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Antiepileptic Drugs for the Elderly

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Elderly
≥ 65 years

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Epilepsy in older people

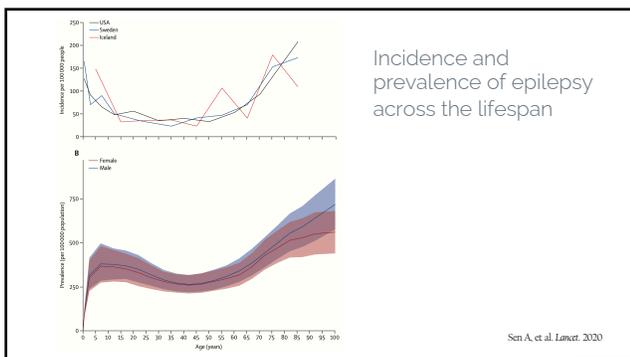
Epidemiology

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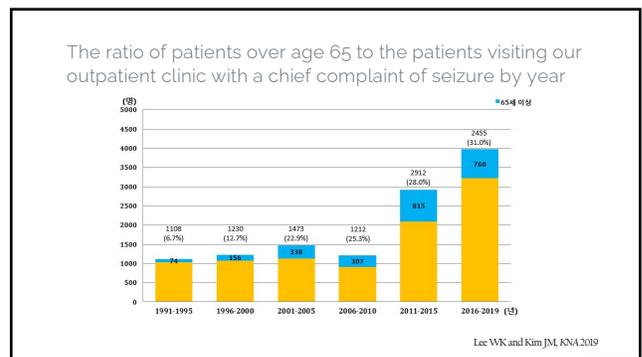
Epilepsy is the third most common neurologic disease in the elderly.



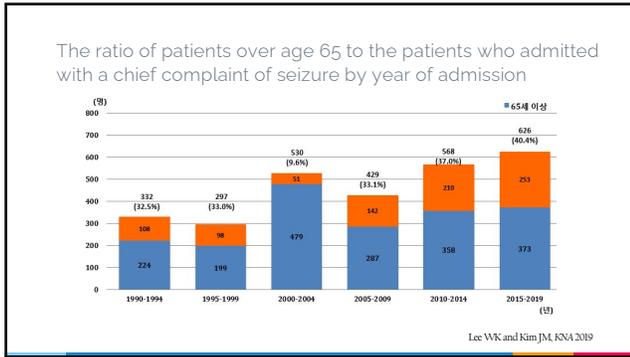
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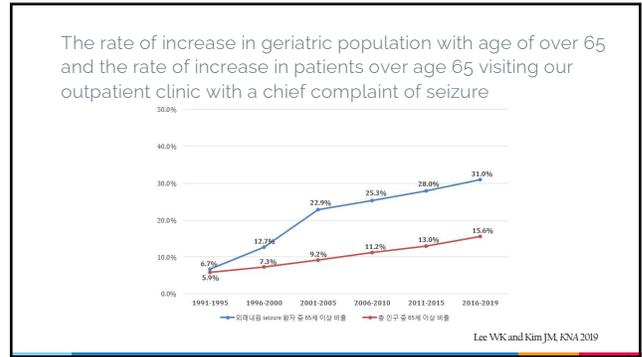
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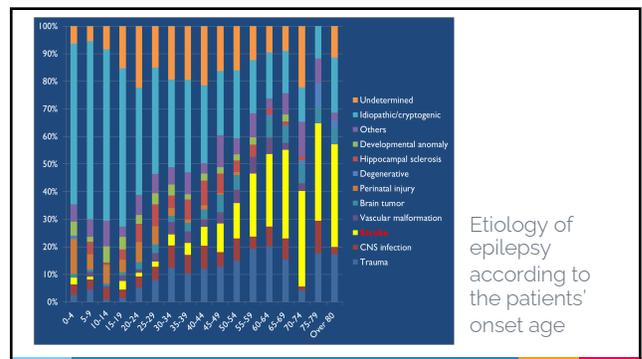


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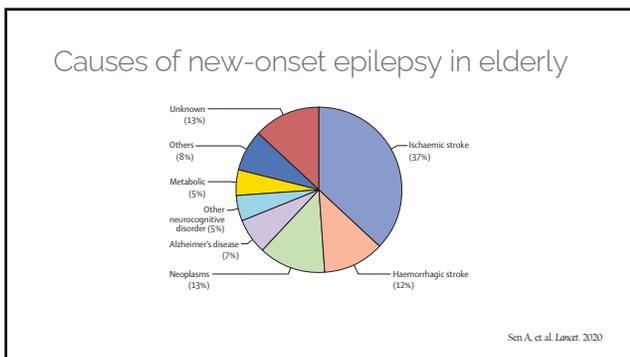
Epilepsy in older people

