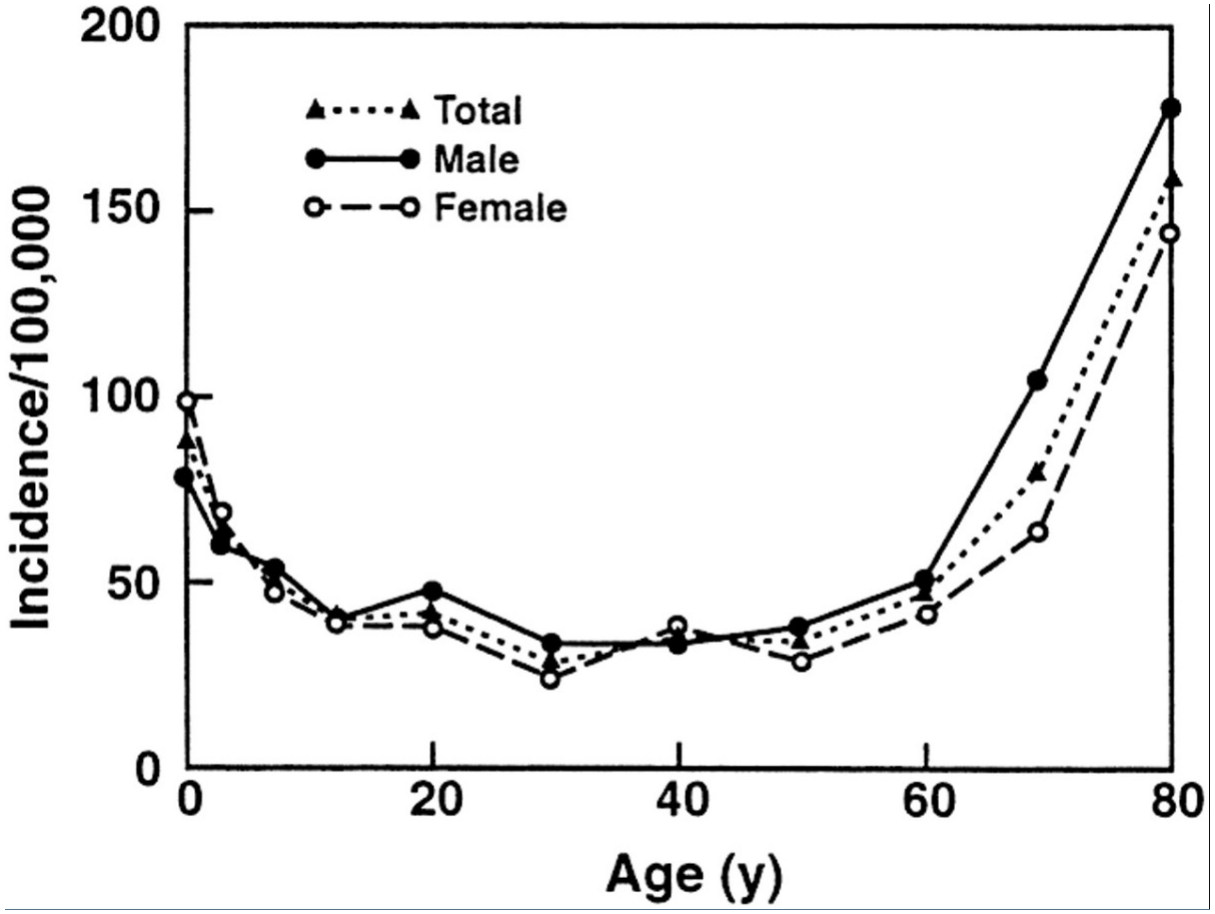
# Epilepsy and Dementia

Michael Doherty, MD, FAAN, FAES

Medical director, Swedish Epilepsy Center




Incidence of epilepsy by age, Rochester, MN, 1935-1984.

Hauser WA. Seizure disorders: the changes with age. Epilepsia 1992;33(suppl4):S6-S14.

