Ketamine for Agitation in the Emergency Department

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Definitions

Agitation: excessive motor or verbal activity

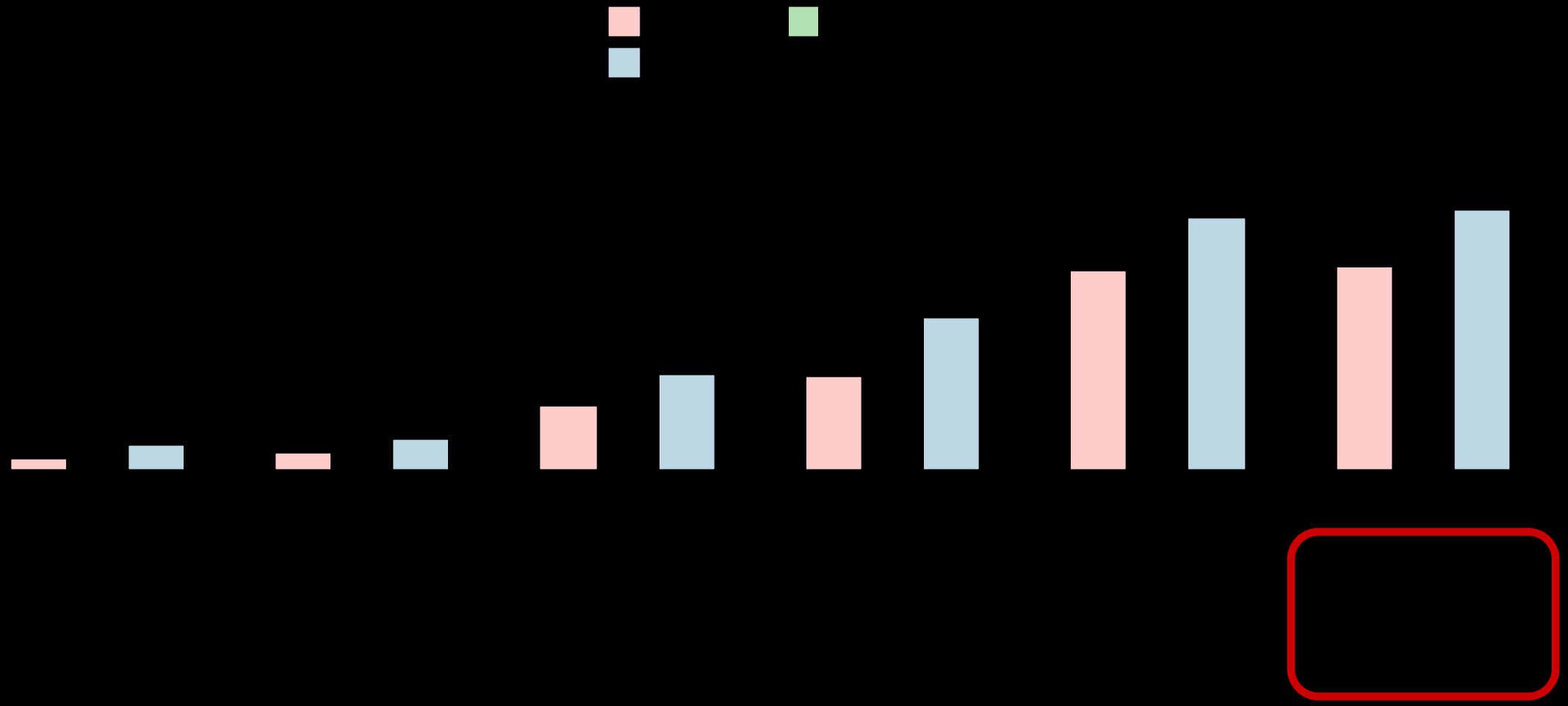
Aggression: used in the literature for both animals and humans

- For humans can be verbal, physical against objects, or physical against people

Violence: physical aggression by people against other people

Hostility: loosely defined - aggression, irritability, suspicion, uncooperativeness, jealousy, etc.

