Choosing AEDs in special situations

Dr. Chusak Limotai, MD., M.Sc., CSCN (C)

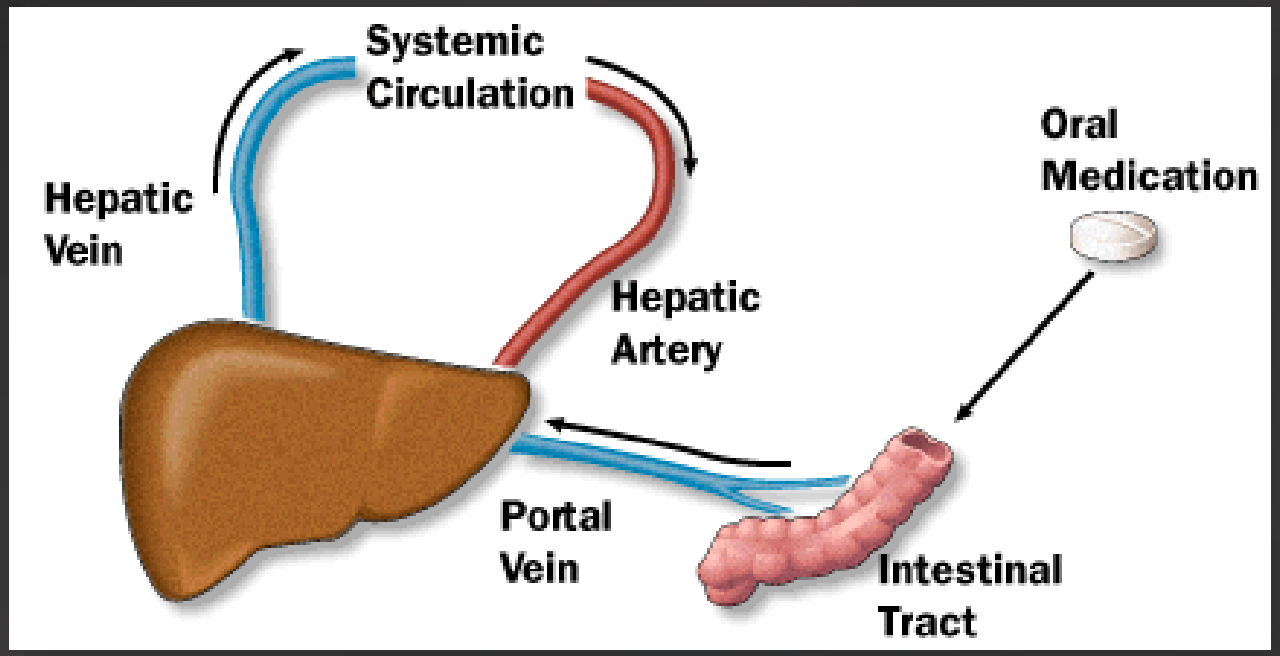
Chulalongkorn Comprehensive Epilepsy Center of Excellence (CCEC)

Talk overview

- Patients with hepatic or renal dysfunction
- Elderly patients
- Pregnant patients
- Psychiatric patients

Patients with hepatic or renal dysfunction

Effects of hepatic dysfunction on AEDs elimination


Systemic
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Medication
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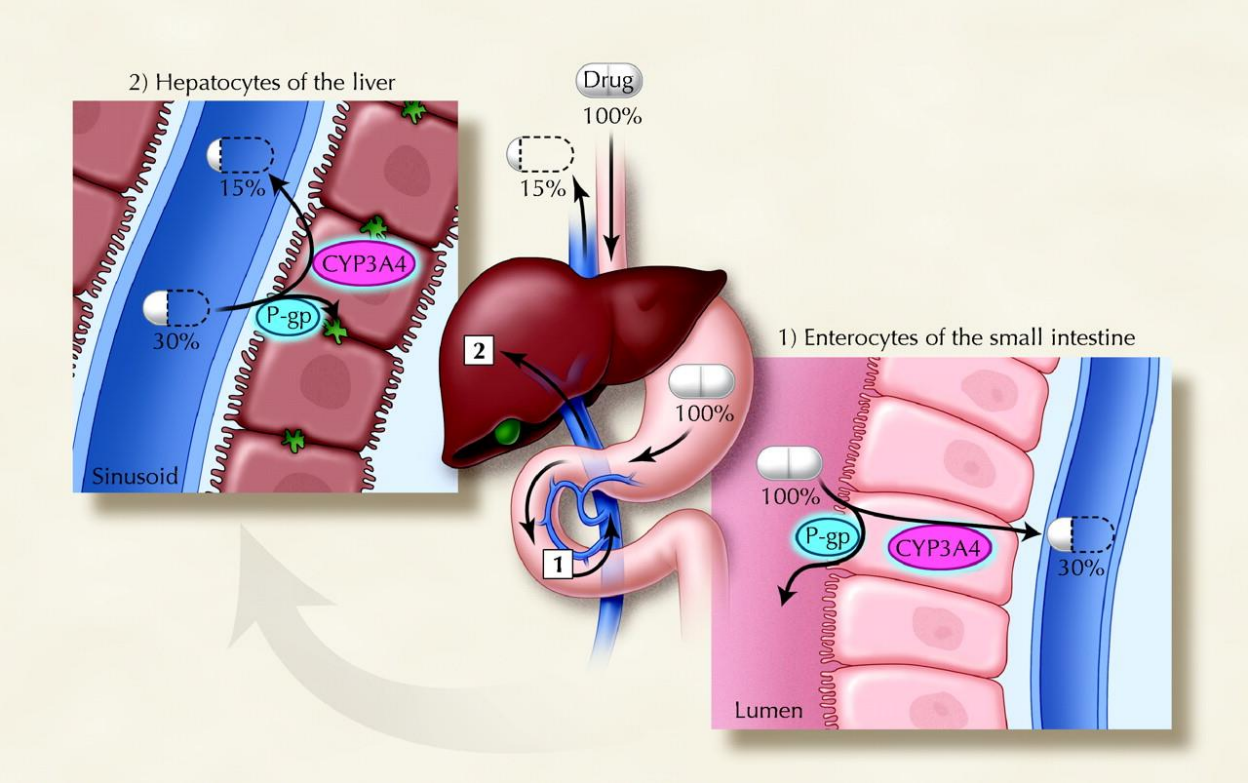
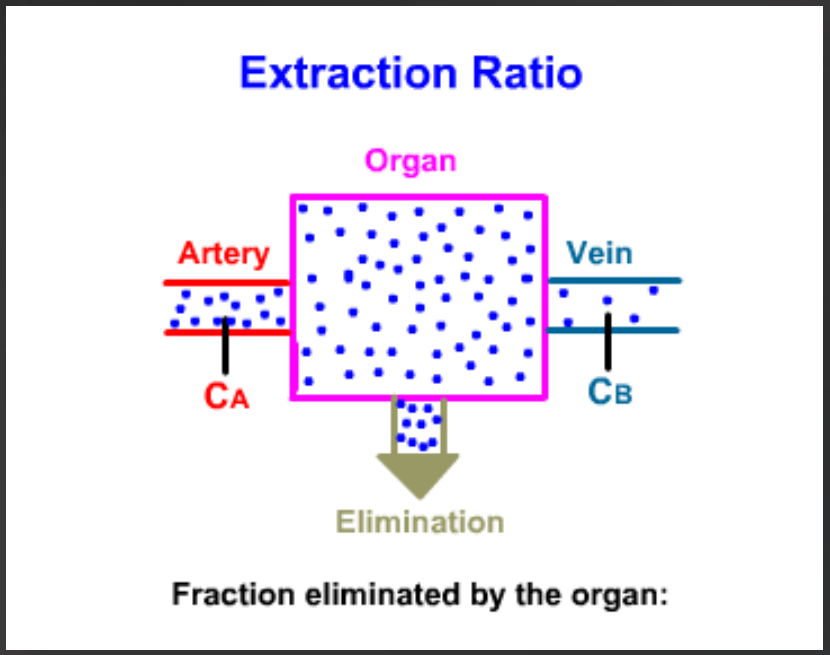
Intestinal
Tract

First pass metabolism



Effects of hepatic dysfunction on AEDs elimination



$$CL_H = Q_H \times E_H$$

CL_H = Hepatic clearance
Q_H = Hepatic flow rate
E_H = Hepatic extraction ratio

$$E_H = \frac{CL_{int} \times f_u}{Q_H + CL_{int} \times f_u}$$

CL_{int} = Hepatic intrinsic clearance (liver's enzymatic capacity)

f_u = unbound fraction of the drug

Extraction ratio (0 → 1)

- **Factors influencing on extraction ratio**

  1) **Hepatic blood flow**
  2) **Protein binding of the drug (unbound fraction)**
  3) **Hepatic intrinsic clearance**

$$E_H = \frac{CL_{int} \times f_u}{Q_H + CL_{int} \times f_u}$$

- High extraction ratio (≥ 0.7): "Flow-dependent"

  $CL_{int} \times f_u >>> Q_H$; $CL_H \approx Q_H$

- Low extraction ratio (≤ 0.3): "Capacity-limited"

  $CL_{int} \times f_u <<< Q_H$; $CL_H \approx CL_{int} \times f_u$

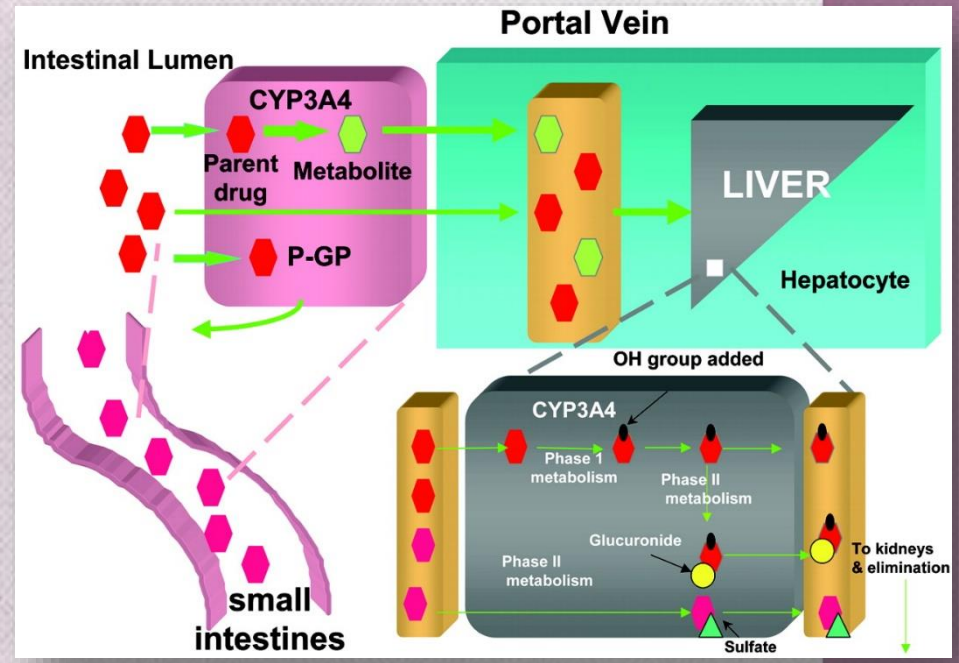
Table 1

Some examples of drugs with high and low hepatic extraction

High extraction ratio	Low extraction ratio
Antidepressants	Non-steroidal anti-inflammatory drugs
Chlorpromazine/haloperidol	Diazepam
Calcium channel blockers	Carbamazepine
Morphine	Phenytoin
Glyceryl trinitrates	Warfarin
Levodopa	
Propranolol	

Sloss A and Kubler P: www.australianprescriber.com; 2009

Drug metabolism (biotransformation)



Phase I: Oxidation (CYP 450), reduction, hydrolysis

Phase II: Conjugation

Liver diseases

- **Acute viral hepatitis (studies with small sample size) :**
  - **activity of the metabolic enzymes is relatively maintained**
  - **doses do not need to be altered in acute hepatitis**

- **Cirrhosis:**
  - **reduced activity of metabolic enzymes and decreased Q_H**
  - **metabolic enzymes are differentially affected depending on the severity of the cirrhosis**

Williams RL et.al: Clin Pharmacol Ther; 1976
Williams RL et.al; Clin Pharmacol Ther; 1977

Child-Pugh Classification

Table 2

Sloss A and Kubler P: www.australianprescriber.com;

Child-Pugh classification [1]

Parameter	Points assigned = 1	Points assigned = 2	Points assigned = 3
Ascites	Absent	Slight	Moderate
Bilirubin, micromol/L	<11	11–45	>45
Albumin, g/L	>35	28–35	<28
Prothrombin time – seconds over control or INR	<4 <1.7	4–6 1.7–2.3	>6 >2.3
Encephalopathy	None	Grade 1–2	Grade 3–4

Total score of 5–6 is grade A or well compensated disease (1 and 2 year survivals are 100% and 85%)

Total score of 7–9 is grade B or disease with significant functional compromise (1 and 2 year survivals are 80% and 60%)

Total score of 10–15 is grade C or decompensated liver disease (1 and 2 year survivals are 45% and 35%)

Depending on hepatic clearance and the therapeutic index of the drug, dose adjustments or drug avoidance may be required in grades B or C chronic liver disease.

