


Pediatric Pharmacy Advocacy Group

**Super Status Epilepticus Expialidocious:
Debate on Treatment Options**

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Disclosures


- The presenters have nothing to disclose related to the content of this presentation.
- Will be referring to medications utilized for non-FDA labeled indications.



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Objectives


1. Choose a first-line benzodiazepine for a child with status epilepticus (SE) in the pediatric intensive care unit (PICU)
2. Select a first-line agent for refractory SE in the PICU
3. Contrast second-line agents for super-refractory SE in the PICU



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Patient Case

- AJ is a 4-year-old female admitted to your PICU after an AVM resection.
- PMH: previously healthy
- Home medications: none
- OR course: no complications
- One-hour after arrival, the PICU RN notices jerking of AJ's right arm & leg.




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Status Epilepticus (SE)

- 20 per 100,000 children each year with 3% mortality

Name	Criteria
Brief Seizure	< 5 minutes
Prolonged Seizure	5-30 minutes
SE	> 30 minute
Refractory SE	40-60 minutes? Two 2 nd line agents?
Super Refractory SE	> 24 hours after refractory therapy?

- Rapid termination of both clinical & electrical activity
- Basic emergency care
 - Circulation, airway, breathing (CAB)
 - Obtain IV access
 - Identify & treat underlying causes




Glauser T, et al. Epilepsy Curr. 2016;16(1):48-61.
Dubey D, et al. Neurol India. 2017;65(Supplement):512-7.
Gurcharran K, et al. Seizure. 2018;33(1099-1311):1830145-6.

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SE Etiologies

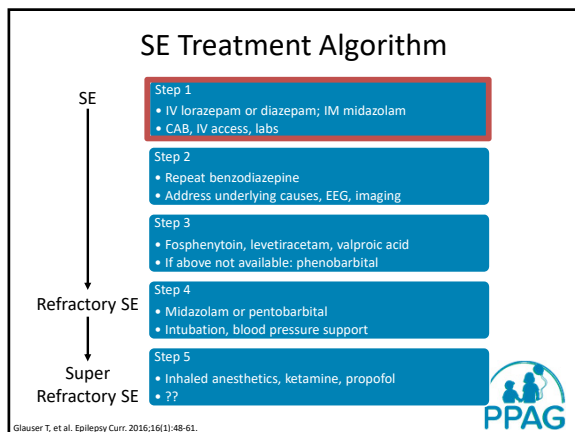
Etiology	%	Common Examples
Remote symptomatic	33	CNS malformation Prior TBI
Acute symptomatic	26	Meningitis Encephalitis Electrolyte disturbance
Febrile	22	Upper respiratory infection Sinusitis
Cryptogenic	15	Absence of acute event and/or metabolic disturbance
Remote symptomatic with acute precipitant	1	Previous CNS insult with concurrent infection

CNS = Central nervous system
TBI = Traumatic brain injury

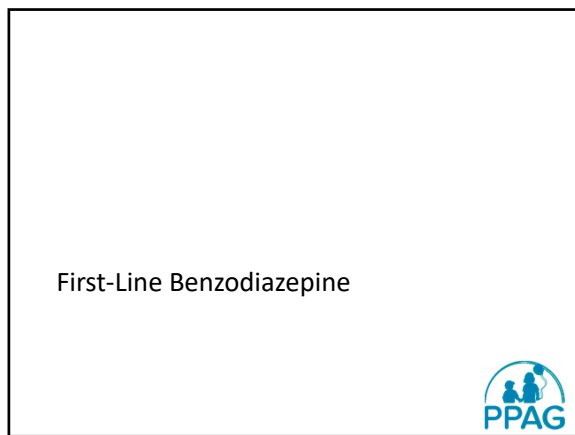


Rivello JJ, et al. Neurology. 2006; 67:1542-50.

