ashp MIDYEAR 2018
Clinical Meeting & Exhibition

Special K: Traditional and Novel Roles of Ketamine in the Critically Ill

James Gilmore, Pharm.D., BCCCP, BCPS
Pharmacy Manager, Critical Care and Emergency Department
Cedars-Sinai Medical Center
Los Angeles, CA

Adrian Wong, Pharm.D., M.P.H., BCCCP, BCPS
Assistant Professor
MCPHS University
Clinical Pharmacist – Medical Intensive Care Unit
Beth Israel Deaconess Medical Center
Boston, MA

Disclosures

All planners, presenters, reviewers, and ASHP staff of this session report no financial relationships relevant to this activity.

Objectives

- Discuss the traditional role of ketamine in adult critically ill patients.
- Evaluate recent literature on the use of ketamine in the critically ill.
- Given a scenario, select practical applications of ketamine for traditional and expanding roles in critically ill patients.

Ketamine Background

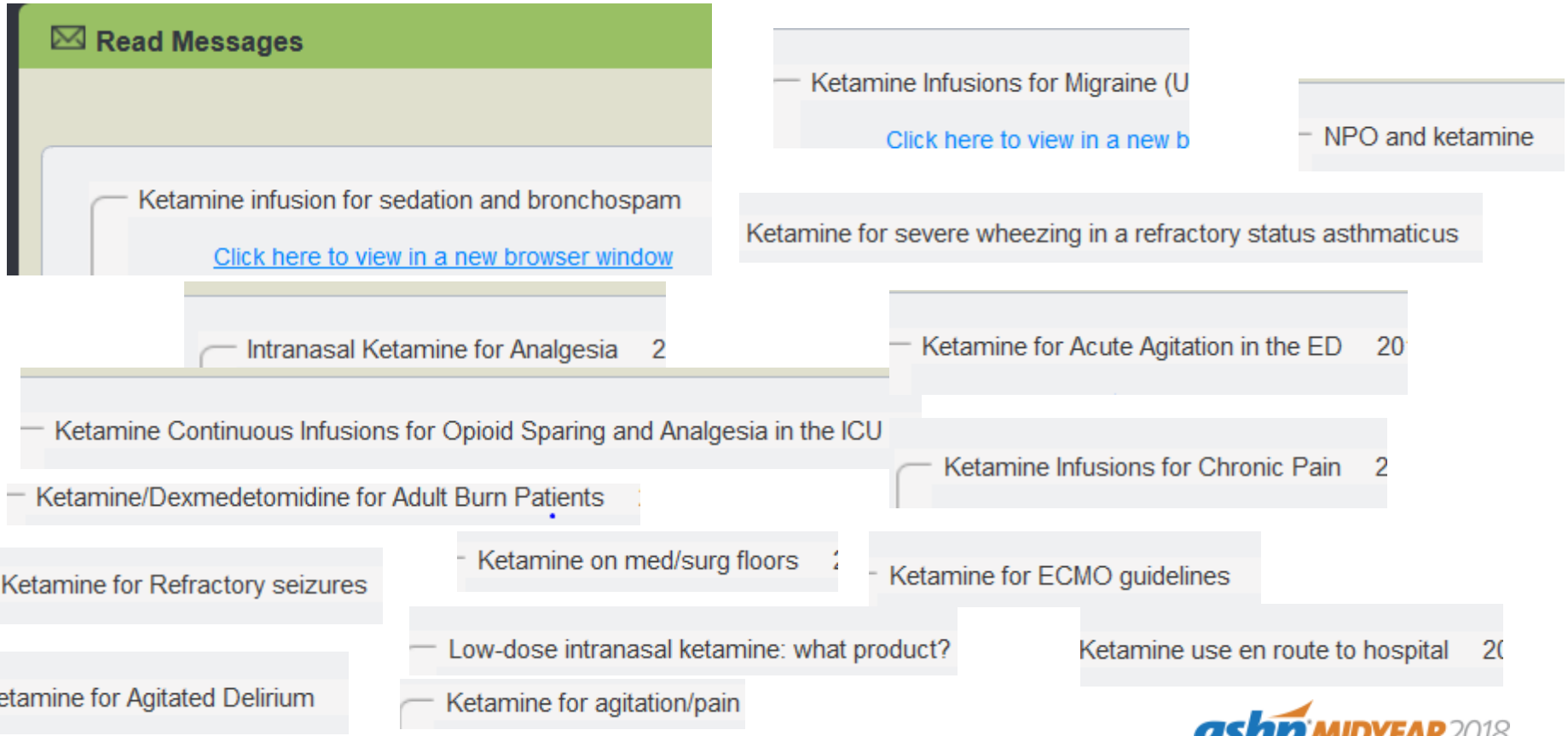
- First synthesized in 1960s
- FDA approval in 1970 as an anesthetic
- Shorter acting, less potent successor to phencyclidine (PCP)
- Claim to fame: dissociative anesthesia
  - Patients appear awake but unable to respond to sensory input
- Rapid analgesia, limited side effect profile led to rise in popularity in anesthesia and (lately) far beyond

Domino EF. *J. Psychedelic Drugs.* 1965. 12, 223–227.
Li L, et al. *Front. Hum. Neurosci.* 2016. *10:612.*

Poll: Your Current Use and Restrictions

- In non-critically ill patients post-operatively?
- In the ICU via continuous infusion as an adjunct for analgesia?
- In the emergency department for procedural sedation?
- Mixed in the same syringe as propofol?
- For alcohol withdrawal?
- Able to be given in the ICU without restrictions?
- Only able to be administered by or under the guidance of an anesthesiologist?

