JOHNS HOPKINS MEDICINE

Sub-dissociative Dosing of Ketamine for Non-procedural Pain in the Emergency Department

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Disclosures

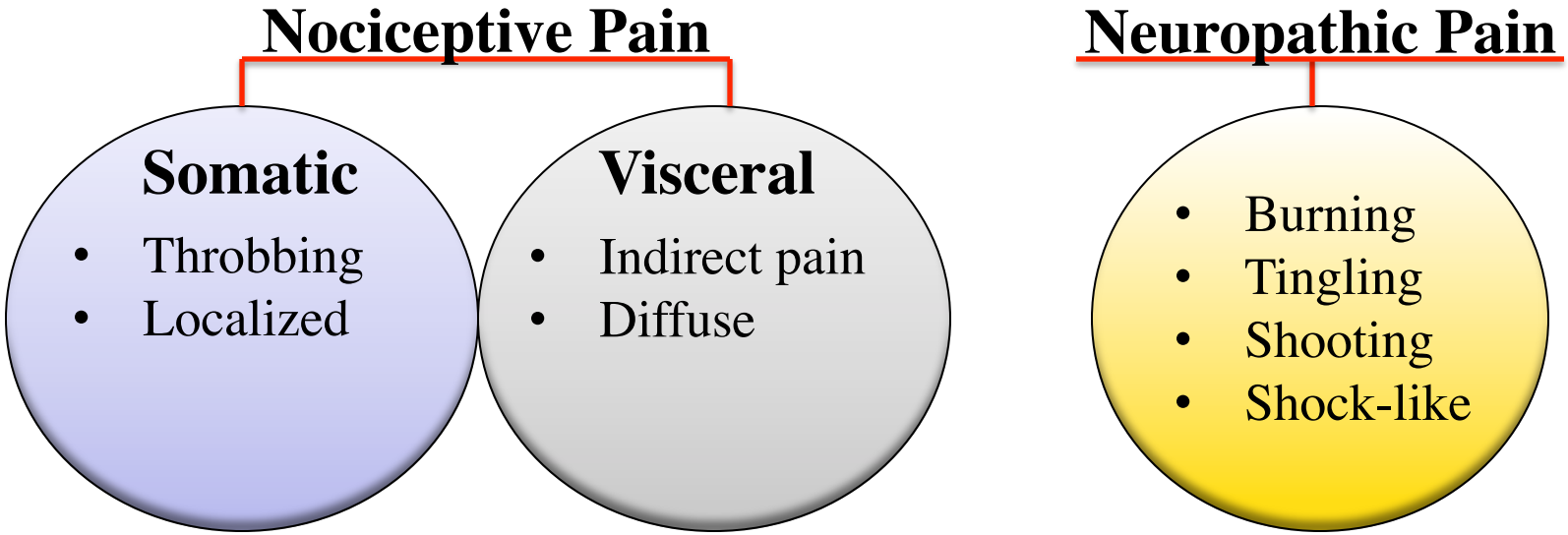
- I have no financial relationships or commercial interests to disclose for this presentation
- This continuing education activity contains discussion of published and/or investigational uses that are not indicated by the FDA. Please refer to the prescribing information for each product for the approved indications, contraindications and warnings.

Learning Objectives

- Identify common treatment options for the three types of pain.
- Evaluate the mechanism and adverse effects that are associated with ketamine.
- Review the literature on the use of ketamine for non-procedural pain in both adults and pediatrics in the Emergency Department (ED).
- Construct an argument for or against the use of ketamine in the ED.

