



National Institute of
Neurological Disorders
and Stroke

NIH Counter**ACT**
Program

Status Epilepticus after Benzodiazepines: Seizures and Improving Long-term Outcomes

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Benzodiazepine-Refractory Status Epilepticus-Mechanisms and Treatment

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Status Epilepticus after Benzodiazepines: Seizures and Improving Long-term Outcomes



Disclaimer

This certifies that the views expressed in this presentation are those of the author and do not reflect the official policy of NIH.

Disclosure

This certifies that I, Jaideep Kapur, have financial relationship that is relevant to the subject matter of the presentation disclosed in the next slide

- Consulting on DSMB Marinus Pharmaceuticals: DSMB
- NIH review panel (CNNT); Grants from NIH
- UVA Brain Institute.
- ILAE North America Board
- American Epilepsy Society Board
- National Advisory Committee, AMFDP, Robert Wood Johnson Foundation
- Received Counter ACT & DOD funding 2006-2013

Status Epilepticus: Research Opportunities

- Why is the apparent incidence of status epilepticus increasing so rapidly?
- Why do NH Black Americans bear a disproportionate burden of SE?
- What receptors and ion channels can be targeted with FDA approved drugs for clinical trials?
- What is the pathophysiology of refractory status epilepticus?
- What are the alternatives to prolonged anesthesia?
- How do we treat non convulsive status epilepticus?

Disparities in Status Epilepticus

The 2010-2019 Nationwide Inpatient Sample data to identify hospitalizations with SE using ICD-9-CM/ICD-10-CM codes.

There were **486,861** SE hospitalizations from 2010-2019, primarily at urban teaching hospitals (71.3%).

SE prevalence was calculated and stratified by demographics.

Logistic regression was used to assess factors associated with EEG monitoring, intubation, tracheostomy, gastrostomy and mortality



Gabriela B Tantillo
Sepulveda, M.D.,
M.P.H. Baylor College
of Medicine

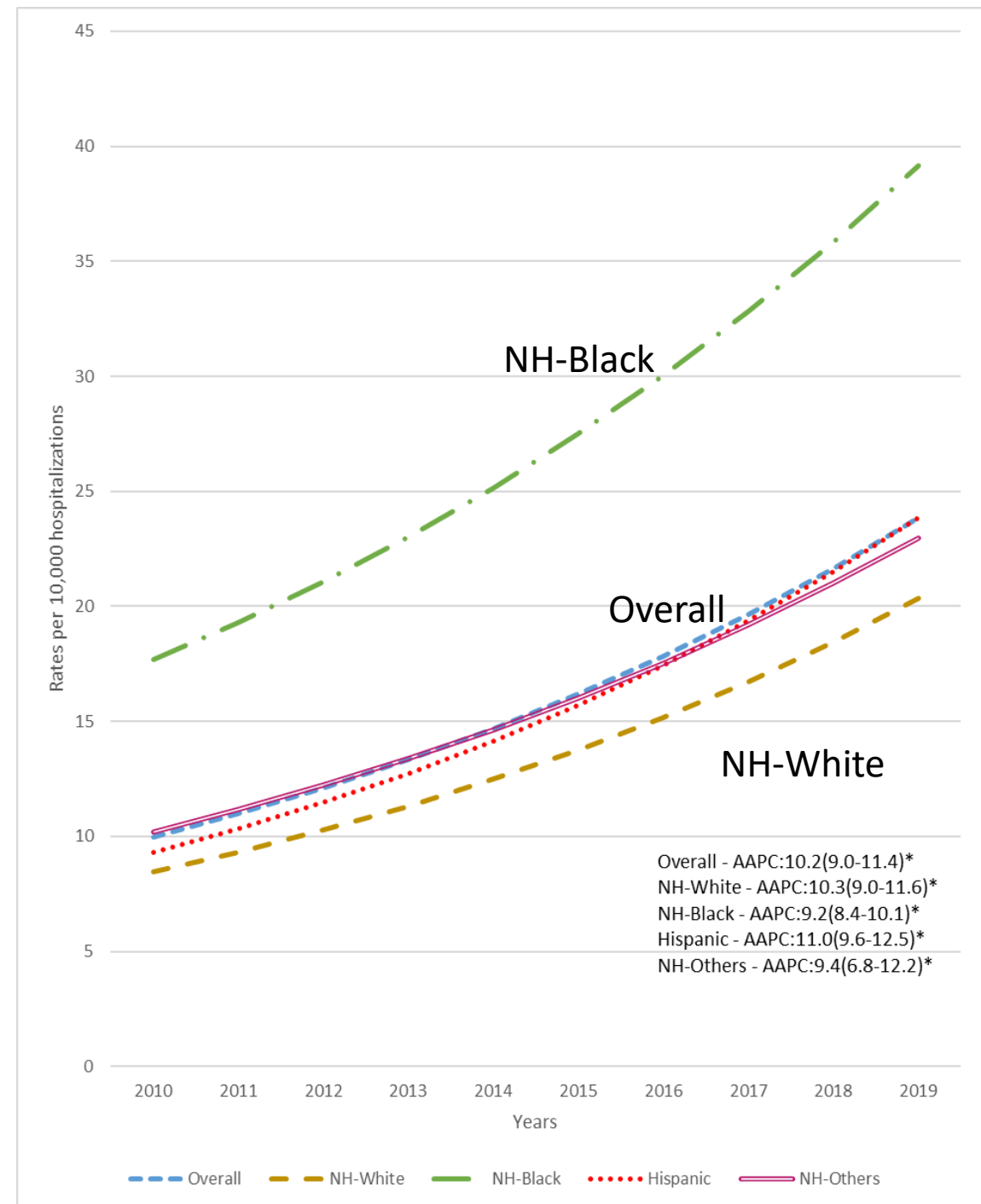
SE Hospitalizations

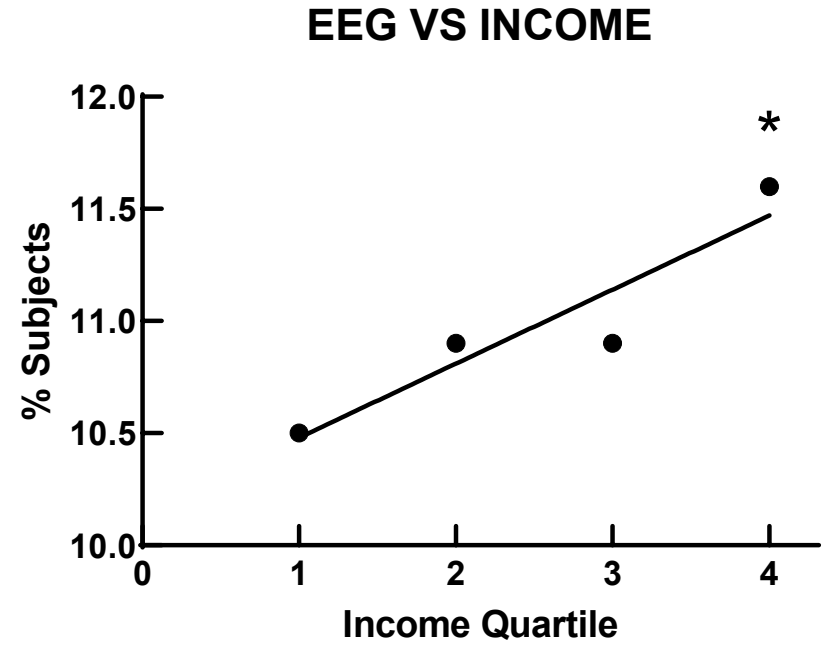
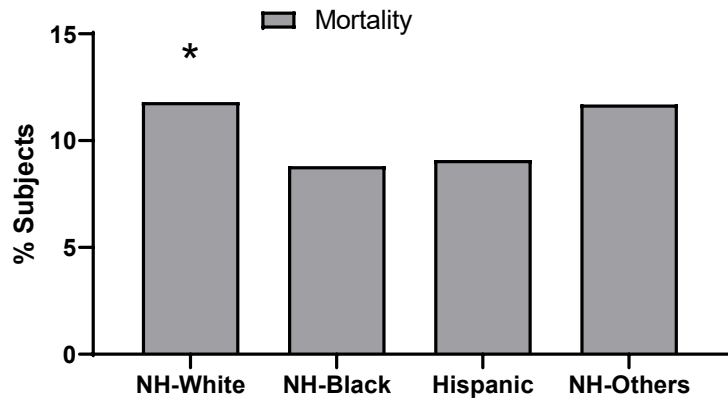
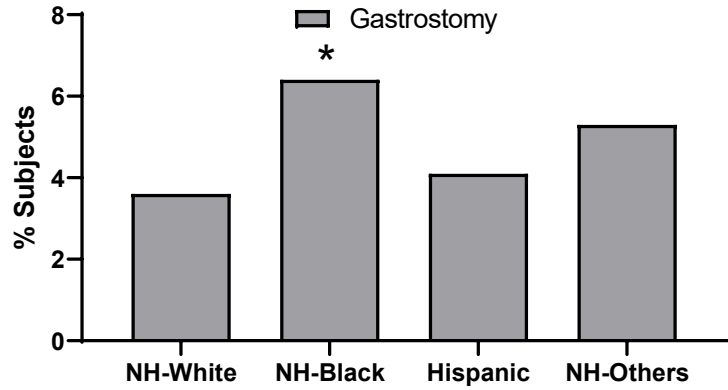
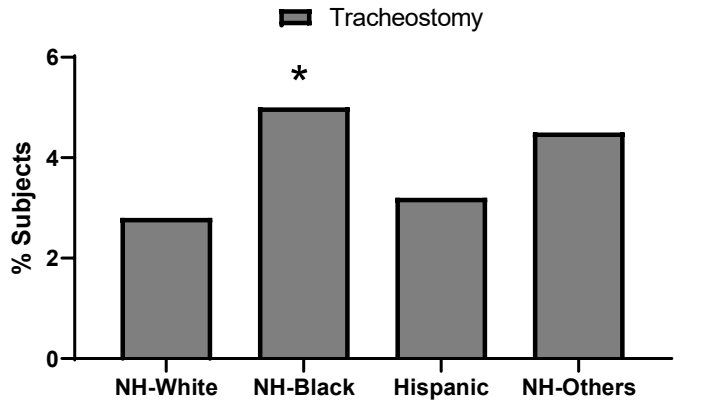
Annual Average Percentage Change

- Overall - AAPC:10.2(9.0-11.4)*
- NH-White - AAPC:10.3(9.0-11.6)*
- NH-Black - AAPC:9.2(8.4-10.1)*
- Hispanic - AAPC:11.0(9.6-12.5)*
- NH-Others - AAPC:9.4(6.8-12.2)*