Ketamine- Everything to Everyone



Ketamine Mechanism/(s)?

- Noncompetitive NMDA antagonist
- At high doses, activates opioid receptors (mu > kappa > sigma)
  - Pain-relieving effects are not reversed by naloxone
- Nicotinic and muscarinic receptor antagonism
- Blockade of sodium and potassium channels
- Activation of D2 and L-type voltage-gated calcium channels
- Facilitation of GABA-A signaling

Cohen SP, et al. Reg Anesth Pain Med. 2018 Jul;43(5):521-546.

Postulated Antidepressant Mechanisms

- Blockade of interneuronal and excitotoxic extrasynaptic NMDA receptors
- Disinhibition of pyramidal cells leading to a glutamate surge
- Activation of prosynaptogenic AMPA receptors
- Activation of synaptogenic intracellular signaling, including TORC1 and brain derived neurotrophic factor
- Increased GABA-B levels
- Inhibition of brain glycogen synthase kinase 3 (similar to lithium)

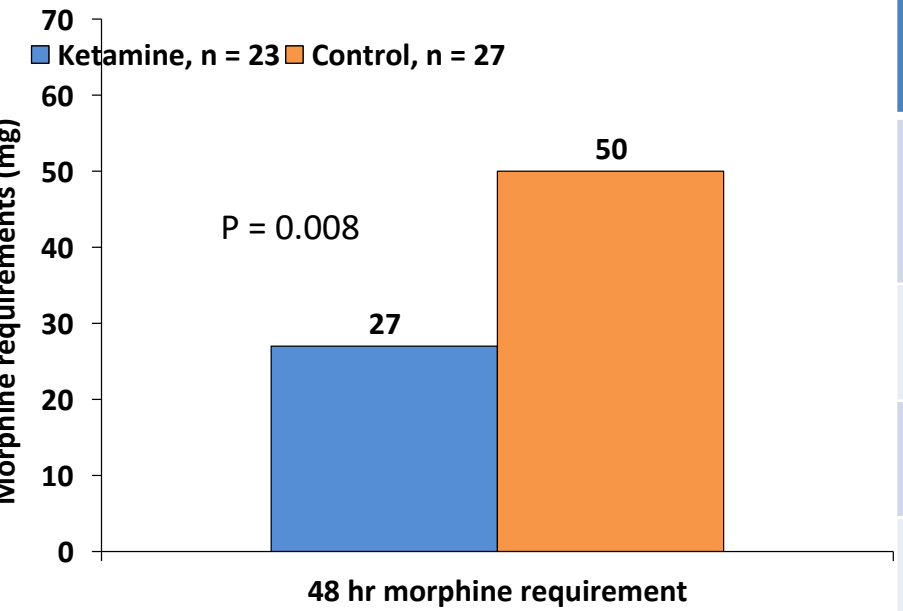
Why We're Here

- Combination of hope and reality check
- At the opioid crossroad
  - Recent surge in opioid use and overdoses has led to a rise in non–opioid-based treatment options
- In preclinical studies, ketamine has been shown to reduce opioid tolerance and hyperalgesia
- Evaluate what evidence we have and don't have for ketamine use in the critically ill

Roles for Ketamine in the ICU

- Traditional
  - Adjunctive analgesia
  - Procedural sedation
- Novel
  - Alcohol withdrawal
  - Depression
  - Post-traumatic stress disorder
  - Status asthmaticus
  - Status epilepticus

Pre-emptive and Post-operative Ketamine plus Morphine vs. Morphine alone



	Ketamine (n=23)	Control (n=27)	p-value
Intra-op sufentanil, mcg†	100 [55]	100 [60]	0.77
Duration of surgery, min†	150 [75]	150 [57]	0.53
Incidence N/V*	1 (4)	10 (37)	**0.01**
Awake at hr 48*	18 (67)	12 (44)	0.09

† Median [IQR]; * number (%); N/V = Nausea and vomiting

Zakine J, et al. Anesth Analg 2008;106:1856-1861

Low Dose Ketamine Impact on Opioid Use in Mechanically Ventilated SICU Patients

- Single center, retrospective, N= 40
- Median dosing 5 mcg/kg/min
- Median duration 1.89 days (0.96-3.06)
- Time from ketamine to extubation 1.44 days (0.58-2.66)
- No significant changes in SBP, DBP, HR or RR in six hours post initiation

Parameter	1 Hr pre	6 Hrs post	P Value
MSO4, mg/hr*	6.66 (4.8-10)	5 (0-6.66)	**0.004**
Phenylephrine equivalent, mg/hr*	70 (25-90)	40 (0-80)	0.019
Propofol, mg/h*	180 (100-250)	150 (12.75-200)	0.014
RASS outside of goal, n	22	20	0.476
RASS >0, n	4	10	**<0.001**
RASS <-1, n	18	10	**<0.001**
*Median (IQR)			

Buchheit JL, J Intensive Care Med. 2017 Jan 1:885066617706907.