Differential effects of severity of cirrhosis on metabolic enzyme activity

- **CYP 2C19**: significantly decreased with even mild liver cirrhosis (CP-A) and remained at a decreased level with increasing severity of disease
- **CYP 2C9, CYP 2E1**: not significantly decreased in mild to moderate liver disease (CP-A, CP-B); but decreased with severe cirrhosis (CP-C)

Frye RF et.al: Clin Pharmacol Ther; 2006

- **UGT, NAT**: significantly decreased in severe cirrhosis

Hoyumpa AM and Schenker S: Hepatology; 1991

Effects of renal dysfunction on AEDs elimination

Renal disease

- Most drugs that are significantly excreted unchanged in the urine, the *relationship between renal clearance and creatinine clearance is linear*
- Creatinine clearance and estimated GFR can be used to estimate doses needed to attain therapeutic concentrations

Dialysis

- Factors determine the drug elimination with dialysis

1) Molecular weight — LOW
2) Protein binding — LOW
3) Volume of distribution — LOW
4) Properties of the dialysis system

Increased elimination; supplemental dose is required

Routes of AED elimination

- ✓ **AEDs exclusively eliminated by liver**

  (***PHT, CBZ, VPA, LTG***, *RFM, STP, TGB,* ***CZP, CLB, DZP, LZP, MDZ****)*

- ✓ **AEDs eliminated unchanged by the kidney**

  (GBP, PGN, VGB)

- ✓ **AEDs eliminated by a combination of liver and kidney**

  (***PB***, ***TPM, LVT, ZNM, LCM, OXC***, *ESL, ETX, FBM, RTG, PRP)*

AEDs exclusively eliminated by liver

AEDs	Indications	Protein binding	Metabolism	Half-life (hours)	Effects of renal disease	Dialyzable	Effects of liver disease
Phenytoin (PHT)	Focal epilepsy	90% 70-80% in ESRD	CYP2C9 (major) CYP2C19 (used when PHT level > 18 µg/ml	7-42	Reduced protein binding, increased free fraction (Half-life Reduced to 8 hours in CRF*)	low 2-4.5%	Acute (viral) hepatitis: no significant effect Cirrhosis: no study
Carbamazepine (CBZ)	Focal epilepsy	70-80%	CYP3A4 (major) CYP1A2, CYP2C8	12-17 and 5-10 h for 10,11-epoxide	Does not affect the protein binding	low	No study
Valproic acid (VPA)	Idiopathic generalized epilepsy, focal epilepsy	90% 70-80% in ESRD	Glucuronidation (major) β-oxidation CYP2C9, CYP2C19, CYP2A6	6-17	Reduced protein binding, increased free fraction but no need to adjust therapeutic range (due to increased Vd#)	Low (<20%)	Acute (viral) hepatitis: no significant effect Moderate to severe alcoholic cirrhosis: increased unbound fraction by twofold
Lamotrigine (LTG)	Idiopathic generalized epilepsy, focal epilepsy	55%	UGT1A4	12-60	No clinical significance	low	Acute (viral) hepatitis: no study Moderate to severe alcoholic cirrhosis: prolonged half-life

AEDs	Indications	Protein binding	Metabolism	Half-life (hours)	Effects of renal disease	Dialyzable	Effects of liver disease
Diazepam (DZP)	Acute seizures	98%	CYP2C19, CYP3A4	24-48	No study	low	Acute hepatitis: no study Cirrhosis (mixed stages) and chronic acute viral hepatitis: prolonged half-life
Clonazepam (CZP)	generalized epilepsy including LGS**	85%	CYP3A4	22-40	No study	low	No study
Clobazam (CLB)	generalized epilepsy including LGS	85%	CYP2C19, CYP3A4	10-30	No study	low	Acute viral hepatitis and cirrhosis: not statistical significance but with trend of decreased protein binding (increased Vd resulting in increased half-life)
Lorazepam (LZP)	Acute seizures	93%	UGT2B15	17-56	No clinical significance	low	Acute hepatitis and cirrhosis: decreased protein binding resulting in a twofold increase in half-life
Midazolam (MDZ)	Acute seizures	95%	CYP3A4 (high extraction ratio)	2-7	No clinical significance (increased free fraction, but no need to adjust dose)	low	Acute hepatitis: no study Severe cirrhosis: reduced clearance due to decreased hepatic blood flow

AEDs	Liver disease	Renal disease	Supplemental dose after dialysis (4 hours of hemodialysis)
Phenytoin (PHT)	May need lower doses with severe cirrhosis	Reduced therapeutic range to 5-10 µg/ml	Usually not necessary. However, significant extraction has been reported with use of high-efficiency dialyzers
Carbamazepine (CBZ)	Lower doses	No need to adjust doses	Not necessary
Valproic acid (VPA)	Caution advised Need to be reduced by at least 50% in moderate to severe cirrhosis	No need to adjust doses	Usually not necessary. However, significant extraction has been reported with use of high-efficiency dialyzers
Lamotrigine (LTG)	Decreased by 50% in moderate cirrhosis (CP*-B) and by 75% in severe cirrhosis (CP-C)	No need to adjust doses	Usually not necessary
Diazepam (DZP)	Prolonged half-life; lower initial dose and slower titration in mild to severe cirrhosis	No need to adjust doses	Not necessary
Clonazepam (CZP)	Prolonged half-life; lower initial dose and slower titration in mild to severe cirrhosis	No need to adjust doses	Not necessary
Clobazam (CLB)	Prolonged half-life; lower initial dose and slower titration	No need to adjust doses	Not necessary
Lorazepam (LZP)	May need larger initial dose due to increased Vd; half-life is also increased	No need to adjust doses	Not necessary
Midazolam (MDZ)	Prolonged half-life; reduced doses in patients with severe cirrhosis	No need to adjust doses	Not necessary

AEDs eliminated unchanged by the kidney

AEDs	Indications	Protein binding	Metabolism	Half-life (hours)	Effects of renal disease	Dialyzable	Effects of liver disease
Gabapentin (GBP)	Focal epilepsy	None	None	5-9	Reduced clearance of unchanged free fraction in a linear relationship with CL_{CR}*	35%	None
Pregabalin (PGN)	Focal epilepsy	None	None	5-7	Reduced clearance of unchanged free fraction in a linear relationship with CL_{CR}*	50-60%	None
Vigabatrin (VGB)	Focal epilepsy, infantile spasm	None	None	5-8	Reduced clearance of unchanged free fraction in a linear relationship with CL_{CR}*	unknown	None

AEDs	Liver disease	Renal disease Adjusted doses according to CL_{CR}				Supplemental dose after dialysis (4 hours of hemodialysis)
		60-89 ml/min	30-59 ml/min	15-29 ml/min	< 15 ml/min	
Gabapentin (GBP)	Not necessary	900-3600 mg/d (BID or TID)	400-1400 mg/d (BID)	200-700 mg/day (QD)	100-300 mg/d (QD)	Necessary: 100-200% of total daily dose
Pregabalin (PGN)	Not necessary	150-600 mg/d (BID or TID)	75-300 mg/d (BID or TID)	25-150 mg/day (QD or BID)	25-75 mg/d (QD)	Necessary: 100-200% of total daily dose
Vigabatrin (VGB)	Not necessary	1000-3000 mg/d	25% dose reduction for GFR > 50 to 80 ml/min	50% dose reduction for GFR > 30 to 50 ml/min	75% dose reduction for GFR > 10 to <30 ml/min	No study

AEDs eliminated by a combination of liver and kidney

AEDs	Indications	Protein binding	Metabolism	Half-life (hours)	Percent renal elimination Effects of renal disease	Dialyzable	Effects of liver disease
Phenobarbital (PB)	Focal and generalized epilepsy	45-60%	CYP2C9 (major), CYP2C19, CYP2E1, glucosidase	36-118	20-25% No study	unknown	Acute hepatitis: no significant effect Moderate to severe cirrhosis: prolonged half-life
Levetiracetam (LVT)	Focal and generalized epilepsy	<10%	Amidase (hydrolysis in blood) (independent of CYP system)	6-8	66% Prolonged half-life	50%	Acute hepatitis: no study Severe cirrhosis: prolonged half-life
Oxcarbazepine (OXC)	Focal epilepsy	38% (active metabolite ; MHD)	Cytosolic arylketone reductase for OXC and UGT for MHD	8-11 for MHD*	27% Prolonged half-life	Unknown (may be significant)	Acute hepatitis: no study Mild to moderate cirrhosis: no significant effect Severe cirrhosis: no study

AEDs	Indications	Protein binding	Metabolism	Half-life (hours)	Percent renal elimination Effects of renal disease	Dialyzable	Effects of liver disease
Topiramate (TPM)	Focal and generalized epilepsy	15%	CYP isoenzymes not identified	21	60-70% Prolonged half-life	50%	Acute hepatitis: no study Cirrhosis: unclear
Zonisamide (ZNM)	Focal and generalized epilepsy	40-60%	CYP3A4 (major), CYP2C19, NAT2** (15%)	27-70	35% Prolonged half-life	unknown	Acute hepatitis: no study Cirrhosis: no study
Lacosamide (LCM)	Focal epilepsy	<15%	Not identified	13	40% Prolonged half-life	50%	Acute hepatitis: no study Mild to moderate cirrhosis: 50-60% higher AUC# (19) Severe cirrhosis: no study

AEDs	Liver disease	Renal disease Adjusted doses according to CL_{CR}				Supplemental dose after dialysis (4 hours of hemodialysis)
		60-89 ml/min	30-59 ml/min	15-29 ml/min	< 15 ml/min	
Phenobarbital (PB)	May need lower dose if moderate to severe cirrhosis (Dose should be reduced by 50%)	May be required in severe renal impairment No need to adjust in mild to moderate renal impairment				Probably necessary, but not well established. Pre- and postdialysis levels recommended for dosing
Levetiracetam (LVT)	May need lower dose if severe cirrhosis (Dose should be reduced by 50%)	500-1000 mg BID	250-750 mg BID	250-500 mg BID	250-500 mg BID	Necessary: 50% pf total daily dose
Oxcarbazepine (OXC)	Unclear	300-600 mg BID	300-600 mg BID	Reduce dose by 50%	Insufficient data, use with caution	No study (probably necessary)

AEDs	Liver disease	Renal disease Adjusted doses according to CL_{CR}				Supplemental dose after dialysis (4 hours of hemodialysis)
		60-89 ml/min	30-59 ml/min	15-29 ml/min	< 15 ml/min	
Topiramate (TPM)	May need lower dose if severe cirrhosis	100-200 mg BID	50-100 mg BID for GFR < 70 ml/min	50-100 mg BID	50-100 mg BID	Necessary: 50% pf total daily dose
Zonisamide (ZNM)	May need lower dose if moderate to severe cirrhosis	200-400 mg QD	200-400 mg QD	Insufficient data, use with caution	Insufficient data, use with caution	May be necessary: 25-50% of total daily dose
Lacosamide (LCM)	May need lower dose. A maximum dose of 300 mg/d in patients with mild to moderate cirrhosis In severe cirrhosis: unclear but likely need lower dose	200-400 mg (BID)	No adjustment necessary	Maximum dose of 300 mg/d for GFR < 30 ml/min	Maximum dose of 300 mg/d for GFR < 30 ml/min	Necessary: 50% pf total daily dose

AED-induced hepatic and renal disease

Hepatic injuries induced by certain AEDs

- **A mild elevation (< 2-3 fold)** of hepatic enzymes (AST, ALT, ALP) during initiation phase (within a month) due to mostly enzyme-inducing AEDs (phenytoin, carbamazepine, phenobarbital) is usually **insignificant**

- A more than 2 to 3 fold increase or an elevation in pre-existing hepatic dysfunction warrants further investigations

Hepatic injuries induced by certain AEDs

Valproate and felbamate are two AEDs associated with high risk of hepatic injury

- For **aromatic ring-containing AEDs (CBZ, PB, PHT, OXC, LTG)**, idiosyncratic hepatotoxicity develops in the context of **"AED hypersensitivity syndrome"**

Zaccara G et.al: Epilepsia; 2007

Conclusion remarks

Selection of AEDs in patients with hepatic dysfunction

- AEDs with wide therapeutic windows are more preferable than narrow-window AEDs (LVT, LTG are better than PHT, CBZ etc.)

