Status epilepticus: evaluation and management

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Disclosures

- I have nothing to disclose

Status epilepticus

- Convulsive status = obvious
- Nonconvulsive status epilepticus = not so much
- 5-37% NCSE in ICU
- 8-30% NCSE in altered mental status

Claassen J, Mayer SA, Kowalski RG, et al. *Neurology*. 2004 May 25;62(10):1743-8.
Jordan KG. *J Clin Neurophysiol*. 1993 Oct;10(4):445-75
Panadian JD, Cascino GD, So EL, et al. *Arch Neurol*. 2004 Jul;61(7):1090-4.
Towne AR, Waterhouse EJ, Boggs JG, et al. *Neurology*. 2000 Jan 25;54(2):340-5
Sutter R, Fuhr P, Grize L, et al. *Epilepsia*. 2011 Mar;52(3):453-7..

Diagnosis

- High index of suspicion!

- Risk factors:
  - Glasgow Coma Scale < 8 (56%)
  - Convulsive seizures before EEG (43-48%)
  - Age < 18 (36%)
  - History of epilepsy (41%)

Abend NS, Arndt DH, Carpenter JL, et al. *Neurology*. 2013 Jul 23;81(4):383-91.
Claassen J, Mayer SA, Kowalski RG et al. *Neurology*. 2004 May 25;62(10):1743-8.
DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. *Epilepsia*. 1998 Aug;39(8):833-40.

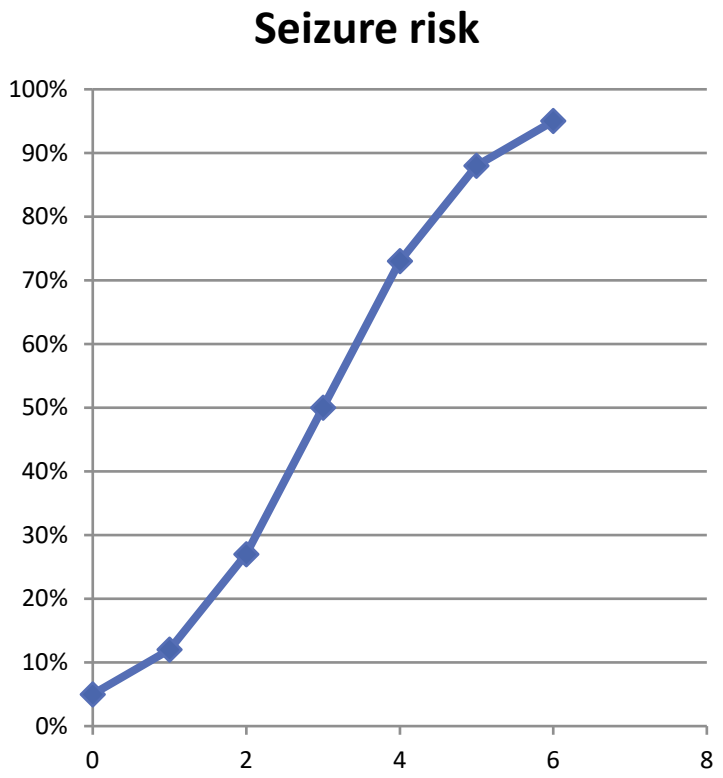
2HELPS2B

	Points
Hz > 2 for any rhythmic or periodic pattern	1
Epileptiform discharges (sporadic)	1
LPDs, LRDA or BiPDs	1
Plus modifier for any feature	1
Seizure history (acute or remote)	1
Brief ictal rhythmic discharges (BIRDs)	2
Total	**? ? ?**

Struck AF, et al. JAMA Neurol. 2017 Dec 1;74(12):1419-1424.

