HOW I MANAGE REFRACTORY & SUPER-REFRACTORY STATUS EPILEPTICUS

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Brain health is our greatest wealth

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Calgary CRITICAL CARE MEDICINE
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~~OUTLINE & OBJECTIVES~~
CONCLUSION

HOW DO I MANAGE RSE & SRSE?

BEST = PREVENTION

AGGRESSIVE
SYSTEMATIC
EVIDENCE-BASED
PRECISION-GUIDED
COMPREHENSIVE

Outline **Objectives** - By the end of this talk, attendees will:

Definitions	Define SE, RSE and SRSE and explain important pathophysiology
Prevention	Explain the importance of proper benzodiazepine dosing in SE
Management	Appreciate common pitfalls of RSE/SRSE management & be equipped with resources to help navigate them.

DEFINITIONS

STATUS EPILEPTICUS (SE)

Sufficiently prolonged **(≥5-10min)** *or repeated seizures*

Table 1. Operational dimensions with t_1 indicating the time that emergency treatment of SE should be started and t_2 indicating the time at which long-term consequences may be expected

Type of SE	Operational dimension 1 Time (t_1), when a seizure is likely to be prolonged leading to continuous seizure activity	Operational dimension 2 Time (t_2), when a seizure may cause long term consequences (including neuronal injury, neuronal death, alteration of neuronal networks and functional deficits)
Tonic–clonic SE	5 min	30 min
Focal SE with impaired consciousness	10 min	>60 min
Absence status epilepticus	10–15 min	Unknown

*Electrographic Status Epilepticus: ≥10 continuous minutes
OR ≥ 20% (12min) / 60min of EEG recording

→Enduring epileptic condition

Will not stop
Neuronal injury
Patient harm

REFRACTORY STATUS EPILEPTICUS (RSE)

seizures ***despite***
adequate doses of BNZ + ASM

SUPER REFRACTORY STATUS EPILEPTICUS (SRSE)

Continuous/recurrent *seizures*
≥24hrs after *onset of* **anesthetic agents**

Epilepsia. 2015; 56(10): 1515-1523.

PATHOPHYSIOLOGY

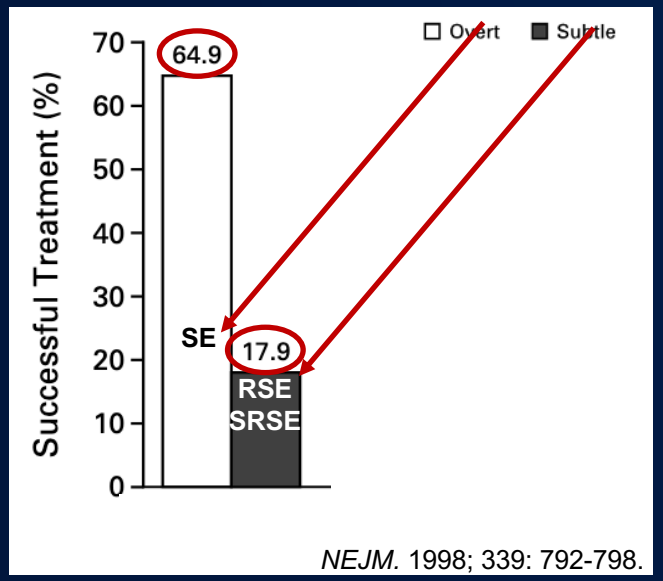
	Time	Definition	Pathophysiology	Death & Disability
Stage I	< 30min	Early/ Impending SE	Protein phosphorylation Ion channel open/close Neurotransmitter release **Receptor trafficking** **↓ $GABA_a$ R** **↑ NMDA R** **↑ AMPA R**	Hosp LOS 3D ICU LOS 5-7D ~5% mortality 45-65% home
Stage II	> 30min - 120min	Established SE		
Stage III	> 120min	Refractory SE	Neuropeptide expression ↑ Substance P ↓ Neuropeptide Y	Hosp LOS 6D ICU LOS 13D 10-40% mortality 35% home
Stage IV	>24hr	Super Refractory SE	Genetic & Epigenetic changes: Gene expression DNA methylation Regulation of mRNA	35-65% mortality

Seizure. 2020: 75: 153-164. / *JAMA Neurology. 2021;* 78(5): 588-595.

