Clinical Versatility: Ketamine in the ICU

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DISCLOSURE

- I have no actual or potential conflicts of interest in relation to this activity.

OBJECTIVES

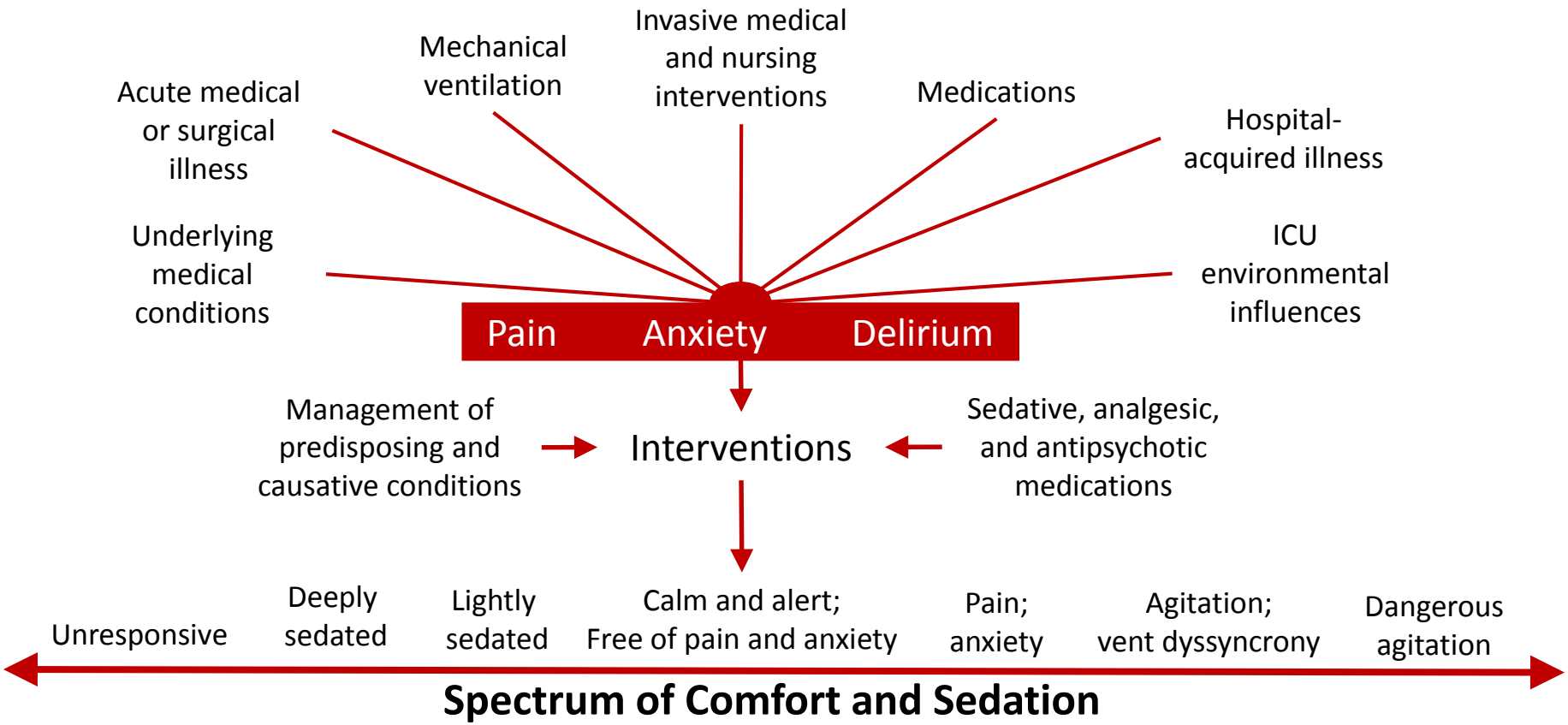
1. Explain the pharmacology and pharmacodynamics effects associated with ketamine in critically ill patients

2. Review considerations for ketamine storage, admixture preparation, and compatibility

3. Recognize potential indications for the use of ketamine in critically ill patients

4. List advantages and limitations to the use of ketamine in the ICU

Predisposing and Causative Conditions



Sessler CN, et al. Chest 2008;133;552-65.

Defining "Ideal" Sedative

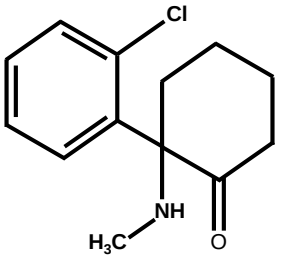
Physical and Pharmacologic Sedative Properties

- ☑ Water-soluble, stable in solution, and long shelf-life
- ☑ Nonirritating following IV or IM administration
- ☑ No/minimal hypersensitivity reactions
- ☑ Rapid, smooth onset of action following IV or IM administration
- ☑ Minimal depression of cardiovascular and respiratory systems
- ☑ Rapid degradation to inactive, nontoxic metabolites
- ☑ Analgesia at subanesthetic levels
- ☐ Rapid, smooth emergence with minimal side effects
- ☑ Low cost

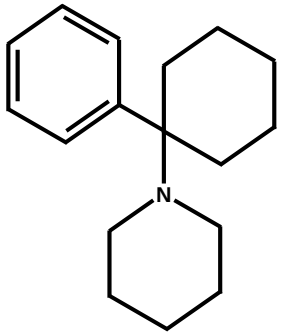
White PF, et al. Anesthesiology 1982 Feb;56(2):119-36.
Reich DL, Silvay G. Can J Anaesth 1989 Mar;36(2):186-97.

