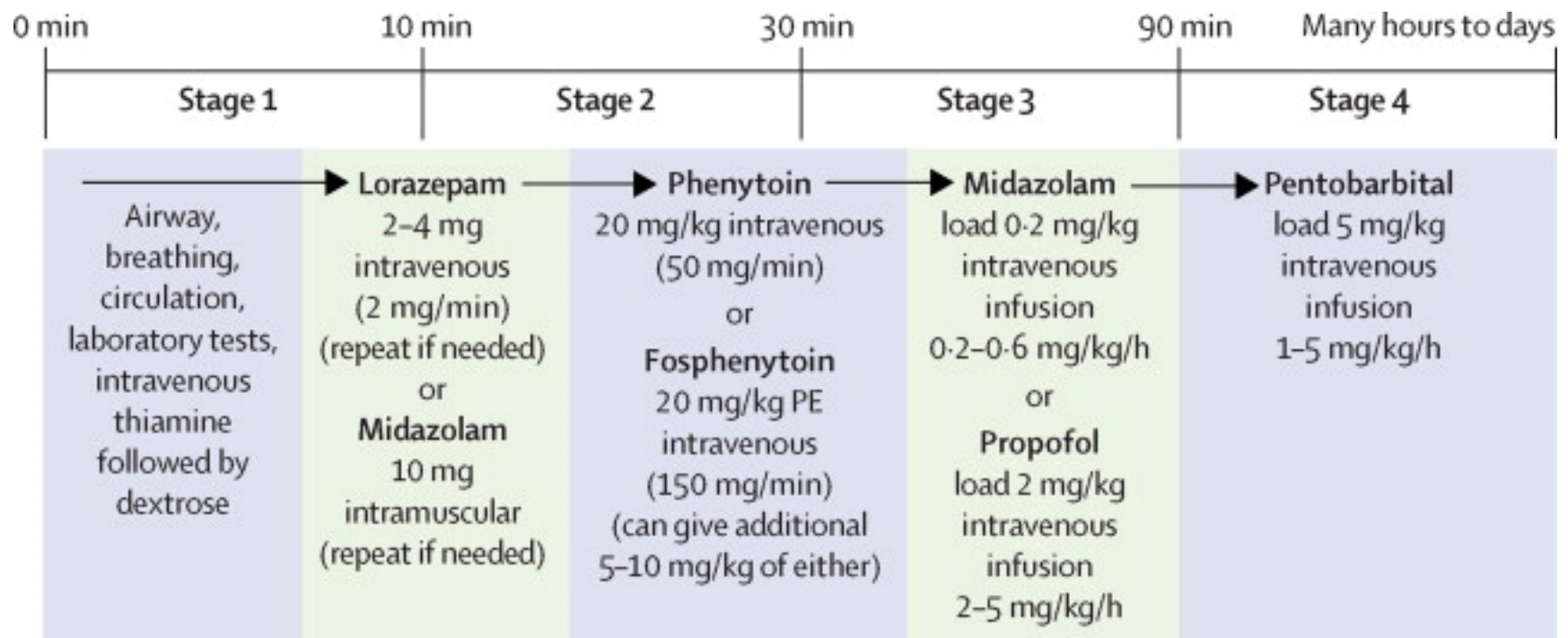


# Potential Future studies

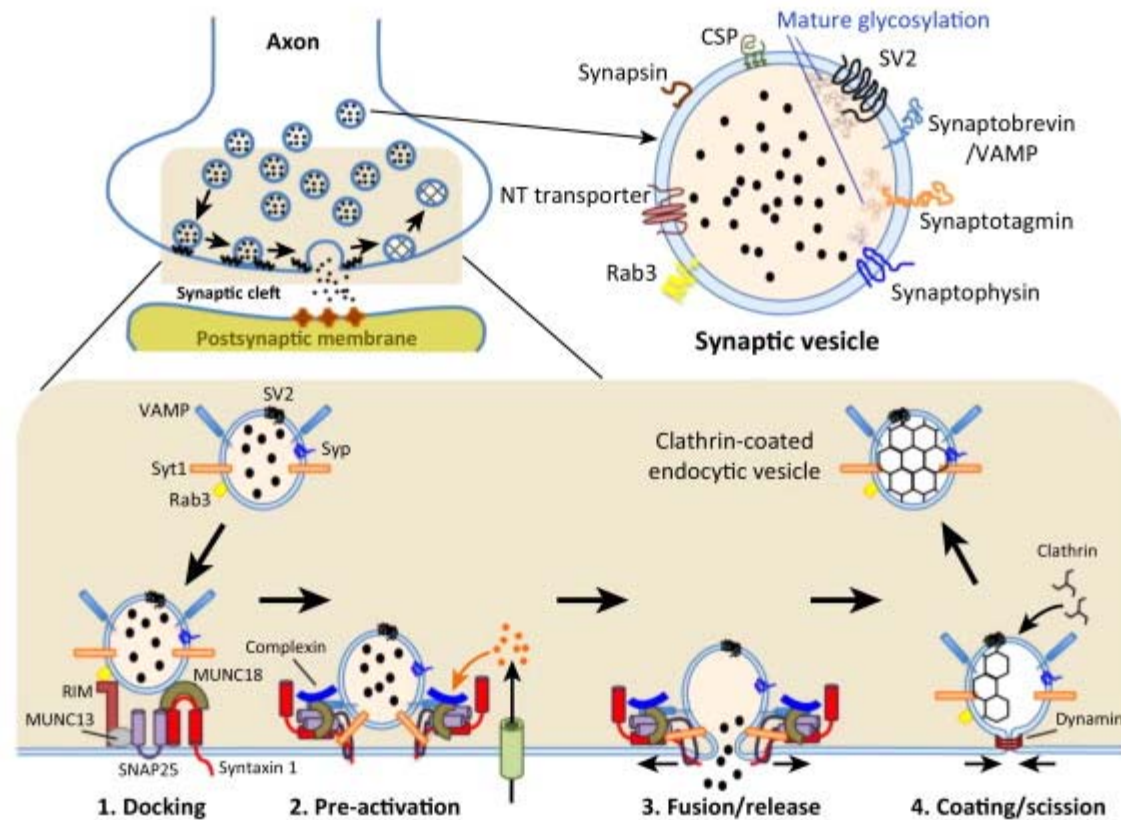


John P Betjemann , Daniel H Lowenstein, Status Epilepticus in adults  
 The Lancet Neurology, Volume 14, Issue 6, 2015, 615 - 624

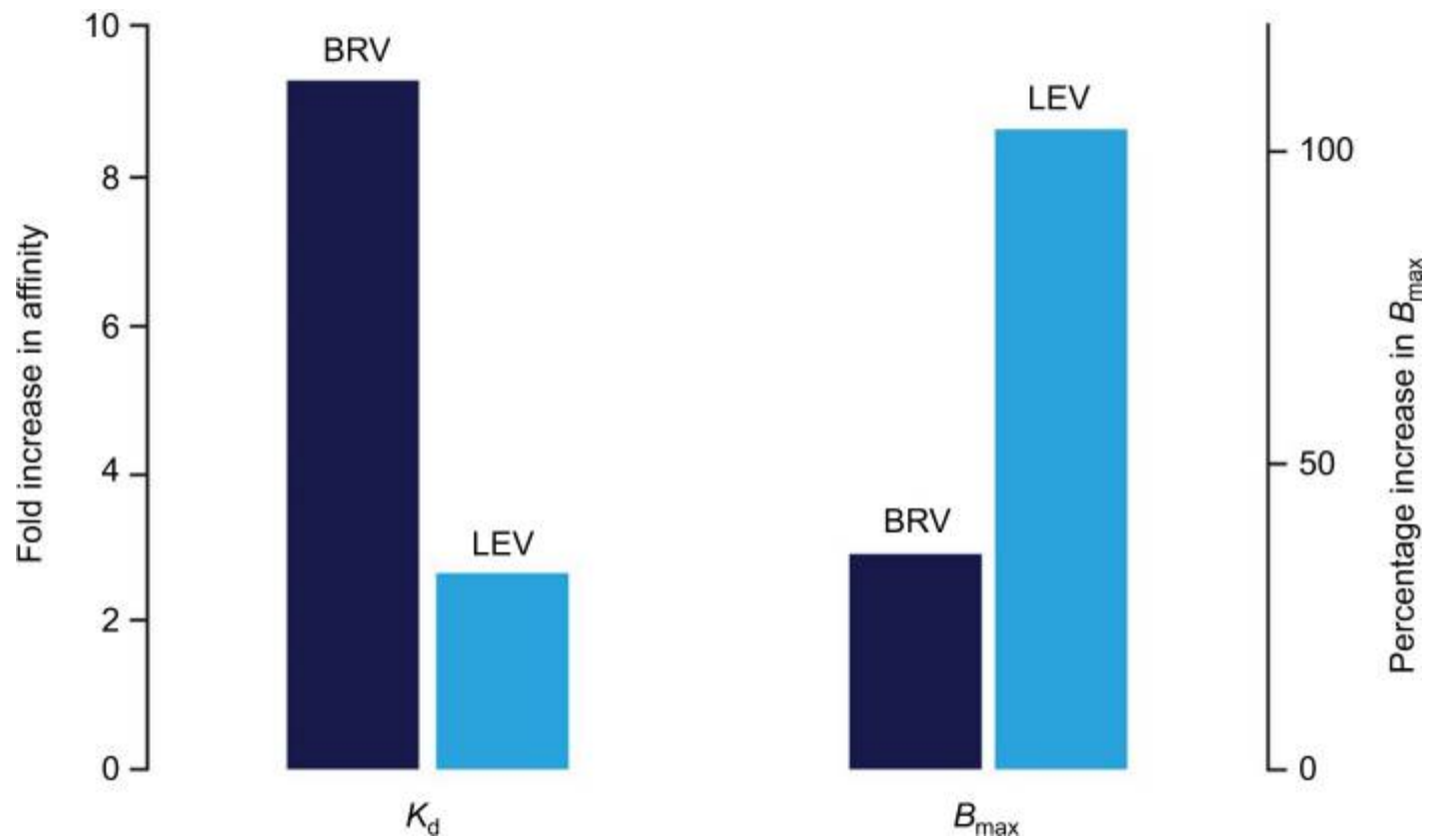
# Add another treatment to midazolam

- AEDs available in solution form
  - Brivaracetam (Briviact).
  - IV solution 50 mg/5ml approved & available. IM absorption not known.
  - Faster brain entry
  - Same mechanism of action as Levetiracetam: It binds to SV2 protein in the presynaptic terminal.
  - Higher affinity to SV2 protein than Lev.
  - Efficacious in therapy of partial seizures (FDA approved).

