2023 GW Epilepsy Board Review & Best Practices

Principles of Management of Epilepsy

Yamane A. Makke, MD

Assistant Professor of Neurology

The GW Epilepsy Center

Disclosures

- None

Outline

1- First seizure, evaluation and management

2- The choice of ASM

3- Pharmacokinetics

4- Drug interactions

5- ASM discontinuation

6- Pharmaco-resistant epilepsy

7- Generics

8- Special populations:

- Elderly
- Pregnancy

First seizure

First seizure

- 8-10% of the population will experience a seizure

- 1 in 26 will develop epilepsy

- Accurate diagnosis:
- *Provoked vs unprovoked*
- *Epileptic vs nonepileptic*

First seizure
Epileptic vs nonepileptic

History & event semiology

First seizure
Epileptic vs nonepileptic

- Aura, ictal and postictal states (aura, event and post-event) description

- Patient and witnesses

- Misdiagnosis rates 4.6%-30%:
- Adults: 19.3% (non-specialists) vs 5.6% (neurologists)
  - Final diagnosis cardiogenic syncope and PNEE
- Pediatrics: 24% -39% of children referred for 1st seizure were found to have non-epileptic events.
  - Final diagnosis: staring, PNEE, syncope, parasomnia and breath-holding spells

- Fisher et al, Epilepsia 2005
- Fisher et al, Epilepsia 2014
- Chowdhury et al, Eur J Neurol 2008
- Leach et al, Seizure 2005
- Udall et al, Arch Dis Child 2004

First seizure
Epileptic vs nonepileptic

List of mimickers and their clinical features

Epilepsy mimic	Clinical clues
Neonates/early infancy	
Benign sleep myoclonus	Myoclonus of one or more limbs or face, occurring in brief clusters lasting <3-5 seconds with pauses of variable duration
	Occurs in sleep only and abolished on waking
	Otherwise normal infant
Jitteriness	Affects one or more limbs, often switching sides from event to event
	Often spreads in nonanatomic pattern
	Increased when the infant is stimulated, startled, or crying but is suppressed when the infant is wrapped or the affected limb is gently restrained
Infants/early childhood	
Benign myoclonus of infancy	Brief jerking of one or more limbs, lasting <5 seconds each, without altered awareness
	Occurs in both wakefulness and sleep
	Otherwise normal infant
Shuddering attacks	Brief stiffening with shivering-like movement, without altered awareness
	Often provoked by excitement or frustration
	Otherwise normal infant
Breath-holding spells, cyanotic or pallid	Triggered by pain, crying, fright
	Child usually cries (crying may be absent with pallid breath-holding), holds their breath at the end of expiration, then becomes briefly tonic
	Associated color change (cyanotic or pallid)
Sandifer syndrome	Back-arching, dystonic posturing of the limbs, and turning/tilting of the head
	May be provoked by feeding and lying flat and may be alleviated with sitting up
	Often seen in neurologically abnormal children
	Caused by gastroesophageal reflux
Spasmus nutans	Rapid eye movements, with head-tilt and nodding, but with retained awareness
Hyperekplexia	Infants are hypertonic but not spastic
	Excessive startle is seen with noise or touch, with flexion of limbs and neck retraction; this at times can be associated with apnea and cyanosis

Epilepsy mimic	Clinical clues
Childhood	
Stereotypies	Mannerisms that may be simple (such as body-rocking, head-banging) or complex (such as finger movements or wrist flexion/extension); these are interrupted by tactile, and at times verbal, stimulation May occur in normal individuals but are seen more commonly in those with autism or intellectual disability
Self-stimulatory behavior	Rhythmic hip flexion and adduction with leg-crossing, often accompanied by a distant expression Can be interrupted, although child may be irritable if interrupted
Benign paroxysmal vertigo	Abrupt onset of anxiety, feeling off balance; child often grasps onto parent May have associated nystagmus
Cyclic vomiting	Paroxysmal events of recurrent emesis that may last hours and be interspersed with symptom-free periods of weeks to months
Daydreaming	Staring off, more likely to occur when engaged in quiet activity such as schoolwork Can be interrupted with tactile stimulation
Parasomnias	Night terrors, sleepwalking, and confusional arousals are behaviors that arise out of deep non-rapid eye movement (REM) sleep most commonly in the first few hours after falling asleep; they typically last >3-5 minutes and occur intermittently These must be distinguished from nocturnal frontal lobe seizures, which are brief (typically <2 minutes), very frequent (multiple per night), and occur throughout the night
Sleep-related rhythmic movement disorders	Body-rocking, rolling, or head-banging during sleep that resolve when the child awakens
Childhood to adulthood	
Tantrums/rage attacks	Tantrums are primarily seen in young children and involve relatively brief periods of behavioral dyscontrol in response to a stimulus; consciousness is not impaired Rage reactions occur predominantly in older children and teens and, although triggered by minor stimuli, are characteristically out of proportion; patients are often aggressive during these periods, which can last for ≥30 minutes
Tics	Involuntary, sudden, rapid, repetitive, nonrhythmic, simple, or complex movements or vocalizations that often occur multiple times per day These are interruptible and can be suppressed, albeit often for only a matter of seconds Tics abate during sleep
REM sleep disorders	Abnormal motor activity typically in the later third of sleep when the individual acts out their dreams The individual can recall the event The events are not as stereotypic as seizures

Epilepsy mimic	Clinical clues
Periodic leg movements in sleep	Repetitive stereotyped flexion of toes, ankles, knees, and hips Resolve with waking
Postural orthostatic tachycardia syndrome (POTS) or orthostatic intolerance	Episodic periods of lightheadedness, chest pain, blurred vision, abdominal pain Comes on with standing and resolves with sitting/lying down
Panic attacks	Brief episodes, lasting minutes only with sudden feeling of impending doom, accompanied by shortness of breath, choking sensation, palpitations, chest pain, paresthesia, dizziness, sweating, trembling, and feeling faint Patient is very frightened but aware No postictal sleepiness/confusion
Narcolepsy/cataplexy	Excessive daytime sleepiness, cataplexy (loss of tone in response to strong emotion), hypnagogic hallucinations, and sleep paralysis
Migraine with aura	Most common aura is visual, typically in one visual field, and is characteristically a scintillating scotoma, which is then followed by a migraine headache Visual phenomena with occipital seizures are more commonly colored and of various shapes
Hemiplegic migraine	Aura of focal weakness with or without speech disturbance; visual symptom and paresthesia onset before typical migrainelike headache Often family history is positive
Psychogenic nonepileptic spells	Two main symptomatologies: (1) unresponsive periods without motor phenomena or (2) motor phenomena with bizarre, irregular jerking and thrashing Often prolonged >15-30 minutes Often minimal postictal phase Frequent and refractory from onset
Paroxysmal kinesiogenic dyskinesia	Brief (<1 minute) attacks of abnormal movement, triggered by a sudden voluntary movement The movements are most commonly dystonic but may be choreiform Affects limbs on one or both sides No altered awareness Family history may be present
Episodic ataxia	Autosomal dominant Brief episodes of cerebellar ataxia triggered by sudden movement, emotion, or illness May have associated dysarthria, nystagmus, titubation, and nausea

Epilepsy mimic	Clinical clues
Adults	
Transient ischemic attacks	Sudden onset of focal neurologic symptoms that typically reflect loss of function (ie, paresis, speech problems, etc), which then resolve completely within 24 hours, and usually within 30-60 minutes Seizures more commonly present with positive symptoms due to an excess of neuronal discharge (visual: flashing lights, zigzag shapes, lines, shapes, objects; somatosensory: pain, paresthesia, or motor features, eg, clonic activity); transient ischemic attacks most commonly involve loss or reduction of neuronal function (eg, loss of vision, hearing, sensation, or limb power)
Any age	
Vasovagal syncope	Typically triggered by prolonged standing, dehydration, change in posture, warm environment, or emotional upset (ie, blood draw) Preceded by lightheadedness, blurred vision, ringing in the ears, pallor, diaphoresis, abdominal discomfort Loss of tone, which may be followed by brief myoclonic jerks or tonic posturing Rapid return to awareness but lightheadedness may remain for a brief period thereafter
Cardiac syncope-long QT	Sudden loss of consciousness with pallor, atonia, or tonic posturing Often triggered by fright, exercise, surprise, and immersion in water Family history of syncope may be present
Neurogenic syncope (Chiari malformation, colloid cyst of the third ventricle)	Headache and sensory symptoms associated with collapse Exacerbated by straining

First seizure
Provoked vs unprovoked

- Provoked seizures:
- Toxins
- Drugs
- Metabolic
- Most have prolonged confusion/behavior change before and after the seizure
- Typically, are generalized convulsive

First seizure
Provoked seizure, examples

- Alcohol withdrawal
- Barbiturate or benzodiazepine withdrawal
- Metabolic (eg, hyponatremia, hypocalcemia, hypoglycemia, hyperglycemia)
- Drugs of abuse (eg, cocaine, amphetamines, phencyclidine)
- Medications (eg, tramadol, imipenem, theophylline, bupropion)

First seizure
Provoked seizure, examples

Category	Mechanism	Other clinical findings	Examples
Increased excitation or withdrawal of central nervous system (CNS) depressants			
γ-Aminobutyric acid (GABA) antagonists	Blockage of GABA-ergic neurons or abrupt withdrawal of CNS depressants	Tremor, tachycardia, hypertension, diaphoresis, nausea, anxiety, irritability, insomnia, hallucinations	Tramadol
			Antibiotics: isoniazid (depletes pyridoxine, which inhibits GABA synthesis from glutamate), penicillin, cephalosporins, carbapenems, fluoroquinolones
			Abrupt withdrawal of GABA-ergic agents such as alcohol, benzodiazepines, baclofen, barbiturates
			Antidepressants and antipsychotics including tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), phenothiazines
Decreased CNS inhibition			
Histamine antagonists	Antagonism at histamine receptors	Confusion, ataxia, hallucinations, delirium, dry mucous membranes, mydriasis	Histamine antagonists including diphenhydramine, doxylamine, hydroxyzine, chlorpheniramine
Adenosine antagonists	Antagonism of adenosine	Cardiac dysrhythmias	Theophylline, caffeine

ECG = electrocardiogram.

