Epilepsy across the lifespan

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Treatment of epilepsy in older adults: Balancing efficacy and polypharmacy

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Treatment

- Provoked seizures: Rx as etiologies (not need ASMs)
- Unprovoked seizures
  - Single seizure or recurrent seizures (epilepsy)
  - ASMs may be appropriate after a single seizure in the elderly

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Pharmacological approaches

- Initial treatment: monotherapy

Choice of a specific ASM
Type of seizures: all ASMs except ethosuximide
Potential side effects (tolerability)
Physiological changes associated with aging
Drug interactions
Comorbidities
Need for rapid titration
Cost

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Seizures in elderly: Comparative efficacy & tolerability of ASMs

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

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Level	ASMs (Elderly recommendation)
A	GBP, LTG
B	None
C	CBZ
D	VPA, TPM
E	Others
F	None

Glauser T,e tal. Epilepsia 2013

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DOI: 10.1111/epi.16068

FULL-LENGTH ORIGINAL RESEARCH

Epilepsia

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

Nastasija Lezaic[1,2] | Geneviève Gore[3] | Colin B. Josephson[4] | Samuel Wiebe[4] | Nathalie Jetté[4,5] | Mark R. Keezer[1,2,6]

Single studies & Head-to-head studies

From 3,417 trials: 18 studies met criteria	Total 1,999 subjects Age > 60
Carbamazepine (CBZ)	10
Lamotrigine (LTG)	9
Levetiracetam (LEV)	5
Valproic acid (VPA)	2
Topiramate (TPM)	2
Gabapentin (GBP)	1
Lacosamide (LAC)	1
Perampanel (PER)	1
Phenobarbital (PB)	1
Phenytoin (PHT)	1
Brivaracetam (BRV)	1
Zonisamide (ZNS)	1

Lezaic N, et al. Epilepsia 2019

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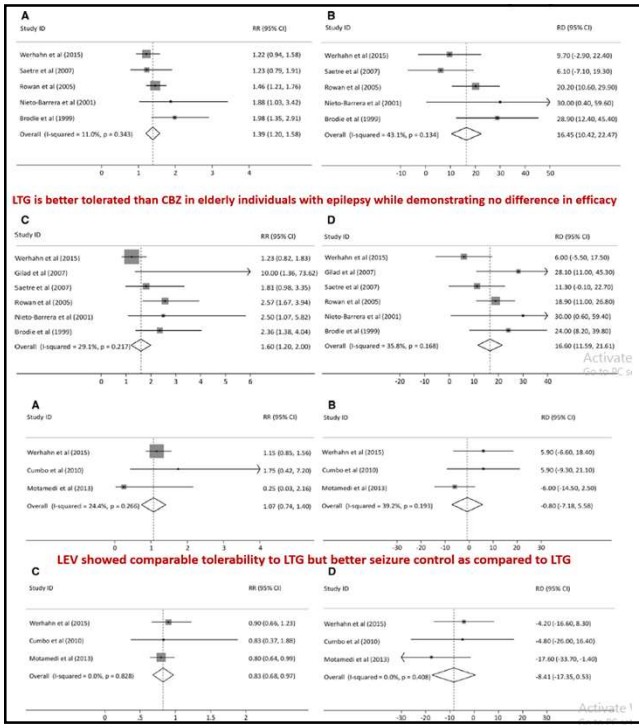

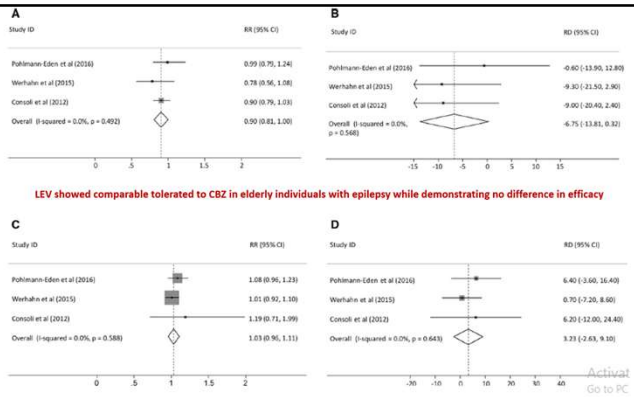

Single studies	ASMs
Provide evidence for the efficacy +/- tolerability in the elderly	VPA GBP, TPM PHT, PER BRV, LAC

