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Clinical Meeting & Exhibition

# Multimodal Analgesia from ERAS to the Critically Ill: Strategies for the Clinical Pharmacist

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# Disclosure

**James Gilmore**

Pacira Pharmaceuticals: Advisory Board

All other planners, presenters, and reviewers of this session report no financial relationships relevant to this activity.

# Objectives

- Describe the consequences of inadequate pain control in the inpatient setting.
- Apply concepts in the selection of analgesic regimens and multimodal approaches in various inpatient settings.
- Recommend strategies to overcome key barriers to multimodal analgesia pharmacotherapy in the inpatient setting.

# Why is Pain Still a Pain?

- Acute pain is very common
- 51.4 million surgical ***in-patient*** procedures were performed in 2010 in the United States
- Almost all patients experience pain after surgery, procedure, or injury
- Survey of 300 US adults undergoing surgery:
  - 86% experienced pain post surgery
  - 75% had moderate to extreme pain in the immediate postsurgical period
  - 74% still had pain post discharge

Gan TJ et al. *Curr Med Res Opin*. 2014;30(1):149-160.

Centers for Disease Control and Prevention. National Center for Health Statistics. www.cdc.gov/nchs/faststats/inpatient-surgery. Accessed July 8, 2015

# Inadequate Acute Pain Management Can Have Consequences

- Chronic pain may develop after surgery as a result of complex biochemical and pathophysiological mechanisms
- Clinically meaningful, severe acute postoperative pain may be a risk factor for the development of chronic pain
- Up to 50% of patients reportedly suffer from chronic pain following common surgery
- Effectively managing acute pain can reduce the risk for pain progression

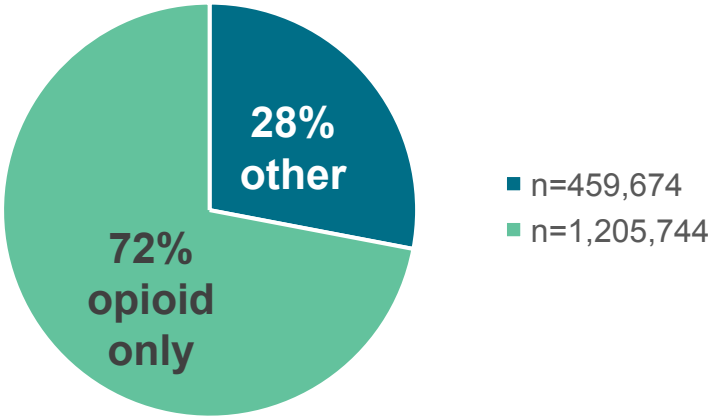

Sinatra R. *Pain Med.* 2010;11(12):1859-1871.
Morrison RS et al. *J Am Geriatr Soc.* 2009;57(1):1-10.
Voscopoulos C, Lema M. *Br J Anaesth.* 2010;105(suppl 1):i69-i85.
Zhou J etal. Nature.com/scienticreports. April 2017

# New Paradigm for Patient Care


Liang BA, Mackey T. *Arch Pathol Lab Med.* 2011; 135(11): 1425-1431.

# Opioids have Historically been the Foundation for Acute Pain Management

- In a 2012 research database of 1,665,418 patients, 72% of inpatients treated with IV analgesia received IV opioid monotherapy




Data from the hospital research database maintained by the Premier healthcare alliance. July 17, 2013.

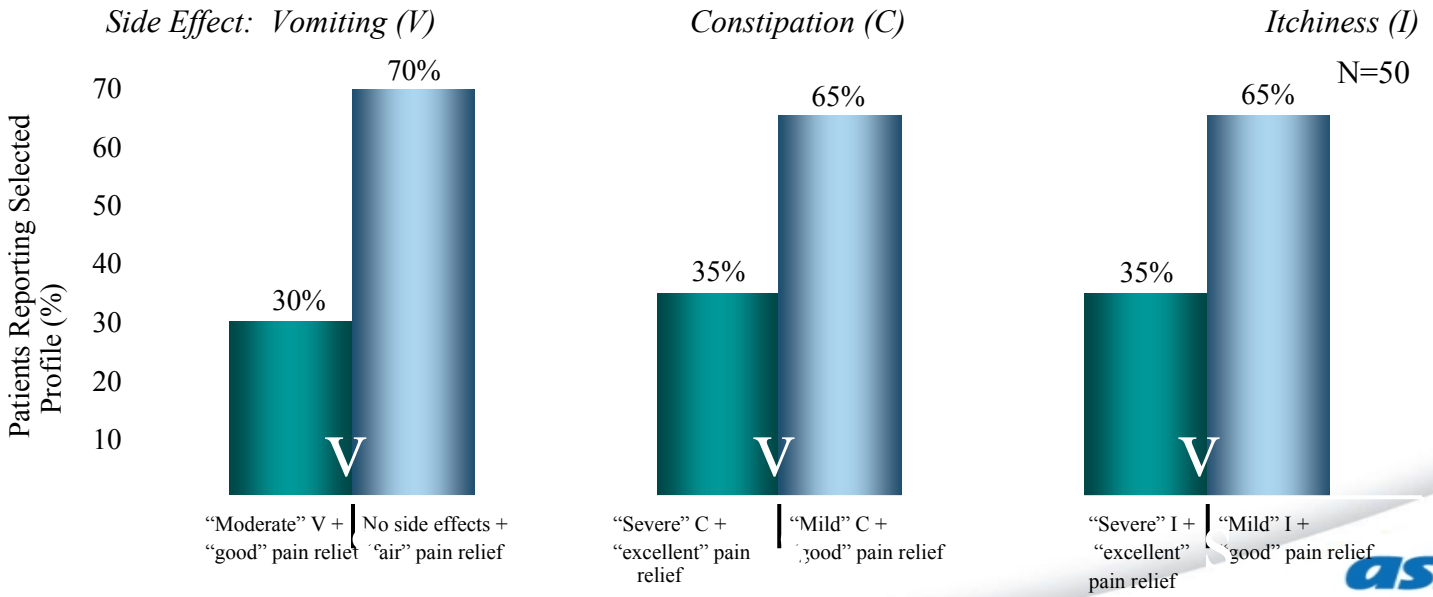
# Opioids

Analgesia

Adverse Effects

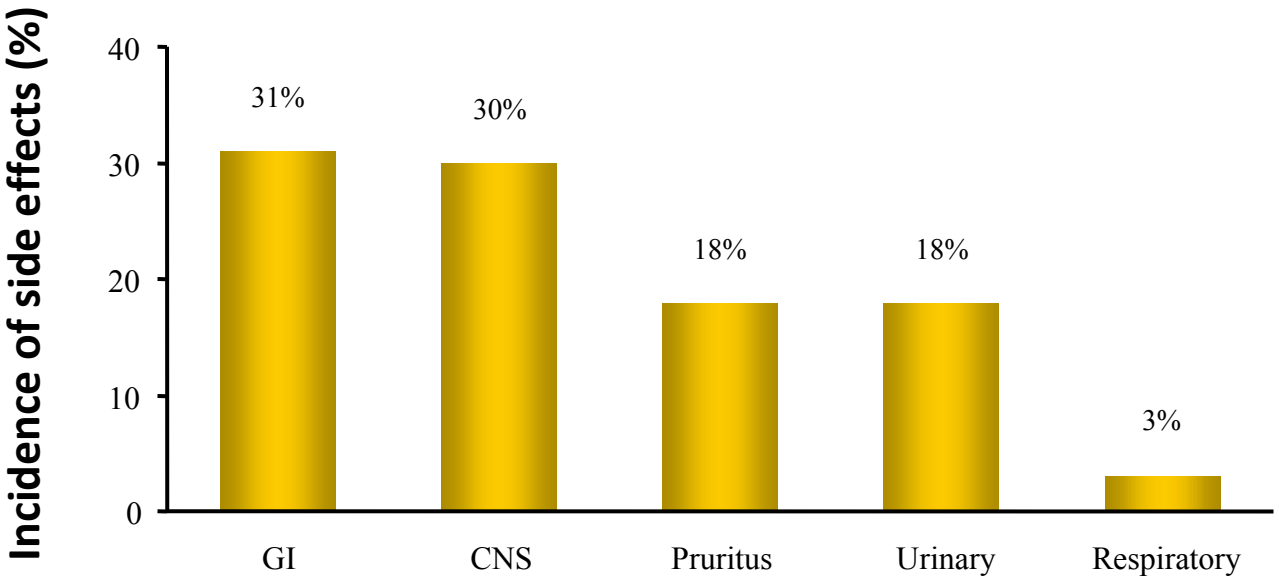
# "Trade-offs" in Pain Management: Patients Have Concerns That May Hinder Treatment

More post-surgical patients chose less pain relief than increased/more severe side effects




Gan et al. *Brit J Anaesthesia*. 2004;92:681-688.

# GI Disturbances Are Among the Most Common Side Effects of Postoperative Opioid Analgesia




Wheeler et al. *J Pain*. 2002;3:159-180.

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# Cost of Opioid Related Adverse Drug Event's in Surgical Patients

- 10yr study, 60,722 adult patients
- 2.7% opioid ADE rate
- N/V = 67%, rash, hives and itching =33.5%
- Increased LOS by 0.53 days
- 29% of preventable ADE's due to analgesics

Oderda GM. J. Pain Symptom Management. 2003

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# Postoperative Opioid Induced Respiratory Depression (OIRD)

- Adults on PCA postoperatively:
  - 41% incidence of hypoxemia (SpO2<90%)
  - 1/178 patients required rescue (positive pressure ventilation)
    - » Overdyk FJ. Anesth Analg 2007;105:415

- 77% of events (naloxone required) occurred in first 24 hours postoperatively
    - » Taylor S. Am J Surg 2005;190:752

# MULTIMODAL TECHNIQUES FOR PERIOPERATIVE PAIN MANAGEMENT

Multimodal analgesia combines two or more analgesic agents or techniques that act by different mechanisms to provide analgesia

American Society of Anesthesiologists (ASA) Task Force recommendations

- Unless contraindicated, all patients should receive an around-the-clock regimen of a non-opioid agent
  - Non-steroidal anti-inflammatory drugs (NSAIDs)
  - Cyclooxygenase-2 specific drugs (COXIBs)
  - Acetaminophen
- Consider supplemental regional anesthesia techniques

# MULTIPLE ORGANIZATIONS RECOMMEND A NON-OPIOID FOUNDATION TO MULTIMODAL ANALGESIA

Society Recommendations

- American Society of Anesthesiologists (ASA)[1]
- American Society of Pain Management Nursing (ASPMN)[2]
- American Society of PeriAnesthesia Nurses (ASPAN)[3]
- American Geriatrics Society (AGS)[4]
- Society for Critical Care Medicine (SCCM)[5]
- Surgical Societies (e.g., American Academy of Orthopaedic Surgeons)[6]

Accrediting and Quality Organizations

- The Joint Commission (TJC)[3]
- Agency for Healthcare Research and Quality (AHRQ)[7]

. ASA Task Force on Acute Pain Management. *Anesthesiology.* 2012; 116: 248-273. 2. Jarzyna D, Jungquist CR, Pasero C, et al. *Pain Manage Nurs.* 2011; 12: 118-145. 3. Wells N , Pasero C, McCaffery M. In Hughes RD, ed. Agency for Healthcare Research and Quality; 2008. 4. The American Geriatrics Society. Pain management in the elderly. http://www.americangeriatrics.org/gsr/anesthesiology/pain_management.pdf. Accessed September 10, 2014. 5. Barr JU, Fraser GL, Puntillo K, et al. *Crit Care Med.* 2013; 41(1): 263-306. 6. AAOS. Sept. 5, 2014. http://www.aaos.org/Research/guidelines/HipFxGuideline_rev.pdf. 7. Hughes RD ed. Patient safety and quality: an evidence-based handbook for nurses. Rockville, MD: Agency for Healthcare Research and Quality; 2008.

