STATUS EPILEPTICUS: DIAGNOSIS AND PREHOSPITAL TREATMENT

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DISCLOSURE

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- Chair, Steering Committee, EPINOV (France)
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Learning Objectives

Key aspects in the diagnosis of status epilepticus

Consequences of misdiagnosis and delay in treatment of status epilepticus

Evidence for effectiveness of pre-hospital treatment of status epilepticus

Key Messages

- Status Epilepticus is often missed in the community
- Longer duration of Status Epilepticus is associated with lower recovery and survival
- Pre-Hospital treatment is associated with better outcomes
  - Shortened duration, lower recurrence, fewer hospitalizations and ICU
- Effective Pre-hospital Medications include
  - Rectal Diazepam
  - Buccal or Intramuscular Midazolam
  - Intravenous Diazepam or Lorazepam

SOME NUMBERS

INCIDENCE (P/100,000)
25 Status Epilepticus
5 Refractory 3 Super R

5% - 17%
Hospital Admissions with SE evolve to SRSE

35% - 43%
Mortality

>50%
Develop cognitive deficits

NUMBER OF DAYS
In THERAPEUTIC COMA = cognitive deficits

60%
Of costs related to SE are due to SRSE

Strzelczyk, et al, Epilepsia 2017

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, ¶Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer, ††Shlomo Shinnar, ‡‡Simon Shorvon, and §§Daniel H. Lowenstein

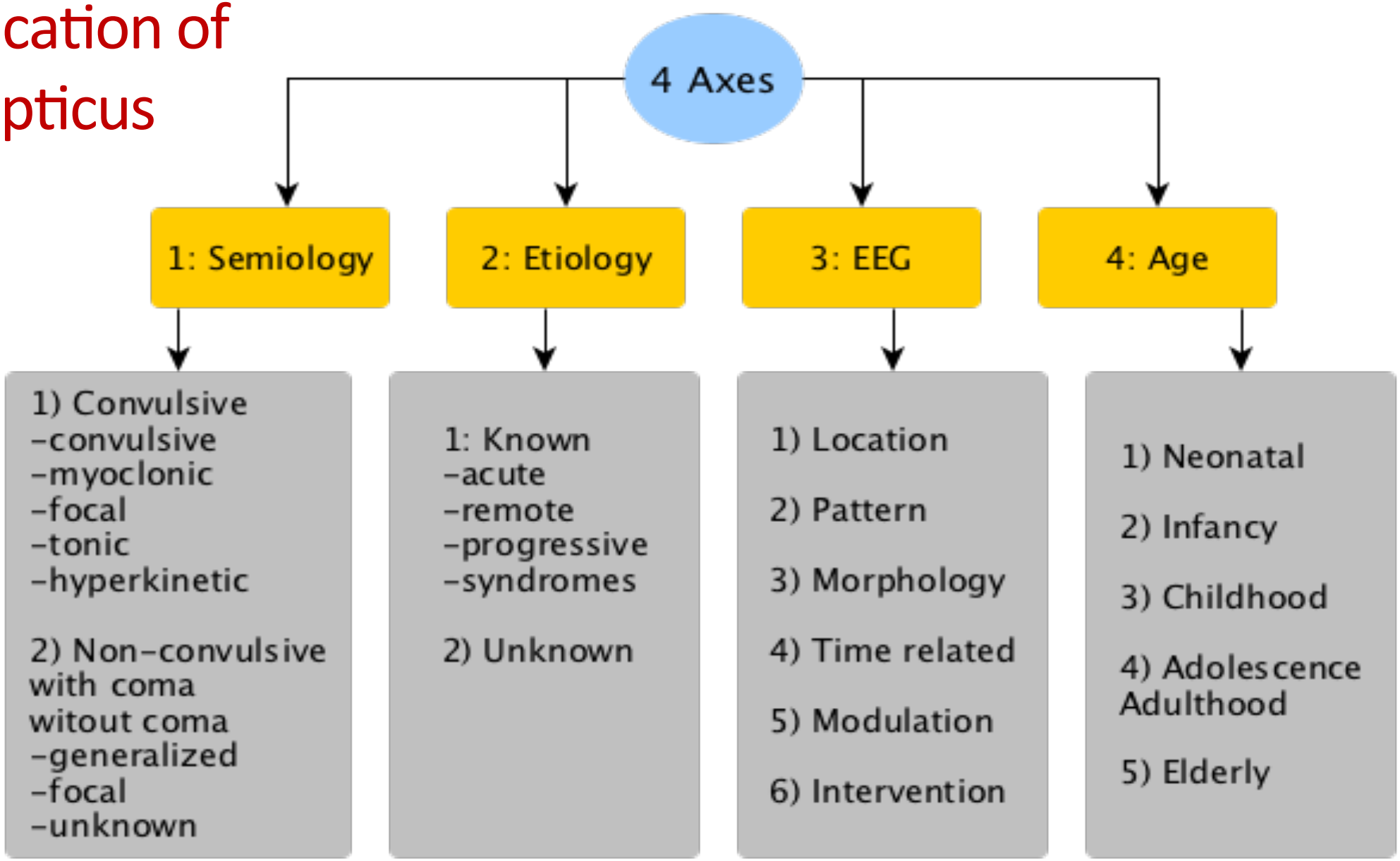
A condition resulting from failure of mechanisms responsible for seizure termination

time point t1 = abnormally prolonged seizures

time point t2 = Can have long-term consequences: neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.

