MAYO CLINIC

Hitting the rESETT Button: Updates in Status Epilepticus

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Learning Objectives

- Report current guideline recommendations and gaps in evidence for the treatment of status epilepticus
- Interpret recent evidence regarding conventional antiepileptic utilization in status epilepticus
- List three considerations in applying new evidence for status epilepticus treatment into clinical practice

Defining Status Epilepticus (SE)

Continuous clinical or electrographic seizure lasting five minutes **or** two or more discrete seizures between which there is incomplete recovery of consciousness

Neurocrit Care. 2012;17(1):3-23.

Epidemiology

- 200,000 patients have episode annually
- One million seizure ED visits annually
- Bimodal age distribution

ED=emergency department

Risk Factors

Infection	Stimulant use
Trauma	Alcohol withdrawal
Metabolic derangement	Subtherapeutic AED levels
Epilepsy	Tumors/Metastases
Drug toxicity	Cerebrovascular accident

AED = antiepileptic drug

Outcomes of Status Epilepticus

Mortality

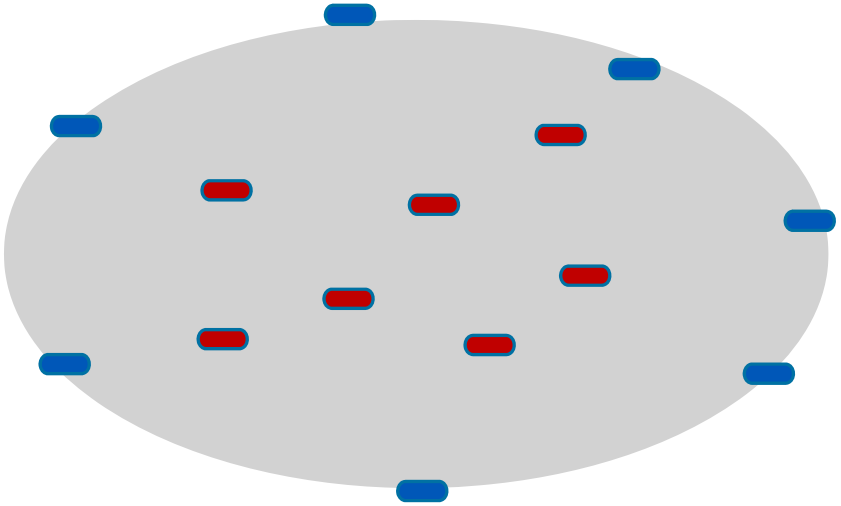
- 30-day mortality 10-27%
- Mortality rates trending down

Morbidity

- Indirect systemic problems arising from convulsive state
  - Impaired ventilation
  - Pulmonary aspiration
  - Metabolic derangements
- Direct neuronal cellular injury from neuronal loss and cell death

Neurocrit Care. ENLS: Status Epilepticus.
Neurocrit Care. 2012;17(1):3-23.