1996 Richmond Study of 43% White 57% Non White population
But among those who had SE 80% were Non White

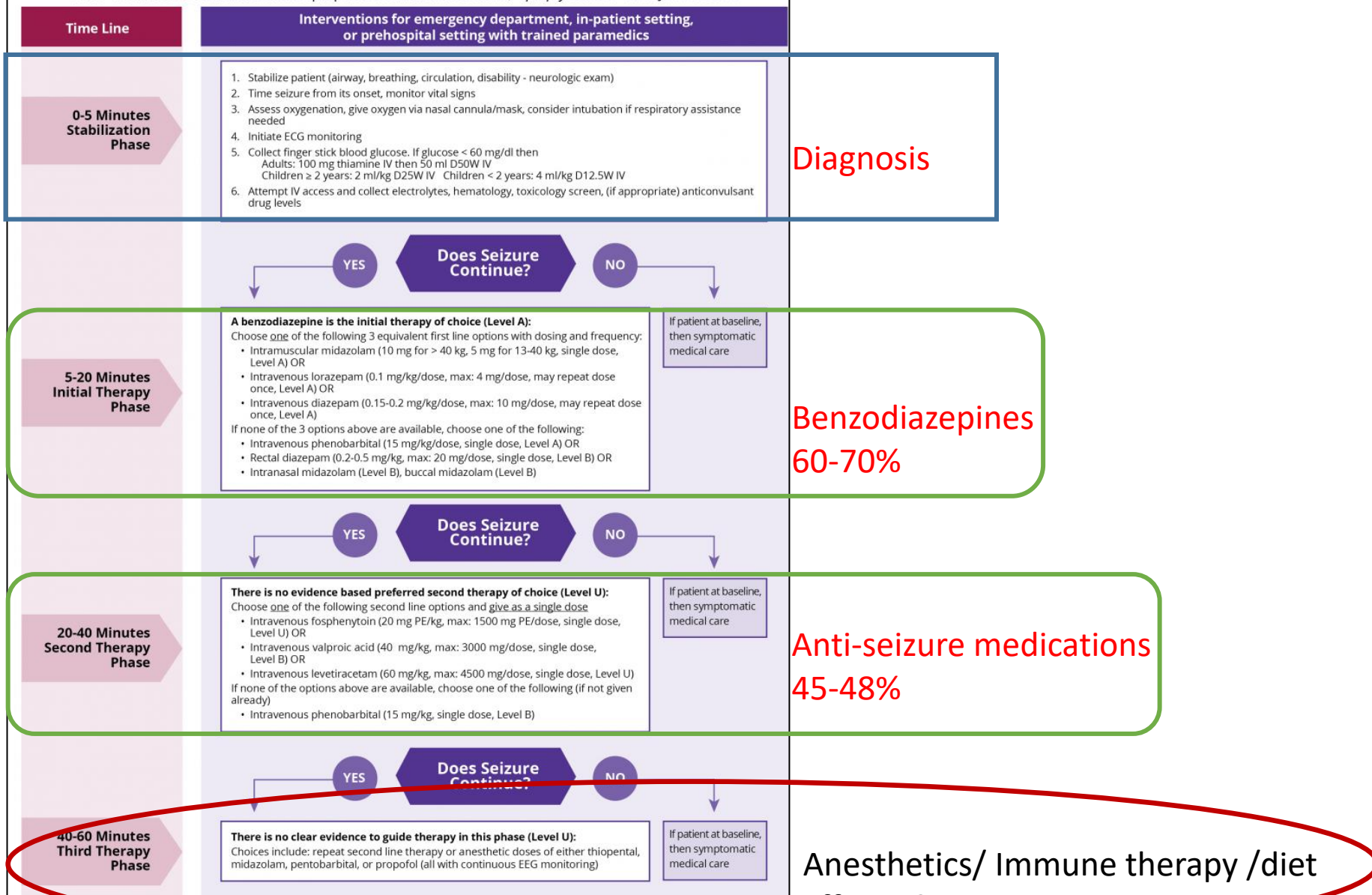
Betjeman et al. PMID: 25915004





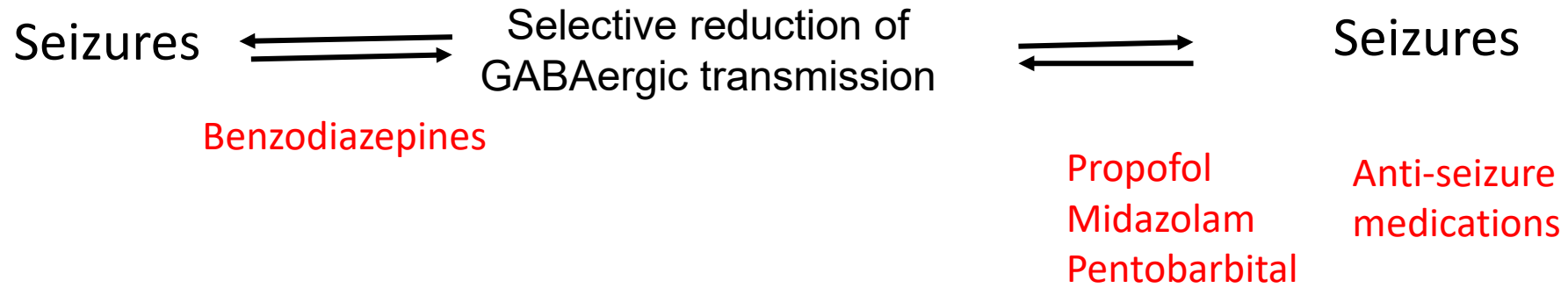
Proposed Algorithm for Convulsive Status Epilepticus

From "Treatment of Convulsive Status Epilepticus in Children and Adults," *Epilepsy Currents* 16.1 - Jan/Feb 2016

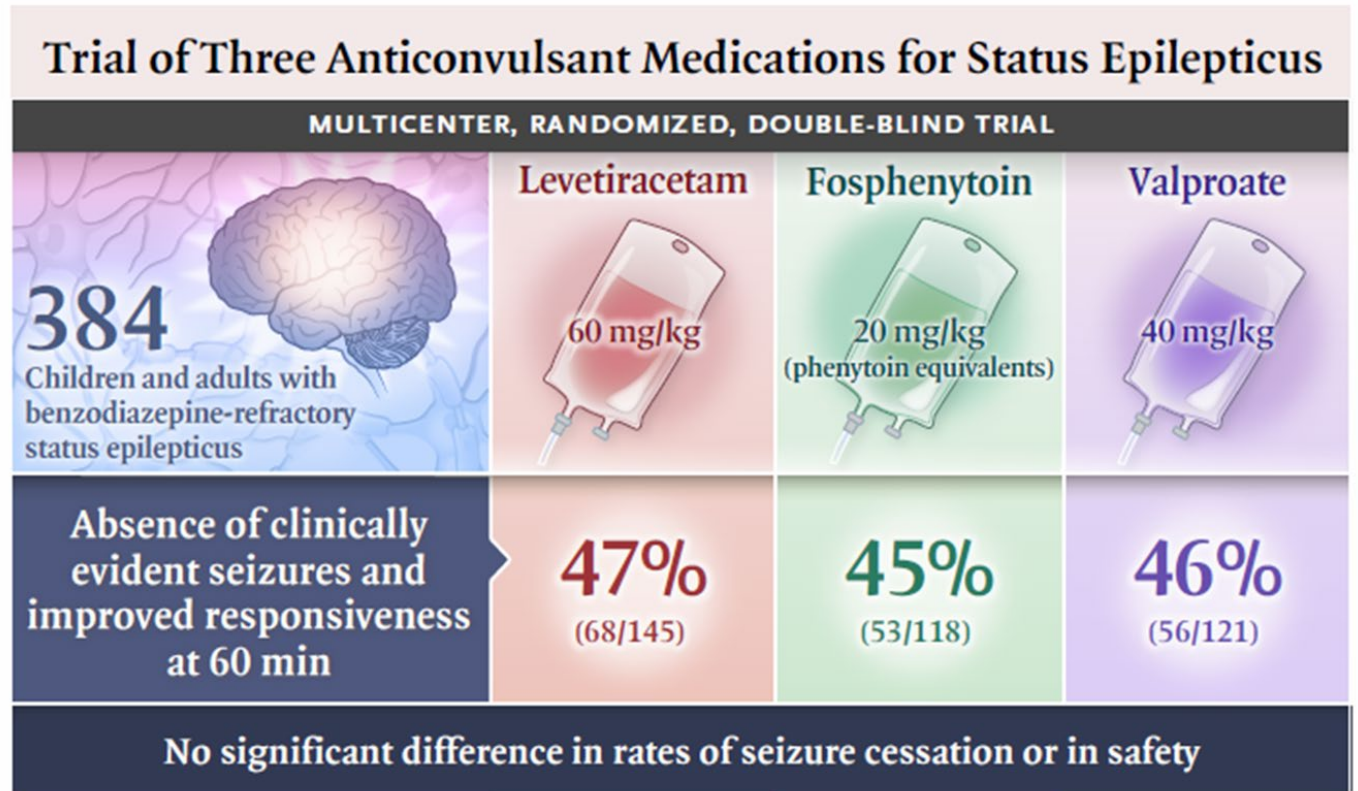


Disclaimer: This clinical algorithm/guideline is designed to assist clinicians by providing an analytic framework for evaluating and treating patients with convulsive status epilepticus. It is not intended to establish a community standard of care, replace a clinician's medical judgment, or establish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