Lezaic N, et al. Epilepsia 2019

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Epilepsia

SPECIAL REPORT

Management of epilepsy in older adults: A critical review by the ILAE Task Force on Epilepsy in the elderly

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• 6381 articles in PubMed, 19 700 results in Google Scholar, and 327 clinical trial registrations

Piccenna L, et al. Epilepsia 2022

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Concerns for taking antiseizure medications

- Neurocognitive adverse effects
  - Memory decline
  - Reduced mobility, increased risk of falls and motor vehicle accidents
  - Depression
- Drug-drug interactions
- Reduced drug metabolism
- Deleterious effects pm bone health: osteoporosis
- Cholesterol homeostasis through enzyme induction
  - Vascular and metabolic disorders

Piccenna L, et al. Epilepsia 2022

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Status epilepticus

Incidence / age group	60-69 years	70-79 years	80 years or older
Convulsive SE	15.5/100,000	21.5/100,000	25.9/100,000

Nonconvulsive SE	Confusion, altered mental status	Aged 60 years or older	16%

Piccenna L, et al. Epilepsia 2022, Leppik IE. Status epilepticus in the elderly. Epilepsia. 2018;59(Suppl 2):140–3.

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Status epilepticus

- ESETT study
  - No difference among fosphenytoin, LEV and valproate in terms of efficacy and adverse events
  - Only 13% pf patients in the study were older adults (>65 years)
  - No subgroup analysis performed

Kapur J, Elm J, Chamberlain JM, Barsan W, Cloyd J, Lowenstein D, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med. 2019;28(381):2103–13.

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6 Practical concerns for an ASM selection for older adults

1. The efficacy of the ASM to prevent seizures
2. The potential of causing adverse effects involving memory, cognition, mood, coordination, balance, sedation, ataxia and other QoL issues
3. Drug-drug interaction with other ASMs or other drugs and natural products
4. Economic and practical factors: cost, availability, drug identification, dose sizes (larger doses → difficult to swallow, difficult titration schedules
5. Avoid some ASMs or select some ASMs in specific comorbidity
6. Long half-life for OD dose

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Surgery

- From case series → advanced age should not be a contraindication for epilepsy surgery
- Resective surgery for mesial temporal sclerosis in older adults have shown excellent seizure freedom, comparable to the younger population
- Increased risk of surgical complications is both a perceived and a reported risk in this population
- The longer duration of disease → proposed effects of secondary epileptogenesis

Murphy M, et al. Epilepsia. 2010., Hughes JR. Arch Neurol. 1985., Morrell F. Arch Neurol. 1985

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Ketogenic diet

- No specific clinical trials have studied a ketogenic diet in older adults with epilepsy

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Clinical practice guidelines for treatment

- Awareness increases
- Recommendations: from a very small number of RCT → level B/II evidence
- Rely on smaller studies investigating older ASMs > newer ASMs
- No guidelines other than drug treatment in the past 5 years

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Seizure control

- ILAE 2013: Gabapentin and lamotrigine and both as more efficacious than carbamazepine, topiramate, or valproic acid
- American Academy of Neurology and American Epilepsy Society: lamotrigine be considered to decrease seizure frequency
- Gabapentin was concluded to be possibly as effective as lamotrigine and better tolerated than carbamazepine-immediate release
- Zonisamide and LEV were also concluded to decrease seizure frequency, although with less efficacy than lamotrigine
- Newer is recommend but no direct study

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Physiological changes during aging affecting pharmacokinetics and pharmacodynamics of ASMs

Parameter	Decreased	Increased
Gastrointestinal motility, secretion,	+/−	
Serum albumin	+	
Body fat/lean mass ratio		+
Total body water	+	
Liver mass and blood flow	+	
Cytochrome P450 enzyme activity	+	
Renal blood flow and weight	+	
Glomerular filtration rate	+	
Filtration fraction		+
Receptor number	+	
Receptor sensitivity	+	

CYP 450 reduced function after age 40, after age 70 reduced 30%
Renal clearance reduced 10% annually

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Co-morbidities & side effects of ASMs

- Cognitive impairment
- Parkinsonism
- Cerebrovascular disease
- Cardiac arrhythmias
- Osteoporosis

