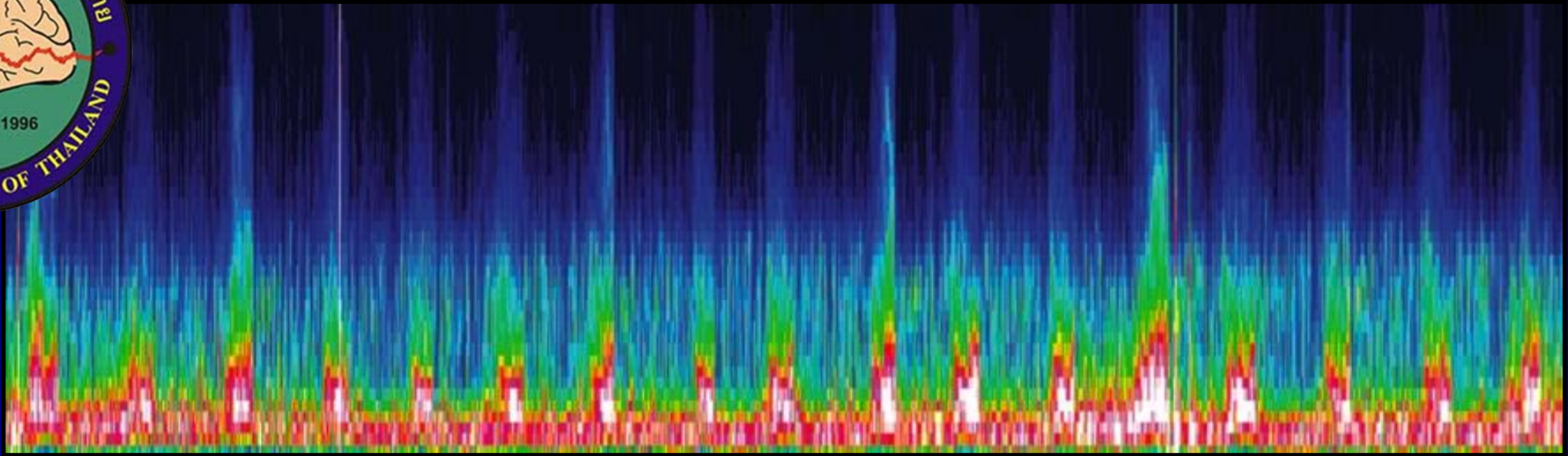




Management of Status Epilepticus: New Evidence and Future Directions

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FACULTY OF MEDICINE

SickKids[®]

Status Epilepticus Has Been Recognized as a Serious Medical Problem Since Antiquity

“If the possessing demon possesses him many times during the middle watch of the night, and at the time of his possession his hands and feet are cold, he is much darkened, keeps opening and shutting his mouth, is brown and yellow as to the eyes ...

It may go on for some time, but he will die.”



Sakikku, Babylonian Textbook of Medicine 1067-1046 B.C.

More Contemporary Definitions...

- “A seizure that persists for a sufficient length of time or is repeated enough to produce a fixed and enduring epileptic condition.”

ILAE, 1989

- Clinical definition: seizures lasting > 30 minutes

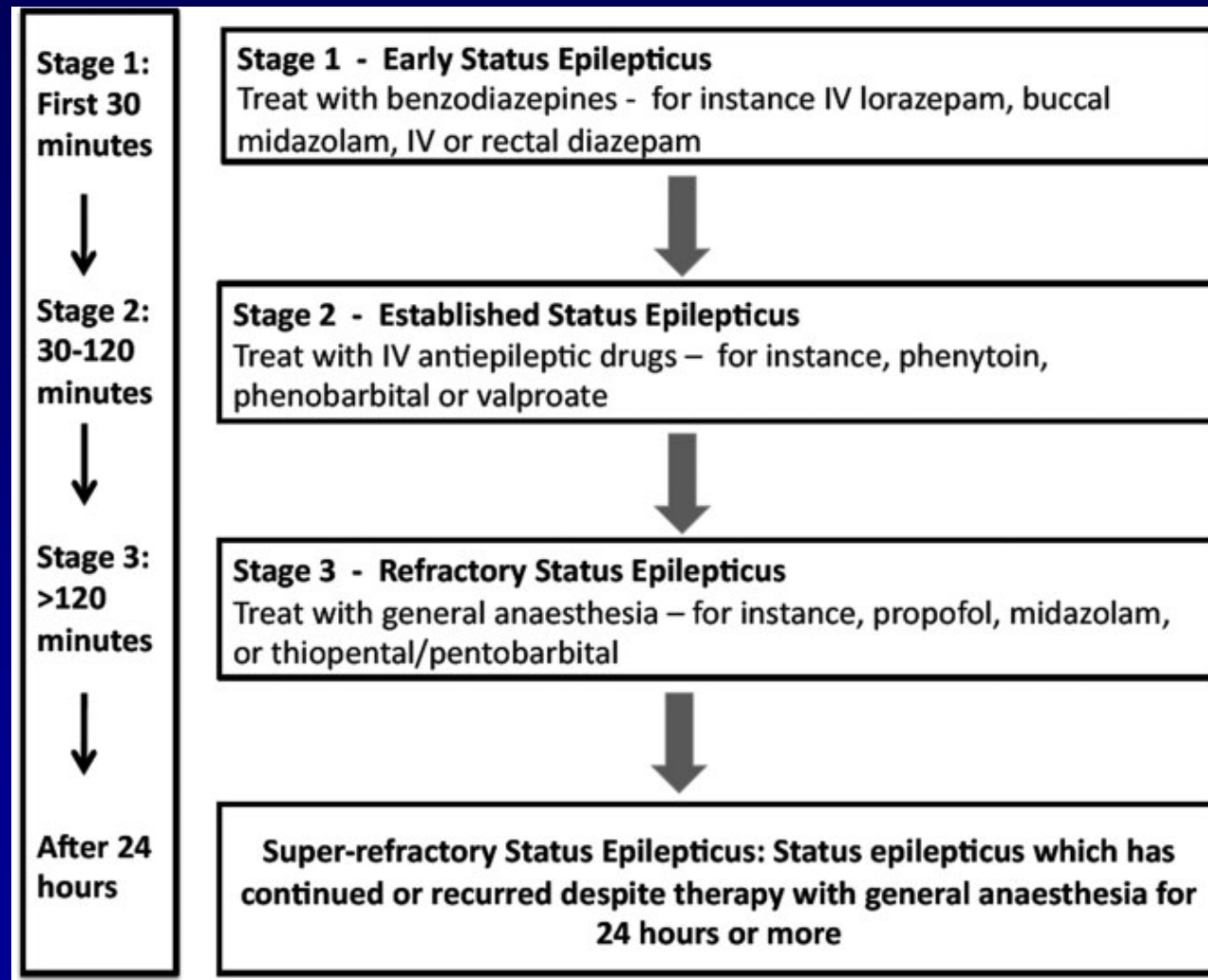
“Operational” Definition

- Seizure lasting 5 minutes or longer
- Repeated seizures without intervening return to consciousness
- Rationale:
 - seizures in naturally cluster by duration into two groups:
 - 76% are < 5 minutes
 - 24% are > 5 minutes, with a mean of 31 minutes

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected		
Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
<u>Tonic-clonic SE</u>	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min ^a	Unknown
^a Evidence for the time frame is currently limited and future data may lead to modifications.		

Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia* 2015, 56(10):1515-1523.

The Stages of Status Epilepticus



Diagnosis

- Diagnosis is easy in the presence of convulsive seizures
- Difficult to differentiate continuous non-convulsive seizures from post-ictal state
 - May present as intermittent altered LOC, lethargy $\pm$ subtle myoclonic jerks
- May require EEG for diagnosis

Convulsive Status Epilepticus is Frequently Followed by Nonconvulsive Seizures

- Among 164 adults with CSE undergoing cEEG
 - 48% had nonconvulsive seizures
 - 14% had nonconvulsive status epilepticus

DeLorenzo et al, Epilepsia 1998

- Among 98 children with CSE undergoing cEEG
 - 33% had electrographic seizures
 - 34% electrographic-only
 - 15% had electrographic status epilepticus

Sanchez Fernandez et al, J Pediatr 2014

Challenges in Identifying Electrographic Seizures

- Seizures in critically ill patients are often not as clear-cut
 - Slower rhythms
 - Atypical waveforms
 - Unclear timing of onset/offset
 - Merge with periodic discharges



ACNS GUIDELINE

American Clinical Neurophysiology Society's Standardized Critical Care EEG Terminology: 2021 Version

Hirsch LJ *et al.* J Clin Neurophysiol 2021;38: 1–29

RHYTHMIC AND PERIODIC PATTERNS (RPPs): MAIN TERMS

- All rhythmic and periodic patterns (RPPs) should be described by main terms 1 and 2, as well as appropriate major and minor modifiers. Not all modifiers will apply to every pattern.

<u>Main term #1 (localization)</u>	<u>Main term #2 (pattern)</u>
(G) Generalized	(PDs) Periodic Discharges
(L) Lateralized	(RDA) Rhythmic Delta Activity
(BI) Bilateral Independent	(SW) (Poly)Spike-&-Wave/Sharp-
(Mf) Multifocal	and-Wave
<i>NEW 2021:</i>	
(UI) <i>Unilateral Independent</i>	

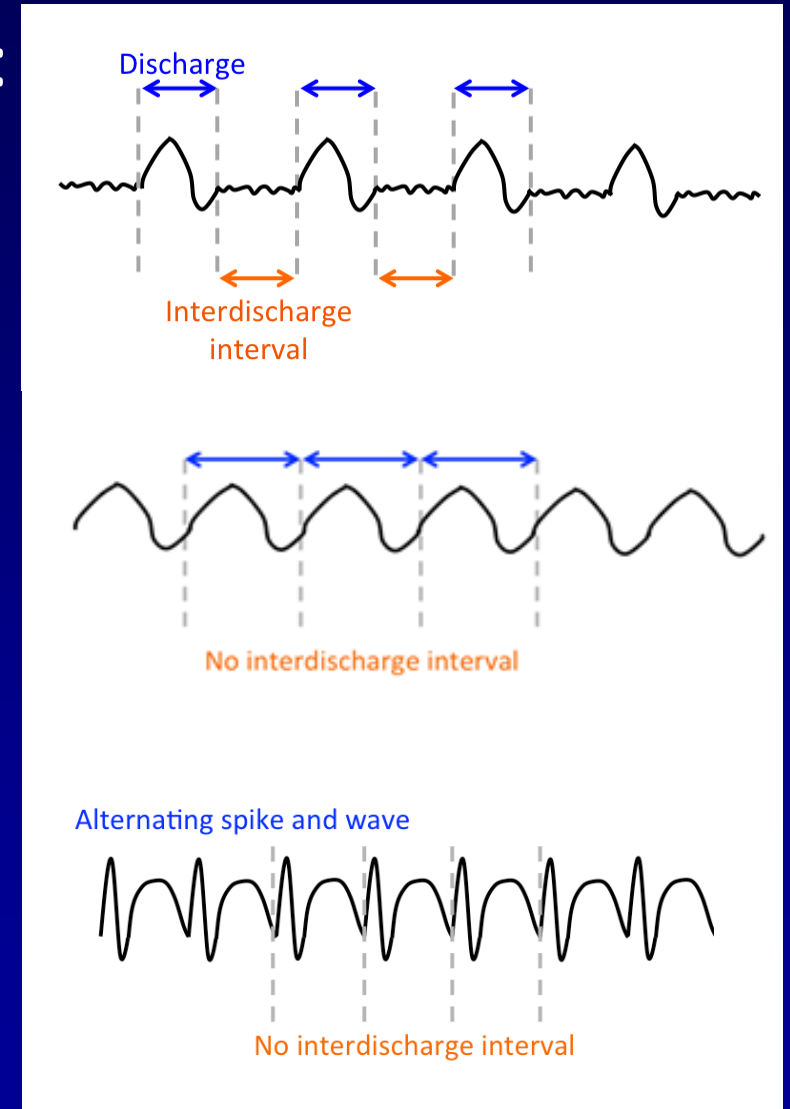
RHYTHMIC AND PERIODIC PATTERNS (RPPs): MAIN TERM 2