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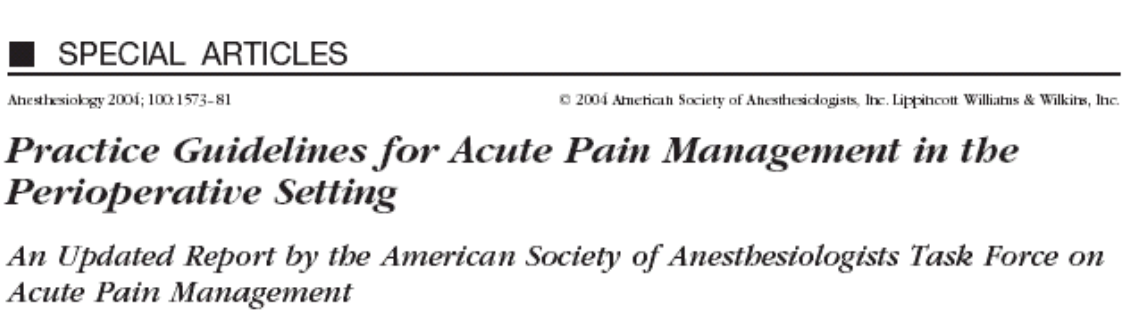


**“Whenever possible, anesthesiologists should employ multimodal pain management therapy. Unless contraindicated, all patients should receive around-the-clock regimen of NSAIDs, Coxibs, or acetaminophen.”**

Savarese JJ etal. J Healthcare Risk Management 2107;37(1)
Chou R etal. The Journal of Pain. 2016. 17(2); 131-157
ASA Task Force on Acute Pain Management. *Anesthesiology*. 2004;100;1573-1581.

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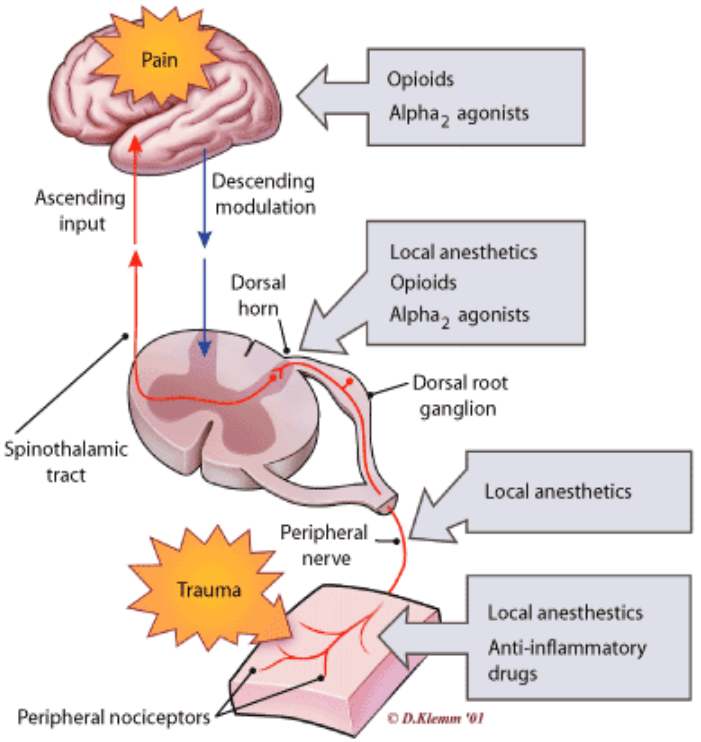
# The Pain Pathway and Interventions that can Modulate Activity at Each Point



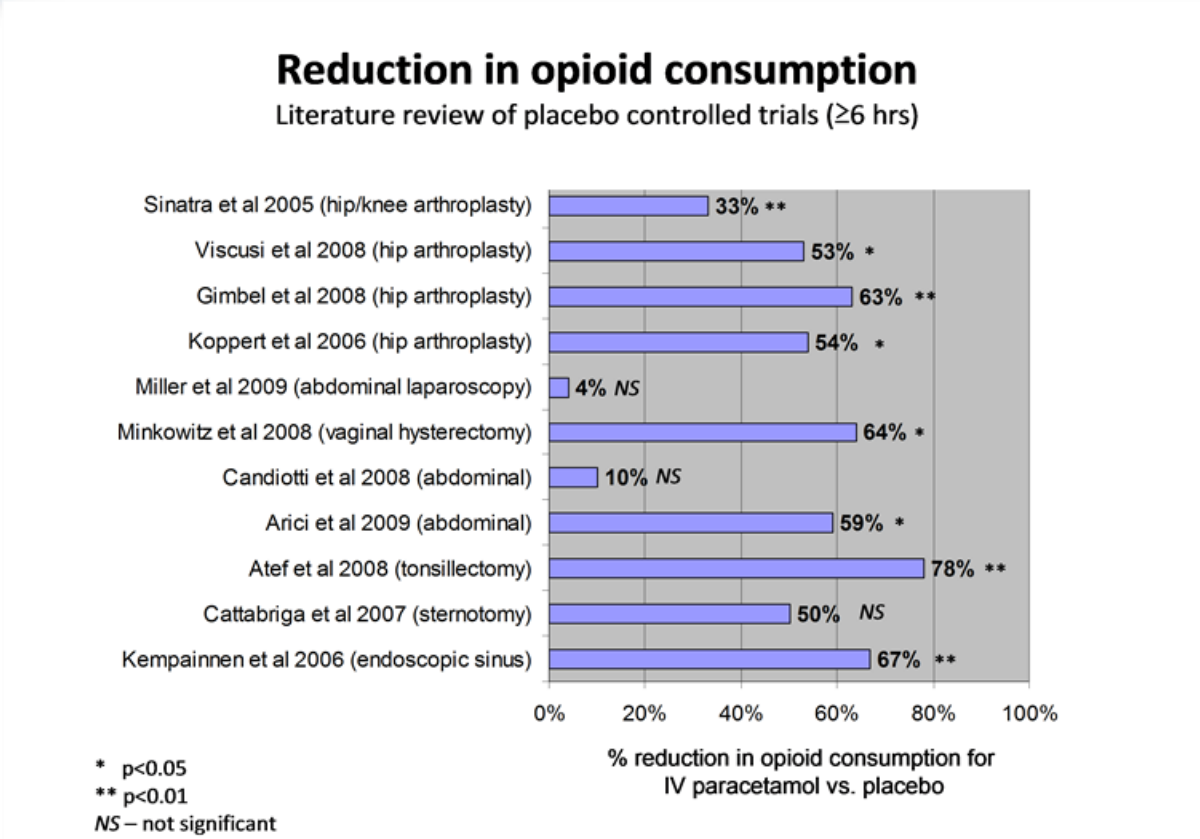

Kehlet H, Dahl JB. The value of "multimodal" or "balanced analgesia" in postoperative pain treatment. Anesth Analg 1993;77:1049.

# Multimodal Approaches: Evidence-based Summary

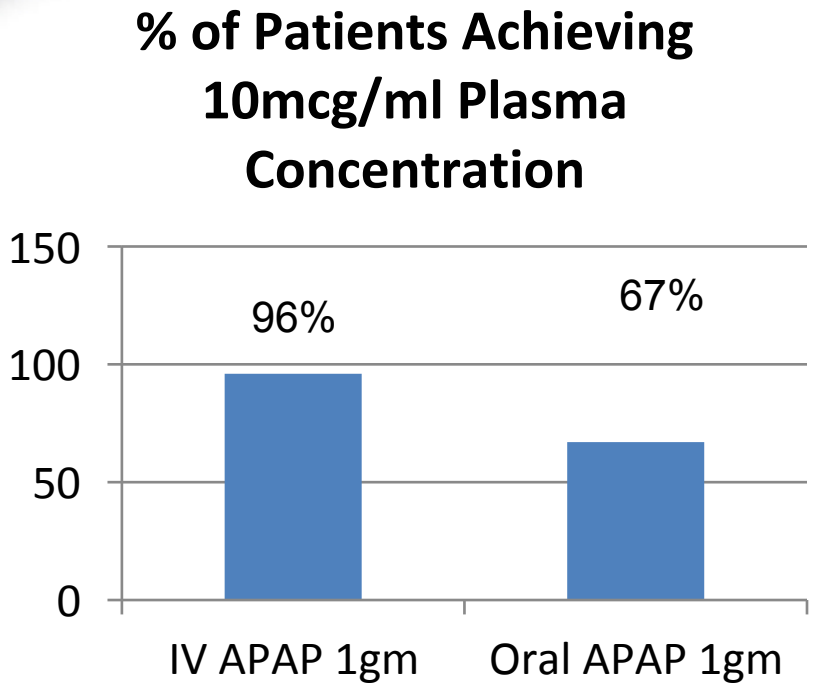
- Acetaminophen (APAP) – oral, single dose
  - Cochrane review[1]
    - 51 studies, 5762 patients, 3277 active, 2425 placebo
      - 50% ↓ in pain with 50% APAP group, 20% placebo group for 4 hours
      - Number needed to treat (NNT) based on dose:
        - APAP 500 mg: 3.5
        - APAP 650 mg: 4.6
        - APAP 1000 mg: 3.6
      - 50% of APAP and 70% of placebo needed additional analgesia
  - A systematic review[2] identified 21 studies comparing APAP alone or in combination with NSAIDs and reported increased efficacy with the combination of 2 agents than with either alone

[1]Toms L et al. *Cochrane Database Syst Rev*. 2008;(4):CD004602.
[2]Ong CK et al. *Anesth Analg.* 2010;110(4):1170-1179.

# Summary of IV Acetaminophen Trials



# Oral Absorption of Acetaminophen During Fasting




- N=106 ENT surgery patients
  - Oral acetaminophen N=52
  - IV acetaminophen N=54
- Plasma levels 30 minutes after and q30 minutes for 4 hrs

Van der Westhuizen J. et al. Anaesth Int Care 2011; 39(2)

# Multimodal Approaches: Evidence-based Summary

- Selective NSAIDs – Single dose Celecoxib
  - Cochrane review - 10 studies, 1785 patients
    - NNT for ≥ 50% decrease in pain over 4 to 6 hours:
      - Celecoxib 200 mg: 4.8
      - Celecoxib 400 mg: 3.5
    - Median time for rescue medication use:
      - Celecoxib 200 mg: 6.6 hours
      - Celecoxib 400 mg: 8.4 hours
      - Placebo: 2.3 hours
    - Proportion of patients requiring rescue medications:
      - Celecoxib 200 mg: 74%
      - Celecoxib 400 mg: 63%
      - Placebo: 91%
    - Adverse events mild to moderate in all groups with no difference in frequency

Derry S et al. *Cochrane Database Syst Rev*. Published Online: 22 OCT 2013

# Multimodal Approaches: Evidence-based Summary

- Injectable NSAIDs
  - Ketorolac and ibuprofen studied in United States
  - Indicated for short-term moderate to severe acute pain that requires analgesia at the opioid level
    - Studies (variety of surgery types) with ketorolac[1,2] compared with placebo suggest patients who received ketorolac:
      - Significant reduction in pain
      - Reduction in opioid consumption (~30%)
      - Facilitation of quicker recovery and rehabilitation
    - Studies with ibuprofen in orthopedic and abdominal surgery[3]
      - At 800-mg dose, reduced morphine use by 22% in first 24 hours
      - Significant reductions in pain at rest and with movement
      - No significant increases compared with placebo in ADRs

1. Cassinelli EH et al. *Spine (Phila Pa 1976).* 2008;33(12):1313-1317.
2. Wong HY et al. *Anesthesiology*. 1993;78(1):6-14.
3. Southworth S et al. *Clin Ther.* 2009;31(9):1922-1935.

