

Mu Over Opioids, Non-Opioid Pain Management Coming Through!

Matthew Li, PharmD, MHA, BCPS, BCCCP

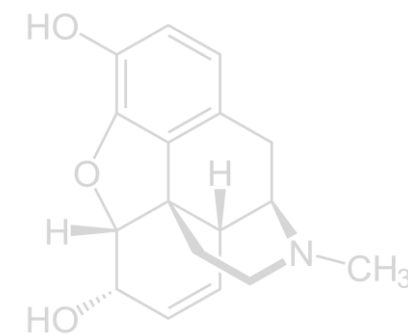
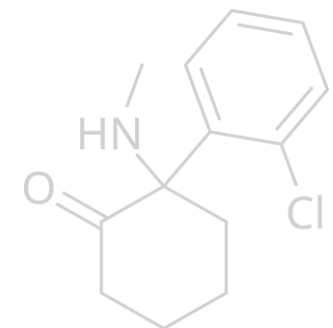
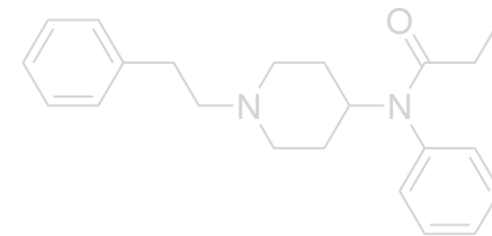
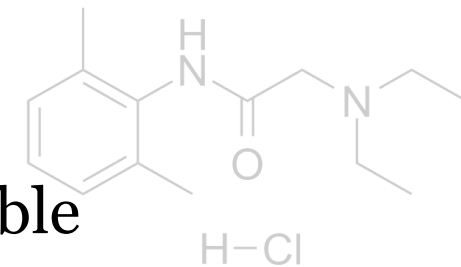
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Disclosure

- The following individual has nothing to disclose concerning possible conflicts of interests related to this presentation
- The unapproved/investigational use of commercial products will be discussed during the educational activity



Objectives

Review

- Review the pathophysiology and etiology of pain in the intensive care unit (ICU)

Highlight

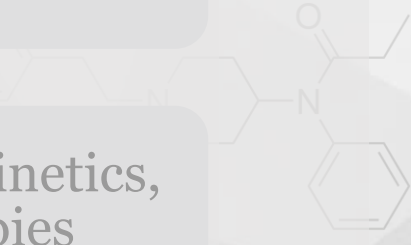
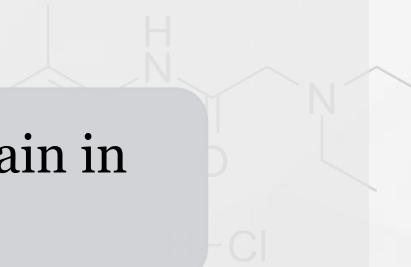
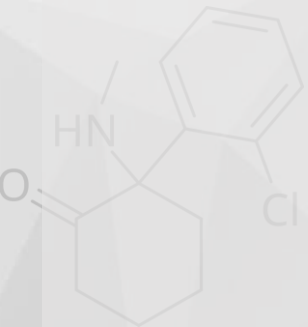
- Highlight the efficacy, safety, and role of opioids in the ICU

Evaluate

- Evaluate the pharmacodynamics, pharmacokinetics, and supporting evidence of non-opioid therapies

Apply

- Apply principles of ICU pain management to a patient case



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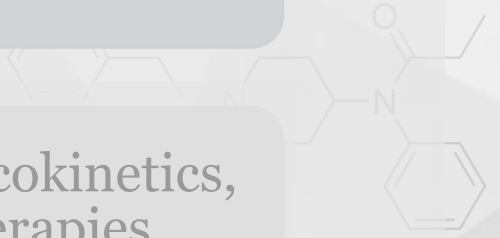
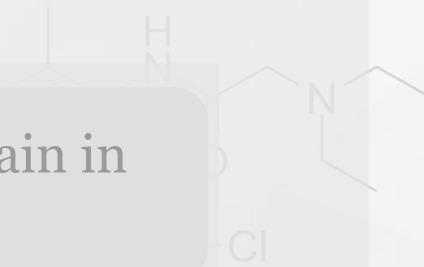
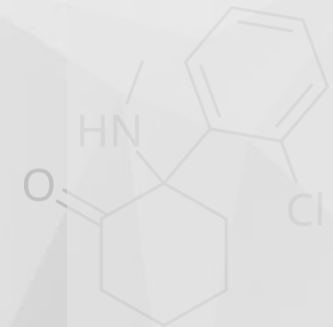
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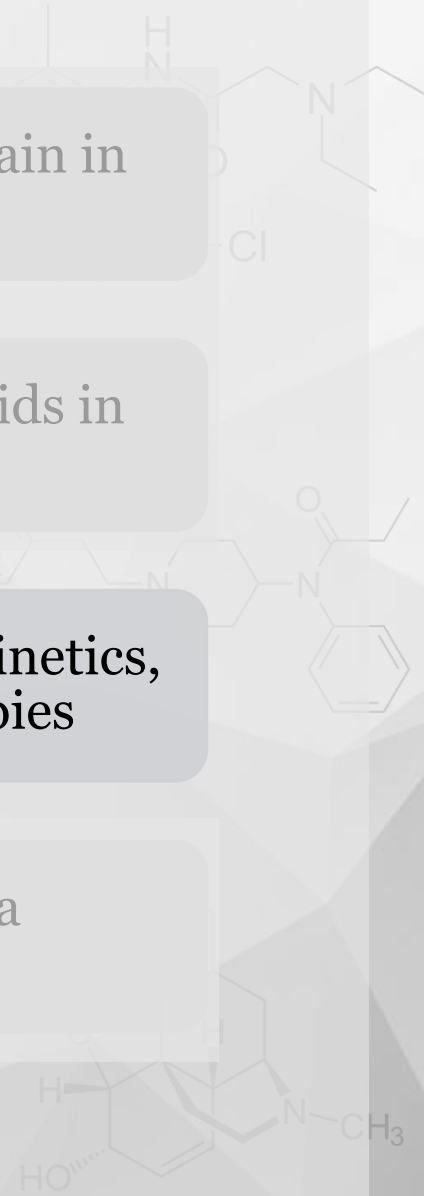
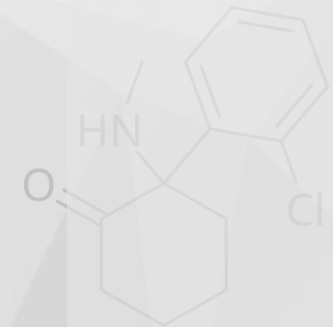
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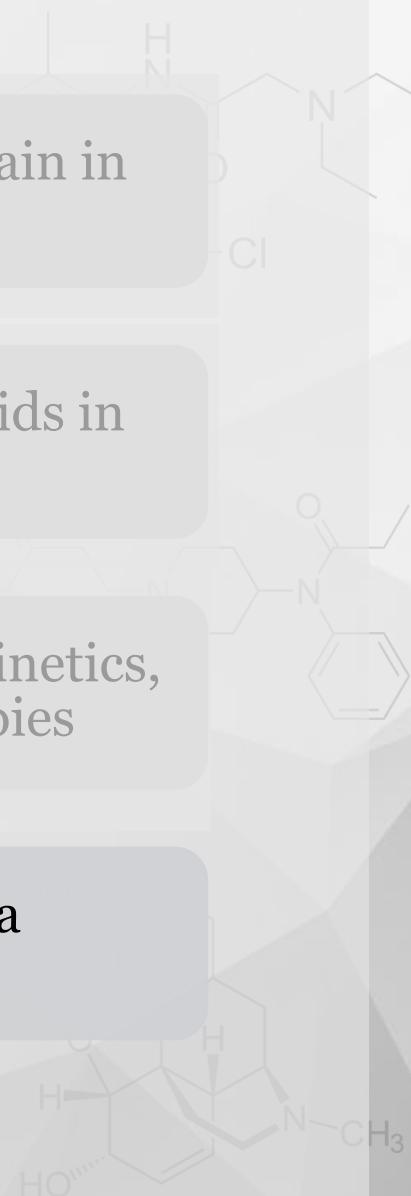
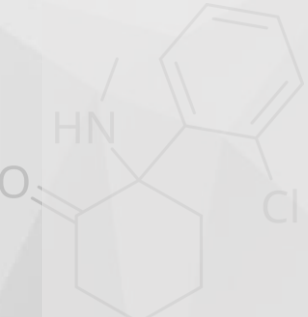
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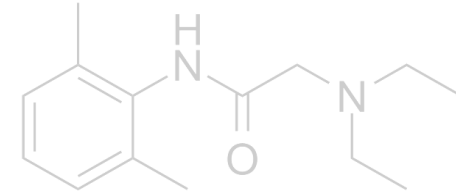
- Apply principles of ICU pain management to a patient case



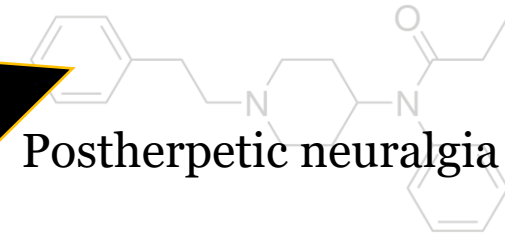
What is Pain?

“An unpleasant sensory and emotional experience associated with actual or resembling that associated with, actual or potential tissue damage”

– International Association for the Study of Pain (2020)



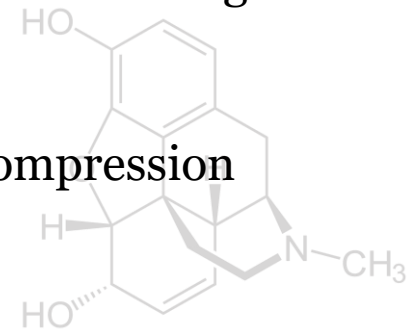
HCl



Postherpetic neuralgia

Trigeminal neuralgia

Spinal root compression



Diabetic

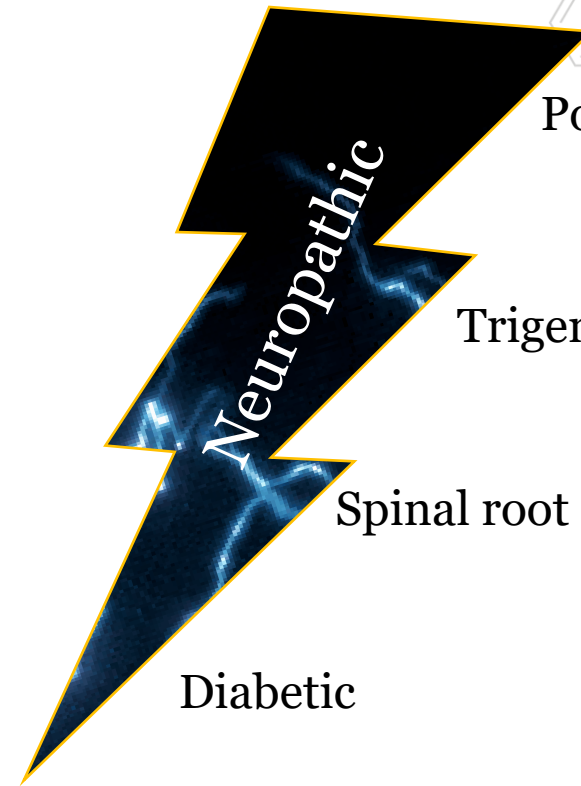


Postoperative pain

Ischemia, infection

Trauma

Neuropathic



Pain: Why Does it Matter?

Inadequate management delays return to work, lowers quality of life, and increases PTSD risk

Untreated Pain



Decreased respiratory function



Increased metabolic demand



Impaired wound healing

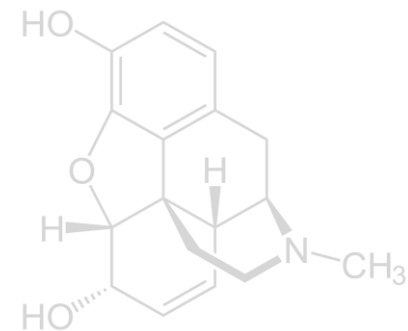


Immunosuppression

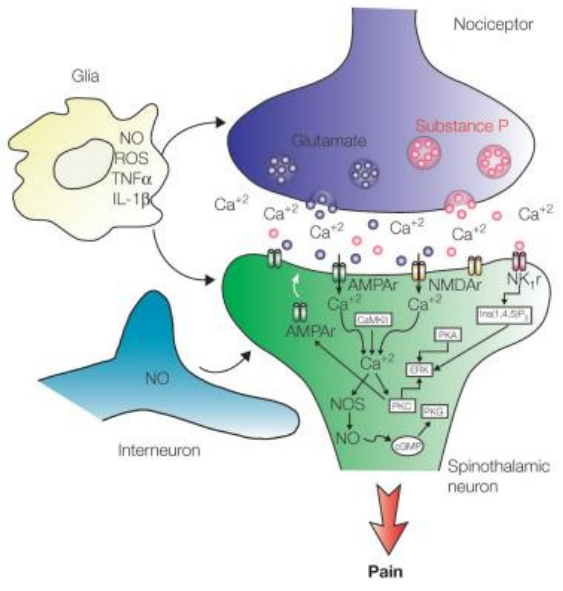
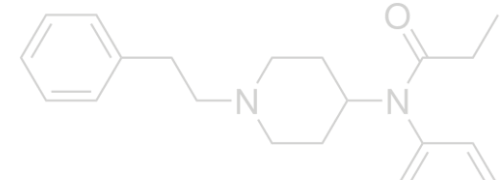
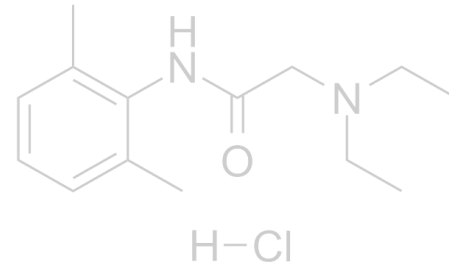
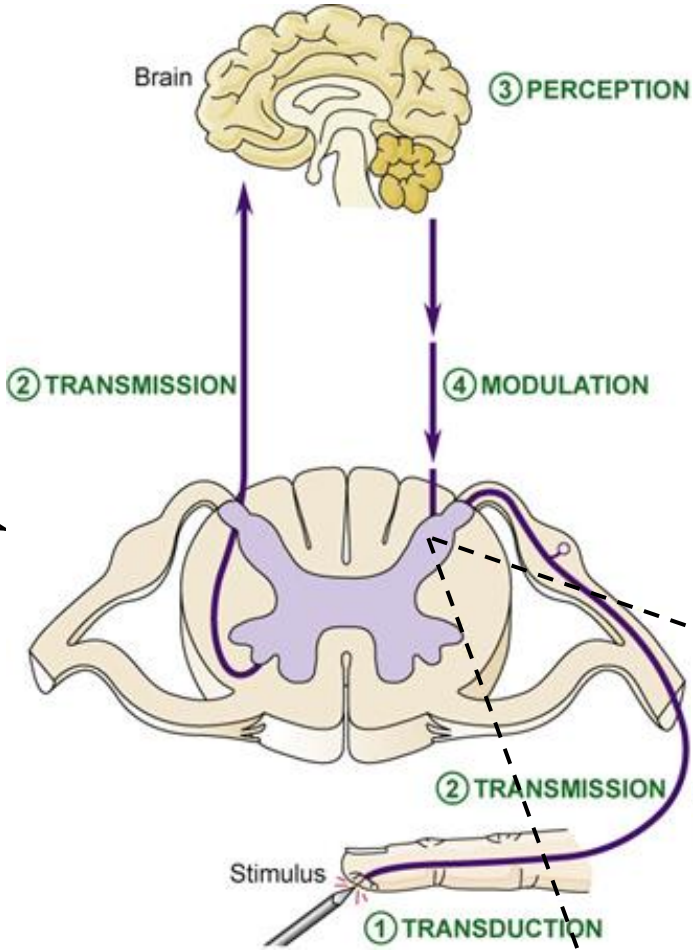
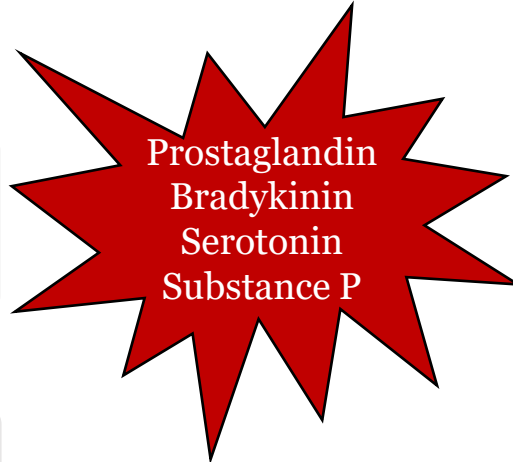
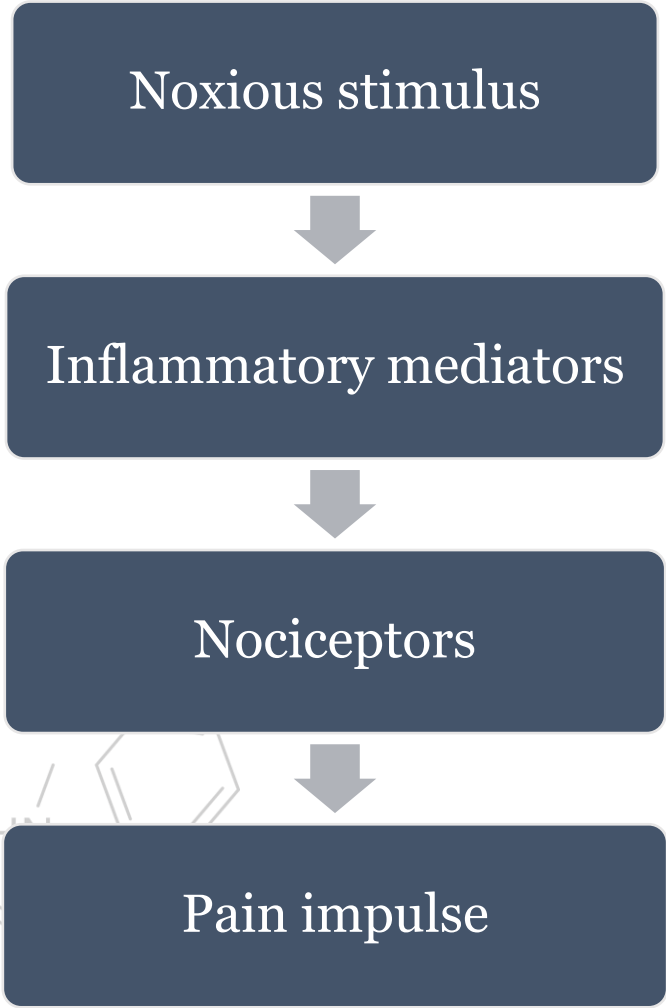


Incidence in ICU

> 50% moderate to severe at rest



Pathophysiology of Pain



Noxious stimulus



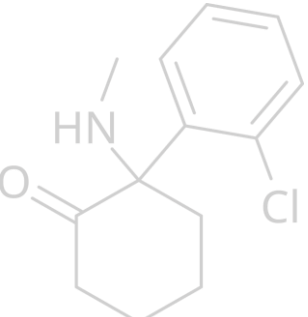
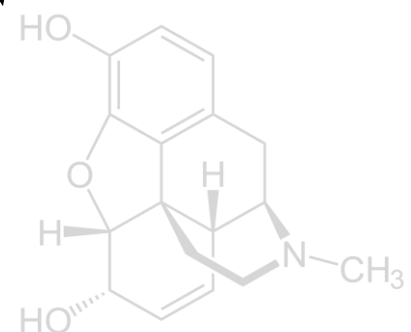
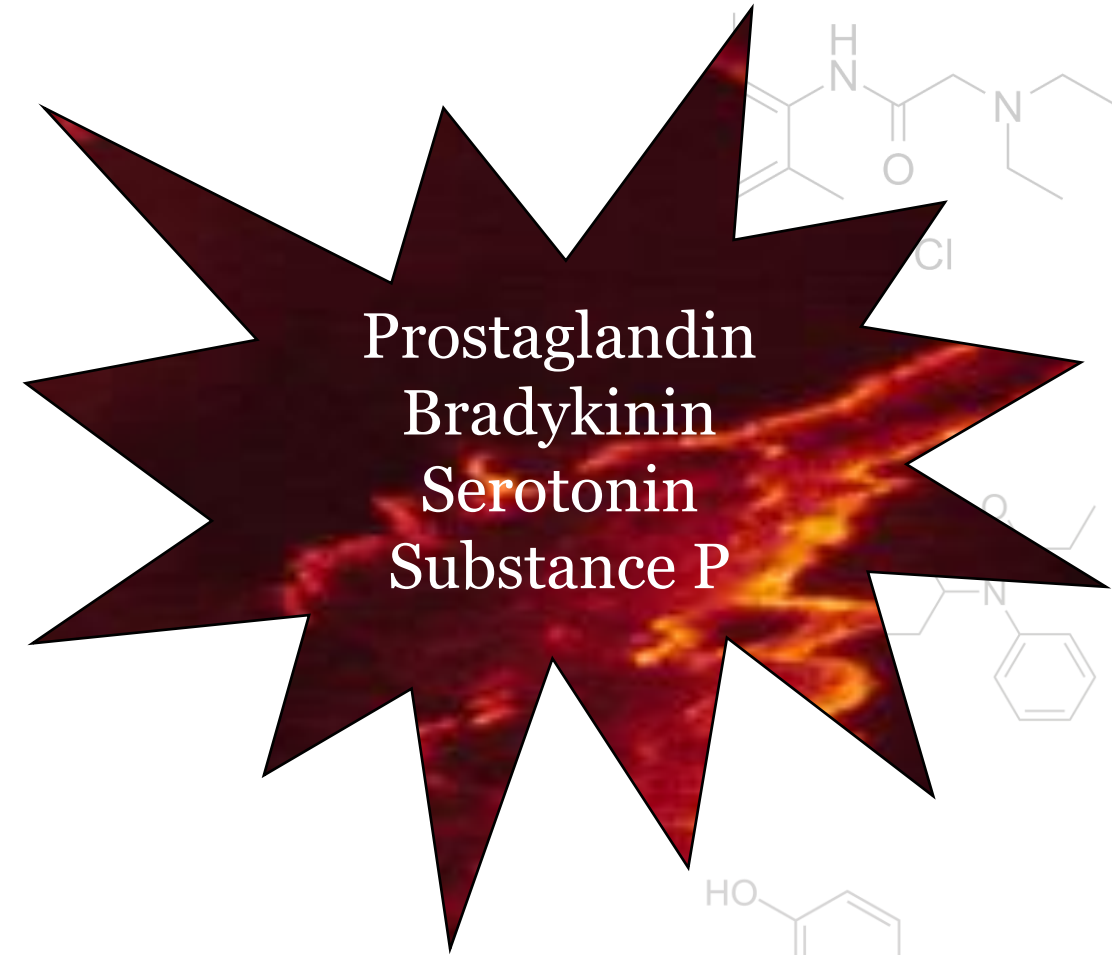
Inflammatory mediators



