Comorbidità e problematiche terapeutiche nell'anziano con epilessia

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Disclosures

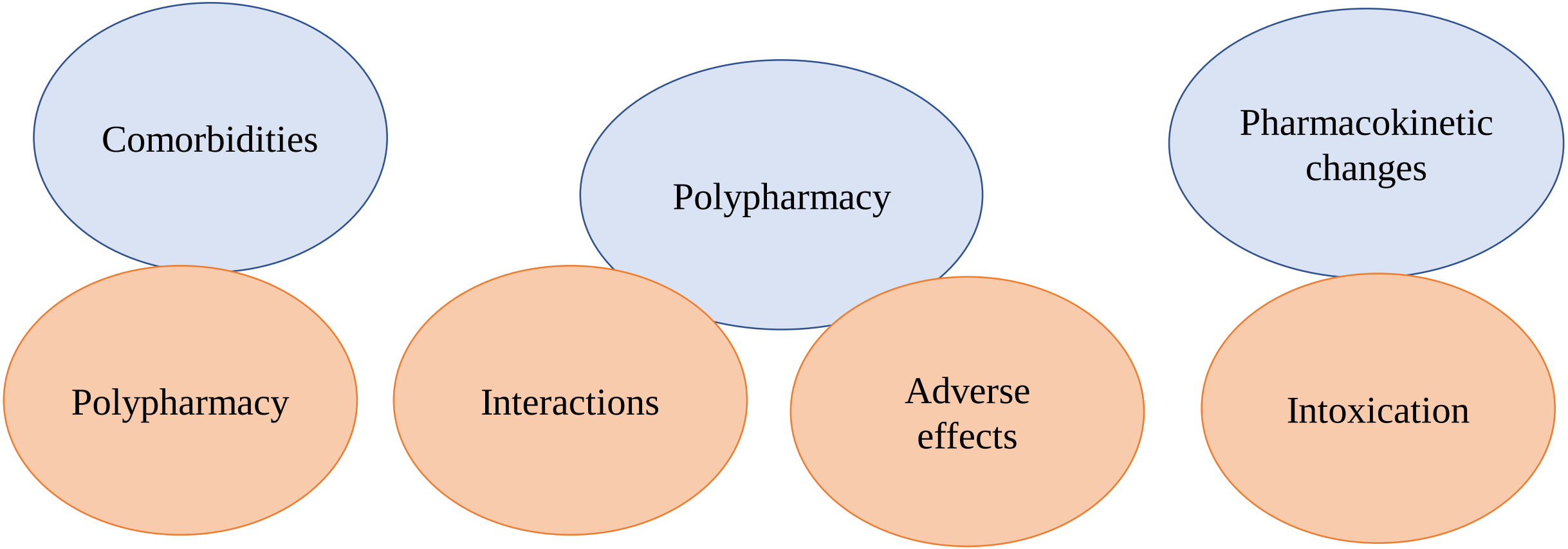
I have received consultancy fees and travel grants from Angelini Pharma, UCB and Eisai.

Outlines

- Introduction
- Comorbidities
- Polypharmacy
- Pharmacokinetic changes
- Drug choice
- Conclusion

Introduction

Considering that modern society is aging, the overall incidence and prevalence of epilepsy is expected to increase and epilepsy incidence is already highest in those older than 65 years.

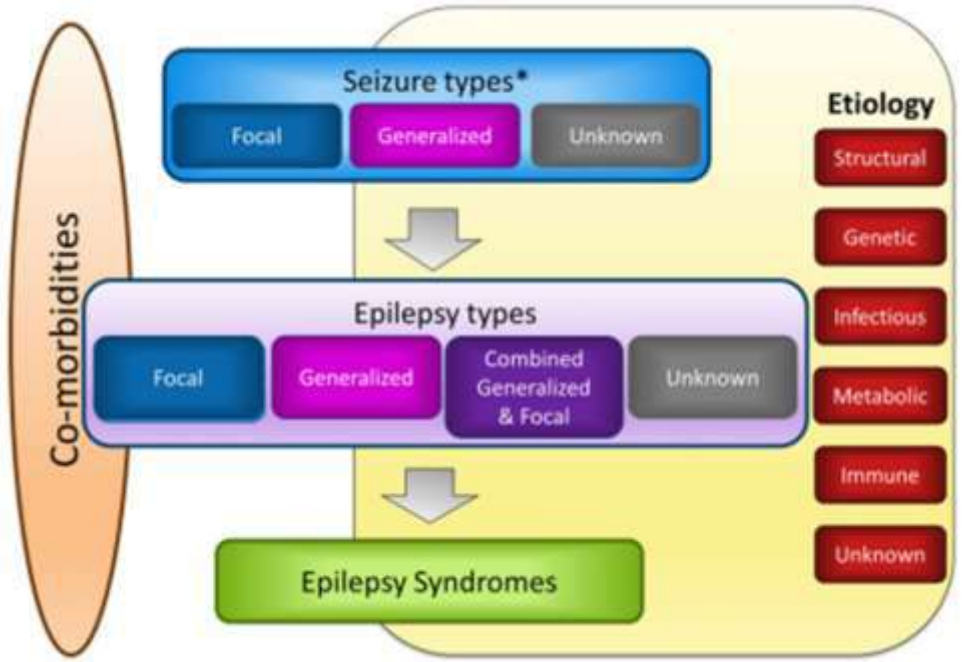


Lee SK, Journal of Epilepsy Research 2018; Sen A et al, Lancet 2020.

Comorbidities

Comorbidity: *any distinct additional clinical entity that existed during the clinical course of a patient's index disease* (A. Feinstein, 1970).

