Mahidol University
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SI-NEURO

Early ASMs Optimization: The Key for Acute Seizure in Adult Patients

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Early Optimizing Usage of ASMs in Epilepsy Patients

- Seizures in the emergency room
  - First unprovoked seizures
  - Acute symptomatic seizures

- Seizures in the inpatient setting
  - Acute symptomatic seizures
  - First unprovoked seizures

Case

- A 67-year-old man with hypertension, dyslipidemia, hypertensive heart disease, atrial fibrillation and recent history of right MCA infarction 1 week ago with left hemiparesis
- Developed aspiration pneumonia during the period of admission
- During the 7th day of hospital admission developed focal to bilateral tonic clonic seizure in the ward
- ได้ valium 5 mg หยุดกระตุก

At ER

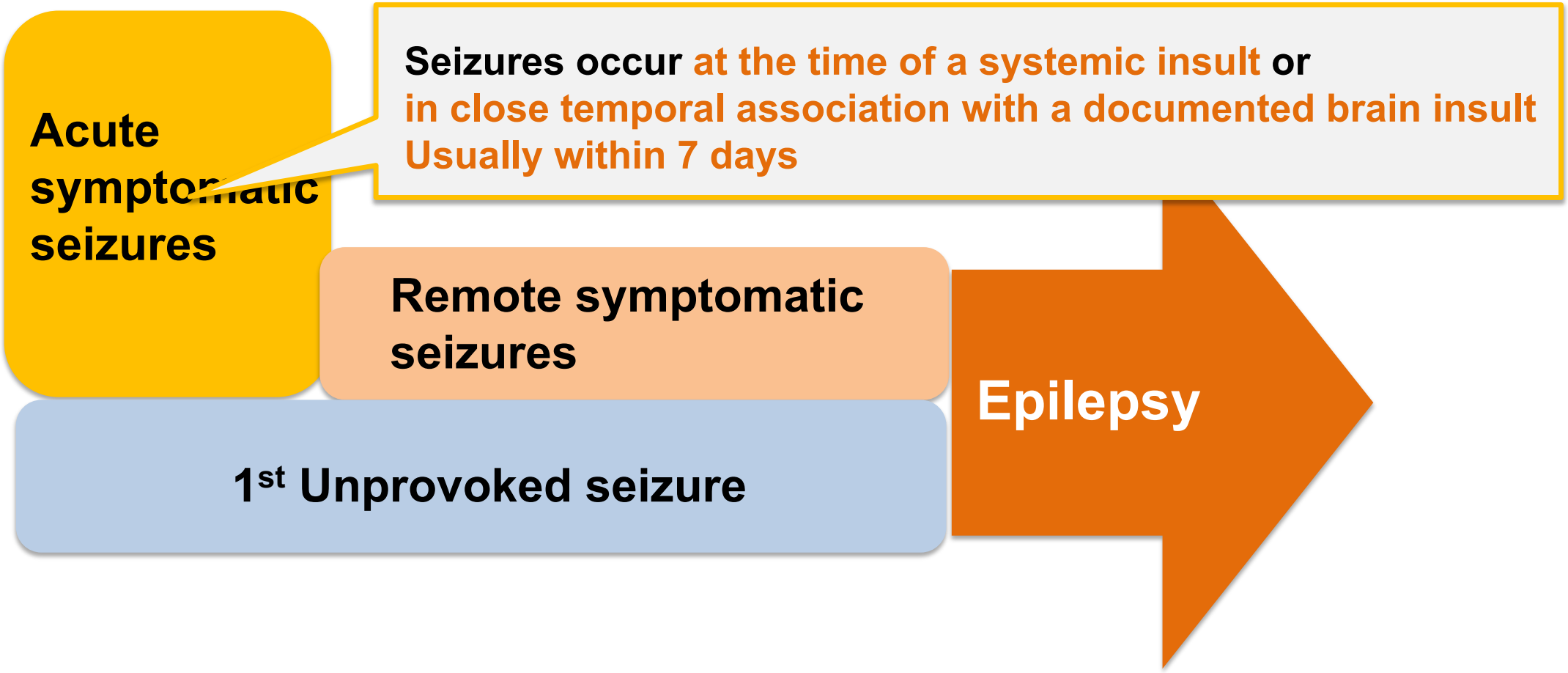
- VS: BT 36.5c, BP 140/85 mmHg, HR 66 bpm (irregular)
- GA: drowsiness, E3V2M6
- NS: mild gaze preference to left side, left facial palsy UMNL, motor tone flaccid left side, motor power right side gr IV, left side gr 0
- CT brain NC: subacute infarction in the right MCA distribution

- หลังจากกลับมาจาก CT brain มี focal to bilateral tonic clonic seizure x 1 min อีกครั้ง terminated by valium 10 mg IV

Medication before this admission

- Carvedilol 10 mg/d
- Warfarin 3 mg/d
- Atorvastatin 40 mg/d
- Amlodipine 5 mg/d
- Clonazepam 0.5 mg/d

Terms


Acute symptomatic seizures
Seizures occur at the time of a systemic insult or
in close temporal association with a documented brain insult
Usually within 7 days
Remote symptomatic seizures
1st Unprovoked seizure
Epilepsy

Acute symptomatic seizure

- Seizures occur at the time of a systemic insult or in close temporal association with a documented brain insult which may be metabolic, toxic, structural, infectious, or due to inflammation.
- The interval between the insult and the seizure may vary according to the underlying clinical condition.