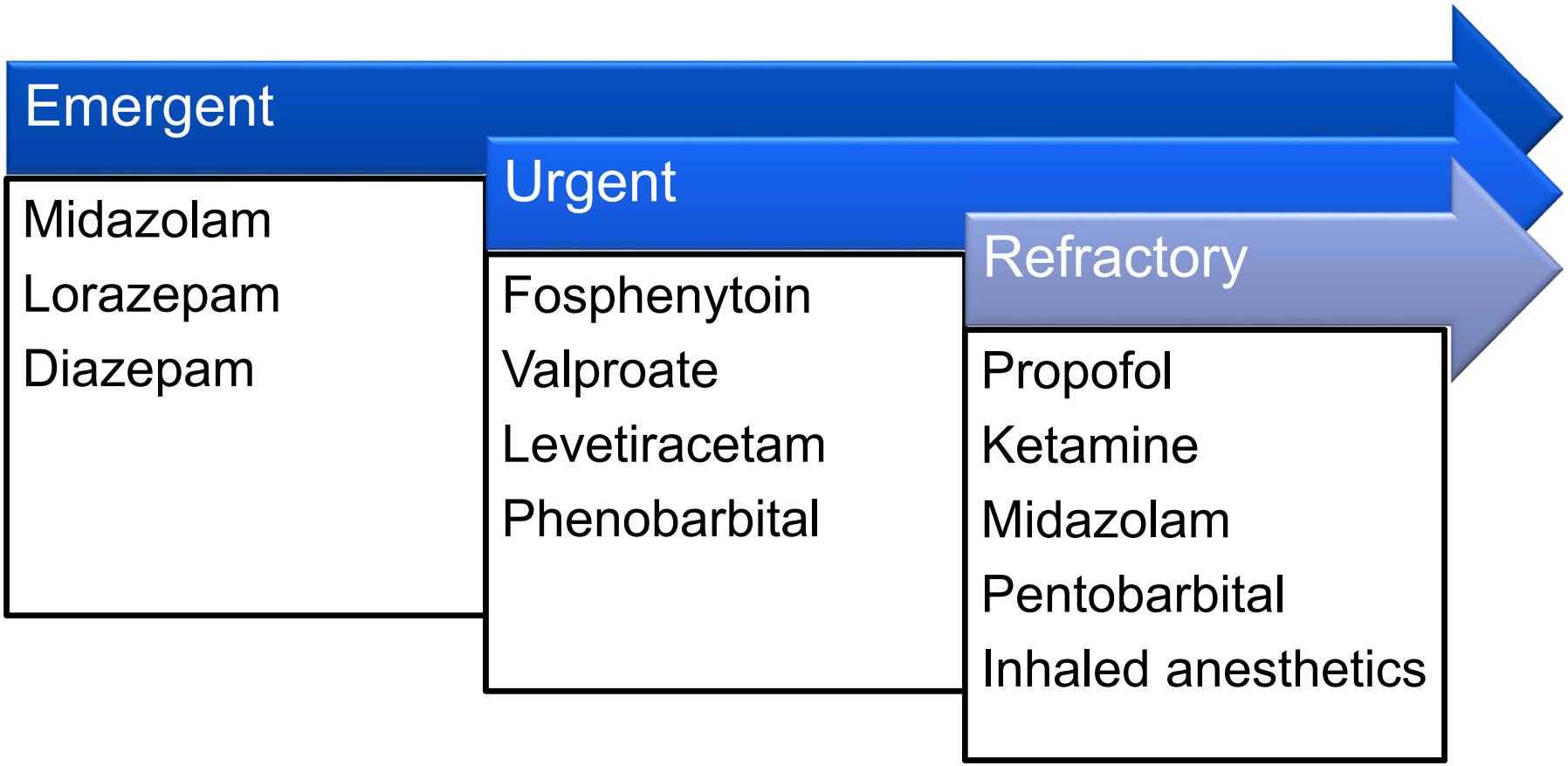
Pathophysiology of SE



GABAa receptors
NMDA receptors

European Journal of Epilepsy. 2019;68:16-21.

Status Epilepticus Treatment Algorithm



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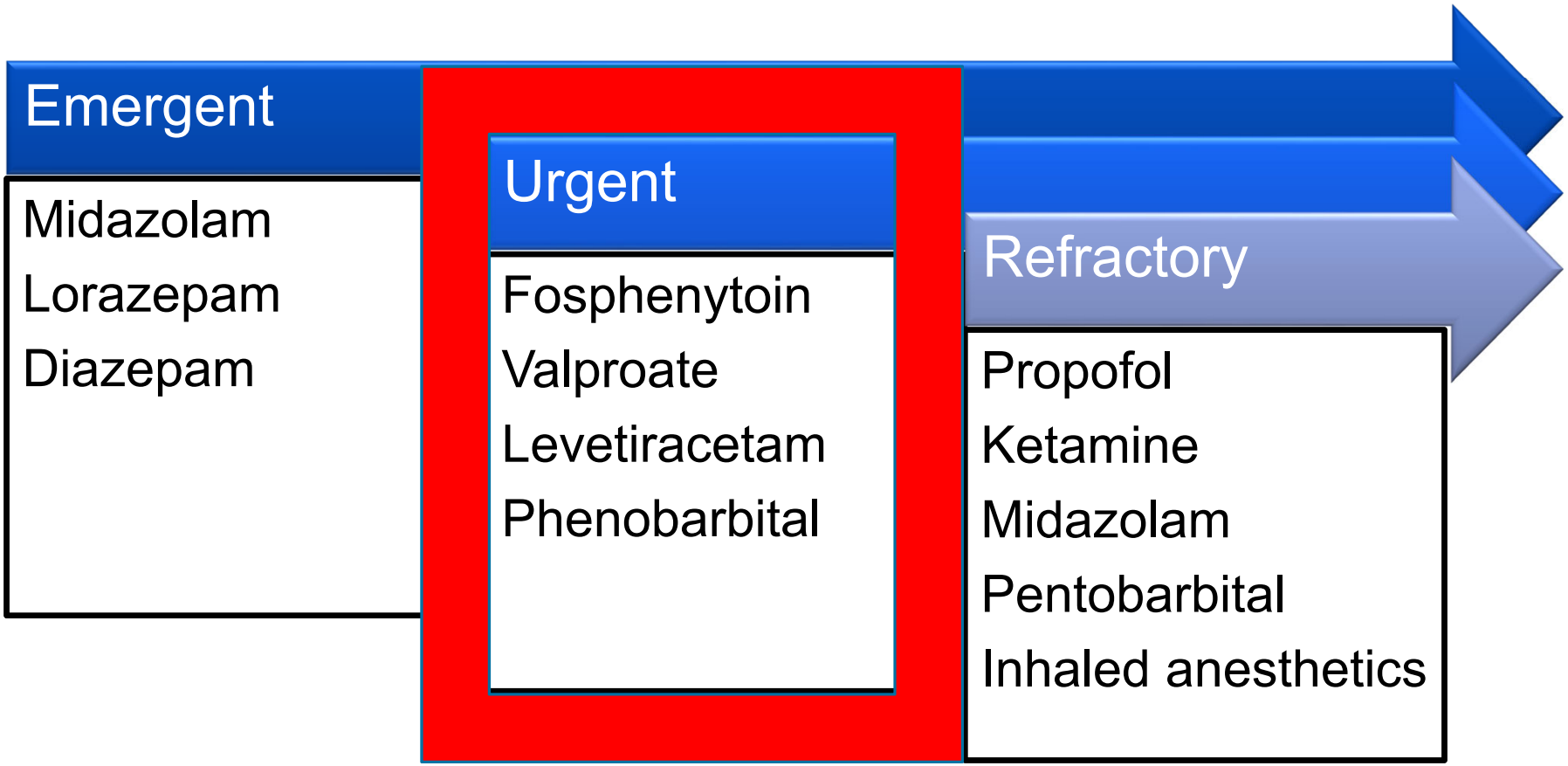
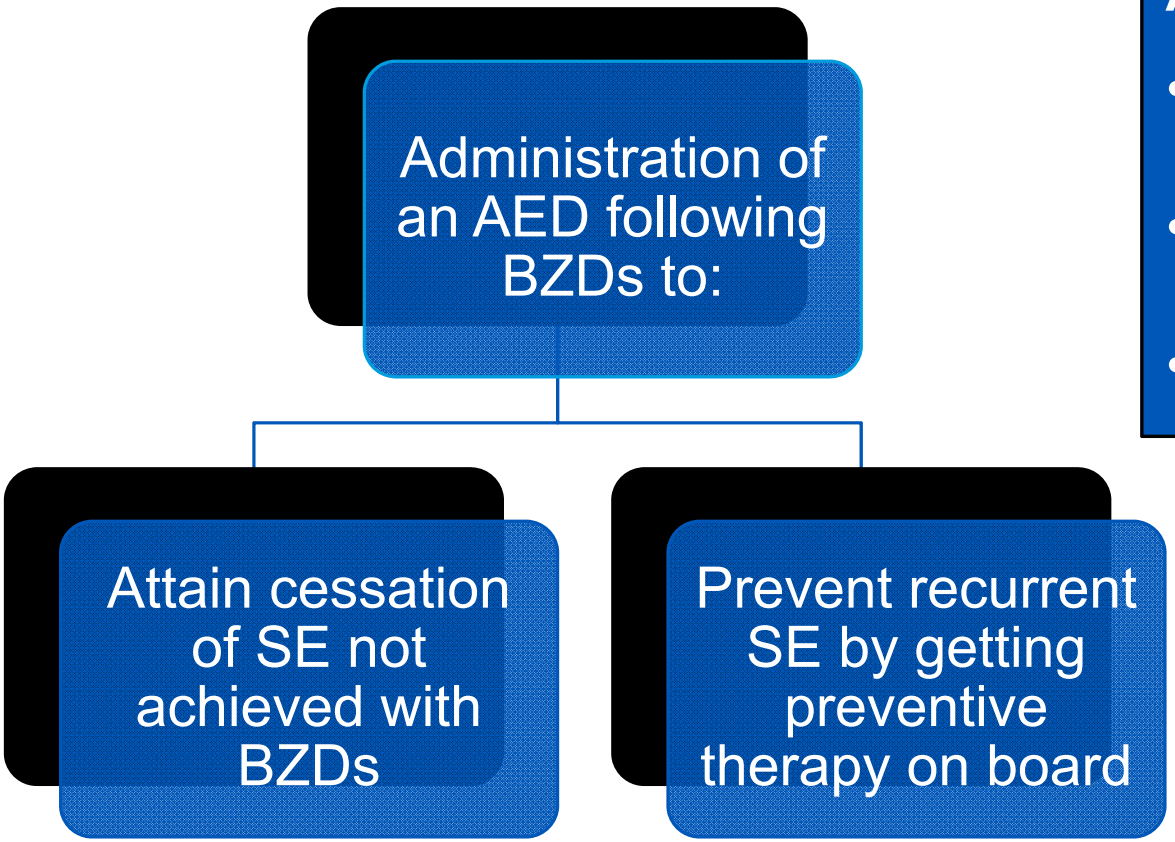
Status Epilepticus Treatment Algorithm