Nociceptors



Pain impulse



Noxious stimulus



Inflammatory mediators



Nociceptors



Pain impulse

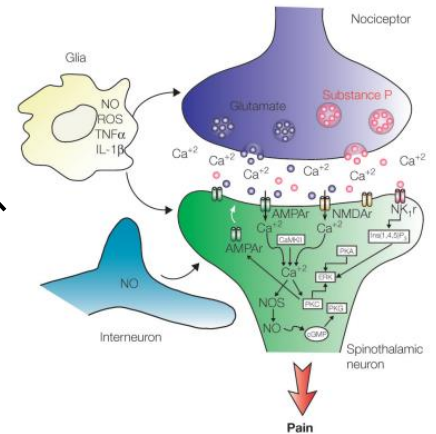
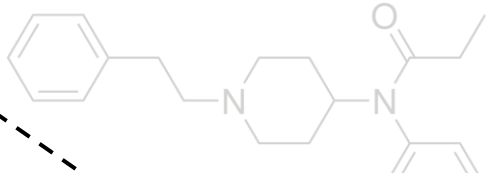
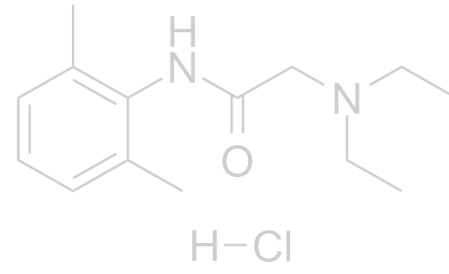
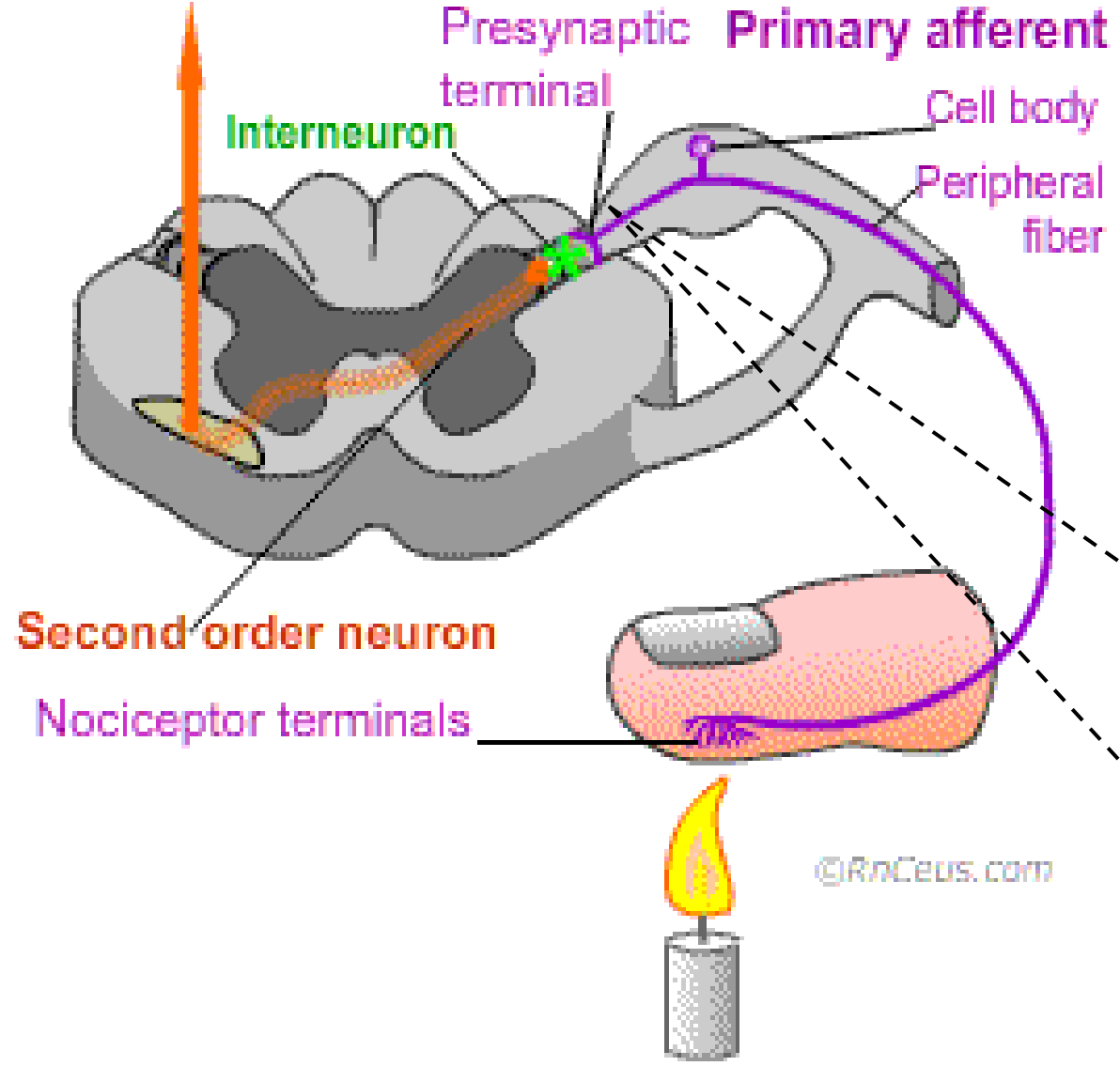
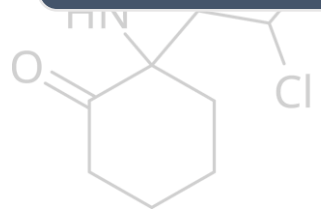


Image source: <https://www.rnceus.com/ages/nociceptive.htm>



Noxious stimulus



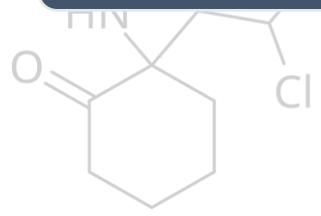
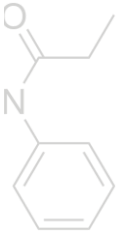
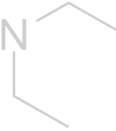
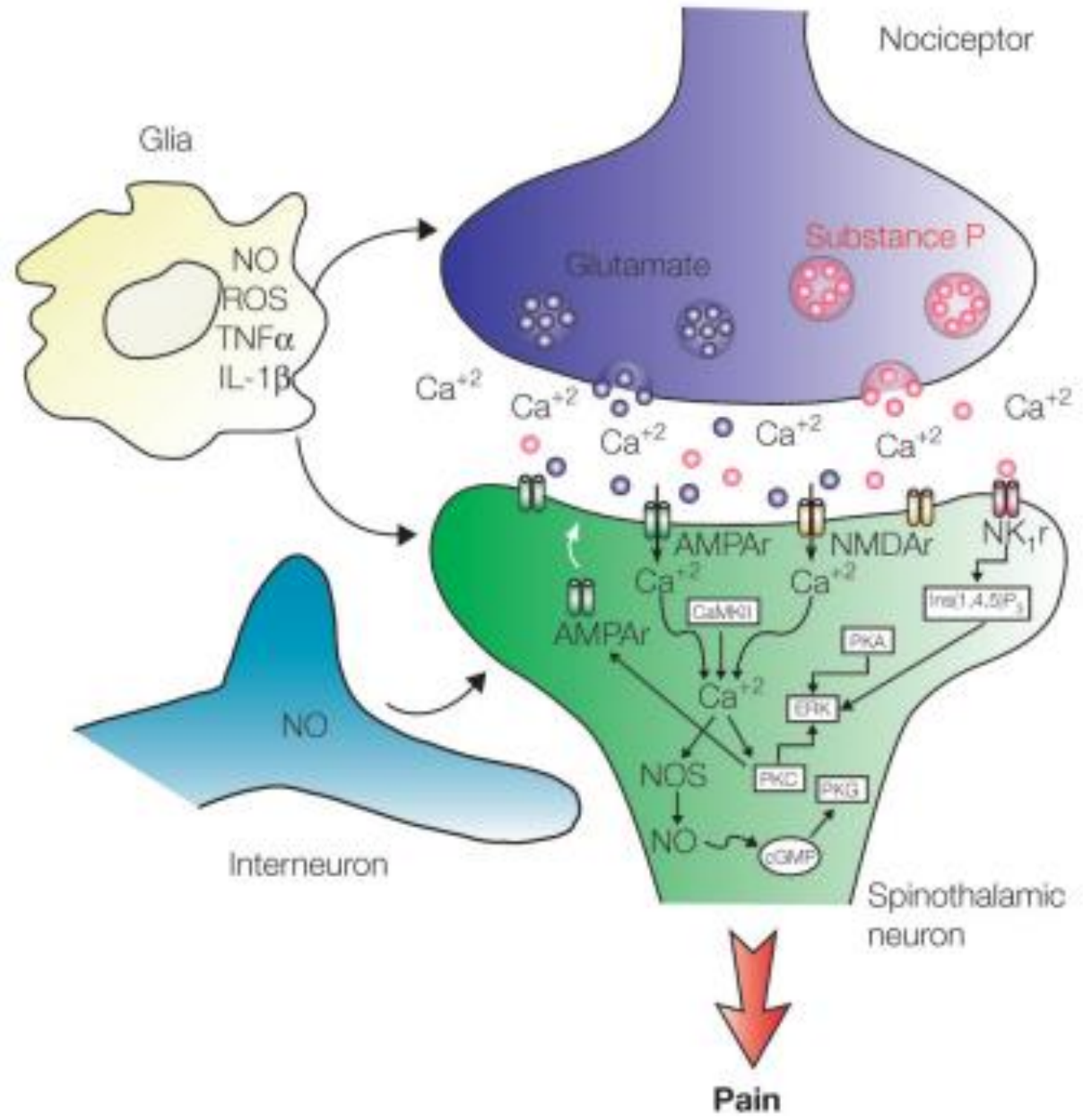
Inflammatory mediators



Nociceptors

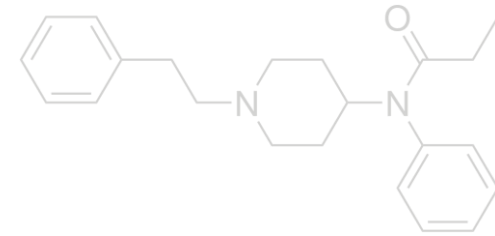
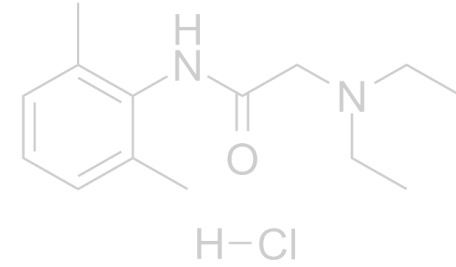


Pain impulse

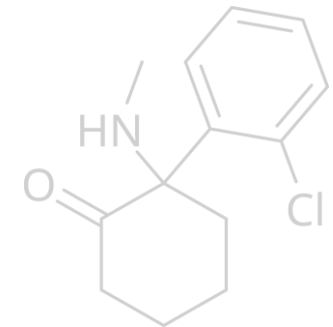
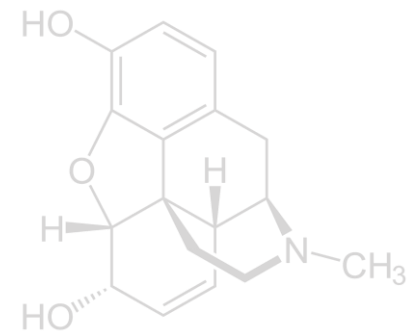
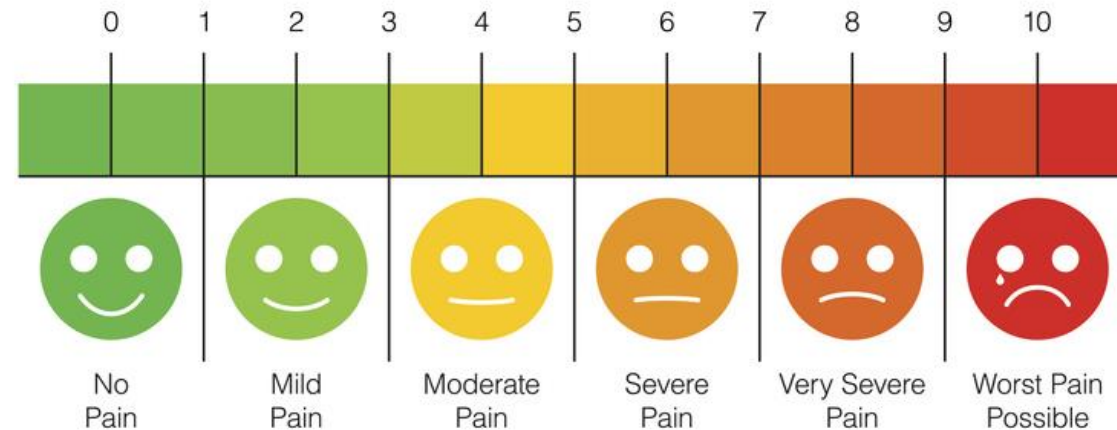


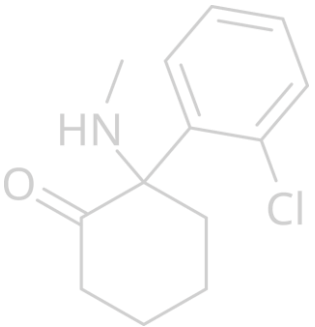
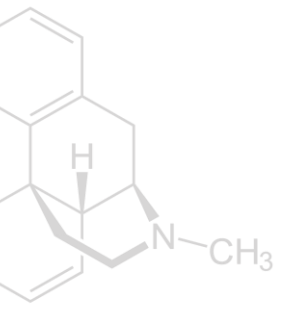
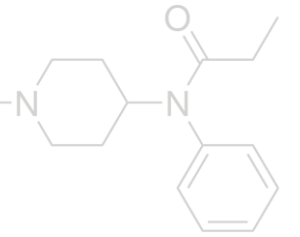
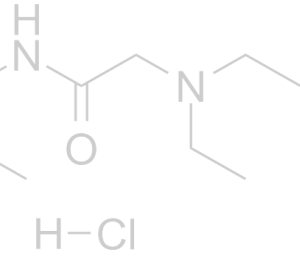
Goal of Pain Management

Achieve **a tolerable pain level** that allows the patient to function



PAIN SCALE

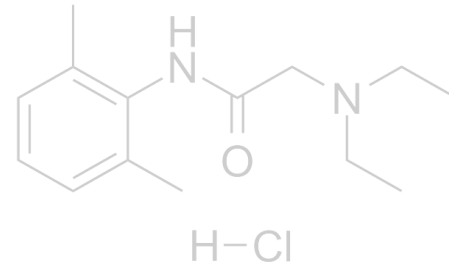






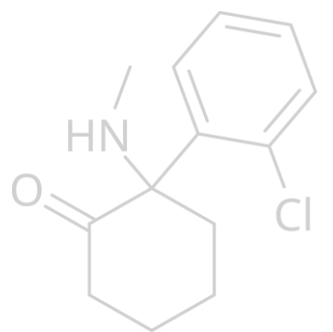
Critical care pain observation tool (CPOT): goal <3

- Vocalization/ Compliance
- Body movements
- Facial expression
- Muscle tension



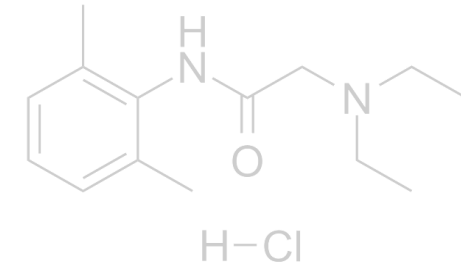
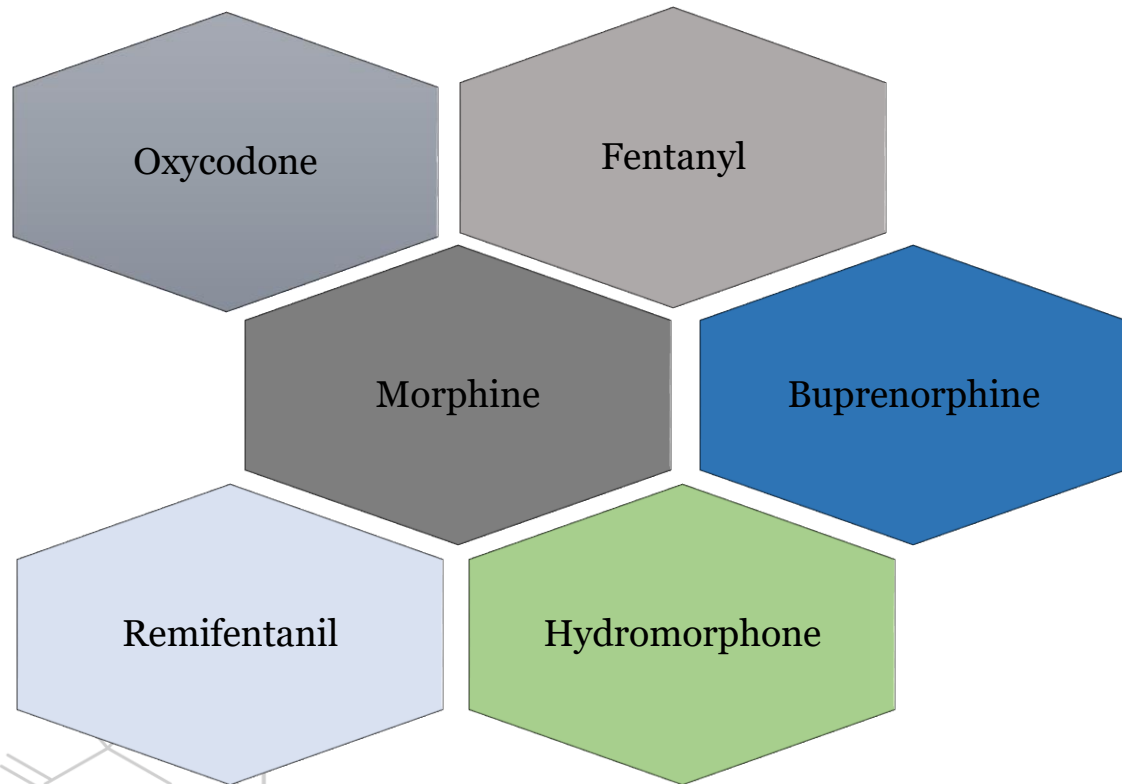
Behavioral pain scale (BPS): goal < 6

Indicator	Score	Description
Facial expressions	1	Relaxed
	2	Partially tightened
	3	Fully tightened
	4	Grimacing
Upper limb movements	1	No movement
	2	Partially bent
	3	Fully bent with finger extension
	4	Permanently retracted
Compliance with mechanical ventilation	1	Tolerating movement
	2	Coughing but tolerating ventilation most of the time
	3	Fighting ventilator
	4	Unable to control ventilation
Total score	__ of 12	

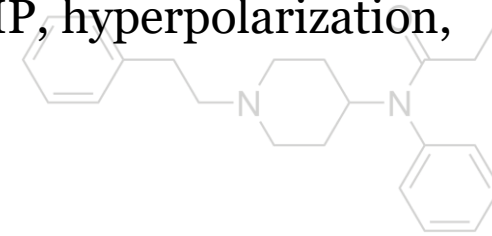


Opioids

- Mainstay of therapy for ICU pain management



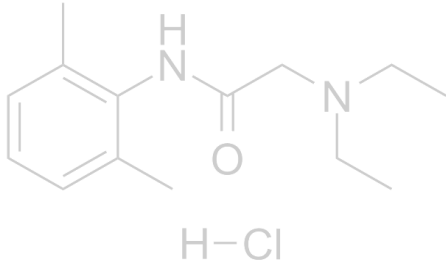
MOA: Binding of an opioid agonist to a G-protein-coupled opioid receptor causes decreased cAMP, hyperpolarization, and reduced neurotransmitter release



Receptor	Action
Mu (M)	Analgesia, dependence, euphoria, respiratory depression, constipation
Kappa (K)	Hyperalgesia, diuresis, dysphoria, negative inotropy/chronotropy
Delta (Δ)	Analgesia, constipation

Multimodal Approach

- Adverse effects of opioids



Central Nervous System



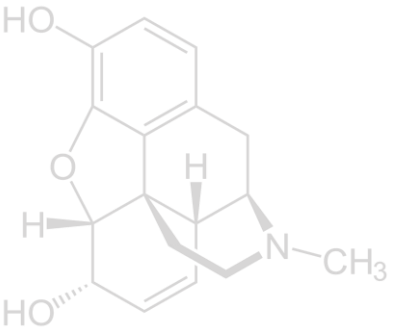
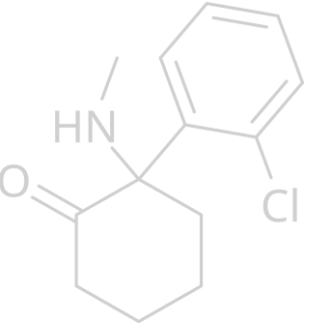
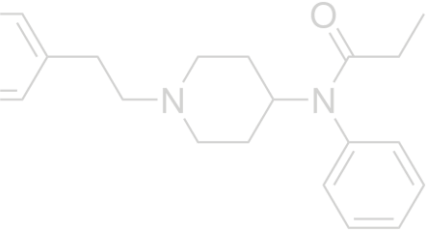
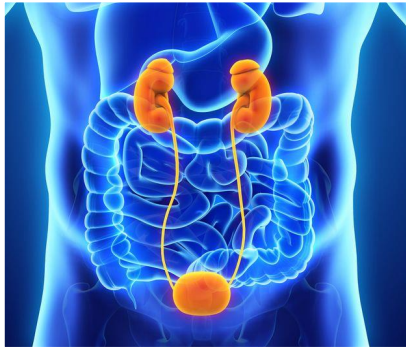
Respiratory



Gastrointestinal



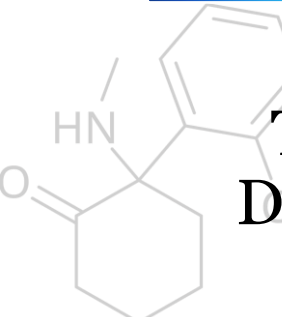
Genitourinary



Central Nervous System



**Sedation
Tolerance
Dependence**



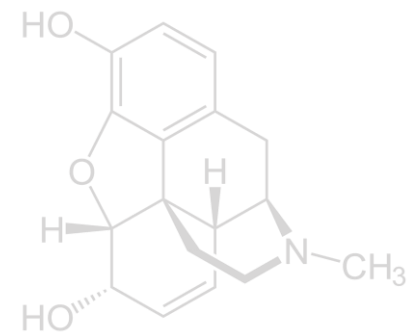
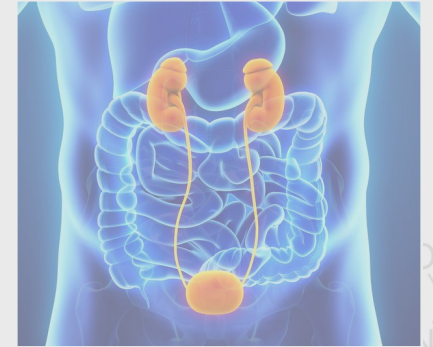
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Gastrointestinal



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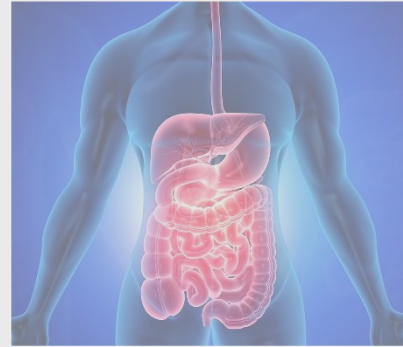
Central Nervous System



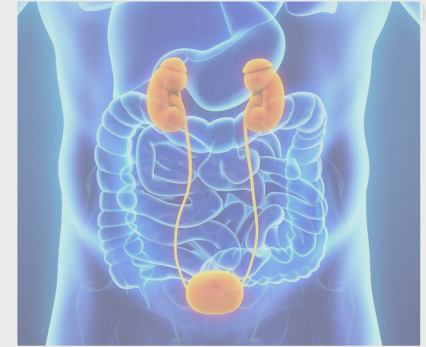
Respiratory



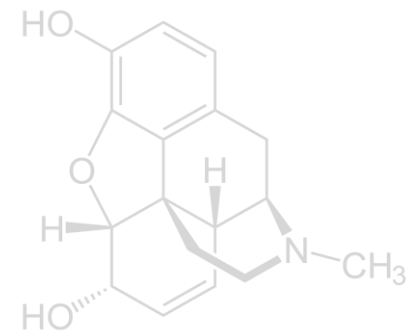
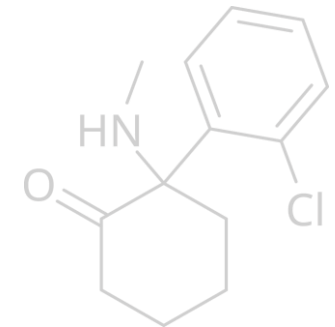
Gastrointestinal



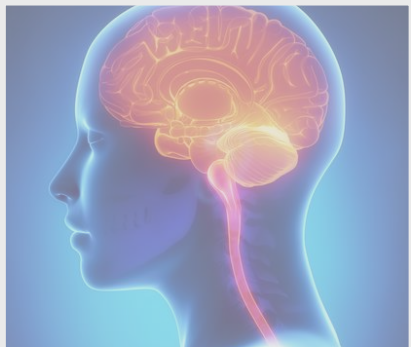
Genitourinary



Respiratory Depression



Central Nervous System



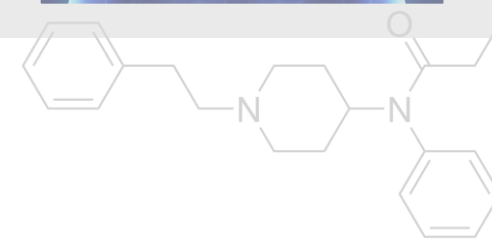
Respiratory



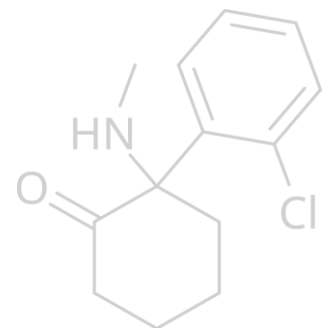
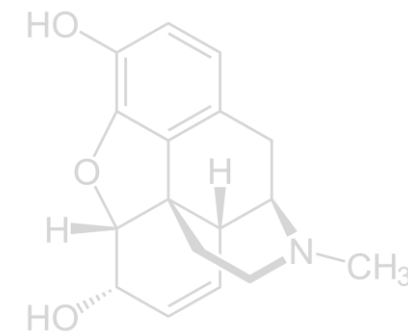
Gastrointestinal



