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Epilepsy in the Elderly

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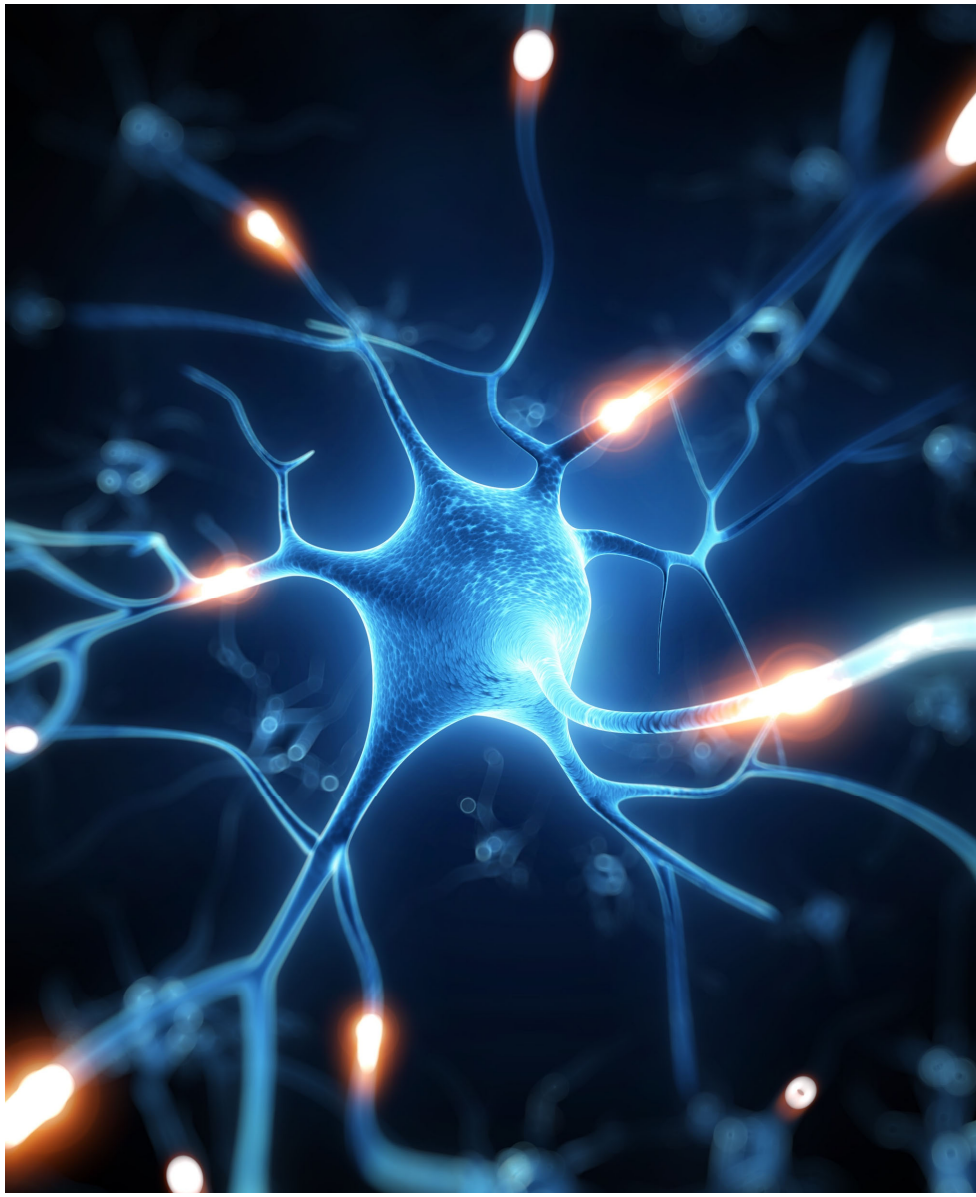
2024 Family Medicine Review
11/2/2024



Disclosures

I have no disclosures.

Education Need/Practice Gap

Gap: Epilepsy is underrecognized and potentially undertreated in the elderly population

Need: The incidence of new onset epilepsy is highest in the elderly population

Objectives

Upon completion of this activity, participants will be able to:

Describe incidence, prevalence, disparities, and etiologies of epilepsy in the elderly.

Outline the differential and evaluate incident epilepsy in the elderly population.

Discuss medication interactions, adverse effects, and physiologic alterations that warrant consideration in the elderly.

Examine evidence for selection of anti-seizure medications in the elderly with epilepsy.

Expected Outcome

Upon completion of this activity, participants will be able to:

Have increased awareness of the incidence and prevalence of epilepsy in the elderly.

Be aware of presenting symptoms that warrants evaluation for seizures in this population.

Become confident with the initial evaluation and treatment considerations for seizures in this population.

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Case Presentation

71 yo man with **atrial fibrillation** and **prior left parietooccipital infarction with hemorrhagic conversion** in 4/2021

He presented with new-onset seizure in 2/2022.

He had been at his baseline, then walked into the house and leaned onto the counter with his head down. Wife asked him if he was okay but speech was nonsensical.

He fell, then rolled onto his back and his entire body became stiff with neck extension, and respirations became labored with face becoming dusky. After ~1 minute, he developed bilateral convulsions.

Wife called EMS and they arrived within 10 minutes. Wife estimates that the stiffness and shaking lasted about 2-3 minutes. He remained somnolent for 5 hours, and noted a left lateral tongue laceration.

Case Presentation

Additional past medical history included hypertension, obstructive sleep apnea, hyperlipidemia, diabetes mellitus II.

He is retired, but frequently works home-building construction projects. He had been driving.

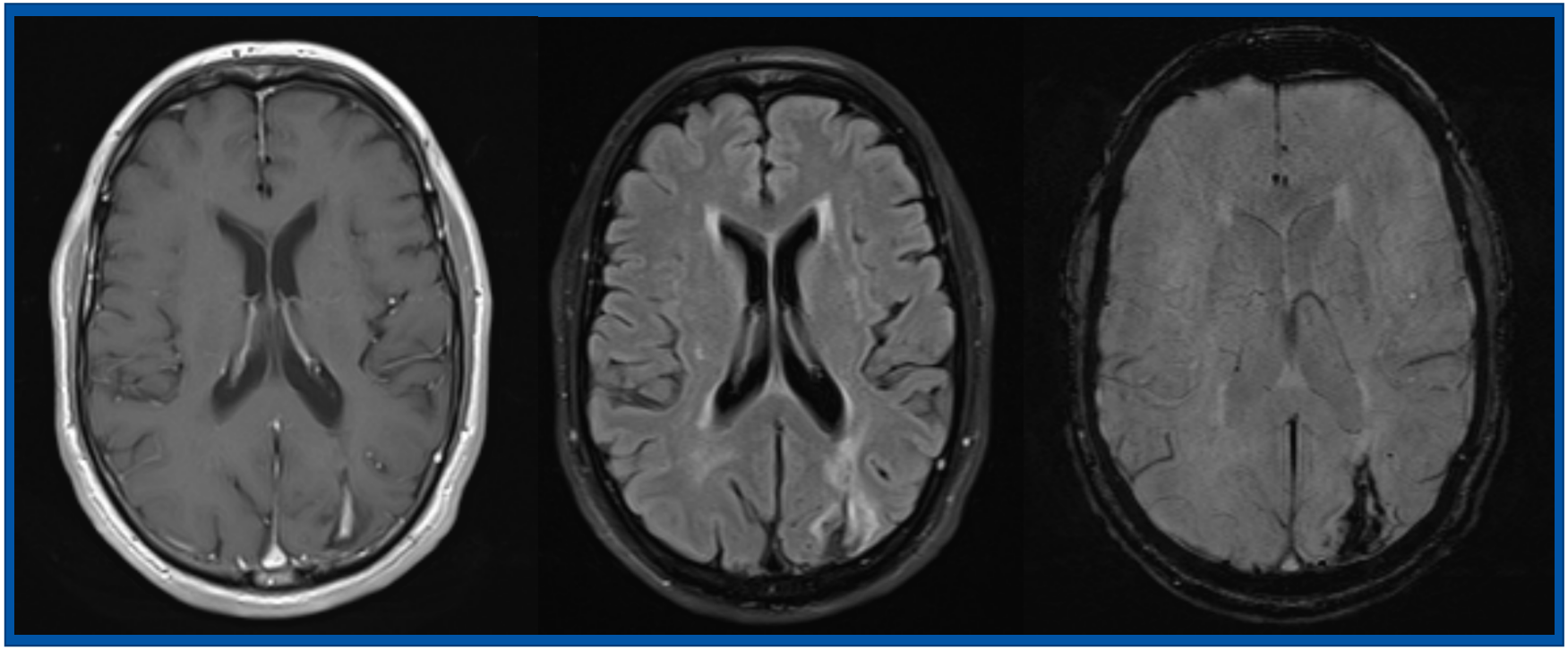
Neurologic Exam reveals a right inferior quadrantanopia.