- ✓ In the context of epilepsy, comorbidities are a heterogenous group of conditions whose pathophysiology can be different in terms of relationship with the epilepsy itself.
- ✓ Comorbidities surely affect the quality of life of patients with epilepsy and seem to be connected with the outcome of the epilepsy itself.



Mula M., Expert Review of Neurotherapeutics, 2020; Scheffer I.E. et al, Epilepsia 2017.

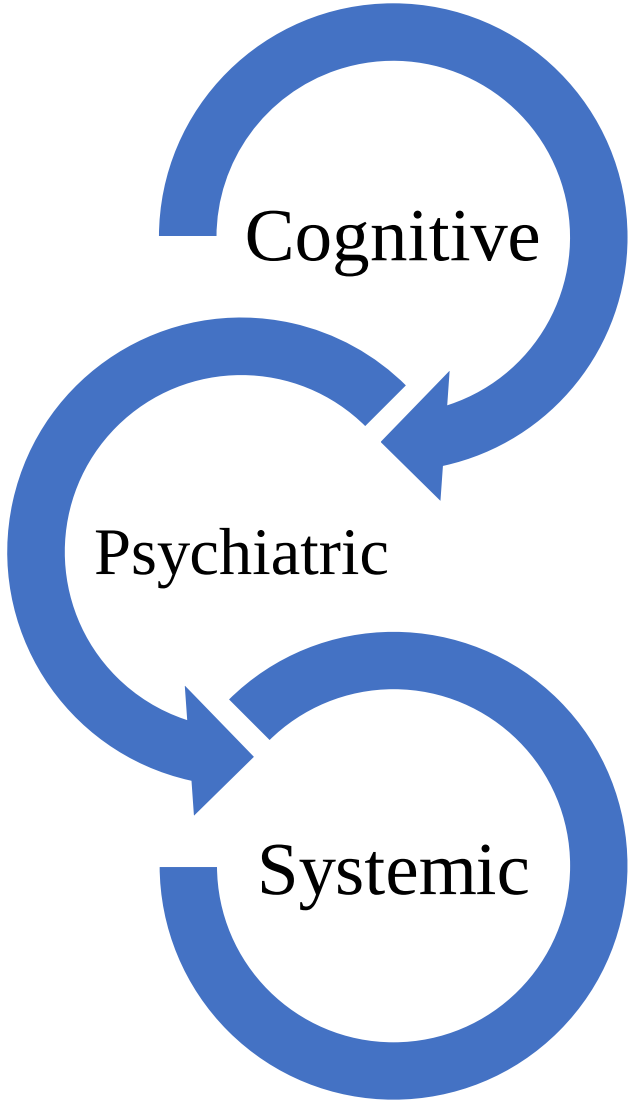
Table 1. Types of comorbidities of epilepsy.

	Type	Mechanism	Examples	Management
1.	Causative	One is the cause of the other	Stroke Traumatic brain injury CNS infections (e.g. neurocysticercosis, HIV) Multiple sclerosis Brain Tumors Heart diseases	Tailored treatment strategies; prevention of drug-drug interactions
2.	Reciprocal	One is associated with increased risk of developing the other and vice versa (complex multifactorial reasons) «bidirectional relationship»	Mood and anxiety disorders Psychosis ADHD Autism Spectrum Disorder Irritable bowel syndrome Headaches Psychogenic non-epileptic seizures Diabetes Suicide	Screening for early diagnosis and management
3.	Mutual	Shared risk factors or etiological mechanisms specific shared etiological factor	Tuberous sclerosis Cerebral palsy Autoimmune encephalitis Intellectual disabilities Anti-GAD antibody associated type 1 diabetes Dementia Headaches Heart diseases	Precision medicine and disease modifying agents
4.	Resultant	Caused by seizures and their treatments	Sexual dysfunction Obesity Osteoporosis Heart diseases Obstructive sleep apnea syndrome Type 2 diabetes	Screening and prevention strategies
5.	Coincidental	By chance	Any condition	Tailored treatment strategies; prevention of drug-drug interactions

HIV = Human immunodeficiency virus; ADHD = attention deficit hyperactivity disorder; CNS = Central nervous system; GAD = glutamic acid decarboxylase

Mula M., Expert Review of Neurotherapeutics, 2020.

Comorbidities



Sen A et al, Lancet 2020.

Comorbidities

Cognitive comorbidity: cognitive and psychological comorbidities and psychosocial difficulties are exacerbated in older people.

Objectives – Cognitive comorbidity at epilepsy onset reflects disease severity and provides a baseline estimate of reserve capacities with regard to the effects of epilepsy and its treatment. Given the high incidence of epilepsy at an older age, this study analyzed objective and subjective cognition as well as quality of life in elderly patients with new-onset focal epilepsy before initiation of anti-epileptic treatment. *Materials and methods* – A total of 257 untreated patients (60–95 years of age) with new-onset epilepsy underwent objective assessment of executive function (EpiTrack) and performed subjective ratings of cognition (Portland Neurotoxicity Scale) and quality of life (QoL; QOLIE-31). *Results* – According to age-corrected norms, 58% of patients (N = 257) demonstrated deficits in executive function; major determinants were cerebrovascular etiology, neurological comorbidity, and higher body mass index. Subjective ratings indicated deficits in up to 27% of patients. Self-perceived deficits were associated with neurological, cardiovascular, and/or psychiatric comorbidity, whereas poorer QoL was related to neurological comorbidity and female gender. Objectively assessed executive functions correlated with subjective social functioning, energy, motor function, and vigilance. *Conclusions* – We found a relatively high QoL, a low rate of subjective impairment, but a high incidence of objective executive deficits in untreated elderly patients with new-onset epilepsy. Neurological status and body mass index, rather than seizure frequency or severity, were risk factors for cognitive impairment. Given the relevance of cognition in the course of epilepsy and its treatment, routine screening before treatment initiation is highly recommended.