	GTC	Focal impaired unawareness	Absence
T1 - start treating as status	5 min	10 min	10-15 min
T2 - treat more aggressively	30 min	60 min	unknown

ILAE Classification of Status Epilepticus

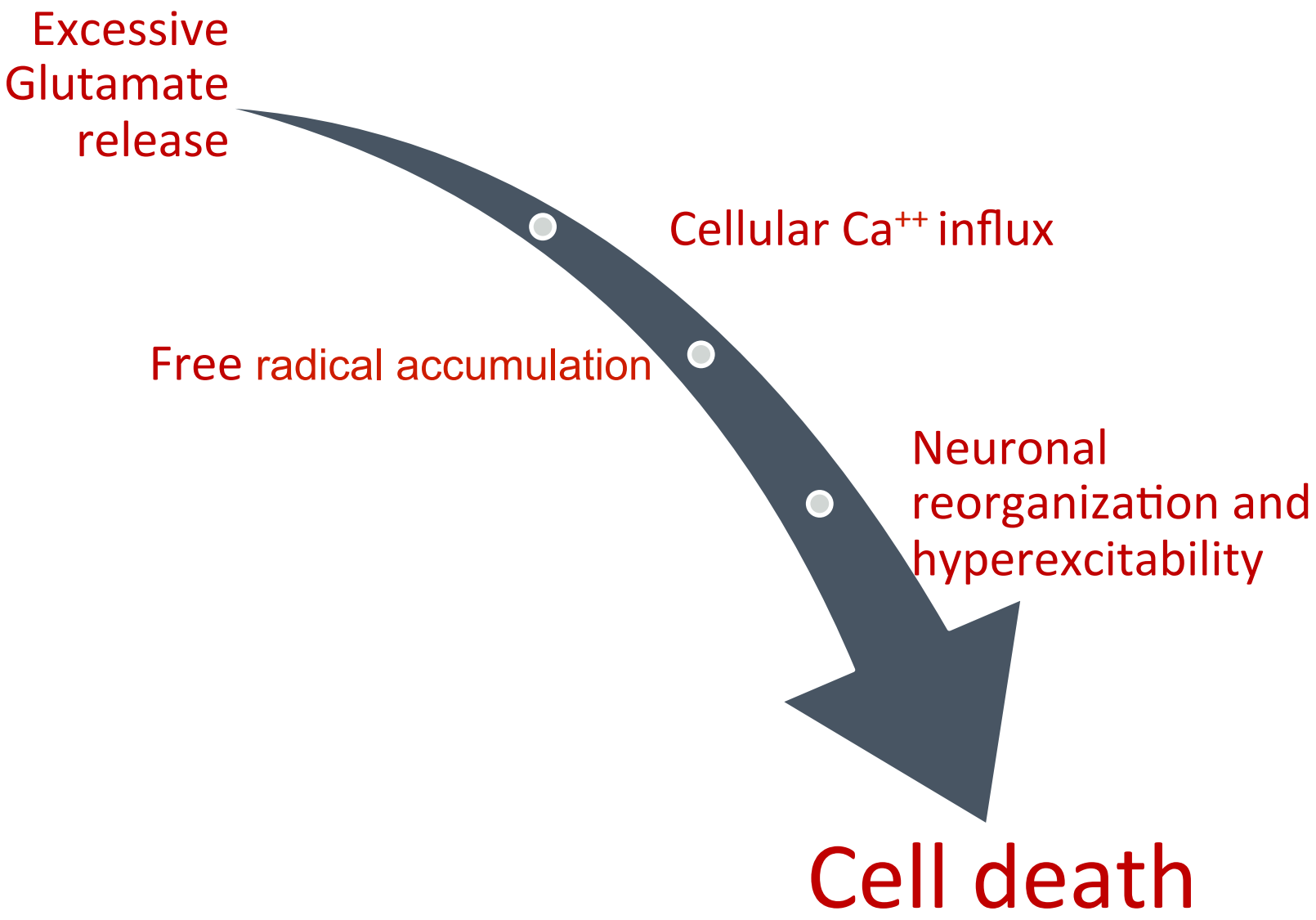


Trinka, Epilepsia 2015

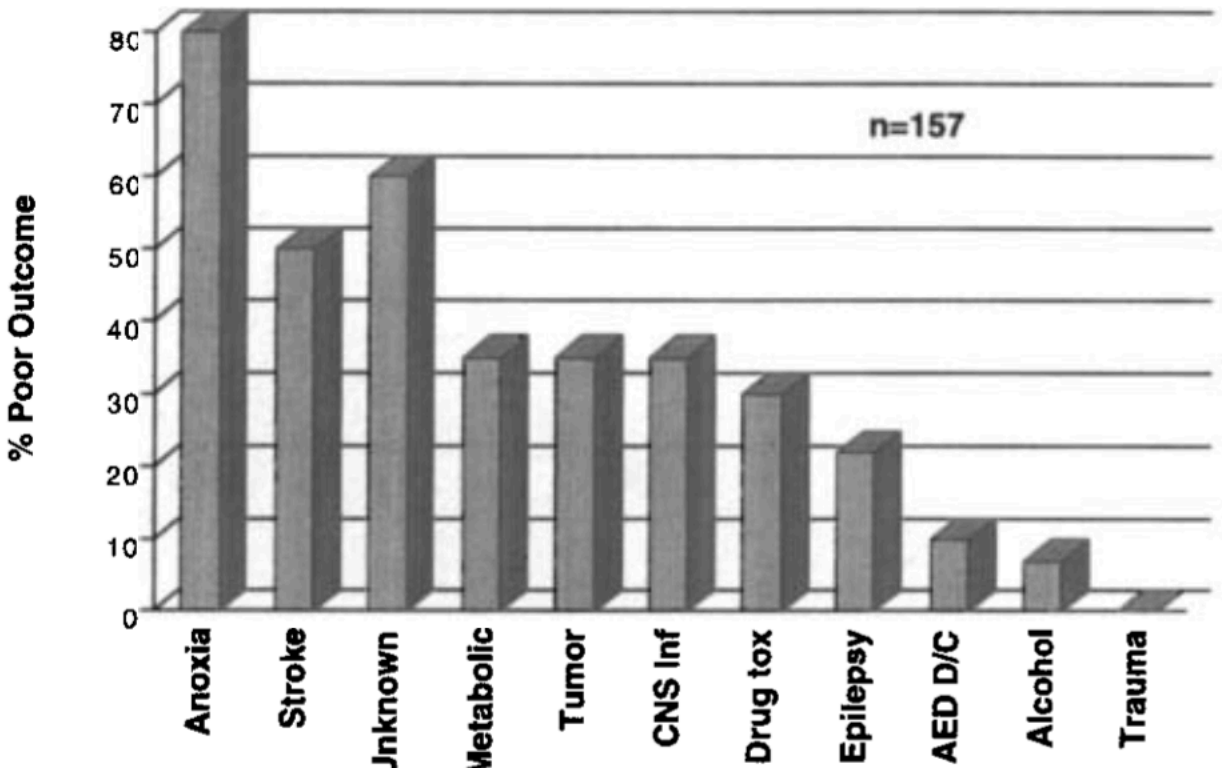
Why is Pre-hospital Treatment of SE Important?