Epilepsia, 51(4):671–675, 2010
doi: 10.1111/j.1528-1167.2009.02285.x

SPECIAL REPORT

Recommendation for a definition of acute symptomatic seizure

*[1]Ettore Beghi, †Arturo Carpio, ‡Lars Forsgren, §Dale C. Hesdorffer, ¶Kristina Malmgren, #Josemir W. Sander, **Torbjorn Tomson, and §W. Allen Hauser

Epilepsia 2010; 51:671–5

■ Seminar in epileptology

Epileptic Disord 2022; 24 (1): 26-49

Epileptic Disorders

Acute symptomatic seizures: an educational, evidence-based review

Matthias Mauritz[1], Lawrence J. Hirsch[2], Peter Camfield[3], Richard Chin[4], Raffaele Nardone[5], Simona Lattanzi[6], Eugen Trinka[1,7,8]

Epileptic Disord 2022; 24: 26-49

- Seizures are considered acute symptomatic if they occur within the first 7 days of cerebrovascular disease [1], TBI , including intracranial surgery [2] and CNS infections [3]
- In multiple sclerosis, acute symptomatic seizures occur as the first presenting symptom or within 7 days of relapse
- Prognosis of acute symptomatic seizures differs from that of unprovoked seizures [4]

1 Jennett et al., 1973; Camilo & Goldstein, 2004
2 Jennett et al., 1973; Annegers et al., 1998
3 Annegers et al., 1988
4 Hesdorffer et al 2009

Table 1. Proposed cutoff values for acute symptomatic seizures in common metabolic disorders

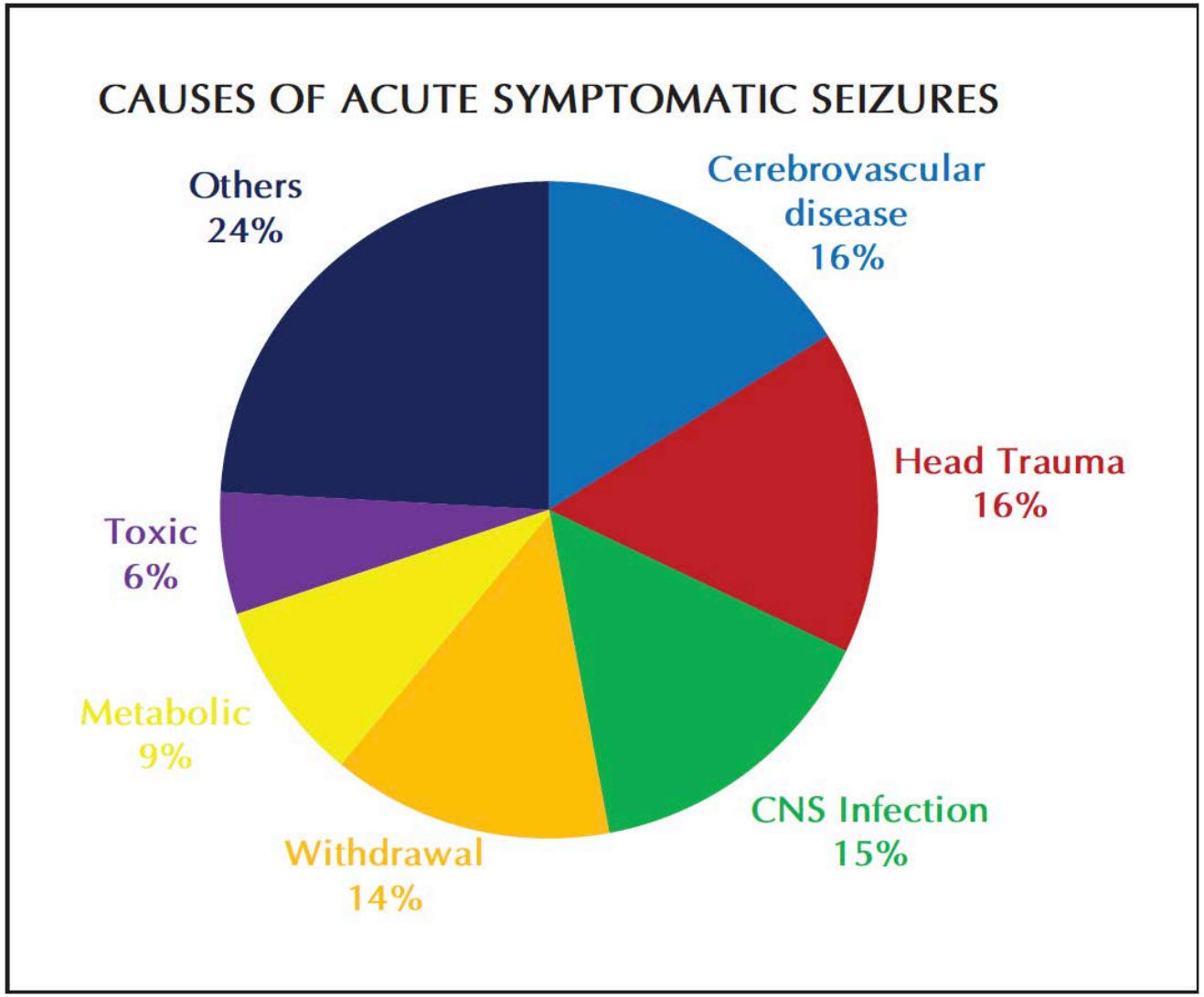
Biochemical parameter	Value
Serum glucose	<36 mg/dl (2.0 mM) or >450 mg/dl (25 mM) associated with ketoacidosis (whether or not there is long-standing diabetes)
Serum sodium	<115 mg/dl (<5 mM)
Serum calcium	<5.0 mg/dl (<1.2 mM)
Serum magnesium	<0.8 mg/dl (<0.3 mM)
Urea nitrogen	<100 mg/dl (>35.7 mM)
Creatinine	>10.0 mg/dl (>884 μM)

Epilepsia 2010; 51:671–675

Epidemiology

- Acute symptomatic seizure: annual incidence 39/100,000
- Unprovoked seizure: incidence 42- 61/100,000/year
- 8.9-fold higher mortality rate in the first 30 days after the seizure event compared to first unprovoked seizures
- Mortality is particularly high in patients with acute symptomatic status epilepticus

Causes of acute symptomatic seizures in the population of Rochester, Minnesota, United States, 1935-1984.