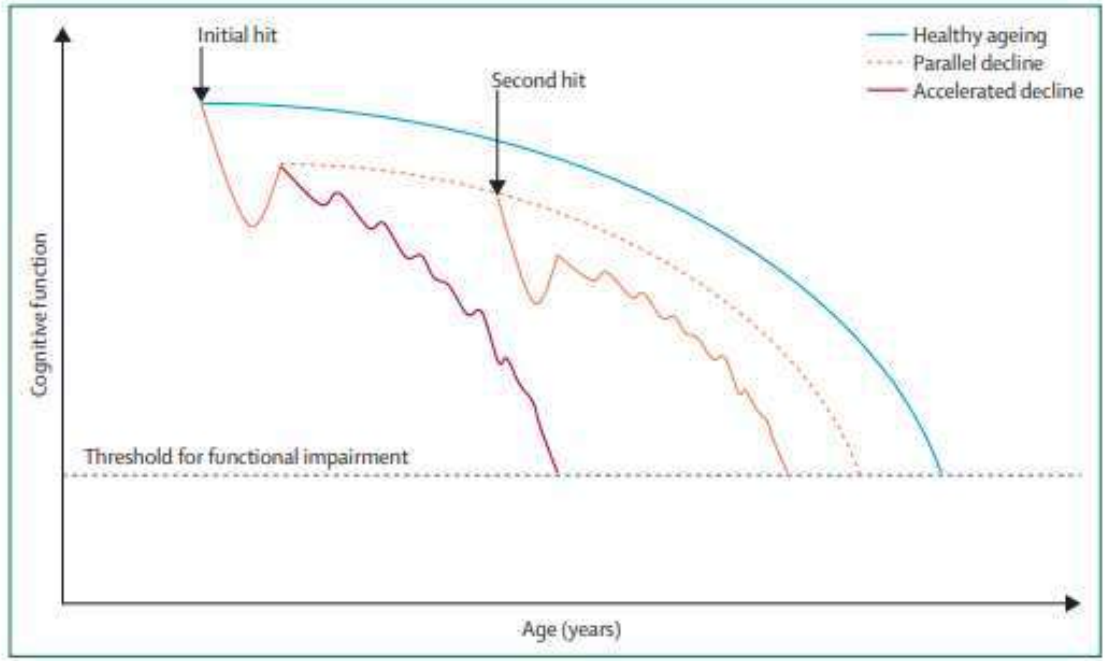


Figure 4: **Potential patterns of cognitive decline in people with epilepsy**

Witt J-A, et al, Acta Neurol Scand, 2014; Sen A et al, Lancet 2020.

Comorbidities

«vicious loop»

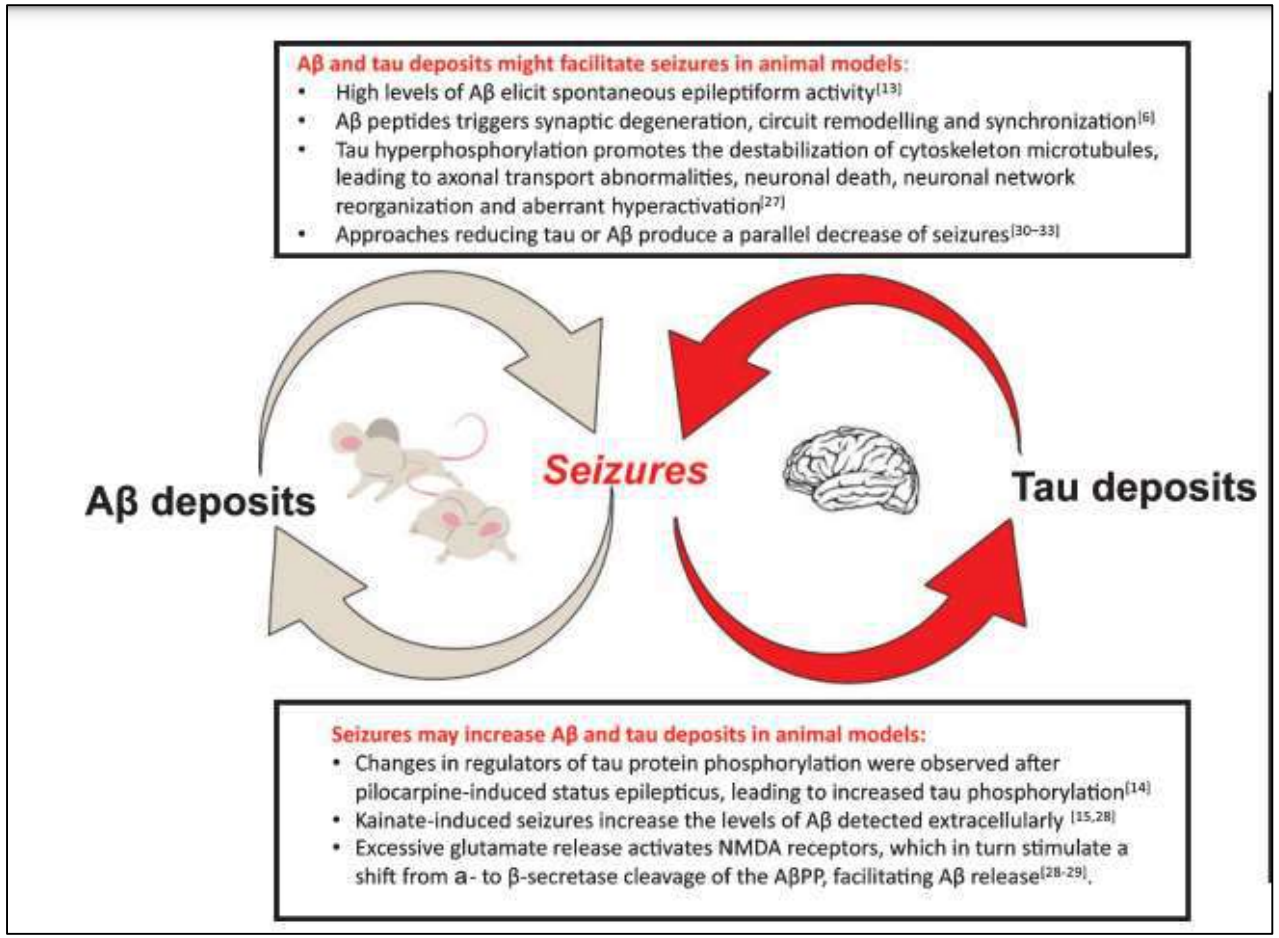
Bidirectional relationship between epilepsy and dementia:

1) People with epilepsy aged 50–75 years seem to have a higher risk of being diagnosed with dementia over the subsequent 8 years;

2) Patients with Alzheimer's disease and vascular dementia are also more likely to develop epilepsy.

10-22% AD patients → seizures

22-54% AD patients → EEG subclinical epileptiform activity.



Patients with AD and seizures or subclinical epileptiform activity experience a faster decrease in cognitive function.

Sen A et al, Lancet 2020; Tombini M et al, J Alzheimers Dis Rep. 2021.

Table 1. Demographic characteristics of a random sample of Medicare beneficiaries and of beneficiaries with epilepsy within the sample, 2005

	Characteristics of beneficiaries (%)				
	All	With epilepsy	Without epilepsy	p	Incidence per 1,000
N total beneficiaries	1,195,188	3,514	1,191,674		2.9
Gender (%)					
Female	58.9	57.3	58.9	0.046	2.9
Male	41.1	42.7	41.1		3.1
Age (%)					
65–74	45.0	33.7	45.1	<0.0001	2.2
75–84	39.3	46.2	39.3		3.5
85+	15.6	20.1	15.6		3.8
Race (%)					
White	88.5	82.9	88.5	<0.0001	2.8
Black	7.3	13.1	7.3		5.3
Hispanic	1.4	1.7	1.4		3.5
Asian	1.3	1.2	1.3		2.9
Other	1.4	a	1.4		2.5
Unknown	0.1	a	0.1		5.6
Comorbidities					
Elixhauser = 0	22.5	0.0	22.6	<0.0001	
1	18.8	2.4	18.8		4.0
2–3	31.6	14.8	31.7		1.4
4+	27.1	82.7	26.9		9.0
Charlson = 0	44.3	7.0	44.4	<0.0001	5.0
1	25.5	15.4	25.5		1.8
2–3	22.4	40.1	22.3		5.3
4+	7.8	37.4	7.7		14.1
Neurologic risks					
Cerebrovascular disease	12.3	64.3	12.2	<0.0001	15.4
Brain tumor	0.8	4.9	0.8	<0.0001	18.6
TBI	0.03	0.9	0.03	<0.0001	9.4
Metastatic cancer	1.4	5.5	1.4	<0.0001	11.6
Dementia	3.7	23.6	3.7	<0.0001	18.5
Psychiatric comorbidities					
Depression	7.4	22.0	7.3	<0.0001	8.8
Psychosis	1.8	15.7	1.7	<0.0001	26.1
Schizophrenia	0.4	2.5	0.4	<0.0001	17.0
Bipolar disorder	0.05	0.5	0.04	<0.0001	29.2
Adjustment disorder	0.9	3.0	0.9	<0.0001	9.6
PTSD	0.05	a	0.05	0.0001	11.2
Substance abuse	0.7	4.6	0.7	<0.0001	18.9

TBI, traumatic brain injury; PTSD, posttraumatic stress disorder; substance abuse includes drug and alcohol abuse.
[a]Cells smaller than 0.3% are omitted due to small numbers.

ilepsy and is associated with more days of

ealth care utilization and costs.

The incidence of epilepsy ranged from 8.8 per 1,000 to 29.2 per 1,000 among older adults with psychiatric comorbidities, higher than the incidence of 2.9 per 1,000 for the overall population and higher than the incidence among people with neurologic conditions (from 9.4 to 18.6 per 1,000).

Falcicchio 2022

Comorbidities

Systemic comorbidity: older people are more prone to multimodal health difficulties.