- Longer duration → brain damage and sequelae
- Longer Duration and etiology are the main determinants of outcome
- Longer duration → lower chance of responding to subsequent AEDs
- Pre-hospital treatment → Improves outcomes

The Excitotoxic Cascade



Prognostic Factors in Status Epilepticus



Lowenstein, Epilepsia 1999

3 Main Risk Factors for Mortality

Factor	Odds Ratio	*p*
Duration >1 hour	9.8	0.003
Etiology: Anoxia	3.7	0.005
Age	1.4	0.02

Duration important across etiologies

Group	Good outcome	Poor outcome	p
	Duration	Duration	
All patients (min)	2.4	11.2	<0.01
AED W/D	1.7	4.6	0.05
Alcohol	1.5	4.1	<0.01
CNS Infection	1.7	18.5	0.05

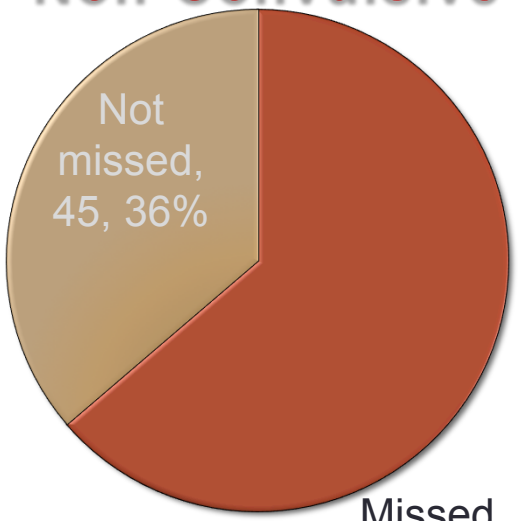
Recognizing Status Epilepticus

150 patients with SE

Swiss Hospital 10 years

Prehospital Diagnosis	SE Suspected	
Epileptic event	**67**	**45%**
SE	32	21%
Seizures	35	23%
No epileptic event	**83**	**55%**
Unknown type	37	25%
Stroke	39	26%
Cardiac event	4	3%
Traumatic brain injury	3	2%

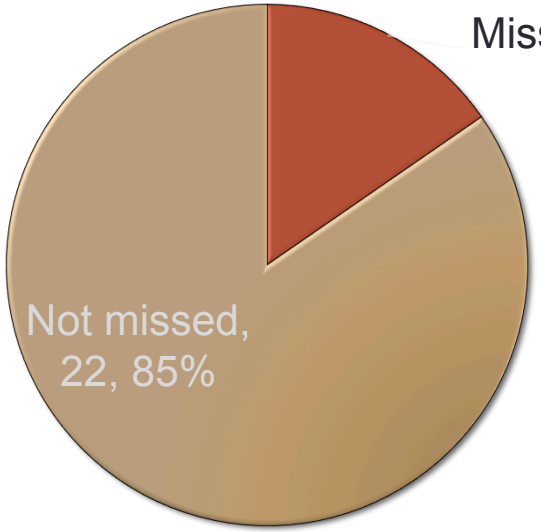
Non-Convulsive



All converted from Convulsive to Non-convulsive

Missed, 79, 64%

Convulsive



Semlack, Neurology 2017

Associations (multivariate*)

Missing SE	OR
• Age (each additional year)	1.06*
• No history of seizures	6.43*
• Fatal etiology	2.04
Not getting benzodiazepines	
• Age (each additional year)	1.05*
• Glasgow CS (each added point)	1.21*
• Missed SE diagnosis (20% vs 50%)	p< 0.001
No recovery to baseline	
• Missed SE diagnosis	3.83*
• Status severity score	1.35*

84% accurate in predicting a Missed Diagnosis of SE

3 things to remember

1. CSE is recognized, but NCSE is frequently missed
2. NCSE is missed with older age and no seizure history
3. Missed NCSE → lack of treatment and no recovery to functional baseline

Semlack et al, Neurology 2017

AVOIDING MISSED DIAGNOSIS

ETIOLOGY?
Most important determinant of Mortality

EMS TRAINING?
might improve detection
What kind of training

EEG – PORTABLE?
Feasible, interpretation?