- AEDs eliminated by kidney are more preferable

  AEDs eliminated exclusively by liver or by a combination of liver and kidney can be used but with adjusted lower doses

- For new-onset acute hepatic dysfunction, valproate, felbamate, and if possible aromatic ring-containing AEDs should be avoided since the risk of further hepatic injury

- Liver cirrhosis has more previous studies and more evidence of higher impacts on metabolism of AEDs than acute (viral) hepatitis

Conclusion remarks

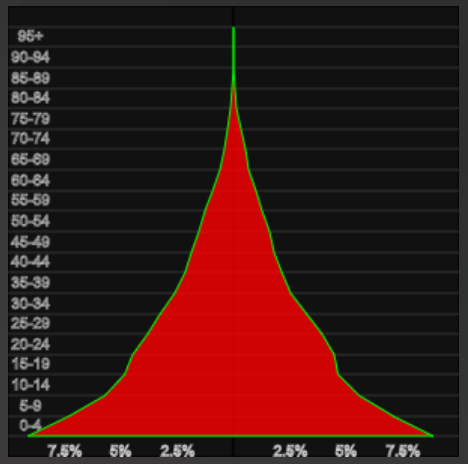
Selection of AEDs in patients with renal dysfunction

- AEDs with wide therapeutic windows are more preferable than narrow-window AEDs (LVT, LTG are better than PHT, CBZ etc.)
- Any AEDs can be used but with adjusted doses according to CL_{CR} or GFR
- For less difficult drug administration, AEDs metabolized at liver may be more preferable
- In patients with dialysis, supplemental doses is required in patients receiving AEDs which are mainly eliminated at kidney
  AEDs with high protein binding and being metabolized at liver are more preferable

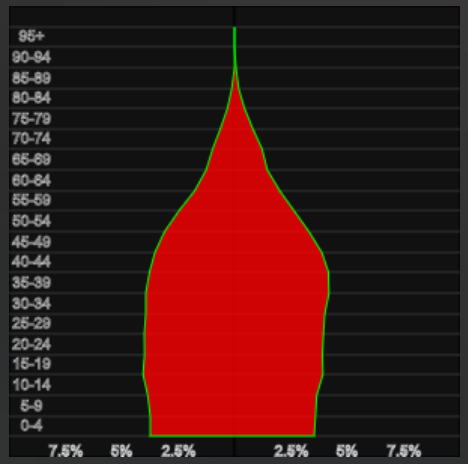
Elderly patients

Thailand population pyramid

1950

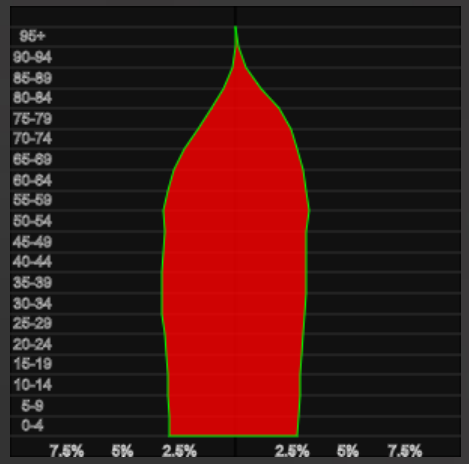


2010



60 yrs

2050



www.world lifeexpectancy.com

Epidemiology of epilepsy in elderly

- Incidence of epilepsy (recurrent unprovoked seizure) in general population

  - developed countries ranges from 24 to 53 per 100,000 patient-years

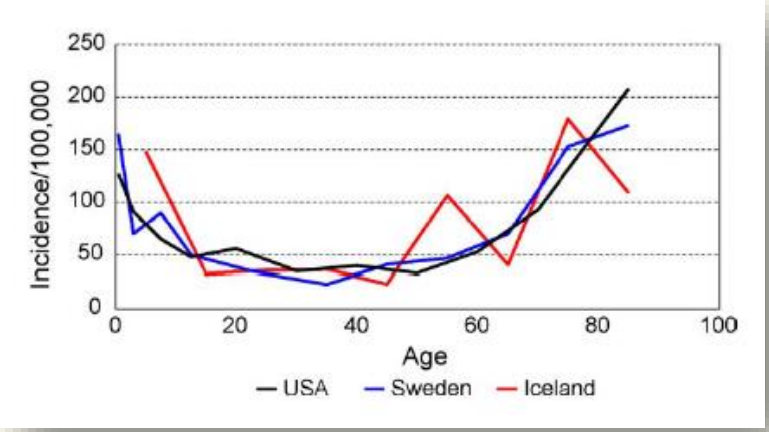
  - developing countries ranges from 64 to 113 per 100,000 patient-years

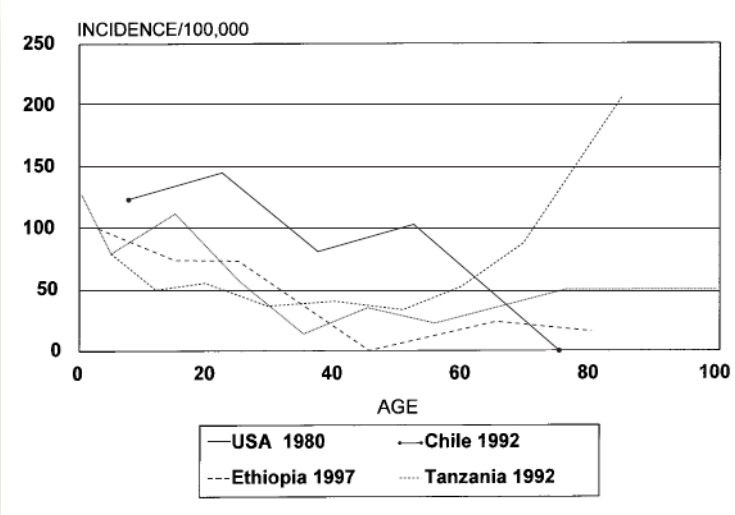
- ***Incidence of epilepsy is high in the elderly***, contrary to the popular belief

  After the age of 70, incidence of epilepsy is higher than during the first 10 years of life

Engel JJr and Pedley TA; Epilepsy: a comprehensive textbook: 2nd edition; 2008: 43-56

U-shaped curve

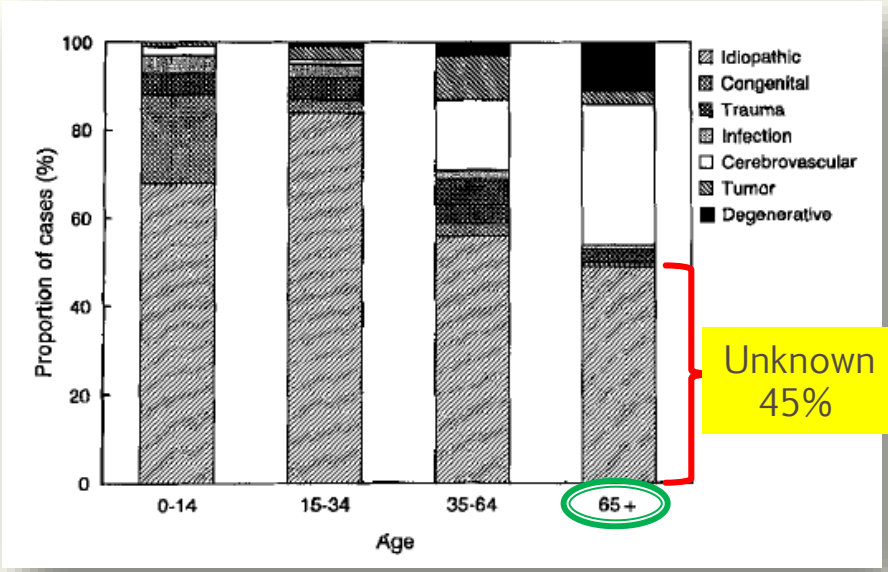




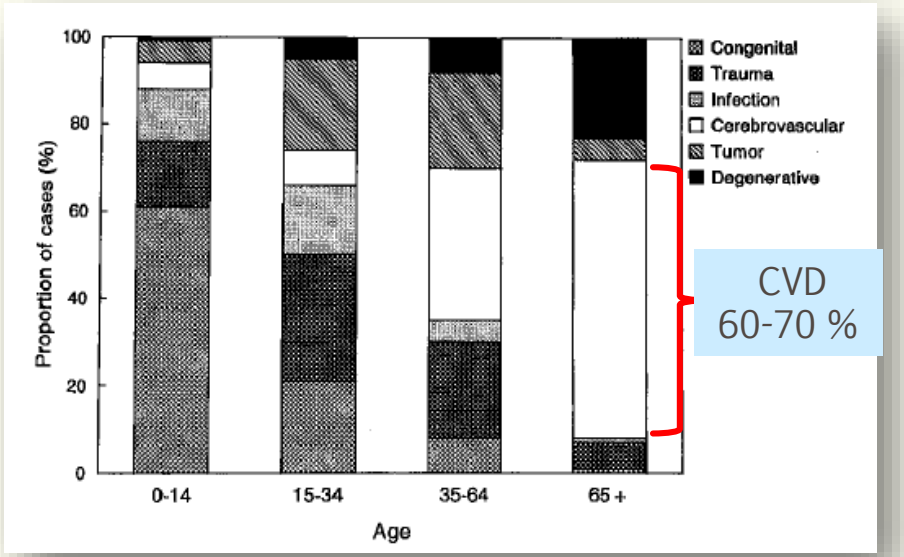
Hauser WA et.al; Epilepsia: 1993
Everitt AD and Sander JW: BMJ: 1998
Cloyd J et.al: Epilepsy Res: 2006
Engel JJr and Pedley TA; Epilepsy: a comprehensive textbook: 2nd edition; 2008: 43-56

Cause of epilepsy in the elderly

Hauser WA et.al; Epilepsia: 1993



Proportion of cases of newly diagnosed epilepsy assigned to specific etiologic categories within age groups



Among cases with known etiology; CVD was the leading cause of epilepsy in the elderly

Association between late-onset seizures/epilepsy and subsequent stroke

- Epileptic seizures/epilepsy and cerebrovascular disease show a ***"bidirectional relation"***

- The hypothesis of ***"Vascular heralding epilepsy"*** emerged in 1978 and has been supported by subsequent studies

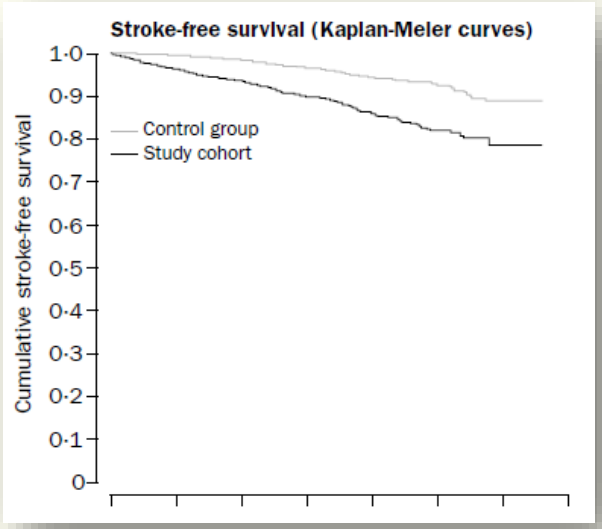
  - **The onset of seizures in late life is associated with a striking increase in the risk of stroke**