Ketamine Chemistry

- Arylcycloalkylamine structurally related to PCP
- Commercially available as a racemic mixture of the hydrochloride salt in the United States
  - S-(+)-ketamine and R-(-)-ketamine
- Each enantiomer with unique pharmacodynamic profiles



Ketamine



Phencyclidine

Reich DL, Silvay G. Can J Anaesth 1989 Mar;36(2):186-97.

General Ketamine Pharmacology

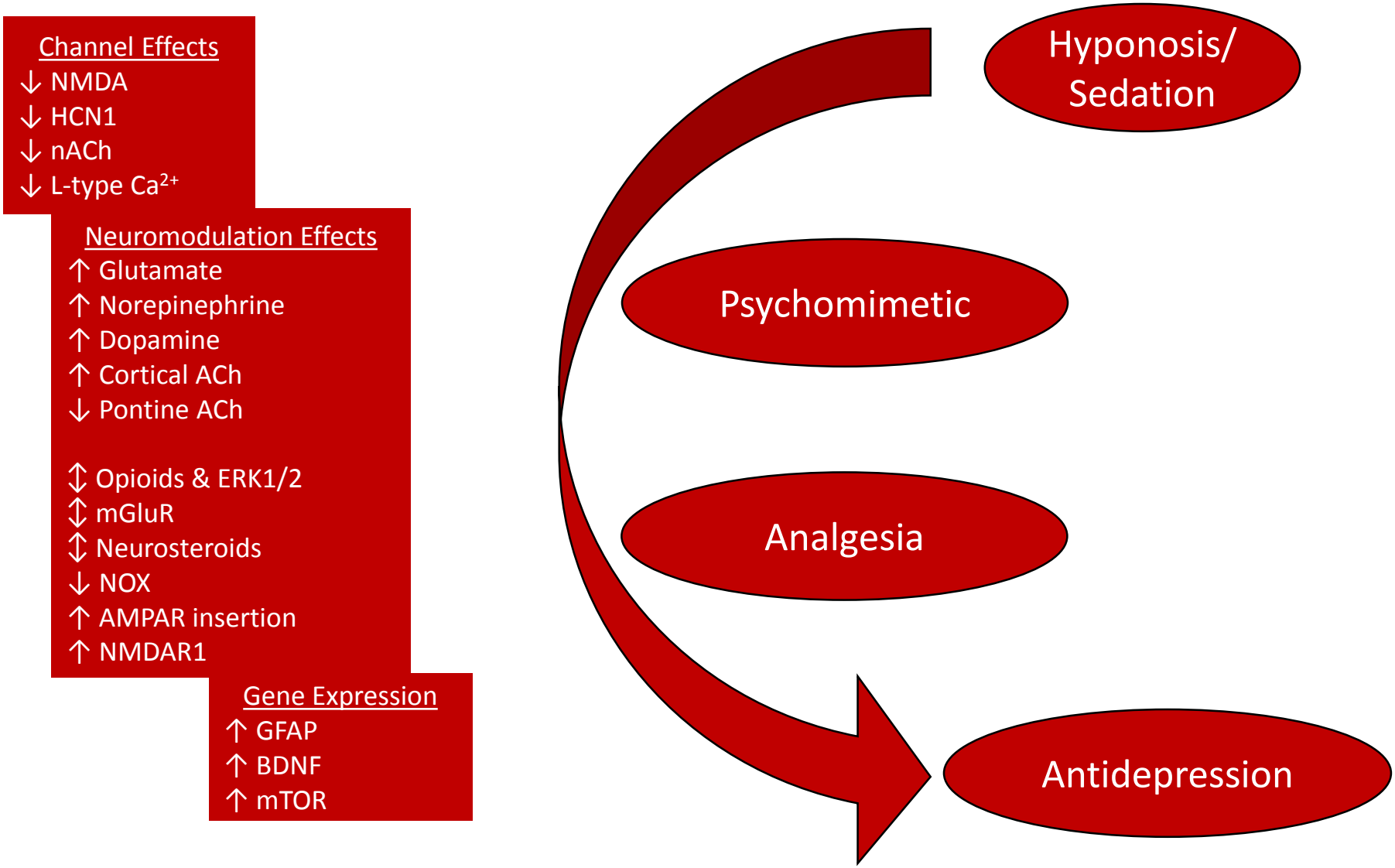
- Nonbarbiturate anesthetic
- Analgosedative or sedatoanalgesic?
  - N-methyl-D-aspartate (NMDA) receptor antagonist
    - Sedative
  - Mu and kappa opioid receptor agonist
    - Analgesic

Benken ST, Goncharenko A. J Pharm Pract. 2017 Oct;30(5):576-581.
Erstad BL, Patanwala AE. J Crit Care. 2016 Oct;35:145-9.
Patanwala AE, et al. J Intensive Care Med. 2017 Jul;32(6):387-395.