In a study by Ramsay et al., out of 593 old patients with new-onset epilepsy

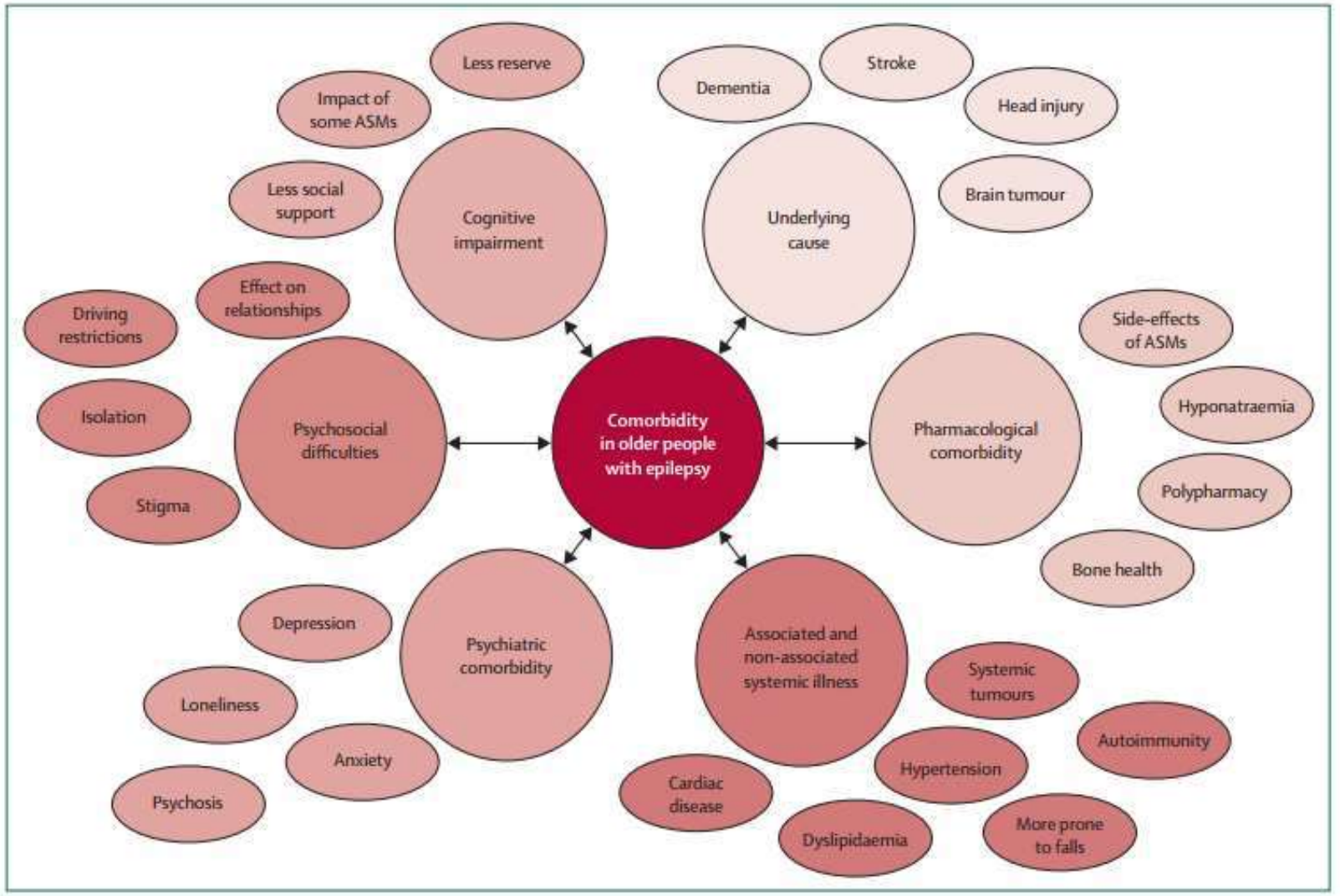
64% of them had hypertension, 50% have had previous stroke,

half of them had a cardiological disorder, 1/3 had diabetes and less than ¼ reported a history of neoplasm.

Increased cardiovascular risk factors → Increased risk of brain lesions causing epilepsy

Ramsay E et al, Neurology 2004; Suller Marti A et al, Neurologia (Engl Ed) 2019.

Polypharmacy



Sen A et al, Lancet 2020.

