Non-Opioid Pain Management: In the ED and Beyond

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Objectives

- Describe the pathophysiology of pain
- Compare and contrast alternatives to opioids for pain management
- Analyze supporting literature for non-opioid pain options
- Recommend appropriate medication therapy given a patient case

What is Covered

- Strategies and approaches to acute pain in ED
- Paradigm shifts in perceptions of pain management
- New data on combination therapy of acetaminophen + ibuprofen
- New data on ketorolac
- Ketamine
- Intravenous lidocaine

What is Not Covered

- ICU Pain Management
- Neuropathic Pain
- Chronic Pain
- Cancer Pain

Epidemiology

- 33,091 overdose deaths involving an opioid in 2015
- ED only accounts for 4.7% of opioid prescriptions, but is frequently where patients are first introduced to opioids
- Percentage of ED visits in which an opioid is prescribed rose from 20.8% in 2001 to 31.0% in 2010
- 17% of patient's prescribed an opioid for acute pain were still taking the medication 1 year after initial ED visit

Combatting the Epidemic

- Prevent new cases of addiction
  - Keep opioid naïve patients naïve
- Balance benefit of pain relief with risk of addiction
  - Identification of high risk patients
- Shared understanding with patient on goals
  - Goal to reduce pain enough to function, not eliminate
- Acute pain improves within days
  - Only 2-3 days of opioids is needed

Red Flags for Opioid Abuse Potential

- Adolescents and young adults
- History of substance use (including tobacco)
- Social isolation or dysfunction
- Existing psychiatric disease
- Concomitant use of sedatives

PHYSIOLOGY OF PAIN

5 PHASES OF ADAPTIVE PAIN

TRANSDUCTION
CONDUCTION
TRANMISSION
PERCEPTION
MODULATION

NMDA RECEPTORS
OPIOID RECEPTORS

NA+ CHANNELS

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PAIN MANAGEMENT

ACETAMINOPHEN + IBUPROFEN

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Acetaminophen + Ibuprofen

- Possible synergistic effect by decreasing pain through multiple mechanisms
- Combination used in Australia, New Zealand, and Europe
- Limited data to date – postoperative and dental pain

- Advantages
  - Cost-effective
  - Limited adverse effects
- Disadvantages
  - Perception & guidance

Hot off the Press

JAMA | Original Investigation

Effect of a Single Dose of Oral Opioid and Nonopioid Analgesics on Acute Extremity Pain in the Emergency Department
A Randomized Clinical Trial

Andrew K. Chang, MD, MS; Polly E. Bijur, PhD; David Esses, MD; Douglas P. Barnaby, MD, MS; Jesse Baer, MD

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Non-Opioid vs. Opioid Extremity Pain

- Patients aged 21 to 64 presenting to ED with acute extremity pain
- Randomized, double-blind, treatment control
- 4 intervention groups
  - 400 mg ibuprofen + 1000 mg acetaminophen
  - 5 mg oxycodone + 325 mg acetaminophen
  - 5 mg hydrocodone + 325 mg acetaminophen
  - 30 mg codeine + 325 mg acetaminophen
- Primary: NRS pain score at 2 hours
- Secondary:
  - NRS pain score at 1 hour
  - Severity of pain – none, mild, moderate, severe

Chang AK, etal. JAMA. 2017

Non-Opioid vs. Opioid Extremity Pain

- 411 patients enrolled
  - 101 patients – APAP + ibuprofen
  - 104 patients – oxycodone + APAP
  - 103 patients – hydrocodone + APAP
  - 103 patients – codeine + APAP
- Notable demographics
  - 60% latino, 31% black
  - 62% presented with muscle strain or sprain
  - 22% presented with extremity fracture

Chang AK, etal. JAMA. 2017

Non-Opioid vs. Opioid Extremity Pain

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Chang AK, etal. JAMA. 2017

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Non-Opioid vs. Opioid Extremity Pain