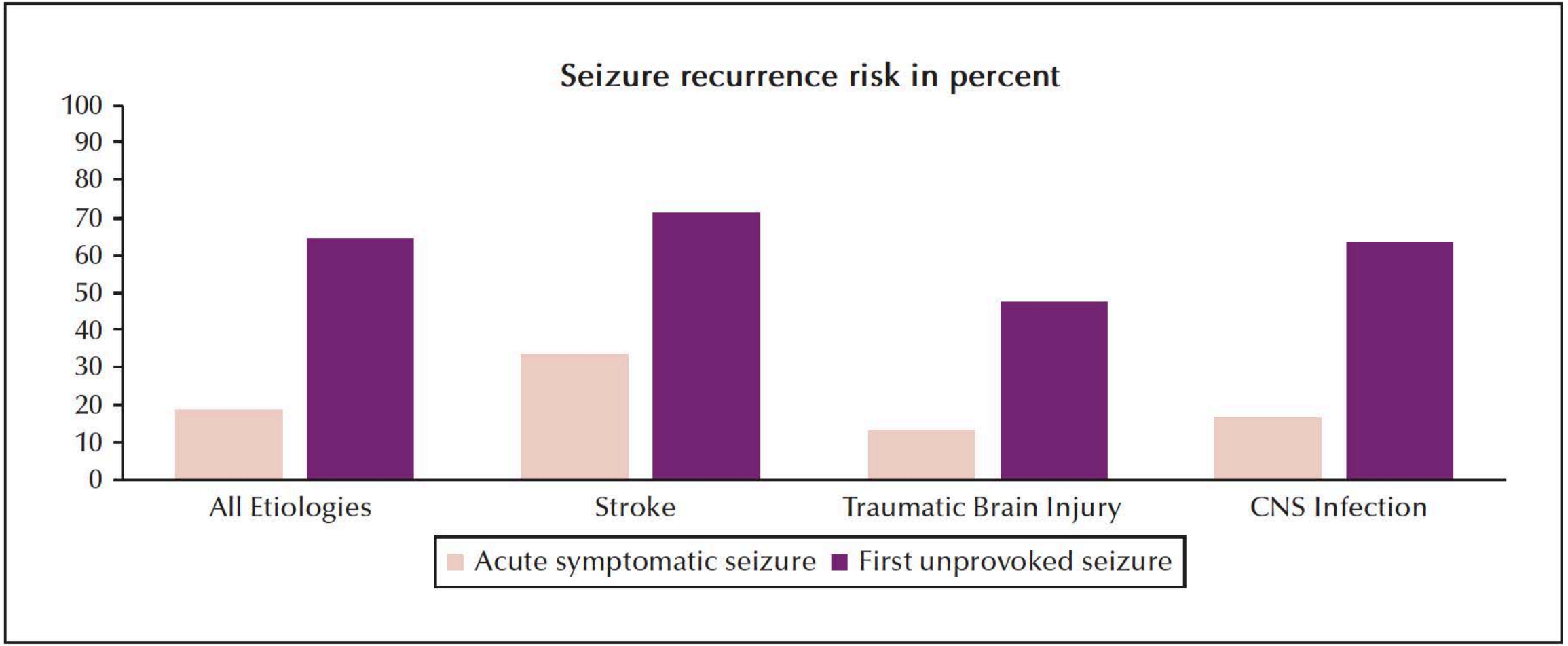


Annegers JF, et al. Epilepsia 1995; 36: 327-33

Etiology	Risk for acute symptomatic seizures	Risk factors
Ischemic stroke	Relatively low (3-6%)	Cortical lesion, lesion size, secondary haemorrhagic transformation, clinical severity, infections, premorbid status, large-artery atherosclerosis
Haemorrhagic stroke	High (10-18%)	Cortical lesion, bleeding volume, midline shift, clinical severity, MCA aneurysm in SAH
Cerebral venous thrombosis	Very high (up to 40%)	Haemorrhagic lesions, thrombosis of superior sagittal sinus and cortical veins, motor deficits
Viral encephalitis	Very high (40-60%)	Depressed level of consciousness, cortical lesions, younger age, herpes-simplex virus 1
Bacterial meningitis	High (17-27%)	Depressed level of consciousness, streptococcus pneumoniae, focal abnormalities on brain imaging
Autoimmune encephalitis	Very high (33%-100%)	Antibodies against NMDA, GABA A, GABA B, LGI1 receptor
Brain trauma	Moderate (2-15%)	Skull fracture, penetrating injury, intracranial haemorrhage, younger age, need for neurosurgical intervention
Hyponatremia	Relatively low (5%)	Lower levels of serum sodium, acuteness of development
PRES	Very high (60-75%)	
Anoxie encephalopathy	Very high (up to one third)	Hypothermia, rewarming

Mauritz M, Hirsch LJ, Camfield P, et al. Epileptic Disord 2022; 24: 26-49

Risk of seizure recurrence after acute symptomatic and unprovoked seizures



Most of the patients can be wean off ASMs after certain periods after acute insults

Mauritz M, Hirsch LJ, Camfield P, et al. Epileptic Disord 2022; 24: 26-49

Acute symptomatic seizure: Treatment

- The aim of treatment with ASMs is to prevent further acute symptomatic seizures
- However, data on how long to treat patients with acute symptomatic seizures with ASMs is largely lacking
- The duration of treatment with ASMs needs to be individualized for every patient and will depend on factors such as the underlying etiology

Considerations when treating acute symptomatic seizures

- High seizure recurrence rate in the acute setting → often need ASMs that can be given IV to achieve quick therapeutic levels
- High morbidity and mortality
- Patients often have multiple medical problems or are critically ill patients
- Patients often are on multiple medications

Available IV antiseizure medications

	Route of administration	Adult dose	Pediatric dose
Phenytoin	IV (<25-50 mg/min)	15-20 mg/kg	20 mg/kg at 25 mg/min
Fosphenytoin	IV (<50-100 mg PE/min)	15-20 mg PE/kg	na
Phenobarbital	IV (<100 mg/min)	10-20 mg/kg	15-20 mg/kg
Valproate	IV (50-200 mg/min)	20-40 mg/kg	20-40 mg/kg
Levetiracetam	IV (100-300 mg/min)	20-60 mg/kg	30-40 mg/kg
Lacosamide	IV (over 15-60 min)	200-400 mg	

Shorvon S. Curr Opin Neurol 2011;24:165–170

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus

Jaideep Kapur, M.B., B.S., Ph.D., Jordan Elm, Ph.D., James M. Chamberlain, M.D., William Barsan, M.D., James Cloyd, Pharm.D., Daniel Lowenstein, M.D., Shlomo Shinnar, M.D., Ph.D., Robin Conwit, M.D., Caitlyn Meinzer, Ph.D., Hannah Cock, M.D., Nathan Fountain, M.D., Jason T. Connor, Ph.D., and Robert Silbergleit, M.D., for the NETT and PECARN Investigators*

N Engl J Med 2019;381:2103-13.