Receptor Pharmacology

- Binds to PCP-binding site of NMDA receptor complex
- NMDA normally excitatory; calcium-gated
  - Glutamate, aspartate, glycine act as agonists
  - Opening of channels and depolarization of neuron
- Block/interfere with sensory input to higher centers of CNS; memory processes

Bergman SA. Anesth Prog 1999;46:10-20.
Reich DL, Silvay G. Can J Anaesth 1989 Mar;36(2):186-97.



NMDA, N-methyl-D-aspartate; HCN1, hyperpolization-activated cyclic nucleotide channel; ACh, acetylcholine; nACh, nicotinic acetylcholine receptors; ERK, extracellular signal-regulated kinases; mGluR, metabotropic glutamate receptors; AMPAR, α-amino-3-OH-5-methylisoxazole-4-propionic acid receptor; NOX, NADPH oxidase; GFAP, glial fibrillary acidic protein; BDNF, brain-derived neurotrophic factor; mTOR, mammalian target of rapamycin

Sleigh J, et al. *Trends in Anaesthesia and Critical Care* 2014(4):76-81.

“True” Analgosedative

- Produces mixture of antinociceptive actions at subdissociative doses
  - Modifies response to spectrum of opioid receptors, endogenous aminergic systems, and inhibition of nitric-oxide synthase
- Comparable to morphine for acute pain

Shikanai H, et al. J Anesth 2014 Jun;28(3):390-8.
Koizuka S, et al. Can J Anaesth 2005 May;52(5):498-505.
Gordh T, et al. Ann Med 1995 Apr;27(2):229-34.
Motov S, et al. Ann Emerg Med 2015 Sep;66(3):222-9.

Pharmacokinetic Properties

- Highly bioavailable after administration

Route	Onset of Action	Duration of Action
IV	30 – 60 seconds	5 – 15 minutes
IM	180 – 240 seconds	12 – 25 minutes

- Undergoes hepatic biotransformation into multiple metabolites
  - Norketamine with 1/3 anesthetic potency

Reich DL, et al. Can J Anaesth 1989 Mar;36(2):186-97.
Stollings JL, et al. Ann Pharmacother 2014 Jan;48(1):62-76.

Sedative Comparisons

Agent	IV Dose	Onset of Action	Elimination Half-Life	Avoid	Consider
Midazolam	0.1 – 0.3 mg/kg	60 – 90 s	1 – 4 hours	Hemodynamically unstable, liver failure	Anxious; predicted difficult intubation
Fentanyl	1 – 3 mcg/kg	< 30 s	2 – 4 hours	Not tolerate decrease in minute ventilation	Blunt sympathetic response needed
Methohexital	1.5 mg/kg	< 30 s	5 – 10 min	Septic shock, hypotension	Head injuries, elevated ICP, HS
Propofol	1 – 2 mg/kg	15 – 45 s	5 – 10 min	Hypotension, low ejection fraction	HS, head injuries, elevated ICP
Etomidate	0.3 mg/kg	15 – 45 s	3 – 12 min	Septic shock, seizure disorder	Hemodynamic instability
Ketamine	1 – 2 mg/kg	30 – 60 s	5 – 15 min	Hypertension, ↑ oral secretions	Hemodynamic instability, asthma

RSI, rapid sequence intubation; IV, intravenous; ICP, intracranial pressure; HS, hemodynamically stable

Stollings JL, et al. Ann Pharmacother 2014 Jan;48(1):62-76.

Cardiovascular Effects

- Produces a dose-related rise in rate-pressure product with transient cardiac index increase
- Exerts sympathomimetic effects by stimulating CNS outflow and decreasing catecholamine reuptake
- Net systemic vascular resistance change minimal

White PF, et al. Anesthesiology 1982 Feb;56(2):119-36.
Stollings JL, et al. Ann Pharmacother 2014 Jan;48(1):62-76.

Pulmonary Effects

- Does not produce significant respiratory depression
- Rapid bolus dosing produces significant, maintained reductions in P_aO_2
- Demonstrates bronchial smooth muscle relaxation and antagonizes spasmodic potential of histamine

White PF, et al. Anesthesiology 1982 Feb;56(2):119-36.
White JM, Ryan CF. Drug Alc Review 1996;15:145-155.

Miscellaneous Effects

- Increases skeletal muscle tone and occasionally muscle spasms
- Decreases serum free fatty acids
- Elevates plasma cortisol, renin, and prolactin
- Attenuates activity and production of nuclear factor-κB, tumor necrosis-α, and interleukin-6

White PF, et al. Anesthesiology 1982 Feb;56(2):119-36.
White JM, Ryan CF. Drug Alc Review 1996;15:145-155.
Hirota K, Lambert DG. Br J Anaesth 2011 Aug;107(2):123-6.

Notable Adverse Effects

- Recovery reactions
  - Emergence reactions: “12%”
  - Recovery agitation: 0 – 30%
- Emesis: 5 – 15%
- Laryngospasm: 0.3%
- Respiratory depression with rapid IVP
- Increase in MAP, ICP, CO

IVP, intravenous push; MAP, mean arterial pressure; ICP, intracranial pressure; CO, cardiac output

Green SM, et al. Ann Emerg Med 2011 May;57(5):449-61.
Erstad BL, Patanwala AE. J Crit Care. 2016 Oct;35:145-9.