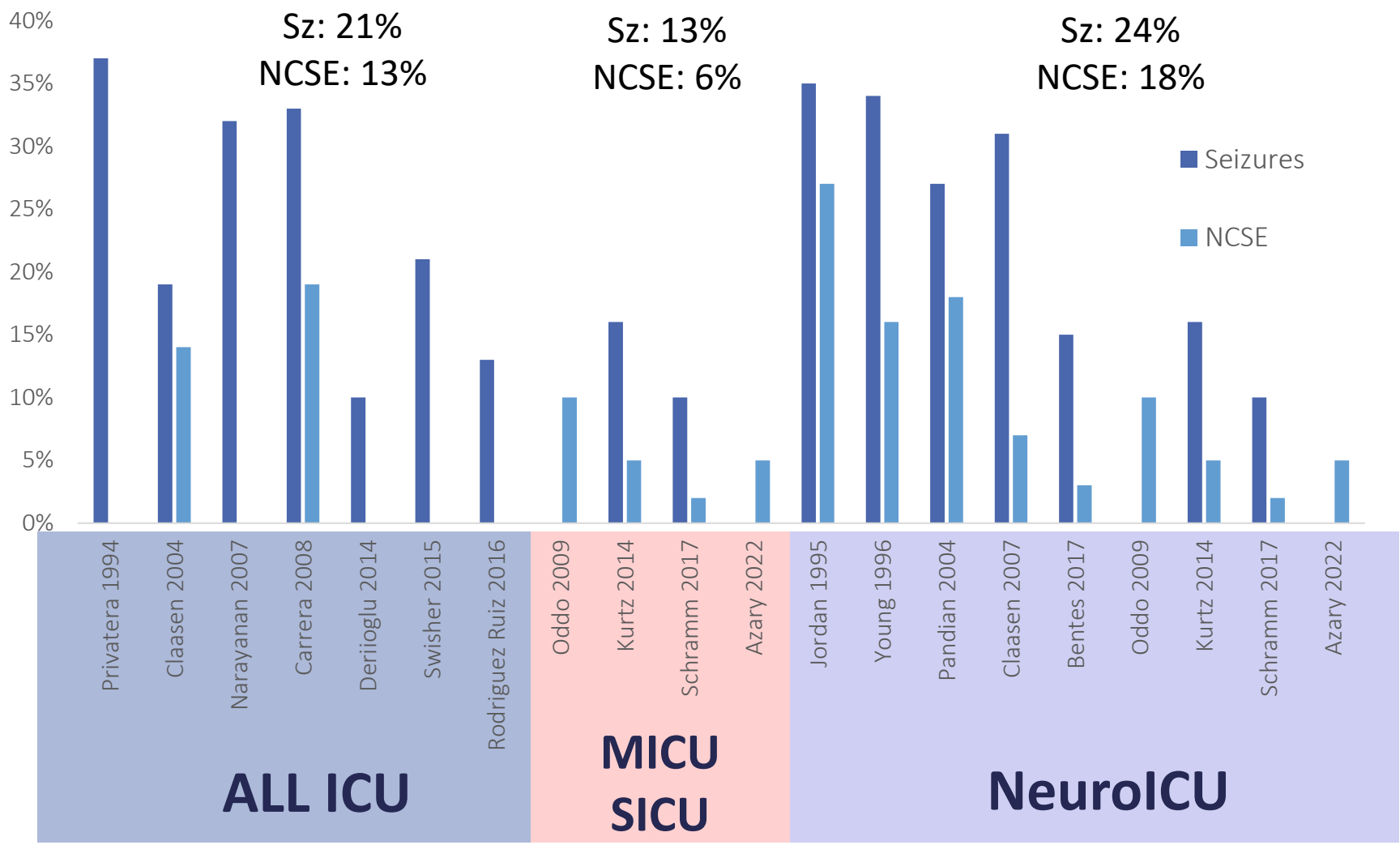
2HELPS2B

Points	Seizure risk
0	5%
1	12%
2	27%
3	50%
4	73%
5	88%
6 - 7	> 95%

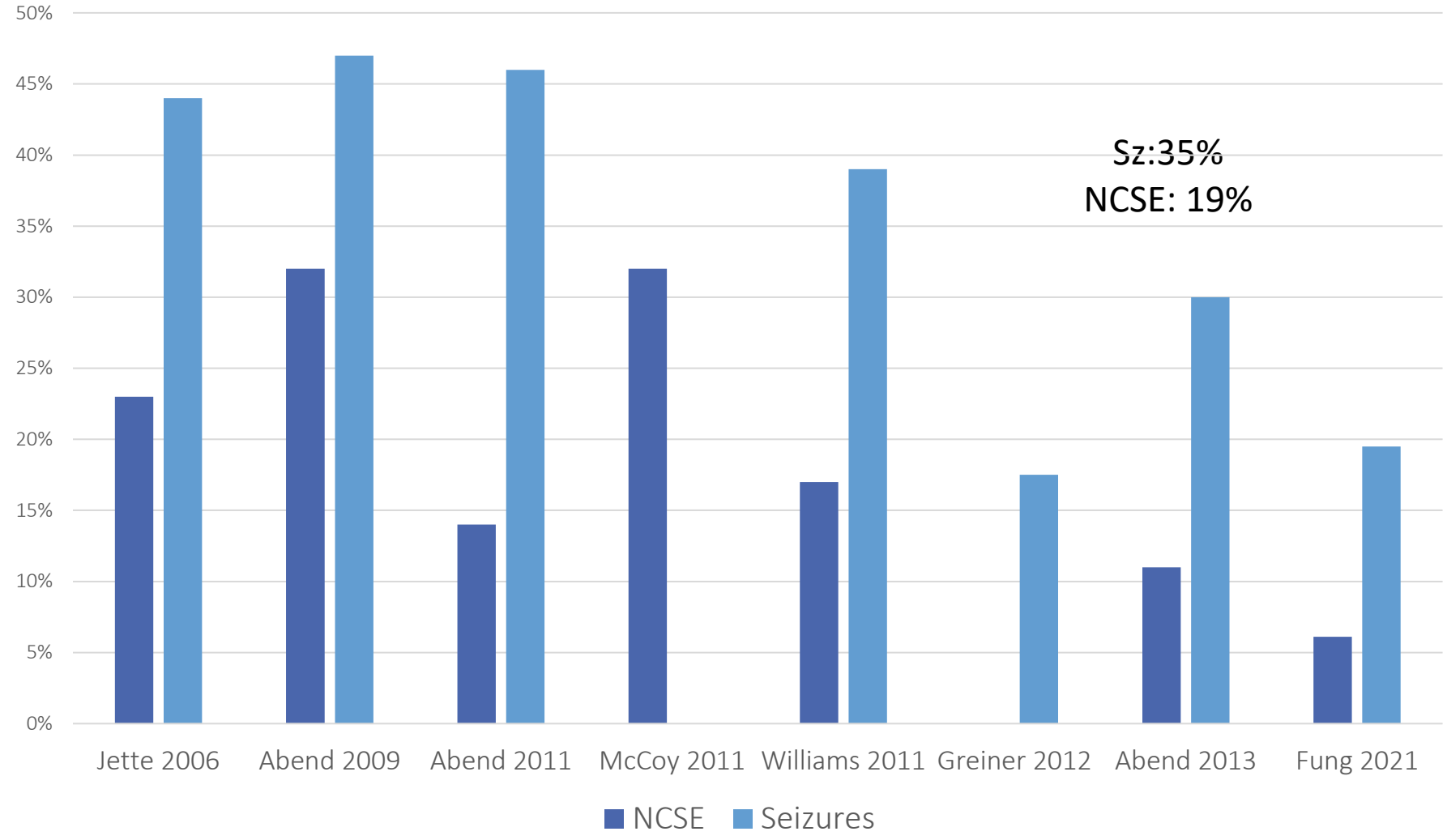


Struck AF, et al. JAMA Neurol. 2017 Dec 1;74(12):1419-1424.

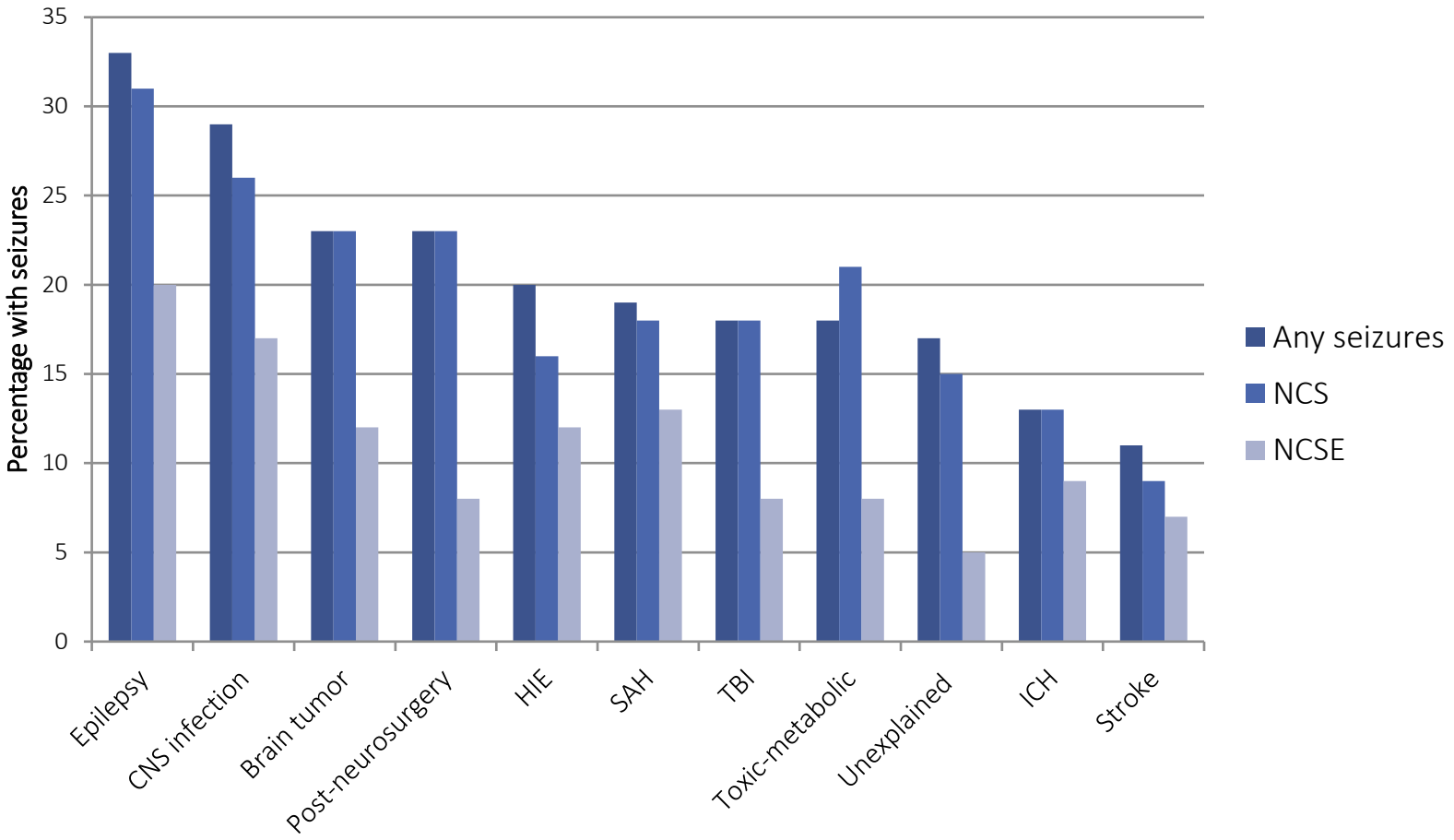
Incidence of seizures in Adult ICUs



Incidence of seizures in Pediatric ICUs



Seizures by diagnosis

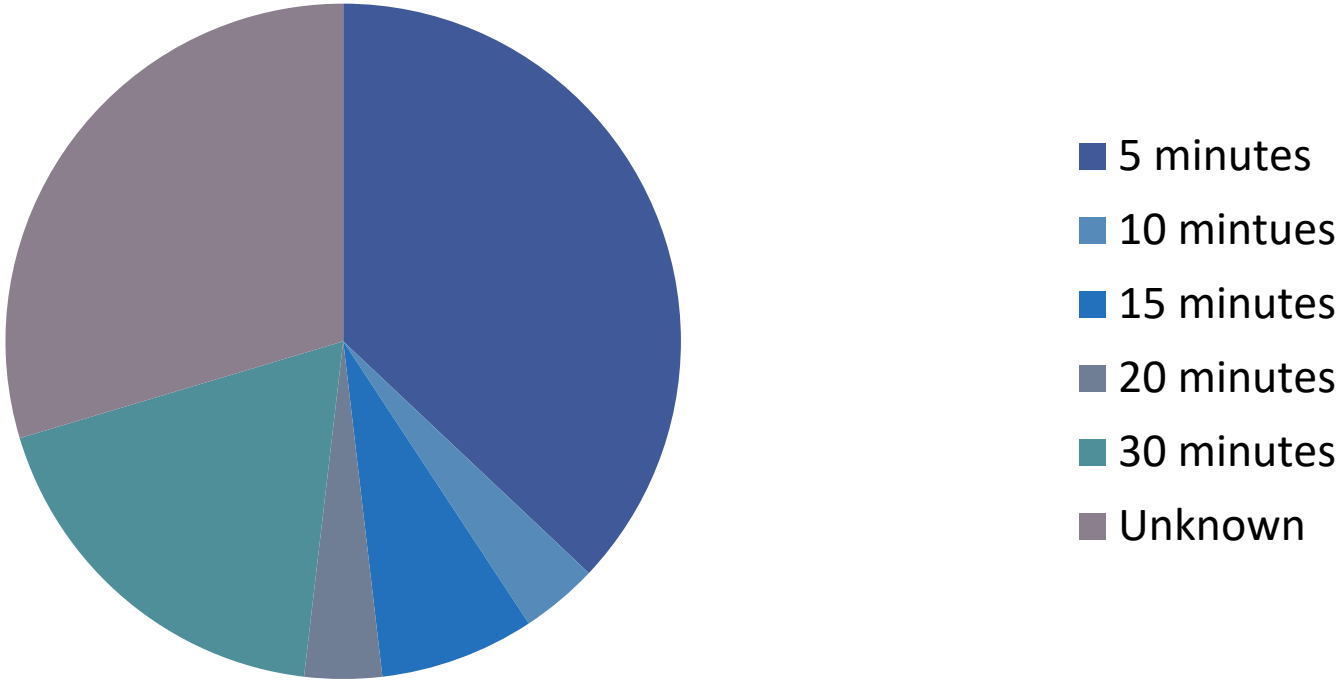


Data from Claassen J, Mayer SA, et al. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology*. 2004 May 25;62(10):1743-8.

