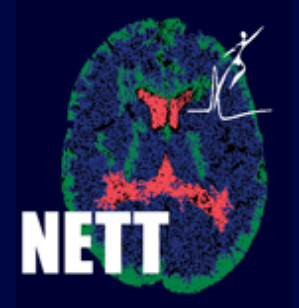


The Rapid Anticonvulsant Medications Prior to Arrival Trial



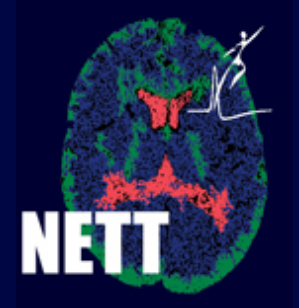
This work was primarily supported by award 5U01NS056975-04 from the National Institute of Neurological Disorders and Stroke (NINDS), the Office of the Director, National Institutes of Health (OD), BARDA, and the NIH CounterACT program

Seizures



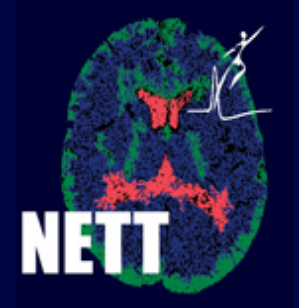
- Common
- Usually stop within a few minutes and without treatment
- Long-term damage is rare

Status Epilepticus



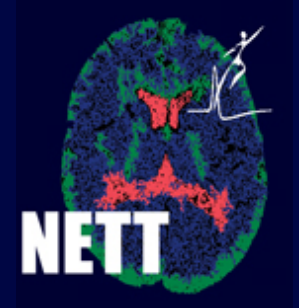
- >5 minutes of convulsions
- Up to 30% mortality
- Early treatment → easier to stop → better

Status Epilepticus



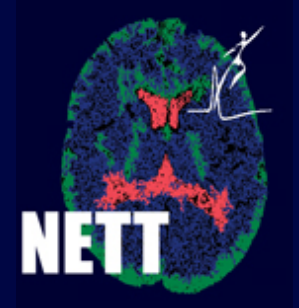
- >5 minutes of convulsions
- Up to 30% mortality
- Early treatment → easier to stop → better
- True EMS emergency

Status Epilepticus

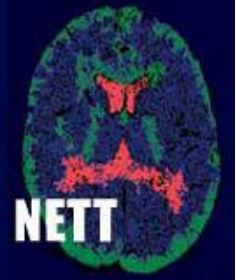


- Benzodiazepines are treatment of choice
 - Diazepam IV/IO/PR
 - Lorazepam IV/IO

Status Epilepticus



- Benzodiazepines are treatment of choice
 - Diazepam IV/IO/PR
 - Lorazepam IV/IO
 - Midazolam IM?



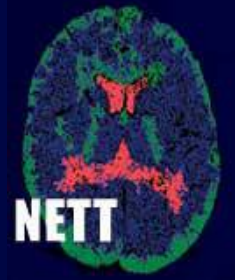
Aims

Primary Hypothesis

- IM midazolam is as effective as IV lorazepam at stopping convulsions prior to ED arrival

Secondary Hypotheses

- Convulsions stop more rapidly with treatment with IM midazolam versus IV lorazepam
- There is no difference in safety between the two treatments



Inclusions

- Convulsive seizure activity for > 5 minutes
- Patient is still seizing
- Estimated weight > 13 kg



Exclusions

- Major trauma precipitating seizure
- Hypoglycemia
- Known allergy to midazolam or lorazepam
- Sensitivity to benzodiazepines
- Cardiac arrest or heart rate <40 beats/minute
- Known pregnancy
- Prisoner

Randomized to:

