Treatment of Epilepsy across the Ages: from Adolescence to Elderly

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Epilepsy management through a patient's life

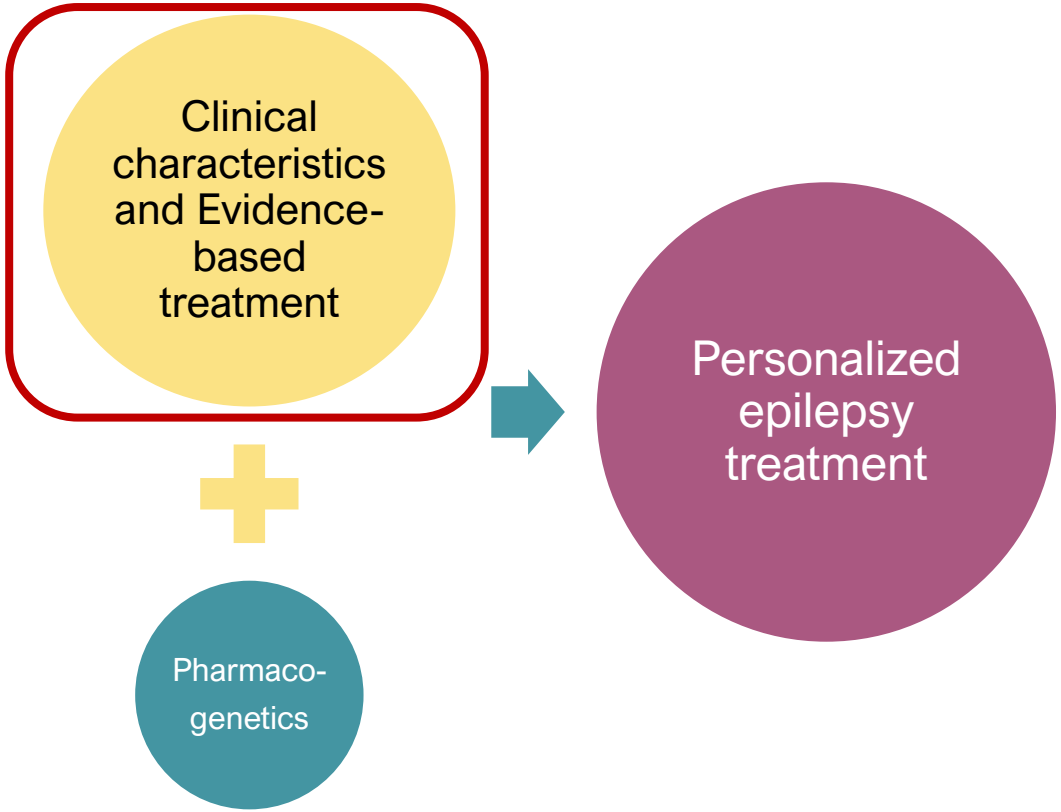
Talk Overview

1. Adolescence
2. Adults
   - ❖ Efficacy evidences of ASMs in adults
   - ❖ Child-bearing age women
3. Elderly

Introduction

- ASM selection can be "**personalized**," based on patient characteristics such as **age, gender, and the presence of comorbidities**

- These patient characteristics may be related to the **efficacy, safety, and tolerability of AEDs** and can help determine the most appropriate drug therapy for an individual



Which drug ?

- ** Seizure types **
- Age and sex
- Associated medical conditions
- Potential side effect on QOL
- Medical expertise
- Regulatory aspects and cost

"Case-by-case basis”

Other than seizure types

- Changes in brain function at different ages
- Changes in underlying epilepsy etiology

Few evidences

- Changes in pharmacokinetics
- Changes in frequency and types of adverse effects

1. Adolescence

14 years old

1st GTC

16 years old

an episode of staring associated with automatic movements

Epilepsy in adolescence

- **First onset of epilepsy in adolescence**
  - ✓ JAE, JME
  - ✓ HS

- **Impacts of epilepsy in this age**
  - ✓ **"Disrupting self-esteem"**
  - ✓ Adversely affecting the ability to conform to one's peers
  - ✓ Interfering with independence

Nordli DR Jr; Epilepsia 2001

Seizure type or epileptic syndrome	Level of evidence	AEDs
Adults with partial-onset seizures	**A** B C D	**CBZ, PHT, LEV, ZNS** VPA GBP, LTG, OXC, PB, TPM, VGB CZP, PRM
Adults with generalized-onset tonic clonic seizures	A B C D	None None CBZ, LTG, OXC, PB, PHT, TPM, VPA GBP, LEV, VGB
Elderly adults with partial-onset seizures	**A** B C D	**LTG, GBP** None CBZ TPM, VPA
Juvenile myoclonic epilepsy (JME)	A B C D	None None None **TPM, VPA**

ILAE 2013

Evidence of efficacy and effectiveness of AEDs in adult epileptic seizures/syndromes

Glauser T et.al; Epilepsia: 2013

VPA and TPM are known to be in the highest level of evidence to treat JME, “Should it be appropriate to use VPA or TPM in child-bearing potentials ?”

Juvenile myoclonic epilepsy (JME) is a common epilepsy syndrome, comprising 5%-10% of all epilepsies

CNS Drugs 2019

Treatment of Juvenile Myoclonic Epilepsy in Patients of Child-Bearing Potential

Historically, VPA has been shown to control symptoms in > 80% of JME patients

Anna Serafini[1] · Elizabeth Gerard[2] · Pierre Genton[3] · Arielle Crespel[4] · Philippe Gelisse[4]

Table 1 Main antiepileptic drugs used in women of childbearing potential with juvenile myoclonic epilepsy

Drugs	Special notes	Standard dosage	Side effects	Precautions
Lamotrigine	Drug of choice	100–300 mg/day	Skin allergy, hypersensitivity syndromes	Slow titration, can be used in pregnancy, does not significantly affect the efficacy of CHC
Levetiracetam	Drug of choice	1000–2000 mg/day	Psychiatric disturbances, insomnia	Can be used in pregnancy, CHC not affected
Valproate	Second-line drug	500–1000 mg/day	Weight gain, tremor (dose related), hair loss (temporary), hepatitis, pancreatitis, polycystic ovarian syndrome	Contraindicated in pregnancy, CHC not affected
Topiramate	Second-line drug	100–300 mg/day	Cognitive and psychiatric disturbance, nephrolithiasis, paresthesia, weight loss, acute myopia	Teratogenic, CHC affected if dose > 200 mg/day
Zonisamide	Second-line drug	200–500 mg/day	Cognitive dysfunction, nephrolithiasis, weight loss	Not teratogenic but the small number of pregnancies precludes any conclusions, CHC not affected
Perampanel	Second-line drug	4–8 mg/day	Psychiatric disturbances	No information for pregnancy, CHC affected if dose > 10 mg/day

CHC combined hormonal contraception

Given the high rate of malformations and cognitive side effects associated with prenatal exposure, **the use of VPA should be severely restricted in women of childbearing potential and limited to those**

(1) using effective contraception and

(2) with persisting GTC seizures despite adequate trials of lower-risk drugs, including at least LTG or LEV or the combination of LTG and LEV, and

(3) experiencing side effects from these drugs

Lifestyle advice is an integral part of the treatment and includes **avoidance of common triggers**, such as
sleep deprivation,
excess alcohol,
inopportune awakening, and
an emphasis on the importance of compliance with medication

Comparative effectiveness of antiepileptic drugs in juvenile myoclonic epilepsy

People with JME were identified from a **large clinical database** from the **EpiPGX** consortium, an international multicenter research project on epilepsy pharmacogenetics (www.epipgx.eu)