# Multimodal Approaches: Evidence-based Summary

- Local Anesthetics – Wound Infiltration
  - Useful in a variety of surgeries
    - Cardiothoracic, abdominal, gynecological, colorectal, head and neck, orthopedic
    - General conclusions from studies:
      - Effective in a variety of surgical sites
      - Neither infection nor toxicity appears to be a significant clinical issue
      - Preoperative blockage superior to postoperative
      - Pain is reduced both at rest and on mobilization
      - Opioid requirements are less
      - Decreased occurrence of acute and chronic pain 3 and 6 months after surgery shown in 1 study with breast cancer surgery

Scott NB. *Anaesthesia*. 2010;65(suppl 1):67-75.

# Multimodal Approaches: Evidence-based Summary

- Intravenous Lidocaine
  - Meta-analysis after abdominal surgery
    - 8 trials, 161 patients received lidocaine (active arm), 159 saline (placebo arm)
      - Both arms could receive as-needed opioids
    - Lidocaine IV groups showed:
      - Decreased duration of ileus
      - Length of hospital stay
      - Postoperative pain intensity
      - Incidence of PONV
      - 30%–50% reduction in opioid consumption

Marret E et al. *Br J Surg*. 2008;95(11):1331-1338.

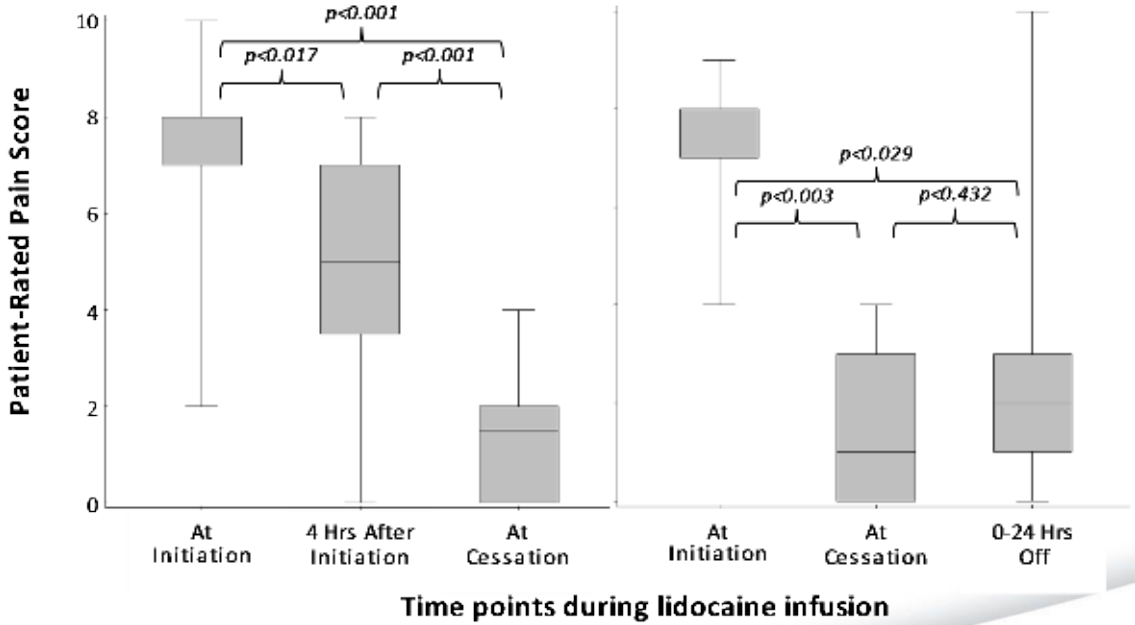
# Multimodal Approaches: Evidence-based Summary

- Intravenous Lidocaine
  - Systematic review (various surgeries, including: abdominal, tonsillectomy, total hip, coronary bypass)
    - 16 trials, 395 patients received lidocaine (active arm), 369 saline (placebo arm)
      - All could receive as-needed opioids
    - In patients who received IV lidocaine IV:
      - Pain scores were reduced at rest and with cough or movement for up to 48 hours postoperatively in abdominal surgery patients
      - No impact on postoperative analgesia in patients undergoing tonsillectomy, total hip arthroplasty, or coronary artery bypass surgery
      - Decreased duration of ileus
      - Length of hospital stay shortened
      - Postoperative pain intensity lessened
      - Incidence of PONV decreased
      - Up to 85% reduction in opioid consumption

McCarthy GC et al. *Drugs*. 2010;70(9):1149-1163.

# Time Course of Analgesia

**Figure 3.** Boxplots of pain scores at varying time-points during and after lidocaine infusions




Gibbons K, etal. Pediatr Blood Cancer. Jan, 2016

# Multimodal Approaches: Evidence-based Summary

- Ketamine Intravenous – Systematic Review
  - 70 studies, 4701 patients (2652 ketamine, 2049 placebo)
  - Summary
    - Patients receiving ketamine reported a reduction in total opioid consumption and an increase in the time to first analgesic dose needed across all studies ($P < .001$).
      - The greatest efficacy of ketamine was found for thoracic, upper abdominal, and major orthopedic surgical subgroups
    - Despite using less opioid, 25 out of 32 treatment groups (78%) experienced less pain than the placebo groups

Laskowski K et al. *Can J Anaesth.* 2011;58(10):911-23.

# Multimodal Approaches: Evidence-based Summary

- Ketamine continued:
  - Hallucinations and nightmares were more common with patients receiving ketamine, but there was no association with increased sedation
  - In patients in whom ketamine was reported as efficacious for pain, postoperative nausea and vomiting was less frequent in those patients who received ketamine
  - The analgesic effect of ketamine was independent of the type of intraoperative opioid administered, the timing of ketamine administration, and the ketamine dose administered

# Why Gabapentin or Gabapentenoids?

- Reduce physiologic sensitization and attenuate hyperexcitability
- Timing doesn't matter
- Seems to affect both NMDA and non-NMDA receptors
- Anxiolytic properties
  - significant pre-induction reduction of anxiety
- Pregablin has an improved bioavailability and faster onset

# Multimodal Approaches: Evidence-based Summary

- Gabapentinoids - Systematic Review of RCTs
  - Gabapentin: 22 trials, 1640 patients
  - Pregabalin: 8 trials, 707 patients
  - Summary:
    - Gabapentin provided better postoperative analgesia and in sparing rescue analgesics than placebo in the 6/10 RCTs that administered gabapentin as preemptive analgesia only
    - 14 RCTs suggested that gabapentin did not reduce PONV when compared with placebo
    - Pregabalin provided better postoperative analgesia and in sparing rescue analgesics than placebo in 2/3 RCTs that evaluated the effects of pregabalin alone vs placebo
    - 4 studies reported no pregabalin effects on preventing PONV
    - Both agents reduced opioid consumption by ~30%

Dauri M et al. *Curr Drug Targets*. 2009;10(8):71633.26

# Prevention of Chronic Postsurgical Pain

- Meta-analysis of studies of CPSP > or = 2 months post surgery
- 11 trials: 8 with Gabapentin, 3 with Pregablin
  - 50% success with Gabapentin, 100% success with Pregablin
- Moderate to large reductions
- Increased patient function

Clarke H. Anesth Analg. 2012

# Summary of Recommendations

| Drug | Pain Intensity | Analgesic Opioid Consumption | Opioid-related Side Effects | Prevention of Chronic Postsurgical Pain | Side Effects |
|---|---|---|---|---|---|
| Ketamine | ↓ | ↓ | ↓ | Inconsistent | Psychomimetic (hallucinations, dreams) |
| Pregabalin | ↓ | ↓ | ↓ | Yes | Sedation, dizziness |
| Gabapentin | ↓ | ↓ | ↓ | Yes | Sedation, dizziness |
| IV Lidocaine | ↓ | ↓ | ↓ | Possible | None noted, but monitor |
| Systemic α2 agonist | ↓ | ↓ | ↓ | No data | Hypotension, bradycardia |

Shankar R et al. *Anaesth Crit Care Pain*. 2013;13(5):152-157.

# ERAS's: Enhanced Recovery After Surgery
# What Does it Mean for us?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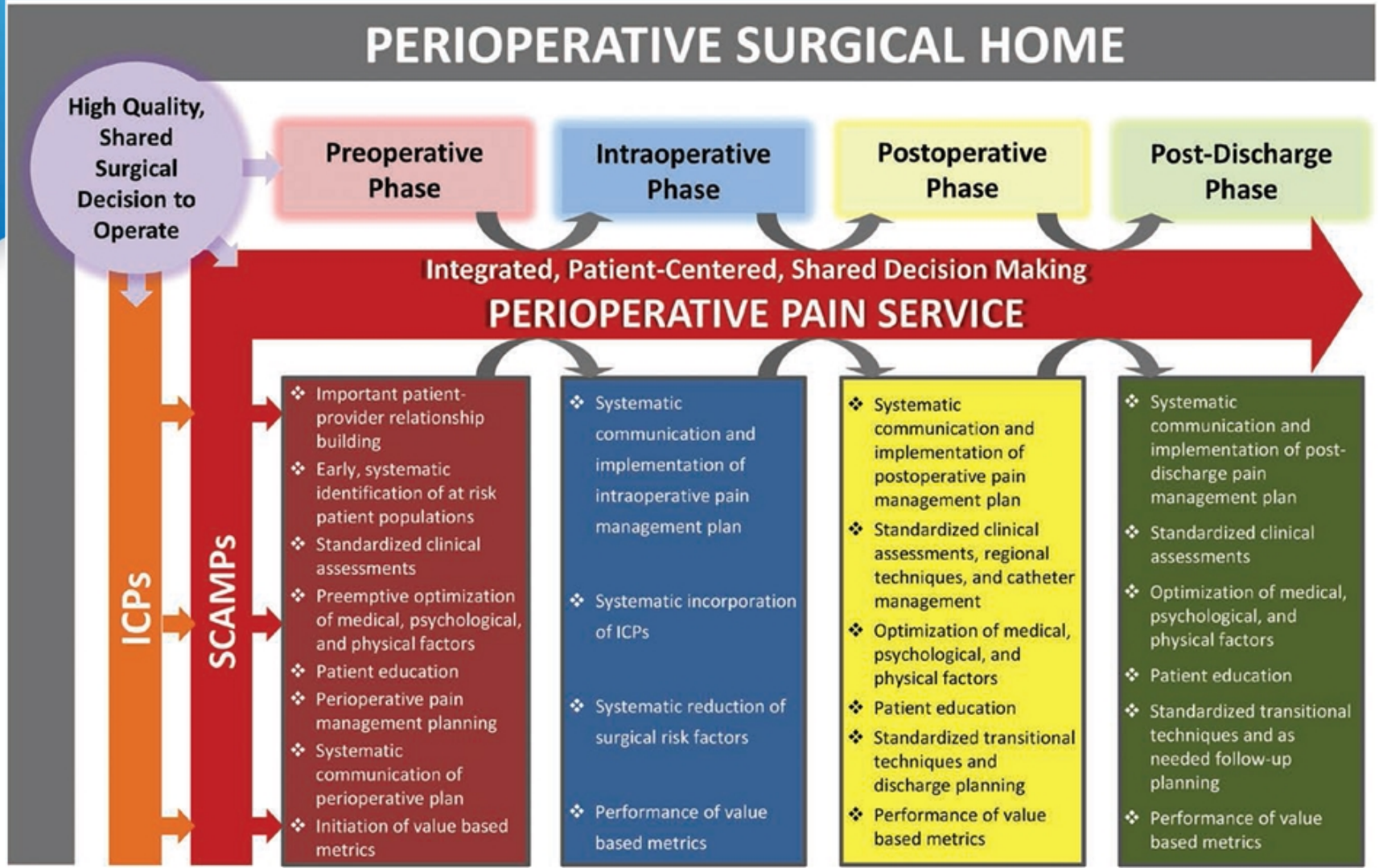
# Why Do We Need ERAS'S