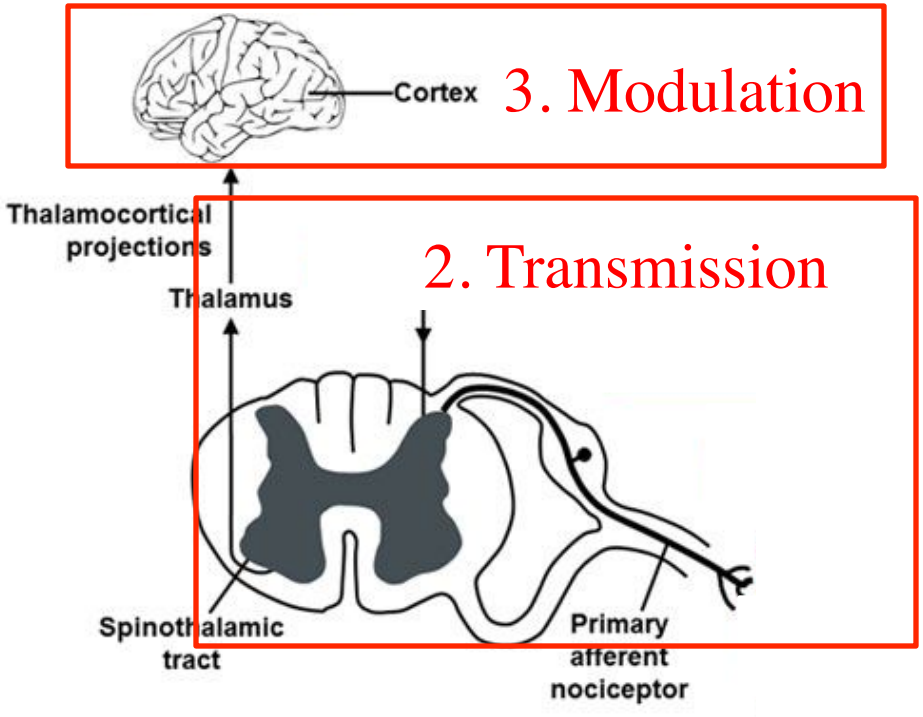
Review of Pain

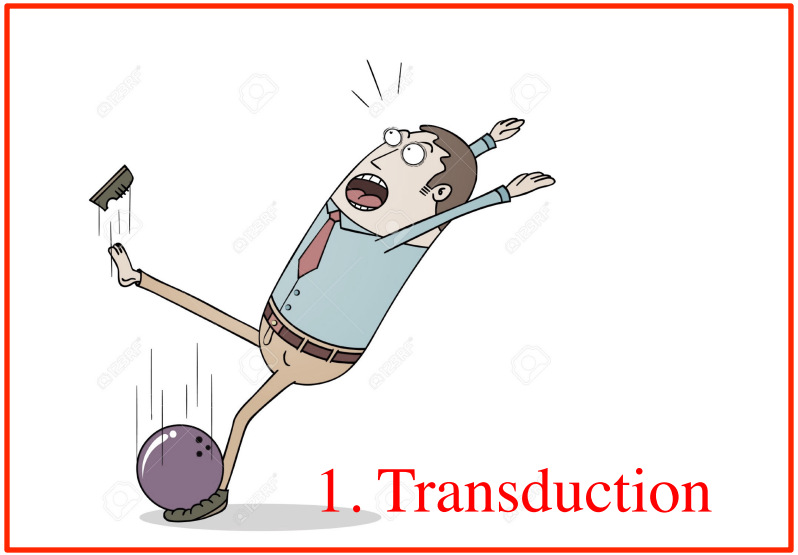
- "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage"



IASP Task Force on Taxonomy, 2 :209-214, 1994

Pathophysiology





Pain Management

Somatic	Visceral	Neuropathic
• Acetaminophen • NSAIDS • Tramadol • Opioids • Ketamine	• Acetaminophen • NSAIDS • Tramadol • Opioids • Ketamine	• Gabapentinoids • Serotonin-Norepinephrine Receptor Inhibitors (SNRIs) • Tricyclic Antidepressants (TCAs) • Local anesthetics • Tramadol • Opioids • Ketamine

Dworkin et al. *Pain* 132.3 (2007): 237-251.

Pain Management in the ED

- Opioids are the mainstay agents for moderate-severe pain
  - Most common agents
    - Morphine
    - Fentanyl
    - Hydromorphone
    - Oxycodone
  - Common adverse effects
    - Hypotension, respiratory depression, sedation

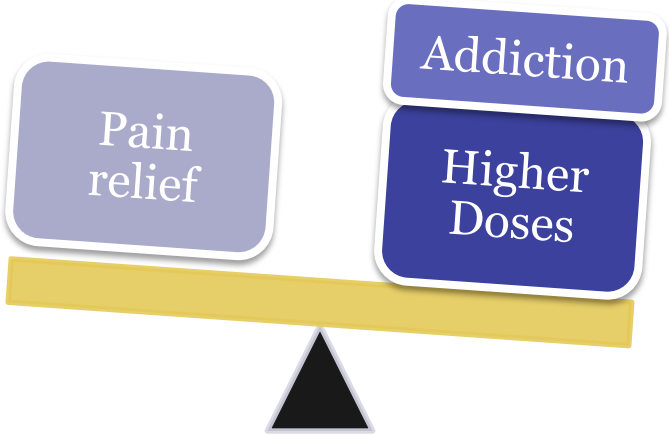
Active Learning #1

KM is a 34 y/o M that presents to the ED s/p MVC with a femur fracture with sharp pain (10/10) that radiates down his leg. (BP= 141/92, RR=15). What type of pain is KM experiencing and what drug should be used to treat this pain?

A. Visceral, NSAIDs
B. Neuropathic, gabapentin
C. Neuropathic, opioids
D. Somatic, opioids

Challenges of Opioids

- Opioid-naïve patients
  - Patients are at a higher risk of over sedation and respiratory depression
- Opioid-tolerant patients
  - Definition of tolerance
  - Opioid-induced hyperalgesia
- Opioid-epidemic