Causes & Risk factors

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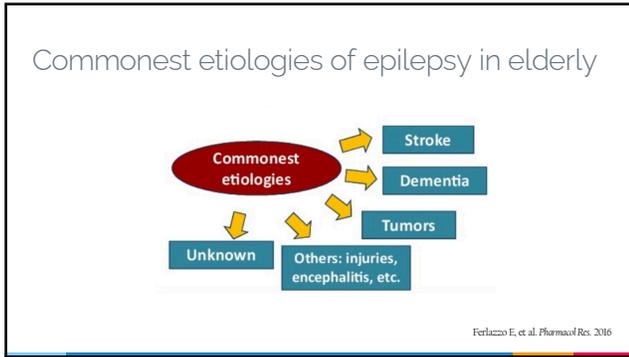
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Etiology of seizures and epilepsy in the elderly

Acute symptomatic seizure	Value (%)	Epilepsy	Value (%)
Acute stroke	30-54	Cryptogenic epilepsy	~50
Metabolic or electrolyte imbalance	10-15	Stroke	30-50
Tumors	~10	Dementia	10-20
Trauma	~10	Tumors	4-6
Drug-related seizure	~10	Trauma	1-3
CNS infection	2-3		

Lee SK, J Epilepsy Res. 2019

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Stroke

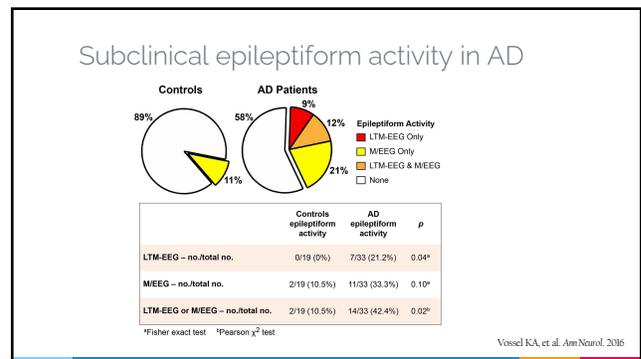
- ▷ A history of stroke and/or findings of cerebral arteriosclerosis on neuroimaging represented the largest group of patients with epilepsy.
- ▷ The risk of developing epilepsy in the first year after a stroke is 20 times higher than those without stroke .
- ▷ The cumulative seizure rate after stroke has been found to be 6.1% after 1 year, 9.5% after 5 years, and 11.5% after 10 years.
- ▷ Among all types of strokes, patients with hemorrhagic lesions, mostly involving the cerebral cortex, are most susceptible to the development of epilepsy.

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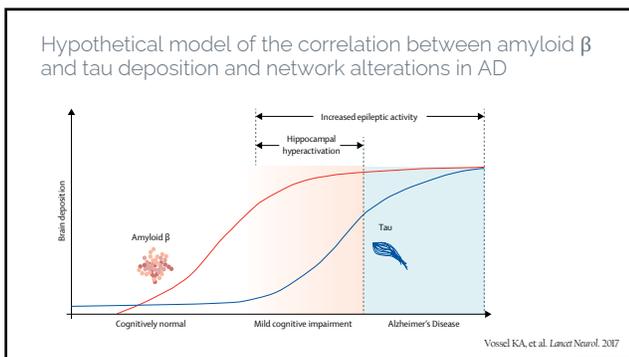
Neurodegenerative diseases

- ▷ Patients with all types of dementias are at a 5- to 10-fold increased risk of epilepsy compared to an age-matched population without dementia.
- ▷ The risk appears highest in patients with Alzheimer dementia (AD) for which the risk of epilepsy is 3 to 87 times greater compared to those without AD.
- ▷ The onset of epilepsy in patients with AD occurs within 0.4 to 9.3 years after dementia symptoms begin.
- ▷ The severity of dementia may increase the incidence of seizures as well. Seizures can occur in 1.5% to 16% of patients with mild dementia, compared to 9% to 64% of patients with severe dementia.

