NewYork-Presbyterian Hospital

STATUS EPILEPTICUS (SE) TREATMENT ALGORITHM IN ADULTS

There exists a lack of prospective controlled trials regarding the appropriate doses or targeted therapeutic levels for refractory status epilepticus. Many of the recommended doses or targeted therapeutic levels are higher than referenced in the literature and based upon expert opinions at NYPH. There is a lack of consensus among neurocritical care clinicians and epileptologists on the pharmacological approach to treatment of generalized convulsive status epilepticus after failure of a benzodiazepine. The suggestions below should not replace clinical judgment.

Definitions: SE is defined as clinical and/or electrographic seizure activity for ≥ 5 minutes or recurrent seizure activity without recovery between seizures.

	MEDICATIONS	NOTES/COMMENTS
Within 1st 5 minutes	**Emergent Initial (1st line)** **Lorazepam** 4 mg IV over 2 minutes; if still seizing, repeat X 1 in 5 minutes **Urgent Control (2nd line)** **Fosphenytoin/Phenytoin, Valproate, or IV bolus of home AED** *Alternative*: Phenobarbital, Levetiracetam	•ABCs; Obtain IV access; FSBG •Begin continuous monitoring of O_2, HR, BP •Draw blood for: CBC, ABG, BMP, Ca, Mg, PO_4, LFTs, troponin, phenytoin, valproate, carbamazepine, other AED levels •50 mL D50W IV unless blood glucose level known & not low •If no rapid IV access, give midazolam 10 mg IM (preferred), intranasally, or buccally (use IV midazolam solution by any of these routes) or give diazepam (Diastat) 20 mg PR (IV diazepam solution can be given PR if Diastat is not available)
Refractory SE	**Midazolam** drip with boluses **Alternatives** (if not given above) 1. Propofol, drip with boluses 2. Fosphenytoin/phenytoin 3. Valproate 4. Levetiracetam 5. Phenobarbital 6. Lacosamide (only if failure of or contraindication to options above)	•Proceed to continuous infusion AED. However, in patients with NCSE who are hemodynamically stable and have not required intubation, consider additional intermittent bolus AEDs if not previously administered •Avoid valproate + phenytoin due to drug interactions •If 1st continuous AED fails, switch or add additional continuous anesthetic and/or add a second AED •Continue adding agents until cessation of clinical and electrographic seizures
Super-refractory ≥30 minutes	• If seizing >30 minutes should be on at least one continuous anesthetic IV drip with boluses every 5 minutes (if BP stable) until cessation of clinical or electrographic seizures • If still seizing, continue optimizing AED dosing, consider adding another AED, changing to a different continuous infusion AED (e.g., propofol or midazolam) or adding another continuous infusion anesthetic (e.g., pentobarbital or ketamine) until cessation of clinical or electrographic seizures or futility is determined.	

Refer to dosing table for all doses

Other Considerations:

•Begin **continuous EEG monitoring** as soon as possible if the patient does not awaken rapidly or if any continuous IV treatment is used
• Administer Thiamine 100 mg IV followed by dextrose once patient stabilized
•Toxicology screen (urine and blood); HCG for women of reproductive age
•12-lead EKG
•Obtain neuroimaging after convulsive activity controlled

TREATMENT PEARLS

- Obtain fingerstick blood glucose
- When checking post-load drug levels, wait 2 hours post infusion for fosphenytoin, phenytoin and valproate.
- Continuous IV infusion duration of treatment: Once seizures are controlled, continue same dose for at least 24 hours prior to consideration of wean.
- Loading doses do not require adjustment for renal or hepatic insufficiency.
- Maintain euthermia.
- If paralytics must be used, assure continuous EEG.
- When weaning continuous infusions particularly pentobarbital, consider adding phenobarbital