# Epilepsy in older patients,:

- 90 per 100,000 in people between 65 and 69
- more than 150 per 100,000 for those older than 80

| | Older patients | Younger patients |
|---|---|---|
| Age | 65.2 ± 8.53 | 33.6 ± 6.75 |
| Gender (female) | 19 (39%) | 20 (40%) |
| Age at seizure onset | 53.6 ± 20.23 | 23.4 ± 12.12 |
| Mean duration of epilepsy (years) | 11.7 ± 15.74 | 10.2 ± 9.72 |
| Seizure frequency | | |
| No seizures for >1 year | 10 (20%) | 4 (8%) |
| One seizure every 6 months to 1 year | 14 (28%) | 9 (18%) |
| One seizure every 2–3 months | 12 (24%) | 10 (20%) |
| More than 1 seizure per month | 14 (28%) | 27 (54%) |
| Epilepsy risk factors | | |
| Vascular | 10 (20%) | 3 (6%) |
| Traumatic brain injury | 15 (30%) | 15 (30%) |
| Central nervous system infection | 3 (6%) | 2 (4%) |
| Central nervous system tumor | 4 (8%) | 3 (6%) |
| History of febrile seizures | 3 (6%) | 10 (20%) |

Silveira DC, Jehi L, Chapin J, Krishnaiengar S, Novak E, Foldvary-Schaefer N, Najm I. Seizure semiology and aging. Epilepsy Behav. 2011 Feb;20(2):375-7. doi: 10.1016/j.yebeh.2010.12.033

| | Older patients | Younger patients |
|---|---|---|
| Age | 65.2 ± 8.53 | 33.6 ± 6.75 |
| Gender (female) | 19 (39%) | 20 (40%) |
| Age at seizure onset | 53.6 ± 20.23 | 23.4 ± 12.12 |
| Mean duration of epilepsy (years) | 11.7 ± 15.74 | 10.2 ± 9.72 |
| Seizure frequency | | |
| No seizures for >1 year | 10 (20%) | 4 (8%) |
| One seizure every 6 months to 1 year | 14 (28%) | 9 (18%) |
| One seizure every 2–3 months | 12 (24%) | 10 (20%) |
| More than 1 seizure per month | 14 (28%) | 27 (54%) |
| Epilepsy risk factors | | |
| Vascular | 10 (20%) | 3 (6%) |
| Traumatic brain injury | 15 (30%) | 15 (30%) |
| Central nervous system infection | 3 (6%) | 2 (4%) |
| Central nervous system tumor | 4 (8%) | 3 (6%) |
| History of febrile seizures | 3 (6%) | 10 (20%) |

Seizure types in older and younger patients.

| Seizure type | Older patients | Younger patients | *P* value[a] |
|---|---|---|---|
| Dialeptic | 30 (60%) | 26 (52%) | 0.4203 |
| Automotor | 9 (18%) | 7 (14%) | 0.5854 |
| Complex motor | 1 (2%) | 1 (2%) | 1.00 |
| Aphasic/dysphasic | 6 (12%) | 3 (6%) | 0.4870 |
| Unilateral tonic or clonic | 4 (8%) | 9 (18%) | 0.1371 |
| Generalized tonic–clonic | 28 (56%) | 40 (80%) | 0.0101 |

[a] $P<0.0028$ (significant).


- Silveira DC, Jehi L, Chapin J, Krishnaiengar S, Novak E, Foldvary-Schaefer N, Najm I. Seizure semiology and aging. Epilepsy Behav. 2011 Feb;20(2):375-7. doi: 10.1016/j.yebeh.2010.12.033.

***Table 1*** *Comparative features of epilepsy in the young and old*

| Feature | Young | Old |
|---|---|---|
| Number of seizure types | Many | Few |
| Seizure types | Multiple (frequently GTCC) | Three (frequently CPS) |
| Seizure frequency | Often high | Low |
| Postictal state | Relatively brief | Relatively prolonged |
| Potential for injury | Relatively low | Relatively high |
| Causes | Many | Few |
| Response to AEDs | Variable (poor to excellent) | Usually good (incomplete data) |
| Tolerance to AEDs | Variable (usually good) | Often poor (incomplete data) |
| Required doses of AEDs | High | Low |
| Speed of AED titration | High | Low |

GTCC = generalized tonic–clonic convulsions; CPS = complex partial seizures; AED = antiepileptic drug.