- Main term 2 (pattern description) includes:

- **PD**: Periodic Discharges

- **RDA**: Rhythmic Delta Activity

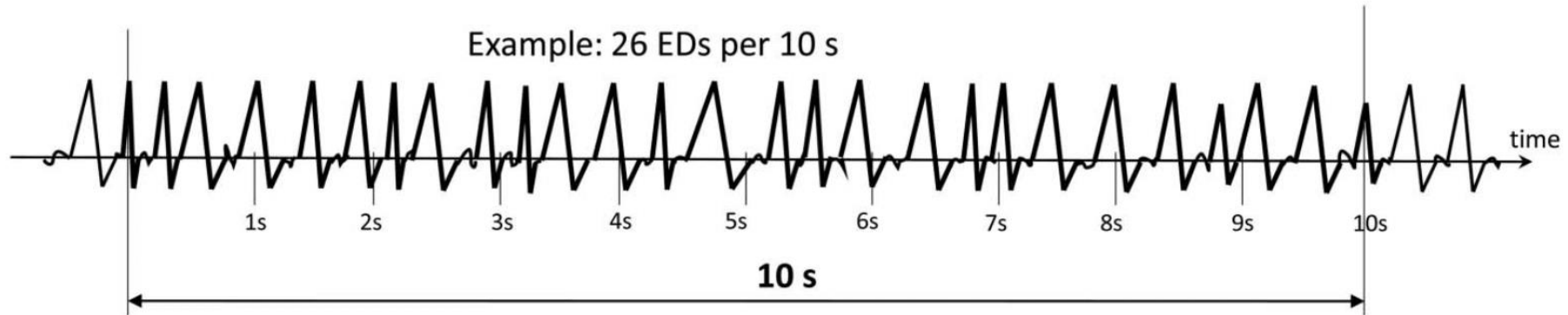
- **SW**: Spike-and-Wave, Sharp-and-Wave or Polyspike-and-Wave



Electrographic Seizures

by ACNS Critical Care EEG Terminology

Epileptiform discharges averaging **>2.5 Hz** for **≥10 s** (>25 discharges in 10 s)



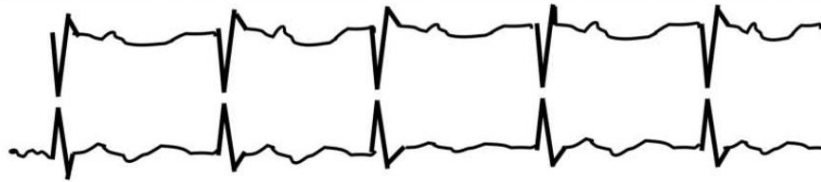
If this pattern continued for 10 continuous minutes, OR if seizures comprised $\geq 20\%$ (i.e., ≥ 12 minutes) of any given hour, this would also qualify as electrographic status epilepticus (ESE).

Electroclinical Seizures

by ACNS Critical Care EEG Terminology

Any EEG pattern with either:

Definite clinical correlate time-locked to the pattern (of any duration)



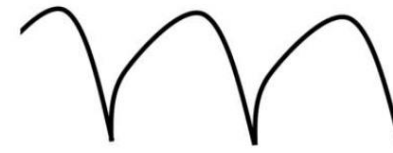
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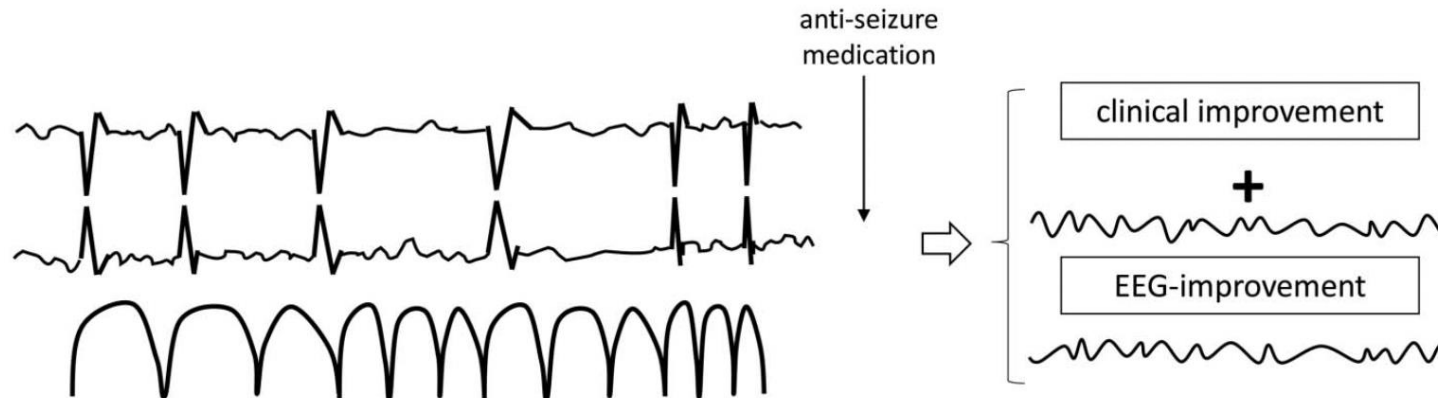
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OR

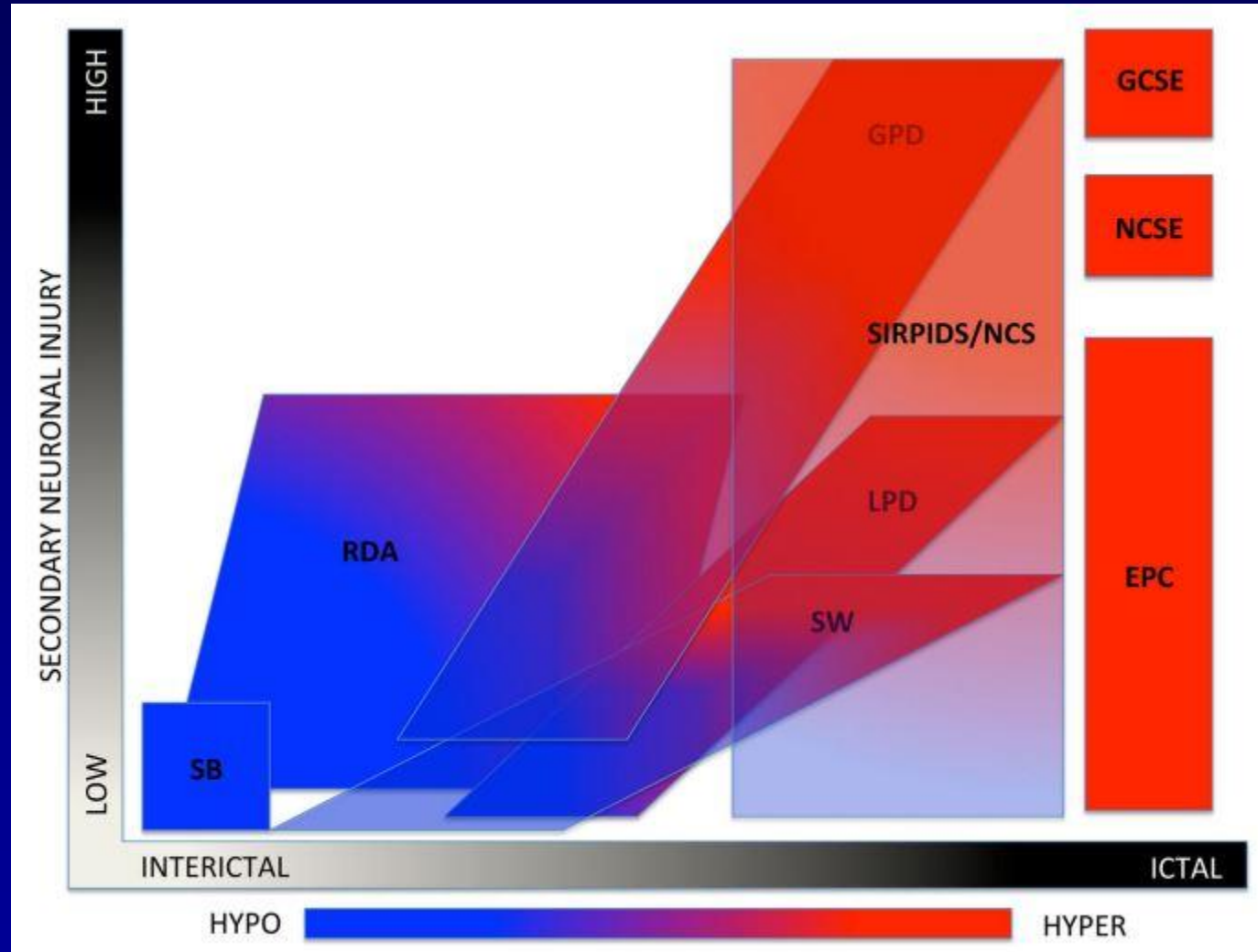
EEG **AND** clinical improvement with a parenteral (typically IV) anti-seizure medication



“Dividing EEG patterns in encephalopathic or comatose patients into a strict dichotomy of “ictal” or “not ictal” is not only extremely difficult, but can be misleading to clinicians and therefore potentially detrimental to patient care.”

Editorial comment – L.J. Hirsch

Ictal-Interictal Continuum



ICTAL-INTERICTAL CONTINUUM (IIC)

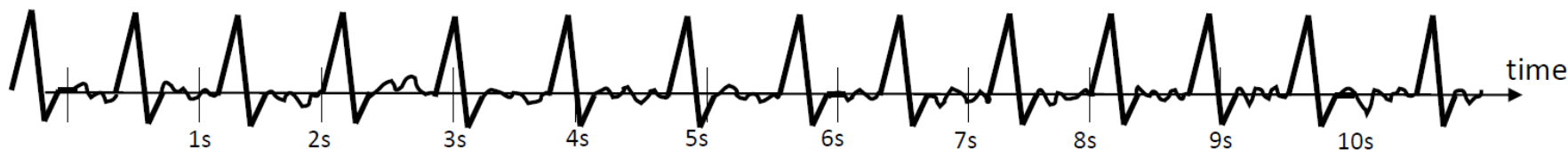
This term is synonymous with “possible ESz” or “possible electrographic SE.” The IIC is a purely electrographic term that is not a diagnosis; it requires careful interpretation in the full clinical context. A pattern on the IIC is a pattern that does not qualify as an ESz or ESE, but there is a reasonable chance that it may be contributing to impaired alertness, causing other clinical symptoms, and/or contributing to neuronal injury. Thus, it is potentially ictal in at least some sense and often warrants a diagnostic treatment trial, typically with a parenteral antiseizure medication.