ESETT study drug doses, formulation, and maximal administration rates.

Study drug (formulation)	Dose mg/kg	Study maximum	
		Rate mg/kg/min	Dose mg
Fosphenytoin (16.66 mgPE/ml)	20	2 (PE)[1]	1500 (PE)
Valproate (33.33 mg/ml)	40	4 [2]	3000
Levetiracetam (50 mg/ml)	60	6	4500

All were infused over 10 min at a rate determined by patient weight

Issues of using ASM in the critically ill patients

- Side effects of ASMs that are even more important in the critically ill patients eg. cardiac arrhythmia, hypotension
- Drug- drug interactions
- Altered pharmacokinetic of ASMs in critical care patients
- Patients with liver and renal impairment

Cardiovascular monitoring for IV ASMs

	Route of administration	Adult dose
Phenytoin	IV (<25-50 mg/min)	15-20 mg/kg
Fosphenytoin	IV (<50-100 mg PE/min)	15-20 mg PE/kg
Phenobarbital	IV (<100 mg/min)	10-20 mg/kg
Valproate	IV (50-200 mg/min)	20-30 mg/kg
Levetiracetam	IV (100-300 mg/min)	2000-4000 mg
Lacosamide	IV (30-60 min/ up to 15 min)	200-400 mg

Shorvon S. Curr Opin Neurol 2011;24:165–170

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Effects of AEDs on commonly used inpatient medications

ADDED DRUG	Warfarin	Steroids	Haloperidol	Lithium	Nimodipine	Simvastatin	Quetiapine
PHT *	↑, then ↓	↓			↓	↓	↓
PB	↓	↓	↓		↓		
CBZ *	↓	↓	↓	↑	↓	↓	↓
VPA *	↑				↑		

Varelas PN, et al. Current Pharmaceutical Design 2017;23: 6533-49

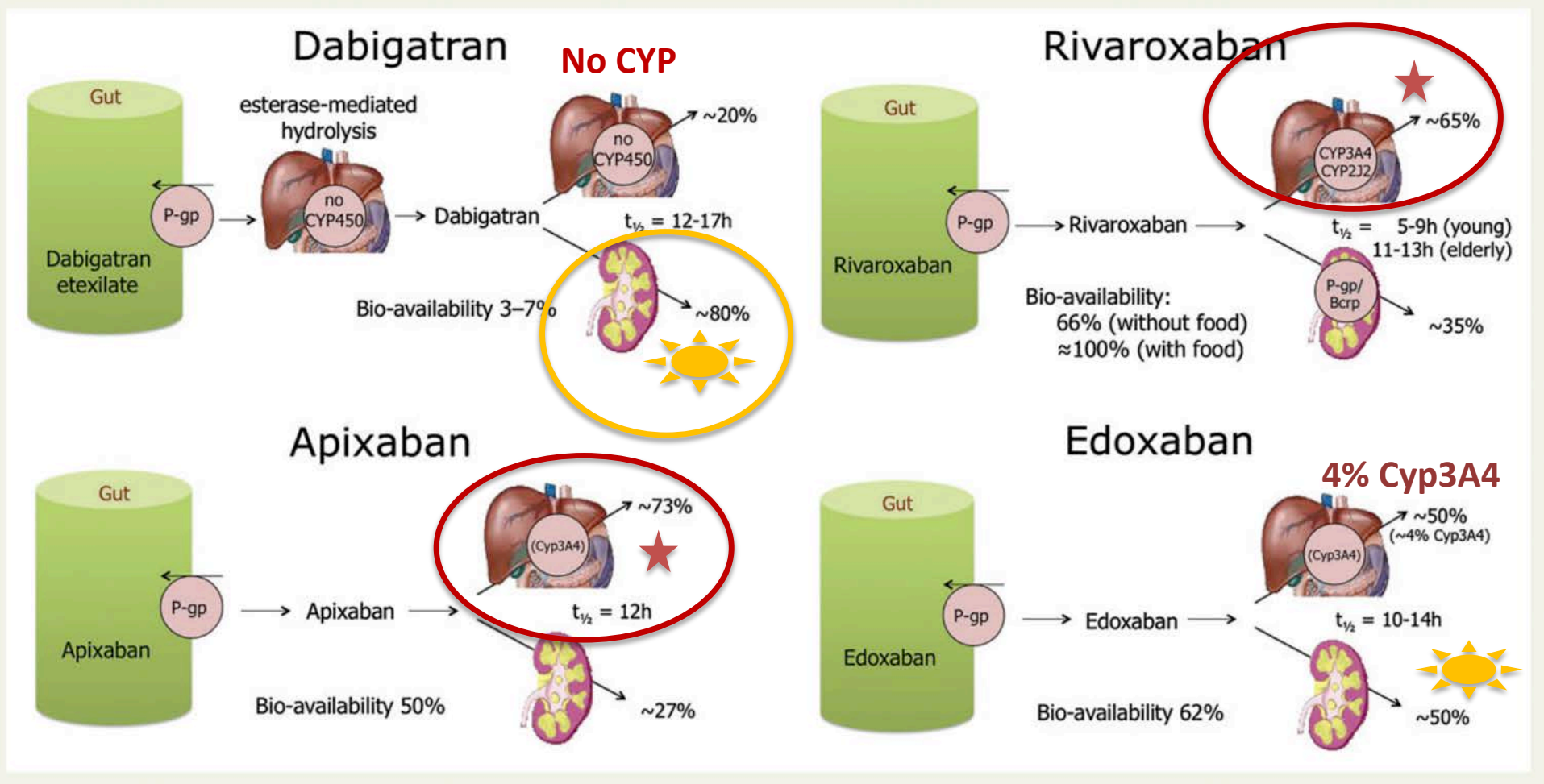
Drug interaction with warfarin

- Metabolites through CYP3A4, 2C9
- Phenytoin, phenobarbital and carbamazepine reduce the concentration of warfarin by up to 50-65%
- Phenobarbital and carbamazepine also reduce the anticoagulation effects of warfarin metabolites
- Newer AEDs do not have significant interaction with anticoagulant

Interaction between AEDs and NOACs

- Intestinal absorption and renal elimination of NOACs are dependent on the intestinal and renal permeability glycoprotein (P-gp) efflux transporter protein system
- Some NOACs are substrates of the hepatic CYP3A4 enzymes
- Induction of P-gp or CYP3A4 might decrease serum NOAC levels, reduce anticoagulant effects and lead to an increase in embolic risk.