BENZOS IF ↓LOC?
Risk of overtreatment, morbidity, unnecessary intubation, hospitalization

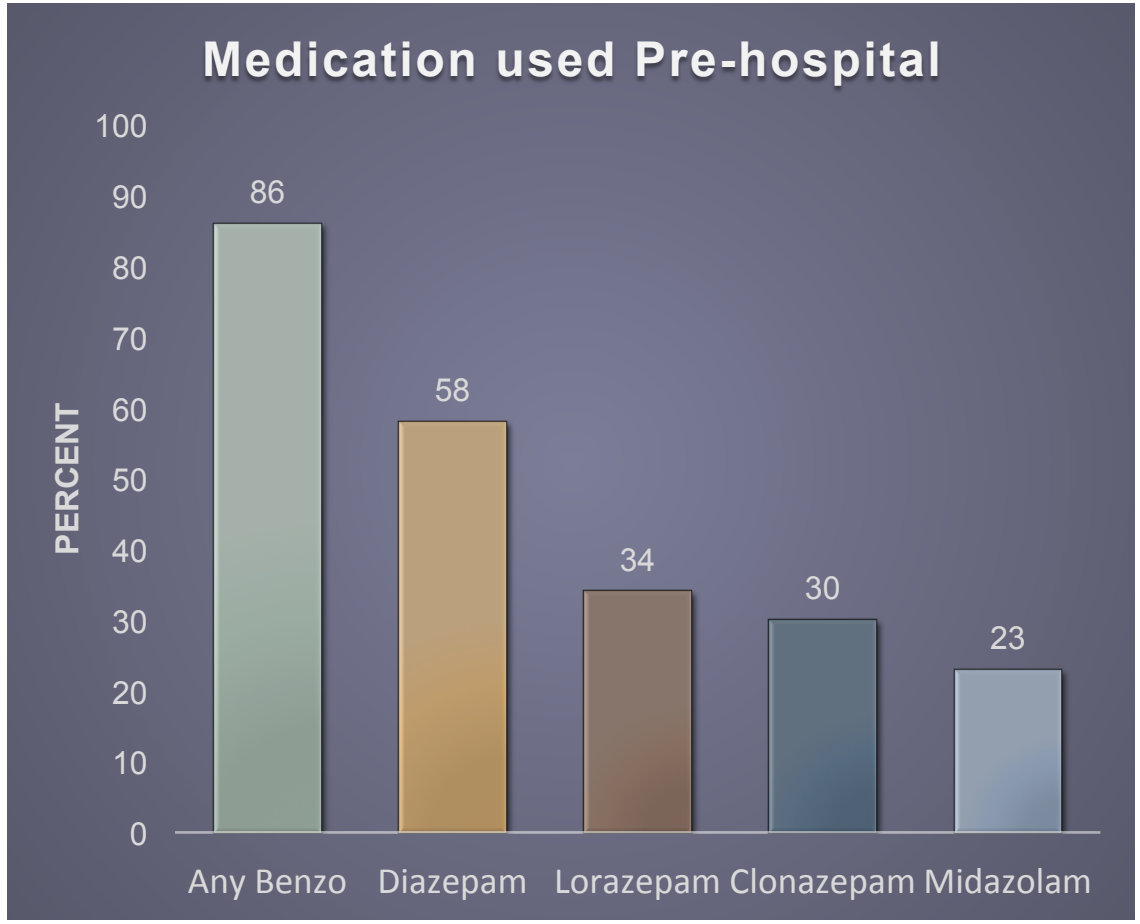
PSYCHOGENIC?
Challenging management, risk of overtreament

FOCUS ON CSE?
Worse consequences of missing diagnosis than NCSE

Semlack, Neurology 2017

15 studies on timing to treatment

- Time to treatment
  - Prehospital Median 35 min (22 to 70)
  - Hospital Median 8 min
- Prehospital treatment
  - 52% by EMS, 13 % by Family
  - 67% by Family if history of CSE
- Later treatment
  - Longer seizures
  - Decreased response to Benzos
  - Increased in-hospital mortality



Gainza-Lein et al, Seizure 2018

Factors related to delays in Pre-hospital management

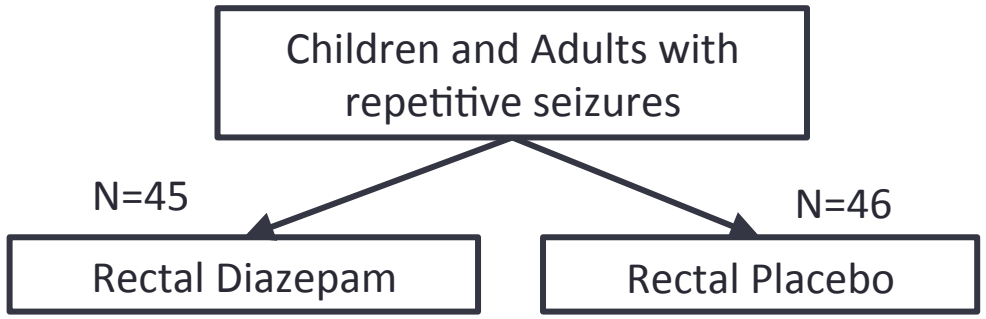
- 92 patients, CSE, Helsinki area
- Delays in management
  - Focal seizures → delay diagnosis, treatment, anesthesia
  - Non-tertiary care hospital

Variable	Time median	Range min–max
Onset-to-initial-treatment	35 min	0 min–77 h 5 min
Onset-to-first-ED	2 h 2 min	0 min–58 h 29 min
Onset-to-tertiary-hospital	2 h 25 min	37 min–277 h 40 min
Onset-to-diagnosis	2 h 10 min	6 min–70 h 40 min
Onset-to-anesthesia	2 h 55 min	0 min–81 h 45 min