Ketamine Supplies and Storage

- Available in 10 mg/mL (20-mL), 50 mg/mL (10-mL), and 100 mg/mL (5-mL) multidose vials
  - 100 mg/mL concentration must be diluted prior to use
- Store between 68 – 77°F (20 – 25°C)
- Protect from light
- Vials can be colorless to slightly yellow
  - Darkens with prolonged exposure to light, but does not impact potency

ASHP's Interactive Handbook on Injectable Drugs, 2015. Bethesda, MD: American Society of Health-System Pharmacists. Accessed 2018 August.
Ketalar® (ketamine hydrochloride injection) [package insert]. Rochester, MI: JHP Pharmaceuticals, LLC; March 2012.

Admixture Preparation

- No “standard” concentration
- Can be added to 5% dextrose or 0.9% sodium chloride
- 10 mg/mL vials made isotonic with sodium chloride
  - 10 mg/mL: 300 mOsm/kg; 50 mg/mL: 387 mOsm/kg
- Variable stability at room temperature depending on concentration, but minimum is six days

ASHP's Interactive Handbook on Injectable Drugs, 2015. Bethesda, MD: American Society of Health-System Pharmacists. Accessed 2018 August.
Ketalar® (ketamine hydrochloride injection) [package insert]. Rochester, MI: JHP Pharmaceuticals, LLC; March 2012.

Additional Considerations

- Compatible with many additives, drugs in syringes, and Y-site injections
- Can be administered via a central or peripheral line

Dispensing Group: YELLOW (Moderate Cost/High Frequency/ Moderate Risk)	
Actions required prior to dispensing: Pharmacy Technician responsibilities: 1. **First Dose:** Prepare initial dose of product 2. **Subsequent scheduled dose:** prepare dose 3. **Extra Dose** requests (missing dose, next bag, etc.): a. Call nurse and ask for a second search of tube stations, patient bins, and bedside b. If workflow permits, send delivery technician directly to patient care area to help procure drug. c. If dose not found, reprint label and prepare for dispensing Pharmacist responsibilities: 2. Verify product and see technician responsibilities for extra dose dispensing	
Delivery method: Can be tubed	**Storage:** See medication guidelines for further storage information.

ASHP's Interactive Handbook on Injectable Drugs, 2015. Bethesda, MD: American Society of Health-System Pharmacists. Accessed 2018 August.
Ketalar® (ketamine hydrochloride injection) [package insert]. Rochester, MI: JHP Pharmaceuticals, LLC; March 2012.

Administration Pearls

- No dose-related adverse effects (AE) within range of clinical doses
- Lower doses may be associated with faster recovery time
- Subdissociative IM ketamine displayed fewer airway and respiratory AE

Green SM, et al. Ann Emerg Med 2011 May;57(5):449-61.
Shah A, et al. Ann Emerg Med 2011;57:425-33.
Green SM, Johnson NE. Ann Emerg Med 1990;19:1033-46.

Absolute Contraindications

- Age – airway complications identified in patients younger than three months
  - Differences in airway anatomy and likelihood of laryngeal excitability
- Mental state – known to exacerbate schizophrenia
- Caution in severe hepatic dysfunction (e.g., cirrhosis) and high-risk coronary artery disease with moderate- or high-dose infusions

Green SM, et al. Ann Emerg Med 2011 May;57(5):449-61.
White PF, et al. Anesthesiology 1982 Feb;56(2):119-36.
Lahti AC, et al. Neuropsychopharmacology 1995 Aug;13(1):9-19.
Schwenk ES, et al. Reg Anesth Pain Med 2018 Jul;43(5):456-466.

Relative Contraindications

Major procedures stimulating the posterior pharynx (e.g., endoscopy)

History of airway instability, tracheal surgery, or tracheal stenosis

Active pulmonary infection or disease, including upper respiratory infections

Known or suspected cardiovascular disease (e.g., angina; heart failure; hypertension [blood pressures above 140/90]; coronary artery disease) due to concerns with sympathomimetic properties

Central nervous system masses, abnormalities, or hydrocephalus (potentially-increased intracranial pressure). ***Minimal effect assuming normal ventilation and corresponding cerebral vasodilatory effect may improve overall perfusion.***

Glaucoma or acute globular injury given conflicting evidence of increased intraocular pressures

Thyroid disease or medications given potential for enhanced sympathomimetic response

Green SM, et al. Ann Emerg Med 2011 May;57(5):449-61.
White PF, et al. Anesthesiology 1982 Feb;56(2):119-36.
Green SM, Johnson NE. Ann Emerg Med 1990;19:1033-46.
Green SM, et al. J Pediatr Gastroenterol Nutr 2001;32:26-33.
Reich DL, Silvay G. Can J Anaesth 1989 Mar;36(2):186-97.
Takeshita H, et al. Anesthesiology 1972;36:69-75.
Bourgoin A, et al. Crit Care Med 2003 Mar;31(3):711-7.
Yoshikawa K, Murai Y. Anesth Analg 1971;50:199-202.
Kaplan JA, Cooperman LH. Anesthesiology 1972;35:229-30.