Genitourinary



Nausea
Constipation



Central Nervous System



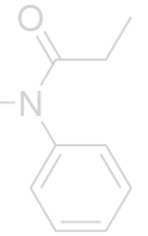
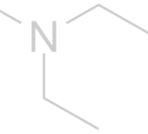
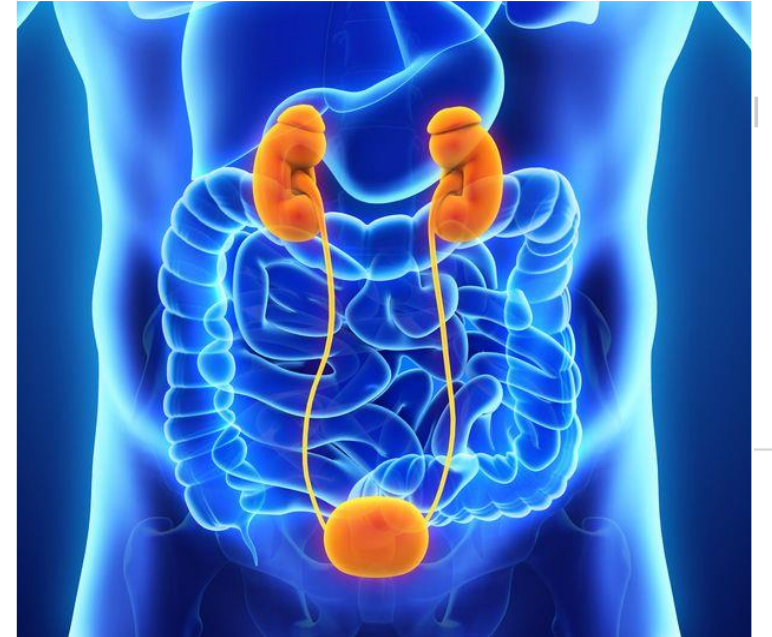
Respiratory



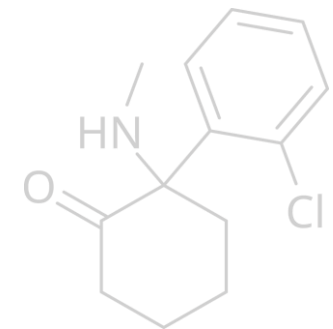
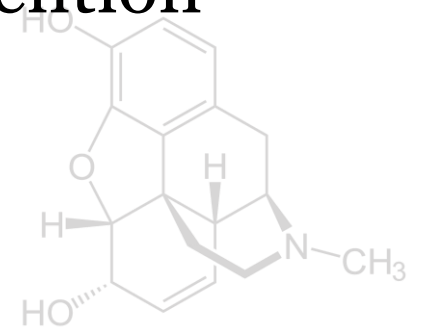
Gastrointestinal



Genitourinary



Urinary Retention



Central Nervous System



Sedation
Tolerance
Dependence

Respiratory



Respiratory
Depression

Gastrointestinal

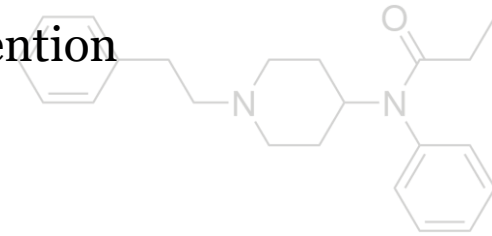
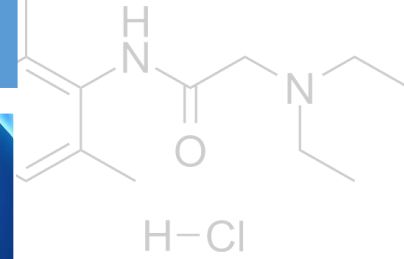


Nausea
Constipation

Genitourinary

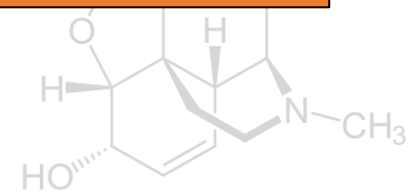
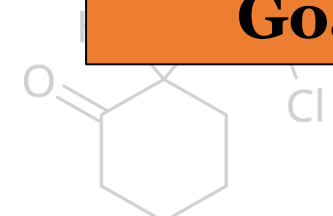


Urinary Retention

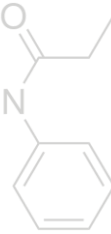
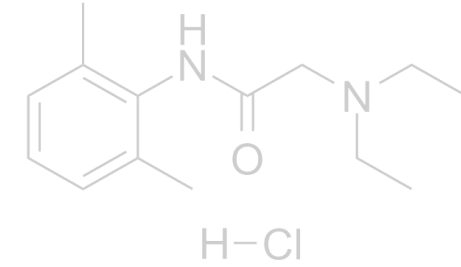


Combination of opioid and non-opioid agents with different mechanisms of action

Goal: limit opioid exposure without sacrificing patient comfort



Multimodal Analgesia



Multimodal Analgesia in Trauma

- Retrospective pre-post cohort of trauma ICU patients (N = 127)
- Implementation of multimodal pain order set reduced cumulative opioid dose received
- No difference in pain scores at day 5, discharge, ICU LOS, hospital LOS

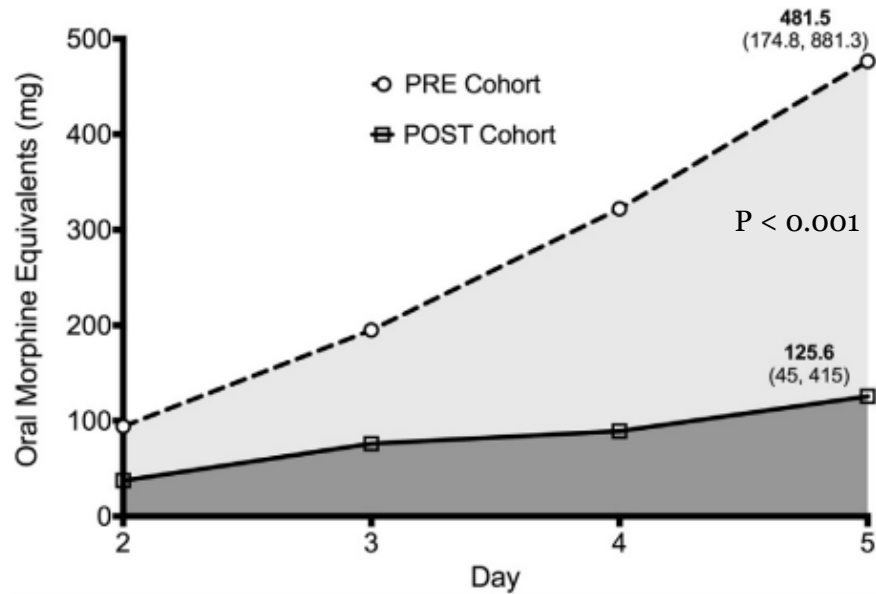
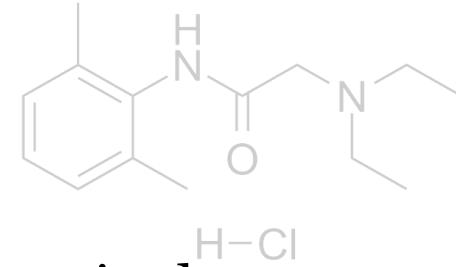


Figure 2. Cumulative opioid exposure.

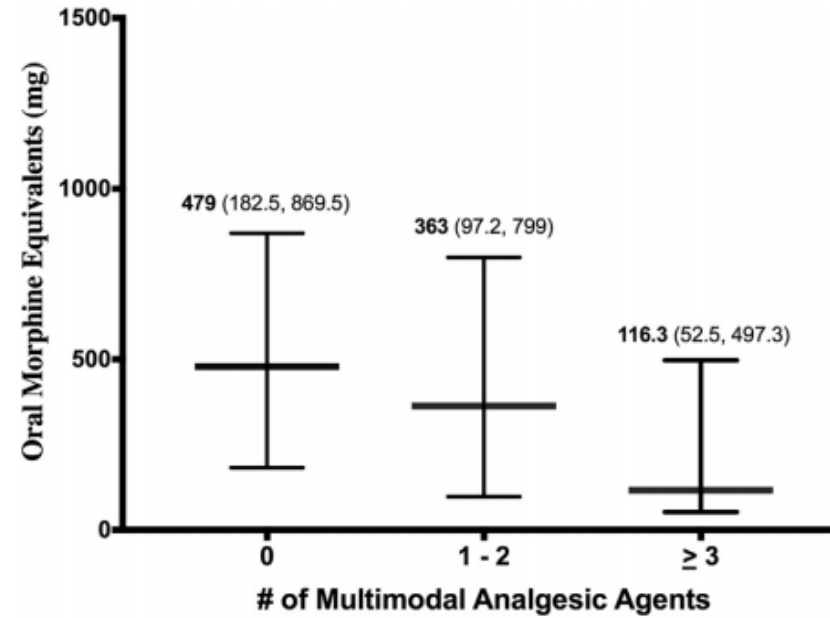
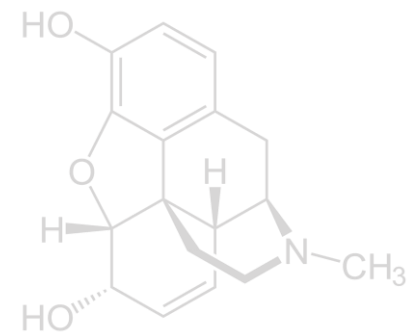
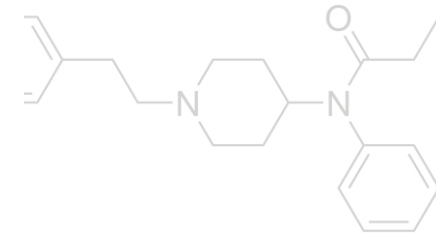


Figure 3. Cumulative opioid exposure vs number of multimodal agents.



Multimodal Analgesia in Trauma

- Retrospective pre-post cohort of trauma ICU patients (N = 127)
- Implementation of multimodal pain order set reduced cumulative opioid dose received
- No difference in pain scores at day 5, discharge, ICU LOS, hospital LOS

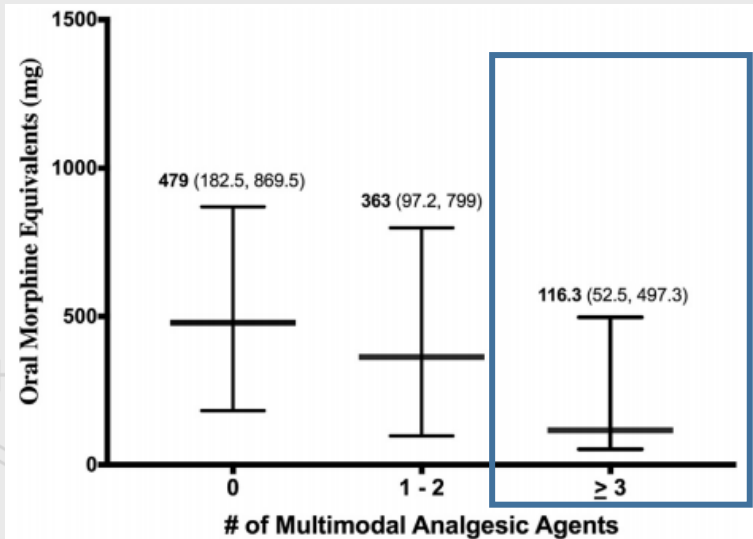


Figure 3. Cumulative opioid exposure vs number of multimodal agents.

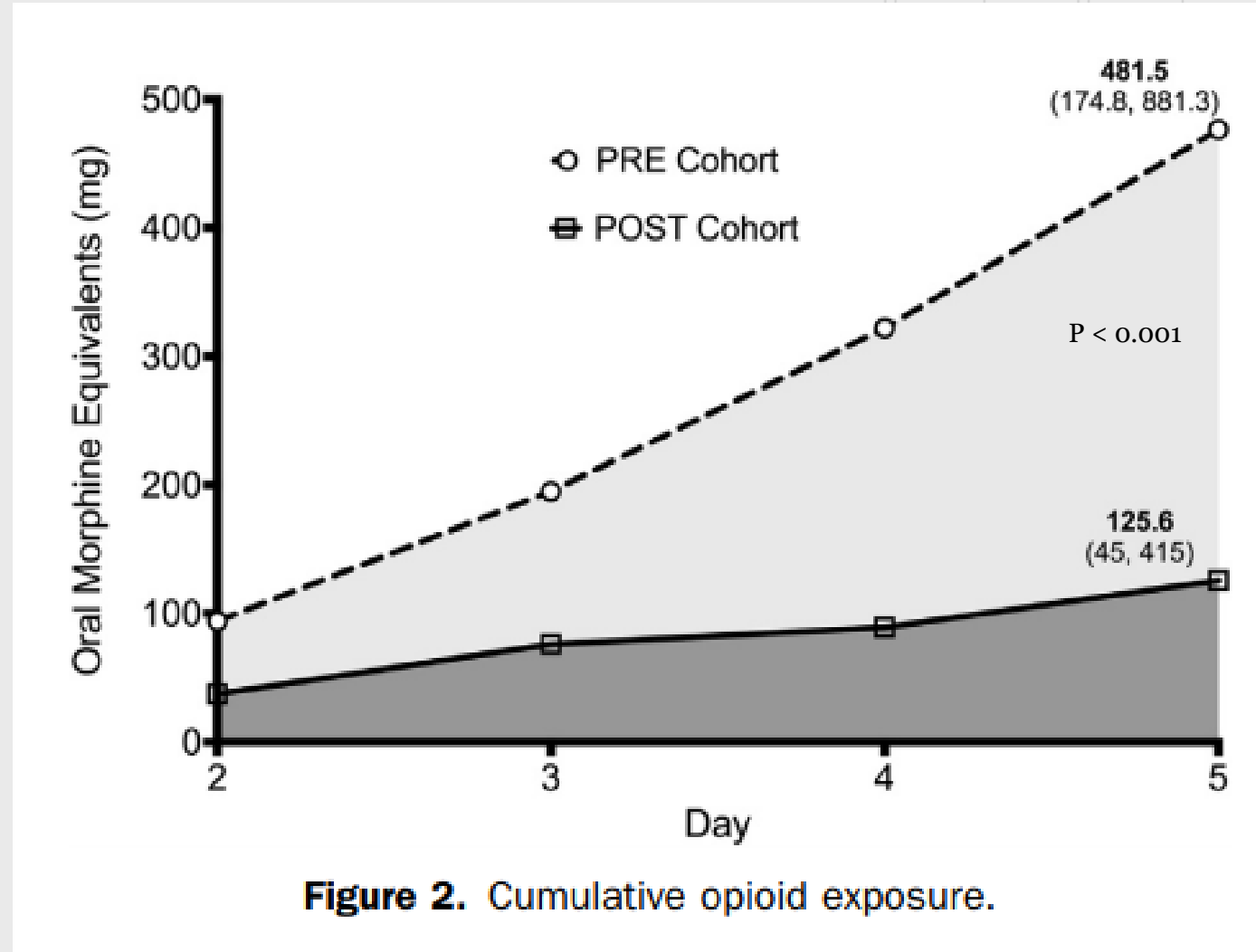


Figure 2. Cumulative opioid exposure.

Multimodal Analgesia in Trauma

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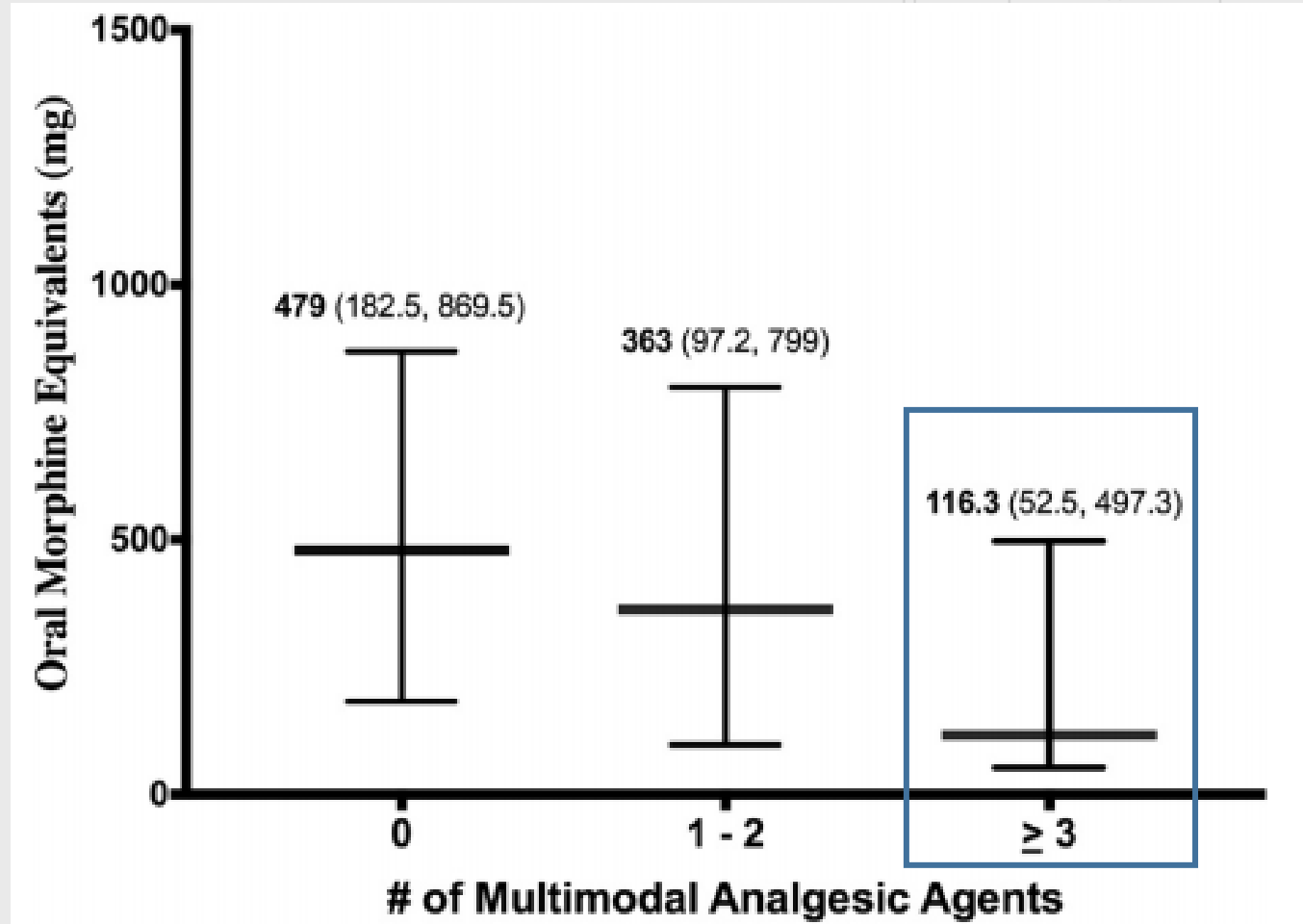
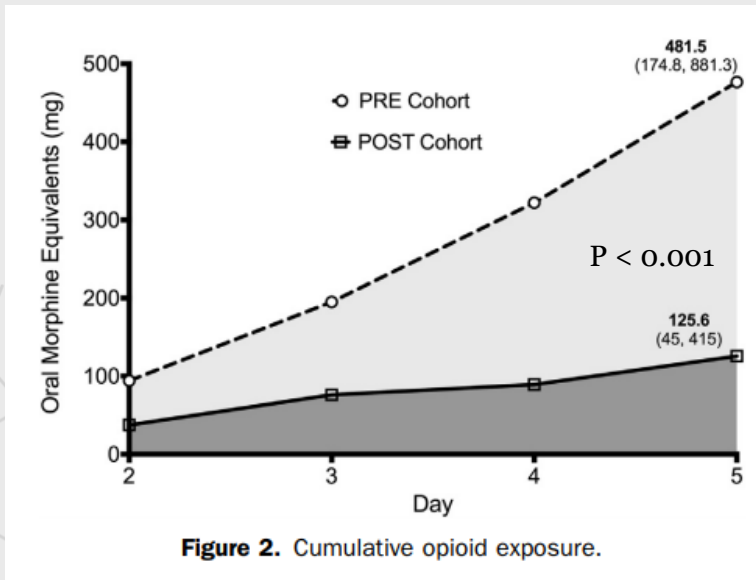
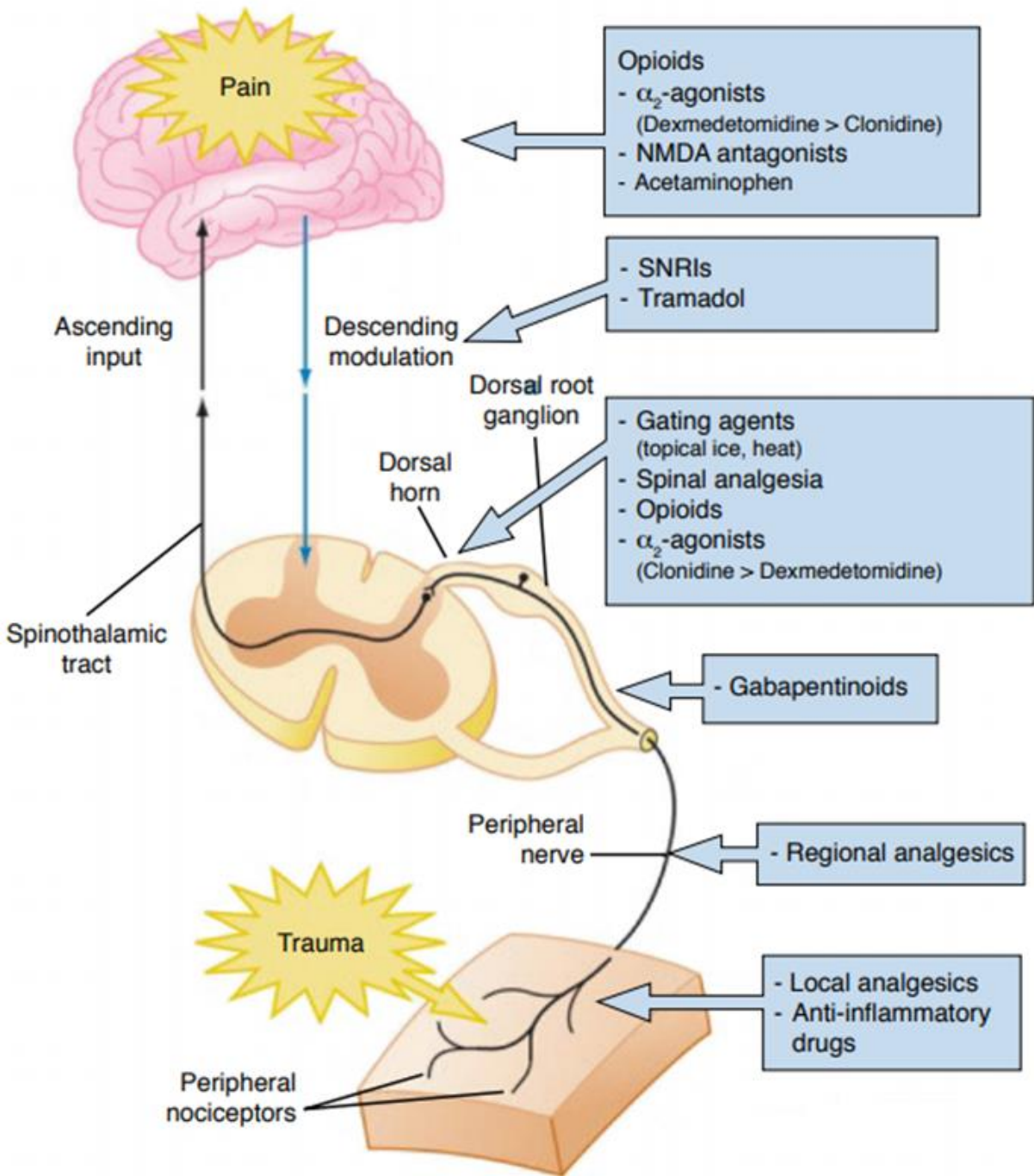