Mechanisms by which toxins lead to provoked seizures

- Increased excitation
- Decreased inhibition
- Withdrawal of central nervous system depressants

Do not treat provoked seizures with ASMs

First seizure
Acute vs remote symptomatic

- Within 7 days of stroke/TBI/active CNS infection → Acute symptomatic
- >7 days → Remote symptomatic
- Acute symptomatic, 80% less chances of recurrence

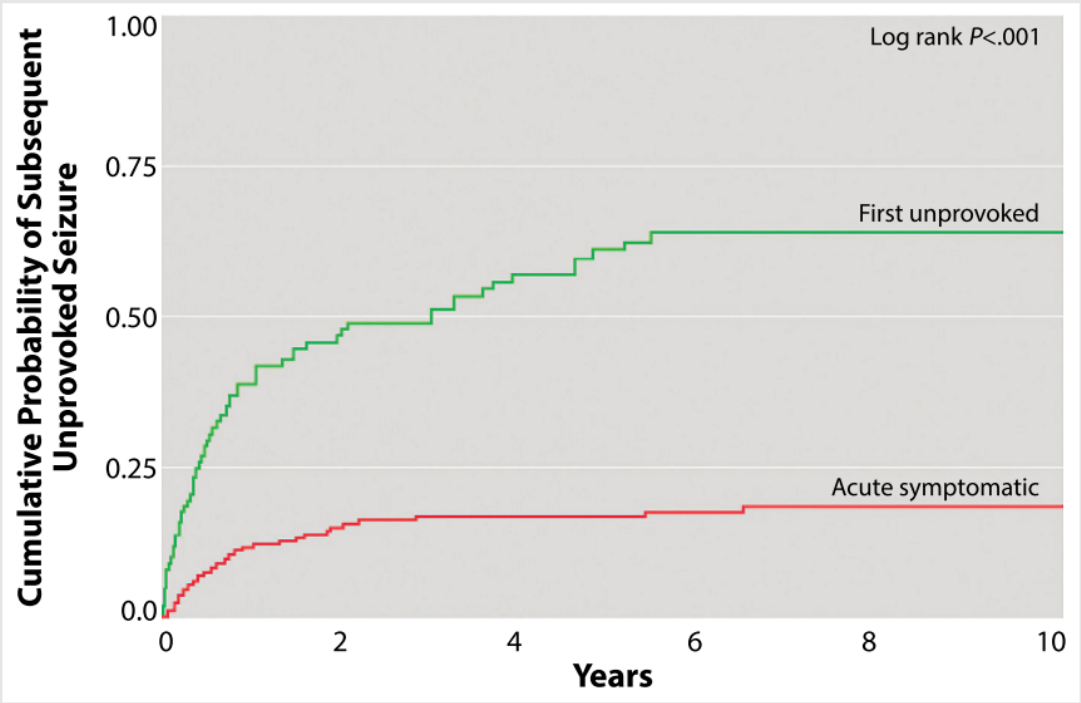


FIGURE 2-2 Risk of subsequent seizure over 10 years after acute symptomatic seizure during acute illness (eg, stroke, central nervous system infection, traumatic brain injury) compared with risk of subsequent seizure in patients with remote symptomatic unprovoked seizure (ie, previous stroke, central nervous system infection, traumatic brain injury).

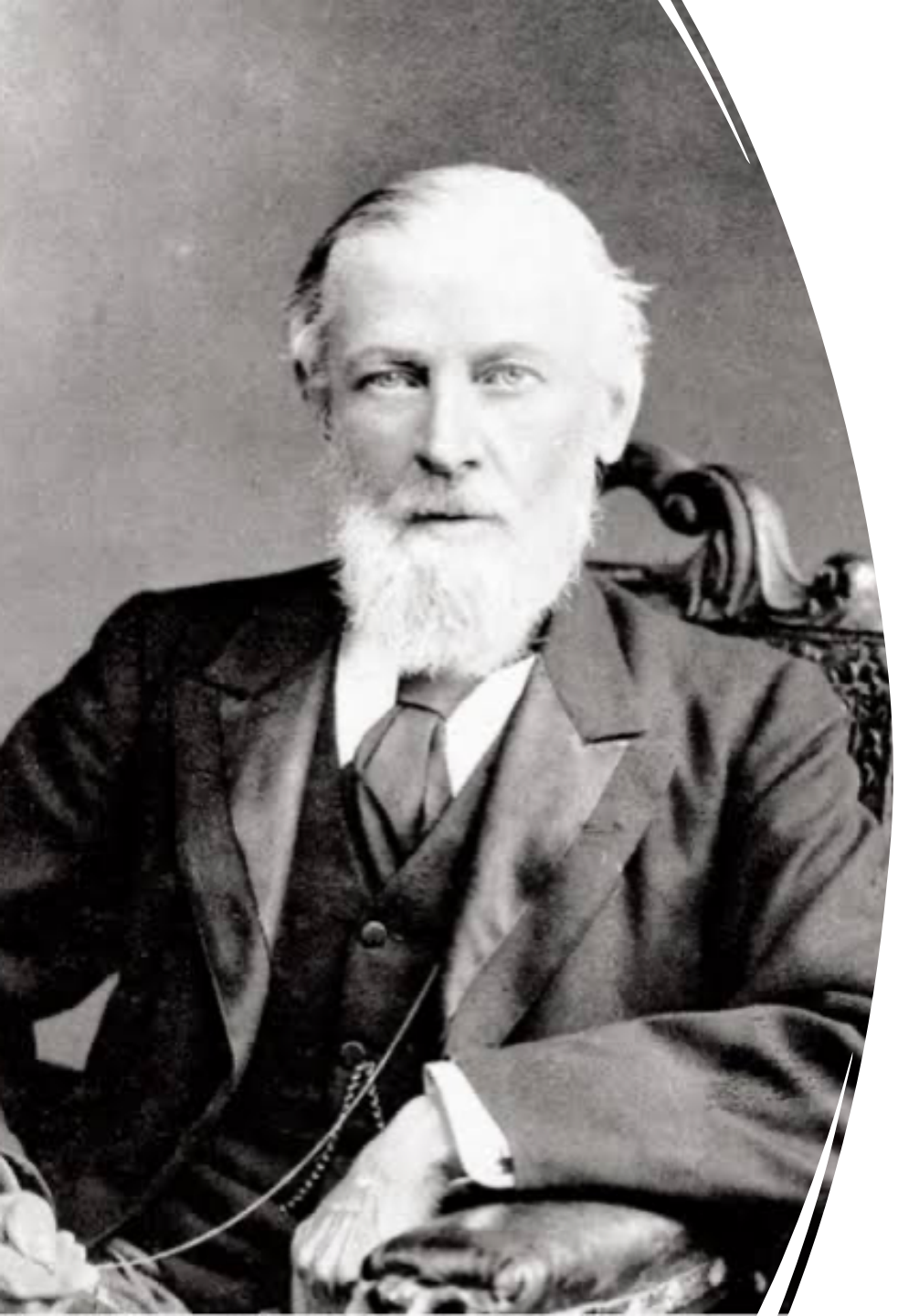
First seizure
Acute vs remote symptomatic

	Acute (%)	Remote (%)
Stroke	33	71.5
TBI	13.4	46.6
CNS Infection	16.63	63.5

Acute: within one week, remote: after one week

Risk of seizure recurrence after first symptomatic seizure (Hesdorffer et al.)

First unprovoked seizure
Assessing the risk of recurrence



"Each attack facilitates the occurrence of another by increasing the instability of the nerve elements"

"Seizures beget seizures"

Is this true?

Gowers, 1881

First unprovoked seizure
Single vs multiple within 24 hours

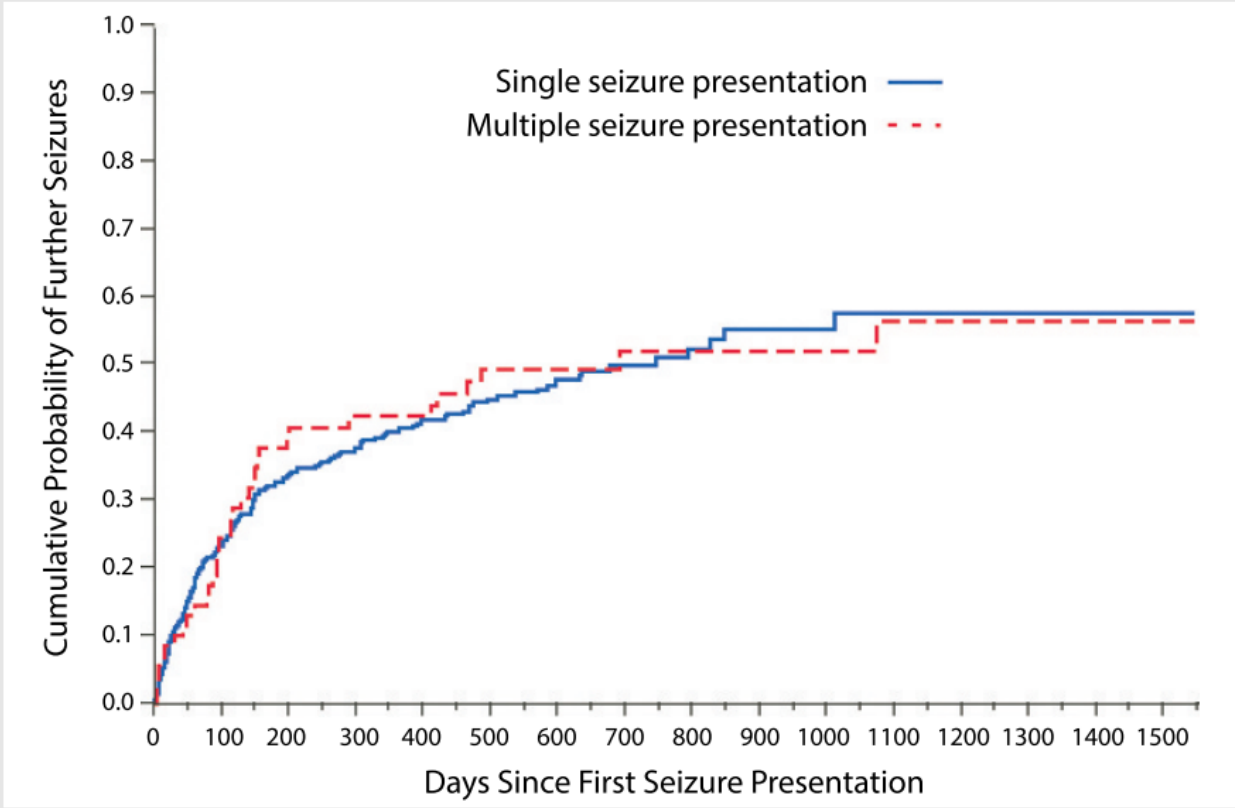
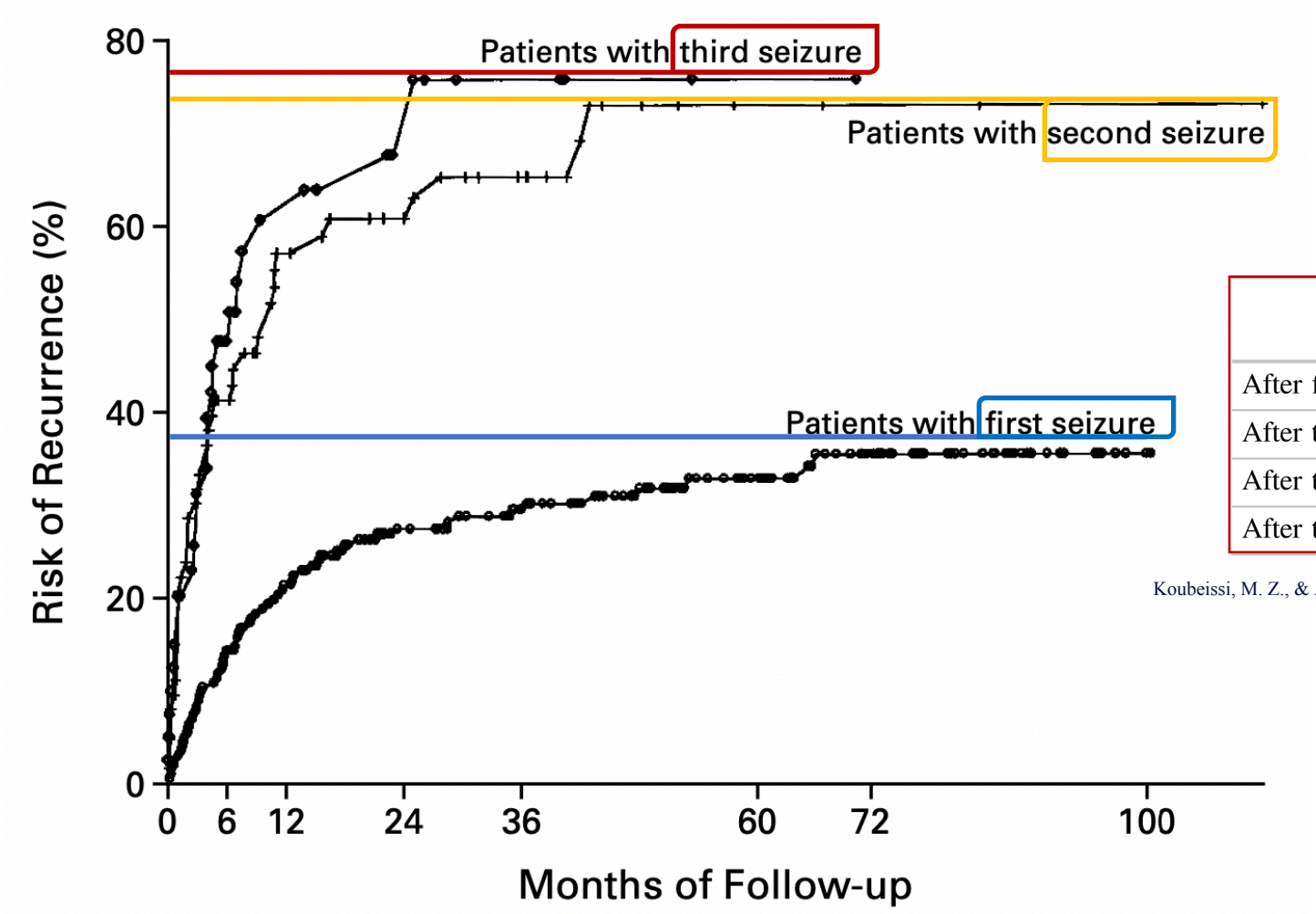


FIGURE 2-1 Data showing no difference in cumulative chance of seizure recurrence whether patients presented with a single seizure (n = 425) or multiple seizures (n = 72).