Impact of Ketamine Use on Adjunctive Analgesic and Sedative Medications in Critically Ill Trauma Patients

- Single center, single arm, retrospective chart review, N=36
- Ketamine infusion initiated second line after fentanyl / Propofol
- Avg ketamine infusion 0.64 ± 0.39 mg/kg/hr in first 24 hours
- 22 pts (61.1%) remained on ketamine for 72 hours

	PRE-K	POST-K	p-value
Opioids, mg IV MME	431.3 (206-1012.4)	272.5 (52.5-772.5)	**0.029**
Opioids, PRN, MME	51.3 (23-123.1)	62.5 (12.5-170)	0.681
Dexmedetomidine mcg/kg/hr	0.7 (0.6-1.1)	0.9 (0.7-1.4)	**0.002**
Propofol, mcg/kg/hr	35.4 (23.1-49.4)	22.8 (14-32.9)	**0.002**
BZD, mg midaz. Equiv	14.3 (1.3-564.3)	17.2 (9.19- 193.9)	0.735

* Median (IQR)

Pruskowski, et al. Pharmacotherapy. 2017;37(12):1537–1544

Ketamine for Procedural Sedation in Burns

- Primary literature largely small RCTs in healthy volunteers exposed to burns
- Ketamine IV (bolus, Infusion, combination) demonstrated reduction in secondary hyperalgesia compared to placebo
- Ketamine combined with morphine abolished the wind-up pain phenomenon for the entire duration of the individual periods studied
- Side effects largely described as weak to moderate

Ilkjaer S. et al. Br J Anaesth 1996;76:829– 34.
Warncke T, et al. Pain 1997;72:99–106
Mikkelson S, et al. Anesthesiology 1999;90:1539–45.
Schulte H, et al. Anesth Analg 2004;98:1574–80.
McGuiness SK, et al. Pain Med. 2011 Oct;12(10):1551-8.

Advantages of Ketamine in Deep Sedation

- Reduced risk of respiratory depression
  - Further reduced when administered as slow infusion compared to bolus
- Reduced hemodynamic implications
- Preserved muscle tone
- Preserved protective airway reflexes
- Bronchodilatory effects
- Reduction of use of opioids

Clattenburg EJ, et al. Acad Emerg Med. 2018 Sep;25(9):1048-1052
Gregoretti C, et al. Drugs 2008; 68 (17): 2427-2443

Guidelines this Year for Ketamine

- Society of Critical Care Medicine
  - Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU
- American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists
  - Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Acute Pain Management
  - Consensus Guidelines on the Use of Intravenous Ketamine Infusions for Chronic Pain

Guideline Recommendations- PADIS 2018

- *Question:*
  - Should ketamine be used as an adjunct to an opioid (vs an opioid alone) for pain management in critically ill adults?
- *Recommendation:*
  - We suggest using low-dose ketamine (0.5 mg/kg IVP x 1 followed by 1-2 µg/kg/min infusion) as an adjunct to opioid therapy when seeking to reduce opioid consumption in postsurgical adults admitted to the ICU (conditional recommendation, very low quality of evidence).

Devlin JW, et al. Crit Care Med. 2018 Sep;46(9):e825-e873

Ketamine for Acute Pain Guidelines

- Perioperative use in surgery with moderate to severe postoperative pain (B)
- Perioperative use in patients with opioid tolerance (B)
- As analgesic adjunct in opioid-tolerant patients with sickle cell crisis (C)
- As analgesic adjunct in patients with OSA (C)
- Dosing:
  - Bolus up to 0.35 mg/kg
  - Infusion: up to 1 mg/kg/hour

Schwenk ES, et al. Reg Anesth Pain Med 2018;43 (5):456-466

Ketamine for Chronic Pain Guidelines

- For spinal cord injury pain, weak evidence for short-term improvement (C)
- In complex regional pain syndrome, moderate evidence to support improvement for up to 12 weeks (B)
- For other pain conditions such as mixed neuropathic pain, fibromyalgia, cancer pain, ischemic pain, headache, and spinal pain, there is weak or no evidence for immediate improvement (D)
- A positive response should include objective measures of benefit in addition to satisfaction such as ≥ 30% decrease in pain score or comparable validated measures for different conditions (C)

Cohen SP, et al. Reg Anesth Pain Med. 2018 Jul;43(5):521-546.