Status Epilepticus

Historically, many definitions

Amount of time necessary to qualify as status epilepticus



Trinka E, et al. Epilepsia. 2015 Oct;56(10):1515-23.
Yasiry Z, Shorvon S. Seizure. 2014;23:167–7

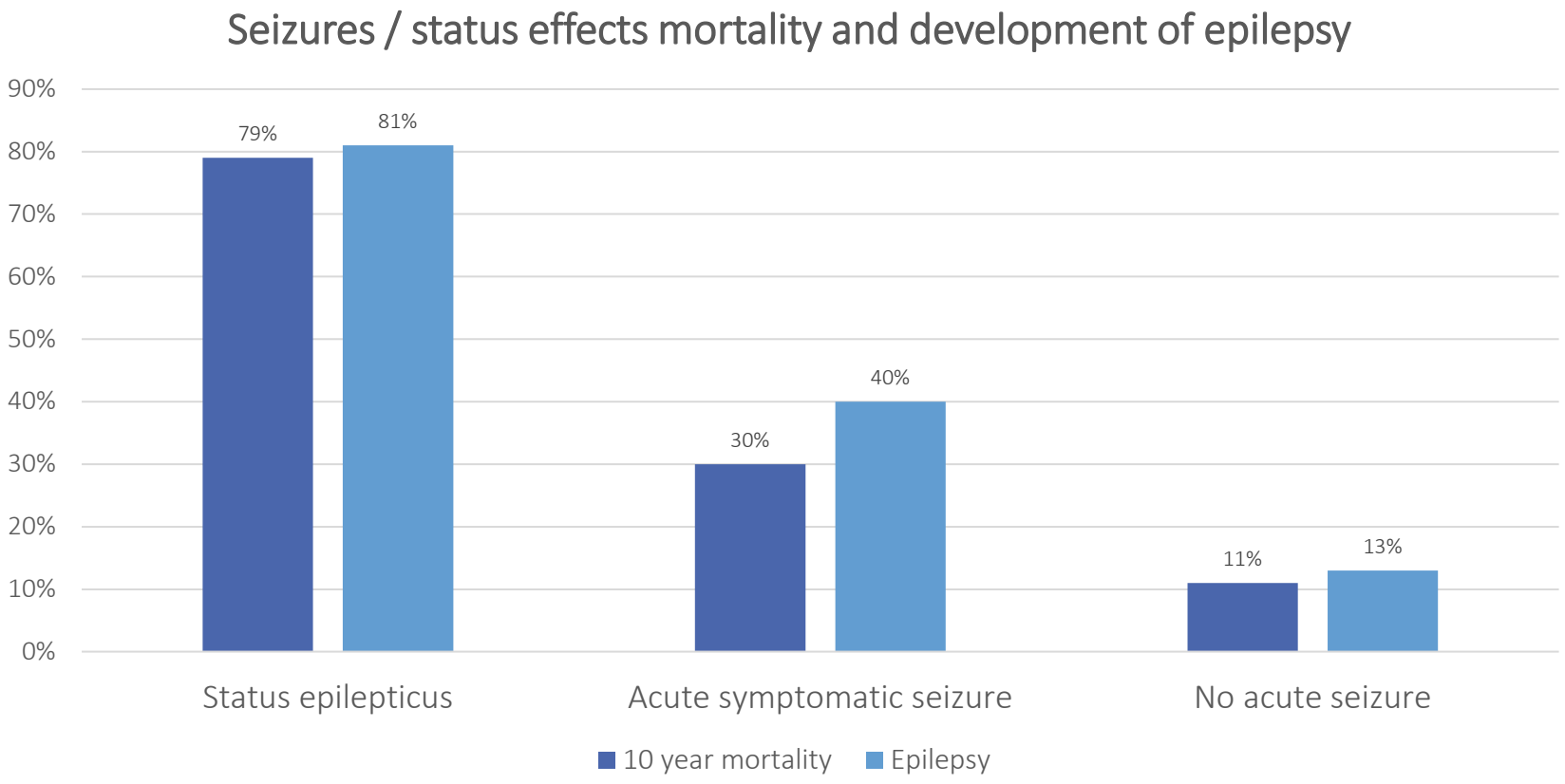
Status epilepticus: definition

- **5 minutes**: Seizures do not stop
- **30 minutes**: Adverse health consequences

82 minutes!

Meldrum BS, Brierley JB. Arch Neurol. 1973;28(1):10–17.
Trinka E, et al. Epilepsia. 2015 Oct;56(10):1515-23.

Time matters!



Data from Sinka L, et al. *JAMA Neurol*. 2023 Apr 10:e230611.

Status Epilepticus Treatment

Goals

- Stop seizure activity quickly
- Allow for full recovery
- Identify / treat underlying etiology

No. 1 rule of status epilepticus:

The longer you seize, the longer you seize

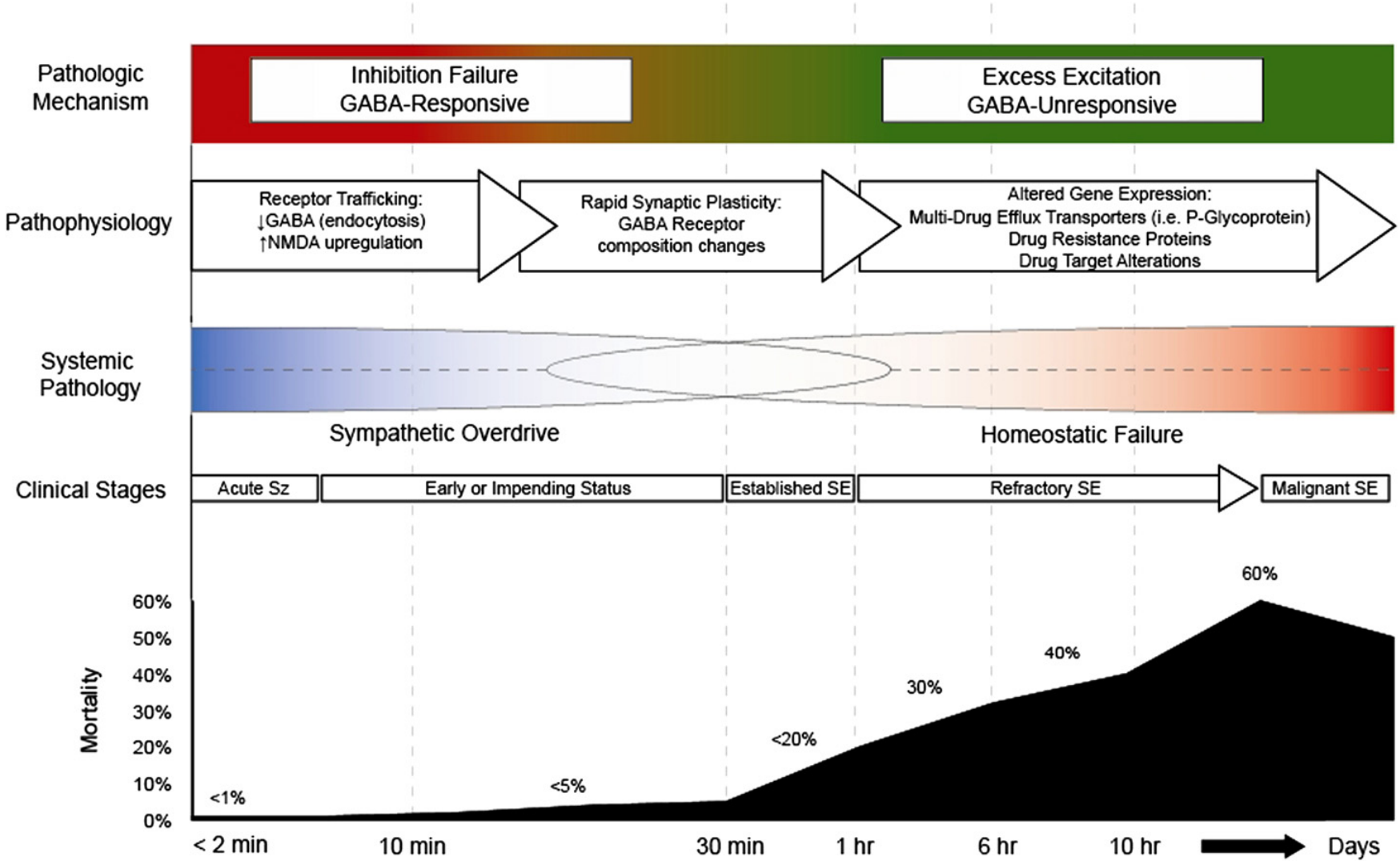
Treatment success: start tx early!

- Early treatment → improved response!
  - 82% respond to 1st line therapy if < 0.5 hours
  - < 40% respond to 1st line tx if SE > 2 hours

- Patients with overt GCSE respond better:
  - Overt GCSE: 56% response
  - Subtle GCSE: 15% response

Lowenstein et al, Neurology 1993

VA cooperative study, NEJM 1998



From Foreman B, Hirsch LJ. Epilepsy emergencies: diagnosis and management. Neurol Clin. 2012 Feb;30(1):11-41

The first five minutes

- **Step one:** Ensure ABCs
  - Hypotension = ICU admission
  - **Do not treat hypertension**
  - Not everyone needs intubation (!)
    - Incidence of aspiration PNA from GTC <0.3%!
- **Step two:** Ensure IV access
- **Step three:** CBC, Panel 7, tox screen, ASM levels (if appropriate), glucose

DeToledo JC, Lowe MR. *Neurology* 2001 Feb 13; 56(3): 290-1.

