Antiseizure Medications and Challenges in the Covid19 Pandemic- Focus on Drug Interactions

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at.linkedin.com/pub/eugen-trinka/a7/6a0/a08
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Agenda

- Organization of a Neurological Department during Covid-19
- Principles of Treatment of Status epilepticus
- Relevant Interaction for acute Seizure and Status Treatment
- Conclusions

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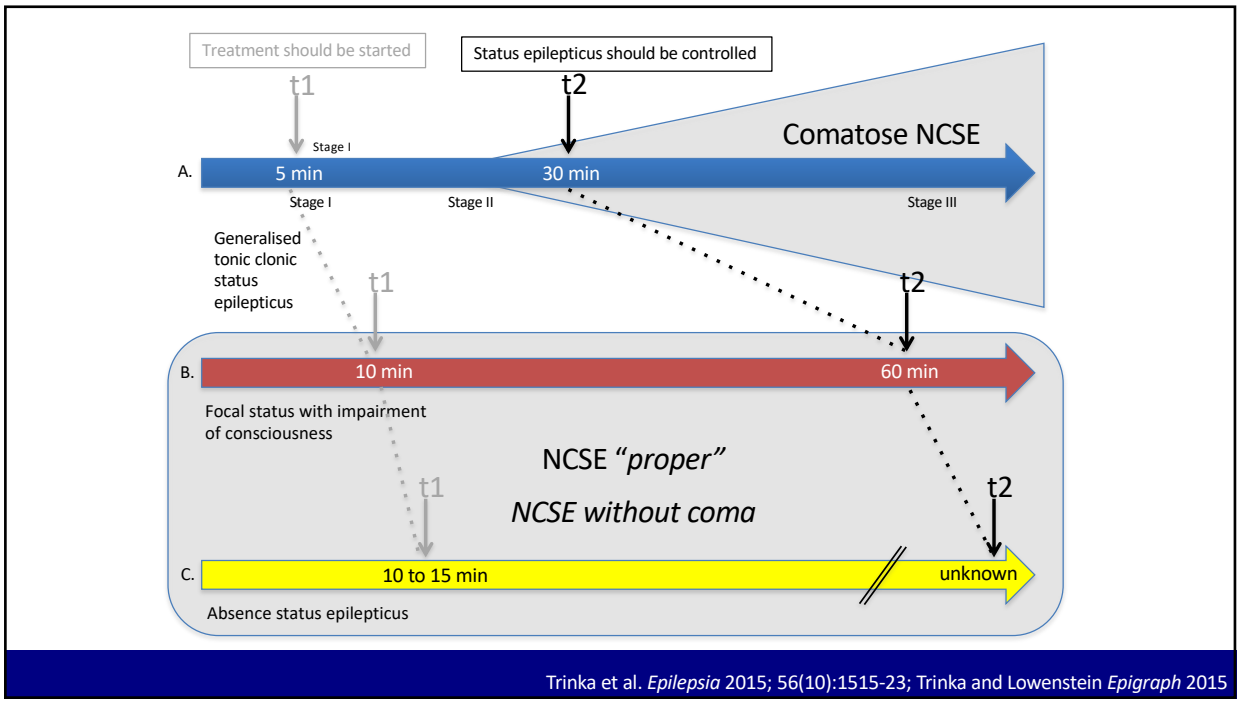

Trinka et al. *Epilepsia* 2015; 56(10):1515-23; Trinka and Lowenstein *Epigraph* 2015

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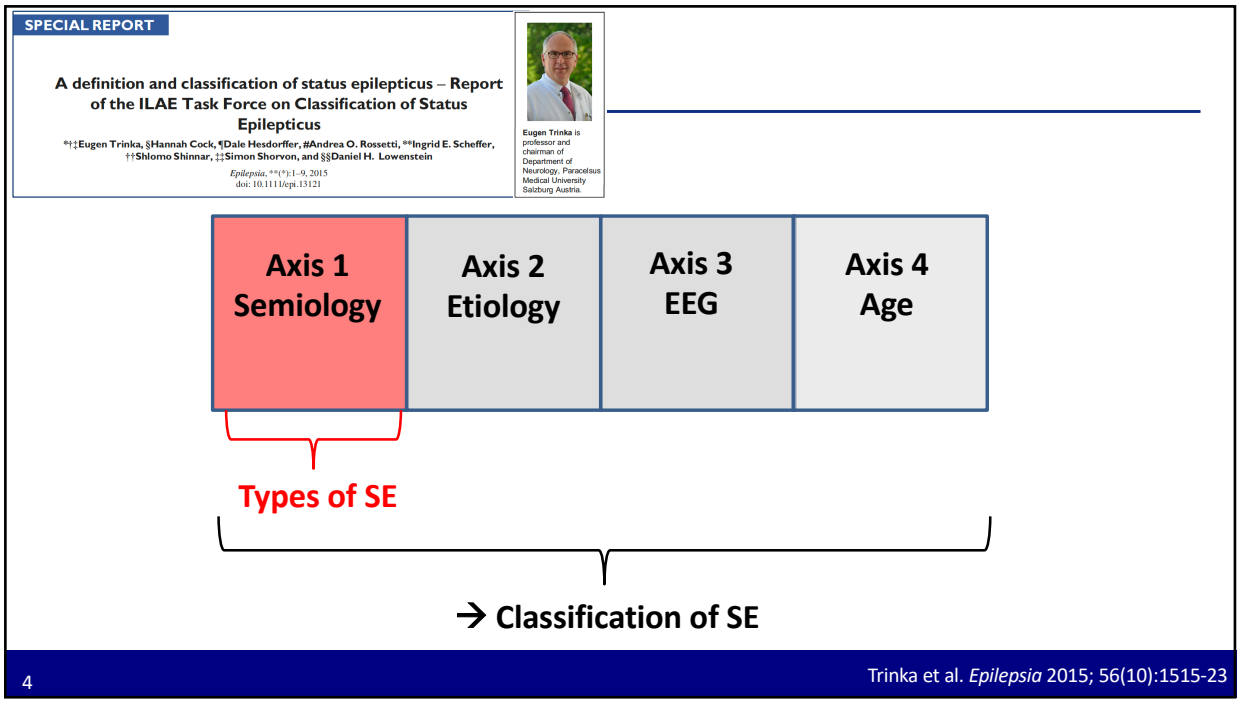

