Alabama Academy of Neurology Annual Conference
August 21, 2021
Grand Bohemian Hotel, Mountain Brook

ALABAMA ACADEMY OF NEUROLOGY

Status Update

What's new in the Management of Status Epilepticus?

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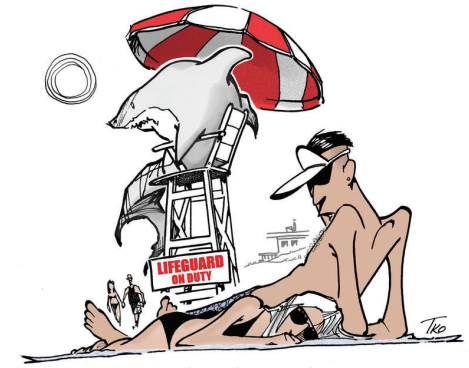
Disclosures

No conflict...

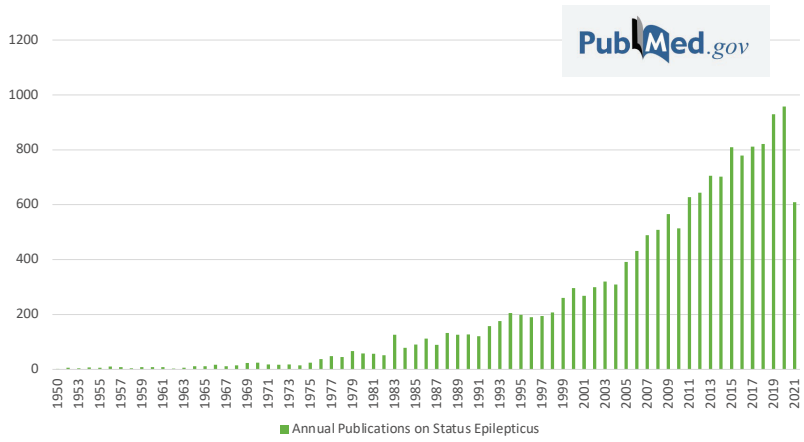
...only interest.

Site-PI for Eisai Inc. sponsored Phase 4 trial on safety and tolerability of Perampanel as monotherapy or first add-on therapy.

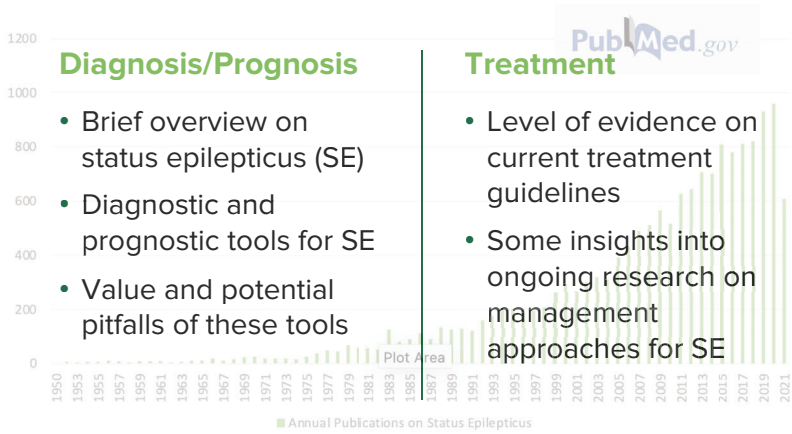


"So, I'm the only one who sees a conflict of interest here?"

Publications on SE since 1950



Learning Objectives



Diagnosis/Prognosis

- Brief overview on status epilepticus (SE)
- Diagnostic and prognostic tools for SE
- Value and potential pitfalls of these tools

Treatment

- Level of evidence on current treatment guidelines
- Some insights into ongoing research on management approaches for SE

Trinka, E. et al. 2015. *Epilepsia*, 56(10), 1515-1523.

SE Definition – ILAE International League Against Epilepsy Task Force

Long-term Consequences:
- Neuronal injury and death
- Alternation of neuronal networks (i.e. late-onset epilepsy)

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)	
		TREATMENT INITIATION		AGGRESSIVENESS OF TX
Tonic-clonic SE	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.

Kantanen, A.-M. et al. 2015. *Epilepsy & Behavior, 49*, 131-134. Ferlisi, M. & Shorvon, S. 2012. *Brain, 135*(Pt 8), 2314-2328.
Giovannini G. et al. *Epilepsy Behav* 2015;49:141–145. Strzelczyk A. et al. *Epilepsia* 2017;58:1533–1541. Santamarina E, et al. *Epilepsy Behav* 2015;49:138–140.

SE Treatment (Tx) Progression

< 30 min | 30 to 120 min | > 120 min | > 24 hours

Stage 1
Early SE
Stabilization
1st Line Tx: benzodiazepines
→ Transport to ER

Stage 2
Established SE
Evaluation for acutely reversible causes and 2nd Line Tx: IV anticonvulsants

Stage 3
Refractory SE
Intubation; Tx for subacute/chronic causes and 3rd Line Tx: IV anesthetics

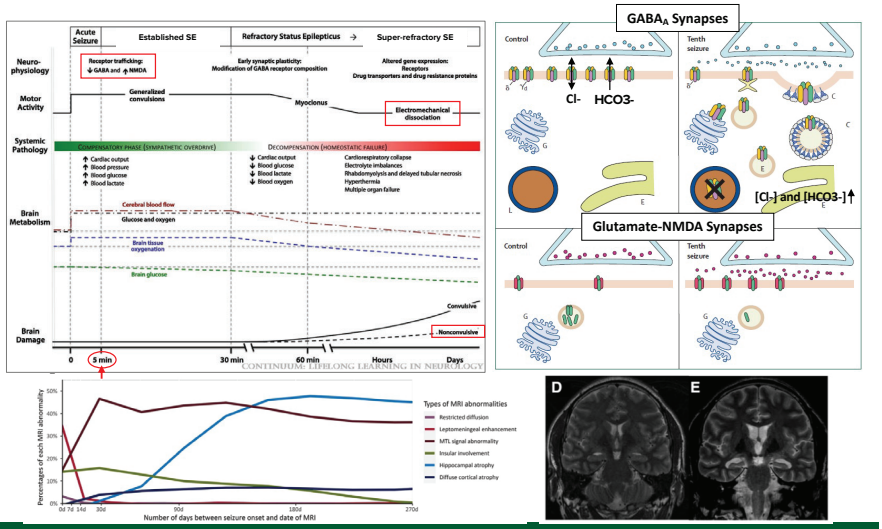
Stage 4:
Super-refractory SE
In-depth assessment of treatable causes; recurrent anesthesia trials; experimental Tx

LOS
Mortality and Morbidity
New Onset Epilepsy and Healthcare Cost

Risk factors: age > 60; acute or chronically progressive etiology and **nonconvulsive SE with coma**

Hirsch, LJ. Et al. *CONTINUUM.* 19(3, Epilepsy):767-794, June 2013. Chen, J. W. Y. 2006. *The Lancet Neurology, 5*(3), 246-256. Chen, J. W. Y. at al. 2007. *Acta Neurologica Scandinavica, 115*(s186), 7-15. Murdoch, D. 2007. *Current opinion in neurology, 20*(2), 213-216. Kim et al. 2020. *Epilepsia.* 2020;61:1735–1748 .

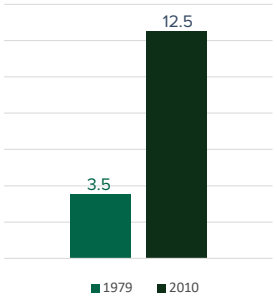
Pathophysiology of SE



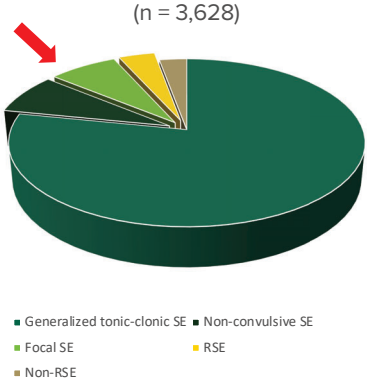
Sadeghi et al. *Seizure.* 81 (2020) 210–221. Lu et al. *Epilepsy & Behavior* .112 (2020) 107459.