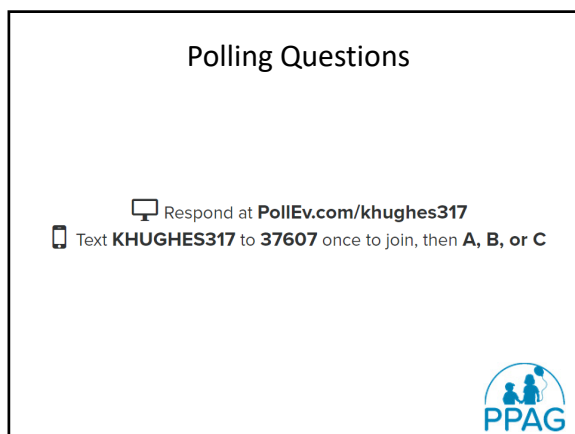
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Polling Question #1

Which IV benzodiazepine do you use first-line for treatment of seizures?

Diazepam **A**

Lorazepam **B**

Midazolam **C**




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Benzodiazepine Comparison

Agent	Onset (min)	Half-life (hr)	CNS Duration	IV Dose
Diazepam	IV: 1-3 PR: 2-10	15-50	60-90 min	0.2-0.5 mg/kg/dose (max 10 mg/dose)
Lorazepam	IV: 15-30 IM: 30-60	6-17	>6 hrs	0.05-0.1 mg/kg/dose (max 4 mg/dose)
Midazolam	IM: 5-15 IV: 1-5	3-4.5	30-60 min	0.05-0.1 mg/kg/dose (max 6 mg/dose)

Ng YT, et al. J Paediatr Child Health. 2013; 49:432-7.
Loddenkemper T, et al. Curr Treat Options Neurol. 2011; 13:560-73.
Pediatric Fundamental Critical Care Support, 2nd edition. SCCM. 2013.
Johnson PN, et al. Ann Pharmacother. 2017;51:656-62.




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Lorazepam: A History in Adults

- 1983 class II study (n = 70)
 - Lorazepam 4mg x 1 dose 78% success, x 2 doses 89% success
 - Diazepam 10 mg x 1 dose 58% success, x 2 doses 76% success
- 1998 Veteran's Affairs (n = 146 in each arm)
 - Lorazepam 0.1 mg/kg vs. diazepam 0.15 mg/kg + phenytoin
 - No overall difference
- 2001 Paramedics (n = 205)
 - Lorazepam 2 mg vs. diazepam 5 mg vs. placebo
 - Both superior to placebo
 - Lorazepam 59.1% vs. diazepam 42.6% seizures terminated prior to ED arrival

Glauser T, et al. Epilepsy Curr. 2016;16(1):48-61.



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Lorazepam vs. Diazepam: The Basics

Study	Intervention	Patients	Outcomes
2014 Class I	Lorazepam (L) 0.1 mg/kg max 4 mg vs. Diazepam (D) 0.2 mg/kg max 8 mg	Emergency department Convulsive SE N = 273	<ul style="list-style-type: none"> No difference in termination @ 10 minutes (~72%) No difference in safety profile
1995 Class III	L 0.05-0.1 mg/kg IV vs. D 0.3-0.4 mg/kg IV or PR	Emergency department Convulsive SE n = L 33, D 53	<ul style="list-style-type: none"> No difference to seizure cessation or # seizures/24 hours 2nd dose needed: L 8/33 vs. D 25/53 (p<0.05) Additional agent needed: L 1/33 vs D 17/53 (p<0.01)

Glauser T, et al. *Epilepsy Curr.* 2016;16(1):48-61.
 Appleton R, et al. *Dev Med Child Neurol* 1995;37:682-8.
 Chamberlain JM, et al. *JAMA* 2014;311:1652-60.