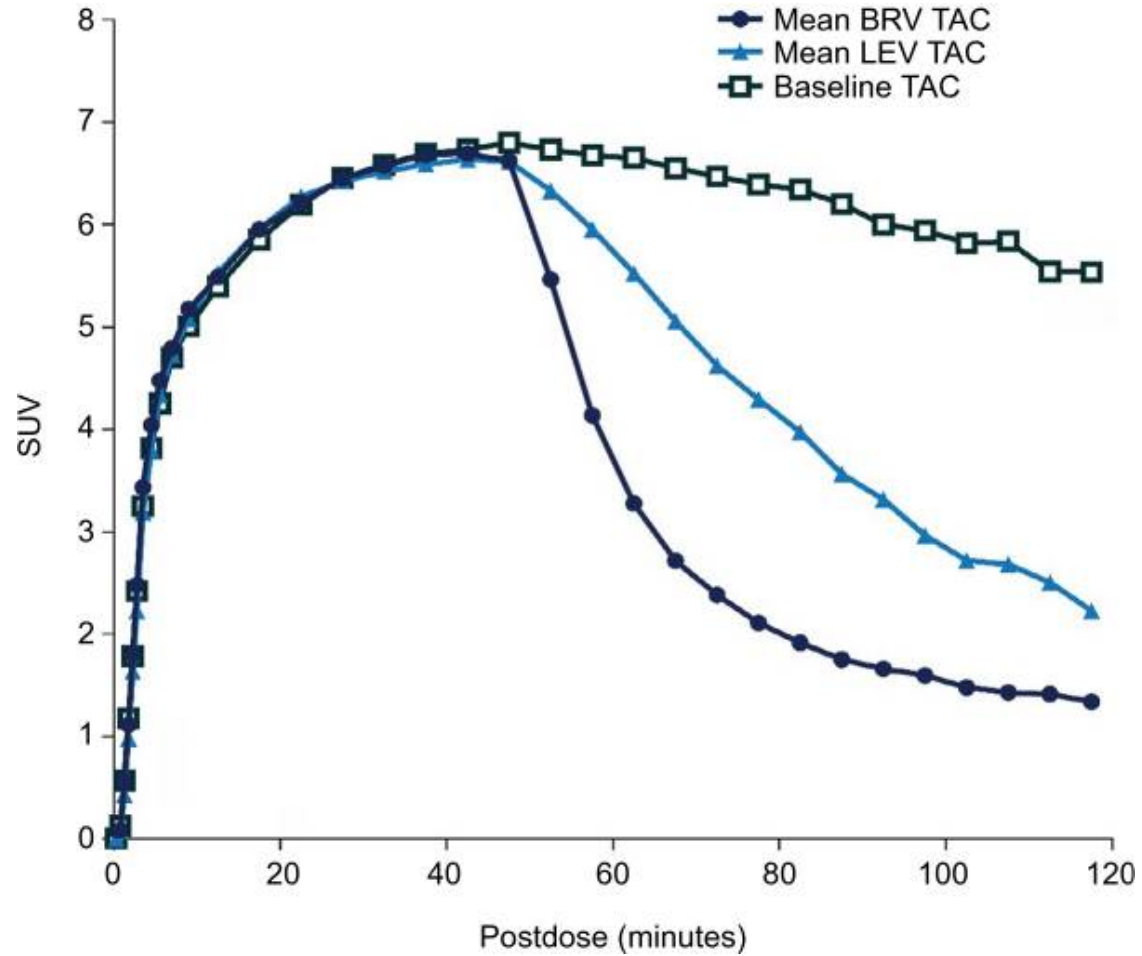
# Mechanism of action

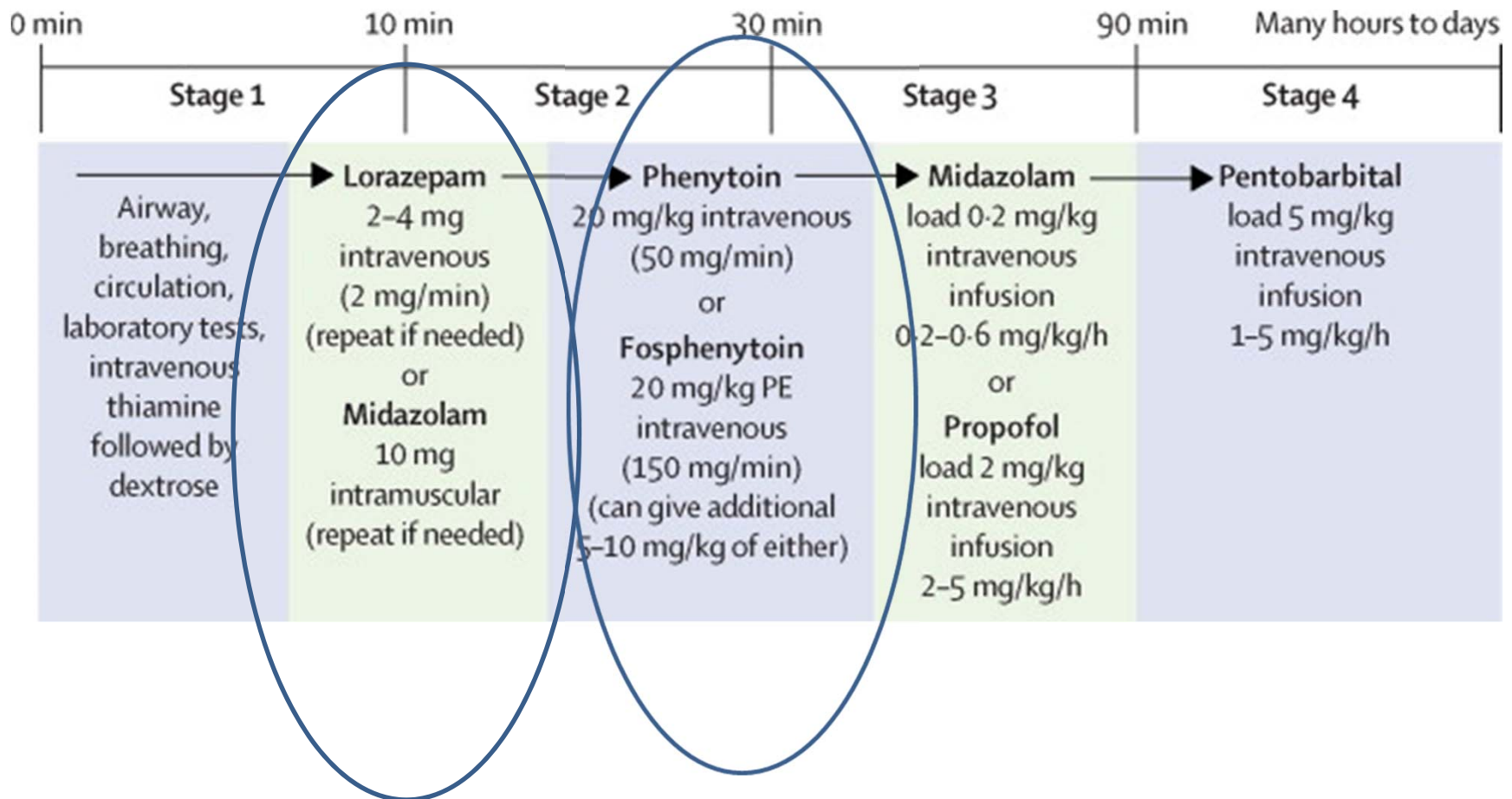


# BRV higher affinity lower maximal binding than BEV



# BRV in brain: PET Imaging





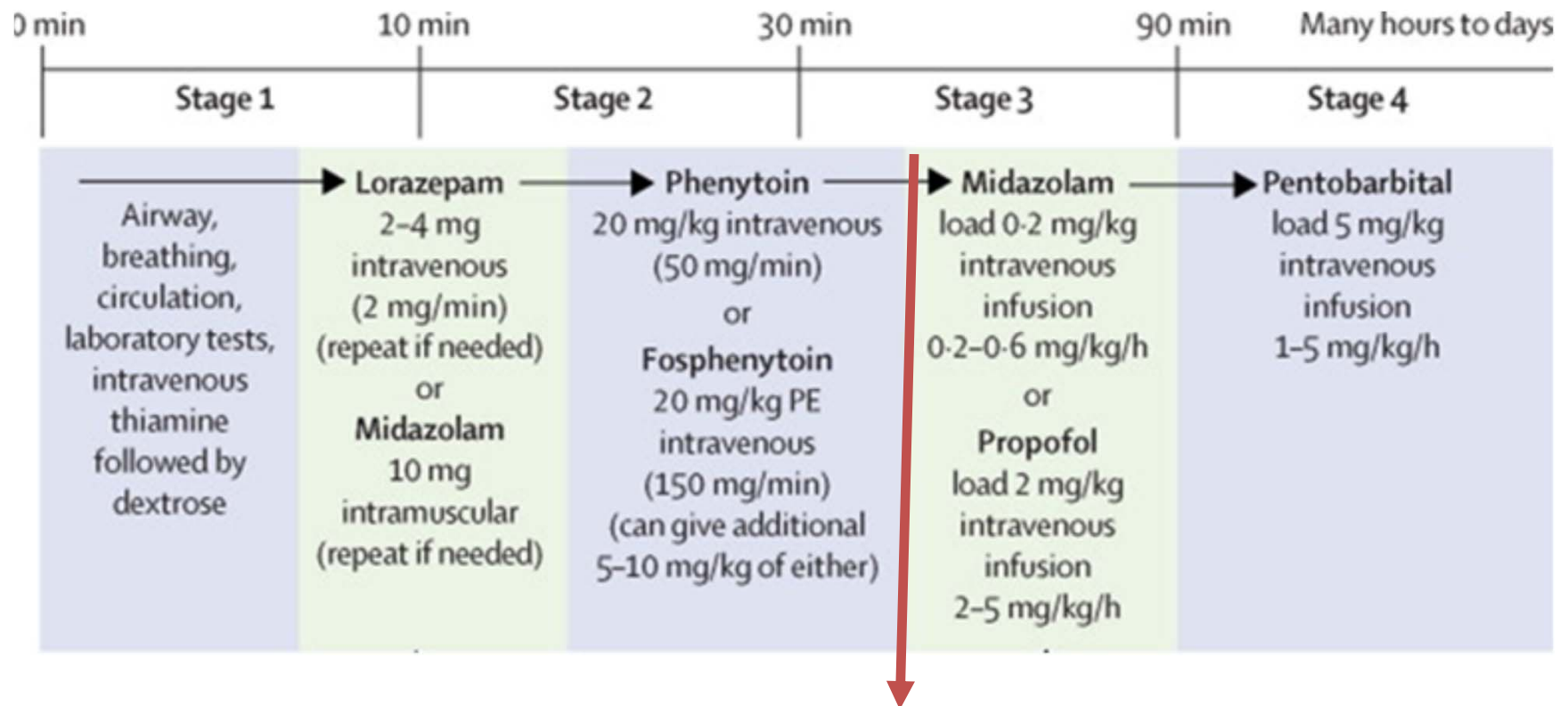
John P Betjemann , Daniel H Lowenstein, Status Epilepticus in adults  
 The Lancet Neurology, Volume 14, Issue 6, 2015, 615 - 624

# BRV Current state

- UCB holds patent.
- IM absorption unknown.