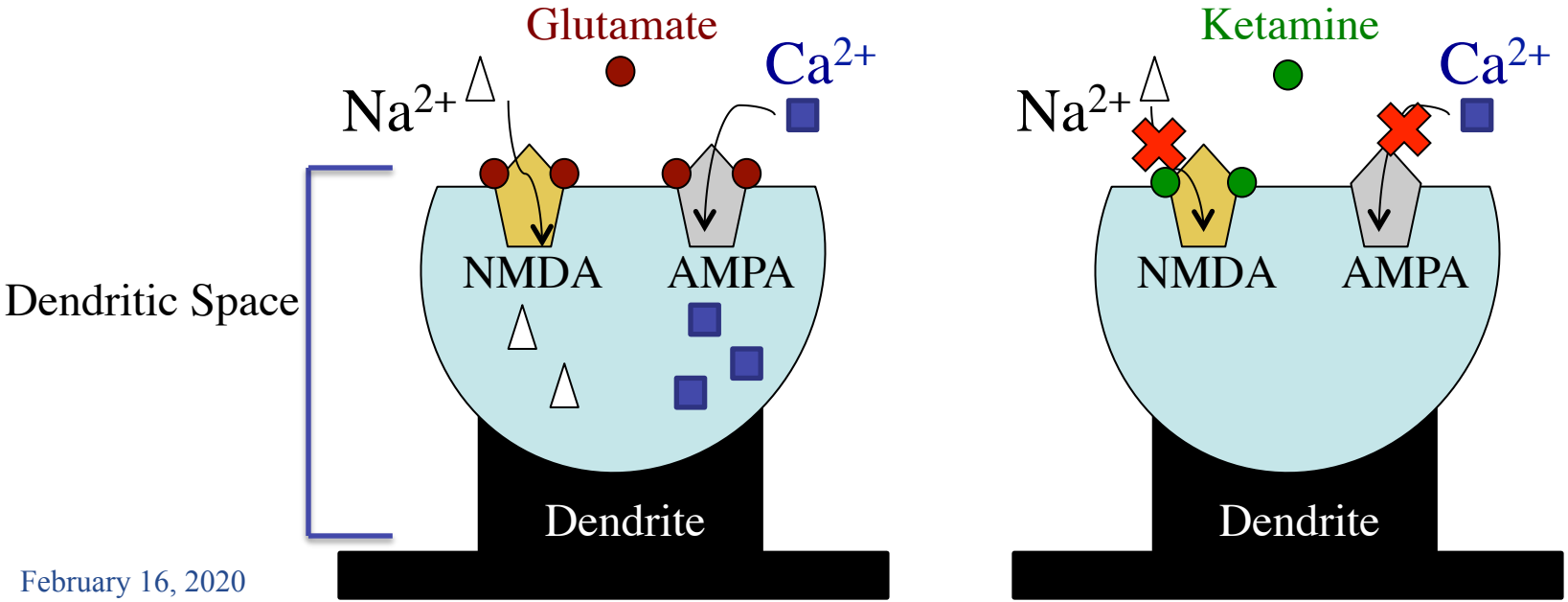
Ketamine: Alternative to Opioids

- Ketamine is most commonly used for the induction of anesthesia
- Studies have investigated the use of ketamine in perioperative pain management[1-2]
- Reductions in somatic, neuropathic, and cancer-related pain have been reported[2]

CNS drugs 21(3) (2007): 185-211.
Biomedicine & Pharmacotherapy, *60*(7), 2006. 341-348.

Review of Ketamine

- MOA- noncompetitive N-methyl d-aspartate (NMDA) receptor antagonist



Ketamine Properties

Onset	Duration	Metabolism	Elimination
30 seconds	10-15 minutes	N-dealkylation to Norketamine	Renal
Adverse effects: Emergence phenomena, sympathomimetic effect			
Absolute contraindications: Patients with schizophrenia, children younger than 3 months old			
Relative contraindications: hypertensive patients, pulmonary compromise			

Ketamine Uses

	Dissociative Dosing	Subdissociative Dosing
Uses	Procedural Sedation Rapid sequence intubation	Acute Pain
Dose	1-2 mg/kg	< 0.6 mg/kg
Properties	Amnestic, analgesic	Analgesic
Adverse Effects	Hypertension Bradyarrhythmias Respiratory depression	?

Active Learning #2

Which of the following side effects are associated with a dissociative dose of ketamine?

A. Hallucinations
B. Hypertension
C. Tachypnea
D. Both A and B
E. All of the above

Miller *et. al.* (2015)

Miller, J. P., et al. "Low-dose ketamine vs morphine for acute pain in the ED: a randomized controlled trial." AJEM (2015): 402-408

Miller, J., *et. al.* (2015)

Purpose	• Compare the ability of low-dose ketamine and morphine to reduce moderate to severe pain
Study Design	• Prospective, randomized, double-blinded, superiority trial
Timeframe	• February 2012 to March 2013

Patient Selection

Inclusion Criteria

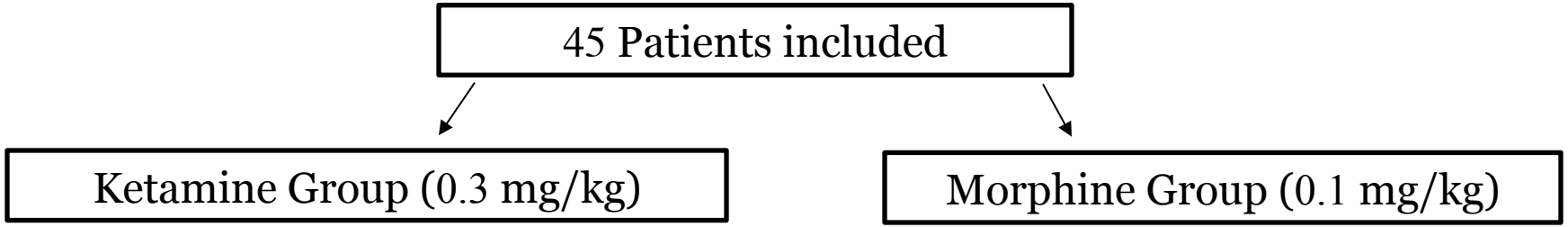
- 18-59 y/o
- Abdominal, flank, low back or extremity pain that thought warranted opioid treatment

Exclusion Criteria

- SpO_2 sat <95%
- RR <10, or >30 BPM
- SBP <90, or >180 mmHg
- HR <50, or >120 BPM
- Chronic use of opioids or tramadol outpatient
- Ischemic heart disease, HF
- Evidence of increased ICP or an intracranial mass, head trauma

Miller, Joshua P., et al. AJEM (2015): 402-408

Study Design



Primary Endpoint	Assess the maximum change in pain score based on the verbal numeric rating scale (NRS) from baseline.
Secondary Endpoint	Vital Signs, adverse events, need for rescue medications, Richmond agitation sedation scale (RASS)

