resistance

- **Mechanisms**

(speculative and unproven)

  - overdosage (CBZ)
  - metabolic derangement (hyponatremia in CBZ/OXC)
  - varying effects of NT facilitation in different epileptic syndromes
  - drug interactions
  - sedation (tonic seizure in LGS)

"If possible, continue AED until it is clear that the seizure increase is not transient"

Age and sex

- **Age**
  - VPA-induced liver toxicity in children < 2 yrs
  - PHT-induced acne, hirsutism, gum hypertrophy and coarsening of facial features when taking during childhood: **consideration against the first-line use of PHT in children and young females**
  - LTG/GBP comparably effective as CBZ, but better tolerable in elderly

- **Sex**
  - VPA-induced teratogenicity in childbearing-age women
  - CBZ, PHT, PB, Primidone, OXC, TPM ≥ 200 mg/d (enzyme-inducing AEDs): increase metabolism of OCP (decrease efficacy)

Associated medical conditions

- **AEDs benefit other conditions**
  - **VPA, TPM, GBP**
  - ✓ migraine
  - **GBP, PGB, CBZ, OXC, LTG**
  - ✓ neuropathic pain/ post-stroke pain
  - **CBZ, OXC, VPA, LTG**
  - ✓ mood stabilizer
- **AEDs used in specific conditions**
  - **LVT, GBP, PGB**
  - ✓ hepatic impairment
  - ✓ adjusted dose in renal insufficiency /supplement if dialysis
  - **LVT, GBP, PGB, LCM**
  - ✓ HIV taking ARV (may consider VPA, LTG, but may need to increase LTG dose; may need to reduce ARV dose if taking VPA)
  - **VPA, LVT, GBP, PGN**
  - ✓ low risk of hypersensitivity
  - **LTG, GBP**
  - ✓ elderly

Associated medical conditions

- **Avoidance**
  - **VPA, CBZ, GBP, PGB, RTG (wt gain)**
  - ✓ avoid in obese pts
  - **TPM, ZNM**
  - ✓ not be 1st line in pts with renal calculi
  - **Enzyme-inducing AEDs**
  - ✓ avoid in pts with chronic medical conditions
- **Potential side effects**
  - **LVT (PB in children)**
  - ✓ produce irritability
  - **TPM, PB, Primidone, VGB**
  - ✓ cause depression
  - **LTG, FBM (stimulant)**:
  - ✓ cause anxiety and insomnia

CASE 1

- 18 yo gentleman, university student, BW 86 kg
- Seizure started at age 17 yrs
- Seizure types:
  - Vocalization with GT/GTC, duration 5 min, 7 episodes in life since onset (Dec 2012), Last episode 2 wks ago
- Medicine: TPM 50 mg BID from another hospital
- EEG, MRI: normal
- Co-morbidity
  - Difficulties with word finding and memory since taking TPM
- Allergic to sulfa drug (face swelling)

Considerations

- Seizure type and epileptic syndrome
- Age and sex
- Associated medical conditions
- Potential side effect on QOL
- Medical expertise
- Regulatory aspects and cost

Which drug ?

- **Broad spectrum**

  Valproic acid

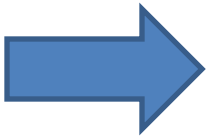
  Lamotrigine

  Benzodiazepines

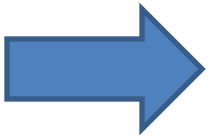
  Phenobarbital

  Topiramates

  Levetiracetam



VPA, LVT



LVT

- **Narrow spectrum** (focal epilepsy is still possible)

  Carbamazepine

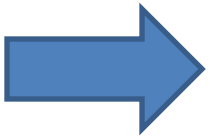
  Phenytoin

  Oxcarbazepine

  Gabapentin

  Pregabalin

HLA-B*1502 requested and revealed positive result



OXC
GBP
PGN

Effectiveness of first AED

TABLE 2. SUCCESS OF ANTIEPILEPTIC-DRUG REGIMENS IN 470 PATIENTS WITH PREVIOUSLY UNTREATED EPILEPSY.

VARIABLE	NO. (%)
Response to first drug	222 (47)
Seizure-free during continued therapy with first drug	207 (44)
Remained seizure-free after discontinuation of first drug	15 (3)
Response to second drug	61 (13)
Seizure-free during monotherapy with second drug	41 (9)
Remained seizure-free after discontinuation of second drug	20 (4)
Response to third drug or multiple drugs	18 (4)
Seizure-free during monotherapy with third drug	6 (1)
Seizure-free during therapy with two drugs	12 (3)
Total	301 (64)

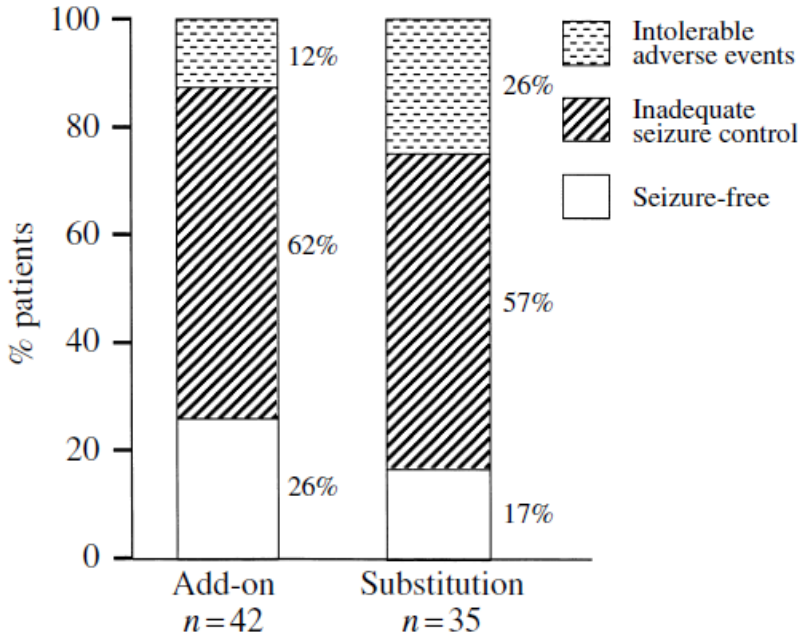
- **Seizure-free for at least 1 yr**
  - 1st drug: 47%
  - 2nd drug mono: 13%
  - 3rd drug mono: 1%
  - two drugs: 3%