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The intersections of Alzheimer's disease, epilepsy and vascular disease

Obesity
Dyslipidaemia
Hyperuricaemia
Insulin resistance
Carotid intima thickening
Small vessel disease

Stroke
Coronary artery disease
Heart failure
Diabetes
Hypertension

Amyloid plaques
Tau tangles
Vascular disease

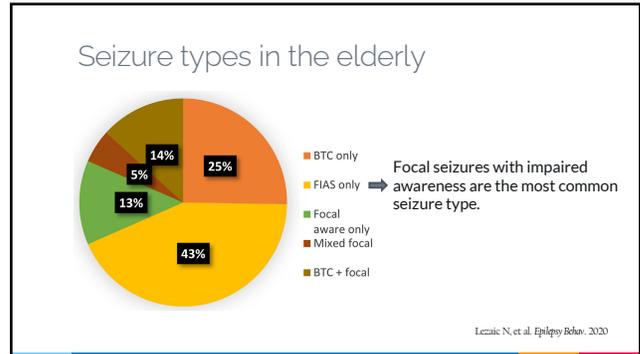
A. Seri, et al. *Brain.* 2018

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Epilepsy in older people

Diagnosis

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Proposed differences in presentation between the elderly and younger adults.

Features	Elderly	Younger adults
Auras	Less reported	More common
Automatisms	Less observed	More common
Motor features (focal and/or generalized)	Infrequent	Frequent
Semiology of FIAS	Simpler & shorter	More elaborate
Subtle episodes of transient confusion	More frequent	Less frequent
Postictal state (confusion, aphasia, paresis) after a secondary generalized seizure	Hours-days	5-15min

Source: Lezaic N, et al. Epilepsy Behav. 2020

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- ### Factors complicating a timely diagnosis
- ▷ Atypical clinical presentation
 - ▷ Lack of awareness of epilepsy in this population
 - ▷ Incomplete history of potential seizure event, etc.

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- ### Differential diagnosis of epilepsy and other seizure disorders in the elderly
- Neurological**
 - TIA
 - TGA
 - Endocrine/metabolic**
 - Hypoglycemia
 - Hyponatremia
 - Cardiovascular**
 - Vasovagal syncope
 - Sleep disorders**
 - REM sleep behavior disorder
 - Parasomnia, including sleep eating disorder or sleepwalking
 - Other reflex syncope**
 - Sick sinus syndrome
 - Other arrhythmia
 - Postural hypotension
 - Psychological**
 - Nonepileptic psychogenic seizure
- Source: Lee SK. J Epilepsy Res. 2019

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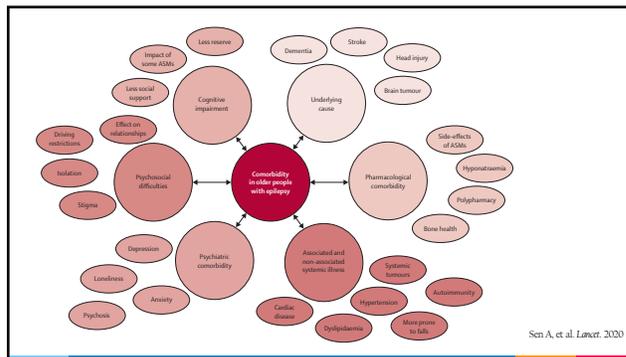
- ### Investigation of suspected seizures
- ▷ Basic blood work (full blood count, urea, creatinine, electrolytes, liver function tests, glucose)
 - ▷ Brain imaging (CT or MRI)
 - ▷ Electroencephalography (EEG) or Video-EEG monitoring
 - ▷ CSF analysis in appropriate cases
 - : eg. if an infective, haemorrhagic, malignant, or inflammatory cause is suspected
 - ▷ Screening for autoantibodies (especially LGI1, CASPR2, paraneoplastic antibodies, etc.); older people with explosive-onset epilepsy, particularly if associated with substantial cognitive and psychological comorbidity

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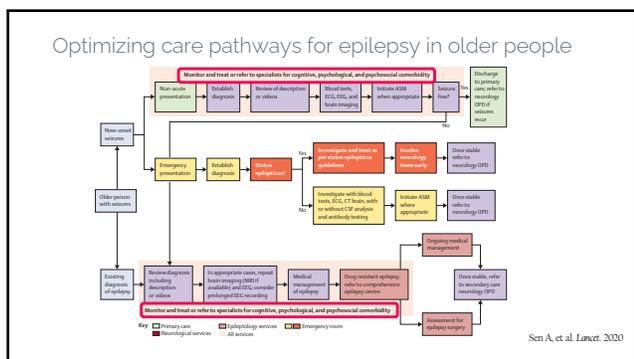
Epilepsy in older people