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Trinka et al. *Epilepsia* 2015; 56(10):1515-23

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SPECIAL REPORT

A definition and classification of status epilepticus – Report of the ILAE Task Force on Classification of Status Epilepticus

*†‡Eugen Trinka, §Hannah Cock, ¶Dale Hesdorffer, #Andrea O. Rossetti, **Ingrid E. Scheffer, ††Shlomo Shinnar, ‡‡Simon Shorvon, and §§Daniel H. Lowenstein

Epilepsia, **(*):1–9, 2015
doi: 10.1111/epi.13121

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(A) With prominent motor symptoms
- A.1 Convulsive SE (CSE, synonym: tonic–clonic SE)
  - A.1.a. Generalized convulsive
  - A.1.b. Focal onset evolving into bilateral convulsive SE
  - A.1.c. Unknown whether focal or generalized
- A.2 Myoclonic SE (prominent epileptic myoclonic jerks)
  - A.2.a. With coma
  - A.2.b. Without coma
- A.3 Focal motor
  - A.3.a. Repeated focal motor seizures (Jacksonian)
  - A.3.b. Epilepsia partialis continua (EPC)
  - A.3.c. Adversive status
  - A.3.d. Oculoclonic status
  - A.3.e. Ictal paresis (i.e., focal inhibitory SE)
- A.4 Tonic status
- A.5 Hyperkinetic SE

(B) Without prominent motor symptoms (i.e., nonconvulsive SE, NCSE)
- B.1 NCSE with coma (including so-called "subtle" SE)
- B.2 NCSE without coma
  - B.2.a. Generalized
    - B.2.a.a Typical absence status
    - B.2.a.b Atypical absence status
    - B.2.a.c Myoclonic absence status
  - B.2.b. Focal
    - B.2.b.a Without impairment of consciousness (aura continua, with autonomic, sensory, visual, olfactory, gustatory, emotional/ psychic/experiential, or auditory symptoms)
    - B.2.b.b Aphasic status
    - B.2.b.c With impaired consciousness
  - B.2.c Unknown whether focal or generalized
    - B.2.c.a Autonomic SE

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Trinka et al. *Epilepsia* 2015; 56(10):1515-23

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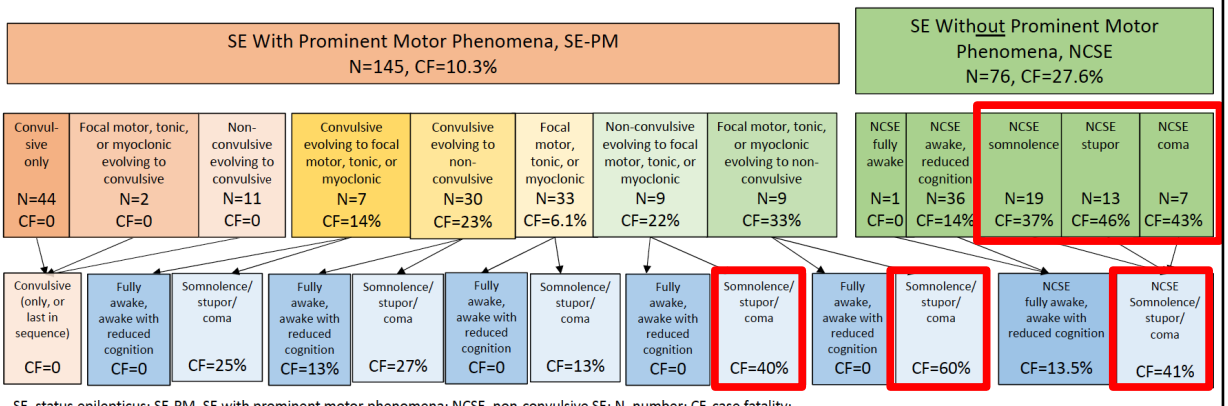
Evolution of semiology, level of consciousness and case fatality



SE, status epilepticus; SE-PM, SE with prominent motor phenomena; NCSE, non-convulsive SE; N, number; CF, case fatality;

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Leitinger, Trinka et al. *Epilepsia* 2019; 60:53-62

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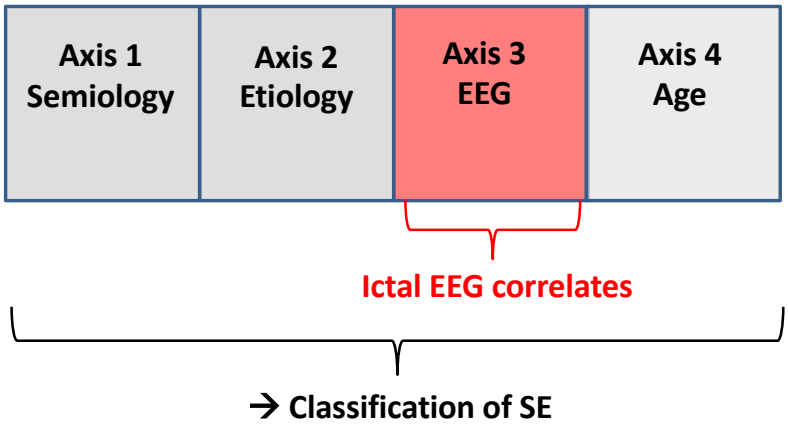
Classification of Status epilepticus