Medically controlled: 64%

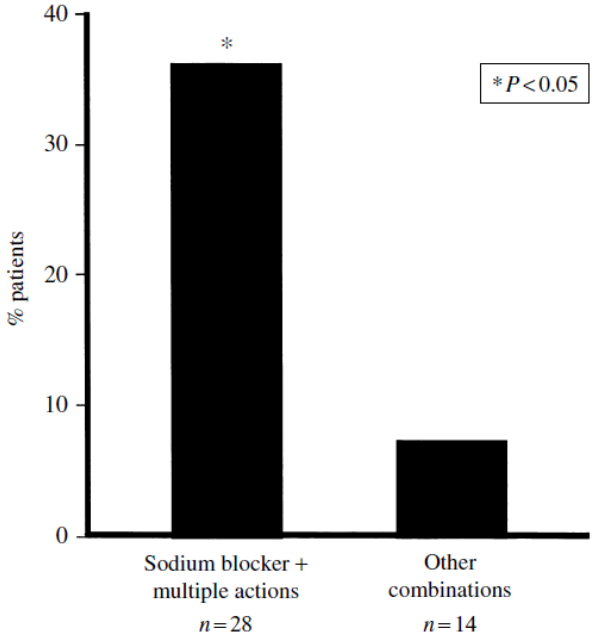
Medically refractory: 36%

Kwan P and Brodie M; Epilepsia 2001

Substitution Vs add-on after the first drug fails



No significant difference in efficacy and intolerable side effects observed between alternative monotherapy and add-on therapy



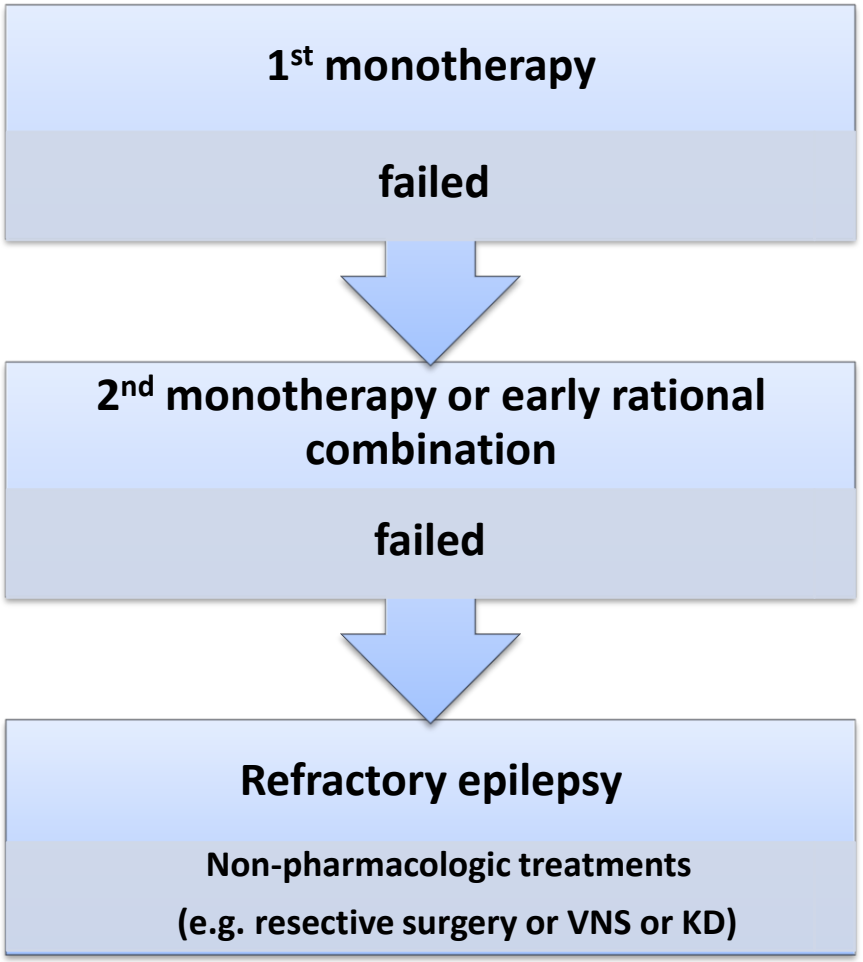
More pts become seizure-free in combination between **sodium channel blockers and a drug with multiple mechanisms** as opposed to other combinations

Kwan P and Brodie M; Seizure 2000

Early rational combinations is possible

- Explosion of new AEDs with better tolerability
- Less drug interactions
- Mechanistic diversity of new AEDs

ILAE definition (2009)
Drug-resistant (refractory) epilepsy as *"a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules (whether as monotherapies or incombination) to achieve sustained seizure freedom"*



AED mechanism of action

Different mechanistic groups suitable for combination therapy.

1 Sodium channel blockers
   (a) Fast-inactivated state—phenytoin, carbamazepine, lamotrigine, oxcarbazepine, eslicarbazepine
   (b) Slow-inactivated state—lacosamide

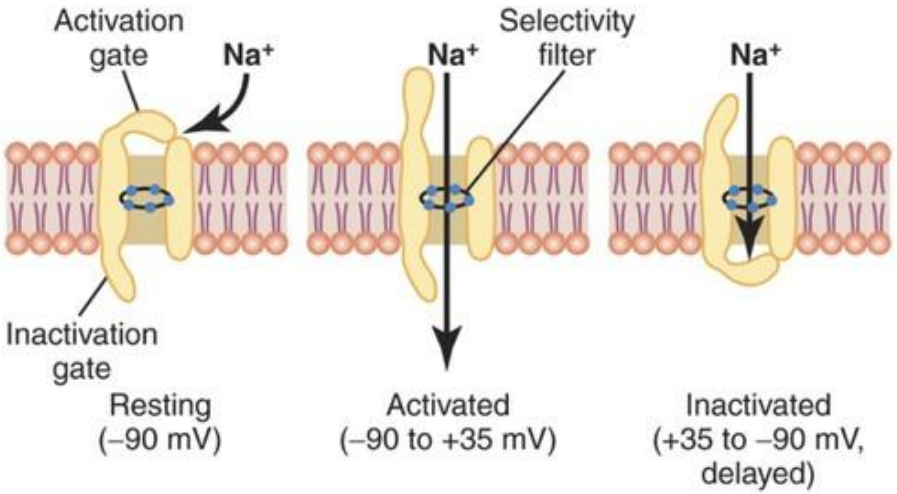
2 Calcium channel blockers
   (a) Low voltage activated channel—ethosuximide
   (b) High voltage activated channel—gabapentin, pregabalin

