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ศิริราชพยาบาล

AED choices in elderly patients

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Challenges in DIAGNOSIS

- History is THE MOST IMPORTANT.
- 30% of epilepsy in elderly are MISDIAGNOSED at first evaluation
- History-taking from patient can be difficult
  - Language, cognitive impairment.
- History from reliable caregiver/ witness is crucial.
  - Initial symptoms, pallor, cyanosis, abnormal movements, tongue biting, urinary incontinence, and impaired conscious level.
  - Postictal state: confusion, headache, weakness

Various presentation

Atypical presentation

- Aura: are not common and may have nonspecific symptom e.g. dizziness
- Postictal symptoms:
  - Confusion, Todd's paresis, aphasia
  - Can stay longer

Seizure characters	Young adults	Elderly
Aura	66-76%	33-54%
Ictal: subtle, brief confusion	0%	18%
Multiple phases to evolution	67%	24%
GTC	80%	56%
Postictal sleepiness or unresponsiveness	45%	67%

Challenges in MANAGEMENT

Antiepileptic drugs

When to start?

What to start?

No seizure

No side effects

When to start

- Usually > 1 unprovoked SZ
- After a single unprovoked SZ
  - brain lesion on imaging
  - an epileptiform on EEG
  - at patient's or family's request

FIRST Seizure Trial Group

- Old age was found to be a significant predictor of seizure recurrence.

		Remissions			
		1 year		2 years	
	No. pts.	No. (%)	RR* (95% CI)†	No. (%)	RR* (95% CI)†
Treatment after first seizure					
No‡	204	170 (83.3)		122 (59.8)	
Yes	215	186 (86.5)	1.17 (0.95–1.45)	146 (67.9)	1.22 (0.97–1.56)
			1.03 (1.28–0.85)§		1.04 (1.30–0.82)§
Age (yrs)					
<16	114	95 (83.3)	0.80 (0.63–1.01)	72 (63.2)	0.90 (0.68–1.18)
16–60‡	277	241 (87.0)		182 (65.7)	
>60	28	20 (71.4)	0.67 (0.42–1.05)	14 (50.0)	0.69 (0.40–1.19)

Musicco M, et al. NEUROLOGY 1997;49:991-998

What to start?

No seizure

- Efficacy

No side effects

- PK-PD
- Comorbidity
- Drug-drug interaction (polytherapy)
- Tolerability
- Cognitive SE

Elderly are more prone to the adverse effects.
"Start low, go slow"

Ideal Properties for AEDs in elderly

- High efficacy & Good tolerability
- No or rapid titration
- No risk of allergic or idiosyncratic reaction
- Low interaction potential
- Favorable pharmacokinetics
  - Linear kinetics
  - No dose adjustment in renal impairment
  - No hepatic enzyme induction or inhibition
  - Once daily dosage
- RCT in elderly age group

Antiepileptic Drugs

Old	Newer (2nd gen)	Newest (3rd gen)
Phenobarbital 1919	Felbamate 1993	**Pregabalin 2005**
Phenytoin 1938	**Gabapentin 1993**	Rufinamide 2009
Primidone 1954	**Lamotrigine 1994**	**Lacosamide 2009**
Ethosuximide 1960	**Topiramate 1996**	Vigabatrin 2009
Carbamazepine 1974	Tiagabine 1997	**Clobazam 2011**
Valproic acid 1978	**Levetiracetam 1999**	Ezogabine 2011
	Oxcarbazepine 2000	**Perampanel 2012**
	Zonisamide 2000	Eslicarbazepine 2014