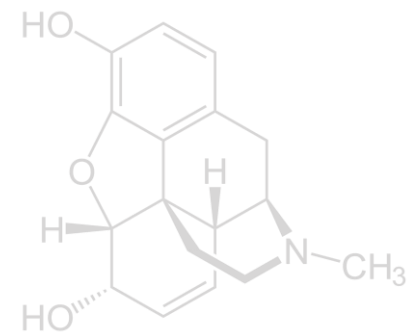
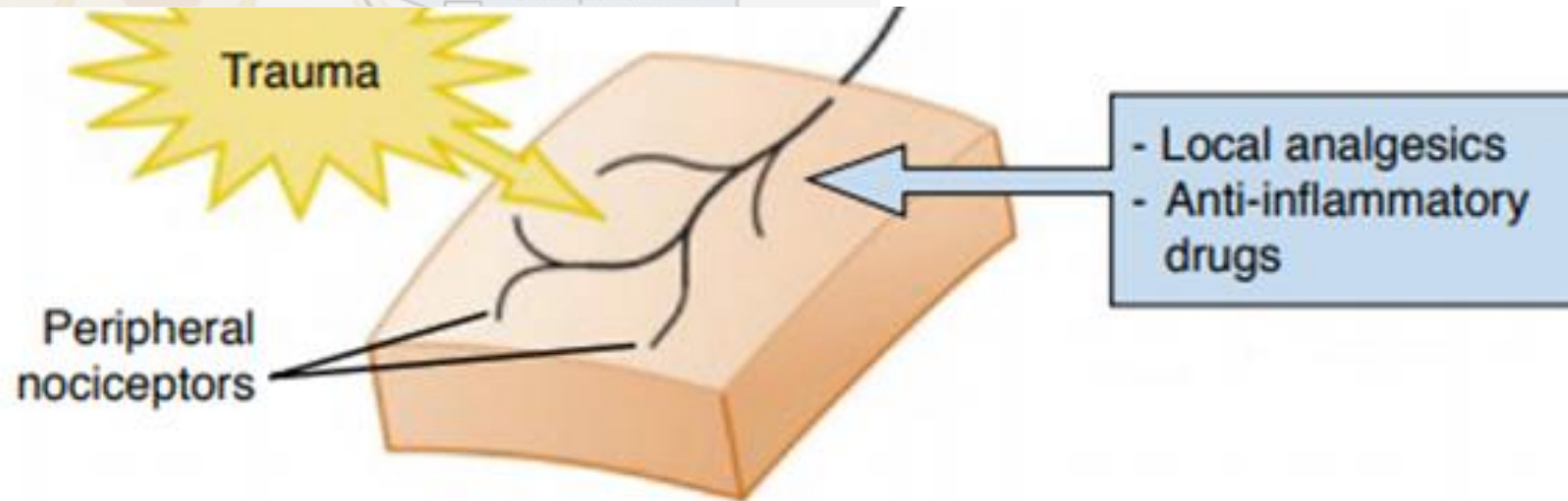
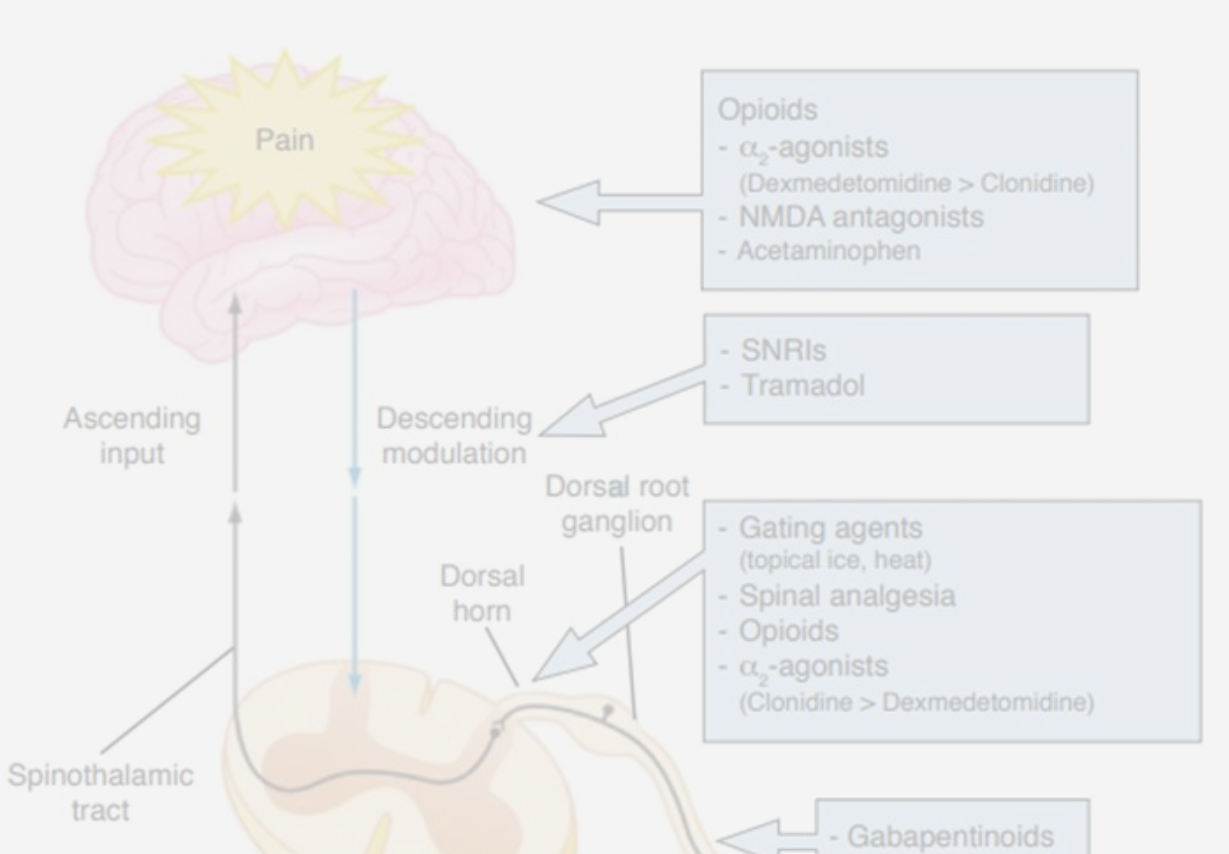
Figure 3. Cumulative opioid exposure vs number of multimodal analgesic agents.



On Today's Menu



On Today's Menu



NSAIDs

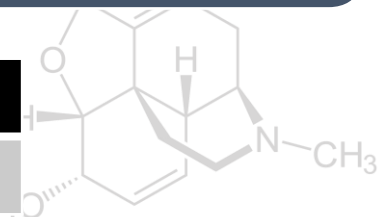
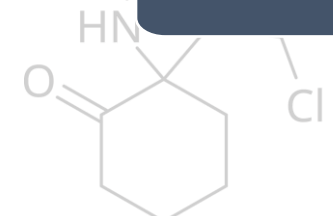
Antipyretic, analgesia, anti-inflammatory

Effective at reducing pain in emergency and post-surgical populations

Reduces opioid requirements and opioid-related complications

Mitigate surgical stress

Ibuprofen	Ketorolac	Naproxen	Celecoxib
400 mg	15 mg	250 mg	200 mg



NSAIDs

Antipyretic, analgesia, anti-inflammatory

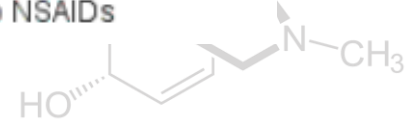
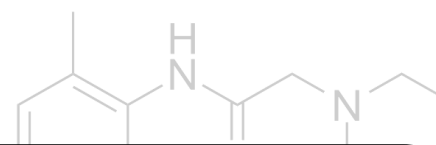
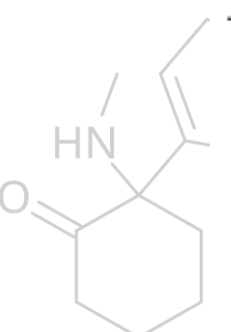
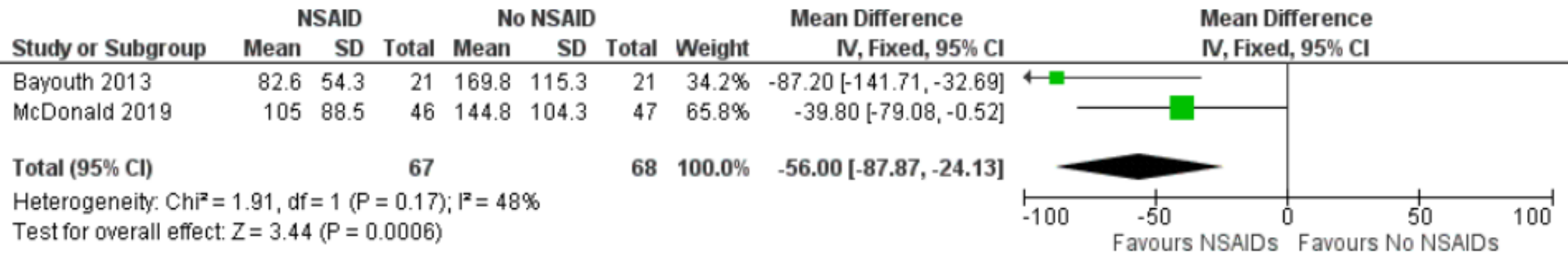
Effective at reducing pain in emergency and post-surgical populations

Reduces opioid requirements and opioid-related complications

26% decrease in opioid consumption

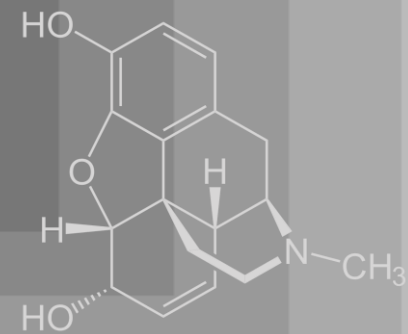
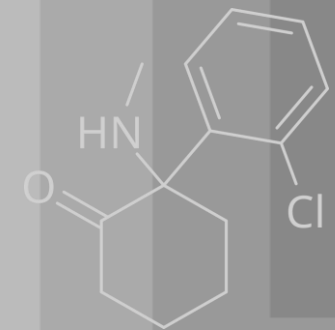
30% decreased odds of nausea and vomiting

47% decreased odds of sedation





Adverse Effects of NSAIDs

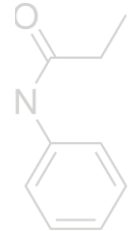
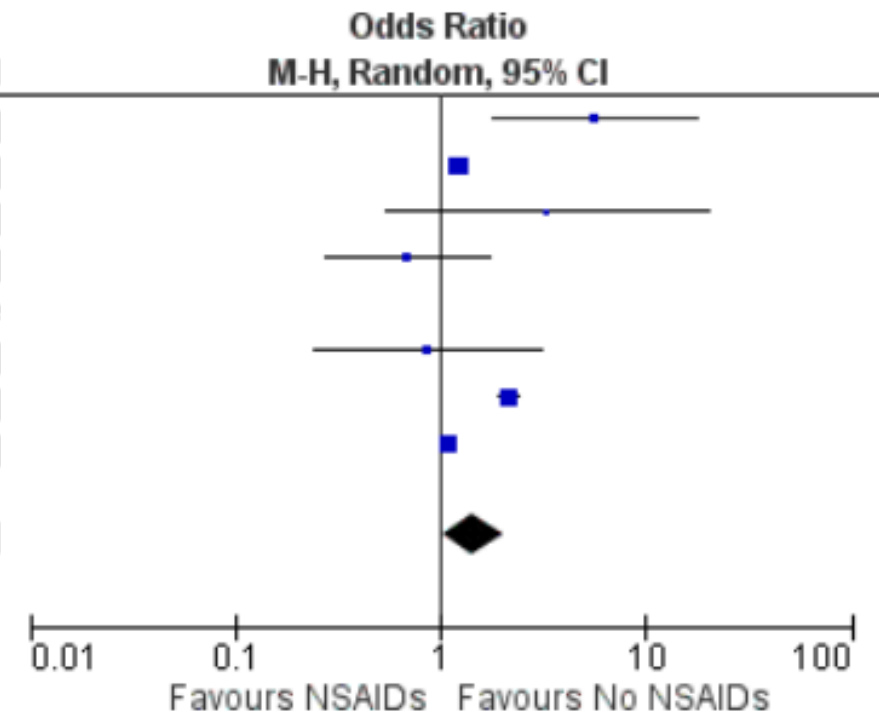


Efficacy and safety of non-steroidal anti-inflammatory drugs (NSAIDs) for the treatment of acute pain after orthopedic trauma: a practice management guideline from the Eastern Association for the Surgery of Trauma and the Orthopedic Trauma Association



Study or Subgroup	NSAID		No NSAID		Weight	Odds Ratio M-H, Random, 95% CI
	Events	Total	Events	Total		
Burd 2003	11	38	5	74	6.2%	5.62 [1.79, 17.70]
George 2020	456	25001	4188	279720	25.8%	1.22 [1.11, 1.35]
Hunter 2019	3	98	2	210	2.9%	3.28 [0.54, 19.98]
McDonald 2019	10	58	13	56	8.5%	0.69 [0.27, 1.73]
Moed 1994	0	16	0	19		Not estimable
Sagi 2014	10	59	4	21	5.2%	0.87 [0.24, 3.13]
Tucker 2020	392	2570	1179	15119	25.4%	2.13 [1.88, 2.41]
Zura 2016	661	23847	7276	286483	26.0%	1.09 [1.01, 1.19]
Total (95% CI)		51687		581702	100.0%	1.45 [1.04, 2.01]

Total events 1543 12667
 Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 90.55$, $df = 6$ ($P < 0.00001$); $I^2 = 93\%$
 Test for overall effect: $Z = 2.22$ ($P = 0.03$)



Non-union rate: 2.99% (NSAID) vs. 2.18% (no NSAID), OR 1.45, 95% CI [1.04 – 2.01]



Risk of Nonunion with Nonselective NSAIDs, COX-2 Inhibitors, and Opioids



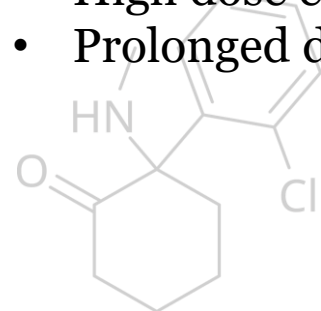
Michael D. George, MD, MSCE, Joshua F. Baker, MD, MSCE, Charles E. Leonard, PharmD, MSCE, Samir Mehta, MD, Todd A. Miano, PharmD, MSCE, and Sean Hennessy, PharmD, PhD

- Nonunion diagnosis within 1 year: 0.9% (2,996)

	No.	Nonunion Diagnosis and Procedure to Treat		Nonunion Diagnosis	
		Nonunion (no. [%])	aOR (95% CI)	Nonunion (no. [%])	aOR* (95% CI)
NSAID/COX-2 analysis					
Neither	279,720	2,250 (0.8%)	Reference	4,188 (1.5%)	Reference
Nonselective NSAID	22,590	236 (1.0%)	1.07 (0.93-1.23)	387 (1.7%)	1.08 (0.96-1.20)
COX-2	2,411	51 (2.1%)	1.84 (1.38-2.46)	69 (2.9%)	1.48 (1.16-1.89)

Filling prescription for NSAID **prior** to fracture increased risk for nonunion

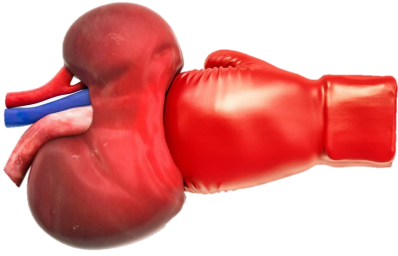
- Cannot Rule Out
- High dose effect
 - Prolonged duration effect



In patients with traumatic fractures, NSAIDs appear to reduce post-trauma pain, reduce the need for opioids and have a small effect on non-union. We conditionally recommend the use of NSAIDs in patients suffering from traumatic fractures as the benefit appears to outweigh the small potential risks.

- Eastern Association for the Surgery of Trauma*
- Orthopedic Trauma Association*

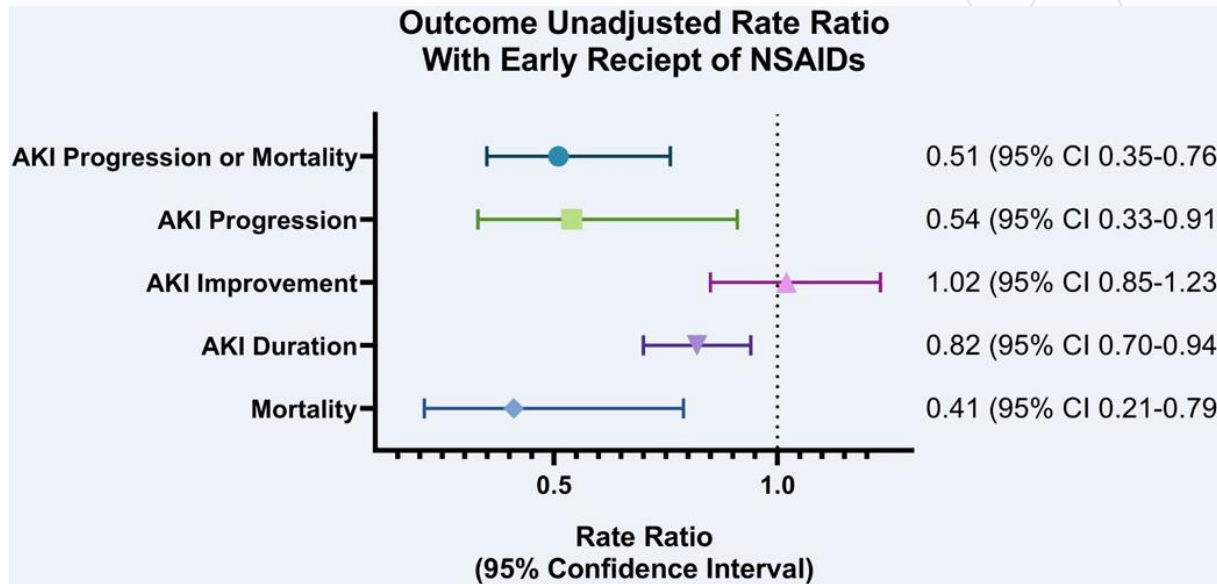




Do Early Non-Steroidal Anti-Inflammatory Drugs for Analgesia Worsen Acute Kidney Injury in Critically Ill Trauma Patients? An Inverse Probability of Treatment Weighted Analysis

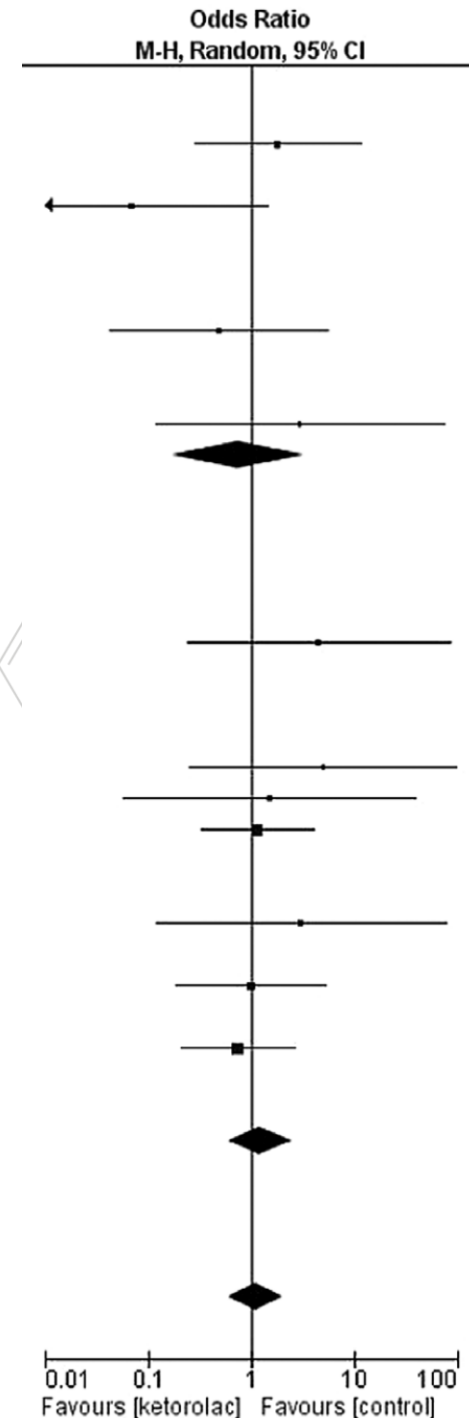
Gabrielle E Hatton, MD^{a,b,d}, Cynthia Bell, MS^c, Shuyan Wei, MD^{a,b,d}, Charles E Wade, PhD^{a,b}, Lillian S Kao, MD MS^{a,b,d}, John A Harvin, MD MS^{a,b,d}

ALL PATIENTS (N=2,340)	NO EARLY NSAIDS (N=2,072)	EARLY NSAIDS (N=268)	P VALUE
Progression or Mortality within 7 d	382 (18%)	25 (9%)	<0.001
AKI Progression	221 (11%)	15 (6%)	0.01
AKI Improvement	673 (33%)	87 (33%)	1.0
AKI Duration	0 (0-1) Mean 1.0	0 (0-1) Mean 0.8	0.05
Mortality	138 (9%)	10 (4%)	0.006



Ketorolac Does Not Increase Perioperative Bleeding: A Meta-Analysis of Randomized Controlled Trials

Ryan M. Gobble, MD, Han L. T. Hoang, MD, Bart Kachniarz, BA, Dennis P. Orgill, MD, PHD



Postoperative bleeding: 2.5% (ketorolac) vs. 2.1% (control), P = 0.72

No difference in low-dose vs. high-dose groups

Total OR 95% CI: **1.12 [0.61, 2.06]**

Superior pain control with ketorolac vs. placebo or acetaminophen



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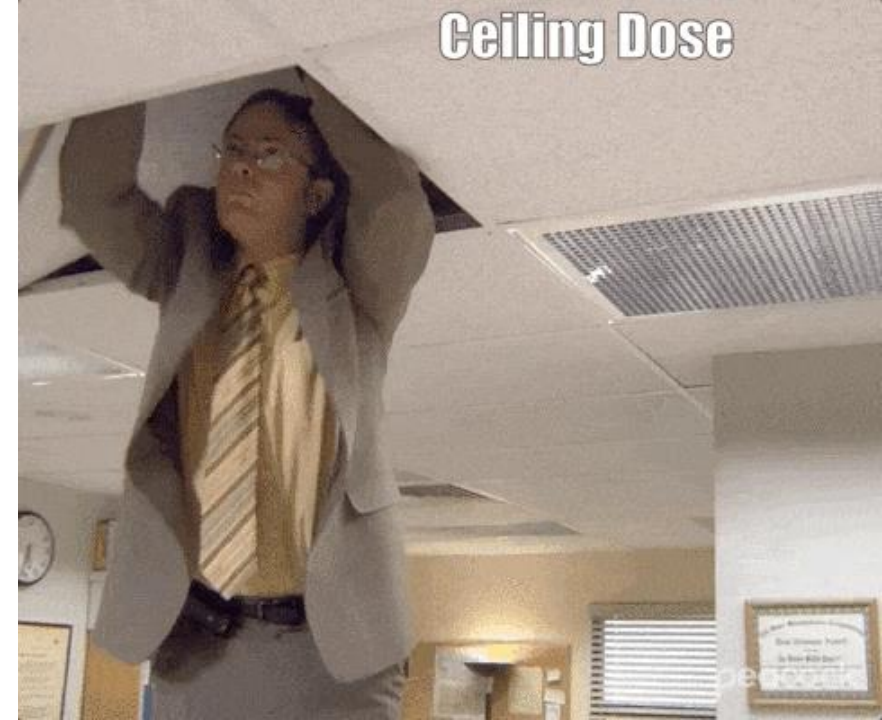
After 30 mg IM ketorolac Q6H x 5 days
Bleed time prolonged from 4.9 min to 7.8 min
No increase in clinically significant bleeding



Comparison of Intravenous Ketorolac at Three Single-Dose Regimens for Treating Acute Pain in the Emergency Department: A Randomized Controlled Trial

Sergey Motov, MD*; Matthew Yasavolian, MD; Antonios Likourezos, MA, MPH; Illya Pushkar, MPH; Rukhsana Hossain, MPH; Jefferson Drapkin, BS; Victor Cohen, PharmD; Nicholas Filk, PharmD; Andrew Smith, PharmD; Felix Huang, MD; Bradley Rockoff, MD; Peter Homel, PhD; Christian Fromm, MD

- IV ketorolac 10, 15, and 30 mg
- N = 240 (80 each dose group)
- No difference in numeric pain scale at baseline or at 30 minutes
- Similar rates of rescue medication and adverse events



Ceiling Dose

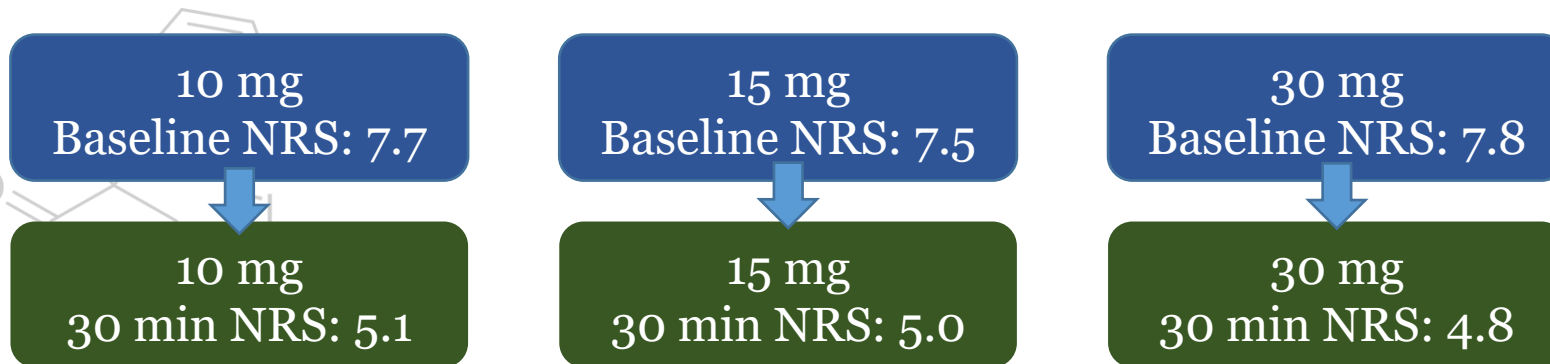
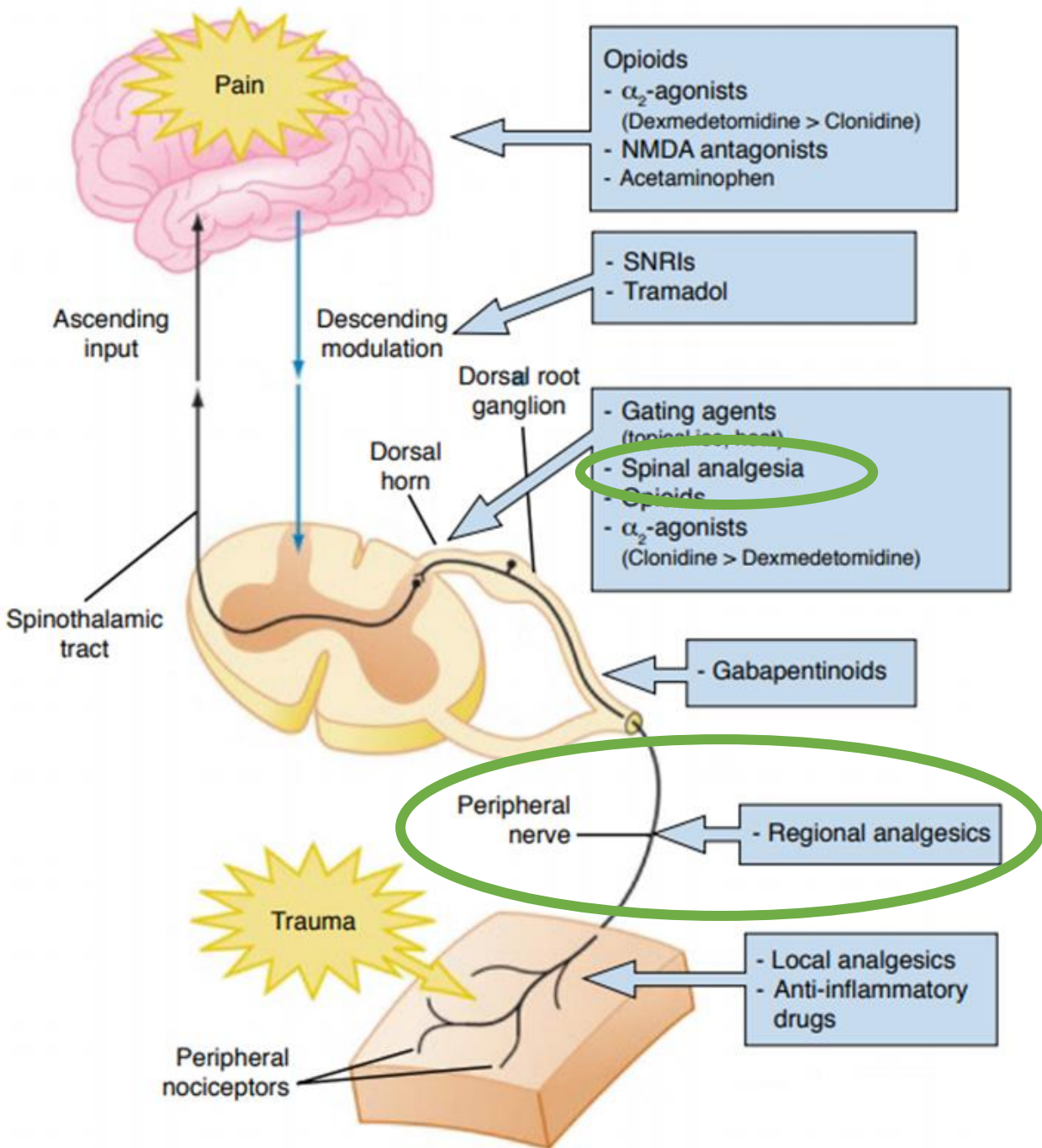


Table 4. Common adverse effects across the 3 ketorolac dose groups.