3 GABA-ergic drugs
   (a) Prolongs chloride channel opening—barbiturates
   (b) Increased frequency of chloride channel opening—benzodiazepines
   (c) Inhibits GABA-transaminase—vigabatrin
   (d) Blocks synaptic GABA reuptake—tiagabine

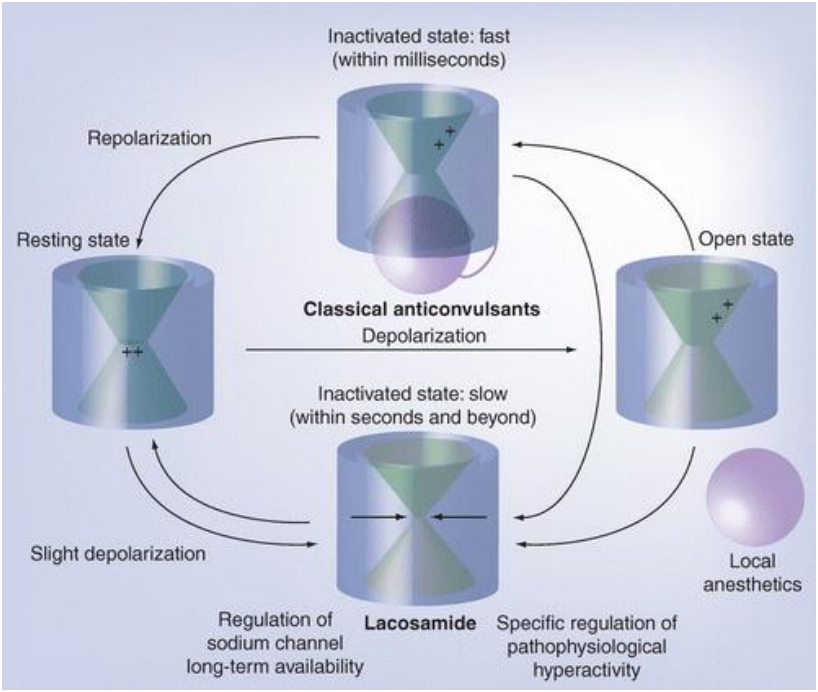
4 Synaptic vesicle protein 2A modulation—levetiracetam

5 Carbonic anhydrase inhibition—acetazolamide

6 Multiple pharmacological targets—sodium valproate, felbamate, topiramate, zonisamide, rufinamide



Sodium channel
-Activation gate
-Inactivation gate



Sodium channel
- Fast inactivation
- Slow inactivation

Rational polytherapy

- Rational combinations
  - ✓ evidence is still lacking
  - ✓ common sense: combine with different, perhaps multiple mechanisms of action
  - ✓ "LTG + VPA": synergism

- Avoidance
  - ✓ similar mechanisms with similar side effects profiles
    - CBZ + LTG
    - CBZ + LCM
    - OXC + LCM
    - LTG + LCM
  - ✓ certain combinations produce more side effects

- PB + VPA: sedation, weight gain
- PHT + CBZ: dizziness, diplopia
- VPA + LTG: dizziness, increased risk of SJS (but very efficacious in some patients)

Pisani F et.al; Epilepsia 1999
Brodie MJ and Yuen AWC; Epilepsy Res 1997

LTG dosing

- **LTG added to enzyme-inducing AEDs**
  - Week 1 and 2: 50 mg/day
  - Week 3 and 4: 100 mg/day
  - Increase by 100 mg/day every 1-2 weeks
  - Usual targeted dose: 300-500 mg/D
- **LTG added to a regimen containing VPA**
  - Week 1 and 2: 25 mg AD
  - Week 3 and 4: 50 mg/day
  - Increase by 25-50 mg/day every 1-2 weeks
  - Usual targeted dose: 100-400 mg/D (if adding to VPA alone: usual targeted dose at 100-200 mg/day)

Old versus New AEDs

- New AEDs which shown similar efficacy and equal or better tolerability than old AEDs in focal epilepsy
  - ✓ **LTG**
  - ✓ **OXC**
  - ✓ **ZNM**
  - ✓ **LVT**
- New AEDs which shown inferior efficacy to CBZ in focal epilepsy
  - ✓ **VBG**
  - ✓ **TGB**
  - ✓ **GBP**
- LTG, TPM are inferior to VPA in treating generalized epilepsy

- **Advantages of new AEDs**

✓ Comparable efficacy with old AEDs (inconclusive one AED is more or less effective)

✓ Mostly better tolerability

✓ Less drug interactions (much less or no protein binding/ most drugs are not hepatic metabolism)

Brodie MJ et.al; Neurology 2012
Marson AG et.al; Lancet 2007
Kalviainen R et.al; Arch Neurol 1995
Mattson RH et.al; NJEM 1992

Drug level monitoring

- **“Therapeutic range” :** The plasma concentration at which most patients respond

- Therapeutic decisions must be based primarily on direct evaluation of clinical response rather than drug measurement alone

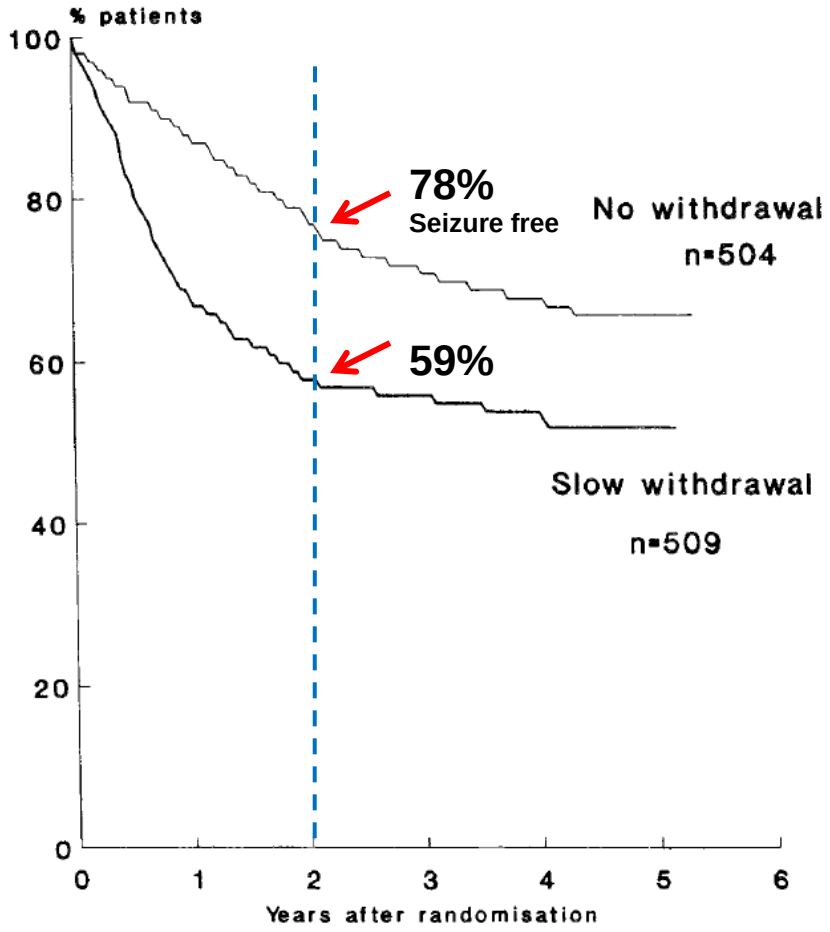
- AED therapy can often be optimized on purely clinical grounds