Comorbidities

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Epilepsy in older people

Treatment

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- ### Age-related physiologic changes
- ▷ Decreases in renal clearance
 - ▷ Decreases in hepatic blood flow and liver size
 - ▷ Decreases in gastrointestinal absorption
 - ▷ Decreases in serum albumin (and thus decreased protein binding), etc.
- Greater sensitivity to adverse effects of AEDs
- “Starting at a low dose & Titrating slowly”**
- Carlson C, et al. *Continuum*. 2016

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AEDs to avoid in patients with hepatic or renal failure

Hepatic failure	Renal failure
Benzodiazepines	Gabapentin
Carbamazepine	Levetiracetam
Felbamate	Pregabalin
Phenytoin	Vigabatrin
Phenobarbital	
Primidone	
Rufinamide	
Valproic acid	

Carlson C, et al. *Continuum*. 2016

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Risk factors of bone disease in patients with epilepsy

▷ **Fall-related fractures**

Patients with epilepsy are at risk for seizure-related falls in addition to falls caused by ataxia, sedation, and gait instability due to either the neurologic pathology underlying the epilepsy or the side effects of AEDs used to treat seizures.

▷ **Direct effects of AED treatment on bone health**

Several AEDs have been linked with bone disease. These mostly include cytochrome P450 enzyme inducers, such as phenytoin, phenobarbital, primidone, and carbamazepine. A long AED treatment duration has been convincingly linked to increased bone disease risk, with the most obvious correlation seen with more than 12 years of treatment.

Carlson C, et al. *Continuum*. 2016

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Selected specific considerations relating to prescription of AEDs in older people

	Potential effect on cognition	Potential effect on mood	Other specific considerations
Carbamazepine	Cognitive side-effects can be more marked in older people	Mood stabilizer	Enzyme inducing: high propensity for drug-drug interaction; side-effect of dizziness can lead to falls; negative effects on lipid metabolism and can increase cardiac markers; enzyme inducing medications can have greater adverse effect on bone health than other antiseizure medications
Phenytoin	Usually cognitively neutral	Can sometimes have adverse effects on mood	Narrow therapeutic window; extensive drug-drug interactions (eg, apixaban); negative effects on lipid metabolism and cardiac markers; dizziness can result in falls; enzyme-inducing medication can have greater adverse effects on bone health than other AEDs
Sodium valproate	Can affect cognition; also hyperammonemic encephalopathy	Mood stabilizer	Thrombocytopenia; weight gain; tremor, especially at higher doses

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Selected specific considerations relating to prescription of AEDs in older people

	Potential effect on cognition	Potential effect on mood	Other specific considerations
Lamotrigine	Usually cognitively neutral	Mood stabilizer	Risk of rash around 1-30; can be associated with insomnia, vivid dreams, and nightmares; might associate with tremor
Levetiracetam	Usually cognitively neutral	Can have adverse effects on mood (eg, irritability, anxiety, low mood)	Lack of drug-drug interaction
Oxcarbazepine	Can be associated with hyponatremia which could result in confusion, apathy, and lethargy	Probably no substantial adverse effect on mood	Enzyme-inducing agent; enzyme-inducing medications can have greater adverse effect on bone health than other antiseizure medications; dizziness could result in falls
Gabapentin	Usually cognitively neutral	Can be anxiolytic and benefit mood	Lack of drug-drug interaction

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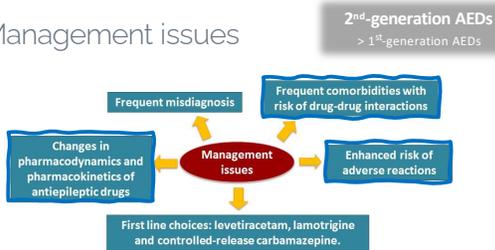
Selected specific considerations relating to prescription of AEDs in older people

	Potential effect on cognition	Potential effect on mood	Other specific considerations
Topiramate	Can have adverse effects on cognition; word-finding difficulty in particular	Can have adverse effects on mood	Nephrolithiasis; weight loss; complex side-effect profile
Zonisamide	Can have adverse effects on cognition; word-finding difficulty in particular	Can have adverse effects on mood	Quite similar side-effect profile to topiramate, but overall probably better tolerated
Lacosamide	Usually cognitively neutral	Generally thought to have a benign psychological profile, but can occasionally have adverse effects on mood	Possibility of palpitations and prolongation of PR interval (all patients); rarely atrial fibrillation and atrial flutter (usually with higher intravenous loading of drug); check electrocardiogram before initiating
Pregabalin	Usually cognitively neutral	Can be anxiolytic and benefit mood	Also frequently used to help with chronic pain; can associate with ankle oedema and increased risk of falls in older people