Adverse Effects	Ketorolac Group (%)		
	10 mg	15 mg	30 mg
Dizziness	14 (17.5)	16 (20.0)	12 (15.0)
Nausea	9 (11.3)	11 (13.8)	8 (10.0)
Headache	8 (10.0)	2 (2.5)	3 (3.8)
Itching	0	1 (1.3)	1 (1.3)
Flushing	0	1 (1.3)	0

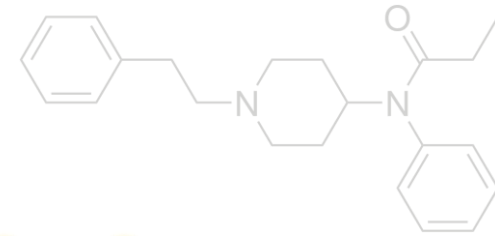
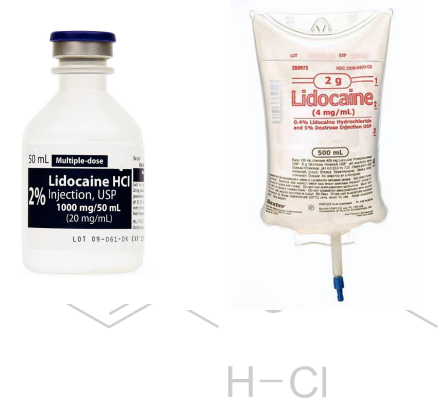


On Today's Menu



Lidocaine IV

- Anti-nociceptive, anti-hyperalgesic, anti-inflammatory
- MOA: block Na channels, prevents over-sensitization of CNS
- Indications: severe neuropathic and opioid refractory pain



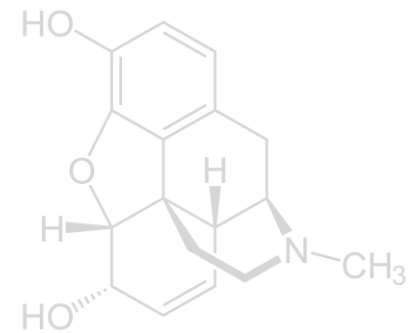
Absolute Contraindications

Conduction blocks
Hypersensitivity
Pregnancy



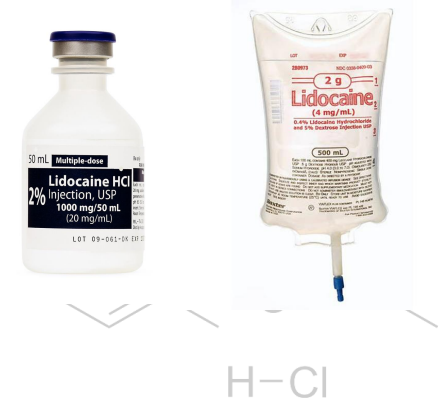
Relative Contraindications

CYP1A2 or 3A4 inducers
Renal dysfunction
Hepatic dysfunction



Lidocaine IV

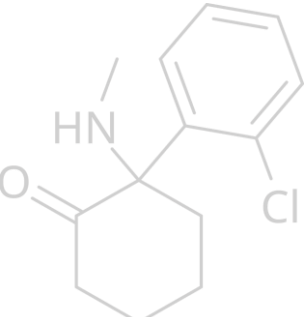
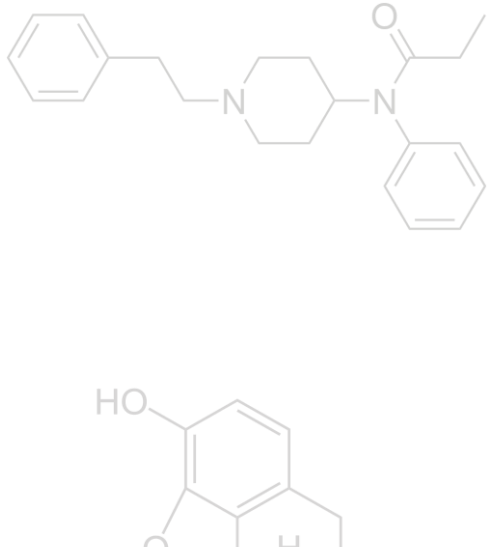
- **Heterogeneous evidence:** Overall low quality
 - Abdominal
 - Renal colic
 - Neuropathic
 - Musculoskeletal
 - Migraine



Benefits
Reduces PONV
Reduces constipation
Improves analgesia



Safety
Narrow therapeutic index
Limited data on lidocaine levels in studies



Foo I, et al. Anaesthesia. 76:238-250.
Masic D, et al. Pharmacotherapy. 2018;38(12):1250-1259.

Lidocaine IV

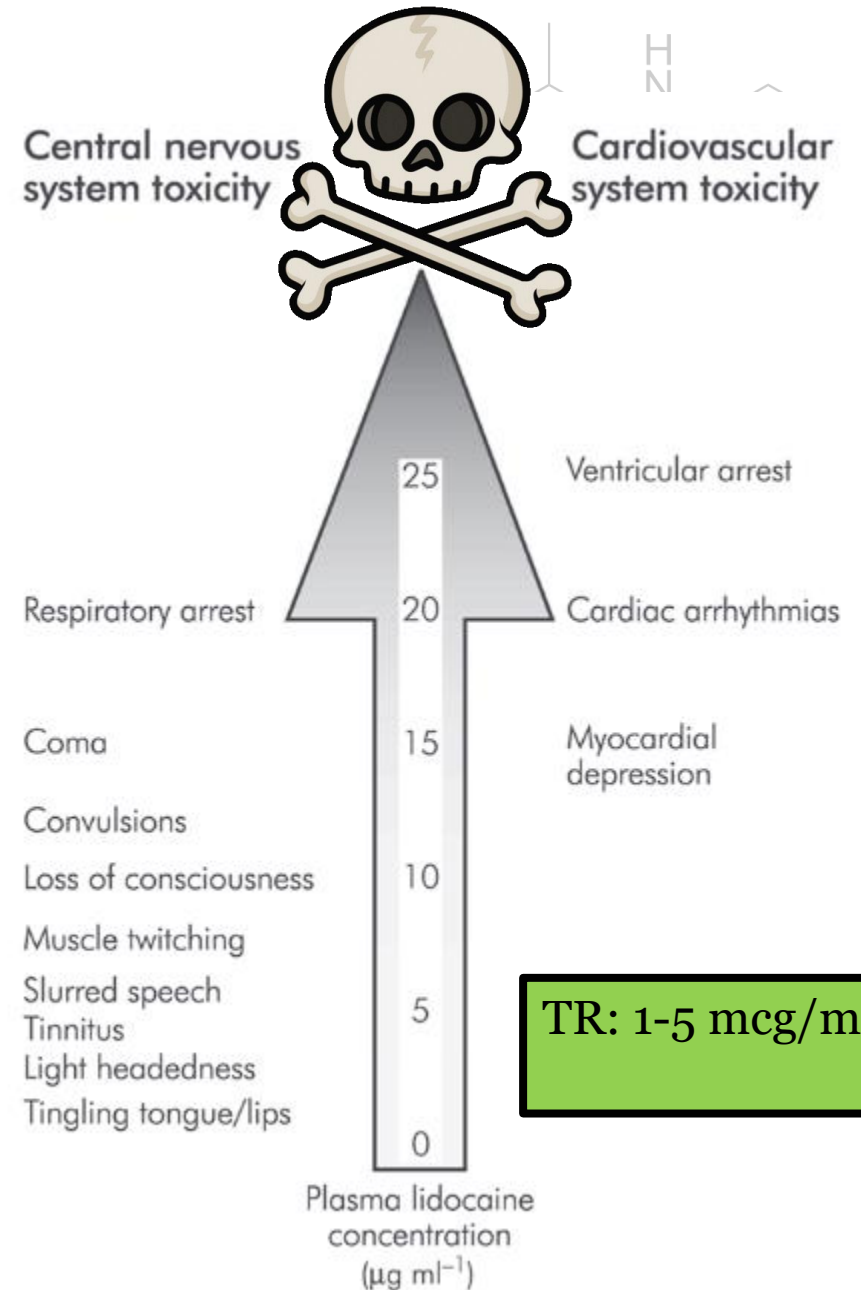
- 1.5 mg/kg IBW IV infusion (load) over 10 minutes
 - Max 100 mg
- 1 mg/kg/h IBW (maintenance)
- Total duration: 24-48 hours
- Sample Monitoring (vitals, EKG, pulse oximetry)

Q15 minutes for first hour

Q1 hour for 12 hours

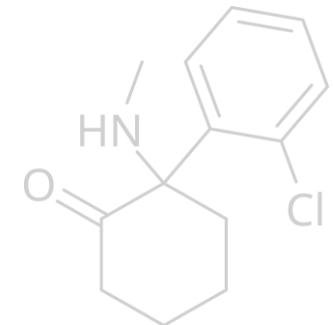
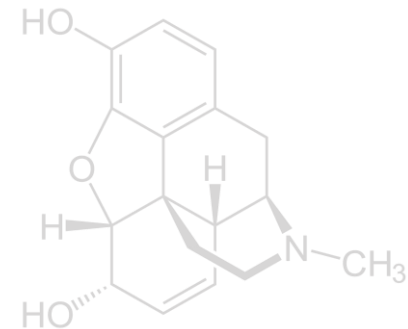
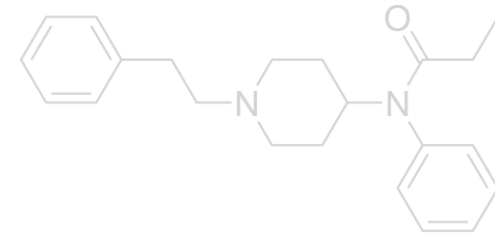
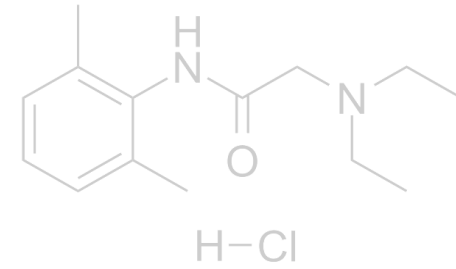
Q2 hour for 36 hours or until discontinuation

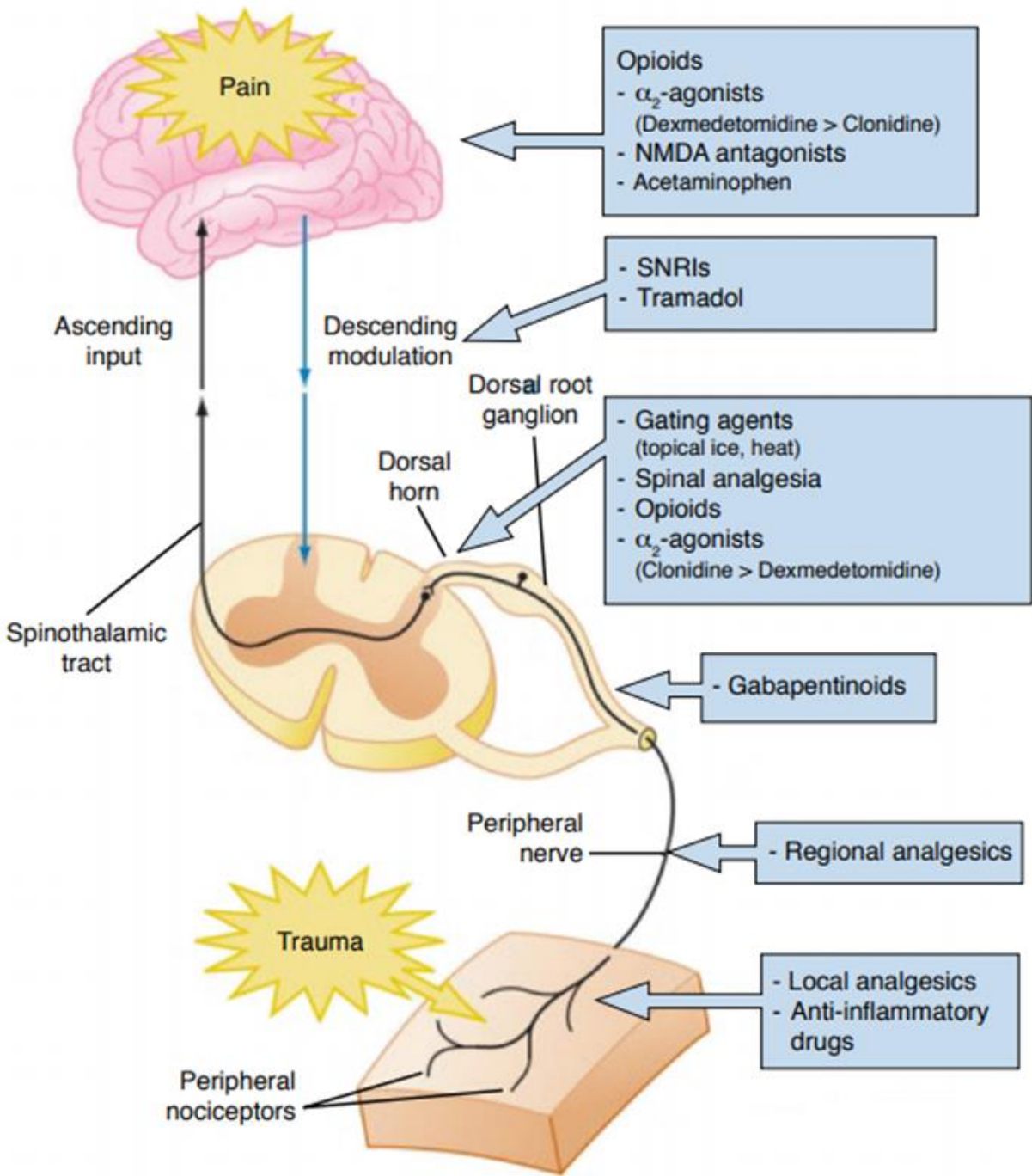
If restarting at lower rate, restart at Q1 hour



Lidocaine IV: Additional Considerations

- Evaluate for contraindications
- Use in accordance with approved hospital policy or protocol
- Ensure standards for smart IV pump technology are established
- Avoid concomitant use of local anesthetics

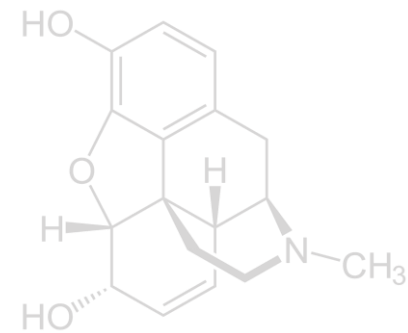
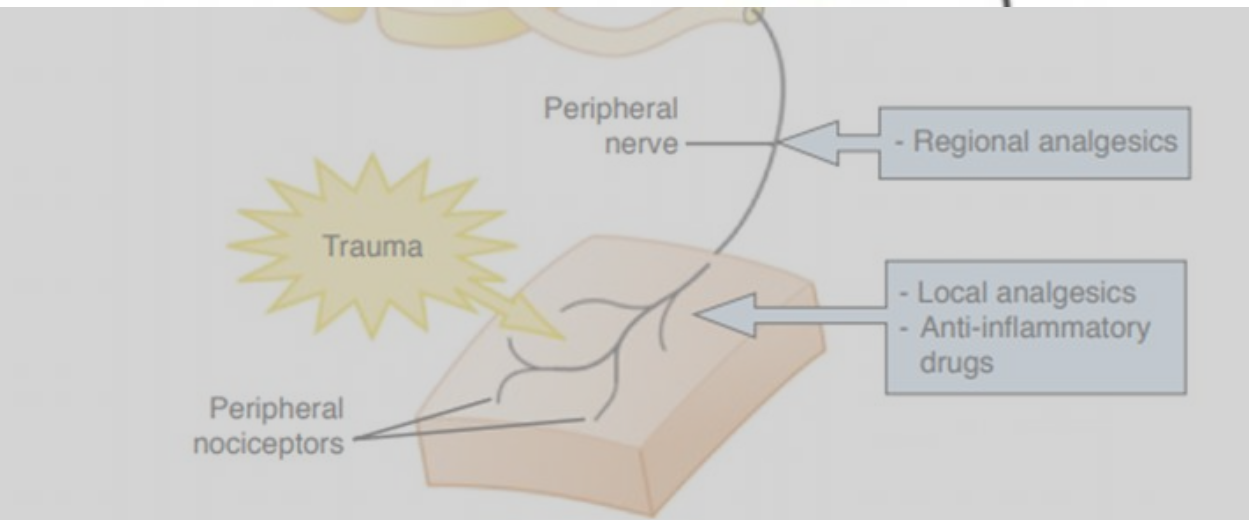
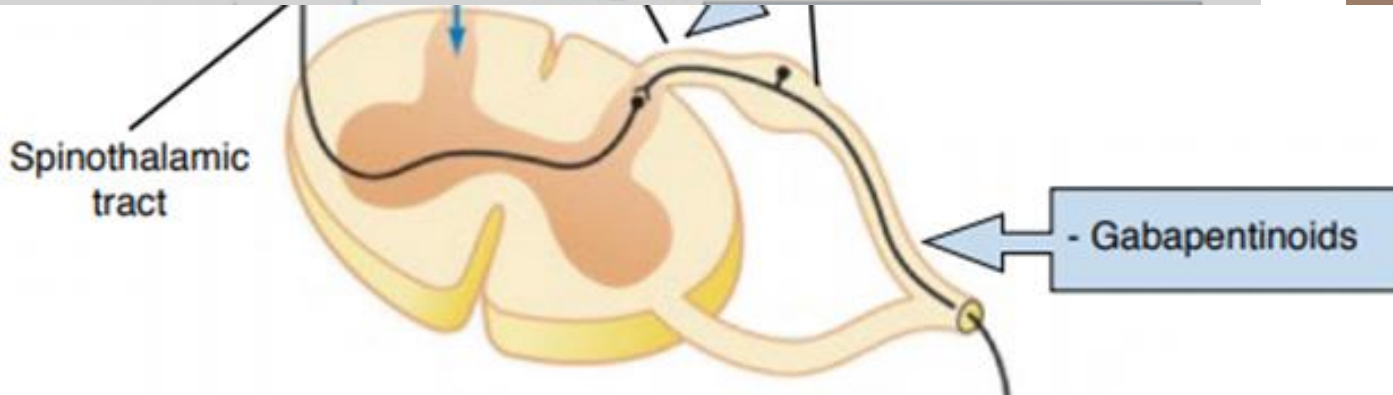
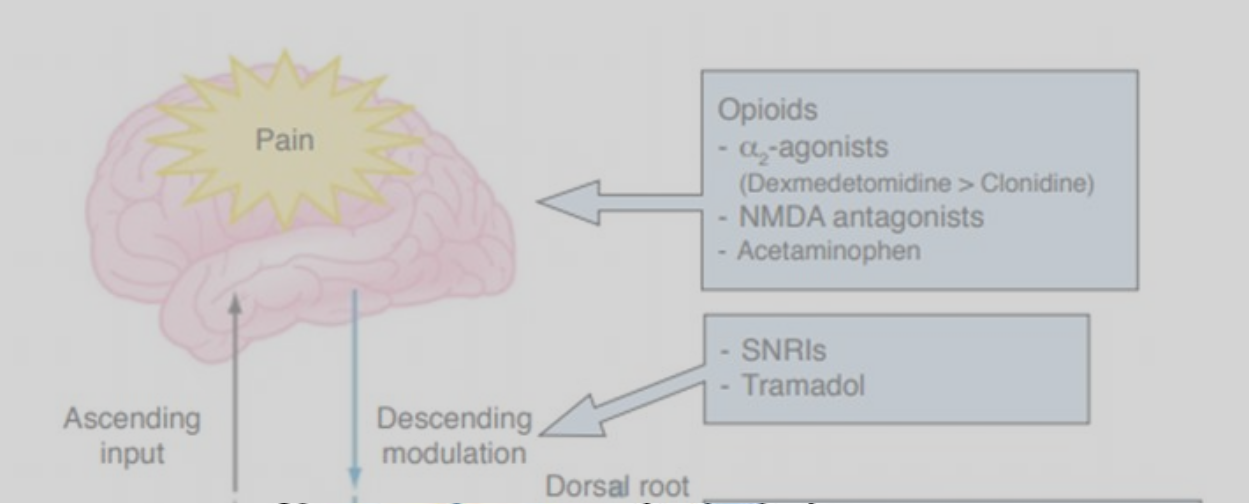




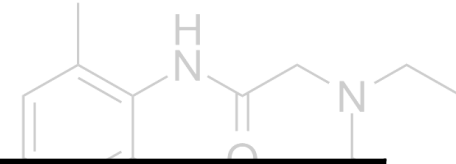
On Today's Menu



On Today's Menu



Gabapentinoids





	Gabapentin	Pregabalin
Mechanism	Bind voltage-gated calcium channels possessing the alpha-2-delta-1 subunit in CNS, modulating release of excitatory neurotransmitters	
Absorption	Limited to small intestine Highly variable Non-linear pharmacokinetics	Small intestine and ascending colon Linear pharmacokinetics
Peak	3 hours	1 hour
Distribution	0.8 L/kg	0.5 L/kg
Interactions	Not metabolized by CYP enzymes	
Excretion	Renal	
Efficacy		Increased binding affinity for alpha-2-delta More potent (~2.4x) in neuropathic pain
Safety	Respiratory depression (use concomitant opioids and benzodiazepines with caution)	

Verret M, et al. Anesthesiology 2020;133:265-79.

Bockbrader HN, et al. Clin Pharmacokinet. 2010 Oct;49(10):661-9.