First unprovoked seizure

Assessing the risk of recurrence (2 years or more)



	Recurrence rate (%)
After first unprovoked seizure	40
After two unprovoked seizures	73
After three unprovoked seizures	76
After treating first unprovoked seizure	15

Koubeissi, M. Z., & Azar, N. J. (2017). *Epilepsy Board Review: A Comprehensive Guide*. Springer.

Hauser et.al 1998

First unprovoked seizure
Assessing the risk of recurrence

		Seizure rate	
		Untreated (%)	Treated (%)
Italian FIRST study 1993 (n = 397)	**6 months**	**41**	**17**
	24 months	**51**	**25**
UK MESS study 2005 (n = 1443)	**6 months**	**26**	**18**
	24 months	**39**	**32**

Koubeissi, M. Z., & Azar, N. J. (2017). *Epilepsy Board Review: A Comprehensive Guide*. Springer.

First unprovoked seizure
Assessing the risk of recurrence

- 80% of seizure recurrence occurs within 2 years

- 50% of recurrence occurs within 6 months

Berg AT. Neurology 1991;41:965-72

First unprovoked seizure
Evaluation

- Level B evidence for EEG and brain imaging (MRI)
- MRI > CT
- Abnormal MRI in 15 % (with 1.5 T study, Hakami et al) vs 23% (3 T)
- Abnormal initial routine EEG in 51 % (additional 35 % on the 2nd sleep-deprived EEG)

First unprovoked seizure
Evaluation-EEG findings and risk of recurrence

Etiology	Risk of recurrence
Idiopathic	32%
Symptomatic	57%

EEG	Risk of recurrence
Normal	27%
Epileptiform	58%

Etiology	EEG	Risk of recurrence
Idiopathic	Normal	24%
Symptomatic	Abnormal	65%

Koubeissi, M. Z., & Azar, N. J. (2017). *Epilepsy Board Review: A Comprehensive Guide*. Springer.

First unprovoked seizure
Assessing the risk of recurrence

- **Factors associated with an increased risk of recurrence:**

- Prior brain lesion or insult (remote symptomatic)

- Epileptiform EEG abnormality

- Significant brain-imaging abnormality

- Nocturnal seizure

Krumholz A, et al, Neurology 2015

First unprovoked seizure
Treatment

- Highest risk of recurrence in the first 1-2 years (21%–45%-Level A)

- If single unprovoked seizure with normal work-up→ wait for a second seizure

- Patients at increased risk of having seizure recurrence (>60% in the next 10 years)→ start ASM

First unprovoked seizure
Treatment

Finding	Level of evidence for increased risk of recurrence
Prior brain insult (stroke/trauma etc)	Level A
EEG with epileptiform activity	Level A
Significant brain-imaging abnormality	Level B
Nocturnal seizure	Level B

Krumholz A,Neurology 2015;84:1705-13

First unprovoked seizure
Treatment

- Although immediate ASM initiation (compared to waiting for 2nd)→ likely to reduce the risk of recurrence (Level B)→may not improve QOL (Level C)

- Over the longer term (3 years), immediate ASM treatment is unlikely to improve the prognosis for sustained seizure remission (Level B)

- Risk for ASM AEs (mild and reversible) is 7% to 31% (Level B)

Krumholz A,Neurology 2015;84:1705-13

Pharmaco-resistant epilepsy
Remission rates with therapy

Epilepsy Type	Remission rate
IGE (GGE)	66%
Focal epilepsy	57%

Focal epilepsy etiology	Remission rate
CVA	70 %
Cortical dysplasia	60%
MTS	52%
TBI	35%

Brodie MJ. Epilepsia 2012;54 (Suppl 2):S5-8.

The choice of ASM

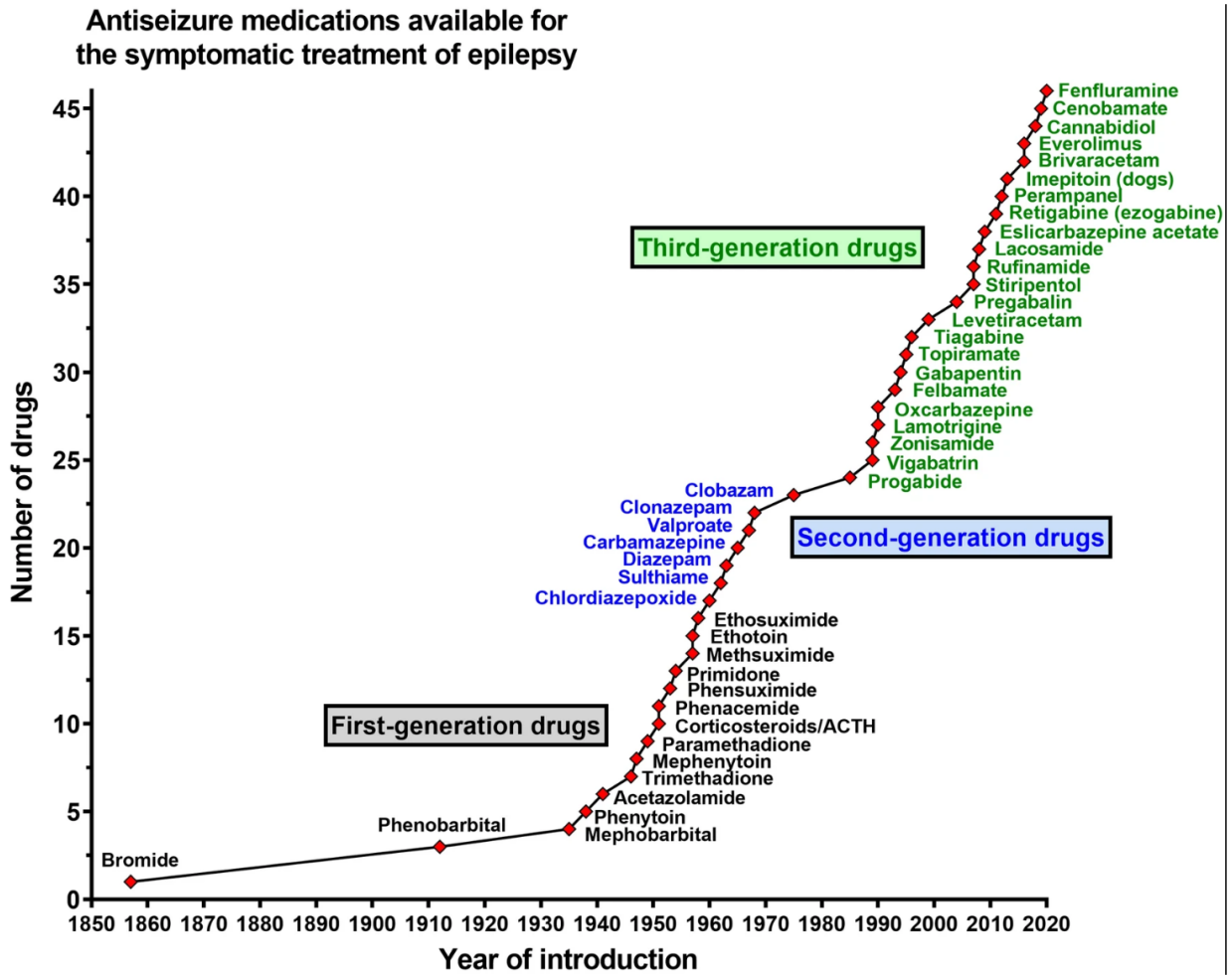
The choice of ASM
Treatment goals

- Seizure freedom
- Least side effects
- Monotherapy
- Easy regimen

The choice of ASM
Treatment goals

- Always, one ASM upon initiating therapy
- Choice should be with the least potential side effects
- Improve adherence (QD vs BID)
- Increase dose until seizure free or side effect emergence

The choice of ASM
ASM evolution



Modified from Löscher and Schmidt [11]. For further details, see Löscher et al. [30]. *ACTH* adrenocorticotropic hormone

Many options! How to select ASMs?

The choice of ASM
Selection criteria

- Seizure type/classification
- Epilepsy syndrome
- Established drug efficacy for a particular seizure type or epilepsy syndrome
- Safety
- Tolerability profile
- Co-morbidities (weight, cognition, psychiatric, other)
- Side-effect profile
- Metabolic status (renal, hepatic)
- Drug-drug interactions
- Drug formulations
- Ease of administration/titration
- Pregnancy or contraception
- Prior allergies and cross reactivity
- Cost
- Availability

Koubeissi, M. Z., & Azar, N. J. (2017). *Epilepsy Board Review: A Comprehensive Guide*. Springer.

The choice of ASM
Epilepsy type

Broad spectrum AEDs	Narrow spectrum AEDs
Valproate	Phenytoin*
Felbamate	Ezogabine*
Phenobarbital#	Perampanel*
Lamotrigine	Lacosamide*
Topiramate	Carbamazepine~
Zonisamide	Gabapentin~
Levetiracetam	Pregabalin~
Benzodiazepines	Tiagabine~
Primidone	Oxcarbazepine~
	Vigabatrin@
	Rufinamide
	Ethosuximide

Rufinamide is minimally effective against focal seizures, Ethosuximide is only approved for absence seizures, * = Spectrum not yet fully identified or mixed, ~ = May exacerbate some generalized seizures such as myoclonus and absence, @ = Considered narrow spectrum but exceptionally useful in infantile spasms, # = May trigger absence seizures or worsen Lennox-Gastaut syndrome or myoclonic epilepsies

- *Avoid in Dravet*
- *May worsen myoclonus*

Could be mixed spectrum

May exacerbate Myoclonic/Absence and other generalized seizures

Absence seizures

Koubeissi, M. Z., & Azar, N. J. (2017). *Epilepsy Board Review: A Comprehensive Guide*. Springer.