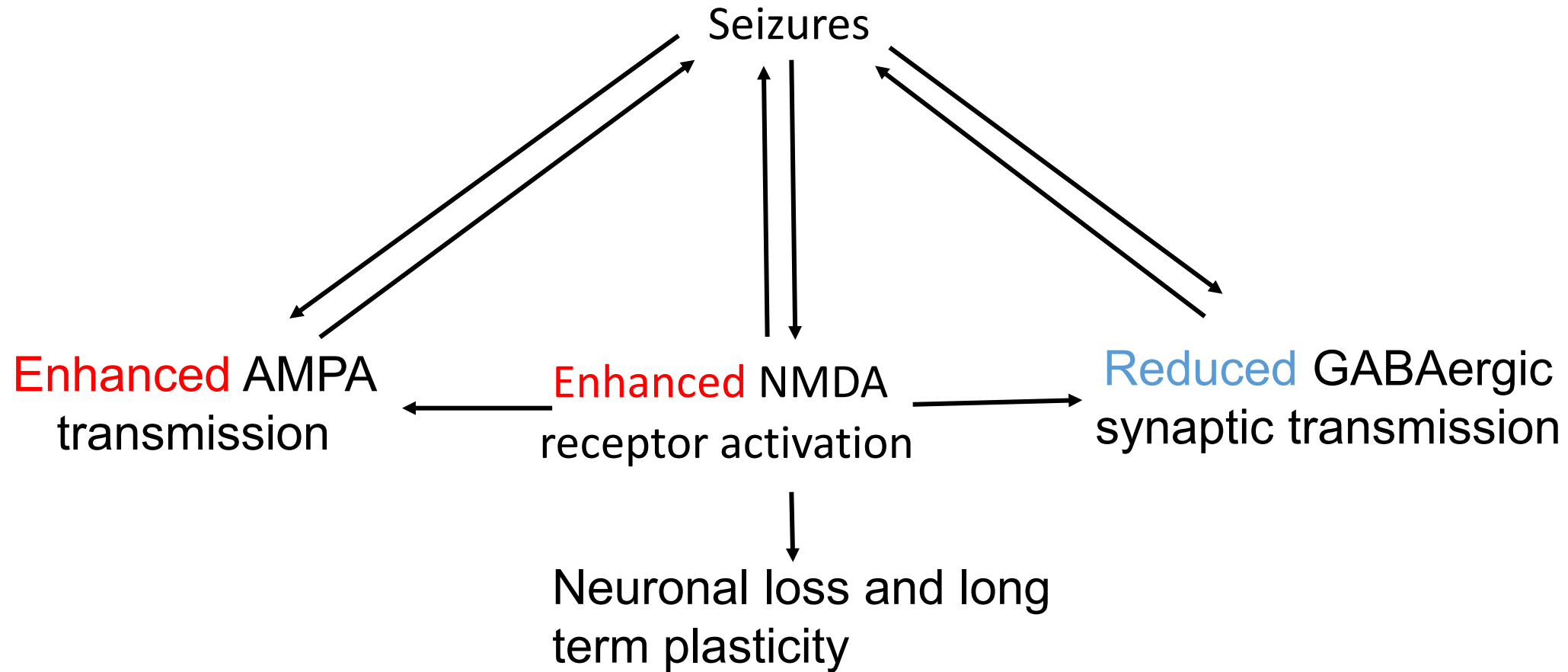
2016 © Epilepsy Currents



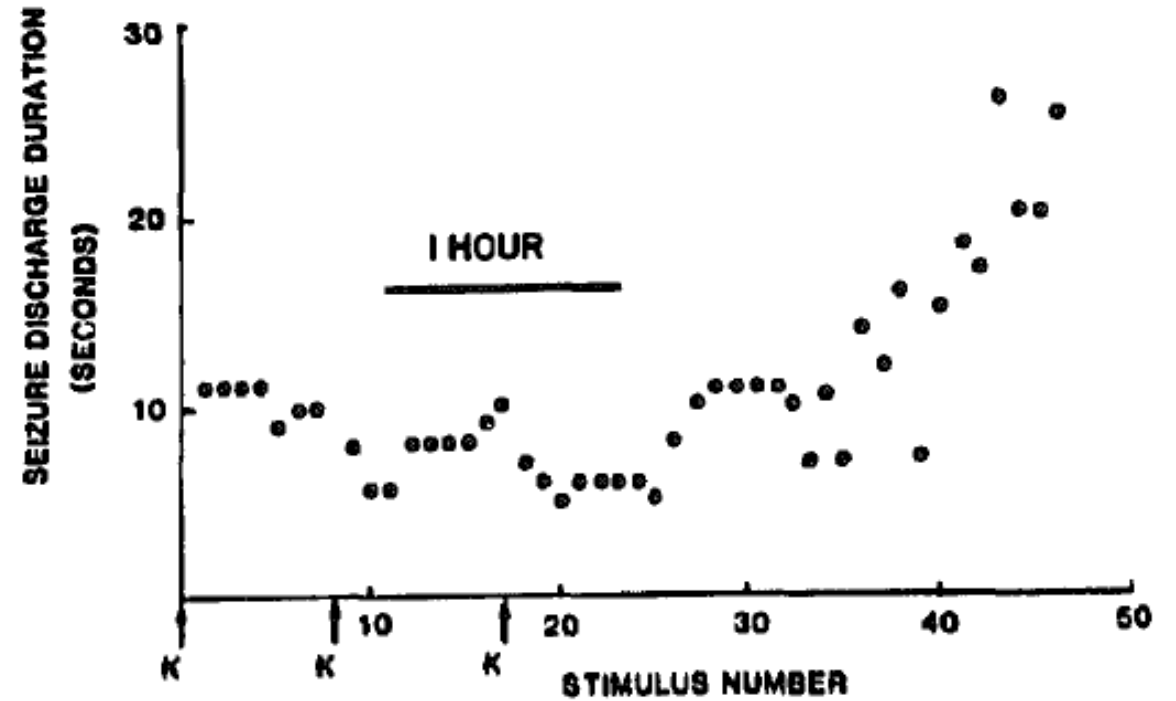
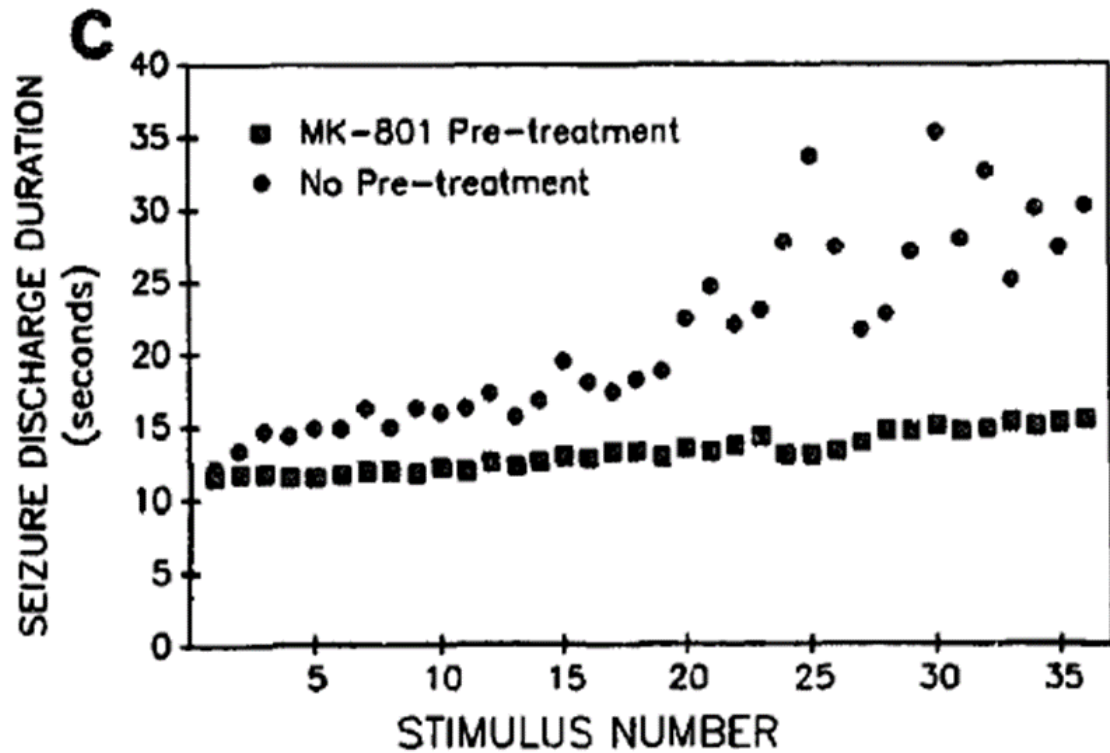
The NEW ENGLAND JOURNAL of MEDICINE

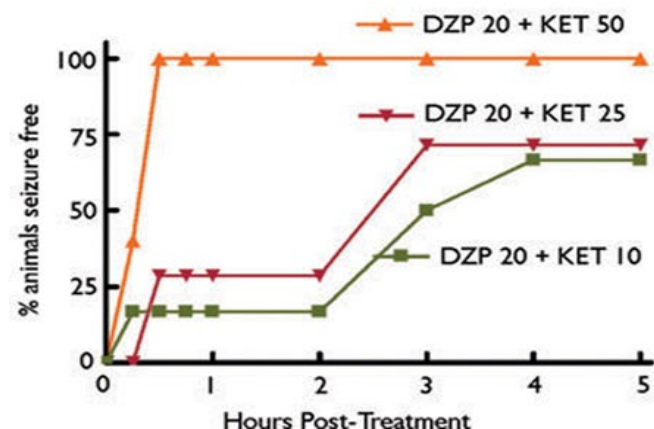
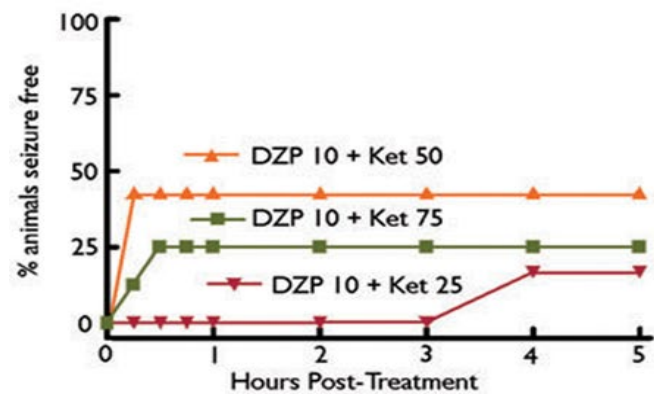
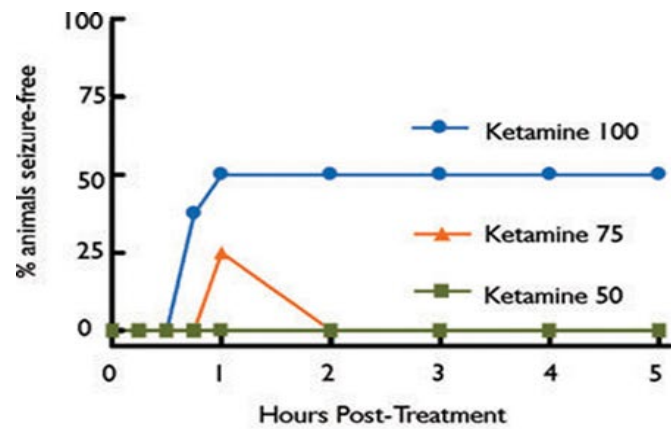
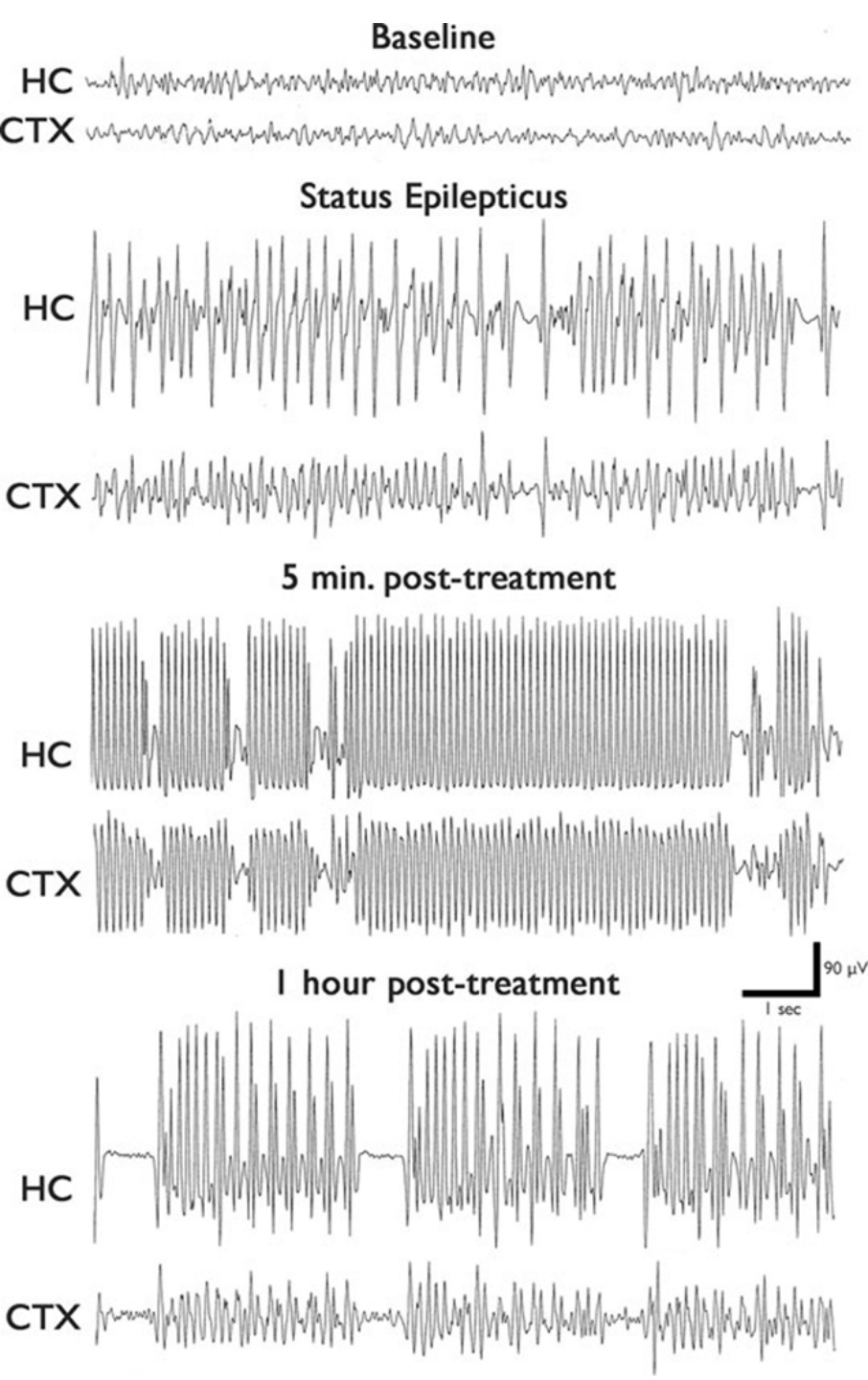