7 Trinka et al. *Epilepsia* 2015; 56(10):1515-23

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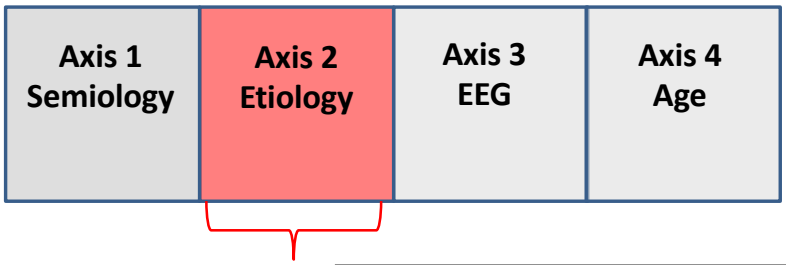
Classification of Status epilepticus



The Causes of SE

1. **Known** (syn. **symptomatic**)
   - a) Acute (e.g.: stroke, intoxication, malaria, encephalitis, etc.)
   - b) Remote (e.g. posttraumatic, post-encephalitic, post-stroke, etc.)
   - c) Progressive (e.g. glioblastoma, Lafora disease and other PMEs)
   - d) SE in defined electroclinical syndromes
2. **Unknown** (syn. **cryptogenic**)

8 Trinka et al. *Epilepsia* 2015; 56(10):1515-23

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Causes of Refractory and super-refractory SE: Global Audit on 776 patients

Aetiologies *(can be multiple per patient)*	N	%
Unknown (cryptogenic)	**200**	**26.1%**
Infections, all	148	19.6%
Vascular (incl. stroke)	111	14.5%
Anoxic (incl. cardiac arrest)	85	11.1%
Antiseizure drug reduction/withdrawal	**56**	**7.3%**
Cerebral tumour	47	6.1%
Miscellaneous[2]	43	5.6%
Trauma	42	5.5%
Metabolic	36	4.7%
Alcohol	35	4.6%
Immunological, all	24	3.1%
Genetic/chromosomal	18	2.3%
Other toxins	12	1.6%
Mitochondrial disease	11	1.4%

New onset SE (NORSE) is a clinical presentation, in a patient without active epilepsy or other pre-existing relevant neurological disorder, with new onset of refractory status epilepticus without a clear acute or active structural, toxic or metabolic cause, (which can be identified within 72h)[2]

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1: Ferlisi, Hocker, Shorvon, Trinka, et al. *Epilepsia* 2018; 2: Hirsch and Trinka et al. *Epilepsia* 2018

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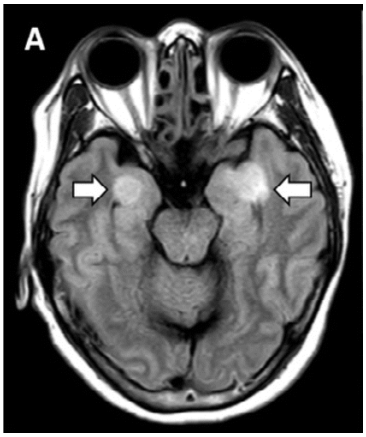
Potential Causes of Status epilepticus during Covid-19 pandemic

- Withdrawal of antiseizure medication dur to lack of supply, or other reasons
- Stress
- Fever
- Metabolic derangement: exsiccosis, hyperglycaemia, hyper- or hyponatremia
- Direct SARS-Cov-2 involvement: Encephalitis, encephalopathy, **cytokine storm**
- Indirect SARS-Cov-2 involvement: Stroke, Sinus venous thrombosis,



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https://www.diagnosticimaging.com/covid-19/brain-images-reveal-possible-covid-19-related-cytokine-storm

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Strategies for treatment of SE

Strategy 1:
Identify and treat the cause of SE

Strategy 2:
Early treatment to prevent long term consequences and brain damage

Strategy 3:
Staged treatment approach tailored to the pathophysiologic changes of SE

Trinka et al. *Drugs* 2015; Trinka et al. *Expert Opinion on Pharmacotherapy* 2016;17(4):513-34

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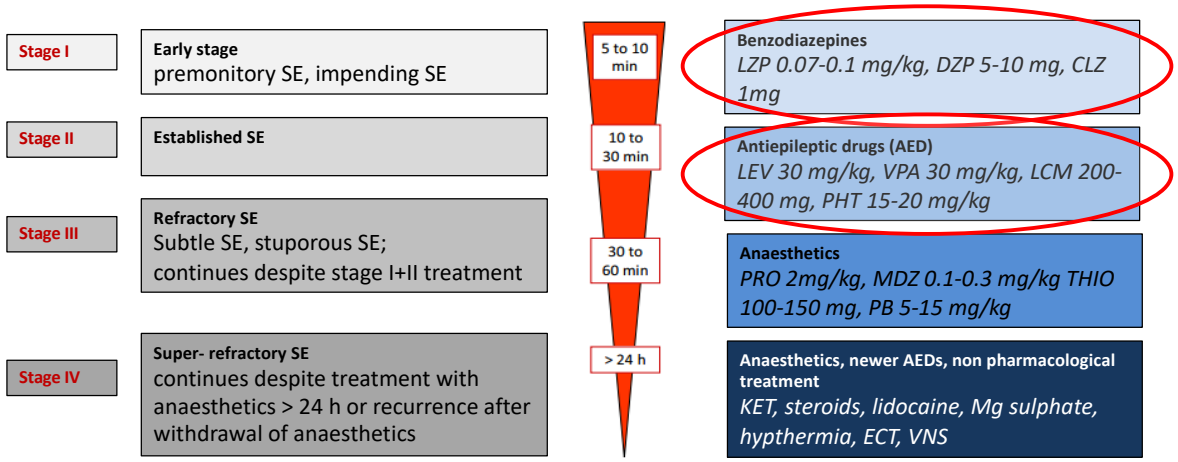
Staged Treatment Approach for Convulsive Status Epilepticus