Efficacy: Treatment responding rate

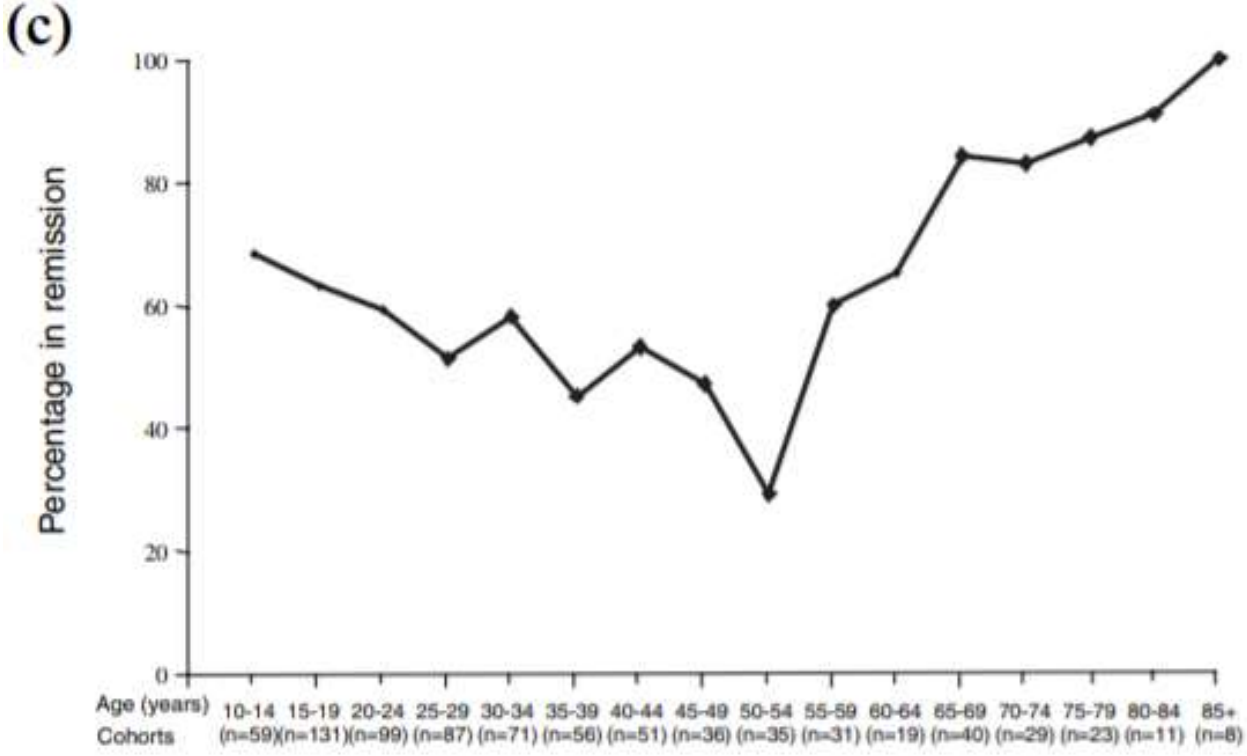
Table 1 Pharmacological outcomes in newly diagnosed epilepsy by age at starting treatment

Patient groups	Age (years)	*n*	Remission (%)	Relapse (%)	Uncontrolled (%)
Adolescent	< 20	170	65*	12	23
Adult	20–64	520	53	4	43
Elderly	> 64	90	85**	1	14

Up to 80% of patients with onset in old age respond to AEDs.

Mohanraj R, Brodie MJ. European Journal of Neurology 2006, 13: 277–282

Efficacy: Remission rate



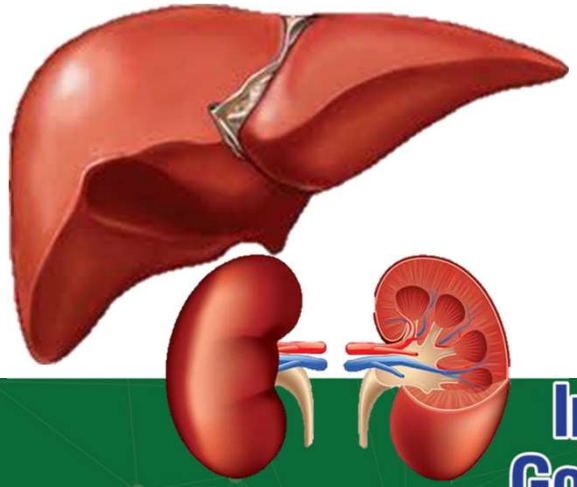
Epilepsy in the elderly generally responds well to treatment.

Mohanraj R, Brodie MJ. European Journal of Neurology 2006, 13: 277–282

Pharmacology in old age

PK

- Absorbtion
- Protein binding
- Hepatic metabolism
- Enzyme inducibility
- Renal elimination



PD

- Brain neurotransmitters
- Receptor function
- Autonomic pharmacology
- Homeostatic mechanisms

Easily get neurotoxicity

Easily get idiosyncratic reaction

"Start low, go slow"

Treatment of epilepsy in elderly

- AED metabolism: renal and hepatic impairment
- AEDs are hepatic metabolized;
  - PB, PHT, CBZ (OXC, ESL), VPA
  - ZNS, LTG, PER
- Factors increase AED levels
  - Hypoalbuminemia
  - Low protein binding affinity
- AED that are renal excreted;
  - GBP, PGB, LEV, LCM, TPM

AED: Old generation

	Advantages	Disadvantages
Phenobarbital (PB)	Broad spectrum Once daily Cheapest	**Sedation** **Cognitive impairment** **Behavioral problems** **Enzyme induction, Bone loss**
Phenytoin (PHT)	Once daily No titration Cheap	**Sedation** **Rash** ****Saturation kinetics** **Enzyme induction, Bone loss**
Carbamazepine (CBZ)	**Goal standard for focal SZ** **Studied in elderly** Relatively cheap	**Rash** **Enzyme induction, Bone loss** ****HypoNa** ****Slow titration**
Na Valproate (VPA)	Broad spectrum Rapid titration Relatively cheap	Tremor Weight gain **Enzyme inhibition, Bone loss** ****Parkinsonism**

Drug-drug interaction

Enz inducer

- CBZ, PHT, PB, primidone
- Interact w/
  - warfarin, antiarrhythmia, theophylline, corticosteroid, antidepressant, CMT.
- Metabolize Vit D → bone loss

Drug-drug interaction

Enz inhibitor

- AED: Sodium Valproate (VPA)
- Others: cimetidine, erythromycin, isoniazid, verapamil, and diltiazem

- VPA does not induce hepatic drug metabolism, although it can reduce bone mineral density.
- Mechanism: possibly by interfering osteoblastic function.