Polyph… DOACs

The induction of hepatic cytochrome P450 3…

efflux transporter protein …

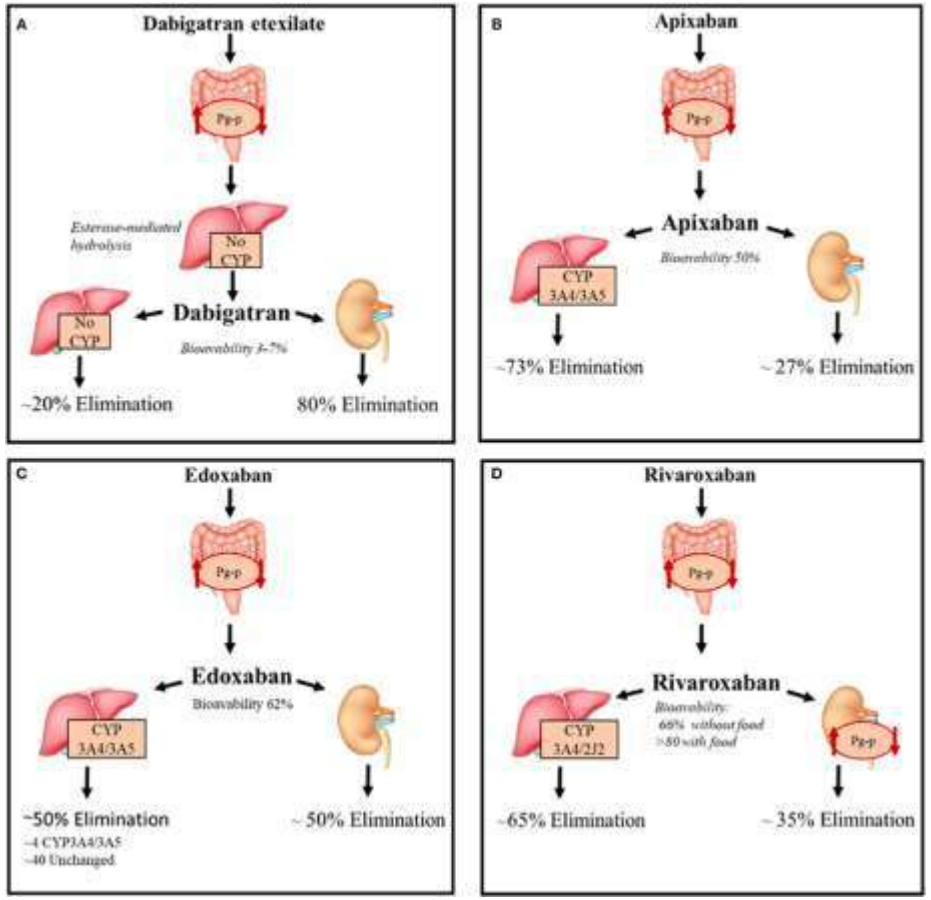


Table 7 Anticipated effects of common antiepileptic drugs on non-vitamin K antagonist oral anticoagulants plasma levels

	Via[426, 539-541]	Dabigatran etexilate	Apixaban	Edoxaban	Rivaroxaban
P-gp substrate		Yes	Yes	Yes	Yes
CYP3A4 substrate		No	Yes (≈25%)	No (<4%)	Yes (≈18%)
Drug					
Brivaracetam	–	No relevant interaction known/assumed			
Carbamazepine	Strong CYP3A4/P-gp induction; CYP3A4 competition	↓29%[541]	↓50% (SmPC)	SmPC	SmPC
Ethosuximide	CYP3A4 competition	No relevant interaction known/assumed			
Gabapentin	–	No relevant interaction known/assumed			
Lacosamide	–	No relevant interaction known/assumed			
Lamotrigine	P-gp competition	No relevant interaction known/assumed			
Levetiracetam	P-gp induction; P-gp competition				
Oxcarbazepine	CYP3A4 induction; P-gp competition				
Phenobarbital	Strong CYP3A4/possible P-gp induction		SmPC	SmPC	SmPC
Phenytoin	Strong CYP3A4/P-gp induction; P-gp competition	SmPC[543]	SmPC	SmPC	SmPC
Pregabalin	–	No relevant interaction known/assumed			
Topiramate	CYP3A4 induction; CYP3A4 competition				
Valproic acid	CYP3A4/P-gp induction/inhibition				Ref 544
Zonisamide	CYP3A4 competition; weak P-gp inhibition	No relevant interaction known/assumed (SmPC)			

Galgani A et al, Front Neurol 2018; Steffel J et Al, Europace 2021.

Polypharmacy- DOACs

- ✓ BRIVAFIRST is a retrospective study conducted across 62 Italian centers.
- ✓ March 2018–March 2020
- ✓ Included patients were receiving stable treatment with ≥1 ASMs during the prior 90 days.
- ✓ Only patients with focal epilepsy and with a 12-month follow-up after initiating BRV were included.

Drugs & Aging (2022) 39:297–304
https://doi.org/10.1007/s40266-022-00931-4

ORIGINAL RESEARCH ARTICLE

Adjunctive Brivaracetam in Older Patients with Focal Seizures: Evidence from the BRIVAracetam add-on First Italian netwoRk Study (BRIVAFIRST)

Simona Lattanzi[1] · Laura Canafoglia[2] · Maria Paola Canevini[3,4] · Sara Casciato[5] · Emanuele Cerulli Irelli[6] · Valentina Chiesa[3] · Filippo Dainese[7] · Giovanni De Maria[8] · Giuseppe Didato[9] · Giovanni Falcicchio[10] · Martina Fanella[6] · Edoardo Ferlazzo[11] · Massimo Gangitano[12] · Filippo Sean Giorgi[13,14] · Angela La Neve[10] · Oriano Mecarelli[6] · Elisa Montalenti[15] · Alessandra Morano[6] · Federico Piazza[16] · Patrizia Pulitano[6] · Pier Paolo Quarato[5] · Federica Ranzato[17] · Eleonora Rosati[18] · Laura Tassi[19] · Carlo Di Bonaventura[6] · BRIVAFIRST Group Membership

Results There were 1029 patients with focal epilepsy included in the study, of whom 111 (10.8%) were aged ≥65 years. The median daily dose of brivaracetam at 3 months was 100 [interquartile range, 100–175] mg in the older group and 100 [100–200] mg in the younger group ($p = 0.036$); it was 150 [100–200] mg in both groups either at 6 months ($p = 0.095$) or 12 months ($p = 0.140$). At 12 months, 49 (44.1%) older and 334 (36.4%) younger patients had a reduction in their baseline seizure frequency by at least 50% ($p = 0.110$), and the seizure freedom rates were 35/111 (31.5%) and 134/918 (14.6%) in older and younger groups, respectively ($p < 0.001$). During the 1-year study period, 20 (18.0%) patients in the older group and 245 (26.7%) patients in the younger group discontinued brivaracetam ($p = 0.048$). Treatment withdrawal because of insufficient efficacy was less common in older than younger patients [older: $n = 7$ (6.3%), younger: $n = 152$ (16.6%); $p = 0.005$]. Adverse events were reported by 24.2% of older patients and 30.8% of younger patients ($p = 0.185$); the most common adverse events were somnolence, nervousness and/or agitation, vertigo, and fatigue in both study groups.

