

Non-opiate Alternatives for Treating Acute Pain in the Emergency Department

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Disclosure

- I have no actual or potential conflicts of interest to disclose.

Objectives

- Discuss opiate prescribing trends and documented abuse in the United States
- Assess the current literature on non-opiate options for different types of acute pain
- Describe ways other institutions have implemented non-opiate pain management options in the emergency department

Opioid Epidemic

Overdose Deaths

- Overdose rates were highest among people aged 25 to 54 years
- Rates higher among non-Hispanic whites and American Indians or Alaskan Natives, compared to non-Hispanic blacks and Hispanics
- Men were more likely to overdose, but the mortality gap between men and women is closing

Additional Risks

- In 2014, almost 2 million Americans abused or were dependent on prescription opioids
- As many as 1 in 4 people who receive prescription opioids long term for noncancer pain in primary care setting struggles with addiction
- Over 1000 people are treated in emergency departments for misusing prescription opioids every day

Opioid Prescription Rates

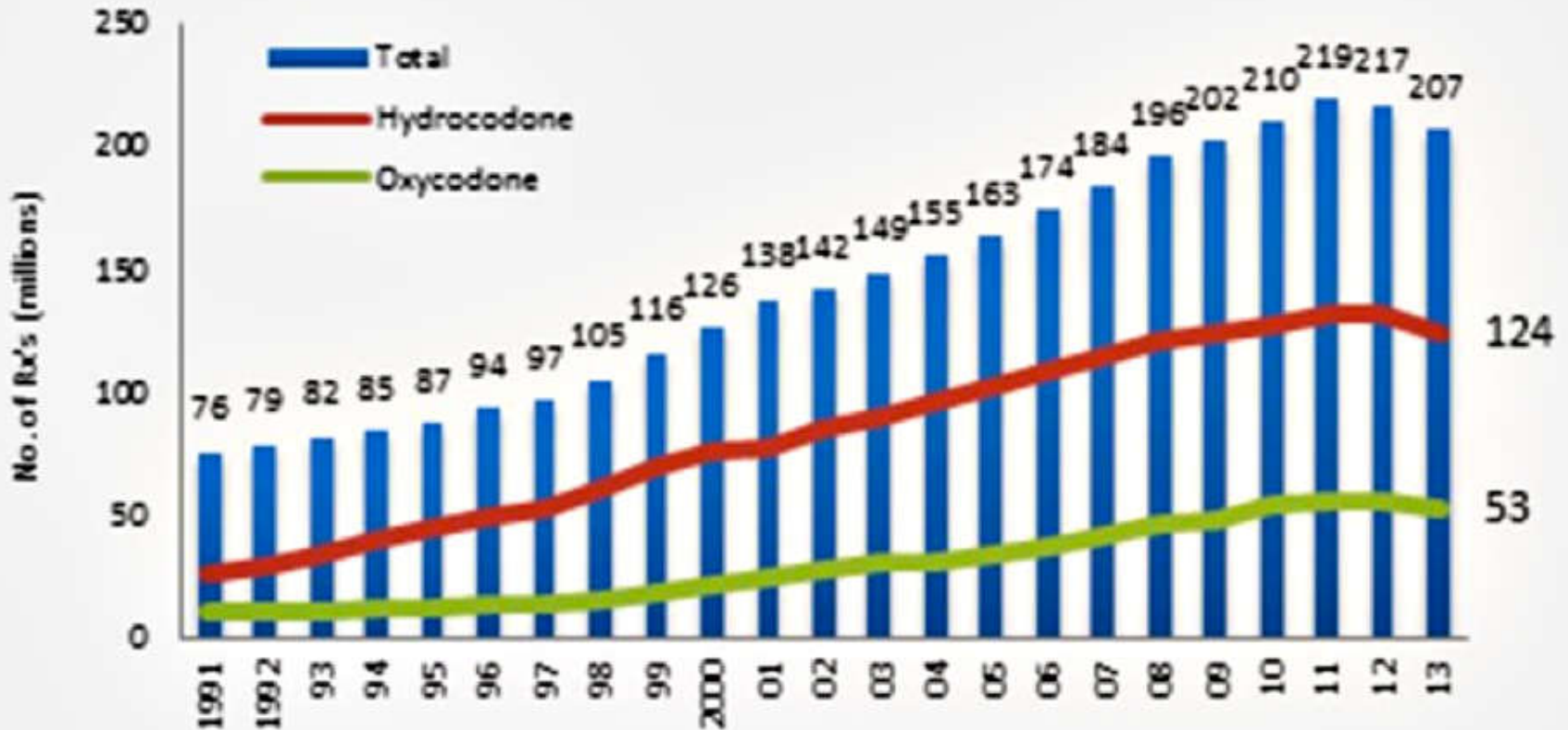


Figure 1. Opioid Prescriptions Dispensed by US Retail Pharmacies. IMS Health, Vector One: National, Years 1991-1996, Data Extracted 201. IMS Health, National Prescription Audit, Years 1997-2013, Data Extracted 2014.

How Did We Get Here?

Vital Signs

1. Body temperature
2. Pulse rate
3. Respiratory rate
4. Blood pressure
5. Pain Assessment

The 5th Vital Sign

- American Pain Society introduced the phrase in 1996
- Initiative that emphasizes that pain assessment is as important as assessment of the standard 4 vital signs
- Veterans Health Administration included this in their national pain management strategy
- Adopted by the Joint Commission on Accreditation of Healthcare organization (JCAHO) in Standard RI 1.2.8, 2000 and PE1.4, 2000

Does It Work?