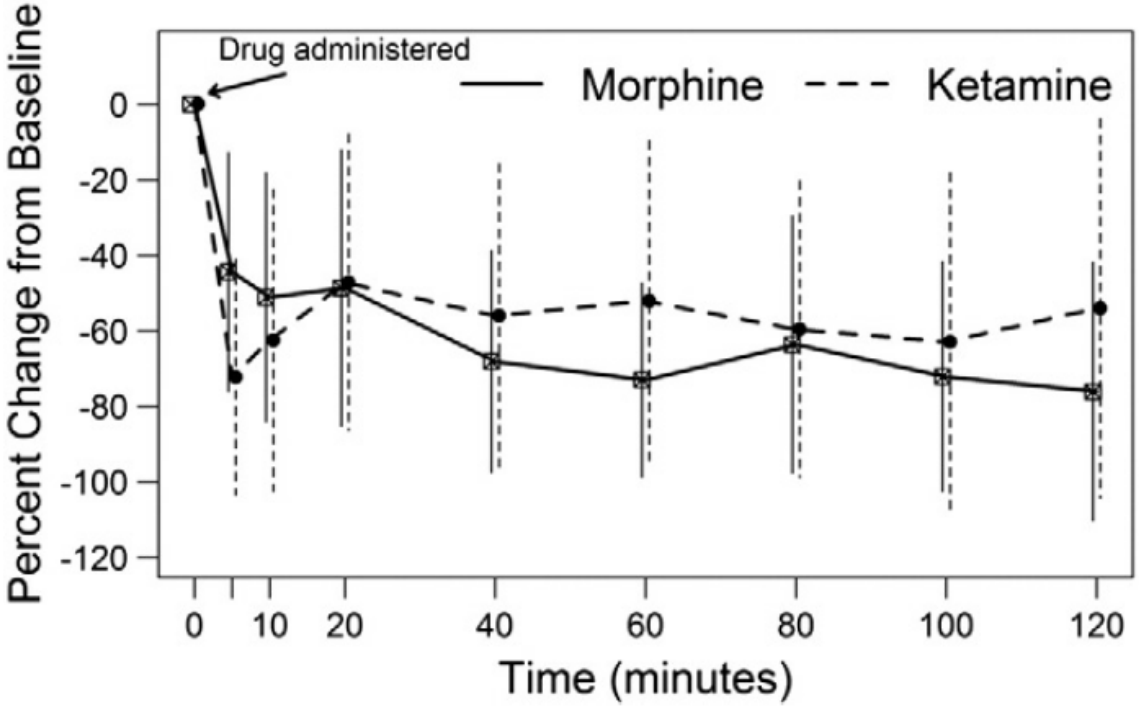
Study Population

	Morphine	Low-dose ketamine	Both treatment groups
Age (y), mean (SD)	29 (10)	31 (12)	30 (11)
Male sex	9 (43)	14 (58)	23 (51)
Vital signs, mean (SD)			
Systolic blood pressure (mm Hg)	121 (11)	126 (14)	124 (13)
Pulse rate (BPM)	74 (11)	76 (11)	75 (11)
Respiratory rate (RPM)	18 (3)	18 (3)	18 (3)
Oxygen saturations (%)	98 (1)	98 (2)	98 (2)
Baseline NRS pain score, mean (SD)	7.14 (1.5)	7.13 (1.7)	7.14 (1.6)
Pain location			
Abdomen	15 (71)	15 (65)	30 (68)
Back	4 (19)	8 (35)	12 (27)
Extremity	2 (10)	0 (0)	2 (5)

All results reported as no. (%) unless otherwise indicated. BPM, beats per minutes; RPM, respirations per minutes.

Miller, Joshua P., et al. AJEM (2015): 402-408

Reduction of pain from baseline



Miller, Joshua P., et al. AJEM (2015): 402-408

Need for repeat analgesia

Repeat dosing of analgesia reported by treatment group

	Morphine	Low-dose ketamine	*P*	Total
Second dose, n (%)			.37[a]	
Yes	8 (38)	13 (54)		21 (47)
No	13 (62)	11 (46)		24 (53)
Total	21	24		45
Third dose, n (%)			.47[b]	
Yes	3 (14)	6 (25)		9 (20)
No	18 (86)	18 (75)		36 (80)
Total	21	24		45

[a] χ^2 Test.
[b] Fisher exact test.

Adverse effects

Adverse effects reported by total events

Adverse effects	Morphine (n = 8)	Low-dose ketamine (n = 12)	Total
Nausea	2	3	5
Dysphoria	0	4	4
Hallucinations	0	3	3
Dizziness	1	2	3
Headache	3	0	3
Drowsiness	2	0	2
Vomiting	1	1	2
Lightheaded	1	0	1
Decreased oxygen saturation	1	0	1
Numbness	0	1	1
Pruritus	1	0	1
Total	12	14	26

n = number of patients experiencing an adverse effect. Some patients reported multiple adverse effects.

Miller, Joshua P., et al. AJEM (2015): 402-408

Summary

Strengths	• Randomized, double blind, superiority trial
Limitations	• Small sample size • Lack of generalizability • Weight based dosing of the medications not a common practice.
Author's Conclusion	• Use of ketamine appears to be safe and feasible option for the treatment of many types of pain
Application	• Both ketamine and morphine reduce pain. • More adverse effects were reported with ketamine • Evidence is not strong to suggest ketamine use in opioid-naïve patients

Motov et al. (2015)

Motov, S., et al. "Intravenous Subdissociative-Dose Ketamine Versus Morphine for Analgesia in the Emergency Department: A Randomized Controlled Trial." *Ann. of Emerg. Med.* (2015).

Motov, S., et al. *Ann. of Emerg. Med.* (2015).

Motov et al. (2015)

Purpose	• Compare the reduction in NRS pain scores between ketamine and morphine.
Study Design	• Prospective, randomized, double-blind trial
Timeframe	• June 2013 to May 2014

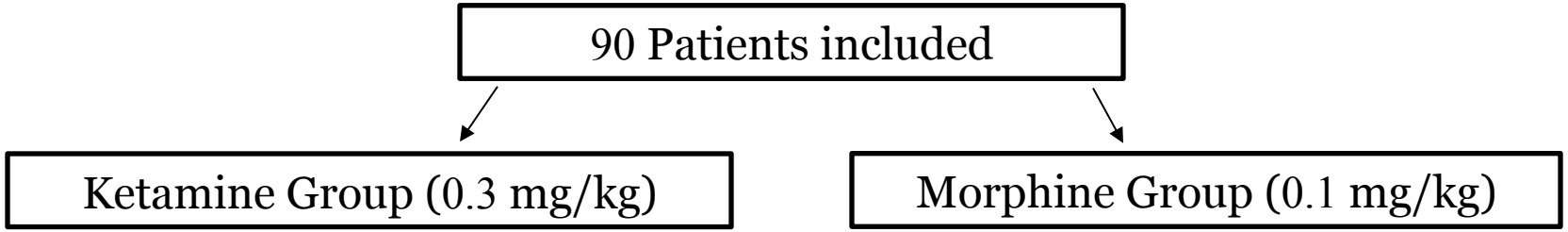
Motov, S., et al. *Ann. of Emerg. Med.* (2015).