Epidemiology of SE

Incidence of CSE per 100,000 people/year

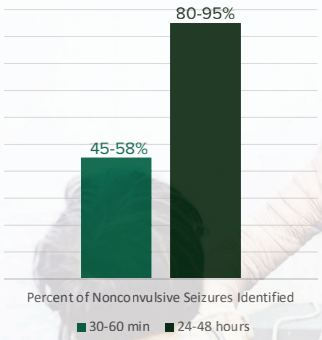


Combined SE-types of 85 studies (n = 3,628)



Young, B. G. et al. 1996. *Neurology, 47*(1), 83-89. Hirsch, L. J. et al. 2005. *Journal of clinical neurophysiology, 22*(2), 128-135. Towne AR et al. Neurology. 2000;54(2):340-345. Alvarez, V. et al 2015. *Epilepsia, 56*(6), 933-941.

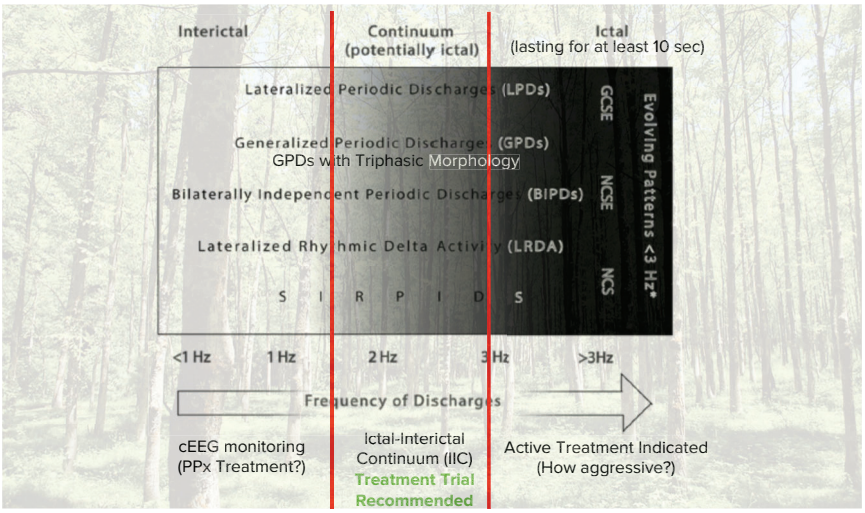
NCSE: You can only treat what you can see



- **8 to 48%** of critically ill adults and **6 to 47%** of critically ill children with altered mental status have **nonconvulsive seizures.**
- ACNS: **EEG-monitoring** as soon as nonconvulsive seizure-activity is suspected
- Patients without early (within first 2h) epileptiform discharges: **< 5% chance of seizures in the next 72h**

O'Rourke, D. et al. 2016. *Neurocritical care*, *24*(2), 233-239. Rodríguez, V. et al. 2016. *Clinical Neurophysiology*, *127*(4), 2056-2064.

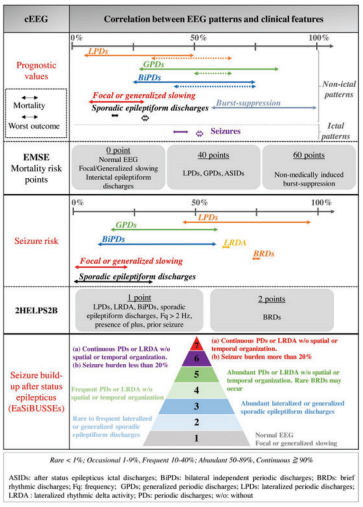
The Problem with continuous EEG Monitoring



Rossetti, A. O. et al. 2006. *Neurology*, *66*(11), 1736-1738. González-Cuevas, M. et al. 2016. *European journal of neurology*, *23*(10), 1534-1540. Leitinger, M. et al. 2015b. *Neurocritical care*, *22*(2), 273-282. Gao et al. 2016. *Critical Care* (2016) 20:46. Hanin, A. et al. *Neurophysiologie Clinique* 51.2 (2021): 101-110.

Evolution of SE Prediction Scores

- Status Epilepticus Severity Score (**STESS-3**): Level of consciousness upon presentation, SE type, previous h/o seizures, age (>65) – **mSTESS-3** including premorbid mRS
- Epidemiology-Based Mortality Score of SE (**EMSE-64**): SE etiology, age, comorbidities and worst EEG pattern
- Encephalitis-NCSE-Diazepam resistance-Image-abnormalities-Tracheal intubation (**END-IT-3**) Score: encephalitis, NCSE, diazepam resistance, image abnormalities (unilateral lesions, bilateral lesions or diffuse cerebral edema) and intubation
- **2HELPS2B** Score: prior seizure and EEG patterns (range 0 to 7 covering 5 to 95% risk for seizure



Rosetti et al. *JAMA Neurol*. 2020;77(10):1225-1232.

Continuous EEG[1)] vs. Routine EEG[2)]

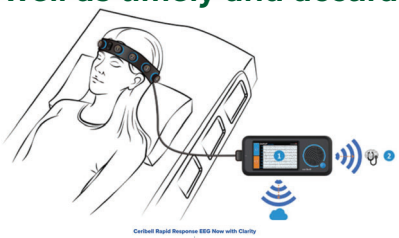
[1)] 30-to-48-hour recording; [2)] two 20-to-30 min recordings within 48 hours

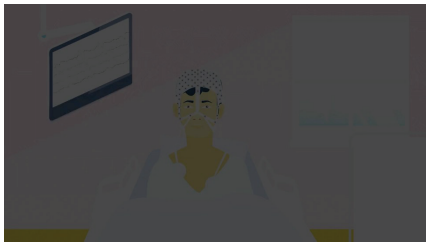
Table 3. Exploratory Analyses: Associations of Secondary Outcome Measures With EEG Type[a]

Outcome	No. (%) rEEG (n = 183)	No. (%) cEEG (n = 185)	Relative risk (95% CI)	*P* value
Features of ictal-interictal continuum detected, without seizures/SE	102 (55.7)	128 (69.2)	1.24 (1.06-1.46)	.009
Seizures/SE detected	8 (4.4)	29 (15.7)	3.59 (1.68-7.64)	.001
Changes in antiseizure drug prescription within 60 h following start of EEG intervention[b]	21 (11.5)	39 (21.1)	1.84 (1.12-3.00)	.01
Changes in sedation prescription within 60 h following start of EEG intervention[b]	8 (4.4)	13 (7.0)	1.61 (0.683-3.79)	.27
Need of additional EEG after intervention	41 (22.8)[c]	56 (31.1)	1.37 (0.97-1.93)	.08
In-hospital infection requiring antibiotics	56 (30.8)	47 (25.7)	0.82 (0.61-1.11)	.20
Length of ventilation need, median (range), h	123 (0-837)	138 (0-1214)	NA	.47
Length of hospital stay in survivors, median (range), d	25.3 (2.6-393.3)	24.5 (1.4-161.1)	NA	.84
Time to death since randomization, median (range), d	8.5 (0-157)	6 (0-176)	NA	.07

Vespa, PM. et al. *Critical care medicine*48.9 (2020): 1249. Hobbs, K et al. *Neurocritical care* 29.2 (2018): 302-312. Wright, NMK et al. *Emergency Medicine Journal* (2021). Kamousi, Baharan, et al. *Neurocritical Care* 34.3 (2021): 908-917.

How to Increase Access to EEG monitoring as well as timely and accurate interpretation?





Reviewer	Sessions reviewed	Sensitivity (%)	Specificity (%)
1	240	62.5	94.8
2	198	20.0	99.5
3	257	88.9	94.3
4	89	66.7	95.2
Clarity	353	100.0	93.0

- Wait-time to EEG: **5 min vs. 4 h**
- Diagnostic accuracy: **90% vs. 65%** (compared to using clinical judgement alone)
- Diagnostic confidence: **86% vs. 40%** (compared to using clinical judgement alone)

Godau J. et al. *Neurocrit Care.* 2021 Jul 30. doi: 10.1007/s12028-021-01273-6. Epub ahead of print.