Measuring Pain as the 5th Vital Sign does Not Improve Quality of Pain Management

Table 3. Comparison of Care Between Preintervention and Postintervention Groups

Process Indicator	Preimplementation Quality Rate (%) (n=300)*	Postimplementation Quality Rate (%) (n=300)*	P-Value for Pre/Post Comparison [†]
Subjective assessment	49.3	48.7	.866
Exam for pain complaint	26.0	26.0	.924
Other orders to assess pain	11.7	8.3	.171
New pain prescription	8.7	11.0	.331
Change existing pain meds	6.7	4.3	.208
Any other form of treatment	11.7	13.7	.461
Follow-up plan made	10.0	8.7	.567
Composite evaluation	50.0	50.3	.867
Composite treatment	26.0	28.3	.517
Any attention to pain	52.0	53.0	.802

*Variables have the potential to be affirmative in 100% of patients, regardless of the presence or absence of pain.

[†]P > .05 for all comparisons between pre and post groups using random effects (to account for physician clustering) logistic regression analysis; post hoc analysis indicated that a minimal difference of 6% to 10% could be detected between the groups.

Measuring Pain as the 5th Vital Sign

- Over one-fifth of patients who reported substantial pain had no attention to pain in the medical record
- Fewer than half of the patients had therapeutic interventions at the time of visit
- Additional interventions are needed to improve providers awareness of patient's pain

JCAHO's Response

Joint Commission Statement on Pain Management

April 18, 2016

Statement on pain management from David W. Baker, MD, MPH, FACP, Executive Vice President, Healthcare Quality Evaluation, The Joint Commission:

Addressed and Explained 5 misconceptions of JCAHO's standards

1. Endorses pain as a vital sign
2. Requires pain assessment for all patients
3. Requires that pain be treated until pain score reaches zero
4. Standards push doctors to prescribe opioids
5. Pain standards caused a sharp rise in opioid prescriptions

JCAHO's Response

1. Does not endorse pain as a vital sign
2. "Pain assessed in all patients" was eliminated in 2009 from all programs except Behavior Health Care Accreditation. JCAHO wants each hospital to have their own policies on patient's pain assessment
3. Advocated for individualized approach and not dependent on a set algorithm according to pain scores
4. Current standards do not push clinicians to prescribe opioids.