Patient Selection

- Inclusion Criteria
  - 18-55 y/o with acute pain
  - Abdominal, flank, back, musculoskeletal pain
  - Pain rated >5 out of 10
- Exclusion Criteria
  - Weight < 45 kg or > 115 kg
  - SBP <90, or >180 mmHg
  - HR <50, or >150 BPM
  - RR <10, or >30 BPM
  - Chronic use of opioids or tramadol outpatient
  - Ischemic heart disease, HF
  - Evidence of increased ICP or an intracranial mass, head trauma

Motov, S., et al. *Ann. of Emerg. Med.* (2015).

Study Design



Primary Endpoint	• Reduction in NRS between ketamine and morphine at 30 minutes post-administration.
Secondary Endpoint	• Need for rescue analgesia (Fentanyl 1 mcg/kg) at 30-60 minutes • Safety

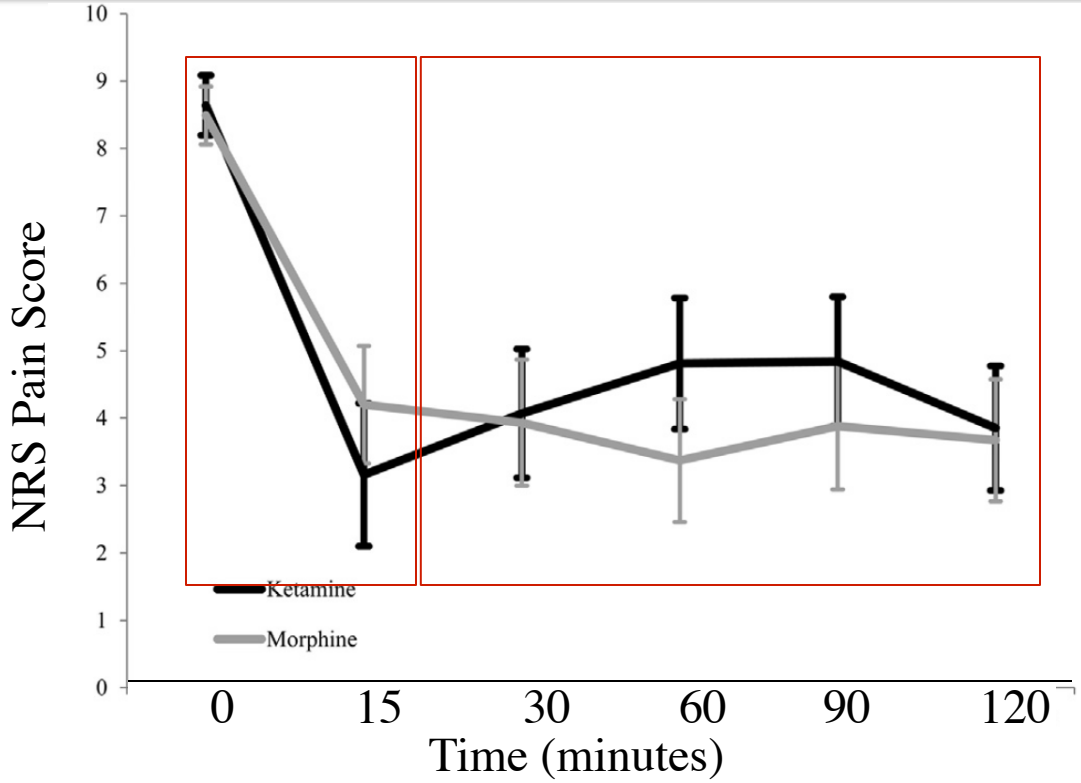
Motov, S., et al. *Ann. of Emerg. Med.* (2015).

Study Population

Characteristics	Ketamine	Morphine	Difference (95% CI)
Age, mean (SD),y	35 (9.5)	36 (10.5)	-1 (-5.1 to 3.3)
Female, No. (%)	30 (67)	28 (62)	5 (-16 to 25)
Weight, mean (SD), kg	74 (15.9)	78 (16.6)	4 (11.4 to 2.2)
Systolic BP	125 (18.2)	127 (16.1)	-2 (-8.8 to 5.6)
Diastolic BP	76 (13.2)	74 (12.7)	2 (-3.6 to 7.3)
Pulse (BPM)	79 (14.8)	79 (15.0)	0 (-6.8 to 5.6)
Abdominal Pain (%)	33 (73)	31 (69)	4 (-15 to 24)
Flank Pain (%)	7 (16)	9 (20)	-4 (-21 to 12)
Other Pain*	5 (11)	5 (11)	0 (-13 to 13)

Motov, S., et al. *Ann. of Emerg. Med.* (2015).

Change from baseline NRS



Motov, S., et al. *Ann. of Emerg. Med.* (2015).

Change from baseline NRS

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 (−2.40 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)
120	3.9 (2.9)	3.7 (2.9)	0.2 (−1.09 to 1.46)

Motov, S., et al. *Ann. of Emerg. Med.* (2015).

Need for rescue analgesia

Time Interval*	Group		Difference (95% CI)
	Ketamine	Morphine	
Fentanyl rescue incidence, No. (%)			
15	0	0	0
30	4 (9)	1 (2)	7 (−2.9 to 16.3)
60	4 (9)	6 (14)	−5 (−18.1 to 9.0)
90	5 (11)	5 (12)	−1 (−13.1 to 14.1)
120	12 (29)	5 (12)	17 (0.8 to 34.2)

Motov, S., et al. *Ann. of Emerg. Med.* (2015).