The choice of ASM
Epilepsy type

Indication	Try	Avoid
Seizure type		
Focal or secondary generalized	LTG, LEV, OXC, LCM, TPM > CBZ, > VPA, ESL, PHT	
Primary Generalized (GTC)	VPA, LEV, LTG, TPM, ZNS	
Primary Generalized (Absence)	ESX, VPA > LTG	PHT, CBZ, GBP, TGB, VGB
Primary Generalized (Myoclonic)	LEV, VPA, CLZ	PHT, CBZ, GBP, TGB, VGB, PGB
Rolandic (centrotemporal)	LEV, OXC	
Other factors		
Young women	LTG, LEV, LCM	VPA > > CBZ, PHT
Depression	LTG	PHT, PHB, PRM,
Labile, impulsive	VPA, CBZ, LTG, OXC, TPM	LEV
Liver disease	LEV, LTG, PGB	VPA, PHT, CBZ
Obesity	TPM, ZNS	VPA, GPN, PGB
Pain	GBP, PGB, CBZ, OXC	
Headache	TPM, VPA, GBP, PGB	
Type A personality (baseline irritability)		LEV
Polytherapy (non AEDs)	LEV, PGB, GBP	Enzyme Inducers
Asian (Han Chinese or Taiwanese)		CBZ, OXC (if have to use **check HLA-b 1502**)

SJS/TEN

Antiseizure drug/ seizure type	Focal seizures	GTCS	Absence	Myoclonic	Lennox–Gastaut syndrome	Infantile spasm	Dravet's syndrome
Brivaracetam	+	+		+			
Cannabidiol					+	+[a]	+
Carbamazepine	+	+	–	–			–
Cenobamate	+						
Clobazam	+	+			+		+[e]
Clonazepam			+	+		+	
Eslicarbazepine	+		–	–			
Ethosuximide			+				
Felbamate	+[b]				+		
Fenfluramine							+
Gabapentin	+	?+	–	–			–
Lacosamide	+	?+					
Lamotrigine	+	+	+	?+[c]	+		
Levetiracetam	+	+	?+	+			
Oxcarbazepine	+	+	–	–			–
Perampanel	+	+					
Phenobarbital	+	+	–	?+			
Phenytoin	+	+	–	–			–
Pregabalin	+			–			
Primidone	+	+	–				
Retigabine[g]	+						
Rufinamide	+				+		
Stiripentol							+[f]
Tiagabine	+		–	–			
Topiramate	+	+		+	+	+	+[e]
Valproate	+	+	+	+[d]	+	+	+[e]
Vigabatrin	+	?+	–	–		+[a]	
Zonisamide	+	+	?+	+		+	

Note that although there is evidence to support the use of these drugs for these seizure types, the drugs may not be indicated for this use by the US Food and Drug Administration.

+Effective;?+ possibly effective; – worsen seizure.

[a] Especially when associated with tuberous sclerosis complex.
[b] Can cause aplastic anemia and severe hepatitis, used only for patients who respond poorly to other agents.
[c] Possibly effective but may worsen myoclonic seizures in some cases.
[d] Preferred in patients with concomitant GTCS or myoclonic seizures (myoclonic absence seizure).
[e] None of these is very effective in Dravet's syndrome.
[f] In combination with clobazam and valproate.
[g] Has been discontinued by the manufacturer, and it is no longer available.

Hakami, Neuropsychopharmacol Rep. 2021 Sep; 41(3): 336–351

The choice of ASM
Mechanism of action

Mechanistic categorization of current antiseizure drugs based on foremost targets at therapeutic concentrations

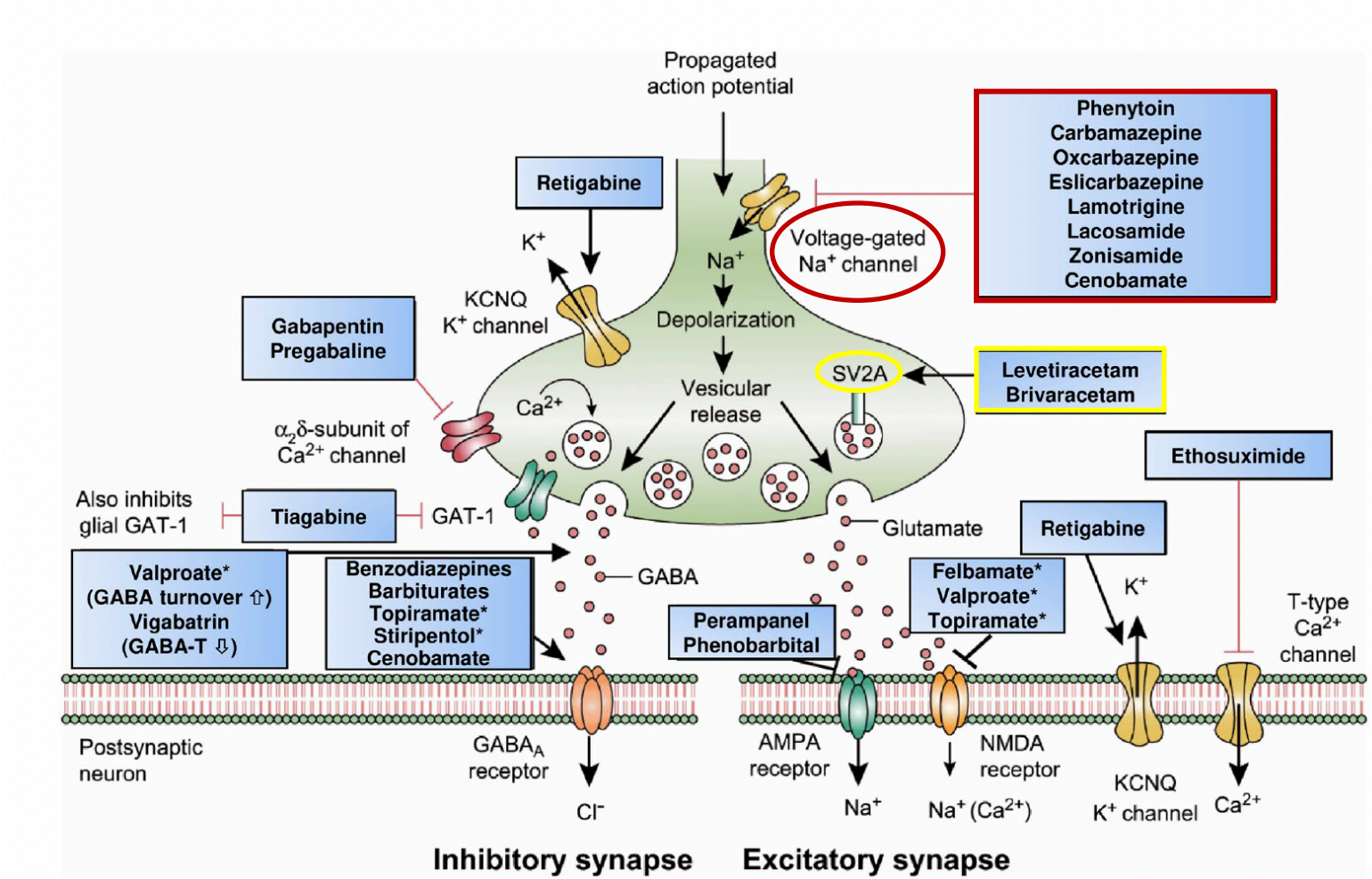
Target and mechanism[a]	Antiseizure drug
Inhibition of voltage-gated sodium channels	Phenytoin, fosphenytoin, carbamazepine, cenobamate, lamotrigine, oxcarbazepine, eslicarbazepine, lacosamide, and possibly topiramate, zonisamide, rufinamide, and phenobarbital
Inhibition of α2δ subunit of voltage-gated calcium channels	Gabapentin, pregabalin
Inhibition of T type voltage-gated calcium channels	Ethosuximide
Activation of $GABA_A$ receptor	Phenobarbital, benzodiazepines, and possibly topiramate, felbamate, retigabine, and stiripentol.
Inhibition of GABA transporter (selective)	Tiagabine
Inhibition of GABA transaminase enzyme	Vigabatrin
Modulation of synaptic vesicle protein 2A	Levetiracetam, brivaracetam
Various actions on multiple targets	Valproate, felbamate, topiramate, zonisamide, and cannabidiol
Opening KCNQ2-5 (Kv7.2-Kv7.5) voltage-gated potassium channels	Retigabine (ezogabine)[b]
Inhibition of NMDA-type glutamate receptors	Felbamate, topiramate and phenobarbital
Inhibition of AMPA-type glutamate receptors	Perampanel

[a] Fenfluramine's mechanism of action for the treatment of seizures associated with Dravet syndrome is unknown.

[b] Production of the drug retigabine has been discontinued by the manufacturer, and it is no longer available.

Hakami, Neuropsychopharmacol Rep. 2021 Sep; 41(3): 336–351

The choice of ASM
Mechanism of action



Löscher W, Klein P. CNS Drugs 2021;35:935

The choice of ASM
Monotherapy and add-on recommendations

Recommendations for add-on and monotherapy in adults and pediatric patients >4 years of age with new-onset epilepsy based on an assessment of current literature and published guidelines

Seizure type	First-line (Monotherapy or add-on)	Second-line (Monotherapy or add-on)	Third-line (Add-on)
Focal-onset seizures, including focal to bilateral tonic-clonic seizure	Lamotrigine[a]	Carbamazepine	Cenobamate[e]
		Levetiracetam	Clobazam
		Zonisamide	Retigabine
		Phenytoin	Felbamate
		Valproate	Rufinamide
		Topiramate[b]	Pregabalin
		Oxcarbazepine[b]	Tiagabine
		Gabapentin[b]	Vigabatrin
		Phenobarbital[c]	
		Brivaracetam[d]	
		Eslicarbazepine[d]	
		Lacosamide[d]	

Hakami, Neuropsychopharmacol Rep. 2021 Sep; 41(3): 336–351

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Generalized tonic-clonic seizures (GTCS)	Valproate[f]	Carbamazepine Phenytoin Lamotrigine Topiramate Levetiracetam Brivaracetam Perampanel Zonisamide Clobazam Phenobarbital	

Hakami, Neuropsychopharmacol Rep. 2021 Sep; 41(3): 336–351

The choice of ASM
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Myoclonic seizure	Valproate	Lamotrigine[g]	
		Topiramate	
		Levetiracetam	
		Brivaracetam	
		Clonazepam	
		Zonisamide	
Absence seizures	Ethosuximide	Lamotrigine	
	Valproate	Clonazepam	
		Levetiracetam	
Unclassified seizures[h]	Valproate	Lamotrigine	
		Levetiracetam	
		Topiramate	

