2023 GW Epilepsy Board Review & Best Practices

Status Epilepticus Review

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Case 1: 21 y/o female college student

- 2 days viral syndrome: headache, mild fever
- 12 hours confusion, bizarre behavior (shrieking at dorm counselor, confused, ran into bathroom)
- Agitated, confused, disoriented in ED
- Fever, serum wbc 15,000, electrolytes NL
- Repeated seizures with staring, limb shaking, & stiffening lasting 1-2 minutes, recur every 5 minutes
- Evaluation and treatment?

Case 1: 21 y/o female college student

- iv lorazepam 2 mg; seizures cease, levetiracetam 2000 mg, persisting confusion
- Toxicology screen NL; CSF: wbc 300 (80% lymphocytes), rbc 150, protein 90, glucose 55
- CT: possible inferior temporal blood & swelling
- Seizures recur: 5 TC seizures in 1 hour, temperature 40°, BP 90/50, pulse 110 bpm
- Diagnosis and treatment?

Evolving definition of status epilepticus

- 1981 ILAE: prolonged or repeated seizures without recovery
- 1993: EFA—seizure lasting 30 minutes
  - *Animal data showing loss of autoregulatory mechanisms; metabolic decompensation, risk of excitotoxicity with irreversible neuronal injury (Meldrum BS)*
- 2015 ILAE: convulsive SE
  - *T1: failure of seizure to terminate without intervention—typically 5 minutes*
  - *T2: neuronal & network injury—typically 30 minutes*

Recognizing stages of status epilepticus

- **Initial treatment: BZD**
  - ***Seizures despite initial BZD tx= established SE***
- **Second step therapy with Antiseizure medications (ASMs), e.g. PHT, LEV, LCM, PB, VPA**
  - ***Persisting seizures: resistant SE (rSE)***
- **Anesthesia tx (midazolam, propofol, ketamine, pentobarbital, thiopental)**
  - ***Persisting seizures >24 hours: super refractory SE***

Status Epilepticus: Convulsive

- **ILAE: 2015:** Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point T1). It is a condition, which can have long-term consequences, including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures" (after time point T2). Usual T1: 5 minutes; T2: 30 minutes.
- **Established SE**: seizures persisting with early BZD treatment
- **Refractory SE:** seizures persisting despite BZD & iv ASM, usually >60 minutes
- **Super Refractory SE:** seizure >24 h despite anesthesia)

Status Epilepticus: non-TC seizure types

- **Myoclonic (with/without coma)**: generalized epilepsy, neurodegenerative, infectious/inflammatory, toxic/metabolic, post-anoxic
- **Focal motor**: often focal lesions, includes epilepsia partialis continua, often with Rasmussen syndrome,, hyperglycemia, ictal paresis
- **Tonic status**: autonomic manifestations, mostly children (LGS), ictal beta often
- **Hyperkinetic**: motor seizures, proximal limbs/axial muscles, often premotor; from sleep; genetic causes (ADNFLE)
- **Nonconvulsive with and without coma**

Facts: convulsive SE:

- 5% of epilepsy patients present with SE or experience SE
- Convulsive SE obvious, serious; outcome correlates with early tx and etiology
- Nonconvulsive SE subtle:
  - *eye lid twitching, confusion, prior history of seizures or precipitants usually*
- Annual incidence: 18 to 41 per 100,000
- Approximately 5% presenting with SE, psychogenic

SE: epidemiology

- **Country incidence rates: 9 to 40 per 100,000**
  - ***18/100,00 Rochester MN study***
  - ***35/100,000 Salzburg, Austria study***
  - ***Increased rates with infants, elderly & with EEG screening***

Ascoli M, Ferlazzo E, Gasparini S, Mastroianni G, Citraro R, Roberti R, Russo E. Epidemiology and Outcomes of Status Epilepticus. Int J Gen Med. 2021

SE: etiologies

- **Richmond SE study: epilepsy (low ASM levels); remote etiologies (most structural) & stroke—either acute or remote**
- **Acute Causes:**
  - ***stroke most common***
  - ***Others: anoxic injury, infection, alcohol intoxication/withdrawal, metabolic (hyponatremia & low or high glucose) autoimmune, encephalitis.***
- **Chronic causes: structural most common (tumor, stroke trauma).**

Ascoli M, Ferlazzo E, Epidemiology and Outcomes of Status Epilepticus. Int J Gen Med. 2021

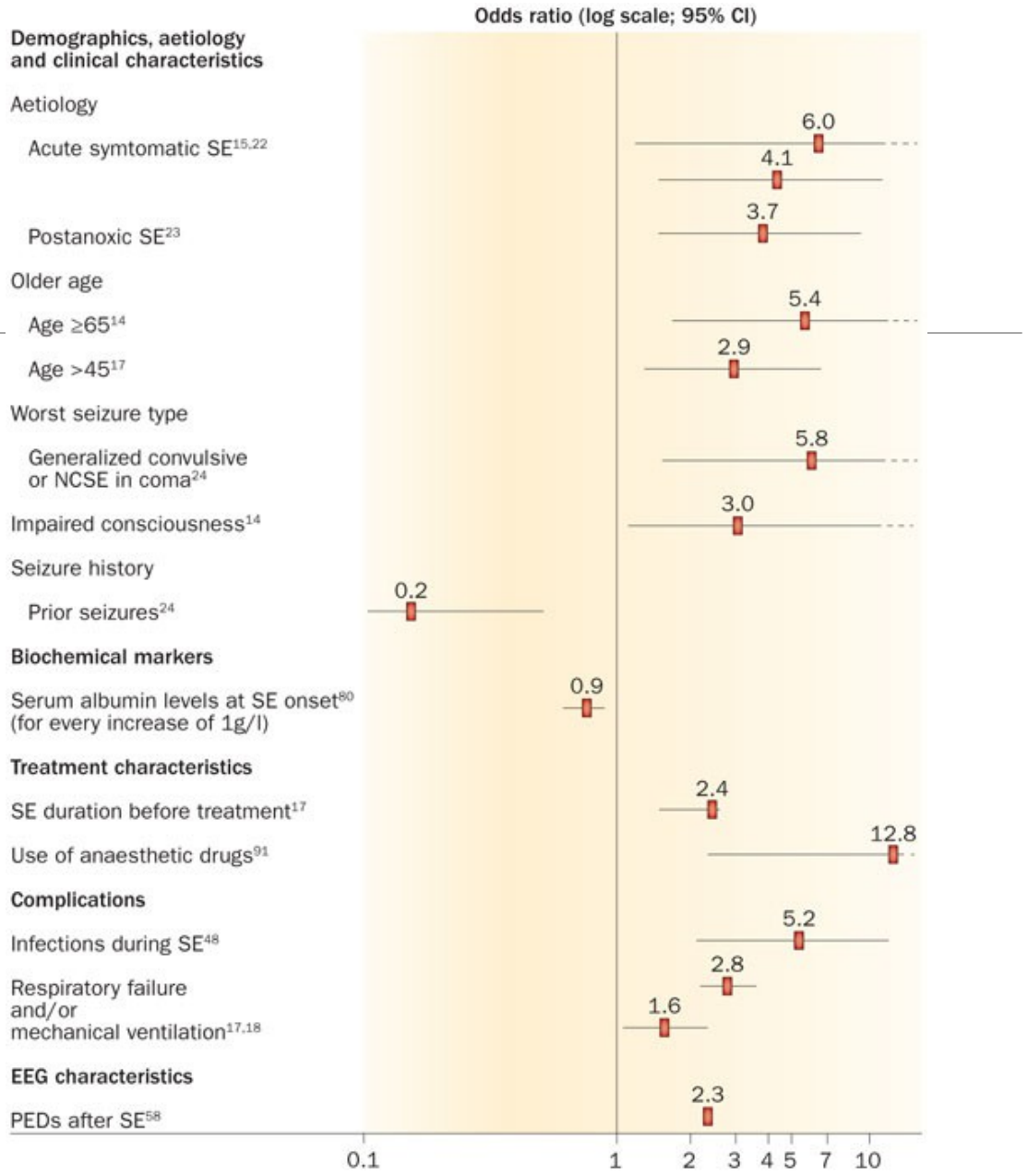
Common causes: status epilepticus

- Uncontrolled epilepsy: 5% new onset
- Cerebral injury: brain contusion, CVA, hemorrhage, hypoxia
- Brain tumor: primary & metastatic
- Electrolyte disturb: hypoglycemia,hyponatremia, low calcium
- Drug/alcohol overdoses or withdrawal: Alcohol ↓ 18 to 30 hrs; cocaine, amphetamine overdoses
- Encephalitis/meningitis: herpes, other viruses
- NORSE: New Onset Refractory SE (50% auto-immune/paraneoplastic)

SE: Prognosis

- 12-43% progress to refractory SE (persists despite BZD & second ASM; anesthesia often required)
- 10-15% progress to super-refractory SE (persists >24 hours despite anesthesia tx)
- Mortality correlates with etiology & delayed treatment (30% mortality).
- Prognosis scales:
  - *STESS: Level of consciousness, worst seizure type, age, history of seizure*
  - *EMSE: etiology, duration, comorbidity, age, EEG level of consciousness, modified Rankin*

Odds ratios of risk factors for death in SE:



Sutter, R., Kaplan, P. & Rüegg, S. Outcome predictors for status epilepticus—what really counts. *Nat Rev Neurol* **9**, 525–534 (2013)

SE: Mortality

- Nonrefractory SE: 9.6%
- Refractory SE: up to 39.5% mortality
- Super Refractory SE: up to 37.5%
- New onset refractory SE (NORSE): 23%
- Childhood: SRSE: 10%; RSE: 1.9%; non-refractory SE: 0%
- Recurrent SE: 2% versus initial 22%
- Higher mortality: ICH, psychosis, DM, renal/hepatic disease, >4 days hospitalization.
- Higher mortality (18%) with PB/thiopental treatment –vs- lower (<10%) midazolam/propofol.

Trinka E et al. Frontiers in Epidemiology; 2023.

Treatment guidelines:

- 0-5 minutes: Stabilization of patient
- 5-20 minutes: BZD; may repeat in 5-10 minutes
- 20-40 minutes: a single dose of non-BZD ASM
- 40-60 minutes (or five minutes after second BZD dose at 15 minutes): initiate EEG & treat with third-line ASM
- Intubation or second non-BZD ASM
- Anesthesia for rSE

Treatment Algorithm: SE

Time:		**Notes**
<10mins	IV Access **Lorazepam** 2-4 mg IV push over 2 min; Repeat after 5 min only if seizures	CAB: Circulation Airway, Breathing Thiamine 100 mg iv; dextrose
10-30 min	Levetiracetam, Valproate, Phenytoin iv load Or Phenobarbital 15 mg/kg IV; 60 mg/min max,	Labs: Glucose, BMP, Ca, Mg, P, LFTs, ABG
>30 min	Additional lorazepam load; Midazolam, propofol, phenobarbital loads	Screen etiologies: Head CT; history, LP-CSF