Neurocrit Care. 2012;17(1):3-23.

Urgent Control Therapy



Adequate BZD Dosing:

- Lorazepam 4 mg IV (0.1 mg/kg)
- Midazolam 10 mg IM or NAS (0.4 mg/kg)
- Diazepam 0.5 mg/kg PR

BZDs = benzodiazepines IV=intravenous IM=intramuscular PR=rectal AED=antiepileptic drug

Neurocrit Care. 2012;17(1):3-23.
Britton, J. AME: Status Epilepticus. Updated March 24th, 2020.

Guideline Recommendations for Urgent Control Therapy

- Fosphenytoin
- Valproate
- Levetiracetam
- Phenobarbital

Neurocrit Care. 2012;17(1):3-23.

Considerations for Antiepileptic Choice

- Side effect profile
- Infusion rate
- Ease of administration
- Routes (PO available)
- Drug interactions
- Availability and necessity for TDM
- Teratogenicity

TDM = therapeutic drug monitoring PO=by mouth

Fosphenytoin & Phenytoin

Dosing: 20 mg PE/kg

- No dose cap included in recommendations

Administration: 150 mg PE/min IV

Adverse Effects: hypotension, cardiac arrhythmias, SJS/TEN, hepatotoxicity, pancytopenia

Considerations

- Narrow therapeutic window requiring TDM
- CYP450 inducer
- Familiarity with dosing and use in SE

TDM =therapeutic drug monitoring
SJS=Stevens-Johnson syndrome
TEN= toxic epidermal necrolysis
CYP= cytochrome P450

Fosphenytoin [package insert]. New York, NY: Pfizer, 2020.

Valproate

Dosing: 40 mg/kg

Administration: Up to 10 mg/kg/min IV

Adverse Effects: hepatotoxicity, thrombocytopenia, teratogenicity, hyperammonemic encephalopathy, pancreatitis, DRESS

Considerations

- Wide therapeutic window with TDM available
- CYP450 Inhibition
- Can administer faster than full loading dose of phenytoin

DRESS= drug rash with eosinophilia & systemic symptoms
TDM= therapeutic drug monitoring
CYP= cytochrome P450

Valproate [package insert]. Chicago, IL: AbbVie, 2013.
Epilepsia. 2007;48(3):478-483.

Levetiracetam

Dosing: 20-40 mg/kg IV

Administration: IVP or IVPB over 5-15 min

Adverse Effects: Irritability/mental status changes, neutropenia

Considerations

- Does not undergo significant CYP450 metabolism
- Can administer dose quickly
- Favorable side effect profile
- Wide therapeutic window with TDM available

IVP=IV push
IVPB=IV piggyback
CYP=cytochrome P450
TDM=therapeutic drug monitoring

Levetiracetam [package insert]. Smyrna, GA: UCB Pharmaceuticals, 2009.