Case Presentation

Medications:

- Apixaban
- Atorvastatin
- Amlodipine
- Finasteride
- Losartan
- Tamsulosin
- Metoprolol
- Albuterol
- Metformin
- Omeprazole
- Montelukast

Case Presentation



T1 Post-Contrast | T2 FLAIR | Susceptibility Weighted (SWI)

MRI Brain 9/2021

(5 months following stroke)

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What medication for seizure would you start?

Carbamazepine 0%

Gabapentin 0%

Lacosamide 0%

Lamotrigine 0%

Levetiracetam 0%

Oxcarbazepine 0%

Phenytoin 0%

Topiramate 0%

Valproate 0%

Zonisamide

SEE MORE

Case Presentation

He was started on levetiracetam 500mg twice daily in the emergency department.

He had a routine EEG, which was normal.

Case Presentation

At follow up with neurology – no further seizures, but reported lethargy with levetiracetam.

~~Levetiracetam~~ ➡ Lacosamide 100mg twice daily ➡ Significant nausea.
~~Lacosamide~~ ➡ Oxcarbazepine 300mg twice daily ➡ **Seizure** in transition + Dizziness
~~Oxcarbazepine~~ ➡ Zonisamide 100mg daily ➡ Severe nausea and vomiting
~~Zonisamide~~ ➡ Levetiracetam 750mg twice daily ➡ Tolerated this time.

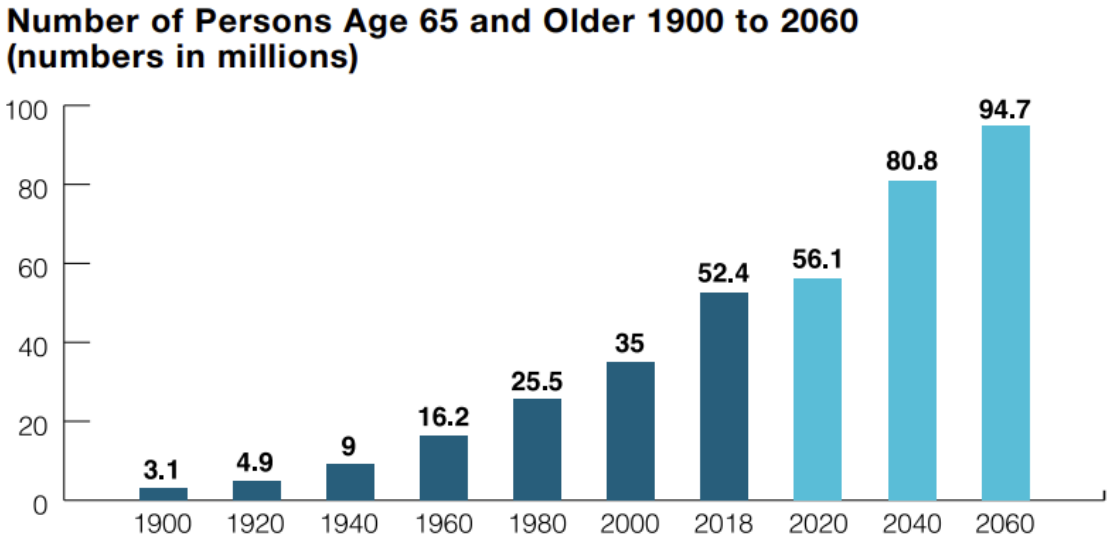
He experienced an episode of confusion, then loss of consciousness while driving in 3/2023, in which he ran his vehicle off of the road. His levetiracetam was increased to 1000mg twice daily, which he tolerated.

No further suspicious events since at time of last follow up.

Epidemiology

For this discussion, we will consider ≥ 65 years as the age threshold for elderly-onset epilepsy

Concept of “frail elderly”



Note: Increments in years are uneven. Lighter bars (2020, 2040, and 2060) indicate projections.

Source: U.S. Census Bureau, Population Estimates and Projections

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Epidemiology

Epilepsy is a disorder of the brain characterized as an enduring predisposition to generate epileptic seizures

Epilepsy is the 3rd most common neurological disorder in the elderly.

1. Stroke
2. Dementia
3. **Epilepsy**

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Ferlazzo E, Sueri C, Gasparini S, Aguglia U. Challenges in the pharmacological management of epilepsy and its causes in the elderly. Pharmacol Res. 2016 Apr;106:21-26. doi: 10.1016/j.phrs.2016.02.013. Epub 2016 Feb 16. PMID: 26896787.

Incidence and Prevalence

The incidence and prevalence of epilepsy is highest in patients over 65 years old

<u>Community:</u>
Incidence: **2.4/1000** people/year
Prevalence:**10.8-11.5/1000** people

Worldwide variations present

<u>Nursing Home:</u>
Point prevalence: **7.8%**

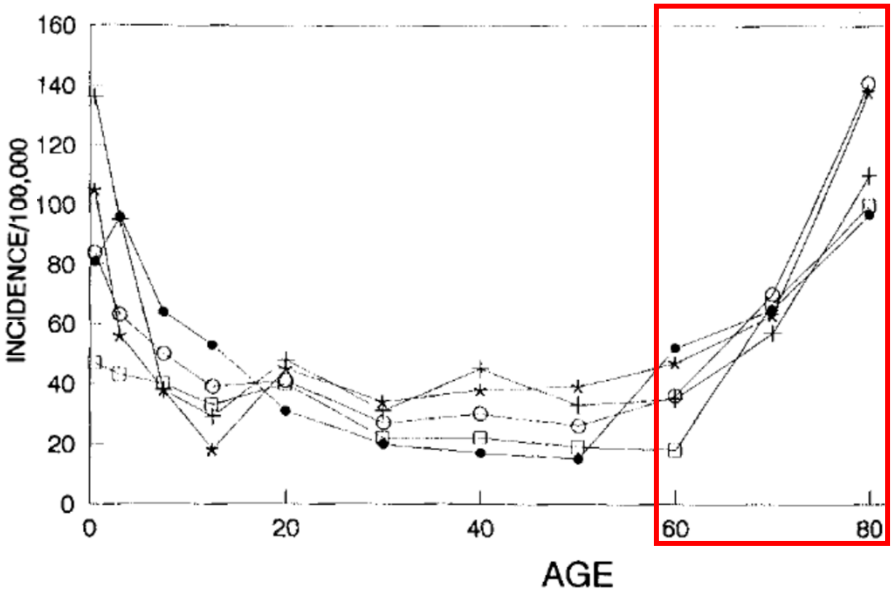

FIG. 17. Time trends in age-specific incidence/100,000 of epilepsy in Rochester, Minnesota, 1935–1984: 1935–1944 (solid circles), 1945–1954 (plus signs), 1955–1964 (stars), 1965–1974 (squares), 1975–1984 (open circles).

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Hauser WA, Annegers JF et al. Incidence of Epilepsy and Unprovoked Seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 34(3):453-468, 1993
E. Faught et al. Neurology 2012;78:448-453
Birnbaum AK, Leppik IE, Svensden K, Eberly LE. Prevalence of epilepsy/seizures as a comorbidity of neurologic disorders in nursing homes. Neurology. 2017 Feb 21;88(8):750-757. doi: 10.1212/WNL.0000000000003629. Epub 2017 Jan 20. PMID: 28108639; PMCID: PMC5344078
. Beghi E, Giussani G, Costa C, DiFrancesco JC, Dhakar M, Leppik I, Kwan P, Akamatsu N, Cretin B, O'Dwyer R, Kraemer G, Piccenna L, Faught E; ILAE Task Force on Epilepsy in the Elderly (2017-2021). The epidemiology of epilepsy in older adults: A narrative review by the ILAE Task Force on Epilepsy in the Elderly. Epilepsia. 2023 Mar;64(3):586-601. doi: 10.1111/epi.17494. Epub 2023 Jan 10. PMID: 36625133.