PROBABILITY OF VIOLENT BEHAVIOR AND CURRENT-YEAR PSYCHIATRIC DIAGNOSIS



Topics to Cover

- What is Excitation Delirium Syndrome (ExDS)?
- Standard of Treatment for Agitation and ExDS in the ED
- Ketamine use in Pre-hospital setting
- Ketamine used as a third-line agent for ExDS in the ED
- Ketamine used as a first-line agent for ExDS in the ED
- Ketamine’s function
- Ketamine in Pediatric Patients in ED
- Ketofol (Ketamine and Propofol blend) for ExDS
- Ketamine for Analgesia
- Future Research

Excitation Delirium Syndrome (ExDS)

- Definition: “An extreme form of arousal that is associated with increased verbal and motor activity”
- Without motor paralysis or hypotonia

Hopper, 2015

Etiology of ExDS

- Toxicology
  - ETOH intoxication/withdrawal
  - Stimulant intoxication (methamphetamine, PCP, cocaine)
  - Anabolic steroids, sedative-hypnotics
- Metabolic
  - Hypoglycemia
  - Hypoxia
- Neurological
  - Stroke
  - Intracranial pathology (hemorrhage, tumor)
  - CNS infection
  - Seizure
  - Dementia
- Other Medical Conditions
  - Hyperthyroidism
  - Shock
  - AIDS
  - Hypothermia, Hyperthermia
- Psychiatric
  - Psychosis (including psychotic depression)
  - Mania
  - Schizophrenia
  - Paranoid delusions
  - Personality disorders (Antisocial behavior)

Moore, 2017

Why is ExDS so important?

- 8% of agitated patients not sedated after 2 doses of either an antipsychotic or benzodiazepine
- Endangers safety of patient & hospital staff
- Wastes hospital staff's time
- Adds financial cost to Emergency Department care
- Disrupts ED environment and affects the care of other patients
- Increases stress in patients, visitors, and staff

Isbister, 2016

Standard of Treatment for Agitation in the ED

- First line:

  Always attempt Verbal De-escalation
  - If verbal de-escalation fails → may need to resort to physical restraints
  - Physical restraints indicated if: imminent danger to self, others, or environment
  - Use physical restraints to permit chemical sedation
  - Chemical sedation typically entails benzodiazepines, typical antipsychotics, or atypical antipsychotics

Hopper, 2015 & Moore, 2017

Standard Chemical Sedatives in ExDS	Nature of Sedative
Benzodiazepines	AE: Respiratory depression, somnolence, paradoxical disinhibition
- Versed (Midazolam)	Faster onset of action than lorazepam
- Ativan (Lorazepam)	Longer duration than midazolam
Typical Antipsychotics	Not used in treating withdrawal; Risk of QT prolongation
- Droperidol	Onset of action: 15 - 30 minutes
- Haloperidal	Onset of action: 30 – 60 minutes

Moore, 2017

ExDS Subtype	Standard Recommended Treatment
Severe violence	Typical Antipsychotic, Benzodiazepine, OR Typical Antipsychotic + Benzodiazepine
Substance intoxication/withdrawal or ETOH withdrawal	Benzodiazepine
Psychiatric etiology	1st Line: Typical Antipsychotic 2nd Line: Atypical Antipsychotic (ziprasidone, olanzapine, risperidone)
Undifferentiated Agitation	1st Line: Benzodiazepine 2nd Line: Typical Antipsychotic

Moore, 2017

Importance of Alternative Sedation

- Current standard of treatment:
  - Requires about 15 – 25 minutes for onset of sedation
  - Associated with respiratory depression, hemodynamic instability, or QT prolongation
  - Often requires frequent re-dosing
  - Often unsafe in pediatric patients

