Potential Future studies
<table>
<thead>
<tr>
<th>Time</th>
<th>Stage</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 min</td>
<td>Stage 1</td>
<td>Airway, breathing, circulation, laboratory tests, intravenous thiamine followed by dextrose</td>
</tr>
<tr>
<td>10 min</td>
<td>Stage 2</td>
<td>Lorazepam 2–4 mg intravenous (2 mg/min) (repeat if needed) or Midazolam 10 mg intramuscular (repeat if needed)</td>
</tr>
<tr>
<td>30 min</td>
<td>Stage 3</td>
<td>Phenytoin 20 mg/kg intravenous (50 mg/min) or Fosphenytoin 20 mg/kg PE intravenous (150 mg/min) (can give additional 5–10 mg/kg of either)</td>
</tr>
<tr>
<td>90 min</td>
<td>Stage 4</td>
<td>Midazolam load 0.2 mg/kg intravenous infusion 0.2–0.6 mg/kg/h or Propofol load 2 mg/kg intravenous infusion 2–5 mg/kg/h</td>
</tr>
<tr>
<td>Many hours to days</td>
<td>Stage 4</td>
<td>Pentobarbital load 5 mg/kg intravenous infusion 1–5 mg/kg/h</td>
</tr>
</tbody>
</table>
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 Leveteracetam: 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 and lower maximal binding than BEV.
BRV in brain: PET Imaging
<table>
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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

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Stage</th>
<th>Treatment Details</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>Airway,</td>
<td>Stage 1:</td>
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<tr>
<td></td>
<td>breathing,</td>
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<tr>
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<td>circulation,</td>
<td>needed) or</td>
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<td>laboratory</td>
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<td></td>
<td>intravenous</td>
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<tr>
<td></td>
<td>thiamine</td>
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<td>followed by</td>
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<td></td>
<td>dextrose</td>
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<td>30-90</td>
<td>Stage 4</td>
<td>Stage 4:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>- Pentobarbital load 5 mg/kg intravenous infusion 1-5</td>
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<td></td>
<td></td>
<td>mg/kg/h</td>
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</table>
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

Rhythmlink inc.
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.

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 deterikne 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
Refractory SE: Ketamine + Diazepam

% treated in 60 minutes

Ketamine Dose (mg/kg)
NMDA receptors play a key role in SE

![Diagram showing the role of NMDA receptors in SE](image-url)
Ketamine trial

• Eligibility
  – Failed ESETT.
  – Seizures present on EEG.

• Randomization: Midazolam drip + Ketamine. Vs Midazolam.

Wean at 24 hours.

Primary outcome: Failure to wean.