- Reducing opioids postoperative have decreased length of stay up to 29%
- High dose opioid regimens incur over $1.6 million in avoidable costs annually
- Chronic postsurgical pain results in $635 billion in healthcare costs
- Costs of complications in major surgical procedures increased 5 fold
- Major complications estimated at $11,500 per patient


PERIOPERATIVE SURGICAL HOME
High Quality, Shared Surgical Decision to Operate
Preoperative Phase
Intraoperative Phase
Postoperative Phase
Post-Discharge Phase
Integrated, Patient-Centered, Shared Decision Making
PERIOPERATIVE PAIN SERVICE
ICPs
SCAMPs
Important patient-provider relationship building
Early, systematic identification of at risk patient populations
Standardized clinical assessments
Preemptive optimization of medical, psychological, and physical factors
Patient education
Perioperative pain management planning
Systematic communication of perioperative plan
Initiation of value based metrics
Systematic communication and implementation of intraoperative pain management plan
Systematic incorporation of ICPs
Systematic reduction of surgical risk factors
Performance of value based metrics
Systematic communication and implementation of postoperative pain management plan
Standardized clinical assessments, regional techniques, and catheter management
Optimization of medical, psychological, and physical factors
Patient education
Standardized transitional techniques and discharge planning
Performance of value based metrics
Systematic communication and implementation of post-discharge pain management plan
Standardized clinical assessments
Optimization of medical, psychological, and physical factors
Patient education
Standardized transitional techniques and as needed follow-up planning
Performance of value based metrics

# What Does The Data Show?

- Colorectal Surgery
  - Overall reduction in direct costs of $7129/patient, increased patient satisfaction
  - Length of stay reduced by 1.6 days
- Breast flap reconstruction
  - 1 day decrease in  length of stay, decreased opioid consumption
- Radical cystectomy
  - Decreased length of stay by 1.2 days
- Gynecologic/oncology
  - 50% decrease in complications
  - Cost savings of $2245 per patient
- Hip Fracture
  - 1/3 decrease in postop complications
  - Decreased length of stay
  - Decrease in total morphine daily equivalents

# Key Concepts of ERAS Protocols

- Regular administration of acetaminophen and NSAID's unless contraindicated
- Use of small dose opioids for breakthrough pain
- Oral opioids preferred
- Utilize adjunct medications such as gabapentin, local anesthetics, ketamine, alvimopam, dexamethasone

Standardize, Standardize, Standardize

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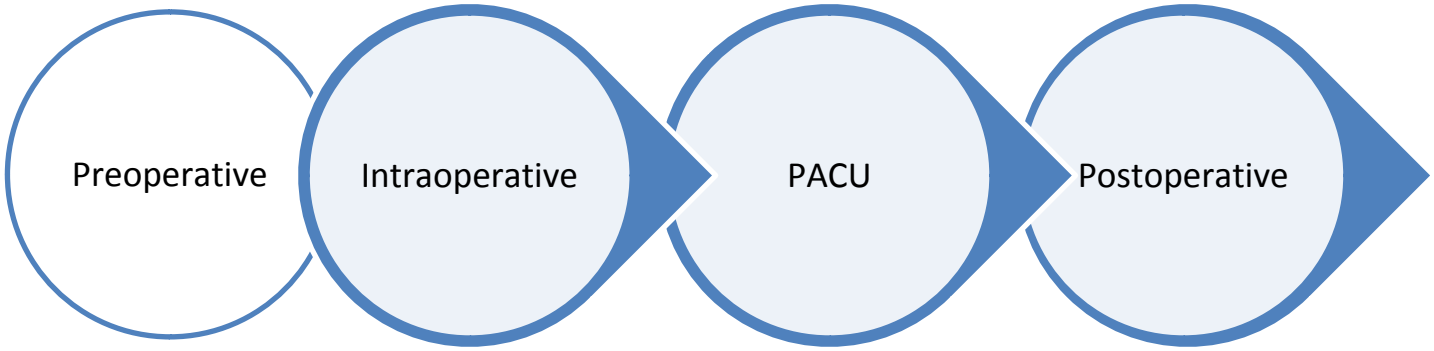
# Challenges with ERAS's

- Most protocols have over 20 unique process elements
- Process measures span the continuum of perioperative care
- Cover a number of geographical locations and hundreds of providers
- Sustainability and continuous evaluation
- Compliance

Grant MC etal. JCJQPS, 2017;43:524-533

# Example of an Enhanced Recovery Protocol for Multimodal Analgesia



# Michigan Medicine RAMP (Rapid Analgesic Medication Protocol) What have we learned?

- Primary THA/TKA guidelines for opioid naïve patients
  - Pre-operative (one time prior to OR)
    - Celecoxib 400mg po x 1
    - Gabapentin 600mg po x 1
    - Acetaminophen 1gm po x 1
    - Clonidine patch 0.1mg (remove after 24 hours)

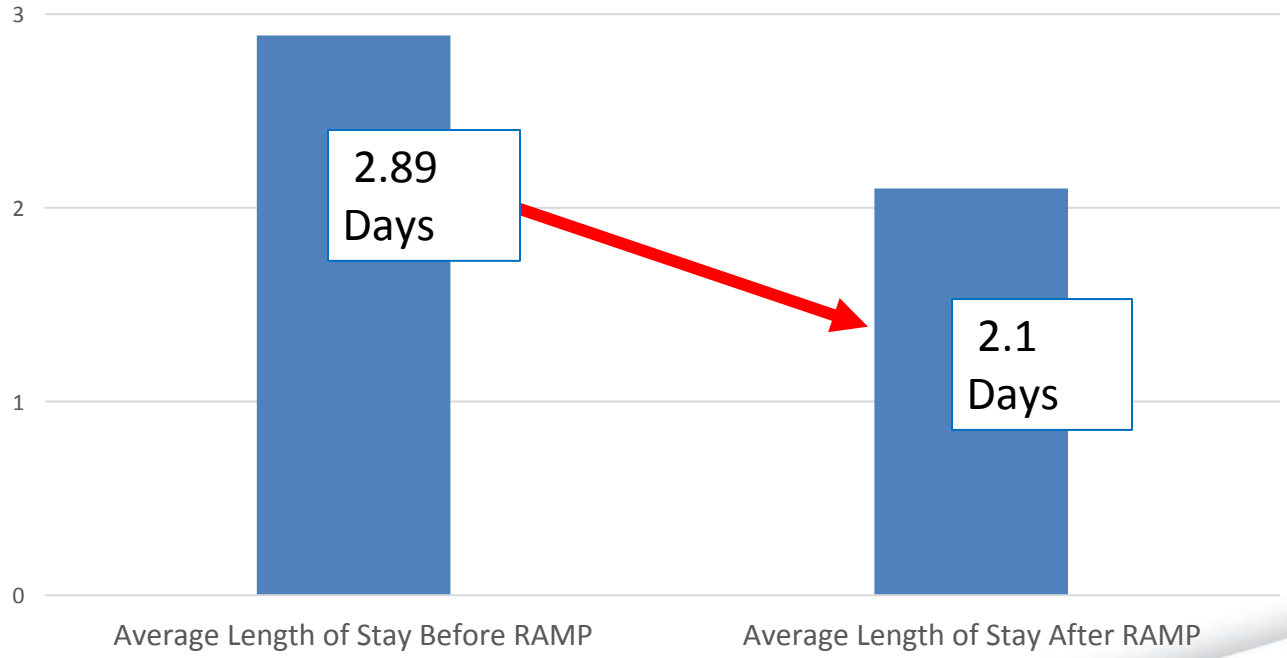
# RAMP cont.

- Intra-operative
  - Neuraxial anesthesia preferred
  - Antiemetic dexamethasone 4mg IV for all cases
  - Local anesthetic injection of bupivacaine 0.25% with epinephrine 1:200,000, 30ml
  - Ketorolac 30mg at skin closure

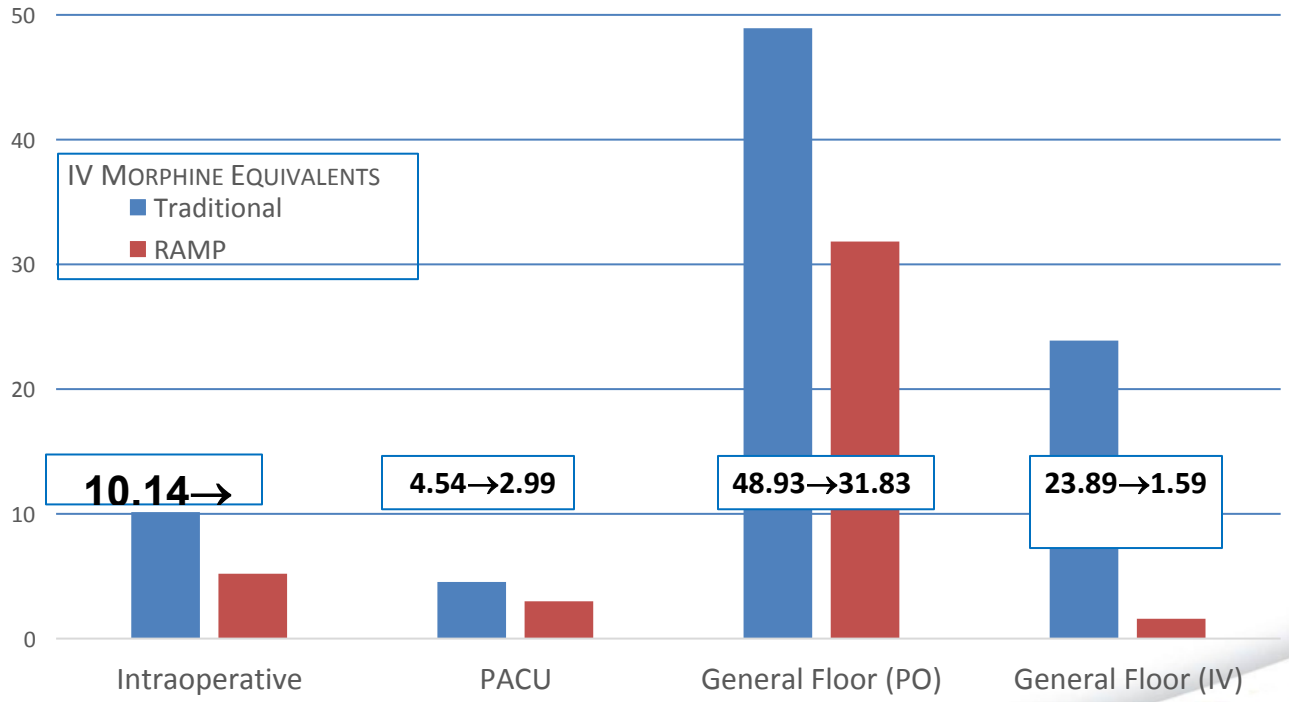
# RAMP cont.