Katri Silvennoinen[1,2] | Nikola de Lange[3] | Sara Zagaglia[1,2,4] | Simona Balestrini[1,2,4] | Ganna Androsova[3] | Merel Wassenaar[5] | Pauls Auce[6,7] | Andreja Avbersek[1] | Felicitas Becker[8] | Bianca Berghuis[5] | Ellen Campbell[9] | Antonietta Coppola[10,11] | Ben Francis[12] | Stefan Wolking[8] | Gianpiero L. Cavalleri[13] | John Craig[9] | Norman Delanty[13,14] | Michael R. Johnson[15] | Bobby P. C. Koeleman[16] | Wolfram S. Kunz[17] | Holger Lerche[8] | Anthony G. Marson[6,7] | Terence J. O'Brien[18] | Josemir W. Sander[1,2,5] | Graeme J. Sills[6] | Pasquale Striano[19,10] | Federico Zara[20] | Job van der Palen[21] | Roland Krause[3] | Chantal Depondt[22] | Sanjay M. Sisodiya[1,2] | the EpiPGX Consortium*

Fewer females than males received VPA (76.2% vs 92.6%, $P = 0.001$)

305 people with 688 AED trials of VPA, LTG, LEV, CBZ, and TPM

VPA was associated with the highest response rate (42.7%); LEV ranked second (37.5%) (not statistical significant difference)

The relative frequency of VPA trials shows a decreasing trend since 2003 while there is an increasing trend for LEV

Epilepsia Open 2018

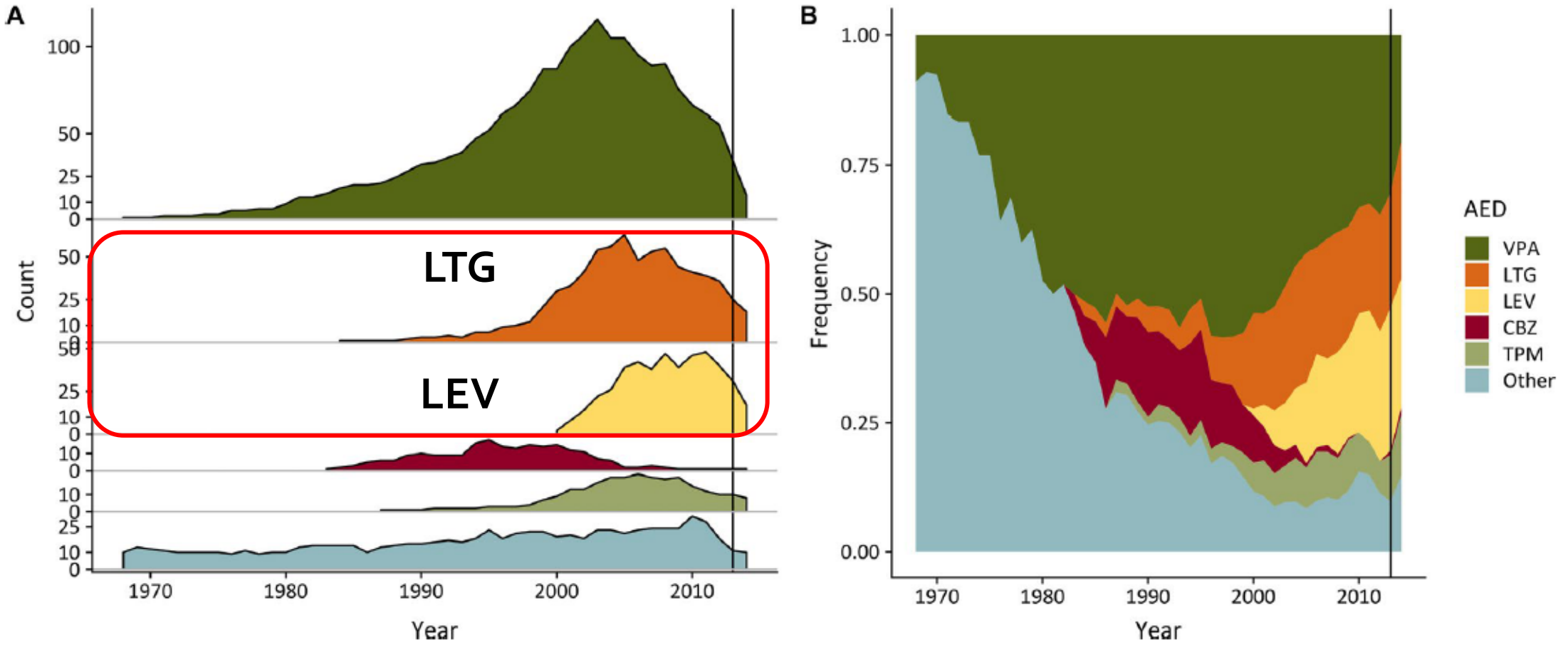


FIGURE 2 The secular prevalence of AED trials between 1968 and 2014. The extreme right vertical line indicates the 2013 recommendation by the UK Medicines and Healthcare products Regulatory Agency to restrict valproate use, and referral of valproate to the European Medicines Agency Pharmacovigilance Risk Assessment Committee[36]

In people with JME, VPA is an effective AED; **LEV emerged as an alternative**

VPA is now contraindicated in women of childbearing potential without special precautions

With appropriate selection and safeguards in place, VPA should remain available as a therapy, including as an alternative for women of childbearing potential whose seizures are resistant to other treatments

Issues in adolescence

- **Adherence to drug regime**
- **Sensitive to adverse effects that alter the appearance**
  - ✓ Weight
  - ✓ Cosmetic side effects
  - ✓ Hair
- **Cognitive side effects**
- **Psychiatric side effects**

Nordli DR Jr; Epilepsia 2001
French JA & Staley BA Epilepsy Currents 2012

Adherence to drug regime

- Simply forgetting to take their medication
- Stigmatizing and differentiates them from their peers

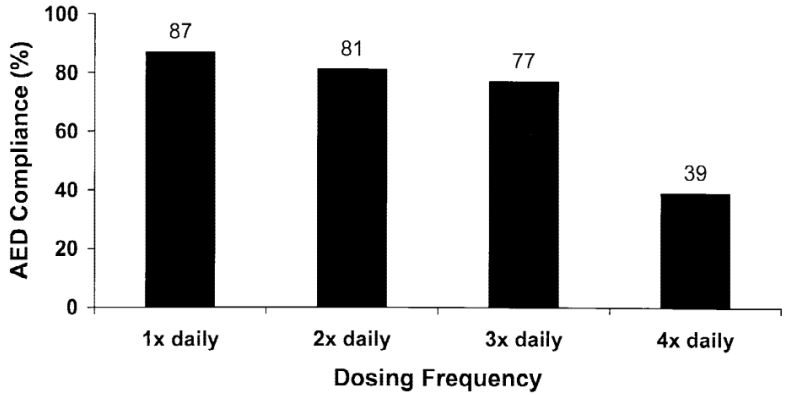


TABLE 1. *Serum half-life of various antiepileptic drugs*

Antiepileptic drugs	$T_{1/2}$ (h)
Carbamazepine	5–20
Ethosuximide	30–60
Felbamate	14–23
Gabapentin	5–9
Lamotrigine	15–60
Levetiracetam	7
Oxcarbazepine (10-monohydroxy)	10–15

Because taking medication may become viewed as the distinguishing feature of their illness, daytime doses may be a potent disincentive against compliance, and **b.i.d. dosing may help**

Nordli DR Jr; Epilepsia 2001
Cramer JA et al.; JAMA 1989

•. 2012

Adverse effects that alter the appearance

- **Weight**
  - ✓ Gain: VPA; GBP; PGN; VGB; CBZ
  - ✓ Loss: TPM; ZNM; FBM
  - ✓ Neutral: PHT; LTG; LEV
- **Cosmetic side effects**
  - ✓ Gingival hyperplasia, hirsutism, facial coarsening: PHT
  - ✓ Hair loss: VPA; CBZ