The first five minutes

- **Step four:** Glucose + thiamine
- **Step five:** Antiseizure therapy

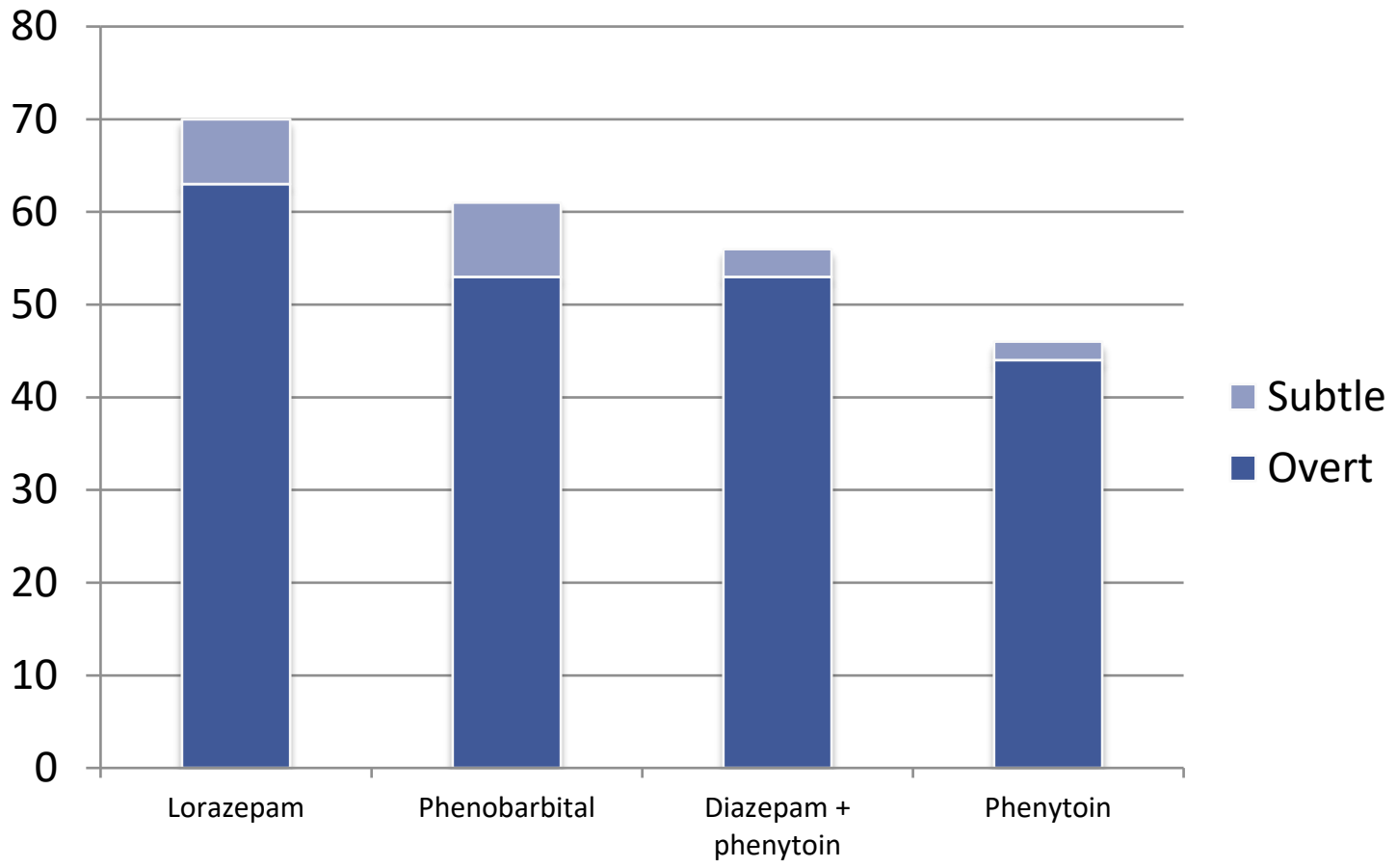
Midazolam IM
10 mg (> 40 kg)

IV lorazepam
0.1 mg / kg
Max 4 mg

IV diazepam
0.15 – 0.2 mg/kg
Max 5 mg

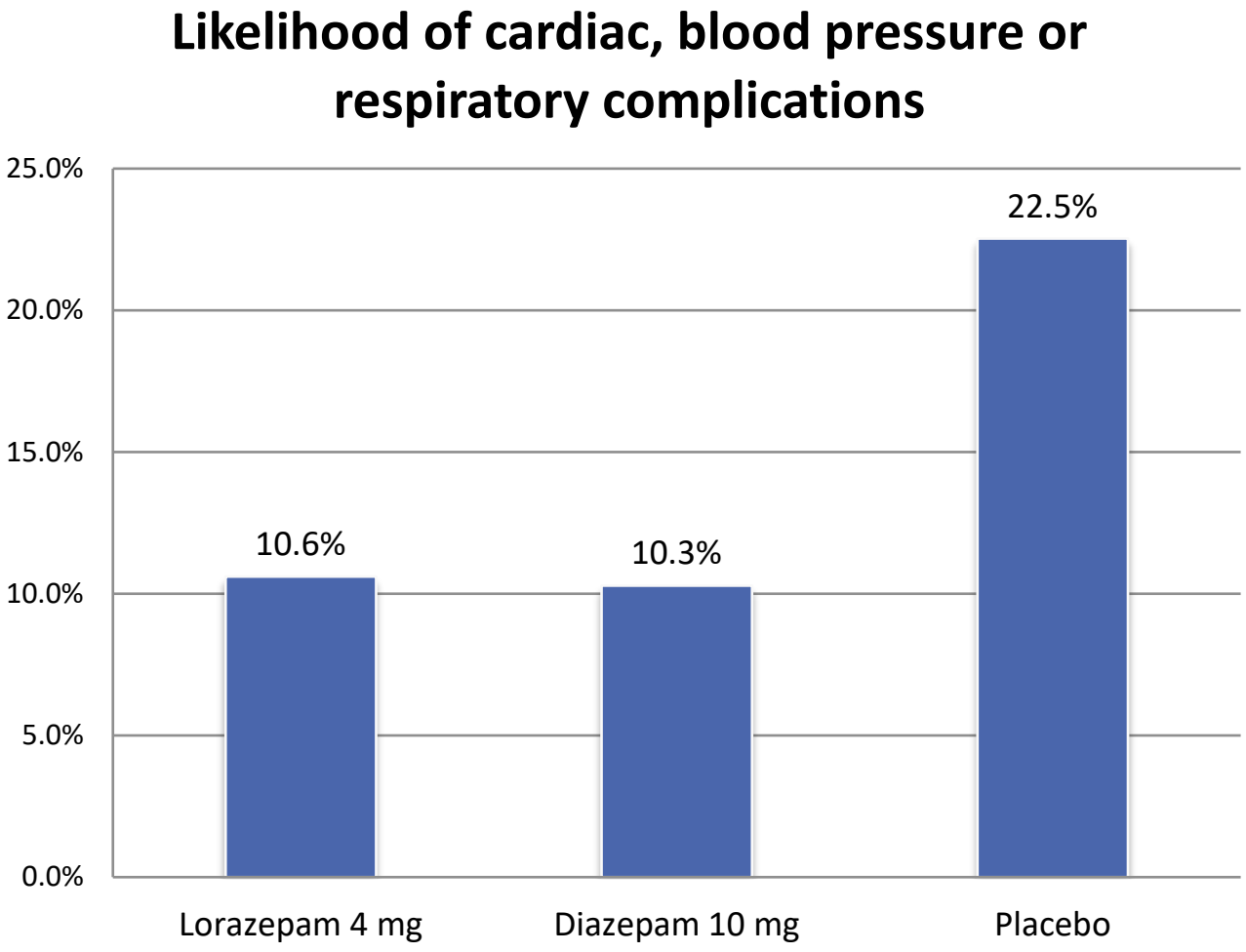
Glauser T, et al. Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society. Epilepsy Curr. 2016 Jan-Feb;16(1):48-61

First line treatment:
VA Status Epilepticus Cooperative Study



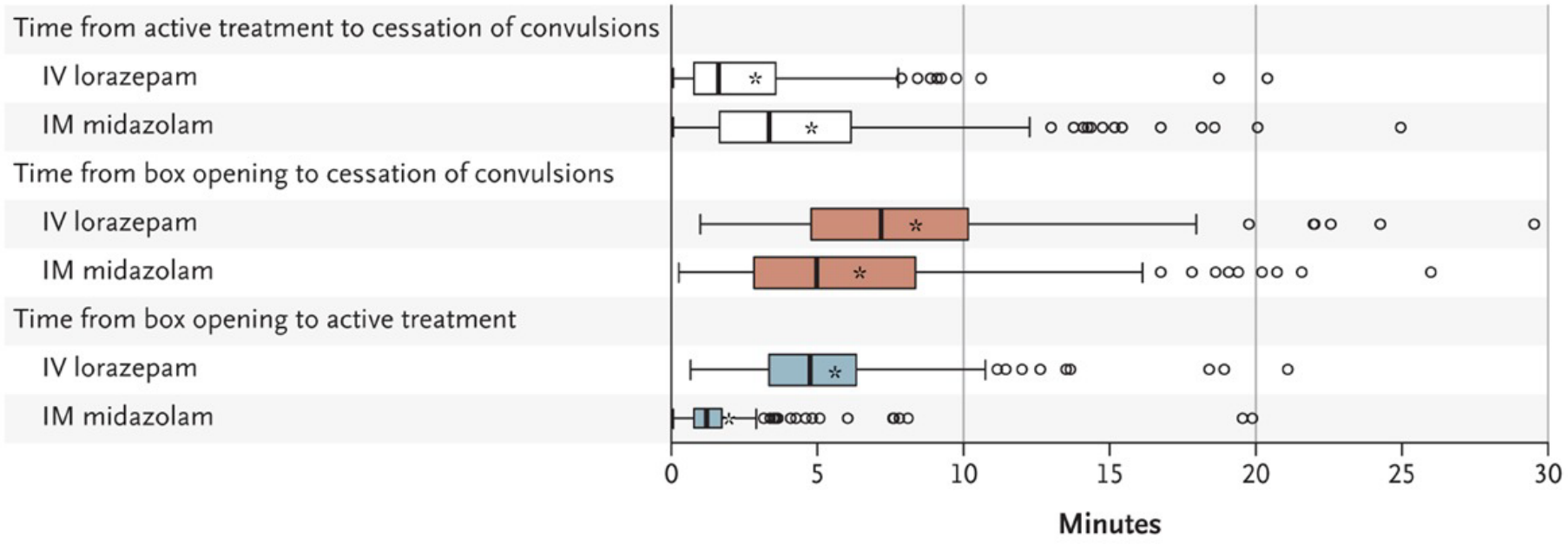
Data from Treiman DM, et al. N Engl J Med. 1998 Sep 17;339(12):792-8.

Benzodiazepines are safer than seizures



Data from Alldredge BK, et al. N Engl J Med. 2001 Aug 30;345(9):631-7

RAMPART trial



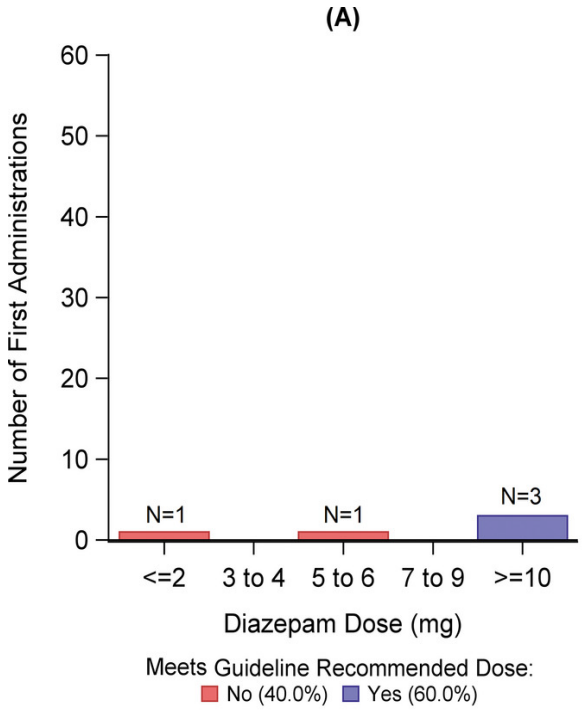
Silbergleit R, et al. N Engl J Med. 2012 Feb 16;366(7):591-600.