Drug level monitoring

- **Indications**

1) To minimize the difficulties in dosage adjustment, particularly in pts with polytherapy
2) The presence of physiological or pathological conditions
3) Establish a DDx of drug toxicity
4) When poor compliance is suspected
5) Critically-ill pts for whom clinical toxicity cannot be evaluated
6) Individualized therapeutic drug concentration

When to discontinue AEDs ?



- After a seizure, risk of a seizure in the next year – 50%

  After 1-year seizure free – 20%

  After 4-5 years seizure free – 10%

- **Considering AED discontinuation**
  - ✓ Adults: 2-5 yrs after seizure remission

MRC AED withdrawal study group; Lancet 1991

Some factors adversely affect the risk of seizure relapse after AED discontinuation

- ✓ Short duration of seizure freedom prior to drug withdrawal
- ✓ Epilepsy with onset in adolescence or adulthood
- ✓ JME
- ✓ Remote symptomatic epilepsy
- ✓ Hx of myoclonic seizures
- ✓ Hx of multiple seizure types
- ✓ Hx of primary or secondarily GTC
- ✓ Prolonged period before achieving seizure control
- ✓ Seizure while on treatment
- ✓ Seizure control requiring multiple drug therapy
- ✓ Abnormal EEG (?)
- ✓ Learning disability
- ✓ Associated neurological handicaps
- ✓ Previous failed attempts to stop medication

How do we practice ?

- **Increased risk for relapse**
  - JME
  - Adolescent or adult onset
  - Focal epilepsy (semiology, EEG, imaging)
  - Associated neurological deficit/mental retardation
  - Previous failed attempts to stop medication
  - Previous multiple seizure types/multiple AEDs

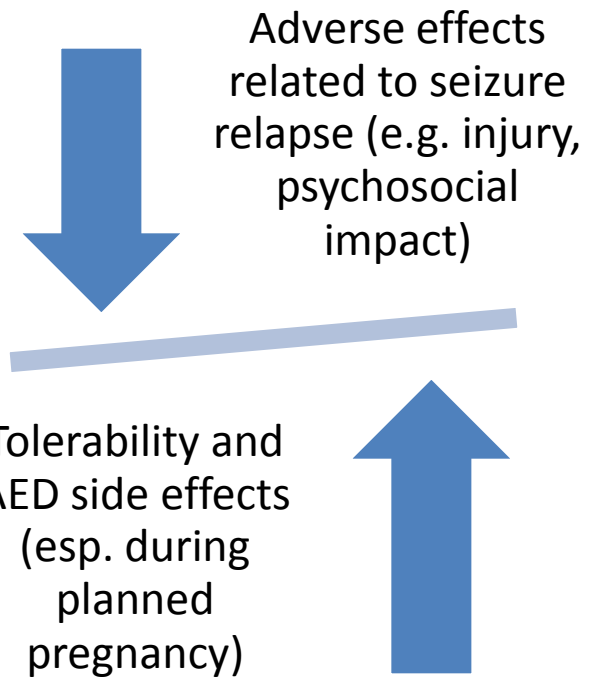
→ **If seizure relapse, greater psychosocial impact in adults than children**

→ **Most of self-remission epileptic syndromes are in childhood (CAE, BCERS)**

How do we practice ?

Discussion with the patient is the key!!!

- ✓ Provide statistic evidence to the patient
- ✓ Longer seizure remission is better (2-5 yrs)
- ✓ Balance risk of adverse effect associated with relapse of seizure and AED side effects
- ✓ Mild, brief, focal seizure, nocturnal occurrence is preferable to consider discontinuing the AEDs
- ✓ Clinical decision depends upon the patient
- ✓ If seizures recur after AED discontinuation, reinstitution of treatment leads to a good outcome, with -90% of patients again attaining another 2-year remission.



CASE 2

- 82 yo gentleman
- Presented with altered LOC which has occurred since 30 min prior to arriving the ER
- At ER: stuporous, equally spontaneous movements of all limbs, intubated
  - BP 200/120 mmHg