Casetta I et al; Neuroepidemiology 1997
Mercke Y et al; Ann Clin Psychiatry 2000
Antel J & Hebebrand J; Handb Exp Pharmacol 2012

Cognitive side effects

TABLE 3. *Categorical evaluation of the sedation and cognitive dysfunction in antiepileptic drugs*

Favorable medications	Unfavorable medications
Felbamate	Barbiturates
Gabapentin	Benzodiazepines
Lamotrigine	Tiagabine
Oxcarbazepine	Topiramate
Valproate	Vigabatrin

Psychiatric side effects

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**

JAMA Neurology | Original Investigation

JAMA Neurol 2019

Prediction Tools for Psychiatric Adverse Effects After Levetiracetam Prescription

Colin B. Josephson, MD, MSc, FRCPC; Jordan D. T. Engbers, PhD; Nathalie Jette, MD, MSc; Scott B. Patten, MD, PhD; Shaily Singh, MD, DM; Tolulope T. Sajobi, PhD; Deborah Marshall, PhD; Yahya Agha-Khani, MD; Paolo Federico, MD, PhD; Aaron Mackie, MD; Sophie Macrodimitris, PhD; Brienne McLane, MD; Neelan Pillay, MB ChB; Ruby Sharma, PhD; Samuel Wiebe, MD, MSc

Two prediction models for psychiatric adverse effects related to LEV

1. One for the overall population
2. One for those without a history of a psychiatric sign, symptom, or disorder during the study period

To derive prediction models to estimate the risk of psychiatric adverse effects from LEV use

The Health Improvement Network (THIN) database based in the United Kingdom (inclusive January 1, 2000, toMay 31, 2012

Histories of febrile seizures, status epilepticus, longer duration of epilepsy, psychiatric comorbidities and behavioral issues, and cognitive impairment
were associated with psychiatric adverse effects from LEV use
Coadministration of LTG was associated with a protective effect

A total of 14.1% (165 of 1173) experienced a psychiatric symptom or disorder within 2 years of index prescription

Significant factors from multivariate analysis

Female sex
(odds ratio [OR], 1.41; 95% CI, 0.99-2.01; P = .05)

Increasing social deprivation
(OR, 1.15; 95%CI, 1.01-1.31; P = .03)

Depression
(OR, 2.20; 95%CI, 1.49-3.24;P< .001)

Anxiety
(OR, 1.74; 95%CI, 1.11-2.72; P = .02)

Recreational drug use
(OR, 2.02 95% CI, 1.20-3.37; P = .008)

Overall
Risk score =
–2.34
+ **0.27** × (female sex)
+ **0.82** × (history of depression)
+ **0.47** × (history of anxiety)
+ **0.74** × (history of recreational drug use)

2. Adults

Efficacy evidences of ASMs in adults

Newly-diagnosed epilepsy

INITIAL MONOTHERAPY

ILAE 2006 and 2013

Epilepsia, 54(3):551–563, 2013
doi: 10.1111/epi.12074

SPECIAL REPORT

Updated ILAE evidence review of antiepileptic drug efficacy and effectiveness as initial monotherapy for epileptic seizures and syndromes

*Tracy Glauser, †Elinor Ben-Menachem, ‡Blaise Bourgeois, §Avital Cnaan, ¶Carlos Guerreiro, #Reetta Kälviäinen, **Richard Mattson, ††Jacqueline A. French, ‡‡Emilio Perucca, §§Torbjorn Tomson for the ILAE Subcommission on AED Guidelines

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2013

This review included applicable articles from 1940 until March 2012

Seizure type or epileptic syndrome	Level of evidence	AEDs
Adults with partial-onset seizures	**A** B C D	**CBZ, PHT, LEV, ZNS** VPA GBP, LTG, OXC, PB, TPM, VGB CZP, PRM
Adults with generalized-onset tonic clonic seizures	A B C D	None None CBZ, LTG, OXC, PB, PHT, TPM, VPA GBP, LEV, VGB
Elderly adults with partial-onset seizures	**A** B C D	**LTG, GBP** None CBZ TPM, VPA
Juvenile myoclonic epilepsy (JME)	A B C D	None None None **TPM, VPA**

Evidence of efficacy and effectiveness of AEDs in adult epileptic seizures/syndromes

AAN & AES 2018

- Jan 2003 – November 2015

CLB, VGB, and the **8 second-generation** and **6 third-generation AEDs** **(ESL, EZG, LCM, PER, PGB, RFN)**

Seizure type or epileptic syndrome	Level of evidence	AEDs
Adults with partial-onset seizures	A B C	None LTG LEV, ZNS
Elderly adults (≥ 60 yrs) with partial-onset seizures	A B C	None LTG GBP
Children with absence epilepsy	A B	None ETX or VPA before LTG

No high-quality studies suggest the remaining AEDs effective to treat new-onset epilepsy

Kanner AM et.al; Neurology: 2018

Initial monotherapy in newly-diagnosed epilepsy

Seizure type or epileptic syndrome	Level of evidence	AEDs			
		ILAE 2006	ILAE 2013	AAN & AES 2004	AAN & AES 2018
Adults with partial-onset seizures	A B	CBZ, PHT VPA	CBZ, PHT, **LEV, ZNS** VPA	**GBP, LTG, TPM, OXC** -	- LTG
Elderly adults (≥ 60 yrs) with partial-onset seizures	A B	LTG, GBP -	LTG, GBP -	**NA**	- LTG
Children with absence seizure in childhood absence epilepsy	A B	- -	ETX, VPA -	- LTG	- ETX or VPA before LTG
Children with partial-onset seizures	A	OXC	OXC	-	-

FDA approved ESL and LCM as add-on or monotherapy in persons ≥4 years old and PER as monotherapy

2. Adults

Child-bearing age women

14 years old

1st GTC

16 years old

an episode of staring associated with automatic movements

16 years old

an episode of staring associated with automatic movements

30 years old

Wants to have kids

Pregnancy & Teratogenicity of the AEDs

Level of MCM risk

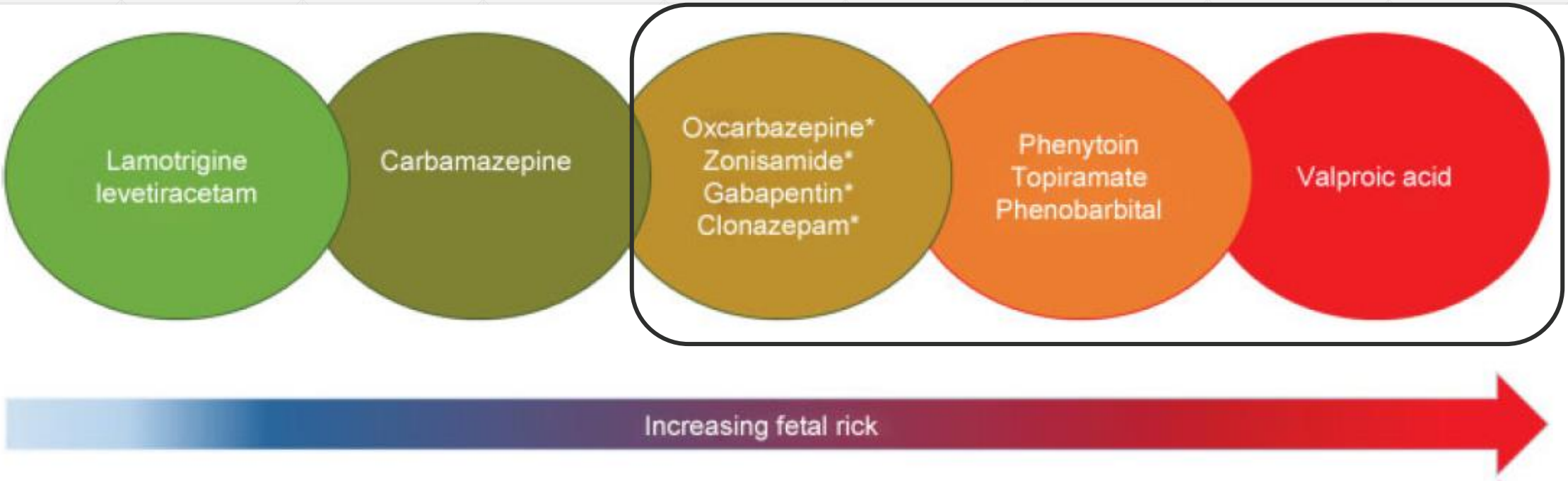


Fig. 2 Preferential selection of AEDs for WWE of childbearing age, based on the available risk profile data at the time of writing. The risk profiles include data about major congenital malformations, fetal growth, and neurodevelopmental outcomes when available, with consideration of the range of relative risks reported from multiple studies, number of patients studied, and confidence intervals.
*Neurodevelopmental outcomes are not yet known.