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Titration

- **To minimize the risk of side effects, the old dictum of "start low, go slow" could be modified to "start lower, go slower" in the elderly**
- Frequent seizures or status epilepticus in elderly
  - Parenteral form, Loading dose, Rapid titration
  - But lower rate than younger patients

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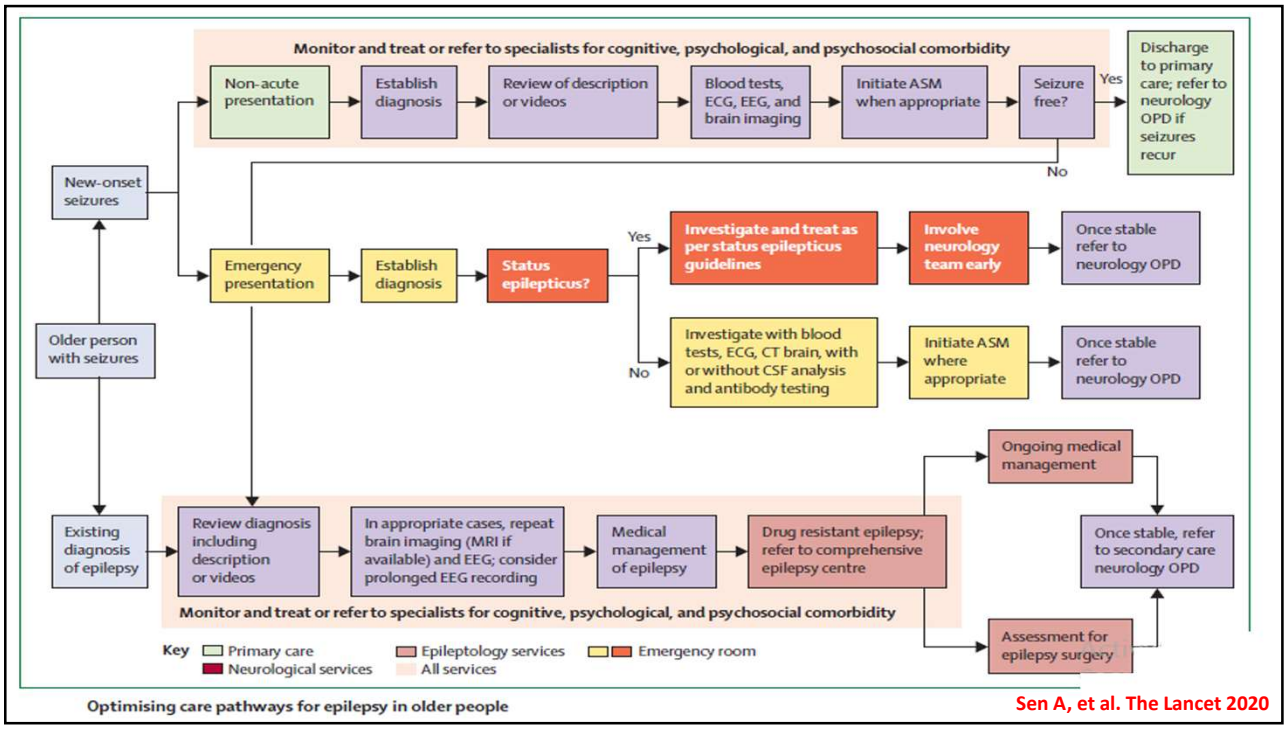

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Prognosis: compare to young adults

- Better response to Rx at lower doses (Drug-resistant epilepsy is uncommon)
- More often to be able to discontinue Rx after 2 years (but unclear if ASMs can be safely withdrawn)
- More side effects/drug interactions from ASMs
- Adherence to medications can be problematic due to cognitive and psychiatric comorbidities
- Epilepsy surgery, especially temporal lobectomy, can be performed in older patients with good results
- In general, the rate of post-operative complications a little higher and seizure outcomes tend to be a little worse

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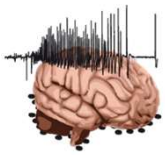
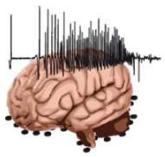


Summary



- Being an elderly with epilepsy is not the same as being a younger age with epilepsy

- Epilepsy and Aging – A bidirectional relationship

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