Phenobarbital

Dosing: 20 mg/kg IV

Administration: Infuse at rate of up to 100 mg/min

Adverse Effects: Prolonged sedation, hypotension, bradycardia, respiratory depression, anemia, withdrawal

Considerations

- Must be administered slowly
- CYP450 inducer
- Long half life
- Requires ICU level of care

CYP=cytochrome P450
TDM=therapeutic drug monitoring

Phenobarbital [package insert]. Quebec, Canada: Sandoz, 2015.

Patient Case

PH is a 36 yo female who presents to the ED with convulsive seizure activity reported to have started around 15 minutes ago. She has a history of traumatic brain injury (TBI) and is not currently on any home medications. EMS administered one dose of lorazepam 4 mg IV, and on arrival she is given a repeat dose which does not stop her seizure.

What guideline approved antiepileptic agent would you use for urgent control therapy in PH?

A. Fosphenytoin

B. Valproate

C. Levetiracetam

D. Phenobarbital

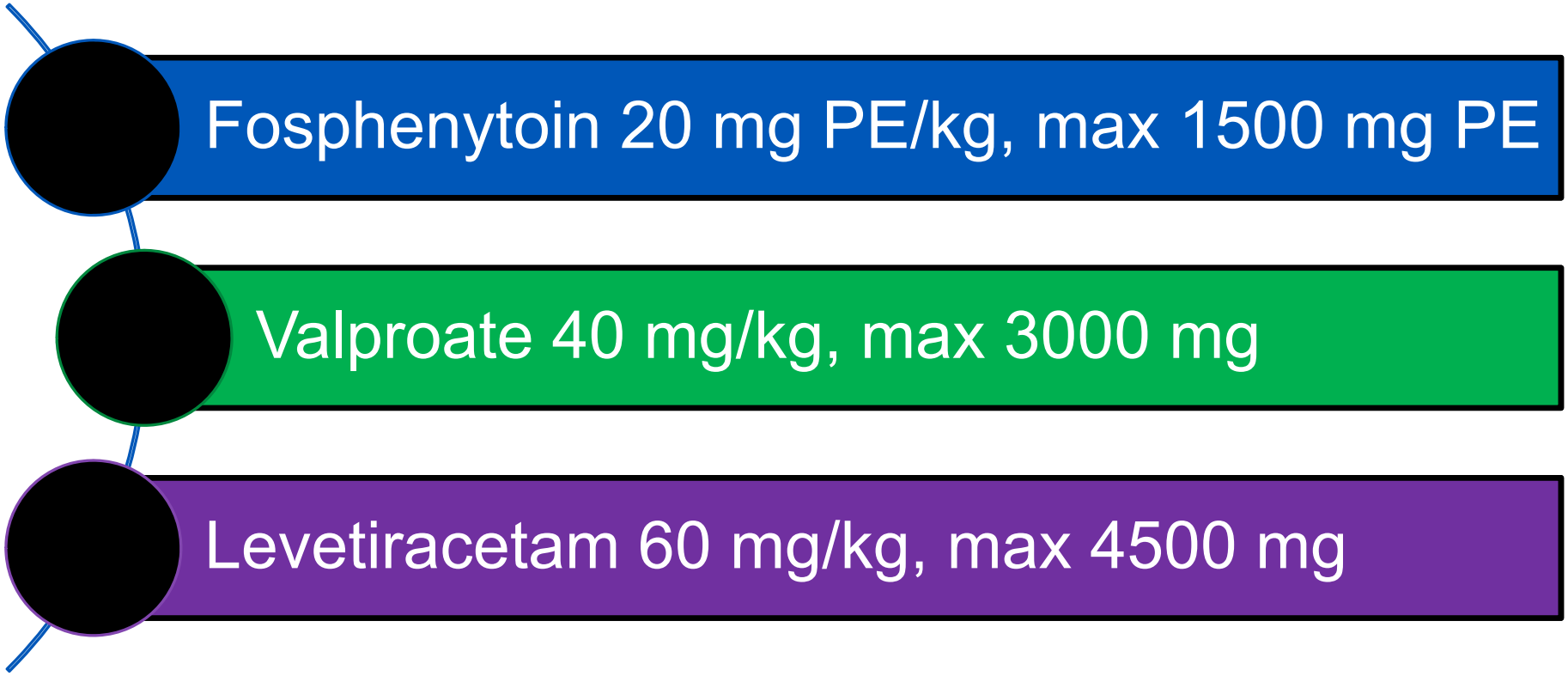
ESETT (2019)

Randomized controlled trial evaluating AEDs for urgent control in patients unresponsive to treatment with benzodiazepines

Inclusion Criteria	Exclusion Criteria
Ages 2 years and older	Seizure due to major trauma, hypoglycemia, hyperglycemia, or cardiac arrest
Generalized convulsive seizure lasting more than 5 minutes	Pregnant or incarcerated patients
Continued convulsions 5 minutes after last dose of BZD	Receipt of agents other than BZDs prior to enrollment
Treated with an acceptable dose of BZD: Midazolam 10 mg (IV or IM) Lorazepam 4 mg (IV) Diazepam 10 mg (IV or PR)	Known allergies or contraindications to any of the selected antiepileptic agents
Seizure and BZD administration could occur prior to ED arrival	

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

ESETT Interventions



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

ESETT Outcomes

Primary

- Absence of clinically apparent seizures and improving responsiveness at 60 minutes without additional AEDs

Secondary

- Time to termination of seizures
- ICU admission
- ICU & hospital length of stay