- 17.8% of patients received rescue analgesia
  - Predominantly oxycodone
  - No difference in need observed between groups
- Post-hoc analysis in severe pain patients also displayed no difference
- Conclusion:
  - Acetaminophen 1000 mg + ibuprofen 400 mg showed no difference in pain reduction at 2 hours from opioid analgesia and may be an effective initial option for pain management

Chang AK, etal. JAMA. 2017

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KETOROLAC

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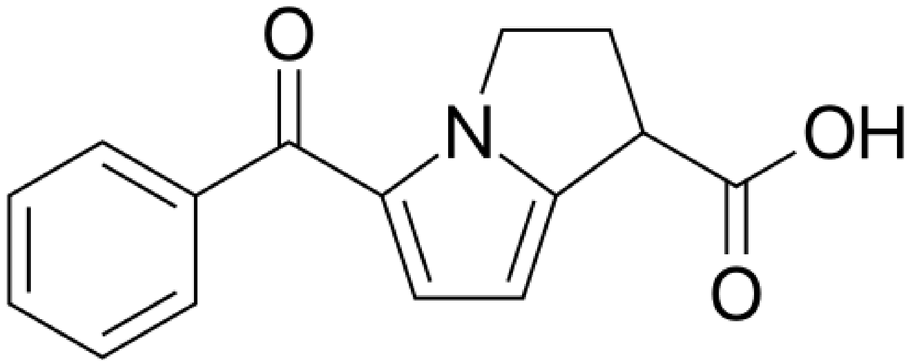
Ketorolac

- Potent NSAID analgesic
- Available in tablets and injectable for IV/IM
  - IV/IM – 15 mg, 30 mg, 60 mg
  - PO – 10 mg

- Advantages
  - Powerful analgesic
  - Many studied uses
  - Cost effective
- Disadvantages
  - Significant drug-drug interactions
  - Adverse effects
    - Nausea, vomiting, dyspepsia, dizziness
    - Nephrotoxicity
    - GI hemorrhage – DOSE DEPENDENT



Ketorolac Dosing in ED

- Patients aged 18-65 presenting to ED with acute flank, abdominal, musculoskeletal, or headache pain with NRS pain score > 5
- Randomized, double-blind, single center
- 3 intervention groups
  - Ketorolac 10 mg
  - Ketorolac 15 mg
  - Ketorolac 30 mg
- Primary: reduction in NRS at 30 minutes
- Secondary: rates of adverse effects and patients requiring rescue analgesia

Motov S, etal. Ann Emerg Med. 2017

Ketorolac Dosing in ED

- 240 patients enrolled
  - 80 patients received 10 mg
  - 80 patients received 15 mg
  - 80 patients received 30 mg
- Notable demographics
  - 45% male
  - 38% abdominal pain, 33% flank pain, 24% musculoskeletal pain

Motov S, etal. Ann Emerg Med. 2017

Mean Pain Scores (SD)

	Baseline	30 minutes	1 hour	2 hours	Significance to baseline
10 mg	7.73 (1.65)	5.13 (2.71)	4.56 (2.77)	3.77 (2.96)	Significant reduction
15 mg	7.54 (1.61)	5.05 (2.56)	4.09 (2.93)	3.60 (2.37)	Significant reduction
30 mg	7.80 (1.55)	4.84 (2.86)	4.11 (2.93)	3.44 (3.00)	Significant reduction
Signifiance between groups	Not significant	Not significant	Not significant	Not significant	

Ketorolac Dosing in ED

- No difference in use of rescue morphine
- No difference in rates of adverse effects
  - Dizziness (17.5%)
  - Nausea (11.6%)
  - No patients had a GI hemorrhage
- Conclusions
  - Patients experience no greater reduction in analgesia with higher doses of ketorolac compared to 10 mg dosing