The following patterns can be considered to be on the ictal-interictal continuum (IIC):

A. Any PD or SW pattern that averages >1.0 Hz and ≤ 2.5 Hz over 10 s (>10 and ≤ 25 discharges in 10 s);

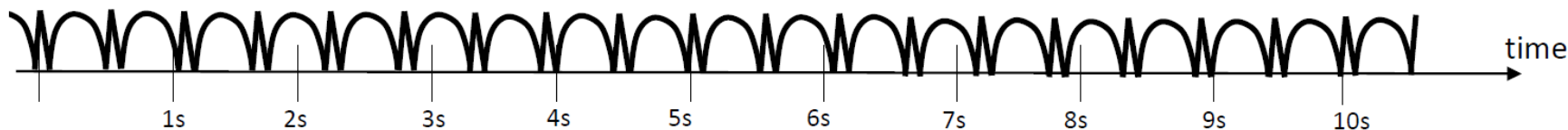
PD

Example: 12 EDs per 10 s



SW

Example: 18 EDs per 10 s

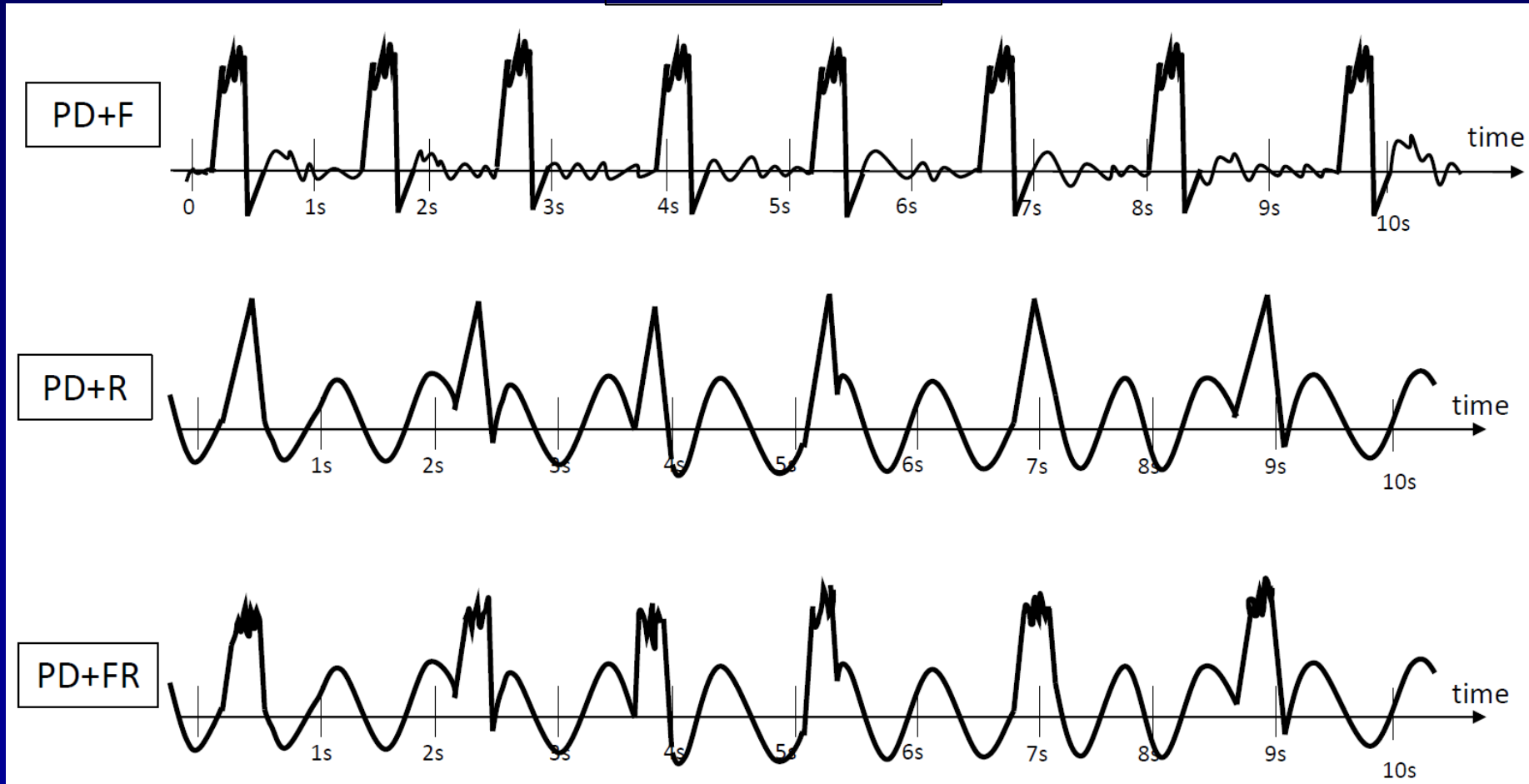


OR...

ICTAL-INTERICTAL CONTINUUM (IIC)

B. Any PD or SW pattern that averages ≥ 0.5 Hz and ≤ 1.0 Hz over 10 seconds (≥ 5 and ≤ 10 discharges in 10 s), AND has a plus modifier or fluctuation;

PLUS-MODIFIERS

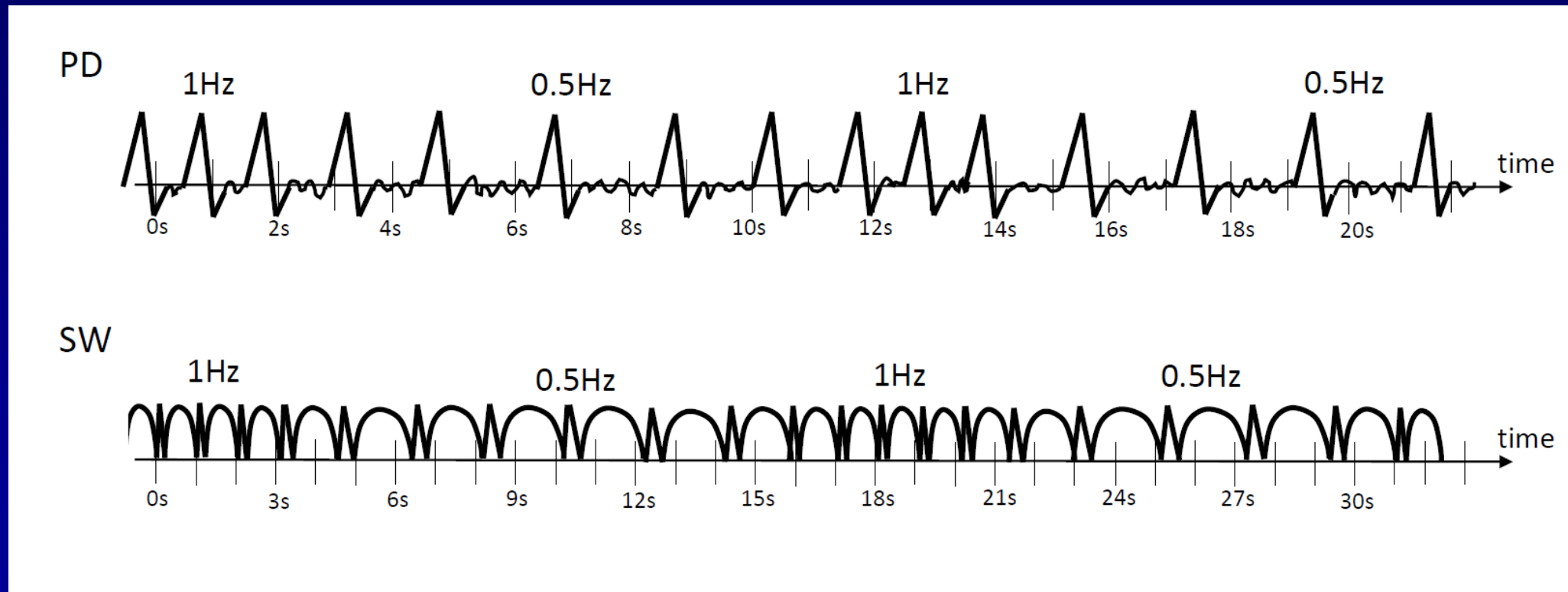


OR...

ICTAL-INTERICTAL CONTINUUM (IIC)

B. Any PD or SW pattern that averages ≥ 0.5 Hz and ≤ 1.0 Hz over 10 seconds (≥ 5 and ≤ 10 discharges in 10 s), AND has a plus modifier or fluctuation;

FLUCTUATION

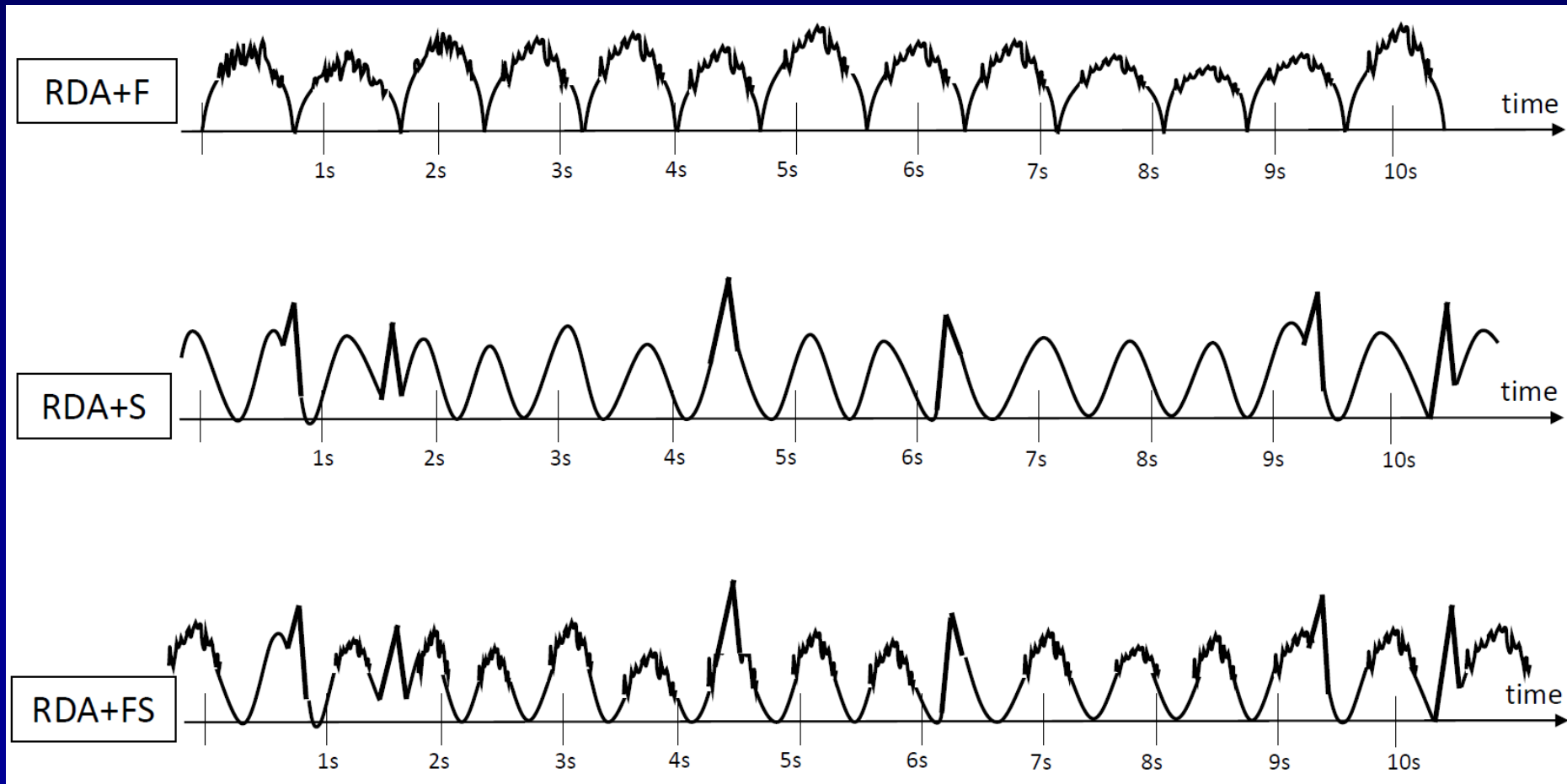


OR...

ICTAL-INTERICTAL CONTINUUM (IIC)

C. Any lateralized RDA (LRDA, BIRDA, UIRDA, MfRDA) averaging >1 Hz for ≥ 10 s (at least 10 waves in 10 s) with a plus modifier or fluctuation.