Adverse Effects

- More adverse effects with ketamine than with morphine in the first 15 minutes (38%, CI=18.2-57.4)
- Common adverse effects
  - Dizziness
  - Disorientation
  - Mood changes
  - Nausea

Motov, S., et al. *Ann. of Emerg. Med.* (2015).

Conclusions

Strengths	• Randomized, double blind trial • Dosing is similar to other comparative studies
Limitations	• Small study • Possible unblinding of healthcare workers
Author's Conclusion	• Ketamine is as effective as morphine in reducing pain at 15-30 minutes • Ketamine groups experienced significantly more adverse effects than the morphine group.
Application	• At doses of 0.3mg/kg, ketamine provides quick relief of pain and comparable to morphine. • Ketamine group required more rescue medication at 120 minutes.

Motov, S., et al. *Ann. of Emerg. Med.* (2015).

Review

	Miller et al.	Motov et al.
Treatment	• Ketamine 0.3 mg/kg • Morphine 0.1 mg/kg	• Ketamine 0.3 mg/kg • Morphine 0.1 mg/kg
Population	• 30 years old • Abdominal pain • No opioid use prior to study	• 35 years old • Abdominal pain • Opioid use within 4 hours
Rescue Analgesia	• Allowed for additional boluses of allocated study group	• Fentanyl 0.1 mcg/kg
Conclusions	• Ketamine has quick onset associated with an initial reduction of pain • Ketamine group required more rescue medication at 120 minutes. • Side effects are more commonly reported with ketamine groups	

Beaudoin et al. (2014)

Beaudoin, Francesca L., et al. "Low-dose Ketamine Improves Pain Relief in Patients Receiving Intravenous Opioids for Acute Pain in the Emergency Department: Results of a Randomized, Double-blind, Clinical Trial." *Acad. Emerg. Med.* (2014)

Study Design

Purpose	• Compare the effectiveness of low-dose ketamine as adjunct treatment to morphine versus morphine alone
Study design	• Pilot, prospective, randomized, double-blind trial
Timeframe	• December 2012 to September 2013

Beaudoin, Francesca L., et al. *Academic Emergency Medicine* 21.11 (2014): 1193-1202.

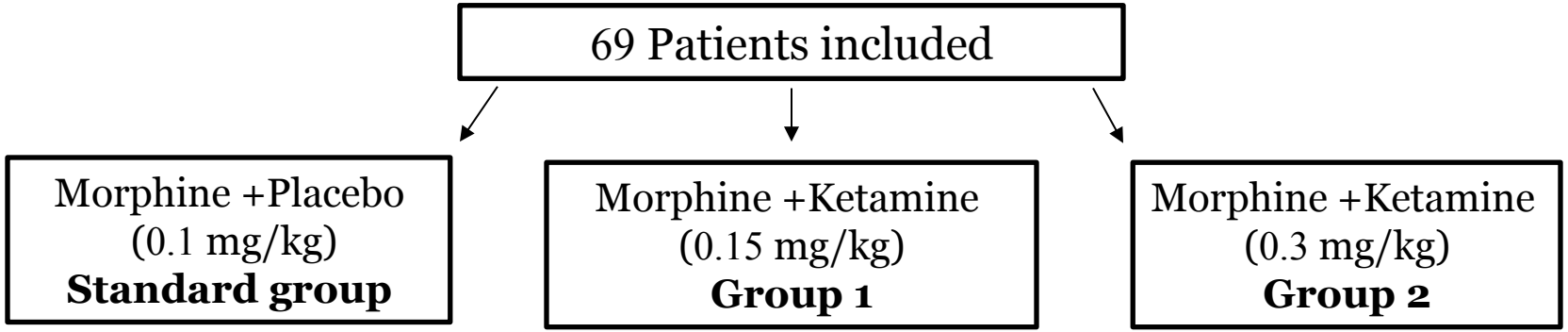
Patient selection

- Inclusion Criteria
  - 18-65 y/o with acute pain
  - Pain rated >5 out of 10
  - Patients that had received analgesia and pain >5/10

- Exclusion Criteria
  - Renal impairment (Scr >2)
  - Neurologic, respiratory, hemodynamic instability
  - History of stroke
  - Liver failure
  - History of cardiac disease

Beaudoin, Francesca L., et al. *Academic Emergency Medicine* 21.11 (2014): 1193-1202.

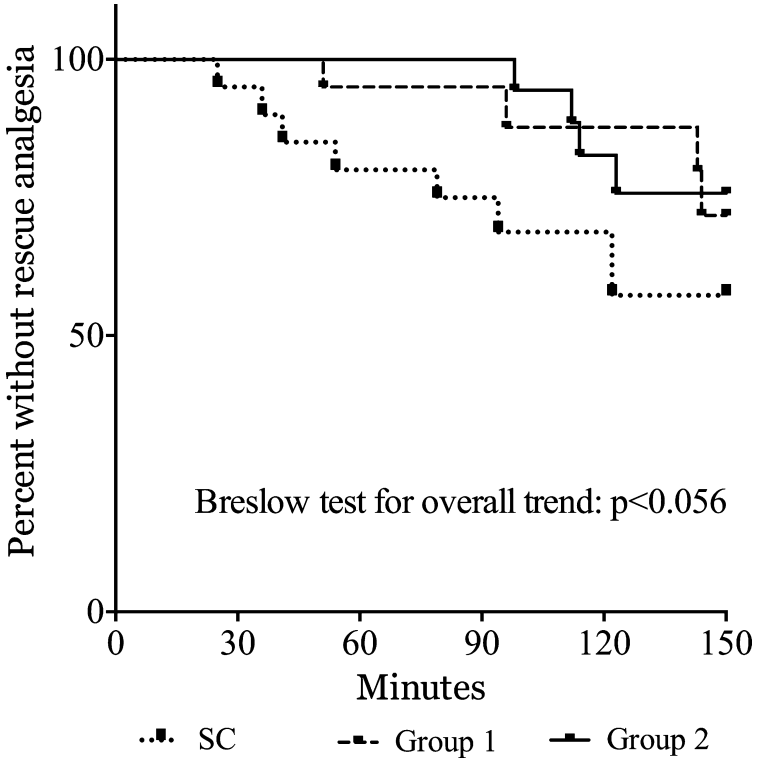
Study Design



Primary Endpoint	• Summed pain-intensity difference (SPID) over 2 hours
Secondary Endpoint	• NRS at each time point • Amount of rescue analgesia • Safety

Beaudoin, Francesca L., et al. *Academic Emergency Medicine* 21.11 (2014): 1193-1202.