IM Active
Treatment

or

IV Active
Treatment

IM Route

Autoinjector
midazolam

+

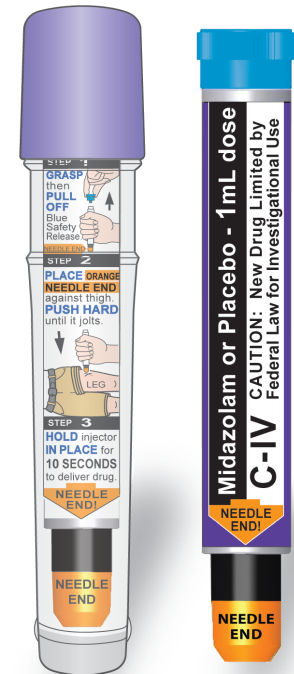
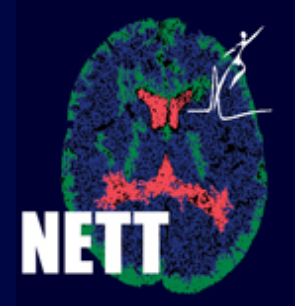
IV Route

IV syringe
placebo

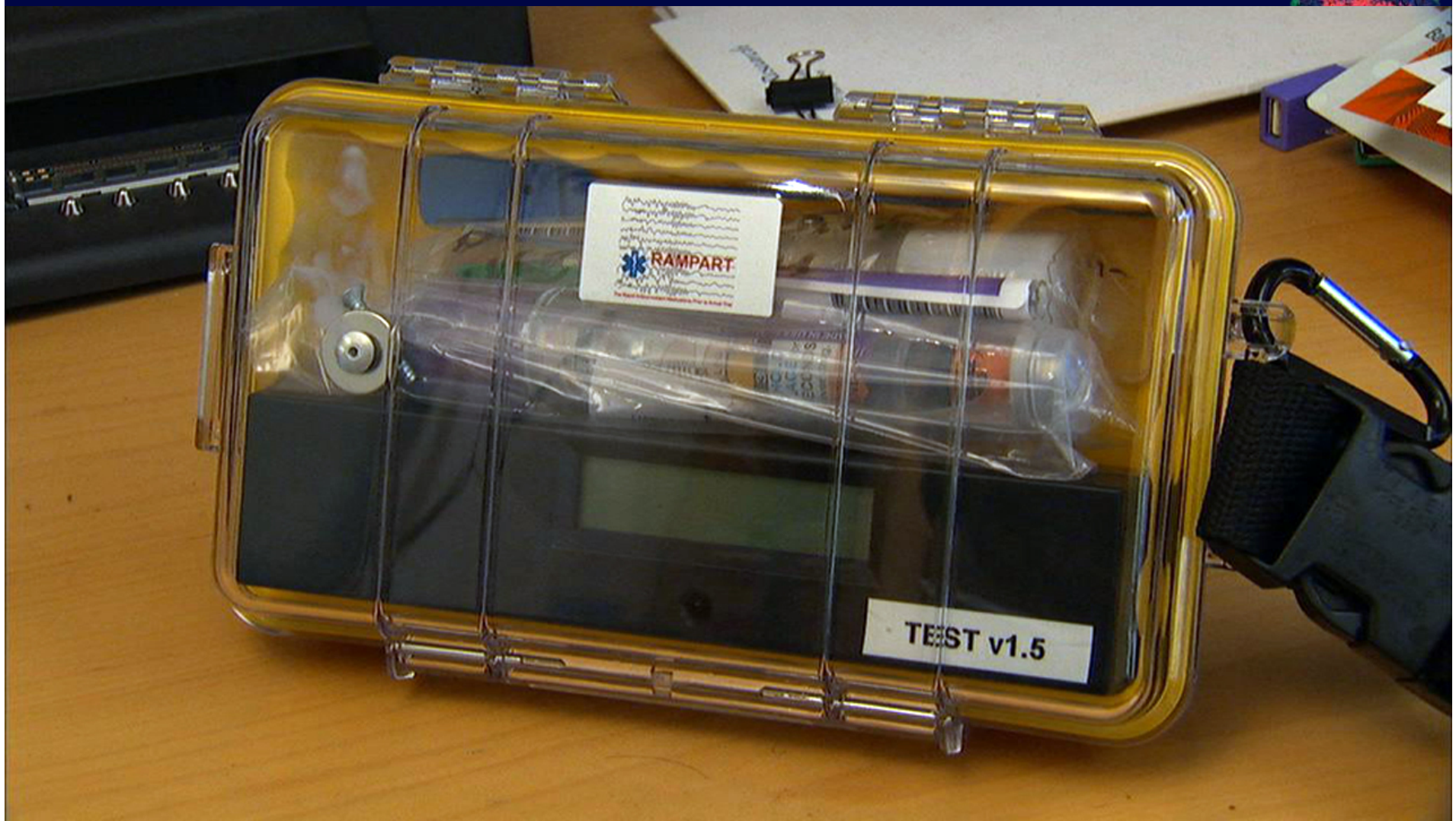
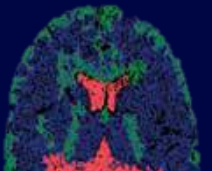
Autoinjector
placebo