Disparities

Multiple, diverse studies demonstrate higher incidence and risks of late onset epilepsy in black men and women:

- 2018: **4.71** vs **2.88** per 1000 person-years (95% CI, 4.12-5.40 and 95% CI, 2.60-3.18; incidence rate ratio, 1.66; 95% CI, 1.41-1.95).
- 2009: Odds ratio of new-onset epilepsy **1.75** (95% CI 1.54-1.98) vs white cohorts.

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Pugh MJ, Knoefel JE, Mortensen EM, Amuan ME, Berlowitz DR, Van Cott AC. New-onset epilepsy risk factors in older veterans. J Am Geriatr Soc. 2009 Feb;57(2):237-42. doi: 10.1111/j.1532-5415.2008.02124.x. PMID: 19207140.
Pisu M, Richman J, Szaflarski JP, Funkhouser E, Dai C, Juarez L, Faught E, Martin RC. High health care costs in minority groups of older US Medicare beneficiaries with epilepsy. Epilepsia. 2019 Jul;60(7):1462-1471. doi: 10.1111/epi.16051. Epub 2019 Jun 6. PMID: 31169918; PMCID: PMC6685539.
Ip Q, Malone DC, Chong J, Harris RB, Labiner DM. An update on the prevalence and incidence of epilepsy among older adults. Epilepsy Res. 2018 Jan;139:107-112. doi: 10.1016/j.eplepsyres.2017.11.022. Epub 2017 Dec 5. PMID: 29220741.

Etiology

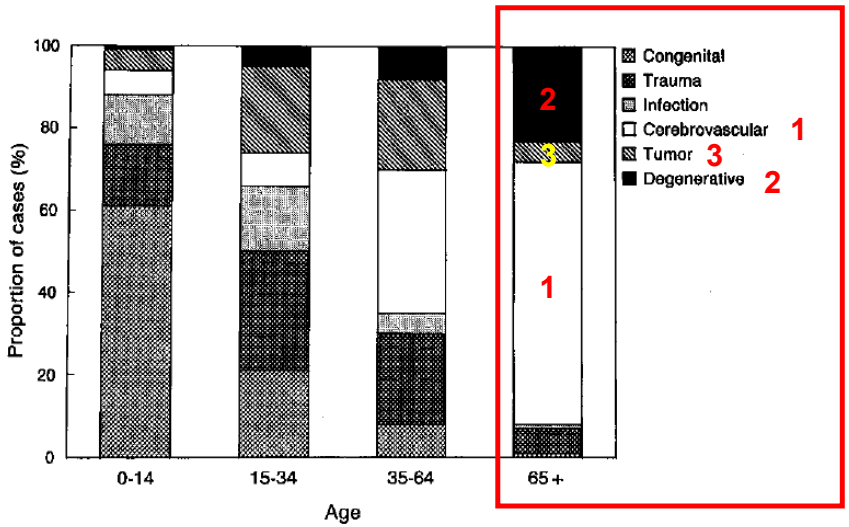


FIG. 11. Proportion of cases of newly diagnosed epilepsy assigned to specific etiologic categories within age groups among those with assigned etiologies. Area: congenital (dashed), trauma (widely dotted), infection (hatched), cerebrovascular (closely dotted), tumor (black), degenerative (crosshatched).

Hauser WA, Annegers JF et al. Incidence of Epilepsy and Unprovoked Seizures in Rochester, Minnesota: 1935-1984. Epilepsia. 34(3):453-468, 1993.

For epilepsy:

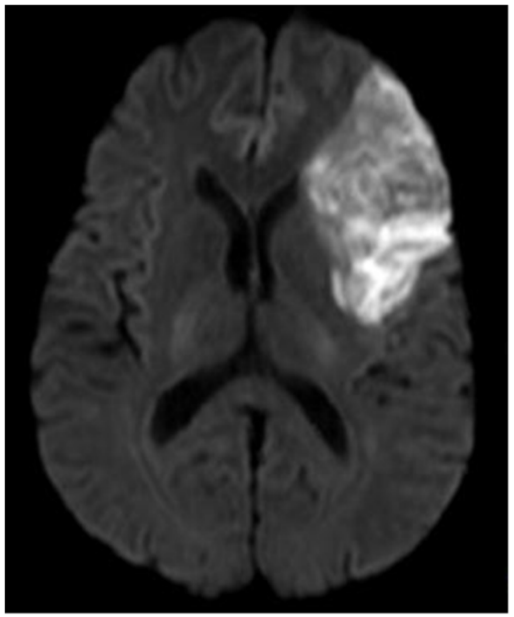
1. Stroke/Cerebrovascular disease
2. Neurodegenerative disease
3. Neoplasm
4. Head trauma

~ 25% of cases are of unclear etiology

Cerebrovascular Disease

Most common cause of new-onset epilepsy in the elderly.

- ~34% of late-onset epilepsy cases
- Higher risk with remote symptomatic seizures



1. Hemorrhagic infarcts involving cortex
2. Cortical infarcts
3. Subarachnoid hemorrhage

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Johnson EL, Krauss GL, Lee AK, Schneider ALC, Dearborn JL, Kucharska-Newton AM, Huang J, Alonso A, Gottesman RF. Association Between Midlife Risk Factors and Late-Onset Epilepsy: Results From the Atherosclerosis Risk in Communities Study. JAMA Neurol. 2018 Nov 1;75(11):1375-1382. doi: 10.1001
Birnbaum AK, Leppik IE, Svensden K, Eberly LE. Prevalence of epilepsy/seizures as a comorbidity of neurologic disorders in nursing homes. Neurology. 2017 Feb 21;88(8):750-757. doi: 10.1212/WNL.0000000000003629. Epub 2017 Jan 20. PMID: 28108639; PMCID: PMC5344078.

Cerebrovascular Disease

Midlife vascular risk factors have been associated with increased risk for late onset epilepsy, even in the absence of stroke.

- Hypertension
- Diabetes
- Smoking

Presence of leukoaraiosis may have negative impact on seizure control.

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Johnson EL, Krauss GL, Lee AK, Schneider ALC, Dearborn JL, Kucharska-Newton AM, Huang J, Alonso A, Gottesman RF. Association Between Midlife Risk Factors and Late-Onset Epilepsy: Results From the Atherosclerosis Risk in Communities Study. JAMA Neurol. 2018 Nov 1;75(11):1375-1382. doi: 10.1001
Tartara E, Micalizzi E, Scanziani S, Ballante E, Paoletti M, Galimberti CA. Late-Onset Focal Epilepsy: Electroclinical Features and Prognostic Role of Leukoaraiosis. Front Neurol. 2022 Feb 23;13:828493. doi: 10.3389/fneur.2022.828493. PMID: 35295838; PMCID: PMC8919697.

Neurodegenerative Disease

~17% of epilepsy in elderly, confers a 5-10-fold increased risk.

This risk is markedly higher in those with Alzheimer Disease

- Earlier age of onset
- Presence of familial AD
- Potentially disease severity

Some similarities to the pathology of mesial temporal lobe epilepsy

- Cell loss/gliosis in CA1 region of hippocampus – hyperexcitability

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Wyllie, E.. (2020). Wyllie's treatment of epilepsy: Principles and practice: Seventh edition.
Association of epileptiform abnormalities and seizures in Alzheimer disease Alice D. Lam, Rani A. Sarkis, Kyle R. Pellerin, Jin Jing, Barbara A. Dworetzky, Daniel B. Hoch, Claire S. Jacobs, Jong Woo Lee, Daniel S. Weisholtz, Rodrigo Zepeda, M. Brandon Westover, Andrew J. Cole, Sydney S. Cash Neurology Oct 2020, 95 (16) e2259-e2270; DOI: 10.1212/WNL.0000000000010612
Ferlazzo E, Sueri C, Gasparini S, Aguglia U. Challenges in the pharmacological management of epilepsy and its causes in the elderly. Pharmacol Res. 2016 Apr;106:21-26. doi: 10.1016/j.phrs.2016.02.013. Epub 2016 Feb 16. PMID: 26896787.
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Neoplasm

5-11.8% of cases

- Seizure (notably focal) may be a common presenting symptom of a brain tumor in this age group

Primary neoplasms more oft implicated

- Meningioma
- Glioblastoma
- Sellar tumors
- Lymphoma
- Brain metastases

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Ferlazzo E, Sueri C, Gasparini S, Aguglia U. Challenges in the pharmacological management of epilepsy and its causes in the elderly. Pharmacol Res. 2016 Apr;106:21-26. doi: 10.1016/j.phrs.2016.02.013. Epub 2016 Feb 16. PMID: 26896787.
Chen H, Judkins J, Thomas C, Wu M, Khoury L, Benjamin CG, Pacione D, Golfinos JG, Kumthekar P, Ghamsari F, Chen L, Lein P, Chetkovich DM, Snuderl M, Horbinski C. Mutant IDH1 and seizures in patients with glioma. Neurology. 2017 May 9;88(19):1805-1813. doi: 10.1212/WNL.0000000000003911. Epub 2017 Apr 12. PMID: 28404805; PMCID: PMC5419985.