The doom loop of status epilepticus



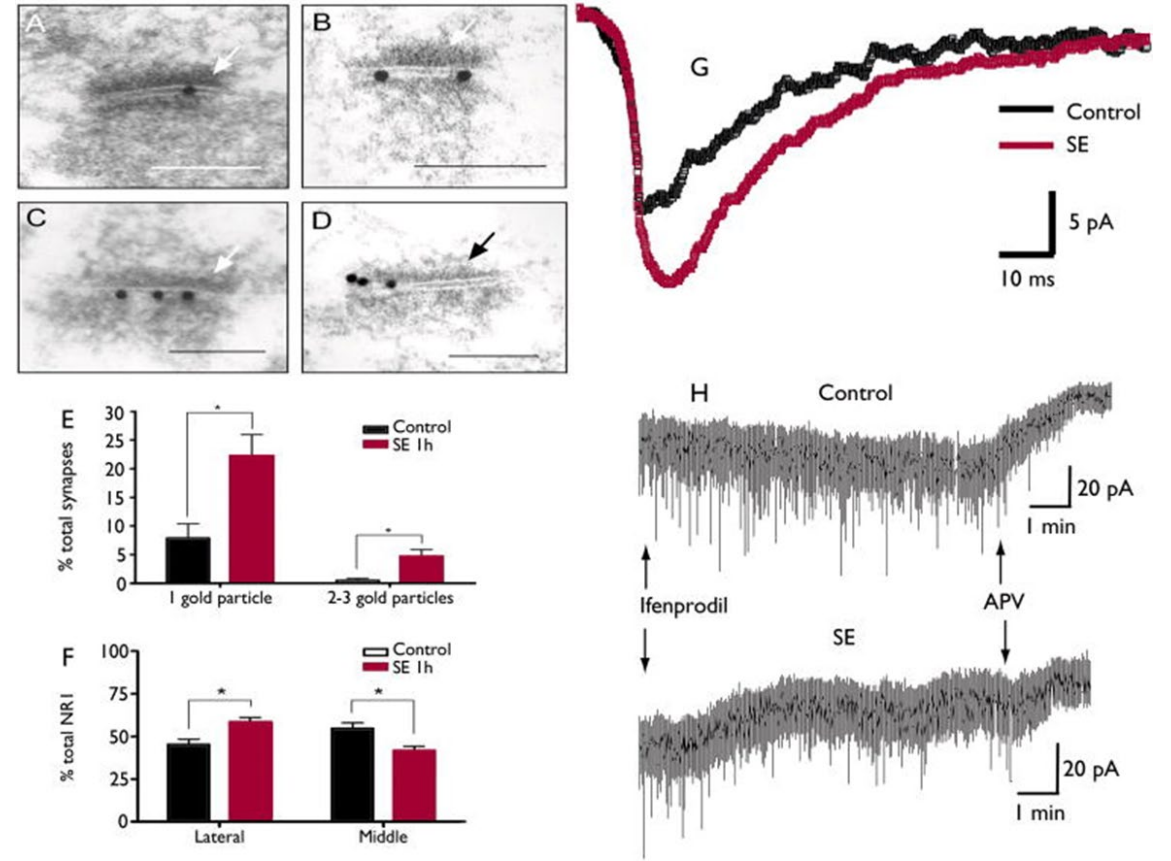
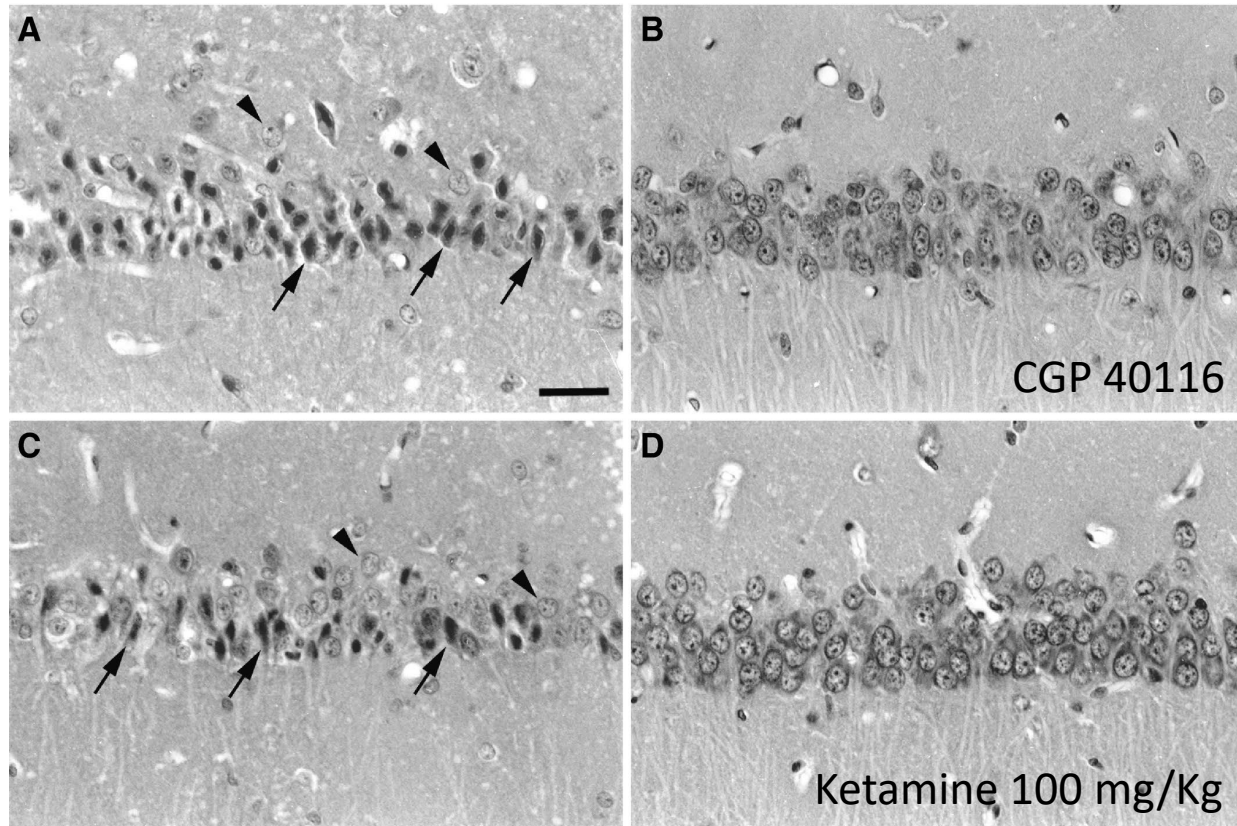
NMDA antagonist Ketamine blocks the doom loop



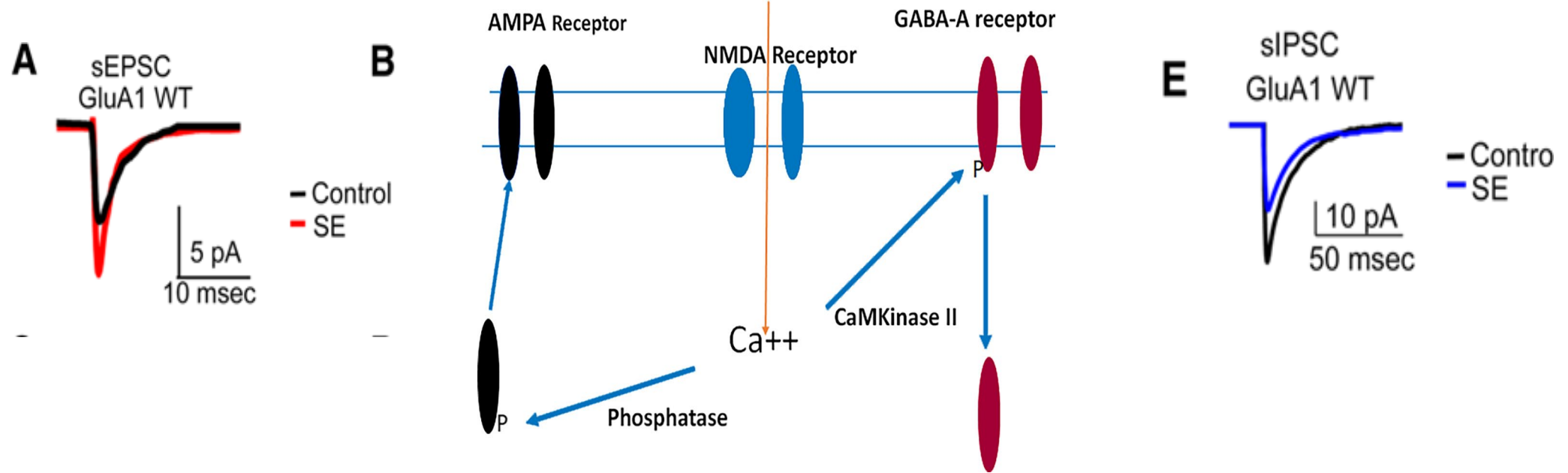


PMID: 17941842, 28225161

Starting ketamine for neuroprotection earlier than its current use as an anesthetic/antiepileptic drug late in refractory status epilepticus