IV AED Options

Benzodiazepines
- Diazepam
- Lorazepam
- Midazolam

Phenytoin

Fosphenytoin

Phenobarbital

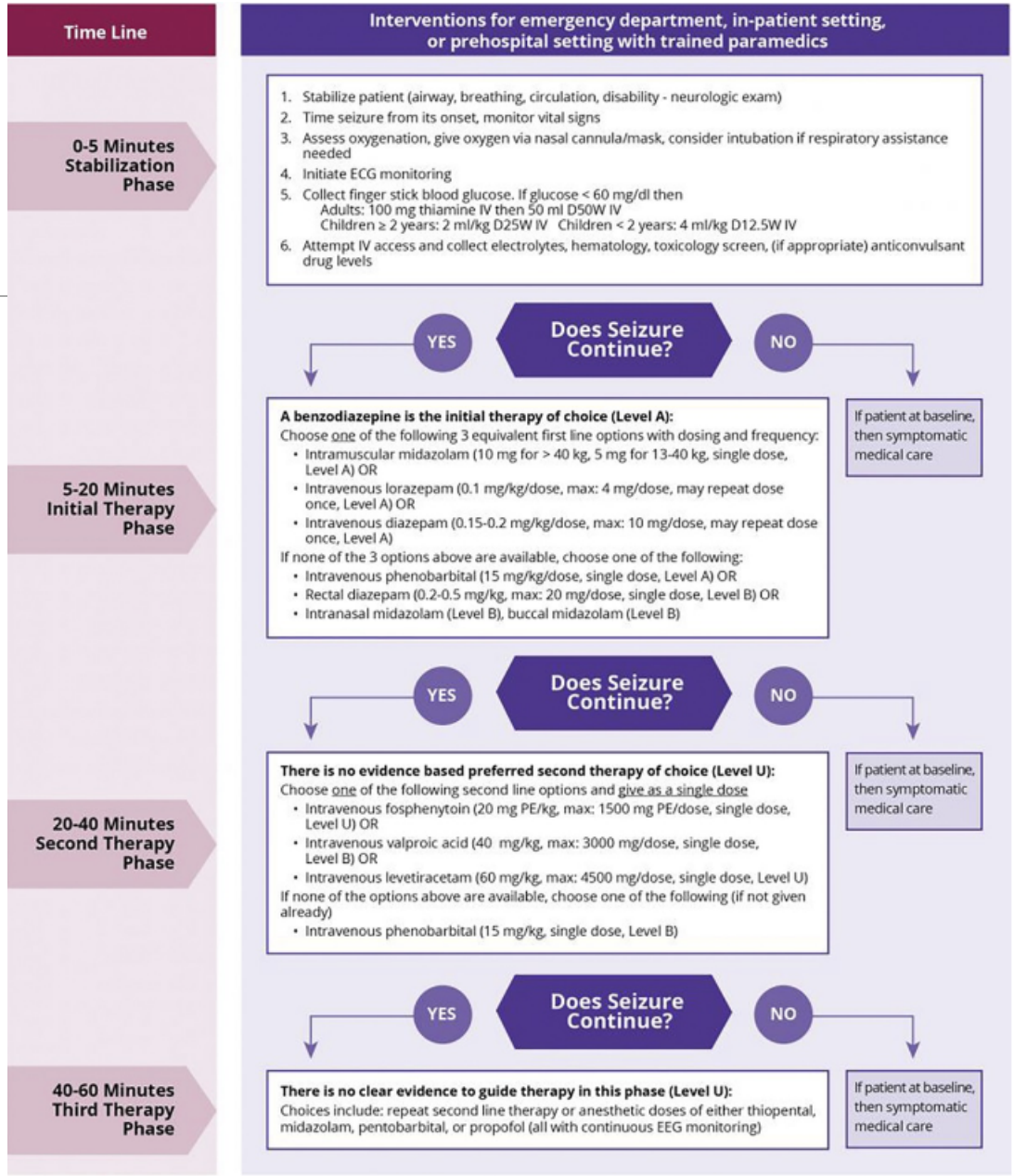
Valproate sodium

Levetiracetam

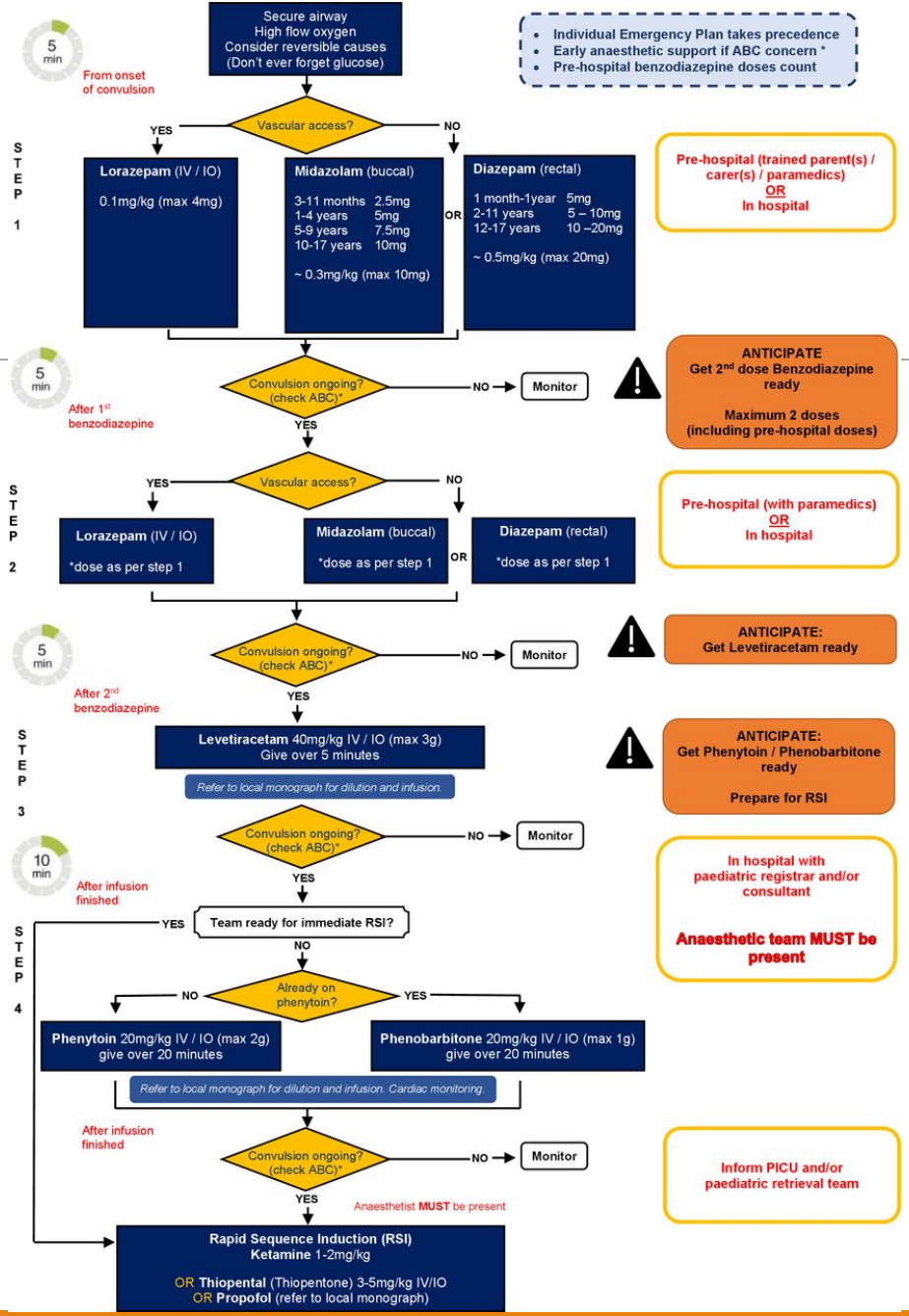
Lacosamide

Anesthetic agents

American Epilepsy Society: Convulsive SE Treatment Guideline



Pediatric SE therapy: APLS guidance:



Bacon M, Appleton R, Bangalore H, et al. Arch Dis Child Educ Pract Ed 2023;108:43–48.

Established status epilepticus treatment trial

The NEW ENGLAND JOURNAL of MEDICINE

Trial of Three Anticonvulsant Medications for Status Epilepticus

MULTICENTER, RANDOMIZED, DOUBLE-BLIND TRIAL

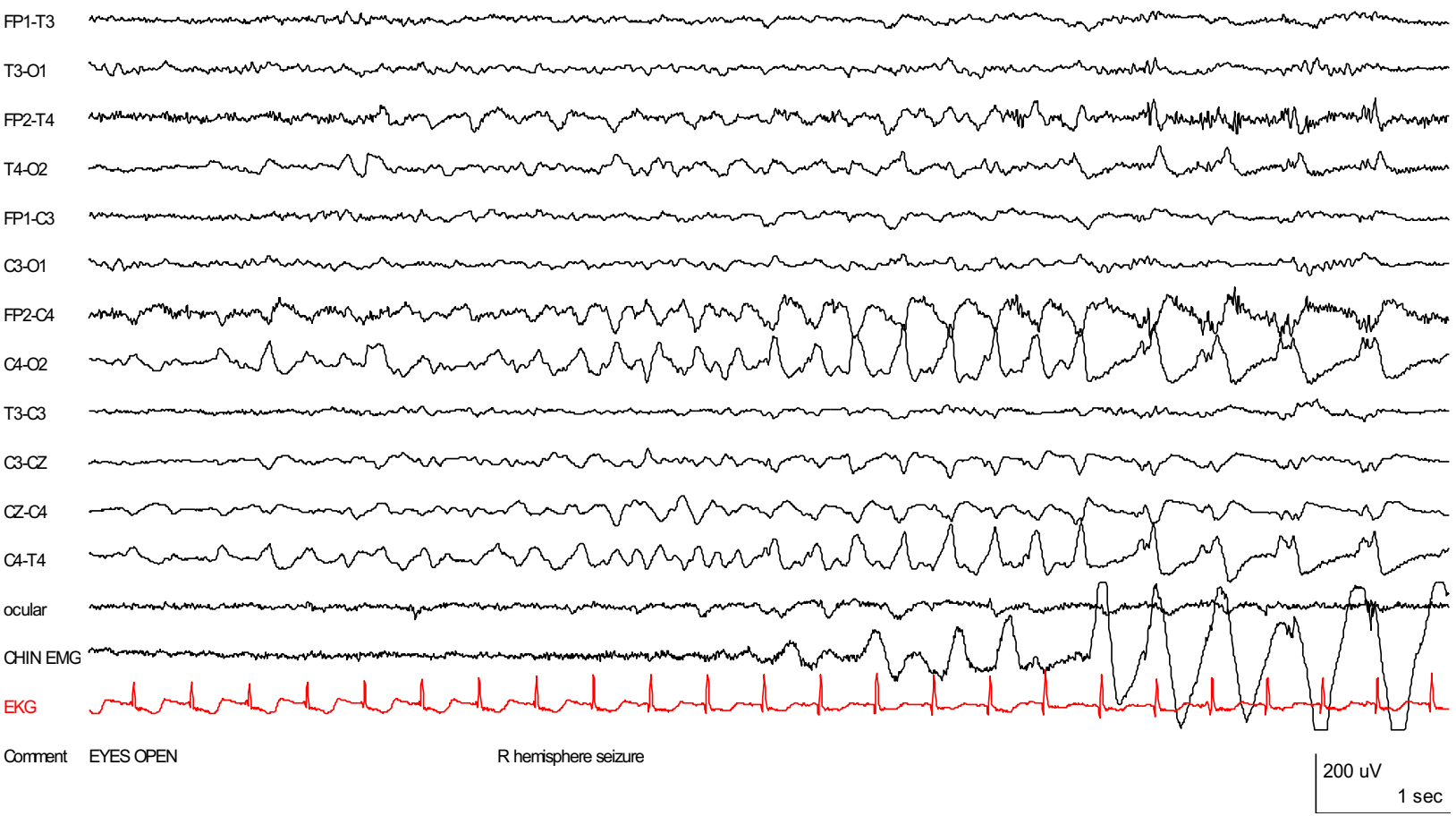
384
Children and adults with benzodiazepine-refractory status epilepticus

	Levetiracetam	Fosphenytoin	Valproate
	 60 mg/kg	 20 mg/kg (phenytoin equivalents)	 40 mg/kg
Absence of clinically evident seizures and improved responsiveness at 60 min	47% (68/145)	45% (53/118)	46% (56/121)

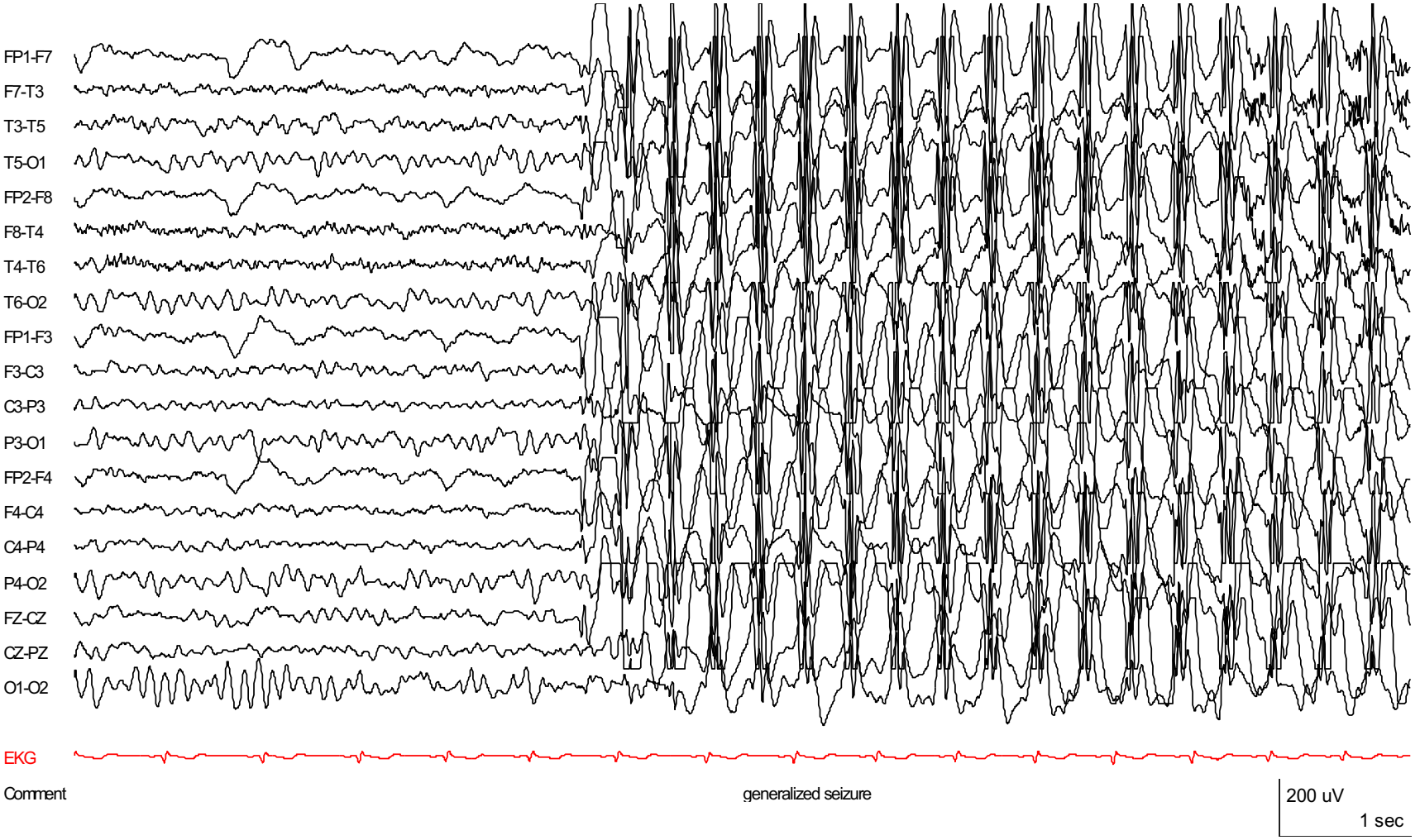
No significant difference in rates of seizure cessation or in safety