Cavalcante AN, et al. Anesth Analg 2017;125:141-6

Effect of Perioperative Pregabalin on Postoperative Quality of Recovery in Patients Undergoing Off-Pump Coronary Artery Bypass Grafting (OPCABG): A Prospective, Randomized, Double-Blind Trial

Deepak Prakash Borde, MD, DNB, FCA, FTEE   • Savani Sameer Futane, DNB, PDCC •
Balaji Asegaonkar, MD, DNB • ... Manish Puranik, MS, MCh • Antony George, MD, DM •
Shreedhar Joshi, MD, DM • [Show all authors](#)

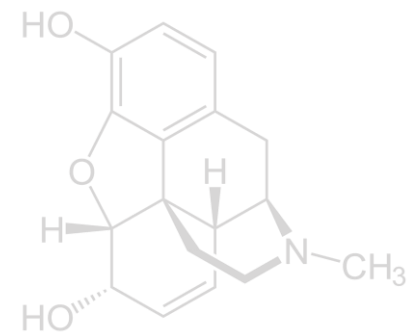
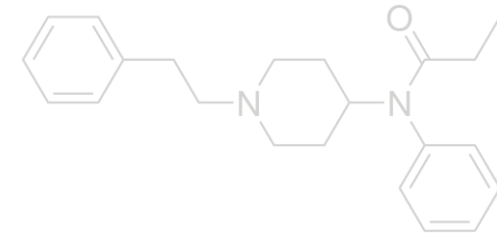
- Assessed quality of recovery via postoperative quality of recovery (QoR-40) questionnaire
 - Baseline and 24 hours post extubation
- N = 71 (37 pregabalin, 34 control)

**One-time dose
(1 hour before surgery)**



Pregabalin 150 mg

**Two days
(After extubation)**

Pregabalin 75 mg
Q12H



Effect of Perioperative Pregabalin on Postoperative Quality of Recovery in Patients Undergoing Off-Pump Coronary Artery Bypass Grafting (OPCABG): A Prospective, Randomized, Double-Blind Trial

Deepak Prakash Borde, MD, DNB, FCA, FTEE   • Savani Sameer Futane, DNB, PDCC •

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Shreedhar Joshi, MD, DM • [Show all authors](#)

**One-time dose
(1 hour before surgery)**

Pregabalin 150 mg

**Two days
(After extubation)**

Pregabalin 75 mg
Q12H

**Pregabalin
Significantly Improved QoR-40**

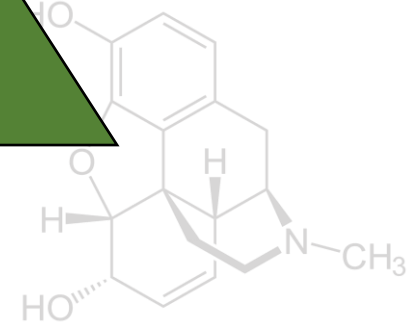
Pain
P = 0.02

Physical comfort
P = 0.04

**Improved
QoR-40**
P = 0.002

Emotional state
P = 0.005

Decreased need for rescue analgesia
Increased dizziness vs. control (1 vs. 5, P = 0.01)



ANESTHESIOLOGY

Perioperative Use of Gabapentinoids for the Management of Postoperative Acute Pain

A Systematic Review and Meta-analysis

Michael Verret, M.D., M.Sc., François Lauzier, M.D., M.Sc., Ryan Zarychanski, M.D., M.Sc., Caroline Perron, M.Sc., Xavier Savard, M.D. candidate, Anne-Marie Pinard, M.D., M.Sc., Guillaume Leblanc, M.D., M.Sc., Marie-Joëlle Cossi, Ph.D., Xavier Neveu, M.Sc., Alexis F. Turgeon, M.D., M.Sc., and the Canadian Perioperative Anesthesia Clinical Trials (PACT) Group*

281 trials (N = 24,682)

Lower postoperative pain intensity

6, 12, 24, and 48 hours

- Did not meet threshold for **clinical significance***
- Met statistical significance

Less opioid use

- Mean difference: -7.9 mg IV morphine, 95% CI [-8.82 to -6.98]

Less postoperative nausea/vomiting

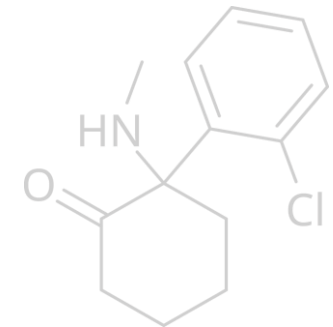
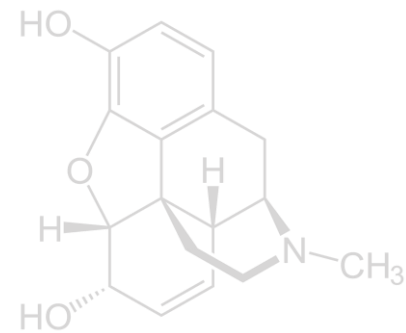
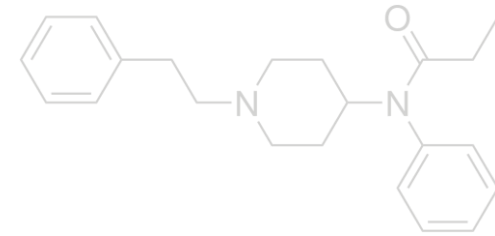
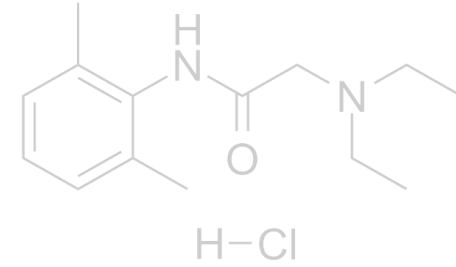
- RR 0.77; 95% CI [0.72 to 0.82]

Gabapentinoids:

- Administered before surgery (71% trials)
- Administered before and after surgery (25% trials)
- Single dose (68% trials)

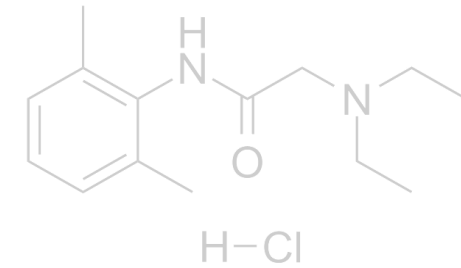
*Clinical significance: Reduction in pain intensity score > 10 points on 100-point scale

Skeletal Muscle Relaxants: Methocarbamol




Skeletal Muscle Relaxants: Methocarbamol

- MOA: direct CNS depression; no direct effects on skeletal muscle
- Available IM, IV, PO



Efficacy of Methocarbamol for Acute Pain Management in Young Adults With Traumatic Rib Fractures

Lindsay P. Deloney, PharmD, BCPS¹ ,
Melanie Smith Condeni, PharmD, BCPS, BCCCP¹,
Cassandra Carter, PharmD¹, Alicia Privette, MD, FACS¹,
Stuart Leon, MD¹, and Evert A. Eriksson, MD, FACS¹

Annals of Pharmacotherapy
1-6
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DOI: 10.1177/1060028020964796
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N = 50 (22 pre-protocol, 28 post-protocol)

Ages 18-39 years

3 or more rib fractures

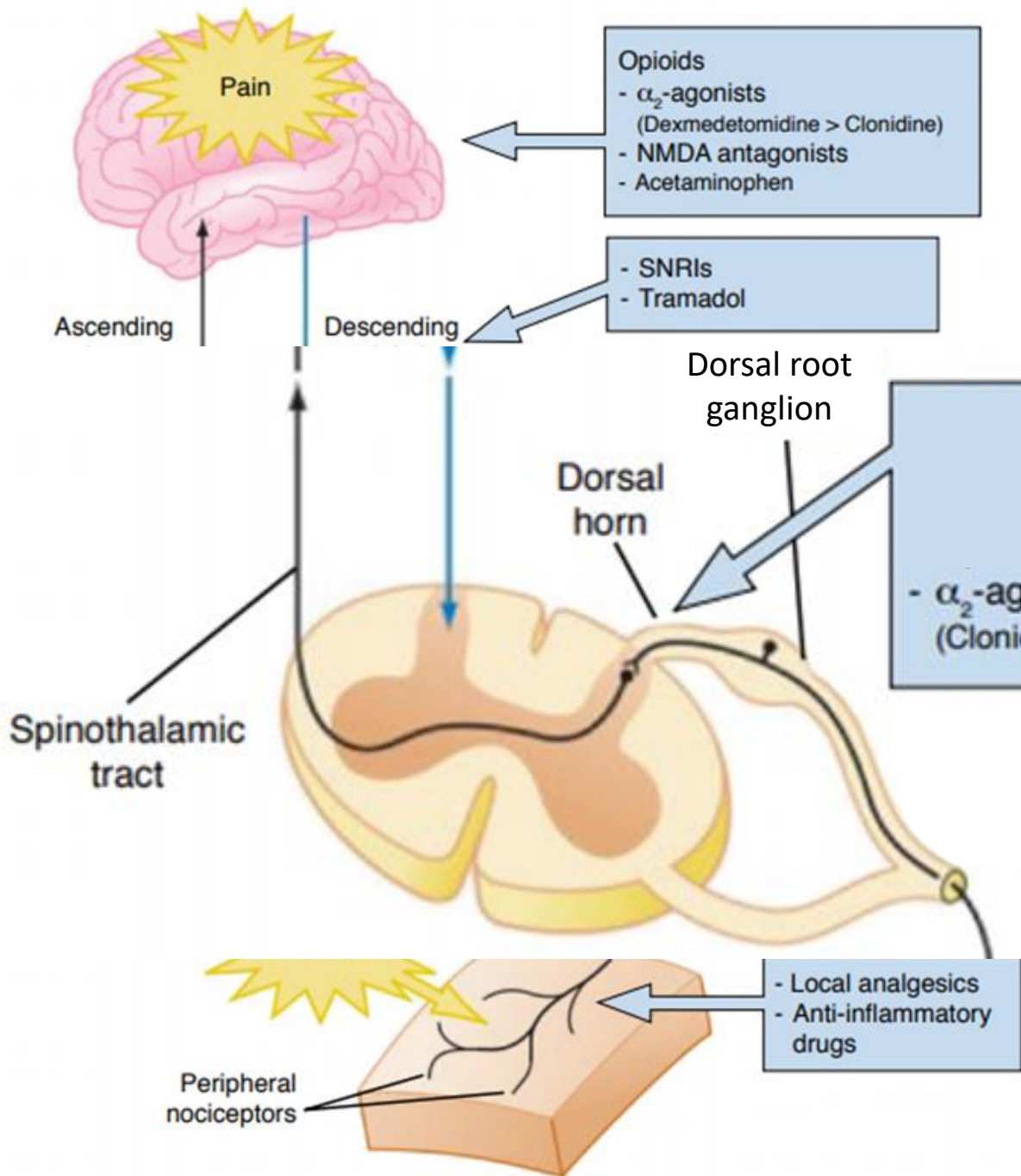
Dosing: 500 mg Q6H – 1500 mg Q6H

Use associated with lower median cumulative opioids (219 vs. 337 mg OME, P=0.01)

Decreased LOS (3 vs. 4 days, P=0.03)

No difference in PNA incidence





On Today's Menu

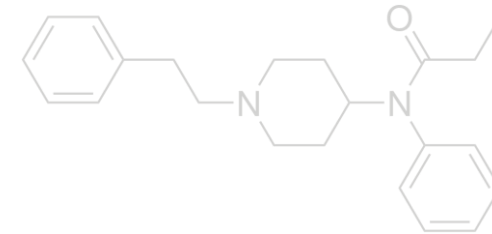
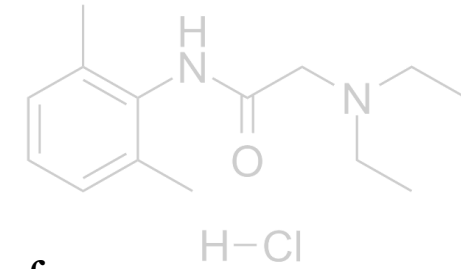
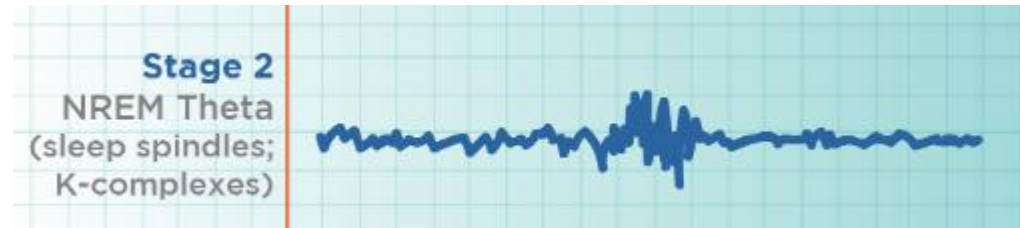


Dexmedetomidine

Mechanism

Selective binding to alpha-2A receptors in CNS, which inhibits adenylyl cyclase, reducing levels of adenosine monophosphate and leading to **hyperpolarization of noradrenergic neurons**

- Negative feedback loop
- Attenuates sympathetic response
- Mimics physiologic stage 2 sleep



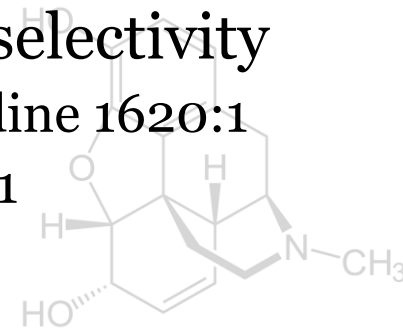
Considerations

- Withdrawal from alpha-2 upregulation (30%)
 - Conflicting evidence to indicate if duration, max/median doses, or weaning prior to discontinuation affect this
 - **Doses > 0.8 mcg/kg/h**

FUN FACT

Alpha-2: alpha-1 selectivity

- Dexmedetomidine 1620:1
- Clonidine 220:1

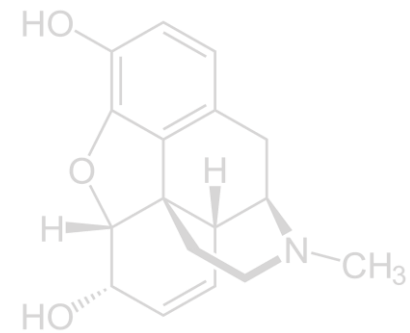
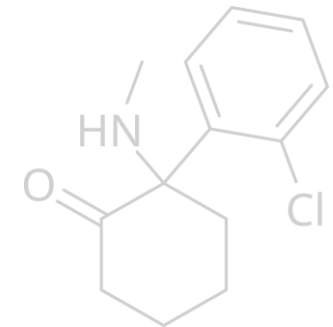
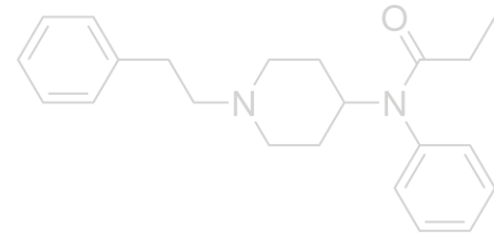
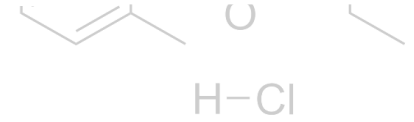


Dexmedetomidine in Enhanced Recovery After Surgery (ERAS) Protocols for Postoperative Pain

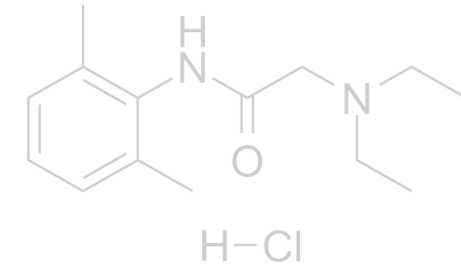
Alan David Kaye¹ • David J. Chernobylsky² • Pankaj Thakur³ • Harish Siddaiah³ • Rachel J. Kaye⁴ • Lauren K. Eng² • Monica W. Harbell⁵ • Jared Lajaunie⁶ • Elyse M. Cornett³

Dexmedetomidine

- Reduces opioid consumption by 30% at 24 hours post-operatively
- Reduces pain intensity
- Decreases postoperative nausea and vomiting
- No effect on recovery time
- Useful adjunct in regional anesthesia



Future of Dexmedetomidine



Drug Fever?

Compared with standard of care, dexmedetomidine is associated with greater incidence of temperatures greater than 38.3C (43.3% vs. 32.7%) or 39C (19.4% vs. 12.5%)

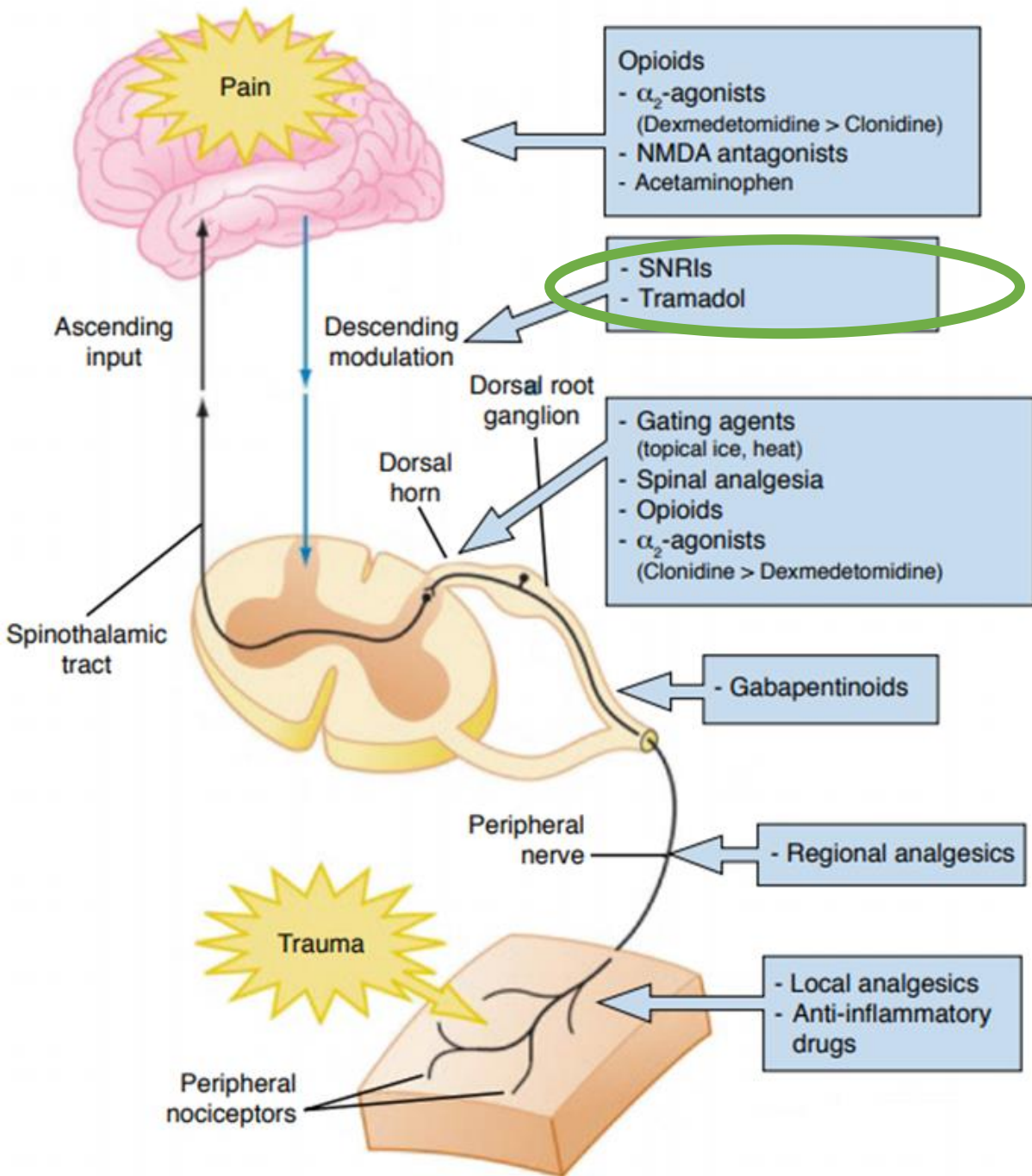
Alternative Routes: PCA, Sublingual

Dexmedetomidine versus control in PCIA

Effectiveness			Adverse reactions			Inflammatory levels		
Analgesic effects	Sedative effects	Patient satisfaction	Nausea vomiting	Pruritus	Bradycardia	Hypotension	IL-6	TNF- α
+	=	+	-	+	=	-	-	-



Igalmi 120 or 180 mcg film
Max 360 mcg/day

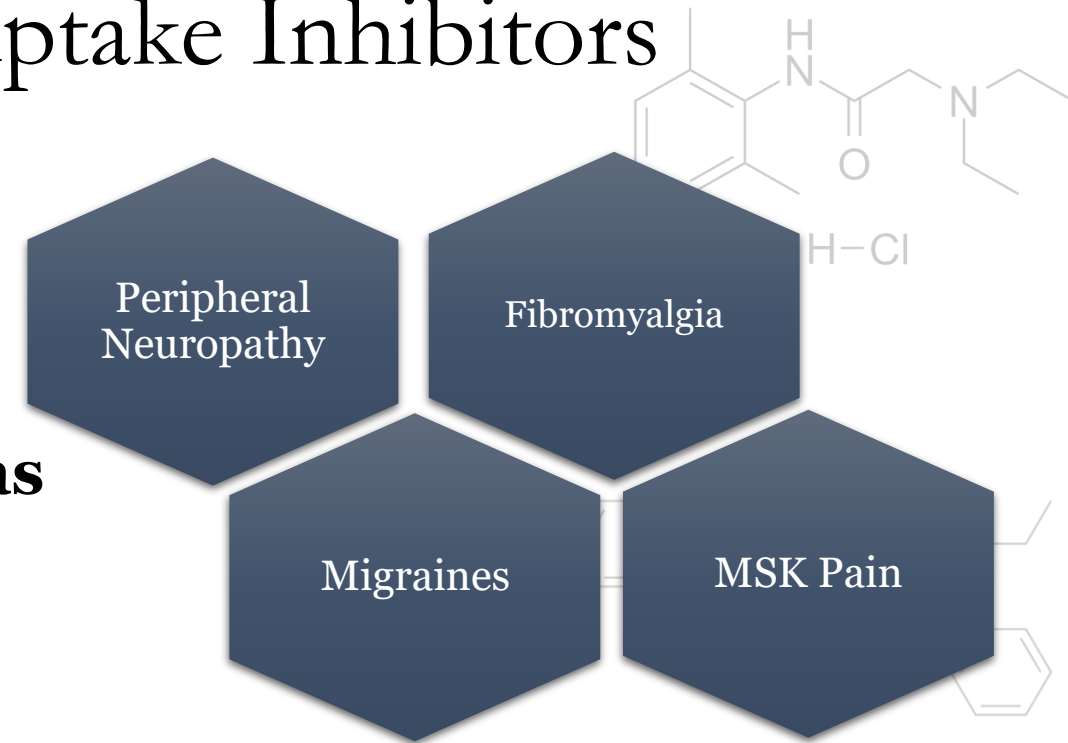


On Today's Menu

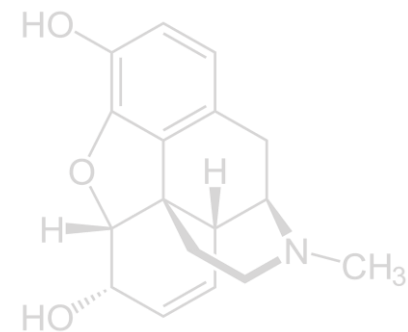


Serotonin-Norepinephrine Reuptake Inhibitors

- Duloxetine, milnacipran, desvenlafaxine, venlafaxine, tramadol
- ADR: bleeding, serotonin syndrome
- **Inconsistent results to benefit routinely as part of multimodal analgesia regimen**



Inhibits Presynaptic Neuronal Reuptake of Serotonin	Direct Serotonin Receptor Agonist	Inhibits Serotonin Metabolism
Cocaine, meperidine, dextromethorphan, St. John's Wort	Fentanyl, triptans, metaxalone	Monoamine oxidase inhibitors



Tramadol TramaDONT



“This patient’s pain is severe, acetaminophen isn’t enough”

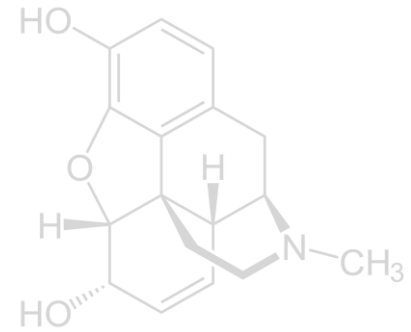
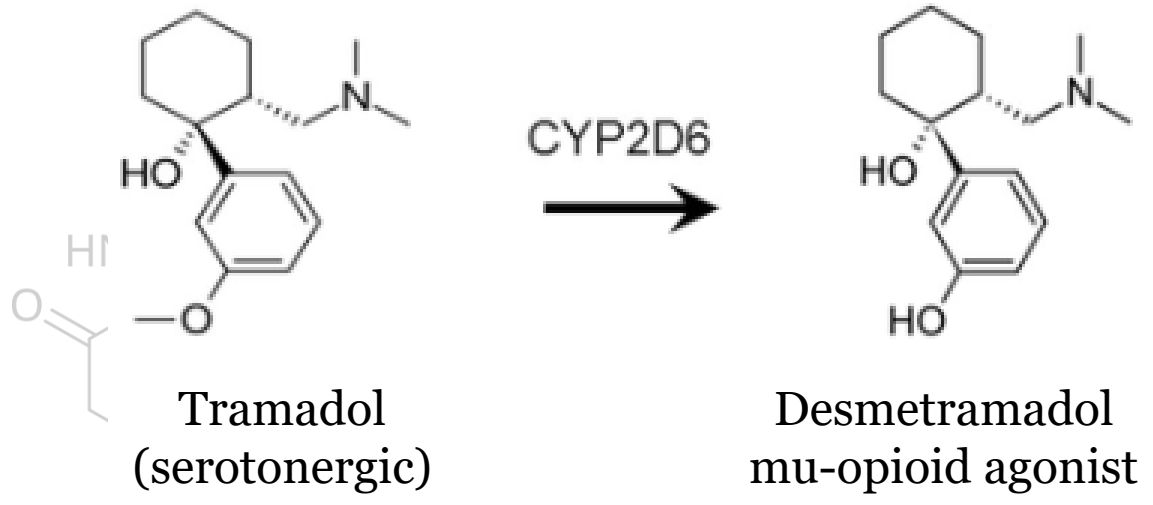
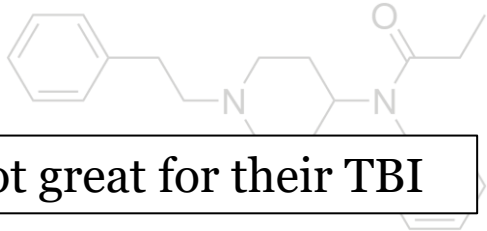
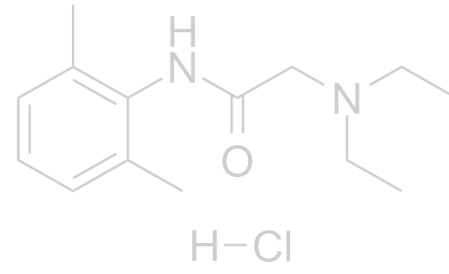
It’s an SNRI (prodrug).