Safety

- Hypotension or cardiac arrhythmia
- Intubation
- Acute seizure recurrence

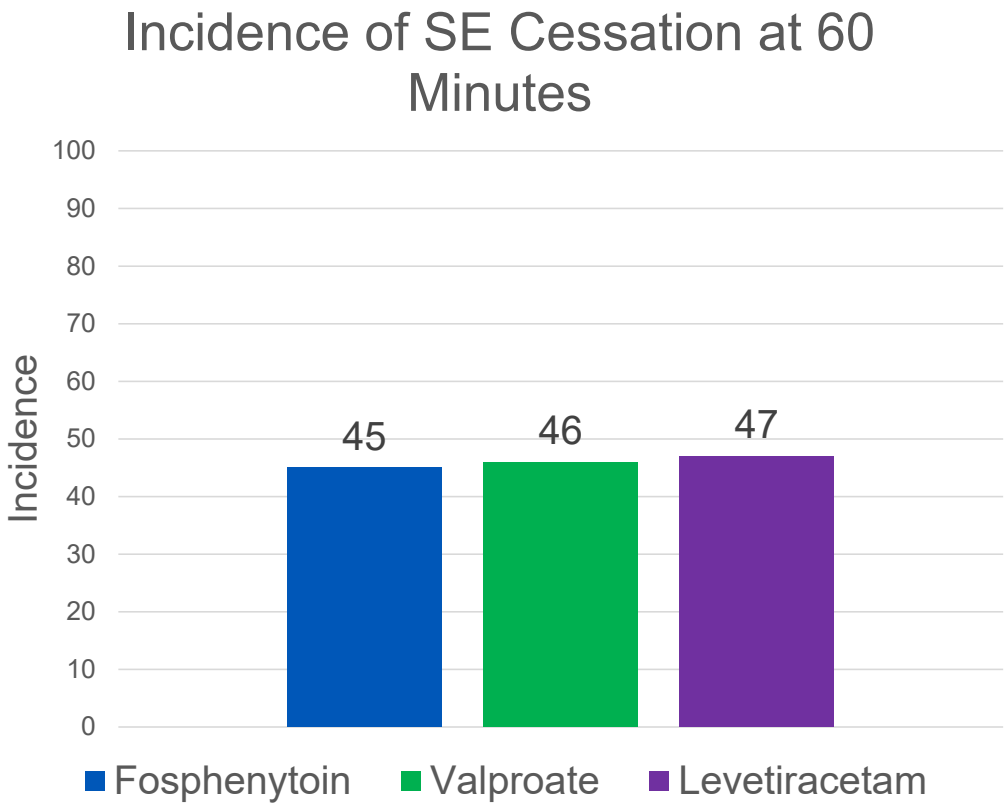
NEJM. 2019;381(22):2103-2113.

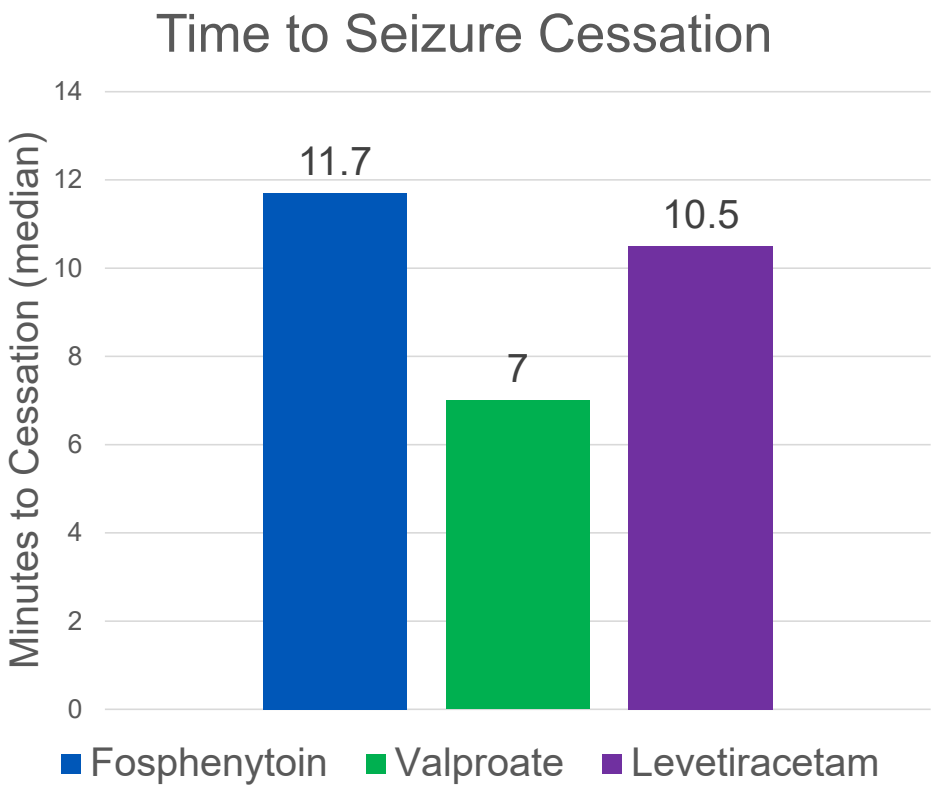
ESETT Baseline Characteristics

Characteristic	Levetiracetam (n=145)	Fosphenytoin (n=118)	Valproate (n=121)
Age, mean (year)	33.3	32.8	32.2
Male sex (%)	77	71	65
History of epilepsy (%)	66.9	67.8	68.6
Final diagnosis of SE (%)	88.3	88.1	84.3
Lorazepam dose equivalents, median (mg)	4.7	4.9	5.0
Duration of seizure at enrollment, median (minutes)	62	59	61.5
Benzodiazepines given prior to hospital arrival, (%)	61.4	57.6	51.2