Kämppi et al, Neurocritical care 2015

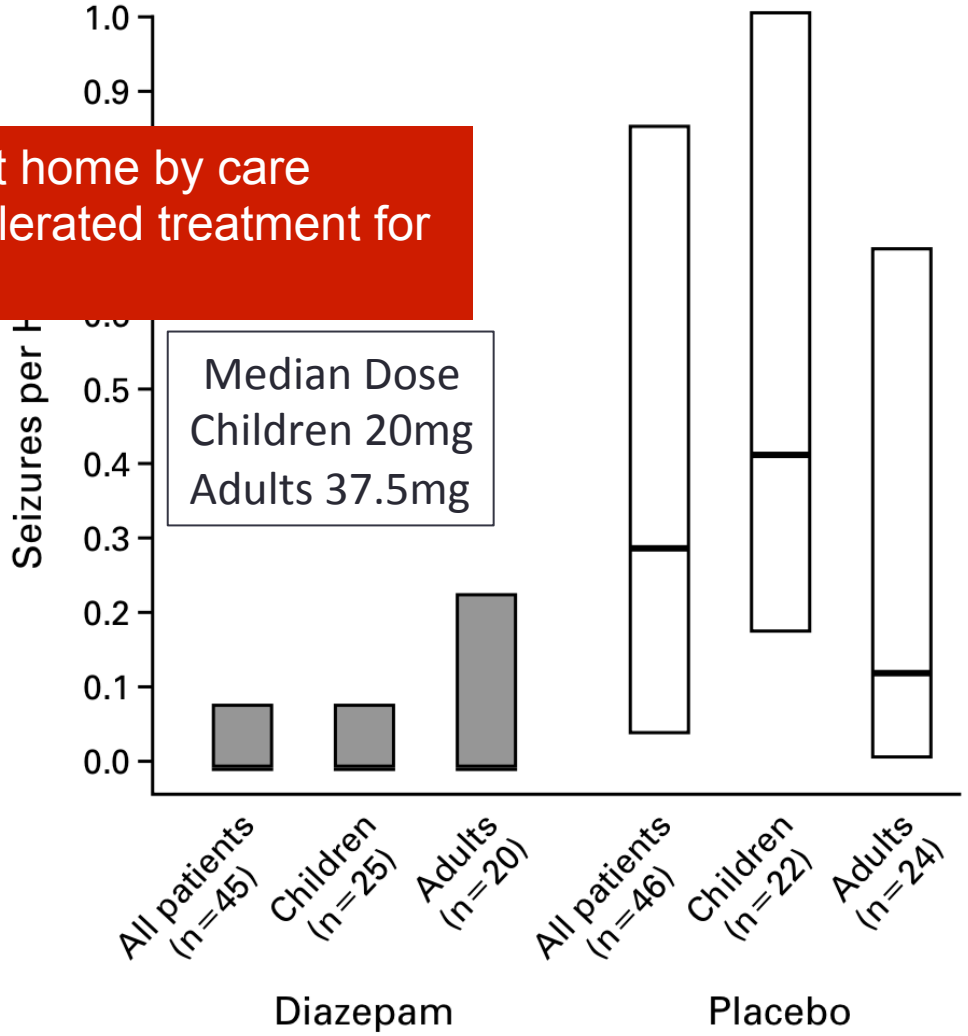
Rectal Diazepam vs Placebo

Dreifuss et al, NEJM 1998



Time to Recur

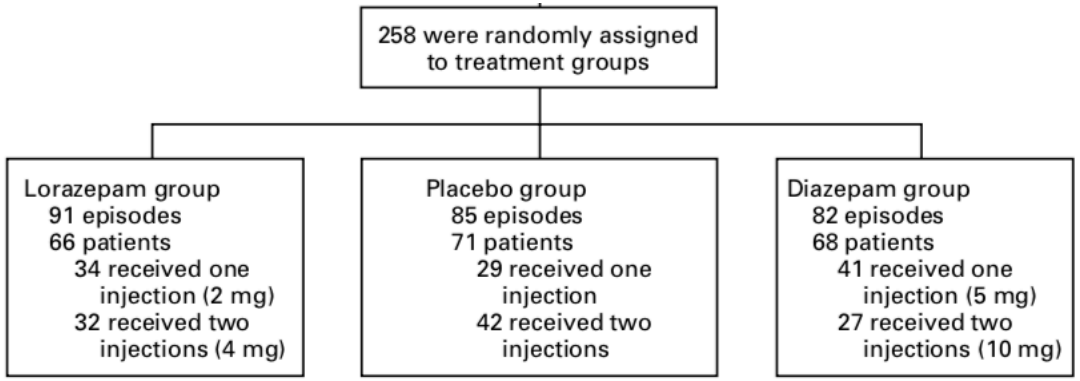
Rectal diazepam administered at home by care givers, is an effective and well tolerated treatment for acute repetitive seizures



The New England
Journal of Medicine

VOLUME 345 AUGUST 30, 2001 NUMBER 9

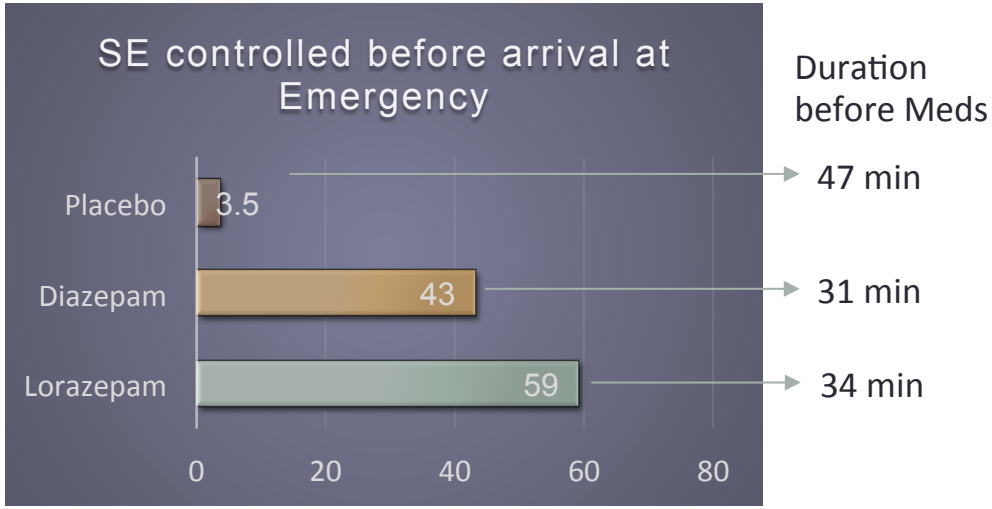
INTRAVENOUS



LZP 2 → 4 mg DZP 5→ 10 mg

- 258 episodes in 205 patients
- Adults, Convulsive SE
- Trained EMS personnel
- Randomized, controlled, blinded

Benzodiazepines are safe and effective out-of-hospital Lorazepam is likely to be a better therapy than diazepam.