Not Quite Perfect

Side Effects

- Nausea, Vomiting
- Hypertension
  - Hypotension (in specific populations)
- Hypersalivation
- Increased ICP
- Emergence Phenomenon

Administration Considerations

- Specialized staff training for may be required

Contraindications (relative)

- Poorly controlled cardiovascular disease
- Pregnancy
- Active psychosis
- Severe hepatic disease (avoid), moderate hepatic disease (caution)
- Elevated intracranial pressure
- Elevated intraocular pressure
- Active substance abuse

Ketamine and Intracranial Pressure

- Generally taught that ketamine increases ICP
- Increase in cerebral artery perfusion may benefit patients with neurological injury
- Systematic review found no association between ketamine and increased cerebral perfusion pressures or several other outcomes
- Risk/benefit of ketamine should be approached on a case-by-case basis

Cohen L, et al. Ann Emerg Med. 2015 Jan;65(1):43-51.e2.
Li L, et al. *Front. Hum. Neurosci. 10:612.*

Emergence Phenomenon

- Patients receiving ketamine are known to experience disorientation, strange dreams, and hallucinations
- Limits ketamine utility in ICU patients already at risk for neurological disturbances
- May be able to diminish this response using midazolam
  - Unknown if prophylactic benzodiazepine vs rescue dose is better for patients
  - If using midazolam for rescue is it worth it to use ketamine in the first place?

Green SM, et al. *Ann Emerg Med*. 2011;57(5):449-461.
Wieruszewski PM, et al. AACN Adv Crit Care. 2018 Summer;29(2):101-106

Assessment Question

Which of the following patients is most appropriate for ketamine according to the 2018 Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU?

A. JD a 35 y.o. M presenting with hyperactivity and acute agitation in the emergency department
B. PS a 69 y.o. F s/p gastrectomy with Roux-en-Y reconstruction in the SICU for post operative respiratory failure in whom opioids are being limited
C. KA a 21 y.o. admitted to a general surgical floor after MVC whose admission is being complicated by EtOH withdrawal
D. VC a 72 y.o. F with depression admitted to the MICU with septic shock on fentanyl for analgesia

Novel Uses of Ketamine in the ICU

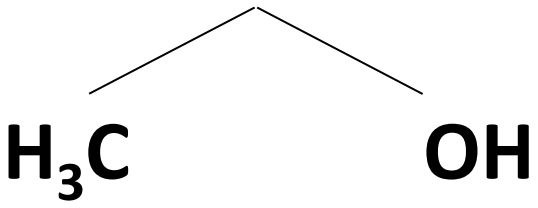
Alcohol withdrawal / Status epilepticus

Alcohol Abuse and Withdrawal

- Most commonly abused mood-altering substance
  - Affects 8.5% of US adult population (2011)
- Associated with $195 billion in healthcare expenditures
  - Medical consequences = $26 billion
- Alcohol withdrawal syndrome (AWS)
  - Mild → severe symptoms
  - Mortality 15% → 5% (2005)

National Institute on Alcohol Abuse and Alcoholism web site. DeBellis R et al. *J Int Care Med*. 2005;20:164-73.
U.S. Department of Health and Human Services. 10th ed. 2010;364-71.