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

ESETT Results

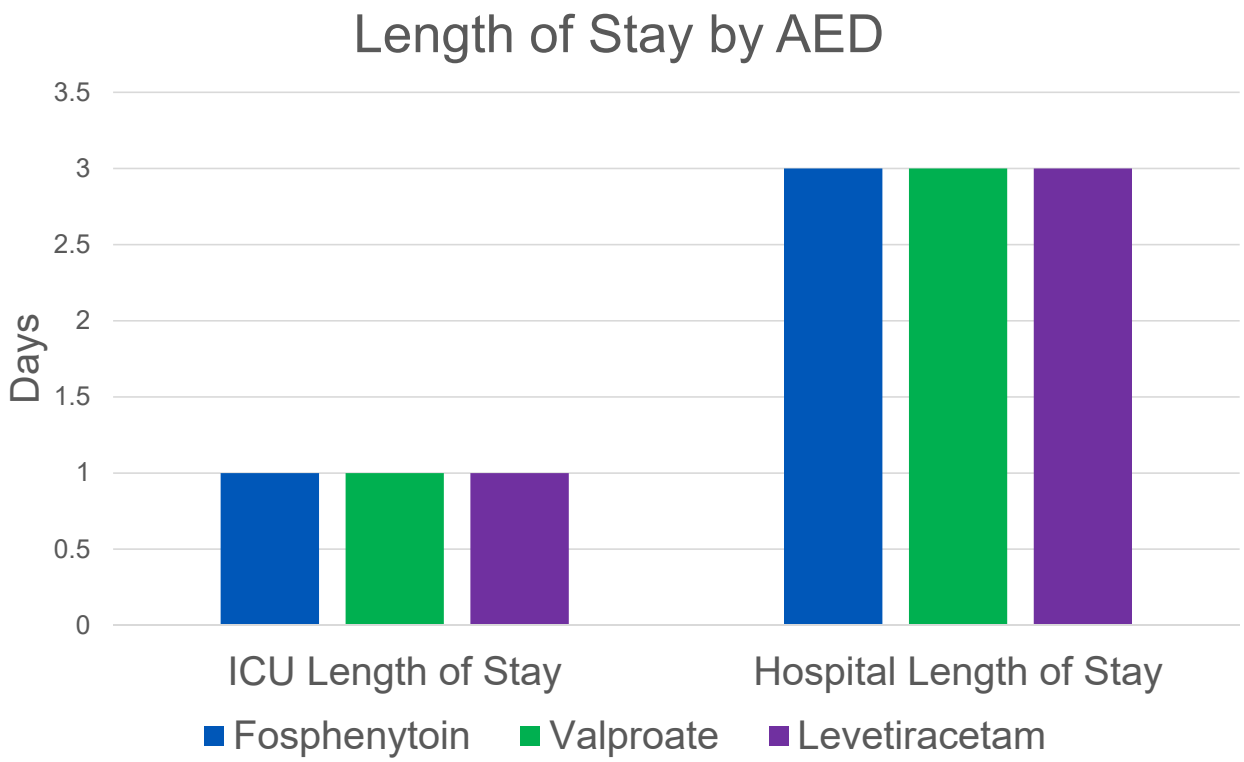




No significant differences noted

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

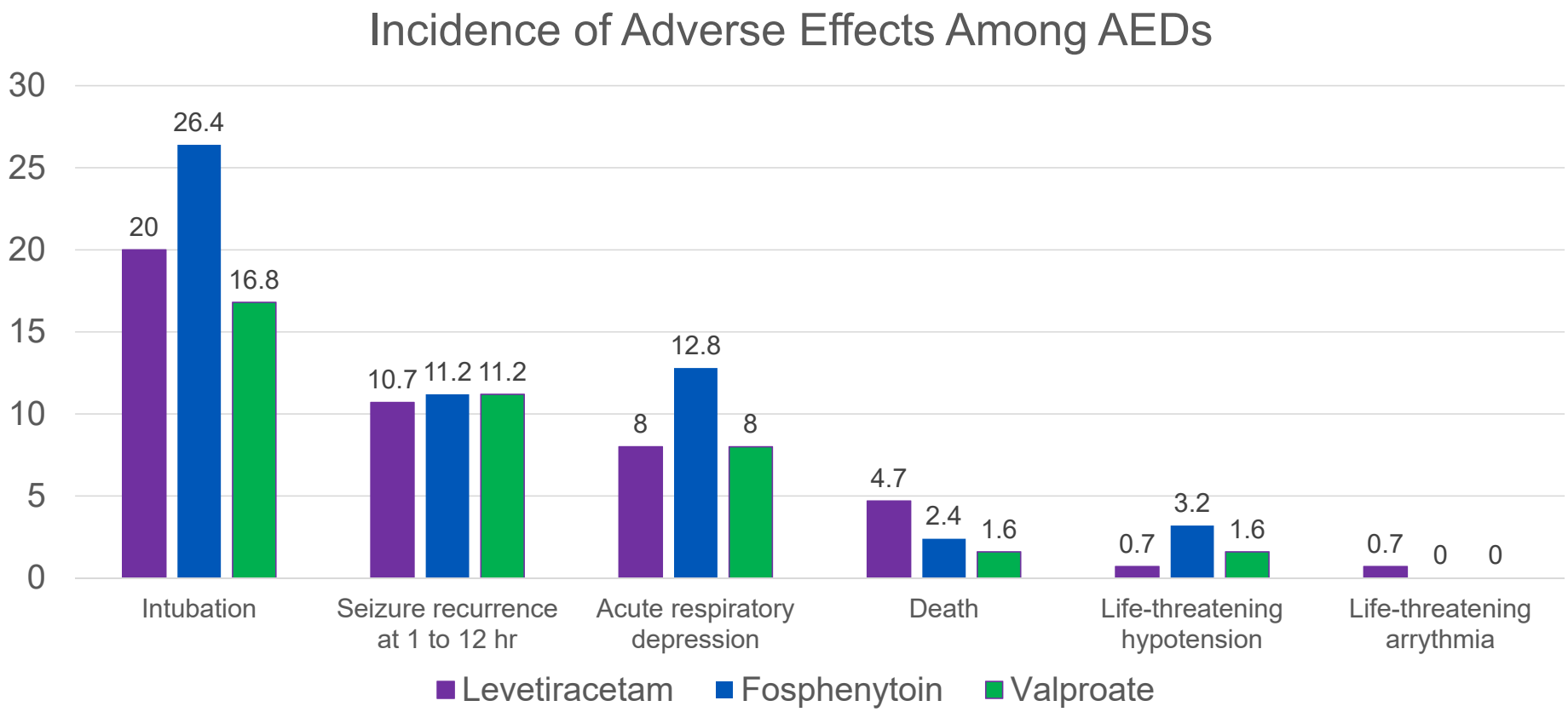
Secondary Outcomes



Admission to ICU:
Fosphenytoin 59.3%
Levetiracetam 60%
Valproate 58.7%

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

Safety Outcomes



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

ESETT Strengths & Weaknesses

Strengths

- Included children and adults
- Chosen safety outcomes were appropriate
- Well-designed with quick enrollment

Weaknesses

- Relative dosing of AEDs
- Arbitrary dose cap
- BZD inclusion criteria did not include repeat BZD dose
- ~50% cases unblinded to treatment team
- Primary outcome used lengthy time frame of cessation at 60 minutes

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

ESETT Unanswered Questions

- Which AED provides the best chance of success with urgent control therapy?
- Is the studied dose cap appropriate? Are we under dosing obese patients?
- How should we or shouldn't we alter dosing of our other standard AEDs?
- What is the dose ceiling of levetiracetam, and have we reached it yet?
- How can we administer these higher doses of levetiracetam?

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

Levetiracetam Administration Issues

Large doses of IV levetiracetam required	• What is the safest and fastest way to administer these doses?
IV push appropriate if diluted 1:1 with normal saline	• Only feasible for small doses
IV piggyback reasonable for large doses	• Limited by ability to compound at the bedside

Patient Case

PH is a 36 yo female who presents to the ED with convulsive seizure activity reported to have started around 15 minutes ago. She has a history of TBI and is not currently on any home medications. EMS administered one dose of lorazepam 4 mg IV, and on arrival she is given a repeat dose.

If PH weighs 82 kg, what antiepileptic and dose would you choose to treat PH with?

- Fosphenytoin 1500 mg PE
- Fosphenytoin 1640 mg PE (20 mg/kg)
- Levetiracetam 4500 mg
- Levetiracetam 4900 mg (60 mg/kg)

Additional Evidence for Urgent Control Therapy

- 2020 systematic review and meta-analysis comparing levetiracetam & fosphenytoin
  - Nine randomized controlled trials
  - 1732 patients assessed
  - Dosing of levetiracetam in studies was 20-40 mg/kg except for ESETT