J. Kapur et al. 10.1056/NEJMoa1905795

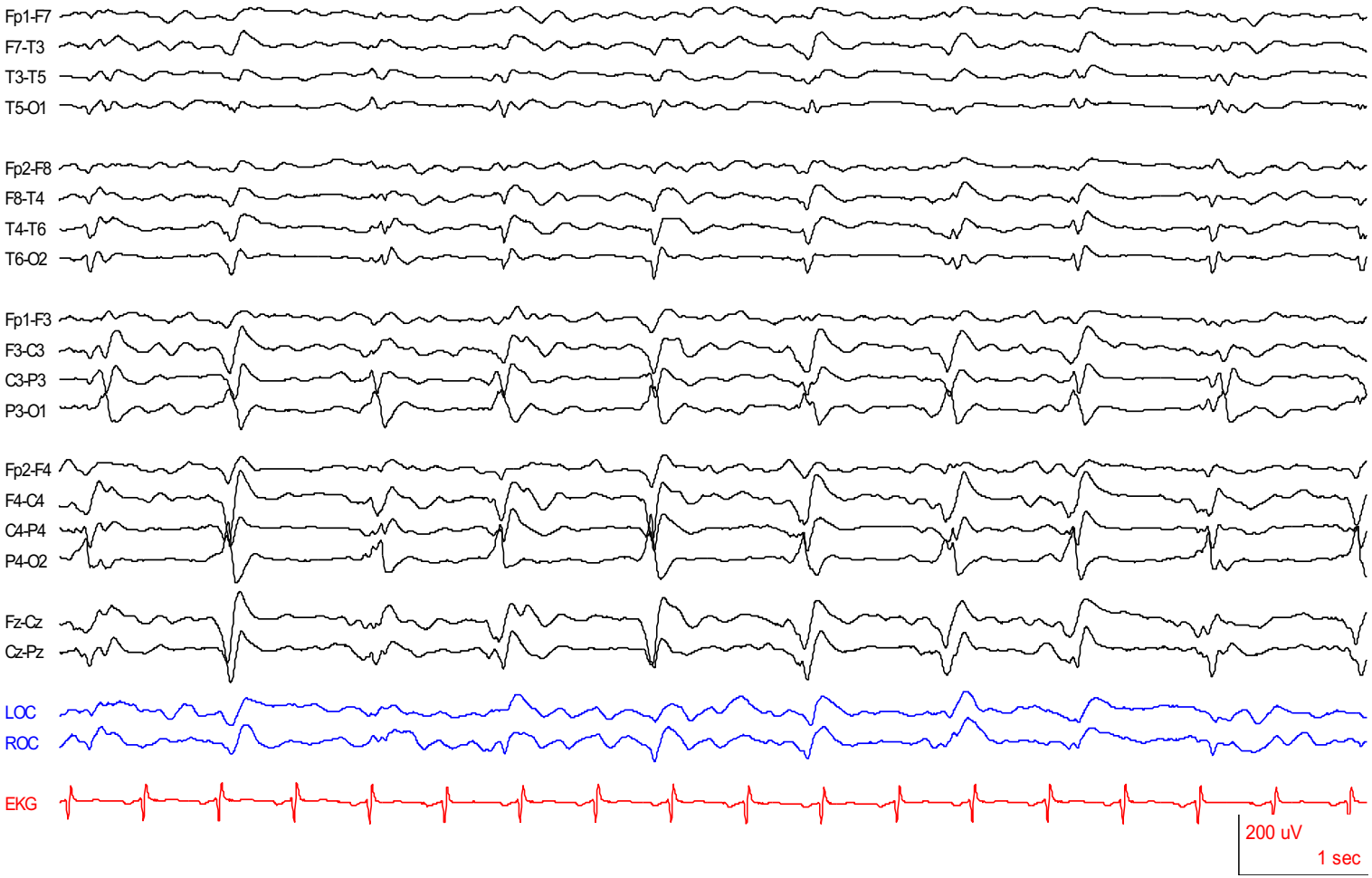
Onset of focal seizure



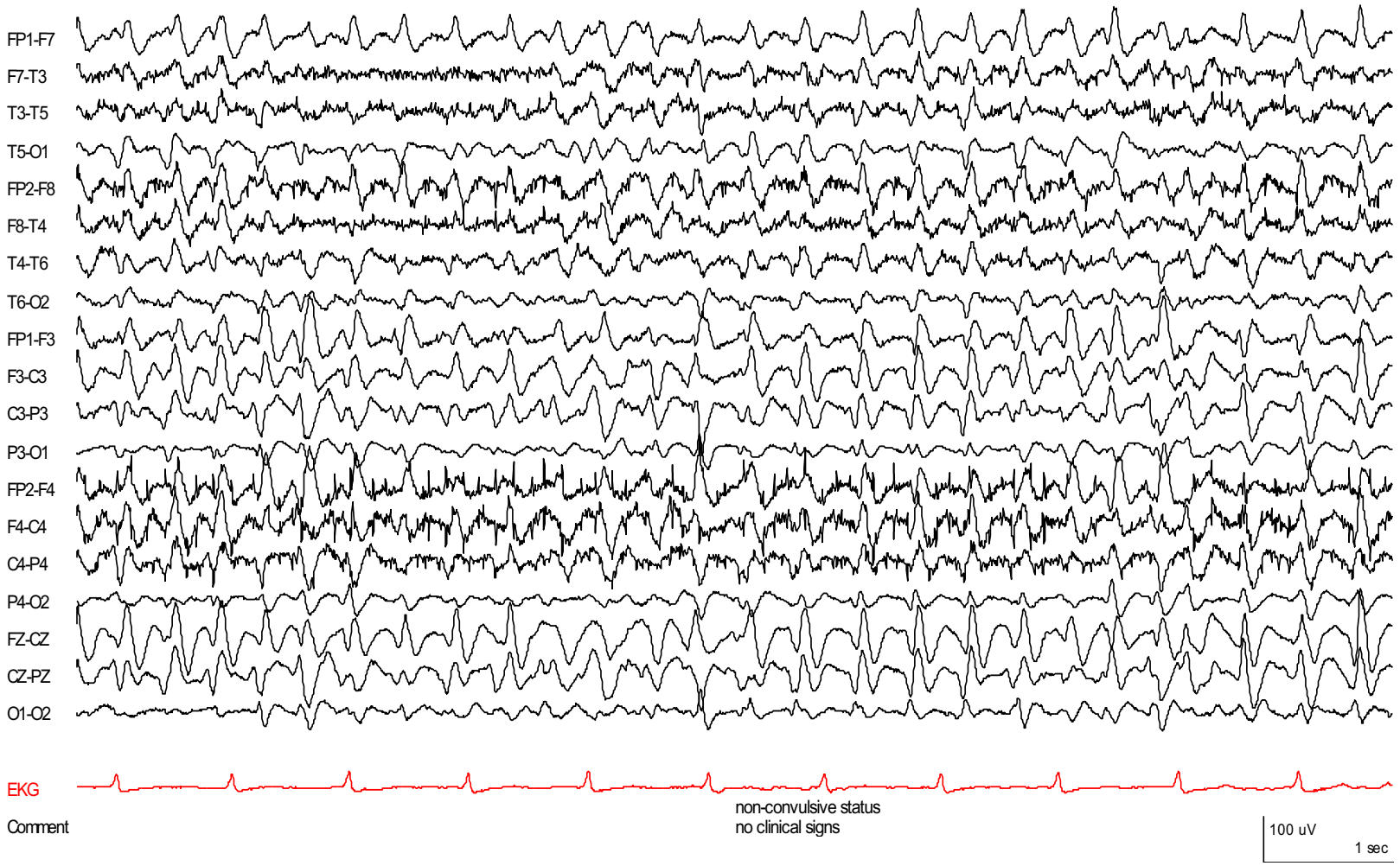
Onset of generalized seizure



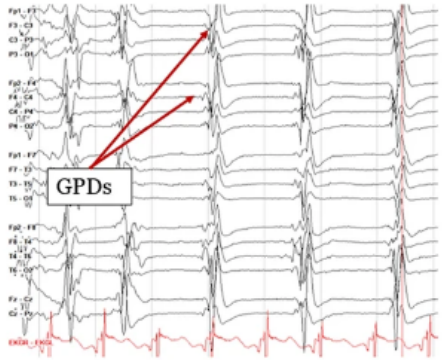
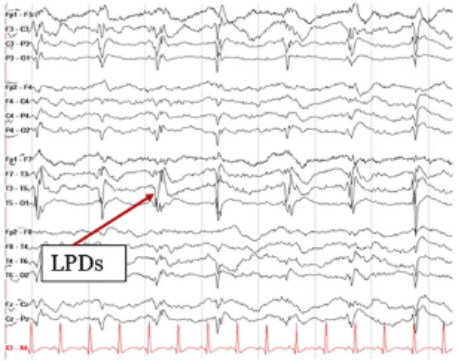
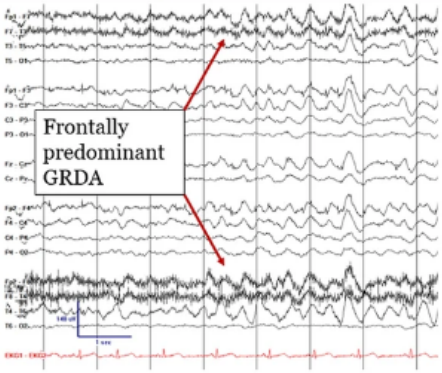
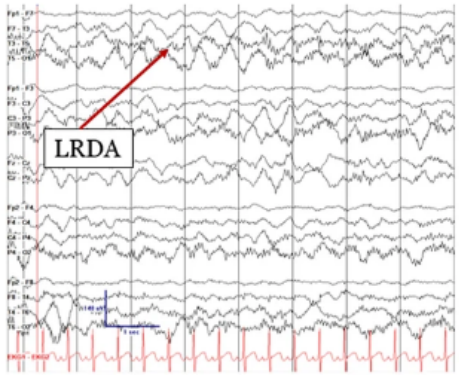
Late status epilepticus (PD)



Non-convulsive status epilepticus



Periodic & rhythmic patterns in critical care EEG: seizure associations

EEG Pattern	Generalized		Lateralized	
Periodic Discharges (PDs) [102-113]		Incidence: 3-7% Associations: - Status epilepticus - Hypoxic-ischemic brain injury - Toxic-metabolic encephalopathy - Anesthetic wean Seizure risk: 63-100%		Incidence: 0.5-7% Associations: - Stroke - Intracranial hemorrhage - Meningoencephalitis - Anesthetic wean Seizure risk: 61-100%
Rhythmic Delta Activity (RDA) [102, 103,114-118]		Incidence: 1.6-2.4% Associations: - Toxic-metabolic encephalopathy - Midline lesions Seizure risk: No strong association with seizures		Incidence: 0.8-1.6% Associations: - Focal structural abnormality - Post-ictal slowing Seizure risk: 64-100%