5. The JCAHO pain standards caused a sharp rise in opioid prescriptions?

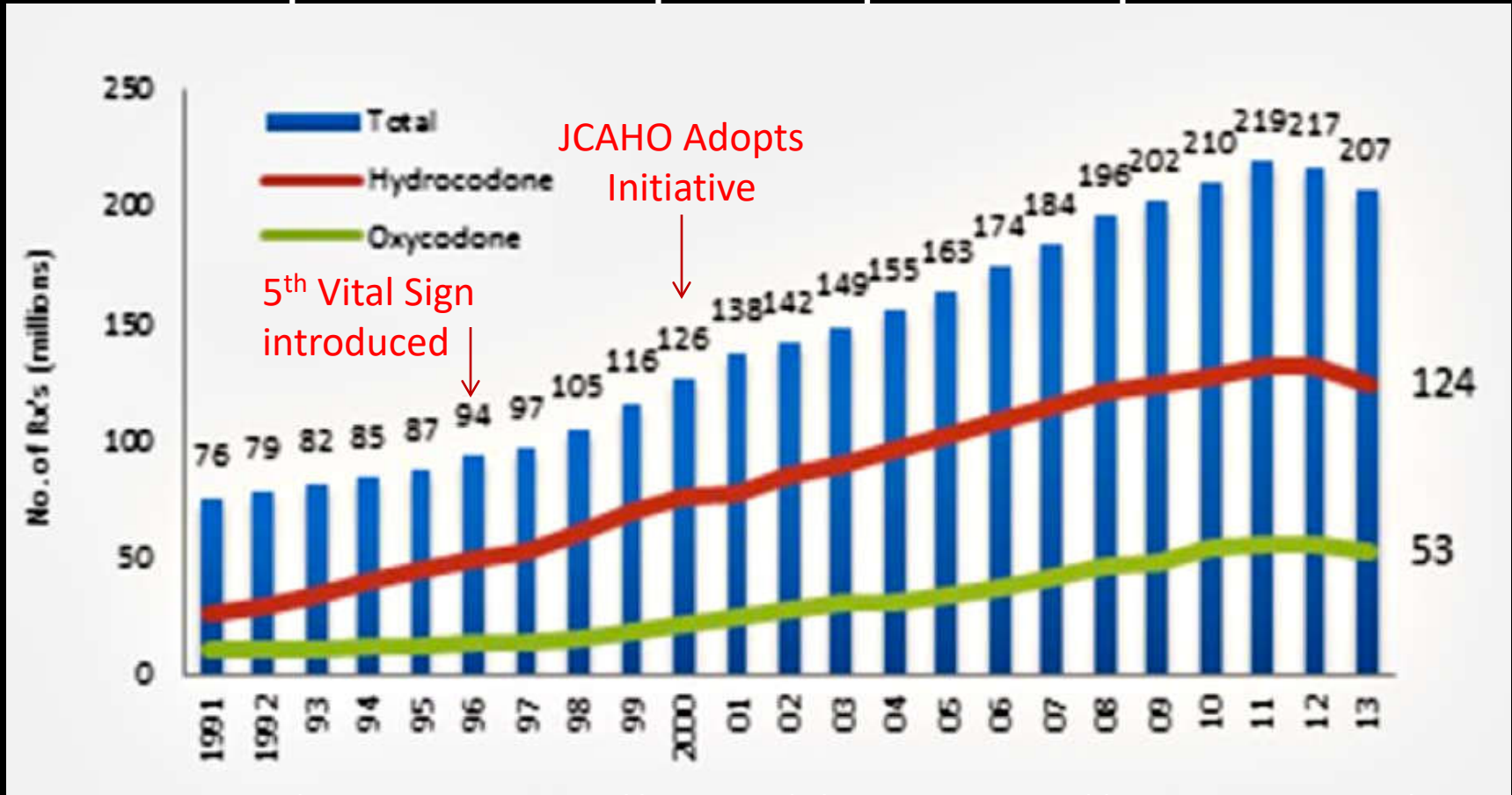
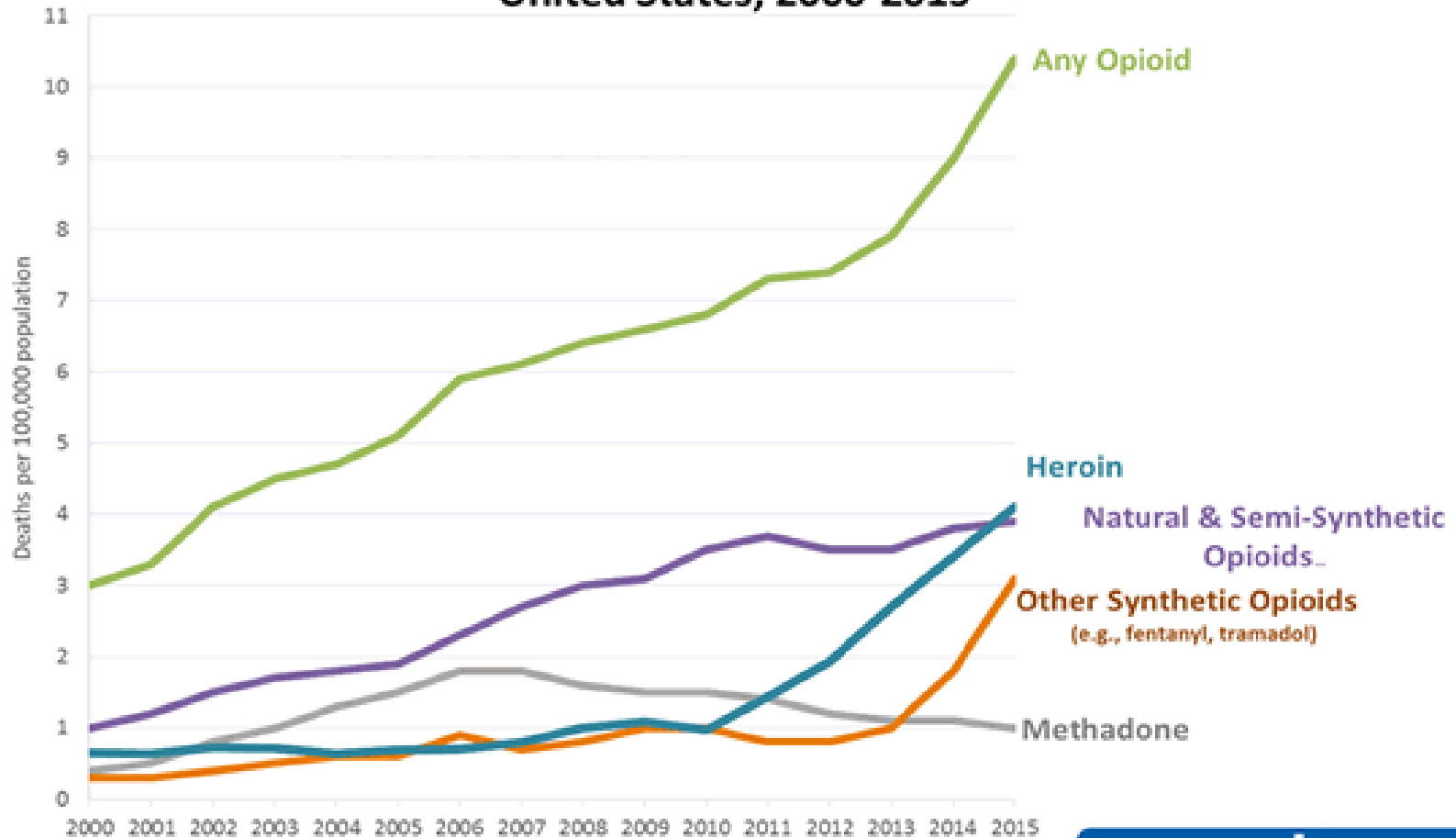


Figure 1. Opioid Prescriptions Dispensed by US Retail Pharmacies. IMS Health, Vector One: National, Years 1991-1996, Data Extracted 2011. IMS Health, National Prescription Audit, Years 1997-2013, Data Extracted 2014.