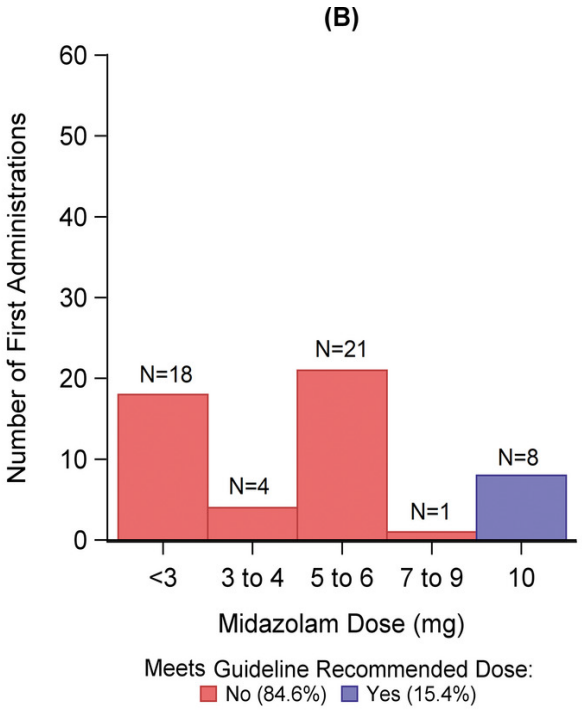
Fear and loathing and benzodiazepines

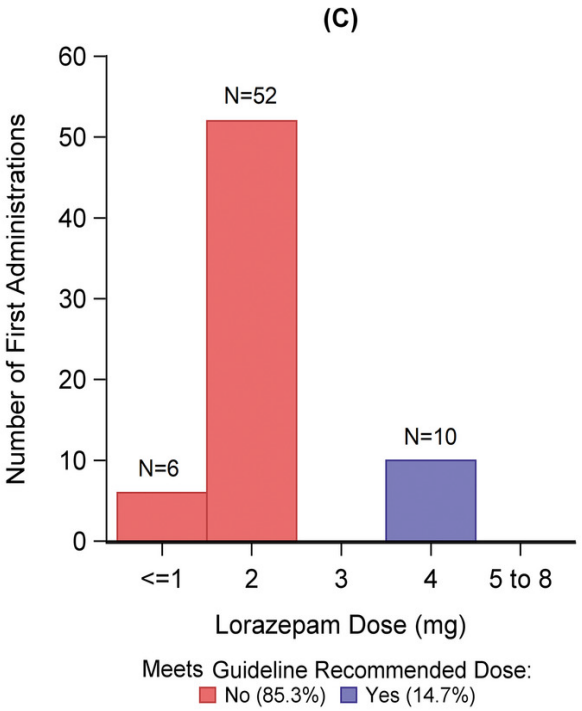
- Weight based guidelines:
  - Lorazepam 4 mg
  - Diazepam 5 mg
  - Midazolam 5 or 10 mg
- 84-95% of adult centers under-dose lorazepam
- ESETT trial: 30% 1st dose benzos appropriate

Alvarez V, et al. *Epilepsia*. 2015 Aug;56(8):1275-85.
Braun J, et al. *J Neurol Sci*. 2017 Nov 15;382:126-130.
Sathe AG, et al. *Acad Emerg Med*. 2019 Jun 4.

ESETT benzodiazepine dosing







Sathe AG, et al. Acad Emerg Med. 2019 Aug;26(8):940-943.

2nd line therapy

Treatment protocol

Fosphenytoin
20 mgPE / kg
(max 1500 mgPE)

Levetiracetam
60 mg/kg
(max 4500 mg)

Valproate 40
mg/kg
(max 3000mg)

Kapur J, et al. N Engl J Med. 2019 Nov 28;381(22):2103-2113.

Established Status Epilepticus Treatment Trial (ESETT)

- Inclusion:
  - **Appropriate benzos!**
  - > 2 years old
  - ER seizures > 5 minutes after benzos
- Primary outcome: clinically improved seizures and improved responsiveness (no EEG!)
- Primary safety outcome: cardiac arrhythmia, hypotension

Kapur J, et al. N Engl J Med. 2019 Nov 28;381(22):2103-2113.

Established Status Epilepticus Treatment Trial (ESETT)

Excluded:

- Major trauma
- Hypoglycemia
- Hyperglycemia
- Cardiac arrest
- Postanoxic patients
- Pregnancy
- Incarceration
- Prior treatment with ASM

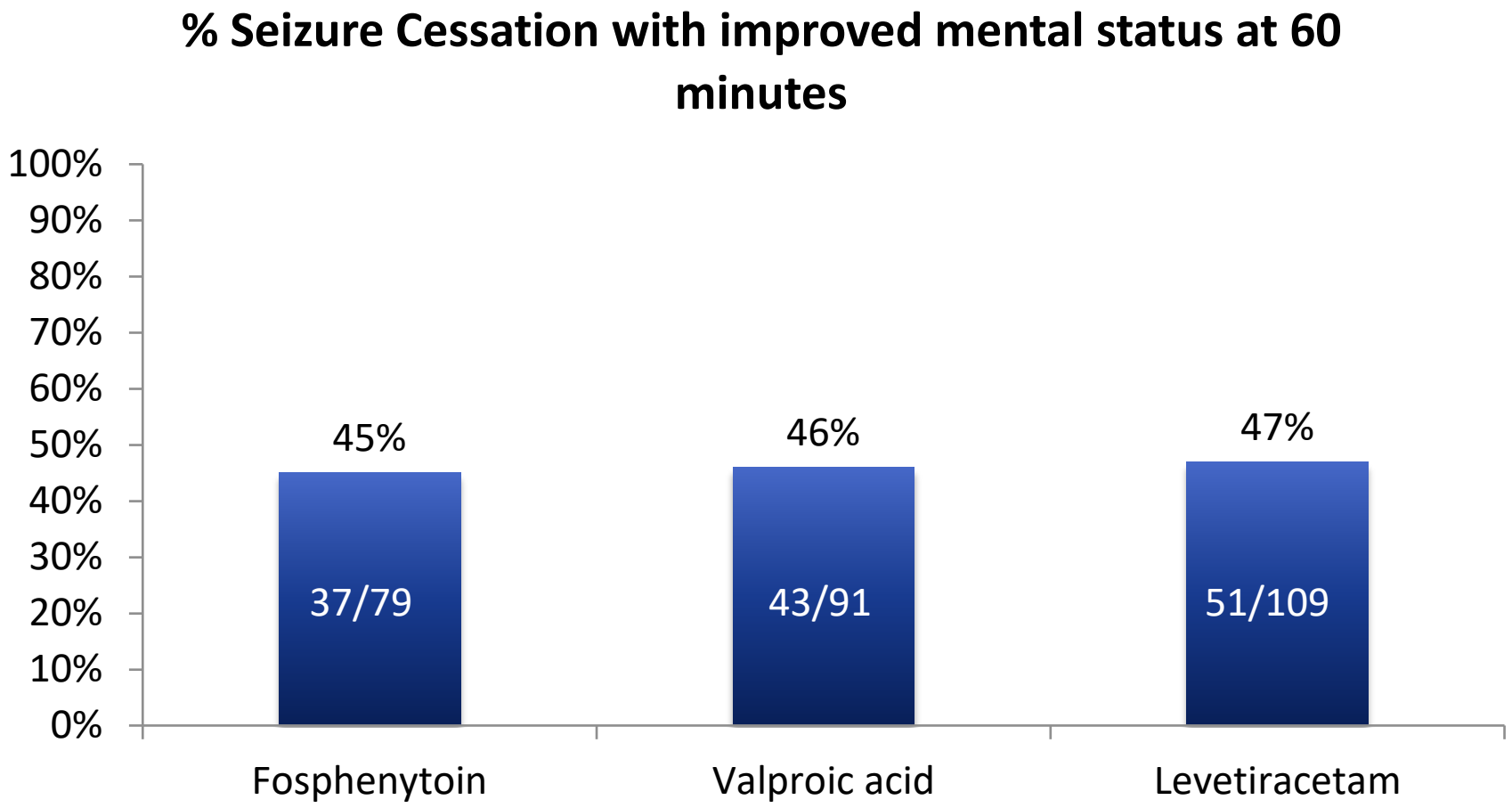
Kapur J, et al. N Engl J Med. 2019 Nov 28;381(22):2103-2113.