GPD: generalized periodic discharges, *GRDA:* generalized rhythmic delta activity, *LPD:* lateralized periodic discharges, *LRDA:* lateralized rhythmic delta activity

Benedetti GM. Neurocritical Care; 2023

Early Status Epilepticus: First stage in/out of hospital

TIME	DRUG TREATMENT		GENERAL MEASURES	EMERGENCY INVESTIGATIONS
5-20 min	Adults	Children		
	Lorazepam i.v. 4 mg bolus or	Lorazepam i.v. 0.1 mg/kg (max 4 mg) or	Airway; oxygen	Glucose, Na, K, Ca
	Diazepam i.v. 10 mg	Diazepam i.v. 0.3 mg/kg (max 10 mg)	Cardiorespiratory function and regular monitoring; ECG, blood pressure, SpO2	Levels of AEDs Toxicology screening
			Intravenous access; i.v. glucose, thiamine, pyridoxine (children) Treat acidosis	Kidney and liver function tests

If seizure continues → Established Status Epilepticus treatment

Kalvianen R, Epilepsia (S8), 2007

Established Status Epilepticus: Second stage: treatment in ED or hospital

TIME	DRUG TREATMENT	GENERAL MEASURES	EMERGENCY INVESTIGATIONS
20-60 min	Fosphenytoin i.v. 15-18 mg PE/kg at max. rate of 150 mg PE/min or	Cardiorespiratory function and monitoring	CT scan for etiology
	Levetiracetam; Lacosamide; VPA	ECG, blood pressure, SpO2, use pressors if needed	CSF for CNS infection
	or in children: Phenobarbital i.v. 15-20 mg/kg max. rate of 100 mg/min	Identify and treat medical complications	EEG for “pseudostatus” or NCSE evolution

If seizure continues → Refractory status epilepticus treatment

PE: phenytoin equivalents; SpO2: pulse oximetry.

Kalvianen R, Epilepsia (S8), 2007

Refractory Status Epilepticus: Third stage: treatment in ICU

TIME	DRUG TREATMENT	GENERAL MEASURES	EMERGENCY INVESTIGATIONS
> 60 min	General anesthesia Thiopental; 3-5 mg/kg blous, then 3-5 mg/kg/h or Pentobarbital 10-15 mg/kg, then 0.5-1 mg/kg/h or Midazolam; 0,2 mg/kg boluses max. 2 mg/kg, then 0.05-2 mg/kg/h or in adults: Propofol; 1-2 mg/kg boluses, max. 10 mg/kg, then 2-10 mg/kg/h	ventilatory and hemodynamic treatment Increased intracranial pressure; measure and treat if signs Anesthesia continued for 12-24 h after last clinical or electrographic seizure Optimize maintenance AED treatment	Continuous EEG monitoring: electrographic seizures, depth of anesthesia (burst-suppression) Monitor K, Na, glucose, lactate, levels of AEDs

Kalvianen R, Epilepsia (S8), 2007

Parenteral Drugs for refractory SE:

Medication	Loading dose (IV, unless specified)	Maintenance dose (IV, unless specified)	Approximate terminal serum $t_{1/2}$ (hours)	Serum level (μg/mL)[a]	Important considerations
ACTH	>2 years = 40-80 U; IM or SC <2 year = 150 U/m^2	>2 years = 40 U IM/d <2 years = 75 U/m^2 IM BID for 2 weeks	0.25 (IV)	–	
Brivaracetam	Unknown	11-19 kg = 2.5 mg/kg BID; 20-49 kg = 2 mg/kg BID; 50+ kg = 100 mg BID (age 4+ years); 100 mg BID (adult)[b]	9	–	
Ketamine	1-2.5 mg/kg	3-10 mg/kg/h[c]	2.5		Combine with BDZ. Avoid in neonates and third trimester of pregnancy
Lacosamide	5-10 mg/kg over 15-30 minutes[d] (FDA-approved "loading dose" is 200 mg in adults)	13 mg/kg/d divided BID (children); 200 mg BID (adult)[b]	15	4-12	Atrial arrhythmia; first, second, and third degree heart block. Rarely: ventricular arrhythmia, deat
Levetiracetam	60 mg/kg over 15 minutes (max 4500 mg)	21 mg/kg BID (<6 months), 25 mg/kg BID (0.5-4 years), 30 mg/kg BID (4-16 years), 1500 mg BID (adult)[b]	7	20-50	
IVIg	0.4-2 g/kg/d for 3 to 5 days		NA	–	
Magnesium sulfate	50 mg/kg (max 4 g)	20-40 mg/kg/h		30-60	
Methylprednisolone succinate	10-30 mg/kg/d for 3 to 5 days	Sometimes after 3-5 days: oral prednisone 1 mg/kg/d		–	
Midazolam	0.2-0.5 mg/kg	0.1-2.0 mg/kg/h[c] or 2.0-40 μg/kg/min	Initially = 1-4.5 (child), 2-7 (adult); prolonged = up to 24	Variable	Clearance is fastest in infants and slows marked with prolonged administration
Pentobarbital	5-15 mg/kg at max rate of 50 mg/min	0.5-5 mg/kg/h[c]	15-22		
Propofol	1-2 mg/kg bolus every 3-5 minutes up to max of 10 mg/kg	1-15 mg/kg/h initially, then max 5 mg/kg/h[c]	Initially = 0.67, prolonged = 4-7, >10 days = 24-72		Children: avoid or use only briefly due to risk of PRIS
Pyridoxine	100 mg every 5 minutes. ×5 doses	15-30 mg/kg/d PO or IV			
Valproic acid	40 mg/kg over 10-60 minutes (max up to 20	5-15 mg/kg every 6 hours, starting 30 minutes	9-16	50-150	

Treatment of Refractory Convulsive Status Epilepticus: A Comprehensive Review by the American Epilepsy Society Treatments Committee. Epilepsy Curr 2020

Pharmacological characteristics of anesthetics used in refractory SE

	Barbiturates	Propofol	Midazolam
ELIMINATION HALF-LIFE AFTER PROLONGED ADMINISTRATION	THP: 14–36 h	1–2 h	6–50 h
	PTB: 15–22 h		
ACCUMULATION	+++	(+)	++
TACHYPHYLAXIS		(+)	+++
HYPOTENSION	+++	+++	++
OTHER ADVERSE EFFECTS	Immunological suppression	Infusion syndrome*	
LOADING DOSE (mg/kg)	THP: 2–7	2	0.1–0.3
	PTB: 5–15		
MAINTENANCE DOSE (mg/kg/h)	THP: 3–5	2–10	**0.05–0.6**
	PTB: 1–5		
REMARKS	Long wash-out time	Limit to 48 h, Combine with BDZ	Increasing doses needed with time

THP, thiopental; PTB, pentobarbital; BDZ, benzodiazepines.
*hypotension, arrhythmia, hyperthermia, acidosis, rhabdo, ARF, hepatitis

ACNS: indications for prolonged cEEG

- Persistent abnormal mental status following generalized convulsive status epilepticus or other clinically evident seizures
- Acute supratentorial brain injury with altered mental status
- Fluctuating mental status or unexplained alteration of mental status without known acute brain injury
- EEG patterns along the ictal-interictal continuum such as periodic discharges and lateralized rhythmic delta activity
- Clinical risk for seizures potentially masked by pharmacologic paralysis, e.g. extracorporeal membrane oxygenation (ECMO), targeted temperature management for cardiac arrest
- Paroxysmal clinical events suspected to be possible seizures

Herman ST, Abend NS, Bleck TP, et al. J Clin Neurophysiol 2015;32(2):87–95.

2HELPS2B risk score system for prediction of subsequent electrographic seizures during an initial screening EEG

1 point each:

2H: Frequency exceeding 2 Hz

E: Independent sporadic epileptiform discharges

L: Lateralized rhythmic or periodic patterns, including lateralized periodic discharges, bilateral independent discharges, or lateralized rhythmic delta activity

P: Plus features, including superimposed rhythmic, fast, or sharp activity

S: Prior seizure history, epilepsy, or suspicion for acute clinical seizure

2 points:

2B: Brief ictal rhythmic discharges (not reaching the 10-second threshold for definitive electrographic seizure)

2HELPS2B Screening EEG Risk Score	Predicted Seizure Risk	Actual Seizure Risk[a]
0	<5%	3-4%
1	12%	12-15%
2	27%	34%
3	50%	52-55%
4	73%	71-75%
5+	88%	84-93%

Struck AF, Ustun B, Ruiz AR, et al. JAMA Neurol 2017;74(12):1419–1424.

Summary of data regarding barbiturates, midazolam & propofol in the treatment of refractory SE

	Barbiturates	Propofol	Midazolam
Mortality	48%	52%	46%
Acute failure in SE control (first 6 h of treatment)	8%	27%	20%
Breakthrough seizures (during agent's administration)	12%	15%	51%
Withdrawal seizures (<48 h after agent's discontinuation)	43%	46%	63%
Hypotension requiring vasopressors	77%	42%	30%

Rossetti AO, Epilepsia. 2007. 48: S8

Treatment of Refractory Status Epilepticus[1]

- **Intubate and ventilate; transfer to ICU**
- **Place on EEG monitor**
- **Place arterial/central catheters if indicated**
- Midazolam ***or*** Propofol

  0.2 mg/kg slow bolus — 1-2 mg/kg bolus

  0.75-10 μg/kg/min — 2-10 mg/kg/h
- **Endpoint: suppression of EEG spikes**
- **Continue phenytoin and/or phenobarbital**
- **Taper midazolam or propofol at 12 h to assess seizures**

1. Lowenstein DH, Alldredge BK. *N Eng J Med.* 1998;338:970-976.

Systemic complications of SE:

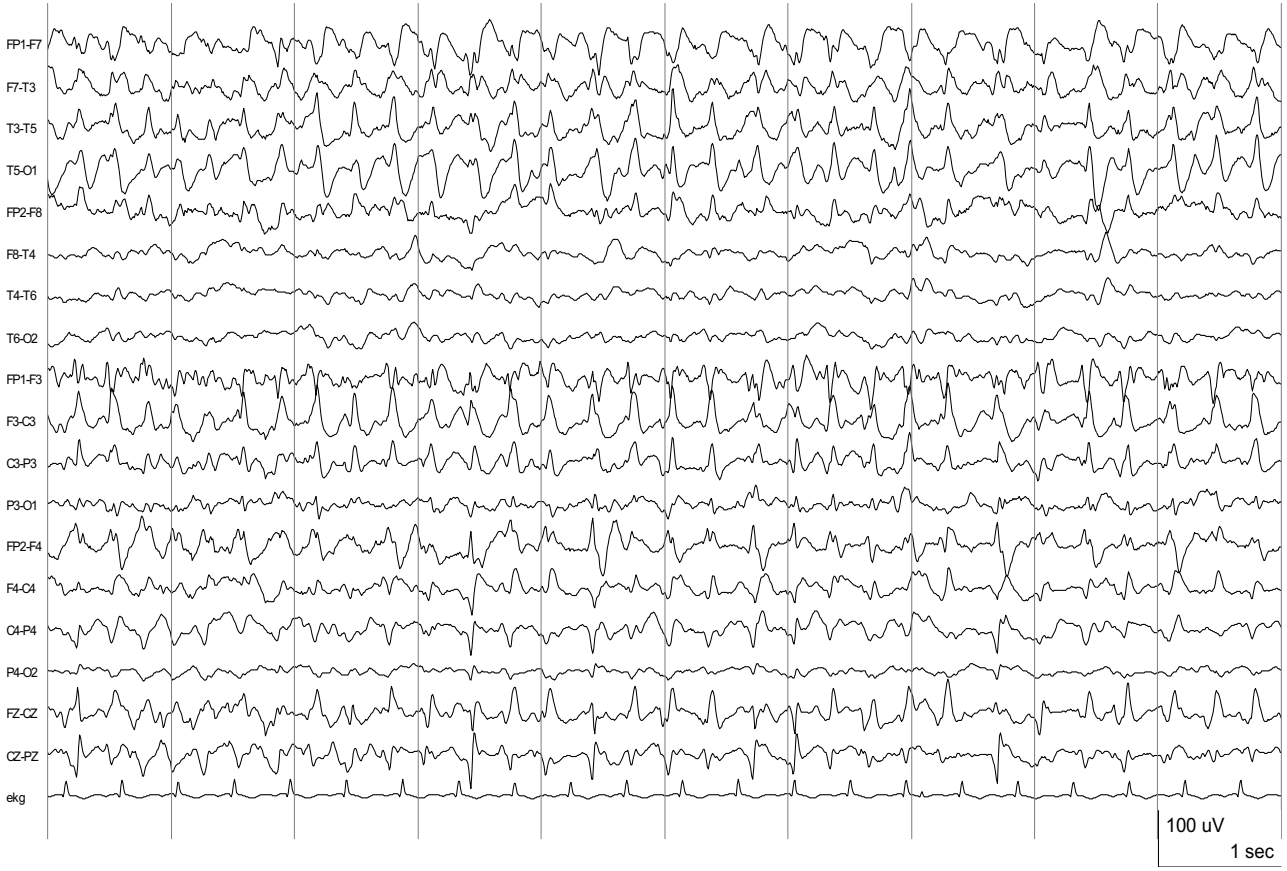
- **Medical complications:**
  - ***Arrhythmia, hypotension***
  - ***respiratory failure, hypoxia, aspiration pneumonia***
  - ***PE, fever, sepsis***
- **Anesthetic & PHT complications**
  - ***Propofol infusion syndrome (>48 h)***
  - ***Phenytoin (hypotension, tissue injury)***
- **Cognitive impairment: "Time is brain"**
- **Others (ICU/coma related)**

Sutter R, Dittrich T, Semmlack S, Rüegg S, Marsch S, Kaplan PW. Crit Care Med. 2018 Jan;46(1):138-145

15 year old in NCSE in Monze Mission Hospital

- TC seizure, collapsed, two days coma
- Woke up after lorazepam injection

NCSE: >2.5 cps rhythmic sharp/slow waves



NCSE treatment: non-BZD iv doses

TABLE 2 Recommendations for nonbenzodiazepine medication: initial doses, incremental doses, and maximum doses for a diagnostic intravenous antiseizure medication trial.