    Positive Doll's eye in both directions,

    Asymmetric pupils size: 4 mm at Rt, 3 mm at Lt, both RTL

    No long tract signs

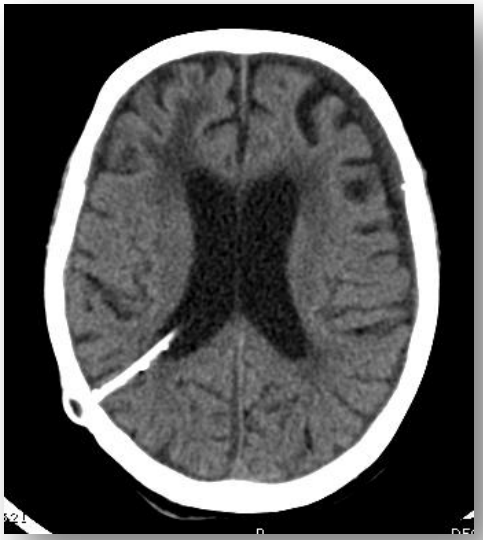
    Blood glucose 187 mg/dl

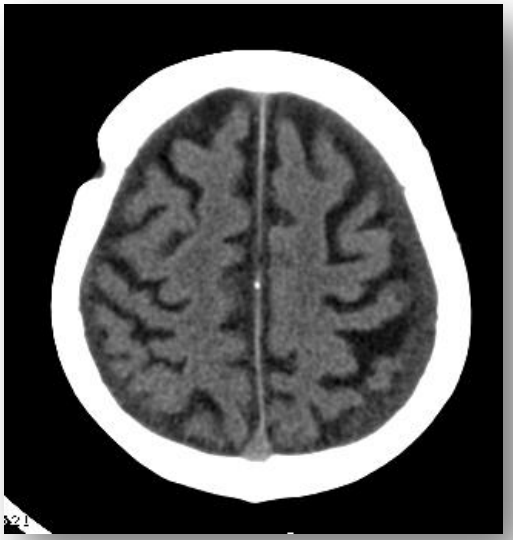
    EEG: normal sinus rhythm
- Underlying:
  - DM, HTN
  - 10 yrs ago: SDH at Rt frontal with right-sided limb clonic seizures requiring AED (details unknown) with subsequent discontinuation
  - NPH requiring shunt insertion

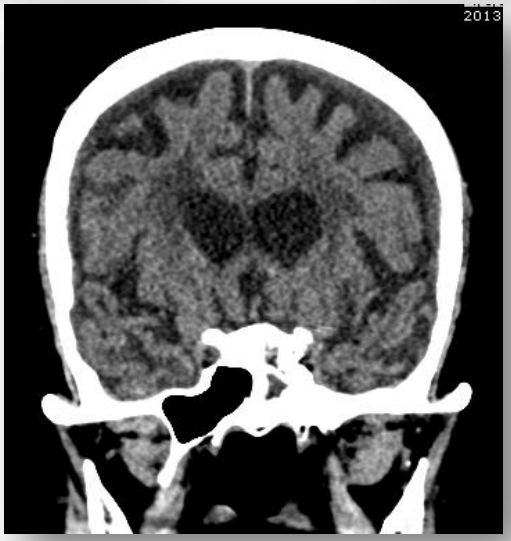
Hospital courses

- **At ward:** intubated and still obtunded with occasionally intermittent spontaneous limbs movements
- Gradually regained consciousness after 12 hours after the episode onset
- Spontaneous eye opening and followed simple commands at 24 hrs after the onset
- **Labs:** unremarkable, except for low Mg++ level

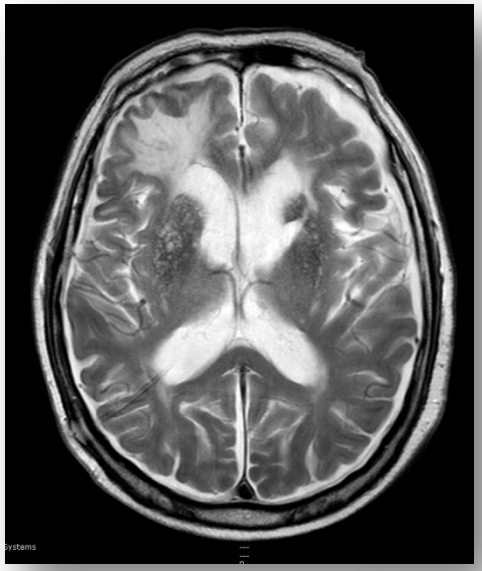
CT brain at ER (4 Aug 2013)

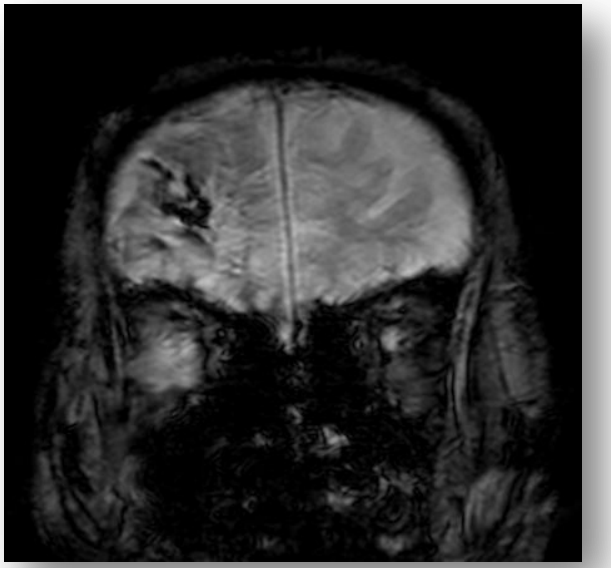


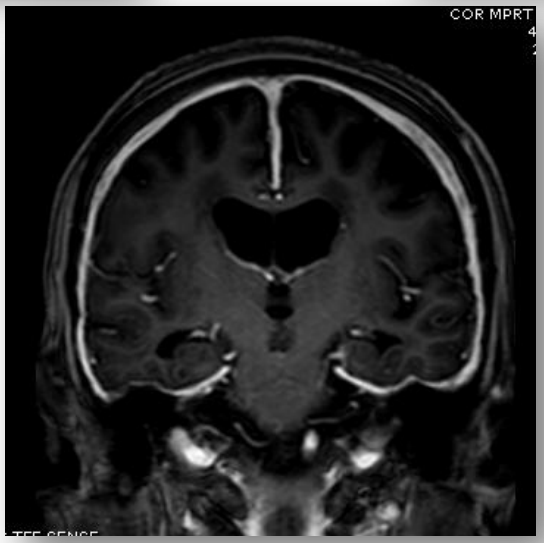




MRI brain at ward (still obtunded)







What's the DDx?