- Post-operative
  - Celecoxib 200mg po x1 POD 1
  - Gabapentin 100mg TID
  - Acetaminophen 500mg q4hrs
  - Omeprazole 20mg po daily
  - Dexamethasone 10mg IV x 1, 8 hrs after initial dose
  - Ketorolac 15mg IV q6hrs x 3

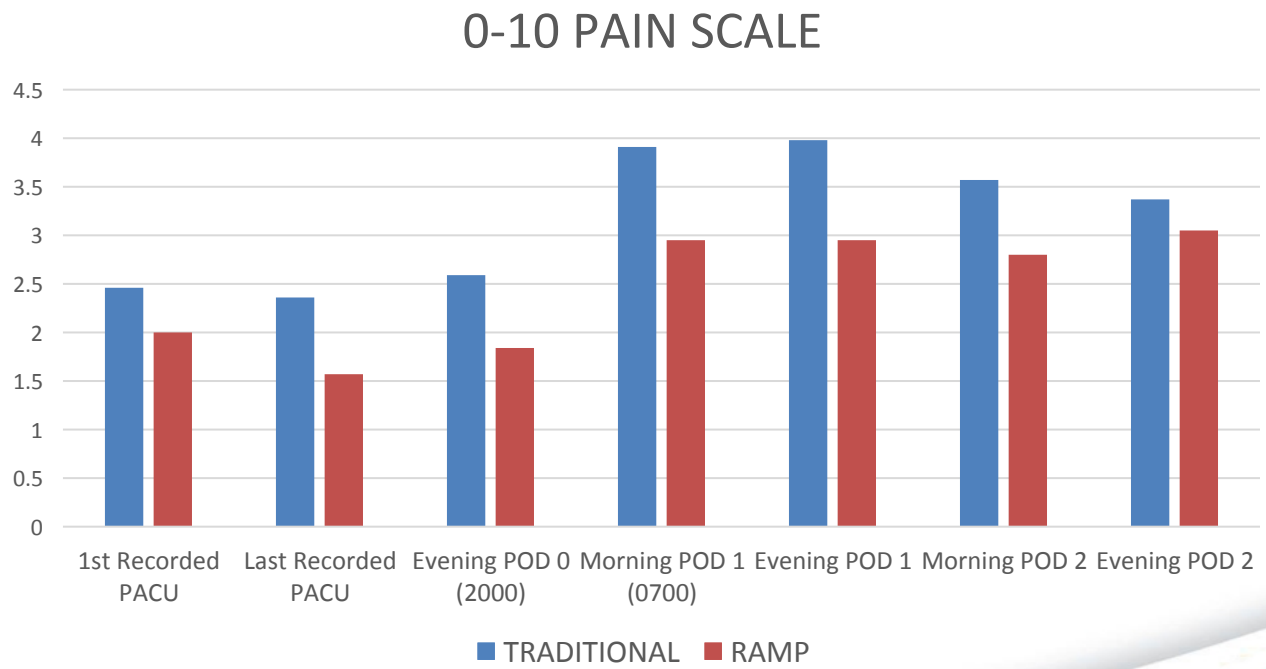
# Decrease in Average Length of Stay



# Decrease in Amount of Opioids Used



# Decrease in Patient Reported Pain Scores



# Financial Impact After RAMP Implementation

- 75% reduction in admissions to Skilled Nursing Facility
  - SNF discharges ↓ from 38% to 9%
- 50% reduction in all cause 30-day readmissions
- 27% reduction in length of stay
- 95% reduction in IV opioid use
  - PCA use eliminated—minimal oral opioid use
  - Significant ↓ in opioid side effects, e.g. nausea, pruritus
- 35% reduction in oral opioid use
- Improved reported pain scores

# Patient Case

- MJ is a 45 year old female scheduled for gynecologic oncology surgery. She weighs 35kg, and has a history of smoking, asthma, and chronic pain. The best surgical plan for her for enhanced recovery should consider all but which of the following upon the day of surgery.
  1. Prophylaxis for nausea and vomiting
  2. Intraoperative infiltration of a long acting local anesthetic
  3. Preoperative administration of oral celebrex and gabapentin
  4. Postoperative prn doses of acetaminophen and ketorolac
  5. PCA postop day one followed by short acting oral opioids for breakthrough pain

# Question #2
# True or False

The foundation of enhanced recovery after surgery protocols is the reliance on opioids as the primary analgesic

1. True
2. False

# Outrun Pain!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# Role of Analgesia in the ICU

- Acute Pain in a leading stressor for ICU patients
- ICU patients experience pain either from their illness or injury or from procedures performed by ICU clinicians
- Inadequate management can cause physical stress, sleep disturbances, and psychological distress delaying discharge and impacting life after discharge

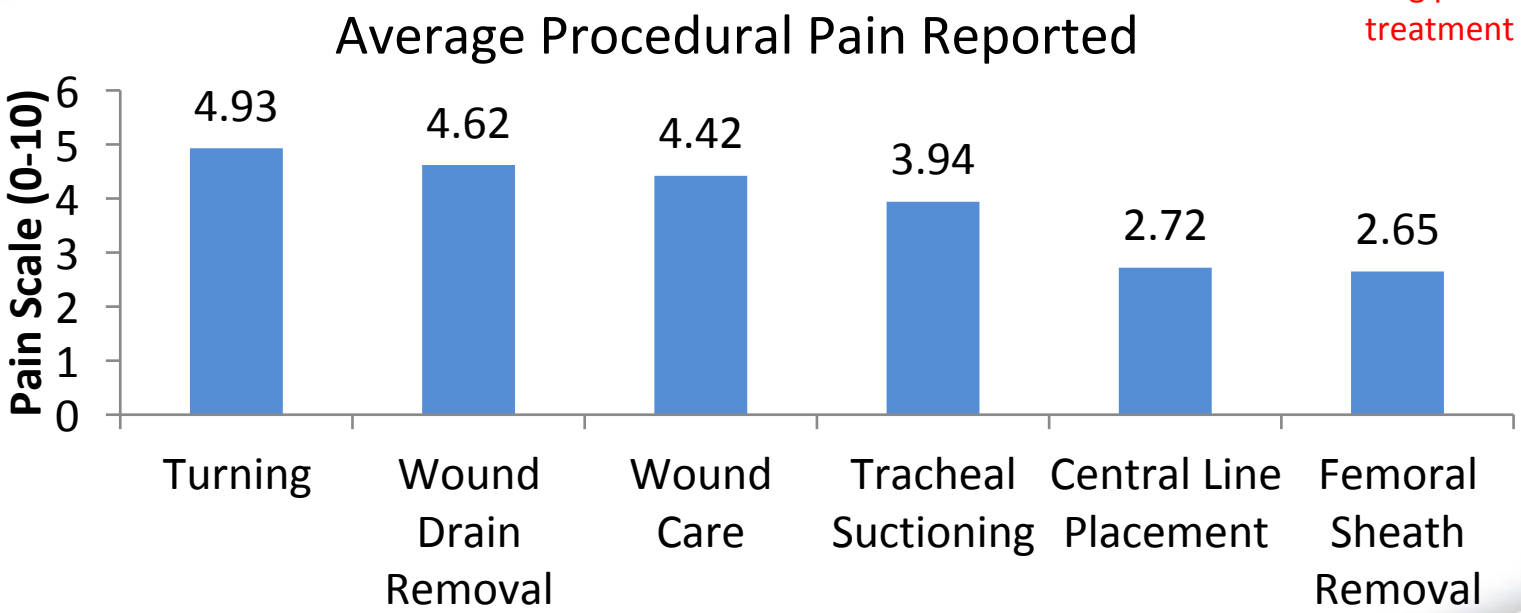
Chanques G et al. Anesthesiology 2007;107:858–60.
Puntillo KA, et al. Am J Respir Crit Care Med 2014;189:39–47
Timmers TK, et al. Arch Surg 2011;146(4):412–8.

# Factors in Management of ICU Analgesia

- Pain Types
  - Visceral, somatic, neuropathic
- Baseline Pain
- Optimized delivery of patient care
  - Assessment, methods of administration, drug-drug interactions
- Critical Illness Factors
  - Altered PK/PD, End Organ Dysfunction

# Thunder II

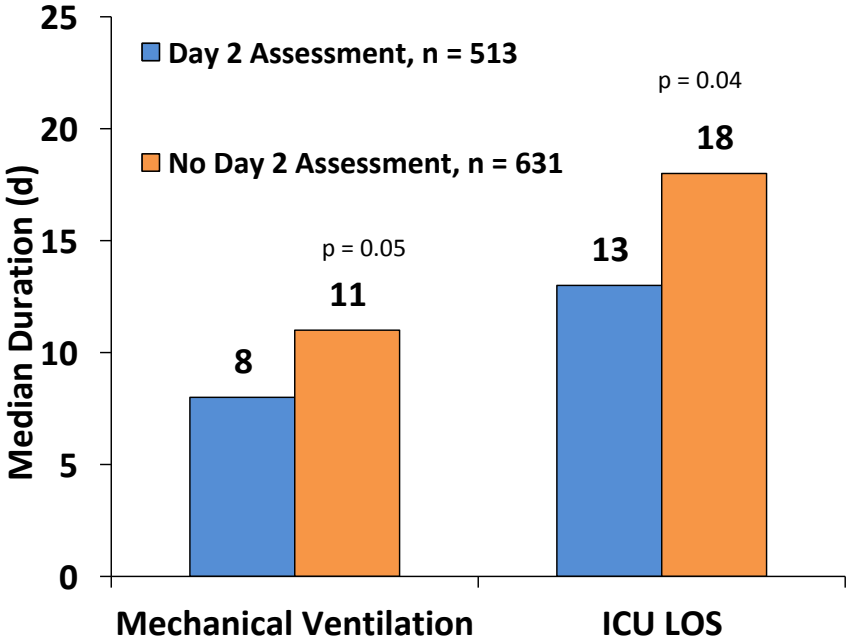
Routine ICU care is painful warranting pre-emptive treatment




Single center descriptive practice analysis of 6201 critically ill patients (5957 adults) with documented pain scores to common procedures in the ICU.

Puntillo KA et al. Am J Crit Care. 2001;10(4):238-51.

# Improved Outcomes Associated with Pain Assessment in the ICU

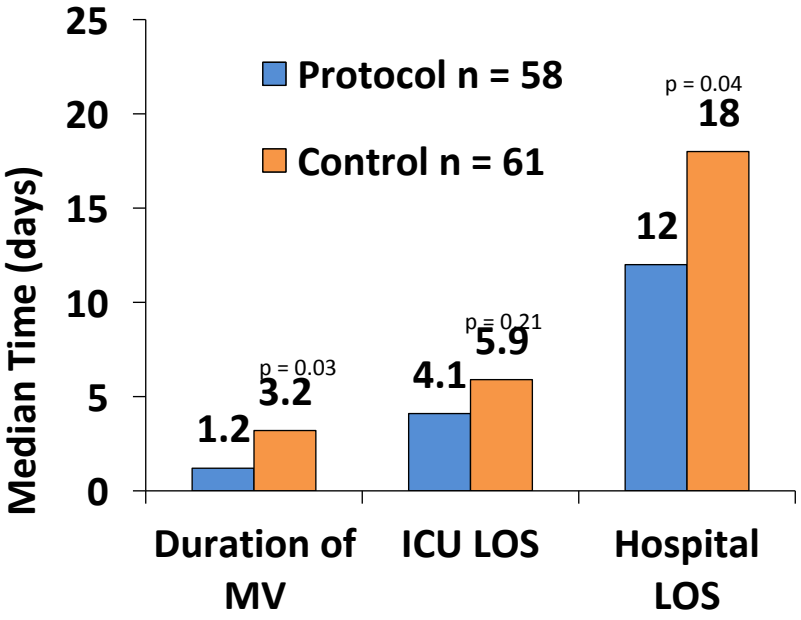



| | No Day 2 Assessment | Day 2 Assessment | P value |
|---|---|---|---|
| Any opioid | 600 (95) | 474 (92) | 0.06 |
| Non-opioid | 184 (29) | 217 (42) | < 0.01 |
| Any sedative | 544 (86) | 384 (75) | < 0.01 |
| Midazolam | 411 (65) | 295 (57) | < 0.01 |
| Propofol | 133 (21) | 86 (17) | 0.06 |

All data presented as n (%)