Established Status Epilepticus Treatment Trial (ESETT)

- N=384
- ~ 9-10% of patients with NEE (in all arms)
- Median sz duration: 62 minutes

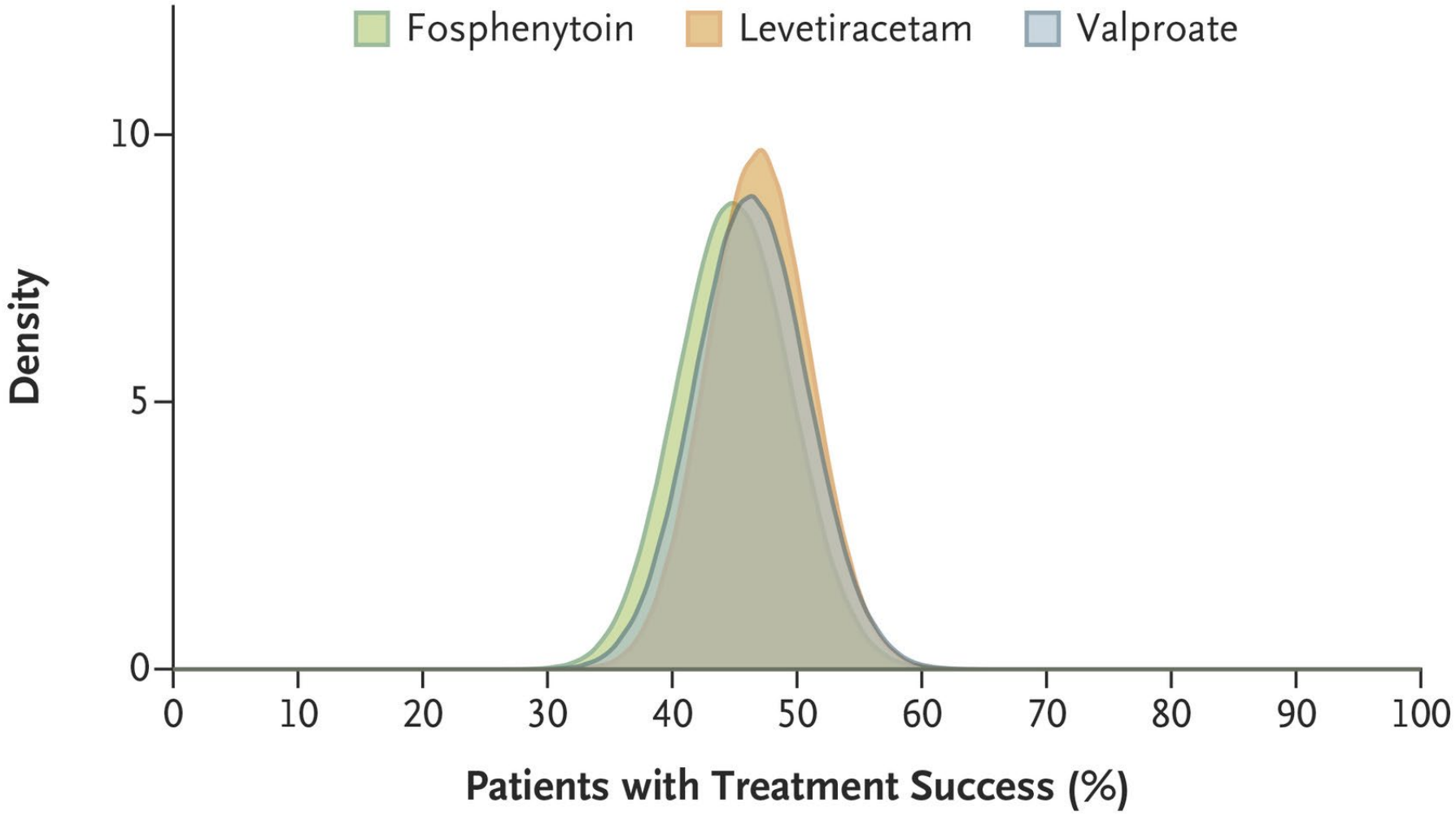
Kapur J, et al. N Engl J Med. 2019 Nov 28;381(22):2103-2113.

Established Status Epilepticus Treatment Trial (ESETT)



Data from Kapur J, et al. N Engl J Med. 2019 Nov 28;381(22):2103-2113.

Established Status Epilepticus Treatment Trial (ESETT)



Kapur J, et al. N Engl J Med. 2019 Nov 28;381(22):2103-2113.

Established Status Epilepticus Treatment Trial (ESETT)

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)

Kapur J, et al. N Engl J Med. 2019 Nov 28;381(22):2103-2113.

Established Status Epilepticus Treatment Trial (ESETT)

Table 3. Safety Analyses.*

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)

* No significant differences among the groups were detected for safety outcomes.

Kapur J, et al. N Engl J Med. 2019 Nov 28;381(22):2103-2113.

Third line treatment: Refractory status epilepticus

3rd line therapy

Seizures → subclinical

EEG required!

3rd line therapy

Midazolam

Propofol

Ketamine

and when all else fails…

Pentobarbital

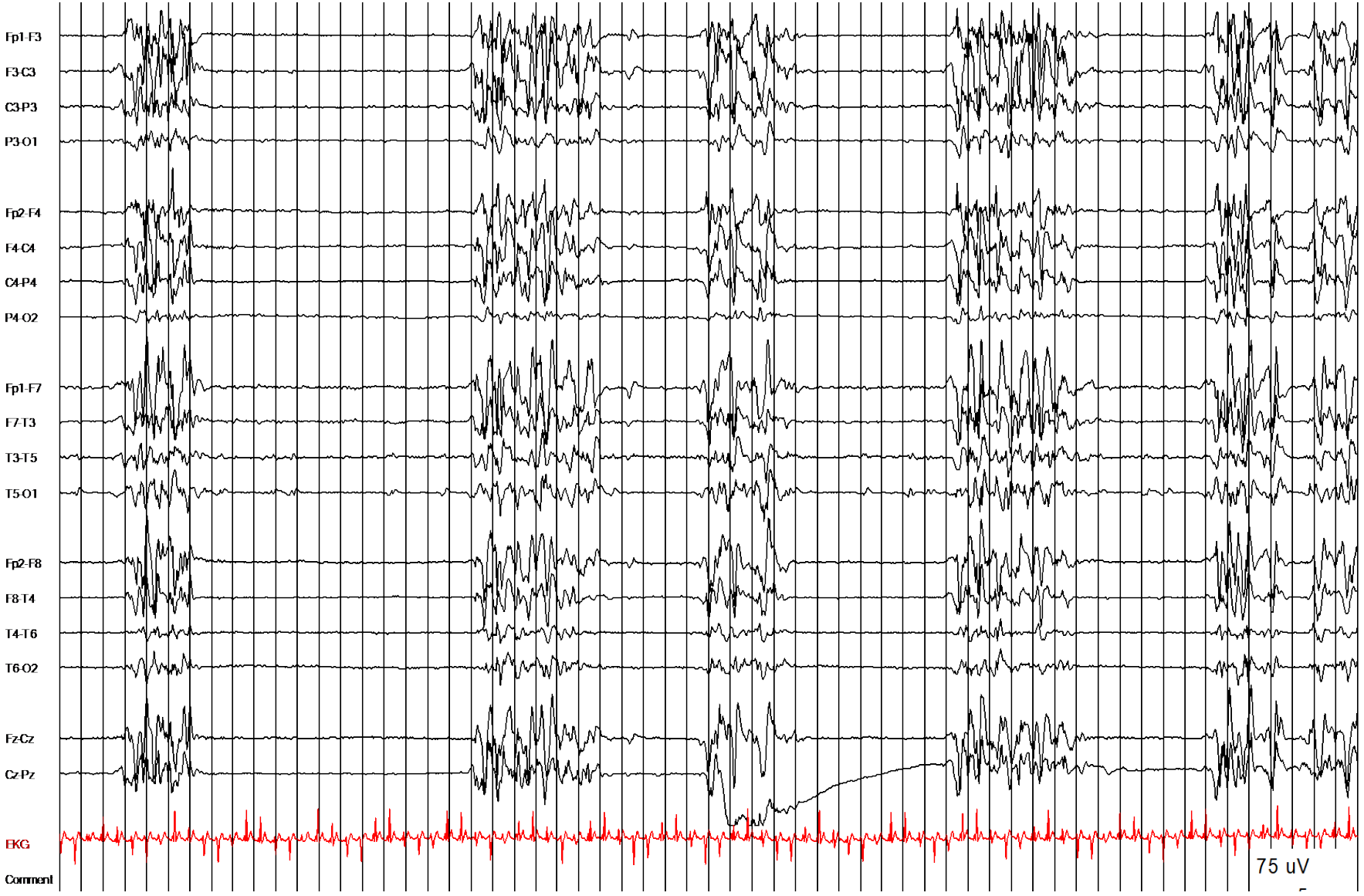
Depth of suppression

Disagreement about depth of sedation:

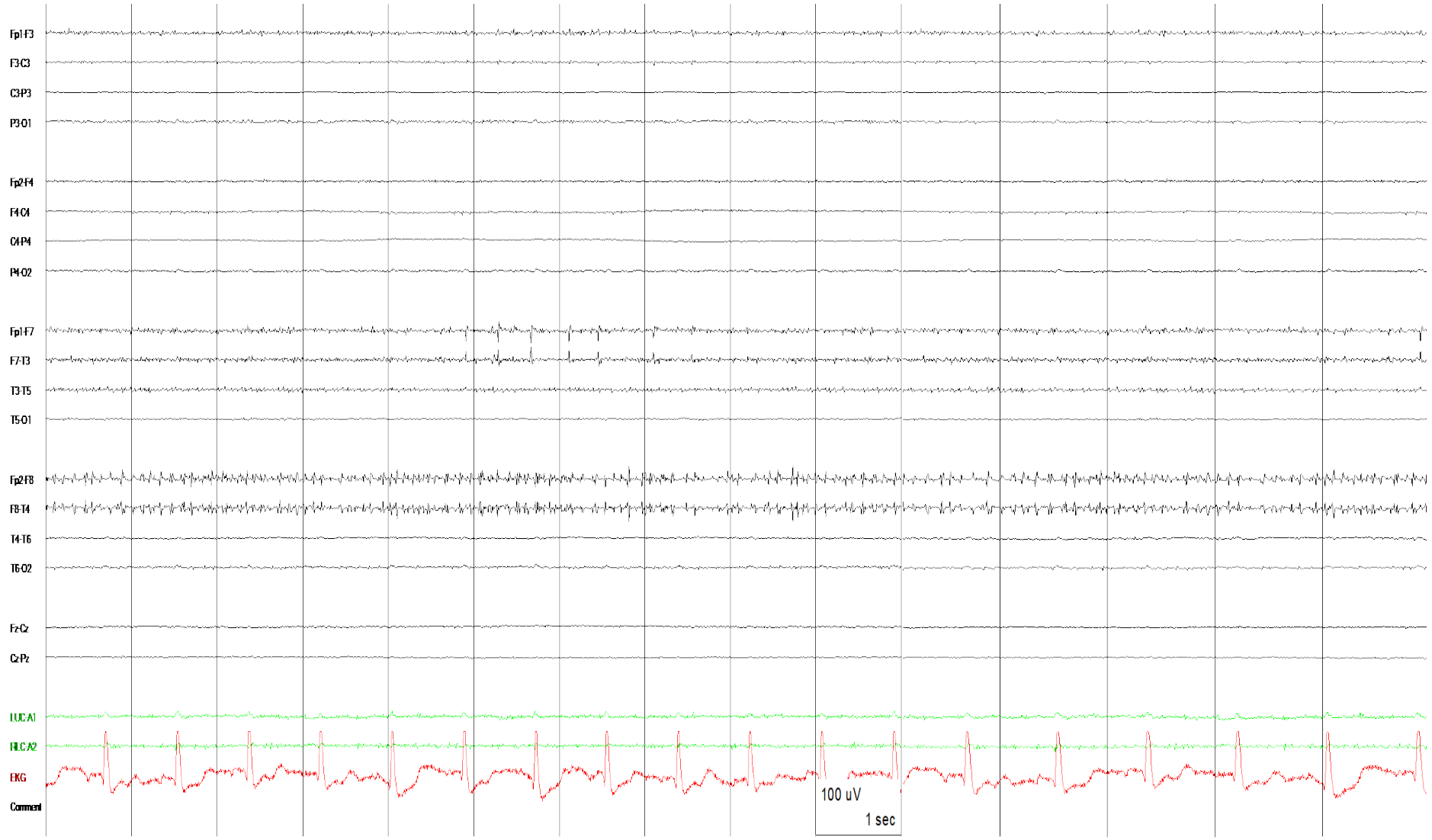
- EFNS guidelines: Either burst-suppression or isoelectric EEG
- NCS guidelines: Burst-suppression (8-20 second intervals), diffuse beta, seizure cessation or isoelectric EEG