+

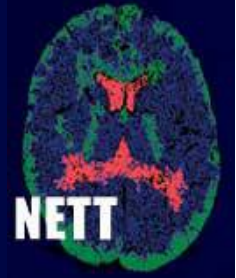
IV syringe
lorazepam



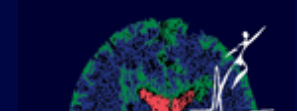
- Midazolam 5mg/10mg IM dose
- Lorazepam 2mg/4mg IV dose



EMS training and deployment



- 4,314 medics trained
- 40 EMS Services in 14 States
 - Fire Service (67%)
 - Third Service or Hospital Based (33%)
- Wide ranging EMS system sizes
 - >100,000 runs/year (20%)
 - <5,000 runs/year (27%)
- Ambulances, Supervisor Units, Engines



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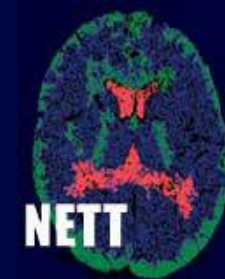
FEBRUARY 16, 2012

VOL. 366 NO. 7

Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D.,
Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

Enrollment

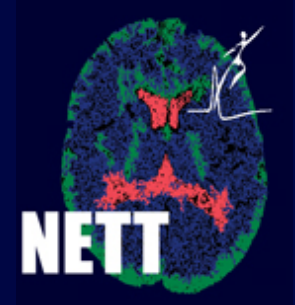


- 893 subjects were enrolled 1023 times
- Only the first enrollment of those enrolled more than once is included
- 732 in the Per Protocol (PP) population

Table 1. Characteristics of the Subjects at Baseline.*

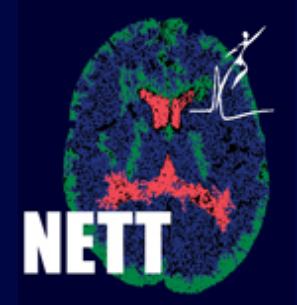
Characteristic	IM Midazolam (N = 448)	IV Lorazepam (N = 445)
Age		
Mean (range) — yr	43±22 (0–102)	44±22 (1–94)
Age group — no. (%)		
0–5 yr	32 (7)	29 (7)
6–10 yr	15 (3)	20 (4)
11–20 yr	28 (6)	21 (5)
21–40 yr	114 (25)	112 (25)
41–60 yr	169 (38)	169 (38)
≥61 yr	90 (20)	94 (21)
History of epilepsy — no. (%)		
Yes	293 (65)	295 (66)
No	111 (25)	103 (23)
Not documented	44 (10)	47 (11)
Final diagnosis — no. (%)		
Status epilepticus	404 (90)	399 (90)
Nonepileptic spell	31 (7)	32 (7)
Undetermined	13 (3)	14 (3)





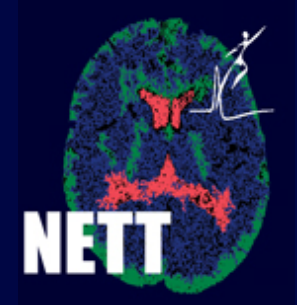
Outcome	Intention-to-Treat Analysis† (N = 893)	
	IM Midazolam (N = 448)	IV Lorazepam (N = 445)
Primary outcome		
Seizures terminated, no rescue therapy given		
No. of subjects	329	282
% of subjects (95% CI)‡	73.4 (69.3–77.5)	63.4 (58.9–67.9)

- Those given IM midazolam stopped seizing 10% more often.