PREVENTION

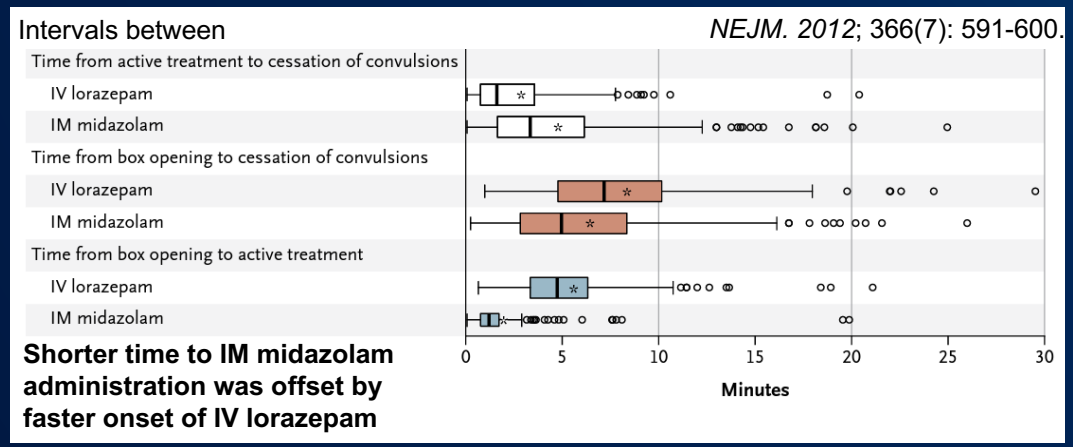
Benzodiazepines (Level A)

Lorazepam
0.1mg/kg IV
max = 2-4mg/min → 8mg

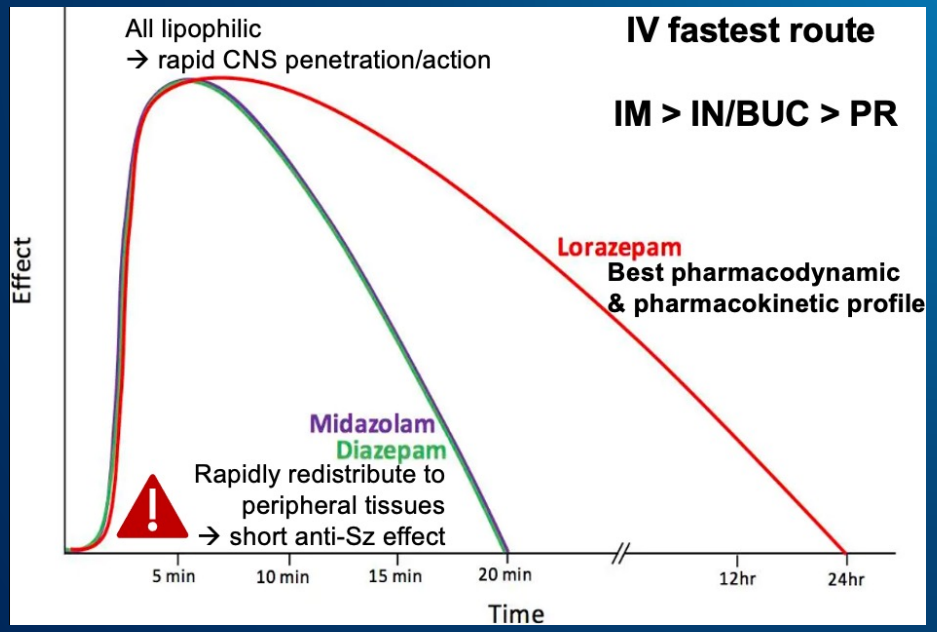


NEJM. 1998; 339: 792-798.