  - Many patients who present with otherwise unexplained seizures are found to have occult cerebrovascular disease

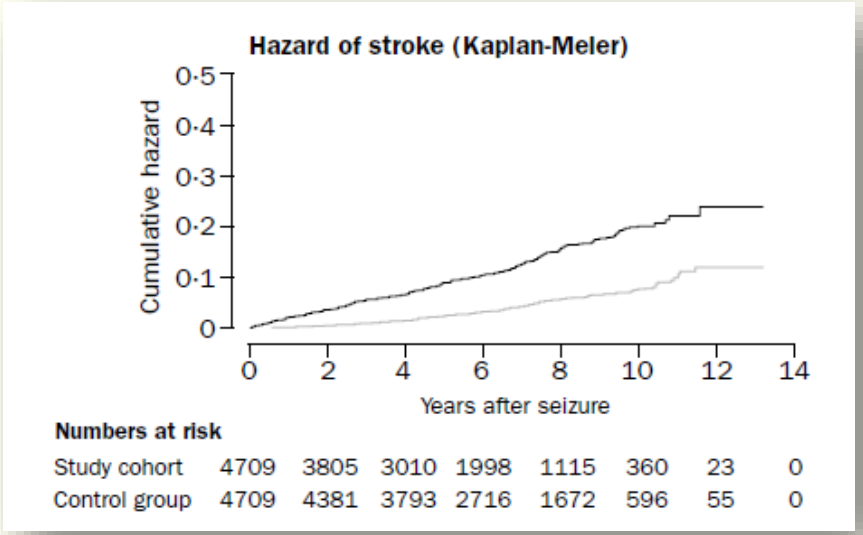
- Epileptic seizures might be a harbinger of future stroke

Shinton RA et.al; Lancet: 1987
Cleary P et.al; Lancet: 2004
Brigo F et.al; Epilepsy & behavior: 2014

Association between late-onset seizures/epilepsy and subsequent stroke



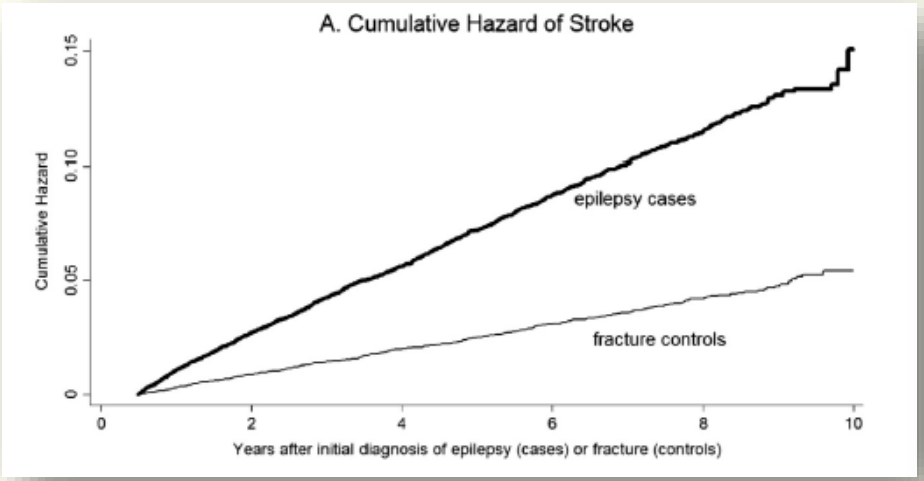
The **relative hazard of stroke** at any point for people with seizures compared with the control group was **2.89** (95% CI 2,45-3.41)

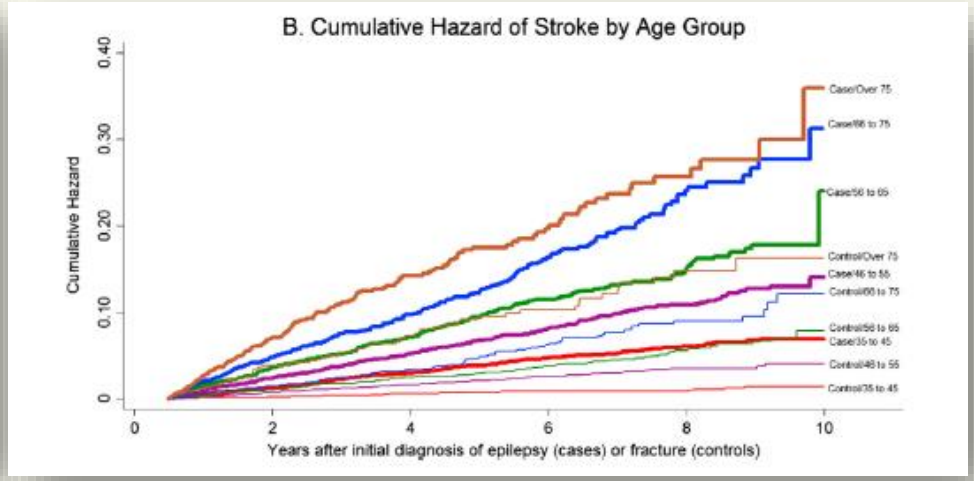


The hazard of stroke over time in studied patients and control group

Cleary P et.al; Lancet: 2004

Stroke after adult-onset epilepsy (aged ≥ 35 years)





Cases with epilepsy showed a
60% higher risk of stroke (HR 1.6; 95% CI 1.42-1.80)

The risk of stroke in cases with epilepsy increased faster and was similar to that in controls who were ≥ 10 yrs older

Adult-onset epilepsy (age ≥ 35 yrs) warrants consideration for occult CVD as an etiology of epilepsy

Wannamaker BB et.al; Epilepsy & behavior: 2015

Vascular determinants of epilepsy

- There may be a relationship between vascular factors and the risk of late-onset epilepsy

- presence of any of these indicators (myocardial infarction, peripheral vascular disease, hypertension, serum total cholesterol, and left ventricular hypertrophy) was ***twice*** as common among subjects with late-onset epilepsy as compared with subjects without epilepsy (OR = 2.0, 95% CI 0.9-4.2)

Li X et.al; Epilepsia: 1997

TREATMENT WITH AEDS

Age-related change in pharmacokinetics and pharmacodynamics

Pharmacokinetics

- **Renal excretion is declined with age**
- Absorption, protein binding, and hepatic drug metabolism are not altered in old age, except in those who are frail or malnourished
- The fat content rises, where the water content decreases in aging body (Vd of lipophilic drug is increased eg. Diazepam)

Pharmacodynamics

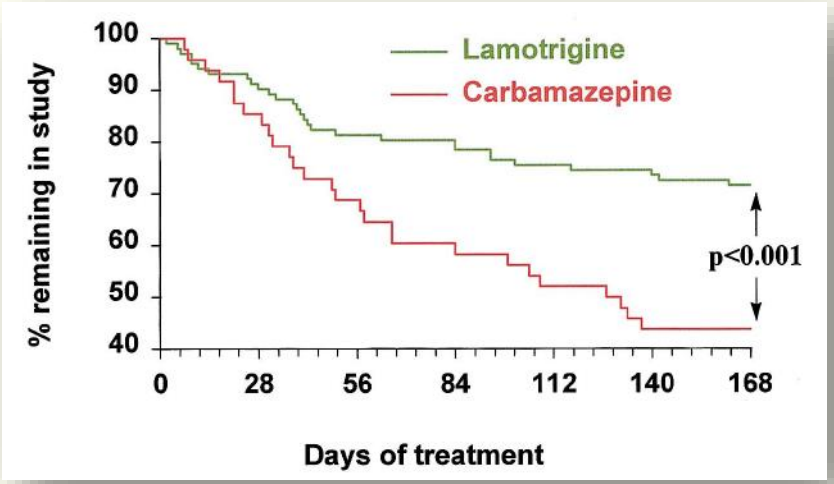
- **Counterregulatory (homeostatic) processes are attenuated**
- The incidence of adverse effects is higher in the elderly, despite the general decline in receptor number or responsiveness

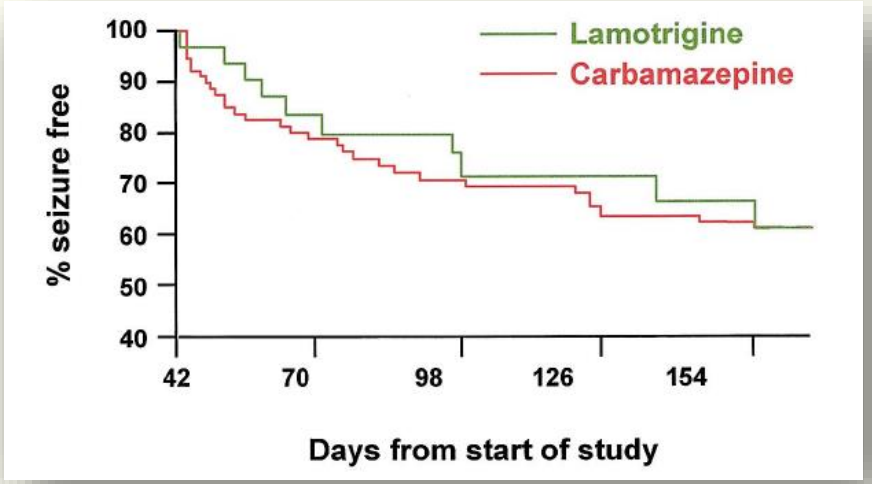
“The elderly people are more vulnerable to develop the side effects from the drugs”

ElDesoky ES; American Journal of Therapeutics: 2007; Turnheim K; Experimental Gerontology: 2003

RCTs in the AED treatment of epilepsy in the elderly

3 RCTs in the elderly

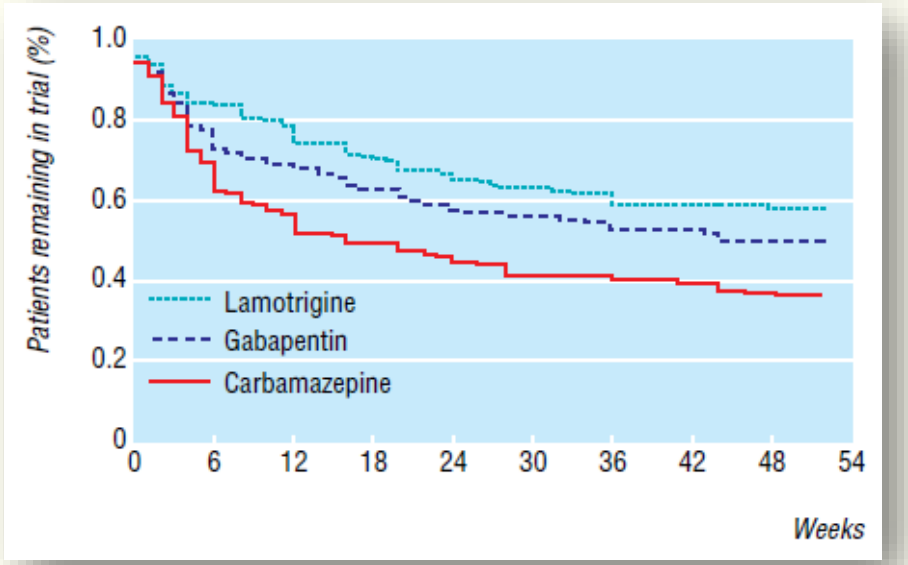


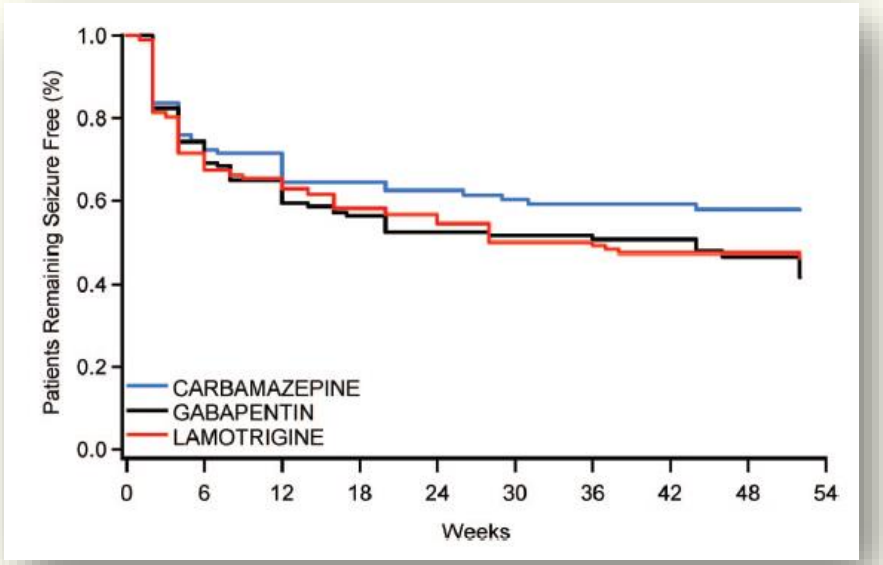


Comparable efficacy between CBZ and LTG, but significantly more patients in CBZ group withdrew from the study due to the side effects