Hakami, Neuropsychopharmacol Rep. 2021 Sep; 41(3): 336–351

The choice of ASM
Common adverse events

Antiseizure drug	Systemic adverse effects	Neurologic adverse effects	Rare idiosyncratic reactions
Brivaracetam	Nausea, vomiting, constipation, fatigue	Headache, somnolence, dizziness, abnormal coordination, nystagmus, mood changes	
Carbamazepine	Nausea, vomiting, diarrhea, a plastic anemia, leukopenia, hyponatremia (common reason for discontinuation), hepatotoxicity, rash, pruritus	Ataxia, dizziness, blurred vision, diplopia, headache	Erythematous maculopapular rash (Steven-Johnson syndrome and toxic epidermal necrolysis), teratogenicity
Cenobamate	Nausea, vomiting, fatigue, hyperkalemia, QT shortening	Somnolence, dizziness, headache, balance disorder, diplopia	Drug reaction with eosinophilia and systemic symptoms (DRESS)/multiorgan hypersensitivity (at high doses)
Eslicarbazepine	Nausea, vomiting, diarrhea, hyponatremia, rash	Dizziness, drowsiness, headache, somnolence, diplopia, ataxia, blurred vision, tremor	
Ethosuximide	Nausea, vomiting	Sleep disturbance, drowsiness, hyperactivity	
Felbamate	Nausea, vomiting, anorexia, weight loss	Insomnia, dizziness, headache, ataxia	Aplastic anemia, severe hepatitis/hepatic failure
Gabapentin	Infrequent	Somnolence, dizziness, ataxia, headache, tremor, and fatigue	
Lacosamide	Nausea, vomiting, increased cardiac conduction (PR interval)	Dizziness, ataxia, diplopia, headache	
Lamotrigine	Nausea, rash, cardiac arrhythmias	Dizziness, tremor, diplopia	Steven-Johnson syndrome
Levetiracetam	Fatigue, infection, anemia, leukopenia	Somnolence, dizziness, agitation, anxiety, irritability, depression, psychosis	
Oxcarbazepine	Nausea, rash, hyponatremia (more common)	Somnolence, headache, dizziness, vertigo, ataxia, diplopia	
Perampanel	Weight gain, fatigue, nausea	Dizziness, somnolence, irritability, gait disturbance, falls (with high dose), aggression, mood alteration	
Phenobarbital	Nausea, rash	Somnolence, ataxia, dizziness, confusion, cognitive dysfunction, tolerance, dependence	
Phenytoin	Gingival hyperplasia, hirsutism, megaloblastic anemia, peripheral neuropathy, osteoporosis, rash	Nystagmus (early sign of phenytoin administration), diplopia, ataxia, somnolence	
Pregabalin	Weight gain, peripheral edema, dry mouth	Somnolence, dizziness, ataxia, headache, and tremor	
Rufinamide	Nausea, vomiting, leukopenia, cardiac conduction (QT interval shortening)	Somnolence, fatigue, dizziness, ataxia, headache, diplopia	
Tiagabine	Abdominal pain, nausea, lack of energy	Dizziness, difficulty concentrating, somnolence, nervousness, tremor, language problems	
Topiramate	Anorexia, weight loss, paresthesia, fatigue	Nervousness, psychomotor slowing, language problems, depression, anxiety, mood problems, tremor	Acute glaucoma (may require prompt drug withdrawal).
Valproate	Gastrointestinal irritation, weight gain, hair loss, easy bruising	Ataxia, somnolence, tremor	Hepatotoxicity, teratogenicity, and thrombocytopenia
Vigabatrin	Fatigue	Somnolence, headache, dizziness, agitation, confusion, psychosis.	Irreversible bilateral concentric visual field defect
Zonisamide	Weight loss, nausea, anorexia	Somnolence, dizziness, confusion, headache, psychosis	Potentially serious skin rashes

Hakami, Neuropsychopharmacol Rep. 2021 Sep; 41(3): 336–351

Pharmacokinetics

- Pharmacokinetics: determines relationship between dose and concentration
- Absorption: entry of drug into blood
- Distribution
- Elimination: removal of active drug from the blood by metabolism and excretion

Pharmacokinetics of ASMs

Antiseizure drug	Bioavailability %	Peak concentration (hr)	Plasma protein binding (%)	Elimination half-life (hr)	Route of elimination	Therapeutic serum concentration (mcg/mL)
Brivaracetam	~ 95	1	≤ 20	7-10	++	0.2-2
Carbamazepine	75-85	4-5	70-80	10-17	++++	4-11
Cannabidiol	10-20	2.5-5	>94	56-61	++++	NE
Cenobamate	88	1-4	60	50-60	+++	NE
Clobazam	90-100	1-3	80-90	36-42	++++	0.03-3
Clonazepam	>80	1-4	80-90	24-48	+++	10-70[a]
Eslicarbazepine	>90	1-4	<40	13-20	++++	5-35
Ethosuximide	95-100	3-7	0	30-60	++	40-100
Felbamate	>90	3-5	22-36	16-22	++	30-60
Gabapentin	50	2-3	0	5-9	-	3-21
Lacosamide	100	1-2	<30	12-14	+	3-10
Lamotrigine	~ 90	1-3	55	8-35	+++	3-13
Levetiracetam	~ 95	1-2	<10	6-8	-	5-41
Oxcarbazepine	100	4-5	75	10-17	++++	3-36
Perampanel	100	0.5-3	95-96	70-110	+++	0.1-1
Phenobarbital	>90	0.5-4	55	90	++	12-30
Phenytoin	85-90	5-7	90	24	+++[b]	10-20
Pregabalin	~90	1-2	0	4.5-7	-	2-6
Primidone	>90	2-6	10	8-15	++	8-12
Rufinamide	>90	4-6	35	6-10	++	4.5-31
Stiripentol	Variable	2-3	99	4.5-13	+	4-22
Tiagabine	~90	0.5-2	96	2-9	+++	0.02-0.2
Topiramate	~80	2-4	15	20-30	+	2-10
Valproate	>90	2-4	90	15	++++	50-100
Vigabatrin	100	1	0	5-8	-	20–160[a]
Zonisamide	>90	2-6	40-60	50-68	++	10-38

Pharmacokinetics of ASMs
Absorption

- Near complete for all ASMs

- *Exceptions:*

1- Gabapentin: saturable amino acid transport system: 900 mg= 60%, 2400 mg = 34%, 3600 mg = 33% (% absorbed)

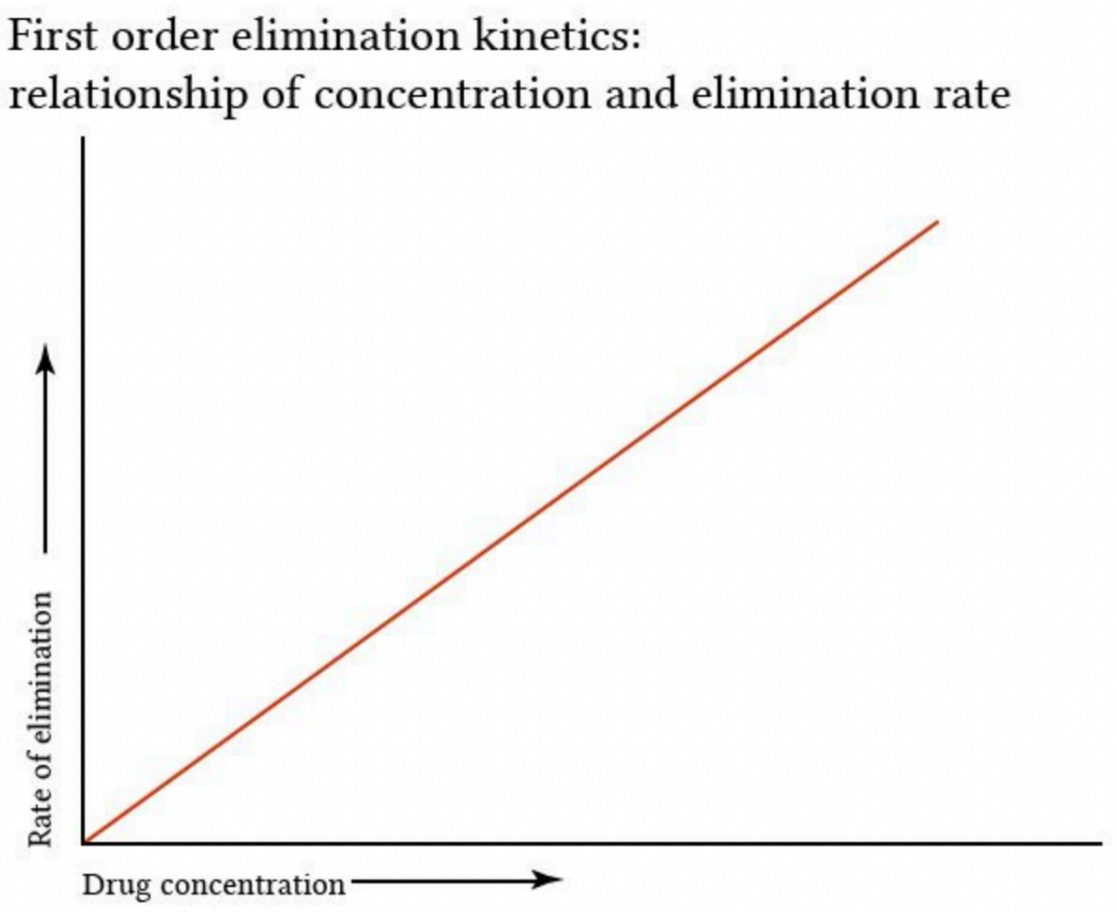
2- Rufinamide: dose limited absorption at doses of > 400 mg>> at high doses, non-proportional increase in blood levels

Pharmacokinetics of ASMs
Distribution

- > 85% protein binding is clinically significant (PHT, CBZ, VPA, TGB, MDZ, PER)
- Linear except for VPA: at 100 µg/ml → free level rises more than total because protein binding is saturated
- Low albumin states (neonates, elderly, pregnancy, hepatic & renal disease) protein binding is important →total concentration decreases more than unbound concentration → free > total concentration (check both T & F levels)
- Perampanel: 95% protein bound, but no protein-binding based drug-drug interaction (blood concentration is in nanomolar range, not micromolar)

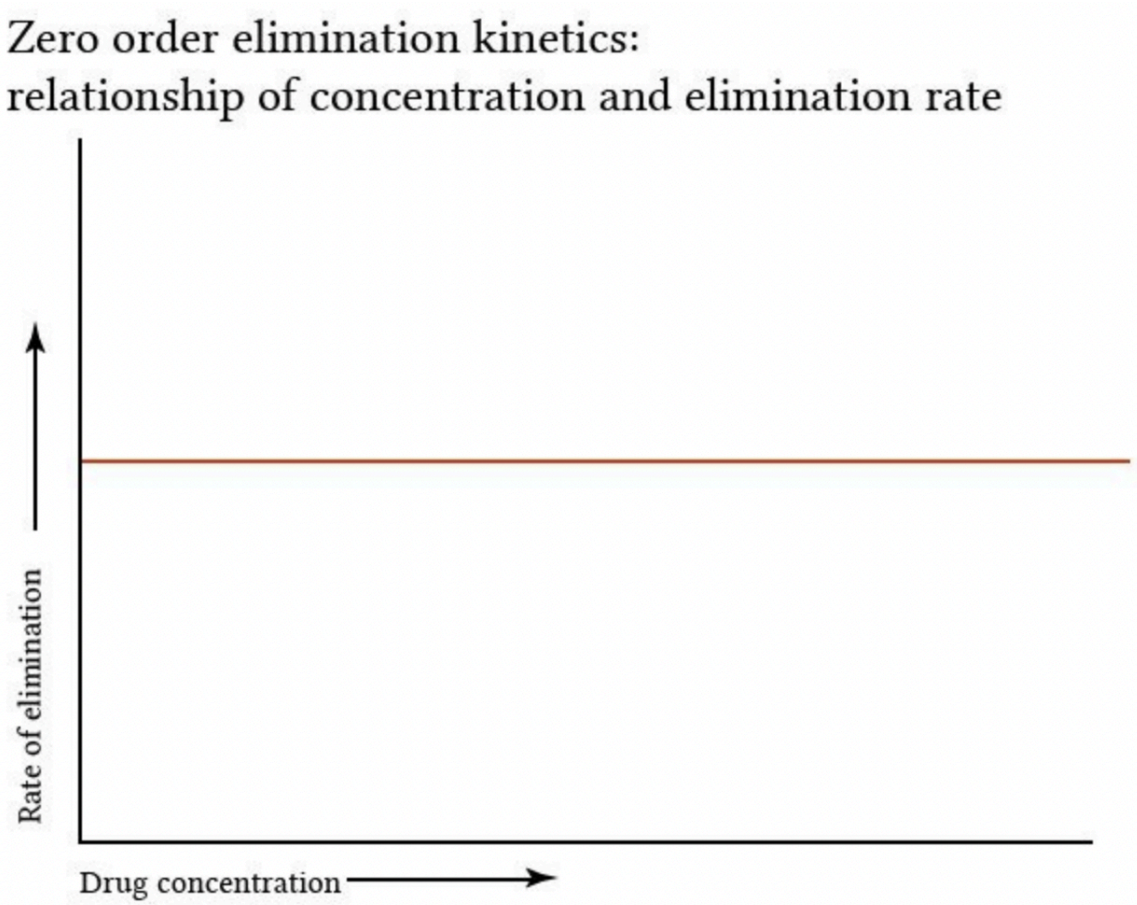
Pharmacokinetics of ASMs
Elimination

Linear for ASMs



Pharmacokinetics of ASMs
Elimination

Except PHT → metabolism is saturated



Pharmacokinetics of ASMs
Elimination

- $T_{1/2}$ x 4-5 results in elimination of >90% of drug>>steady state = 5x$T_{1/2}$