Bone loss

Recommendation (limited available data)

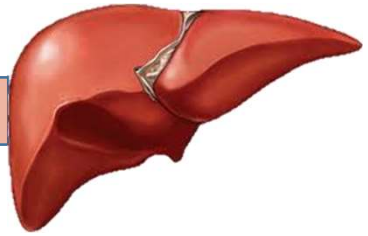
- Screening DEXA scan in high risk AEDs; EIAEDs & VPA (no clear interval of the screening)
- Supplement both calcium and Vit D
  - Ideal dosage is still lacking
  - Calcium 1000 – 1500 mg/d
  - High dose Vit D 4000u/d

AED: New generation

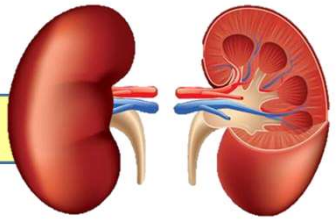
	Advantages	Disadvantages
Lamotrigine	Broad spectrum Good tolerability Few interactions	Slow titration Rash
Topiramate	Broad spectrum Weight loss	Slow titration Cognitive impairment Renal stone
Oxcarbazepine	Good tolerability	Rash HypoNa
Levetiracetam	No allergic reactions No interactions Rapid titration	Behavioral problems
Zonisamide	Broad spectrum Once daily No interactions	Slow titration Rash Renal stones

None of which have superior efficacy to the old gen

AED to avoid in liver/renal failure



- **Hepatic Failure**
  - Benzodiazepines
  - Carbamazepine
  - Felbamate
  - Phenytoin
  - Phenobarbital
  - Primidone
  - Rufinamide
  - Valproic acid and its derivatives



- **Renal Failure**
  - Gabapentin
  - Levetiracetam
  - Pregabalin
  - Vigabatrin

Hyponatremia

- Oxcarbazepine > Carbamazepine
- Esp. combination w/ thiazide or other diuretics
- Usually asymptomatic

Comorbidities

AEDs to Use Cautiously or Avoid	
Liver dz	VPA, PHT, PB, CBZ, LTG
Renal fail	LEV, GBP, PB, PGB, TOP, ZNS
h/o renal stone	ZNS, TOP
Arrhythmia	CBZ, PHT
Pancreatic dz	VPA, CBZ
Hypothyroidism	CBZ, OXC, PHT
Hyponatremia	CBZ, OXC
Osteopenia	PHT > CBZ, PB
Obesity	VPA, PGB, GBP
Anorexia	FBM, TOP, ZNS

Comorbidities

AEDs to Use Cautiously or Avoid (cont.)	
Bleeding diathesis	VPA (dose-related thrombocytopenia)
Blood dyscrasia	CBZ (idiosyncratic leukopenia)
Peripheral edema	PGB
h/o hypersense	AED w/ risk of rash (PHT, CBZ, LTG)
Psychiatric d/o	LEV, PB
Taking warfarin	↓ warfarin: PHT, PB, CBZ
	↑ warfarin: VPA
Cognitive impairment	PB, PHT, primidone
Ataxia	PHT, PB, BDZ, CBZ

Ideal Properties for AEDs in elderly

- High efficacy & Good tolerability
- No or rapid titration
- No risk of allergic or idiosyncratic reaction
- Low interaction potential
- Favorable pharmacokinetics
  - Linear kinetics
  - No dose adjustment in renal impairment
  - No hepatic enzyme induction or inhibition
  - Once daily dosage
- RCT in elderly age group

Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy

Martin J. Brodie [a,*], Peter W. Overstall [b], Luigi Giorgi [c], The UK Lamotrigine Elderly Study Group