# EEG in treatment of convulsive SE



# Who needs EEG to screen for SE?

- All patients who do not show improvement in consciousness/ responsiveness following treatment of generalized convulsive SE
- Patient who has acute supratentorial brain injury with altered mental status.
  - traumatic brain injury, subarachnoid hemorrhage, intracerebral hemorrhage, encephalitis, acute ischemic stroke, and during and after therapeutic hypothermia following cardiac arrest

# Comatose Patients in ICUs at risk for seizures

- Witnessed convulsive seizures/status epilepticus prior to coma (30-48%).
- Intracerebral hemorrhage (29%).
- Central Nervous system infection (26%).
- Brain Tumor (23%).
- Severe head trauma (22%).
- Subarachnoid hemorrhage (18%).

# Obtaining EEG in Emergency department

## Challenges technical

- Placing electrodes at appropriate location.
- Attaching low impedance electrodes rapidly to skin.
- Measuring impedance.
- Amplifying the signal
- Recording
- Storage

# Advances integrated EEG system

- The system is comprised of a headband and a small hand-held control unit.
- The elastic fabric headband has 10 electrode assemblies, each consisting of a passive scalp-contacting prongs to prepare scalp for electrode contact, silver/silver-chloride electrode, a reservoir filled with conductive electrolyte gel, mechanism for dispensing gel onto patient scalp,
- A cable attached to the headband to allow connection to an EEG acquisition/recording device.
- The EEG electrode cable plugs into a digital recorder and transmitter, a tablet computer monitor. Instructions for use are included in the tablet computer



# Ronner et al.

- Results: The inter-observer agreement of an EEG diagnosis of seizure was limited.
- The overall kappa score for the five experienced raters was 0.5,
- and the kappa score for less experienced raters was 0.29.
- Kappa values for the individual Young's criteria were highly variable, indicating discrepancies in the interpretation of specific phenomena. Especially, some types of periodic discharges gave rise to different interpretations

# ACNS efforts to characterize EEG patterns

- Define unequivocal seizure patterns.
- Define periodic patterns.

Working group: Hirsch LJ, LaRoche SM, Gaspard N, Gerard E, Svoronos A, Herman ST, Mani R, Arif H, Jette N, Minazad Y, Kerrigan JF, Vespa P, Hantus S, Claassen J, Young GB, So E, Kaplan PW, Nuwer MR, Fountain NB, Drislane FW.

# Improving interpretation

- ILAE taskforce:
- Advances in electrophysiologic techniques may provide us with increased capability to utilize EEG in the emergency setting and allow better delineation of the highly dynamic changes of EEG patterns in the near future.



# ILAE Proposed terminology

- Location: generalized (including bilateral synchronous patterns), lateralized, bilateral independent, multifocal.
- Name of the pattern: Periodic discharges, rhythmic delta activity or spike-and-wave/sharp-and-wave plus subtypes.
- Morphology: sharpness, number of phases (e.g., triphasic morphology), absolute and relative amplitude, polarity.
- Time-related features: prevalence, frequency, duration, daily pattern duration and index, onset (sudden vs. gradual), and dynamics (evolving, fluctuating, or static).
- Modulation: stimulus-induced vs. spontaneous.
- Effect of intervention (medication) on EEG.

# Salzburg study

- Diagnostic accuracy of the Salzburg EEG criteria for non-convulsive status epilepticus: a retrospective study.
- 100 patients suspected of Non convulsive SE. 100 with abnormal EEG.
- Inter-rater agreement was high for both the Salzburg criteria ( $k=0.87$ ) and for the reference standard ( $k=0.95$ ).
- Therapeutic changes occurred significantly more often in the group of patients fulfilling Salzburg criteria (42 [84%] of 50 patients) than in those who did not (11 [16%] of 70;  $p<0.0001$ ).

# Other SE studies using EEG

- IV lacosamide IV phosphenytoin in refractory SE in the ICU (TRENDS, Phase 2)
  - NCT01458522. Study completed PI Aatif Husain Results pending.
- IV allopregnanolone in super-refractory SE.(phase 3).
  - NCT02477618.
  - Study completed.

Both studies point to feasibility of using EEGo diagnose and determine the outcome of SE