Alcohol in the Body



Acute →

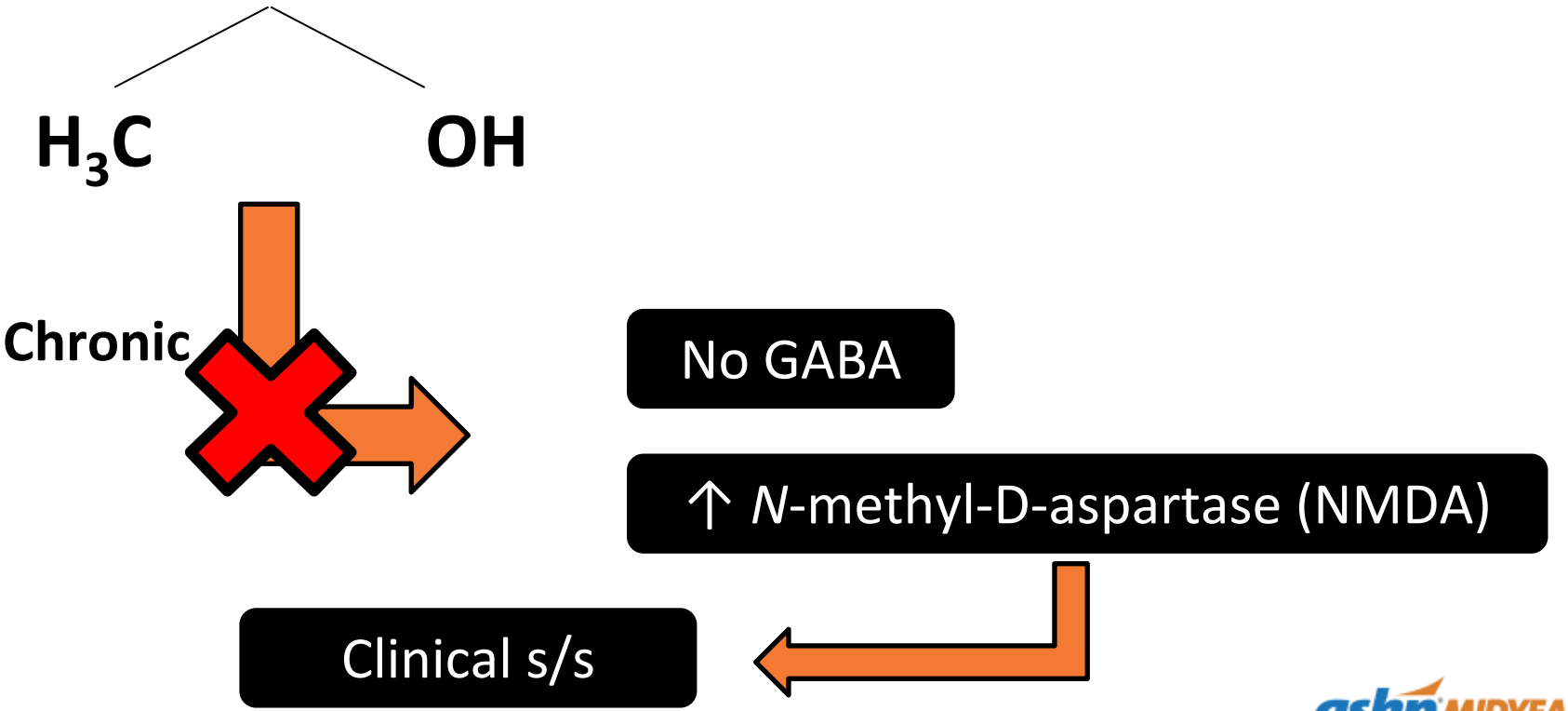
↑ γ-amino-butyric acid (GABA)