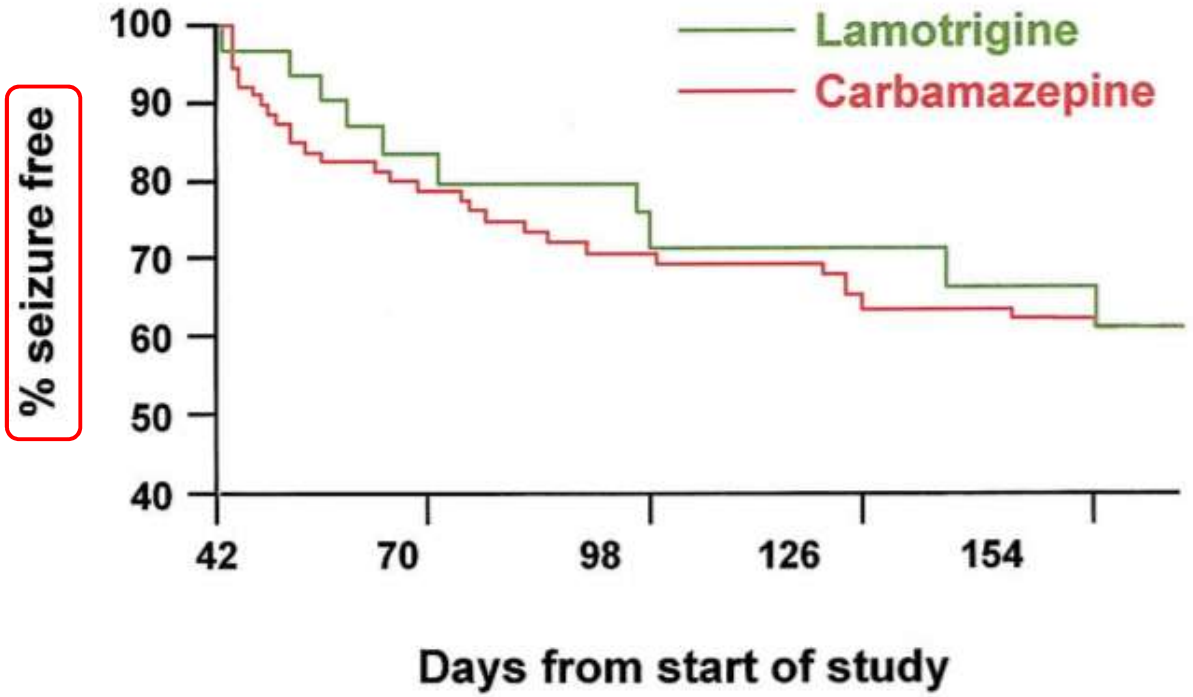
P: age >65 yo (mean 77)
I: randomized to LTG or CBZ
C: efficacy and tolerability over 24 wks

Abstract

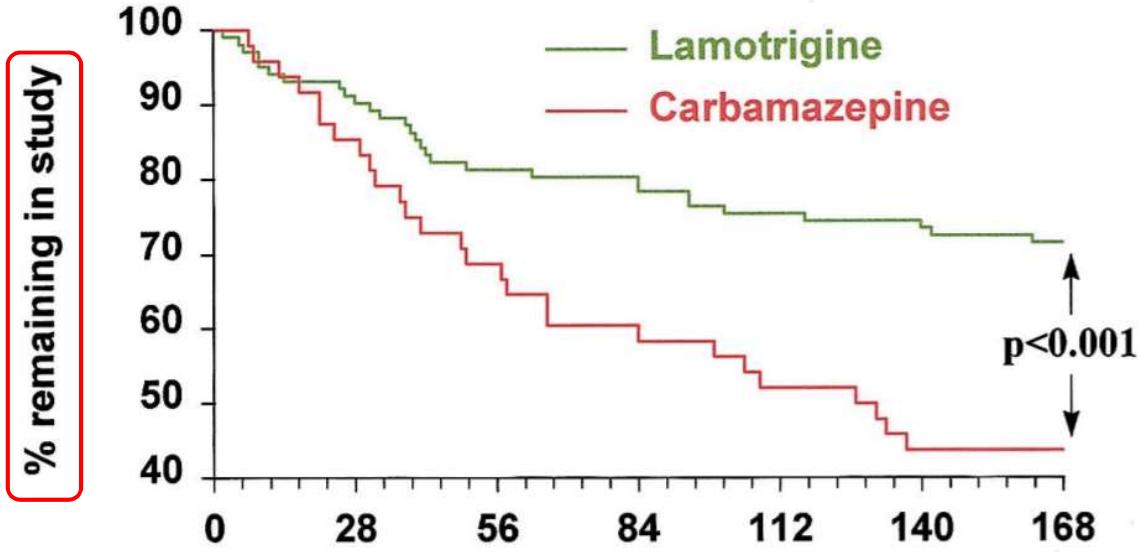
In a multicentre, osed epilepsy were randomised in a 2: ng a short titration period, the dosage 4 weeks. The main difference between BZ 42%). This was in part a consequer TG-treated patients also complained le ough there was no difference between the drugs in time to first seizure, a greater percentage of LTG-treated patients remained seizure-free during the last 16 weeks of treatment (LTG 39%, CBZ 21%; $P = 0.027$). Overall, more patients continued on treatment with LTG than CBZ (LTG 71%, CBZ 42%; $P < 0.001$) for the duration of the study. The hazard ratio for withdrawal was 2.4 (95% CI 1.4–4.0) indicating that a patient treated with CBZ was more than twice as likely to come off medication than one taking LTG. In conclusion, LTG can be regarded as an acceptable choice as initial treatment for elderly patients with newly diagnosed epilepsy.