NMDA receptors play central role in SE

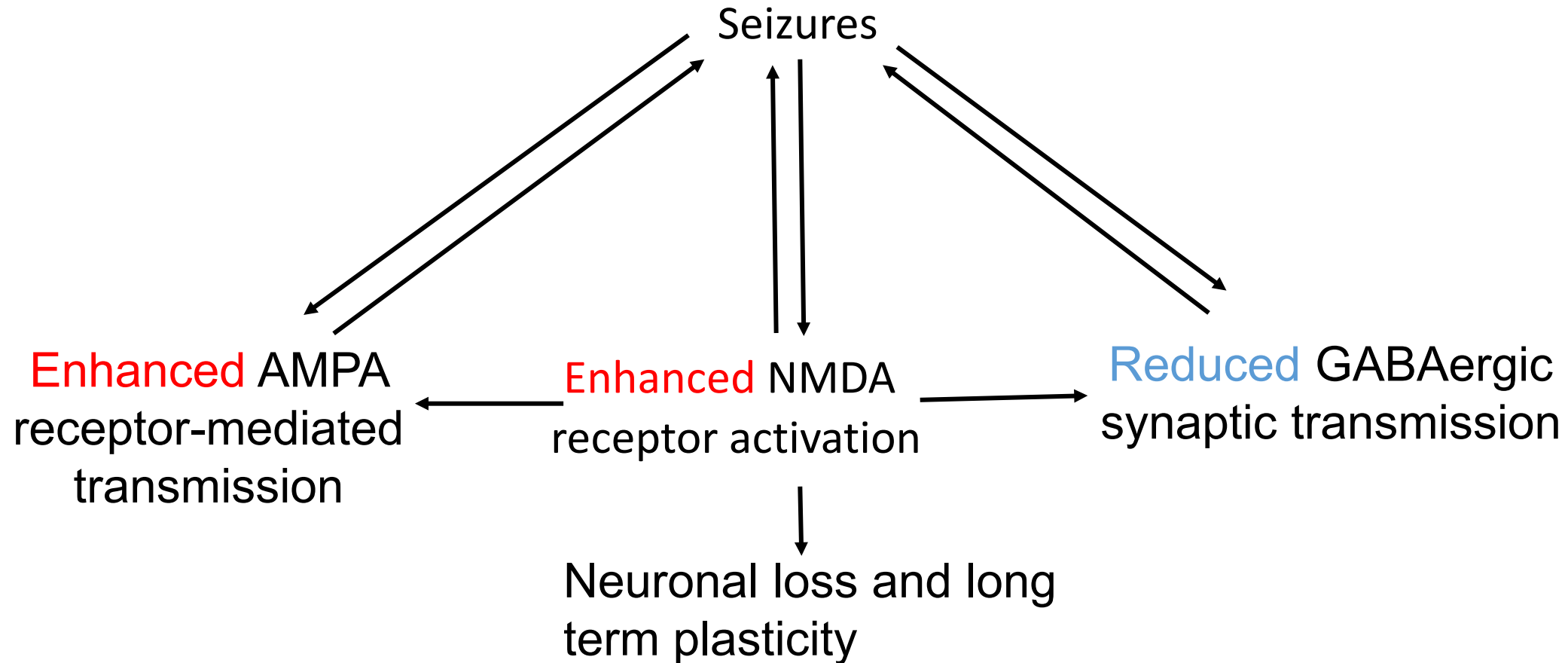


KESETT

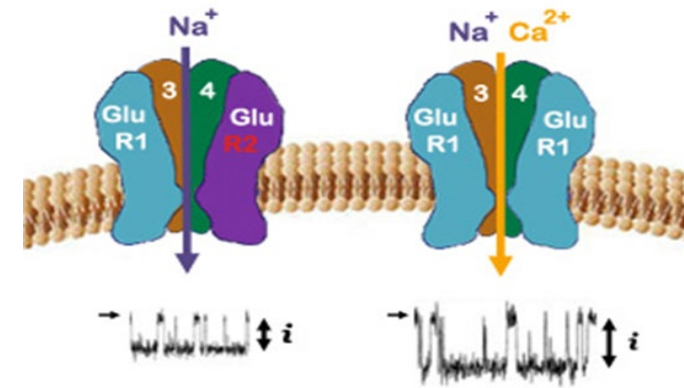
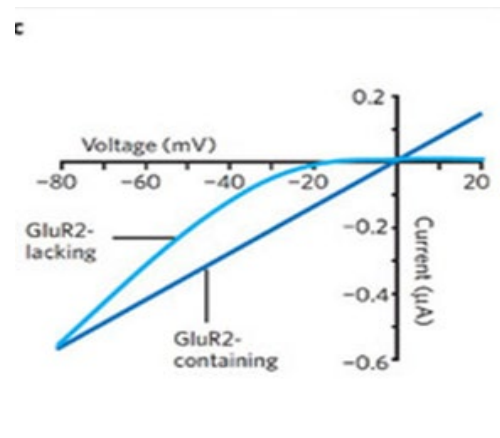
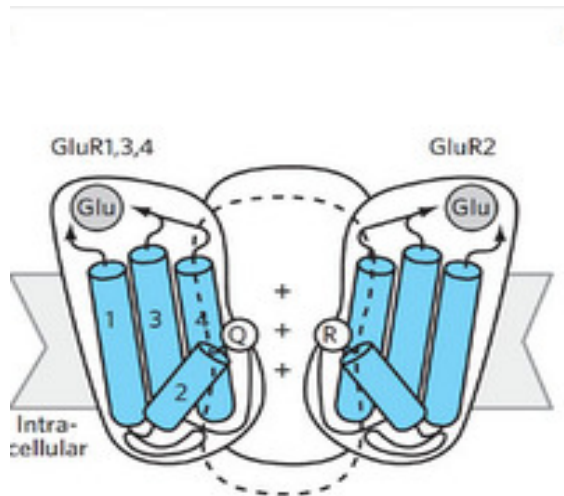
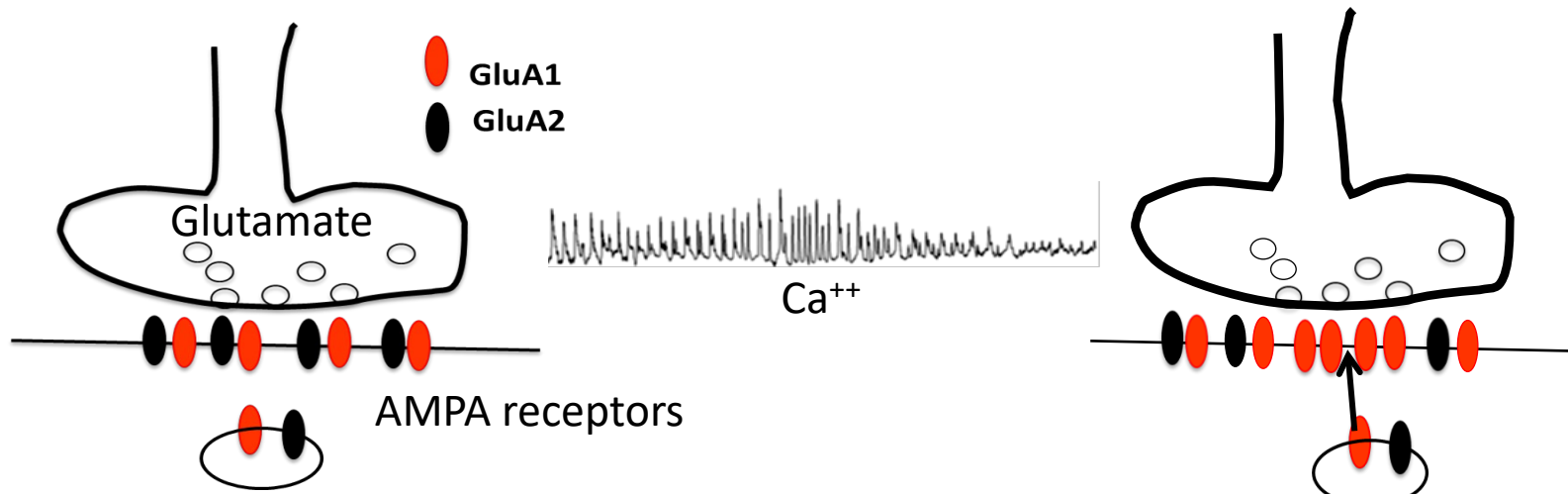
Ketamine add-on therapy for established status epilepticus trial (KESETT), a **proposed** phase III randomized, double-blind clinical trial to test whether ketamine (1 or 3 mg/Kg) added to the standard therapy, levetiracetam (LEV 60 mg/Kg), is more effective than LEV alone in treating status epilepticus after benzodiazepines have failed.