Brodie MJ et.al; Epilepsy Res: 1999

LTG and GBP versus CBZ





Rowan AJ et.al; Neurology: 2005

LTG versus sustained-release CBZ

An International Multicenter Randomized Double-Blind Controlled Trial of Lamotrigine and Sustained-Release Carbamazepine in the Treatment of Newly Diagnosed Epilepsy in the Elderly

*Erik Saetre, †Emilio Perucca, ‡§Jouko Isojärvi and ¶Leif Gjerstad on behalf of the LAM 40089 Study Group

LTG and CBZ showed comparable effectiveness, with a trend for higher seizure-free rates for CBZ and better tolerability for LTG

Saetre E AJ et.al; Epilepsia: 2007

ILAE guideline in 2013

- **LTG and GBP** were established as Level A recommendation in the elderly with partial-onset seizures

Glauser T et.al; Epilepsia: 2013

A survey of common AED being used for the elderly with epilepsy

Antiepileptic drug	% (n = 9,628)
Phenobarbital	2.5
Phenytoin	67.0
Carbamazepine	8.5
Valproate	5.6
Gabapentin	11.0
Lamotrigine	1.6
Levetiracetam	2.3
Topiramate	1.0
Oxcarbazepine	0.6

PHT was the most commonly used AED in the elderly

(data from South Texas Veterans Health Care System)

Pugh MV et.al; Neurology: 2008

A survey of common AED being used for the elderly with epilepsy

AED type	2000	2001	2002	2003	2004
Phenobarbital	59 (3.2%)	57 (2.9%)	54 (2.8%)	42 (2.0%)	34 (1.9%)
Phenytoin	1,301 (70.6%)	1,372 (69.4%)	1,251 (64.3%)	1,389 (64.5%)	1,164 (66.1%)
Standard	245 (13.3%)	281 (14.2%)	322 (16.5%)	306 (14.2%)	215 (12.2%)
New	238 (12.9%)	268 (13.6%)	320 (16.4%)	416 (19.3%)	348 (19.8%)
Total	1,843	1,978	1,947	2,153	1,761

Even though there had been launched of clinical guidelines and clinical recommendations for AEDs in older patients with epilepsy, *PHT was the most commonly used AED* and there was little change in its use in elderly over this 5 years period

Standard includes CBZ + VPA
New includes GBP, LTG, LVT, OXC, TPM

AEDs and cognitive-enhancing drugs

Alzheimer Medications	PHT	CBZ	PB	BZD	VPA	OXC	LEV	TOP	GBP	LTG	ZNS	PGB
Donepezil (D)	↓	↓	↓	—	—	↓	—	—	—	—	—	—
Galantamine (G)	↓	↓	↓	—	—	↓	—	—	—	—	—	—
Rivastigmine (R)	none	none	none	none	none	none	none	none	none	none	—	none
Tacrine (T)	none	none	none	none	none	none	none	none	none	none	—	none
Memantine (M)	none	none	none	none	none	none	none	none	none	none	—	none

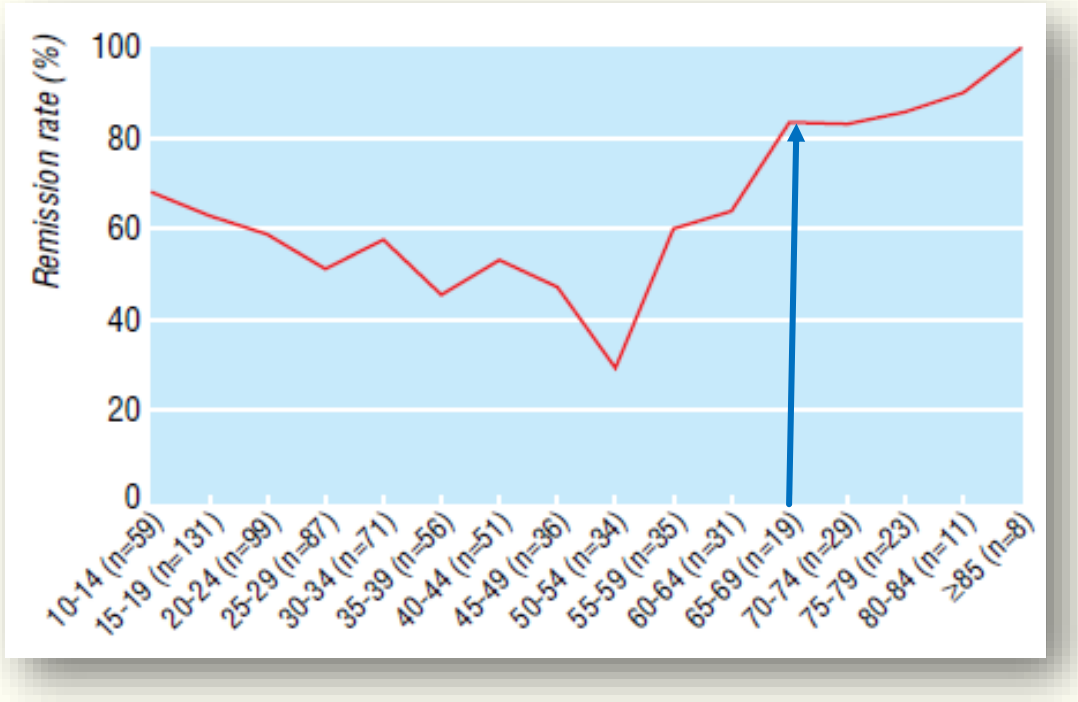
Rivastigmine and Memantine have no drug interactions with AEDs

Sigmund J et.al; Am J Alzheimers Dis Other Demen: 2010

Drug interaction between AEDs and commonly drugs used in the elderly

Drugs	Clinically significant drug interaction
Anticoagulant: Warfarin	**Yes: PHT, CBZ, PB, VPA** **No: LEV, LTG, GBP, TGB, TPM dose < 200 mg/d**
Antiplatelets: Aspirin, Clopidogrel, Dipyridamole	**No** ** TPM is a weak CYP2C19 inhibitor (CYP 2C19 is an enzyme used for Clopidogrel metabolism)
Antihypertensive drugs	**Yes: Calcium channel blockers** (CYP 3A4 inhibitor) increase level of CBZ and PHT; lipophilic beta blockers **propranolol, timolol, metopolol** **No**: ACE-I, thiazide, hydrophilic beta blockers
Statins	**Yes: CBZ, PHT decrease level of simvastatin and atorvastatin**
Anti-diabetic drugs	**No**

Remission rates according to age at starting treatment



- 80-85% of the elderly with epilepsy were in seizure-remission after the first AED
- Only 10-15% of the patients were medically intractable

Mohanraj R and Brodie MJ et.al; Eur J Neurol: 2006

Pregnant patients

CASE

- 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

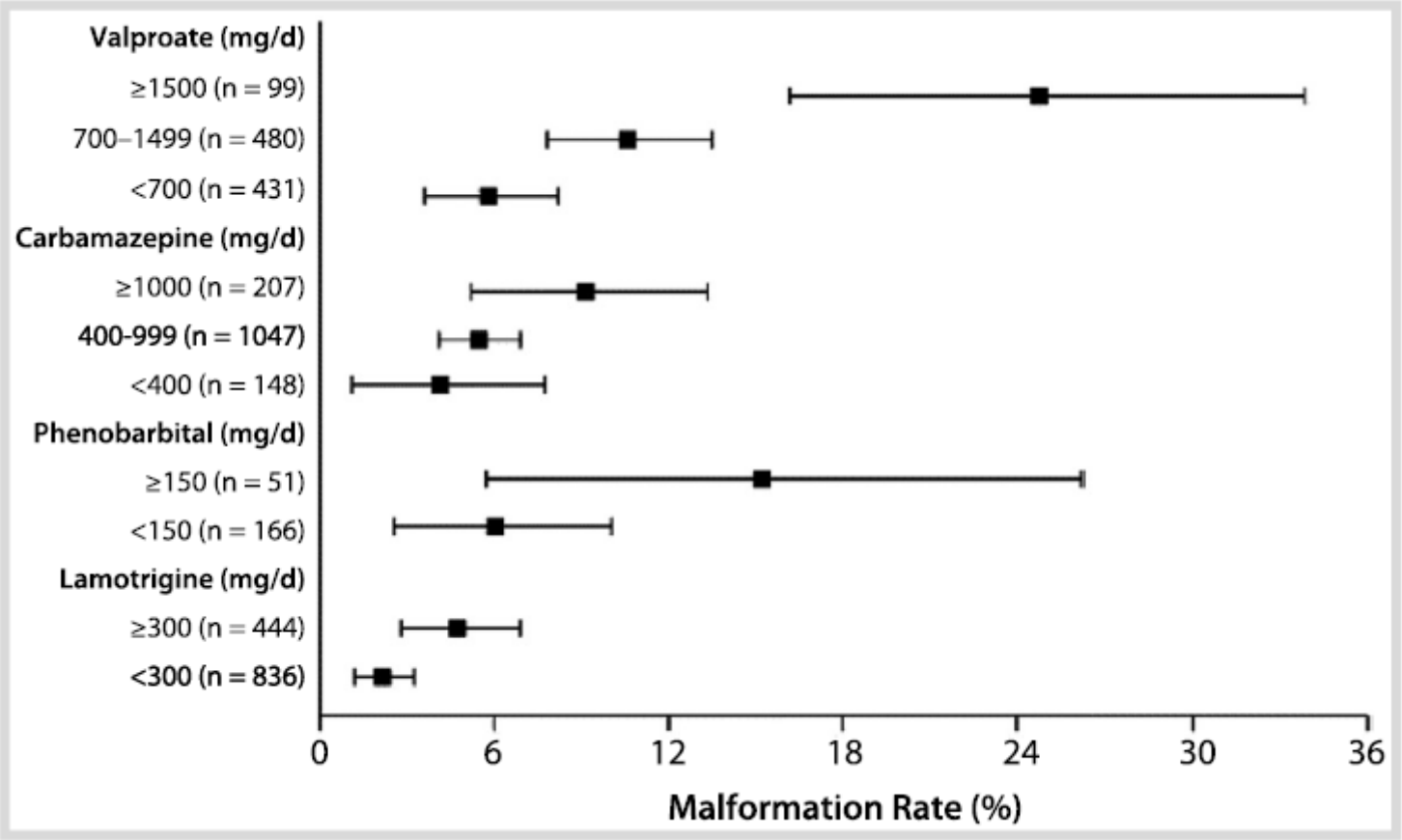
(B) Switching the VPA to another AED e.g. LTG