(A) TIA

(B) Epileptic seizure

(C) Transient increased ICP

(D) Intoxication

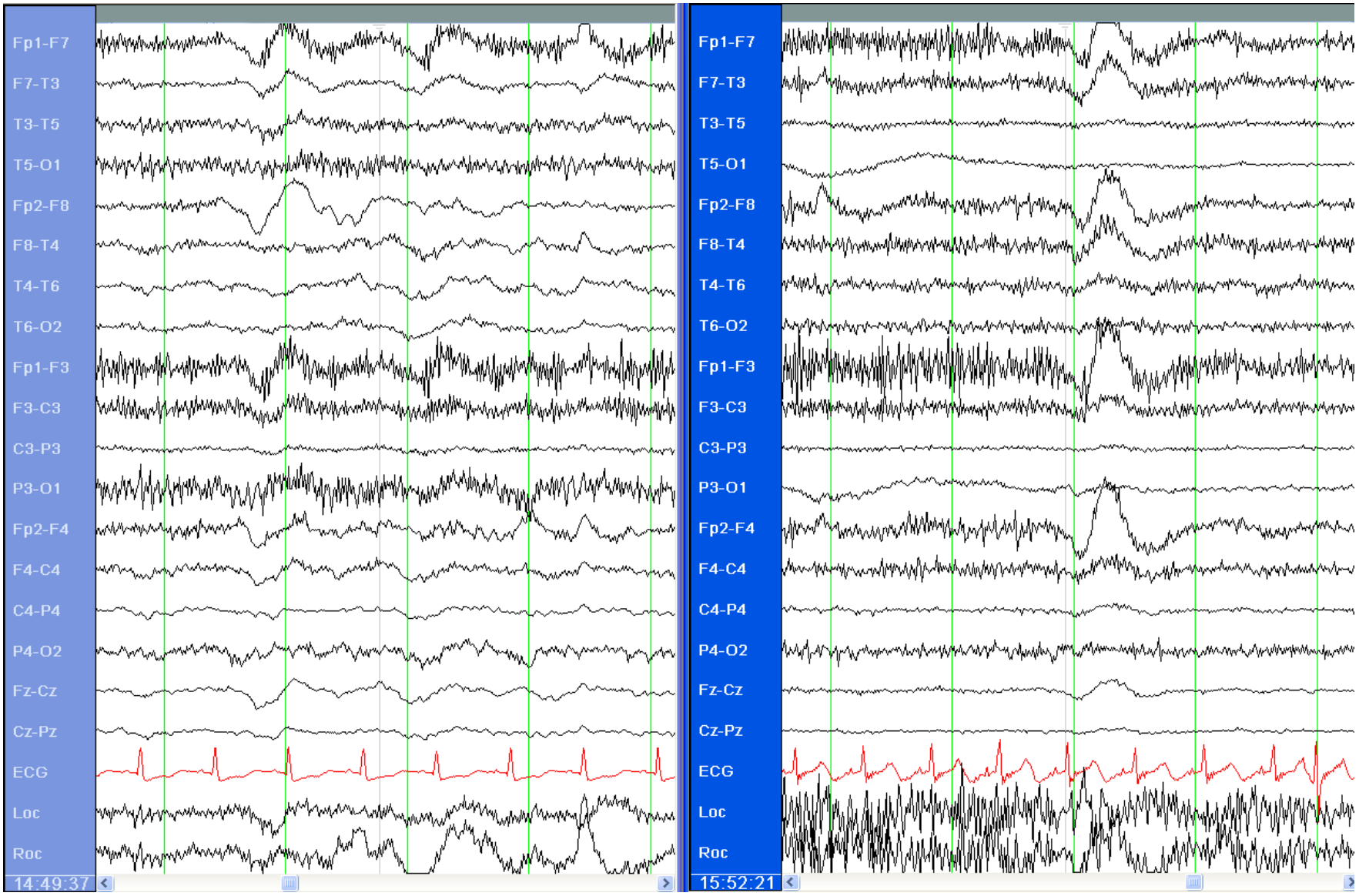
(E) Metabolic derangement

5 Aug 2013

(30 hrs after the onset, alert)

8 Aug 2013

5 uV/mm



CASE 3

- 29 yo lady, LHD, housewife
- Seizure started at age 15 yrs
- Only seizure type
  - **Generalized tonic seizure**
  - **Frequency: 0-1/ 3 months**
- MRI: left F-T-P encephalomalacia with porencephaly
- Medication:
  - **VPA 400 mg BID (800 mg/day)**
  - **Folic acid 5 mg/d**
  - **previous allergy to PHT (rash)**
- **At clinic, informed us that she has got pregnant with GA at 10 weeks , G1P0A0**

- What should the treating physician do with her AED ?

(A) Reducing the VPA dosage to < 500 mg/d

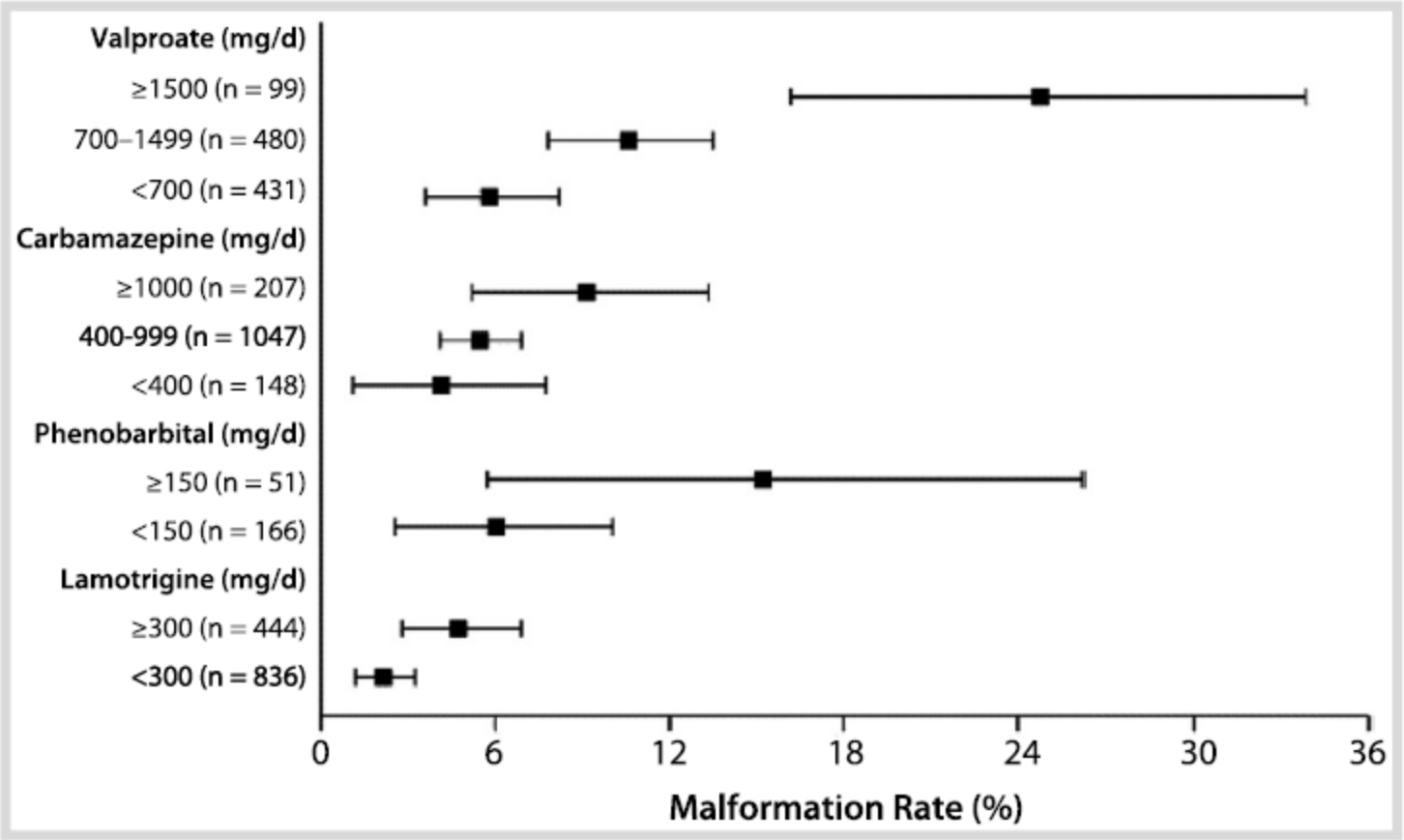
(B) Switching the VPA to another AED e.g. LTG