Absorption and metabolism of the different new anticoagulant drugs



DE-RA

ESC European Society of Cardiology

Europace (2021) **00**, 1–65
doi:10.1093/europace/euab065

POSITION PAPER
EHRA PRACTICAL GUIDE

2021 European Heart Rhythm Association Practical Guide on the Use of Non-Vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation

Jan Steffel[1]*, Ronan Collins[2], Matthias Antz[3], Pieter Cornu[4], Lien Desteghe[5,6], Karl Georg Haeusler[7], Jonas Oldgren[8], Holger Reinecke[9], Vanessa Roldan-Schilling[10], Nigel Rowell[11], Peter Sinnaeve[12], Thomas Vanassche[12], Tatjana Potpara[13], A. John Camm[14], and Hein Heidbüchel[5,6]

Steffel J, et al. Europace 2021; 0:1-65

	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%[542]	-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)			

Other interaction between other drugs and ASMs

Therapeutic class	Selected examples	Antiepileptic drugs
Psychotropic agents	Fluoxetine, sertraline, trazodone	↑ Phenytoin
	Trazodone, fluoxetine, risperidone	↑ Carbamazepine
	Sertraline	↑ Valproic acid
Antimicrobials	Erythromycin, clarithromycin, ketoconazole, fluconazole	↑ Carbamazepine
	Ritonavir	
	Sulfonamides	↑ Phenytoin
	Carbapenems (imipenem, doripenem, meropenem, ertapenem)	↓ Valproic acid
Cardiovascular agents	Amiodarone	↑ Phenytoin (a dose reduction of approximately 25% is recommended)
	Diltiazem	↑ Carbamazepine, phenytoin (risk of toxicity)
	Clopidogrel	↑ Phenytoin
Analgesics	Acetaminophen	↓ Lamotrigine
Immunosuppressants	Methotrexate	↓ Valproic acid, carbamazepine

↑ and ↓ indicate increased and decreased levels and/or effects, respectively

Farrokh S, et al. Critical Care 2018;22:153

Epilepsia Open

SHORT RESEARCH ARTICLE

Carbapenems and valproate: A consumptive relationship

*†Peter Bede, ‡Diane Lawlor, ‡Damodar Solanki, and *§Norman Delanty

Epilepsia Open, 2(1):107–111, 2017
doi: 10.1002/epi4.12030

Table 1. Summary of the demographic and clinical profile of the cases

Case	Age	Sex	Pre-meropenem VPA dose	Last pre-meropenem VPA level	Duration of meropenem therapy	VPA measured after initiation of meropenem	VPA level during meropenem therapy	Patient symptomatic of low VPA	Intervention	Normalization of VPA levels post-meropenem therapy
1	55	Female	800 mg BD	19	+14 days	24 h	8	Yes; seizures	Increased dose + bolus + alternative AED	*RIP*
2	42	Male	600 mg BD	41	10 days	24 h	<3	No	No	4 weeks
3	24	Female	600 mg TDS	45	3 days	72 h	9	Yes; seizures	Increased dose + bolus + alternative AED	*RIP*
4	42	Male	625 mg BD	N/A	24 + 7 days	Meropenem introduced first	6	Yes; seizures	Increased dose + bolus	4 weeks
5	78	Male	600 mg BD	27	3 days	72 h	9	No, but intubated	Meropenem discontinued	*RIP*
6	25	Male	1,300/1,200 mg	106	7 days	7 days	11	Yes; seizures	No	Checked 2 months later
7	69	Female	300 mg BD	40	10 days	72 h	<3	Yes; hypomania	Increased dose	8 days

AED, antiepileptic drug; BD, twice a day; RIP, patient deceased; TDS, three times a day.

Epilepsia Open 2017;2:107-11

Issues of using ASM in the critically ill patients

- Side effects of ASMs that are even more important in the critically ill patients eg. cardiac arrhythmia, hypotension
- Drug- drug interactions
- Altered pharmacokinetic of ASMs in critical care patients
- Patients with liver and renal impairment

Altered pharmacokinetic of ASMs in ICU setting

- Decrease enteral absorption of medications due to decreased blood flow, dysmotility and interaction with enteral nutrition
- Bioavailability of active drugs is also affected by alterations in volume of distribution for hydrophilic medications
- Hypoalbuminemia increases the unbound (free) fraction of highly albumin-bound medications
- Induced hypothermia reduce the systemic clearance of many medications mediated by CYP450 (such as phenytoin or propofol), between 7 and 22% for every degree of Celsius below 37

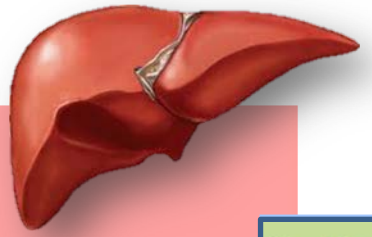
Farrokh S, et al. Critical Care 2018;22:153

Patients with hepatic and renal impairment

: IV form of antiseizure meds

:ASMs that excrete via renal route:

how should we use them?