PLUS-MODIFIER

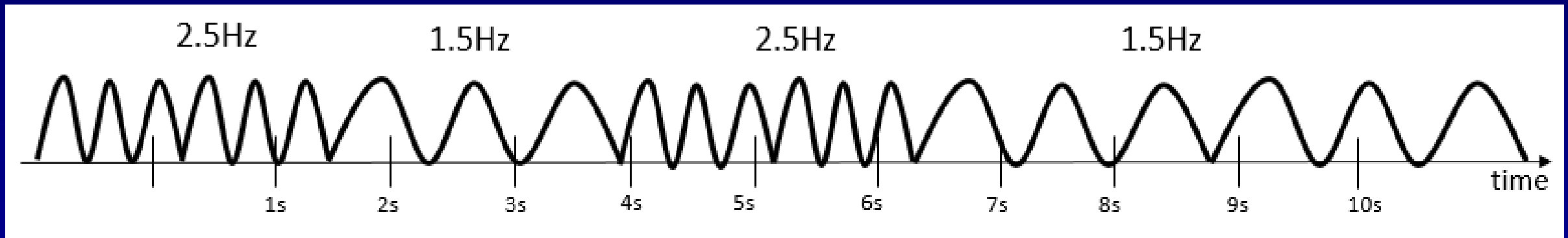


OR...

ICTAL-INTERICTAL CONTINUUM (IIC)

C. Any lateralized RDA (LRDA, BIRDA, UIRDA, MfRDA) averaging > 1 Hz for ≥ 10 s (at least 10 waves in 10 s) with a plus modifier or fluctuation.

Fluctuation



Treatment of Status Epilepticus

- Early treatment is paramount
 - In experimental models of SE, neuronal injury begins after 20-60 min of continuous seizures
 - SE becomes more difficult to control as the duration increases

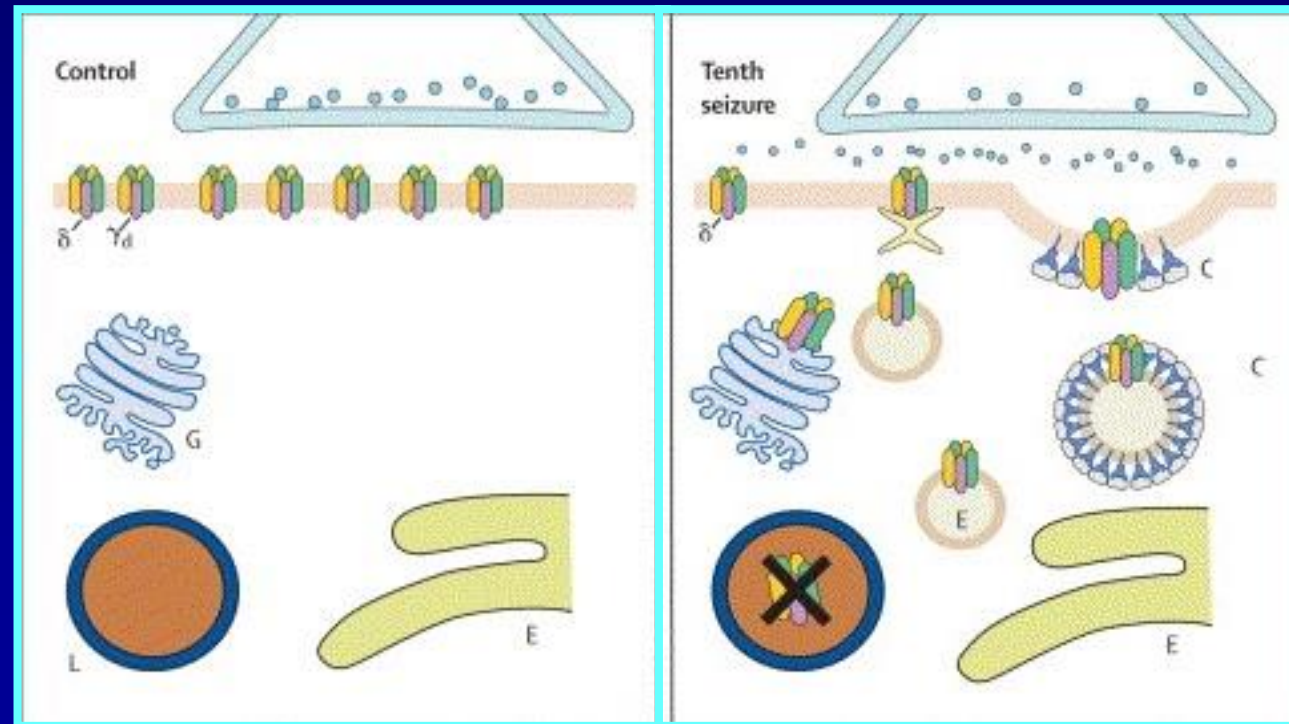
Concept of Progressive Time-Dependent Pharmacoresistance

- Proven in animal models and borne out by clinical experience
- Barbiturates, benzodiazepines lose potency over time
 - 20-fold reduction in potency within 30 minutes
 - Due to a failure of GABA-mediated inhibition
 - Extremely high doses required to stop seizures
 - Leads to toxicity that precludes their use
 - e.g. cardiovascular depression
- NMDA-blockers remain effective, even late

Pathophysiologic Basis of Refractoriness

within seconds – minutes

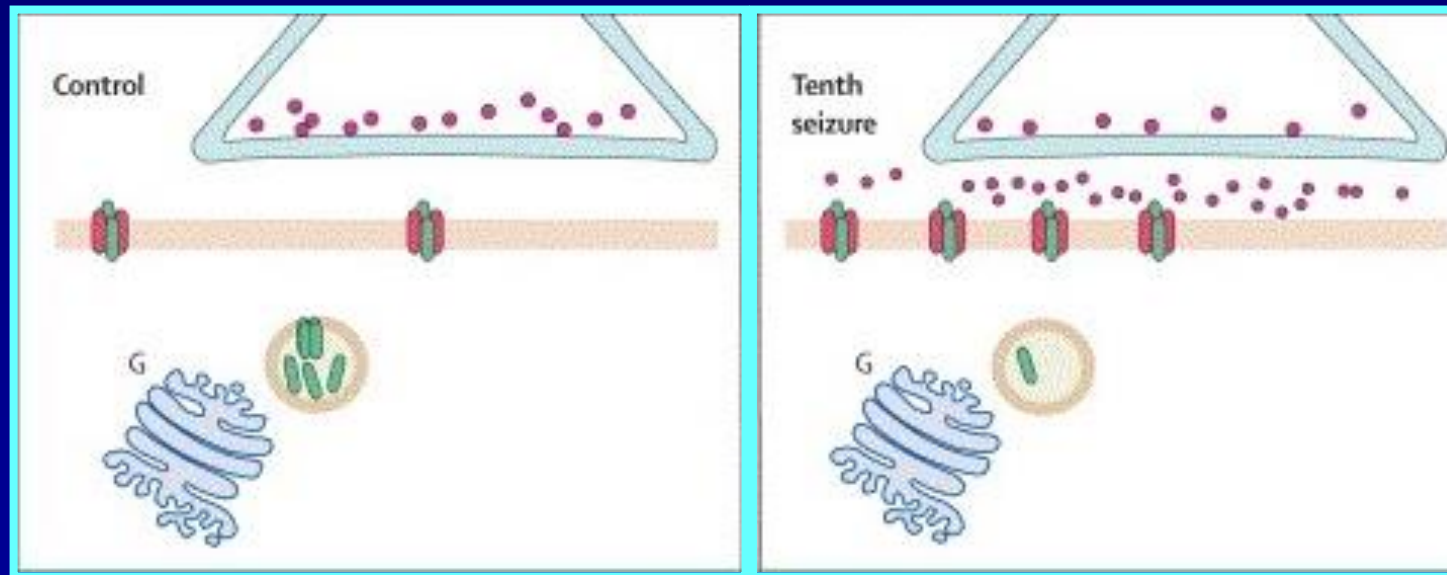
- Endocytosis of GABA_A receptors
- Failure of GABA_A inhibition



Pathophysiologic Basis of Refractoriness

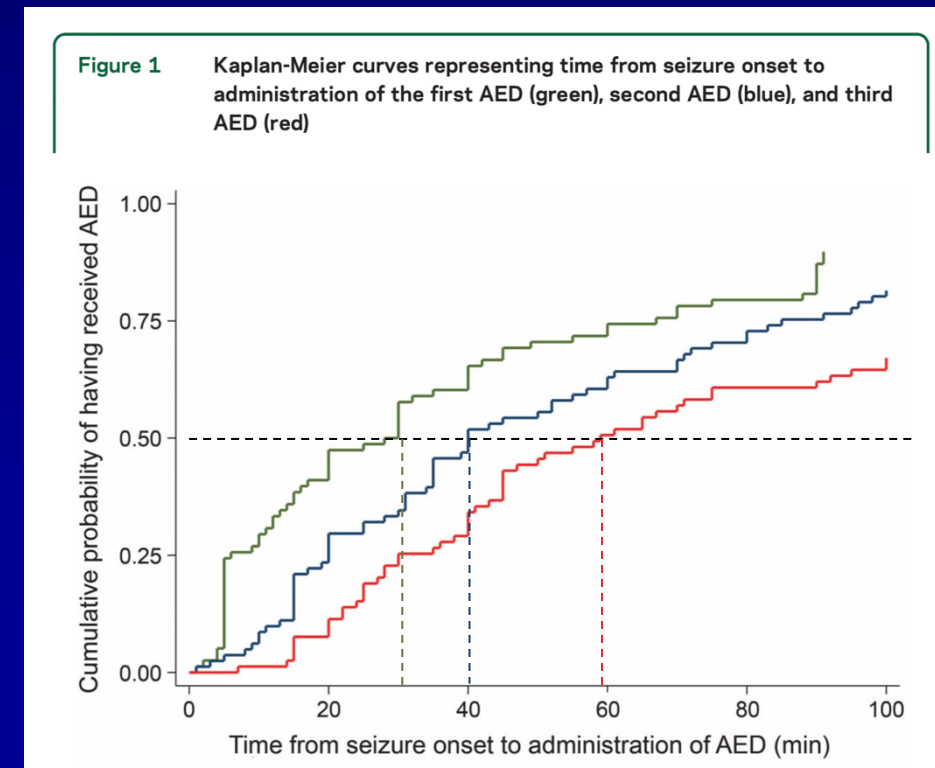
within seconds – minutes

- Mobilization of NMDA receptors
- Gain of excitatory function



Treatment Delays Are Common

- Time from SE onset to treatment is commonly delayed in both pre-hospital and in-hospital settings
 - Prospective multicenter cohort of 81 children with convulsive SE
 - Median time to:
 - First AED dose: 28 min
 - Second AED dose: 40 min
 - Third AED dose: 59 min