Scheppke, 2014

	Haloperidol[1,2]	Aripiprazole*[1]	Olanzapine*[1]	Ziprasidone*[3]	Loxapine Inhalation*[4]	Lorazepam[5,6]
	Intramuscular (IM)	IM†	IM†	IM†	Inhalation†	IM, Oral
	20 min	30 min	15-45 min	15 min	2 min	IM: 60-90 min; Oral: 2 h
	18 h	75 h	34-38 h	2.2-3.4 h	6-8 h	12-15 h
	2-5 mg/ 4-8 h	9.75 mg/ 2 h	10 mg/ 20 min	10-20 mg/ 10 mg q2h, 20 mg q4h	10 mg/ None within 24 h	IM: 0.5-1 mg, Oral: 1-2 mg/ 30-60 min
	18 mg	30 mg	20 mg	40 mg	10 mg	NA
	Ready to use. Room temperature storage	Ready to use. Room temperature storage	Must be dissolved in sterile water (5 ng/mL) and used within 1 hour	Must be dissolved in sterile water (1.2 mL) and used within 1 hour	Ready to use. Room temperature storage	Oral: Ready to use. IM: administer undiluted

* FDA-approved for treatment of agitation associated with schizophrenia or bipolar I disorder
† FDA-approved route of administration for agitation associated with schizophrenia or bipolar I disorder

1. Gonzalez D, et al. *Curr Res Med Opin*. 2013;29:241-50. 2. Haloperidol Injection, USP (Prescribing Information. Schaumburg, IL. Sagent Pharmaceuticals, 2011. 3. Ziprasidone Mesylate (Prescribing Information). New York, NY. Roerig (Pfizer, Inc.), 2012. 4. Loxapine Inhalation (Prescribing Information). Horsham, PA. Teva Pharmaceuticals USA, 2012. 5. Baker SN. *Adv Emerg Nurs J*. 2012;34:306-18. 6. Lorazepam Injection (Prescribing Information). Deerfield, IL. Baxter Pharmaceuticals, 2009.

Research on Pre-hospital use of Ketamine

- Scheppke *et al*. – Assessed 52 EMS run sheets for transports that involved a single IM injection (4 mg/kg) of ketamine

  Protocol: administer IM midazolam after ketamine sedation to prevent emergence phenomenon (agitation)

  - 50 of 52 were sedated in ≤ 3 minutes
  - 3 of 52 became hypoxic (after midazolam administration)
    - 1 required ET intubation
    - 2 required bag valve mask ventilation
  - 26 of 52 patients did not receive midazolam, because EMS paramedics deemed patients already excellently sedated with ketamine alone

Scheppke, 2014 & Melamed, 2007

Research on Pre-hospital Use of Ketamine

- Cole *et al.* -- a prospective cohort study
  - Appropriate Sedation = Altered Mental Status Scale ≤ 0

IM Sedative	Time to sedation (p < 0.0001)
Ketamine (5mg/kg) (n = 64)	5 minutes
Haloperidol (10 mg) (n = 82)	17 minutes

Table 4. Complications.

	Ketamine	Haloperidol
Hypersalivation[a]	38% (21/56)	0 (0/69)
Emergence Reaction	10% (5/52)	0 (0/69)
Vomiting	9% (5/57)	3% (2/71)
Dystonia	5% (3/56)	3% (2/69)
Laryngospasm	5% (3/55)	0 (0/69)
Akathisia	2% (1/53)	0 (0/69)
Deaths	0	1% (1/82)

[a]Treatments for hypersalivation: suctioning (4), atropine (6), intubation (11).

- Ketamine associated with:
  - Significantly faster onset of action than IM haloperidol
  - Higher side effect profile