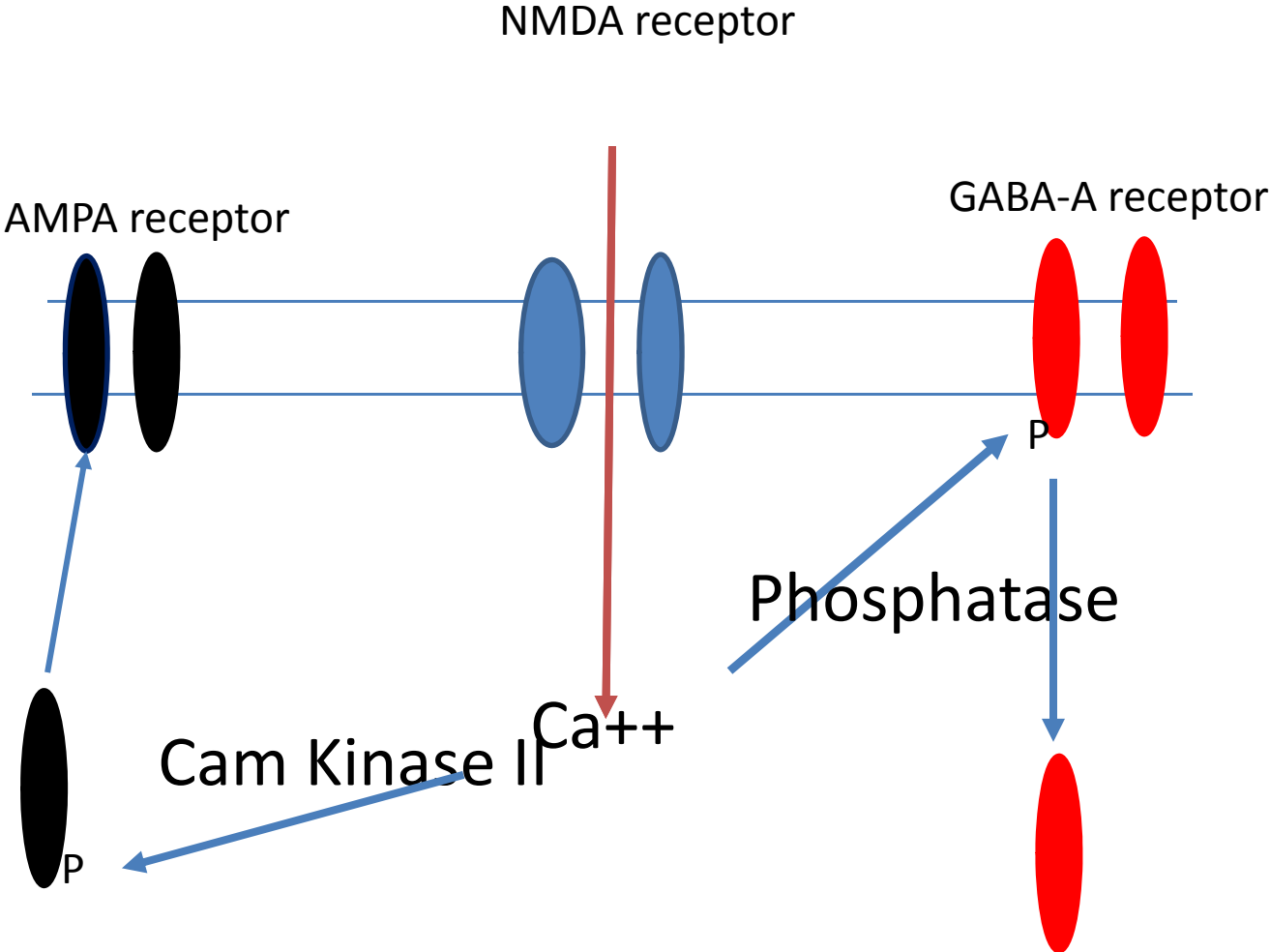
# Potential EEG based studies

- Early versus conventional diagnosis and treatment of subtle or non convulsive SE.
- Novel therapies for generalized convulsive SE:
- Early ( skipping second line) versus delayed general anesthesia.

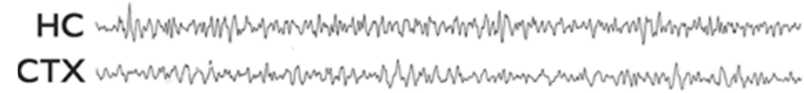
# Refractory SE: Ketamine

- Anesthetic: initiation and maintenance of anesthesia.
- NMDA receptor antagonist.
- A large number of case reports and case series in super-refractory SE.
- Safety data available.
- Dosing data