A. James Rowan Neurology Nov 1998, 51 (5 Suppl 4) S28-S33; DOI: 10.1212/WNL.51.5_Suppl_4.S28

# But what about Alzheimer's an epilepsy…… the bidirectional risk?

- 10% of all late onset epilepsy thought to be neurodegenerative
- Most others are vascular related
- Seizures promote Amyloid β and tau deposits
- Epilepsy can occur in late-stage Alzheimer's
- Is there a bidirectional risk?

Zhang D, Chen S, Xu S, Wu J, Zhuang Y, Cao W, Chen X, Li X. The clinical correlation between Alzheimer's disease and epilepsy. Front Neurol. 2022 Jul 22;13:922535. doi: 10.3389/fneur.2022.922535

# The cognition of young vs old patient with chronic temporal lobe epilepsy?

- Older patients with epilepsy were more likely to score $Z < -1.5$ on the RAVLT (54.1 vs 32.8%)
- more likely to be on disability due to their seizures (23.0 vs 5.7%).
- higher grades of white matter hyperintensities correlated with worse performance on Trail Making Test A
- higher number of anti-epileptic drugs (AEDs) correlated with worse performance on Trail Making Test B regardless of age

- Older meds may predispose to vascular risks eg Carbamazepine and Cholesterol, BP; Valproic acid and metabolic syndrome

Sarkis RA, McGinnis S, Rushia SN, Park S, Ansari EE, Willment KC. Growing older with drug-resistant epilepsy: cognitive and psychosocial outcomes. J Neurol. 2018 May;265(5):1059-1064. doi: 10.1007/s00415-018-8805-z

# Epilepsy in Alzheimer's

- Seizures are often Non-motor, subtle and long (focal onset impaired awareness)
  - Subtypes include myoclonus 8-10%, often in younger patients
  - Unprovoked seizures 10-22%
- Better picked on ambulatory or long duration studies
- Down's Syndrome (APP gene) up to 84% with seizure
- Untreated seizure will hasten cognitive decline
- In mouse models of Alzheimer's seizures may occur prior to amyloid/tau disruption
- Does Amyloid β contribute to epilepsy in Alzheimer patients?
- Braak staging of temporal lobe epilepsy patients without Alzheimer's is moderated with 94% showing hyperphosphorylated tau


- Vossel KA, Tartaglia MC, Nygaard HB, Zeman AZ, Miller BL. Epileptic activity in Alzheimer's disease: causes and clinical relevance. Lancet Neurol. 2017 Apr;16(4):311-322. doi: 10.1016/S1474-4422(17)30044-3.

# Epilepsy in Alzheimers

- ***Alzheimer's disease should be assessed carefully for epileptiform activity and silent seizures if patients 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***

(Myoclonus should also trigger paraneoplastic evaluation)

Vossel KA, Tartaglia MC, Nygaard HB, Zeman AZ, Miller BL. Epileptic activity in Alzheimer's disease: causes and clinical relevance. Lancet Neurol. 2017 Apr;16(4):311-322. doi: 10.1016/S1474-4422(17)30044-3.

# Hippocampal Atrophy occurs in

- Alzheimer disease
- Temporal lobe epilepsy
- Encephalitis that targeted temporal lobe disproportionately (EG herpes simplex)
- Paraneoplastic encephalitis

# Hippocampus serves as the memory engine

- Uses a lot of glucose
- Easy to screw its functions up

# Ambulatory EEG may pics up abnormalities

- Sharp waves and incidental spikes can often be seen
- Ambulatory EEG is error prone and expensive
- Very prone to over calls

# Epilepsy Meds and Dementia-Downsides

- Some can induce depression and mimic dementia-pseudodementia
  - Levetiracetam
- Some Sedate and limit participation and attention:
  - Pretty much any anti seizure med but worse in benzodiazepine and barbiturate families
- Some trigger insomnia that ruins sleep that then hurts memory
  - Lamotrigine, Zonisamide
- Many are play dirty with other meds (valproic acid, phenobarb)
- Some can worsen word recall
  - Zonisamide
  - Topiramate
  - High dose of any anti-seizure med

# Epilepsy Meds and Dementia- upsides

- Correctly treated temporal lobe epilepsy MAY limit further memory decline
- Some have mood stabilizing effects (valproic acid, lamotrigine)
- Some have mild sedative effects (phenobarbital)
- Some are better at myoclonus that others (levetiracetam, zonisamide, valproic acid)

Commonly prescribed antiepileptic drugs for older adults with cognitive impairment

| | 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 |

## Retention/response rate in Alzheimer's

- Leveitracetam (500-2000 mg/day): 84% retention rate, 72% response rate
- Lamotrigine (25-100 mg/d)  100% retention rate, 59% response rate
- Phenobarb (50-100mg/day)83% retention rate 64% response rate, 30% sleepy

- No significant differences in side effects for these three meds!