Monitoring

- Supplemental oxygen while breathing room air
- Occasional head repositioning for optimal airway patency or suction of pharynx
- Pulse oximetry, vitals, and capnography
- For ICU use:
  - BPS, CPOT, RASS, SAS, CAM-ICU, ICDSC

BPS, Behavioral Pain Scale; CPOT, Critical-Care Observation Tool; RASS, Richmond Agitation Sedation Scale; SAS, Sedation-Agitation Scale; CAM-ICU, Confusion Assessment Method for the ICU; ICDSC, Intensive Care Delirium Screening Checklist

Green SM, et al. Ann Emerg Med 2011 May;57(5):449-61.
White PF, et al. Anesthesiology 1982 Feb;56(2):119-36.
Krauss B, Green SM. N Engl J Med 2000;342:766-80.
Krauss B, Hess DR. Ann Emerg Med 2007;50:172-81.
Barr J, Fraser GL, Puntillo K, et al. Crit Care Med 2013 Jan;41(1):263-306.

Being “Jack” – Potential Uses

- Acute pain management
- Adjunctive pain, agitation, and delirium treatment
- Alcohol withdrawal
- Status epilepticus (SE)
- Rapid sequence intubation (RSI)

Acute Pain: Patient Identification

- Several broad patient categories for subanesthetic ketamine
  - Expected post-operative pain to be severe
    - Abdominal, thoracic, orthopedic (e.g., limb; spine)
  - Opioid tolerant or dependent presenting for surgery or with exacerbation of chronic pain condition
  - Increased risk for opioid-mediated respiratory depression (e.g., obstructive sleep apnea)

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

Acute Pain: Dose Range

- Ketamine produced analgesia at plasma concentrations of 100 to 200 ng/mL
  - General anesthesia: 9000 to 25000 ng/mL
- Range includes a 0.3 to 0.5 mg/kg IV bolus, with or without an infusion started at 0.1 to 0.2 mg/kg/hr
- Data suggesting profound analgesic effect and **decrease** in opioid consumption for up to six weeks

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

Ketamine Versus Morphine

- Prospective, randomized, double-blind trial in adult patients in the ED experiencing moderate pain
- Randomized to ketamine 0.3 mg/kg or morphine 0.1 mg/kg IV push over 3 to 5 minutes
- Primary outcome: reduction in pain at 30 minutes
- Secondary outcome: incidence of rescue analgesia at 30 and 60 minutes

Motov S, et al. Ann Emerg Med. 2015 Sep;66(3):222-229.e1.

Time Interval*	Group		Difference (95% CI)
	Ketamine	Morphine	
Pain NRS, mean (SD)			
Baseline	**8.6 (1.5)**	**8.5 (1.5)**	**0.1 (-0.46 to 0.77)**
15	**3.2 (3.5)**	**4.2 (2.9)**	**-1.0 (-2.4 to 0.31)**
30	**4.1 (3.2)**	**3.9 (3.1)**	**0.2 (-1.19 to 1.46)**
60	**4.8 (3.2)**	**3.4 (3.0)**	**1.4 (0.13 to 2.75)**
90	**4.8 (3.1)**	**3.9 (3.1)**	**0.9 (-0.37 to 2.28)**
Complete resolution of pain, N (%)			
15	**20 (44)**	**6 (13)**	**31 (13.1 to 49.2)**
30	**12 (27)**	**11 (24)**	**3 (-16.3 to 20.7)**
60	**9 (21)**	**12 (27)**	**-6 (-25.6 to 11.6)**
90	**7 (16)**	**9 (21)**	**-5 (-21.5 to 12.2)**

NRS, numeric rating scale; SD, standard deviation; CI, confidence interval
*Time in minutes from medication administration

Motov S, et al. Ann Emerg Med. 2015 Sep;66(3):222-229.e1.

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- Alcohol withdrawal
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Adjunctive Analgosedation

- Retrospective study of 40 adult patients being mechanically ventilated patients in an SICU
- Impact of low-dose ketamine continuous infusions (i.e. 1-5 mcg/kg/min) as adjunctive analgesia
- Primary outcome: slope of change in morphine equivalents 12 hours pre- and post-ketamine infusion

Buchheit JL, et al. J Intensive Care Med. 2017 Jan 1:885066617706907. doi: 10.1177/0885066617706907.

Adjunctive Analgosedation

Parameter	24 Hours Preketamine	24 Hours Postketamine	P value
ME (mg/hr)	6.66 (3.33 – 10)	0 (0 – 3.33)	<0.001
Vasopressor? (N)	16	18	0.651
PE equivalent (mg/hr)	70 (25 – 95)	50 (30 – 77.5)	0.236
Propofol (mg/hr)	150 (80 – 200)	32.5 (0 – 150)	0.002
RASS outside goal (N)	15	17	0.797
SBP (mmHg)	115 (100 – 134)	118.5 (102 – 136.5)	0.462
DBP (mmHg)	54 (47 – 61)	57.5 (53.5 – 64.5)	0.12
HR (BPM)	77 (72 – 89)	90 (80 – 98)	0.01
RR (BPM)	20 (15 – 25)	19.5 (15 – 26)	0.918
COMA Score	4 (1.5 – 10)	6 (4 – 12)	0.082

ME, morphine equivalents; PE, phenylephrine; RASS, Richmond Agitation Sedation Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate, COMA, Critical Care Observation of Motor Activity

Buchheit JL, et al. J Intensive Care Med. 2017 Jan 1:885066617706907. doi: 10.1177/0885066617706907.