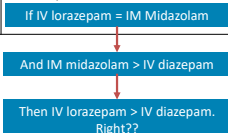


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Lorazepam vs. Diazepam: The Full Story

Study	Intervention	Patients	Outcomes
2010 Class III	L 0.1 mg/kg IV vs. D 0.2 mg/kg + Phenytoin 18 mg/kg	Emergency department Convulsive SE N = 178	<ul style="list-style-type: none"> 100% seizure cessation in both groups
Class I	Midazolam IM 5 mg (13-40 kg) vs 10 mg (>40 kg) L 2 mg (13-40 kg) vs 4 mg (>40 kg)	Paramedics Convulsive SE N = 893 adults + children ≥ 13 kg (120 children)	<ul style="list-style-type: none"> 63-73% seizure cessation pre-hospital IM midazolam is non-inferior to IV lorazepam

Glauser T, et al. *Epilepsy Curr.* 2016;16(1):48-61.
 Sreenath TG, et al. *Eur J Paediatr Neurol* 2010;14:162-8.
 Silbergliet R, et al. *N Engl J Med* 2012;366:593-600.



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Lorazepam 2008 Cochrane Review

- Articles 1966-2007
 - Lorazepam, diazepam, & midazolam
 - Phenytoin, phenobarbitone, & paraldehyde
- 4 studies with 383 patients included
 - IV lorazepam 70% vs. IV diazepam 65% (95% CI 0.77-1.54)
 - ↓ adverse effects with lorazepam


Appleton R, et al. *Cochrane Database Syst Rev.* 2008; Jul 16 (3): CD001905.



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Diazepam


- Faster onset of action than lorazepam, 1-3 vs 5-15 min
- Pharmacokinetic profile:
 - CNS duration: Lorazepam (>6 hr) vs Diazepam (60-90 min)
 - NOT predictive of efficacy



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Back to the 2008 Cochrane Review

- No statistical difference between lorazepam vs diazepam:
 - 19/27 (70%) vs 22/34 (65%)
 - RR 1.09 (95% CI: 0.77-1.54)
- Respiratory depression:
 - Noted in only 1 study included
 - Diazepam vs lorazepam: 35% vs 22%
 - Hold that thought....




Appleton R, et al. Cochrane Database Syst Rev. 2008; Jul 16 (3): CD001905.

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IV Diazepam vs. IV Lorazepam

- **Objective:** To determine if lorazepam has better safety/efficacy than diazepam for SE
- **Methods:**
 - Multi-centered double-blind RCT from 2008-2012 for 3-18 year-olds with SE
 - Primary efficacy outcome was cessation of SE within 10 min
 - Primary safety outcome was defined as the need for assisted ventilation for respiratory depression




Chamberlain, JM et al. JAMA. 2013; 311:1652-60.

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IV Diazepam vs. IV Lorazepam (Cont'd)

- Results:**
 - Cessation of seizures: No difference between diazepam and lorazepam: 101/140 (72.1%) vs 97/133 (72.9%), absolute efficacy difference 0.8% (95% CI: -11.4 to 9.8)
 - No difference with assisted ventilation
 - ↑ number of patients sedated with lorazepam
- Conclusions:** Results **DO NOT** support lorazepam over diazepam
 - PK Profile does NOT predict efficacy**




Chamberlain, JM et al. JAMA. 2013; 311:1652-60.

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Polling Question #2

Which IV benzodiazepine WILL you use first-line for treatment of seizures?


- Diazepam
- Lorazepam
- Midazolam



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Summary: Diazepam vs. Lorazepam

- Don't wait to get IV access
- Similar efficacy IV diazepam and lorazepam
- Possibly ↓ adverse effects with lorazepam
- Consider availability & drug shortages



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First-Line Agent
Refractory Status Epilepticus



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Patient Case

- AJ has received 2 doses of IV lorazepam and convulsions have stopped. The EEG technician reports AJ is still seizing.



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Polling Question # 3

What is the next step for AJ?