- <u>Dosing consideration with renal disease and the elderly:</u>

- Reduce dose of LM, GB, PGB, LEV, LCM

- <u>Liver Metabolism/CYP-450 inducers:</u> Changes in metabolism over time (auto-induction) or with polytherapy (enzyme induction or inhibition):

- PB,PHT,CBZ: auto-induction, levels fall 4 weeks after starting induce metabolism of each other and other ASMs

- VPA: inhibits UGT 1A9,1A4; CYP-450 > increases levels of LMT, PHT, PB

- ESL: inhibits CYP-2C19 > increases levels of PHT

- CBD/CNB: inhibit CYP-2C19 > increases levels of n-desmethyl-CLB (and decreases level of CLB, with CNB)

Pharmacokinetics of ASMs
Liver metabolism

- CYP-450: 3 families of individual isoenzymes : CYP1-3.
- ASMs are metabolized by 4 isoenzymes, CYP3A4/5, CYP2C9, CYP2C19
- CYP3A4 accounts for 30% of all hepatic CYP & metabolism of >50% of all drugs
- A drug may be substrate for > 1 enzyme

- Uridine Glucoronyl Transfearses (UGT): 2 families:
- UGT1: glucuronidate drugs, xenobiotics and endobiotics;
- UGT2: glucuronidate endobiotics including steroids

Pharmacokinetics of ASMs
Liver metabolism

- CYP-450: Inducers:
  PB,PHT,CBZ: CYP 1A2, A28/9, 3A4, (+2A6,2B6)
  OXC,TPM, FB, ESL, CNB: CYP 3A4

- CYP-450: Inhibitors:
  VPA, FB: 2C19: ↑concentrations of PHT,PB
  TPM, OXC, ESL: 2C19: ↑concentrations of PHT
  CBD, CNB: 2C19 ↑concentrations of CLB active metabolite (N-Desmethyl CLB)

- UGT: Inhibitors:
  VPA: UGT1A9: ↑concentrations of LMT, lorazepam
  UGT1A4: ↑concentrations of LMT
  UGT2B7: ↑concentrations of lorazepam

Pharmacokinetics of ASMs
Liver disease

- ↓ CYP-450 synthesis → ↑ ASM levels of CYP-metabolized ASMs

- CYP2C19 activity is first affected with mild liver disease, 3A4 and 2C9 activity in severe liver disease

- ↓ albumin synthesis: ↓ ASM protein binding

Pharmacokinetics of ASMs
Renal disease

- ↓ albumin concentration:↓ ASM protein binding
- ↓ renal clearance: ↑ level of renally excreted drugs

Pharmacogenetics of ASMs

- Genetic variation in functionality and expression of transporters may affect clinical outcome
- Polymorphism of ASMs target in the brain may affect effectiveness
- Genetic variation in drug metabolism and elimination may contribute to interindividual variability in drug response

Pharmacogenetics of ASMs
Pgp

- Several ASMs, are Pgp substrates → genetic variation in the ABCB1 [multidrug resistance 1 (MDR1)] gene that encodes Pgp may have dramatic consequences for the pharmacological behavior of substrate drugs
- ABCB1 gene is composed of 29 exons
- A synonymous SNP in exon 27 (C3435T) → first variant to be associated with altered protein expression in the human intestinal
- Levels of phenytoin (PHT) correlate with the C3435T polymorphism in the ABCB1 gene
- Epilepsy patients with the CC genotype are more likely to have low PHT levels (<10 lg/ml) than patients with the TT phenotype
- Some patients with MRE & high expression of brain Pgp have persistently subtherapeutic plasma levels of CBZ, VPA or PHT (despite high doses) → absorption and/or elimination may be affected by increased expression of Pgp in the periphery

Pharmacogenetics of ASMs
CYP 450/UGT substrates

- There is genetic polymorphism in the expression of CYP1A2, 2B6, 2C8, 2C9, **2C19**, 2D6, 3A5, and UGT1A1
- Poor metabolizers: monozygous for the mutant gene. High ASM level
- Extensive metabolizers: homozygous or heterozygous for the gene. Low ASM level
- Ultra-metabolizers: have multiple copies of the gene; only described for CYP 2D6 polymorphism
- CYP 2C9, CYP2C19 Extensive metabolizers (EM) and poor metabolizers (PM): impact PHT and possibly clobazam, CBD and cenobamate
- In PHT combined polymorphisms of CYP2C9/19 (rare in Caucasians) have clinical impact

Pharmacogenetics of ASMs
CYP 450/UGT substrates

- CYP2D6: predominant variant in Asians and African Americans are alleles with reduced enzyme activity >> ethnic variability in proportion of poor metabolizers

- ASMs affected: PHT, CBZ, VPA

- NB HLA-B*1502 in south east Asians (Taiwanese); and HLA-A*3101 in Europeans/Japanese: CBZ Stevens-Johnsons

Drug-drug interaction

Affected Drug Classes					
AEDs Susceptible to Interactions	**AEDs**	**Antidepressants and Antipsychotics**	**Oral Contraceptives**	**Antimicrobal Drugs**	**Various (e.g. Warfarin, Antineoplastic Drugs, Immuno-Suppressants)**
Enzyme inducers that will decrease serum concentrations of affected drugs					
Carbamazepine, phenobarbital, phenytoin, primidone	Benzodiazepines, ethosuximide, lamotrigine, oxcarbazepine, pregabalin, rufinamide, stiripentol, tiagabine, topiramate, zonisamide, valproic acid,	*Typical:* Chlorpromazine, haloperidol *Atypical:* Aripiprazol, clozapine, olanzapine, quetiapine, risperidone, ziprasidone Antidepressants: Clomipramine Imipramine	Estrogen component of combination pills	Doxycycline, indinavir, itraconazole, metronidazol, praziquantel	Warfarin Antineoplastic agents (e.g. cyclophosphamide, irinotecan, methotrexate, tamoxifen) Immuno-suppressants: Ciclosporin, tacrolimus Varia: Cortisol derivatives, dextropropoxyphene, dihydropyridine calcium antagonists, fentanyl, statines, methadone, theophylline, thyroxine
Eslicarbazepine and oxcarbazepine	Lamotrigine, phenobarbital, phenytoin, (mainly induction)		Estrogen component of combination pills		
Felbamate	Carbamazepine Clobazam				
Topiramate	Phenytoin (in some cases)		Estrogen component of combination pills (topiramate doses >200 mg/day)		Carboanhydrase inhibitors, digoxin, hydrochlortiazide, metformin, pioglitazone,

Affected Drug Classes					
AEDs Susceptible to Interactions	**AEDs**	**Antidepressants and Antipsychotics**	**Oral Contraceptives**	**Antimicrobal Drugs**	**Various (e.g. Warfarin, Antineoplastic Drugs, Immuno-Suppressants)**
Enzyme inhibitors that will increase serum concentrations of affected drugs					
Valproic acid	Carbamazepine, ethosuximide, lamotrigine, phenobarbital, rufinamide	Amitriptyline, nortriptyline		Carbapenem antibiotics: Imipenem, meropenem, panipenem	Cisplatin, etoposide
Felbamate	Clonazepam phenobarbital, phenytoin, valproic acid		Estrogen component of combination pills		Warfarin
Rufinamide	Carbamazepine, lamotrigine, phenobarbital, phenytoin (mainly inhibition)		Estrogen component of combination pills		Triazolam
Stiripentol	Carbamazepine, clobazam, phenytoin, phenobarbital, valproic acid				Various potential interactions*

AEDs=Antiepileptic drugs. The list is not all-including but relevant examples are given. Several references are used, see text for details and selected reviews, [7-13] and the spc of the various drugs. Oral contraceptives and warfarin are described in more detail in Table 4. **In vitro* studies suggest a potential for interactions with most drug classes metabolized by CYP3A4, 1A2, 2C19.

Johannessen, S.I., & Landmark, C.J. (2010). Antiepileptic Drug Interactions - Principles and Clinical Implications. *Current Neuropharmacology, 8*, 254 - 267.

Table 1. Interactions between antiseizure medications with clinical significance.

	Phenobarbital	Phenytoin	Primidone	Ethosuximide	Carbamazepine	Valproate	Clonazepam	Clobazam	Vigabatrin	Zonisamide	Lamotrigine	Oxcarbazepine	Felbamate	Gabapentin	Topiramate	Tiagabine	Levetiracetam	Pregabalin	Rufinamide	Stiripentol	Lacosamide	Eslicarbazepine	Perampanel	Brivaracetam	Cannabidiol	Cenobamate	Fenfluramine
Phenobarbital		↑±	+	-	-	↑±	↑-		-	-	-	±	±			-				+			-	-		+	
Phenytoin			↑-	+	±	↑+	↑-	±	-	-	-	±	±		±	-				+		-	-	±	+	±	
Primidone				-	↑-	↑±	±			-	-	-	-			-				±			-				
Ethosuximide					-	±					-									+							
Carbamazepine						↑-	-	-	+	-	↑-	-	-		-	-	↑			+		↑-	-	↑±		-	
Valproate							↑-	±			↑+		+		↑				+	+					↑		
Clonazepam																											
Clobazam																				↑+					↑+	+	
Vigabatrin																											
Zonisamide																											
Lamotrigine												↑			+							-			+	-	
Oxcarbazepine																						↑	±				
Felbamate																											
Gabapentin																											
Topiramate																						-	-				
Tiagabine																				+							
Levetiracetam																											
Pregabalin																											
Rufinamide																											
Stiripentol																									+		+
Lacosamide																											
Eslicarbazepine																											
Perampanel																											
Brivaracetam																									+		+
Cannabidiol																											
Cenobamate																											
Fenfluramine																											

(↑) Increase in adverse effects intensity; (↓) decrease in adverse effects intensity; (+) increase in serum concentration of one or both antiseizure medications and possibly intensification of anticonvulsant activity; (-) decrease in serum concentration of one or both antiseizure medications and possibly diminution of anticonvulsant activity; (±) increase in serum concentration of one and decrease in serum concentration of another antiseizure medication given in combination. Fosphenytoin is not mentioned in the table due to similarity of its interaction potential with phenytoin.