Cole, 2016

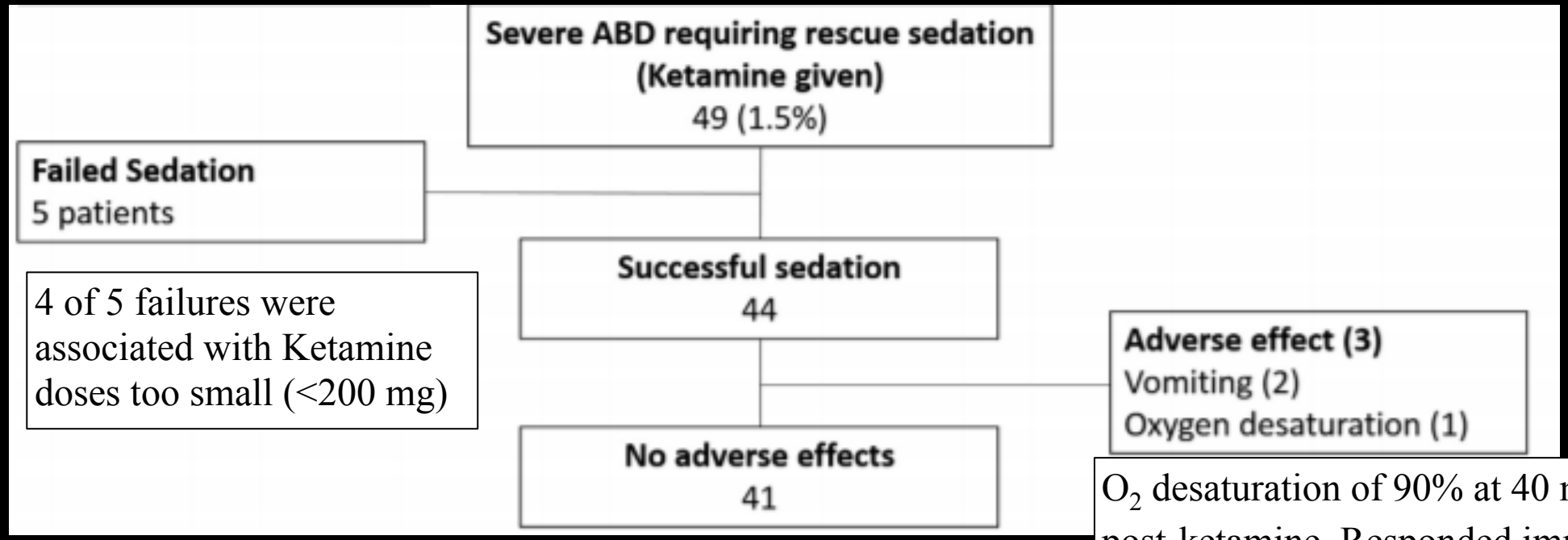
Ketamine as a Third-line Agent

- 49 of 1292 DORM II Study patients failed sedation with 2 doses of IM droperidol 10 mg
  - Isbister *et al.* -- Administered 4-6 mg/kg IM ketamine to these 49 patients
  - Inclusion Criteria: Patient …
    - **(1) still needed restraints** and
    - **(2) still 2-3 on Sedation Assessment Tool**
      - Sedation was considered to be 0-1 on the Sedation Assessment Tool

Isbister, 2016

- No emergence phenomenon (agitation) reported
- No significant change in Systolic Blood Pressure and Pulse
- Average time to sedation (SAT ≤ 1) after IM ketamine = 20 minutes

ABD: Acute Behavioral Disturbance



O_2 desaturation of 90% at 40 minutes post-ketamine. Responded immediately to O_2 administration.

Isbister, 2016

Ketamine as a First-line for ExDS

- Riddell *et al.* – Study **time to sedation** using ketamine versus Versed, lorazepam, haloperidol, and a combination of benzodiazepine and typical antipsychotic
- Ketamine had:
  - Same rate of re-dosing as did benzodiazepines and haloperidol
  - Neutral hemodynamic effect

Riddell, 2017

Agitation Reduction: Agitation Score ≤ 2

Treatment	Sample Size	Dose Administered	Time until Agitation Reduction* (p = 0.032)	48-Hr ED Bounceback (p = 0.062)	Number Requiring Re-Dosing (p = 0.199)
Ketamine	n = 24	4-6 mg/kg IM or 1-2 mg/kg IV	6.57 minutes	2 (8.3%)	14 (58.3%)
Versed	n = 19	5-10 mg IM or 5 mg IV	14.95 minutes	2 (10.5%)	15 (78.9%)
Ativan	n = 33	1-2 mg IM/IV	17.73 minutes	2 (6.1%)	26 (78.8%)
Haldol	n = 14	5-10 mg IM	13.43 minutes	1 (7.1%)	7 (50%)
BZD + Haldol	n = 10		23.30 minutes	0 (0%)	7 (70%)