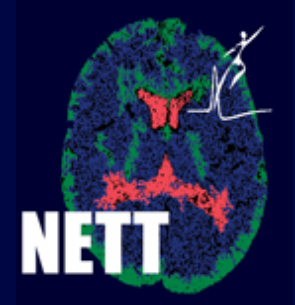
Outcome	Intention-to-Treat Analysis† (N = 893)	
	IM Midazolam (N = 448)	IV Lorazepam (N = 445)
Secondary outcomes		
Endotracheal intubation within 30 min after ED arrival		
No. of subjects — %	63 (14.1)	64 (14.4)
Relative risk (95% CI)	0.98 (0.70–1.34)	

- No difference in need to intubate
- Intubation rate less than previous studies



Outcome	Intention-to-Treat Analysis† (N = 893)	
	IM Midazolam (N = 448)	IV Lorazepam (N = 445)
Secondary outcomes		
Recurrent seizure within 12 hr after ED arrival		
No. of subjects — %	51 (11.4)	47 (10.6)
Relative risk (95% CI)	1.08 (0.74–1.56)	
Hypotension		
No. of subjects — %	12 (2.7)	13 (2.9)
Relative risk (95% CI)	0.92 (0.42–1.98)	

- No difference in recurrent seizures or hypotension



Outcome	Intention-to-Treat Analysis† (N = 893)	
	IM Midazolam (N = 448)	IV Lorazepam (N = 445)
Secondary outcomes		
Hospitalization		
No. of subjects — %	258 (57.6)	292 (65.6)
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 treated patients less likely to be admitted or go to the ICU

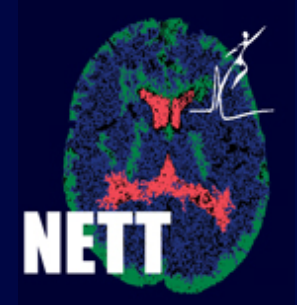
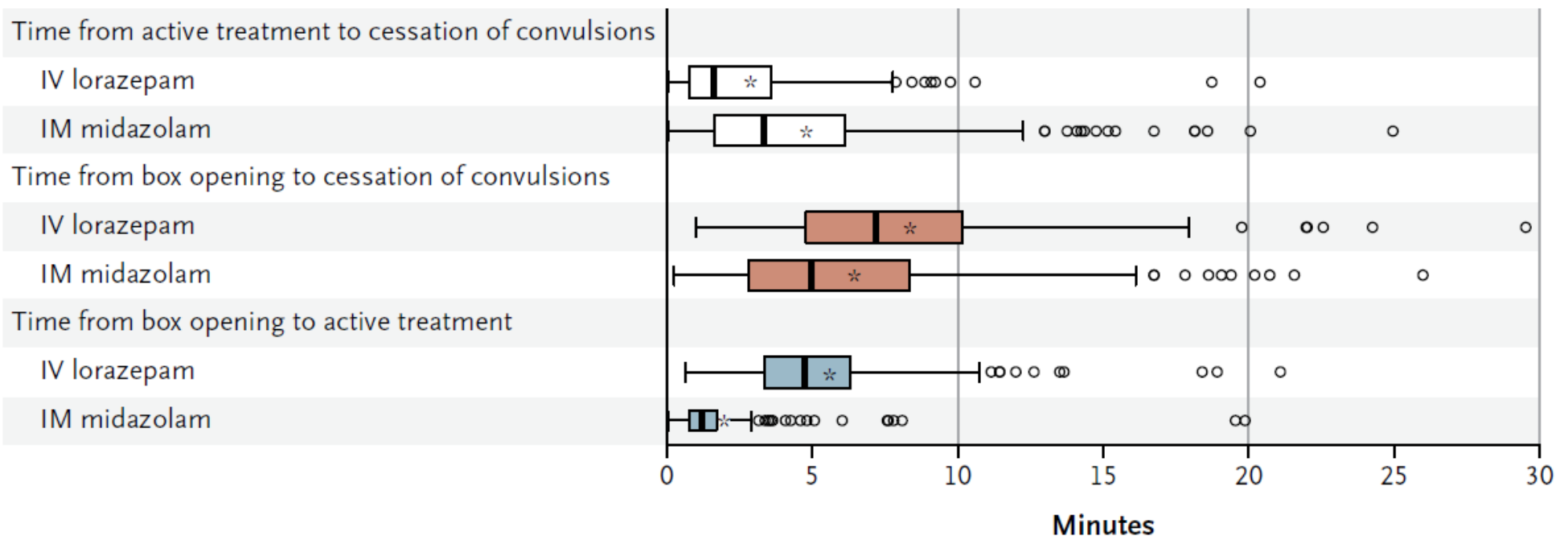
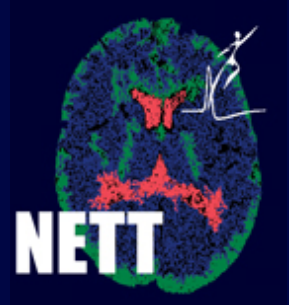