Midazolam
0.2mg/kg IV/IM/IN/BUC
max = 10mg



Shorter time to IM midazolam administration was offset by faster onset of IV lorazepam



Diazepam
0.15mg/kg IV, max = 10mg x 2

0.3-0.5mg/kg PR, max = 20mg

⚠ often **underdosed** – only 30% ESETT dosed properly ⚠

MANAGEMENT

= aggressive, comprehensive, systematic, simultaneous assessment & treatment

Supportive Care
Beware Complications

Stop & Prevent Seizures

Identify & Treat Cause

Evidence based
+
Precision guided

- Emergent/Initial Rx
- Urgent Control Rx
- **Refractory Rx**
- **Super Refractory Rx**

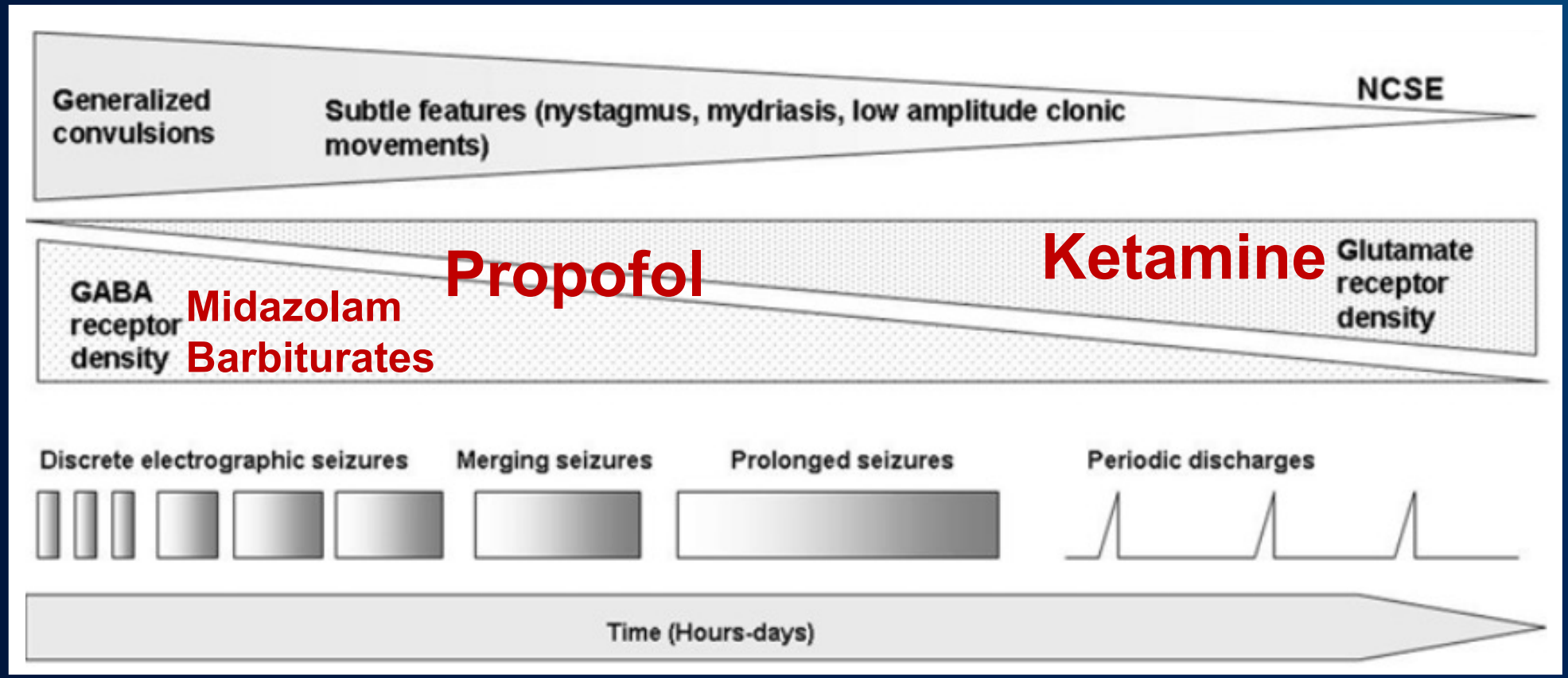
Common pitfalls

Epilepsy Curr. 2016; 16(1): 48-61 / Neurocrit Care. 2012; 17(1): 3-23.