▶ Hepatic Failure

Benzodiazepines

Carbamazepine

Felbamate

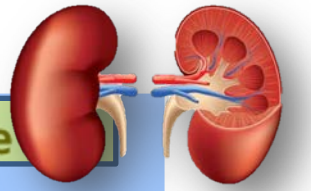
Phenytoin

Phenobarbital

Primidone

Rufinamide

Valproic acid and its derivatives



▶ Renal Failure

Gabapentin

Levetiracetam

Pregabalin

Vigabatrin

Extracorporeal removal of ASMs

Methods	Key factors for removal	Key properties of ASMs removed by this method	ASMs
Intermittent HD	Remove free fraction of drugs Key factors for removal via HD - Low protein binding - Low VD - Low molecular weight - Renally eliminated	Usually well described in the drug's prescribing information May need supplemental dosing after HD	LEV, LCM PB
CRRT	Estimations of drug removal can be performed to estimate the removal of medications by CRRT based on flow rates, as well as drug and filter properties	ASMs that are eliminated via HD (to more extent)	LEV, LCM, PB, TPM

CRRT= continuous renal replacement therapy,

Dosing adjustment for patients with impaired renal function

Creatinine clearance (mL/min)	Dosage (mg)
Gabapentin	
>60	400 tid
30-60	300 bid
15-30	300 od
<15	300 every other day
hemodialysis	200-300* supplement
Levetiracetam	
>80	500-1500 bid
50-80	500-1000 bid
30-50	250-750 bid
<30	250-500 bid
hemodialysis	500-1000*q 24 hr then 250-500 mg supplement

***with supplement dose after HD**

ASMs removal by CRRT and recommended dosages

Antiepileptic drug	Initial dosing considerations
Carbamazepine	Not significantly removed by CRRT
	Not dose adjustment required
	Monitor carbamazepine level
Gabapentin	Not sufficient data
	Initiate dosing for CL_{CR} 20–50 mL/min [1]
Lacosamide	Not sufficient data
	Likely removed by CRRT; no dose adjustment
Levetiracetam	Regular dosing has been recommended; half-life and volume of distribution close to those in patients with normal renal function
	Suggested initial dose 1 g q12 h [6–8]
	Monitor drug concentration, if available
Phenobarbital	No initial dose adjustment
	Possible significant removal by CRRT
	Monitor phenobarbital level
Phenytoin/ Fosphenytoin	No initial dose adjustment
	Monitor free phenytoin
	Albumin correction equations might not be accurate; however; free fraction is expected to be elevated if albumin <3 g/dL
Topiramate	Not sufficient data
	Likely removed by CRRT
	Initiate dosing for CL_{CR} 20–50 mL/min [1]
Valproic acid	No initial dose adjustment
	Monitor free valproic acid level, if available
	If free concentration not available, monitor total concentration
	Free fraction might be >20 % especially in patients with low albumin

CL_{CR} creatinine clearance, *q12h* every 12 hours

Mahmoud SH. Clin Drug Investig 2017; 37:7–23

Extracorporeal removal of ASMs

Methods	Key factors for removal	Key properties of ASMs removed by this method	ASMs
PLEX	Remove whole plasma (free fraction and protein bound portion) Key factor in removal of a drug with PLEX - volume of distribution - duration/frequency of PLEX - exchange volume	In general, drugs with low VD (< 0.2 L/kg) predominantly reside in the vascular compartment and PLEX would be expected to remove a significant portion of the total body stores of these drugs	VPA (0.2) PB, LEV, TPM, PGB, BRV (0.5)
ECMO	Sequester drugs given the large surface area of the tubing and membranes which can result in an increase in the VD initially, while later releasing the drug into the circulation resulting in an unpredictable effect	Lipophilic and highly protein-bound drugs are considered to be particularly vulnerable	Midazolam Propofol Phenobarbital

ECMO= extracorporeal membrane oxygenation

ECMO is typically associated with reduced drug clearance as a result of alterations of end-organ perfusion. ECMO is also often combined with some form of RRT, further complicating predictability.

NARRATIVE REVIEW

Antiseizure medication dosing and monitoring in the intensive care unit: a practical narrative review

Andrew J. Webb[1*], Brooke Barlow[2], Stephanie L. Seto[3], Carolina B. Maciel[4], Joanna Brennan[5] and Aaron M. Cook[6]

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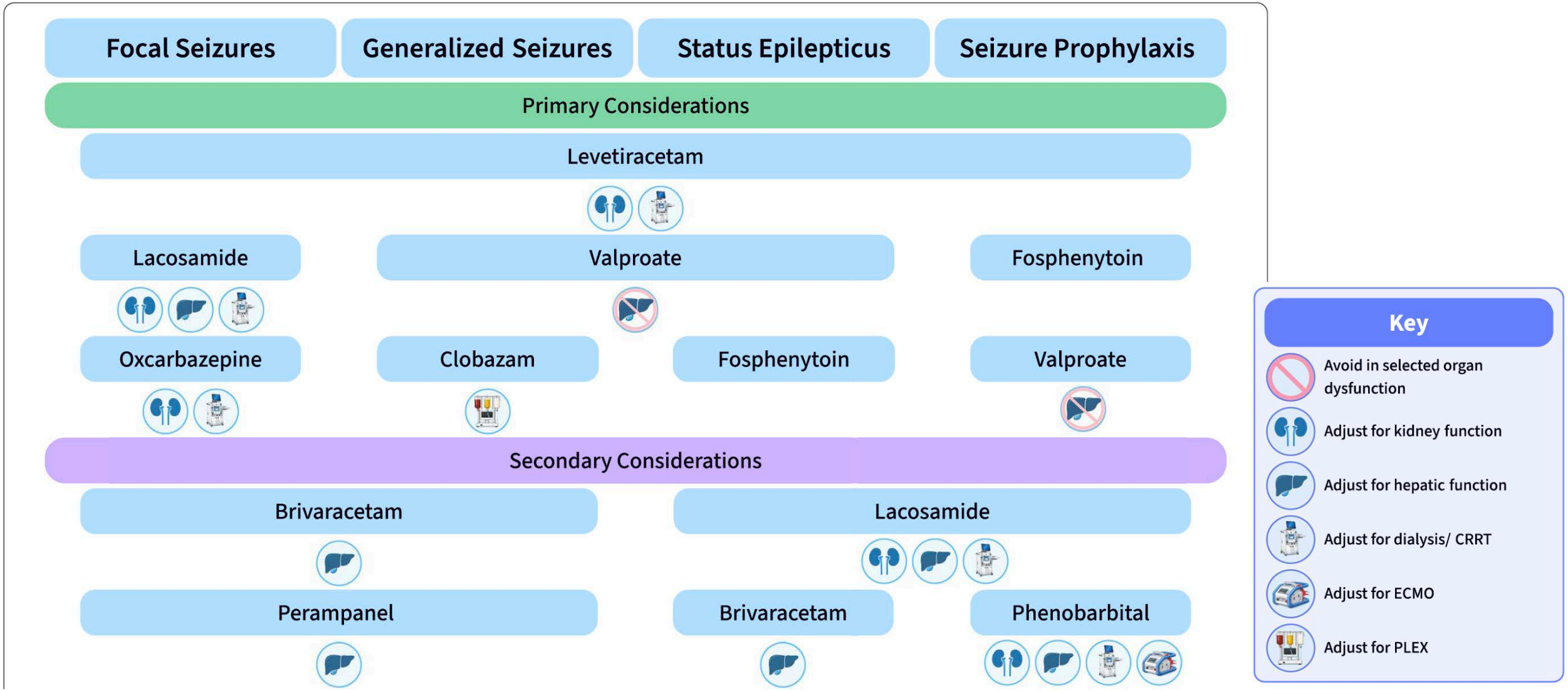
Intensive Care Med 2026
https://doi.org/10.1007/s00134-026-08550-y