The Eye as the Window to the Brain

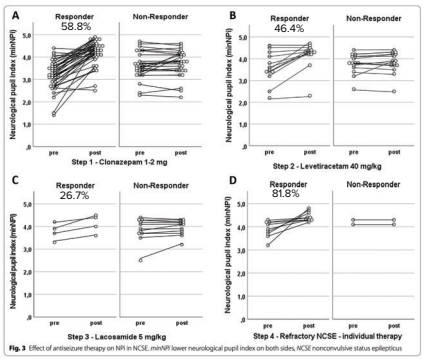
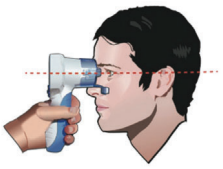
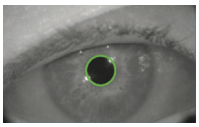


Fig. 3 Effect of antiseizure therapy on NPi in NCSE. minNPI lower neurological pupil index on both sides, NCSE nonconvulsive status epilepticus

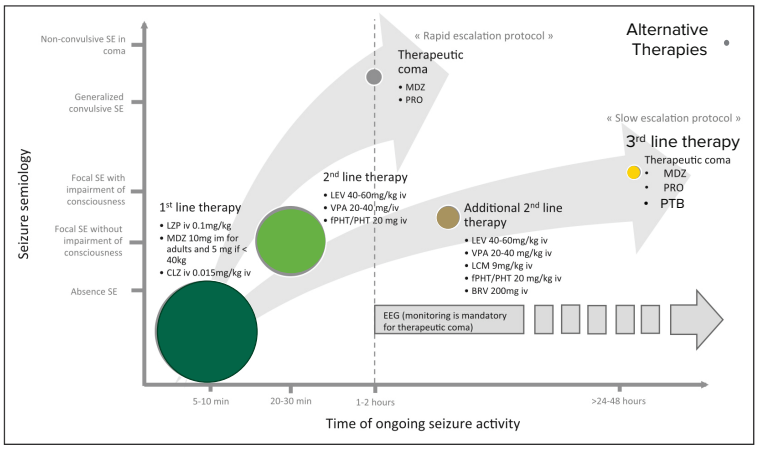




- 58 (87.9%) cases had abnormal baseline minNPi
- In 45 (77.6%) minNPi normalized after successful NCSE Tx
- Remaining 13 cases showed significant increase of baseline to final minNPi, although absolute minNPi remained within abnormal range

Rossetti, Andrea O., and Vincent Alvarez. *Current Opinion in Neurology* 34.2 (2021): 172-181.

Suggested SE Treatment Algorithm



First Line Treatment: Benzodiazepines

Agent	Dose (maximum)	Route	Onset (min)	Duration of Action	Bioavailability (%)	Volume of Distribution (L/kg)	Metabolism	Excretion	$T_{1/2}$ (h)
Lorazepam (Ativan® Injection)	0.1 mg/kg (4 mg)	IV	1-6	4-6 h	100	1.3	Liver to inactive metabolites	Hepatic metabolism to inactive metabolites	12
	-	IM	12–19		83–100				
Lorazepam (Ativan Intensol®)	0.1 mg/kg (4 mg)	SL	Readily	-	90				
Lorazepam (Ativan® Sublingual tablets) *	0.1 mg/kg (4 mg)	SL	15–17	-	>90				
Midazolam (Versed®)	0.2 mg/kg (10 mg)	IV	1.5–2.5	30–80 min	100	1–3	CYP3A4 to active metabolite	Renal	3–4
Midazolam (Versed®)	0.2 mg/kg (10 mg)	IM	5–15	2–6 h	>90				3–5
Midazolam (Nayzilam®)	0.2 mg/kg (15 mg)	IN	3–10	23 min	44				2–6
Midazolam	0.2 mg/kg (15 mg)	IV injection given IN	6–14	-	44–83				2–4
Midazolam (Buccolam®, Epistatus®) *	0.5 mg/kg (30 mg)	Buccal	5–15	-	75–87				3–4
Midazolam (Versed®)	0.5 mg/kg (30 mg)	IV injection given Buccal	~15	-	75				-
Diazepam (Valium®)	0.15 mg/kg (10 mg)	IV	1–3	15–30 min	100	0.8–1.2	CYP2C19 and CYP3A4 to active metabolites	Renal	33–45
Diazepam (Valium®)	-	IM	~15	-	>90				60–72
Diazepam (Valtoco®)	0.2 mg/kg (20 mg)	IN	2–10	15–30 min	97				~49
Diazepam	0.2 mg/kg (20 mg)	IV injection given IN	1–10	-	Up to 74				17–33
Diazepam (Diastat®)	0.2 mg/kg (20 mg)	PR	2–10	15–30 min	90				~46

CNS Characteristics	Lorazepam	Diazepam	Midazolam
Lipophilicity	Low	High	High
CNS half-life	Long	Short	Short
CNS penetration	Slow	Fast	Fast
CNS concentration	5–15% of serum	3–12% of serum	3–14% of serum
Onset of EEG slow-wave, minutes	3.8 ± 3.1	0.89 ± 3.1	0.29 ± 0.04
Duration of EEG slow-wave, minutes	28.3 ± 10.1	7.5 ± 1.4	6.3 ± 1.9

CNS, central nervous system; EEG, electroencephalogram.

- **Level A** evidence for SE Treatment
- Associated with lower mortality and morbidity, lower use of ASM upon arrival at hospital, shorter seizure-duration
- **Most effective within first 30 min** (the sooner the better)
- Respiratory complication: 1-18%
- Somnolence: 1.5-68%
- Desired pharmacokinetic profile:
  - Easy and fast to administer
  - Fast onset (high and reliable bioavailability, good CNS penetration)
  - Limited duration of side-effects
  - Low chance for breakthrough Sz's

Almohaish et al. 2021. *J. Clin. Med.* **2021**, *10*, 1754.

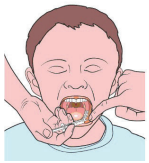
Benzodiazepines: Route of Administration

Table 4. Administration route advantages and disadvantages [55–64].

Route	Advantages	Disadvantages
Intravenous	• Fastest onset of action • No bioavailability concerns • Bypass first-pass metabolism • Large volume can be administered • Reliable route for sedated or comatose patients	• Highly trained individuals required to administer • May require physical restraint • Injection site irritation, extravasation, or infection • Development of tolerance with continuous infusions
Intramuscular	• Bypass first-pass metabolism • Prolonged action	• Trained individuals required to administer • May require physical restraint • Painful • Variable absorption • Injection site irritation or infection • Limited volume can be administered (2–5 mL)
Intranasal	• Easily administered • Rapid absorption • Bypass first-pass metabolism • Direct drug delivery to blood-brain-barrier	• Small volume (≤0.2 mL) hard to measure • Short retention time • Nasal discharge may alter the absorption • Nasal irritation
Buccal and Sublingual	• Rapid absorption • Bypass first-pass metabolism • Low risk of infection	• Variable absorption • Unpalatable • Challenging to place and maintain in the correct location • Risk of aspiration
Rectal	• Bypass first-pass metabolism • Ease of administration in infant emergencies • Low risk of infection	• Rectal irritation or proctitis with ulceration • Less convenient for adults

VALTOCO® (diazepam nasal spray) C-IV

Nayzilam® C-IV (midazolam) nasal spray



Staccato® Alprazolam, a drug-device-combination designed to deliver alprazolam with a single, normal breath, to rapidly terminate an epileptic seizure

- Potential to be the first **on-demand, single use treatment**
- **Rapid seizure termination** (30 sec – 2 min)
- Phase 2b clinical trial completed (end 2019); phase 3 to start H2 2021
- Potential to deliver on-demand, rapid seizure termination for 20 – 30% of people living with epilepsy

Diastat® AcuDial™ (diazepam rectal gel)

Guterman, EL. et al. *Neurology* 95.24 (2020): e3203-e3212. Gainza-Lein, M. et al. *Seizure* 68 (2019): 22-30. Kämppi, L. et al. *Seizure* 55 (2018): 9-16.

Treatment Hesitation at a High Price?

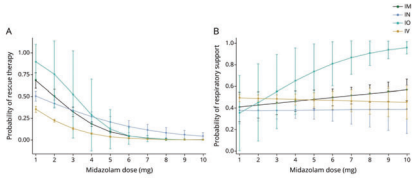
Treatment Delay

- Decreased response to benzodiazepines
- Need for recurrent doses of rescue therapy
- Prolonged seizures
- Greater need of continuous infusions
- Potential brain injury
- Increased in-hospital mortality

Underdosing

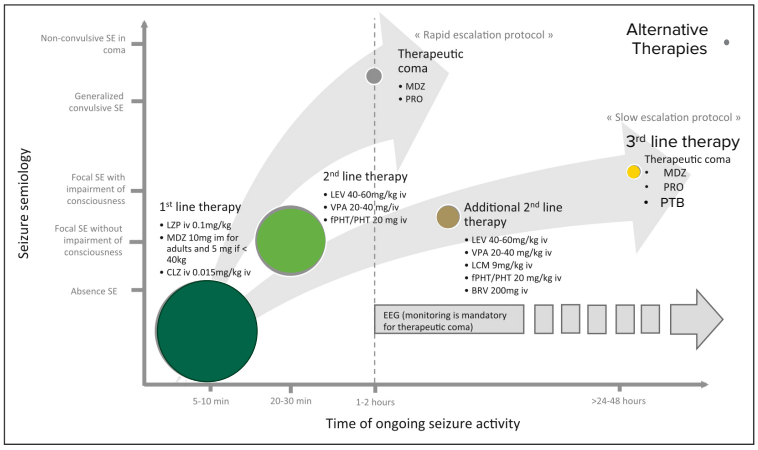
- Increased need for respiratory support (i.e. intubation)
- Increased admissions to ICU