Riddell, 2017

Ketamine's Function

- Noncompetitively antagonize NMDA-Receptors
- Promotes sympathomimetic functions
  - Causes bronchodilation through ß2 – agonistic action
  - No significant change in systolic blood pressure or pulse within 1 hour of administration (as seen with many sedatives and anesthetics)
  - Preserves respiratory drive, and laryngeal reflex (keeps airways patent)

- Function in treating ExDS: allows fast initial workup via inducing a "trance-like" cataleptic state
- Downside of ketamine: (1) Does not fix underlying cause of agitation, (2) May require re-dosing, (3) Impairs patient's ability to participate in assessment

Hopper, 2015; Jones, 2013; Pourmand, 2017; and Riddell, 2017

Ketamine's Dissociative State

- Separates **Cortical** (external stimuli reception) from **Limbic System** (which integrates peripheral stimuli into CNS)

- Dissociative threshold
  - Additional dosage does not deepen or enhance "level of sedation"
- Independent of Sedation Spectrum

  Conscious sedation ←→ Deep sedation (LOC and loss of airways reflex)

Hopper, 2015 and Riddell, 2017

Ketamine Adverse Effects

Side Effect	Potential Remedies	Nature of Side Effect
Emesis	- Zofran (NNTB ≥ 9) - Administer with Propofol (anti-emetic)	Highest in adolescence
Recovery Agitation/ Emergence Phenomenon	Adults: co-treat with 0.03 mg/kg of IV Midazolam (after Ketamine sedation) (NNTB = 6)	
Nystagmus		
Spontaneous Head Movement	Manual head positioning to maintain airways	Because no muscle paralysis
↑ Intracranial Pressure	Administer with Propofol (will actually ↓ ICP)	Only minimal increase Use Ketamine with care if recent head trauma

Himmelseher, 2005; Hopper, 2015; Howes, 2004; and Riddell, 2017

Ketamine Absolute Contraindications

(1) < 3 months old
- ↑ risk of laryngospasm (and apnea in severe cases)

(2) Schizophrenia
- potential of emergence phenomenon to exacerbate psychosis

Lathi, 1995

IV vs IM

Route	Advantages	Loading Dose	Maintenance Dose	Onset of Action
IV	Ideal for **Lengthy Procedures** - Easy redosing **Adults**: - less emesis - shorter recovery time	1.5 mg /kg – 2 mg/kg	0.5 mg/kg – 1 mg/ kg	1-2 minutes
IM	Ideal in **Pediatrics** Ideal if Pt **too combative**	4-5 mg/kg		3 minutes

Hopper, 2015

Ketamine for Pediatric Patient in ED

- Ideal to avoid physical restraints in pediatrics
  - Prefer distraction therapy

<u>Metanalysis shows:</u>

- Emergence phenomenon: 8%
  - Children more tolerant of Emergence
    - Mostly perceived as non-bothersome “sensory misinterpretation”
    - Best tolerated by <10y/o
  - Midazolam not lessen likelihood of emergence
  - Avoid ketamine in children with h/o psychosis or flashbacks
- Vomiting: 8.5%
  - No reported incidence of aspiration

Howes, 2004

Sub-Dissociative Dose of Ketamine – McGlown *et al.* (2-2.5 mg/kg)

- Administered in 501 children for minor emergent procedures
- 2% exhibited emergence phenomenon

Report of Accidental Ketamine Overdose in Pediatric Patients – Green *et al*

- 3 children received 5X maximal dose
- 5 children received 10X maximal dose
- 1 child received 100X maximal dose
- No apneic episodes or respiratory depression