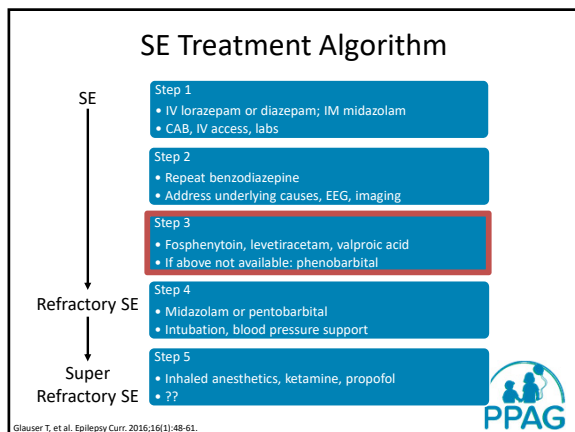
Proceed with normal ICU care as convulsive seizures have stopped

Load AJ with levetiracetam 60 mg/kg IV x 1

Start midazolam 0.1 mg/kg/hr




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2nd Line Anti-Epileptics

IV Medication	Dose
Fosphenytoin	20 mg PE/kg, max 1500 mg PE/dose
Levetiracetam	60 mg/kg, max 3000 mg/dose
Valproic Acid	40 mg/kg, max 4500 mg/dose
If none of the above available:	
Phenobarbital	15 mg/kg



Glauser T, et al. Epilepsy Curr. 2016;16(1):48-61.

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Polling Question #4


What is your first line therapy for refractory SE?

Midazolam

Pentobarbital

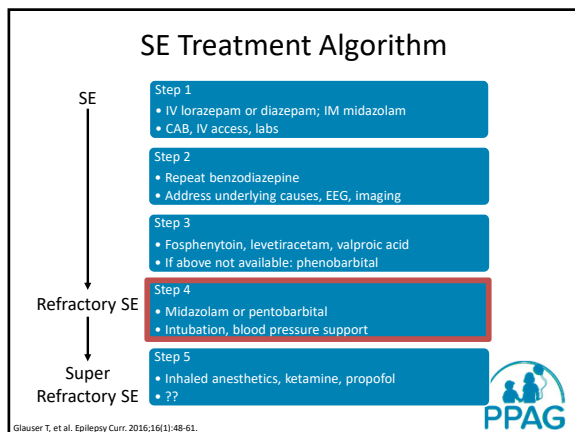
Ketamine

Propofol

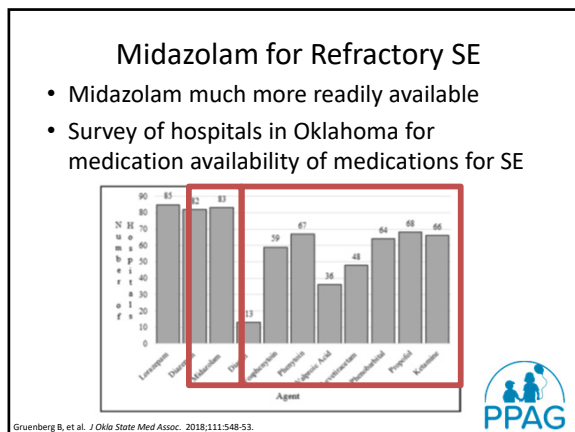


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Refractory SE Systematic Review

- **Objective:** Review best evidence for agents to use for refractory SE, including midazolam and anesthetics
- **Methods:**
 - Reviewed MEDLINE and EMBASE prior to 12/31/2013
 - Protocol described
 - Report had to include at least 5 patients
 - Included high-dose benzodiazepine or anesthetic




Wilkes R, et al. Pediatr Crit Care Med. 2014; 15:632-9.

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Refractory SE Systematic Review (Cont'd)

- **Results:** 16 studies (n = 645)
 - Midazolam (9 studies) with 76% efficacy
 - Barbiturates* (4 studies) with 65% efficacy
 - Anesthetics/hypothermia** (3 studies) used after failure of other agents and with prolonged onset
- **Conclusions:**
 - Data with poor quality overall
 - Hierarchy of treatment: midazolam > barbiturates > anesthetics/hypothermia

*Thiopental (n = 1 study); pentobarbital (n = 3 studies)
**Hypothermia (n = 1 study); ketamine (n = 1 study); isoflurane (n = 1 study)




Wilkes R, et al. *Pediatr Crit Care Med*. 2014; 15:632-9.