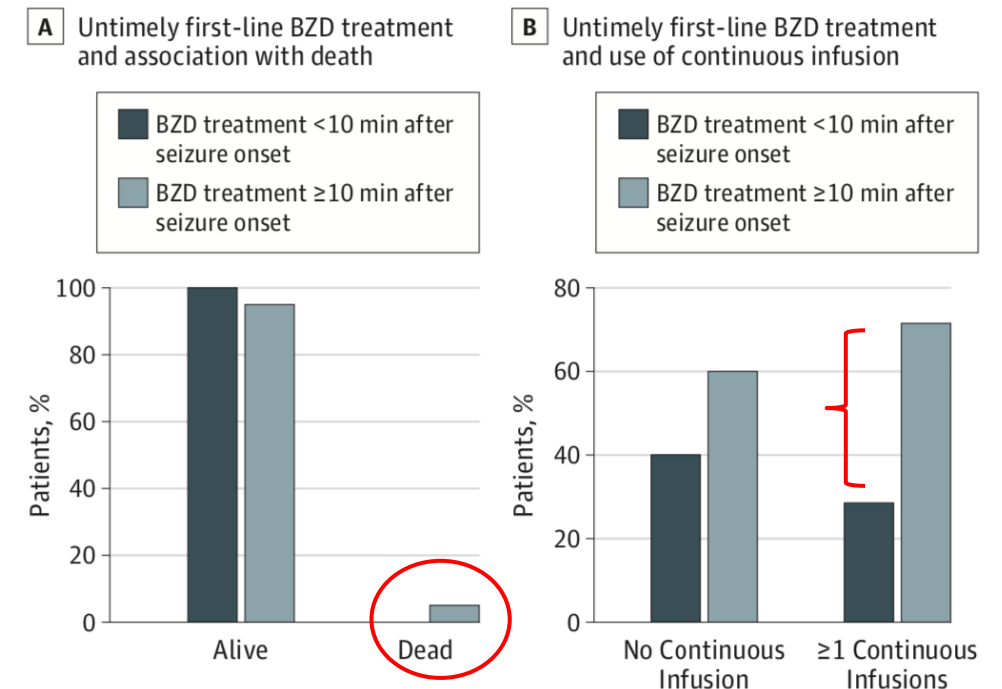


Treatment Delays are Associated with Worse Outcome

- Multicenter prospective cohort study of 218 children with refractory convulsive SE
- Dichotomized into two groups:
 - First-line benzodiazepine received <10 min
 - First-line benzodiazepine received ≥10 min
- Multivariate analysis: patients who received **untimely first-line benzodiazepine** had
 - **Higher odds of death** (OR 11, P=0.02)
 - **Greater odds of receiving continuous infusion** (OR 1.8, P=0.047)
 - **Longer convulsive seizure duration** (OR 2.6, P=0.02)

Gáinza-Lein et al. JAMA Neurol. 2018;75(4):410-418.

Figure 1. Untimely First-line Benzodiazepine (BZD) Treatment and Association With Outcome



A, All 7 patients who died prior to hospital discharge received untimely first-line BZD treatment (≥10 minutes). B, Of the 112 patients (51.4%) who received a continuous infusion as treatment for refractory convulsive status epilepticus, 80 (71.4%) received untimely first-line BZD treatment.

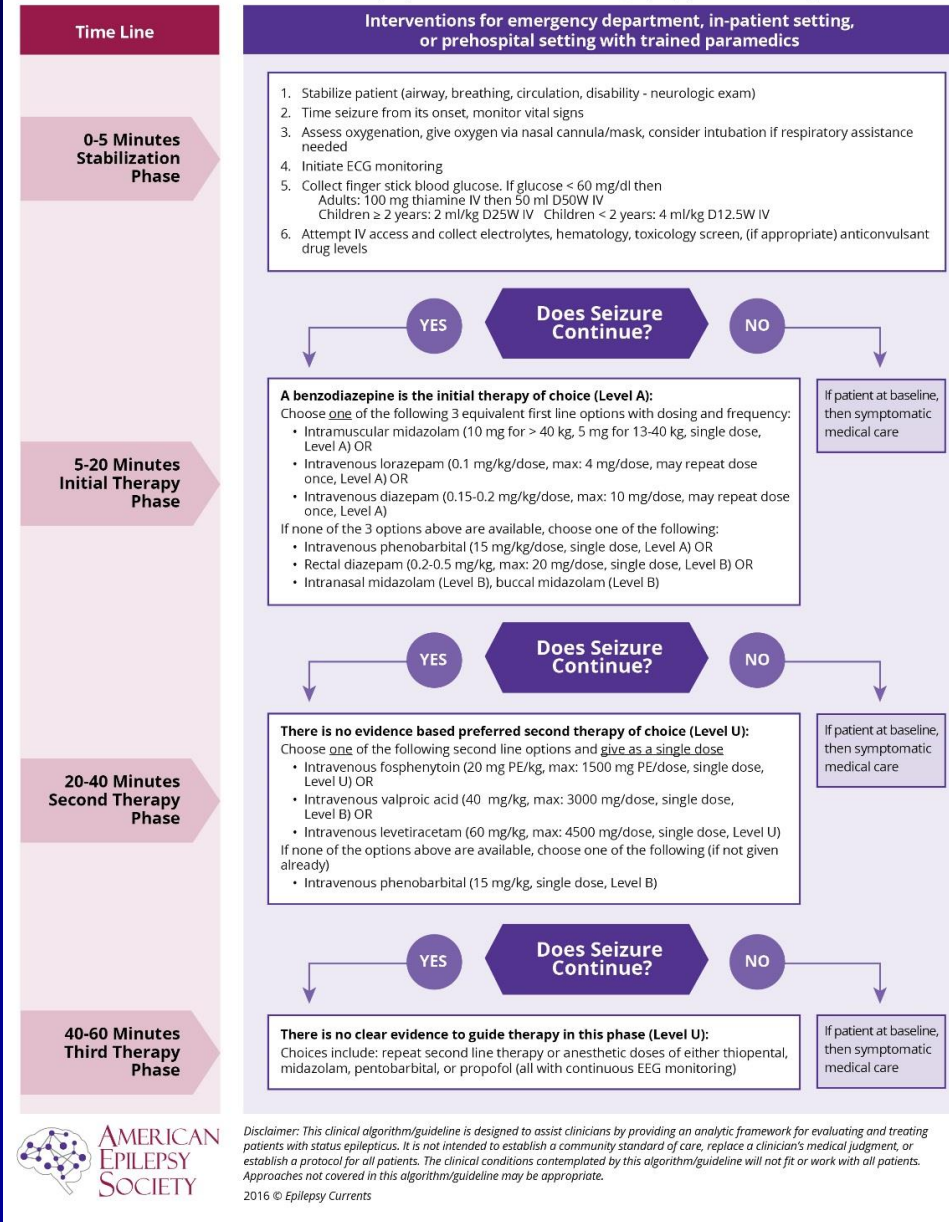
Guidelines Can Improve Timeliness of Treatment

- Guidelines should be evidence-based whenever possible
- Until recently, evidence has been lacking

2016 American Epilepsy Society Guideline

Proposed Algorithm for Convulsive Status Epilepticus

From "Treatment of Convulsive Status Epilepticus in Children and Adults," *Epilepsy Currents* 16:1 - Jan/Feb 2016



Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytic framework for evaluating and treating patients with status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish a protocol for all patients. The clinical conditions contemplated by this algorithm/guideline will not fit or work with all patients. Approaches not covered in this algorithm/guideline may be appropriate.

2016 © Epilepsy Currents

Epilepsy Currents
Vol. 16, No. 1, pp. 48-61.

0-5 Minutes Stabilization Phase

1. Stabilize patient (airway, breathing, circulation, disability - neurologic exam)
2. Time seizure from its onset, monitor vital signs
3. Assess oxygenation, give oxygen via nasal cannula/mask, consider intubation if respiratory assistance needed
4. Initiate ECG monitoring
5. Collect finger stick blood glucose. If glucose < 60 mg/dl then
Adults: 100 mg thiamine IV then 50 ml D50W IV
Children $\geq$ 2 years: 2 ml/kg D25W IV Children < 2 years: 4 ml/kg D12.5W IV
6. Attempt IV access and collect electrolytes, hematology, toxicology screen, (if appropriate) anticonvulsant drug levels

**5-20 Minutes
Initial Therapy
Phase**

A benzodiazepine is the initial therapy of choice (Level A):

Choose one of the following 3 equivalent first line options with dosing and frequency:

- Intramuscular midazolam (10 mg for > 40 kg, 5 mg for 13-40 kg, single dose, Level A) OR
- Intravenous lorazepam (0.1 mg/kg/dose, max: 4 mg/dose, may repeat dose once, Level A) OR
- Intravenous diazepam (0.15-0.2 mg/kg/dose, max: 10 mg/dose, may repeat dose once, Level A)

If none of the 3 options above are available, choose one of the following:

- Intravenous phenobarbital (15 mg/kg/dose, single dose, Level A) OR
- Rectal diazepam (0.2-0.5 mg/kg, max: 20 mg/dose, single dose, Level B) OR
- Intranasal midazolam (Level B), buccal midazolam (Level B)

Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART)

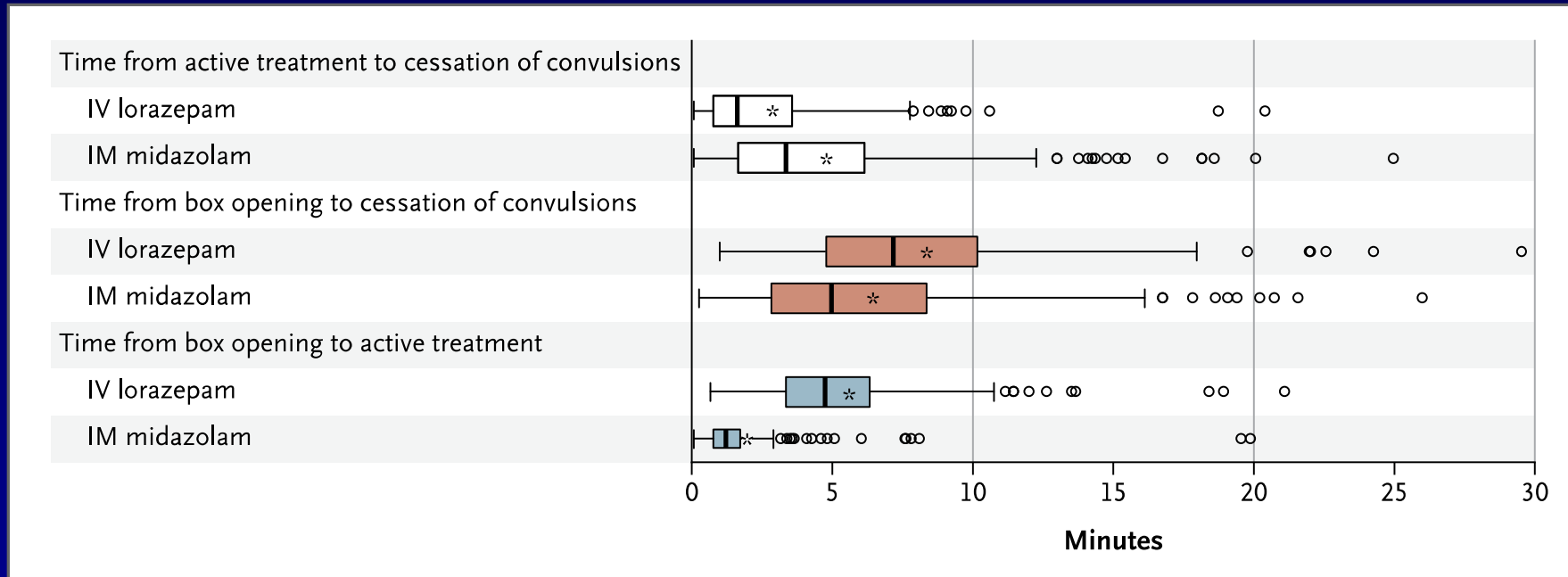


Figure 3. Intervals between Active Treatment and Cessation of Convulsions, Box Opening and Cessation of Convulsions, and Box Opening and Active Treatment.

The shorter time to IM drug administration was offset by the faster onset of action after IV drug administration, resulting in similar latency periods until convulsions were terminated. Time to IV administration includes the nominal time (about 20 seconds) needed to administer the drug by means of IM autoinjector. Asterisks indicate means, boxes interquartile ranges, bold vertical lines within boxes medians, I bars 1.5 times the interquartile range, and circles outliers.