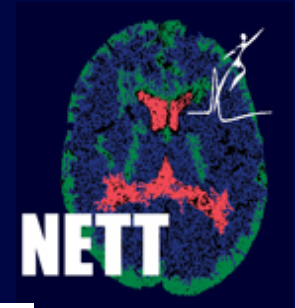
Figure 3. Intervals between Active Treatment and Cessation of Convulsions, Box Opening and Cessation of Convulsions, and Box Opening and Active Treatment.



- IM given in 1.2 minutes
- IV given in 4.8 minutes

In conclusion, intramuscular midazolam is noninferior to intravenous lorazepam in stopping seizures before arrival in the emergency department in patients with status epilepticus treated by paramedics. Intramuscular midazolam is also as safe as intravenous lorazepam. The group of subjects treated with intramuscular midazolam had a higher rate of discharge from the emergency department than the group treated with intravenous lorazepam and had similar or lower rates of recurrent seizures and endotracheal intubation. The intramuscular administration of midazolam by EMS is a practical, safe, and effective alternative to the intravenous route for treating prolonged convulsive seizures in the prehospital setting.





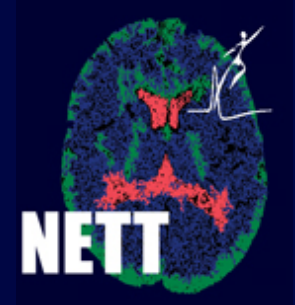
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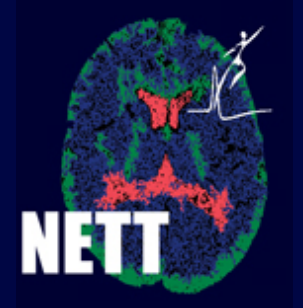


Intramuscular versus Intravenous Benzodiazepines for Prehospital Treatment of Status Epilepticus

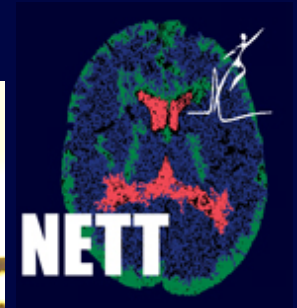
Lawrence J. Hirsch, M.D.



The study reported by Silbergleit and colleagues is an important step in this direction. As soon as a practical intramuscular autoinjector for midazolam becomes widely available, the findings in this study should lead to a systematic change in the way patients in status epilepticus are treated en route to the hospital.



On behalf of the entire RAMPART team,
THANK YOU for your trust and dedication.
Together, we have changed medicine.



Jason.McMullan@uc.edu

IV not administered

		IM N=448	IV N=445
IV not administered	n(% of total ITT)	216 (48%)	148 (33%)
Reason			
n(% of total ITT)			
Seizure stopped before IV could be started		174 (39%)	95 (21%)
Medics unable to start IV before ED arrival		27 (6%)	42 (9%)
Other		15 (3%)	11 (2%)