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IV Pentobarbital Toxicity

- Contains 40% v/v of PG
- WHO recommends max of 25 mg/kg/day of PG
- PG included in several other IV formulations:
 - Lorazepam (80% v/v)
 - Phenytoin (40% v/v)
- Associated with acute kidney injury and metabolic acidosis

PG = propylene glycol
v/v = volume/volume
WHO = World Health Organization




Chandler CJ, et al. *J Pediatr Intensive Care*. 2014; 3:73-7.
Miller MA, et al. *Ann Pharmacother*. 2006; 40:1502-6.

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Cost Comparison of Midazolam vs. Pentobarbital

- Significantly less expensive compared to others for refractory seizures
- Initial dose for 20-kg, 6 year-old:

IV Medication	Initial Dose	Cost
Midazolam	0.1 mg/kg/hr	\$1.60-4.16
Pentobarbital	1 mg/kg/hr	\$72.62-84.00
Propofol	1 mg/kg then 20 mcg/kg/min	\$4.38-10.95
Ketamine	36.5 mcg/kg/min	\$7.83-29.06



Gruenberg B, et al. *J Ohio State Med Assoc*. 2018;111:548-53.

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Pentobarbital for Refractory SE


- Midazolam most common first-line agent but only 65-76% success rate
- Barbiturates show good response to midazolam failures

	Midazolam Failure	Barbiturate Response
2014 Systematic Review	125/521 (24%)	65%
2016 prospective observational study	12/42 (29%)	8/12 (67%)
2016 Retrospective chart review*	13/34 (38%)	13/13 (100%)

*phenobarbital

- Overall 94% response rate with midazolam + pentobarbital

Wilkes R, et al. Pediatr Crit Care Med 2014;15:632-9.
Tasker RC, et al. Pediatr Crit Care Med 2016;17(10):968-75.
Gulati S, et al. Brain Dev 2018;40:316-24.




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Questioning Midazolam's Efficacy & Safety

- 2014 Literature Review cited 396/521 patients (76%) responded to midazolam with mean time of 271 minutes
 - Endpoint of clinical seizure cessation in 7/9 studies
 - When continuous EEG used: ~7 fold ↑ in time to cessation and ~4 fold ↑ in dose
- 2 cases of metabolic acidosis with midazolam
 - HCl for solubility + benzyl alcohol preservative
 - Non-anion gap acidosis due to HCl

Wilkes R, et al. Pediatr Crit Care Med 2014;15:632-639.
Singh S, et al. Indian J Crit Care Med 2018;22(2):119-21.




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Pentobarbital vs. Midazolam

	Pentobarbital	Midazolam
The good		
Efficacy	✓	✓
# of studies		✓
EEG evidence	✓✓	✓
Therapeutic monitoring	✓	
The bad		
Wide dosing range	1-10 mg/kg/hr	0.1-0.84 mg/kg/hr
Frequency of titrations	q6-12h	Q5-15min
Renal clearance		✓
Tachyphylaxis		✓
Hypotension	✓✓	✓
Need for intubation	✓✓	✓
Delirium		✓

PPAG logo



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Polling Question #5


What WILL BE your first line therapy for refractory SE?

Midazolam

Pentobarbital

Ketamine


Propofol



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Summary: Midazolam vs. Pentobarbital


- Midazolam should be used first-line for refractory SE due to ↓ adverse effects
 - 76% response rate
 - 2% of patients needed vasoactives
- Use continuous EEG to guide therapy
- More studies are needed



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Patient Case

- AJ was started on midazolam at 0.1 mg/kg/hr and titrated up to 0.4 mg/kg/hr within 6 hours of initiation with no improvement in her EEG.
- Pentobarbital is initiated at 10 mg/kg/hr x 1 hour then started at 1 mg/kg/hr.
- Over the course of the next 48 hours, AJ receives multiple pentobarbital boluses and the infusion is titrated up to 5 mg/kg/hr.
- The EEG technician reports AJ is still seizing.