Conclusions Adjunctive brivaracetam was efficacious, had good tolerability, and no new or unexpected safety signals emerged when used to treat older patients with uncontrolled focal seizures in clinical practice. Adjunctive brivaracetam can be a suitable therapeutic option in this special population.

Limitation of the study: unavailability of information about comorbidities and concomitant medications.

Polypharmacy – Antidepressants

- ✓ The use of tricyclic antidepressants is not advisable in subjects with epilepsy, especially the elderly due to adverse effects (from dry mouth or sedation to severe toxic reactions such as cardiac arrest or delirium).
- ✓ The selective serotonin receptor inhibitors (SSRIs) have a very low seizure potential. All of them inhibit some P-450 isoenzymes. Paroxetine and fluoxetine are potent inhibitors of CYP2D6, and fluvoxamine inhibits CYP1A2 and CYP2C19, and possibly CYP3A4 and CYP2D6.

	Daily dose (mg)	Half-life	Time to reach steady state	Findings in the elderly
Fluoxetine	20–80	1–4 days	>4 wk	Minimal differences
Fluvoxamine	50–300	15 h	10 days	Similar AUC and half-life
Paroxetine	20–50	20 h	7–14 days	Greater steady-state variability
Sertraline	50–150	26 h	5–7 days	Higher concentrations
Citalopram	10–60	36 h	6–10 days	Decreased clearance, prolonged half-life
Venlafaxine	75–375	5–11 h	1–3 days	24% increase in steady-state half-life; increased metabolite concentrations
Nefazodone	200–400	2–4 h	1 day	Larger AUC and longer half-life
Mirtazapine	15–45	20–40 h	5–10 days	Longer half-life

Zaccara G et al. Epilepsia 2002.

Polypharmacy – Antipsychotic drugs

- ✓ The use of conventional antipsychotics has often been limited by proconvulsive or adverse effects.
- ✓ Of particular concern in the elderly are anticholinergic reactions (dry mouth, constipation, confusion and hallucinations), extrapyramidal symptoms, cardiac conduction disturbances and cognitive slowing.

	Half-life (h)	Minimal time to steady state (days)	Starting dose (mg)
Clozapine	5–14	3	12.5
Risperidone	9–20	5	0.5
Active metab.	24	—	—
Olanzapine	30–75	5	2.5
Quetiapine	6.2	1	12.5

BETTER SAFER PROFILE!

Risperidone	Olanzapine	Quetiapine
Hepatic metabolism (CYP2D6)	Hepatic metabolism (CYP1A2; CYP2D6)	Hepatic metabolism (CYP3A4)
Renal excretion (active metabolite)	Renal excretion	Renal excretion (73%)
1/3 the dose used in younger patients	Its elimination half-life in elderly men is longer by 68%	↓ clearance (30-50%) in the elderly

Zaccara G et al. Epilepsia 2002.

Polypharmacy

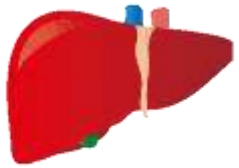
There is no standard cut point to the number of medications for the definition of polypharmacy.

Consequences of polypharmacy:

- ✓ The "burden" of taking multiple medications;
- ✓ Greater health care costs;
- ✓ Increased risk of adverse drug events;
- ✓ Drug-drug interactions (DDIs);
- ✓ Medication non-adherence;
- ✓ Reduced functional capacity;
- ✓ Multiple geriatric syndromes.

Maher Jr LR et al, Expert Opin Drug Saf. 2014.

Pharmacokinetic changes



✓ Reduced hepatic metabolic rate → lower start/total dose;
start slowly/increase slowly;
select ASM without or few hepatic metabolism.

✓ Reduced hepatic synthesis rate → screen and care for malnutrition;
select low/absent protein binding ASM.

✓ Reduced renal elimination rate → select ASMs without active renally excreted metabolites;
check for renal function;
encourage patients to drink fluids.

From 35° IEC ILAE Congress 2022.

Pharmacokinetic changes

Protein Binding	Liver	Kidneys	Heart
High (>60%)	**Problematic**	**Caution**	**Problematic**
Perampanel Benzodiazepines Phenytoin Valproic acid Carbamazepine Cenobamate	Valproic acid Carbamazepine Phenytoin Barbiturates BDZ (exc. Lorazepam!) Cenobamate	Pregabalin Gabapentin Levetiracetam Midazolam Topiramate Zonisamide	Phenytoin Lacosamide Carbamazepine
Low (<30%)	**Suitable**	**Suitable**	**Suitable**
Levetiracetam Gabapentin Pregabalin Lacosamide Topiramate Brivaracetam	Levetiracetam Gabapentin Pregabalin Topiramate Lacosamide Lamotrigine Brivaracetam Perampanel Oxcarbazepine	Valproic acid Oxcarbazepine Carbamazepine BDZ (exc. Midazolam) Lacosamide Brivaracetam Perampanel Lamotrigine	All other ASMs

From 35° IEC ILAE Congress 2022.

Drug choice

✓ Levetiracetam, lamotrigine and lacosamide are the ASMs of choice in older people with epilepsy.

✓ A significant decrease in prescriptions has been observed for carbamazepine.

✓ Valproate continues to be frequently prescribed among older adults.

✓ Newer ASMs, such as brivaracetam and perampanel, are being used with increasing frequency.

Hochbaum M et al, Epilepsy Behav. 2022.

Drug choice

Lamotrigine	**PROS:** does not make patients tired, mood drifting and drive enhancing (antidepressant). **CONS:** slow titration schedule, no emergency drug, action tremor, insomnia and allergic skin rush.
Lacosamide	**PROS:** fast onset of action, i.v. loading, high efficacy in focal epilepsies, no psychiatric adverse effects. **CONS:** sedation, conduction block.
Levetiracetam	**PROS:** fast onset of action, i.v. loading, no interactions. **CONS:** sedation, psychiatric adverse effects, behavioral changes.