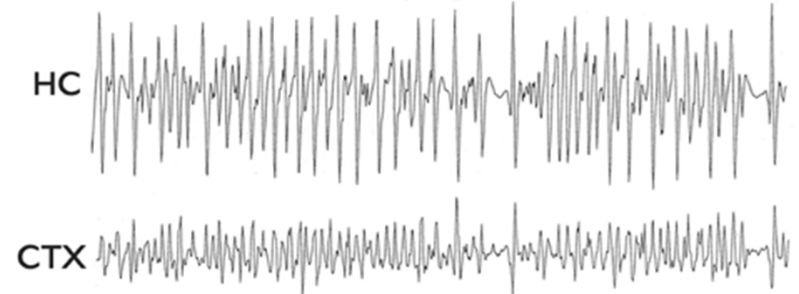
# NMDA receptors play a key role in SE



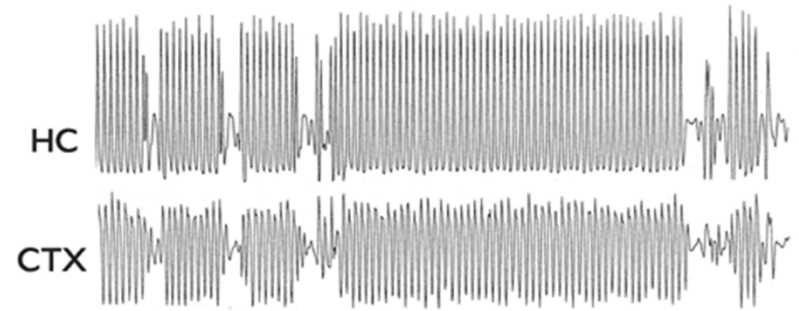
**Baseline**



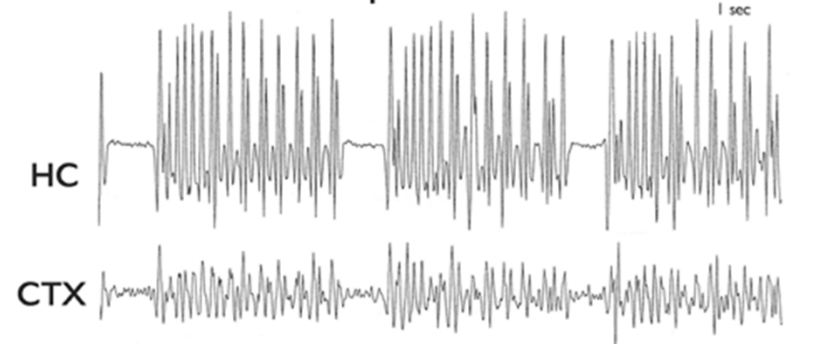
**Status Epilepticus**



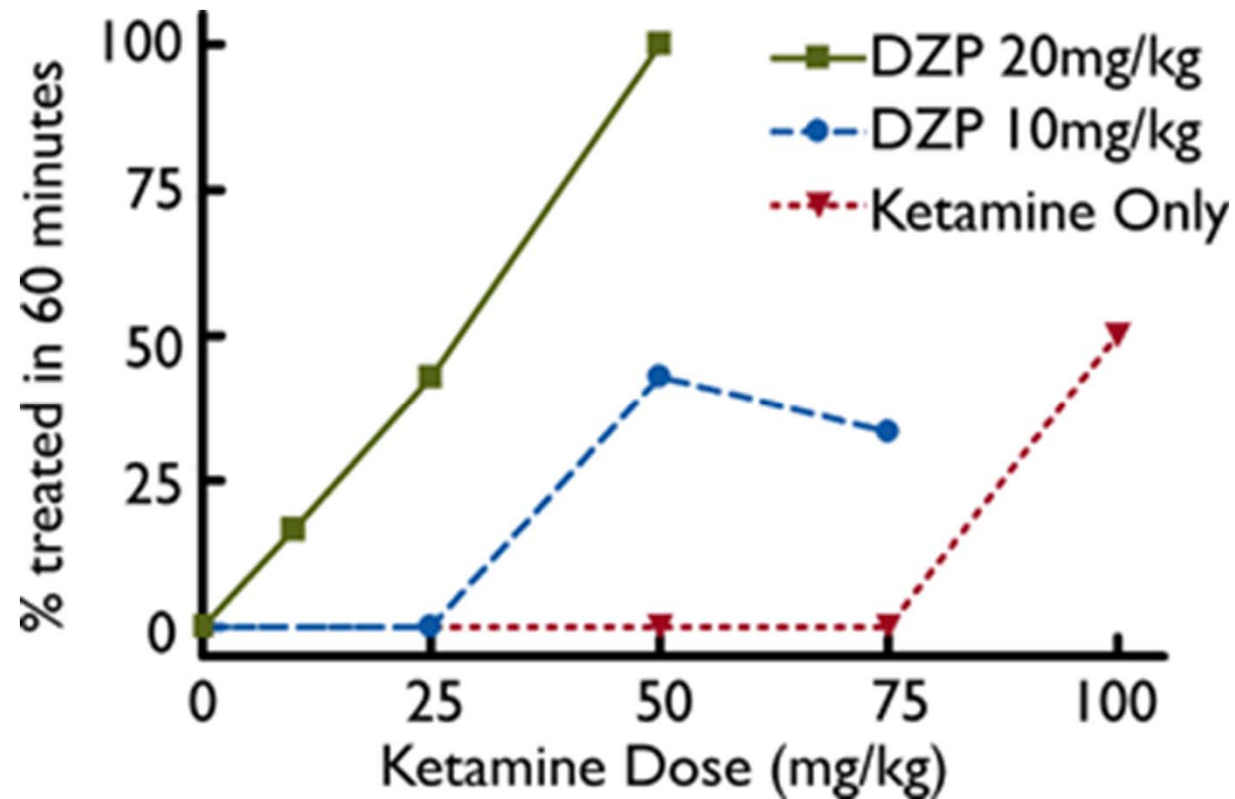
**5 min. post-treatment**



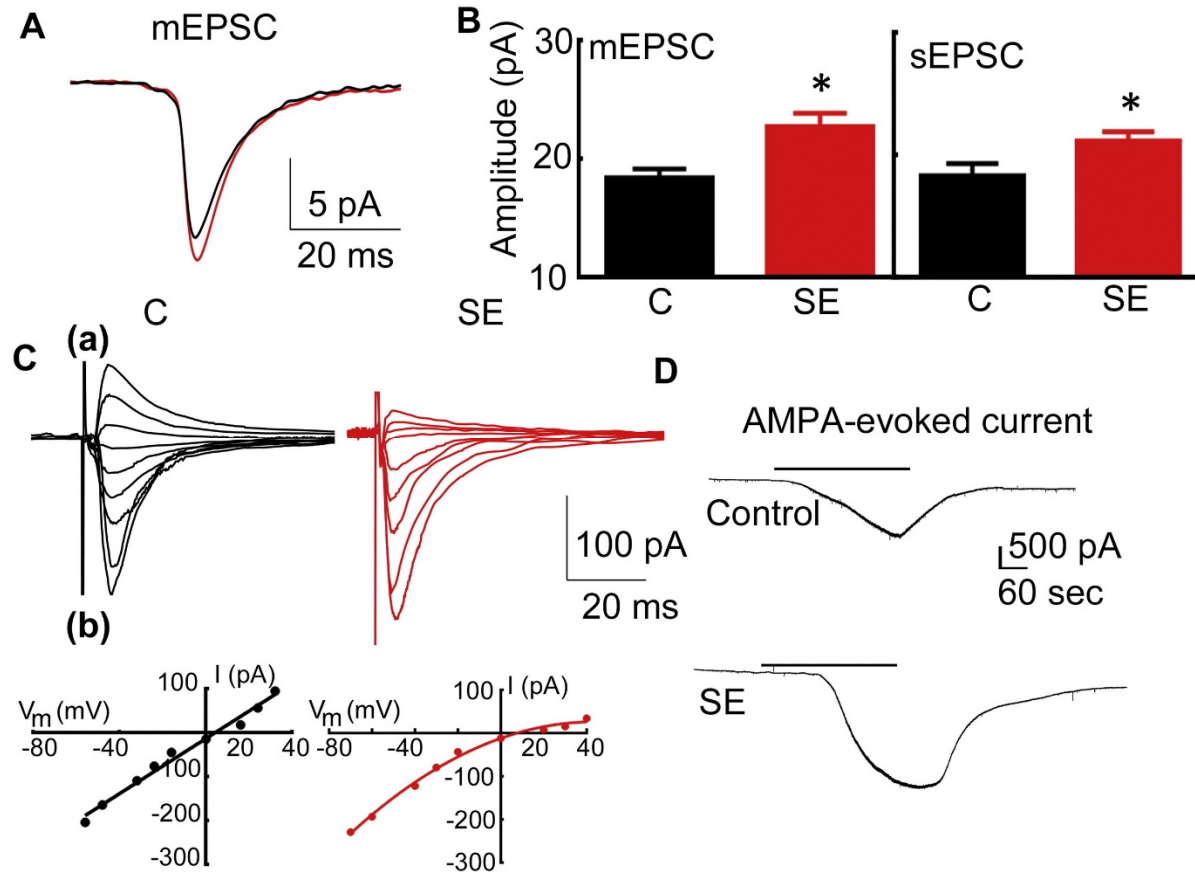