Trinka et al. *Drugs* 2015; Trinka et al. *Expert Opinion on Pharmacotherapy* 2016;17(4):513-34

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Alternative routes for treatment of convulsive SE[1,2]

Stage 1

Early phase

Premonitory SE, impending SE

5-10 Min

Midazolam 10 mg *buccal* (5 mg in the elderly or in patients <50 kg); if necessary can be repeated once after 10 min. Alternatively, use 10 mg/2 mL injection via buccal route.

OR

Midazolam 10 mg *intramuscularly* (5 mg in the elderly or in patients <50 kg); if necessary can be repeated once after 10 min.

OR

Diazepam 10 mg *rectal* (5 mg in the elderly or in patients <50 kg); if necessary can be repeated once after 10 min.

1: Trinka et al. *Drugs.* 2015 Sep;75(13):1499-521.; 2: Trinka et al. *Expert Opin Pharmacother.* 2016;17(4):513-34

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RESEARCH ARTICLE

Factors Predicting Cessation of Status Epilepticus in Clinical Practice: Data From a Prospective Observational Registry (SENSE)

Christoph Kellinghaus, MD,[1,2] Andrea O. Rossetti, MD, FAES,[3] Eugen Trinka, MD, MSc, FRCP,[4,5] Nicolas Lang, MD,[6] Theodor W. May, PhD,[7] Iris Unterberger, MD,[8] Stephan Rüegg, MD, FAES,[9] Raoul Sutter, MD,[10] Adam Strzelczyk, MD,[11,12] Christian Tilz, MD,[13] Zeljko Uzelac, MD,[14] and Felix Rosenow, MD[11,12]

Comparative Effectiveness

- Prospective registry of adult patients with SE in Austria, Germany and Switzerland
- Incident episodes of 1,049 patients
- Uni- and multivariate statistics predicting cessation of SE within 1 hour (for generalized convulsive SE [GCSE]) and 12 hours (for non-GCSE)

- Etiology: remote (32%) and acute (31%) symptomatic; 43% had GCSE.
- Median latency between SE onset and first treatment was **30 minutes** in GCSE and **150 minutes** in non-GCSE
- 1st IV compound **BDZ in 86% in GCSE and 73% in non-GCSE**
- Bolus doses were lower than recommended by current guidelines in 76% of GCSE patients and 78% of non-GCSE patients.
- SE was ongoing 1 hour after initiating treatment n 319 GCSE (70%) and in 342 non-GCSE patients (58%) 12 hours after initiating treatment
- BDZ as 1st line treatment and a higher cumulative dose of anticonvulsants were associated with shorter time to cessation of SE (Multivariate Cox regression).

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Kellinghaus et al. *Ann Neurol* 2019; Jan 20. doi: 10.1002/ana.25416

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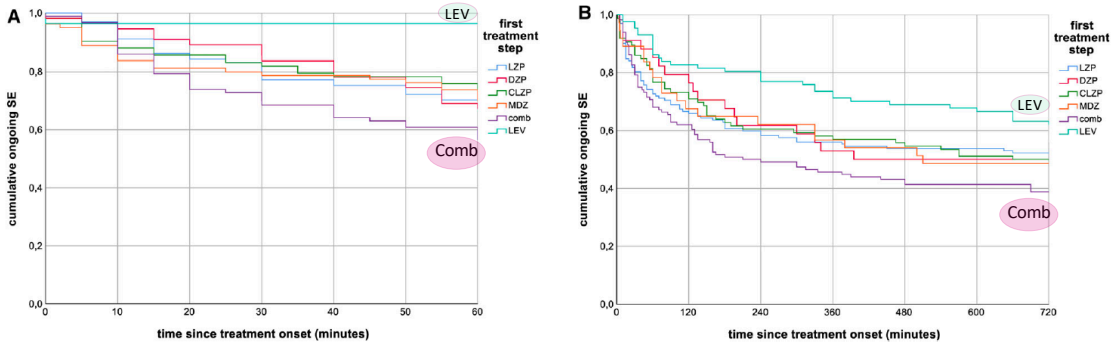

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Kellinghaus et al. *Ann Neurol* 2019; Jan 20. doi: 10.1002/ana.25416

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IV Antiepileptic Drugs used in established SE: Overview

	Phenytoin	Levetiracetam	Valproate	Phenobarbital	Lacosamide
Mechanisms	Na Channel Blocker (fast inactivation)	SV2A	Multiple mechanisms of action	$GABA_A$	Na Channel Blocker (slow inactivation)
Loading dose	18-20mg/kg	30-70mg/Kg	20-30mg/Kg	20mg/Kg	5-6mg/Kg
max rate	50mg/min	500mg/min	10mg/kg/min	100mg/min	40-80mg/min
Class III/IV evidence	++	+++	+++	+	++
Disadvantages	Infusion site reaction hypotension, cardiac arrhythmia non linear PK	low BBB permeability	idiosyncratic toxicity (brain, liver pancreas), high protein binding	infusion site reaction, cardiac toxicity, hypotension, sedation	cardiac arrhythmias (?)
Advantages	Long standing experience	good tolerability, linear PK, lack of relevant interactions, broad spectrum	excellent tolerability, linear PK, broad spectrum	good efficacy	good tolerability, linear PK, lack of sedation and relevant interactions