Most Common Overdosed Opioids

- Methadone
- Oxycodone
- Hydrocodone

Overdose Deaths Involving Opioids, by Type of Opioid, United States, 2000-2015



SOURCE: CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA; US Department of Health and Human Services, CDC; 2016. <https://wonder.cdc.gov/>.

www.cdc.gov
Your Source for Credible Health Information

Taking Measures to Combat Opioid Abuse

- Sept. 2016, “Prescription Opioid and Heroin Epidemic Awareness Week”
- Encourage U.S. attorneys to share information across state lines
- The Food and Drug Administration (FDA) announced a \$40,000 prize to encourage software developers to create a mobile app for users to identify and react to an overdose
- The VA would announce funding to support Veterans Drug court to encourage judges to order treatment for veterans with substance abuse problems

Taking Measures to Combat Opioid Abuse

- Hospital emergency department (ED) institute “opioid free” periods
- Development of an opioid reduction protocol in an emergency department

Common Locations of Pain in the ED

- Abdominal
- Chest
- Headache, pain in head
- Back
- Not referable to a specific body system

Most Common Prescribed Medications

Given In The ED

1. Promethazine
2. Ketorolac
3. Acetaminophen (APAP)
4. Ibuprofen
5. Morphine
6. APAP/Hydrocodone

Prescribed at Discharge

1. APAP/Hydrocodone
2. Ibuprofen
3. Acetaminophen
4. APAP/oxycodone
5. Amoxicillin
6. Cephalexin

Non-opioid Alternatives

- NSAIDs
- Intranasal Ketorolac
- Intravenous Acetaminophen
- Ketamine
- Propofol
- Intravenous Lidocaine

Non-Steroidal Anti-Inflammatory Drugs

- Provide analgesia
- Reduce inflammation by preventing the synthesis of thromboxanes and prostaglandins through inhibition of cyclo-oxygenase-1 (COX-1) and COX-2 enzymes
- Recommended mainstay treatment for patients with osteoarthritis or other types of musculo-skeletal pain

Two Types

- Non-selective
- COX-2 inhibitors

Non-Steroidal Anti-Inflammatory Drugs

Non-Selective

- Ibuprofen
- Naproxen
- Ketorolac IV/PO/IN?

Can be purchased over-the-counter (except ketorolac)

COX-2 Inhibitors

- Celecoxib
- Meloxicam
- Piroxicam

Require a prescription

Non-Steroidal Anti-Inflammatory Drugs

- Risk factors for Gastrointestinal injury
 - Age > 65
 - History of gastrointestinal bleeding
 - Use of medications such as aspirin, warfarin, or oral corticosteroids
 - History of myocardial infarction, chronic renal insufficiency, chronic liver disease, poorly controlled hypertension, or diabetes
 - Short term use (i.e. < 1 month)
 - Use of maximum dose NSAIDs
 - Presence of Helicobacter pylori infection
- Increased risk of myocardial infarction, naproxen appears to be less harmful
- Increase plasma potassium concentration
- Decrease renal function in patients taking angiotensin-converting enzyme inhibitors (ACE-I) or angiotensin receptor blockers (ARB)

Intranasal Ketorolac

Intranasal Ketorolac

- Novel delivery method
- Thought to improve tolerability and limit adverse reactions
- Shown to provide significant reduction in postoperative pain, similar to intravenous or intramuscular forms
- One spray (15.75mg) in each nostril every 6 - 8 hours, maximum of 4 doses per day



Acute Pain Management with IN NSAIDs, Opioids, or Both

- Prospective
- Observational cohort of convenience sample
- Presented with acute musculoskeletal or visceral pain
- Did not require admission
- Comply with daily telephonic follow-up
- Treatment was not directed by the study but by the treating ED clinician
- Patients were discharged with either NSAIDs, opioids, or combination therapy for with a 5 day supply
- IN ketorolac was prescribed to both NSAID and combination group if the physician was comfortable with prescribing to that patient

Acute Pain Management with IN NSAIDs, Opioids, or Both

- Maximum pain scores improved day to day more effectively with a ketorolac based approach
- Self-reported rates of return to work and work effectiveness were higher in the IN ketorolac group than with opioids or combination therapy
- Overall satisfaction was higher with the IN ketorolac based treatment than with opioid monotherapy
- IN ketorolac is a novel delivery approach for short term post-ED outpatient analgesia

Acetaminophen

Mechanism of Action:

- Inhibit the synthesis of prostaglandins in the central nervous system
- Works peripherally to block pain impulse generation
- Produces antipyresis from inhibition of hypothalamic heat-regulating center

Acetaminophen

- Efficacy superior to placebo in treating hip and knee osteoarthritis pain, number to treat between 4 and 16
- Not considered superior to NSAIDs for the treatment of acute osteoarthritis pain

Intravenous (IV) Acetaminophen

Indication

- Management of mild to moderate pain
- Management of moderate to severe pain with adjunctive opioid analgesics
- Reduction of fever

Dosage

- 1000mg IV every 6 hours
- 650mg IV every 4 hours to a maximum of 4000mg per day



Intravenous (IV) Acetaminophen

- 14 publications of IV APAP use for acute pain in the ED
- 3 trials showed significant pain score reduction (2/3 were compared to IV morphine, the other piroxicam)
- 8 randomized trials showed no detectable differences in pain scores
- 4 trials, the use of rescue analgesia was fewer in the IV APAP group versus the comparator
 - Of those trials, only one detected a significant decrease in the number of patients who required rescue opioids, favoring IV APAP (17/54 (31%) patients in IV APAP vs 30/54(55%) patients in IV morphine)

Intravenous (IV) Acetaminophen

Conclusion

- Limited evidence to support the use of IV APAP as the primary analgesic for acute pain
- There are no known trials that evaluate a cost-benefit analysis on the use of IV APAP