Payen JF et al. Anesth 2009;111:1308-1316

# Pain-Sedation-Delirium Protocol in Trauma: University of Cincinnati

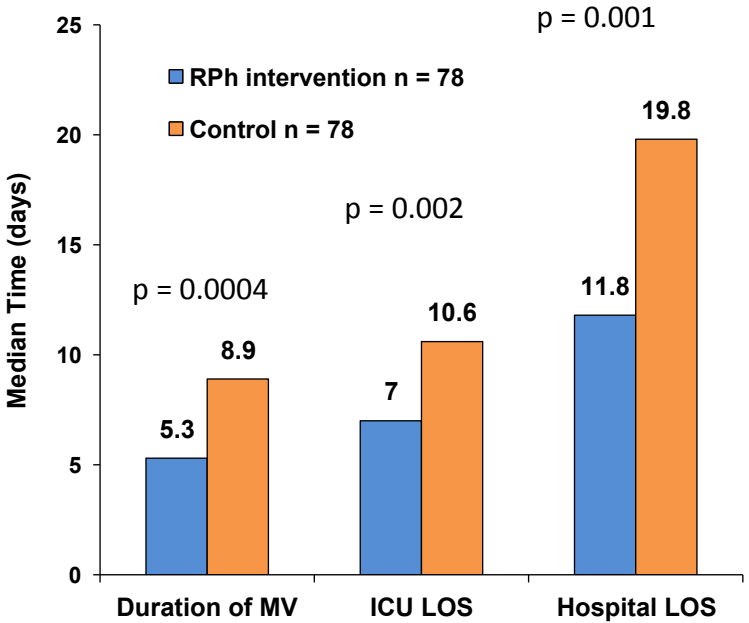



| | Protocol | Control | P value |
|---|---|---|---|
| Propofol infusions† | 52 (90) | 49 (81) | 0.25 |
| Propofol,mcg* | 10,057 ± 14,616 | 19,232± 22,477 | 0.01 |
| MSO4,mcg* | 1,641± 1,250 | 2,465±1,242 | <0.001 |
| Lorazepam infusions† | 8 (16) | 24 (39) | 0.003 |

*Data presented in mean ** Data presented in median †Data presented as n (%)
CIVS; Continuous intravenous infusion sedation

Robinson BR, et al. J Trauma. 2008 Sep;65(3):517-26.

# Pharmacist Enforced Adherence to an ICU Sedation Guideline



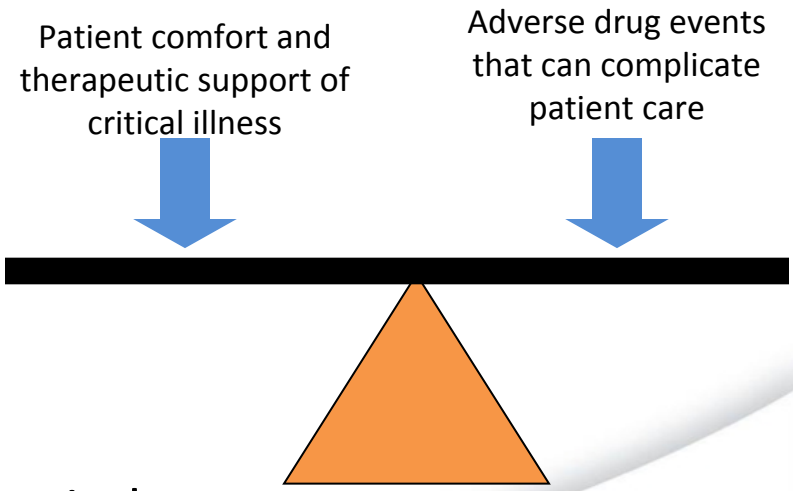

| | RPh | Control | P value |
|---|---|---|---|
| Alcohol/drug overdose† | 15 (19.2) | 6 (7.7) | 0.03 |
| Lorazepam equivalents/vent day, mg* | 65.2 ± 114.1 | 74.8 ± 76.1 | 0.54 |
| Fentanyl equivalents/vent day, mcg* | 102.5 ± 328 | 400 ± 1026 | 0.02 |

*Data presented in mean †Data presented as n (%)

Marshall J, et al. Crit Care Med. 2008 Feb;36(2):427-33

# Considerations When Implementing multimodal analgesia in the ICU

- Pharmacologic rationale
- Impact on pain control
- Analgesic consumption
- Adverse drug events
- Patient outcomes
- Expenditure on both medication and hospital resources



# Pain Assessment in the ICU

- Assessing pain and sedation in all ICU patients using validated tools will aid in recovery and economic impact
  - Reduction in ventilator support
  - Reduction in ICU stay
  - Decreased need for hypnotic drugs
- Analgosedation with established protocols allows early mobilization
  - Reduced hospital and ICU LoS
  - Improved functional mobility at hospital discharge

| Assessment Tools for communicative Patients | Tools for patients unable to communicate pain |
|---|---|
| NRS | BPS |
| VAS | CPOT |
| | NPS |
| | BPAT |

# 2013 SCCM PAD Guidelines

- We recommend that intravenous (IV) opioids be considered as the first-line drug class of choice to treat non-neuropathic pain in critically ill patients (+1C)
- We suggest that nonopioid analgesics be considered to decrease the amount of opioids administered (or to eliminate the need for IV opioids altogether) and to decrease opioid-related side effects (+2C)
- We recommend that thoracic epidural anesthesia/analgesia be considered for postoperative analgesia in patients undergoing abdominal aortic aneurysm surgery (+1B)

Barr J, et al. Crit Care Med. 2013 Jan;41(1):263-306

# Unclear From the PAD Guidelines

- Which non-opiates to use across clinical scenarios?
- Dosing/ dosing strategies
- When to initiate
  - Analgosedation
  - Prior to procedures, painful stimuli

# Why so much uncertainty for multimodal therapy?

- "A lack of direct comparisons between opioids and nonopioids hinders conclusions regarding the effect of nonopioid analgesics, particularly in ICU patients"

- What do we know, what are we extrapolating, and how do we address gaps in the literature

Barr J, et al. Crit Care Med. 2013 Jan;41(1):263-306

# Pharmacologic Multimodal Pain Treatment Options

| Modality | Side Effects |
|---|---|
| Opiates | Class Effects: Respiratory Depression, decreased motility<br>Agent Specific concerns |
| Acetaminophen | Hepatotoxicity, Nausea/Vomiting<br>IV: Hemodynamic Instability |
| NSAIDs | GI toxicity, Renal Failure, Bleeding |
| Alpha-2 Agonists | Hypotension, Bradycardia, Tachycardia |
| NMDA Antagonists | Hallucinations, Tachycardia, Hemodynamic Changes |
| Anticonvulsants | Hallucinations, Withdrawal, seizures |

Riker RR, Fraser GL. Pharmacotherapy. 2005 May;25(5 Pt 2):8S-18S
Devlin JW, et al. Crit Care Med. 2010 Jun;38(6 Suppl):S231-43.

# Other Multimodal Therapies

| Modality | Examples | Side Effects | Types of Pain |
|---|---|---|---|
| Intervention w/ local analgesia | Epidural, Nerve Block, TAP Block | Anesthetic toxicity, epidural hematoma, nerve injury | Acute postsurgical pain, fractures |
| PT/OT | Mobility, Range of Motion, Rehabilitation, skills training | Minimal Risks | Acute post surgical pain, chronic pain |
| Complementary | Music, Animals, TENS | Unknown | All types |
| Psychologic | Stress Reduction, Cognitive-behavioral Therapy | Unknown | Chronic Pain, PTSD |

Kohler M, et al. Pain Manag. 2016 Nov;6(6):591-602.

# Opioids

- Commonly administered parenterally or via the epidural route
- Patient-controlled analgesia can be used for cognitively intact patients
- Close monitoring for side effects including respiratory depression, sedation, urinary retention and constipation is necessary

- Specific Opiate Adverse effects
  - Fentanyl
    - Chest wall rigidity
    - Accumulation in certain patients
  - Morphine
    - Cholecystitis
  - Remifentanil
    - ↑ ammonia levels
  - Meperidine
    - Tremors/seizures
  - Methadone
    - QTC prolongation

Sessler CN, et al. Chest. 2008. 133(2) 552-565
Payen J et al. *Anesthesiology 2007.* 106(4), 687–695;
Barr J, et al. Crit Care Med. 2013 Jan;41(1):263-306

# Strategies to Optimize Opiates in the ICU and After

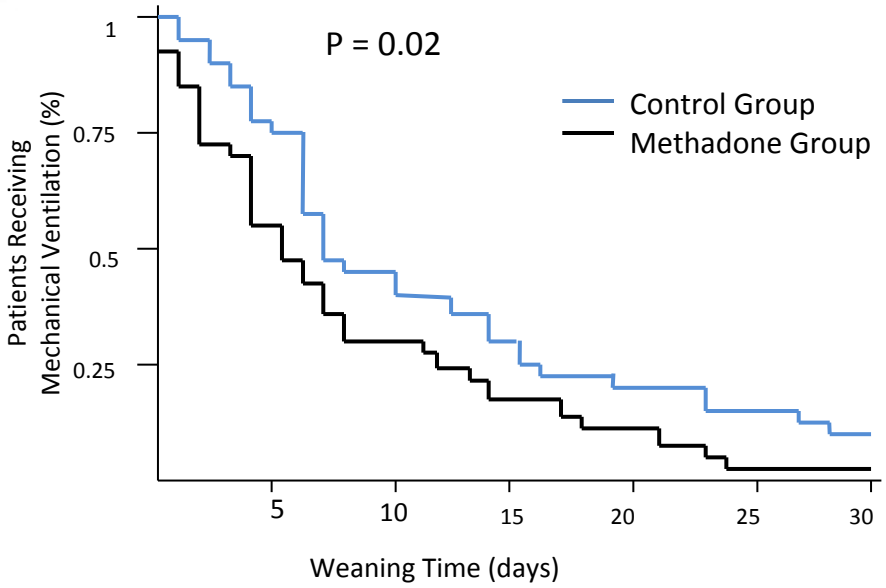
- Careful assessment (including psychosocial factors)
- Provision of effective analgesia despite reduced efficacy of opioids
- Attenuation of tolerance and opioid-induced hyperalgesia (OIH)
- Prevention of opioid abstinence syndrome
- Close communication with other health-care professionals
- Appropriate discharge planning

# Tolerance and Opioid-Induced Hyperalgesia

- Tolerance: Same dose no longer resulting in continued efficacy
- OIH- induce increased sensitivity to nociceptive stimuli

- Strategies to attenuate:
  - Rotation—switching to a different opioid
  - Use of NMDA receptor antagonists (e.g., ketamine)
  - In some cases, modulators of the alpha-2-delta calcium channel (gabapentin, pregabalin)

# Enteral Methadone While Weaning Fentanyl Infusion




| | Methadone (n=37) | Control (n=31) | P value |
|---|---|---|---|
| Baseline Fentanyl Dose, mcg* | 40,608 ± 24,882 | 41,284 ± 20,545 | 0.9 |
| Weaning time (survivors), d† | 4 | 7 | 0.004 |
| MV-free days† | 20 | 16 | 0.13 |
| Duration of MV, d† | 15 | 20 | 0.14 |
| ICU LOS, d† | 19 | 25 | 0.19 |
| Hospital LOS | 44 | 47 | 0.62 |
| Signs of opioid withdrawal | 10 (27) | 12 (39) | 0.3 |

*Data presented as mean ± SD; †Data presented as median; MV = mechanical ventilation

Wanzuita R, et al. Crit Care. 2012 Mar 15;16(2):R49.