Meierkord H, et al. *Eur J Neurol*. 2010 Mar;17(3):348-55.

Brophy GM, et al. *Neurocrit Care*. 2012 Aug;17(1):3-23.


Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
EKG
Comment
75 uV


Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
EKG
Comment
100 uV
5 sec


Fp1-F3
F3-C3
C3-P3
P3-O1
Fp2-F4
F4-C4
C4-P4
P4-O2
Fp1-F7
F7-T3
T3-T5
T5-O1
Fp2-F8
F8-T4
T4-T6
T6-O2
Fz-Cz
Cz-Pz
LUC-A1
RLC-A2
EKG
Comment
100 uV
1 sec

Depth of suppression

RSE weaned off anesthetic agents:

- N=37
  - Interburst interval, burst-suppression ratio, length of bursts did not predict success
  - Epileptiform activity within bursts → ↓ success
  - Lower amplitude bursts (< 125 μV) → ↑ success
- Second study also found that "highly epileptiform bursts" → ↓ success

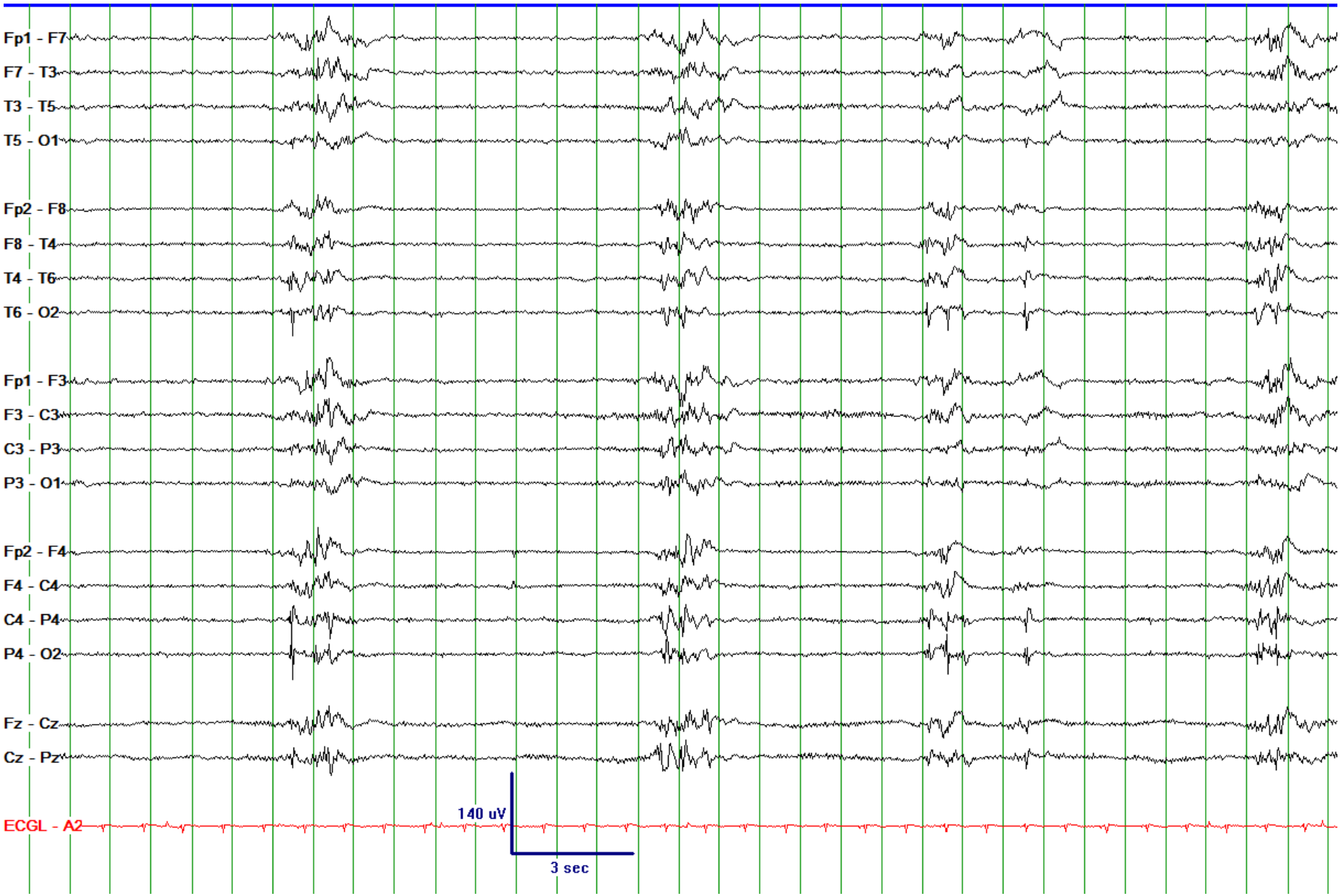
Krishnamurthy KB, Drislane FW. *Epilepsia*. 1999 Jun;40(6):759-62.
Thompson SA, Hantus S. *J Clin Neurophysiol*. 2016 Feb;33(1):66-71.

What the heck is a highly epileptiform burst?

- ≥ 2 epileptiform discharges in most bursts at ≥ 1 Hz

- OR rhythmic, potentially ictal-appearing pattern occurs at ≥ 1 Hz in most bursts

Hirsch LJ, et al. J Clin Neurophysiol. 2021 Jan 1;38(1):1-29.


Fp1 - F7
F7 - T3
T3 - T5
T5 - O1
Fp2 - F8
F8 - T4
T4 - T6
T6 - O2
Fp1 - F3
F3 - C3
C3 - P3
P3 - O1
Fp2 - F4
F4 - C4
C4 - P4
P4 - O2
Fz - Cz
Cz - Pz
ECGL - A2
140 uV
3 sec

Other options ???

Lacosamide

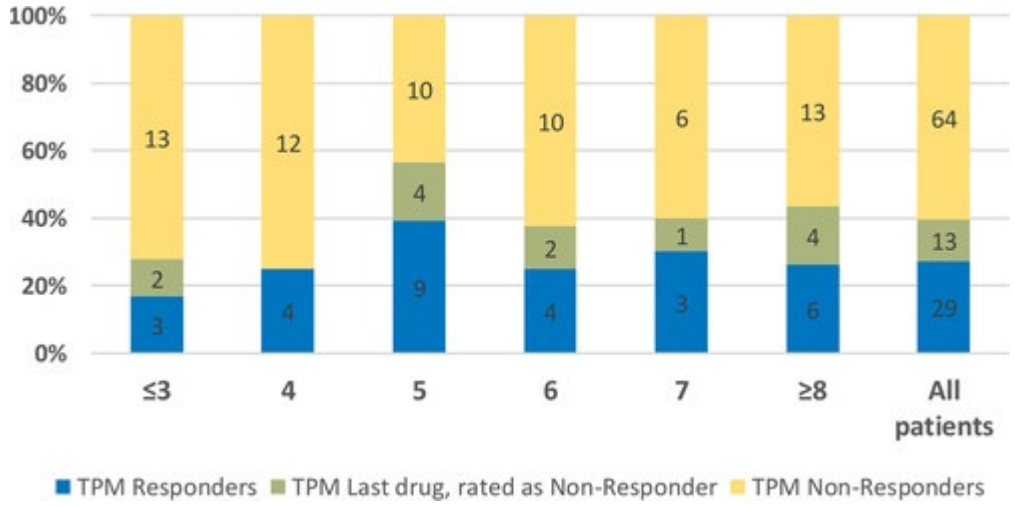
- > 500 reported cases (Class IV evidence)
- On average → 3rd Rx
  - Efficacy 57%
  - ↓ effectiveness later
- 400 mg load → ↑ seizure freedom at 3 hours

Strzelczyk A, et al. Epilepsia. 2017 Jun;58(6):933-950.

Topiramate

TPM and refractory status:

- Median dose 400 mg / day
- 32% response rate in refractory status
- 20% response rate in super refractory status



Fechner A, et al. Epilepsia. 2019 Dec;60(12):2448-2458.