MANAGEMENT

SEDATION

GABA Agonism vs NMDA Antagonism

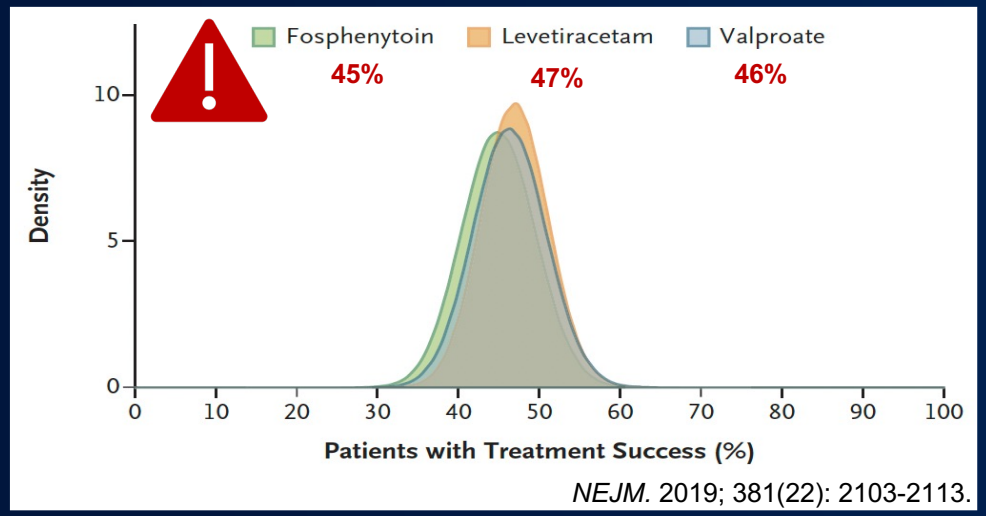


CJNS. 2012; 39(2): 157-169.

MANAGEMENT

SEDATIVE	MOA	DOSE (IV)	SIDE EFFECTS	CONSIDERATIONS
Midazolam Level B	$GABA_A$ agonist	0.2mg/kg load 0.05-2mg/kg/hr	↓ RR, ↓ BP NAGMA (HCl) WAGMA (BA)	Active metabolites renally cleared + peripheral redistribution → ↑ context sensitive T1/2 Mixed in HCl/benzyl alcohol (BA) Tachyphylaxis
Propofol Level B	$GABA_A$ agonist NMDA antagonist Inhibits glutamate release	1-2mg/kg load 20-200mcg/kg/min	↓ RR, ↓ BP HyperTG PRIS – cardiogenic shock, bradycardia, rhabdomyolysis, AKI, WAGMA (PG)	Mixed in propylene glycol (PG) Adjust feeds to account for 1.1kcal/mL PRIS: ↑ risk with young age, neurologic dx, prolonged infusions.
Ketamine Level U	NMDA antagonist	1.5mg/kg load 1-10mg/kg/hr	↑ BP, ↑ HR	Consider early use?
Pentobarbital Level B	$GABA_A$ agonist	5-15mg/kg load 0.5-5mg/kg/hr	↓ RR, ↓ Temp ↓ BP (SVR/inotropy) Ileus, WAGMA (PG) ↓ immune system	Mixed with propylene glycol (PG) CYP inducer → Med interactions