  - Dosing of fosphenytoin was 20 PE mg/kg
  - Primary outcome time frames differed
    - Many studies assessed seizure cessation within 5-30 minutes

Epilepsy & Behavior. 2020;107286. Epub ahead of print.

Additional Evidence for Urgent Control Therapy

- Primary outcome: cessation of seizures
  - 74% success rate in levetiracetam group
  - 71% success rate in fosphenytoin group
- Higher rates of success observed than what was seen with ESETT
  - Likely due to differences in primary outcomes
- Minimal efficacy differences in AEDs for urgent control therapy
  - Consider alternative factors when choosing an agent

Epilepsy & Behavior. 2020;107286. Epub ahead of print.

Implementing ESETT into Practice

- Results of ESETT have not yet been incorporated into new guideline for status epilepticus
- Ask Mayo Expert has incorporated ESETT dosing strategies into their treatment algorithm and recommendations for SE
- Levetiracetam continues to be favored in practice due to side effect profile and ease of administration compared to other agents
- Most significant change has been related to levetiracetam dosing

Lacosamide

Dosing: 200-400 mg IV

Administration: IVPB over 15 minutes or IV push

Adverse Effects: hypotension, bradycardia, injection site reactions, prolonged PR interval, diplopia

Considerations

- Favorable side effect profile
- Schedule V controlled substance
- No induction or inhibition of CYP450 enzymes
- Theoretical increased efficacy for patient already seizing

Lacosamide [package insert]. Smyrna, GA: UCB Pharmaceuticals, 2008.

TRENdS RCT (2018)

Evaluated noninferiority of lacosamide vs fosphenytoin for nonconvulsive seizures

Interventions

- 400 mg IV lacosamide
- 20 mg PE/kg IV fosphenytoin

Primary Endpoint

- Absence of electrographic seizures for 24 hours

Results

- 63.3% success with lacosamide vs 50% with fosphenytoin (p=0.02)

Lacosamide is noninferior to fosphenytoin for control of nonconvulsive seizures

Ann Neurol. 2018;83:1174-1185.

Lacosamide in Status Epilepticus

Systematic review and meta-analysis examining success rates of lacosamide in SE

No direct efficacy comparison

Extracted efficacy and safety outcomes for patients receiving lacosamide for SE

20 case series or retrospective studies were used to identify 522 patients

50% of included patients had non-convulsive SE and 32% had focal motor SE

Doses ranged from 200-400 mg IV

Epilepsia. 2017;58(6):933-950.