(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

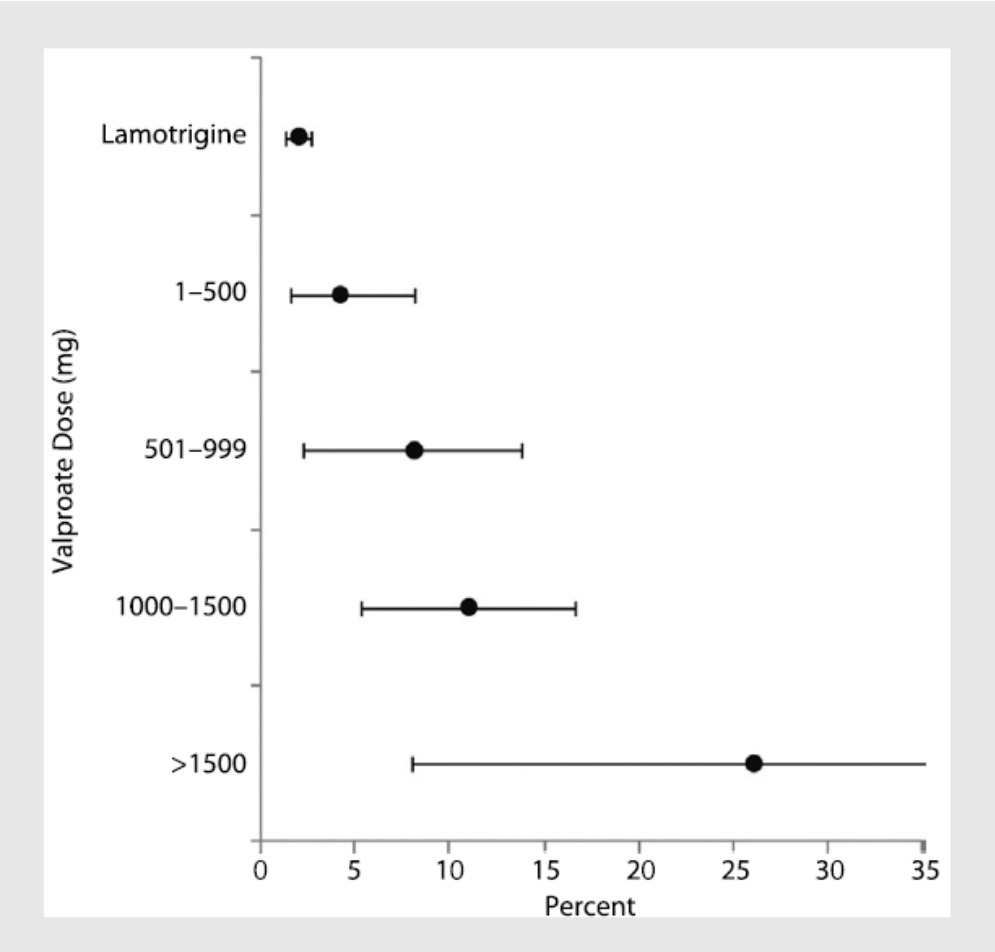
Tissues	Malformations	Postconceptional Age
CNS	Neural tube defect	28 d
Heart	Ventricular septal defect	42 d
Face	Cleft lip	36 d
	Cleft maxillary palate	47–70 d

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



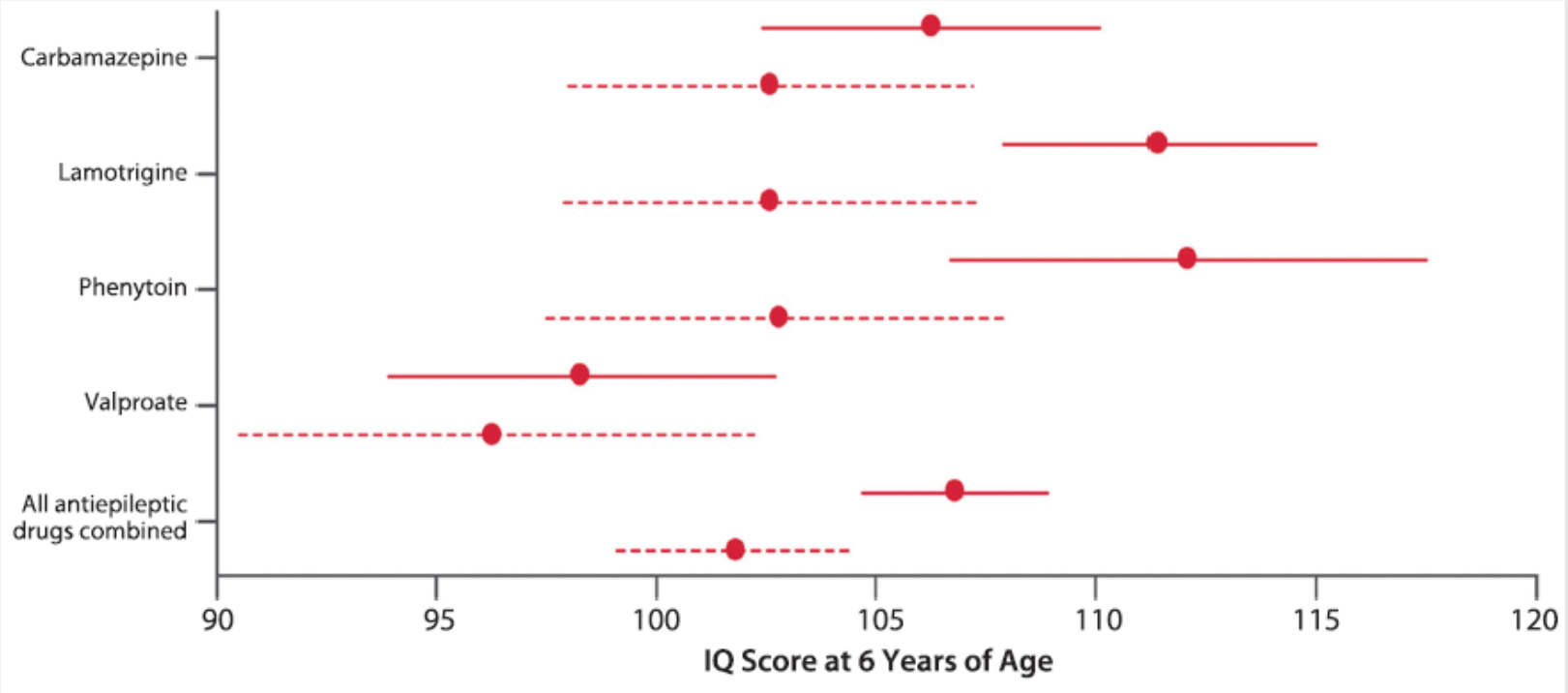
Tomson T et al, Lancet Neurol 2011

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)

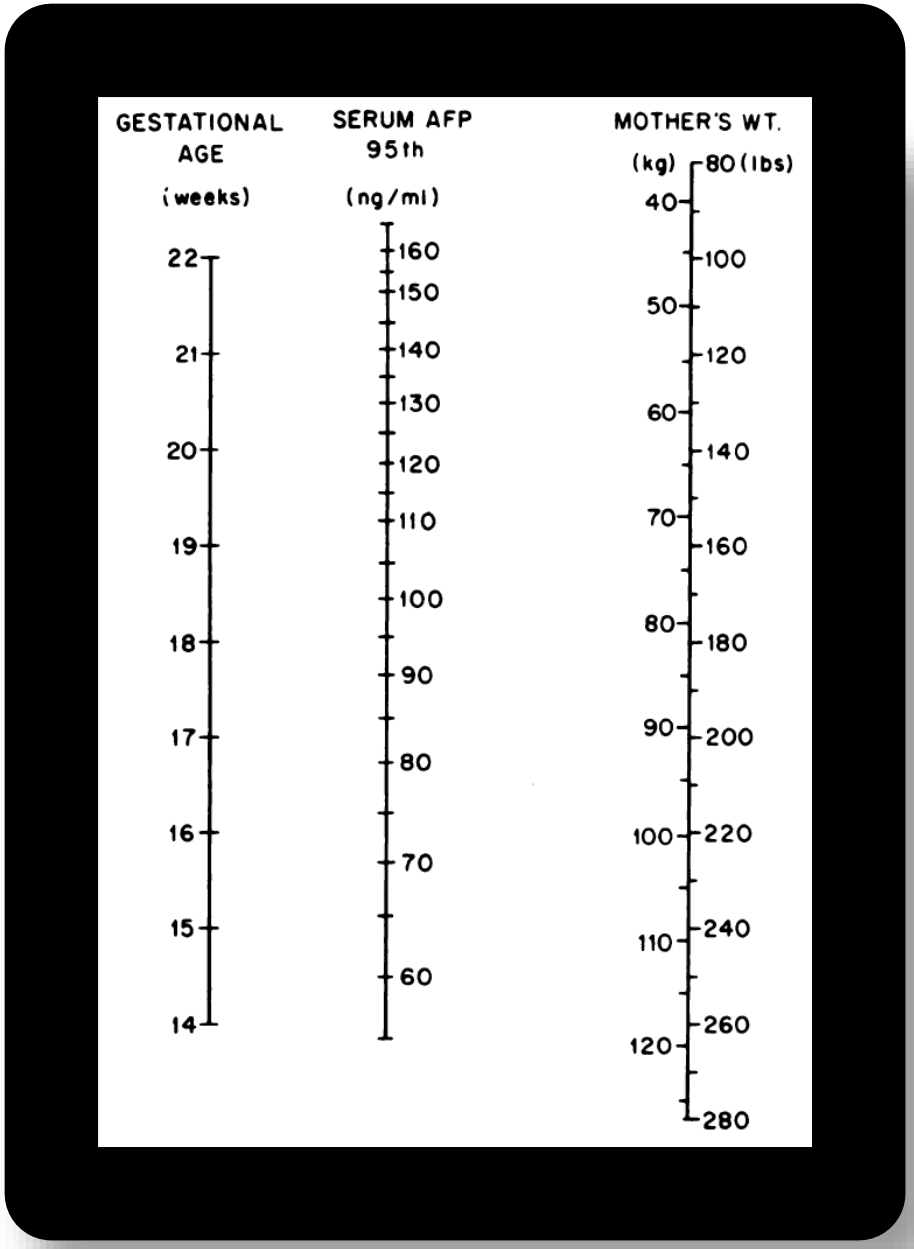
- **VPA level** while taking VPA 800 mg/d

✓ 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

Introduction

- Exposure to antiepileptic drugs (AEDs) in the first trimester of pregnancy increases the risk of major congenital malformations (MCM) from the background risk of 1-2.4% to 4-9% (either monotherapy or polytherapy, 2-3 times)
- MCM was higher in polytherapy (6-9%) than monotherapy (3-5%)

Holmes LB et.al. NJEM 2001; Morrow J et.al, JNNP 2006; Molgaard-Nielsen D and Hviid A, JAMA 2011

- Risk of MCM is higher in VPA monotherapy (6.2-9.3%, OR 2.59-4.24 compared with CBZ) or polytherapy with VPA (OR 2.5, compared with polytherapy without VPA)

Morrow J et.al, JNNP 2006; Hermandez-Diaz S et.al, Neurology 2012

What are **TRUE** regarding adverse effects of valproic acid (VPA) in women with epilepsy (WWE)?

A. VPA carries the higher risks of major congenital malformations (MCMs) as compared with other antiepileptic drugs
B. VPA has adverse effects on child development at age 3 and 6 years
C. Breastfeeding in WWE using VPA negatively impacts on child development
D. A and B

Answer

D

Risk of MCM in newer AEDs

National and International AED Pregnancy Registry

- North American AED Pregnancy Registry (US and Canada): 1997-2011
- UK Epilepsy and Pregnancy Registry (UKEPR): 1996-2011
- International Lamotrigine Pregnancy Registry: 1992-2009
- Danish Health Registry: 1996-2008
- Australian Pregnancy Registry (APR): 1999-2010

Which new AED was classified by US FDA in 2011 as Pregnancy Category D given a recent data of increased risk of cleft lip?

A. Topiramate
B. Gabapentin
C. Oxcarbazepine
D. Levetiracetam

Answer

A

AEDs	Risk of MCM (%)
VPA	9.3% (30/323)
PB	5.5% (11/199)
CBZ	3.0% (31/1,033)
PHT	2.9% (12/416)
TPM	4.2% (15/359)
LVT	2.4% (11/450)
LTG	2.0% (31/1,562)
OXC	2.2% (4/182)
GBP	0.7% (1/145)
CZP	3.1% (2/64)

Comparative safety of antiepileptic drugs during pregnancy

North American AED Pregnancy Registry

ABSTRACT

Objective: To assess the safety of the newer antiepileptic drugs (AEDs) during pregnancy.

Methods: The study population was pregnant women who enrolled in the North American AED Pregnancy Registry between 1997 and 2011. Data on AED use and maternal characteristics were collected through phone interviews at enrollment, at 7 months' gestation, and postpartum. Malformations were confirmed by medical records. The risk of major malformations was calculated among infants exposed to specific AEDs in monotherapy during the first trimester of pregnancy and among an unexposed group. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated with logistic regression.