	Levetiracetam	Valproate	Lacosamide	Brivaracetam	Fosphenytoin[a]	Phenobarbital[b]
Choice	**1**	**1**	**1**	**1**	**2**	**3**
Starting dose	40 mg/kg	30 mg/kg	6 mg/kg	4 mg/kg	15 mg PE/kg	10 mg/kg
Administration time	5 min	5 min	10 min	5 min	10–15 min (maximum 150 mg/min)	15+ min
With additional boluses up to a maximum dose of (whichever is lower):						
Maximum total loading dose, weight based	60 mg/kg	40 mg/kg	8 mg/kg	6 mg/kg	20 mg PE/kg	20 mg/kg
Maximum total loading dose, absolute	4500 mg	3000 mg	600 mg	450 mg	1500 mg PE	1500
Special measures			ECG monitoring		ECG monitoring	

Diagnosing nonconvulsive status epilepticus. Leitinger M et al. Epilepsia 2023.

A nonconculsive SE response scale

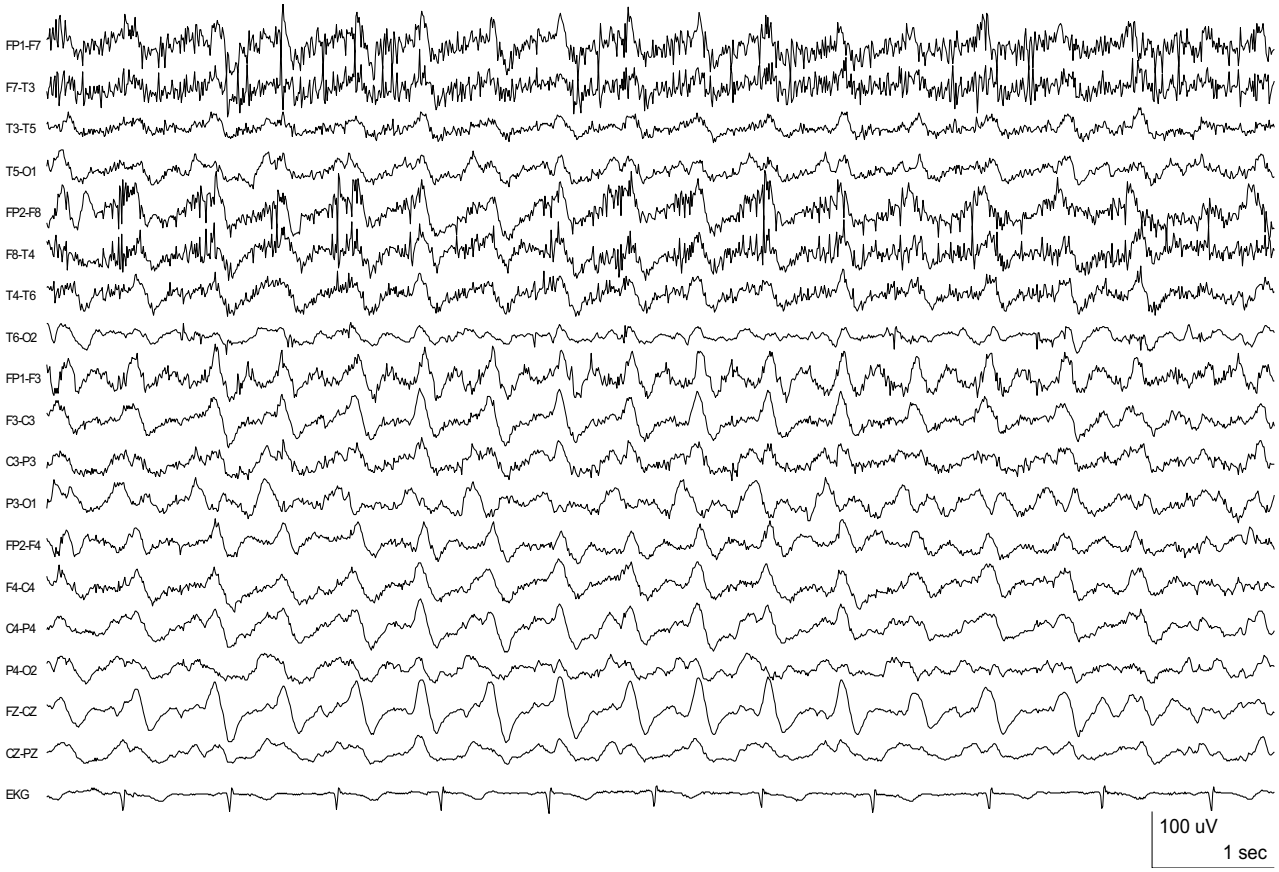
TABLE 4 The NRS for measurement of clinical improvement in response to intravenous antiseizure medication.

Level 10: Normal
Level 9: Speaks or writes words with clear sense, oriented to person, year, and city or region, but behavior or performance different than normal
Level 8: Speaks or writes words with clear sense, but disoriented to person, year, and city or region
Level 7: Speaks or writes words or syllables, incomprehensible or confused
Level 6: Follows commands (verbally or by demonstration) (e.g., open/close eyes, raise arms, say "1, 2, 3")
Level 5: Directed gaze to examiner (or responsive vertical eye movement in locked-in syndrome), does not follow any commands (neither verbal nor by demonstration)
Level 4: Opens eyes spontaneously or to verbal stimulus or to light touch (no directed gaze), does not follow any commands
Level 3: Opens eyes to (strong) tactile stimulus (right or left shoulder, nose), does not follow commands (neither verbal nor by demonstration)
Level 2: Localizes to/wards off painful stimuli
Level 1: No purposeful response to painful stimuli

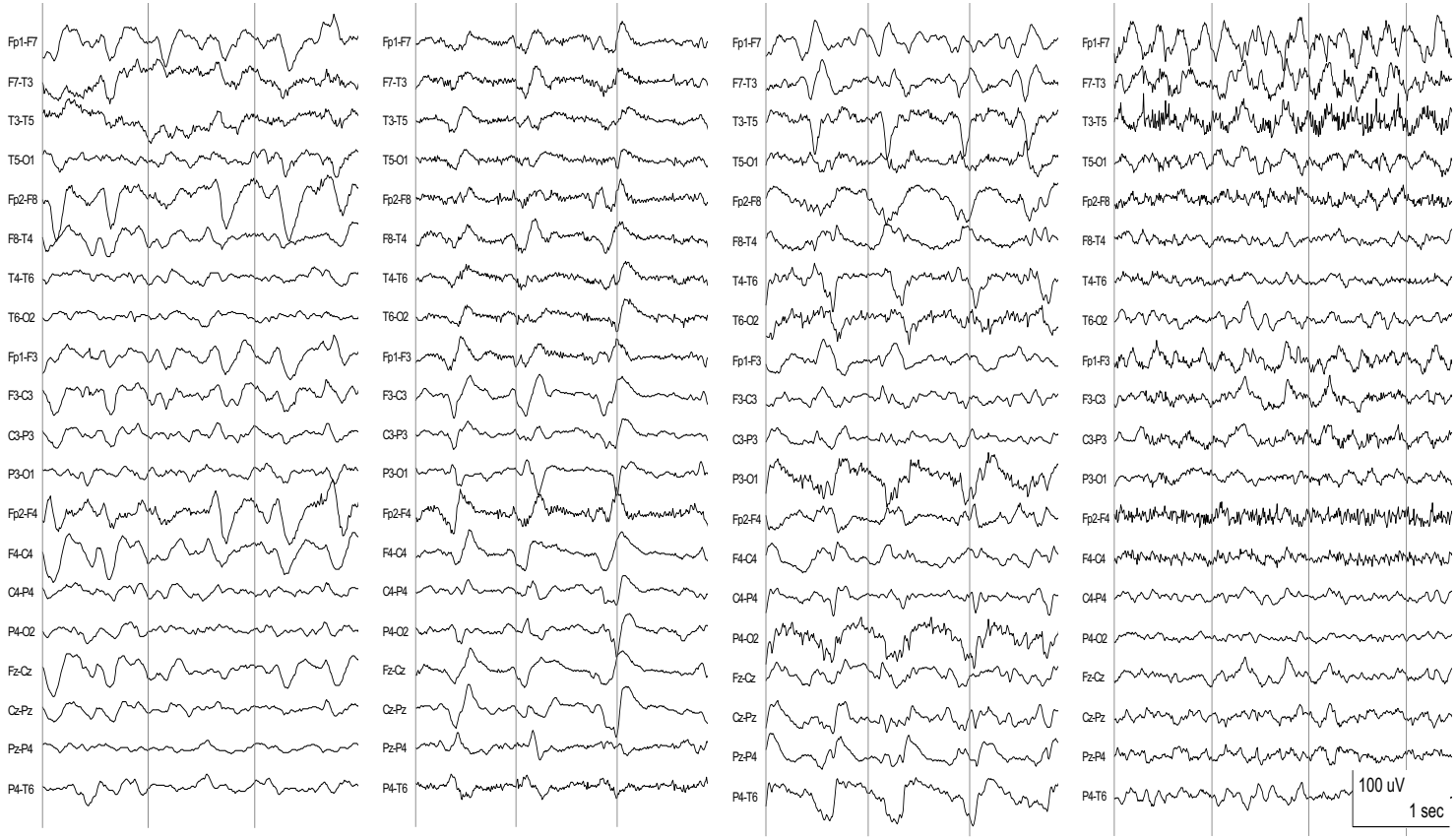
Pitfalls in treating status epilepticus

- Not distinguishing epilepsy & acute symptomatic seizures (e.g. hemorrhage with seizures)
- Over-treating patients whose seizures have stopped (unneeded sedation/intubation)
- Not recognizing nonconvulsive status epilepticus (pt “not waking up”)
- Not recognizing psychogenic status epilepticus
  - *5% of patients with SE*
  - *Asymmetric limb flailing, resists examination, stop/start with encouragement*