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 FEBRUARY 16, 2012 VOL. 366 NO. 7

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Silbergleit et al 2012

- 4314 paramedics in 79 receiving hospitals in USA
- Randomized, controlled, blinded, non inferiority
- Excluded: trauma, hypoglycemia, cardiac arrest, bradycardia <40 per minute, allergy, pregnant

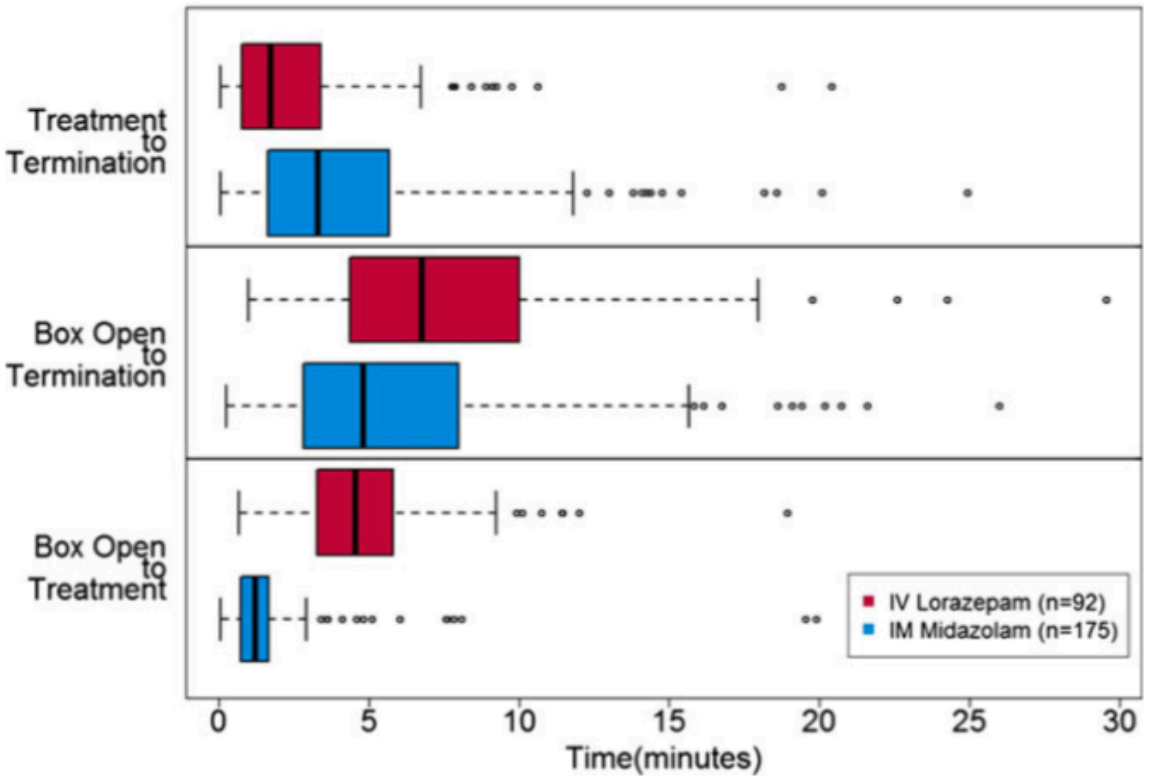
- BTC Seizure >5 minutes
- Randomization
  - 448 = 20 mg MDZ IM + IV placebo
  - 445 = 4 mg LZP IV + IM placebo

	MDZ	
Hospitalization		
No. of subjects — %	258 (57.6)	
Relative risk (95% CI)	0.88 (0.79–0.98)	
ICU admission		
No. of subjects — %	128 (28.6)	161 (36.2)
Relative risk (95% CI)	0.79 (0.65–0.95)	

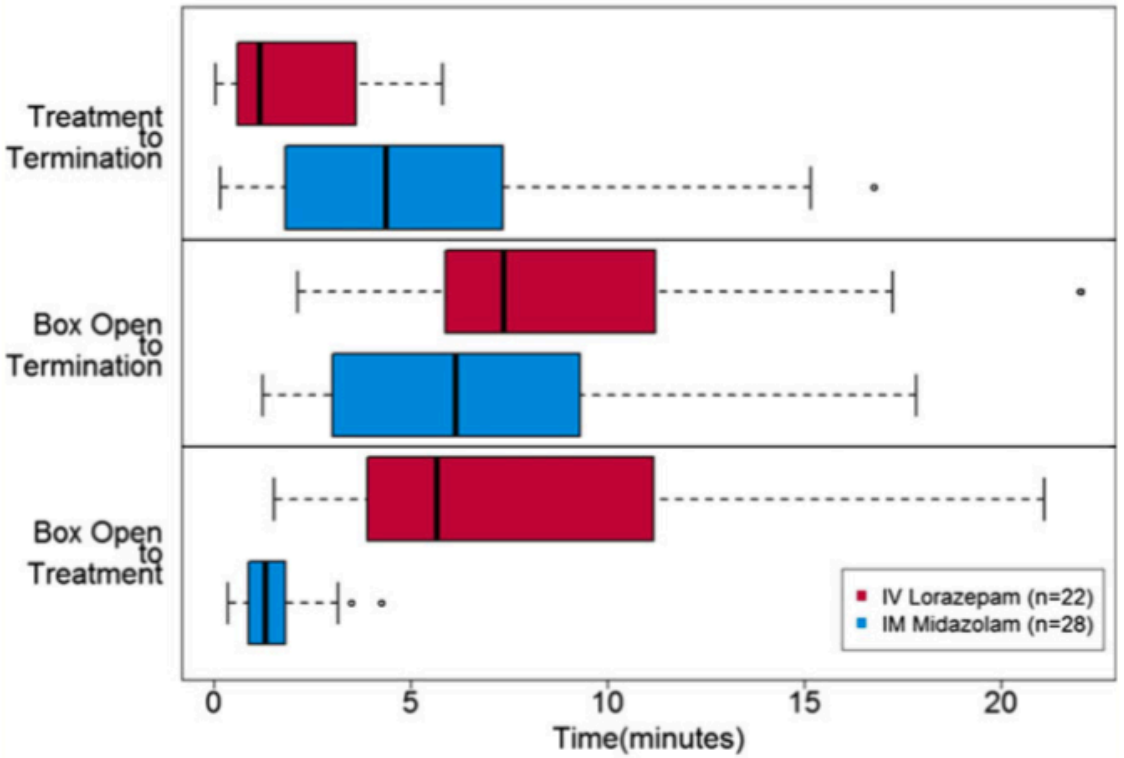
IM Midazolam is at least as safe and effective as IV Lorazepam