Results: The risk of major malformations was 9.3% (30 of 323) for valproate, 5.5% (11 of 199) for phenobarbital, 4.2% (15 of 359) for topiramate, 3.0% (31 of 1,033) for carbamazepine, 2.9% (12 of 416) for phenytoin, 2.4% (11 of 450) for levetiracetam, and 2.0% (31 of 1,562) for

Comparable, p = 0.56

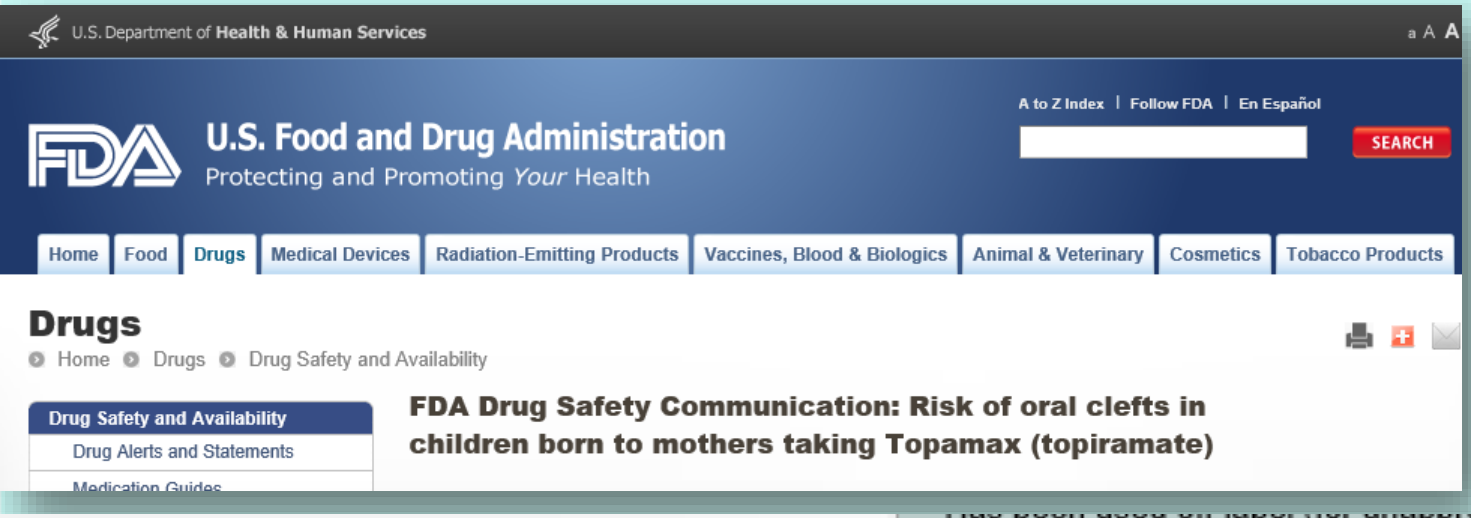
Seizure control during pregnancy

VPA: 23% had seizures during pregnancy

LTG: 31% had seizures

VPA, PB, TPM was associated with an increased risk of cleft lip (>10/1,000) compared with that of a reference population (1/1,000)

Hernandez-Diaz S et.al, Neurology 2012



In 2011: FDA reclassified TPM to be in **Pregnancy Category D** (previously Category C)

other conditions, some of which may not be considered serious.

- From January 2007 through December 2010, approximately 32.3 million topiramate prescriptions were dispensed and approximately 4.3 million patients filled topiramate prescriptions from the outpatient retail pharmacies in the U.S.[2]

Topiramate was previously classified as a Pregnancy Category C drug, which means that data from animal studies suggested potential fetal risks, but no adequate data from human clinical trials or studies were available at the time of approval. However, because of new human data that show an increased risk for oral clefts, topiramate is being placed in Pregnancy Category D. Pregnancy Category D means there is positive evidence of human fetal risk based on human data but the potential benefits from use of the drug in pregnant women may be acceptable in certain situations despite its risks.

(see Data Summary)

Final results from 18 years of the International Lamotrigine Pregnancy Registry

M.C. Cunnington, PhD
J.G. Weil, MD
J.A. Messenheimer, MD
S. Ferber, MSc
M. Yerby, MD, MPH
P. Tennis, PhD

ABSTRACT

Objective: To monitor for a signal for major teratogenicity following in utero lamotrigine exposure.

Methods: Health care providers reported lamotrigine exposure during pregnancy, and subsequent outcomes, on a voluntary basis. Prospective reporting early in pregnancy was encouraged. Major congenital malformations (MCMs) were classified according to the Centers for Disease Control and Prevention (CDC) criteria and were reviewed by a pediatrician on the Registry's Scientific

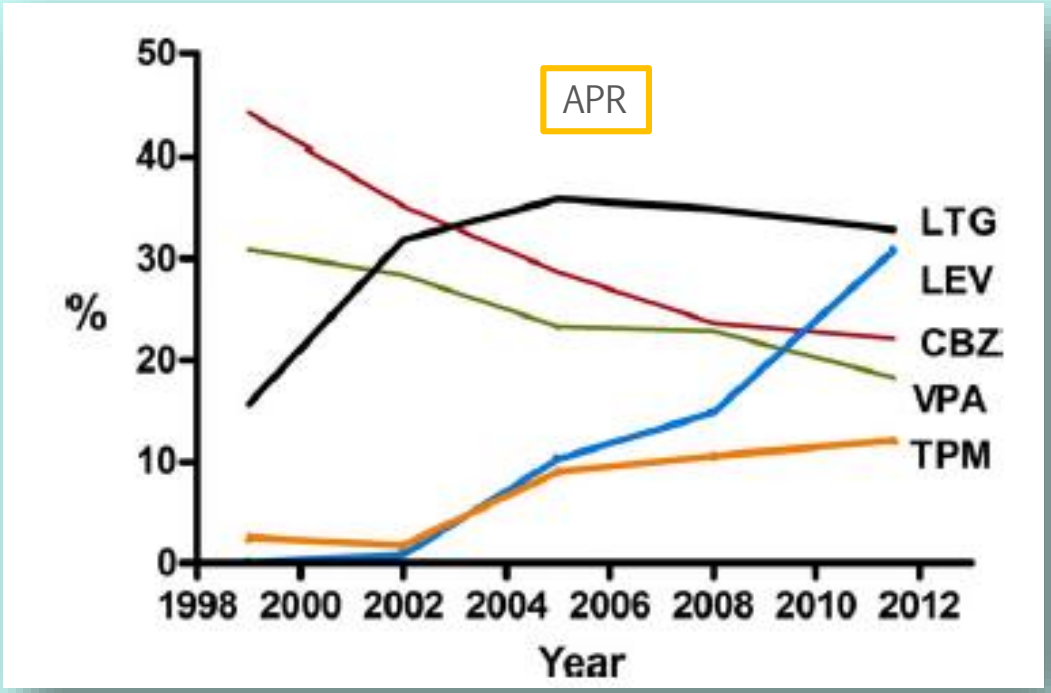
First trimester maximal daily dose, mg	No. of exposures	Major congenital malformations, %
>0-100	276	2.5
101-200	556	1.6
201-300	274	3.6
301-400	220	1.4
401-600	153	3.3
601-1,200	44	—
Missing dose	35	2.9
All	1,558	2.2

- Over 18 yrs, 35 infants with MCMs were observed among 1,558 first trimester LTG exposure: 2.2% similar to general population
- LTG+VPA: 10.7%, LTG + other AEDs: 2.8%
- No observed increased MCM with increasing LTG dose

Cunninton MC et.al., Neurology 2011

LTG was among the 2 most common AEDs (LTG, LVT) prescribed in women with epilepsy in US from 1999 through 2004

Meador KJ et.al., Epilepsy Behav 2009



Vajda FJE et.al, Epilepsia 2014

AEDs	Risk of MCM (%)
LTG, OXC, GBP, TPM, LVT	3.2% (49/1,532) Controls 2.4% (OR 0.99)
LTG	3.7% (38/1,019)
OXC	2.8% (11/393)
TPM	4.6% (5/108)
GBP	1.7% (1/59)
LVT	0% (0/58)

Newer-Generation Antiepileptic Drugs and the Risk of Major Birth Defects

Ditte Mølgaard-Nielsen, MSc
Anders Hviid, MSc, DrMedSci

THE PREVALENCE OF ANTIEPILEPtic drug use in pregnant women is 0.2% to 0.5%.[1-3] While their main indication is

Context Epilepsy during pregnancy is a therapeutic challenge. Since the 1990s, the number of licensed antiepileptic drugs has substantially increased, but safety data on first-trimester use of newer-generation antiepileptic drugs and birth defects are limited.

Objective To study the association between fetal exposure to newer-generation antiepileptic drugs during the first trimester of pregnancy and the risk of major birth defects.

Danish Health Registry

Molgaard-Nielsen D and Hviid, JAMA 2011

Clinical Study

Teratogenicity of the newer antiepileptic drugs – the Australian experience

F.J.E. Vajda [a,b,*], J. Graham [c], A. Roten [c], C.M. Lander [d,e], T.J. O'Brien [a,b,c], M. Eadie [d,e]

[a] Department of Medicine, University of Melbourne, Royal Parade, Parkville, Victoria 3050, Australia
[b] Department of Neuroscience, Royal Melbourne Hospital, Parkville, Victoria, Australia
[c] Department of Neurology, University of Melbourne, Parkville, Victoria, Australia
[d] Department of Neurology, Royal Brisbane and Women's Hospital, Brisbane, Queensland, Australia
[e] Department of Medicine, University of Queensland, Brisbane, Queensland, Australia

APR

AEDs	Risk of MCM (%)
LTG	5.2% (12/231)
TPM	3.2% (1/31)
LVT	0% (0/22)
PHT	2.9% (1/35)
VPA	16.3% (35/215)
CBZ	6.3% (19/301)

The new AEDs appeared no more teratogenic than traditional drugs in monotherapy

Vajda FJE et.al, J Clin Neurol 2012

Neurodevelopment in fetus with intrauterine AED exposure

	N	Mean age-6 IQ (95% CI)	p value (vs below-median dose valproate)	p value (vs above-median dose valproate)
Carbamazepine (median dose 700 mg per day)				
Below group median	28	107 (102–112)	0·3994	0·0002
Above group median	33	106 (102–110)	0·5990	0·0004
Lamotrigine (median dose 433 mg per day)				
Below group median	31	106 (102–111)	0·4854	0·0003
Above group median	43	109 (105–113)	0·1154	<0·0001
Phenytoin (median dose 398 mg per day)				
Below group median	20	108 (103–114)	0·2551	0·0002
Above group median	20	106 (101–112)	0·5501	0·0011
Valproate (median dose 1000 mg per day)				
Below group median	23	104 (99–109)	NA	0·0065
Above group median	26	94 (90–99)	0·0065	NA