Time to first treatment		Prehospital time to first treatment	Time to EMS arrival		Time to hospital arrival	
Median	Range	Median (range)	Mean	Range	Mean	Range
17 (218 pts)	5–45[a]	25 (10–60)[a] (139 pts)	16 (63 pts)	10–25[a]	45[a] (106 pts)	30–80[a]
30 (67 pts) 60 (151 pts)	0–485 0–10080	– –	– –	– –	145[a] (70 pts) –	37–16660[a] –
28 (81 pts)	6–67	30 (12–60)[a] (64 pts)	49.4 (26 pts)	2–875	81.8 (50 pts)	11–920
45 (99 CSE pts)	5–2880 (99 CSE pts)	–	–	–	–	–
30 (161 pts)	1–175	22.3 (12.5 min + 9.8 min) (161 pts)	20 (161 pts)	0–95	38 (161 pts)	0–239
35 (81 pts)	0–4625	–	9 (68 pts)	0–45	69 (68 pts)	10–182
70[a] (109 pts)	–	70[a] (109 pts)	30[a] (109 pts)	–	105[a] (109 pts)	–
90 (101 CSE pts)	50–187	–	–	–	–	–
– – –	– – –	– – –	– – –	– – –	42[a] (542 pts) 39[a] (182 pts) 48 (37 pts)	3–3960 5–514 –
34 (mean) (66 pts) –	17.8 (SD) –	– –	– –	– –	50.2 (66 pts) –	– –
– 42.4 (1134 all pts), 40.2 (902 CSE pts)	– 0–10080 (all pts), 0–485 (CSE pts)	– 35.1 (473 CSE pts)	– 22.0 (427 pts)	– 0–875	– 56.0 (1391 pts)	– 0–16660



Rossetti, Andrea O., and Vincent Alvarez. *Current Opinion in Neurology* 34.2 (2021): 172-181.

Suggested SE Treatment Algorithm

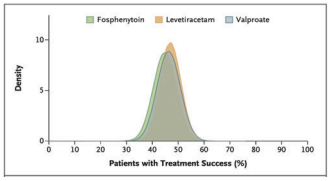


Kapur et al. 2019. *NEJM 381*(22), 2103-2113.

Second Line Treatment: Nonsedating Anitseizure Medications (established evidence)

Established Status Epilepticus Treatment Trail (ESETT)

- 384 patients with **established CSE** enrolled and randomly assigned to:
  - Levetiracetam (145 patients)
  - Fosphenytoin (118 patients)
  - Valproate (121 patients)
- Primary Outcome: Cessation of **clinical seizure-activity** and improving mental status within 60 min after administration
- Secondary Outcomes:
  - Time to termination of clinical seizures
  - Rates of intubation
  - Admission to ICU
  - Mortality



Outcome	Levetiracetam (N = 150)	Fosphenytoin (N = 125)	Valproate (N = 125)
	number of patients (percent)		
Life-threatening hypotension within 60 min after start of trial-drug infusion	1 (0.7)	4 (3.2)	2 (1.6)
Life-threatening cardiac arrhythmia within 60 min after start of trial-drug infusion	1 (0.7)	0	0
Endotracheal intubation within 60 min after start of trial-drug infusion	30 (20.0)	33 (26.4)	21 (16.8)
Acute seizure recurrence 60 min to 12 hr after start of trial-drug infusion	16 (10.7)	14 (11.2)	14 (11.2)
Acute anaphylaxis	0	0	0
Acute respiratory depression	12 (8.0)	16 (12.8)	10 (8.0)
Hepatic aminotransferase or ammonia elevations	1 (0.7)	0	1 (0.8)
Purple glove syndrome	0	0	0
Death	7 (4.7)	3 (2.4)	2 (1.6)
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 (7.3–20.9)	7.0 (4.6–14.9)

Chamberlain, JM. et al. *The Lancet* 395.10231 (2020): 1217-1224. Dalziel SR. et al. *Lancet.* 2019;393(10186):2135-2145. Lyttle MD. et al. *Lancet.* 2019;393(10186):2125-2134.

Second Line Treatment: Nonsedating Anitseizure Medications (established evidence)

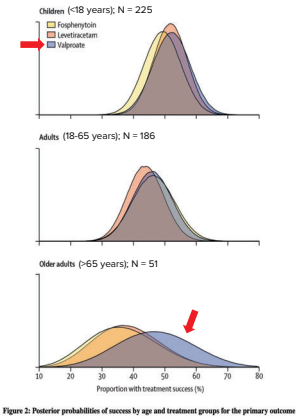


Figure 2: Posterior probabilities of success by age and treatment groups for the primary outcome

ESETT Subgroup Analysis

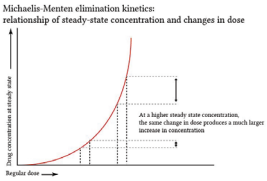
- Extending enrolment for children
- Primary outcome: same as ESETT
- Safety outcome(s): life-threatening hypotension, cardiac arrhythmia, intubation.
- Enrolled 478 patients and 462 included in analysis:
  - Levetiracetam (175 patients)
  - Fosphenytoin (142 patients)
  - Valproate (145 patients)

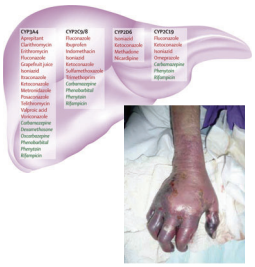
ConSEPT and EcLiPSE Trial

- Open-label trials comparing efficacy of Phenytoin (PHT) vs Levetiracetam (LEV) as 2nd line in children with SE
- ConSEPT – PHT: 60% vs LEV: 50%
- EcLiPSE – no significant difference

The Slow and Agonizing Death of Phenytoin

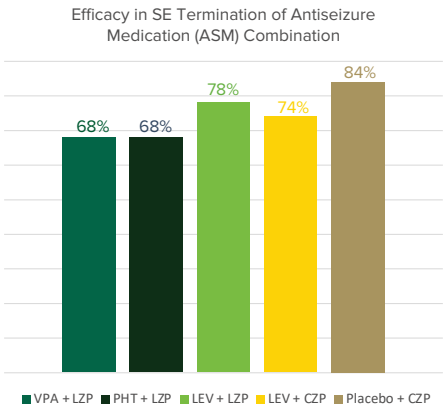
- Narrow mechanism of action
- Complex pharmacokinetics and pharmacogenomics
- Drug-drug interactions
- Unique adverse effects
- Formulation issues that make administration difficult

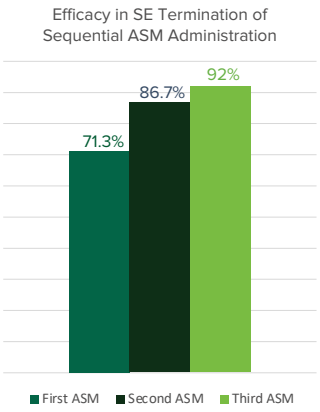




Mundlamuri RC. et al. *Epilepsy Res.* 2015;114(1):52-58. Navarro, V. et al. *The Lancet Neurology* 15.1 (2016): 47-55.

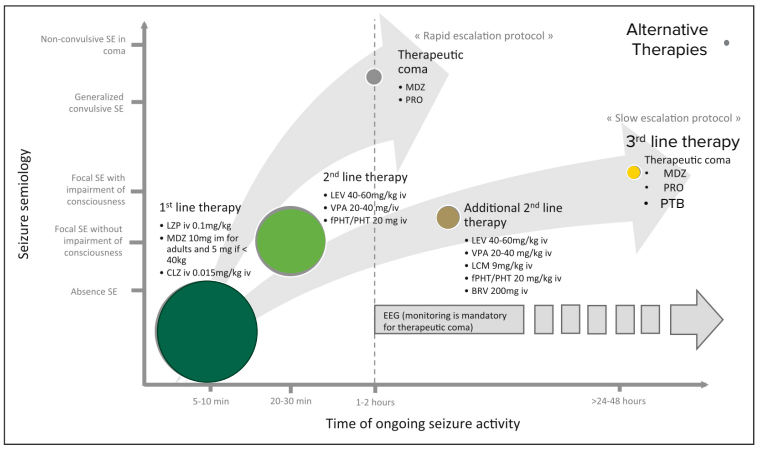
Efficacy of Combined and Sequential Treatments





Rossetti, Andrea O., and Vincent Alvarez. *Current Opinion in Neurology* 34.2 (2021): 172-181.