Chronic →

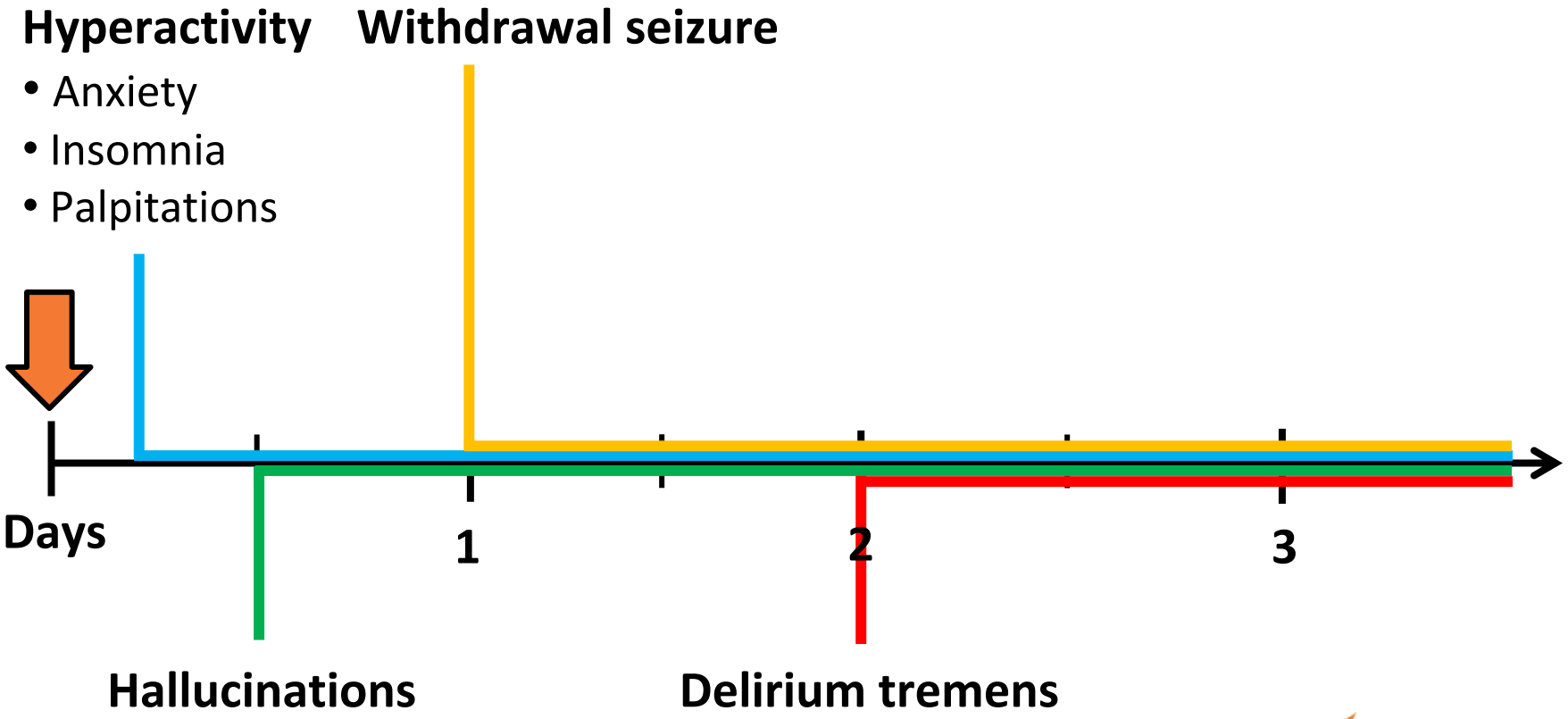
↓ GABA

↑ *N*-methyl-D-aspartase (NMDA)

Alcohol Withdrawal Syndrome (AWS)



Signs of Symptoms



Management of AWS

- Benzodiazepines (BZDs) generally first line therapy for alcohol withdrawal (AWS)
- Other potential options
  - Dexmedetomidine
  - Phenobarbital
  - Propofol
  - Symptomatic treatment
- Subset of patients with severe AWS may not respond to BZDs (18.5%)
- ? role of NMDA antagonists for these patients

Bayard M, et al. *Am Fam Physician*. 2004;69:1443-50.
Benedict NJ, et al. *In press*

Adjunct Ketamine for AWS – Study 1

Purpose	Determine efficacy of adjunctive ketamine in adult patients with AWS
Design	Retrospective, single-center, observational study (4/2011-3/2014)
Patients (n=23)	- Predominately male (60.9%) - AWS-related ICU admission (73.9%)
Results	- Mean time from 1st treatment to ketamine 33.6 hr (SD 29.1) - Median treatment dose 0.20 mg/kg/hr (IQR 0.12, 0.23) - Mean duration of therapy 55.8 hr (SD 30.5) - No change in sedation scores within 6 hr of initiation - Median change in benzodiazepines at 12 and 24 hr (-40.0, -13.3 mg, respectively)

Wong A, et al. *Ann Pharmacother*. 2015;49:14-9.

Adjunct Ketamine for AWS – Study 2

Purpose	Determine efficacy of guideline using adjunctive ketamine on outcomes in patients with severe AWS
Design	Retrospective, single-center, study (pre-, post-guideline)
Patients (n=63)	- Severe AWS defined as ICU admission and delirium tremens - Pre (n=29) (1/2008-3/2011), post (n=34) (4/2011-1/2015)
Protocol	Pre: Benzodiazepines, phenobarbital Guideline: Ketamine 0.15-0.3 mg/kg/hr until resolution of delirium; bolus (0.3 mg/kg) optional; plus standard of care
Results	- Decreased need for intubation: OR 0.14 (95% CI 0.04-0.49) - Decreased benzodiazepine use: 1508 vs. 2525 mg, p=0.02 - Decreased ICU length of stay 2.83 d (95% CI -5.58 - (-)0.089)

Pizon AF, et al. *Crit Care Med*. 2018;46:e768-71.

Adjunct Ketamine for AWS – Study 3

Purpose	Determine effect of ketamine on AWS symptom control and lorazepam infusion requirements in the medical ICU
Design	Prospective, single-center, observational study (8/2012-8/2014)
Patients (n=30)	- Severe AWS defined as CIWA-Ar >20
Results	- Mean time to ketamine initiation from lorazepam infusion 41.4 hr - "All patients" with symptom control within 1 hr of ketamine start - Intubation needed for progressing AWS (n=2) - Mean infusion rate 1.6 mg/kg/hr - Significant decrease in lorazepam infusion rate (-4 mg/hr, p=0.01)

CIWA-Ar = Clinical Institute Withdrawal Assessment, Revised

Shah P, et al. *J Med Toxicol*. 2018;14:229-36.

Adjunct Ketamine for AWS – Summary

	Study 1 (n=23)	Study 2 (n=34)	Study 3 (n=30)
Population	All patients	DTs and admitted to ICU	RAW, admitted to ICU
Previous AWS	n=4 (17.4%)	n=7 (20.6%)	Unknown
Adjunct[a]	n=5 (21.7%)	Unknown	n=7 (23.3%)
Time	- Time from first AWS tx: 33.6 hr - Time from RAW: 12.3 hr	Unknown	41 hr after lorazepam infusion

[a] Defined as only ketamine + benzodiazepine

DTs = delirium tremens; RAW = resistant alcohol withdrawal

Adjunct Ketamine for AWS – Summary

	Study 1 (n=23)	Study 2 (n=34)	Study 3 (n=30)
Dose and Duration	- Loading dose (n=8) - Median infusion: 0.20 - Median: 55.8 hr	- Loading dose (n=19) - Mean infusion: 0.19 - Median: 47 hr	- Initial: 0.75 - Mean max: 1.6 - Mean: 53.7 hr
Findings	- ↓ BZD use: 12, 24 hrs - One case of over-sedation	- ↓ need for intubation - ↓ BZD use - ↓ ICU LOS - One case of over-sedation	- Quick symptom control - ↓ in lorazepam infusion dose - Two cases of hypertension

BZD = benzodiazepine; LOS = length of stay

Assessment Question

MV is a 45 y/o M with known alcohol abuse admitted s/p MVA two days prior. He is now exhibiting signs of AWS, including delirium tremens, and has been administered 100 mg of diazepam in the past hour. Which of the following would you recommend for MV to manage his AWS?