1: Trinka et al. *Drugs* 2015;75(13):1499-521

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ORIGINAL ARTICLE

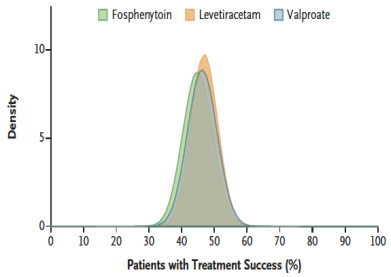
Randomized Trial of Three Anticonvulsant Medications for Status Epilepticus

Jaideep Kapur, M.B., B.S., Ph.D., Jordan Elm, Ph.D., James M. Chamberlain, M.D., William Barsan, M.D., James Cloyd, Pharm.D., Daniel Lowenstein, M.D., Shlomo Shinnar, M.D., Ph.D., Robin Conwit, M.D., Caitlyn Meinzer, Ph.D., Hannah Cock, M.D., Nathan Fountain, M.D., Jason T. Connor, Ph.D., and Robert Silbergleit, M.D., for the NETT and PECARN Investigators*

Randomized, double-blind, phase III, adaptive trial design
Children and adults with BDZ resistant SE (N=384)
IV LEV vs. IV fPHT vs IV VPA

- Prespecified stopping rule for futility of finding one drugto be superior or inferior
- A planned interim analysis led to the trial being stopped

Outcome and Population	Levetiracetam (N=145)	Fosphenytoin (N=118)	Valproate (N=121)
Primary efficacy outcome: cessation of seizures and improvement in consciousness at 60 min without other anticonvulsant medications			
Intention-to-treat population			
No. with outcome	68	53	56
Percent of patients with outcome (95% credible interval)	47 (39–55)	45 (36–54)	46 (38–55)
Probability that treatment is the most effective	0.41	0.24	0.35
Probability that treatment is the least effective	0.24	0.45	0.31
Per-protocol population			
No. with outcome/total no.	51/109	37/79	43/91
Percent of patients with outcome (95% credible interval)	47 (38–56)	47 (36–58)	47 (37–57)
Probability that treatment is the most effective	0.31	0.34	0.36
Probability that treatment is the least effective	0.34	0.35	0.31



Kapur et al. *N Engl J Med* 2019;381:2103-13.

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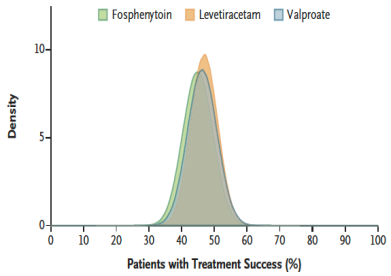
Outcome	Levetiracetam (N=150)	Fosphenytoin (N=125)	Valproate (N=125)
	number of patients (percent)		
Life-threatening hypotension within 60 min after start of trial-drug infusion	1 (0.7)	4 (3.2)	2 (1.6)
Life-threatening cardiac arrhythmia within 60 min after start of trial-drug infusion	1 (0.7)	0	0
Endotracheal intubation within 60 min after start of trial-drug infusion	30 (20.0)	33 (26.4)	21 (16.8)
Acute seizure recurrence 60 min to 12 hr after start of trial-drug infusion	16 (10.7)	14 (11.2)	14 (11.2)
Acute anaphylaxis	0	0	0
Acute respiratory depression	12 (8.0)	16 (12.8)	10 (8.0)
Hepatic aminotransferase or ammonia elevations	1 (0.7)	0	1 (0.8)
Purple glove syndrome	0	0	0
Death	7 (4.7)	3 (2.4)	2 (1.6)



Kapur et al. *N Engl J Med* 2019;381:2103-13.

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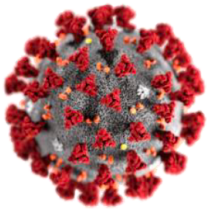
Drugs used in covid-19 treatment

Antimalaria drugs:
- Chloroquine
- Hydroxychloroquine

Antiviral drugs:
- Remdesivir (experimental)
- Lopinavir/Ritonavir
- Darunavir/cobicistat
- Oseltamivir
- Favipiravir
- Atazanavir
- Ribavirin
- Nitazoxanide

Immunomodulating drugs:
- Interferon-beta
- Tocilizumab
- Anakinra
- Emapamulab
- Sarilumab

Antibacterial drugs:
- Azithromycin
- Ceftriazone
- Piperacillin/tazobactam



Based on recommendations and reports from:
WHO, China, South-Korea, US, EMA,

https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected . March 13th 2020
https://www.eahp.eu/sites/default/files/covid-19-clinical-information-and-treatment-guidelines_0.pdf
https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19
https://www.covid19-druginteractions.org
https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html
https://sph.nus.edu.sg/wp-content/uploads/2020/03/COVID-19-Science-Report-Therapeutics-30-Mar.pdf
https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

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- Sarilumab

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- Piperacillin/tazobactam

More than anecdotal evidence:
- Pathophysiological reasoning
- Open Trials
- Broader patient named programs

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↑ *Potential increased exposure of the co-medication;*
↓ *Potential decreased exposure of the co-medication;*
⇈ *Potential increased exposure of COVID drug;*
⇊ *Potential decreased exposure of COVID drug;*
↔ *No significant effect;*
♥ *One or both drugs may cause QT and/or PR prolongation.*