What About Trauma?

- Retrospective analysis of 36 patients

Comparison of Analgesics and Sedatives Pre- and Post-Ketamine Use			
	Pre-ketamine	Post-ketamine	p value
Opioids, mg IVME	431.3 (206.3 – 1012.4)	272.5 (52.5 – 772.5)	0.029
PRN opioids, mg IVME	51.3 (23.1 – 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/min	35.4 (23.1 – 49.4)	22.8 (14 – 32.9)	0.002
Benzodiazepines*	14.3 (1.3 – 564.3)	17.2 (9.2 – 193.9)	0.7358

*, represented as milligrams of midazolam equivalents
IVME, intravenous morphine equivalents; PRN, as needed

Pruskowski KA, et al. Pharmacotherapy. 2017 Dec;37(12):1537-1544.

Impact on Delirium and Coma

Variable	Ketamine (N=39)	Non-Ketamine (N=40)	P value
Analgesia and Sedation			
% Goal RASS (-2 to 0)	70 (47 – 87)	84 (68 – 93)	0.19
% Goal CPOT/BPS	99 (93 – 100)	91 (77 – 96)	0.044
Delirium and Coma			
Delirium present, n (%)	29 (74)	34 (85)	0.274
Coma present, n (%)	16 (41)	6 (15)	0.013
Delirium- or coma-free days	6 (2 – 9)	4 (3 – 7)	0.351
ICU LOS, days	11 (7 – 24)	8 (5 – 13)	0.019
Hospital LOS, days	15 (11 – 28)	12 (7 – 20)	0.30
In-hospital mortality, n (%)	11 (28)	5 (13)	0.099

RASS, Richmond Agitation Sedation Scale; CPOT, Critical Care Pain Observation Tool; BPS, Behavioral Pain Scale; ICU, intensive care unit; LOS, length of stay

Shurtleff V, et al. J Intensive Care Med. 2018 Jan 1:885066618767619. doi: 10.1177/0885066618767619.

Caveats to Consider

- Higher proportion of ketamine patients on vasopressor and inotrope therapy
- Ketamine not started until 48 hours into admission
- 69% of ketamine patients also on propofol
  - Received over double total propofol (14.1 vs 5.6 gm) for a longer median duration
- Received more midazolam in a clinically significantly shorter duration of therapy

Shurtleff V, et al. J Intensive Care Med. 2018 Jan 1:885066618767619. doi: 10.1177/0885066618767619.

Being “Jack” – Potential Uses

- Acute pain management
- Adjunctive pain, agitation, and delirium treatment
- **Alcohol withdrawal**
- Status epilepticus (SE)
- Rapid sequence intubation (RSI)

Impact on Alcohol Withdrawal

- Retrospective observational cohort of 63 patients
  - 29 pre-guideline; 34 post-guideline
- Delirium tremens as defined by DSM V criteria
- Pre-guideline: benzodiazepines and phenobarbital
- Post-guideline: add IV ketamine infusion at 0.15-3 mg/kg/hr with or without 0.3 mg/kg IV bolus

Pizon AF, et al. Crit Care Med. 2018 Aug;46(8):e768-e771.

Ketamine Versus No Ketamine

Outcome	Ketamine (N=34)	No Ketamine (N=29)	P value
Mean ICU days	5.7	11.2	<0.001
Mean hospital days	12.5	16.6	0.03
Mean benzodiazepine dose, mg DE	1508.2	2525.1	0.02
Dexmedetomidine use, n (%)	9 (31)	3 (8.8)	0.10
Mean dexmedetomidine time, d	1.77	2.33	0.4
Intubations, n (%)	10 (29.4)	22 (75.9)	<0.001
Mean benzodiazepine dose, mg DE	833.6	3016.1	0.01
Propofol use, n (%)	9 (90)	20 (90.9)	0.9
Mean propofol time, d	2.4	4.57	0.03

DE, diazepam equivalents; d, days; ICU, intensive care unit

Pizon AF, et al. Crit Care Med. 2018 Aug;46(8):e768-e771.

Dosing Characteristics

Parameter	Ketamine (N=34)
Ketamine loading dose, n (%)	19 (55.9)
Initial infusion dose, mg/kg/hr*	0.24 (0.10)
Infusion dose during therapy, mg/kg/hr*	0.19 (0.10)
Duration of ketamine treatment, hr†	47 (35 – 71)
Total ketamine dose, mg†	825.4 (440 – 1456)
Benzodiazepine dose in DE, pre-ketamine, mg†	333.4 (106.6 – 626.6)
Benzodiazepine dose in DE, post-ketamine, mg†	450 (295 – 700)
Total benzodiazepine dose in DE, mg†	892.5 (453.3 – 1,646.6)

*, represented as mean (SD); †, represented as median (interquartile range)
DE, diazepam equivalents

Pizon AF, et al. Crit Care Med. 2018 Aug;46(8):e768-e771.

Being “Jack” – Potential Uses

- Acute pain management
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- Alcohol withdrawal
- **Status epilepticus (SE)**
- Rapid sequence intubation (RSI)

Impact on Status Epilepticus

- NMDA receptors upregulated and activity increased in late SE
  - Blocks cation exchange and reduces epileptiform burst discharges, inhibiting conduction of excitation
- Neuroprotective as it blocks Ca^{2+} influx, resulting in anti-inflammatory and antioxidant effects
- Change in intracranial pressure very small and may actually be associated with a net reduction

Fang Y, Wang X. Seizure. 2015 Aug;30:14-20.