A. Dexmedetomidine
B. Ketamine
C. Lorazepam
D. Phenobarbital
E. Other

Summary: Ketamine and AWS

- Appears to be well tolerated
  - Few cases of adverse events; emergence phenomenon
- Efficacy questionable
  - ↓ in BZDs → normal course of AWS?
  - Length of stay
- More data to support this indication necessary
  - Benefit in select patients
  - Dosing

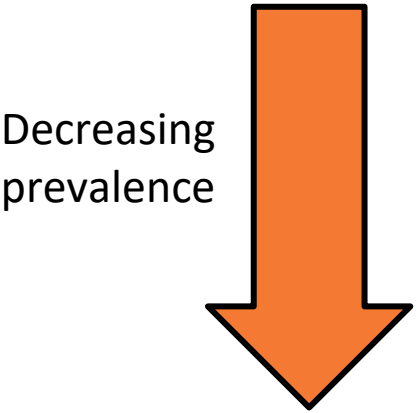
Status Epilepticus (SE)

- Definition is variable
  - ≥5 min of
    - Continuous clinical and/or electrographic seizure activity, or
    - Recurrent seizure activity without recovery between seizures
  - Convulsive vs. non-convulsive
- Estimated incidence of 12.5/100,000 persons/year
- Mortality: short-term: 7.6-22%; long-term: 43%

Dham BS, et al. *Neurocrit Care*. 2014;20:476-83.
Brophy GM, et al. *Neurocrit Care*. 2012;17:3-23.

Etiology of SE

- Subtherapeutic levels of antiepileptics
- Cerebrovascular accidents
- Congenital abnormalities
- Metabolic (e.g., sepsis)
- Anoxic brain injury
- Central nervous system (CNS) infection
- Drug toxicity



Dham BS, et al. *Neurocrit Care*. 2014;20:476-83.

Goals of Therapy

- Stop clinical and electrographic seizure activity
- Symptomatic management
  - Airway
  - Access
- Identify and manage underlying cause
  - CNS infection: antimicrobials
  - Drug toxicity: antidotes
  - History of epilepsy: loading doses of AEDs

Brophy GM, et al. *Neurocrit Care*. 2012;17:3-23.
Glauser T, et al. *Epilepsy Curr*. 2016;16:48-61.

Recommended Therapies

- Emergent treatment
  - BZDs: lorazepam, midazolam
  - GABA agonists
    - Class IIb, level A: Phenytoin/fosphenytoin; phenobarbital; valproate sodium
    - Class IIb, level C: Levetiracetam
- Urgent treatment
- Refractory treatment
  - Pentobarbital; lacosamide; topiramate

Brophy GM, et al. *Neurocrit Care*. 2012;17:3-23.

Role of Ketamine

- Role of NMDA antagonism after GABA agonists have been utilized
  - Oversaturation of GABA receptors
  - Overactivity of NMDA
- Use in refractory status epilepticus (SE) or super-refractory SE
  - Refractory (RSE): No response to adequate doses of standard treatment (e.g., benzodiazepine and second antiepileptic drug [AED]) of SE
  - Super-refractory (SRSE): RSE continuing ≥24 hr after initiation of anesthetic infusions

Brophy GM, et al. *Neurocrit Care*. 2012;17:3-23.
Glauser T, et al. *Epilepsy Curr*. 2016;16:48-61.

SE Guidelines

- Neurocritical Care Society (2012)
  - Emerging therapy; 9 articles detailing use in refractory SE; no recommendation
- American Epilepsy Society (2016)
  - No mention

Brophy GM, et al. *Neurocrit Care*. 2012;17:3-23.
Glauser T, et al. *Epilepsy Curr*. 2016;16:48-61.

Data in Children

Purpose	Determine safety and efficacy of ketamine for RSE in children
Design	Prospective, single-center (Italy), observational study of ketamine protocol (11/2009-2/2015)
Patients (n=13)	- Age range (2 months-11.5 years) - Most common etiology: cortical development malformation
Protocol	Two boluses of 2-3 mg/kg 5 min apart, then infusion of 5-10 mcg/kg/min up to max of 60 mcg/kg/min
Results	- Median dose 30 mcg/kg/min - Median duration of ketamine 3 days - Prevented admin of traditional anesthetics → no intubation (n=5) - Treatment failure in 5 children

Ilvento L, et al. *Epilepsy Behav*. 2015;49:343-6.