Other Causes

Head Trauma

- Higher risk of falls

Autoimmune/Paraneoplastic

- Voltage Gated Potassium Channel
  - LGI1 and CASPR2
- Anti-Hu (small cell lung cancer)

Explosive-onset focal aware seizures with autonomic features

Faciobrachial dystonic seizures in an LGI1 VGKC-complex antibody-mediated encephalitis

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Liu S, Yu W, Lü Y. The causes of new-onset epilepsy and seizures in the elderly. Neuropsychiatr Dis Treat. 2016 Jun 17;12:1425-34. doi: 10.2147/NDT.S107905. PMID: 27382285; PMCID: PMC4918803.
Sen A, Wang J, Laue-Gizzi H, Lee T, Ghougassian D, Somerville ER. Pathognomonic seizures in limbic encephalitis associated with anti-LGI1 antibodies. Lancet. 2014 Jun 7;383(9933):2018. doi: 10.1016/S0140-6736(14)60684-X. PMID: 24910233. Manfredi M, Giallonardo AT, Di Bonaventura C. Late-onset seizures and epilepsy: Electroclinical features suggestive of autoimmune etiology. Front Neurol. 2022 Aug 12;13:924859. doi: 10.3389/fneur.2022.924859. PMID: 36034285; PMCID: PMC9412019.

Status Epilepticus in the Elderly

Incidence of status epilepticus is highest in those ≥ 60 years old.

- **15.5**/100,000 (**60-69**)
- **21.5**/100,000 (**70-79**)
- **25.9**/100,000 (**80+**)

Mortality is increased.

Non-convulsive SE is common.

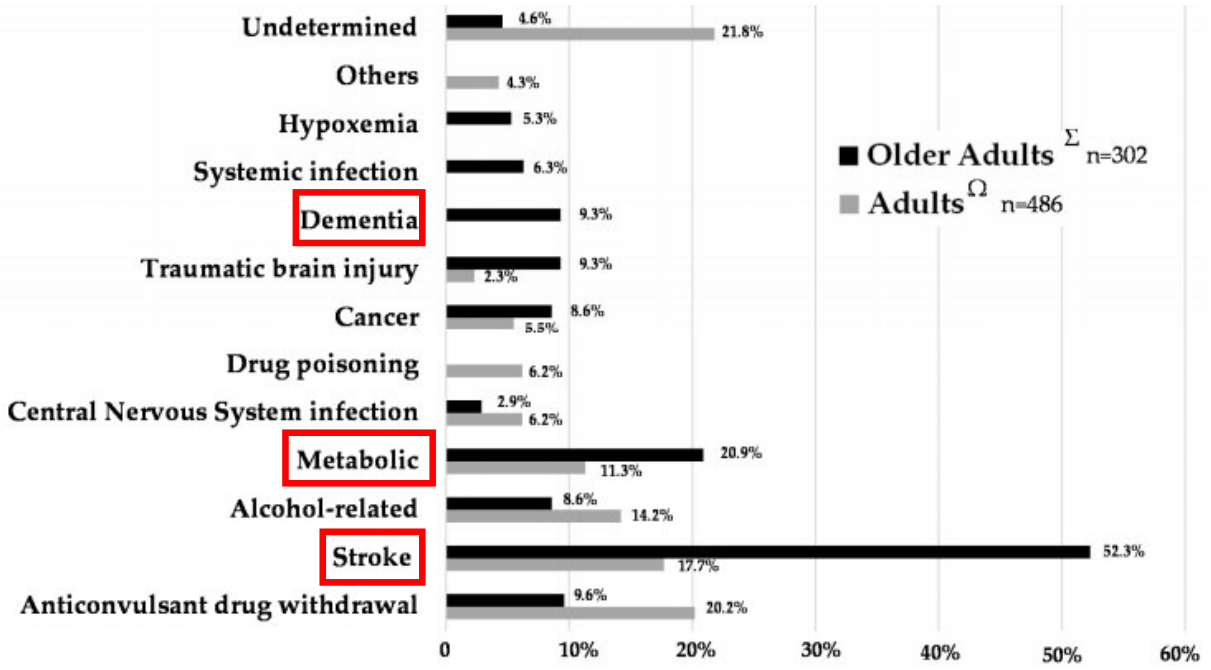

Figure 4. Comparison of causes of status epilepticus in 486 adults and 302 older adult patients.

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Leppik IE. Status epilepticus in the elderly. Epilepsia. 2018 Oct;59 Suppl 2:140-143. doi: 10.1111/epi.14497. Epub 2018 Aug 29. PMID: 30159881.
Legriel S, Brophy GM. Managing Status Epilepticus in the Older Adult. J Clin Med. 2016 May 11;5(5):53. doi: 10.3390/jcm5050053. PMID: 27187485; PMCID: PMC4882482
Verma A, Kumar A, Pathak P, Mishra AK. Clinical Profile and Predictors of In-Hospital Mortality in De Novo Convulsive Status Epilepticus in the Elderly Populace. J Epilepsy Res. 2022 Dec 30;12(2):48-52. doi: 10.14581/jer.22009. PMID: 36685739; PMCID: PMC9830029..

Seizure Types in the Elderly

Focal seizures are the most common seizure type.

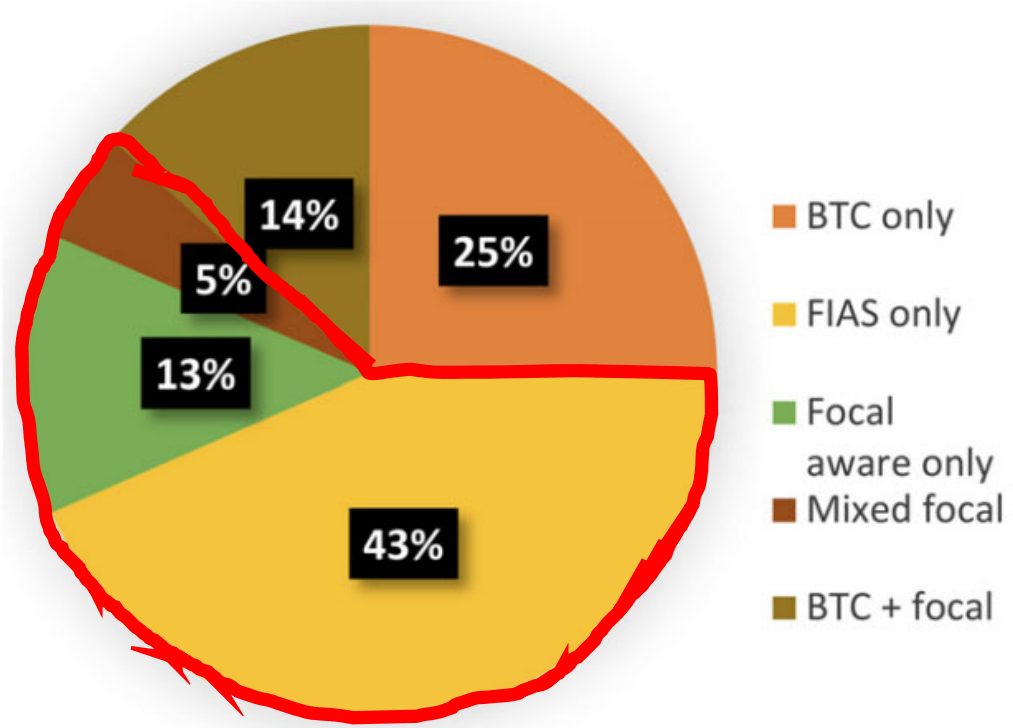

Fig. 2. Seizure semiology in new-onset epilepsy in the elderly. BTC = Bilateral tonic–clonic; FIAS = Focal onset with impaired awareness seizure.