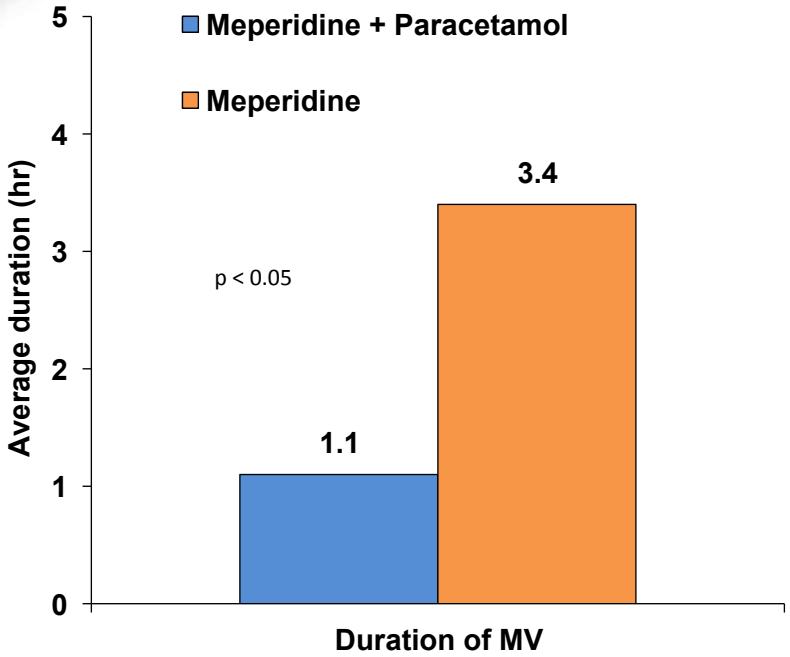
# Acetaminophen

- Multiple meta-analyses have concluded that 24-h consumption of morphine significantly decreases with acetaminophen
  - no significant reduction in pain scores
  - did not significantly decrease the incidence of respiratory depression or sedation
- Low side-effect profile when dose appropriately

- Decrease doses possibly avoided in patients with an acute hepatitis/ hepatic insufficiency or in cases of cachexia due to decreased levels of glutathione

Elia N et al. Anesthesiology. 2005 Dec;103(6):1296-304.
Maund E et al. Br J Anaesth. 2011 Mar;106(3):292-7.
Remy C et al. Br J Anaesth. 2005 Apr;94(4):505-13.

# Adjunctive IV paracetamol with meperidine vs. meperidine alone

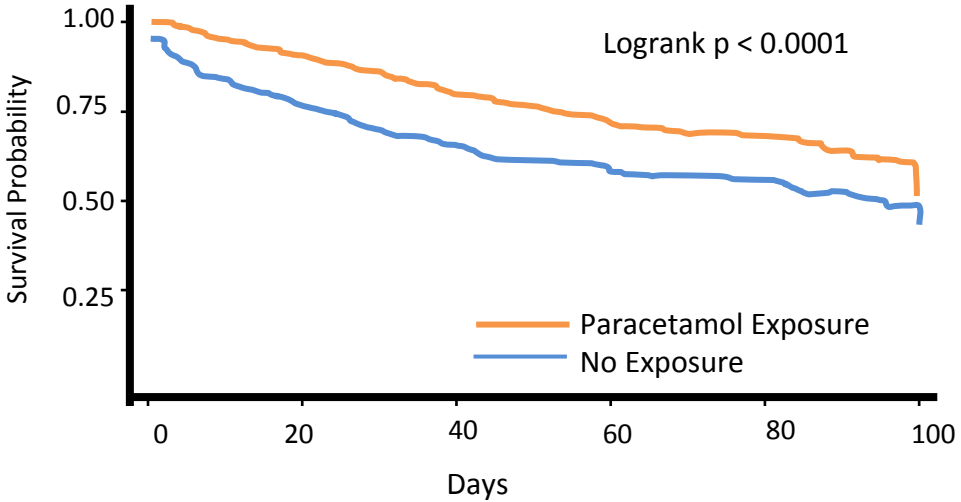



| | Meperidine (n=20) | Meperidine + Paracetamol (n=20) | P value |
|---|---|---|---|
| Meperidine consumption, mg* | 198 ± 66 | 77 ± 18 | < 0.05 |
| BPS until extub* | 5.7 ± 2.1 | 3.7 ± 0.8 | < 0.01 |
| VAS after extub.* | 2.6 ± 0.3 | 2.4 ± 0.6 | < 0.01 |
| BPS at extub.* | 3.6 ± 1.2 | 2.5 ± 0.8 | < 0.05 |
| N/V requiring treatment† | 7 | 1 | < 0.05 |

*Data presented as mean ± SD; †Data presented as n
VAS: Visual Analog Scale; BPS: Behavioral Pain Scale

Memis D, et al. J Crit Care 2010 25:458-462

# Paracetamol Therapy and Outcome of Critically Ill Patients: a Multicenter Retrospective Observational Study



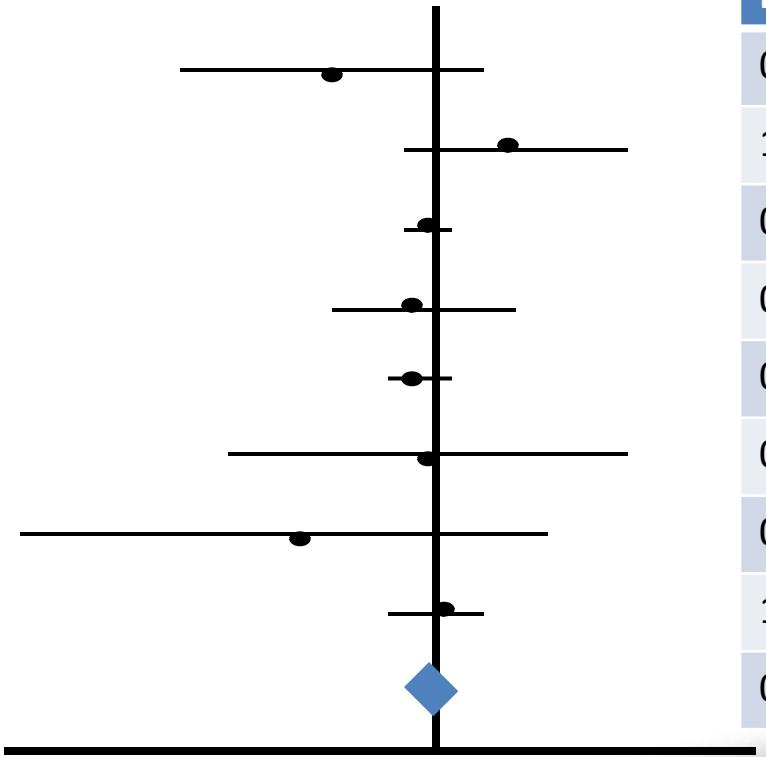

| # at Risk | | | | | | |
|---|---|---|---|---|---|---|
| No | 5772 | 1236 | 410 | 197 | 110 | 57 |
| Yes | 10046 | 3095 | 1110 | 515 | 266 | 143 |

| | N | Adjusted OR (95% CI) | P-Value |
|---|---|---|---|
| All Patients | 15818 | 0.60 (0.53- 0.68) | <0.001 |
| Surgery | 9994 | 0.72 (0.85-0 0.91) | 0.006 |
| No Surgery | 5824 | 0.59 (0.48 – 0.66) | <0.001 |
| Fever | 4397 | 0.76 (0.61-0.93) | 0.009 |
| No Fever | 11421 | 0.54 (0.46 – 0.64) | <0.001 |
| Medical, Fever and Infection | 681 | 0.67 (0.42 – 1.05) | 0.08 |

Suzuki S, et al. Crit Care. 2015; 19:162

# Antipyretic Therapy in Sepsis

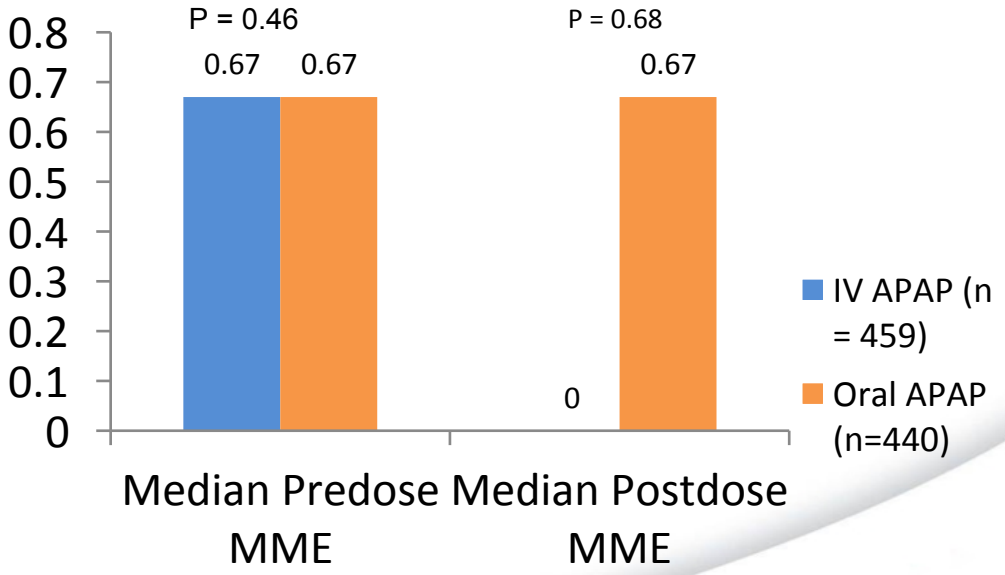
| Study | RR (95% CI) | %Weight |
|---|---|---|
| Bernard et al (1991) | 0.44 (0.13, 1.43) | 1.76 |
| Haupt et al (1991) | 1.83 (0.73, 4.60) | 2.90 |
| Bernard et al (1999) | 0.93 (0.74, 1.17) | 45.54 |
| Memis et al (2004) | 0.88 (0.39, 1.95) | 3.83 |
| Schortgen et al (2012) | 0.88 (0.65, 1.19) | 26.71 |
| Niven et al (2013) | 0.96 (0.20, 4.69) | 0.99 |
| Janz et al (2015) | 0.31 (0.04, 2.50) | 0.56 |
| Young et al (2015) | 1.02 (0.70, 1.48) | 17.71 |
| Overall P = 0.0% p = 0.652 | 0.93 (0.79, 1.09) | 100 |



Drewry AM, et al. Crit Care Med. 2017 May;45(5):806-813. 1

# IV or Oral Acetaminophen in Neuro ICU

| Time | IV APAP PID* | Oral APA PID* | P- Value |
|---|---|---|---|
| 30 M | 4 (3-5) | 1 (0-4) | < 0.0001 |
| 1 h | 4 (0-4) | 3 (2-4) | 0.94 |
| 2 h | 4 (2.75 – 5) | 4 (3, 4) | 0.25 |
| 3 h | 4 (3-5) | 4 (3-5) | 0.32 |
| 6h | 4 (3-5) | 4 (4-5) | 0.92 |
| * Median (IQR) | | | |




Nichols DC, et al. Neurocrit Care. 2016 Dec;25(3):400-406.