**20-40 Minutes
Second Therapy
Phase**

There is ~~no~~ evidence based preferred second therapy of choice (Level A):

Choose one of the following second line options and give as a single dose

- Intravenous fosphenytoin (20 mg PE/kg, max: 1500 mg PE/dose, single dose, Level U) OR
- Intravenous valproic acid (40 mg/kg, max: 3000 mg/dose, single dose, Level B) OR
- Intravenous levetiracetam (60 mg/kg, max: 4500 mg/dose, single dose, Level U)

If none of the options above are available, choose one of the following (if not given already)

- Intravenous phenobarbital (15 mg/kg, single dose, Level B)

Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus

- A Multicenter, Randomized, Blinded, Comparative Effectiveness Study of Fosphenytoin, Valproic Acid, or Levetiracetam in the ED Treatment of Patients With Benzodiazepine-Refractory SE (age > 2 years).
- Response-adaptive comparative-effectiveness design, Bayesian analysis
 - **Fosphenytoin** 20 mg/Kg IV (max 1500 mg) over 10 min
 - **Valproic acid** 40 mg/Kg IV (max 3000 mg) over 10 min
 - **Levetiracetam** 60 mg/Kg IV max 4500 mg) over 10 min
- Patients randomly assigned to receive one of the three trial drugs, initially in a 1:1:1 ratio. After 300 patients were assigned to a treatment group, response-adaptive randomization was initiated with the goal of maximizing the likelihood of identifying the most effective treatment.

Table 2. Efficacy Analyses.*

Outcome and Population	Levetiracetam (N = 145)	Fosphenytoin (N = 118)	Valproate (N = 121)
Primary efficacy outcome: cessation of seizures and improvement in consciousness at 60 min without other anticonvulsant medications			
Intention-to-treat population			
No. with outcome	68	53	56
Percent of patients with outcome (95% credible interval)	47 (39–55)	45 (36–54)	46 (38–55)
Probability that treatment is the most effective	0.41	0.24	0.35
Probability that treatment is the least effective	0.24	0.45	0.31
Per-protocol population			
No. with outcome/total no.	51/109	37/79	43/91
Percent of patients with outcome (95% credible interval)	47 (38–56)	47 (36–58)	47 (37–57)
Probability that treatment is the most effective	0.31	0.34	0.36
Probability that treatment is the least effective	0.34	0.35	0.31
Adjudicated-outcomes population			
No. with outcome	67	57	60
Percent with outcome (95% credible interval)	46 (38–54)	48 (39–57)	50 (41–58)
Probability that treatment is the most effective	0.17	0.35	0.48
Probability that treatment is the least effective	0.51	0.29	0.20
Secondary efficacy outcomes			
Admission to ICU — no. (%)	87 (60.0)	70 (59.3)	71 (58.7)
Median length of ICU stay (IQR) — days	1 (0–3)	1 (0–3)	1 (0–3)
Median length of hospital stay (IQR) — days	3 (1–7)	3 (1–6)	3 (2–6)
Median time from start of trial-drug infusion to termination of seizures for patients with treatment success (IQR) — min†	10.5 (5.7–15.5)	11.7 (7.5–20.9)	7.0 (4.6–14.9)

Conclusions

- levetiracetam, fosphenytoin, and valproate each led to seizure cessation and improved alertness by 60 minutes in approximately half the patients
- the three drugs were associated with similar incidences of adverse events

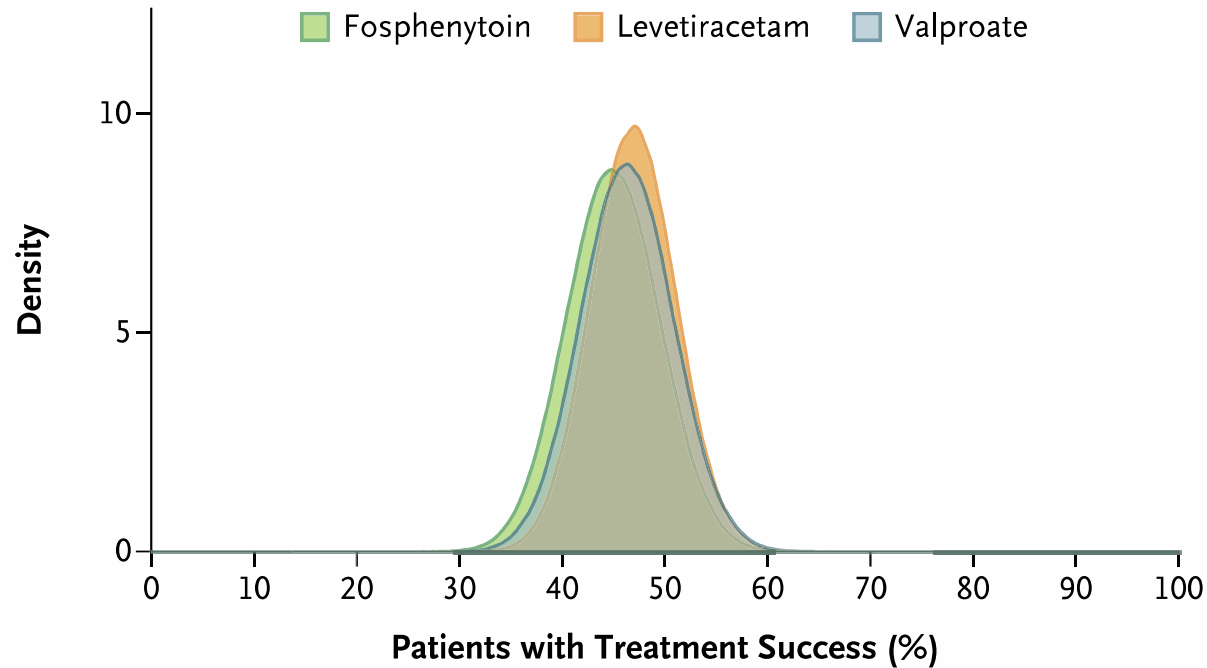


Figure 2. Posterior Probabilities of Success According to Treatment Group for the Primary Outcome of Cessation of Status Epilepticus at 60 Minutes.

The relative posterior probabilities of treatment success with regard to the primary outcome for each drug are shown. The percentage of patients with treatment success was 47% (95% credible interval, 39 to 55) in the levetiracetam group, 45% (95% credible interval, 36 to 54) in the fosphenytoin group, and 46% (95% credible interval, 38 to 55) in the valproate group.

Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial

Stuart R Dalziel, Meredith L Borland, Jeremy Furyk, Megan Bonisch, Jocelyn Neutze, Susan Donath, Kate L Francis, Cynthia Sharpe, A Simon Harvey, Andrew Davidson, Simon Craig, Natalie Phillips, Shane George, Arjun Rao, Nicholas Cheng, Michael Zhang, Amit Kochar, Christine Brabyn, Ed Oakley, Franz E Babl, on behalf of the PREDICT research network

“Levetiracetam is not superior to phenytoin “

Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial

*Mark D Lyttle, Naomi E A Rainford, Carrol Gamble, Shrouk Messahel, Amy Humphreys, Helen Hickey, Kerry Woolfall, Louise Roper, Joanne Noblet, Elizabeth D Lee, Sarah Potter, Paul Tate, Anand Iyer, Vicki Evans, Richard E Appleton, with support of Paediatric Emergency Research in the United Kingdom & Ireland (PERUKI) collaborative**

“Levetiracetam could be an appropriate alternative to phenytoin “

Lancet 2019 May 25;393(10186):2135-2145.

Lancet 2019 May 25;393(10186):2125-2134

Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial

James M Chamberlain, Jaideep Kapur, Shlomo Shinnar, Jordan Elm, Maija Holsti, Lynn Babcock, Alex Rogers, William Barsan, James Cloyd, Daniel Lowenstein, Thomas P Bleck, Robin Conwit, Caitlyn Meinzer, Hannah Cock, Nathan B Fountain, Ellen Underwood, Jason T Connor, Robert Silbergleit, for the Neurological Emergencies Treatment Trials* and the Pediatric Emergency Care Applied Research Network investigators†

- Extension of ESETT in children
- Double-blind RCT of fosphenytoin, valproate and levetiracetam
- Confirms findings of EcLiPSE and ConSEPT open label studies and extends these findings to valproate
- All 3 anticonvulsants are appropriate first-choice second-line drugs in children with benzodiazepine-refractory status epilepticus

Lancet 2020; 395: 1217–24

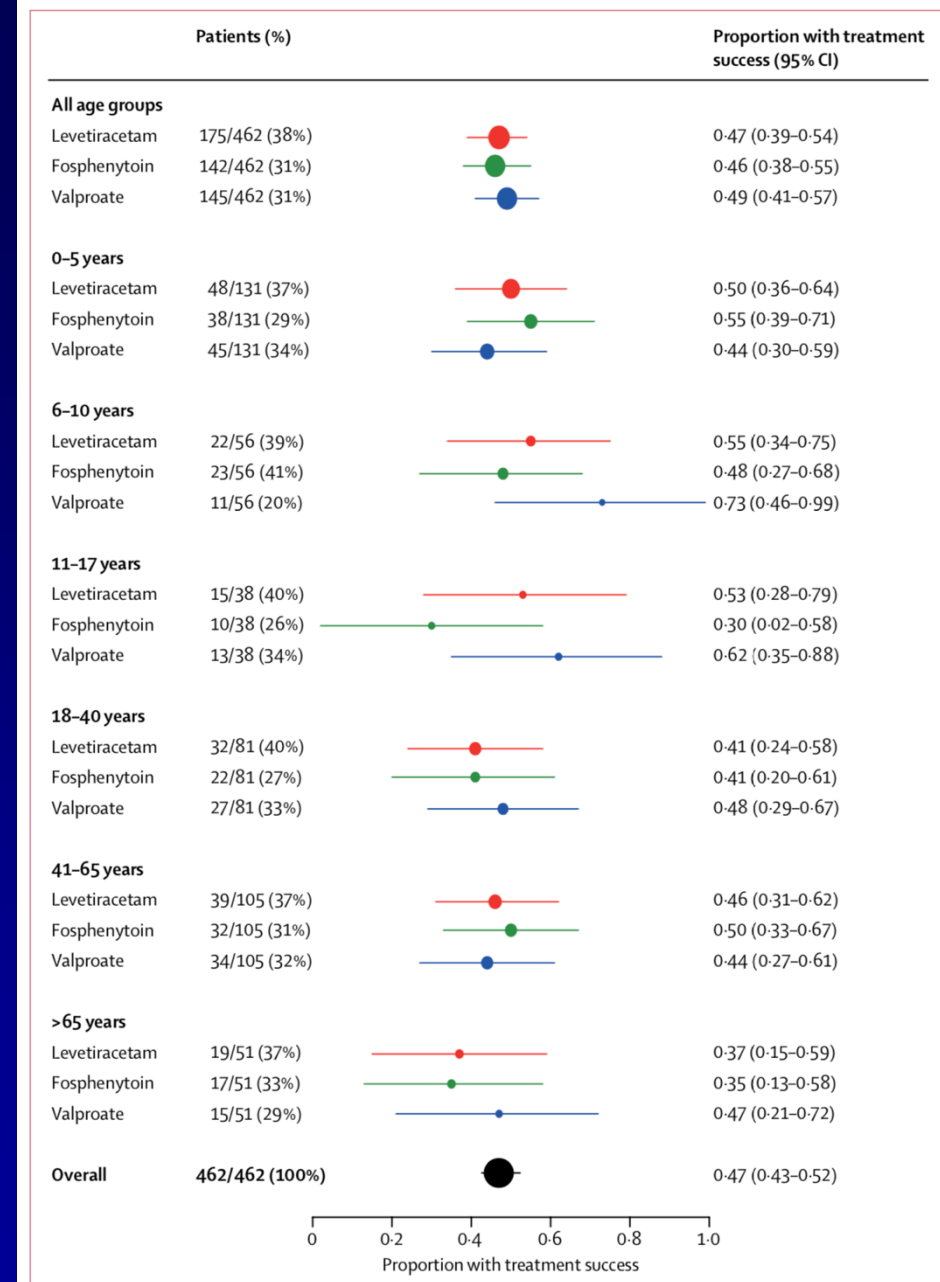


Figure 3: Forest plot of proportion of treatment success for the primary outcome by age ranges, post hoc
The size of the circle in each row is representative of the number of patients in that group and the error bars show 95% CIs. These narrower age groupings were determined post hoc.