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Pugh MJ, Knoefel JE, Mortensen EM, Amuan ME, Berlowitz DR, Van Cott AC. New-onset epilepsy risk factors in older veterans. J Am Geriatr Soc. 2009 Feb;57(2):237-42. doi: 10.1111/j.1532-5415.2008.02124.x. PMID: 19207140.
Lezaic N, Roussy J, Masson H, Jetté N, Keezer MR. Epilepsy in the elderly: Unique challenges in an increasingly prevalent population. Epilepsy Behav. 2020 Jan;102:106724. doi: 10.1016/j.yebeh.2019.106724. Epub 2019 Dec 7. PMID: 31816480.

Seizure Types in the Elderly

New onset generalized epilepsy is rare in the elderly.

> *"convulsive idiopathic generalized epilepsy with an onset over 60 years of age is comparable to the Loch Ness monster: aside from a handful of authors, no one has seen such an entity".*
>
> - Loiseau, 1998

Punia et. al 2023: **12** patients; literature review 1973-2022: **10** patients

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Loiseau J., Crespel A., Picot M.C. Idiopathic generalized epilepsy of late onset. *Seizure*. 1998;7:485-487.
Francesco Brigo, Veronica Tavernelli, Raffaele Nardone, Eugen Trinka. *De novo* late-onset absence status epilepticus or late-onset idiopathic generalized epilepsy? A case report and systematic review of the literature. Epileptic Disorders. 2018;20(2):123-131. doi:10.1684/epd.2018.0961
Alzahrany M, Punia V. Extreme late onset of genetic generalized epilepsy in older adults and the elderly: A cohort study and literature review. Epilepsia Open. 2023 Mar;8(1):193-199. doi: 10.1002/epi4.12671. Epub 2022 Nov 20. PMID: 36366877; PMCID: PMC9977743.

Seizure Types in the Elderly

Focal seizures are different in the elderly

Seizure Types (most common)	• Focal seizures • Status Epilepticus

Ictal Characteristics	• Short duration (seconds)
	• Subtle features:
	  • Staring/loss of awareness
	  • Confusion
	  • Amnesia

Postictal Features	• Long period of confusion (days to weeks) • Easily mistaken for delirium • Easily mistaken for mood disorder or a “funny turn”

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Stefan H, May TW, Pfäfflin M, Brandt C, Füratsch N, Schmitz B, Wandschneider B, Kretz R, Runge U, Geithner J, Karakizlis C, Rosenow F, Kerling F. Epilepsy in the elderly: comparing clinical characteristics with younger patients. Acta Neurol Scand. 2014 May;129(5):283-93. doi: 10.1111/ane.12218. Epub 2014 Feb 3. PMID: 24495079.
Vu LC, Piccenna L, Kwan P, O'Brien TJ. New-onset epilepsy in the elderly. Br J Clin Pharmacol. 2018 Oct;84(10):2208-2217. doi: 10.1111/bcp.13653. Epub 2018 Jul 28. PMID: 29856080; PMCID: PMC6138506.
Theodore WH. The postictal state: effects of age and underlying brain dysfunction. Epilepsy Behav. 2010 Oct;19(2):118-20. doi: 10.1016/j.yebeh.2010.06.031. Epub 2010 Aug 17. PMID: 20724220; PMCID: PMC2952737.

Differential Considerations

Diagnosis can be delayed, and misdiagnosis is common:

1. Atypical presentation
2. General lack of awareness of prevalence in elderly
3. Incomplete history

1.7 years on average until diagnosis of epilepsy

<u>Differential:</u>

- Syncope/Cardiac
- Migraine
- Transient ischemic attack
- Metabolic disturbances
- Sleep disorders
- Transient global amnesia
- Amyloid “spells”/transient focal neurological episodes
- Psychogenic non-epileptic spells

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Wyllie, E.. (2020). Wyllie's treatment of epilepsy: Principles and practice: Seventh edition.
Ramsay RE, Rowan AJ, Pryor FM. Special considerations in treating the elderly patient with epilepsy. Neurology. 2004 Mar 9;62(5 Suppl 2):S24-9. doi: 10.1212/wnl.62.5_suppl_2.s24. PMID: 15007161.

Evaluation of New Onset Epilepsy/Seizures in Elderly

Brain imaging – MRI preferred over CT.

- Particularly important in this population.

EEG

Laboratory evaluation

Lumbar puncture

Other studies based on differential:

- Cardiac studies
- Sleep studies
- Neuropsychological testing

Treatment Challenges - Physiology

Important changes in physiology:

- Decline in hepatic metabolism.
- Decline in renal function yearly after age 60.
- Gastrointestinal physiology changes.
- Decreased protein binding.
- Increased proportion of adipose tissue.

Bruun E, Virta LJ, Kälviäinen R, Keränen T. Co-morbidity and clinically significant interactions between antiepileptic drugs and other drugs in elderly patients with newly diagnosed epilepsy. Epilepsy Behav. 2017 Aug;73:71-76. doi: 10.1016/j.yebeh.2017.05.022. Epub 2017 Jun 14. PMID: 28622547.

Treatment Challenges – Drug-Drug Interactions

Medication Interactions:

Wyllie, E.. (2020). Wyllie's treatment of epilepsy: Principles and practice: Seventh edition
. Barbieri MA, Perucca E, Spina E, Rota P, Franco V. Cenobamate: A Review of its Pharmacological Properties, Clinical Efficacy and Tolerability Profile in the Treatment of Epilepsy. CNS Neurol Disord Drug Targets. 2023;22(3):394-403. doi: 10.2174/1871527321666220113110044. PMID: 35049441.

INDUCERS		INHIBITORS	
MEDICATION	**ENZYME**	**MEDICATION**	**ENZYME**
Phenytoin	CYP450; UGT; PGP	**Valproate**	UGT; CYP450
Phenobarbital	CYP450; UGT; PGP	Brivaracetam	Epoxide hydrolase
Primidone	CYP450; UGT; PGP	Cannabidiol	CYP450; UGT
Carbamazepine	CYP450; UGT; PGP		
Clonazepam	CYP450; UGT		
BOTH			
Lamotrigine	UGT		UGT, CYP450
Oxcarbazepine	CYP450		CYP450
Eslicarbazepine	CYP450		CYP450
Felbamate	CYP450		CYP450; β-oxidation
Topiramate	CYP450		CYP450
Cenobamate	CYP3A4, 2B6		CYP2C19

Treatment Challenges - Important Interactions

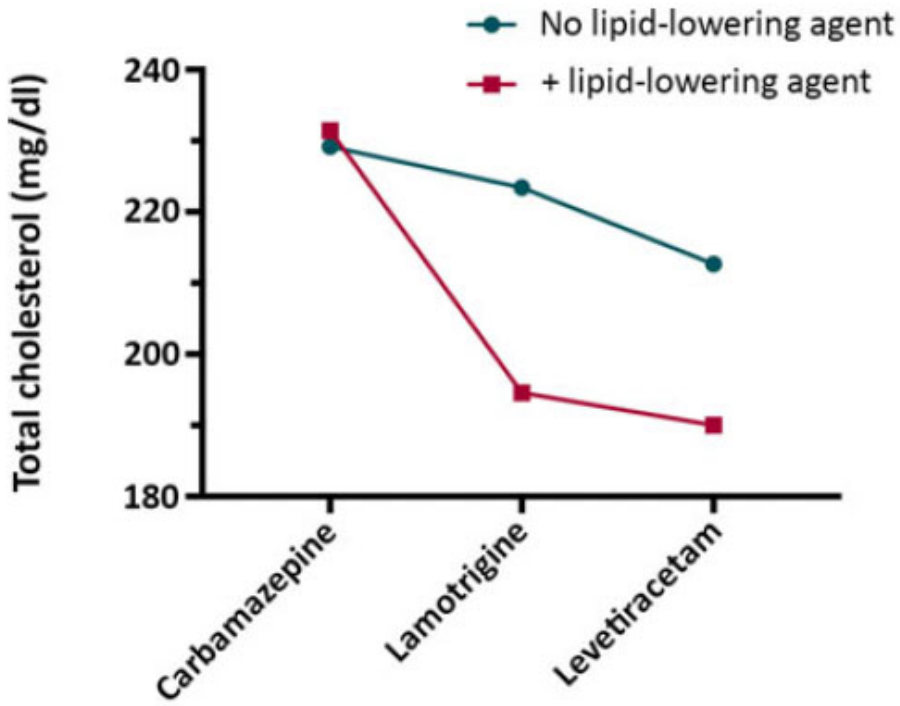
Warfarin
- Induced by CBZ, PHT = ↓INR
- Inhibited by VPA = ↑INR