Ketamine

Indications

- Anesthesia/sedation
- Analgesia
- Depression

Mechanism of Action

- Non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor

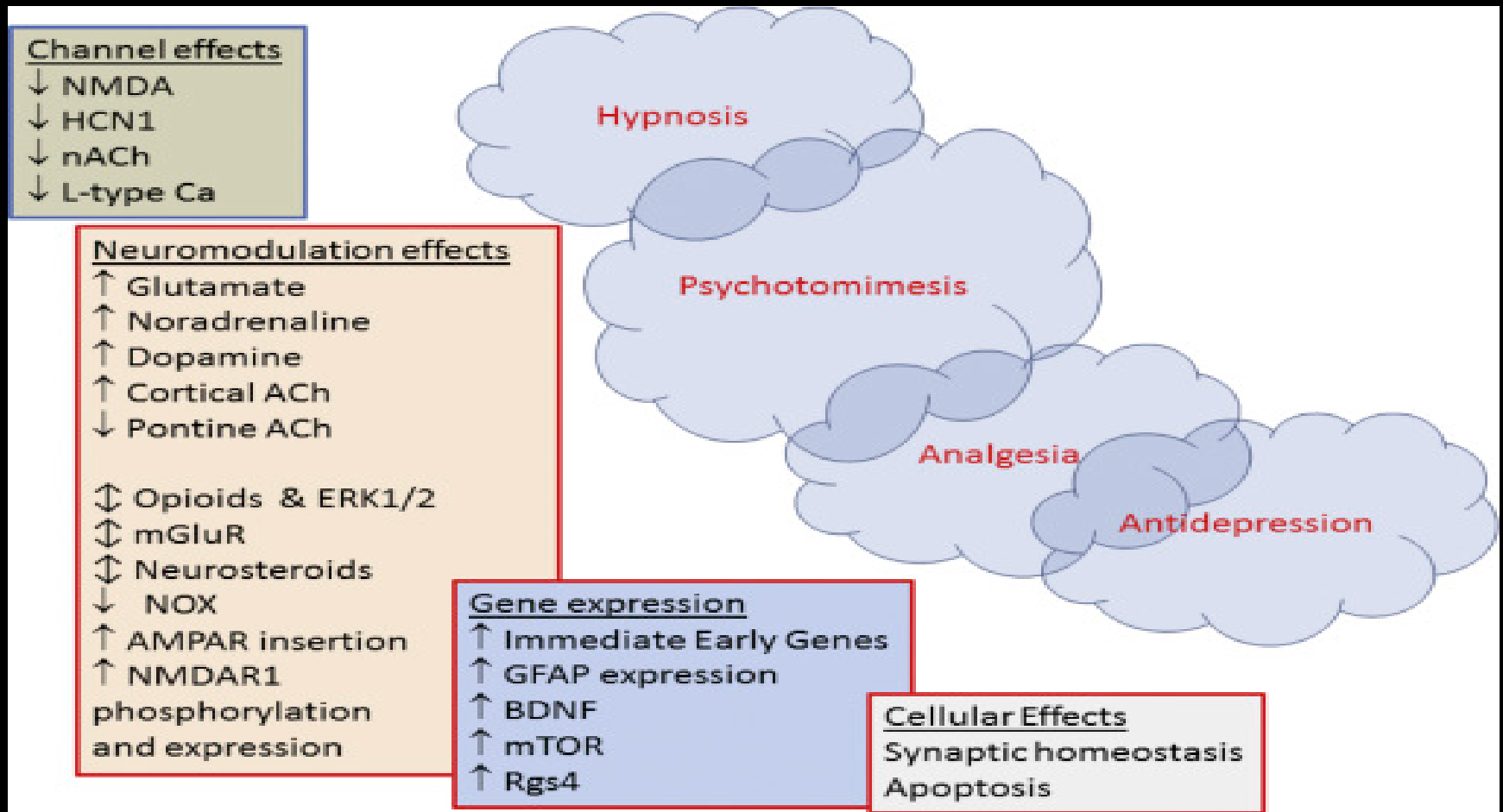


Ketamine

Dissociative anesthesia

- Hypnosis, which includes psychotmimetic affects at low concentrations
- At higher concentrations, increased sedation and unconsciousness
- Intense analgesia (anti-nociception)
- Increased sympathetic activity
- Maintenance of airway tone and respiration

Ketamine



Ketamine

Induction of Anesthesia Dose

- 6.5 – 13mg/kg intramuscular (IM)
- 1 – 4mg/kg intravenous (IV)

Maintenance of Anesthesia Dose

- 0.1 – 0.5mg/minute
- Supplemental dose of one-half to the full induction dose

Ketamine

Subdissociative Dose

- 0.1 – 0.6mg/kg as an adjunct dose to opioid analgesics
- Shown to confer potent, opioid sparing effects and to provide analgesia for pain that is poorly controlled by opiates

Ketamine vs Morphine

Design

- Prospective
- Randomized
- Double blind
- Compared safety and efficacy of ketamine with morphine for acute pain
- Randomized by predetermined randomization list

Inclusion

- Adults 18-55
- Acute abdominal, flank, back, or musculoskeletal
- Pain score of 5 or more on the 11 point numeric rating scale

Exclusion

- Pregnancy/breastfeeding
- Altered mental status
- Allergy to either drug
- Weight less than 46kg or more than 115kg
- Hemodynamic instability

Ketamine vs Morphine Intervention

- Ketamine 0.3mg/kg in 10mLs of 0.9% sodium chloride (NS)

Or

- Morphine 0.1mg/kg in 10mLs of NS
- Medication was delivered to the nurse in a blinded fashion
- Administered IV push over 3 - 5 minutes