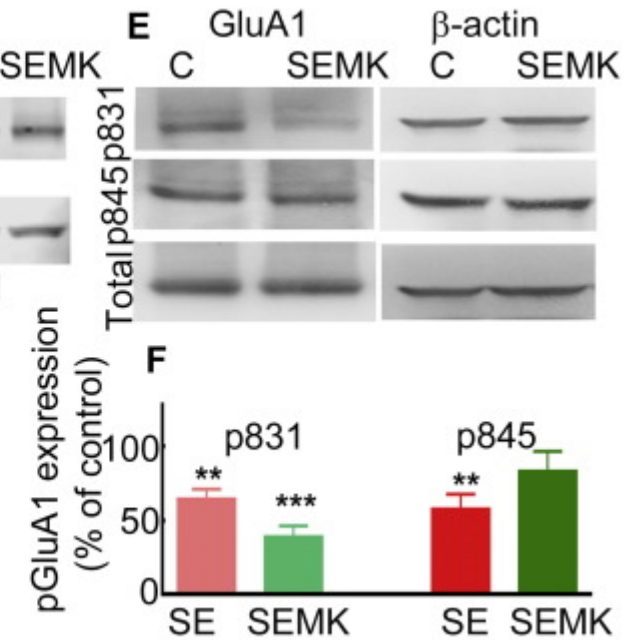
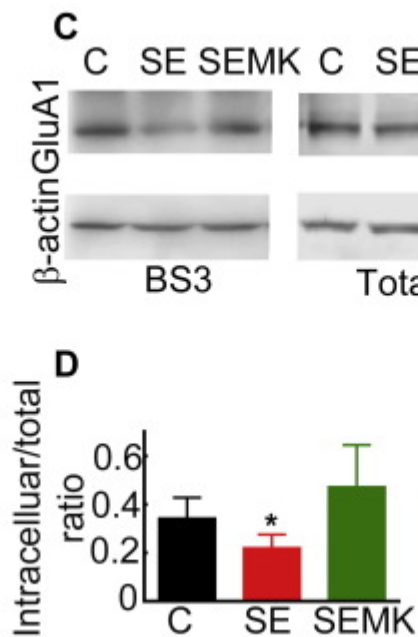
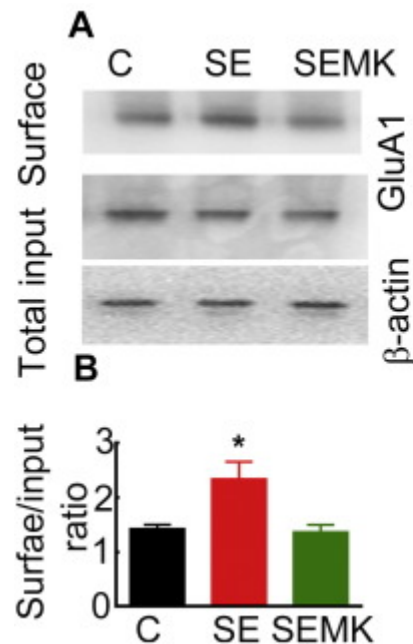
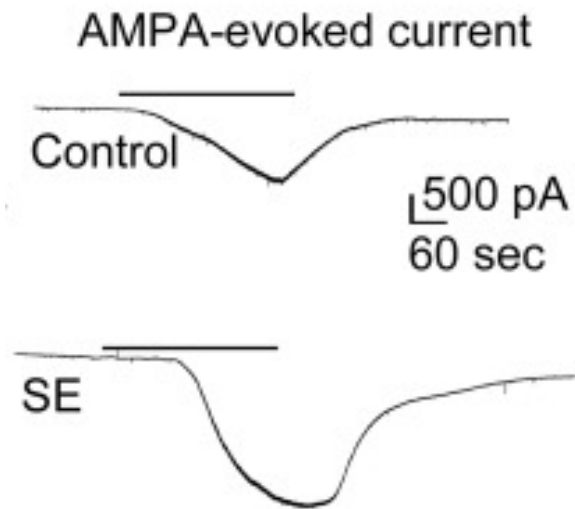
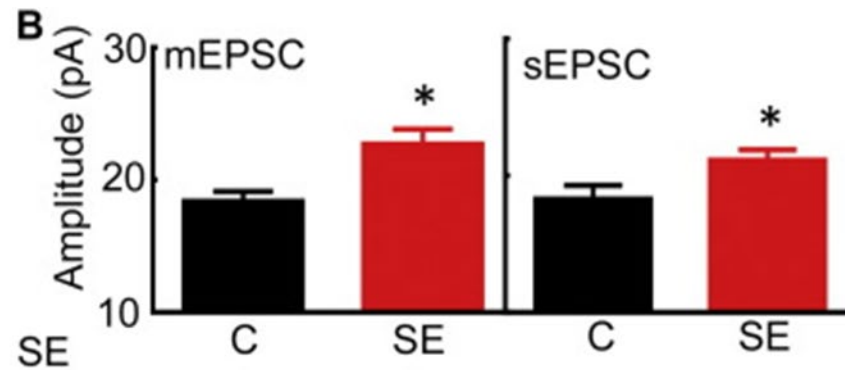
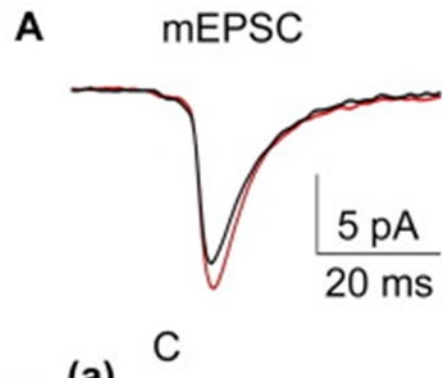


The doom loop of status epilepticus

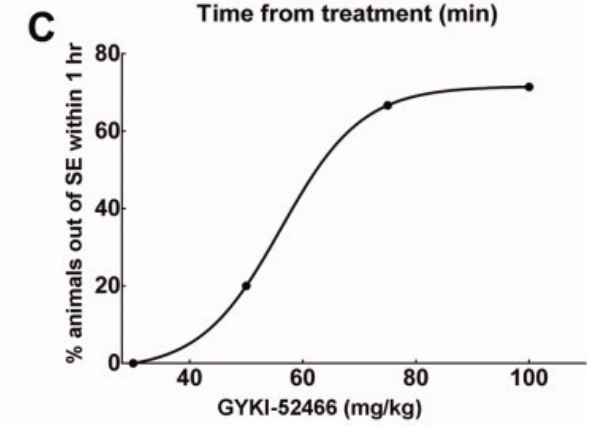
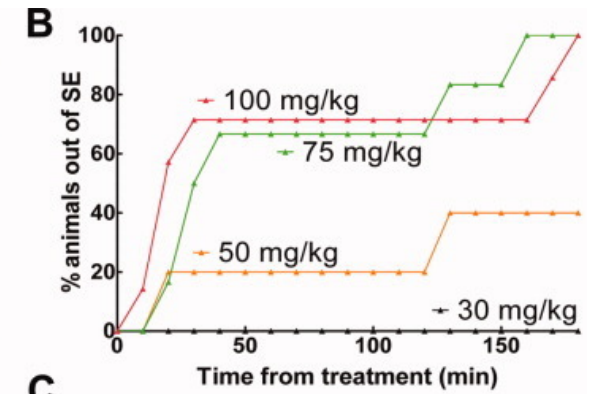
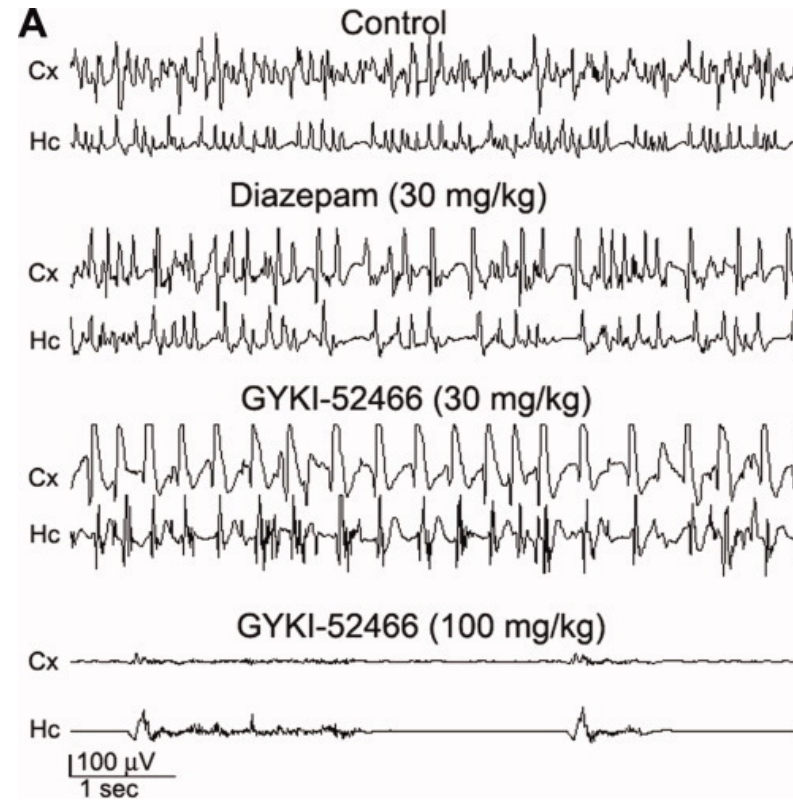
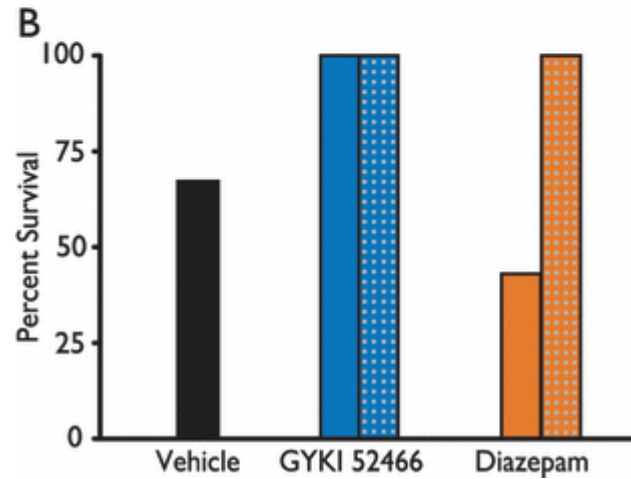
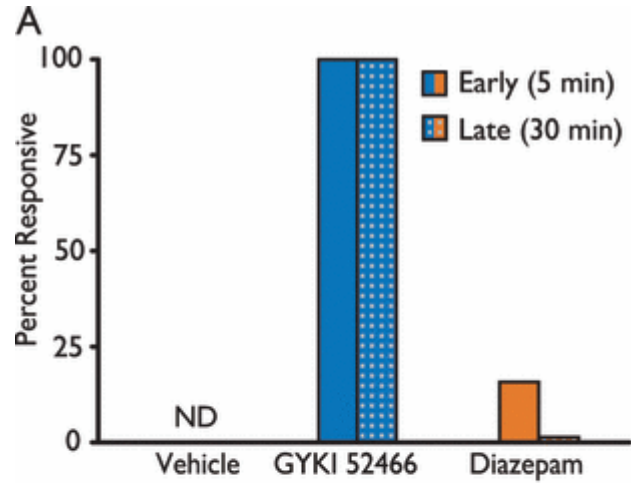