Voinescu PE & Pennell PB; Semin Neurol 2017

Comparative risk of major congenital malformations with eight different antiepileptic drugs: a prospective cohort study of the EURAP registry

Lancet Neurol 2018

Torbjörn Tomson, Dina Battino*, Erminio Bonizzoni, John Craig, Dick Lindhout, Emilio Perucca, Anne Sabers, Sanjeev V Thomas, Frank Vajda, for the EURAP Study Group†*

Data from pregnancies in women who were exposed to antiepileptic drug monotherapy at conception, prospectively identified from 42 countries contributing to EURAP

Primary outcome:

The **risk of major congenital malformations assessed at 1 year after birth** in offspring exposed prenatally **to one of eight commonly used antiepileptic drugs** (carbamazepine, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, topiramate, and valproate)

Lancet Neurol 2018

	Dose range (mg/day)	Number of pregnancies exposed	Number of major congenital malformation events	Prevalence of major congenital malformation events (95% CI)
Lamotrigine	25–1300	2514	74	2·9% (2·3–3·7)
Carbamazepine	50–2400	1957	107	5·5% (4·5–6·6)
Valproate	100–3000	1381	142	10·3% (8·8–12·0)
Levetiracetam	250–4000	599	17	2·8% (1·7–4·5)
Oxcarbazepine	75–4500	333	10	3·0% (1·4–5·4)
Phenobarbital	15–300	294	19	6·5% (4·2–9·9)
Topiramate	25–500	152	6	3·9% (1·5–8·4)
Phenytoin	30–730	125	8	6·4% (2·8–12·2)

Table 2: Prevalence of major congenital malformations in offspring exposed prenatally to one of eight different antiepileptic monotherapies

Risks of major congenital malformation associated **with lamotrigine, levetiracetam, and oxcarbazepine** were within the range reported in the literature for offspring **unexposed to antiepileptic drugs**

	Number of pregnancies exposed	Number of major congenital malformation events	Prevalence of major congenital malformation events (95% CI)	p value
Lamotrigine				
≤325 mg/day	1870	46	2·5% (1·8–3·3)	0·0145
>325 mg/day	644	28	4·3% (2·9–6·2)	..
Carbamazepine				
≤700 mg/day	1276	58	4·5% (3·5–5·8)	0·0140
>700 mg/day	681	49	7·2% (5·4–9·4)	..
Valproate				
≤650 mg/day	600	38	6·3% (4·5–8·6)	<0·0001
>650 to ≤1450 mg/day	666	75	11·3% (9·0–13·9)	..
>1450 mg/day	115	29	25·2% (17·6–34·2)	..
Phenobarbital				
≤80 mg/day	73	2	2·7% (0·3–9·5)	0·0390
>80 to ≤130 mg/day	161	10	6·2% (3·0–11·1)	..
>130 mg/day	60	7	11·7% (4·8–22·6)	..

When a dose dependency for the risk of major congenital malformation was identified, comparisons also included specific dose ranges at time of conception.

Table 3: Association between prevalence of major congenital malformations and exposure to one of the four monotherapies in which a dose response was detectable

Lancet Neurol 2018

Other issues
in child-bearing age women

Contraceptive methods

Sazgar M; CONTINUUM (MINNEAP MINN) 2019

ASMs and contraceptive failure

AEDs causing contraceptive failure (enzyme-inducing AEDs)	AEDs causing contraceptive failure at higher dose	AEDs with no known effects on contraceptive failure
Carbamazepine Oxcarbazepine Eslicarbazepine Acetate Phenytoin Phenobarbital Primidone Rufinamide Clobazam	Topiramate (> 200 mg/d) Perampanel Felbamate	Ethosuximide Gabapentin Tiagabine Vigabatrin Lacosamide Lamotrigine Levetiracetam Retigabine/ ezogabine Valproic acid Zonisamide Clonazepam

Table 2 Antiepileptic drug effects on the metabolism of hormonal contraceptive agents and recommended contraceptive methods

Degree of induction of metabolism of sex steroid hormones	Strong inducers	Weak inducers	Noninducers
Antiepileptic drug	Phenobarbital Phenytoin Carbamazepine Primidone Oxcarbazepine Perampanel	Topiramate Lamotrigine[a] Felbamate Rufinamide Clobazam Eslicarbazepine	Ethosuximide Valproate Gabapentin Clonazepam Tiagabine Levetiracetam Zonisamide Pregabalin Vigabatrin Lacosamide
Recommended contraceptive methods	IUD Depo-provera	IUD Progestin implant Depo-provera [b] Some OCPs	IUD, Progestin implant, Depo-provera, OCPs, Patches, Vaginal Rings

Copper IUDs (nonhormonal) and Levonorgestrel-releasing IUDs.

Voinescu PE & Pennell PB; Semin Neurol 2017

3. Elderly

16 years old

an episode of staring associated with automatic movements

30 years old

Wants to have kids

30 years old

Wants to have kids

60 years old

still has frequent seizures

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

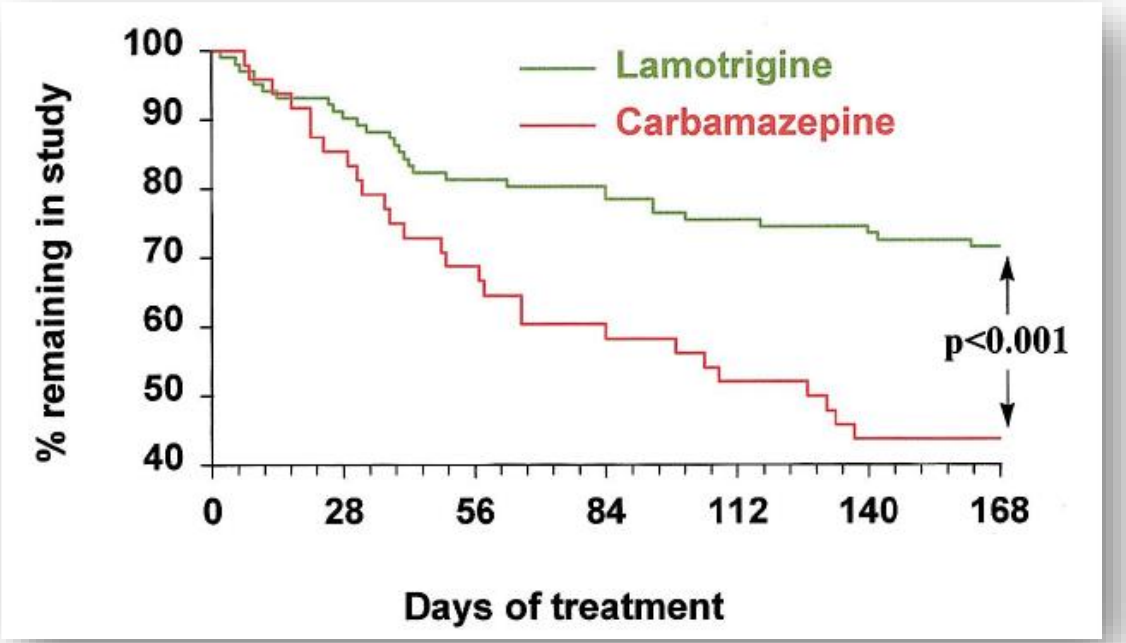
- **Counterregulatory (homeostatic) processes are attenuated**
- The incidence of adverse effects is higher in the elderly, despite the general decline in receptor number or responsiveness