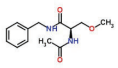
Suggested SE Treatment Algorithm



Brigo, F. et al. *CNS drugs* 33.8 (2019): 771-781. Husain, AM. et al. *Annals of neurology*. 83.6 (2018): 1174-1185.

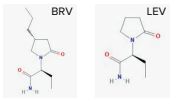
Second Line Treatment: Nonsedating Antiseizure Medications (weak evidence)

Lacosamide (Vimpat; LCM)



- Treatment of Recurrent Electrographic Nonconvulsive Seizures (TRENdS):
  - Total of 74 randomized patients
  - LCM 400 mg vs. fPHT 20 mg/kg
  - Primary outcome: Sz-absence for 24 hours
- Sz-control:
  - LCM: 63.3%
  - fPHT: 50%
- Treatment emergent adverse events ~25% in both arms (LCM: dose-dependent AV-block)
- LCM non-inferior to fPHT in treatment of recurrent nonconvulsive seizures

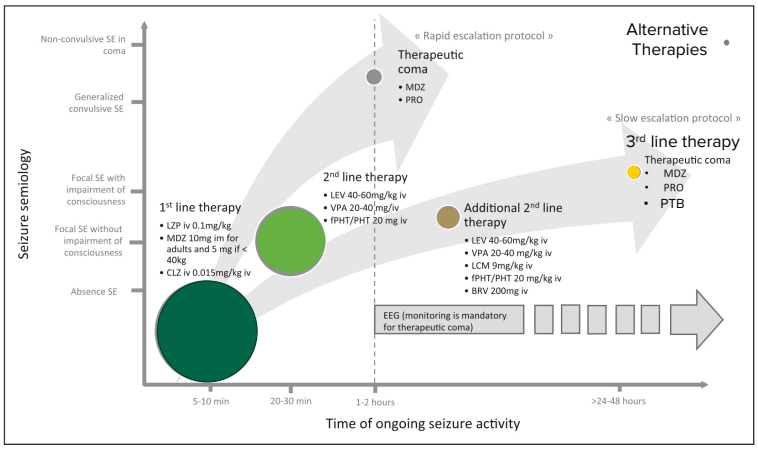
Brivaracetam (Briviact; BRV)



- No controlled trials available
- Review of 7 studies with 37 patients including case reports
- Efficacy: 27 to 50%
- Time to effect: 15 min to 94 hours
- No serious adverse events
- Yet, highly variable dosing, medication order and treatment delay
- Concern: decreased efficacy with coadministration of LEV

Rossetti, Andrea O., and Vincent Alvarez. *Current Opinion in Neurology* 34.2 (2021): 172-181.

Suggested SE Treatment Algorithm



Glauser, T. et al. 2016. *Epilepsy currents*, *16*(1), 48-61. Brophy, G. M. et al. 2012. *Neurocrit Care*, *17*(1), 3-23. Meierkord, H. et al. 2010. *Eur J Neurol*, *17*(3), 348-355. Vossler, DG. et al. *Epilepsy currents*. 20.5 (2020): 245-264.

Third Line Treatment: Therapeutic Coma

Neurocritical Care Society

"The intensity of treatment is usually dictated by cEEG findings, with the goal of treatment being cessation of electrographic seizures or burst suppression. [...] **The optimal duration of maintaining electrographic seizure control in patients with RSE is not known since there are few data to indicate what duration of treatment is needed to maintain control**. Customarily, electrographic seizure control is maintained **for 24–48 h**, followed by gradual withdrawal of the continuous infusion AED." (2012)

European Federation of Neurologic Societies

"Depending on the anaesthetic used in the individual in-house protocol, we recommend titration against an **EEG burst suppression pattern with propofol and barbiturates**. If **midazolam** is given, **seizure suppression is recommended**. This goal should be maintained **for at least 24 h**." (2010)

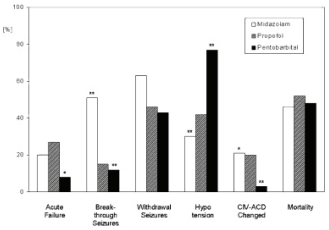
American Epilepsy Society

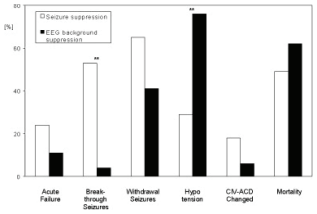
"There is **no clear evidence** to guide therapy in the 3rd phase (40 to 60 min into SE)." (2016) – "[...] mostly insufficient evidence exists on the efficacy of stopping clinical **CRSE** using BRV, LCM, LEV, valproate, KET, MDZ, PTB, and PRO either as the last ASM or compared to others of these drugs. **Triple-masked, randomized controlled trials are needed to compare the effectiveness of parenteral anesthetizing and nonanesthetizing ASMs in the treatment of CRSE**." (2020)

Claassen, J. et al. 2002. *Epilepsia*, *43*(2), 146-153. Rossetti, A. O. et al. 2011. *Neurocrit Care*, *14*(1), 4-10.
Vossler, DG. et al. *Epilepsy currents.* 20.5 (2020): 245-264. Shorvon, S., & Ferlisi, M. 2011. *Brain*, *134*(Pt 10), 2802-2818.

Studies on Therapeutic Coma for RSE

- Usual 1st Line: Propofol (PRO) or Midazolam (MDZ) drip (advantage: "quick and out")
- Pentobarbital (PBT) tends to be utilized for SRSE
- Continuous EEG is essential for assessment of treatment response
- Adverse Effects:
  - Hypotension common problem (need for vasopressors)
  - PRO infusion syndrome (PRIS): acute refractory bradycardia/asystole, fatty liver, rhabdomyolysis, hyperlipidemia
  - PBT – Propylene glycol toxicity: ARF, refractory hypotension, lactic acidosis, arrhythmias
- Mainly class 2a/2b: regardless of anesthetic used, **suppression of the EEG-background** (i. e. burst- or complete suppression) and **early treatment initiation** provides best chances for immediate and sustained seizure control





Alvarez, V et al. 2016. *Neurology*, *87*(16), 1650-1659. Jordan, K. G., & Hirsch, L. J. 2006. *Epilepsia*, *47 Suppl 1*, 41-45. Kaplan, P. W. (2000). *Neurophysiol Clin*, *30*(6), 377-382.
Kowalski, R. G. et al. 2012. *Crit Care Med*, *40*(9), 2677-2684. Rossetti, A. O., et al.2005. *Arch Neurol*, *62*(11), 1698-1702. Sutter, R. et al. 2014. *Neurology*, *82*(8), 656-664.
Caronna et al. 2020. *Acta Neurol Scand.* 2020;142:555–562.

Therapeutic Coma and Poor Outcome?

Retrospective Studies

- Prolonged hospitalizations/ICU-stays which bears significant risk of in-hospital mortality and morbidity
- 4-fold increased risk for infections
- 5.6-fold increased risk for new disabilities upon discharge
- 3 to 12-fold increased risk of death
- Importance to maximize treatment benefits and minimize treatment-exposure related risks

Prospective Study

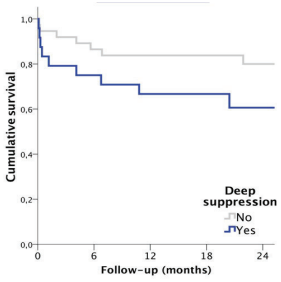
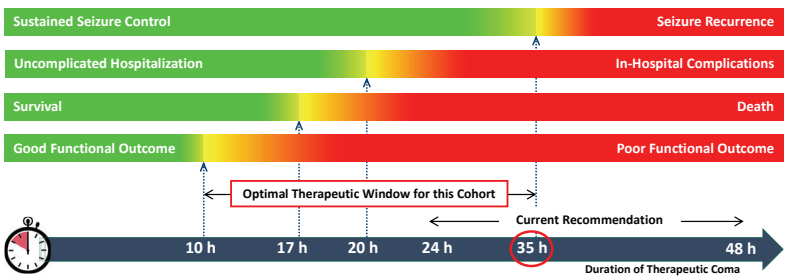


FIGURE 1 Kaplan-Meier curve of deep sedation during 2-year follow-up ($P < .05$)

Muhlhofer et al. *Epilepsia* 2019;60:921-934.