Belcastro V, Costa C, Galletti F, Pisani F, Calabresi P, Parnetti L. Levetiracetam monotherapy in Alzheimer patients with late-onset seizures: a prospective observational study. *Eur J Neurol.* 2007;14:1176–78.

# Change in cognitive performance?

| | MMSE score (min–max) | | | Difference (12 months/baseline) |
|---|---|---|---|---|
| | Baseline | 6 months | 12 months | |
| LEV | 20.29 | 20.49 | 20.51 | +0.23 |
| | (14.00–24.00) | (15.00–24.00) | (14.00–24.00) | (–1.00/+1.00) |
| PB | 20.35 | 19.83 | 18.78 | –1.57 |
| | (15.00–26.00) | (15.00–26.00) | (14.00–25.00) | (–3.00/+1.00) |
| LTG | 20.24 | 20.12 | 19.60 | –0.64 |
| | (14.00–25.00) | (14.00–25.00) | (13.00–25.00) | (–2.00/0) |
| Controls | 19.83 | 20.23 | 20.90 | +1.07 |
| | (14.00–24.00) | (15.00–24.00) | (15.00–24.00) | (–1.00/+3.00) |

*Note*. +, positive score difference indicating clinical improvement; –, negative score difference indicating clinical worsening. Significant differences existed among the three treatment groups at the end of treatment.

ANOVA between treatments for changes at 12 months versus baseline, $P < 0.0001$.

Higher dose300mg LTG in separate trial showed improvements in ADAS recognition and naming tasks

Belcastro V, Costa C, Galletti F, Pisani F, Calabresi P, Parnetti L. Levetiracetam monotherapy in Alzheimer patients with late-onset seizures: a prospective observational study. *Eur J Neurol.* 2007;14:1176–78.

Tekin S, Aykut-Bingöl C, Tanridağ T, Aktan S. Antiglutamatergic therapy in Alzheimer's disease—effects of lamotrigine. *J Neural Transm (Vienna)* 1998;105:295–303

# Levetiracetam for Alzheimer's Disease-Associated Network Hyperexcitability

- randomized double-blinded placebo-controlled crossover clinical trial of 34 adults
- levetiracetam did not change NIH-EXAMINER composite scores (mean difference vs placebo, 0.07 points; 95% CI, -0.18 to 0.32 points; P = .55)
- Among participants with epileptiform activity, levetiracetam treatment improved performance on the Stroop interference naming subscale (net improvement vs placebo, 7.4 points; 95% CI, 0.2-14.7 points; P = .046) and the virtual route learning test (t = 2.36;  P = .02)

Vossel K et a. Effect of Levetiracetam on Cognition in Patients With Alzheimer Disease With and Without Epileptiform Activity: A Randomized Clinical Trial. JAMA Neurol. 2021 Nov 1;78(11):1345-1354. doi: 10.1001/jamaneurol.2021.3310.

# What are we doing in Epilepsy to prevent memory decline?

Weight bearing and other exercise

Avoidance/treatment of sleep apnea, good sleep habits

Maintaining social contacts, interests and a positive mood

Good hearing

Avoidance or treatment of type II diabetes with good sugar controls

Don't snack on sugary foods at night!

Caffeinated coffee may be good, at least in the AM, so might flavonoids (blueberry,  strawberry, cocoa)

Treating elevated blood fats (cholesterol, triglycerides)

Ideally- blood pressure top number at or below 120, bottom number at or below 70

Mediterranean diet, particularly use of olive oil as the main cooking oil

Limited (very limited) alcohol use

If you smoke, quit smoking

Very limited consumption of red meat

Good seizure control

Consider Methylated B12 and Methylated folate