SSRI - fluoxetine
- Inhibit CBZ, PHT, VPA → toxicity

Statins
- Induced by CBZ = ↓statin efficacy

Calcium Channel Blockers
- Inhibit CBZ → CBZ toxicity

Antibiotics – erythromycin
- Inhibit CBZ → CBZ toxicity



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Perucca E, Berlowitz D, Birnbaum A, Cloyd JC, Garrard J, Hanlon JT, Levy RH, Pugh MJ. Pharmacological and clinical aspects of antiepileptic drug use in the elderly. Epilepsy Res. 2006 Jan;68 Suppl 1:S49-63. doi: 10.1016/j.eplepsyres.2005.07.017. Epub 2005 Oct 3. PMID: 16207524.
Mintzer S, Trinka E, Kraemer G, Chervoneva I, Werhahn KJ. Impact of carbamazepine, lamotrigine, and levetiracetam on vascular risk markers and lipid-lowering agents in the elderly. Epilepsia. 2018 Oct;59(10):1899-1907. doi: 10.1111/epi.14554. Epub 2018 Sep 3. PMID: 30178473.

Treatment Challenges – Bone Health

Osteoporosis and osteopenia are common in this population.

Enzyme inducing drugs are associated with greater rate of bone loss.

Interference with Vitamin D metabolism and bone turnover are suspected mechanism.

Supplementation, surveillance, antiosteoporitic drugs, and fall precautions are facets of treatment/prevention

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Main effects of classic and new AEDs on bone and calcium metabolism.

Drug	BMD	25-OHD	Ca/P	PTH	Bone turnover
Classic AEDs					
Benzodiazepines	↓	↓	N	N	↑bALP ↑OC ↑ICTP ↑NTx
Carbamazepine	↓	↓	N	↑	↑bALP ↑OC ↑ICTP ↑NTx
Phenytoin	↓	↓	↓	↑	↑bALP ↑NTx
Phenobarbital	↓	↓	N	–	↑bALP ↑ICTP
Primidone	↓	↓	N	–	–
Valproic acid	↓	N	N	N	↑ALP ↑OC
New AEDs					
Gabapentin	↓	–	–	–	–
Lamotrigine	N	N	N	?	N
Levetiracetam	N	N	N	–	?
Oxcarbazepine	↓	↓	N	↑	↑bALP
Zonisamide[a]	↓	–	–	–	↑PYD

[a] Results from animal studies.

Verrotti A, Coppola G, Parisi P, Mohn A, Chiarelli F. Bone and calcium metabolism and antiepileptic drugs. Clin Neurol Neurosurg. 2010 Jan;112(1):1-10. doi: 10.1016/j.clineuro.2009.10.011. Epub 2009 Nov 12. PMID: 19913352.

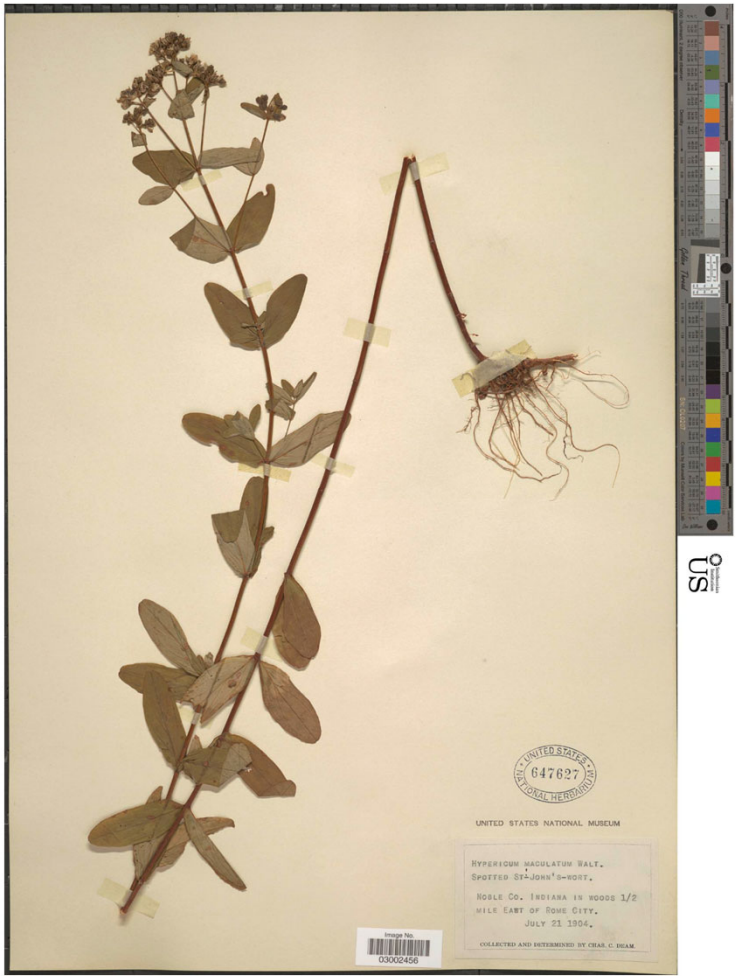
Lazzari AA, Dussault PM, Thakore-James M, Gagnon D, Baker E, Davis SA, Houranieh AM. Prevention of bone loss and vertebral fractures in patients with chronic epilepsy--antiepileptic drug and osteoporosis prevention trial. Epilepsia. 2013 Nov;54(11):1997-2004. doi: 10.1111/epi.12351. Epub 2013 Sep 6. PMID: 24010637.

Treatment Challenges – Complimentary and Alternative Medicine (CAM)

Ginkgo biloba

St. John's Wort

Grapefruit Juice



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Samuels N, Finkelstein Y, Singer SR, Oberbaum M. Herbal medicine and epilepsy: proconvulsive effects and interactions with antiepileptic drugs. Epilepsia. 2008 Mar;49(3):373-80. doi: 10.1111/j.1528-1167.2007.01379.x. Epub 2007 Oct PMID

Girgis MMF, Fekete K, Homoródi N, Márton S, Fekete I, Horváth L. Use of Complementary and Alternative Medicine Among Patients With Epilepsy and Diabetes Mellitus, Focusing on the Outcome of Treatment. Front Neurosci. 2022 Jan 11;15:787512. doi: 10.3389/fnins.2021.787512. PMID: 35087374; PMCID: PMC8787116.

Medication Options

Guidelines for treatment of new-onset focal epilepsy in the elderly

(level of evidence)

ILAE (2013)	AES (2018)	AAN (2018)
Lamotrigine (A)	Lamotrigine (B)	Lamotrigine (B)
Gabapentin (A)	Gabapentin (C)	Gabapentin (C)
Carbamazepine (C)		

Critical review by the ILAE's task force on epilepsy in the elderly 2023

Levetiracetam: increasing chances of long-term seizure freedom

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Seo JG, Cho YW, Kim KT, Kim DW, Yang KI, Lee ST, Byun JI, No YJ, Kang KW, Kim D; Drug Committee of Korean Epilepsy Society. Pharmacological Treatment of Epilepsy in Elderly Patients. J Clin Neurol. 2020 Oct;16(4):556-561. doi: 10.3988/jcn.2020.16.4.556. PMID: 33029960; PMCID: PMC7542002
. Piccenna L, O'Dwyer R, Leppik I, Beghi E, Giussani G, Costa C, DiFrancesco JC, Dhakar MB, Akamatsu N, Cretin B, Krämer G, Faught E, Kwan P. Management of epilepsy in older adults: A critical review by the ILAE Task Force on Epilepsy in the elderly. Epilepsia. 2023 Mar;64(3):567-585. doi: 10.1111/epi.17426. Epub 2022 Oct 20. PMID: 36266921.

Why Lamotrigine and Gabapentin?

