Evidentiary Table for Adult Status Epilepticus Clinical Guidelines
Produced in December 2018 by Aaron Blau, Andrew Perron MD, Jeffrey A. Holmes, MD

#	Author Publication Date	Study/Review	Design	LOE	Results/Recommendations	Comments
1	Glauser, Tracy et al Epilepsy Currents 2016	Evidence-Based Guideline: Treatment of Convulsive Status Epilepticus in Children and Adults: Report of the Guideline Committee of the American Epilepsy Society	Evidenced-Based Clinical Practice Guideline	NA	First Line -A benzodiazepine (specifically IM midazolam, IV lorazepam, or IV diazepam) is recommended as the initial therapy of choice, given their demonstrated efficacy, safety, and tolerability Second Line -There is no evidenced based second therapy of choice. Choose one of the following as a single loading dose: -IV fosphenytoin (20mg/kg, max 1500mg) -IV valproic acid (40mg/kg, max 3000mg) -IV levetiracetam (60mg/kg, max 4500mg) Third Line -There is no clear evidence to guide therapy in this phase. If second therapy fails to stop the seizures, treatment considerations should include repeating second-line therapy or anesthetic doses of either thiopental, midazolam, pentobarbital, or propofol (all with continuous EEG monitoring).	-Strong evidence for first line recommendations. -Insufficient evidence for second and third line recommendations
2	Brophy, Gretchen M et al Neurocritical Care 2012	Guidelines for the Evaluation and Management of Status Epilepticus	Evidenced-Based Clinical Practice Guideline	NA	-In patients with known epilepsy, who have been on an AED before admission, it is reasonable to provide and IV bolus of this AED, if available prior to initiating an additional agent.	-Use of home AED in patients with epilepsy on AED therapy reflects expert opinion -Insufficient evidence for preference in choice of third line therapy -Dosing recommendations based on expert opinion

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<td>- At present, there are insufficient data to suggest whether midazolam, propofol, or pentobarbital is the preferred agent. Propofol is an option but its safety profile needs to be considered as it can cause propofol infusion syndrome. Of the two other compounds, midazolam may cause less hypotension as it does not contain the solvent propylene glycol and may be preferred in selected clinical situations. Pentobarbital may have a higher rate of successfully controlling RSE acutely than midazolam, but may have more adverse effects.

Table 8 RSE dosing recommendations
<table>
<tr><th>Drug</th><th>Initial dose</th><th>Continuous infusion dosing recommendations-titrated to EEG</th><th>Serious adverse effects</th><th>Considerations</th></tr>
<tr><td>Midazolam</td><td>0.2 mg/kg; administer at an infusion rate of 2 mg/min</td><td>0.05–2 mg/kg/hr CI
Breakthrough SE: 0.1–0.2 mg/kg bolus, increase CI rate by 0.05–0.1 mg/kg/hr every 3–4 h</td><td>Respiratory depression
Hypotension</td><td>Tachyphylaxis occurs after prolonged use
Active metabolite, renally eliminated, rapid redistribution (short duration), does NOT contain propylene glycol</td></tr>
<tr><td>Pentobarbital</td><td>5–15 mg/kg, may give additional 5–10 mg/kg; administer at an infusion rate ≤50 mg/min</td><td>0.5–5 mg/kg/h CI
Breakthrough SE: 5 mg/kg bolus, increase CI rate by 0.5–1 mg/kg/h every 12 h</td><td>Hypotension
Respiratory depression
Cardiac depression
Paralytic ileus
At high doses, complete loss of neurological function</td><td>Requires mechanical ventilation
IV contains propylene glycol</td></tr>
<tr><td>Propofol</td><td>Start at 20 mcg/kg/min, with 1–2 mg/kg loading dose</td><td>30–200 mcg/kg/min CI
Use caution when administering high doses (>80 mcg/kg/min) for extended periods of time (i.e., >48 h)
Peds: Use caution with doses >65 mcg/kg/min; contraindicated in young children
Breakthrough SE: Increase CI rate by 5–10 mcg/kg/min every 5 min or 1 mg/kg bolus plus CI titration</td><td>Hypotension (especially with loading dose in critically ill patients)
Respiratory depression
Cardiac failure
Rhabdomyolysis
Metabolic acidosis
Renal failure (PRIS)</td><td>Requires mechanical ventilation
Must adjust daily caloric intake (1.1 kcal/ml)</td></tr>
<tr><td>Thiopental</td><td>2–7 mg/kg, administer at an infusion rate ≤50 mg/min</td><td>0.5–5 mg/kg/h CI
Breakthrough SE: 1–2 mg/kg bolus, increase CI rate by 0.5–1 mg/kg/h every 12 h</td><td>Hypotension
Respiratory depression
Cardiac depression</td><td>Requires mechanical ventilation
Metabolized to pentobarbital</td></tr>
</table>
CI continuous infusion; EEG electroencephalogram; h hour; IM intramuscular; IV intravenous; IVP intravenous push; min minute; PRIS propofol related infusion syndrome

-Recommended that cEEG findings, not serum drug levels, guide therapy in RSE</td>
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<tr>
<td>3</td>
<td>Brigo, Francesco Et al

Epilepsy and Behavior

2016</td>
<td>Direct and indirect comparison meta-analysis of levetiracetam versus phenytoin or valproate for convulsive status epilpeticus</td>
<td>Meta-analysis</td>
<td>I</td>
<td>-Small RCT’s insufficiently powered to detect evidence of no difference between the compared drugs.

-Pooling with meta-analysis suggests clinical equipoise of IV levetiracetam, IV valproate, and IV phenytoin.

-Further investigation required with large RCT (ESETT)</td>
<td>-ESETT ongoing, no published results at this time</td>
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4	Teiman, David M et al NEJM 1998	A Comparison of Four Treatments for Generalized Convulsive Status Epilepticus	RCT	I	Control of SE at 20 min (p=0.02) -IV lorazepam .1mg/kg 64.9% -IV phenytoin 18mg/kg 43.6% -IV phenobarbital 15mg/k 58.2% -IV diazapam .15mg/kg + 55.8% IV phenytoin 18mg/kg	-Large RCT, sufficient power
5	Silbergleit, R et al NEJM 2012	Intramuscular versus intravenous therapy for prehospital status epilepticus.	Non-inferiority RCT	I	Absence of seizure activity on arrival to ED (p=<0.001 for noninferiority) -IM midazolam 10mg 73.4% -IV lorazepam 4mg 63.4%	-Large RCT, sufficient power
6	Gujjar, Arunodaya et al Seizure: European Journal of Epilepsy 2017	Intravenous levetiracetam vs phenytoin for status epilepticus and cluster seizures: A prospective, randomized study	Small RCT	II	Rate of seizure control in SE at 24 hours following second line agent (p=0.62) -IV levetiracetam 30mg/kg 82.3% -IV phenytoin 20mg/kg 76.0%	-Not included in Brigo et al meta-analysis -Small RCT with insufficient power to detect evidence of no difference