Brodie MJ, et al. Epilepsy Research 1999: 37; 81–7

	Lamotrigine	Carbamazepine
Weeks 1–2	25 mg	100 mg
Weeks 3–4	25 mg bd	100 mg bd
Weeks 5–6	50 mg bd	200 mg bd
Weeks 7–24	75–500 mg	200–2000 mg



Brodie MJ, et al. Epilepsy Research 1999: 37; 81–7



Premature discontinuations from lamotrigine or carbamazepine treatment

	Lamotrigine	Carbamazepine
Adverse events	18 (18%)	20 (42%)
Protocol violation	7	3
Consent withdrawn	3	2
Intercurrent death	0	2
Lost to follow-up	2	1
Total	30 (29%)	28 (58%)

	Lamotrigine	Carbamazepine
Rash	3 (3%)	9 (19%)
Somnolence	2 (2%)	3 (6%)
Asthenia	1 (1%)	3 (6%)
Nausea	3 (3%)	1 (2%)
Incoordination	3 (3%)	1 (2%)
All withdrawals	18 (18%)	20 (42%)

Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy

Martin J. Brodie [a,*], Peter W. Overstall [b], Luigi Giorgi [c], The UK Lamotrigine Elderly Study Group

Outcome:
Efficacy – No difference between CBZ and LTG
Tolerability – LTG is significantly better

Abstract

In a multic epilepsy were randomised i hort titration period, the d ks. The main difference bet %). This was in part a consequence of the lower rash rate with LTG (LTG 3%, CBZ 19%; 95% CI 7–25%). LTG-treated patients also complained less frequently of somnolence (LTG 12%, CBZ 29%; 95% CI 4–30%). Although there was no difference between the drugs in time to first seizure, a greater percentage of LTG-treated patients remained seizure-free during the last 16 weeks of treatment (LTG 39%, CBZ 21%; $P = 0.027$). Overall, more patients continued on treatment with LTG than CBZ (LTG 71%, CBZ 42%; $P < 0.001$) for the duration of the study. The hazard ratio for withdrawal was 2.4 (95% CI 1.4–4.0) indicating that a patient treated with CBZ was more than twice as likely to come off medication than one taking LTG. In conclusion, LTG can be regarded as an acceptable choice as initial treatment for elderly patients with newly diagnosed epilepsy.

Brodie MJ, et al. Epilepsy Research 1999: 37; 81–7

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

Summary: *Purpos*

efficacy, and tolerabi

release carbamazepin

nosed epilepsy in the

Methods: Patients

enced at least two unp

clonic seizures, were

CBZ (n = 92) accordi

group design. Trial d

week dose escalation

which dosages could

maintenance and maximum dosages were 25 mg, 100 mg, and 500 mg per day for LTG, and 100 mg, 400 mg, and 2,000 mg per day for CBZ, respectively. The primary end point was retention in the trial.

Result

(73%) completed the

7%) in the CBZ group,

rawal from any cause

he number of subjects

ere seizure free in the

roup and 52 (57%) in

withdrawal occurred

l 23 (25%) subjects in

comparable effective-

-free rates for CBZ and better tolerability for LTG. Differences in outcome compared with previous trials may be related to different dosing rates and use of a sustained-release formulation for CBZ. **Key Words:** Epilepsy—Elderly—Carbamazepine—Lamotrigine—Monotherapy—Randomized controlled trial.