Evaluating Impact in Practice

- Multicenter, retrospective review to examine use, efficacy, and safety of ketamine in refractory SE
- Permanent control in 32% (19/60) of patients
  - Infusion doses higher than 0.9 mg/kg/hour
- Discontinued due to possible adverse events in 5 patients
- Mortality rate lower when SE controlled within 24 hours of ketamine infusion (16 vs 56%, p=0.0047)

Gaspard N, et al. Epilepsia. 2013 Aug;54(8):1498-503.

Being “Jack” – Potential Uses

- Acute pain management
- Adjunctive pain, agitation, and delirium treatment
- Alcohol withdrawal
- Status epilepticus (SE)
- **Rapid sequence intubation (RSI)**

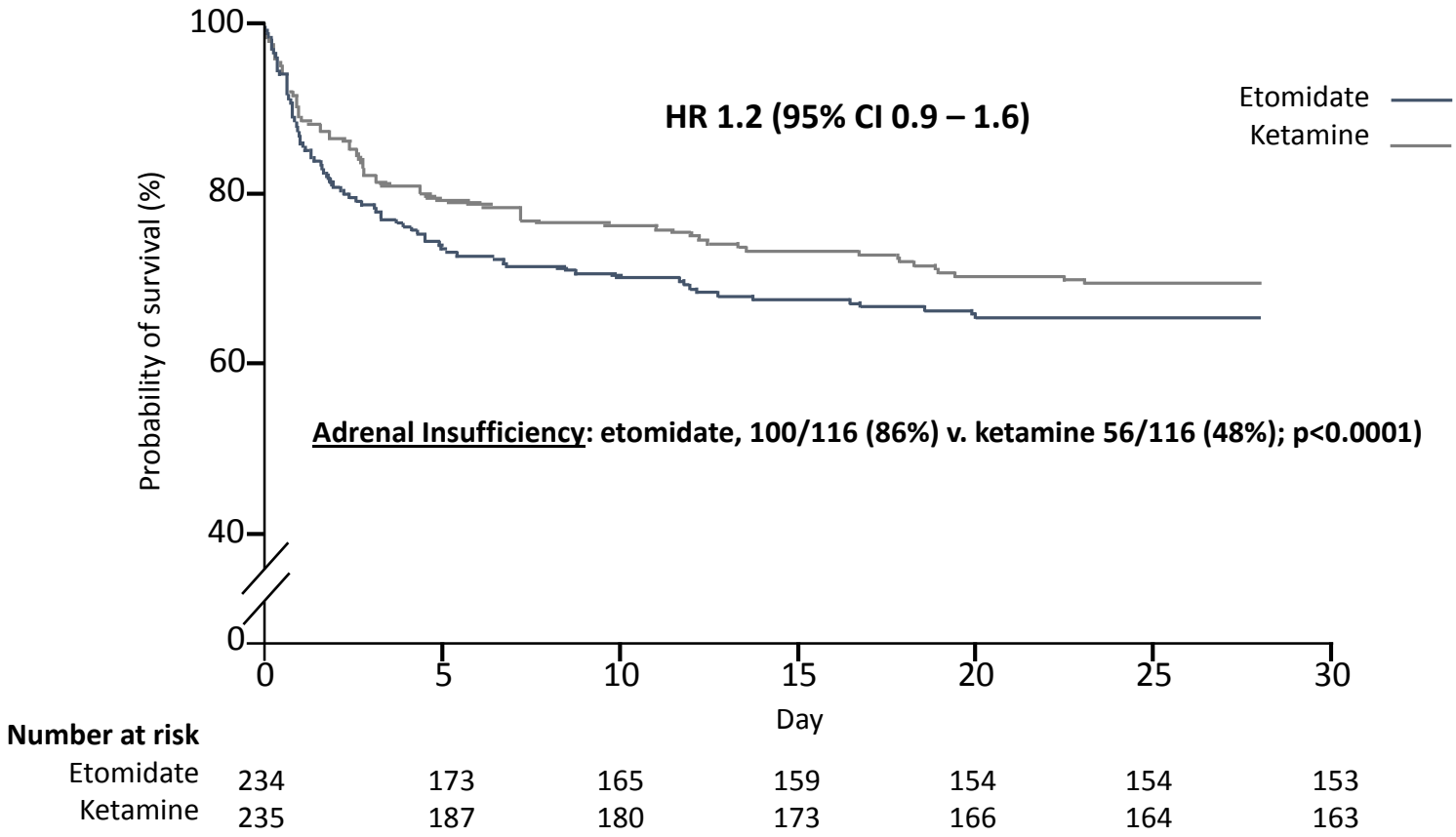
Impact on Rapid Sequence Intubation

- Multicenter, randomized, controlled, single-blind study
- Treatment groups
  - Etomidate 0.3 mg/kg versus ketamine 2 mg/kg
- Primary endpoint
  - Maximum SOFA score during first 72 hours in ICU

SOFA, Sequential Organ Failure Assessment

Jabre P, et al. Lancet. 2009;374: 293-300.