(C) Keeping VPA at the same total dose per day, but splitting to 4 times a day

Relative Timing and Developmental Pathology of Certain Malformations

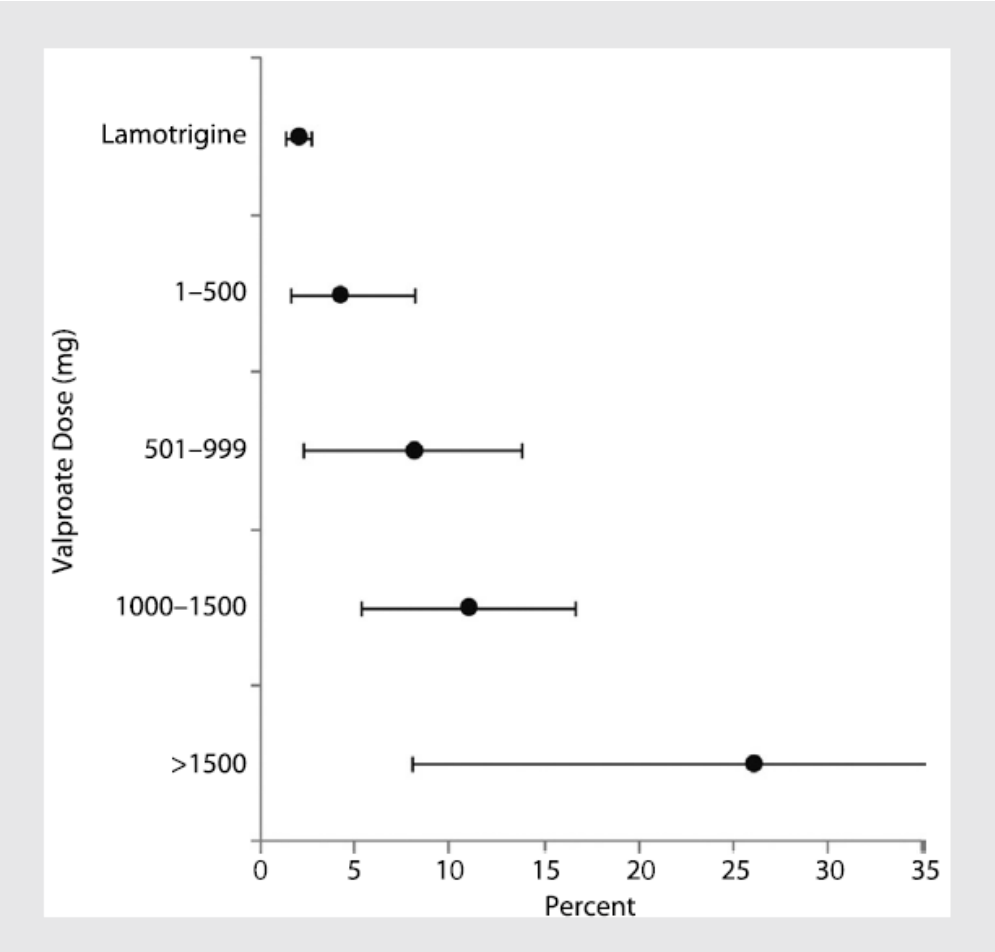
Tissues	Malformations	Postconceptional Age
CNS	Neural tube defect	28 d
Heart	Ventricular septal defect	42 d
Face	Cleft lip	36 d
	Cleft maxillary palate	47–70 d

Rates of major congenital malformations at 1 year after birth in relation to exposure to AED monotherapy according to data from the International Registry of Antiepileptic Drugs and Pregnancy