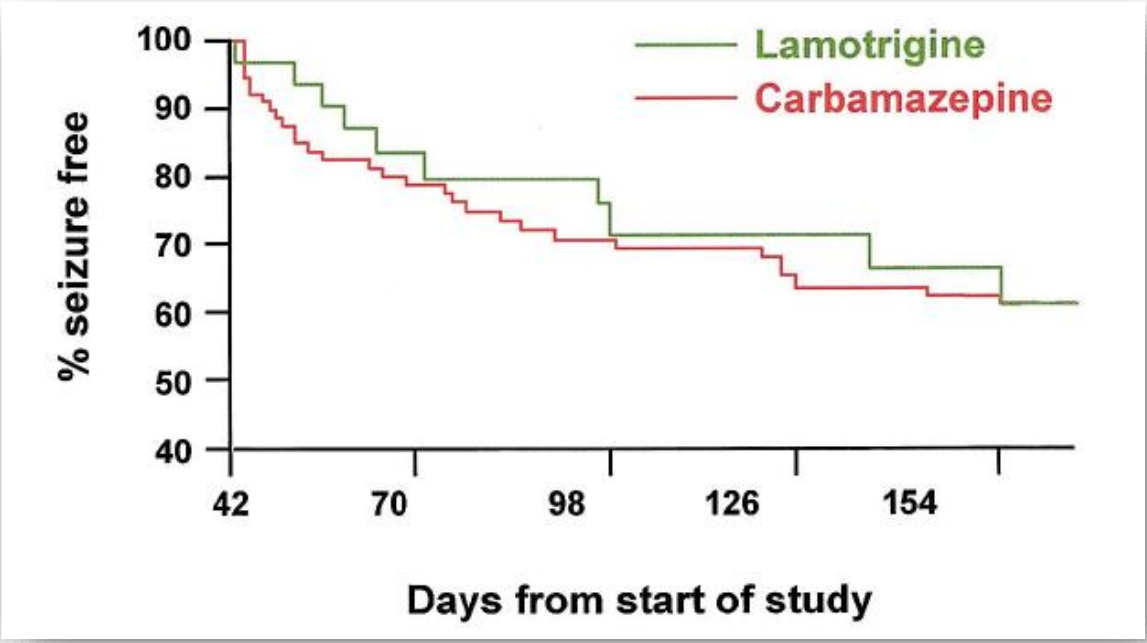
"The elderly people are more vulnerable to develop the side effects from the drugs"

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

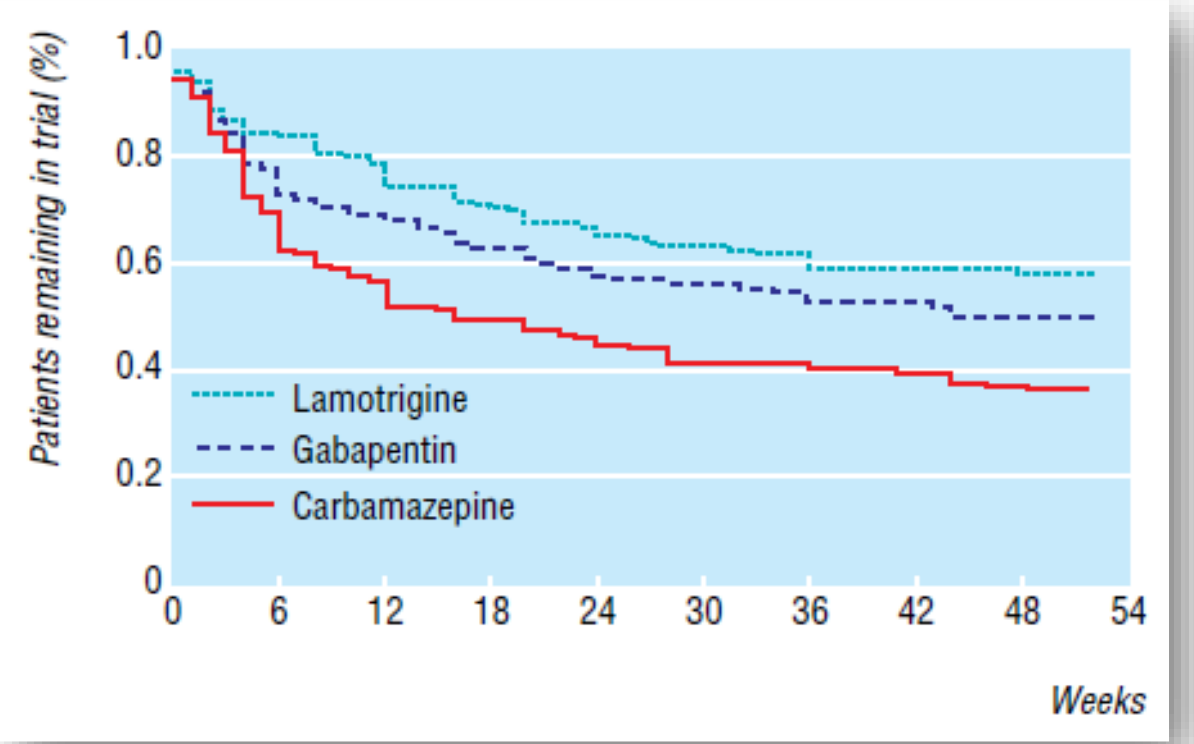


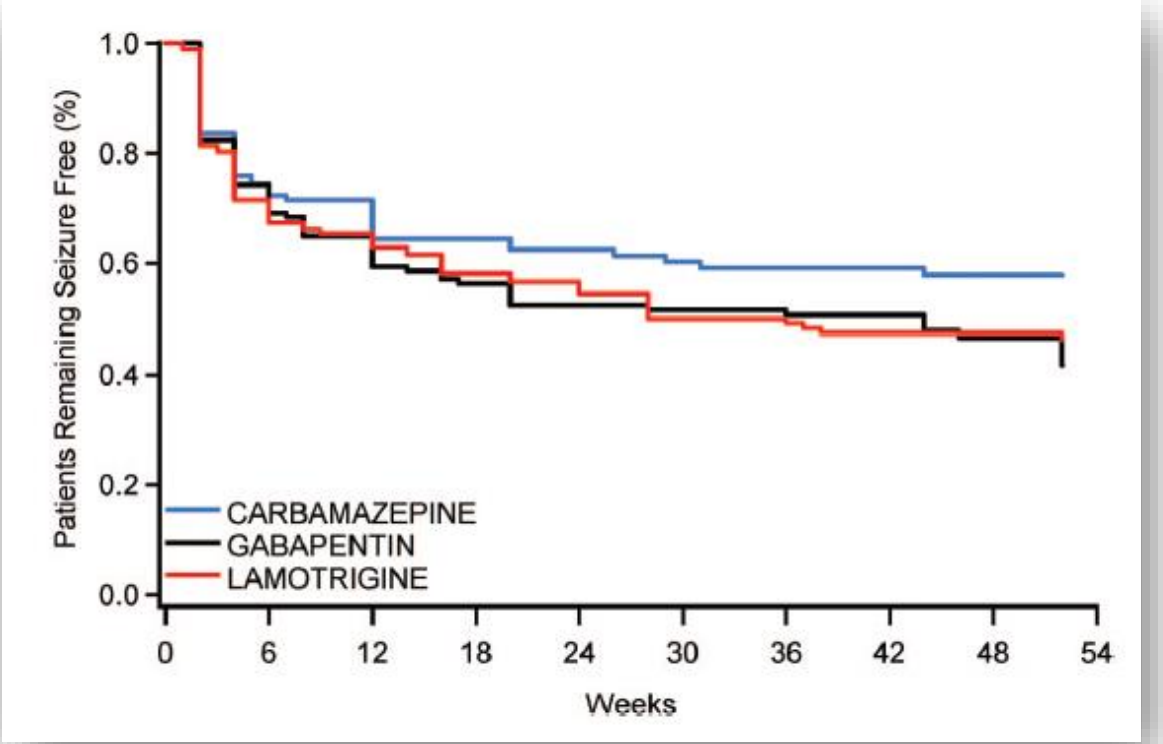


Comparable efficacy between CBZ and LTG, but significantly more patients in CBZ group withdrew from the study due to the side effects