Are there other alternatives?

- Lacosamide, a newer ASM that selectively enhances the slow inactivation of sodium channels
- Has attracted attention as a second- line treatment option due to its favorable pharmacokinetics, minimal drug–drug interactions, and well- tolerated infusion profile.
- Although lacosamide is included in several SE treatment guidelines, large-scale RCTs to establish its efficacy relative to other second- line agents are lacking.

Comparison of lacosamide, levetiracetam, and valproate as second-line therapy in adult status epilepticus: Analysis of a large cohort

Cecil D. Hahn, Jan Novy, Andrea O. Rossetti



Background

- Guidelines for treatment of SE recommend
 - 1st line: benzodiazepines
 - 2nd line: phenytoin, valproate, levetiracetam, phenobarbital, lacosamide, brivaracetam, etc...

Clinical practice guidelines on the management of status epilepticus in adults: A systematic review

Luca Vignatelli¹  | Valentina Tontini¹ | Stefano Meletti²  | Maria Camerlingo³ |
Stefania Mazzoni¹ | Giada Giovannini²  | Elena Pasini¹  | Roberto Michelucci¹  |
Francesca Bisulli^{1,4}  | Paolo Tinuper⁴ | Lidia Di Vito¹ 

Second line:	First choice:	Second choice:
13 CPGs	VPA: 8 e2,e5,e7,e10,e11,e13-e15	LEV: 6 e2,e3,e5,e7,e8,e12
	PHT: 8 e2,e5,e8,e10-e12,e14,e16	PB: 5 e2,e3,e5,e7,e15
	fosPHT: 6 e2,e5,e13-e16	VPA: 3 e3,e8,e12
	DZP+PHT: 2 e1,e3	LCS: 3 e2,e8,e12
	PB: 5 e8,e11-e13,e16	PHT: 2 e7,e15
	LEV: 5 e11,e13-e16	fosPHT: 1 e7
	LZP: 2 e1,e3	TPM: 1 e11
	MDZ (continuous): 1 e16	PROP (continuous): 1 e5
	LCS: 1 e11	

Background

- Considerable variability remains in choice of second-line therapy
- We observed declining use of phenytoin and increasing use of lacosamide
 - selectively enhances the slow inactivation of sodium channels
 - favorable pharmacokinetics
 - minimal drug-drug interactions
 - well-tolerated infusion profile
- Large-scale RCTs to establish efficacy of lacosamide are lacking
- Direct comparisons of ASMs in real-world practice remain limited

Objective

- To compare the real-world efficacy of lacosamide with other commonly used second-line ASMs using an established prospective single-center adult SE cohort

Methods

- Retrospective analysis of an institutional SE registry (Jan 2013–Dec 2022)
 - Adults treated with 2nd line therapy for SE of any cause except cardiac arrest
- Outcomes:
 - SE termination
 - Need for mechanical ventilation
 - Condition at discharge: return to baseline / new disability / death
- Confounders:
 - Sex
 - Status Epilepticus Severity Score (STESS)
 - Adequacy of initial SE treatment and treatment delay
 - Potentially fatal etiology

Results

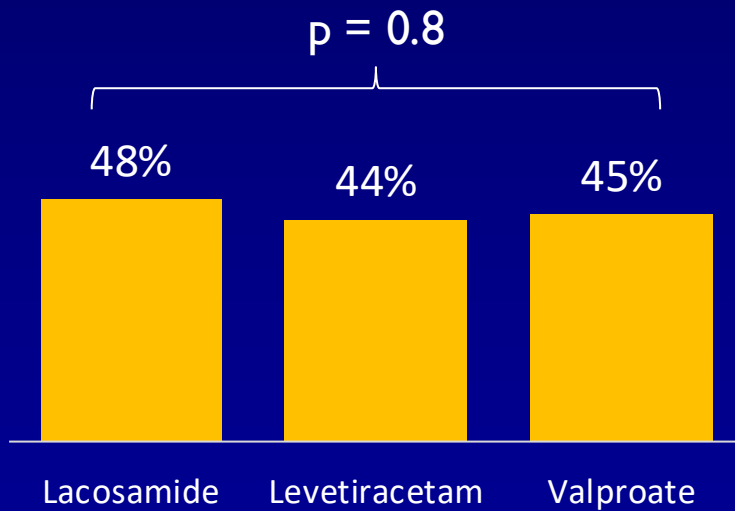
- 961 consecutive adult SE episodes were included over 10 years
- 868 SE episodes required second-line ASM therapy, most commonly:
 - Levetiracetam in 413 episodes (48%)
 - Valproate in 110 episodes (13%)
 - Lacosamide in 75 episodes (9%)
- Other ASMs excluded from analysis because of insufficient usage
 - e.g. phenytoin in 7 episodes (1%)

Univariable Analysis

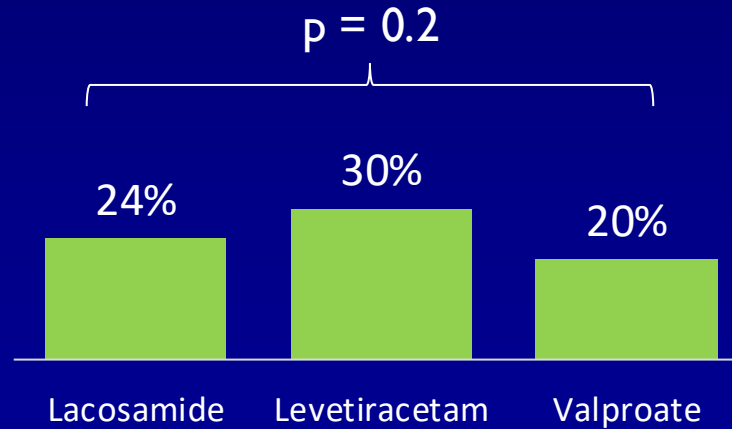
- Potential confounders identified on univariable analysis:
 - STESS
 - treatment delay
 - adequacy of initial SE treatment
- STESS was higher among patients receiving levetiracetam
- Initial SE treatment was more often delayed and inadequate among patients receiving lacosamide

Results

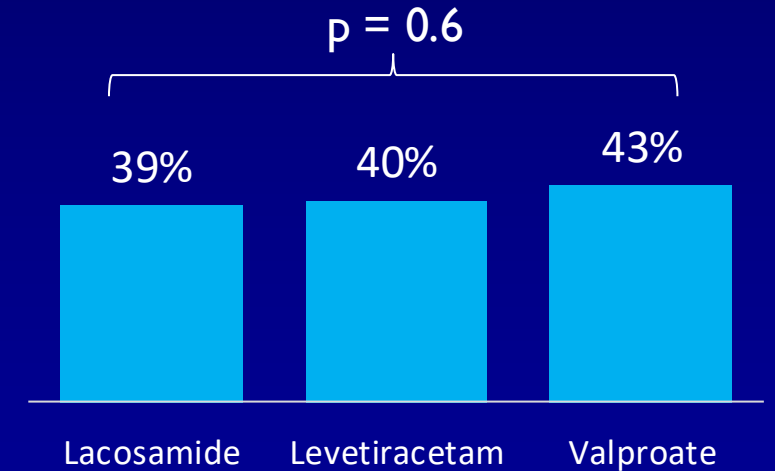
Response to Second-Line Therapy



Need for Mechanical Ventilation

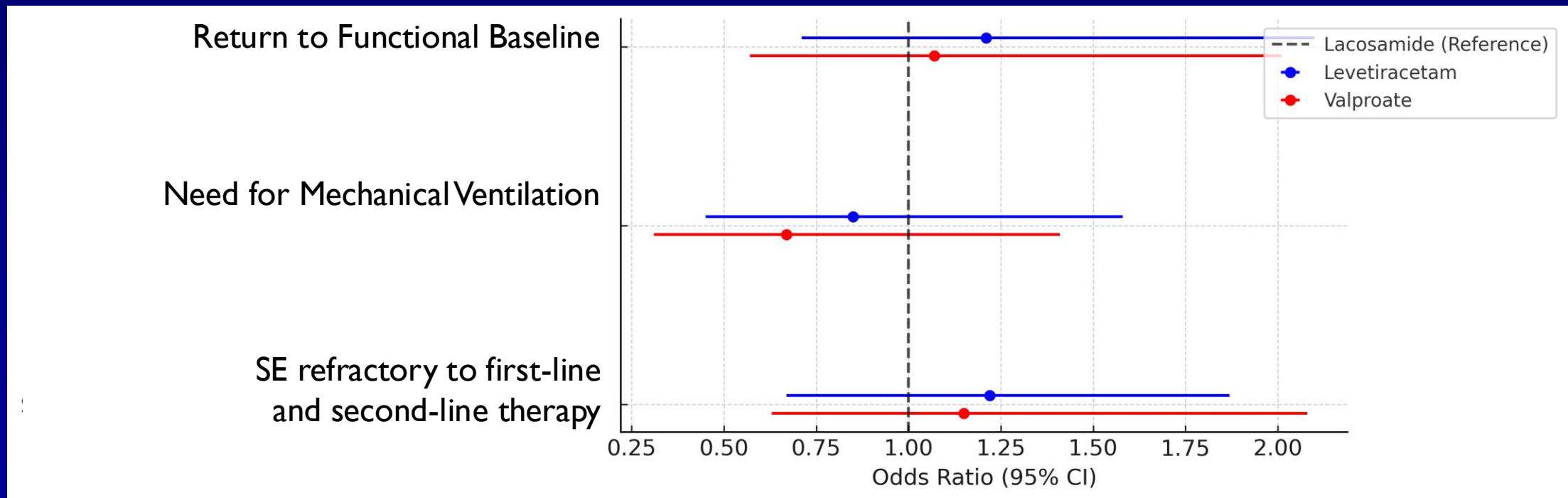


Return to Baseline Functional Status



Multivariable Analysis

- Adjusted for STESS, treatment delay, and adequacy of initial SE treatment
- Second-line use of Lacosamide, Levetiracetam and Valproate was associated with statistically equivalent rates of:



Strengths & Limitations

- Strengths
 - Large real-world comparison of lacosamide vs. other second-line therapies for SE
 - Single-center registry conducted over 10 years provides internal validity
- Limitations
 - Only 1% of our cohort received phenytoin as second-line therapy
 - Concerns re: challenging pharmacokinetics, cardiac side effects, drug interactions
 - Limits the generalizability of our findings
 - Despite multivariable analysis adjusting for known potential confounders, some residual unknown confounding may have remained

Conclusions

- Lacosamide appears to represent a reasonable alternative to levetiracetam and valproate for second line therapy of SE
- Lacosamide warrants consideration for inclusion in future randomized controlled trials of therapy of established SE

Treatment of Recurrent Electrographic Nonconvulsive Seizures (TRENdS)

- Noninferiority, prospective, multicenter, randomized trial of patients **diagnosed with nonconvulsive seizures by cEEG**, comparing:
 - Lacosamide 400mg IV
 - Fosphenytoin 20mg PE/kg
- Primary outcome: absence of EEG seizures for 24 hours
- 74 subjects enrolled (37 LCM, 37 fPHT)
- Seizures controlled with LCM in 63% and with fPHT in 50%
- LCM was non-inferior to fPHT, adverse events similar
- LCM is an alternative to fPHT for treatment of NCS on cEEG