ASM Levels

- Optimization of therapy
- Document positive or negative outcomes
- Compliance
- Monitor drug-drug interactions (eg VPA and LTG)
- Valdated ranges for PHT,PB,CBZ,VPA,LM

Patsalos PN, et al. Epilepsia. 2008 ;49

Convenience

- Once daily use
- Rapid titration
- IV formulation
- Pharmakokinetics
- Lack of interaction

Discontinuation of ASMs

Discontinuation of ASMs
When to consider

- Seizure-free 2–5 years while taking ASMs (mean 3.5 years)
- Single type of focal seizure
- Single type of generalized onset seizures
- Normal neurologic examination results/normal IQ EEG normalized while taking ASMs

Antiseizure Medication Withdrawal in Seizure-Free Patients: Practice Advisory Update Summary Report of the AAN Guideline Subcommittee David Gloss et al on behalf of the AAN Guideline Subcommittee Neurology Dec 2021, 97 (23) 1072-1081

Discontinuation of ASMs
Seizure relapse

- 11–41 % of patients will relapse after the AED discontinuation (depending on the seizure type/etiology)

- Relapse rate lower in children (20 %) and higher in adults (40 %)

- Most relapses occur in the first 1 year of discontinuation (50 % in the first 6 months, 60-90% in the first 1 year)

Antiseizure Medication Withdrawal in Seizure-Free Patients: Practice Advisory Update Summary Report of the AAN Guideline Subcommittee David Gloss et al on behalf of the AAN Guideline Subcommittee Neurology Dec 2021, 97 (23) 1072-1081

Discontinuation of ASMs
Factors associated with a high risk of recurrence

- Long duration of epilepsy before remission
- Short seizure-free interval before ASMs withdrawal
- Older age at onset of epilepsy (in patients >25 years)
- History of febrile seizures
- >10 seizures before remission
- Absence of a self-limiting epilepsy syndrome e.g. absence or rolandic epilepsy
- Developmental delay Epileptiform abnormality on EEG before withdrawal

Laue-Gizzi H. Discontinuation of antiepileptic drugs in adults with epilepsy. *Aust Prescr*. 2021;44(2):53-56. doi:10.18773/austprescr.2021.005

Discontinuation of ASMs

Factors associated with long term (>10 years) seizure freedom

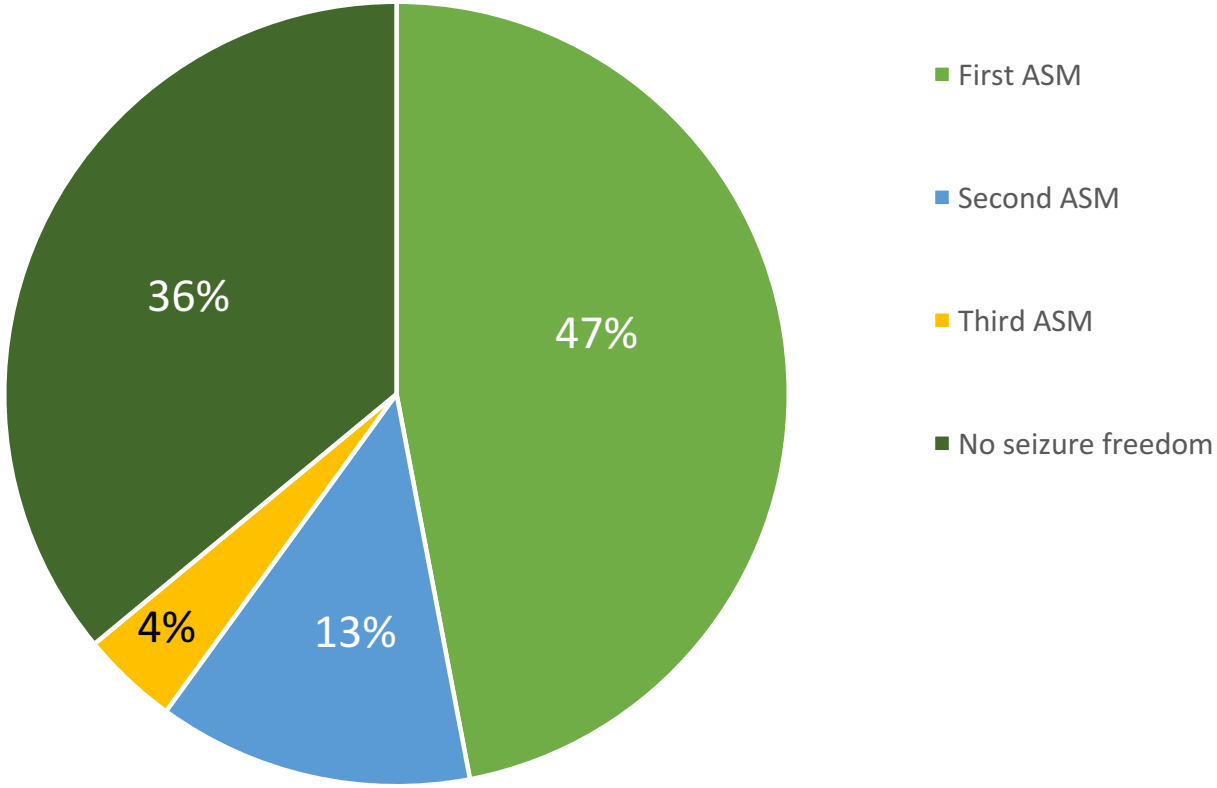
- Short duration of epilepsy before remission
- Long seizure-free interval (years) before ASMs withdrawal
- One or low number of ASMs before withdrawal
- Low number of seizures before remission
- No history of focal seizures
- No epileptiform abnormality on EEG before withdrawal

Laue-Gizzi H. Discontinuation of antiepileptic drugs in adults with epilepsy. *Aust Prescr*. 2021;44(2):53-56. doi:10.18773/austprescr.2021.005

Pharmaco-resistant epilepsy

Pharmaco-resistant epilepsy
Response to ASM

Success of ASM regimens in 470 patients with previously untreated epilepsy



Kwan P, et al. N Engl J Med. 2000;342:314-319.

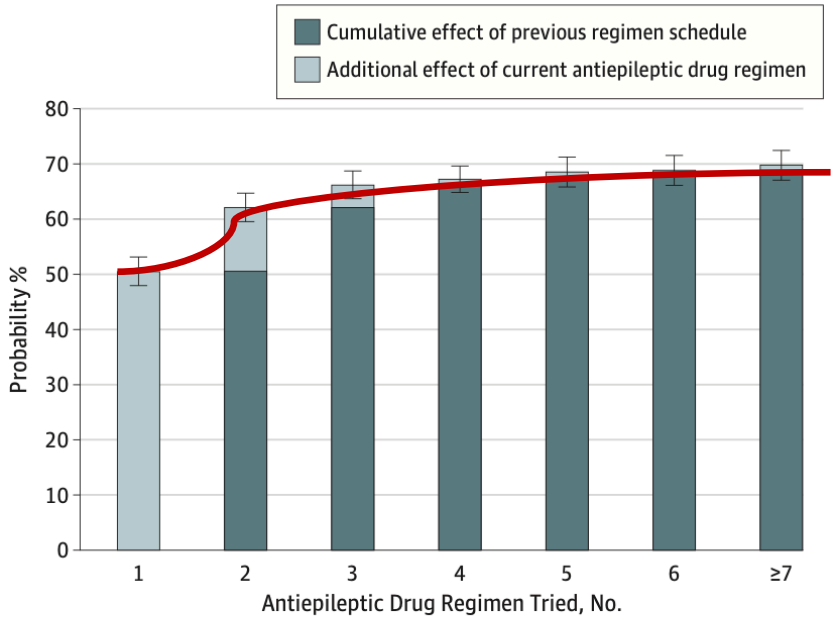
Pharmaco-resistant epilepsy
Reasons of failing 1st ASM

- 55% → idiosyncratic reaction
- 41% → side effects
- 11% → lack of efficacy

Kwan P, et al. N Engl J Med. 2000;342:314-319
Chen Z et al. JAMA Neurol 2018;75:279-286

Pharmaco-resistant epilepsy
Effect of adding ASMs

Figure 3. Increases in Probability of 1-Year Seizure Freedom for Each Additional Antiepileptic Drug Regimen Tried



The percentage of patients achieving seizure freedom via the first, second, third, fourth, fifth, sixth, and seventh AED regimens were 50.5%, 11.6%, 0.99%, 1.34%, 0.28%, and 0.94%, respectively. Please see Table 2 for numbers of patients achieving seizure freedom and total patients in each subgroup.

Chen Z, Brodie MJ, Liew D, Kwan P. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. *JAMA Neurol.*2018;75(3):279–286. doi:10.1001/jamaneurol.2017.3949

Drug resistant epilepsy

"Failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom" ILAE

Kwan, Patrick et al. "Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies." *Epilepsia* vol. 51,6 (2010): 1069-77.

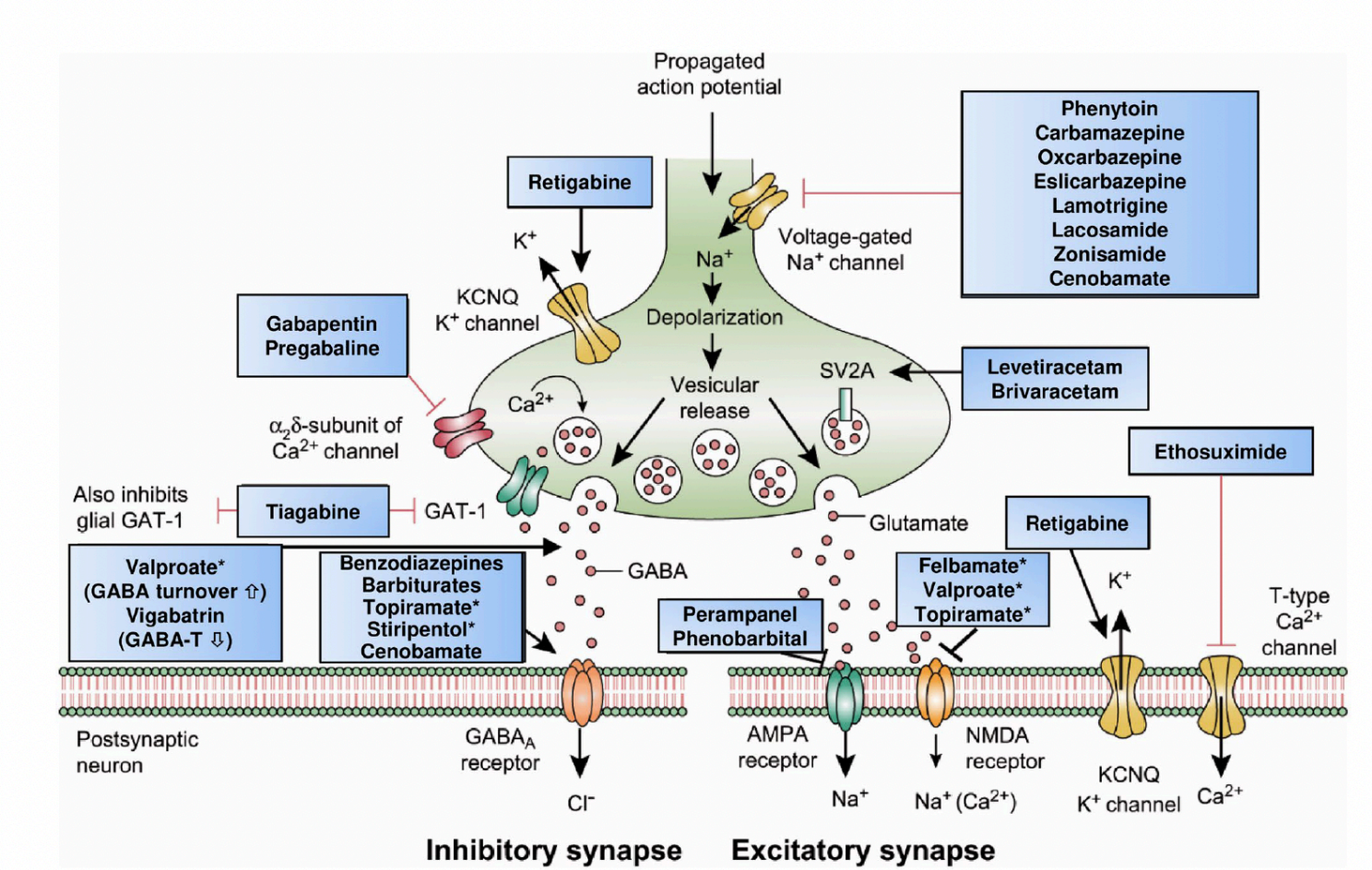
Pharmaco-resistant epilepsy
Predictors

- High seizure frequency (prior to therapy)
- Depression (and other psychiatric comorbidities)
- High dose of 1st ASM
- Family history
- History of febrile seizures