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

Seizure type or epileptic syndrome	Level of evidence	AEDs
Adults with partial-onset seizures	**A** B C D	**CBZ, PHT, LEV, ZNS** VPA GBP, LTG, OXC, PB, TPM, VGB CZP, PRM
Adults with generalized-onset tonic clonic seizures	A B C D	None None CBZ, LTG, OXC, PB, PHT, TPM, VPA GBP, LEV, VGB
Elderly adults with partial-onset seizures	**A** B C D	**LTG, GBP** None CBZ TPM, VPA
Juvenile myoclonic epilepsy (JME)	A B C D	None None None **TPM, VPA**

Evidence of efficacy and effectiveness of AEDs in adult epileptic seizures/syndromes

Relationship Epilepsy and AD

An estimated 10% to 22% of patients with AD develop unprovoked seizures, with higher rates in familial and early-onset cases (< 65 yrs)

The incidence of seizures was 10 times more than expected in a reference population

Hauser WA et al., Neurology 1996; Amatnek JC et al., Epilepsia 2006; Vossel KA et al., JAMA Neurol 2013

Overall, seizures occur more frequently in patients with Alzheimer's disease than in those with non-Alzheimer's disease dementias

Sherzai D et al., Epilepsy & Behav 2014

Presence of myoclonus increased seizure risk by 7·7 times

Seizures occurred in any stage of AD, but myoclonus was often a late manifestation

Samson WN et al., Eur Neurol 1996

Myoclonus, which is generally considered to be due to **cortical hyperexcitability**, is also common in patients with Alzheimer's, with a prevalence of 7–10% and a cumulative risk as high as 80% by late stages of disease

Hauser WA et al., Neurology 1986; Chen JY et al., Arch Neurol 1991

Do you know ?

Epileptic activity can occur at “Early disease stages” and might contribute to pathogenesis

Vossel KA et al., Lancet Neurol 2017

1 **Seizures can accelerate cognitive decline in patients with AD**

2 **Seizures in patients with AD can easily go unrecognized** (non-motor seizures; can overlap with other symptoms of the disease)

3 **Selected low-dose AED is sufficient to treat clinical seizures in patients with AD**

4 **Certain classes of AEDs that reduce network hyperexcitability have disease-modifying properties**

Epileptic activity can occur at "Early disease stages" and might contribute to pathogenesis

Original Investigation

Seizures and Epileptiform Activity in the Early Stages of Alzheimer Disease

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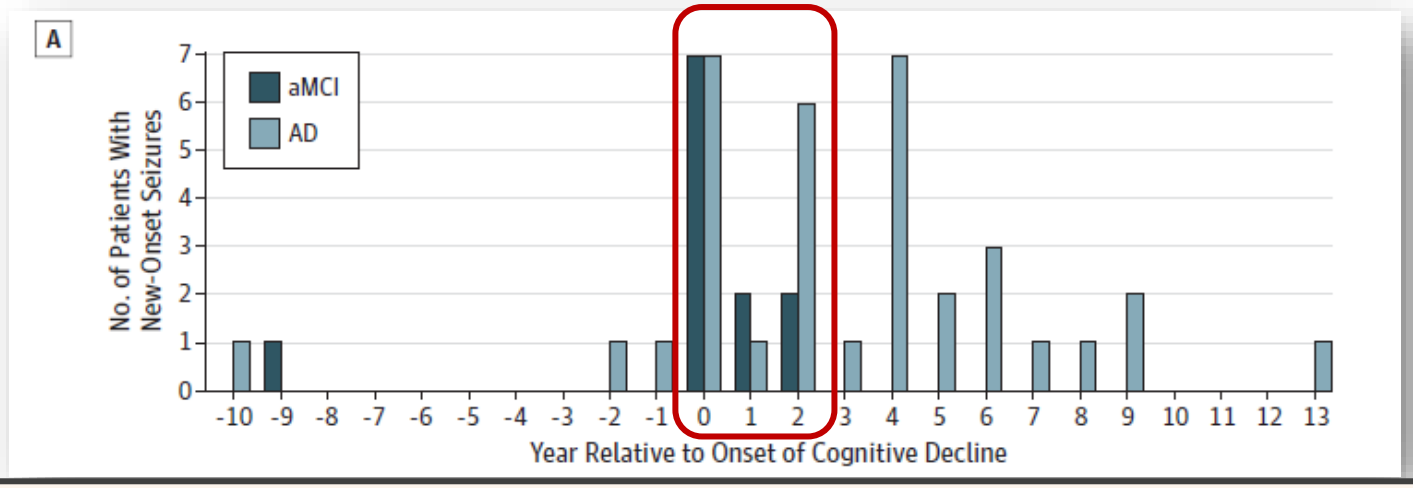
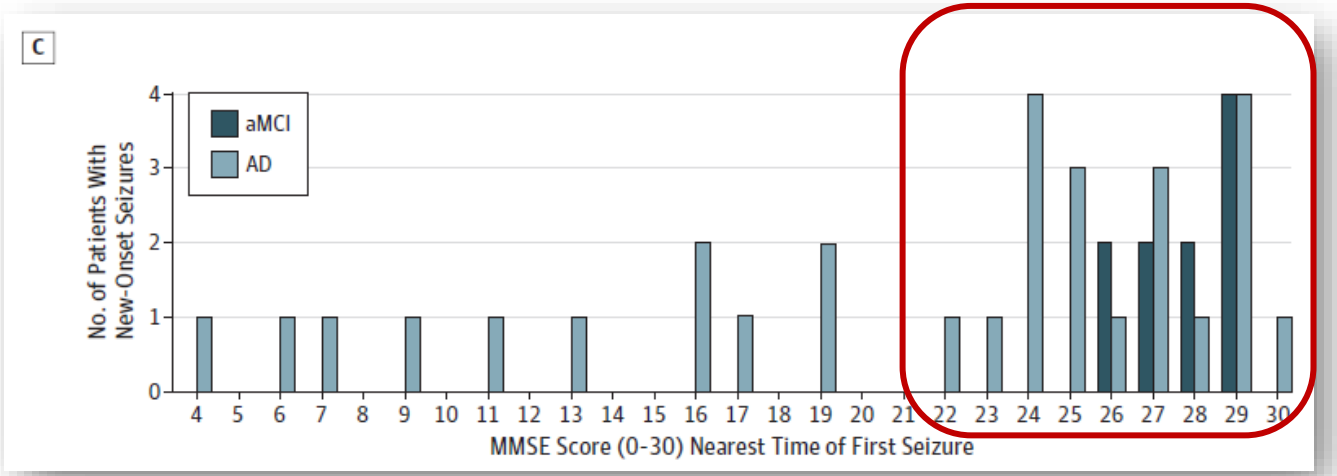
JAMA Neurol 2013



Seizures were coincident with, or followed the onset of cognitive decline

Epileptic Prodromal Alzheimer's Disease, a Retrospective Study of 13 New Cases: Expanding the Spectrum of Alzheimer's Disease to an Epileptic Variant?