Enhanced Excitatory transmission



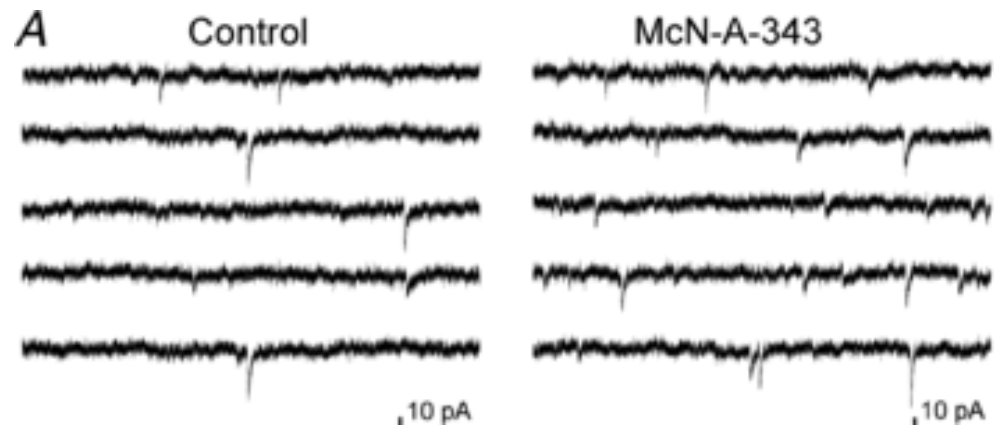
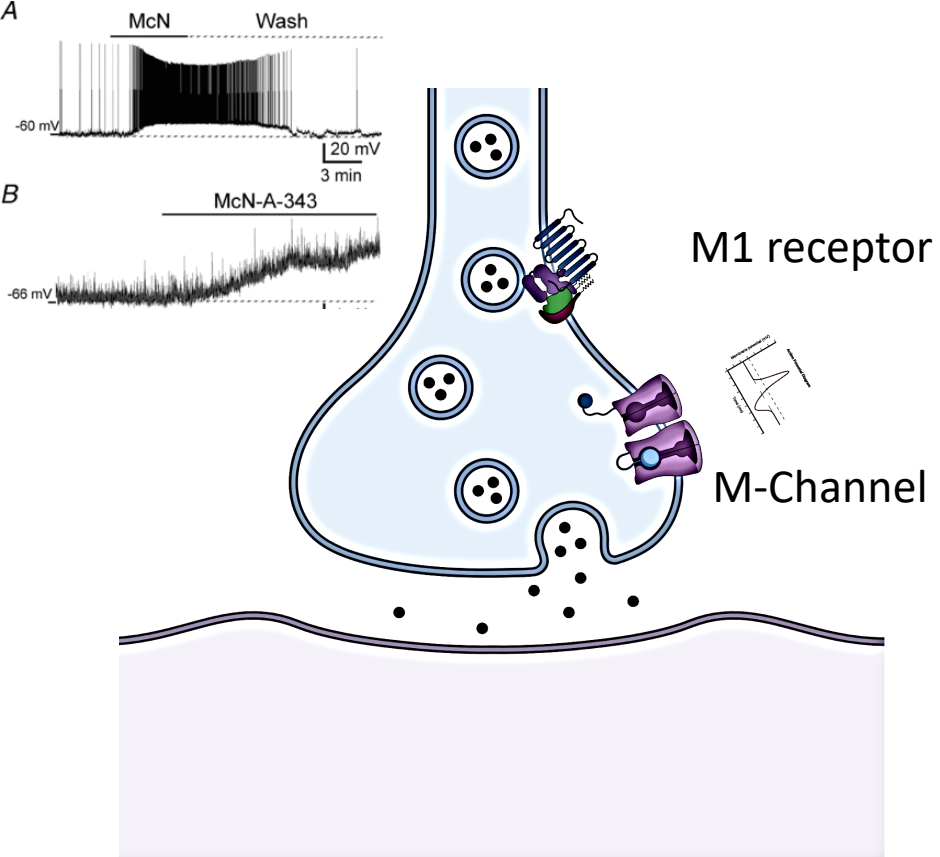


Joshi S, Rajasekaran K, Sun H, Williamson J, Kapur J. Neurobiol Dis. 2017 Jul;103:45-53. doi: 10.1016/j.nbd.2017.03.017. Epub 2017 Apr 2. PMID: 28377128; PMCID: PMC5481781.



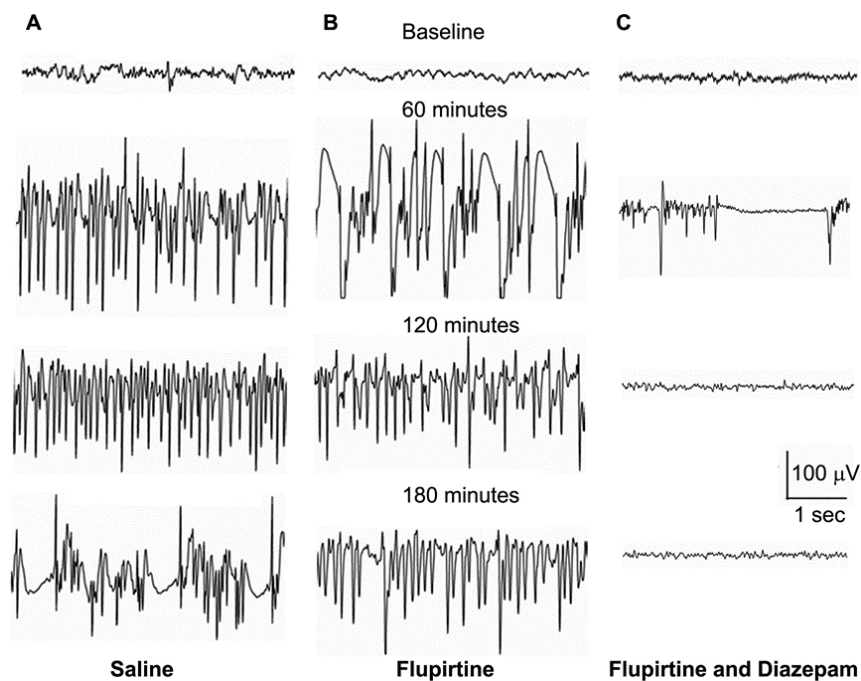
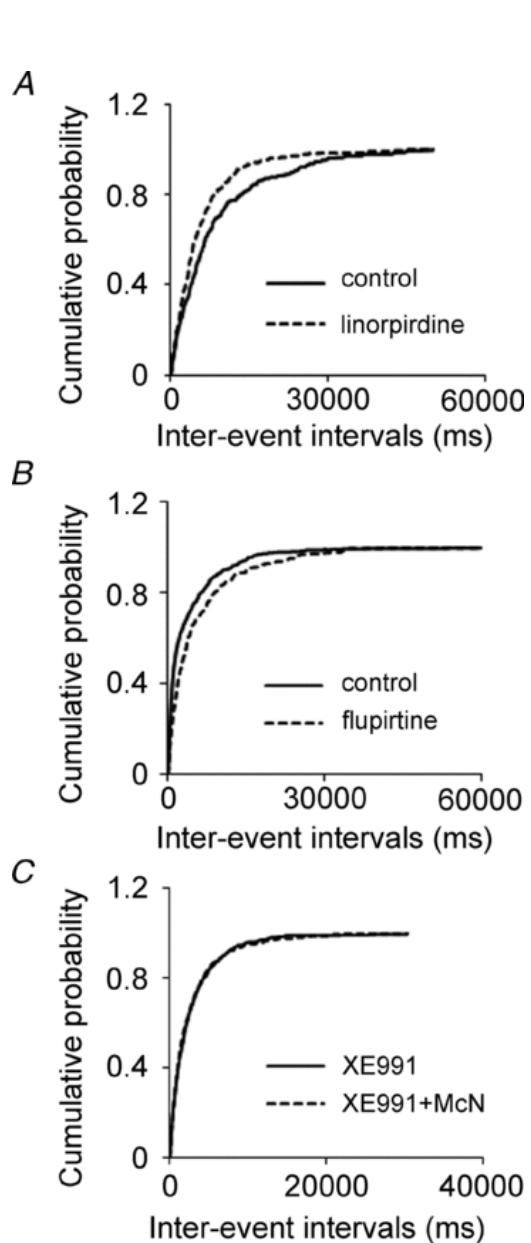
Fritsch B, Stott JJ, Joelle Donofrio J, Rogawski MA. Treatment of early and late kainic acid-induced status epilepticus with the noncompetitive AMPA receptor antagonist GYKI 52466. *Epilepsia*. 2010 Jan;51(1):108-17.

Annals of Neurology, Volume: 72, Issue: 1, Pages: 91-102



M1 activation mimics OP action

M-channel inhibition occludes M1 effect, and mimics it

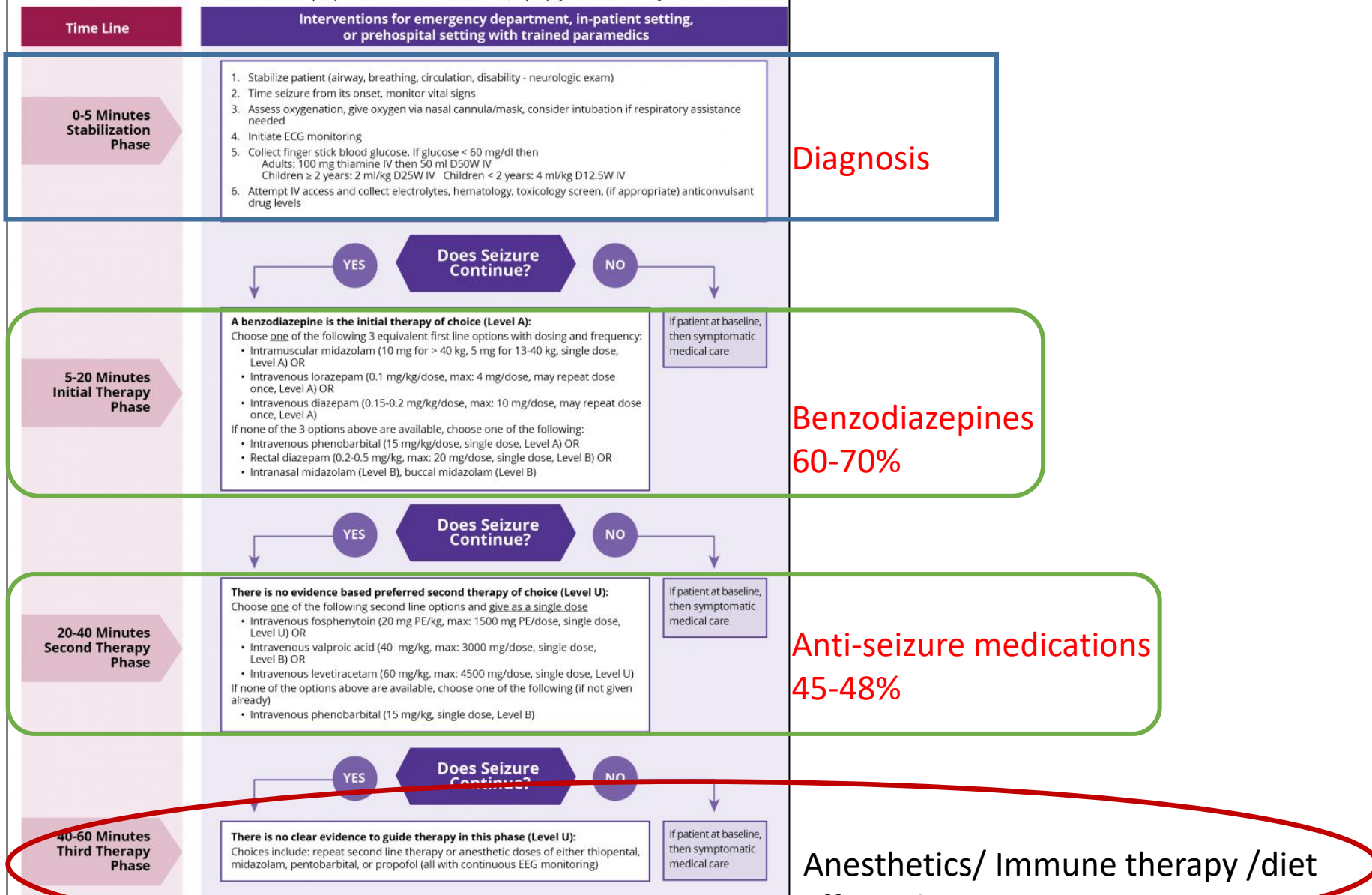


Ezogabine,/retigabine

PMID: 22578704, 23473742,
20107127, 22674722, 29296617

Proposed Algorithm for Convulsive Status Epilepticus

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Causes of refractory SE

- **Acute brain injury** rather than as a consequence of chronic epilepsy.