MANAGEMENT

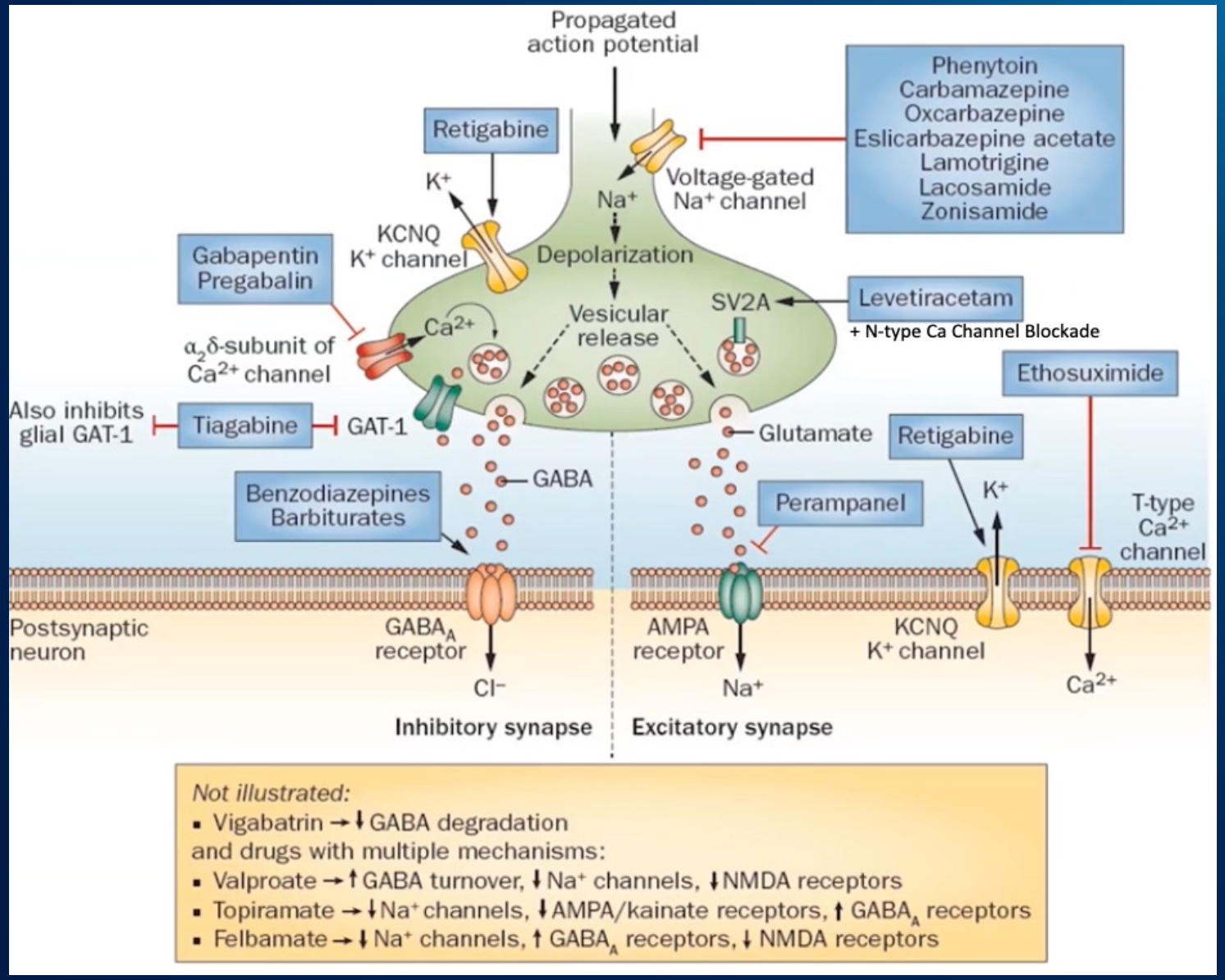


NEJM. 2019; 381(22): 2103-2113.

Individualized, aggressive, systematic selection and titration

CONSIDER

Mix mechanisms
Underlying cause
Comorbidities
Allergies
Renal/Liver function
Drug administration & interactions
Life threatening side effects



Ther Clin Risk Manage, 2013; 9:258-293 / *Neurocrit Care.* 2012; 17: 24-30.