Medication	Dose	Method of In-activation	$t_{1/2}$ (h)	Protein Binding	Drug Interaction	Targeted trough drug levels for status epilepticus	Dose Adjustment in Renal Impairment	Dose Adjustment in Renal Replacement Therapy	Dose Adjust-ment in Liver Impairment	SE, Monitoring, Comments
FOSPHENYTOIN (Cerebyx) Dilute in NS* 2-25 mg/mL	Load: 20 mg PE/kg IV Max IV rate 150 mg/min May give an additional 5 mg PE/kg dose 10 minutes after loading infusion Maintenance: See phenytoin • IV filter and NS flush following administration not required	See phenytoin Conversion half-life to phenytoin ~15 minutes								SE: Hypotension, arrhythmias
PHENYTOIN (Dilantin) Dilute in NS ONLY, final concentration 2-10 mg/mL **Avoid small vein administration**	Load: 20 mg/kg IV; maximum rate 50 mg/min 25 mg/min in elderly or patients with pre-existing cardiovascular conditions May give an additional 5-10 mg/kg dose 10 minutes after loading infusion Maintenance: 5-7 mg/kg/day in 2-3 divided doses Lower doses required in elderly • Infuse through dedicated line with 0.22 -0.55 µm filter • Flush with NS following administration	Hepatic	~10-15 (IV)	90%	Major substrate: CYP 2C9 and 2C19 Induces: CYP 1A2, 2B6, 2C, 3A3/4, 3A5-7	Total: 15-25 mg/L, Free: 1.5-2.5 mg/L (monitor free level when on VPA, midazolam or other highly protein bound medications, low albumin or if critically ill)	None, monitor free levels	None, monitor free levels	Consider dose reduction	SE: Hypotension, arrhythmias, metabolic acidosis (diluted in 40% propylene glycol) Precipitation with many drugs/diluents: D5W, potassium, insulin, heparin, vasopressors, cephalosporins, dobutamine
KETAMINE (Ketalar) 500 mg/500 mL NS (1 mg/mL) 500 mg/250 mL NS (2 mg/mL) 2500 mg/25 mL (100 mg/mL, undiluted)	Load: 1.5 mg/kg q 3-5 min until seizure stops, up to max of 4.5 mg/kg total Initial: 1 mg/kg/h, bolus and increase rate by 0.5-1 mg/kg/h until seizure control Maintenance: 1-10 mg/kg/h	Hepatic	2.5	45%	Major substrate CYP2B6, 2C9, 3A4	None	None	Unclear	Consider dose reduction	SE: Caution in patients with cardiac disease, hypertension, ↑ ICP • Consider combining with benzodiazepine to lower dose requirements
LACOSAMIDE (Vimpat) Dilute in 50 mL NS* 200 mg/20 mL Inj	Initial: 400 mg IV over 15-30 min Maintenance: 200 – 300 mg IV/PO over 30-60 min q 12 hours	Hepatic 60%, Renal 40%	13	<15%	None	None	Maximum 300 mg/day for CrCl < 30 mL/min	HD: 50% removed, maximum 300 mg/day, add 50% of am dose post dialysis. CRRT: normal dosing without renal adjustment	Consider dose reduction	SE: May prolong PR interval

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LEVETIRACETAM (Keppra) Dilute in 100 mL NS* 100 mg/mL solution 500 mg/ 5 mL inj	Load: 1000-3000 mg IV over 5-15min Initial: 3000-6000 mg/day divided in 3-4 divided doses Maintenance: 2000-6000 mg/day IV/PO in 3-4 divided doses	Enzymatic hydrolysis 33%, Renal 67%	~6-8	<10%	None	25-60 mg/L. Unclear relationship between serum levels and efficacy. Dose guided by clinical response.	Reduce dose for CrCl < 80 mL/min	HD: 50% removed, dose q 24 hours; add 50% of am dose post dialysis. CRRT: normal dosing without renal adjustment	None	SE: psychosis, sedation
MIDAZOLAM (Versed) 100 mg/100 mL NS* (1 mg/mL) 500 mg/100 mL NS* (5 mg/mL)	Load: 0.2 mg/kg IV over 2-5 min; repeat 0.2-0.4 mg/kg boluses every 5 minutes until seizures stop, up to a maximum loading dose of 2 mg/kg. Initial rate: 0.1 mg/kg/h. Bolus and increase rate until seizure control Maintenance: 0.05-2.9 mg/kg/h	Hepatic; Active metabolite excreted renally	3-11	95%	Inhibitor CYP 3A, C9, 2C8	None	Consider dose reduction: active metabolite accumulate	None	Consider dose reduction	SE: Hypotension Tachyphylaxis with prolonged use • Accumulates in fat tissue and renal impairment
PENTObarbital (Nembutal) Dilute up to 50 mg/mL NS* 1 g/250 mL NS*(4 mg/mL) 2 g/250 mL NS*(8 mg/mL) 50 mg/mL inj (2mL, 20 mL)	Load: 5 mg/kg IV; repeat 5 mg/kg boluses until seizures stop. Maximum rate: 50 mg/min Initial rate: 1 mg/kg/h Maintenance: 0.5-10 mg/kg/h traditionally titrated to suppression-burst on EEG but titrating to seizure suppression is reasonable as well	Hepatic	~15-50	35-55%	Induces CYP 2A6, 3A4	Monitoring levels not recommended for RSE	None	None	Consider dose reduction	SE: Hypotension, gastric stasis, myocardial suppression, thrombocytopenia, metabolic acidosis (diluted in 68-75% propylene glycol)
PHENObarbital (Luminal) Dilute in NS* Max conc 130 mg/mL 65,130 mg/mL (1 mL)	Load: 20 mg/kg IV; May give additional 5-10 mg/kg dose 10 minutes after initial loading dose. Maximum rate: 60 mg/min Maintenance: 1-3 mg/kg/day in 2-3 divided doses Doses < 300 mg IV over 3-5 min (up to 60 mg/min)	Hepatic 75%, Renal 25%	~ 53-140	20-45%	Induces UGT, CYP 3A4, 2B6, 2C9, 2A6, 1A2	20-50 mg/L	Consider dose reduction	HD: 50% removed, consider additional 50% post dialysis. CRRT: normal dosing without renal adjustment	Consider dose reduction	SE : Hypotension, hypoventilation, metabolic acidosis (diluted in 40% propylene glycol)