Intensive Care Med 2026
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Antiseizure Medications	Renal replacement therapy				ECMO	PLEX
	HD	CRRT				
		< 2 L/h	2–3 L/hr	> 3 L/h		
Brivaracetam	*No adjustment necessary**					
Cannabidiol	*No adjustment necessary**				Higher doses may be needed*†	*No adjustment necessary**
Carbamazepine	*No adjustment necessary*†				Higher doses may be needed*†	Administration post-PLEX†
Cenobamate	*No adjustment necessary**					
Clobazam	*No adjustment necessary*				*No adjustment necessary**	Administration post-PLEX
Lacosamide	Administer 50% of maintenance dose post-HD	50–200 mg q12	50–200 mg q8-12	100–200 mg q6-12	*No adjustment necessary*	
Lamotrigine	*No adjustment necessary**					
Levetiracetam	Administer 50% of maintenance dose post-HD *or* 250–750 mg q12	250–1000 mg q12	500–1250 mg q12	500–1500 mg q6-12	*No adjustment necessary*	
Oxcarbazepine	Slower up-titration, otherwise no adjustment necessary†				*No adjustment necessary*	
Perampanel	*No adjustment necessary**					
Phenobarbital	Administer 50% of maintenance dose post-HD†	Use higher (2–3 mg/kg/day) initial maintenance dosing†				*No adjustment necessary*
Phenytoin	*No adjustment necessary (monitor free concentrations)*†					
Topiramate	Administer 50% of maintenance dose post-HD	Consider initiating at lower dose (25–50 mg q12) and up-titrate guided by tolerability (up to 200 mg q12)			*No adjustment necessary**	
Valproate	*No adjustment necessary (monitor free concentrations)*†					
Zonisamide	Administer 50% of maintenance dose post-HD	Consider initiating at lower dose (25–50 mg q12) and up-titrate guided by tolerability (up to 300 mg q12)			*No adjustment necessary**	

CRRT continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *HD*: hemodialysis, *PLEX* plasmapheresis

* Limited to no data available, recommendations based on expert opinion

† Consider TDM to guide dosing

Intensive Care Med 2026
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Antiseizure Medications	Renal replacement therapy				ECMO	PLEX
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Valproate	*No adjustment necessary (monitor free concentrations)*†					
Zonisamide	Administer 50% of maintenance dose post-HD	Consider initiating at lower dose (25–50 mg q12) and up-titrate guided by tolerability (up to 300 mg q12)			*No adjustment necessary**	

CRRT continuous renal replacement therapy, *ECMO* extracorporeal membrane oxygenation, *HD*: hemodialysis, *PLEX* plasmapheresis

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Intensive Care Med 2026
https://doi.org/10.1007/s00134-026-08550-y

Executive Summary

1. **Critical illness alters ASM pharmacokinetics**. Standard outpatient dosing often does not generalize to ICU patients given changes in volume of distribution, organ dysfunction, augmented renal clearance, and extracorporeal devices (CRRT, ECMO, PLEX). Dosing must be individualized rather than "one-size-fits-all."
2. **Loading doses of many ASMs can accelerate time to effective concentrations in status epilepticus**. Beyond overcoming pharmacokinetic changes seen in critical illness, loading doses help counteract pharmacodynamic changes such as receptor internalization that occur with prolonged seizure activity. Furthermore, maintenance doses often exceed manufacturer dosing recommendations and titration occurs faster than outpatient titration
3. **Therapeutic drug monitoring (TDM) is valuable in the ICU but has important limitations**. Protein binding alterations in critical illness make free drug measurement preferable to total levels for agents like phenytoin and valproate if TDM is pursued. For most newer ASMs, concentration–response targets have not been identified
4. **ASMs have notable drug–drug interactions with common ICU medications**. Clinicians must proactively screen for DDIs with ASMs. A critical example is carbapenems and valproate; carbapenems reduce valproate concentrations by over 70% and cannot be overcome by dose escalation. Complex interactions (e.g., CYP450 enzyme inhibition or induction and protein binding changes) can be seen with many medications used in the ICU
5. **Evidence gaps are substantial, especially for newer ASMs**. Most ASM dosing guidance is extrapolated from outpatient data. Concentration-effect relationships have not been established for the majority of ASMs in critically ill patients, and the tolerability of aggressive ICU dosing strategies remain poorly characterized

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CONCLUSION

Early Maximize Usage of ASMs in Epilepsy Patients

- Seizures in the emergency rooms
  - First unprovoked seizures
  - Acute symptomatic seizures
- Seizures in the inpatient setting
  - Acute symptomatic seizures

Considerations when treating acute symptomatic seizures

- High seizure recurrence rate in the acute setting → often need ASMs that can be given IV to achieve quick therapeutic levels
- High morbidity and mortality
- Patients often have multiple medical problems or are critically ill patients
- Patients often are on multiple medications

Issues of using ASM in the critically ill patients

- Side effects of ASMs that are even more important in the critically ill patients eg. cardiac arrhythmia, hypotension
- Drug- drug interactions
- Altered pharmacokinetic of ASMs in critical care patients
- Patients with liver and renal impairment