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Second-Line Agent
Super Refractory Status Epilepticus



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SE Treatment Algorithm

SE


↓

Refractory SE

↓

Super Refractory SE

- Step 1
 - IV lorazepam or diazepam; IM midazolam
 - CAB, IV access, labs
- Step 2
 - Repeat benzodiazepine
 - Address underlying causes, EEG, imaging
- Step 3
 - Fosphenytoin, levetiracetam, valproic acid
 - If above not available: phenobarbital
- Step 4
 - Midazolam or pentobarbital
 - Intubation, blood pressure support
- Step 5
 - Inhaled anesthetics, ketamine, propofol
 - ??



Glauser T, et al. Epilepsy Curr. 2016;16(1):48-61.

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Polling Question #6


What is your first line therapy for super refractory SE?

Inhaled anesthetics

Ketamine

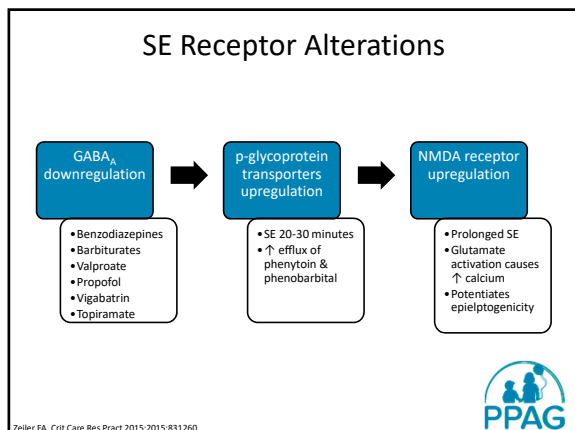
Propofol

Other



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Special “K”etamine

- NMDA receptor
 - Synergism with benzodiazepine & barbiturate
 - Upregulation during RSE ↑ excitotoxicity
 - Antagonism provides some neuroprotection
 - Status epilepticus
 - Traumatic brain injury
- No respiratory drive depression
- Sympathomimetic properties
 - Vasopressor sparing
 - No compounded hypotension

Zeller FA, Crit Care Res Pract 2015;20(5):831-260.
Keros S, et al. J Child Neurol 2017;32(7):636-46.

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Systematic Review of Ketamine for RSE

- 9 studies with 52 children
- Response rate 63.5%
- Dosing
 - Bolus: 0.5-3 mg/kg
 - Infusion: 0.12-10 mg/kg/hr
- AEDs prior to ketamine: 1-11
- Most common 7 day duration (2 hours-27 days)
- No major complications in either children or adults
 - 1 hypersalivation
 - 1 arrhythmia


Zeller FA, et al. Neurocrit Care 2014;20(3):502-13.

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Uptake in Ketamine Use for RSE

- 2010 to 2014: ketamine use in RSE ↑ 4.5 fold
- Initiation after pentobarbital most common
 - Average start on day 11 (5-20) and used for 7 (4-9) days
 - Consistently ~60% response rate as 3rd or 4th line agent
- Single institution treated 5/13 patients with ketamine instead of anesthetics
 - Response in 4/5 patients (80%)
 - Prevented endotracheal intubation

Zeiler FA. Crit Care Res Pract 2015;2015:831260.
 Keros S, et al. J Child Neurol 2017;32(7):638-46.
 Gaspard N, et al. Epilepsia 2013;54:1498-503.
 Beutner J, et al. Epilepsia 2015;56:2134-6.