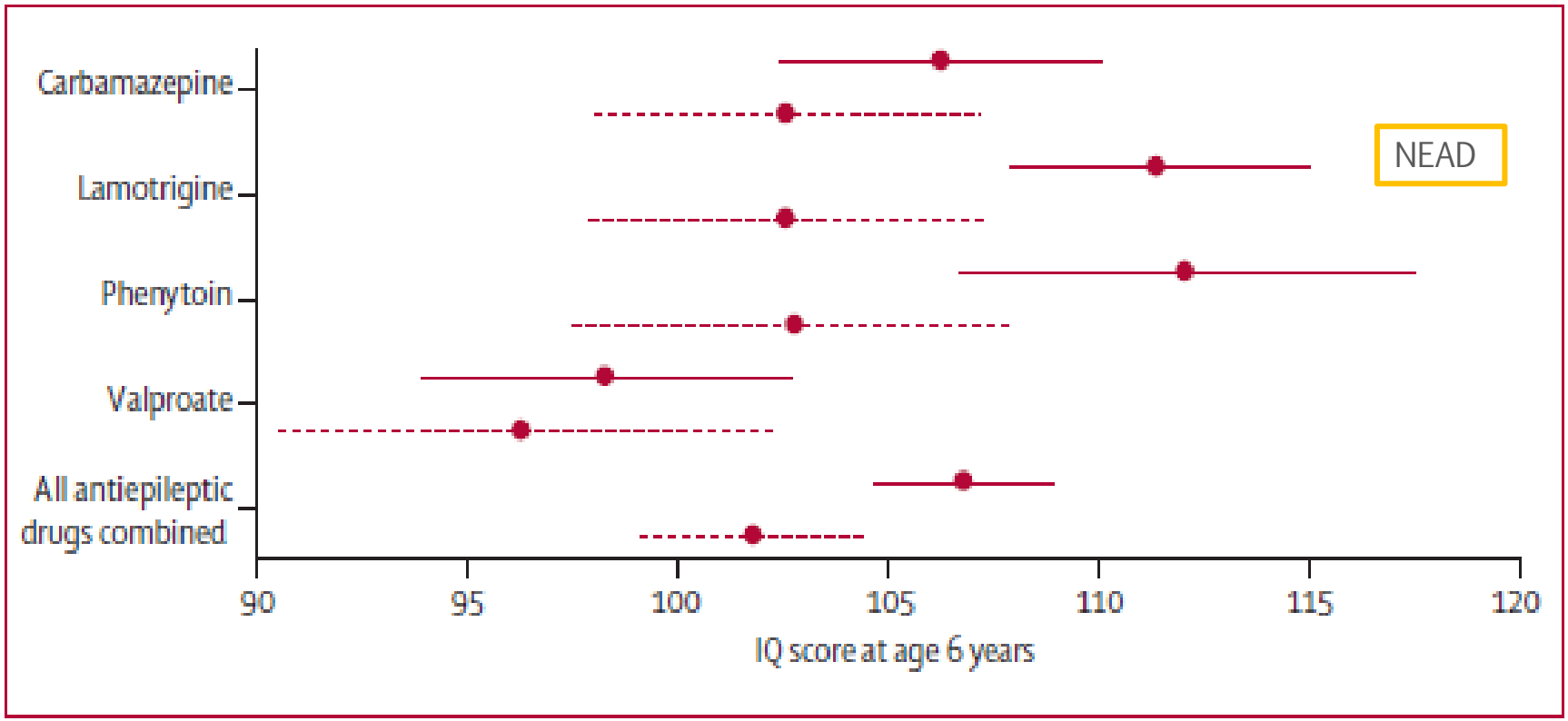
Means were adjusted for maternal IQ, gestational age at birth, and folate. IQ=intelligence quotient.

Table 5: IQ outcomes at age 6 years by median group dose for the age-6-completer sample (n=224)

The Neurodevelopmental Effects of Antiepileptic Drugs (NEAD): 1999-2004, 25 centers in US and UK

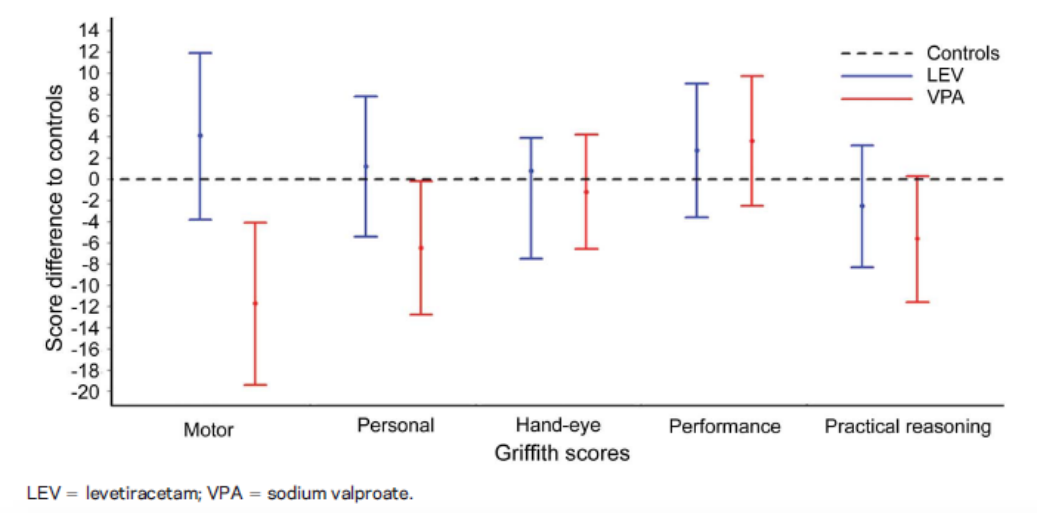
Age-6 IQ was lower after exposure to VPA than CBZ, LTG ,and PHT

Meador KJ et.al, NEJM 2009
Meador KJ et.al., Lancet Neurol2013

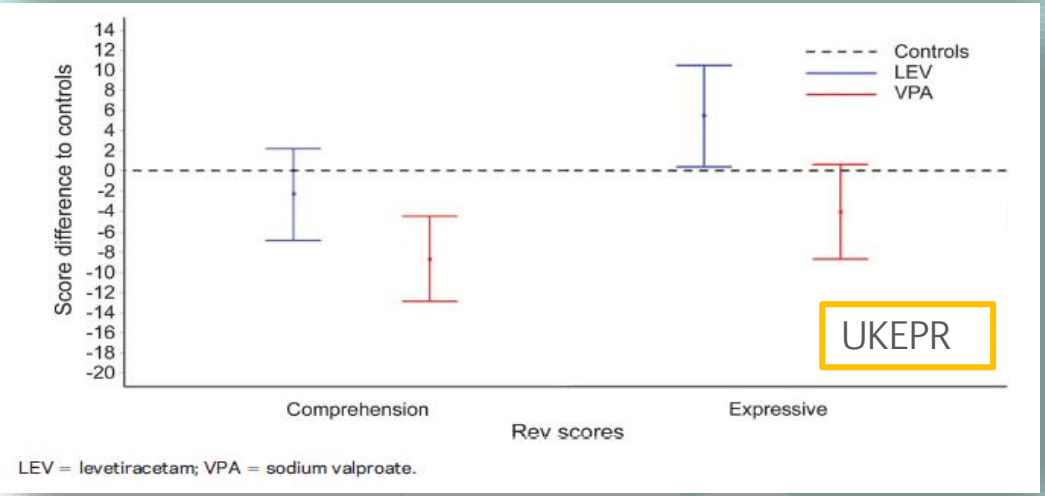


Mean IQs were higher in children exposed to *periconceptional folate* than they were in unexposed children

Meador KJ et.al., Lancet Neurol2013



LEV = levetiracetam; VPA = sodium valproate.



LEV = levetiracetam; VPA = sodium valproate.

At 3 years of age

- Children exposed to LVT in utero (n = 53) did not differ from unexposed control children (n = 131)
- Children exposed to LVT in utero (n = 53) were superior in their language and motor development in comparison to children exposed to VPA (n = 43)

Shallcross R et.al., Neurology 2014

Breastfeeding in WWE

AED group	Breastfed	No.	Age 3 IQ[a]	95% Confidence Intervals[b]
All AEDs	Yes	84	99	96-103
	No	115	98	95-101
Carbamazepine	Yes	26	103	97-108
	No	32	98	93-103
Lamotrigine	Yes	30	104	97-110
	No	36	104	98-110
Phenytoin	Yes	17	91	84-98
	No	23	99	93-105
Valproate	Yes	11	93	82-105
	No	24	90	83-98

The preliminary analysis **fails to demonstrate deleterious of breastfeeding** during AED therapy on cognitive outcomes in children previously exposed in utero

Meador KJ et.al., Neurology 2010

Original Investigation

Early Child Development and Exposure to Antiepileptic Drugs Prenatally and Through Breastfeeding

A Prospective Cohort Study on Children of Women With Epilepsy

Gyri Veiby, MD; Bernt A. Engelsen, MD, PhD; Nils Erik Gilhus, MD, PhD

- 1999-2009 **Norwegian Mother and Child Cohort Study (MoBa)**
- Infants of mother using AEDs (CBZ, VPA, LTG) had a **higher risk of impaired fine motor skills** compared with the reference group (11.5% vs 4.8%, OR 2.1)
  Multiple AEDs use had adverse outcome of both fine motor (25% vs 4.8%, OR 4.3) and social skills (22.5% vs 10.2%, OR 2.6)

- **Continuous breast feeding: less impaired development at age 6 and 18 months**, compared with those with no breast feeding or breastfeeding for less than 6 months
  At 36 months: prenatal AED exposure was associated with adverse development regardless of breastfeeding status during the first year **(suggesting breastfeeding is safe)**

Velby G et.al., JAMA Neurol2013

Adverse Outcome[a]	Reference, %	Mother Treated With AED			
		Breastfeeding ≥6 mo		Breastfeeding <6 mo[b]	
		No. (%)	OR (95% CI)[c]	No. (%)	OR (95% CI)[c]
Child aged 18 mo[d]					
Fine motor skills	12.4	22 (19.6)	1.7 (1.1-2.8)[e]	14 (20.6)	1.7 (0.9-3.1)
Gross motor skills	8.6	13 (11.5)	1.2 (0.7-2.3)	14 (20.0)	2.2 (1.2-4.1)[e]
Autistic traits	7.8	9 (8.7)	1.0 (0.5-2.0)	15 (22.4)	2.9 (1.6-5.2)[e]
Communication skills	10.6	20 (18.0)	1.7 (1.1-2.9)[e]	17 (24.3)	2.6 (1.5-4.5)[e]
Child aged 36 mo[f]					
Autistic traits	1.5	4 (5.0)	3.1 (1.1-8.7)[e]	4 (7.5)	3.8 (1.4-10.8)[e]
Sentence skills	4.8	9 (11.1)	2.3 (1.3-4.7)[e]	6 (11.3)	1.9 (0.8-4.6)
ADHD symptoms	4.0	7 (8.5)	2.2 (1.0-5.2)	1 (1.9)	0.3 (0.1-2.4)
Aggressive symptoms	4.1	4 (4.9)	1.3 (0.5-3.7)	7 (13.0)	2.9 (1.3-6.6)[e]

In summary

- VPA should be avoided in WWE due to diverse negative effects on fetus including

  - higher risk of MCMs either monotherapy or in combination with other AEDs

  - poorer child development

- Increased data about risk of MCMs in newer AEDs

  - largest amount of evidence for LTG

  - Evidence for LVT has recently increased and showed comparable risk of MCMs similar to LTG

- LVT may be superior to LTG in WWE during pregnancy in case of

  - requiring rapid and effective seizure control

  - high risk of AED hypersensitivity

- TPM should be possibly avoided due to significant risk of cleft lip

What are the appropriate goals of management in WWE during pregnancy?

A. Using AED monotherapy
B. Using minimal effective dose of the AED
C. Avoid VPA
D. All are correct

Answer

D

Psychiatric patients

Psychotropic effects	Antiepileptic drugs (AEDs)
Effects on mood	**Positive effects**: **Mood-stabilizing effect** **- LTG** (Bipolar I disorder, depression) **- CBZ** (aggression, anxiety, mania in Bipolar disorder; no benefit in depression) **- VPA** (Bipolar II depression, agitation, impulsive aggression; no benefit in aggression associated with dementia) **GBP, PGB** (anxiety, no mood-stabilizing effect)
	Negative effects: **Aggression (irritability)** → **LVT,** TPM, ZNM, TGB, **GBP (children, pts with developmental disabilities)**, LTG, **Barbiturates**, **BZD** (paradoxical disinhibition syndrome) **Depression** → Barbiturates, LVT (underlying depression), TPM
Effects on psychotic symptoms	**Positive effects: None**
	Negative effects: **Psychosis** → **TGB (8.4%)**, LVT, TPM, ZNM

Ettinger AB, Neurology 2006; Piedad J et.al, CNS Drugs 2012

Psychiatric adverse effects of the AEDs

Pathophysiology

- Interaction between the drug and the underlying epileptic process
- Presents as either; 1) side effects with no prognostic value or 2) the first step in a progressive course leading to some chronic psychiatric disorder
- Pre-existing of limbic injuries pose vulnerability to psychiatric adverse effects from AEDs
- Can be dose-dependent

Patients at risk

- Mental retardation/ neurologically handicapped children
- **Previous psychiatric history eg. depression** for LVT

Opp J et.al, Seizure 2005;
Chatzistefanidis D et.al, Clinical Neuropharmacology 2013

Epilepsy we Together

Thank you for your attention