Available IV antiseizure medications

	Route of administration	Adult dose	Pediatric dose
Phenytoin	IV (<25-50 mg/min)	15-20 mg/kg	20 mg/kg at 25 mg/min
Fosphenytoin	IV (<50-100 mg PE/min)	15-20 mg PE/kg	na
Phenobarbital	IV (<100 mg/min)	10-20 mg/kg	15-20 mg/kg
Valproate	IV (50-200 mg/min)	20-40 mg/kg	20-40 mg/kg
Levetiracetam	IV (100-300 mg/min)	20-60 mg/kg	30-40 mg/kg
Lacosamide	IV (over 15-60 min)	200-400 mg	

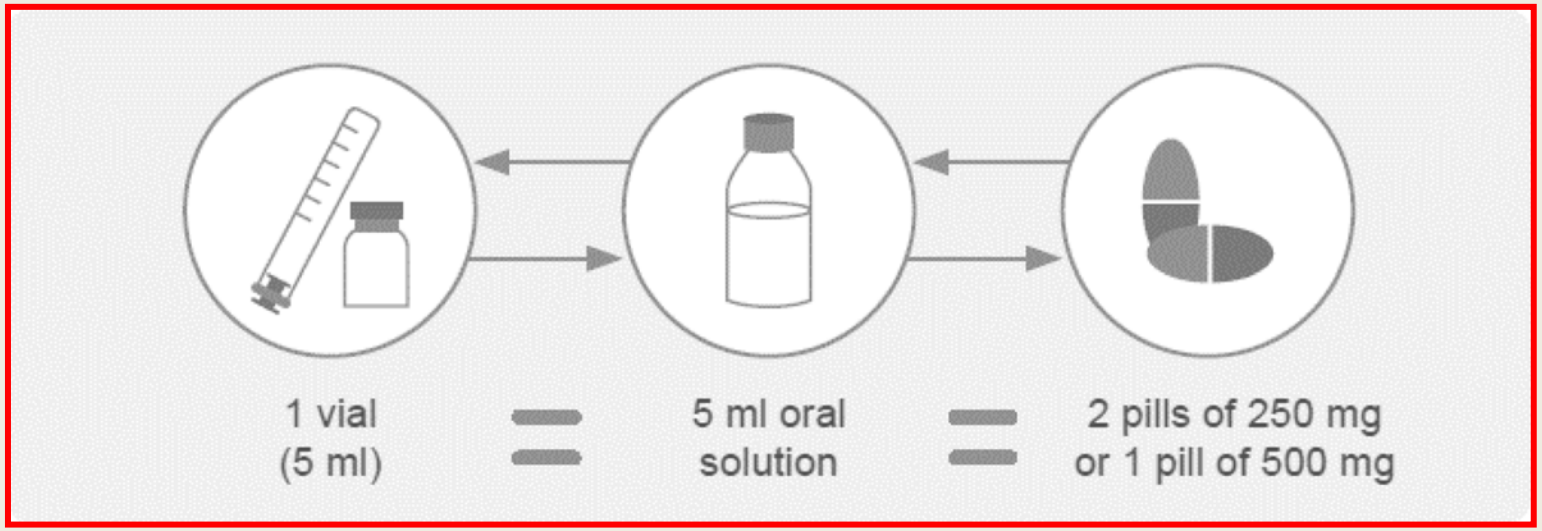
Shorvon S. Curr Opin Neurol 2011;24:165–170

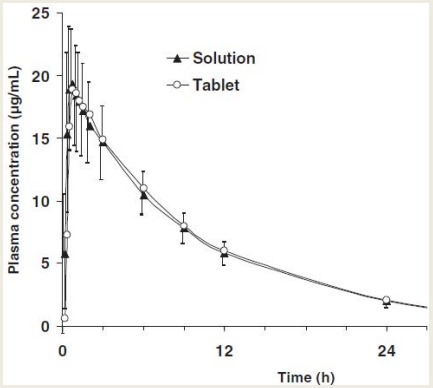
Ideal ASMs

- Broad spectrum/ new mechanism of action
- Good efficacy
- Good tolerability
- Available IV formulation
- Good pharmacokinetic properties
- Low protein binding
- Not a strong enzyme inducer or inhibitor/ no or minimal drug interaction
- Fewer serious adverse events
- Availability/reimbursability

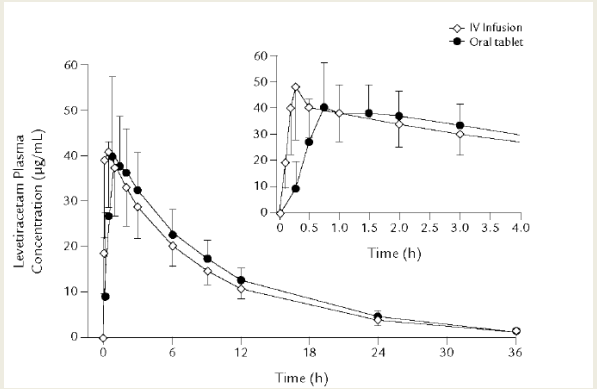
Levetiracetam

Complete line between formulation





Mean levetiracetam plasma concentration-time profile in healthymale and female subjects following single oral 750-mg Doses administered as either a tablet () or a10%solution (). Data are expressed as the mean ± standard deviation (n = 24)[1].



Mean (SD) plasma concentrations of levetiracetam overtime after administration of a single IV (1500 mg) or oral (three 500-mg tablets) dose (n = 17). The inset shows the interval from 0 to 4 hours. Limit of quantification, 0.5 pg/mL[2].

1. Coupez R., Straetemans R., et. al. Levetiracetam: Relative Bioavailability and Bioequivalence of a 10% Oral Solution (750 mg) and 750-mg. J. Clin. Pharmacol. 2003; 43; 1370-6.
2. Ramael S, De Smedt F,Toubianc N, et al. Single-Dose Bioavailability of Levetiracetam Intravenous Infusion Relative to Oral Tablets and Multiple-Dose Pharmacokinetics and Tolerability of Levetiracetam Intravenous Infusion Compared with Placebo in Healthy Subjects. Clin Therapeu. 2006;28:734-44

Questions?