Medication	Dose	Method of In-activation	$t_{1/2}$ (h)	Protein Binding	Drug Interaction	Targeted trough drug levels for status epilepticus	Dose Adjustment in Renal Impairment	Dose Adjustment in Renal Replacement Therapy	Dose Adjust-ment in Liver Impairment	SE, Monitoring, Comments
PROPOFOL (Diprivan) 1 G in 100 mL premixed (10 mg/mL) • Change drug/tubing every 12 hours	Load: 1-2 mg/kg IV over 3-5 min; repeat boluses every 3-5 minutes until seizures stop, up to maximum total loading dose of 10 mg/kg. Initial rate: 20 microgram/kg/min Bolus and increase rate until seizure control Maintenance: 17 – 200 microgram/kg/min See comment column.	Hepatic	~ 4-7 h to 1-3 days	90%	None	None	None	None	None	SE: Hypotension, hypertriglyceridemia, pancreatitis, Propofol Infusion Syndrome (metabolic acidosis, bradycardia, cardiac arrest, rhabdomyolysis) • Monitor pH, HCO_3, CPK & cardiac function, triglycerides • Accumulates in fat tissue • Contraindications: allergy to soy, egg • Avoid doses > 80 microgram/kg/min for >24-48 h
Topiramate (Topamax) Tablet: 25, 100, 200 mg	Load: NA Maintenance dose: 300-1600 mg/day orally (divided in 2 doses)	Renal 70%	19-23	**15-41%**	None	None	CrCl < 70 mL/min: Reduce dose by 50%	HD: 50-100 mg q 12 hours; 50% removed, add additional 50% post dialysis. CRRT: normal dosing without renal adjustment	None	No IV formulation SE : hyperchloremic, non-gap, metabolic acidosis
VALPROATE (Depacon) Dilute: < 2500 mg in 50 mL NS* ≥ 2500 mg in 100 mL NS* max 50 mg/mL 500 mg/5 mL inj	Load: 40 mg/kg IV over 10 min; if still seizing, additional 20 mg/kg over 5 min (max rate 6 mg/kg/min) Initial: 1 g IV q 6 hours	Hepatic	~9-16	90%	Weak inhibitor: CYP 2C19, 2A6, 3A4 Weak inducer: CYP2A6 • Carbapenems ↓ levels significantly (can occur with one dose), concomitant use is **contraindicated** • VPA strongly inhibits lamotrigine metabolism	Total: 80-140 mg/L Free: 7-23 mg/L	None; consider monitoring free levels	None; consider monitoring free levels	Avoid	SE: thrombocytopenia, hepatic toxicity, pancreatitis, , hyperammonemic encephalopathy

Continuous cardiac monitoring recommended for all agents in this setting

*Stable in 5% dextrose in water (D5W) as well. Normal Saline is the standard diluent in the NeuroICUs for medicated drips where stability in normal saline has been established,

ABC= airway, breathing, circulation; AED= antiepileptic drugs; BMP= basic metabolic panel; BZ= benzodiazepines; Ca= calcium; CBC= complete blood count; DPH= phenytoin; FSBG= fingerstick blood glucose; Mg= magnesium; ICP= intracerebral pressure; PE= phenytoin equivalents; PO_4= phosphate; SE: Side effects; UGT= glucoronidation; VPA= valproate

RESPONSIBILITY:

Enterprise Subcommittee of Critical Care Therapeutics

GUIDELINE DATES:

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References:

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