Lacosamide in Status Epilepticus

Overall efficacy rate of 57% observed

Lower rate likely due to use in refractory SE

Comparable efficacy between use in nonconvulsive (57%) and convulsive (61%) SE

Success rate better in focal motor SE (92%)

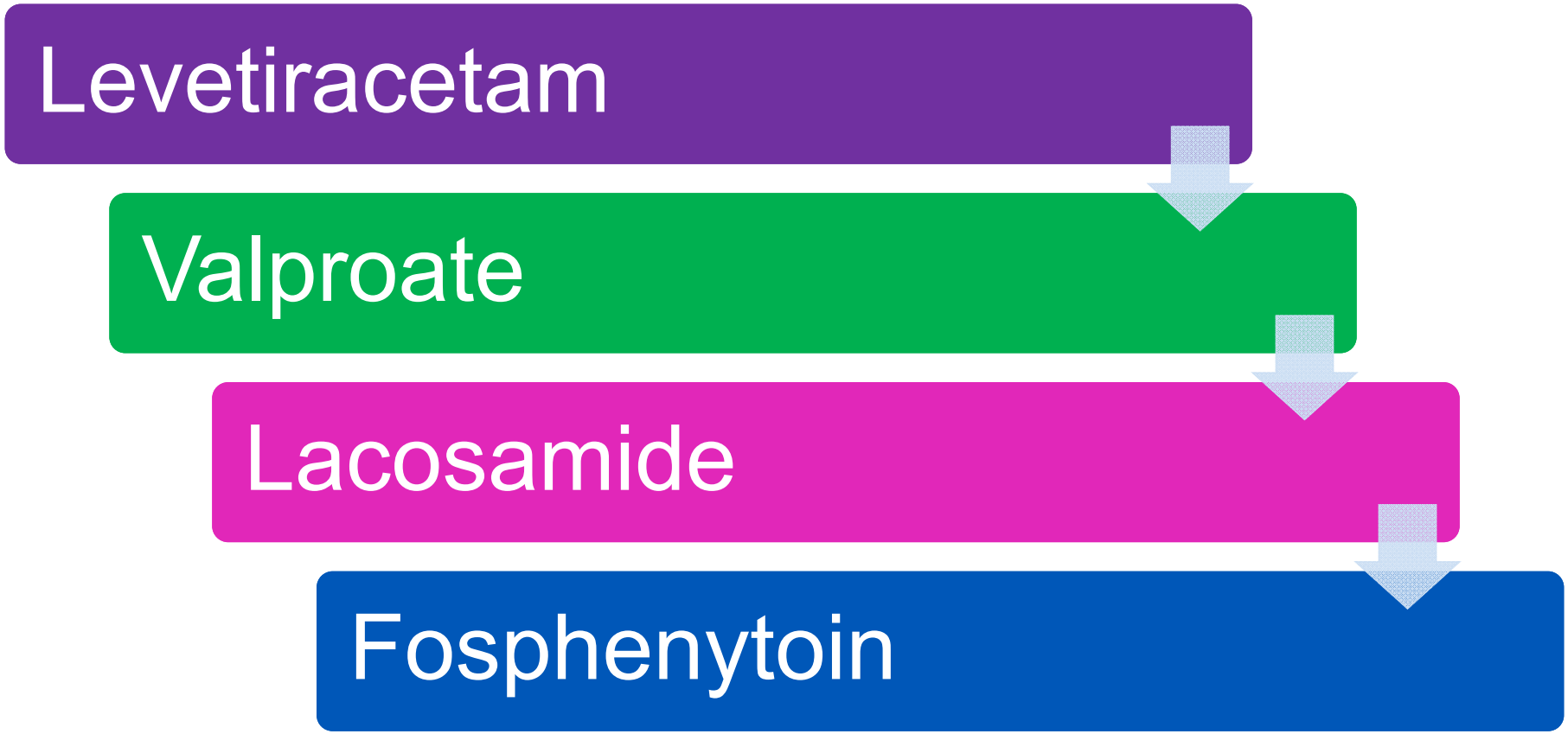
Lacosamide is a promising option for treatment of SE

Epilepsia. 2017;58(6):933-950.

Proposed NCC Guideline Update

For urgent control therapy in status epilepticus levetiracetam (**60 mg/kg up to a maximum dose of 4500 mg**), valproate 40 mg/kg, fosphenytoin 20 mg PE/kg, **or lacosamide 400 mg are recommended**. There is insufficient efficacy evidence to provide recommendations for use of one agent over another. **Antiepileptic choice should be determined using patient-specific clinical factors.**

Algorithm for Urgent Control AEDs



Patient Case

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- The team decides to administer levetiracetam 4500 mg. How will you quickly administer the ordered dose?
  - Infuse 4500 mg IVPB over 15 minutes
  - Infuse 4500 mg IVPB over 45 minutes
  - Administer 4500 mg undiluted IV push over 5 minutes
  - Administer 4500 mg diluted 1:1 with NS as an IV push over 5 minutes

Areas for Future Research

Safety of various levetiracetam administration techniques

Examination of appropriate AED dosing in obese patients

Exploration of newer antiepileptic agents and their potential for rapid delivery

Summary

- No significant differences in efficacy between guideline recommended urgent control therapies in SE
- Antiepileptic choice should be determined using patient-specific factors and safety considerations
- Recent evidence brings into question what AED dosing strategies should be utilized
- Rapid administration of antiepileptic therapies remains elusive
- Exploration of newer AEDs in the treatment of SE is ongoing