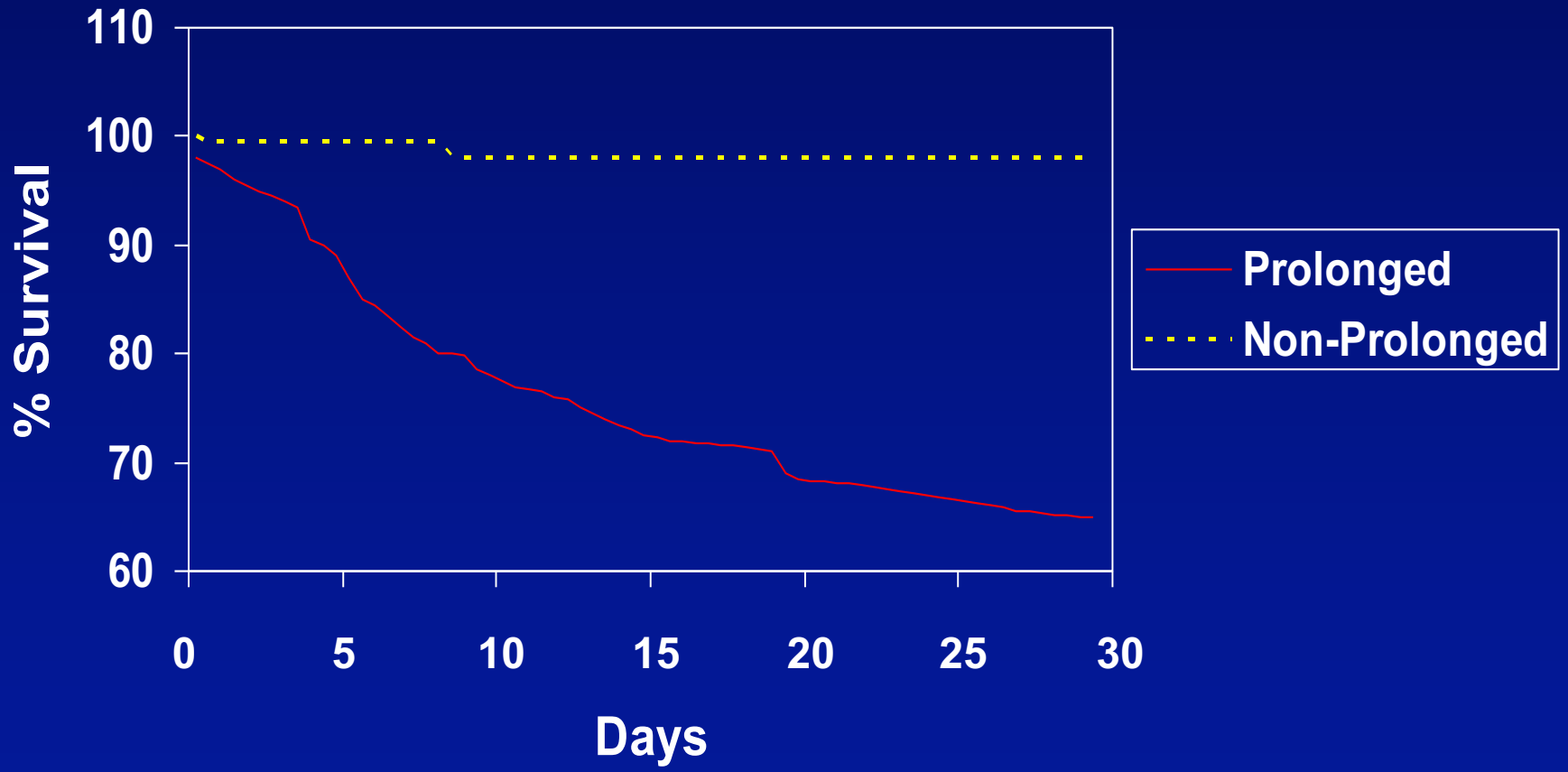
Post-anoxic Coma



Nonconvulsive status epilepticus?

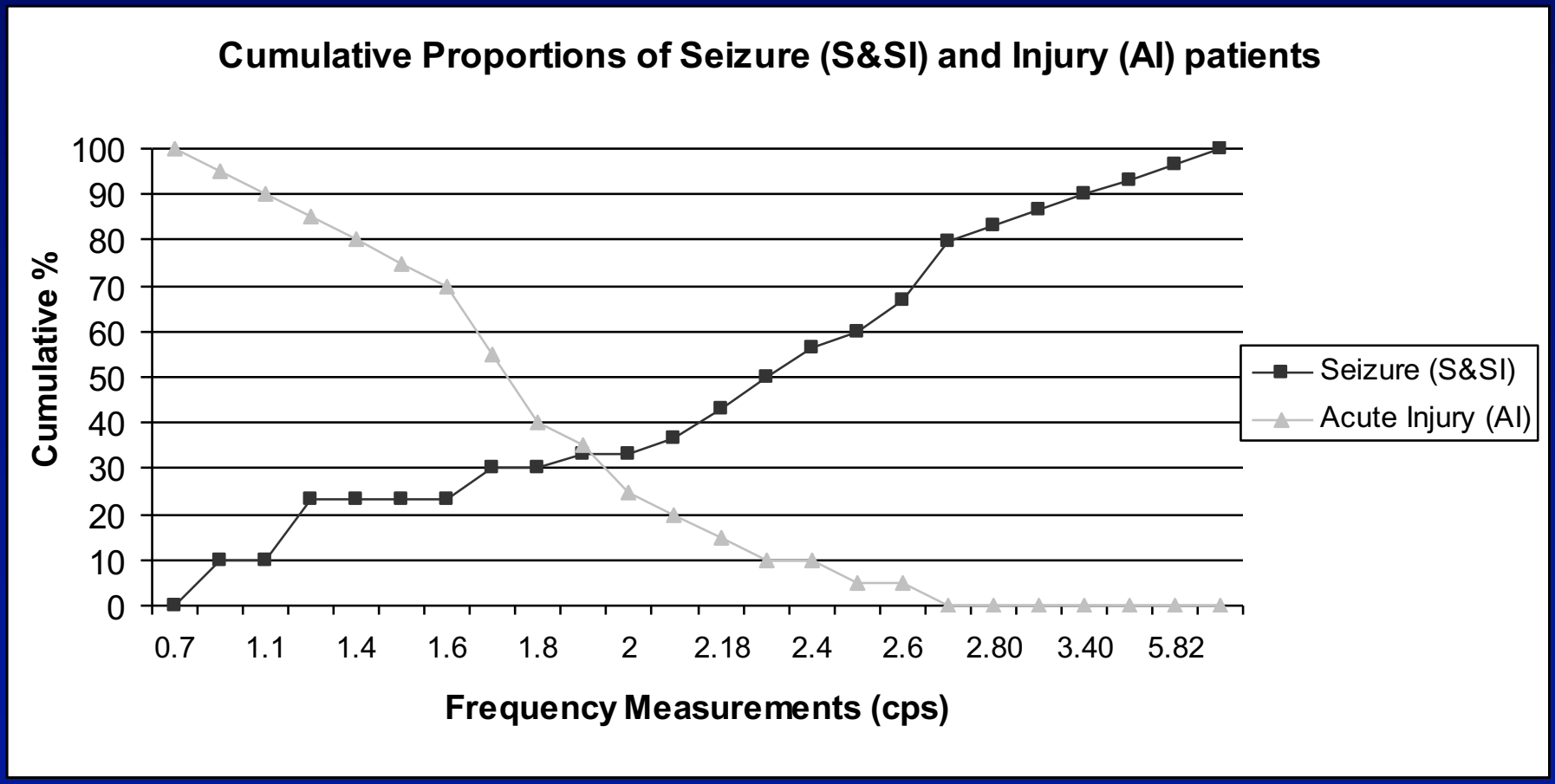


Survival Curves for Patients With Prolonged and Nonprolonged Seizure Duration[1]



1. DeLorenzo RJ, et al. Status epilepticus in children, adults, and the elderly. *Epilepsia.* 1992;33(Suppl 4):S15-S25.

Acute injury –vs- Seizures: EEG frequency



Case 1: 21 y/o female college student

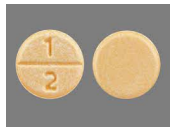
- Seizures recur despite iv lorazepam, LEV & fosphenytoin (5 GTC in 1 hour)
- Additional lorazepam 4 mg iv given; second fosphenytoin iv load: 10 mg/kg; seizure recur
- ED to NCCU transfer: 3 GTC in 15 minutes

Case 1: 21 y/o female college student

- Intubation, iv resuscitation, propofol infusion
- EEG: burst-suppression; 24 hours
- Acyclovir tx, viral serology negative
- Repeated seizure flurries on decreased propofol; converted to pentobarbital then phenobarbital
- Two weeks intubation, seizures gradually decrease from daily to monthly frequency
- Full cognitive recovery at 2 months

Targeting rescue therapies:

Repetitive or prolonged seizures: Define individual seizure patterns in seizure treatment plans:



"2 or more seizures in <2 hours, administer clonazepam 1 mg disintegrating tablet, may repeat once"

"A convulsive seizure in a child lasting >4 minutes, administer rectal diazepam"

"An adult with a major seizure lasting >4 minutes, administer nasal midazolam

"A woman with reliable catamenial (menses) seizures, administer clonazepam 0.5 mg BID for 3-4 days during risk period"

Treatment of status epilepticus: the end

IV Diazepam[1,2]

- Dose: 0.1-0.6 mg/kg (total 2-20 mg)
- Rate of administration (max): 5 mg/min
- Time to stop seizures: 1-3 min
- Duration of action: 15-30 min
- Use: acute treatment of severe seizures

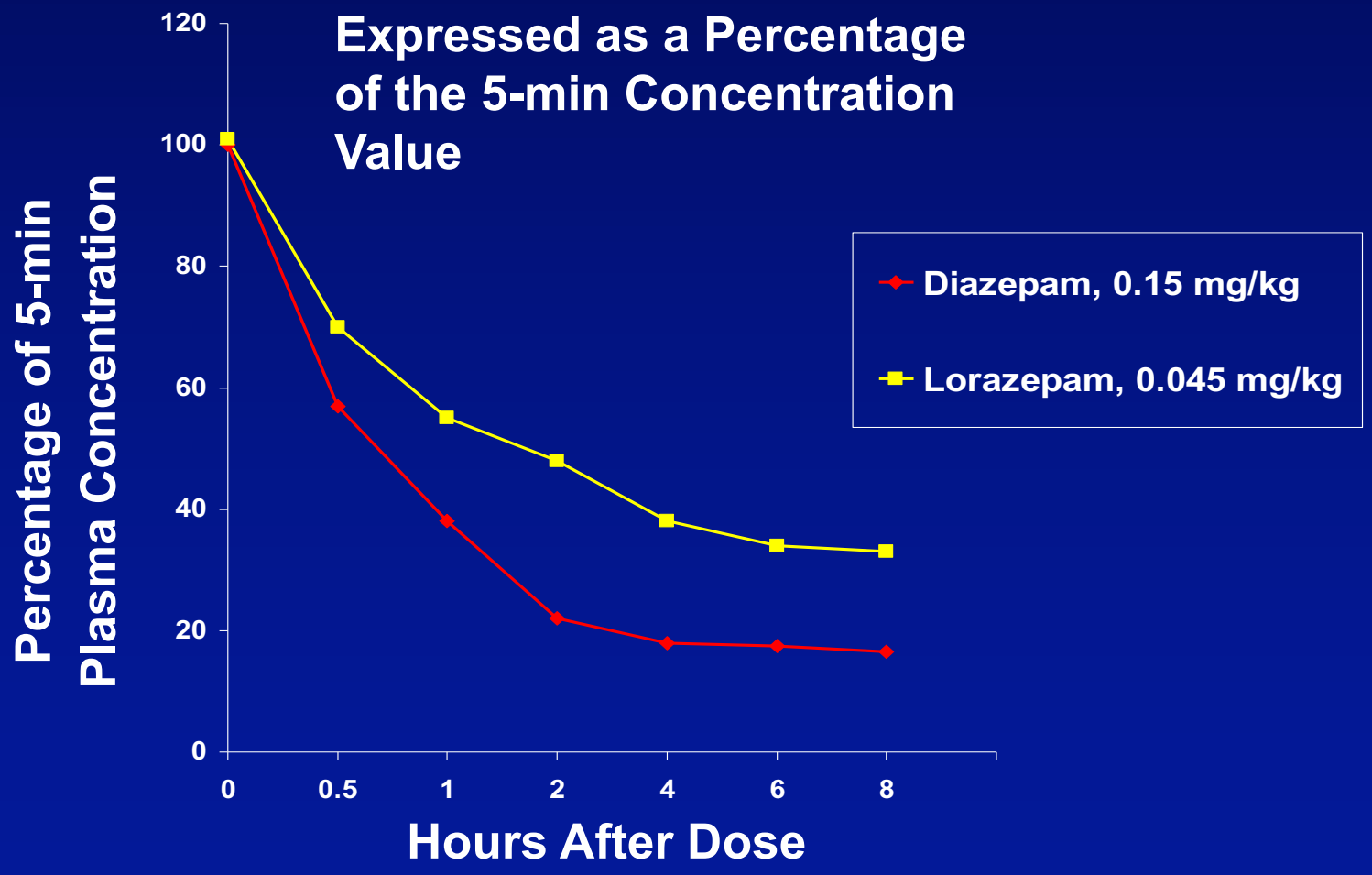
1. Lowenstein DH, Alldredge BK. *N Eng J Med.* 1998;338:970-976.
2. Greenblatt DJ, et al. *J Pharmacol Exp Ther.* 1989:250:134-140.