Sen A, et al. *Lancet*. 2020

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Management issues



Ferlicco E, et al. *Pharmazie*. 2016

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Class 1 RCTs comparing efficacy, effectiveness, and safety of 1st-generation and 2nd-generation AEDs

	Second-generation ASM participants	First-generation ASM participants	Age eligibility (mean age)	Maximum duration of follow-up (weeks)	Efficacy or effectiveness outcomes	Patients with AEs (%)	Patients with AEs leading to withdrawal (%)
Older people (>60 years) with focal epilepsy							
Rowan et al (2005)*	Carbamazepine 1200 mg/day (n=195) Lamotrigine 120 mg/day (n=200)	Carbamazepine 600 mg/day (n=198)	>60 (72)	48	Seizure freedom rate at 12 months was not significantly different across treatments (47% for gabapentin, 51% for lamotrigine, and 64% for carbamazepine); retention at 12 months (PE) was lower for carbamazepine (36%) compared with lamotrigine (56%, p<0.002) and gabapentin (49%, p=0.01)	Not reported; incidence of specific AEs differed across groups	27% (gabapentin), 32% (lamotrigine), 31% (carbamazepine)
Wuhalo et al (2015)†	Levetiracetam 1000-3000 mg/day (n=322) Lamotrigine 300-300 mg/day (n=127)	Carbamazepine-CR 400-1200 mg/day (n=121)	>60 (73)	58	Seizure freedom rate at 58 weeks was not significantly different across treatments (43% for levetiracetam, 33% for lamotrigine, 33% for carbamazepine-CR); retention at week 58 (PE) was higher for levetiracetam (52%) than for carbamazepine-CR (46%, p<0.02); no difference in retention between lamotrigine (55%) and levetiracetam or carbamazepine-CR	89% (levetiracetam), 94% (lamotrigine), 89% (carbamazepine-CR)	17% (levetiracetam), 34% (lamotrigine), 32% (carbamazepine-CR)

E Perucca, et al. *Lancet Neurol*. 2020

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Guidelines of the ILAE and the AES/AAN for elderly patients with focal-onset seizures

Type of seizures	ILAE guidelines (2013) Antiepileptic drugs	Level of evidence	AES/AAN guidelines (2018)
Newly diagnosed/ untreated focal-onset seizures in elderly	Lamotrigine, gabapentin	A	Lamotrigine (Level B)
	Carbamazepine	C	Gabapentin (Level C)
Generalized tonic-clonic seizures	Topiramate, valproate	D	
	Ocarbazepine, levetiracetam, phenytoin, pregabalin, clonazepam, clobazam	E	
	No data	No data	No recommendation
Myoclonic seizures	No data	No data	No recommendation
Absence seizures	No data	No data	No recommendation

The Drug Committee of Korean Epilepsy Society, JCN 2020

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The medical treatment of epilepsy in the elderly : A systematic review and meta-analysis

- ▷ Among the elderly with epilepsy, lamotrigine was better tolerated than carbamazepine.
- ▷ Levetiracetam demonstrated a higher probability of seizure freedom as compared to lamotrigine, with no significant differences in measures of tolerability.
- ▷ There were no significant differences between carbamazepine and levetiracetam in terms of efficacy and tolerability.
- ▷ More data are required to evaluate the newest generation of AEDs, and to compare different AED doses and titration schedules in the elderly with epilepsy.

Lezacic N, et al. *Epilepsia*. 2019.

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Summary & Recommendation

- ▷ Epilepsy in elderly patients has quite different etiology, clinical manifestations, and choice of AEDs compare with other adult patients.
- ▷ In addition to the efficacy of AEDs, their adverse effects and drug interactions as well as comorbid diseases and economic status must be considered when choosing AEDs for treating epilepsy in elderly patients.
- ▷ AEDs that are suitable for treating epilepsy in elderly patients have 1) no interactions with other medications or AEDs, 2) no or low protein binding, 3) good adverse-effect profiles, and 4) little effect on cognitive function.
- ▷ Lamotrigine and levetiracetam are recommended as the treatment of choice for epilepsy in elderly patients.

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