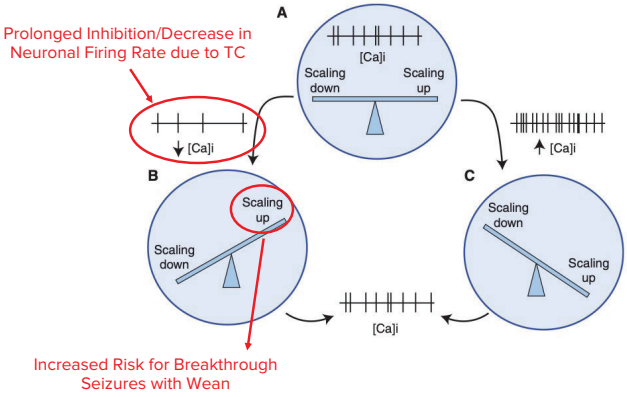
Duration of Therapeutic Coma (TC) and Outcome in RSE

- Duration of TC independently associated with:
  - Prolonged duration of ventilation
  - Total length of stay
  - Increased risk for seizure recurrence
- Duration of TC not independently associated with:
  - Poor functional neurologic outcome upon discharge
  - In-hospital complications
  - Mortality
- Ictal and highly epileptogenic patterns on EEG (i. e. LPDs and seizures) during titration period of TC independently associated with seizure recurrence
- **Higher doses of anesthetic** (= deeper TC) independently associated with **fewer in-hospital complications, shorter duration of mechanical ventilation and total length of stay**



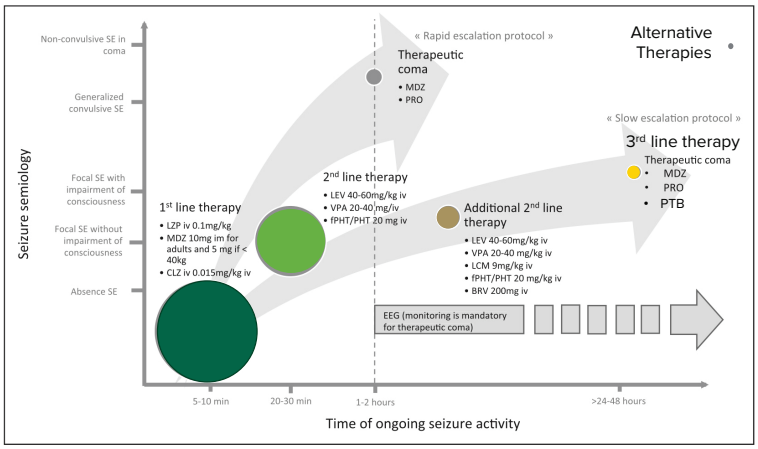
Turrigiano, G. *Cold Spring Harbor perspectives in biology* 4.1 (2012): a005736.

Homeostatic Plasticity Hypothesis



Rossetti, Andrea O., and Vincent Alvarez. *Current Opinion in Neurology* 34.2 (2021): 172-181.

Suggested SE Treatment Algorithm



Ochoa, JG. et al. *Epilepsy Currents* (2021): 1535759721999670.

Studies on Treatment of SRSE

Table 1. Evidence of Therapeutic Interventions for SRSE.

Therapeutic intervention	Level of evidence	Comment
Therapeutic hypothermia	Level C: 1 Class II study 3 Class IV studies 13 Case reports	Risk of serious complications including venous thrombosis, pulmonary embolism, infection, and paralytic ileus
Vagus nerve stimulation	Level U: 27 Class IV studies	Potential bias in the systematic review publication
Ketogenic diet	Level U: Children 5 Class IV studies Level U: Adults: 3 Class IV studies	Retrospective and small sample size studies
Lidocaine	Level U: 5 Class IV studies	Most studies are focused on neonatal seizures
Inhalational anesthetics	Level U: 16 Class IV studies	Risk of potential neurotoxicity
Brain surgery	Level U: 7 Class IV studies	Focal resection of a well-localized ictal zone in noneloquent cortex is recommended
Perampanel	Level U: 4 Class IV	Possible role in the treatment of postanoxic SRSE
Pregabalin	Level U: 3 Class IV studies	Risk of induction of myoclonic status epilepticus
Topiramate	Level U: 1 Class IV 6 Case reports	Enteral administration is well tolerated

Abbreviation: SRSE, super-refractory status epilepticus.

- "[...] insufficient evidence exists that any of the ASMs reviewed, inhalational anesthetics, ketogenic diet, acute VNS, brain surgery, and therapeutic hypothermia are effective treatments."
- "[...] Data supporting the use of these treatments for SRSE are scarce and limited mainly to small case series and case reports and are confounded by differences in patient populations, and comedications, among other factors."

Rosati A, et al. *BMJ open.* 2016;6(6): e011565. Alkhachroum et al. *Neurology* 2020.95:e2286-e2294.

Ketamine – Just too Late to the Party?

Table 1. Summary of Case Series of Ketamine in Refractory or Superrefractory SE.[a]

	N episodes	Age (years)	Top 3 etiologies	Latency (days)	Maximal dose (mg/kg/h)	Response rate	AEs	Mortality
This study	68, all SRSE	53 ± 19	Anoxic NORSE Cerebrovascular	2 [1-5]	2.2 [0.2-10]	65%	Not reported No effect on ICP	46%
Dericioglu et al[13]	7, including 6 with SRSE	66 [44-86]	NORSE Anoxic Stroke	3 [2-7]	2 [1-5]	56%	Transient liver failure	29%
Santoro et al[14]	3, all SRSE	19 [3.5-54]	NMDAR encephalitis	9 [4-32]	3 [3-3]	100%	None	33%
Höfler et al[15]	42, including 39 with SRSE	67 [59-72]	Anoxic Cerebrovascular NORSE	3 [2-7]	2.55 [?]	64%	None	45%
Basha et al[16]	11, all SRSE	56 [33-68]	Epilepsy NORSE Stroke	2 [0-11]	4 [1-5]	36%	Increased ICP	27%
Sabharwal et al[17]	67, all SRSE	62 [8-85]	Anoxic Toxic-metabolic Stroke	?	? [1.5-10.5]	91%	Not reported	39%
Synowiec et al[18]	11, all SRSE	52 [22-82]	Epilepsy Infections	5 [1-11]	1 [0.45-2.1]	64%	No reported	18%
Gaspard et al[12]	60, including 56 with SRSE	24 [0.6-74]	NORSE Anoxic Infections	9 [0-122]	2.75 [0.05-10]	32%	Tachycardia Atrial fibrillation No effect on ICP	45%
Rosati et al[19]	11, including 9 with SRSE	5 [1.3-10]	Epilepsy NORSE	6 [2-26]	2.4 [0.6-3.6]	66%	None	0%

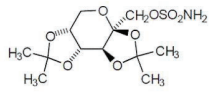
Abbreviations: AEs, adverse events; ICP, intracranial pressure; NORSE, new-onset refractory status epilepticus; SRSE, superrefractory status epilepticus.
[a]Data are presented as median (range), count or percentage.

- Works best in combination with GABA-ergic agents and when administered early
- Modulates some cytokines and might reduce neuroinflammation
- Quick on and off-set; less hypotension (promotion of sympathetic and respiratory stimulation)
- Ongoing multicenter, randomized, controlled, open-label trial comparing efficacy of KET in treatment of RSE in children compared to "standard of care" (i.e. MDZ and PRO) – enrolling since 2016

Fechner A. et al. *Epilepsia.* 2019; 60(12):2448-2458. Ho et al. *Neurocrit Care* (2019) 31:24–29. Lim, SN. et al. *Journal of Neurology.* (2021): 1-14.

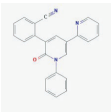
Alternative Antiseizure Medications

Topiramate (Topamax, TPM)



- Retrospective Review of TPM adjunct in 106 patients with RSE (66) and SRSE (40)
- Median initial dose: 100 mg/day
  Median maintenance: 400 mg/day
- Median treatment duration: 12 days
- Efficacy:
  - RSE: 32%
  - SRSE: 20%
- Hyperammonemia (up to 36%, particularly in combo with VPA)

Perampanel (Fycompa, PER)



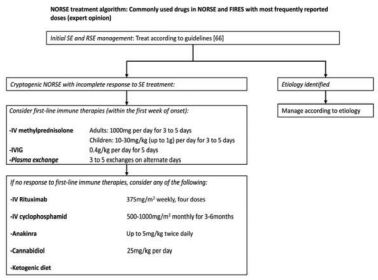
- Few retrospective studies (n = 23 to 81) analyzing efficacy and safety of PER as add-on for RSE and SRSE
- Median initial dose: 4 mg/day
  Median maintenance: 12 mg/day
- Efficacy: 17 to 36%
- High loading (up to 24 mg) and low maintenance dose (between 8 and 12 mg) with better response
- Potentially more effective in CSE, focal motor SE and post-anoxic SRSE

Sculier and Gaspard. *Seizure: European Journal of Epilepsy.* 68 (2019) 72–78. Khawaja, A. M. et al. 2015. *Epilepsy Behav, 47,* 17-23.