IV Lorazepam[1,2]

- Dose: 0.05-0.5 mg/kg (total 1-8 mg)
- Rate of administration (max): 2 mg/min
- Time to stop seizures: 6-10 min
- Duration of action: up to 12-24 h
- Use: acute treatment of seizures

1. Lowenstein DH, Alldredge BK. *N Eng J Med.* 1998;338:970-976.
2. Greenblatt DJ, et al. *J Pharmacol Exp Ther.* 1989:250:134-140.

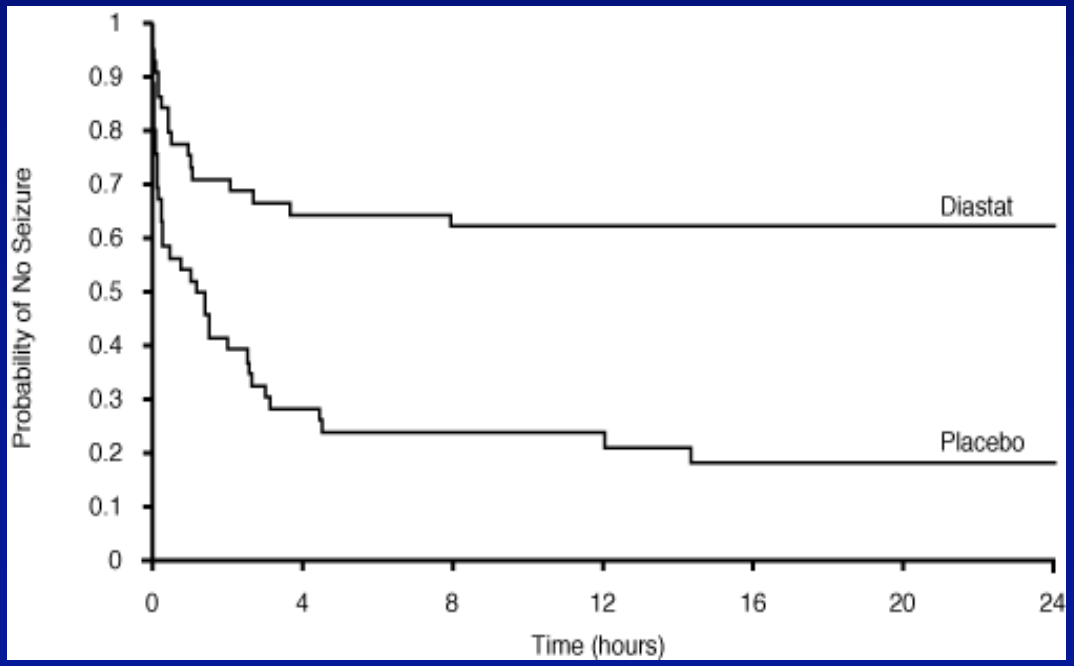
Plasma Diazepam and Lorazepam Concentrations Over Time



1. Greenblatt DJ, et al. *J Pharmacol Exp Ther.* 1989;250:134-140.

Valium rectal gel (Diastat): 10 mg/ 15 mg/ 20 mg

Kaplan-Meier Survival Analysis of Time-to-Next-Seizure



IV Phenytoin

- Prolonged antiseizure effect[1]
- Used in addition to benzos
- Pharmacological action[2]
  - *Blockage of voltage-operated sodium channels*
  - *Leads to decrease in electrical activity*
- Slow administration (≤50 mg/min)
- Requires IV filter, nurse at bedside, simultaneous EKG, specific IV fluid (saline)

1. Lowenstein DH, Alldredge BK. *N Eng J Med.* 1998;338:970-976.
2. Davies JA. *Seizure.* 1995;4:267-271.

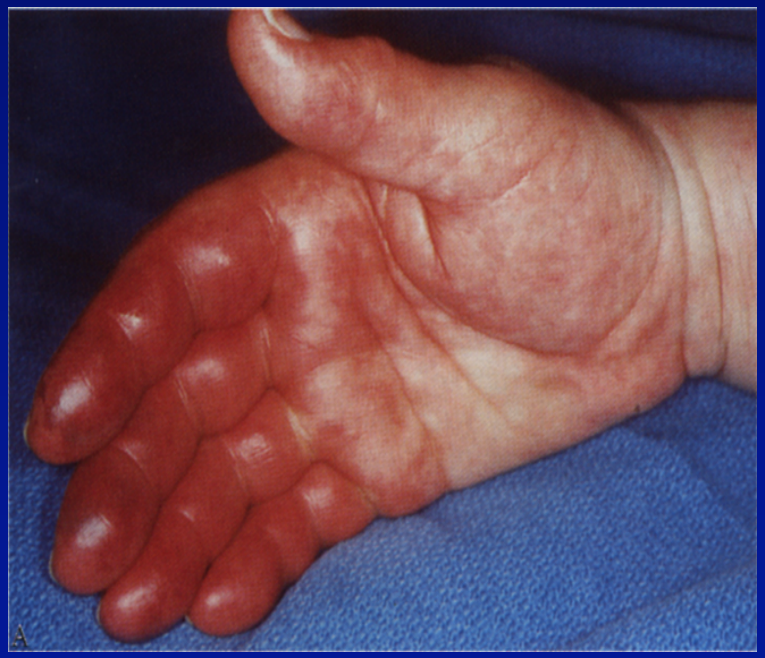
IV Phenytoin

Adverse effects[1,2]

- Hypotension
- Cardiac arrhythmias
- Infusion-site reactions
  - *Phlebitis*
  - *Soft tissue damage*

1. Lowenstein DH, Alldredge BK. *N Eng J Med.* 1998;338:970-976.
2. Wheless J, Venkataraman V. *J Epilepsy.* 1998;11:319-324.

Phenytoin infusion injury

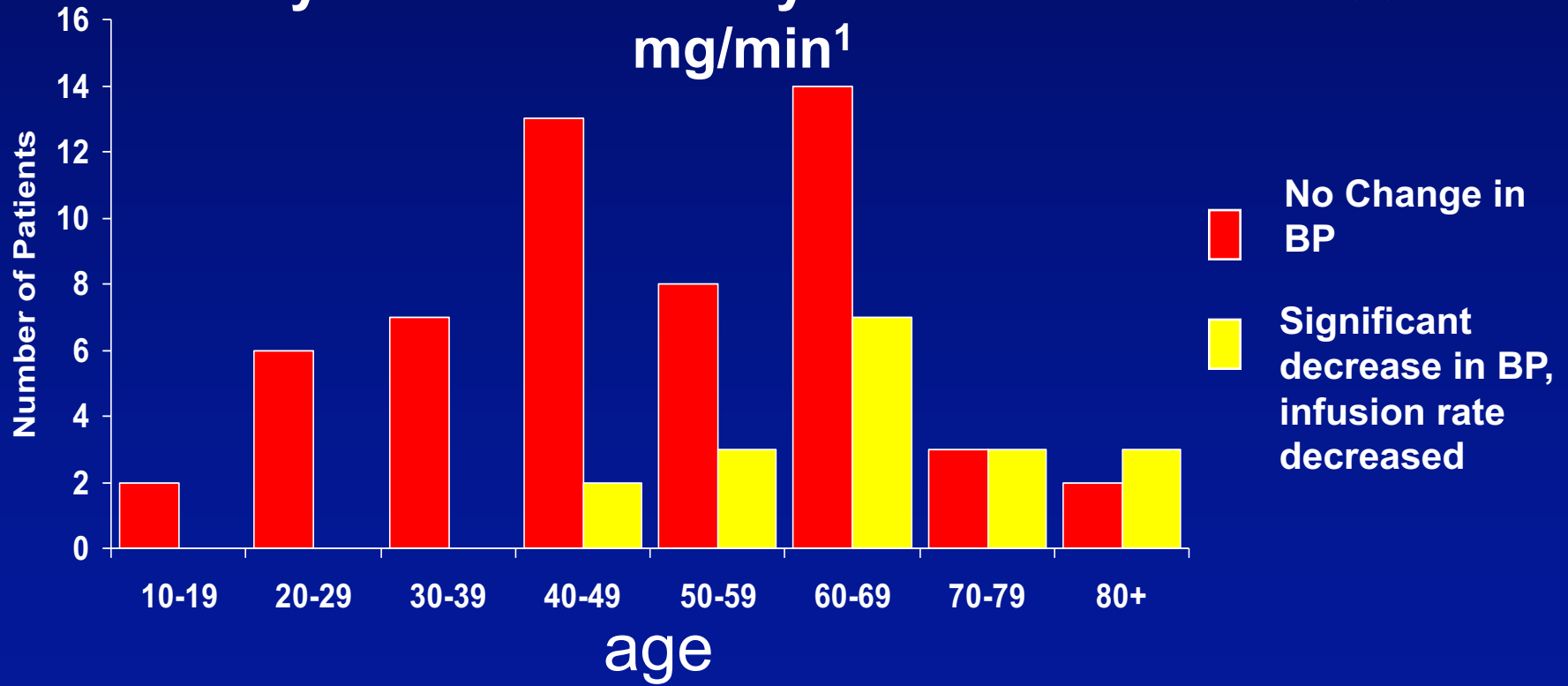


- distal small veins
- “purple glove” syndrome
- increased in elderly
- 5% incidence (Mayo)

(O’Brien, Neurology, 2001)

Phenytoin and Hypotension

Occurrence of Hypotension During Administration of Phenytoin Intravenously at an Initial Rate of 50 mg/min[1]



1. Cranford RE, et al. Intravenous phenytoin: Clinical and pharmacokinetic aspects. *Neurology.* 1978;28:874-880.

IV Fosphenytoin

- Prodrug of phenytoin
- Time of onset and effect similar to phenytoin[1]
- Infusion-site reactions less common[2]
- Can be administered IM
- Adverse effects
  - *Hypotension*
  - *Paresthesia (sacral)*
  - *Cardiac arrhythmias*

1. Lowenstein DH, Alldredge BK. *N Eng J Med.* 1998;338:970-976.
2. Fierro LS, et al. *Am J Health Syst Pharm.* 1996;15:2707-2712.

IV Fosphenytoin[1]

- Dose: 15-20 mg PE/kg
- Dose may need to be adjusted when replacing oral therapy
- Rate of administration: 150 mg PE/min (max) or 3 mg PE/kg/min
- Time to stop seizures: 10-30 min
- Alters phenytoin protein binding immediately postinfusion
- Uses: acute treatment and maintenance therapy

PE=Phenytoin equivalents

1. Lowenstein DH, Alldredge BK. *N Eng J Med.* 1998;338:970-976.

i.v. Valproate Acid (Depacon)

- Bioequivalence demonstrated
  463 subjects
- initial and replacement therapy
- given q 6 h, infuse over 1 hour (<20 mg/min)
- NOT approved for status epilepticus
- Loading tolerated in uncontrolled series: 1.5 to 3.0 mg/kg/min, max 15 mg/kg (mean peak 96 mg/L)

i.v. VPA Safety and Tolerability

Adverse Events Reported in ≥1% of Patients

	Overall (n=318)	Children (<17 yrs) (n=22)	Adults (n=296)
Adverse Events			
Any event	54 (17.0)	4 (18.2)	50 (16.9)
Headache	7 (2.2)	0	7 (2.4)
Reaction, injection site	7 (2.2)	2 (9.1)	5 (1.7)
Nausea without vomiting	7 (2.2)	0	7 (2.4)
Somnolence	6 (1.9)	0	6 (2.0)
Vomiting only	5 (1.6)	0	5 (1.7)
Dizziness	4 (1.3)	0	4 (1.4)
Taste perversion	4 (1.3)	0	4 (1.4)
Injection site inflammation	3 (0.9)	2 (9.1)	1 (0.3)
Injection site pain	3 (0.9)	0	3 (1.0)