P: age >65 yo
I: randomized to LTG or CBZ CR
C: tolerability over 40 wks

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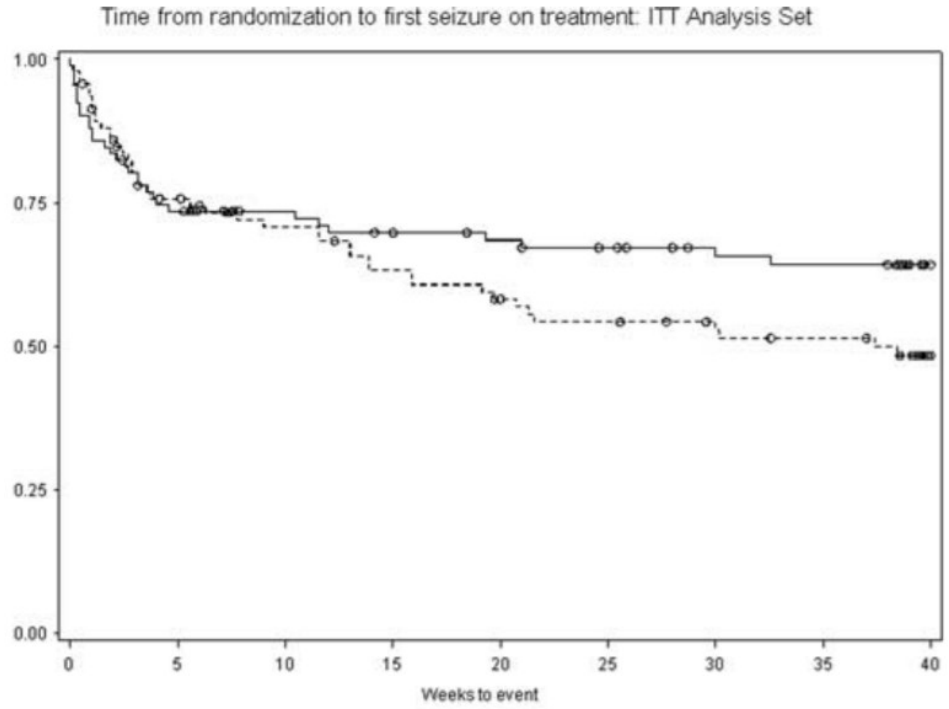
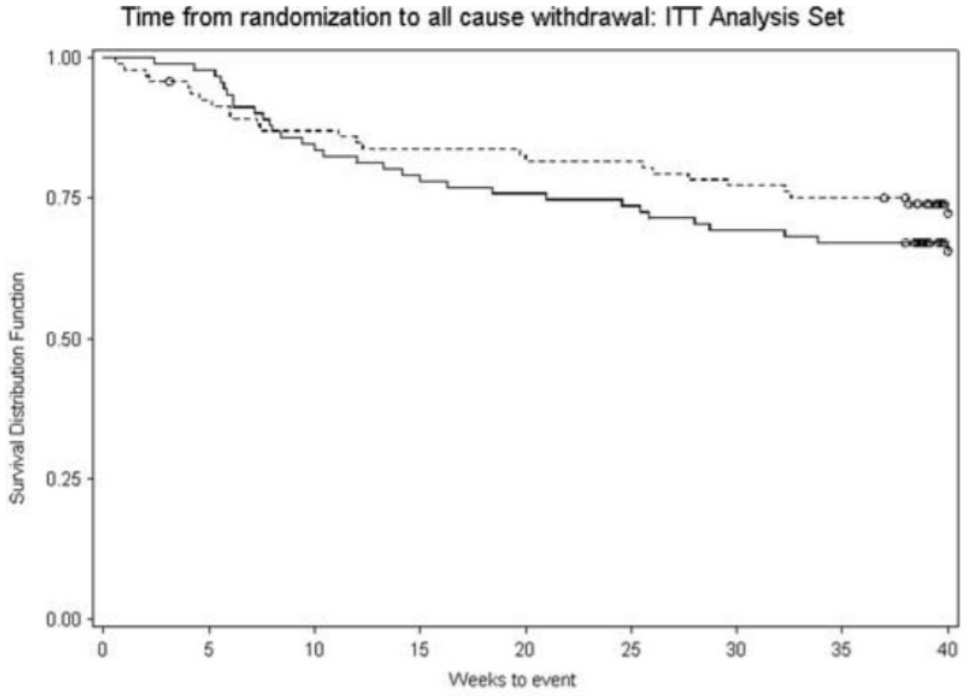




O: No significant difference between efficacy and tolerability

A randomized, double-blind comparison of antiepileptic drug treatment in the elderly with new-onset focal epilepsy

*[1]Konrad J. Werhahn, ††Eugen Trinka, ††Judith Dobesberger, ‡Iris Unterberger, §Petra Baum, ¶Maria Deckert-Schmitz, #Tobias Kniess, **Bettina Schmitz, *Viviane Bernedo, ††Christian Ruckes, ††Anne Ehrlich, and ‡‡[2]Günter Krämer

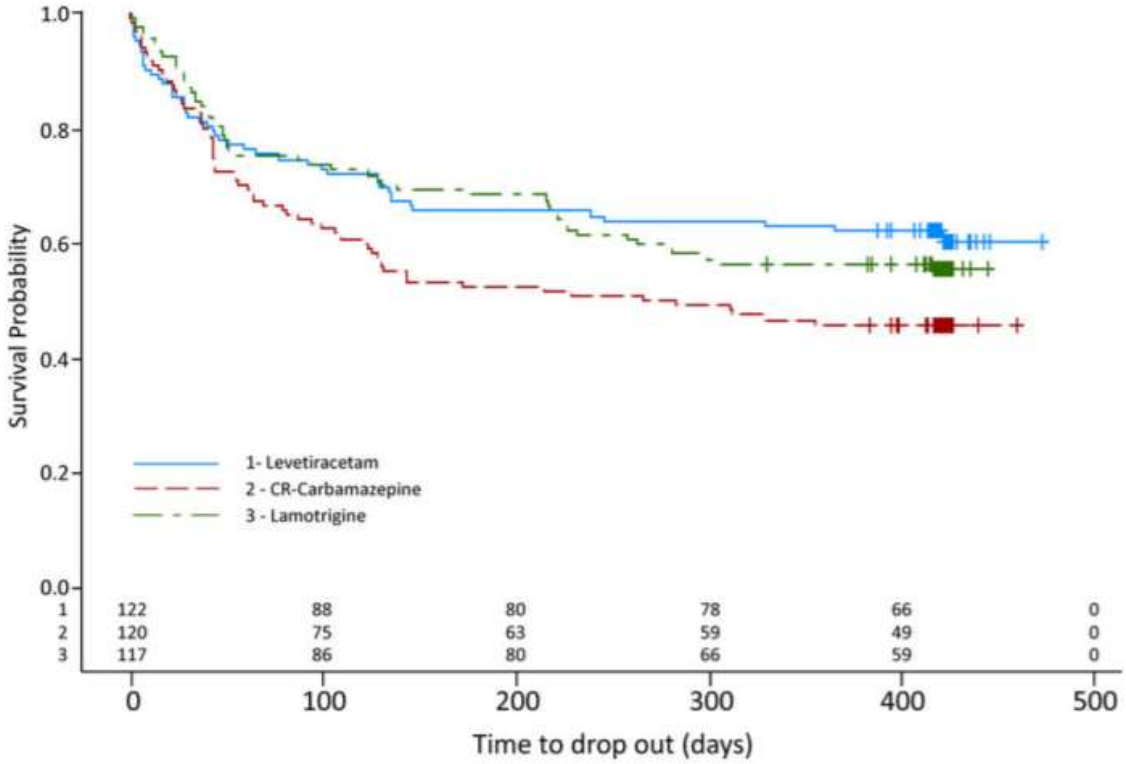
P: age >60 yo
I: randomized to LTG, CBZ CR or LEV
C: efficacy and tolerability