NORSE and Immunotherapy

New-onset RSE

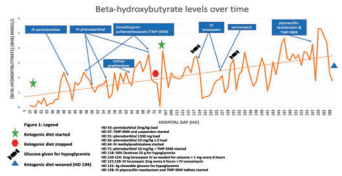
- RSE w/o active epilepsy or any clear acute or active structural, toxic or metabolic cause
- Febrile infection-related epilepsy syndrome (FIRES): febrile illness between 2 weeks and 24 h prior to NORSE
- Mainly affecting school-age children and young adults
- 66% with prodrome of flu-like symptoms preceding NOSRE by 1-14 days
- Starts w/ infrequent and brief repeated focal seizures with secondary bilateralization → SRSE
- Short-term mortality: 12-27%
  Often long-term disability and epilepsy



- 50% potentially caused by autoimmune encephalitis; treatment delay leading to worse outcomes
- Pooled analysis of 91 patients: 42% versus 20% with favorable outcome following immunotherapy
- Immunotherapy less effective in children – potentially higher impact of ketogenic diet

Other Alternative Treatments

Outcome	Hypothermia (N = 138)	Control (N = 130)	Odds Ratio (95% CI)†	P Value
Primary outcome: GOS score of 5 at day 90 — no. (%)‡	67 (49)	56 (43)	1.22 (0.75–1.99)	0.43
Secondary outcomes				
Total seizure duration — min				
Median	75	90	—	0.26
Interquartile range	37–180	45–255		
Progression to EEG-confirmed status epilepticus — no. (%)§	15 (11)	29 (22)	0.40 (0.20–0.79)	0.009
Refractory status epilepticus from day 1 to day 3 — no. (%)				
Refractory status epilepticus on day 3¶	43 (31)	50 (38)	0.68 (0.40–1.15)	0.15
Super-refractory status epilepticus‖	23 (17)	30 (23)	0.64 (0.34–1.19)	0.16



Hypothermia (HT)

Multicenter trial randomly assigning 270 critically ill patients with CSE requiring intubation to either standard of care (SOC) + HT or SOC alone:

- No difference in functional outcome at 90 days
- Rate of progression to EEG-confirmed SE, RSE or SRSE lower in HT group, yet not significant and higher complication rate in HT group
- Common complications: DVT, coagulopathies and infections

Ketogenic diet (KD)

- Only one prospective multicenter study investigating the feasibility, safety, and efficacy of a KD for SRSE in adults 14 patients w/ KD treatment: 11 (78%) had resolution of SRSE, with a median of 5 days
- Only retrospective analysis of KD efficacy in SRSE in children (n = 10 to 16) – Sz-cessation and regain of consciousness: 56 to 70% within 2 to 4 days of reaching ketonuria

Electroconvulsive therapy (ECT): 8 case series (2-11 patients): SRSE cessation in 80%; complete recovery in 27%

Neuromodulation (VNS, TMS, DBS): only by retrospective small case series and case reports; SRSE aborted in >80% - no randomized, prospective, and controlled trials

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Status Update – What's new in the Management of Status Epilepticus?

Any Questions?

References

- Trinka, E., Cock, H., Hesdorffer, D., Rossetti, A. O., Scheffer, I. E., Shinnar, S. et al. (2015). A definition and classification of status epilepticus–Report of the ILAE Task Force on Classification of Status Epilepticus. *Epilepsia*, *56*(10), 1515-1523.
- Kantanen, A.-M., Reinikainen, M., Parviainen, I., Ruokonen, E., Ala-Peijari, M., Bäcklund, T. et al. (2015). Incidence and mortality of super-refractory status epilepticus in adults. *Epilepsy & Behavior*, *49*, 131-134.
- Ferlisi, M., & Shorvon, S. (2012). The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy. *Brain*, *135*(Pt 8), 2314-2328.
- Giovannini G, Monti G, Polisi MM, et al. A one-year prospective study of refractory status epilepticus in Modena, Italy. Epilepsy Behav 2015;49:141–145.
- Strzelczyk A, Ansorge S, Hapfelmeier J, Bonthapally V, Erder MH, Rosenow F. Costs, length of stay, and mortality of super-refractory status epilepticus: a population-based study from Germany. Epilepsia 2017;58:1533–1541.
- Santamarina E, Gonzalez M, Toledo M, et al. Prognosis of status epilepticus (SE): relationship between SE duration and subsequent development of epilepsy. Epilepsy Behav 2015;49:138–140.
- Lu, Mei, et al. "Epidemiology of status epilepticus in the United States: A systematic review." *Epilepsy & Behavior* 112 (2020): 107459.
- Sadeghi, Mahsa, et al. "Outcomes of status epilepticus and their predictors in the elderly–a systematic review." *Seizure*(2020).
- Hirsch, Lawrence J.; Gaspard, Nicolas CONTINUUM: Lifelong Learning in Neurology. 19(3, Epilepsy):767-794, June 2013.
- Chen, J. W. Y., & Wasterlain, C. G. (2006). Status epilepticus: pathophysiology and management in adults. *The Lancet Neurology*, *5*(3), 246-256.
- Chen, J. W. Y., Naylor, D. E., & Wasterlain, C. G. (2007). Advances in the pathophysiology of status epilepticus. *Acta Neurologica Scandinavica*, *115*(s186), 7-15.
- Murdoch, D. (2007). Mechanisms of status epilepticus: an evidence-based review. *Current opinion in neurology*, *20*(2), 213-216.
- Kim, Hyo Jae, et al. "The timelines of MRI findings related to outcomes in adult patients with new-onset refractory status epilepticus." *Epilepsia* 61.8 (2020): 1735-1748.
- Young, B. G., Jordan, K. G., & Doig, G. S. (1996). An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring an investigation of variables associated with mortality. *Neurology*, *47*(1), 83-89.
- Alvarez, V., Drislane, F. W., Westover, M. B., Dworetzky, B. A., & Lee, J. W. (2015). Characteristics and role in outcome prediction of continuous EEG after status epilepticus: A prospective observational cohort. *Epilepsia*, *56*(6), 933-941.
- Zeiler FA, Matuszczak M, Teitelbaum J, Gillman LM, Kazina CJ. Electroconvulsive therapy for refractory status epilepticus: a systematic review. *Seizure* 2016; 35: 23-32.
- Godau J, Bharad K, Rösche J, Nagy G, Kästner S, Weber K, Bösel J. Automated Pupillometry for Assessment of Treatment Success in Nonconvulsive Status Epilepticus. Neurocrit Care. 2021 Jul 30. doi: 10.1007/s12028-021-01273-6. Epub ahead of print. PMID: 34331202.

References cont.