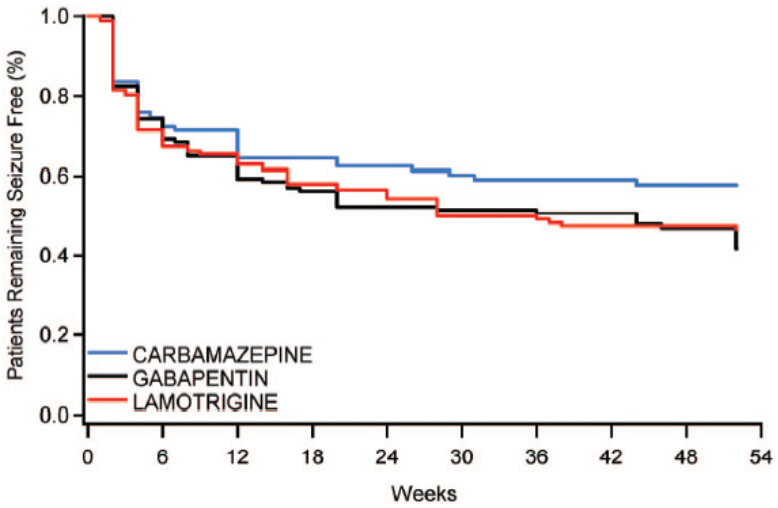

Figure 4. Percentage of patients remaining seizure-free over time (time to first seizure).

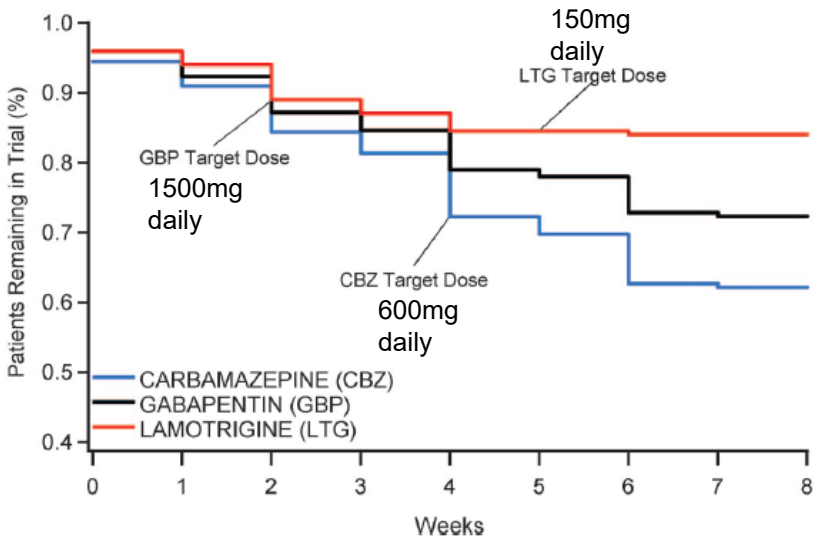

Figure 3. Percentage of patients remaining in the trial over time (6-week titration time).

- No significant difference in seizure free rate at 12 months
- Carbamazepine had poorer retention than lamotrigine or gabapentin

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Rowan AJ, Ramsay RE, Collins JF, Pryor F, Boardman KD, Uthman BM, Spitz M, Frederick T, Towne A, Carter GS, Marks W, Felicetta J, Tomyanovich ML; VA Cooperative Study 428 Group. New onset geriatric epilepsy: a randomized study of gabapentin, lamotrigine, and carbamazepine. Neurology. 2005 Jun 14;64(11):1868-73. doi: 10.1212/01.WNL.0000167384.68207.3E. PMID: 15955935.

Why Lamotrigine and Gabapentin

Other double-blind randomized controlled trials in the elderly:

Brodie '99 – lamotrigine and carbamazepine

- Significantly greater retention in the lamotrigine group; no differences in time to first seizure.

Saetre '05 – lamotrigine and extended-release carbamazepine

- Retention rates in carbamazepine group were higher than in previous studies, however, carbamazepine was more likely to be discontinued due to adverse effects.

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Brodie MJ, Overstall PW, Giorgi L. Multicentre, double-blind, randomised comparison between lamotrigine and carbamazepine in elderly patients with newly diagnosed epilepsy. The UK Lamotrigine Elderly Study Group. Epilepsy Res. 1999 Oct;37(1):81-7. doi: 10.1016/s0920-1211(99)00039-x. PMID: 10515178
Saetre E, Perucca E, Isojärvi J, Gjerstad L; LAM 40089 Study Group. An international multicenter randomized double-blind controlled trial of lamotrigine and sustained-release carbamazepine in the treatment of newly diagnosed epilepsy in the elderly. Epilepsia. 2007 Jul;48(7):1292-302. doi: 10.1111/j.1528-1167.2007.01128.x. Epub 2007 Jun 11. PMID: 17561956.

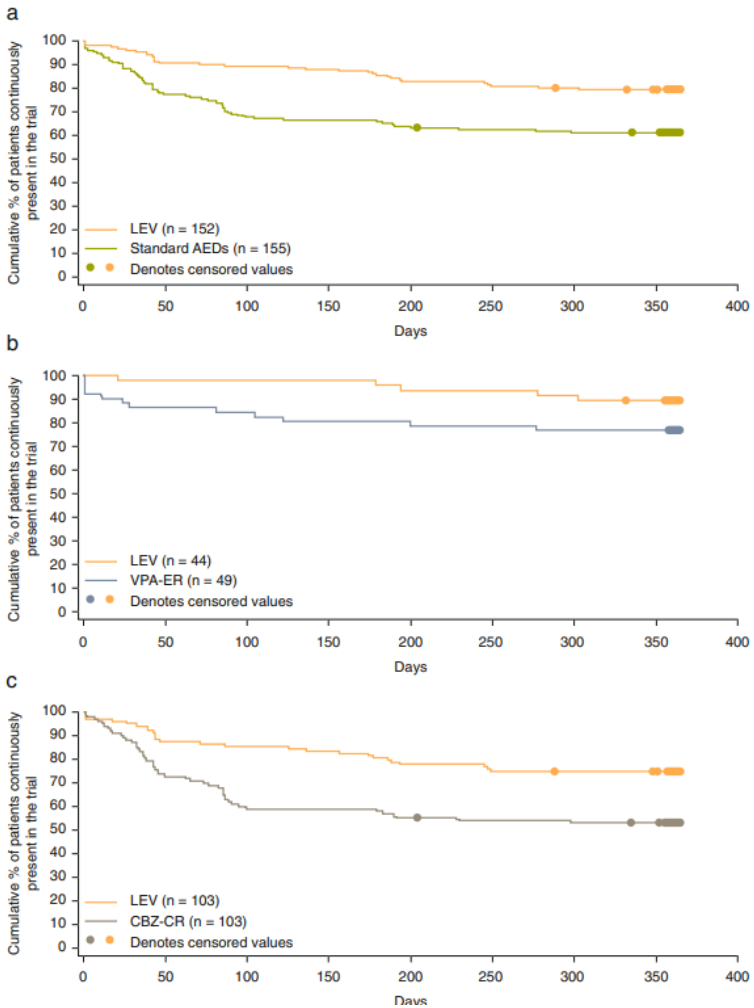
Levetiracetam

In a post-hoc subgroup analysis of an unblinded study, levetiracetam had better retention than standard medications.

Time to first seizure was not significantly different than standard medications.

This raised the possibility that levetiracetam may be reasonable choice for initial therapy in the elderly.

Pohlmann-Eden B, Marson AG, Noack-Rink M, Ramirez F, Tofighy A, Werhahn KJ, Wild I, Trinka E. Comparative effectiveness of levetiracetam, valproate and carbamazepine among elderly patients with newly diagnosed epilepsy: subgroup analysis of the randomized, unblinded KOMET study. BMC Neurol. 2016 Aug 23;16(1):149. doi: 10.1186/s12883-016-0663-7. PMID: 27552848; PMCID: PMC4995751.



Medication Options – “Newer Medications”

MEDICATION	CONSIDERATION
Zonisamide	Tolerable, minimal interactions
Topiramate	Cognitive side effects, clearance decreases with age
Oxcarbazepine	More tolerable than CBZ, hyponatremia
Lacosamide	Minimal interactions
Brivaracetam	Minimal interactions
Perampanel	Once daily dosing. Mood changes in younger patients

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Lezaic N, Gore G, Josephson CB, Wiebe S, Jetté N, Keezer MR. The medical treatment of epilepsy in the elderly: A systematic review and meta-analysis. Epilepsia. 2019 Jul;60(7):1325-1340. doi: 10.1111/epi.16068. Epub 2019 Jun 11. PMID: 31185130.