Chen Z, Brodie MJ, Liew D, Kwan P. Treatment Outcomes in Patients With Newly Diagnosed Epilepsy Treated With Established and New Antiepileptic Drugs: A 30-Year Longitudinal Cohort Study. *JAMA Neurol.*2018;75(3):279–286. doi:10.1001/jamaneurol.2017.3949

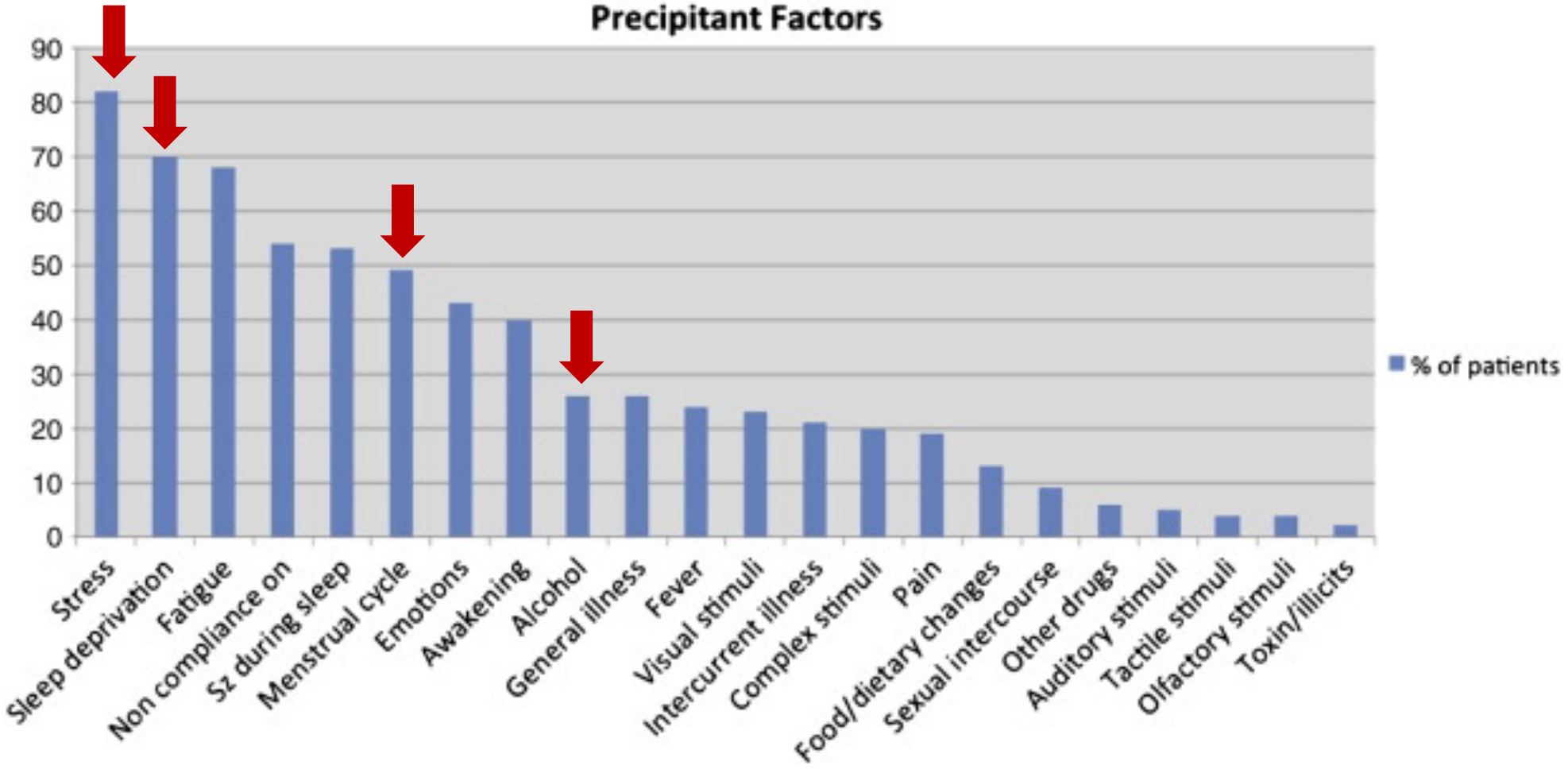
Rational Polypharmacy

- Use ASMs with different mechanism of action



Löscher W, Klein P. CNS Drugs 2021;35:935

Seizure triggers



Ferlisi, Monica, and Simon Shorvon. "Seizure precipitants (triggering factors) in patients with epilepsy." *Epilepsy & behavior : E&B* vol. 33 (2014): 101-5. doi:10.1016/j.yebeh.2014.02.019

ASM generics

Generics

- Bioequivalence = pharmacokinetic parameters Cmax and AUC fall within a specified range. Compares the brand to a single generic.

- Therapeutic equivalence = two products provide equal seizure control and tolerability. Rarely tested, but inferred by bioequivalence.

- Switchability = there is no change in therapeutic effect when one product is switched for another

Liow et al.Neurology 2007;68:1249-50

FDA Bioequivalence Requirements

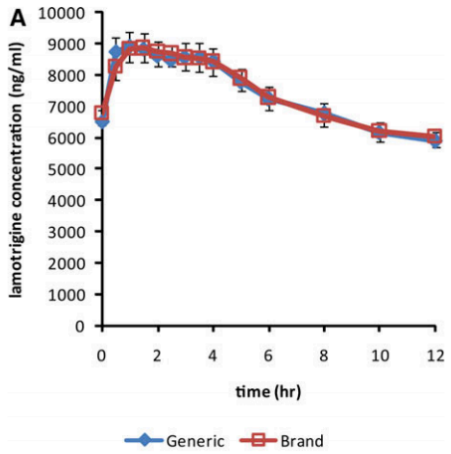
- For both AUC and Cmax, 90% confidence intervals of the ratio of the generic to brand must fall within 80-125% range

Liow et al.Neurology 2007;68:1249-50

AES position statement on generic substitution of AEDs

- …[two] … prospective studies of generic AED substitution… demonstrated bioequivalence of generic[s].. in patients with epilepsy taking concomitant AEDs. …generic products of branded modified-release products (e.g., extended release) are bioequivalent and safely interchangeable.

- Results from these studies have shown no difference in bioequivalence when switching from a brand.. to a generic… or between multiple generic products.



LM brand and generic levels in 33 “AED brittle” patients[1]

[1]Ting T et al. Epilepsia 2015;56:1415—24
Vossler D et al. Epi Curr 2016;209-11
Privitera M et al;Lancet Neurol 2016:15:365-72
Johnson EL et al. Neurology 2016;86;1597-604

Epilepsy in the elderly

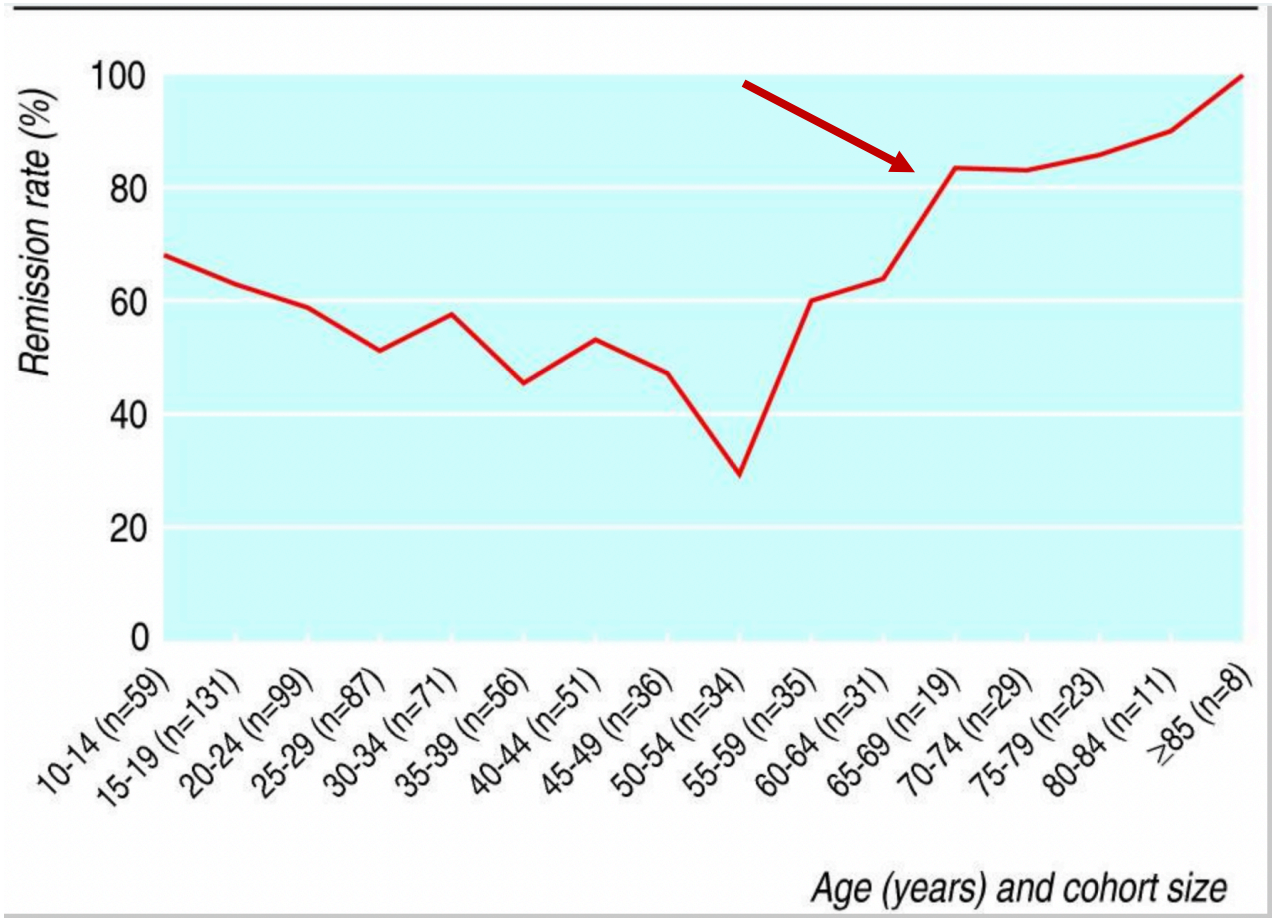
The summary of the percentage of each cause of new-onset epilepsy in the elderly

Cerebrovascular diseases account for 30%–50%.
Primary neurodegenerative disorders account for ~10%–20%.
Head trauma accounts for 10%–20%.
Brain tumors account for nearly 10%–30%.
One-third to one-half of geriatric epilepsies still have undetected causes, to date.

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.

Epilepsy in the elderly
Response to therapy

Response >80%



Brodie MJ, Kwan P. Epilepsy in elderly people. BMJ. 2005 Dec 3;331(7528):1317-22. doi: 10.1136/bmj.331.7528.1317. PMID: 16322020; PMCID: PMC1298856.

Epilepsy in the elderly
Considerations

- More susceptible to side effects
- Low dosing works
- Avoid ASMs with cognitive side effects
- Avoid ASMs with high drug-drug interaction

Thank you