MANAGEMENT

ASM	Mechanism of Action	Loading Dose	Maintenance Dose	Metabolism	Adverse Effects	Comments
4 Clobazam If bnz responsive	$GABA_A$ agonist	variable	20 mg/d in 2 divided doses (range 10–60 mg/d)	Hepatic to active metabolite	Ataxia Somnolence/sedation Upper respiratory infections	Oral/enteral administration only
Fosphenytoin	Increases efflux/decreases influx of sodium across cell membrane	20 mg Phenytoin equivalents/kg IV (max 1500 mg)	4–6 mg Phenytoin equivalents /kg/d in divided doses	Rapid hydrolysis to phenytoin then hepatic	Arrhythmias Hypotension	Administer no faster than 150 mg PE/min Potent CYP inducer resulting in many drug-drug interactions Therapeutic drug monitoring required (total phenytoin level 10–20 mcg/mL or free phenytoin level 1–2 mcg/mL); total level unreliable in hypoalbuminemia and renal impairment Highly protein bound Transition to oral phenytoin when applicable
3 Lacosamide	Enhances slow inactivation of voltage gated sodium channels	200–400 mg IV	200–400 mg/d in 2 divided doses	Hepatic to inactive metabolites	Hypotension PR prolongation	Cardiac monitoring recommended with higher doses and in patients with history of cardiac disease
1 Levetiracetam	Unknown; may interact with N- type calcium channels, facilitates GABA inhibition, interacts with potassium rectifier current, and/or bind to synaptic vesicle proteins	60 mg/kg IV (max 4.5 g)	1000–3000 mg/d in 2 divided doses	Hydrolysis	Agitation/behavior disturbances Somnolence/sedation	Minimal drug interactions and adverse effects
Phenobarbital	Increases GABA activity by altering inhibitory synaptic transmission mediated by $GABA_A$	20 mg/kg IV	1–3 mg/kg/d in divided doses	Hepatic to inactive metabolites	Hypotension Respiratory depression	Contains propylene glycol Therapeutic drug monitoring required (15–40 mcg/mL)
4 Perampanel If ketamine responsive	AMPA receptor antagonist	variable	2-6mg starting described 6-32mg/d max described *Epilepsy & Behavior* 2022; 128:108583	Hepatic to inactive metabolites	Serious psychological and behavioral disturbances including SI (BW)	Major substrate o CYP 3A4 so higher doses may be required with inducers such as carbamazepine, phenytoin, or oxcarbazepine
Topiramate	Block voltage gated sodium channels, increase GABA activity, antagonize AMPA/kainite glutamate receptors, weak carbonic anhydrase inhibitor	Variable	300–1600 mg/d in divided doses	Not extensively metabolized	Metabolic acidosis Somnolence	Oral/enteral administration only
2 Valproic Acid	Increases availability of GABA or may increases the action of GABA; prolongs recovery phase of voltage-gated sodium channels	40 mg/kg IV (max 3000 mg)	10–60 mg/kg/d in divided doses	Hepatic to active metabolites	Hyperammonemia Pancreatitis Thrombocytopenia Transaminitis	Therapeutic drug monitoring required (50–100 mcg/mL) Concomitant use with carbapenem antibiotics should be avoided due to significant and prolonged drops in serum valproic acid level Highly protein bound

J Clin Medicine. 2021; 10: 3028. / *Epilepsy Currents.* 2020; 20(5): 245-264.

MANAGEMENT

ASM-Drug Interactions

Antiepileptic drug	Therapeutic group	Selected examples
Phenytoin, phenobarbital, carbamazepine	Psychotropic agents	↓ Amitriptyline, nortriptyline, imipramine, bupropion, paroxetine, citalopram, Haloperidol, chlorpromazine, olanzapine, risperidone, quetiapine, ziprasidone
Valproic acid		↑ Amitriptyline, nortriptyline, paroxetine
Topiramate		↑ Haloperidol
Phenytoin, phenobarbital, carbamazepine	Antimicrobials	↓ Doxycycline, metronidazole, itraconazole, retrovirals
Valproic acid		↑ Zidovudine
Phenytoin	Cardiovascular agents	↓ Amiodarone, nimodipine, diltiazem, verapamil, ticagrelor, atorvastatin, dabigatran, apixaban, rivaroxaban (↑ warfarin effects with phenytoin load, ↓ warfarin effects with maintenance dose of phenytoin)[a]
Lacosamide		Diltiazem, verapamil (risk of atrioventricular block/ bradycardia), ↓ warfarin
Carbamazepine		↓ Nimodipine, diltiazem, verapamil, ticagrelor, atorvastatin, warfarin, dabigatran, apixaban and rivaroxaban
Phenobarbital		↓ Nimodipine, atorvastatin
Valproic acid		↑ Nimodipine, warfarin
Phenytoin, phenobarbital, carbamazepine	Analgesics	↓ Fentanyl, methadone
Phenytoin, phenobarbital, carbamazepine	Immunosuppressant	↓ Cyclosporine, sirolimus, tacrolimus, corticosteroids