Reduction in SPID



Beaudoin, Francesca L., et al. *Academic Emergency Medicine* 21.11 (2014): 1193-1202.

Reduction in SPID

Variable	Standard Care (n = 20)	Group 1 (n = 20)	Group 2 (n = 20)	p-values: Overall	Group 1 vs. Standard	Group 2 vs. Standard	Group 1 vs. Group 2
Pain intensity							
SPID	4.0 (1.8 to 6.5)	7.0 (4.3 to 10.8)	7.8 (4.8 to 12.8)	0.02	0.04	0.01	0.37
%SPID	21% (10 to 37)	39% (22 to 86)	42% (29 to 80)	0.02	0.05	0.01	0.42
Achieved SPID33%	5 (25%)	10 (50%)	14 (70%)	0.02	0.19	0.01	0.33
Pain intensity decrease							
30 minutes	2 (0.5 to 3)	4 (3 to 6.5)	4 (2 to 6)	0.01	0.00	0.02	0.70
1 hour	2 (1 to 3.5)	4 (2.5 to 6)	4 (1.5 to 7)	0.07	0.06	0.04	0.60
2 hours	2 (0.4 to 3)	2.51 (0.7 to 4)	4 (2 to 7)	0.07	0.32	0.02	0.19
Total patient-perceived pain relief	2.5 (1.0 to 4.3)	4.3 (1.3 to 5.5)	4.5 (3.0 to 6.0)	0.06	0.07	0.12	0.86
SIA score	44.3 (–18.0 to 82.0)	–8.2 (–86.1 to 55.7)	–65.6 (–100 to 21.3)	0.01	0.19	0.00	0.14

Continuous data are presented as median (IQR); categorical data are presented as a number (%).
Standard care = morphine + placebo; group 1 = morphine + 0.15 mg/kg ketamine; group 2 = morphine + 0.3 mg/kg ketamine.
SIA = Silverman integrated analgesic assessment; SPID = summed pain-intensity difference; SPID33% = the proportion of subjects achieving an SPID% score of ≥33%, treatment responders.

Beaudoin, Francesca L., et al. *Academic Emergency Medicine* 21.11 (2014): 1193-1202.

Adverse effects

- Patients in group 2 (higher-dose ketamine+morphine) reported dizziness or lightheadedness at 30 minutes compared with other groups
- No patients reported confusion of dysphoria

Beaudoin, Francesca L., et al. *Academic Emergency Medicine* 21.11 (2014): 1193-1202.

Summary

Strengths	• Randomized, double-blind trial • Dosing
Limitations	• Did not reach adequate power to detect a difference in adverse effects
Author's Conclusion	• The combination of morphine+ ketamine decreased pain intensity when compared to morphine alone. • Morphine with ketamine (0.3 mg/kg) was the only regimen that significantly reduced pain.
Application	• Ketamine (0.3 mg/kg) with morphine may provide a better reduction in pain than morphine alone.

Beaudoin, Francesca L., et al. *Academic Emergency Medicine* 21.11 (2014): 1193-1202.

Graudins et al (2015)

Graudins, A, et al. "The PICHFORK (Pain in Children Fentanyl or Ketamine) Trial: A Randomized Controlled Trial Comparing Intranasal Ketamine and Fentanyl for the Relief of Moderate to Severe Pain in Children With Limb Injuries." *Ann. of emerg. med.* (2015)

Study design

Purpose	• Compare the effectiveness of intranasal ketamine versus intranasal fentanyl in reducing moderate to severe pain in children
Study design	• Randomized, double-blind, control trial
Timeframe	• November 2012 to February 2013

Graudins, Andis, et al. *Annals of emergency medicine* 65.3 (2015): 248-254.

Patient selection

- Inclusion Criteria
  - 3-13 y/o with acute pain with a limb injury
  - < 50 kg
  - Pain rated >6 out of 10
- Exclusion Criteria
  - inability to obtain consent from parent or guardian
  - current treatment with serotonergic antidepressants
  - previous use of IN opioids/ analgesics
  - allergy to any medication
  - aberrant nasal anatomy
  - head trauma
  - LOC

Graudins, Andis, et al. *Annals of emergency medicine* 65.3 (2015): 248-254.

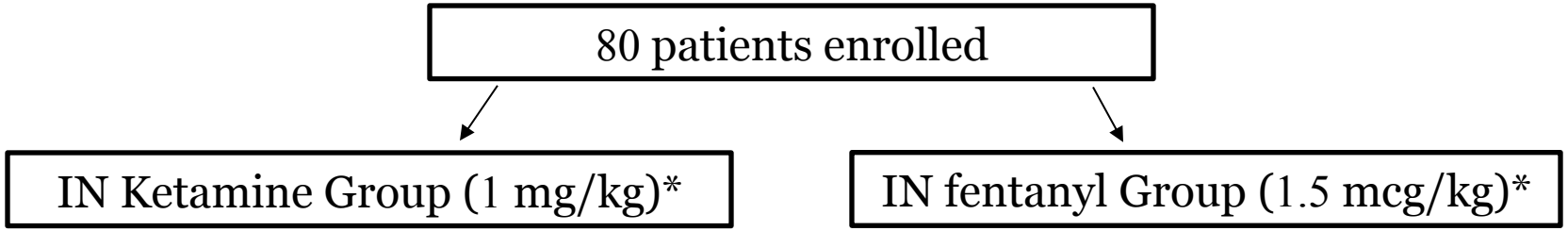
Study population

Table 1. Comparison of baseline characteristics between groups.