Ketamine vs Morphine

- Both groups show statistically significant reductions in mean pain scores
- No statistical significance between the two groups
- At 15 minutes, more patients showed more resolution of pain in the ketamine group
- No rescue analgesia was needed in either group
- No serious or life threatening adverse events occurred in either group

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)
Complete resolution of pain, No. (%)			
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)
120	9 (22)	9 (21)	1 (-17.7 to 18.8)
Reduction of 3+ NRS, No. (%)			
15	34 (75)	31 (69)	6 (-12.3 to 25.6)
30	33 (73)	31 (69)	4 (-14.7 to 23.6)
60	25 (58)	33 (77)	-19 (-38.5 to 1.3)
90	23 (54)	33 (77)	-23 (-43.3 to -3.2)
120	29 (71)	33 (79)	-8 (-27.0 to 11.3)
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)

NRS, Numeric rating scale.
 *Minutes from time of medication injection.
[†]95% CI -0.77 to 1.05 is based on the SD from the mixed-model regression.

Ketamine vs Morphine

Conclusion

- Subdissociative-dose Ketamine at 0.3mg/kg provides analgesic effectiveness and apparent safety comparable to the of morphine for short term treatment of acute moderate to severe pain in the ED

Propofol

Indications

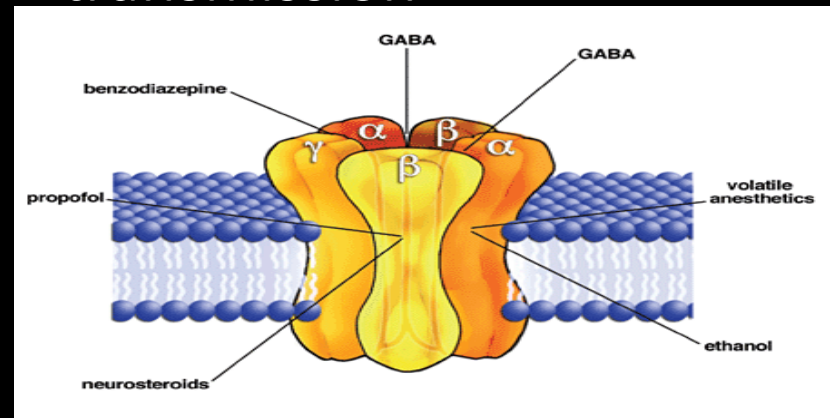
- Anesthesia
- Sedation for intubated mechanically-ventilated patients

Properties

- Quick onset (9-51 seconds)
- Short duration (3-10 minutes)
- Hepatically metabolized

Mechanism of Action

- GABA receptor agonist
- Causes a flux of chloride into the cell
- Produces an inhibitory affect on synaptic transmission



Propofol For Acute Migraines

- Evaluated 4 cases of migraine presenting to the ED
- All 4 failed outpatient treatment

Intervention

- Propofol 1mg/kg IV push over 1 minute until patient fell asleep
- Placed on a cardiac monitor
- Received supplemental oxygen by nasal canula
- Attached to an end tidal CO2 monitor
- Had one to one nursing care during sedation

Propofol for Acute Migraines

- Two patients had been seen multiple times in the previous 12 months with similar presentation

Table. Pain score and length of stay.

	Initial pain score	Discharge pain score	Propofol dose (mg/kg)	Length of stay (LOS) (hours)	Average LOS prior 3 visits (hours)
Patient 1	9	0	1	2.00	4.4 (SD 0.75, 95% CI 3.5-5.2)
Patient 2	9	0	1	2.75	NA
Patient 3	9	0	1	4.80	NA
Patient 4	8	1	1	2.80	4.3 (SD 0.8, 95% CI 3.4-5.2)

LOS, length of stay; SD, standard deviation; CI, confidence interval, NA, not available

Propofol vs Sumatriptan

- Randomized
- Double blind
- Evaluated 91 patients
- 45 patients received propofol
- 46 patients received sumatriptan
- 1 patient in the sumatriptan group was excluded after severe chest tightness
- Baseline demographics were similar

Inclusion

- Age 18 – 45 years
- Presented with symptoms of a migraine headache

Exclusion

- Pregnancy
- Know or suspected coronary or peripheral vascular disease
- Know allergies to study drugs
- Self reported opium addiction
- Diastolic blood pressure > 105mmHg
- Use of ergotamine or 5-HT serotonin agonists with the 24 hours prior to ED admission

Propofol vs Sumatriptan

Propofol Group

- Normal Saline 0.5mL SC once
- Propofol 30 – 40mg IV once

Then

- Propofol 10 – 20mg IV every 3 to 5 minutes to a max dose of 120mg
- Sedated patient to a Ramsey Score of 3 - 4

Sumatriptan Group

- Sumatriptan 6mg SC once
- Normal Saline 3.5mL IV once

Then

- Normal Saline 1.5mL every 4 minutes to a final dose of up to 7.5mL
- Therapy was repeated in one hour if pain score was reduced by less than 4 points

Propofol vs Sumatriptan

- Pain was significantly lower 30 minutes after treatment in the propofol group
- Recurrence rate and need for anti-emetic therapy were significantly lower in the propofol group
- Symptom improvement were similar between both groups
- Chest tightness and rash at site if injection were significantly lower in the propofol group