	ATV	*DRV/c[1]	*LPV/r	RDV[2]	FAVI	CLQ	HCLQ	NITA	RBV	TCZ[3]	IFN-β-1a[4]	OSV
Brivaracetam	↔	↔	↓	↔	↔	↑	↑	↔	↑	↔	↔	↔
Carbamazepine	⇊↑	⇊↑	⇊↑	⇊	↔	⇊	⇊	↔	↔	↓	↔	↔
Cannabidiol	↔	↑	↑	↔	↔	↑	↑	↔	↔	↔	↔	↔
Cenobamate	⇊	⇊	⇊	↔	↔	⇊	⇊	↔	↔	↔	↔	↔
Clonazepam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Clobazam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Diazepam	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Eslicarbazepine	⇊♥	⇊	⇊♥	⇊	↔	⇊	⇊	↔	↔	↔	↔	↔
Ethosuximide	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Felbamate	↓	⇊	↓	↔	↔	♥↓	♥↓	↔	↔	↔	↔	↔
Gabapentin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lacosamide	♥↔	⇑	♥↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lamotrigine	↔	↑	↓	↔	↔	↔	↔	↔	↔	↔	↔	↔
Levetiracetam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Lorazepam	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Oxcarbazepine	⇊	⇊↓	⇊	⇊	↔	⇊	⇊	↔	↔	↔	↔	↔
Perampanel	↑	⇊	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Phenytoin	⇊	⇊	⇊	⇊	↔	⇊	⇊	↑	↔	↓	↔	↔
Phenobarbital	⇊	⇊↓	⇊	⇊	↔	⇊	⇊	↔	↔	↓	↔	↔
Pregabalin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Primidone	⇊	⇊	⇊↓	⇊	↔	⇊	⇊	↔	↔	↓	↔	↔
Retigabine	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Rufinamide	⇊	⇊	⇊	⇊	↔	⇊	⇊	↔	↔	↔	↔	↔
Sulthiame	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Tiagabine	↑	↑	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Topiramate	↔	⇊	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Valproic acid	↔	⇊	⇑	↔	↔	↔	↔	↔	↔	↔	↔	↔
Vigabatrin	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔
Zonisamide	↔	↑	↔	↔	↔	↔	↔	↔	↔	↔	↔	↔

ATV, atazanavir
DRV/c, darunavir/cobicistat
LPV/r, lopinavir/ritonavir
RDV, remdesivir/GS-5734
FAVI, favipiravir
CLQ, chloroquine
HCLQ, hydroxychloroquine
NITA, nitazoxanide
RBV, ribavirin
TCZ, tocilizumab
IFN-β-1a; interferon β-1
OSV, oseltamivir.

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Benzodiazepines used in the treatment of SE: Overview

	Diazepam	Lorazepam	Midazolam	Clonazepam
	Diazepam clearance is increased by enzyme inducers and decreased by inhibitors of CYP3A4 (e.g., cimetidine, erythromycin, itraconazole, ritonavir) and CYP2C19 (e.g., fluvoxamine, omeprazole).	Lorazepam clearance is increased by enzyme inducers and decreased by valproic acid.	Midazolam clearance is increased by enzyme inducers and decreased by CYP3A4 inhibitors such as erythromycin, clarithromycin, ketoconazole, diltiazem, verapamil or cimetidine and Atazanavir (→ up to 4-fold increase)	Clonazepam clearance is increased by enzyme-inducing agents
	Diazepam and other CNS depressants may potentiate reciprocally their actions when administered together	Lorazepam and other CNS depressants may potentiate reciprocally their actions when administered together.	Midazolam and other CNS depressants may potentiate reciprocally their actions when administered together.	Co-administration of CNS-depressing agents may lead to reciprocal potentiation of adverse effects

1: Trinka E and Brigo F , Benzodiazepines for the treatment of epilepsy. In: Treatment of Epilepsies, 5th Ed. Blackwell 2015; 2: Trinka et al. Drugs 2015

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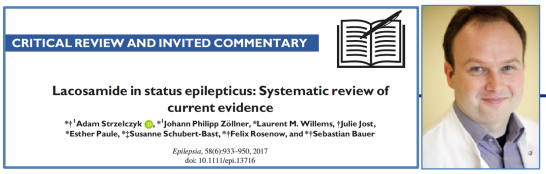
CRITICAL REVIEW AND INVITED COMMENTARY

Lacosamide in status epilepticus: Systematic review of current evidence

*†[1]Adam Strzelczyk, *[2]Johann Philipp Zöllner, *Laurent M. Willems, †Julie Jost, *Esther Paule, *‡Susanne Schubert-Bast, *†Felix Rosenow, and *†Sebastian Bauer

Epilepsia, 58(6):933-950, 2017
doi: 10.1111/epi.13716

IV Lacosamide in SE

Open issues:

- Optimal bolus dose and rate not explored → safety in high dose/high rate
- EEG response not well determined, spectrum of efficacy is unknown
- Clear order effect → Stage I or II
- → **RCT is needed**

- In total, 522 SE episodes (51.7% female) in 486 adults and 36 children and adolescents
- Success rate **57%:** NCSE (57%; 82/145) and CSE (61%; 30/49; p = 0.68) focal motor SE (92%; 34/39, p = 0.013; p < 0.001)
- Most often used bolus: **400mg** (range 50-400mg)@ **40-80mg/min**
- Efficacy with later positioning of LCM decreased from 100% to 20%
- AEs: dizziness, abnormal vision, diplopia, and ataxia