Rohracher A, Kalss G, Kuchukhidze G, Neuray C, Leitinger M, Höfler J, Kreidenhuber R, Rossini F, Volna K, Mauritz M, Poppert N, Lattanzi S, Brigo F, Trinka E. New anti-seizure medication for elderly epilepsy patients - a critical narrative review. Expert Opin Pharmacother. 2021 Apr;22(5):621-634. doi: 10.1080/14656566.2020.1843636. Epub 2020 Nov 12. PMID: 33111598.

Stockis A, Nicolas JM, Sargentini-Maier ML, Krauwinkel W. Pharmacokinetics, Safety, and Tolerability of Brivaracetam in Healthy Elderly Participants. Clin Pharmacol Drug Dev. 2023 Nov;12(11):1121-1127. doi: 10.1002/cpdd.1264. Epub 2023 May 22. PMID: 37212183

. Pascarella A, Gasparini S, Manzo L, Marsico O, Torino C, Abelardo D, Cianci V, Iudice A, Bisulli F, Bonanni P, Caggia E, D'Aniello A, Di Bonaventura C, DiFrancesco JC, Domina E, Dono F, Gambardella A, Marini C, Marrelli A, Matricardi S, Morano A, Paladin F, Renna R, Piccioli M, Striano P, Ascoli M, Ferlazzo E, Aguglia U; PEROC Study Group. Perampanel as only add-on epilepsy treatment in elderly: A subgroup analysis of real-world data from retrospective, multicenter, observational study. J Neurol Sci. 2023 Dec 15;455:122797. doi: 10.1016/j.jns.2023.122797. Epub 2023 Nov 13. PMID: 37976793.

Lamotrigine and Arrhythmia

- Cardiac rhythm and conduction abnormalities: Based on in vitro findings, LAMICTAL could cause serious arrhythmias and/or death in patients with certain underlying cardiac disorders or arrhythmias. Any expected or observed benefit of LAMICTAL in an individual patient with clinically important structural or functional heart disease must be carefully weighed against the risk for serious arrythmias and/or death for that patient. (5.4)

- FDA, 2020

- **ILAE's position:** Paucity of human data to determine this.
  >60 years, obtain EKG

Greatest risk with:

- 2nd or 3rd degree heart block
- Brugada syndrome
- Left bundle branch block
- Right bundle branch block w L ant/post fascicular block
- ARVC

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https://gskpro.com/content/dam/global/hcpportal/en_US/Prescribing_Information/Lamictal/pdf/LAMICTAL-PI-MG.PDF
https://www.ilae.org/files/ilaeGuideline/ILAE_AES_Lamotrigine_advisory_final_EO_CLEAN_ASG2-2021-0225-2.pdf

Other Treatment Considerations

- Cost
- Complex titrations and multiple daily doses lead to non-adherence.
- Increased incidence of adverse effects.
- Higher impetus to treat after first unprovoked seizure, and treatment is more likely to be life-long.
- **Removing or adding an inducer/inhibitor is going to influence everything.**

On the positive side:

- Most elderly patients have good control with monotherapy.
- Age is not a contraindication to epilepsy surgery.

Wyllie, E.. (2020). Wyllie's treatment of epilepsy: Principles and practice: Seventh edition.

Comorbidities

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Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Incident epilepsy in the cognitively normal geriatric population, irrespective of seizure control, impairs quality of life

Saniya Pervin *,[1], Gregory A. Jicha [2], Meriem Bensalem-Owen, Sally V. Mathias

Department of Neurology, University of Kentucky, Lexington 40536, KY, USA

Depression Memory loss SUDEP and increased risk of mortality

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Sen A, Jette N, Husain M, Sander JW. Epilepsy in older people. Lancet. 2020 Feb 29;395(10225):735-748. doi: 10.1016/S0140-6736(19)33064-8. PMID: 32113502.
Sveinsson O, Andersson T, Carlsson S, Tomson T. The incidence of SUDEP: A nationwide population-based cohort study. Neurology. 2017 Jul 11;89(2):170-177. doi: 10.1212/WNL.0000000000004094. Epub 2017 Jun 7. PMID: 28592455.
Kaestner E, Reyes A, Chen A, Rao J, Macari AC, Choi JY, Qiu D, Hewitt K, Wang ZI, Drane DL, Hermann B, Busch RM, Punia V, McDonald CR; Alzheimer's Disease Neuroimaging Initiative. Atrophy and cognitive profiles in older adults with temporal lobe epilepsy are similar to mild cognitive impairment. Brain. 2021 Feb 12;144(1):236-250. doi: 10.1093/brain/awaa397. PMID: 33279986; PMCID: PMC7880670
. Pervin S, Jicha GA, Bensalem-Owen M, Mathias SV. Incident epilepsy in the cognitively normal geriatric population, irrespective of seizure control, impairs quality of life. Epilepsy Behav. 2022 Jan;126:108457. doi: 10.1016/j.yebeh.2021.108457. Epub 2021 Dec 6. PMID: 34883464; PMCID: PMC8792889.

Summary

Epilepsy is more common in the elderly than most realize, and the subtle nature of focal seizures often leads to diagnostic difficulty/delay.

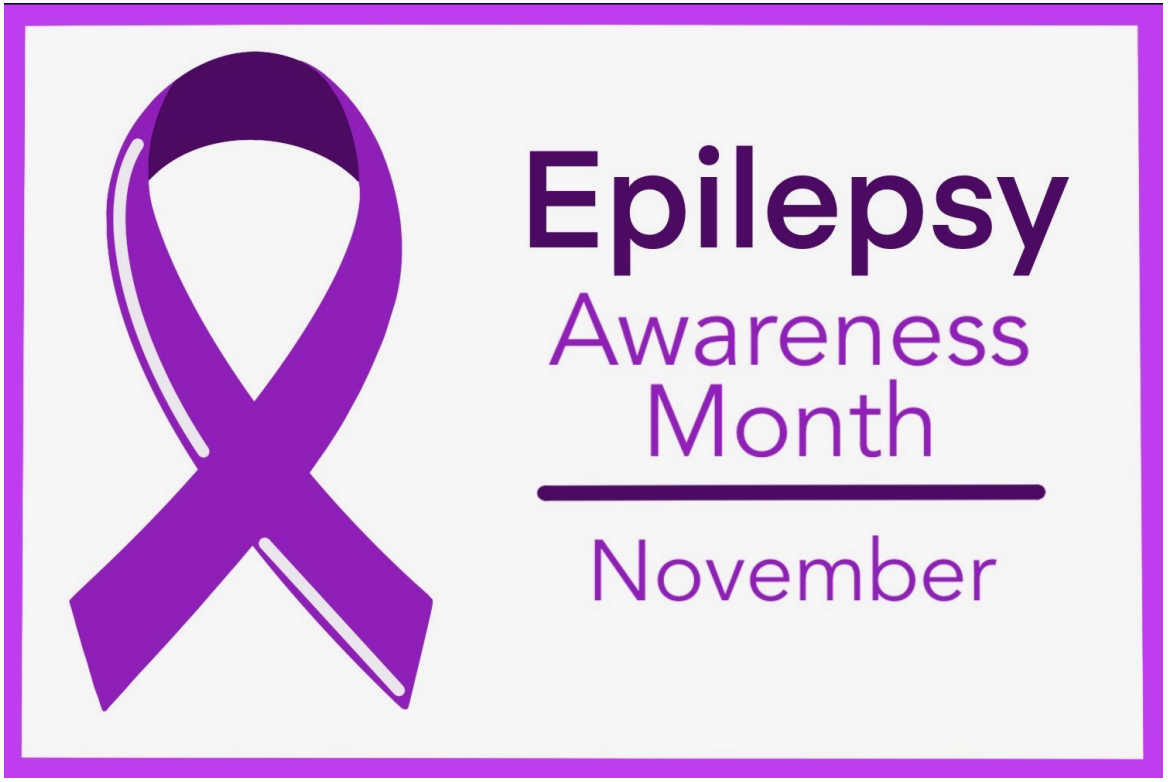
As most seizures are focal, and most focal seizures are of symptomatic etiology, new-onset epilepsy in the elderly requires a prompt and extensive evaluation.

When choosing a seizure medication, all comorbidities, concurrent medications, and physiologic changes that occur with age must be considered.

Lower doses of the “newer generation” of anti-seizure medications (levetiracetam, lamotrigine, gabapentin) appear to be the best tolerated, with emerging data on lacosamide, brivaracetam, perampanel.

The least expensive option with the simplest regimen and fewest drug interactions may be the best choice.

Epilepsy Awareness



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Thank you