Same study: Patients <18 years

Adults



<18 years old (n=120)



Seizures controlled
- 68% MDZ vs 71% LZP

Welch et al, Epilepsia 2015

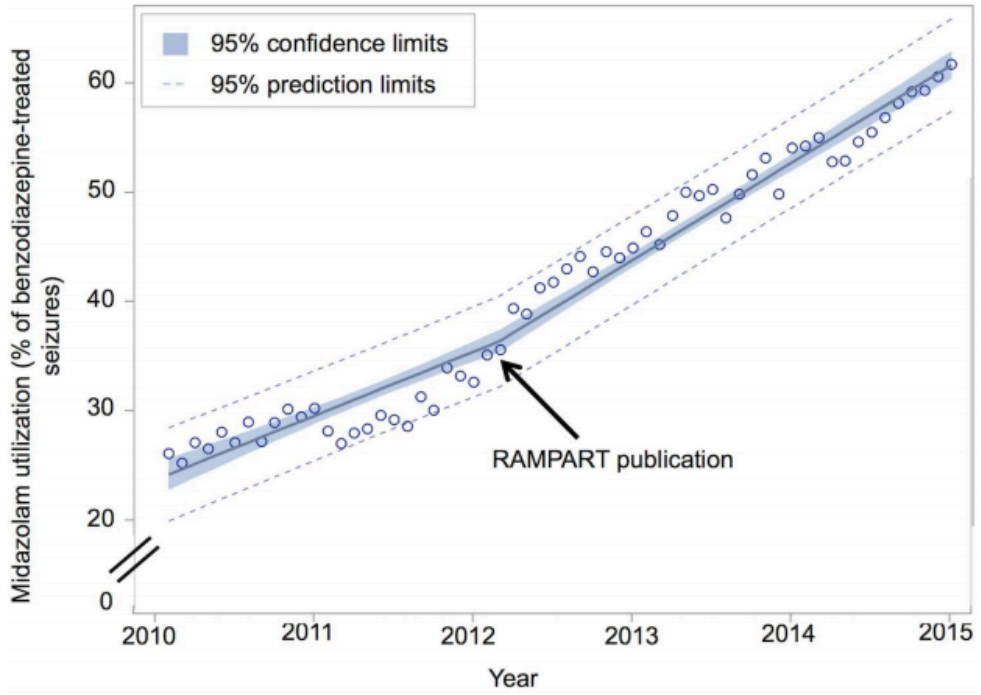
Pre-hospital midazolam for benzodiazepine-treated seizures before and after the Rapid Anticonvulsant Medication Prior to Arrival Trial: A national observational cohort study

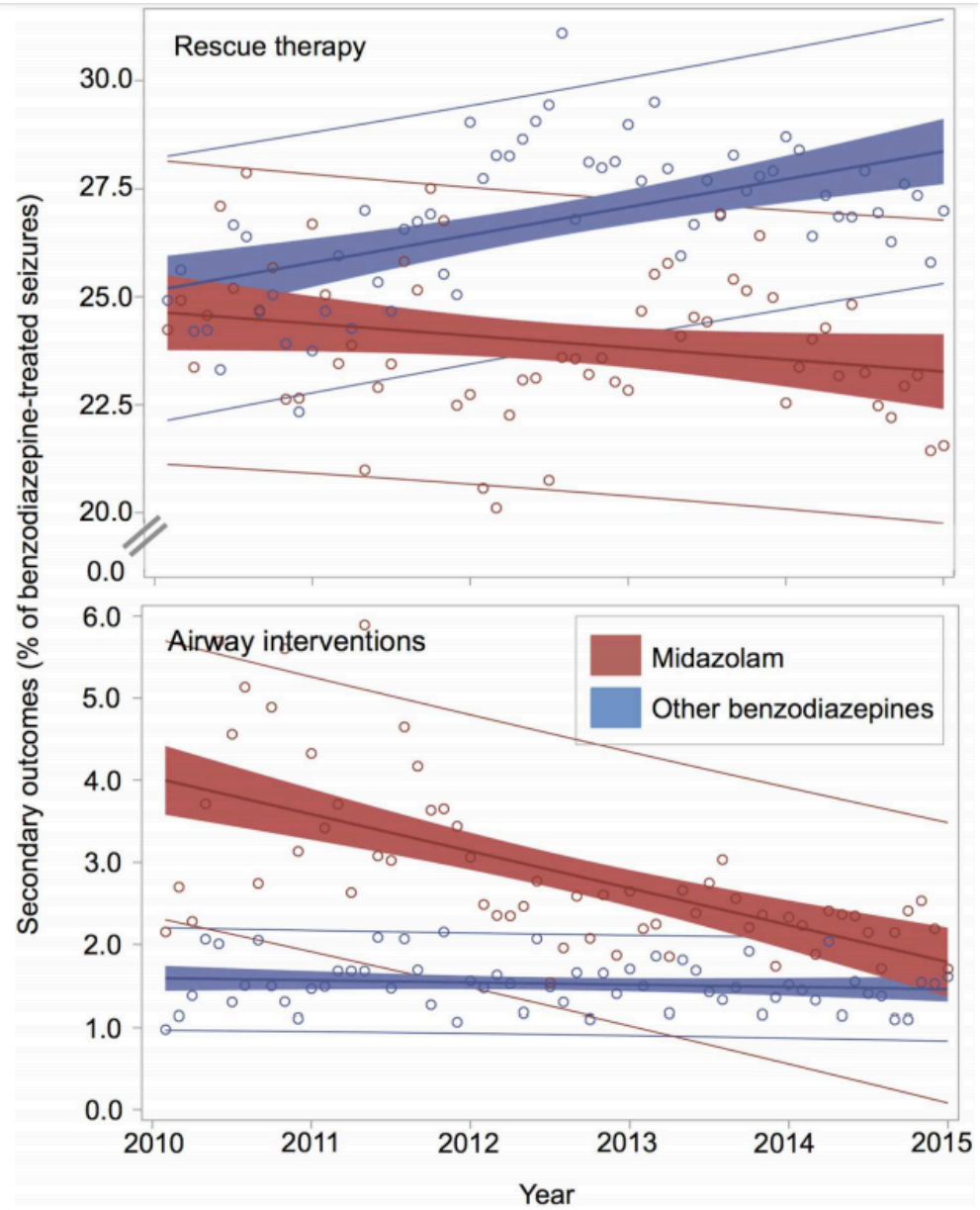
Eytan Shtull-Leber[1☯], Robert Silbergleit[2], William J. Meurer[3☯*]