n = 117, LEV n = 122) in the modified intent-to-treat population (mean age [range] 71.4 [60–95] years). At week 58, the retention rate for LEV was significantly higher than for CR-CBZ (61.5% vs. 45.8%, p = 0.02), and similar to LTG (55.6%). Seizure freedom rates at weeks 30 and 58 were not different across the groups. Twice as many patients receiving CR-CBZ discontinued due to adverse events or death compared to those in the LEV group (32.2% vs. 17.2%; odds ratio 2.28, 95% confidence interval [CI] 1.25–4.19, p = 0.007), whereas discontinuation was intermediate for LTG (26.3%). Median daily doses of completers (n = 195) were CR-CBZ 380.0 mg/day (333.0–384.0), LTG 95 mg/day (94.0–97.0), and LEV 950 mg/day (940.0–985.0).

Significance: In the initial monotherapy of focal epilepsy in the elderly, 1-year retention to LEV was higher compared to CR-CBZ due to better tolerability. Retention of LTG was intermediate and close to LEV, but did not differ significantly from either comparators. NCT00438451, www.clinicaltrials.gov.

Werhahn KJ, et al. Epilepsia. 2015;56(3):450-9.

Discontinuation rate



O: Equal efficacy; CBZ less tolerated

Werhahn KJ, et al. Epilepsia. 2015;56(3):450-9.

Double-blind, RCT

References	Investigated drugs	Main findings
Brodie et al.	LTG vs. IR-CBZ	LTG equally effective and better tolerated than CBZ
Saetre et al.	LTG vs. CR-CBZ	Equal efficacy and tolerability
Werhahn et al.	LTG vs. LEV vs CR-CBZ	Equal efficacy; CBZ less tolerated
Ramsay et al.	TPM 50 mg/day vs. 200 mg/day	Good efficacy; sufficient tolerability for both dosages

Levetiracetam versus Carbamazepine in Patients with Late Poststroke Seizures: A Multicenter Prospective Randomized Open-Label Study (EpIC Project)

D. Consoli[a] D. Bosco[b] P. Postorino[a] F. Galati[a] M. Plastino[b] G.F. Perticoni[c]
G.A. Ottonello[e] B. Passarella[f] S. Ricci[g] G. Neri[d] D. Toni[h]
on behalf of EPIC Study

P: Poststroke epilepsy
I: randomized to CBZ CR or LEV (open-label)
C: efficacy (primary) and tolerability (secondary)

O: similar efficacy,
but LEV caused significantly fewer side effects (p = 0.02)

Consoli D, et al. Cerebrovasc Dis 2012;34:282–289

Open label studies

References	Investigated drugs	Main findings
Kutlu et al.	LEV	Good efficacy and tolerability
Belcastro et al. (2008)	LEV	Good efficacy and tolerability
Belcastro et al. (2007)	LEV	Good efficacy and tolerability

Neurology®

April 18, 2017; 88 (16 Supplement) APRIL 27, 2017

Efficacy and tolerability of lacosamide monotherapy in elderly patients with newly diagnosed epilepsy: subgroup analysis of a non-inferiority trial versus controlled-release carbamazepine (P5.232)

Felix Rosenow, Manuel Toledo, Michel Baulac, Kiyohito Terada, Ting Li, Melissa Brock, Simon Borghs, Marc De Backer, Konrad Werhahn

- Efficacy: LCM similar to CBZ-CR
- Tolerability: better than CBZ-CR

Efficacy and safety of perampanel in the subgroup of elderly patients included in the phase III epilepsy clinical trials