1: Strzelczyk et al. *Epilepsia.* 2017; 58(6):933-950. *2*: Höfler et al. *Epilepsia* 2011; 3: Trinka *Epilepsia* 2011; 4: Höfler and Trinka *Epilepsia* 2013

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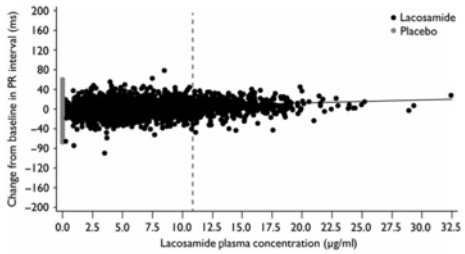
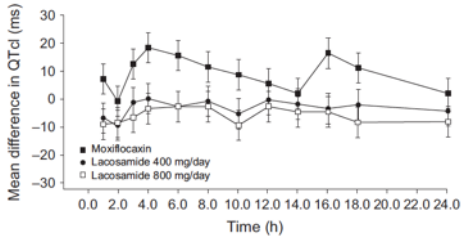
Cardiac Safety of Lacosamide in Elderly with Focal Epilepsy

- Single case reports of AV Block, sinus node dysfunction, or atrial flutter[1-5]
- Pooled data of post-randomization changes from baseline ECG measures in RCTs (n=944, LCM 200mg, 400mg, 600mg vs. n=364, PBO)[6]



"LCM at the maximum recommended dose (400 mg/day) was not clearly associated with any cardiac effect other than a small, dose-related increase in PR interval"[6]

- Randomized, double-blind, positive- and placebo-controlled, parallel-design trial, healthy volunteers
- LCM 400 mg/day (maximum-recommended daily dose, 6 days), LCM 800 mg/day (supratherapeutic dose, 6 days), placebo (6 days), or moxifloxacin 400 mg/day (3 days)



" LCM did not prolong the QTc interval. LCM caused a small, dose related increase in mean PR interval that was not associated with AEs"[7]

1: DeGiorgo *Epilepsy Behav* 2010;18:322–4 2: Krause et al. *Epilepsy & Behavior* 2011; 20:725-727; 3: Chinnasami et al. *Epilepsia*, 54(6):e90–e93, 2013; 4: Nizam et al. *Epilepsia*, 52(10):e153–e155, 2011; 5: Altenmüller et al. *Epilepsia* 45:1640–1644; 6: Rugg et al. *Acta Neurol Scand* 2015; 7: Kropeit et al. *Acta Neurol Scand* 2015

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Hydroxychroroquine adverse effects

- Headache, blurring of vision, diplopia, confusion, **convulsions,** lichenoid skin eruptions, bleaching of hair
- Widening of the QRS interval
- T-wave abnormalities
- **QTc prolongation**

- Careful cardiac assessment is needed in Covid-19 patients before hydroxychloroquine treatment
- Combinations of LCM and hydroxychloroquine are seen critical → cardiac monitoring

25 Goodman and Gilman´s *The Pharmacological Basis of Therapeutics* 11th ed. 2006; p1035

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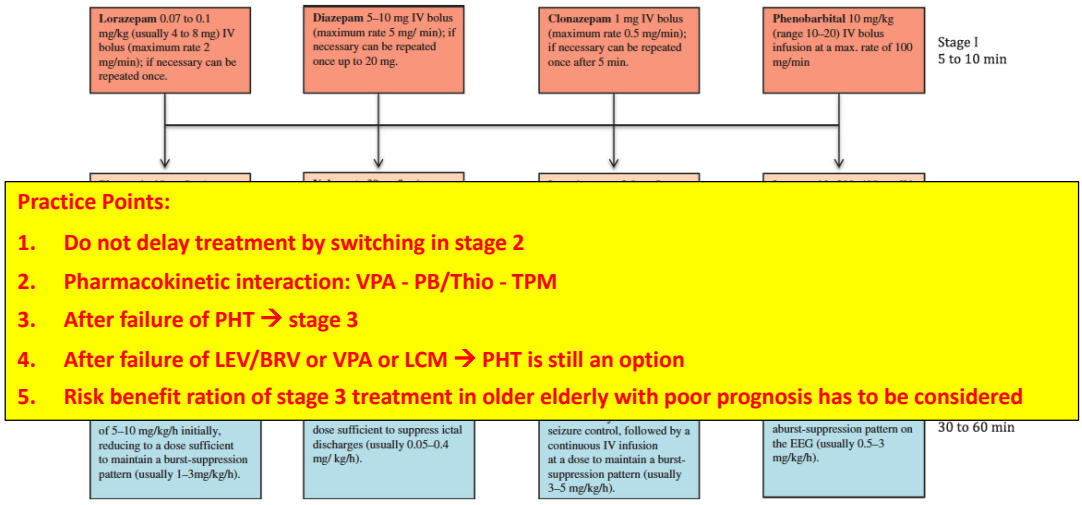
Staged treatment protocol for SE



Practice Points:

1. **Do not delay treatment by switching in stage 2**
2. **Pharmacokinetic interaction: VPA - PB/Thio - TPM**
3. **After failure of PHT → stage 3**
4. **After failure of LEV/BRV or VPA or LCM → PHT is still an option**
5. **Risk benefit ration of stage 3 treatment in older elderly with poor prognosis has to be considered**

Trinka et al. *Expert Opinion On Pharmacotherapy*, 2016 2016;17(4):513-34

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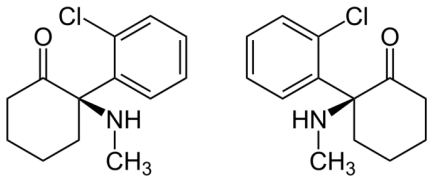
Ketamine