Motov S, etal. Ann Emerg Med. 2017

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KETAMINE

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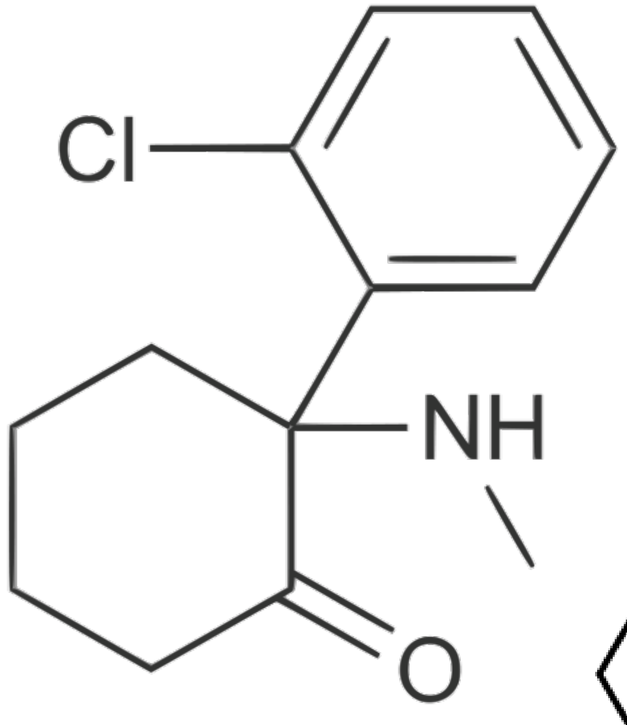
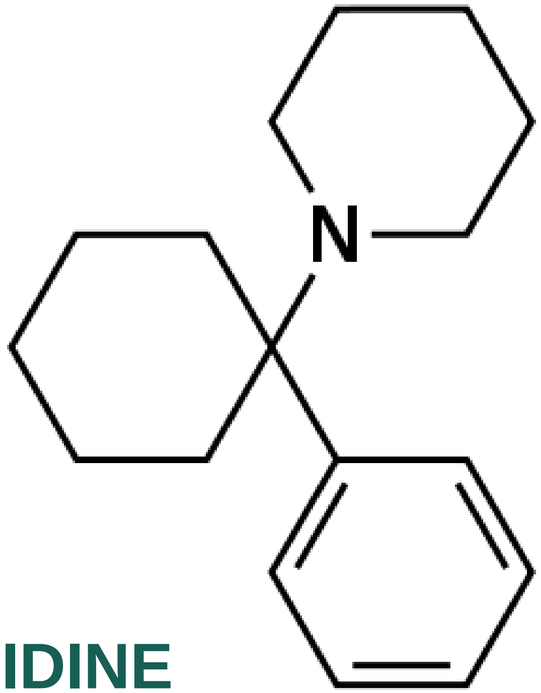
Ketamine

- Functions by binding to NMDA receptors in the CNS
  - Structurally related to PCP
- Racemic mixture
  - Both isomers are effective; however S enantiomer is more potent with fewer emergence reactions
- May be used as alternative or adjunct to opioids



KETAMINE



PHENYLCYCLIDINE

Ketamine

- Studied uses:
  - Acute pain – wide range of etiologies
  - Chronic pain
- Studied routes
  - IV, IM, Intranasal, SubQ

- Dosing
  - Subdissociative: 0.15 – 0.6 mg/kg IV bolus
    - Consider mixing in 50 mL NS and administer over 15 minutes (Motov, 2017)
  - Anesthetic: 1-4.5 mg/kg
- Duration of Effect
  - Peak at 15 minutes
  - May last up to 1-2 hours

Ketamine

- Advantages
  - Large therapeutic window
  - Lack of respiratory depression
- Disadvantages
  - Limited data – small trials in ED and postoperative setting
  - High rates of mild, transient adverse effects
  - Higher cost than opioids
  - State board of nursing

Ketamine Adverse Effects

Subdissociative Dosing	Anesthetic Dosing
Nausea	Hypertension
Dizziness	Tachycardia
Feeling of unreality	Emergence reactions
Hallucination - rare	Elevated intraocular pressures
Mild elevations in blood pressure	Elevations in intracranial pressures?