Cretin B et al., J Alzheimer Dis 2016



MMSE scores obtained nearest the time of the first seizure were clustered toward the upper end of the range

Epileptic activity can occur at "Early disease stages" and might contribute to pathogenesis

Seizures in aMCI and AD generally began early in the disease course when patients had mild impairments on cognitive testing

Vossel KA et al., JAMA Neurol 2013

Seizures can accelerate cognitive decline in patients with AD

Vossel KA et al., Lancet Neurol 2017

Cognitive decline began **before 65 years of age**

- **aMCI – Epilepsy: in 50% of cases**
- **AD – Epilepsy: in 51% of cases**
- aMCI - No epilepsy: in 21% of cases
- AD – No epilepsy: in 26% of cases

AD – Subclinical epileptiform activity

- AD-epilepsy and also showed an **earlier cognitive decline** than patients with AD – No epilepsy (**age 58.9 vs 70.3 years**; *p = .009*)

Vossel KA et al., JAMA Neurol 2013

Based on these observations, patients with AD should be assessed carefully for epileptiform activity and silent seizures if they present with **fluctuations in cognition**, **rapidly progressive cognitive decline**, **early-onset Alzheimer's disease** (eg, onset around age 50 years), and **myoclonus**, given the co-occurrence of myoclonus and seizures

Journal of Neurology
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ORIGINAL COMMUNICATION

June 2020

Seizures in Alzheimer's disease are highly recurrent and associated with a poor disease course

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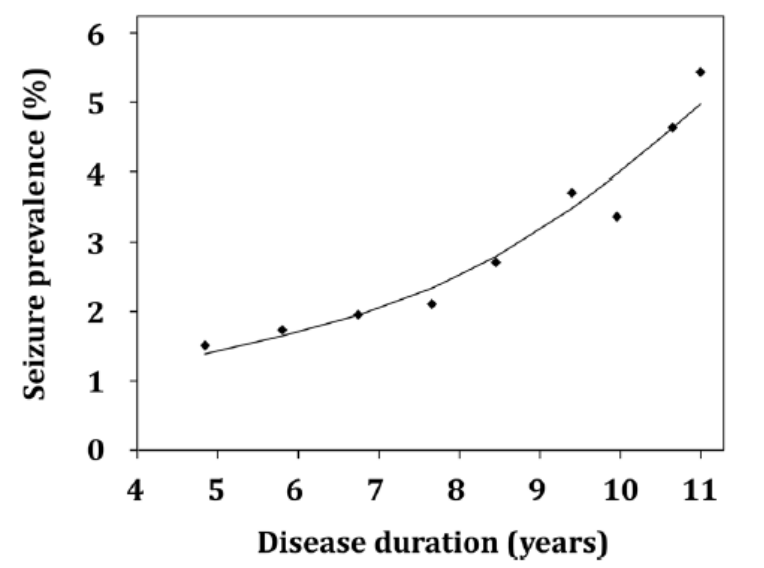
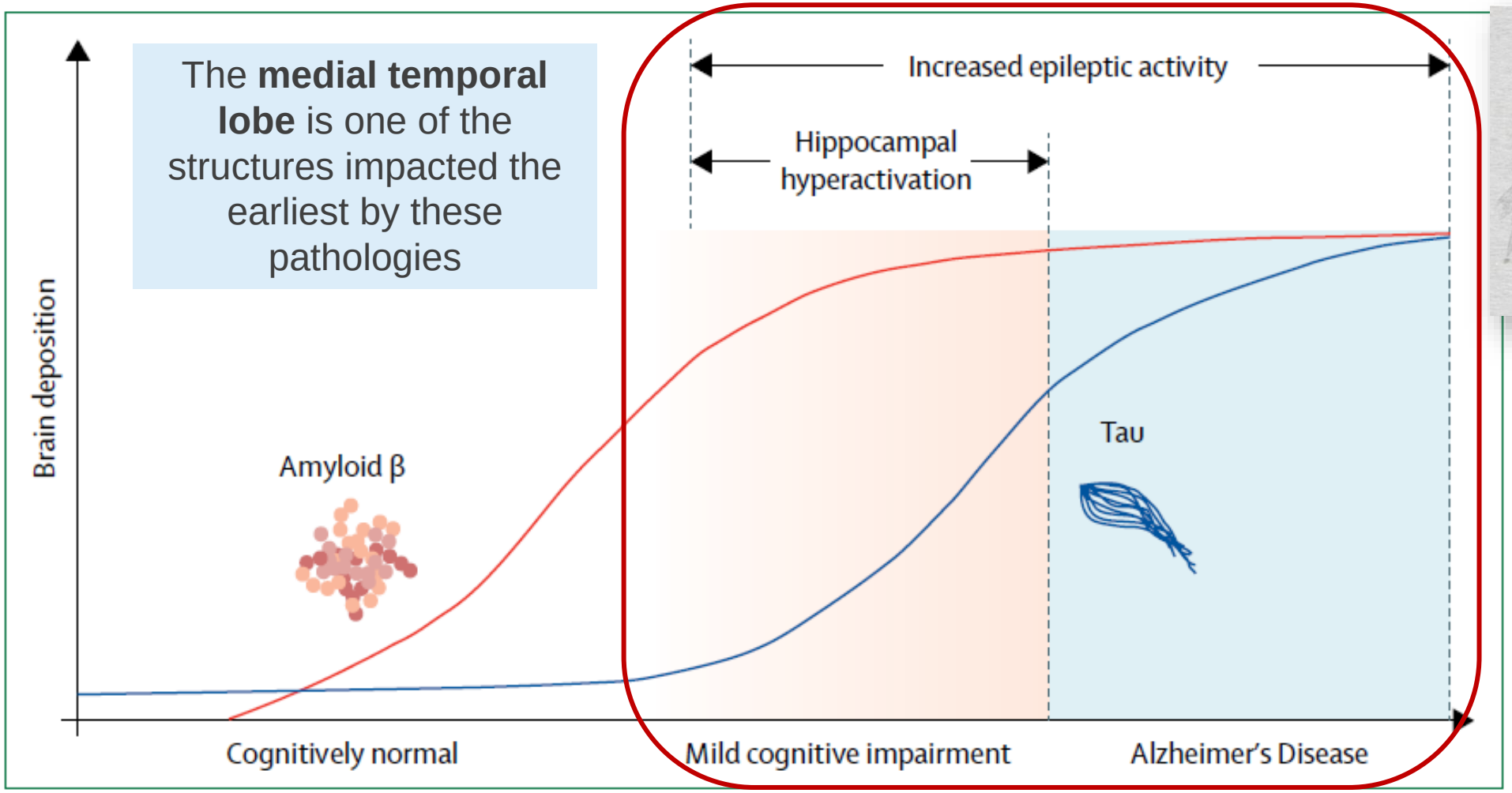


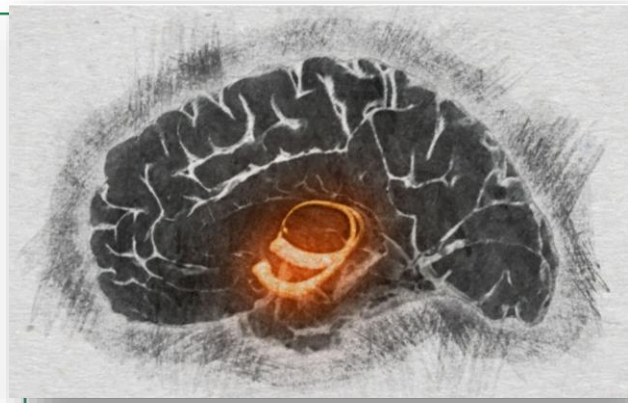
The National Alzheimer's Coordinating Center database containing data from 34 past and present Alzheimer's disease centers (ADCs) in the USA

- Seizure history was associated with an **earlier age of onset of cognitive symptoms**
- **Worse cognitive and functional performance**