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Chronic Ketamine Therapy

- 33-year-old woman with poorly controlled focal epilepsy
- Recurrent focal seizures treated with IV ketamine
 - Continuous infusion titrated to 1.25 mg/kg/hr
 - Enteral ketamine introduced on day 2, titrated up to 250 mg BID
 - Infusion tapered off by hospital day 5
- Continued enteral ketamine for 6 months with ↓ seizure frequency and no adverse effects

Pizzi MA, et al. J Intensive Care 2017;5:54. DOI10.1186/140560-017-0248-6




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Inhaled Anesthetic Agents

- Possess many properties for treatment of refractory SE:
 - Lipophilic nature allows transport in CNS
 - Titrated easily based on EEG monitoring
 - Inhibit glutamate through NMDA-antagonism & agonize GABA_A receptors
- Therapeutic options:
 - Isoflurane & desflurane preferred
 - Sevoflurane possess ↓ NMDA-antagonistic effects


Zeiler AZ, et al. Can J Neurol Sci. 2015;42:106-15.



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Systematic Review of Anesthetics for Refractory SE (Cont'd)

- **Objective:** Review studies in adults & children receiving anesthetics for refractory SE
- **Methods:**
 - Reviewed articles from MEDLINE, BIOSIS, EMBASE, Cochrane Library, & others
 - Evaluated by 2 independent reviewers
 - Graded using Oxford & Grading of Recommendation Assessment Development & Education methodology




Zeller AZ, et al. Can J Neurol Sci. 2015;42:106-15.

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Systematic Review of Anesthetics for Refractory SE (Cont'd)

- **Results:**
 - 19 studies identified with 46 patients
 - Included 46 patients (28 adults & 18 children)
 - No difference in seizure control in adults vs children, 92.9% vs 94%
 - Isoflurane most common
 - Hypotension rating limiting effect
- **Conclusion:** Weak but positive evidence for isoflurane (insufficient data for desflurane)




Zeller AZ, et al. Can J Neurol Sci. 2015;42:106-15.

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Refractory SE Systematic Review...Again

- Summary of results:
 - 16 studies total
 - 2 studies with anesthetics
- Findings:

Agent	Cases	Failed AEDs	Dosing	Duration	Responders (%)
Isoflurane	5	Diazepam, phenytoin, phenobarbital, pentobarbital	Titrated to end-tidal concentration 0.5-2.2%	Range 1-55 hr	5/5 (100)
Ketamine	9	Multiple, midazolam, thiopental	Mean 36.5 (range 10-60) mcg/kg/min	Range 1-17 d	6/9 (67)




Wilkes R, et al. Pediatr Crit Care Med. 2014; 15:632-9.
Kofke WA, et al. Anesthesiology. 1989;71:653-9.
Rosati A, et al. Neurology. 2012;79:2355-8.

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Ketamine & Adverse Events

- ↑ secretions
- ↑ blood pressure & heart rate
- Emergence phenomenon:
 - Golding et al. noted only 3/74 (4.1%)
 - Likely biased on nature of retrospective reports
 - True incidence may be ↑ due to risk of PICU delirium

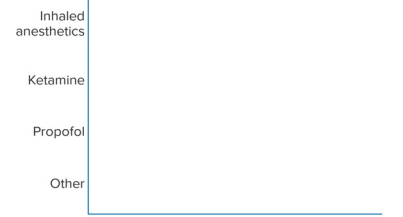
Golding CL, et al. *Ann Pharmacother.* 2016;50:234-41.




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Polling Question #7

What WILL BE your first line therapy for super refractory SE?




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Summary: Ketamine vs. Anesthetics

- Ketamine is a promising therapy for refractory SE & is well tolerated
- Evidence for early use of ketamine still needed



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Conclusions

- IV lorazepam or diazepam are appropriate 1st line options for treatment of SE
- Midazolam should be considered 1st line option for refractory SE
 - ¾ of patients are likely to respond
 - ↓ adverse effects compared to pentobarbital
- Ketamine is a promising treatment of super refractory SE, but data regarding earlier use is needed



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Super Status Epilepticus Expialidocious: Debate on Treatment Options

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