Avoid Ketamine

- Psychiatric illness
- Systolic blood pressure > 180 mmHg
- Heart rate > 150 beats per minute

Ketamine vs. Morphine Acute Pain

- Patients aged 18-55 presenting to ED with acute abdominal, flank, back, or musculoskeletal pain with a NRS > 5
- Prospective, randomized, double-blind
- 2 intervention groups
  - Ketamine 0.3 mg/kg
  - Morphine 0.1 mg/kg
- Primary: reduction in NRS at 30 minutes
- Secondary: Need for rescue analgesia at 30 minutes, 60 minutes, vital sign changes, adverse effects

Ketamine vs. Morphine Acute Pain

- 90 patients enrolled
  - 45 received ketamine
  - 45 received morphine
- Notable demographics
  - 62% female
  - 71% presented with abdominal pain
  - 18% presented with flank pain

Motov S, etal. Ann Emerg Med. 2015

Ketamine vs. Morphine Acute Pain

- More patients required fentanyl rescue in ketamine at 120 minutes: 29% ketamine vs 12% morphine (95% CI 0.8-34.2)
- Adverse effects observed with ketamine
  - Dizziness (53%)
  - Disorientation (29%)
  - Mood changes (13%)
- Conclusions: Ketamine is an effective pain medication; however it is associated with a high rate of mild adverse effects and may need rescue opioids

Motov S, etal. Ann Emerg Med. 2015

Ketamine Additional ED Data

Indication	N	Route	Dose	Comparator	Result	Conclusion	Reference
Renal Colic	53	Nasal	1 mg/kg	Morphine IV 0.1 mg/kg	Ketamine reduced pain from 8.35 to 4.17 on VAS at 30 minutes	No difference in pain reduction seen between ketamine and morphine	Am J Emerg Med 2017
Headache	54	IV	0.3 mg/lg	Prochlorperazine 10 mg	Difference in pain of 18.1 on VAS at 45 minutes	Prochlorperazine superior to ketamine	Ann Emerg Med 2017
Trauma pain	90	Nasal	1 mg/kg	Morphine 0.1 mg/kg IV or Morphine 0.15 mg/kg IM	Ketamine reduced pain by 56 mm on VAS at 40 minutes	No statistical difference between groups	BMC Emerg Med 2016
Moderate-severe pain	39	Nasal	0.7 mg/kg + 0.3 mg/kg rescue	None	100% of patients had at least a 20 mm reduction on VAS at 30 and 60 minutes	Ketamine was an effective pain medication	World J Emerg Med 2016
Moderate-severe pain	45	IV	0.3 mg/kg	Morphine 0.1 mg/kg	Maximum change in NRS for ketamine = 4.9 at 5 minutes, morphine = 5 at 100 minutes	Ketamine is not superior to morphine, but did control pain	AM J Emerg Med 2015

Postoperative Ketamine

- Dosing: 0.15-0.25 mg/kg/hr for 48-72 hours
- Studied as adjuvant to reduce opioid doses and prevent hyperalgesia
  - Abdominal surgery
  - Cardiothoracic surgery
  - Orthopedic surgery
- Modest reduction in pain
  - 0.6 cm reduction at 24 hours (95% CI 0.3-0.8), 1.3 cm reduction at 72 hours (95% CI 0.2-2.4) among 36 trials
- Reduction in opioids consumed
  - Reduced morphine use by 5 mg at 24 hours (95% CI 2.8-7.2), 20.2 mg at 72 hours (95% CI 12.7-27.7) among 36 trials
- Reduced post-op nausea and vomiting
  - RR = 0.71, (95% CI 0.60-0.85) among 30 trials

Wang L, etal. Can J Anaesth. 2016

Assessment Question

Which of the following patients is the best candidate for ketamine for pain?