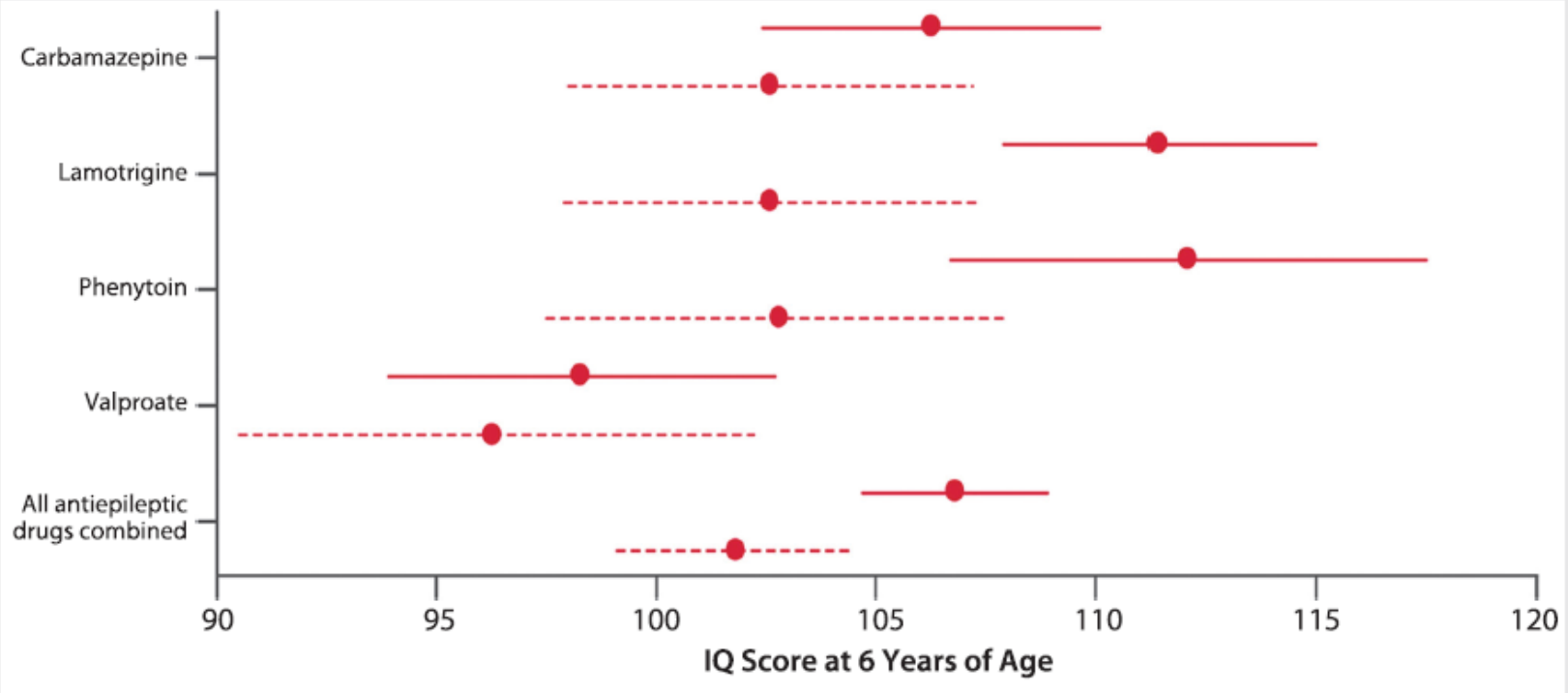
Tomson T et al, Lancet Neurol 2011

Risk of major malformations by average valproate dose (mg) during the first trimester



Hernandez-Dıaz S, et al,Neurology 2012

Child IQ at 6 years of age, by exposure to maternal antiepileptic drug use and periconceptional folate



Meador KJ, et al, Lancet Neurol 2013

What should we do next ?

- **Maternal serum AFP**

✓ examined at 14 wks GA = 38.77 ng/ml (0-10)

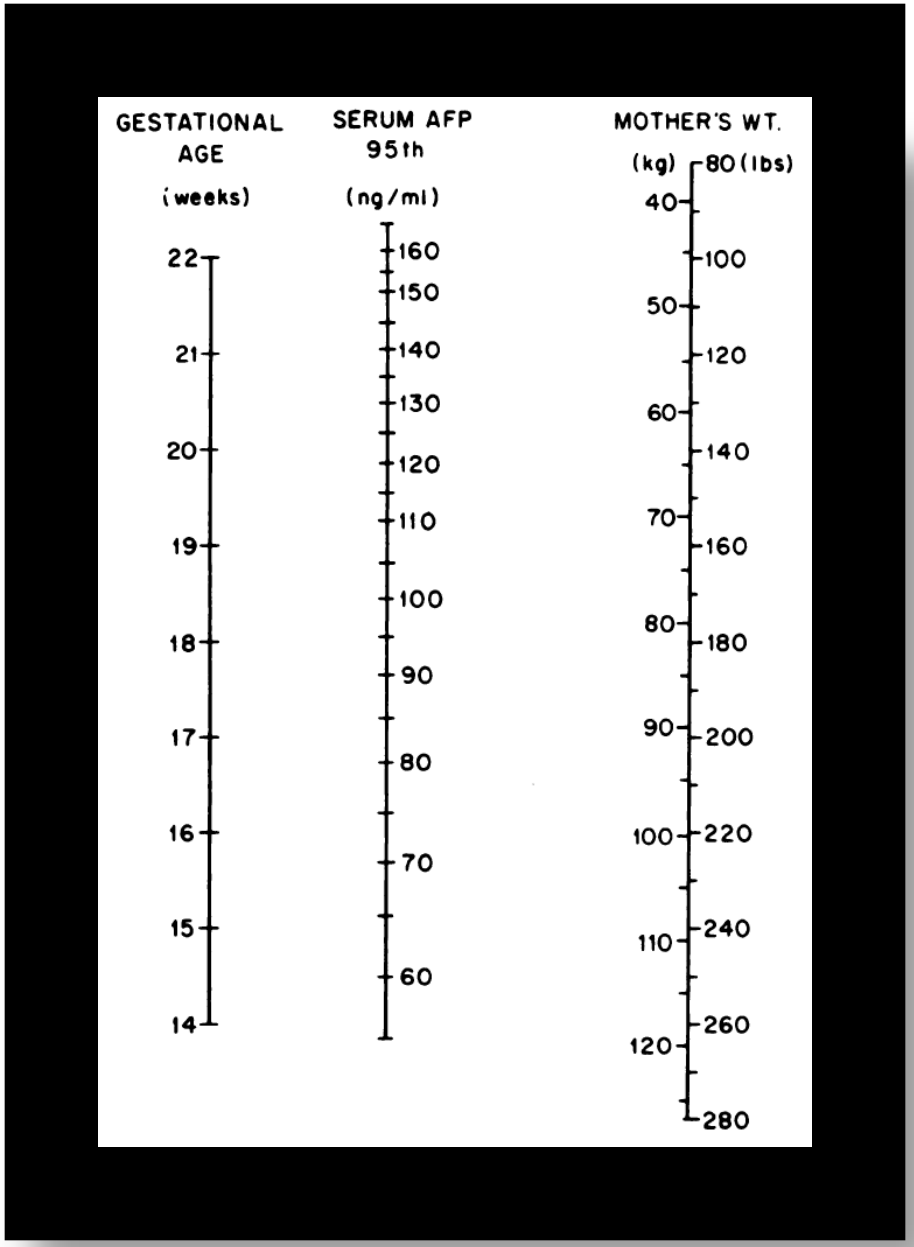
- **VPA level** while taking VPA 800 mg/d

✓ 34 μg/ml (50-100)

- **High-resolution USG** at 14 wks GA

✓ no fetal anomaly

✓ will repeat at 18-20 wks GA



Nomogram constructed to identify 95th percentile serum AFP at each week of gestation for maternal weights between 36.4 kg (80 lbs.) 127 kg (280 lbs.)

Crandall BF et.al; Clin Chem 1983

Chulalongkorn

Comprehensive

Epilepsy

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