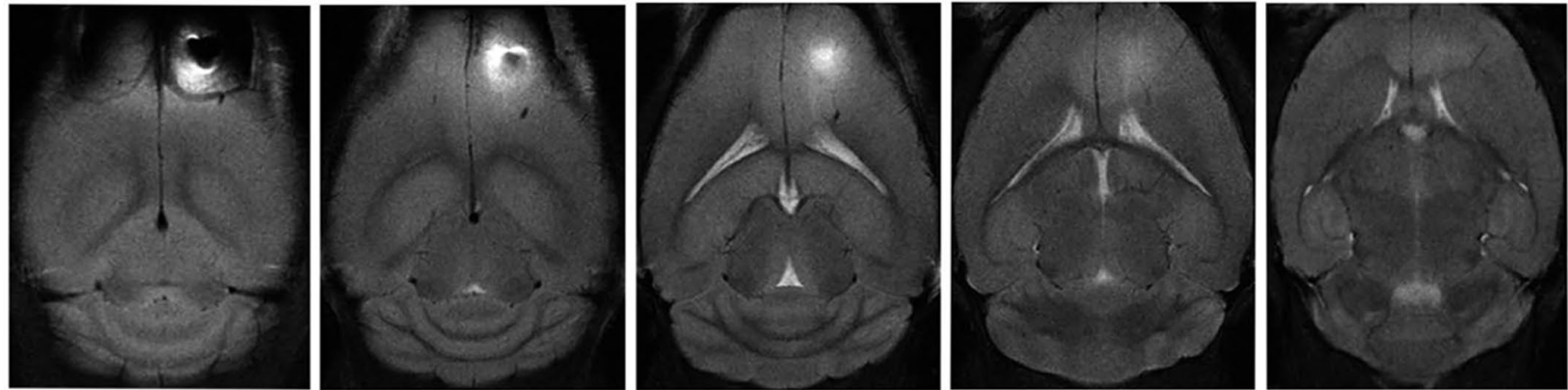
- Stroke/SAH/Lobar hemorrhage & TBI
- Hypoxic injury to the brain.
- Inflammation



- New-onset refractory status epilepticus (NORSE) is defined as a condition, not a specific diagnosis, with new onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause in a patient without active epilepsy.

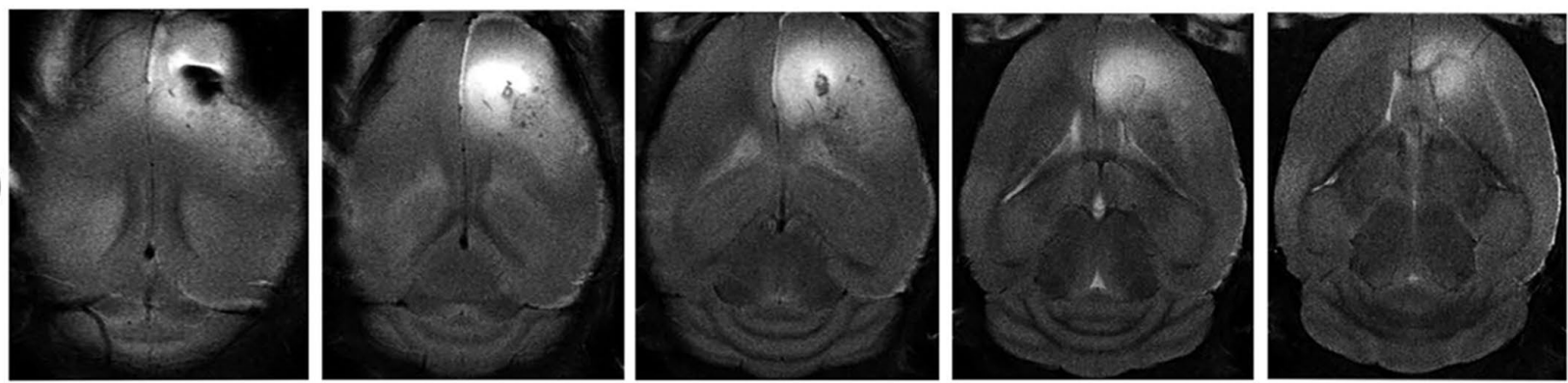
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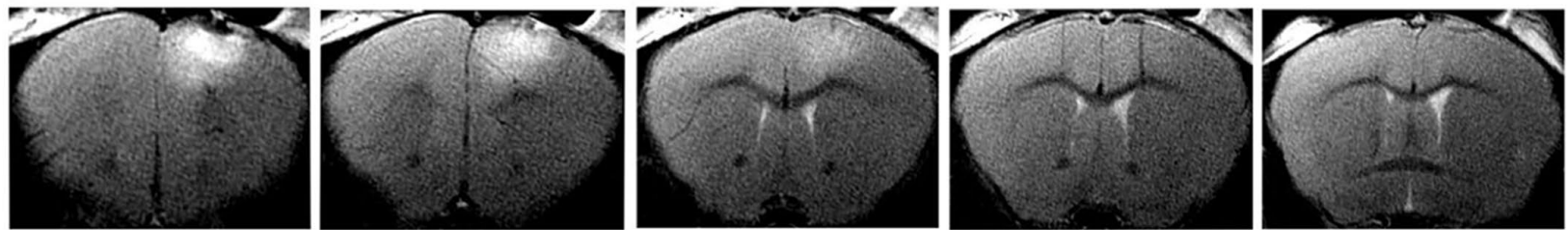
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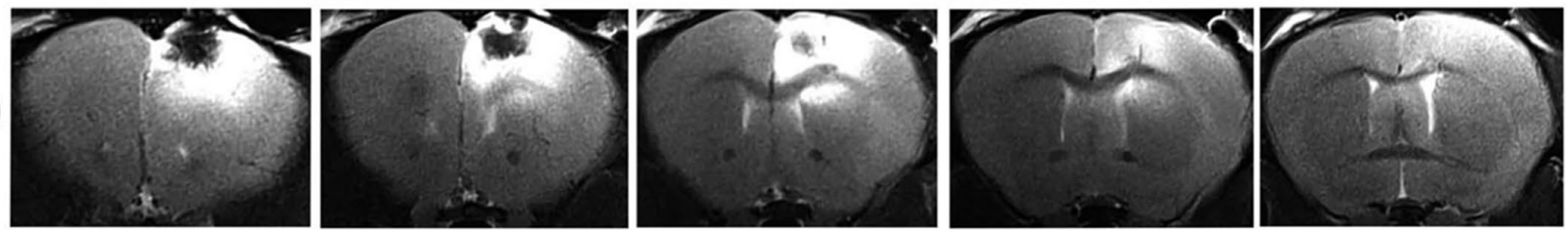
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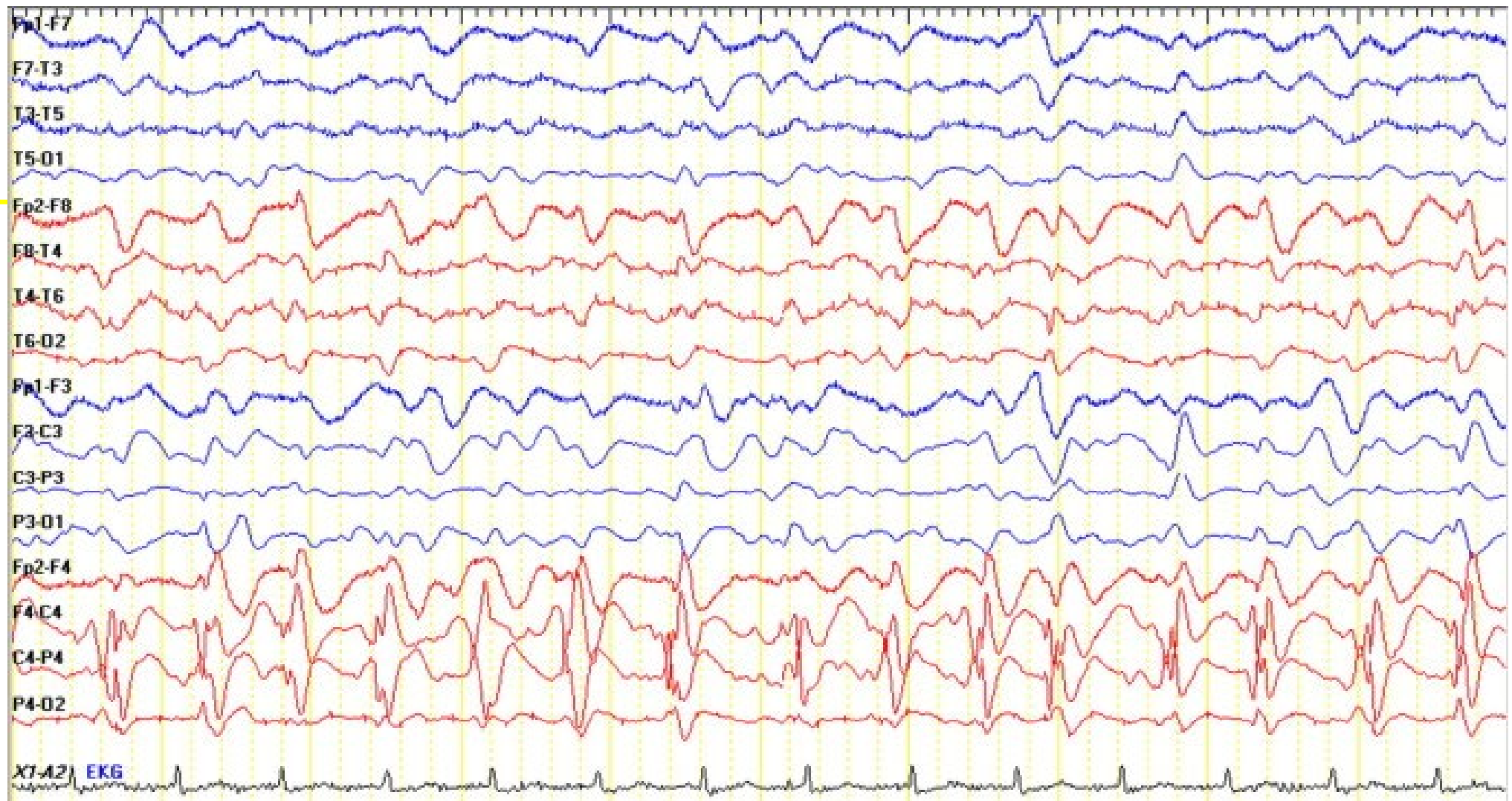


D

T240



Non-convulsive status epilepticus



Risk of prolonged anesthesia

- The risk of prolonged anesthesia is well known, but has only recently come under scrutiny, calling into question the current practice of using anesthesia for prolonged periods in some patients with SRSE.
 - prolonged immobility,
anesthetic use,
immunosuppression,
exposure to an intensive care unit environment
 - Homeostatic plasticity

Non convulsive status epilepticus

- When does non convulsive status epilepticus begin?
- Are benzodiazepines the initial treatment?
- Do we use anti seizure medications and or anesthetics?
- What is the EEG goals (seizure cessation, burst suppression, complete suppression)?
- Is there is a role of immunotherapy in NORSE/FIRES (i.e.; IVIG, plasma exchange, steroids, rituximab)
- Role of ketogenic diet
- What are the mechanisms ?

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