Table 2. Pain Intensity and Response to Therapy in the Patients

Outcome Measurement	Groups		P Value
	Sumatriptan	Propofol	
Pain intensity before treatment	8.71 ± 1.20	9.09 ± 1.02	0.111
Pain intensity 30 minutes after treatment	3.69 ± 2.55	2.62 ± 2.12	0.034
Pain intensity 1 hour after treatment	2.36 ± 2.31	2.69 ± 2.63	0.53
Pain intensity 2 hours after treatment	1.36 ± 1.96	1.62 ± 2.04	0.53
Recurrence within 24 hours of discharge	55.3%	17.1%	0.001
Anti-emetic therapy	33.3%	13.3%	0.045
Response to therapy	80%	84.4%	0.78
Response in first attempt	73.3%	64.4%	0.16

Propofol For Acute Migraines

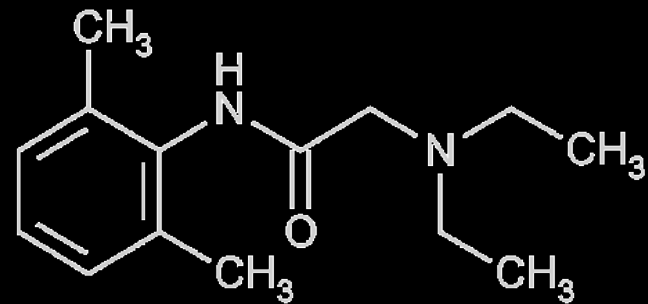
Conclusion

- Shows a promising reduction in headache symptoms using sedative dosing
- Has potential to reduce ED length of stay
- Could be implemented as a rescue therapy option for patients in the ED and hospital setting
- Does require high amount of patient care during treatment
- Potential for patients to develop propofol dependency

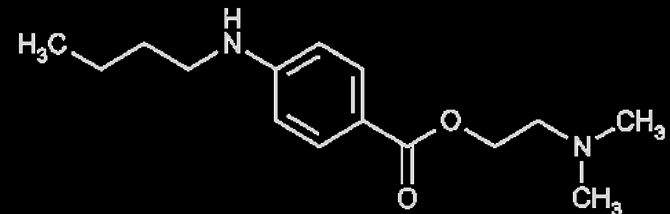
Lidocaine

- Amino amide anesthetic
- Class 1B antiarrhythmic
- Local and regional anesthesia
- Rapid sequence intubation
- Various types of pain
 - Oncological
 - Post-surgical
 - Chronic opioid refractory

Amide (lidocaine)



Ester (tetracaine)



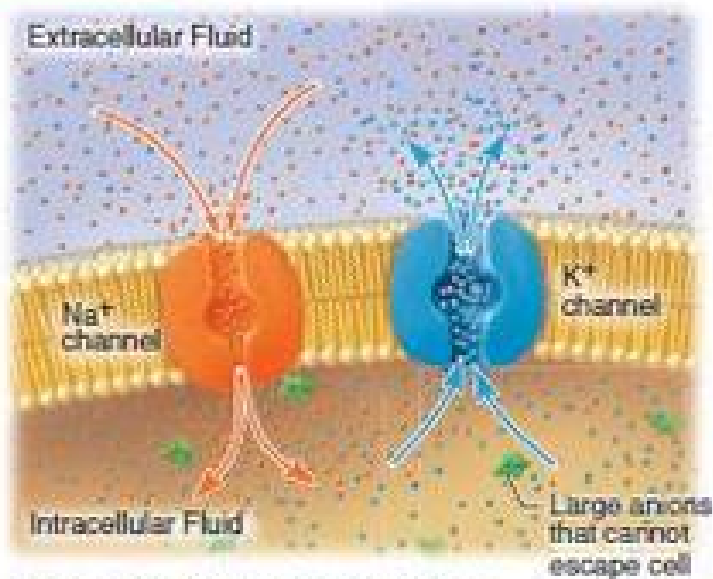
Lidocaine

Mechanism of Action

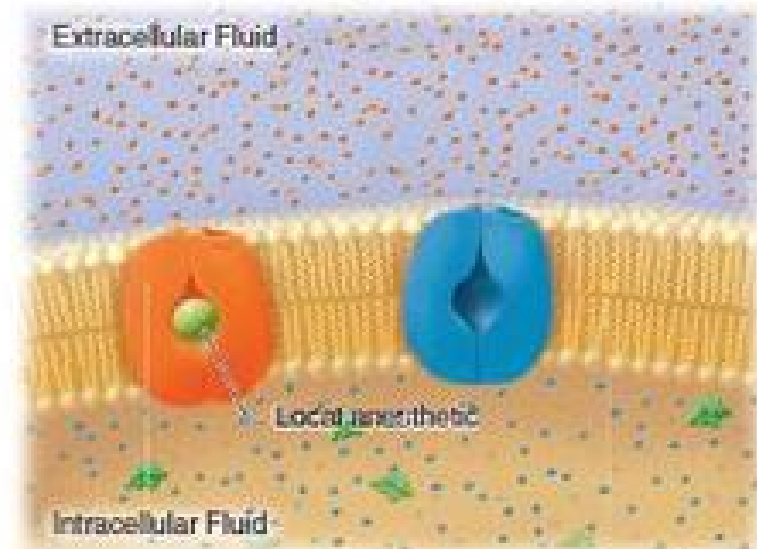
- Blocks the initiation and conduction of nerve impulses by decreasing the neuronal membrane's permeability to sodium ions, which results in inhibition of depolarization with resultant blockade of conduction
- Suppresses automaticity of conduction tissue, by increasing electrical stimulation threshold of ventricle and spontaneous depolarization of the ventricles during diastole by direct action on the tissues (antiarrhythmic)

Lidocaine

Figure 10.1 Action of Local Anesthetics on Nerve Conduction



(a) Depolarization impulse conduction



(b) Local anesthetic blockade of sodium ion channel. No impulse conduction.