ASM-ASM Interactions

	CBZ	CNP	DZP	LAC	LAM	MDZ	OXZ	PEN	PMP	PHB	PHT	TOP
ZON	↓ZON			↓LAC			↓ZON	↓ZON		↓ZON	↓ZON	↓ZON
	↑CBZ											
VPA	↓VPA	? risk of absence seizures			↑ LAM		↓OXZ		↑VPA	↑PHB	↑PHT	↓VPA
	↑CBZ									↓VPA	↓VPA	
TOP	↓VPA		↑ DZP			↓MDZ		↓TOP	↓ PMP	↓TOP	↑PHT	
	↓TOP										↓TOP	
PHT	↓↑CBZ		↓ DZP	↓LAC	↓ LAM	↓MDZ		↓PEN	↓ PMP	↓PHT		
	↓↑PHT											
PHB	↓CBZ		↓ DZP		↓ LAM	↓MDZ	↓OXZ					
PEN	↓CBZ		↓ DZP			↓MDZ						
OXZ	↓CBZ		↑↓DZP			↓MDZ						
	↓OXZ											
MDZ	↓MDZ											
LAM	↓LAM											
LAC	↓LAC											
DZP	↓DZP											
	↑CBZ											
CNP												
BRV	↓BRV											

Critical Care. 2018; 22: 153.

Clin Drug Investig. 2017; 37(1): 7–23.
Intensive Care Med. 1995;21(7):612–20.
Clin Pharmacokinet. 1993;24(5):362–79.
Pharmacotherapy. 2007;27(11):1529–49.

Drugs → ↓ Sz Threshold

Antibiotics	Psychotropic agents	Analgesics	Neurostimulants	Miscellaneous agents
Cefepime	Bupropion	Meperidine[b]	Amantadine	Baclofen
Erythromycin	Haloperidol	Tramadol	Amphetamines	Flumazenil
Imipenem[a]	Phenothiazines		Bromocriptine	
Isoniazid	SSRIs			
Levofloxacin	TCAs			
Linezolid				
Meropenem				
Metronidazole				
Penicillins				

RRT/PLEX Considerations

Drug-related factors	RRT-related factors
• Low protein binding	• Mode of dialysis (CRRT vs. IHD vs. others)
• Low volume of distribution	• RRT filter membrane (sieving coefficient)
• Predominantly renally eliminated	• Dialysis prescription (mode and flow rates)
• Low molecular weight	• Duration/frequency of renal replacement

Drug-ASM Interactions

Therapeutic class	Selected examples	Antiepileptic drugs
Psychotropic agents	Fluoxetine, sertraline, trazodone	↑ Phenytoin
	Trazodone, fluoxetine, risperidone	↑ Carbamazepine
	Sertraline	↑ Valproic acid
Antimicrobials	Erythromycin, clarithromycin, ketoconazole, fluconazole	↑ Carbamazepine
	Ritonavir	
	Sulfonamides	↑ Phenytoin
	Carbapenems (imipenem, doripenem, meropenem, ertapenem)	↓ Valproic acid
Cardiovascular agents	Amiodarone	↑ Phenytoin (a dose reduction of approximately 25% is recommended)
	Diltiazem	↑ Carbamazepine, phenytoin (risk of toxicity)
	Clopidogrel	↑ Phenytoin
Analgesics	Acetaminophen	↓ Lamotrigine
Immunosuppressants	Methotrexate	↓ Valproic acid, carbamazepine