- Phencyclidine derivative; racemic mixture; 1st described 1965; in 1970s 1st clinical use
- **Metabolism**: by N-demethylation → **Norketamine** (active metabolite)
- **Excretion**: renally, elimination half-life of 2–3 h in adults
- **Receptor binding:** blocks the ionotropic NMDA-Glutamate receptor
- **Routes of administration:** IV, IM, SC, oral, rectal, epidural and intranasal, water and lipid soluble[1]
- **Volume of distribution:** Patients 16.0 L/kg vs. healthy controls 5.1 L/kg [2, 3]
- **Bioavailability** IV 90% vs. oral or rectal only 16% [1]



1: Craven Anaesthesia 2007; 2: Hijazi, British Journal of Anaesthesia 2003; 3: Clements et al, Br J Anaesth 1981

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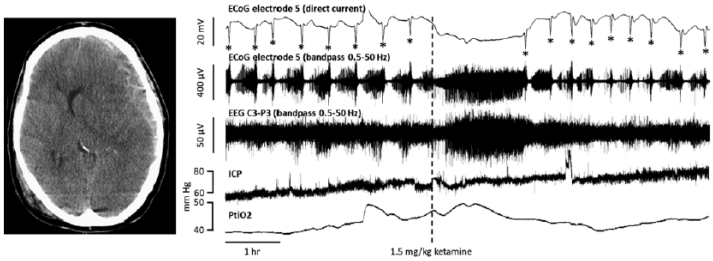
Ketamine sedation for the suppression of spreading depolarizations

- 10 patients with severe TBI or aneurysmal subarachnoid hemorrhage (SAH)
- Standard ECoG strip
- Alternating every-6-hour schedule of ketamine or other sedation agent; subanesthetic basal dose (0.1 mg/kg/hr)

Periods with no or low-dose ketamine (< 1.5 mg/kg/hr) had increased risk of SD compared to periods of ketamine dosage >1.5 mg/kg/hr: odds ratio 13.8



First RCT to supress cortical spreading depression with ketamine (NMDA antagonist)

1: Carlson et al. *J Neurosurg*. 2018 25:1-7; 2: Harding et al. *J Neurosurg* August 3, 2018

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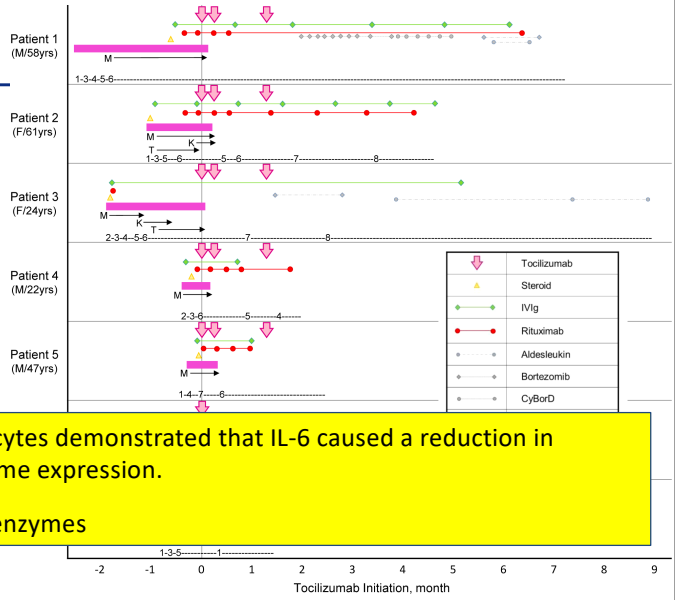
Tocilizumab Treatment for New Onset Refractory Status Epilepticus

Jin-Sun Jun, MD,[1*] Soon-Tae Lee, MD, PhD,[2*] Ryul Kim, MD,[2] Kon Chu, MD, PhD,[2] and Sang Kun Lee, MD, PhD[2]

- 7 patients with new onset refractory status epilepticus (NORSE) refractory to conventional immunotherapy with rituximab (n = 5) or without rituximab (n = 2)
- Treatment with tocilizumab (interleukin-6 receptor inhibitor)
- 2 patients severe infections (sepsis, pneumonia)



- *In vitro* studies with cultured human hepatocytes demonstrated that IL-6 caused a reduction in CYP1A2, CYP2C9, CYP2C19 and CYP3A4 enzyme expression.
- Tocilizumab normalises expression of these enzymes

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1: Kenney-Jung, *Ann Neurol* 2016;80:939–945; 2: Roactemra SmPC

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Shortage of Drug Supply

- Shortage of: Ketamin, Fentanyl, Morphium, Midazolam
- Most Antiviral drugs are delivered through named patient programs or RCTs
- Hydroxychloroquine is still available in most countries
- Tocilizimab is still available
- rTPA is running short due to mass orders of many hospitals in Germany and Austria

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Conclusions

- Epidemiology: SE occurs during the Covid-Pandemic at least as often as usual
- Classification is based on semiology, aetiology, and EEG → Dichotomy CSE vs. NCSE
- Building up a "Covid-safe" fast track for Status (similar to stroke)
- Stage I: IV LZP/DZP OR IM MDZ/BUCC MDZ (children) → Interaction with enzyme inhibiting drugs can lead to increased CNS/respiratory depression
- Stage II/III: Enzyme inducing drugs (PHT, Barbiturates) decrease antiviral drugs and HCLQ
- Stage III: Ketamine may be useful in Cytokine storm → inhibition of NMDA mediated spreading cortical depression
- Tocilizumab normalises expression of CYP P450 enzymes

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