- Hirsch, L. J., Brenner, R. P., Drislane, F. W., So, E., Kaplan, P. W., Jordan, K. G. et al. (2005). The ACNS subcommittee on research terminology for continuous EEG monitoring: proposed standardized terminology for rhythmic and periodic EEG patterns encountered in critically ill patients. *Journal of clinical neurophysiology*, *22*(2), 128-135.
- Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of non- convulsive status epilepticus in comatose patients. Neurology. 2000;54(2):340-345.
- O'Rourke, D., Chen, P. M., Gaspard, N., Foreman, B., McClain, L., Karakis, I. et al. (2016). Response rates to anticonvulsant trials in patients with triphasic-wave EEG patterns of uncertain significance. *Neurocritical care*, *24*(2), 233-239.
- Rodríguez, V., Rodden, M. F., & LaRoche, S. M. (2016). Ictal–interictal continuum: A proposed treatment algorithm. *Clinical Neurophysiology*, *127*(4), 2056-2064.
- Rossetti, A. O., Logroscino, G., & Bromfield, E. B. (2006). A clinical score for prognosis of status epilepticus in adults. *Neurology*, *66*(11), 1736-1738.
- González-Cuevas, M., Santamarina, E., Toledo, M., Quintana, M., Sala, J., Sueiras, M. et al. (2016). A new clinical score for the prognosis of status epilepticus in adults. *European journal of neurology*, *23*(10), 1534-1540.
- Hanin, Aurélie, et al. "Continuous EEG monitoring in the follow-up of convulsive status epilepticus patients: A proposal and preliminary validation of an EEG-based seizure build-up score (EaSiBUSSEs)." *Neurophysiologie Clinique* 51.2 (2021): 101-110.
- Vespa, Paul M., et al. "Evaluating the clinical impact of rapid response electroencephalography: the DECIDE multicenter prospective observational clinical study." *Critical care medicine*48.9 (2020): 1249.
- Hobbs, Kyle, et al. "Rapid bedside evaluation of seizures in the ICU by listening to the sound of brainwaves: a prospective observational clinical trial of Ceribell's brain stethoscope function." *Neurocritical care* 29.2 (2018): 302-312.
- Wright, Norah MK, et al. "Evaluating the utility of Rapid Response EEG in emergency care." *Emergency Medicine Journal* (2021).
- Rossetti, Andrea O., and Vincent Alvarez. "Update on the management of status epilepticus." *Current Opinion in Neurology* 34.2 (2021): 172-181.
- Almohaish, Sulaiman, Melissa Sandler, and Gretchen M. Brophy. "Time Is Brain: Acute Control of Repetitive Seizures and Status Epilepticus Using Alternative Routes of Administration of Benzodiazepines." *Journal of Clinical Medicine* 10.8 (2021): 1754.
- Guterman, Elan L., et al. "Prehospital midazolam use and outcomes among patients with out-of-hospital status epilepticus." *Neurology* 95.24 (2020): e3203-e3212.
- Gaínza-Lein, Marina, et al. "Timing in the treatment of status epilepticus: from basics to the clinic." *Seizure* 68 (2019): 22-30.
- Kämppi, Leena, et al. "The essence of the first 2.5 h in the treatment of generalized convulsive status epilepticus." *Seizure* 55 (2018): 9-16.
- Lambrecq, V., Villéga, F., Marchal, C., Michel, V., Guehl, D., Rotge, J. Y. et al. (2012). Refractory status epilepticus: electroconvulsive therapy as a possible therapeutic strategy. *Seizure*, *21*(9), 661-664.
- Kamousi, Baharan, et al. "Monitoring the Burden of Seizures and Highly Epileptiform Patterns in Critical Care with a Novel Machine Learning Method." *Neurocritical Care* 34.3 (2021): 908-917.

References cont.

- Kapur, J., Elm, J., Chamberlain, J. M., Barsan, W., Cloyd, J., Lowenstein, D., ... & Fountain, N. (2019). Randomized trial of three anticonvulsant medications for status epilepticus. *New England Journal of Medicine*, *381*(22), 2103-2113.
- Dalziel SR, Borland ML, Furyk J, et al. Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial. Lancet. 2019;393(10186):2135-2145.
- Lyttle MD, Rainford NEA, Gamble C, et al. Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial. Lancet. 2019;393(10186):2125-2134.
- Chamberlain, James M., et al. "Efficacy of levetiracetam, fosphenytoin, and valproate for established status epilepticus by age group (ESETT): a double-blind, responsive-adaptive, randomised controlled trial." *The Lancet* 395.10231 (2020): 1217-1224.
- Hall, Elizabeth A., James W. Wheless, and Stephanie J. Phelps. "Status epilepticus: the slow and agonizing death of phenytoin." *J Pediatr Pharmacol Ther* 2020 Vol. 25 No. 1. Pages 4-6.
- Mundlamuri RC, Sinha S, Subbakrishna DK, et al. Management of generalised convulsive status epilepticus (SE): a prospective randomised controlled study of combined treatment with intravenous lorazepam with either phenytoin, sodium valproate or levetiracetam—pilot study. Epilepsy Res. 2015;114(1):52-58.
- Navarro, Vincent, et al. "Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial." *The Lancet Neurology* 15.1 (2016): 47-55.
- Brigo, Francesco, et al. "Intravenous brivaracetam in the treatment of status epilepticus: a systematic review." *CNS drugs* 33.8 (2019): 771-781.
- Husain, Aatif M., et al. "Randomized trial of lacosamide versus fosphenytoin for nonconvulsive seizures." *Annals of neurology*. 83.6 (2018): 1174-1185.
- Glauser, T., Shinnar, S., Gloss, D., Alldredge, B., Arya, R., Bainbridge, J. et al. (2016). Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the Guideline Committee of the American Epilepsy Society. *Epilepsy currents*, *16*(1), 48-61.
- Brophy, G. M., Bell, R., Claassen, J., Alldredge, B., Bleck, T. P., Glauser, T. et al. (2012). Guidelines for the evaluation and management of status epilepticus. *Neurocrit Care*, *17*(1), 3-23.
- Meierkord, H., Boon, P., Engelsen, B., Göcke, K., Shorvon, S., Tinuper, P. et al. (2010). EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol*, *17*(3), 348-355.
- Vossler, David G., et al. "Treatment of refractory convulsive status epilepticus: a comprehensive review by the American Epilepsy Society Treatments Committee." *Epilepsy currents*20.5 (2020): 245-264.
- Ochoa, Juan G., et al. "Treatment of Super-Refractory Status Epilepticus: A Review." *Epilepsy Currents* (2021): 1535759721999670.
- Claassen, J., Hirsch, L. J., Emerson, R. G., & Mayer, S. A. (2002). Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia*, *43*(2), 146-153.
- Stavropoulos, Ioannis, Ho Lim Pak, and Antonio Valentin. "Neuromodulation in Super-refractory Status Epilepticus." *Journal of Clinical Neurophysiology: Official Publication of the American Electroencephalographic Society* (2021).

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References cont.

- Rossetti, A. O., Milligan, T. A., Vulliémoz, S., Michaelides, C., Bertschi, M., & Lee, J. W. (2011). A randomized trial for the treatment of refractory status epilepticus. *Neurocrit Care*, *14*(1), 4-10.
- Shorvon, S., & Ferlisi, M. (2011). The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain*, *134*(Pt 10), 2802-2818.
- Alvarez, V., Lee, J. W., Westover, M. B., Drislane, F. W., Novy, J., Faouzi, M. et al. (2016). Therapeutic coma for status epilepticus: Differing practices in a prospective multicenter study. *Neurology*, *87*(16), 1650-1659.
- Jirsch, J., & Hirsch, L. J. (2007). Nonconvulsive seizures: developing a rational approach to the diagnosis and management in the critically ill population. *Clinical neurophysiology*, *118*(8), 1660-1670.
- Kowalski, R. G., Ziai, W. C., Rees, R. N., Werner, J. K., Kim, G., Goodwin, H. et al. (2012). Third-line antiepileptic therapy and outcome in status epilepticus: the impact of vasopressor use and prolonged mechanical ventilation. *Crit Care Med*, *40*(9), 2677-2684.
- Kaplan, P. W. (2000). No, some types of nonconvulsive status epilepticus cause little permanent neurologic sequelae (or: "the cure may be worse than the disease"). *Neurophysiol Clin*, *30*(6), 377-382.
- Rossetti, A. O., Logroscino, G., & Bromfield, E. B. (2005). Refractory status epilepticus: effect of treatment aggressiveness on prognosis. *Arch Neurol*, *62*(11), 1698-1702.
- Muhlhofer, Wolfgang G., et al. "Duration of therapeutic coma and outcome of refractory status epilepticus." *Epilepsia* 60.5 (2019): 921-934.
- Turrigiano, Gina. "Homeostatic synaptic plasticity: local and global mechanisms for stabilizing neuronal function." *Cold Spring Harbor perspectives in biology* 4.1 (2012): a005736.
- Fechner A, Hubert K, Jahnke K, et al. Treatment of refractory and superrefractory status epilepticus with topiramate: a cohort study of 106 patients and a review of the literature. Epilepsia. 2019; 60(12):2448-2458.
- Ho, Chen-Jui, et al. "Perampanel treatment for refractory status epilepticus in a neurological intensive care unit." *Neurocritical care* 31.1 (2019): 24-29.
- Lim, Siew-Na, et al. "Efficacy and safety of perampanel in refractory and super-refractory status epilepticus: cohort study of 81 patients and literature review." *Journal of Neurology*(2021): 1-14.
- Rosati A, Ilvento L, L'Erario M, et al. Efficacy of ketamine in refractory convulsive status epilepticus in children: a protocol for a sequential design, multicentre, randomised, controlled, open- label, non-profit trial (KETASER01). BMJ open. 2016;6(6): e011565.
- Alkhachroum et al. Ketamine to treat super-refractory status epilepticus. Neurology 2020;95:e2286-e2294.
- Sculier, Claudine, and Nicolas Gaspard. "New onset refractory status epilepticus (NORSE)." *Seizure* 68 (2019): 72-78.
- Katz et al. Pearls and Pitfalls of Introducing Ketogenic Diet in Adult Status Epilepticus: A Practical Guide for the Intensivist. *J. Clin. Med.* 2021, *10*, 881.

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