Consistency in Outcome



Jabre P, et al. Lancet. 2009;374: 293-300.

Shocking Hemodynamics?

- Rates of hypotension reported as high as 24%
- Shock index (pulse rate/systolic blood pressure) may indicate patients at risk if ≥0.9 preinduction

Outcome	HSI (N=31)	LSI (N=81)	95% CI
Hypotension, n(%)	8 (25.8)	2 (2.5)	12 – 45%
Hypertension, n(%)	4 (12.9)	32 (39.5)	4 – 30%

HSI, high shock index (i.e., ≥0.9); LSI, low shock index (i.e., <0.9); CI, confidence interval
Hypotension defined as a systolic blood pressure >90 mmHg preinduction that decreased below 90 mmHg at any time measurement after induction
Hypertension defined as a systolic blood pressure <160 mmHg preinduction that increased above 160 mmHg at any time measurement after induction

Miller M, et al. Ann Emerg Med. 2016 Aug;68(2):181-188.e2.

Pharmacodynamic Advantages

- Produces a dose-related rise in rate-pressure product with transient cardiac index increase
  - Net systemic vascular resistance change minimal
- Does not produce significant respiratory depression
- Demonstrates bronchial smooth muscle relaxation

White PF, et al. Anesthesiology 1982 Feb;56(2):119-36.
White JM, Ryan CF. Drug Alc Review 1996;15:145-155.
Hirota K, Lambert DG. Br J Anaesth 2011 Aug;107(2):123-6.

Pharmacodynamic Advantages

- Known to decrease serum free fatty acids
- Elevates plasma cortisol, prolactin, and renin
- Potential immunomodulatory benefit
  - Decreases activity and production of proinflammatory cytokines

White PF, et al. Anesthesiology 1982 Feb;56(2):119-36.
White JM, Ryan CF. Drug Alc Review 1996;15:145-155.
Hirota K, Lambert DG. Br J Anaesth 2011 Aug;107(2):123-6.

Cost Comparison: IV Drips

Drug	Drip Concentration	Approximate Cost*
Fentanyl	2000 mcg/ 200 mL	$2.24
Remifentanil	5 mg / 100 mL	$354
Hydromorphone	20 mg / 100 mL	$8.38
Lorazepam	40 mg / 250 mL	$14.38
Dexmedetomidine	400 mcg / 100 mL	$45.82
Propofol	1000 mcg / 100 mL	$37.50
Ketamine	500 mg / 100 mL	$9.83

*Represented by average wholesale price

McKesson Pharmaceutical. https://www.mckesson.com. Accessed 7/27/2018.

Potential Barriers

- **NATIONAL SHORTAGE**
- Fear of emergence reactions and agitation
- Unfamiliarity
- State board limitations/restrictions
- Institutional labeling (e.g., anesthesia only)
- Unclear controversy in certain populations

Fear of the Unknown?

- Sedative agents mentioned in SCCM Guidelines:
  - Dexmedetomidine: 59
  - Propofol: 54
  - Midazolam: 32
  - Lorazepam: 24
  - Ketamine: 4

"No studies have compared clinical outcomes in ICU patients sedated with either ketamine or other sedative agents."

Barr J, et al. Crit Care Med 2013 Jan;41(1):263-306.

Post-Test 1: Which of the following statements most accurately describes the pharmacology of ketamine?

A. The primary effects are similar to barbiturates.
B. The analgesic property is solely due to an interaction with opioid receptors.
C. Associated with respiratory depression when used as a continuous infusion.
D. Changes in blood pressure are associated with increase in cardiac output.

Post-Test 2: Which statement best aligns with ketamine and one of its potential indications?

A. It should be considered in patients at risk for cardiac depression when used for acute pain.
B. It has been associated with hypotension in patients used for rapid sequence intubation.
C. It results in better control of agitation in mechanically ventilated, critically surgical patients.
D. It is associated with a substantial increase in intracranial pressure for patients in status epilepticus.

Post-test 3: Which of the following is a potential pharmacologic advantage of ketamine over conventional analgosedative agents for mechanically ventilated patients?

A. Ability to provide concurrent sedation and opioid-sparing analgesia

B. Emergence reactions leading to vivid dreams, hallucinations, irrational behavior, and frank delirium

C. Reduction of vasopressor requirements in patients with shock due to its impact on vascular resistance.

D. Demonstrates modest bronchoconstriction.

SUMMARY

- Ketamine provides dissociative sedation and a cataleptic state through NMDA antagonism
- Employs favorable cardiovascular and pulmonary pharmacodynamic properties
- Many potential and emerging roles in acute and critical care areas
- Potential barriers exist making its entry into routine analgosedative use difficult

SUPPLEMENTAL RESOURCES

1. Erstad BL, Patanwala AE. Ketamine for analgosedation in critically ill patients. *J Crit Care*. 2016 Oct;35:145-9.
2. Patanwala AE, Martin JR, Erstad BL. Ketamine for Analgosedation in the Intensive Care Unit: A Systematic Review. *J Intensive Care Med*. 2017 Jul;32(6):387-395.
3. Schwenk ES, et al. *Reg Anesth Pain Med*. 2018 Jul;43(5):456-466.
4. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. *Ann Emerg Med*. 2011 May;57(5):449-61.

Clinical Versatility: Ketamine in the ICU

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