Variable	Fentanyl (n=37)	Ketamine (n=36)
Age, median (IQR), y	9 (6 to 11)	7 (6 to 9.5)
Male, No. (%) [95% CI]	24 (65) [47.5 to 79.8]	22 (61) [43.5 to 76.9]
Enrollment pain rating, median (IQR), mm	80 (70 to 100)	80 (69 to 96)
Enrollment UMSS, median (range)	0 (0 to 1)	0 (0 to 1)
Median intranasal drug dose administered (IQR)	1.53 μg/kg (1.45 to 1.57)	1.01 mg/kg (0.96 to 1.05)
Patients receiving ibuprofen, No. (%)	33 (89)	33 (92)
Median time to administration of ibuprofen after intranasal drug delivery, (range), min	0 (–70 to 60)	0 (–28 to 50)

Graudins, Andis, et al. *Annals of emergency medicine* 65.3 (2015): 248-254.

Study design



Primary Endpoint	• Median reduction in pain rating at 30 minutes after administration
Secondary Endpoint	• Change in pain rating at 15-60 minutes • Improvement of symptoms • Sedation score • Need for and timing of rescue medication

* All patients received oral ibuprofen (10mg/kg)

Graudins, Andis, et al. *Annals of emergency medicine* 65.3 (2015): 248-254.

Results: Primary Outcome

- At 30 minutes, both ketamine and fentanyl reduced pain by 45 to 40 mm.
- Pain reduction was maintained at 60 minutes
- No statistical significance between the groups.

Graudins, Andis, et al. *Annals of emergency medicine* 65.3 (2015): 248-254.

Results: Secondary Endpoints

Table 3. Comparison of rescue analgesia, satisfaction, and self-reported sedation level between groups.

Variable	Fentanyl	Ketamine	Difference (Ketamine vs Fentanyl) (95% CI)
Rescue analgesia, No. (%)	12/37 (32)	5/36 (14)	−18 (−37 to 3)
Satisfied at final rating, No. (%)	26/36 (72)	29/35 (83)	11 (−9 to 30)
Sedation at final rating, No. (%)			
Too much	1/36 (3)	0/35	−3 (−8 to 3)
Enough	10/36 (28)	18/35 (51)	23 (1 to 45)
None	25/36 (69)	16/35 (46)	−23 (−42 to 2)
Not enough	0/36	1/35 (3)	3 (−3 to 8)
Symptoms improved at final rating, No. (%)	28/36 (78)	31/35 (89)	11 (−28 to 6)

Graudins, Andis, et al. *Annals of emergency medicine* 65.3 (2015): 248-254.

Adverse Effects

- Patients in the ketamine group has a greater overall incidence of adverse effects
- Most common adverse effects
  - Dizziness
  - Drowsiness
  - Bad taste in mouth

Graudins, Andis, et al. *Annals of emergency medicine* 65.3 (2015): 248-254.

Summary

Strengths	• Randomized, double-blind, controlled trial
Limitations	• Selection bias • No placebo arm • Incomplete recording times of ibuprofen • No criteria for rescue medication
Author's Conclusion	• Both medications provide pain reduction after 30 minutes • Consistent findings in previous studies.
Application	• While it may reduce pain, IN ketamine was associated with more adverse effects • More research is needed before ketamine should be used before other agents.

Graudins, Andis, et al. *Annals of emergency medicine* 65.3 (2015): 248-254.

In the pipeline…

Study Design	• Randomized, double-blind, placebo-controlled trial
Purpose	• Evaluate whether patients who receive ketamine as adjunctive treatment to opiates for pain control, better satisfaction with pain control and reduction in total opiate dosage when compared to opiate therapy.
Population (n=116 patients)	• Group 1: Ketamine (0.1 mg/kg) • Group 2: Protocol-based group (morphine or fentanyl)
Results	• Primary endpoint: ketamine group had lower pain scores than the standard group (p=0.015) and required lower opioid doses than standard treatment (p=0.02)

Summary of trials

- Adults
  - Low-dose ketamine reduces pain comparable to morphine
  - Ketamine is associated with more adverse effects (dizziness and drowsiness) than morphine
- Pediatrics
  - IN fentanyl and ketamine reduces pain in pediatrics
  - IN administration is not commonly used
  - Ketamine also associated with dizziness and drowsiness

Active learning #3

Upon review of the use of ketamine for pain, which of the following are false?

A. Ketamine was not found to be beneficial for pain in children
B. A common adverse effect of ketamine was dizziness
C. Ketamine was superior to morphine in treating somatic pain
D. Both A and C

Implementation of ketamine in the ED

- Only physicians can administer intermittent ketamine boluses
- No policy or procedure for ketamine administration for pain management in the ED
- No management of the need for repeat dosing
- Monitoring parameters remain unclear
- Patient population…

Summary

- Increasing abuse of opioids is requiring healthcare workers to find alternatives.
- Ketamine has been shown to have comparable pain lowering effects when use in combination with opioids
- At low doses, ketamine is associated with an increased incidence of dizziness and drowsiness
- More studies are needed before the creation or implementation of ketamine-for-pain protocols

Active learning #4

You are working in the Emergency Department. A 34 y/o F is the victim of a hit and run. She is brought in by EMS. (HR=70, BP=140/95, RR=19). She is found to have a fracture of the right humerus and multiple abrasions. Her pain is 10/10. She reports taking morphine daily to control her fibromyalgia. After receiving a total of 100 mcg of fentanyl IV and 2 mg morphine IV her pain is still rated 10/10.

Dr. House asks if you have ever heard about sub-dissociative dosed ketamine for pain and if you think it would be a good option in this patient. Why, or Why not?

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