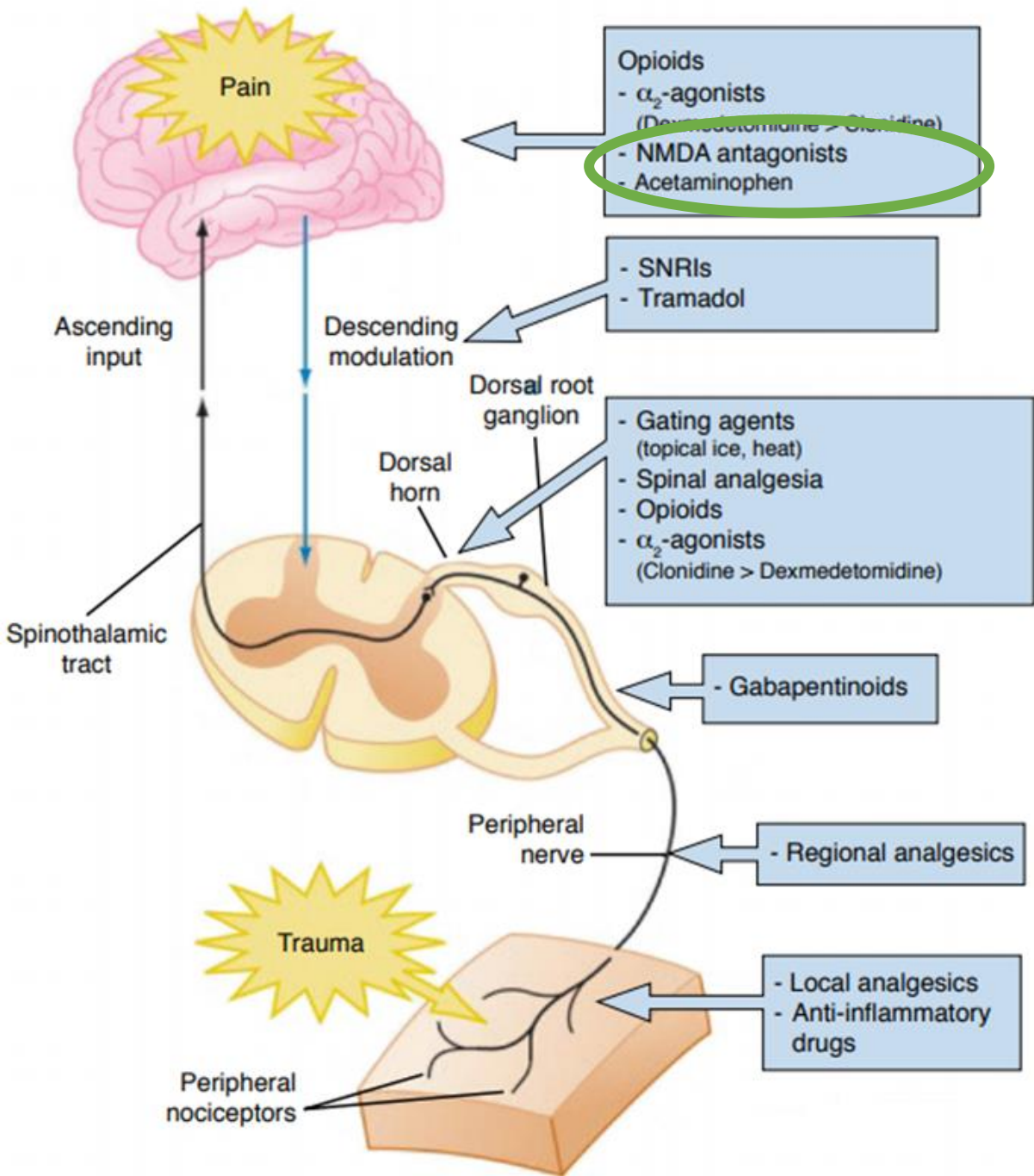
“It’s opioid sparing”

But it’s a μ -opioid receptor agonist

“This trauma patient looks uncomfortable”

It can lower the seizure threshold, not great for their TBI





On Today's Menu



IV Acetaminophen



“You want to make a pharmacist mad? Ask for IV Tylenol”

Review of Intravenous Acetaminophen for Analgesia in the Postoperative Setting

Danielle M. Tompkins, PharmD, BCCCP^{1,2},
Arielle DiPasquale, PharmDc¹, Michelle Segovia, PharmDc¹,
and Stephen M. Cohn, MD, FACS³

IV APAP inferior to NSAIDs for analgesia after bariatric surgery

No difference compared to oral APAP or NSAIDs in abdominal, gynecologic, genitourinary, orthopedic, or renal surgery

Conflicting results in neurological or cardiac surgery

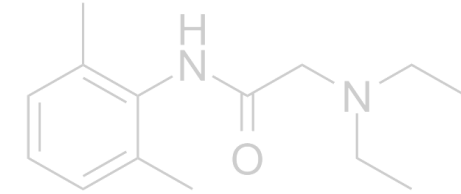
Beneficial PK profile did not translate into improved clinical outcomes

- No benefit of IV over PO or rectal APAP

H-Cl

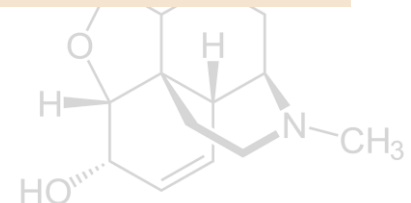


Average Cost Comparison



Medication	Cost per dose ^a	Cost per 24 hours ^b
Acetaminophen (PO)	\$0.01 per 325 mg tablet	\$0.12
Acetaminophen (suppository)	\$0.66 per 650 mg suppository	\$2.64
Acetaminophen (IV)	\$31.72 per 1000 mg/100 mL vial	\$126.88
Ibuprofen (PO)	\$.29 per 600 mg tablet	\$1.16
Ketorolac (IV)	\$1.04 per 30 mg vial	\$4.16
Tramadol (PO)	\$.80 per 50 mg tablet	\$3.20
Oxycodone (PO)	\$.39 per 5 mg tablet	\$1.56
Morphine (IV)	\$2.47 per 2 mg/mL vial	\$9.88
Hydromorphone (IV)	\$4.98 per 0.5 mg/0.5 mL vial	\$19.92

^aPricing based on average wholesale price.
^bCost per 24 h based on average dose scheduled every 6 hours.





Ketamine

Ketamine

MOA: NMDA antagonist

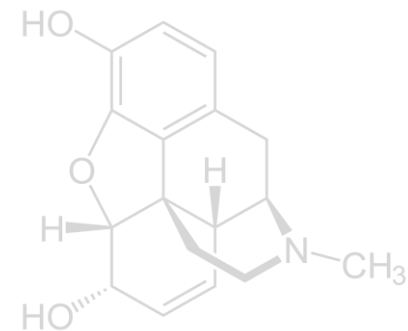
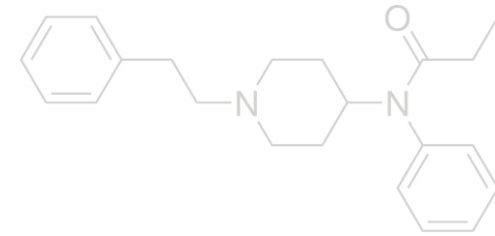
- Hypnotic, amnestic, bronchodilator, antidepressant, analgesic

Dose-dependent effects

- Pain (low-dose): 0.1- 0.3 mg/kg/h
- Sedation (moderate-dose): 0.5 – 1.5 mg/kg/h
- Amnestic (high-dose): up to 7.5 mg/kg/h

Adverse effects

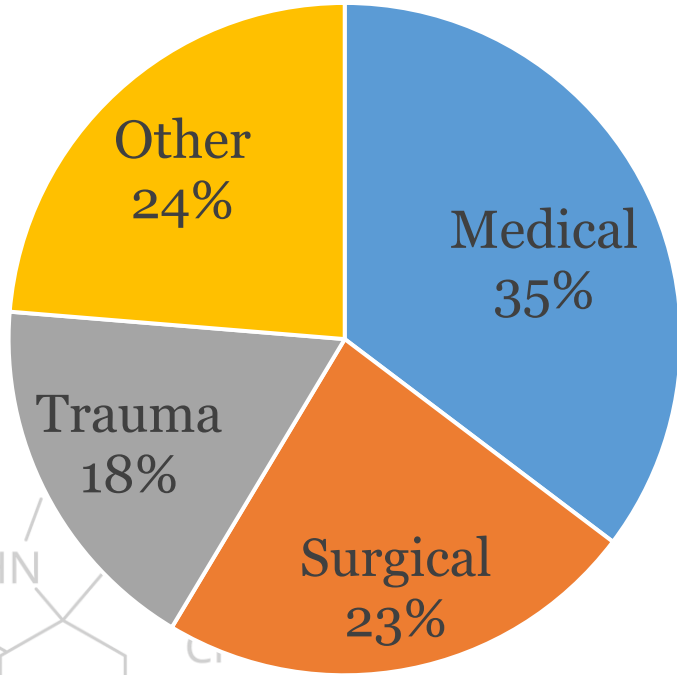
- Laryngospasm
- Increased blood pressure and heart rate
- Cardiac decompensation
- Emergence reactions



Multicenter Retrospective Review of Ketamine Use in the ICU

- Multicenter observational study across 25 institutions in the US

ICU Type



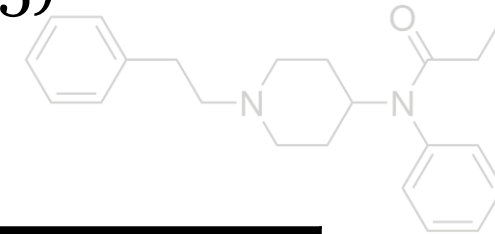
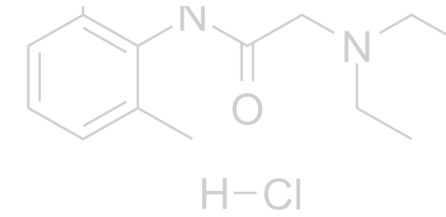
N = 390



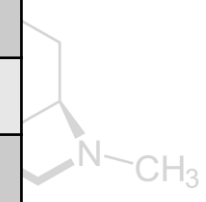
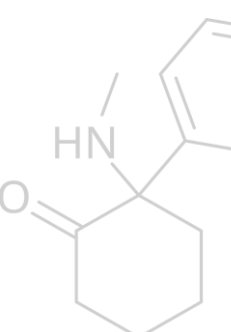
- Christine M. Groth, PharmD, BCCCP, FCCM¹
- Christopher A. Droege, PharmD, BCCCP, FCCM, FASHP²
- Kathryn A. Connor, PharmD, BCCCP³
- Kimberly Kaukeinen, BA¹
- Nicole M. Acquisto, PharmD, BCCCP, FCCM, FCCP, FASHP¹
- Sai Ho J. Chui, PharmD, BCPS, BCCCP⁴
- Michaelia D. Cucci, PharmD, BCPS, BCCCP⁵
- Deepali Dixit, PharmD, BCPS, BCCCP, FCCM⁶
- Alexander H. Flannery, PharmD, PhD, BCPS, BCCCP, FCCM⁷
- Kyle A. Gustafson, PharmD, BCPS, BCCCP⁸
- Nina E. Glass, MD, FACS⁹
- Helen Horng, PharmD, BCCCP¹⁰
- Mojdeh S. Heavner, PharmD, BCPS, BCCCP, FCCM¹¹
- Justin Kinney, PharmD, MA, BCCCP¹²
- Rachel M. Kruer, PharmD, BCCCP, CNSC¹³
- William J. Peppard, PharmD, BCPS, FCCM¹⁴
- Preeyaporn Sarangarm, PharmD, BCPS, BCCCP¹⁵
- Andrea Sikora, PharmD, MSCR, BCPS, BCCCP, FCCM¹⁶
- Velliyur Viswesh, PharmD, BCIDP, BCCCP¹⁷
- Brian L. Erstad, PharmD, MCCM, FCCP, FASHP¹⁸

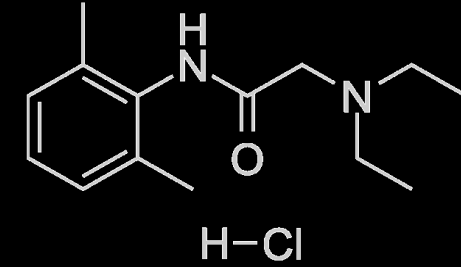
Multicenter Retrospective Review of Ketamine Use in the ICU

- Multicenter observational study across 25 institutions in the US
- Median starting dose 0.2 mg/kg/h (0.1 – 0.5 mg/kg/h)
- Significant increase in proportion of time spent within goal pain score ($P < 0.001$)
- Significant reduction in concomitant opioids and sedatives ($P < 0.005$)
- No difference in delirium ($P = 0.233$)



Time Period	% Goal Pain Score Range	Median IV Morphine Equivalents	Median IV Midazolam Equivalents	Median Propofol Dose
24 hours prior to ketamine	68.9%	120 mg	11 mg	942 mg
0-24 hours	78.6%	118 mg	6 mg	160 mg
25-48 hours	80.3%	80 mg	3 mg	0 mg





Honorable Mentions

Corticosteroids

> 0.11 mg/kg IV dexamethasone x 1

Magnesium

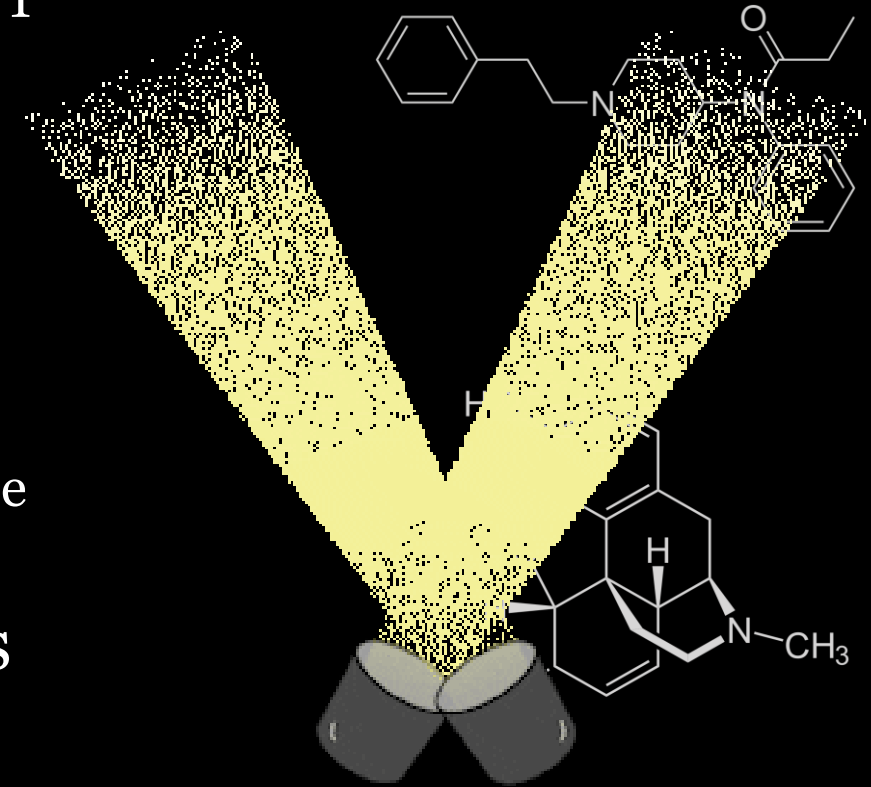
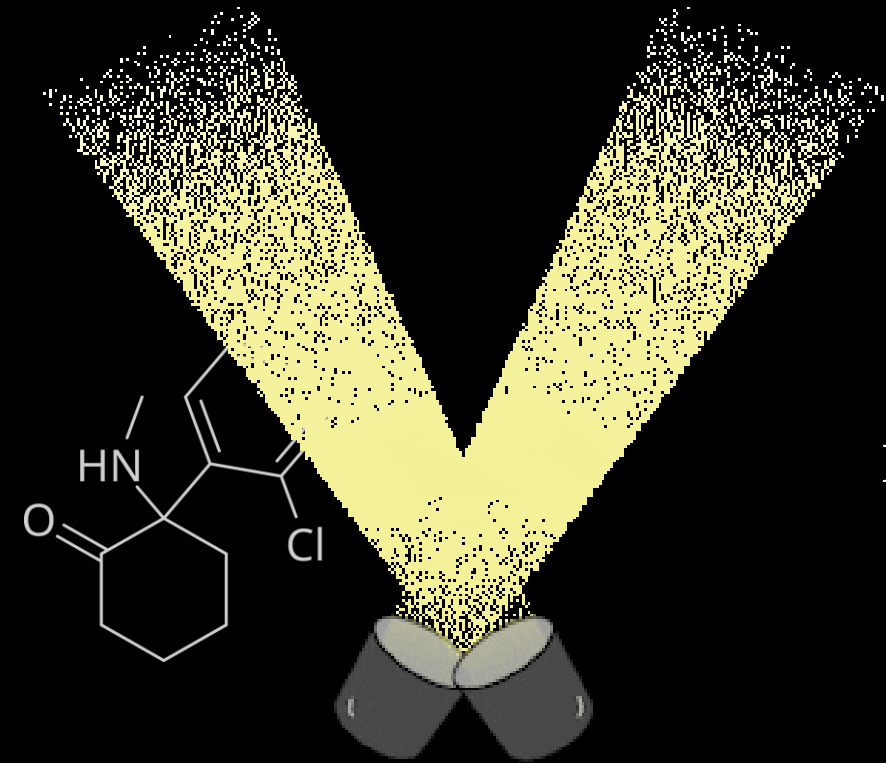
30-50 mg/kg at induction

Volatile Anesthetics

Desflurane, isoflurane, sevoflurane

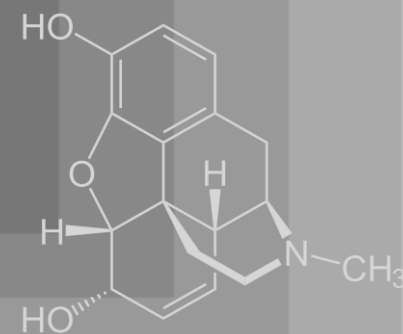
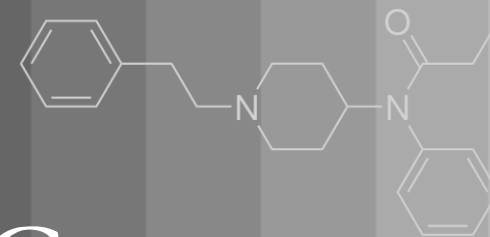
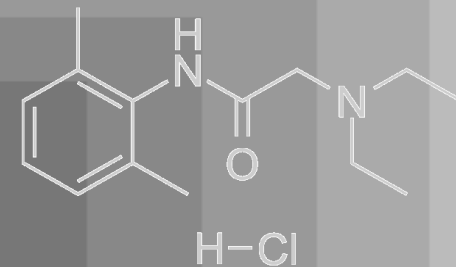
Peripheral Nerve Blocks

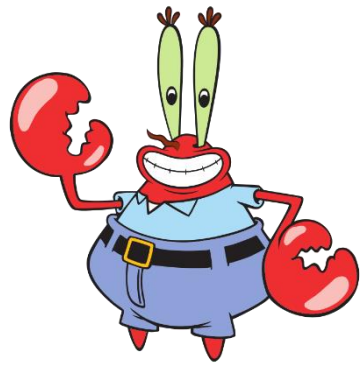
Bupivacaine, ropivacaine





Patient Case





79M



MVC



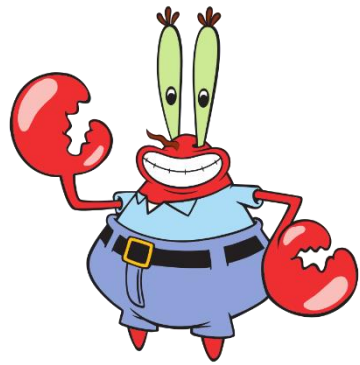
Admitted to TICU

Injuries

- L 3-6 rib fractures
- L open femur fracture
- L ankle fracture
- L open humerus fracture

The team is discussing potential pain regimens for this patient. Which of the following statements is true regarding multi-modal analgesia?

- Multi-modal analgesia has clear mortality benefit compared to opioid monotherapy
- Multi-modal analgesia can decrease opioid consumption
- Multi-modal analgesia should be avoided given the risk for non-union fractures
- Multi-modal analgesia is not appropriate given the extent of traumatic injuries



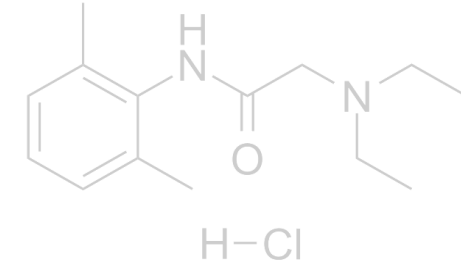
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MVC

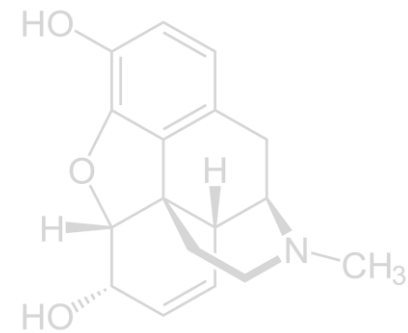
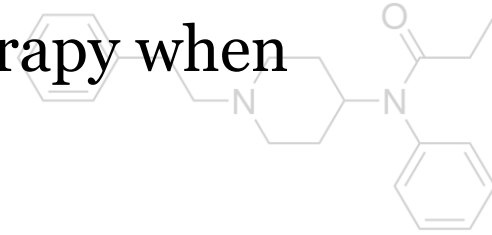


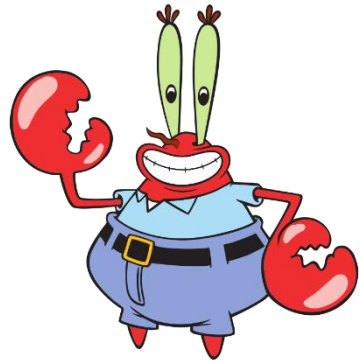
Admitted to TICU



Which of the following is not a contraindication for IV lidocaine therapy when used to manage acute pain?