KESETT Trial

Ketamine Add-on for Established Status Epilepticus



- Scale: ~60 US sites in SIREN network, up to 770 participants
- Design: Multicenter, randomized, double-blind, Bayesian adaptive trial
- Population: benzodiazepine-refractory established SE (adults & children ≥ 1 yr)
- Intervention: Levetiracetam + ketamine (1 mg/kg or 3 mg/kg) vs levetiracetam + placebo
- Rationale: NMDA antagonism may overcome GABA resistance in prolonged seizures
- Primary Outcome: seizure termination at 60 minutes with need for additional treatment
- Hypothesis: addition of ketamine will increase proportion of patients with seizure termination at 60 minutes from 47% to ~ 62%
- Study start: March 2026
- Estimated completion: June 2029

**40-60 Minutes
Third Therapy
Phase**

There is no clear evidence to guide therapy in this phase (Level U):

Choices include: repeat second line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring)

Refractory Status Epilepticus

- Definition
 - A severe form of status epilepticus that does not respond to first and second line treatment with adequate doses of antiepileptic drugs
- Incidence
 - ~ 26% of children with SE
 - ~ 9% of adults with SE

Refractory Status Epilepticus

- Mortality
 - 39% in adults
 - 16% – 21% in children
- Morbidity
 - highest among acute symptomatic cases
 - 2/3 of survivors have neurological impairment
 - most survivors have ongoing epilepsy

Third-Line Therapeutic Options

Drug	Mechanism	Half-life	Precautions
Midazolam	GABA _A agonist	3-4 hours	Rapid tolerance
Pentobarbital	GABA _A agonist	25 hours	Hypotension
Thiopental	GABA _A agonist	14-34 hours	Accumulation due to lipid solubility
Phenobarbital	GABA _A agonist	37-73 hours	Immunosuppression
Propofol	GABA _A agonist	1.5-12 hours	Propofol infusion syndrome (acidosis)
Ketamine	NMDA antagonist	2.5 hours	Hypertension, increased ICP

General Precautions: Sedation, bradycardia, hypotension, cardiac arrhythmia, respiratory depression

Anaesthetic Agents All Have Equivalent Efficacy

Table 2 Overall outcome of anaesthetic therapy

Outcome	Thiopental/pentobarbital (n = 192)	Midazolam (n = 585)	Propofol (n = 143)
Control	64% (123/192)	78% (458/585)	68% (97/143)
No control ever achieved ^a	5% (9/192)	16% (93/585)	11% (16/143)
Breakthrough seizures	0% (0/192)	3% (19/585)	1% (2/143)
Withdrawal seizures	9% (18/192)	< 1% (2/585)	6% (8/143)
Therapy failure because of side-effects	3% (5/192)	< 1% (1/585)	6% (8/143)
Death during therapy	19% (37/192)	2% (12/585)	8% (12/143)

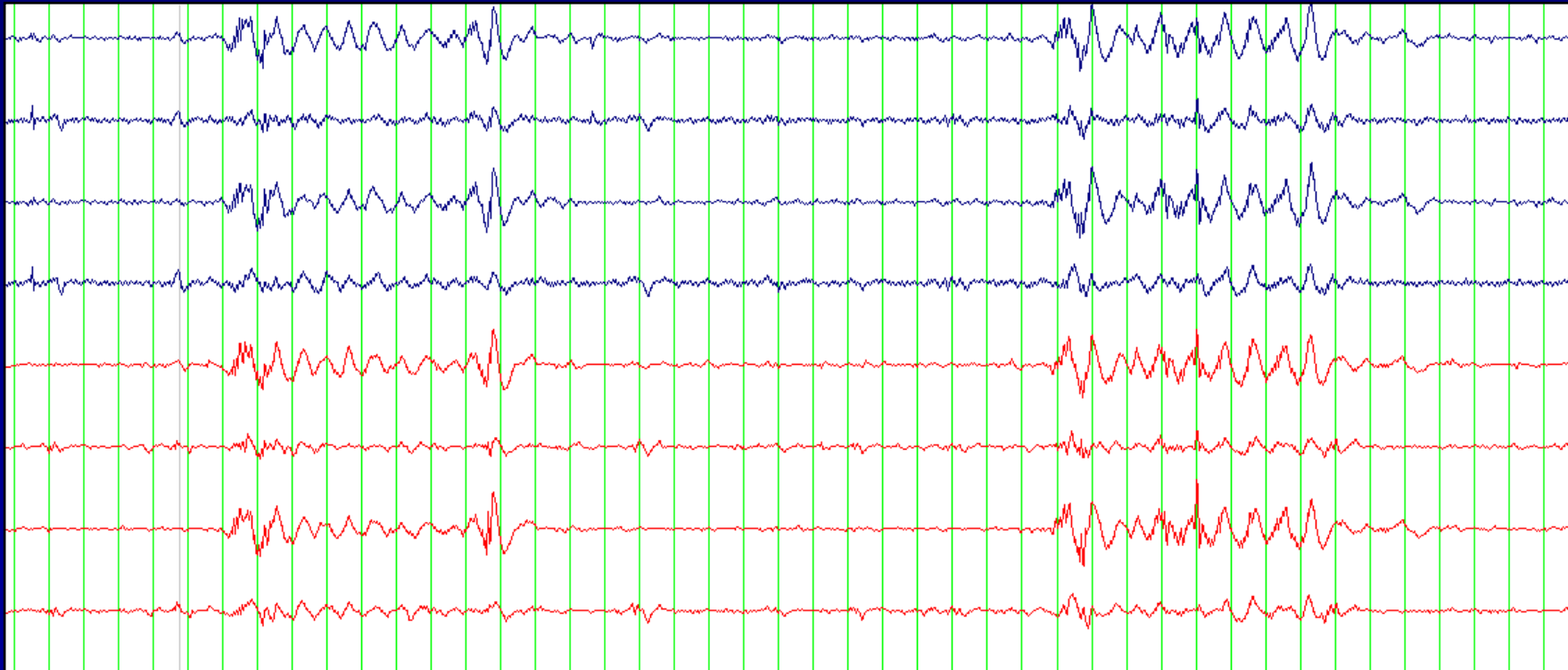
Establishing Treatment Goals

- Controversies
 - End-point for titration of therapy
 - Clinical seizure suppression
 - Electrographic & clinical seizure suppression
 - EEG burst suppression
 - EEG complete suppression
 - Duration of therapy prior to weaning

Burst Suppression

- Definition

- Suppression: 2-10 second periods of unreactive background $<5 \mu\text{V}$
- Burst: epochs of higher voltage irregular slow and sharp wave activity lasting a few seconds
- Different from periodic discharges due to complexity and duration of bursts



De Novo Generalized Periodic Discharges Related to Anesthetic Withdrawal Resolve Spontaneously

Amar B. Bhatt,* Alexandra Popescu,† Elizabeth J. Waterhouse,‡ and Bassel W. Abou-Khalil*

Journal of Clinical Neurophysiology • Volume 31, Number 3, June 2014

“GRAWs”: Generalized periodic discharges related to anesthetic withdrawal

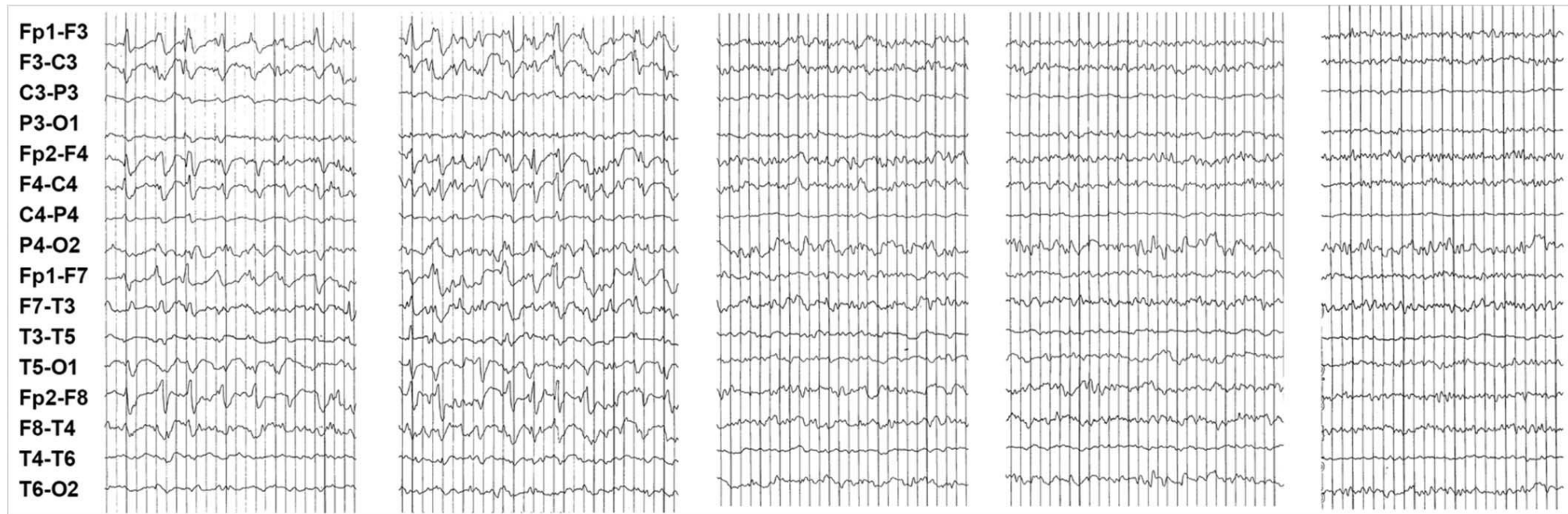


FIG. 1. Spontaneous resolution of GRAWs over 12 hours in case 1. The first panel showed persistent GRAWs that progressively attenuated in the third and fourth panels and resolved in the last panel.

Additional Therapeutic Options

Therapy	Mechanism	Comments
Corticosteroids	Immune suppression 'Membrane stabilizing' effect	Consider if evidence of inflammation, anti-NMDAR
PLEX / IVIG	Immunomodulation	Consider if evidence of inflammation, anti-NMDAR
Hypothermia	Neuroprotection Anticonvulsant effect?	Immunosuppression, acidosis, elevated INR
Ketogenic Diet	Unknown (? gap junctions)	Can be difficult to sustain in ICU setting
Resective Surgery	Disrupt epileptogenic zone	Requires evidence of focality Lesional: MRI Non-lesional: MEG

Prior to Wean... Optimize Conventional AED Therapy

Drug	Mechanism	Dosing	Comments
Valproate	Na, Ca channel blocker GABA _A modulator	30 mg/kg bolus, then 5 mg/kg/h infusion or 40-80mg/kg/day q8h	• IV formulation not available in Canada • Hepatotoxicity • Caution if suspected metabolic disorder • Carnitine depletion
Topiramate	Na, Ca channel blocker GABA _A modulator AMPA, kainate modulator	10 mg/mg initial Increase by 3mg/kg q1-3 days	• PO/NG only • Metabolic acidosis
Levetiracetam	Ca channel blocker GABA modulator Glutamate modulator Synaptic vesicle 2A binding	10-40 mg/kg/day	• IV formulation now available in Canada

Key Points in Management of SE

- Rapid intervention is key
 - time dependent pharmacoresistance
- Develop your own institutional management guideline
 - 1st line – benzodiazepines are all equivalent
 - 2nd line – Valproate, Phenytoin, Keppra are all equivalent
 - 3rd line and beyond: no clear evidence
- EEG monitoring is indicated if patients are
 - Treatment-refractory – to guide therapy
 - Not waking up – to assess for ongoing nonconvulsive seizures