Data in Adults

Purpose	Determine safety and efficacy of ketamine for SRSE
Design	Retrospective, single-center, observational study (2012-2015)
Patients (n=67)	- Median age 62 - Metabolic/toxic injury most common etiology of SRSE (n=18)
Protocol	- No set protocol but dose range 25-175 mcg/kg/min - Combination with propofol
Results	- Ketamine initiated 24-48 hr of SRSE - SRSE resolution rate of 91% - Mortality rate of 39% - Duration of therapy: 1-29 days (mean 6.0) - Appeared safe although vasopressors needed in 79% of patients

Sabharwal V, et al. *Epilepsy Behav*. 2015;52:264-6.

Adverse Effects

- Neurotoxicity in a 44 y/o M
  - Dose up to 7.5 mg/kg/hr over 48 hr, then titrated off over 72 hr
  - Re-evaluation 3 months after admission revealed cerebellar atrophy
  - Attributed to “excessive” NMDA receptor antagonism
- Cardiac arrest in 72 y/o F with no previous cardiac history, admitted with subarachnoid hemorrhage
  - Ketamine initiated at 0.07 mg/kg/hr
  - Hours after → atrial fibrillation → sinus bradycardia → brief episodes of asystole
  - Attributed to depletion of catecholamines in critical illness; ketamine reliant on this for cardiovascular stability
  - Naranjo score of 4

Ubogu EE, et al. *Epilepsy Behav*. 2003;4(1):70-5.
Koffman L, et al. *J Clin Neurosci*. 2018;47:149-51.

Systematic Review (2018)

Purpose	Determine safety and efficacy of ketamine for RSE in adults and children
Design	PubMed, Cochrane, ClinicalTrials.gov
Adults (n=219)	- Median age: 54.5 y (range: 24-67) - Duration of SE to ketamine significantly variable (12h-5 months) - Dose ranged from 0.07-15 mg/kg/hr; duration 6h-29 days - Regimens effective in 70.3% of cases
Children (n=29)	- Age range: 2 mo to 18 years - Duration of SE to ketamine significantly variable (5h-73 days) - Dose ranged from 0.04-10 mg/kg/hr; duration 1-21 days - Regimens effective in 60.9% of cases

Rosati A, et al. *CNS Drugs*. 2018. doi: 10.1007/s40263-018-0569-6.

Use of Enteral Ketamine

- Typically not dosed as enteral formulation
  - Poor bioavailability: 16-30%
  - No commercially available product
- Limited studies evaluating transition of infusion to enteral formulation
  - Adult: Infusion at 1.25 mg/kg/hr, with enteral ketamine titrated to final dose of 250 mg twice daily; ketamine discontinued after 6 months
  - Adult: Infusion started at 0.4 mg/kg/hr and weaned off when total dose ~2500 mg (50 mg/kg), with enteral ketamine dosed at 50 mg twice daily
  - Children: 1.5 mg/kg/day in two divided doses

Pizzi MA, et al. *J Intensive Care*. 2017;5:54.
Yeh P, et al. *Seizure*. 2011;20:723-6.
Mewasingh LD, et al. *Seizure*. 2003;12:483-9.

On the Horizon

- KETASER01
  - Multi-center, open-label randomized controlled trial in children
  - Dosing: two boluses of 2-3 mg/kg 5 minutes apart, then infusion of 5-10 mcg/kg/min to max of 60 mcg/kg/min; 7 days
  - Primary outcome: incidence of resolution of refractory SE
- Ketamine vs. traditional antiepileptics in refractory SE
  - Single center, randomized controlled trial in adults
  - Dosing: bolus of 2.5 mg/kg, then infusion of 3 mg/kg/hr to max of 10 mg/kg/hr
  - Primary outcome: time to burst suppression; termination of seizures

https://clinicaltrials.gov

Summary: Ketamine and SE

- Appears to be well tolerated
- Efficacy data limited
  - Efficacy of 64% in early RSE (<72 h)
  - Efficacy of 32% in RSE (mean duration of RSE 26.5 days to ketamine initiation)
- Randomized controlled trials may be helpful in illustrating role of ketamine in this population
- Place in guidelines; comparative evaluation

Rosati A, et al. *CNS Drugs*. 2018. doi: 10.1007/s40263-018-0569-6.

KEY TAKEAWAYS

1) *Ketamine, even in traditional roles in the ICU, lacks high quality evidence to support routine use*

2) *Novel uses of ketamine suggest its potential use in therapy*
   I. *Alcohol withdrawal: Adjunct to GABA-agonists at doses similar to general anesthesia; ? prevention of intubation*
   II. *Status epilepticus: Adjunct to GABA-agonists; optimal dose unclear; ? place in therapy*

3) *Ketamine appears to be relatively well tolerated, regardless of the clinical situation it has been studied in*