A. 27 year old with a fractured ankle and a history of schizophrenia
B. 74 year old with back pain and a blood pressure of 170/110
C. 55 year old with a myocardial infarction
D. 46 year old with abdominal pain and a tolerance to opioids

PAIN MANAGEMENT

LIDOCAINE

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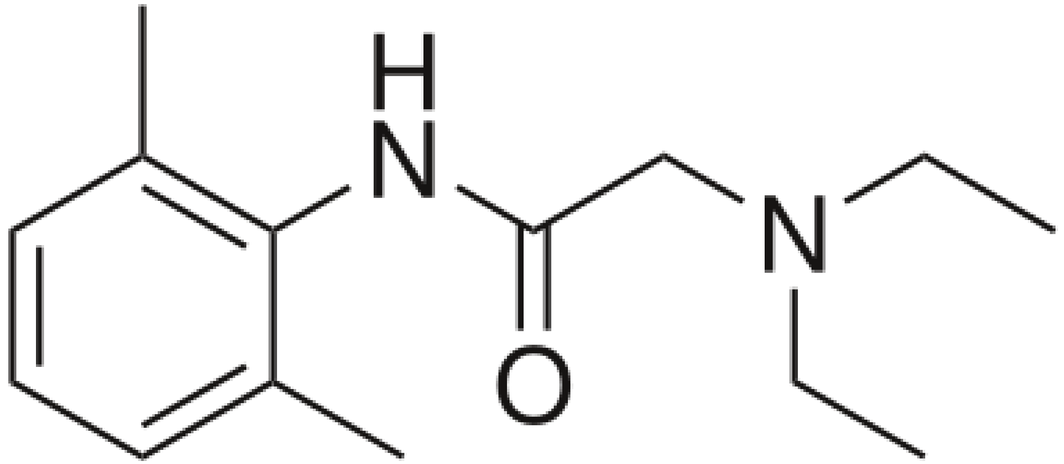
Lidocaine

- Studied uses:
  - Renal colic
  - Back pain
  - Neuropathic pain



- Can be used intravenously, topically, or as a peripheral nerve block
- Role for IV use in patients in whom narcotics are ineffective or not tolerated

Lidocaine

- Dosing:
  - Intravenous lidocaine 2% (20 mg/mL)
    - Patients should be on 1.5 mg/kg actual body weight (max: 200 mg)
    - Dilute in 100-250 mL of D5W or NS
    - Infuse over 10-20 minutes
- Telemetry during administration and monitored for bradycardia

Lidocaine

- Advantages
  - Safe and effective
  - Cost effective

- Disadvantages
  - Potential for medication errors
  - Data limited to small studies and case series
  - Indications in which most effective are limited
  - Consider telemetry monitoring with IV administration

Lidocaine Adverse Effects

- Common
  - Nausea, vomiting, abdominal pain
  - Dizziness
  - Perioral numbness
- Uncommon
  - Metallic taste
  - Tremor
  - Dry mouth
  - Bradycardia

Lidocaine IV vs. Morphine in Renal Colic

- Adults aged 18-65 years presenting to ED with renal colic
- Prospective, randomized, double blind, single center
- 2 intervention groups
  - Lidocaine IV 1.5 mg/kg
  - Morphine IV 0.1 mg/kg
- Primary: reduction in VAS at 5, 10, 15, and 30 minutes
- Secondary:

Lidocaine IV vs. Morphine in Renal Colic

- 240 patients enrolled
  - 120 received lidocaine IV
  - 120 received morphine IV
- Notable demographics
  - 73% patients were male
  - Mean age 36 years old

Soleimanpour H, etal. BMC Urol. 2012

Lidocaine IV vs. Morphine in Renal Colic

Soleimanpour H, etal. BMC Urol. 2012

Lidocaine IV vs. Morphine in Renal Colic

- More patients responded to lidocaine than morphine 90% vs 70% (p=0.00001)
- Lidocaine was well tolerated, with dizziness being the most common adverse effect
- Conclusion: lidocaine is a safe an effective alternative to opioids in managing renal colic