Seizure prevalence increased with duration of AD dementia
(standardized OR = 1.55, 95% CI = 1.39–1.73, $p < 0.0001$)

The **medial temporal lobe** is one of the structures impacted the earliest by these pathologies





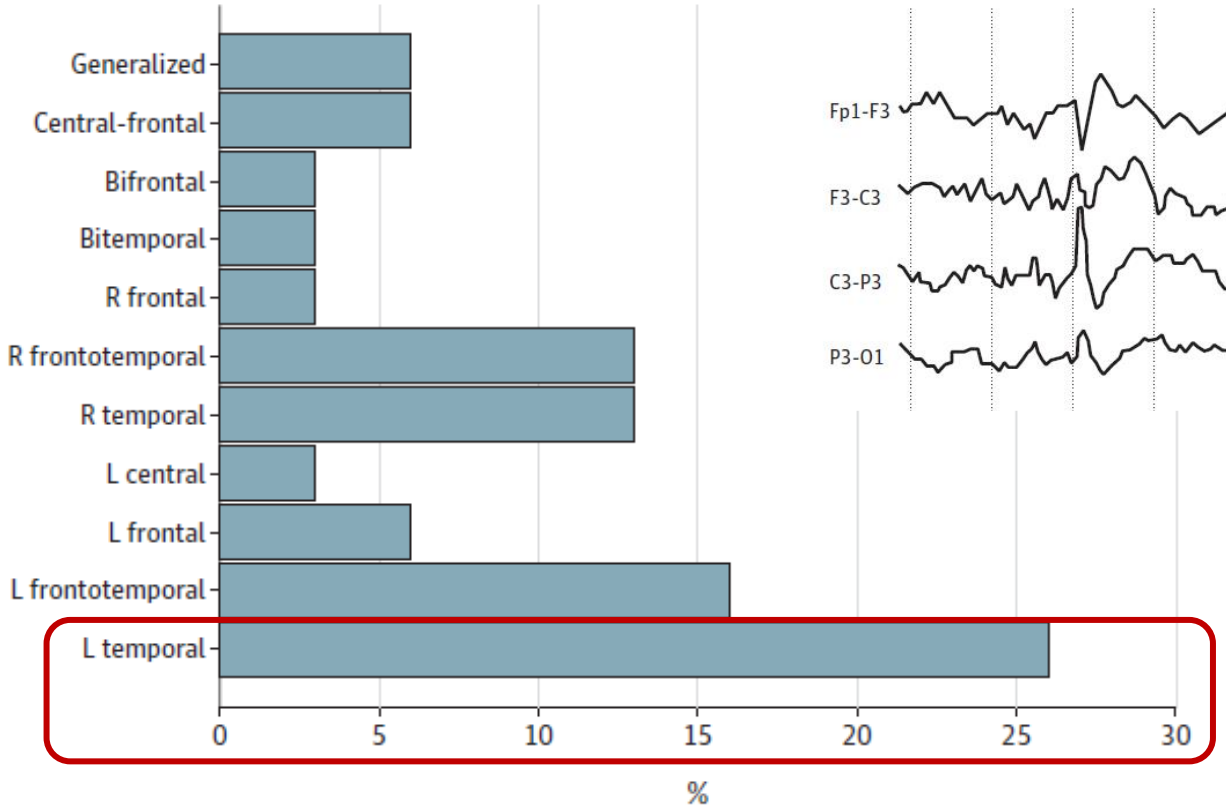
Vossel KA et al., Lancet Neurol 2017

Figure: Hypothetical model of the correlation between amyloid β and tau deposition and network alterations in Alzheimer's disease

Seizures that precede onset of cognitive decline might reflect the epileptogenic potential of amyloid β, which begins to accumulate more than 10 years before clinical signs of dementia

Villemagne VL et al., Lancet Neurol 2013

Figure 2. Distribution of Electroencephalogram Epileptiform Activity



Vossel KA et al., JAMA Neurol 2013

Vossel KA et al., Lancet Neurol 2017

Seizures in patients with AD can easily go unrecognized (non-motor seizures; can overlap with other symptoms of the disease)

55% of the patients with aMCI or AD who had epilepsy (26 of 47) had only **nonconvulsive seizures**

AEDs can reduce excessive glutamate release from excitatory neurons, which might be relevant to epileptogenesis in Alzheimer's disease

	Proposed mechanism	Phase of investigation in Alzheimer's disease
Antiepileptic drug		
Levetiracetam	Binds SV2A and prevents synaptic vesicle release,[65] and increases glutamate transporter expression[89]	Animal model;[6,70] case-control;[58] phase 2 (NCT02002819);[73] and phase 3 (registering in 2017)
Brivaracetam	Binds SV2A with higher affinity than levetiracetam[90]	Animal model[76]
Lamotrigine	Inhibits Na^+ channel activity; more potent at inhibiting glutamate release than other antiepileptic drugs in this class[66]	Animal model;[77] case-control[58]
Topiramate	Inhibits GSK-3β activation and histone deacetylase activity,[70] inhibits Na^+ and Ca^{2+} channels, enhances $GABA_A$ receptor function, and blocks AMPA and kainate receptors	Animal model[70]

Vossel KA et al., Lancet Neurol 2017

Studies of AEDs in older adults with or without dementia

	Dose (mg per day)	Tolerability	Efficacy	Cognitive side-effects?	Other potential adverse effects*	Other uses
Levetiracetam	250–2000	Excellent	Excellent	No	Aggression, asthenia, dizziness, fatigue, headache, irritability, and nausea	Treatment of myoclonus
Lamotrigine	25–500	Excellent	Excellent	No	Asthenia, ataxia, blurred vision, diarrhea, diplopia, dizziness, hypersensitivity reaction, incoordination, insomnia, nausea, rash, somnolence, Stevens-Johnson syndrome, and tremor	Mood stabilisation
Gabapentin	300–1500	Good	Good	Possible	Ataxia, dizziness, fatigue, nystagmus, nausea, peripheral oedema, somnolence, and weight gain	Treatment of insomnia, peripheral neuropathy, postherpetic neuralgia, and migraine prophylaxis
Carbamazepine	600	Fair	Good	Yes	Agranulocytosis, asthenia, ataxia, blurred vision, cardiac dysrhythmia, constipation, decreased bone density, dizziness, hepatotoxicity, hypersensitivity reaction, hyponatraemia, nausea, rash, somnolence, and xerostomia	Mood stabilisation, and treatment of trigeminal neuralgia
Valproic acid	250–1000	Fair	Good	Yes	Alopecia, asthenia, ataxia, constipation, diarrhoea, diplopia, dizziness, gait disturbance, headache, hepatotoxicity, indigestion, nausea, nervousness, nystagmus, peripheral oedema, rash, somnolence, tinnitus, tremor, weakness, and weight gain	Mood stabilisation, migraine prophylaxis, and treatment of myoclonus
Phenytoin	200–300	Poor	Good	Yes	Ataxia, constipation, decreased bone density, dizziness, dysarthria, gingival hyperplasia, hepatotoxicity, hypersensitivity reaction, incoordination, lethargy, muscle hypotonia, nausea, nervousness, nystagmus, and sedation or drowsiness	None
Phenobarbital	50–100	Poor	Excellent	Yes	Asthenia, barbiturate withdrawal, decreased bone density, hypersensitivity reaction, somnolence, and syncope	Long-term sedation

*Partial list that includes common side-effects and serious side-effects. Information collected from several sources.[2,3,58,60–64]

Table 2: **Commonly prescribed antiepileptic drugs for older adults with cognitive impairment**

Vossel KA et al., Lancet Neurol 2017

Epilepsy management through a patient's life

Summary

1. Adolescence
2. Adults
   - ❖ Efficacy evidences of ASMs in adults
   - ❖ Child-bearing age women
3. Elderly

Thank you