NO COGNITIVE IMPAIRMENT!

From 35° IEC ILAE Congress 2022.

A

PIANO TERAPEUTICO AIFA PER LA PRIMA PRESCRIZIONE DI LACOSAMIDE NEL TRATTAMENTO DELLE CRISI AD ESORDIO PARZIALE CON O SENZA GENERALIZZAZIONE SECONDARIA IN ADULTI CON EPILESSIA.

Da compilarsi ai fini della rimborsabilità SSN a cura di specialisti neurologi.

Centro prescrittore _____

Medico prescrittore (cognome, nome) _____

Tel. _____ e-mail _____

Paziente (cognome, nome) _____

Data di nascita _____ sesso M ☐ F ☐ _____ peso (Kg) _____

Codice fiscale |_|_|_|_|_|_|_|_|_|_|_|_|_|_|_|_| Tel. _____

ASL di residenza _____ Regione _____ Prov. _____

Medico di Medicina Generale _____ recapito Tel. _____

Indicazione autorizzata nei pazienti adulti:

Lacosamide è indicato come monoterapia nel trattamento delle crisi ad esordio parziale con o senza generalizzazione secondaria in adulti con epilessia.

Lacosamide è indicato come terapia aggiuntiva:

- nel trattamento delle crisi ad esordio parziale con o senza generalizzazione secondaria in adulti con epilessia;
- nel trattamento delle crisi tonico-cloniche generalizzate primarie (PGTCS) in adulti con epilessia generalizzata idiopatica.

Indicazione rimborsata SSN nei pazienti adulti:

Lacosamide è indicato come monoterapia e come terapia aggiuntiva nel trattamento delle crisi ad esordio parziale con o senza generalizzazione secondaria in adulti con epilessia che hanno fallito* un precedente trattamento con levetiracetam o presentino controindicazioni all'uso di levetiracetam.

Condizioni cliniche e criteri di rimborsabilità

Il/la Paziente deve soddisfare tutte le condizioni sottostanti:
Al paziente è stata diagnosticata epilessia con crisi ad esordio parziale con o senza generalizzazione secondaria, e presenta tutte le seguenti condizioni:

1. Ha un'età uguale o superiore a 18 anni e presenta crisi ad esordio parziale con o senza generalizzazione secondaria.

2. Ha fallito un precedente trattamento con levetiracetam o presenta controindicazioni all'uso di levetiracetam.

*Specificare la causa di fallimento:
inefficacia primaria
inefficacia secondaria (perdita di efficacia)
comparsa di eventi avversi _____ specificare
altro _____

Peculiari **acosamide** sciroppo

roved.

Uso di anticoagulante orale
Comorbidità psichiatrica
Insufficienza renale

Drug choice

Requirements in elderly people with epilepsy:

1. Therapy simplification : monotherapy; ASMs with simple kinetics;
2. Caution : - *«start slow, go slow»;*

- attention to adverse effects and possible DDIs;

- avoid repercussion on cognitive performances.

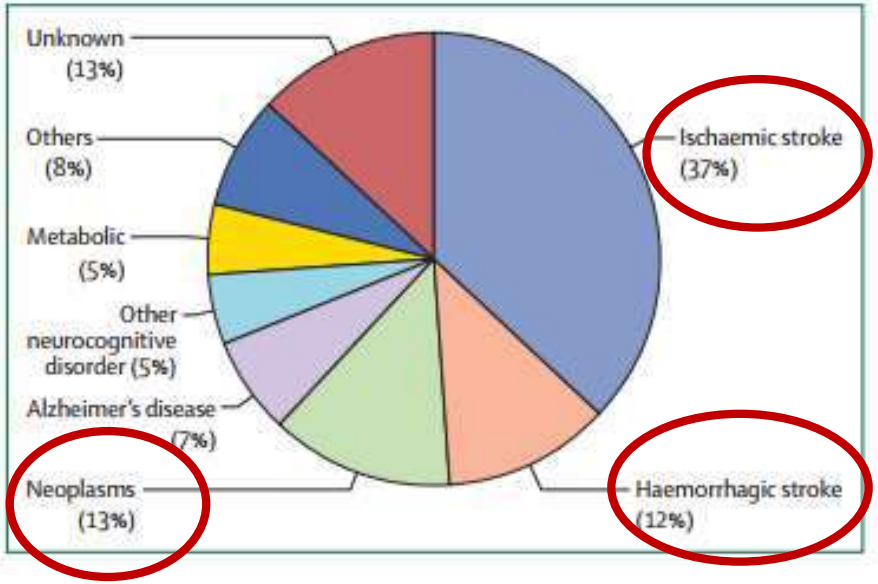
3. Adherence improvement : small pills; once/twice daily dosing.

Main goals:
Tolerability and efficacy

From 35° IEC ILAE Congress 2022.; Striano S et al, Clinical Geriatrics 2020.

Conclusions

- ✓ Observational studies suggest that treatment is more effective in older adults with new onset epilepsy compared with younger adults.
- ✓ Seizure frequency is much lower suggesting that seizures are easier to treat in older people.
- ✓ In older people the initial dose and rate of titration of antiseizure medications is half that used in younger individuals, which aids with tolerability.



Sen A et al, Lancet 2020; Bagshaw J et al, Seizure 2009; Piccenna L et al, Epilepsia 2022.