(a) Depolarization – sodium ions (Na^+) move in and potassium ions (K^+) move out of the cells.

(b) Local anesthetics enter the sodium channel and prevent sodium ion flow and depolarization.

Lidocaine for Acute Pain in the ED (case series)

- Reviewed 17 patients who received IV lidocaine for acute pain
- Common cause of pain
 - Acute fracture (5)
 - Sickle cell pain crisis
 - Acute back pain
 - Abdominal pain

Lidocaine for Acute Pain in the ED (case series)

- Average dose received was 148.53mg (range 75-400mg)
- Only 7 had their pain assessed before and after administration of lidocaine
- Initial pain scores were 9 – 10 / 10 (VAS)
- Average pain reduction of 3 (VAS) in the 7 patients
- One patient suffered a seizure followed by cardiac arrest after receiving an improperly high dose but was quickly resuscitated

Lidocaine vs Morphine for Renal Colic in the ED

- Prospective
- Randomized double blinded
- 240 patients (73% male)
- Conducted at “Tabriz university of Medical Services,” Iran
- Presented with
 - Flank pain
 - Unilateral abdominal pain radiating to genitalia
 - Urinalysis positive for hematuria
- Received a 12-lead echocardiogram (ECG)
- Metoclopramide 0.15mg/kg IV once

Lidocaine vs Morphine for Renal Colic in the ED

- Group I = Lidocaine 1.5mg/kg IV once
- Group II = Morphine 0.1mg/kg IV once
- VAS pain was measured at 5, 10, 15, and 30 minutes after injection
- Trial was considered “accomplished” when pain score was less than 3 for 30 minutes after last dose

Lidocaine vs Morphine for Renal Colic in the ED

Table 2 Comparison of the mean value of pain reduction between two groups

	Group I	Group II	P-value
primary VAS	9.65 ± 0.88	9.74 ± 0.63	0.365
VAS ₅	3.18 ± 2.27	4.45 ± 2.16	0.0001
VAS ₁₀	1.83 ± 1.59	2.89 ± 2.07	0.0001
VAS ₁₅	1.37 ± 1.32	2.55 ± 1.52	0.0001
VAS ₃₀	1.13 ± 1.15	2.23 ± 1.57	0.0001

- Pain relief was better in the lidocaine group
- More considerable pain relief in the lidocaine group
- No major adverse events reported in either group

Lidocaine Conclusion

- Small but growing body of literature to support the use of intravenous lidocaine for acute pain
- Shows benefit in treating central or visceral pain based on its mechanism
- Lidocaine can be used as an opioid sparing option with similar results
- Can be life threatening if dose is not judiciously monitored

How Can we Implement
These Novel Regimens?

Development of an opioid reduction protocol in an emergency department

- ED opioid free period between 0700 to 1500
- Patients 18 years of age and older with a complaint of pain
- Provided non-opioid analgesics based on the strategies developed
- If additional analgesia was necessary, a rescue dose of an opioid would be prescribed
- Patients were not made aware of the opioid-free shift

Interventions

Type of Pain	Regimen
General Pain Score 1 - 4	<ul style="list-style-type: none"> •Ibuprofen 400-800mg once •Acetaminophen 500-1000mg •Gabapentin 300mg once •Prednisone 50mg once •Naproxen 250-500mg once •Butalbital 50mg, acetaminophen 325mg, caffeine 40mg Once
General Pain Score 5 - 10	<ul style="list-style-type: none"> •Acetaminophen 1000mg IV over 15 minutes •Ketamine 0.3mg/kg (ABW) in 100mL of 0.9% sodium chloride over 10 minutes •Ketamine 0.15mg/kg/hr infusion •Ketorolac 10-15 mg bolous
Nephrolithiases, renal colic	<ul style="list-style-type: none"> •Lidocaine 1.5mg/kg IV over 10 minutes
Intractable migraine headaches	<ul style="list-style-type: none"> •Propofol 10-20mg IV bolous every 10 minutes with a max dose of 1.5mg/kg •Ketamine 50mg/mL 1mg/kg IN once

Pain Relief at 30 and 60 mMinutes After Treatment, by Pain Type

	Acute Pain (n=12)	Chronic Pain (n=5)
Median baseline pain score	7.67	7.4
Median pain score at 30 min	6.0	5.6
Median pain score at 60 min	5.5	5.0
Satisfied with pain relief at 30 min, no. (%)	10 (83)	4 (80)
Satisfied with pain relief at 60 min, no. (%)	10 (91)	3 (75)
Pain reduction of $\geq 30\%$ at 30 min, no. (%)	4 (33)	3 (60)
Pain reduction of $\geq 50\%$ at 30 min, no. (%)	2 (17)	1 (20)
Pain reduction of $\geq 30\%$ at 60 min, no. (%)	4 (36)	2 (50)
Pain reduction of $\geq 50\%$ at 60 min, no. (%)	3 (27)	1 (25)

Results/Conclusion

- None of the patients reported taking opioids at home prior to their visit
- One patient was discharged from the ED with a prescription for opioids for management of acute pain
- Ketorolac IV was the most frequently prescribed for acute pain while ibuprofen was prescribed for chronic
- Only 1 of 17 patients received rescue therapy with morphine (acute pain secondary to renal colic)

Non-opioid Alternatives

- NSAIDs
- Intranasal Ketorolac
- Intravenous Acetaminophen
- Ketamine
- Propofol
- Intravenous Lidocaine

Non-opiate Alternatives for Treating Acute Pain in the Emergency Department

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