**1 hour post-treatment**



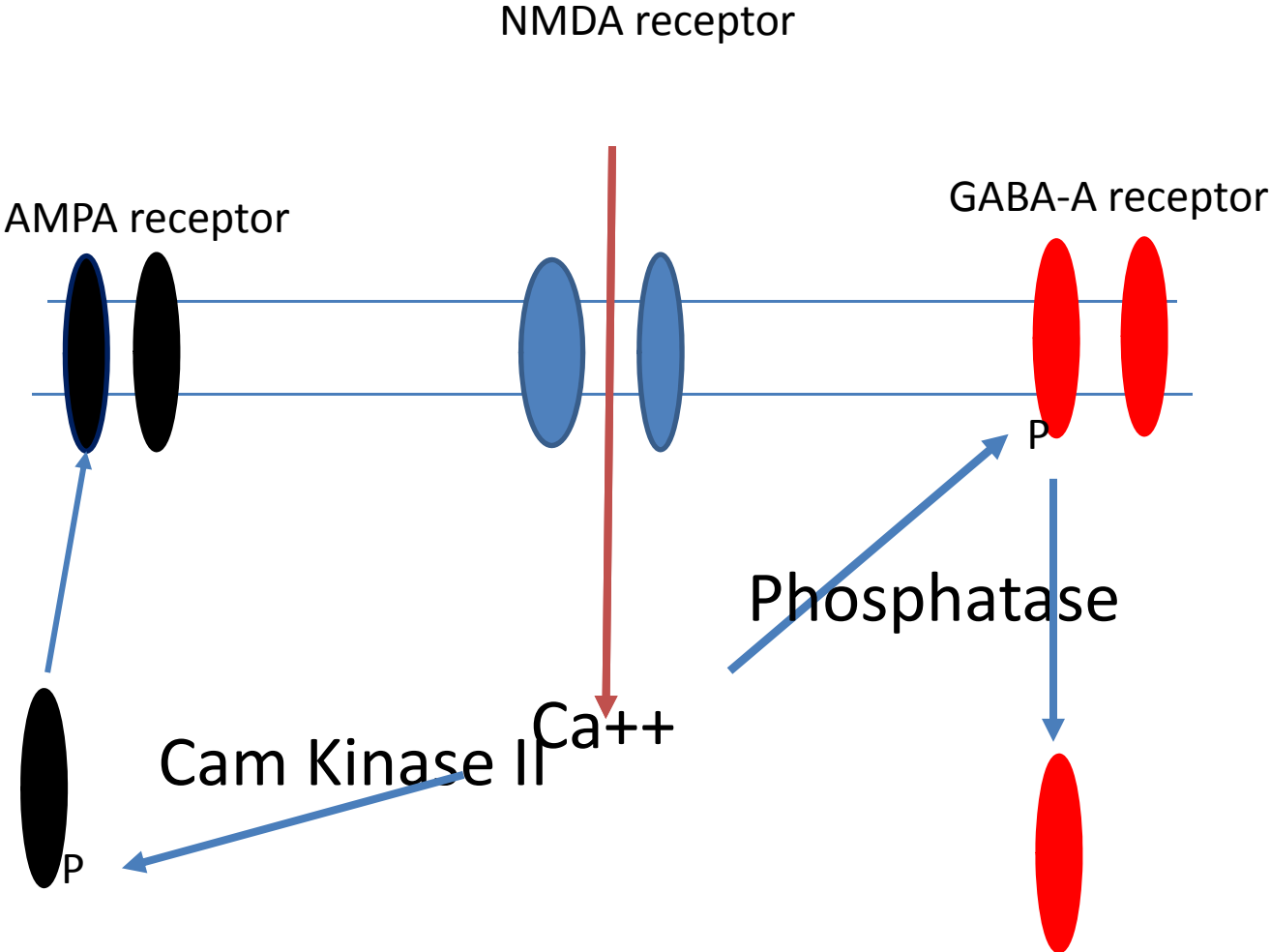
# Refractory SE: Ketamine + Diazepam







# NMDA receptors play a key role in SE



# Ketamine trial

- Eligibility
  - Failed ESETT.
  - Seizures present on EEG.
- Randomization: Midazolam drip + Ketamine.

Vs Midazolam.

Wean at 24 hours.

Primary outcome: Failure to wean.