Ketogenic Diet

- Reported use in 66 children and adults
  - 79% response (N=24)
  - Seizure freedom rates 75-80%
- Rx tried before KD: 3-16
- Days to achieve ketosis: 3.5 – 37
- Time to resolution of status: 4 – 25 days

Cervenka Mcet al. *Neurology*. 2017 Mar 7;88(10):938-943.
Kossoff EH, Nabbout R. *J Child Neurol*. 2013 Aug;28(8):1049-51.
Mahmoud SH, et al. Epilepsia Open. 2019 Nov 24;5(1):10-21.

Ketogenic Diet

- Side effects common:
  - Metabolic acidosis (often persistent)
  - Hyperlipidemia
  - Hypoglycemia
- KD → ↑ risk propofol infusion syndrome (n=1)

Cervenka Mcet al. *Neurology*. 2017 Mar 7;88(10):938-943.
Kossoff EH, Nabbout R. *J Child Neurol*. 2013 Aug;28(8):1049-51.

Ketogenic diet exclusions

- Recent propofol use (last 24 hours)
- Hemodynamic instability
- Pregnancy
- Liver failure
- Hypoglycemia
- Ileus
- Fatty oxidation disorder
- Hyponatermia, hypernatremia or hypercalcemia
- Baseline cholesterol >300 mg / dL
- pH < 7.2

Mahmoud SH, et al. Epilepsia Open. 2019 Nov 24;5(1):10-21.

The kitchen sink…

- Allopregnanolone
- Anakinra
- Azathioprine
- Cannabidiol
- Carbamazepine
- Clobazam
- CSF drainage
- Cyclophosphamide
- Deep brain stimulation
- Electroconvulsive therapy
- Felbamate
- Hypothermia
- IVIg
- Inhaled anesthestics
- Lidocaine
- Magnesium
- Neurosurgery
- Neurosurgery
- Oxcarbazpine
- Perampanel
- Plasma exchange
- Pregabalin
- Responsive neural stimulation
- Rituximab
- Stiripental
- Tacrolimus
- Thiopental
- Tocilzumab
- Transcranial magnetic stimulation
- Vagus nerve stimulation

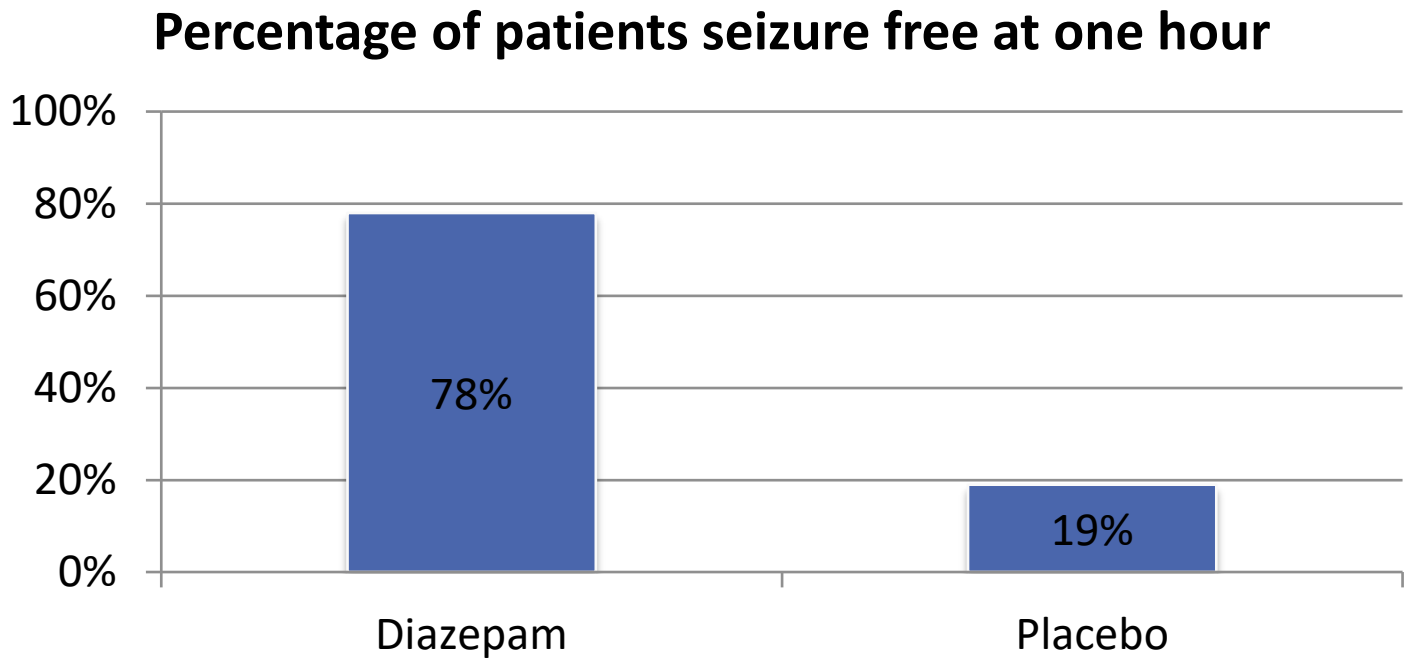
Prevention!

- Waiting for EMS → tx delay
  - Average EMS response time: 7 minutes
  - Rural areas: 14 minutes
  - 10% → 30+ minutes
- With early tx, many seizures do not need hospitalization

Madiraju SK, et al. J Surg Res. 2017 Oct;218:261-270.
Mell HK, et al. JAMA Surg. 2017 Oct 1;152(10):983-984

Rectal diazepam works

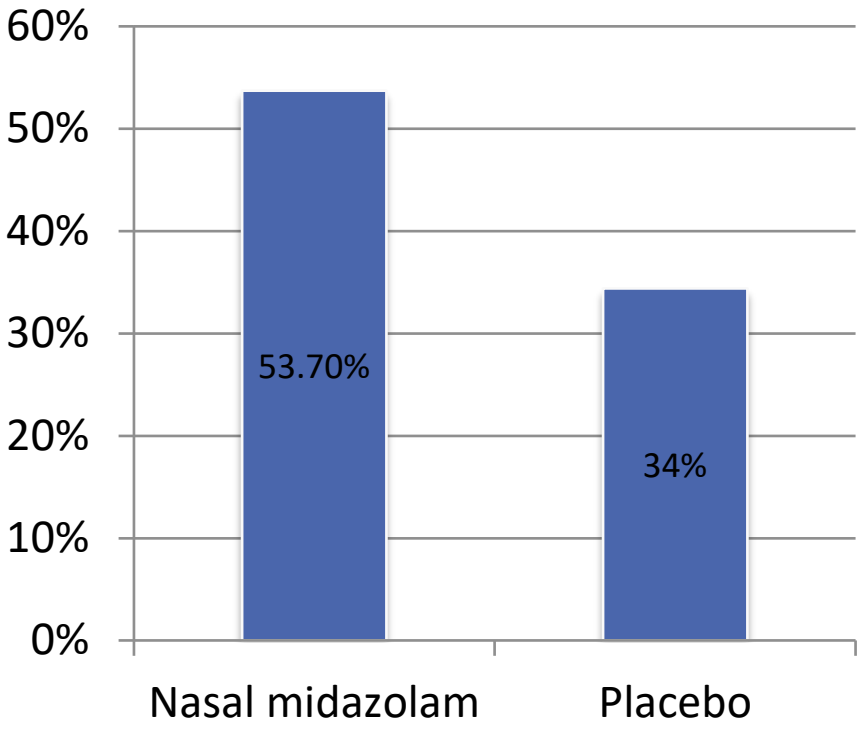
- Reduced seizure frequency
- Improved outcome (as assessed by caregiver)
- Effective in children and adults



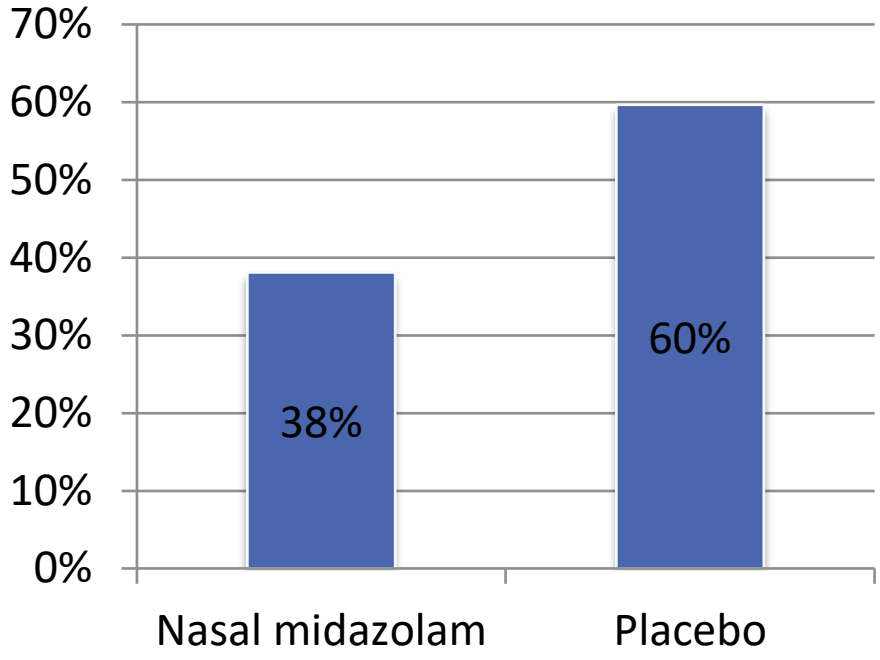
Dreifuss FE, et al. N Engl J Med. 1998 Jun 25;338(26):1869-75.

Nasal midazolam randomized controlled trial

Percentage of patients seizure free at ten minutes



Percentage of patients with seizure recurrence after ten minutes



Detyniecki K, et al Epilepsia. 2019 May 29.

Conclusions

- High index of suspicion for status epilepticus
- Stop underdosing benzodiazepines
- Fosphenytoin = valproate = levetiracetam
- No great evidence on treating RSE