MANAGEMENT

CATEGORY		CONSIDERATIONS	REFERENCE
⚠ Immunotherapy **>50% NORSE AIE/Paraneoplastic**	Solumedrol 1g daily x 3-5d IVIG 2g/kg / 3-5d PLEX q2d x 3-5d Rituximab 375mg/m^2 qwk x4 Cyclophosphamide 500-1000mg/m^2 qmth x3-6	R/O infection. Dx & Rx associated malignancy Beware: Complications Infection risk Evidence evolving for other agents: Anikinra, Tacrolimus, Azathioprine	*Neuro NSx Psych.* 2021;92:757-68. *Seizure.* 2019; 68: 72–78. *Neurology.* 2020; 95: e2280–e2285
⚠ Ketogenic Diet		55-90% success. Pharmacist + dietician essential C/I: N/WAGMA, hepatic failure, pancreatitis Increased risk of PRIS with propofol	*Neurology.* 2014; 82: 665–670. *Neurosci. Lett.* 2017; 637: 4–10. *Neurology.* 2017; 88: 938–943. *Brain Dev.* 2019; 41: 420–427.
Neurosteroids	Brexanolone Ganaxolone	Phase III STATUS RCT (SRSE) negative Phase III RAISE RCT (RSE) underway	*Ann Neurol.* 2017 ;82(3): 342-352.
Neuromodulation	Vagal Nerve Stimulation Electroconvulsive Therapy Transcranial Magnetic Stim	Case reports – 80% success (publication bias) Most often used in peds/EPC	*Brain Stimul.* 2019; 12: 835–844.
NSx resection		Target required. Most used/successful in pediatrics	*Epilepsia.* 2007; 48: 61–65.
Hypothermia	32-34^{o}C	HYPERNATUS = negative RCT	*NEJM.* 2016; 375: 2457–2467.
Other	Inhalational Anesthetics Lidocaine MgSO4 Cannabinoids	High complication rate/morbidity Low complication rate Evolving case reports	CJNS 2015; 42(2): 106-115.. *Seizure.* 2015; 31: 41-48. *Seizure.* 2015; 32 :100-108.

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MANAGEMENT

J Clin Neurophysiol. 2015;32:87-95.
Intensive Care Med. 2013;39:1337–1351.
Neurocrit Care. 2012 17: 3-23.

NEUROCRITICAL CARE SOCIETY

AMERICAN CLINICAL NEUROPHYSIOLOGY SOCIETY • 1946 •

ESICM EUROPEAN SOCIETY OF INTENSIVE CARE MEDICINE

PERFORMANCE INTERPRETATION

Neurocrit Care. 2021; 35(3): 894-912

THERAPEUTIC CONSIDERATIONS

Ictal Interictal Continuum

Semin Respir Crit Care Med 2017;38(06): 793-806.
Clin. Neurophysiol Prac. 2017;2:107-118.
JAMA Neurol. 2017;74(2):181-188

Burst suppression vs Sz suppression

No evidence comparing

Emergence Patterns

J Clin Neurophysiol. 2022; 39(4): 289-294.
Neurocrit Care. 2018; 29(3): 452-462.

MANAGEMENT

COMPLICATIONS

TREATMENT RELATED		DIAGNOSIS RELATED
DIRECT	**INDIRECT**	
Sedatives: ↓ RR, ↓ BP	Delirium Deconditioning (CIN/M)	Cerebral edema Mass effect
PROP: HyperTG – pancreatitis, PRIS - shock, ↓ HR, AKI, rhabdomyolysis, WAGMA	Procedural complications	Intracranial hypertension
MIDAZ: NAGMA PTB: Ileus, immunosuppression, ↓ BP	Infections – VAP, CLABSI, CAUTI	Hydrocephalus
PHY: hepatic dysfunction, rash	DVT/PE/SVT	Stroke/Hemorrhage
VPA: ↓ PLT, liver dysfunction, pancreatitis LCS: AVB	Sacral ulcers	Vasospasm
CBZ: liver dysfunction, SIADH, rash TPX: NAGMA, Nephrolithiasis		Ventriculitis
LTG: Rash LVT/BRV & Perampanel: Nil . . .		CSW/SIADH/DI
Drug interactions!	Shock → MOF	PSH

CONCLUSION

HOW DO I MANAGE RSE & SRSE?

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SYSTEMATIC
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PRECISION-GUIDED
COMPREHENSIVE