- a) Conduction abnormalities
- b) Previous anaphylaxis to bupivacaine
- c) Pregnancy
- d) Recent intra-abdominal procedures





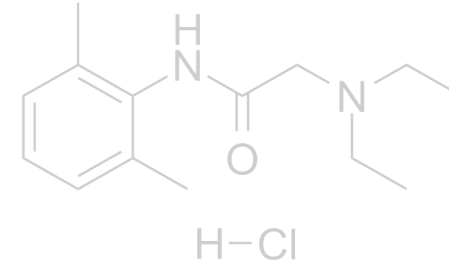
79M



MVC

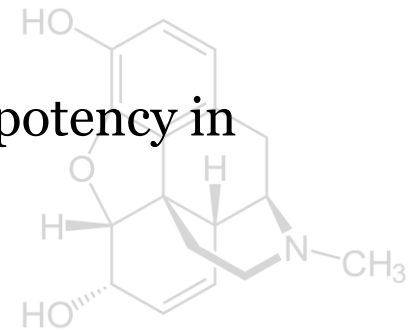
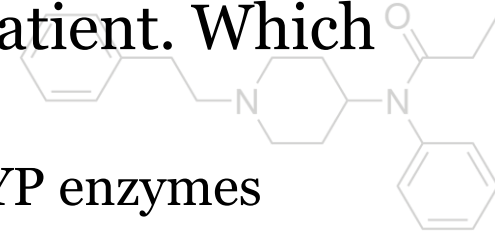


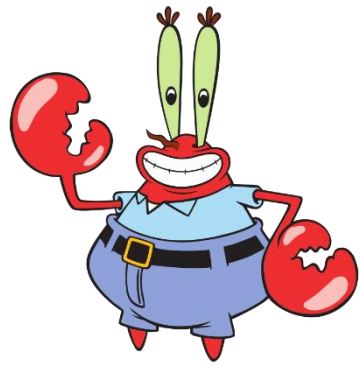
Admitted to TICU



The surgical resident asks you about starting a gabapentin for this patient. Which statement is **incorrect**?

- a) Gabapentinoids have few interactions because they are not metabolized by CYP enzymes
- b) Gabapentinoids should be used with caution because GABA-a agonists can cause respiratory depression
- c) Gabapentin is reasonable but demonstrates non-linear pharmacokinetics
- d) Pregabalin has increased binding affinity compared to gabapentin and has more potency in neuropathic pain





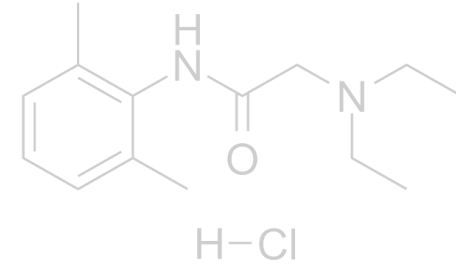
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MVC

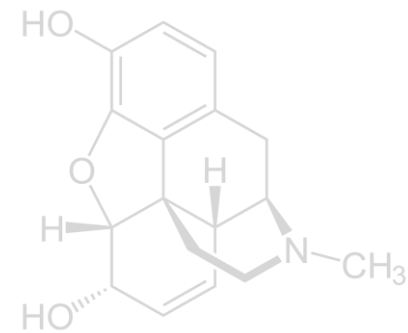
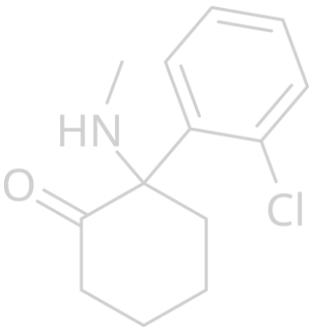
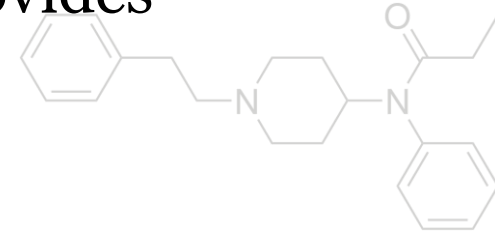


Admitted to TICU



Dexmedetomidine can be considered for adjunctive sedation but provides minimal analgesia without additional clinical benefit.

- a) True
- b) False



Mu Over Opioids, Non-Opioid Pain Management Coming Through!

Matthew Li, PharmD, MHA, BCPS, BCCCP

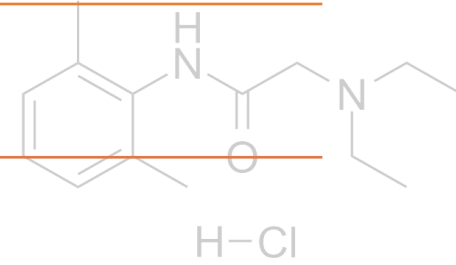
Clinical Pharmacy Specialist – Trauma, Surgical, Burn ICU

Clinical Assistant Professor of Surgery – New York Medical College

Westchester Medical Center
Valhalla, NY

Sample
ERAS
Protocol
Components

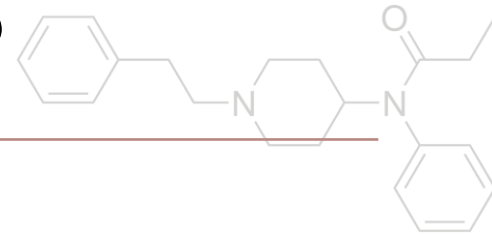
Ketorolac 15 mg IV Q6H x 24 H



Ketamine infusion x 24 H

Gabapentin 300-600 mg PO Q8H x 7 D

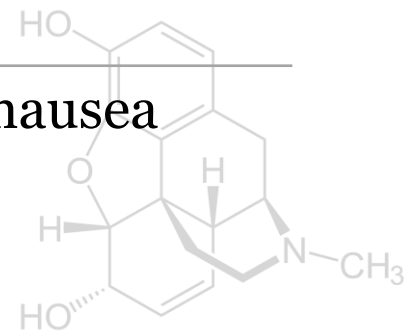
Acetaminophen 1000 mg PO Q8H x 7D



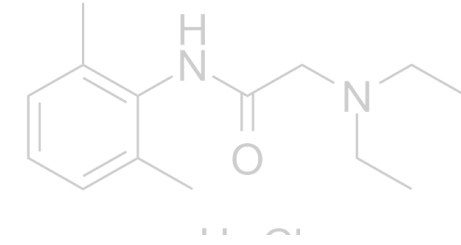
Tizanidine 4 mg Q8H as needed

Oxycodone 5 mg PO Q4H for as needed breakthrough pain

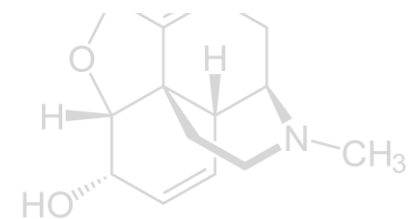
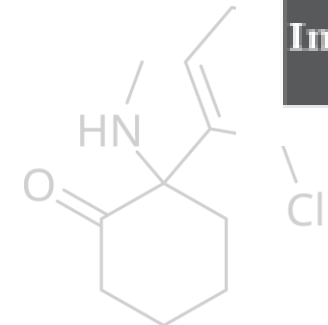
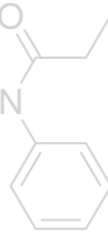
Ondansetron 4 mg PO Q6H as needed for nausea



Types of Pain



	Description	Localization	Description	Etiology	Management
Nociceptive	Tactile on skin and external soft tissues; musculoskeletal	Very localized	Variable but typically sharp, stabbing	Trauma, pressure	Anti-inflammatories, centrally acting agents; opioids as last resort
Visceral	Deeper origin, e.g., gut or brain (colic, obstruction)	Poorly localized (headache, abdominal pain, chest pain)	Dull, achy, colicky, intermittent	Injury or trauma to internal organs	Centrally acting; opioids as last resort, need to pursue cause
Neuropathic	Commonly peripheral extremities (spinal cord injury, herpes zoster, DM neuropathy)	Usually well localized	Burning, piercing, tingling; constant	Chronically damaged nerves from DM, ischemia,	Nerve stabilizers, antidepressants > anti-inflammatory; opioids as last resort
Inflammatory	Soft tissues and joints	Usually well localized	Burning, aching, worse with movement	Soft tissue or joint inflammation locally	Anti-inflammatory; ice, compression; opioids as last resort



Regional Anesthesia in the ICU

WHY

Minimize opioid use

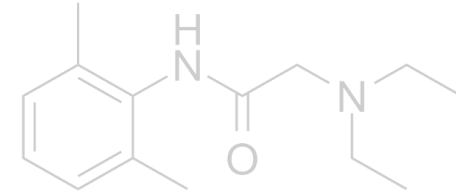
Facilitates rehabilitation

Advantageous when systemic anesthesia for intubation should be avoided

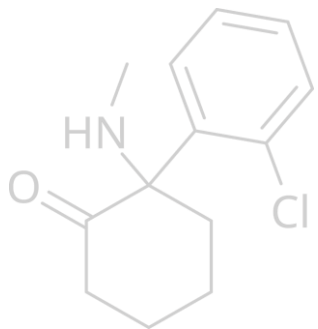
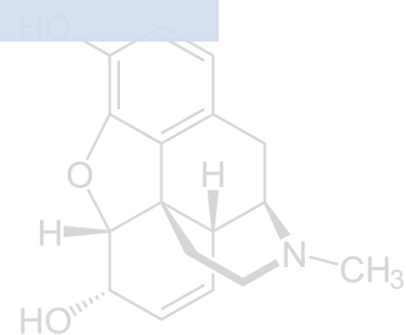
HOW

Effectively manage pain

Interrupts action potentials by reversibly binding to voltage-gated sodium channels



HCl

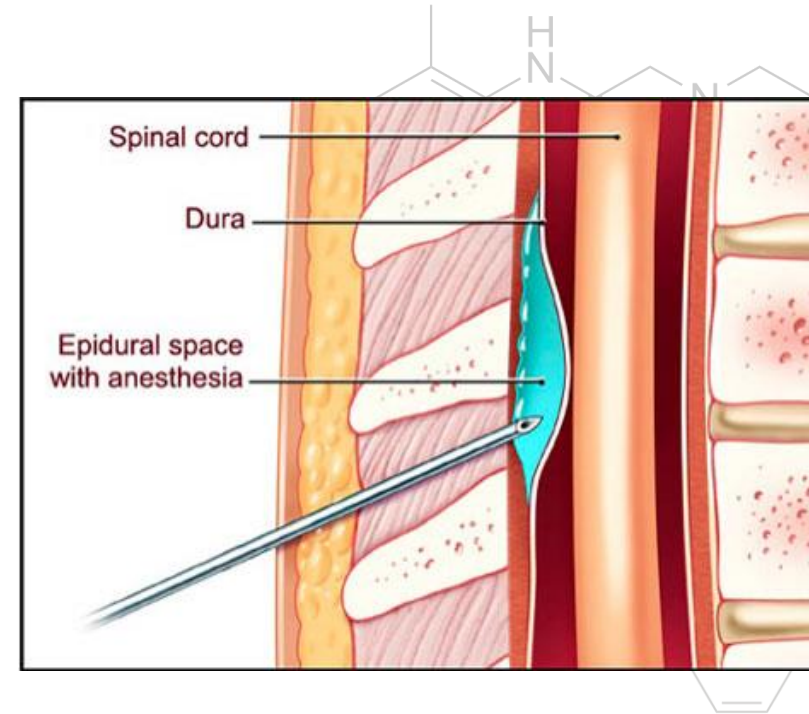


Neuraxial Anesthesia

Spinal, epidural, combined

Commonly used for lower abdominal and lower extremity surgery

- Hemorrhoidectomy
- Hysterectomy
- Knee and hip replacements
- Prostatectomy
- Cesarean delivery
- Inguinal hernia repair



Agent	Dose	Duration
Chloroprocaine 3%	30 – 60 mg	40 – 90 min
Bupivacaine 0.5%, 0.75%	15 – 20 mg	90 – 120 min
Ropivacaine 0.5%, 0.75%	15 – 20 mg	90 – 200 min

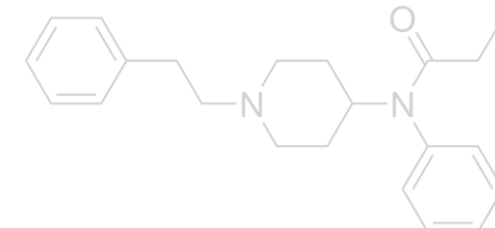
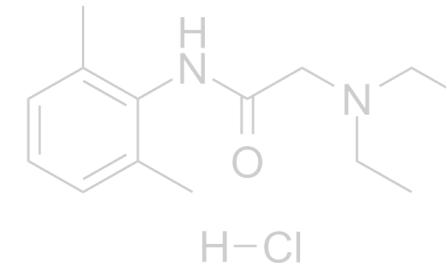
Complications: post-dural puncture headache, hypotension, hematoma, local anesthetic toxicity, total spinal block, nerve injury

Absolute Contraindications

- Epidural abscess
- Hemodynamic instability
- Coagulopathy
- Increased intracranial pressure

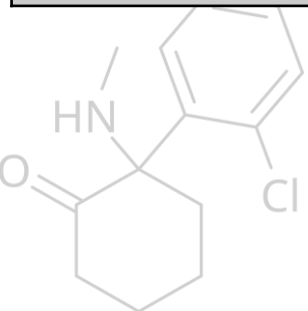
Peripheral Nerve Blocks

- Local anesthetics into tissues around peripheral nerves
- Great for long procedures and for intra-and post-procedural pain
- Similar complications to neuraxial anesthesia



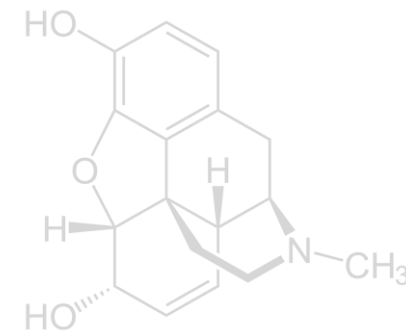
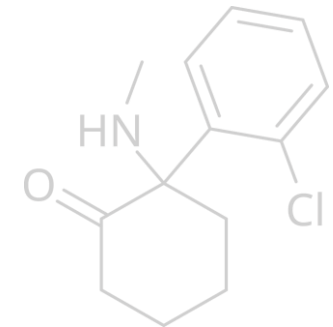
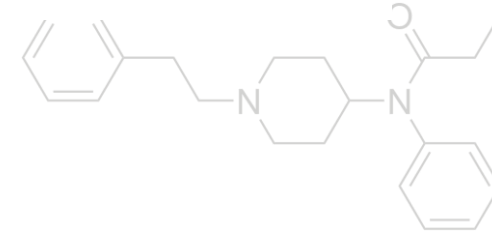
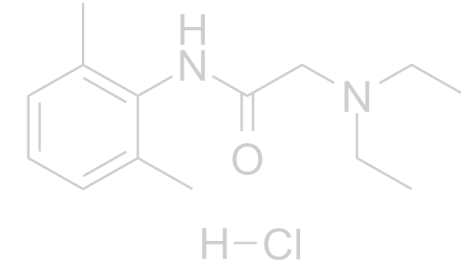
Agent	Volume	Duration
Lidocaine 1%-2%	30 – 50 mL	120 – 240 min
Bupivacaine 0.25%-0.5%	30 – 50 mL	360 – 720 min
Ropivacaine 0.2% - 0.5%	30 – 50 mL	360 – 720 min

Type of Block	Common Procedures
Transversus abdominis plane	Abdominal Groin Chest
Rectus sheath	Chest
Paravertebral	Breast Chest
Brachial plexus and other upper extremity	Shoulder, arm, hand, digit
Femoral nerve	Thigh, femur, knee



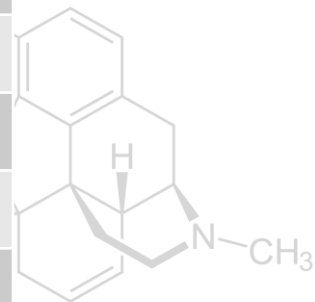
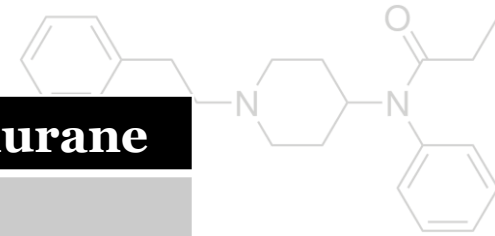
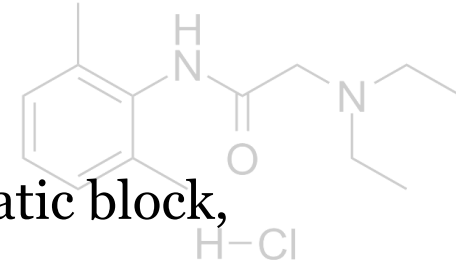
Anticoagulation Considerations During Neuraxial Anesthesia or Peripheral Blocks

- Coagulopathies limit use
- Guideline recommendations from American Society of Regional Anesthesia and Pain Medicine (ASRA)
- Refer to institution specific policies
- Recommendations vary depending on type of blockade and anticoagulant

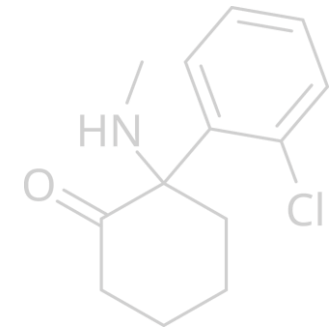


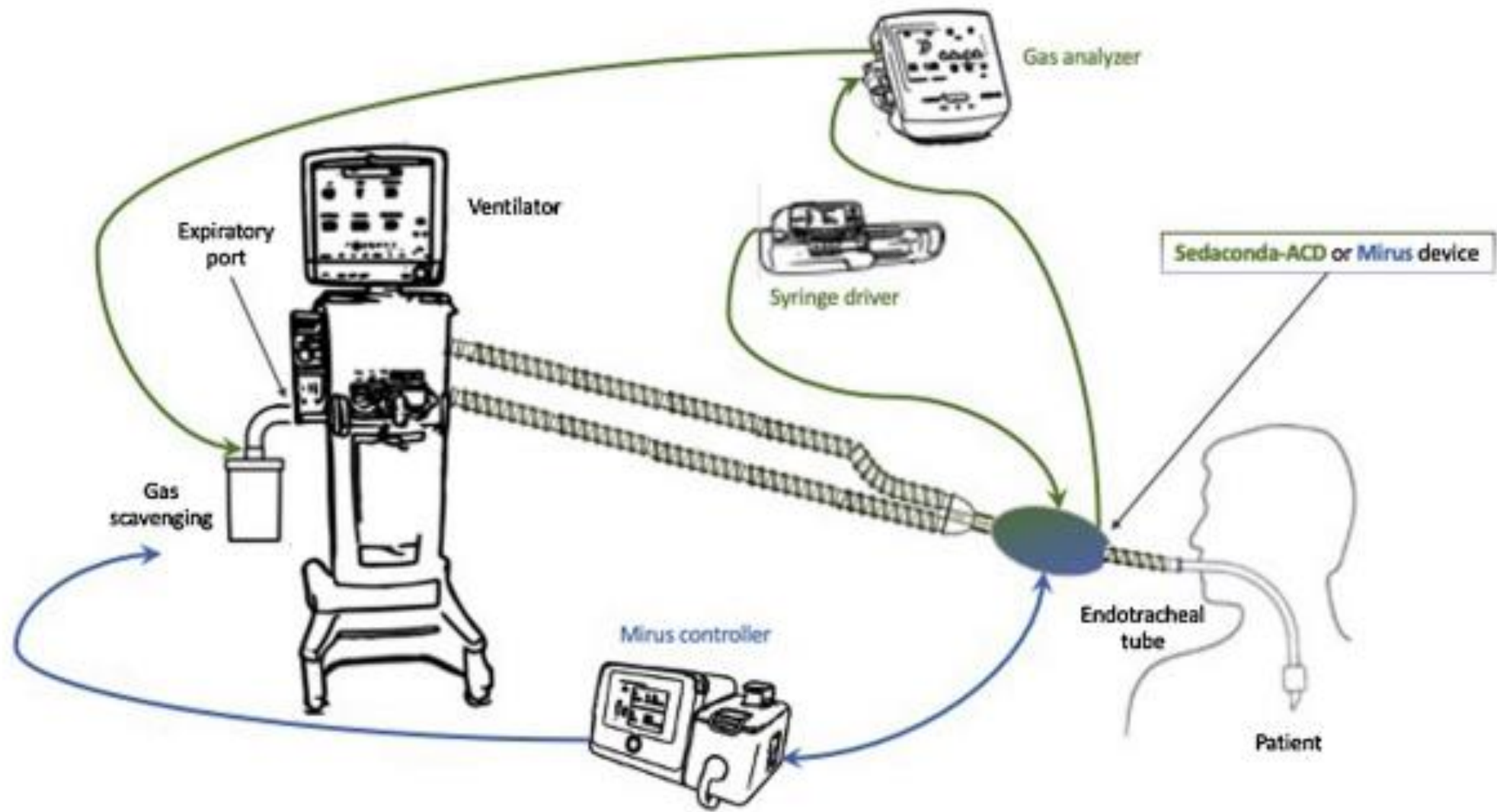
Volatile Anesthetics

- Dose-dependent hypnosis, amnesia, anxiolysis, akinesia, autonomic, and somatic block, and respiratory depression
- Bronchodilator and anticonvulsant
- MOA: GABA agonists, NMDA antagonist
- Modest analgesic properties

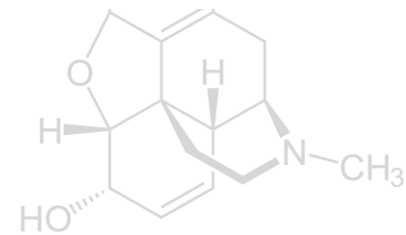


Characteristics	Desflurane	Isoflurane	Sevoflurane
How Supplied	Liquid	Liquid	Liquid
Preservative	No	No	No
Blood-gas partition coefficient	0.42	1.46	0.65
Brain-blood partition coefficient	1.3	1.6	1.7
Recovered as metabolites (%)	0.02	0.2	2-5
Elimination	Lungs	Lungs	Lungs
Hepatic metabolism (%)	0.02	0.2	2-5
Tachyphylaxis	No	No	No



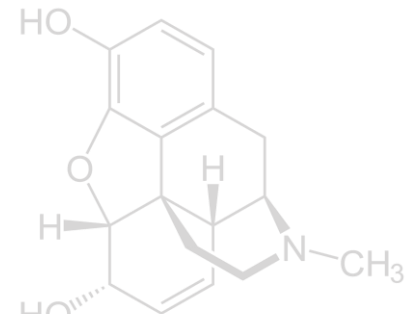
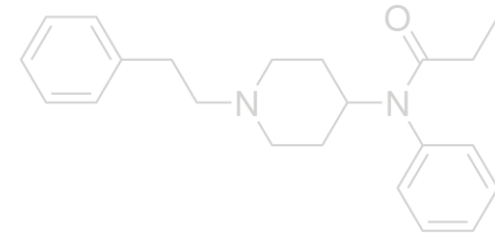
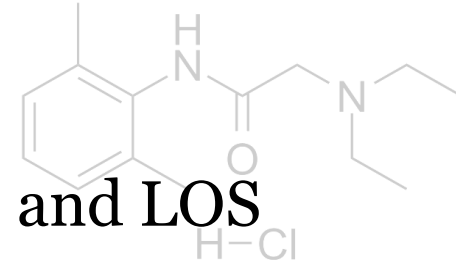


Replacement Frequency
 Sedaconda-ACD: 24 hours
 Mirus System: 7 days



Considerations of Inhaled Anesthetics

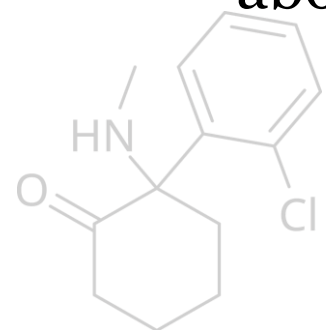
- Conflicting evidence supporting reduction in opioid requirements and LOS
- ADR
 - Dose dependent hypotension (not reflected in studies)
 - Nausea, vomiting
 - Malignant hyperthermia
 - Psychomotor (hallucinations, tremor, chorea)
 - Blunted cerebral autoregulation, increased cerebral vasodilation
- Time-weighted exposure risk for developmental defects and spontaneous abortions



Herzog-Niescery J, et al. *J Clin Monit Comput* 2018;32:667-75

Meiser A, et al. *Lancet Respir Med* 2021;9:1231-40.

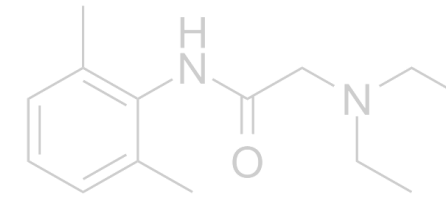
Ariyama J, et al. *J Clin Anesth* 2009;21:567-73.



Jabaudon M, et al. *Anaesth Crit Care Pain Med*. 2022 Oct;41(5):101133.

Larach MG, et al. *Anesth Analg* 2014;119:1359-66.

Summary of Guideline Recommendations



Agent	2018 PADIS	2016 American Pain Society
Acetaminophen	Recommended – conditional, very low quality	Recommended – strong, high quality
Dexmedetomidine	Not addressed for pain	Not addressed
Ketamine	Recommended for postoperative ICU patients – conditional, low quality	Recommended – weak, moderate quality
Lidocaine	Routine use not recommended – conditional, low quality	Recommended – strong, high quality CI in patients post-CABG
Neuropathic agents	Recommended for neuropathic pain in critically ill patients – strong, moderate quality Recommended after cardiac surgery – conditional, low quality	Recommended – strong, moderate quality
NSAIDs	Routine use of COX-1 selective not recommended – conditional, low quality	Recommended – strong, high quality CI in CABG patients
Skeletal muscle relaxants	Not addressed	Not addressed
Volatile anesthetics	Not recommended – strong, very low quality	Not addressed