Green, 1999 & McGlown, 2004

Ketofol – Ketamine & Propofol blend

- Study by Andolfatto *et al.* to see if 1:1 ratio of ketamine to propofol may ameliorate propofol's respiratory depression
- Goal: Use opposing side effects to create "Synergy"
- Compare ketofol (n=142) to propofol (n=142) for ED procedural sedation

Side effects	Ketamine	Propofol
Emesis	↑	↓
Recover agitation (emergence phenomenon)	↑	↓
Respiratory depression	↓	↑
Dose-dependent hypotension	↓	↑

Andolfatto, 2012

- Ketamine
  - added analgesic properties
  - prevented cardiopulmonary depression & muscle rigidity
- Propofol
  - Added anti-emetic properties
  - Prevented emergence phenomenon

Ketofol (n=142)	Propofol (n=142)
13 unsuccessful sedations - 8: emergence phenomenon - 3: procedural agitation - 2: emergence phenomenon + procedural agitation	16 unsuccessful sedations - 14: procedural agitation - 1: muscle rigidity - 1: procedural agitation + muscle rigidity

Ketofol: Decreased Intracranial Pressure
- may make ketofol ideal in head injury patients

Side effects	Ketamine	Propofol	Ketofol
Emesis	↑	↓	↓ Emesis (none reported)
Recover agitation (emergence phenomenon)	↑	↓	↓ Recovery agitation
Respiratory depression	↓	↑	↓ Respiratory depression (compared to Propofol)
Dose-dependent hypotension	↓	↑	↓ Hypotension (compared to Propofol)

Andolfatto, 2012 & Himmelseher, 2005

Ketamine for ED Analgesia

- Ketamine functions through the following:
  - NMDA-receptor antagonism
  - Stimulate delta-opioid receptors → potentiate ERK 1 & 2 phosphorylation → require less opioid binding to mu-opioid receptors for pain relief
  - Inhibits NO Synthase
  - Ketamine may be considered as an alternative to opioids in the ED when:
    - A trial of NSAIDS have failed
    - Opioids are considered high-risk
    - The patient is opioid tolerant

- Miller *et al.*
  - Ketamine (.3mg/kg IV): decreased NRS pain scale by 4.9 in 5 minutes
  - Morphine (.1 mg/kg IV): decreased NRS pain scale by 5.0 in 100 minutes

Jones, 2013; Miller, 2015; & Pourmand, 2017

Other Research Areas

- Educating physicians, nursing, staff on Ketamine use
- Comparing Ketofol to standard sedatives and ketamine in ExDS
- Assessing if Ketamine would be a viable option on inpatient wards
- Directly comparing droperidol versus ketamine in an ED study on ExDS
- Determining the safety profile of ketamine in elderly patients and patients with prior history of cardiovascular disease

Pourmand, 2017

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Altered Mental Status Scale – Cole, 2016

Table 1. The altered mental status scale.

Score	Responsiveness	Speech	Facial Expression	Eyes
+4	Combative, very violent, or out of control	Loud outbursts	Agitated	Normal
+3	Very anxious, agitated, mild physical element of violence	Loud outbursts	Agitated	Normal
+2	Anxious, agitated	Loud outbursts	Normal	Normal
+1	Anxious, restless	Normal	Normal	Normal
0	Responds readily to name in normal tone	Normal	Normal	Clear, no ptosis
−1	Lethargic response to name	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (<half eye)
−2	Responds only if name is called loudly	Slurring or prominent slowing	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)
−3	Responds only after mild prodding	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)
−4	Does not respond to mild prodding or shaking	Few recognizable words	Marked relaxation (slacked jaw)	Glazed and marked ptosis (>half eye)

Sedation Assessment Tool – Isbister, 2016

Table E1. Sedation Assessment Tool.

Score	Responsiveness	Speech
3	Combative, violent, out of control	Continual loud outbursts
2	Very anxious and agitated	Loud outbursts
1	Anxious/restless	Normal/talkative
0	Awake and calm/cooperative	Speaks normally
−1	Asleep but rouses if name is called	Slurring or prominent slowing
−2	Responds to physical stimulation	Few recognizable words
−3	No response to stimulation	Nil