CrossMark

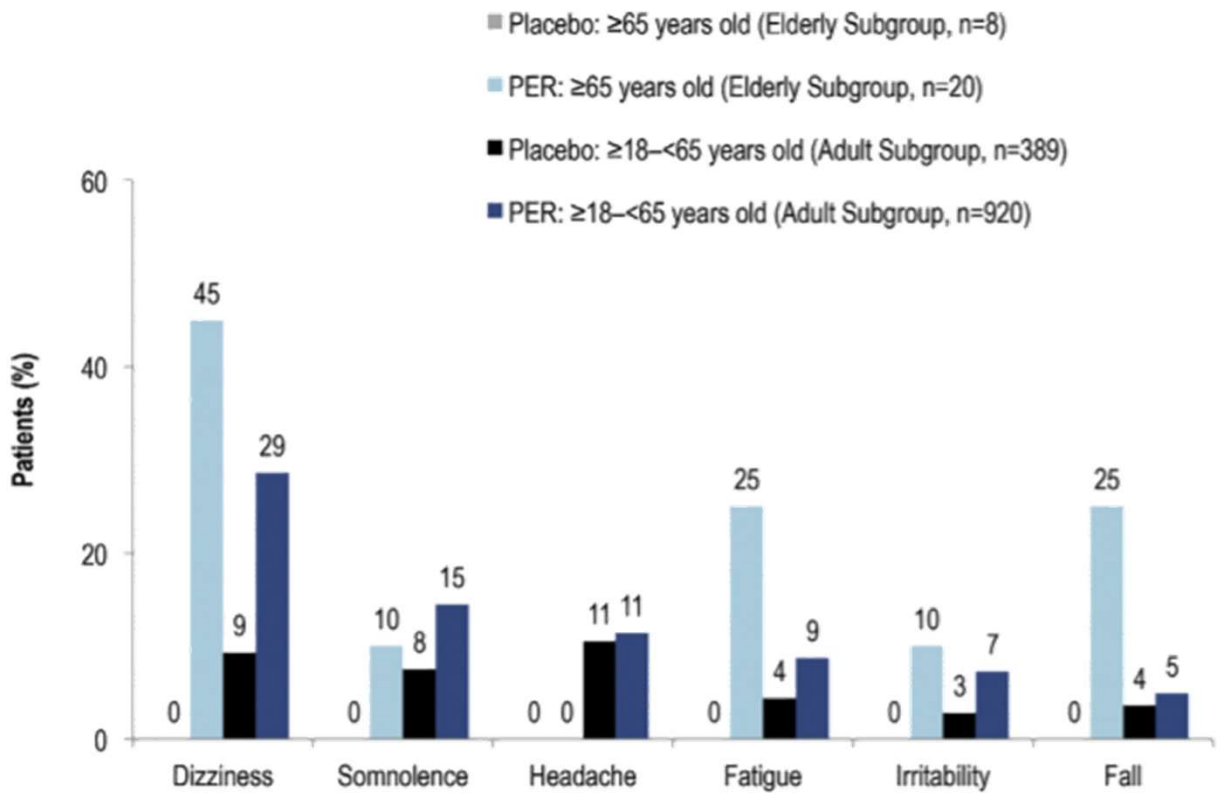
Ilo E. Leppik[a,*], Robert T. Wechsler[b], Betsy Williams[c], Haichen Yang[d], Sharon Zhou[c], Antonio Laurenza[d]

Summary Clinical data regarding use of antiepileptic drugs in the elderly are generally scarce. Therefore, a subanalysis of subjects aged ≥65 years who participated in the 3 phase III perampanel studies was undertaken to determine efficacy and safety in these patients. Efficacy (change in seizure frequency/28 days and 50% responder rate) in the elderly subgroup was found to be consistent with the adult population. Adverse event rates were also largely similar, with some exceptions. Because risks of falls, dizziness, and fatigue were greater in the elderly, careful titration of perampanel in patients aged ≥65 years is suggested, especially at higher doses, where balancing tolerability and clinical response is necessary.

P: subgroup aged > 65

I: phase III perampanel study

C: determined efficacy and safety in elderly compare to adult population and placebo



O: efficacy similar to adult population
Side effect of dizziness, fall, fatigue are greater than in young adults

Leppik IE, et al. Epilepsy Research (2015) 110, 216-20

Summary from trials

- Efficacy is no significantly different between old generation (CBZ-CR) and new generation (LTG, LEV, LCS, PER).
- Tolerability seems to be better when using new generation AEDs.
- New generation AEDs need further RCT studies to compare efficacy and side effects.

Strategy

- No seizure and no (minimal) side effects
- PK-PD, comorbidity, drug-drug interaction should be 1st considered
- Slow titration to an initial maintenance of LTG 50 mg bid or LEV 500 mg bid.
- If do not well tolerated to 1st drug, 2nd should be rapidly substituted.
- If SZs continue, 2nd monotherapy with a different MOA should be tried.

- If AED causes neurotoxicity (eg, dizziness, unsteadiness, tremor), a small decrease dose back to previous tolerated dose is recommended.
- Surgical treatment for refractory epilepsy can also be an option for older people.
- Treatment is usually lifelong as any causative factors provoking the development of epilepsy in old age are not likely to remit.