Soleimanpour H, etal. BMC Urol. 2012

Lidocaine IV vs. Ketorolac Back Pain

- Patients aged 15-55 with acute radicular back pain
- Randomized, double-blind, single center
- 2 intervention groups
  - Lidocaine IV 100 mg
  - Ketorolac IV 30 mg
- Primary: Difference in VAS at 60 minutes
- Secondary: Patient pain relief score at 1 week

Tanen DA, etal. J Emerg Med. 2014

Lidocaine IV vs. Ketorolac Back Pain

- 41 patients enrolled
  - 21 patients received lidocaine
  - 20 patients received ketorolac
- Notable demographics
  - Mean age 37 years
  - Mean weight 88.6 kg

Tanen DA, etal. J Emerg Med. 2014

Lidocaine IV vs. Ketorolac Back Pain

Lidocaine IV vs. Ketorolac Back Pain

- 67% of patients in the lidocaine group required rescue analgesics
- No adverse effects were tracked
- Conclusions: while lidocaine decreased radicular back pain from baseline, it did not reach clinical significance

Tanen DA, etal. J Emerg Med. 2014

Lidocaine Additional Data

Setting	Indication	N	Route	Dose	Comparator	Result	Conclusions	Reference
ED	Critical limb ischemia	63	IV	2 mg/kg	Morphine 0.1 mg/kg	At 60 minutes, lidocaine had a mean reduction of 2.25 in VAS	Lidocaine superior to morphine	Emerg Med J 2015
Meta-analysis	Neuropathic Pain	329	IV	1-5 mg/kg	placebo	Pooled analysis – reduction in VAS by 10.60 mm and superior to placebo (-10.02 mm, p=0.002)	IV lidocaine is effective compared to placebo for neuropathic pain	Anesth Analg 2005
Pain Clinics	Neuropathic Pain	58	Patch 5%	1-4 patches every 12 hours	Placebo	31% of lidocaine patients had a 50% reduction in VAS vs 8.6% placebo and 41% of lidocaine patients had at least a 30% reduction in VAS vs 8.1% placebo	Lidocaine is an effective adjuvant option for focal neuropathic pain	Pain 2003
ED	Postherpatic neuralgia	24	IV	1 mg/kg or 5 mg/kg	Placebo	All 3 infusions reduced VAS score from baseline	Lidocaine IV reduced pain, but no difference seen in dose or placebo	J Pain Symptom Manage 1999

Assessment Question

Which of the following is FALSE about lidocaine for pain management?

A. Intravenous lidocaine has been shown to be efficacious when administered for acute lower back pain
B. Lidocaine doses of 1.5 mg/kg (about 100 mg) have been shown to be safe with few side effects
C. Much of the data for intravenous lidocaine in the ED comes from small studies and case series

Assessment Question

JA is a 53 year old female presenting to the ED with 9/10 pelvic pain. A CT scan reveals a new nephrolithiasis in her ureter. JA's past medical history is significant for back pain and opioid abuse (sober for 3 years). Allergies list GI bleeding with NSAID use. Home medications include: acetaminophen 1000 mg every 6 hours as needed for back pain and omeprazole 20 mg daily. Given her history, JA requests avoiding anything with the potential for addiction.

Which of the following options would be best for JA's pain?

A. Morphine 4 mg IV once
B. Ketamine 0.3 mg/kg IV once
C. Lidocaine 1.5 mg/kg IV once
D. Ketorolac 10 mg IV once

Future Directions

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Key Takeaways

- Consider non-opioid analgesia first, even if moderate-severe pain
  - Acetaminophen 1000 mg + ibuprofen 400 mg
  - Ketorolac at limited doses (10 mg)
- Subdissociative ketamine is an effective alternative to opioids for pain
  - Administer over 15 minutes to reduce adverse effects
- Lidocaine is effective for renal colic and neuropathic indications but needs more research
  - While safe, recommend cardiac monitoring

Questions?

- Email: Craig.P.Worby@hitchcock.org

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