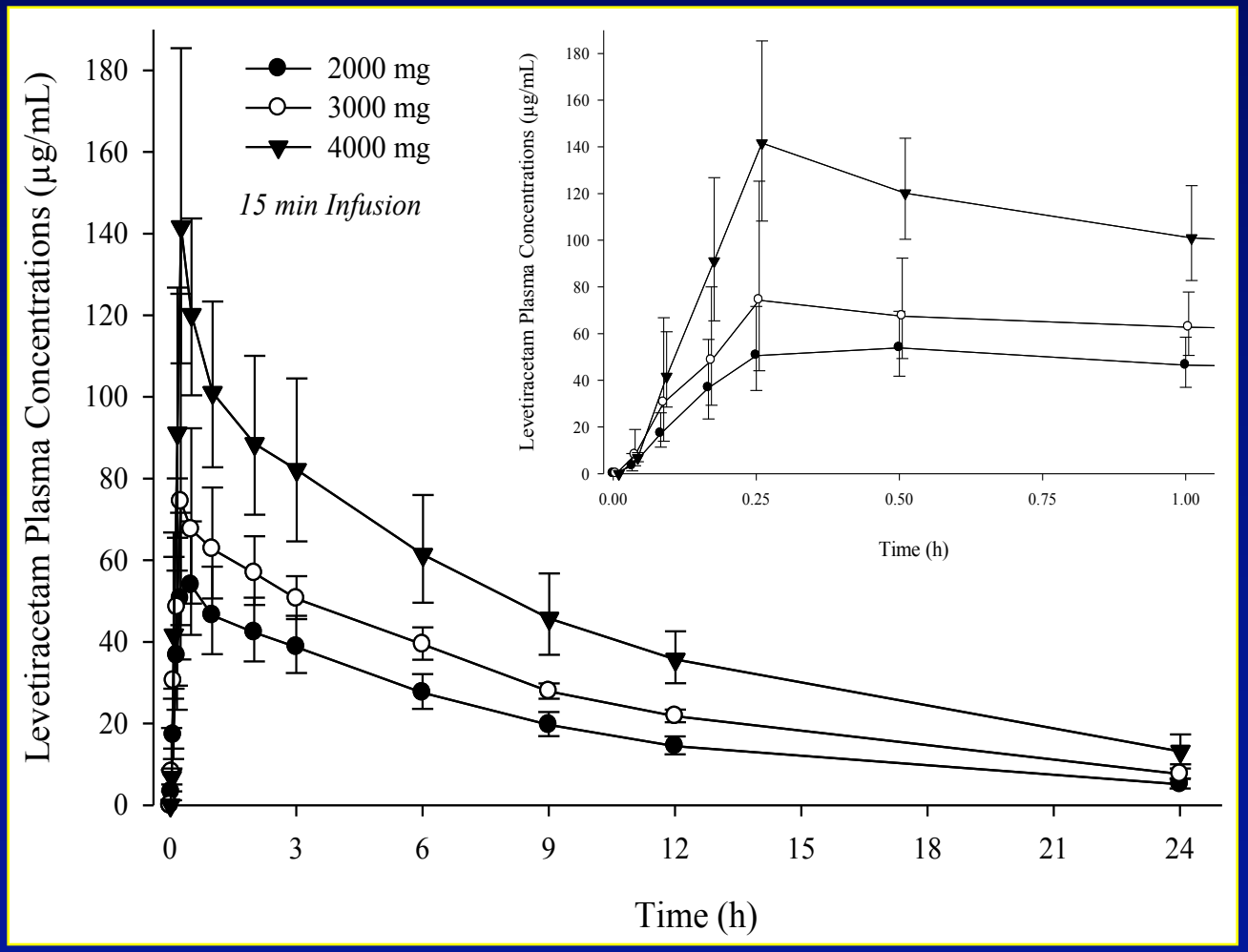
Intravenous Levetiracetam (Keppra)

- **Bioequivalent to oral tablet**
  - *1500 mg iv/po single dose*
  - *Multiple daily doses*
- **Rapid kinetics**
  - *T max equal to infusion rates at 5, 10, 15 minutes*
  - *C max comparable to oral doses at 1500 to 4000 mg/day (40 to 80 mg/l)*
- **Intravenous dosing well tolerated**
  - *Headache, fatigue most common*
- **Non-inducer, no drug interactions, non-sedating, broad-spectrum**

Safety Study Results (15 min infusion)

Average LEV plasma concentration (µg/mL) after single dose administration of 2000, 3000, 4000 mg (15 min infusion)

Inset is 0-1 hour interval

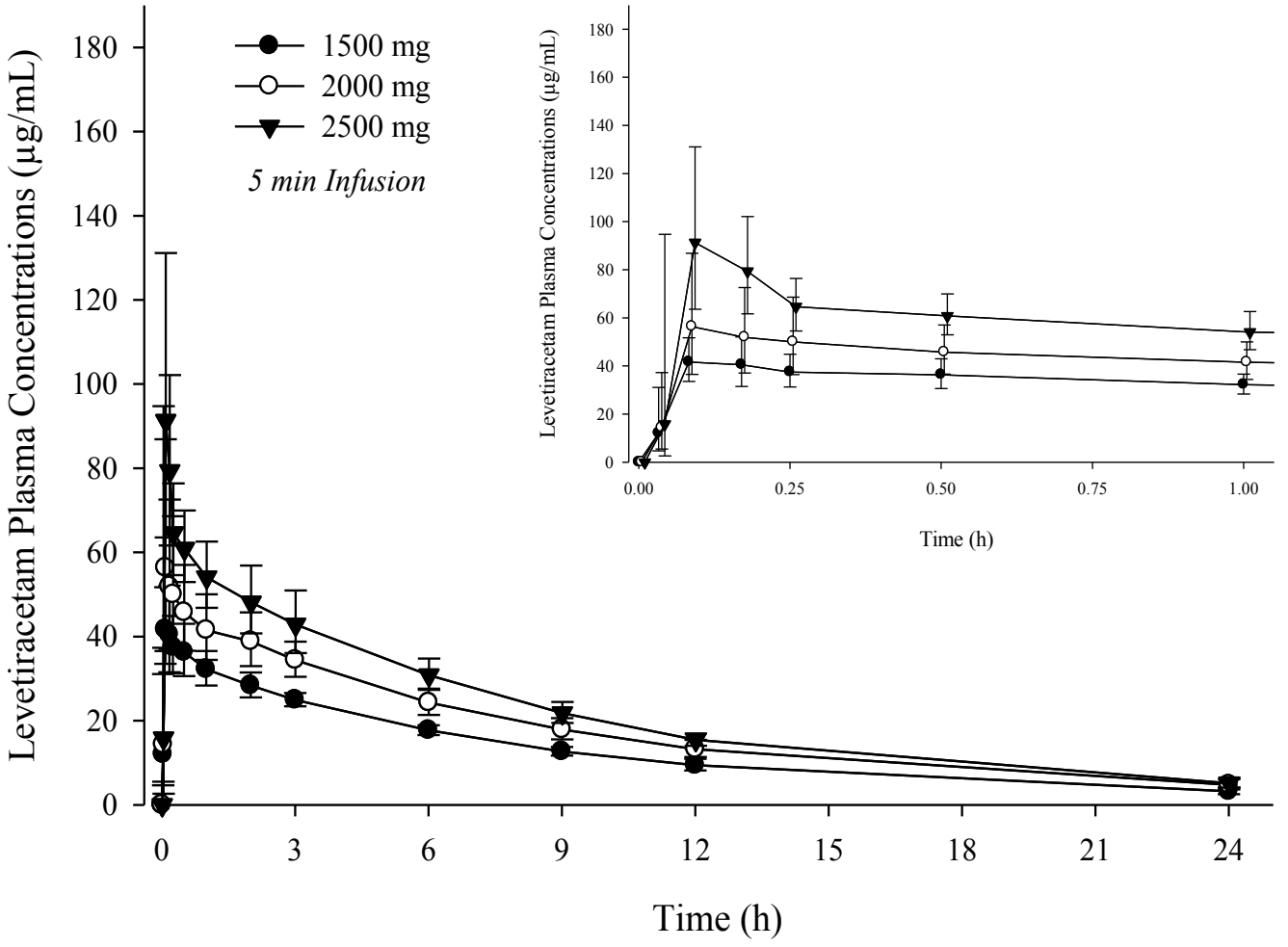


Reference: Ramael et al. Epilepsia. 2006;47:1126-1135.

Safety Study Results (5 min infusion)

Average LEV plasma concentration (µg/mL) after single dose administration of 1500, 2000, 2500 mg (5 min infusion);

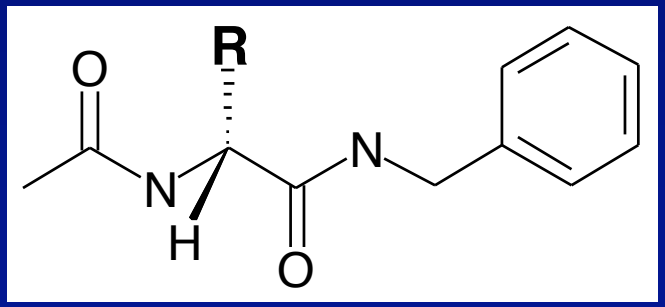
Inset is 0-1 hour interval



Reference: Ramael et al. Epilepsia. 2006;47:1126-1135.

Lacosamide

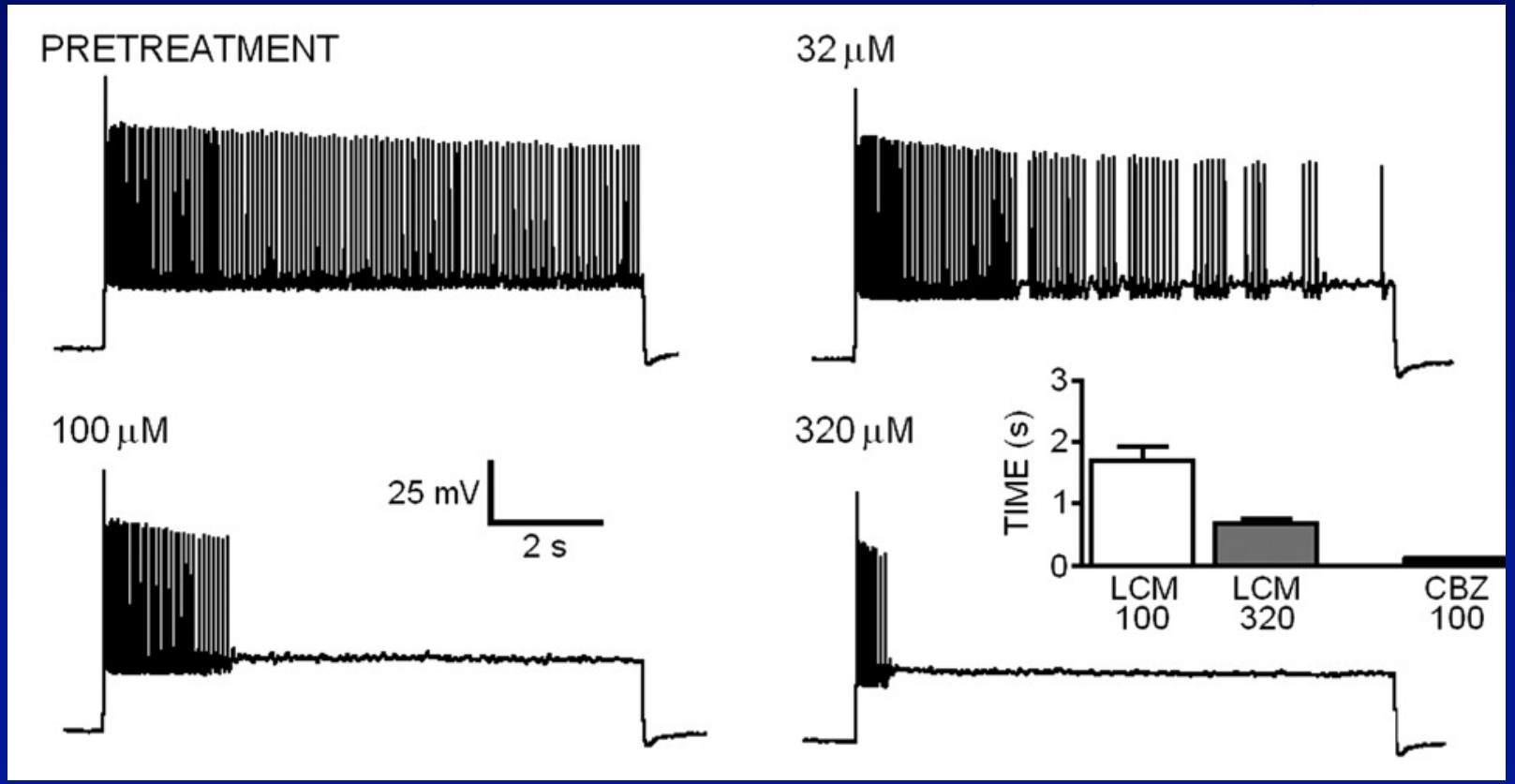
- **Functionalized amino-acid with similarity to D-serine**
- **Modulates neuronal slow sodium inactivation gate**



(R)-2-acetamido-N-benzyl-3-methoxypropionamide

R(+) configuration is active
Molecular Weight: 250.3
Water solubility: 27mg/mL

LCM inhibits voltage-dependent prolonged repetitive spike trains



Errington AC. *Mol Pharmacol* 73:157-169, 2008

Characteristics of Lacosamide Solution for Infusion

- Isotonic solution (10mg/mL LCM)
- Contains identical drug substance as oral lacosamide tablets
- Stable at room temperature
- Does not require dilution prior to administration
- pH 3.5 to 5
- No protein binding or known drug interactions