PLOS ONE

2017

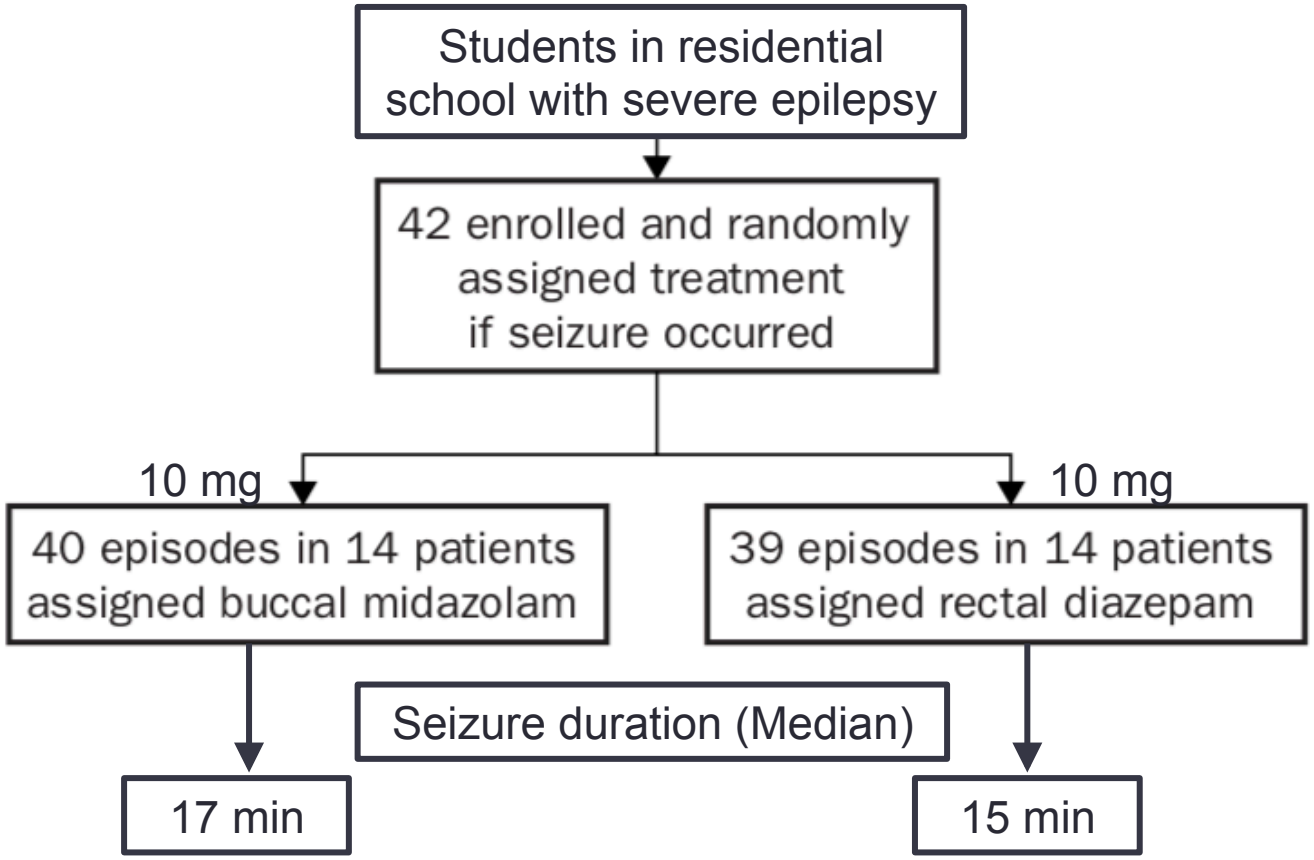
- Observational cohort in United States --2010 through 2014
- Rates of midazolam use as first-line treatment over time
- 156,539 benzodiazepine-treated seizures
- Midazolam use increased from 26.1% in 2010 to 61.7% in 2014
- Rescue therapy and airway interventions declined over time





Stuhli-Leber et al, PLOSone 2017

Buccal Midazolam vs Rectal Diazepam in Children



- Buccal midazolam is at least as effective as rectal diazepam
- More socially acceptable and convenient
- preferred treatment for outside hospital treatment

Scott et al, Lancet 1999