# IV Acetaminophen Considerations in Critically Ill Patients

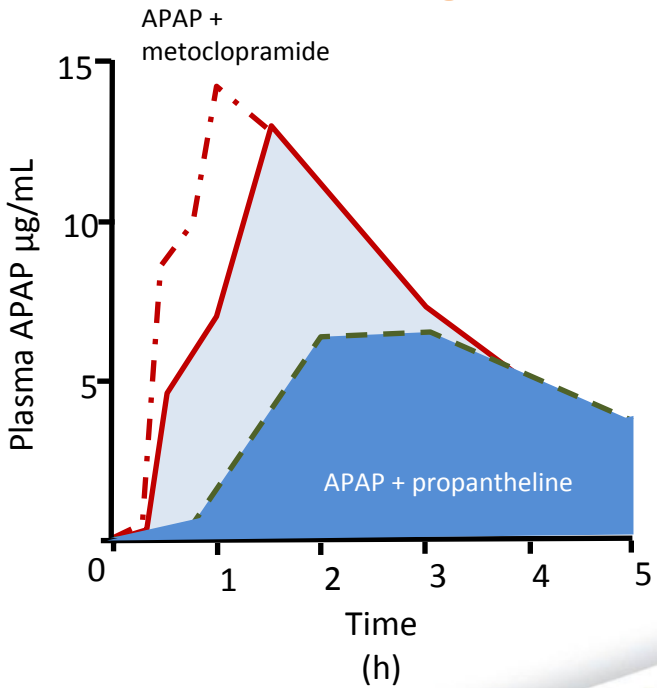
- Cost
- Acetaminophen induced hypotension reported in 13-59% of patients
  - Median time to hypotension 30 minutes
  - Potential mechanisms include COX inhibition, mannitol excipient, vasodilation associated with antipyresis

Cantais A, et al. Crit Care Med. 2016; 44: 2192-2198,

Schell- Chaple HM, et al Crit Care Med. 2017 Jul;45(7):1199-1207.

# Acetaminophen Absorption

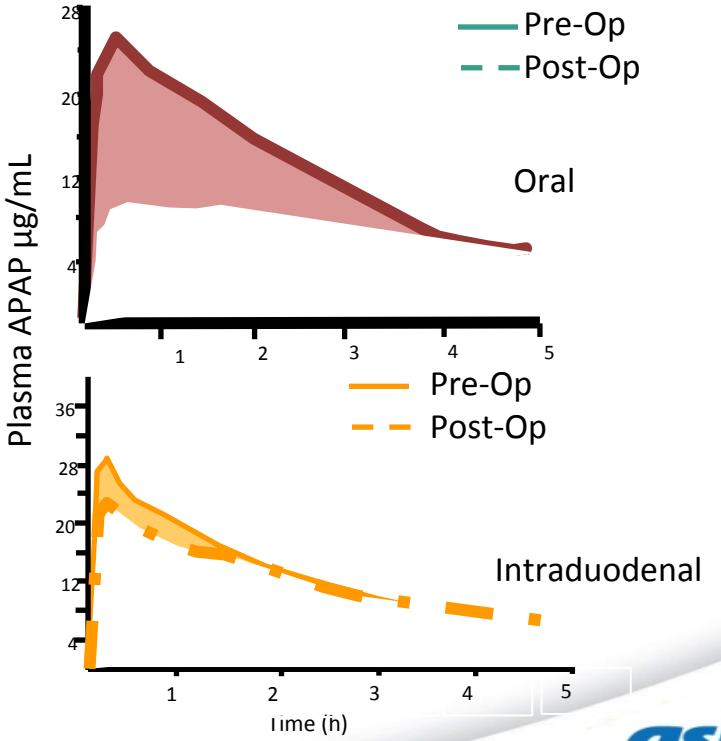
- Rapid, passive diffusion from small intestine
  - $C_{max}$ 1-2 hours after dose
- Pharmacokinetic attributes tied closely to rate of gastric emptying
  - $C_{max}$
  - $T_{max}$
  - AUC




Nimmo J, et al. Br Med J. 1973;1:587–589
Raffa RB, et al. Pain Pract. 2014 Sep;14(7):668-77

# Acetaminophen Absorption in Surgery

- Prospective evaluation of abdominal surgery patients who served as their own control
  - Oral administration postoperatively leads to decreased $C_{max}$
  - Intraduodenal absorption via feeding tube only had minor difference in $C_{max}$





Nimmo J, et al. Br Med J. 1973;1:587–589
Raffa RB, et al. Pain Pract. 2014 Sep;14(7):668-77

# Acetaminophen Absorption Test in the ICU

- No gold standard described in the critically ill, though a commonly used marker in other populations
- Single center, observational, retrospective analysis of 19 MICU/ SICU patients, 28 AAT total conducted
  - 10-15 mg/kg enteral acetaminophen x1, followed by 2 serum concentration drawn within 180 minutes
  - 21/28 tests considered positive
    - Serum concentration $\geq$ 10 µg/mL
  - Age, weight, dose, serum prealbumin similar between responders and non-responders

Rhoades A, et al. Crit Care Med 43(12) Supp 155–156 (Abstract)

# NSAIDs

- Although effective, adverse events and side effects require cautious use
- Use lowest dose for shortest duration
- Closely monitor for side effects including gastrointestinal bleeding, nephrotoxicity and delirium

# Ketorolac Ceiling Dose?

- ED Patients
- No difference in pain scores between 10 mg, 15 mg, 30 mg dose
- Larger validation could mitigate adverse effect risk to be more attractive in higher risk populations

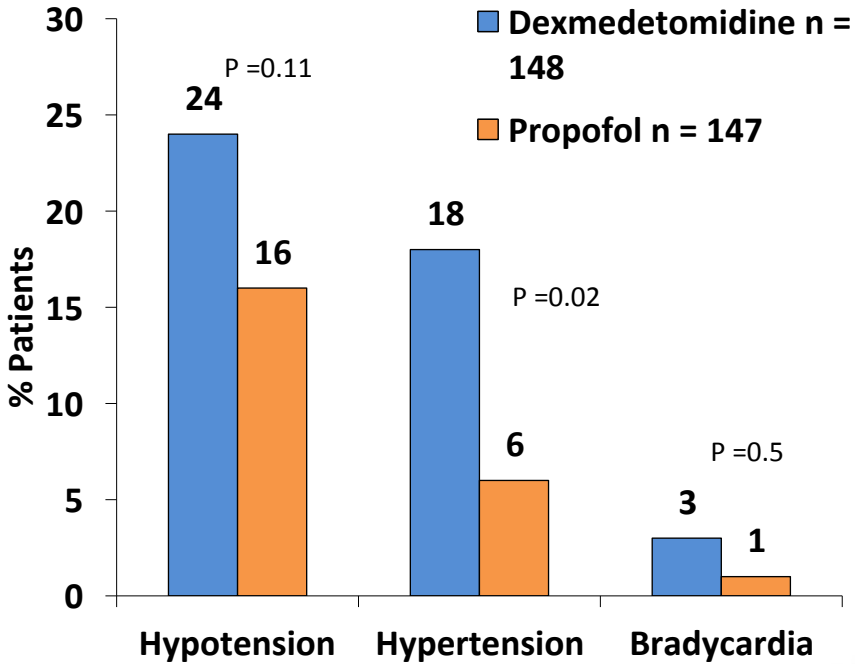
| Rate of rescue morphine over time by number of patients per group | | | |
|---|---|---|---|
| Time, Minutes | 10 mg (%) | 15 mg (%) | 30 mg (%) |
| 15 | 0 | 0 | 0 |
| 30 | 4 (5.0) | 3 (3.8) | 4 (5.0) |
| 60 | 4 (5.2) | 7 (9.0) | 4 (5.3) |
| 90 | 7 (9.3) | 4 (5.5) | 7 (10.3) |
| 120 | 3 (4.6) | 8 (12.7) | 2 (3.2) |

Motov S, et al. Ann Emerg Med. 2017 Aug;70(2):177-184.

# Dexmedetomidine

- Becoming increasingly utilized as benzodiazapine use falls out of favor
- Analgesic effects via α-2 agonism that facilitate descending inhibitory actions in the superficial dorsal horn of the spinal cord
- Efficacy as an analgesic largely seen as secondary endpoint
- Moderate opioid-sparing effect in the early postoperative period
- Light level of sedation, not a respiratory depressant
- Hemodynamic Instability, bradycardia

# Dexmedetomidine-based vs. Propofol Based Sedation after Bypass Surgery

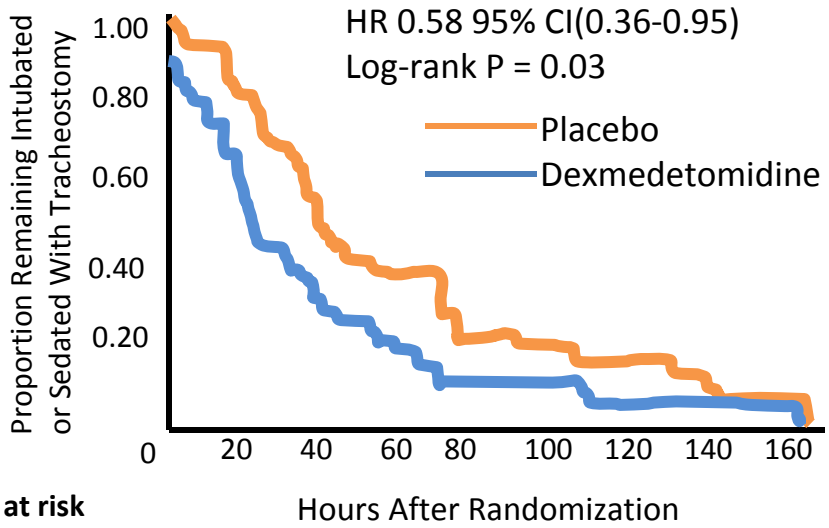



| | Dex | Propofol | P value |
|---|---|---|---|
| Ramsay* | 4.5 | 4.7 | 0.26 |
| Weaning time, mins* | 295 | 300 | NS |
| Extubation time, mins* | 410 | 462 | NS |
| Morphine, mg* | 0.23 | 0.84 | < 0.001 |

*Data presented in mean Hypotension, hypertension, bradycardia not defined

Herr DL, et al. J Cardiothorac Vasc Anesth. 2003 Oct;17(5):576-84.

# Dexmedetomidine in Patients With Agitated Delirium




| # at risk | | | | |
|---|---|---|---|---|
| Dex | 39 | 10 | 4 | 2 |
| Placebo | 32 | 13 | 6 | 2 |

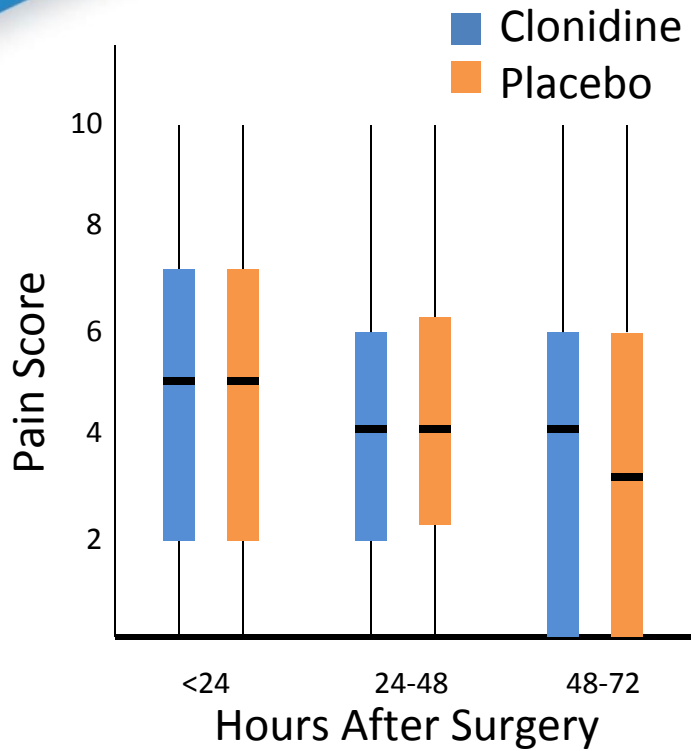
| | Dex n= 39 | Placebo n= 32 | P-Value |
|---|---|---|---|
| Propofol use* | 28 (71.8) | 28 (87.5) | 0.11 |
| Propofol Dose** | 980 (280-3050) | 5390 (1880 – 10803) | <0.001 |
| Morphine use* | 5 (12.8) | 11 (34.4) | 0.03 |
| Morphine Dose** | 19 (13-29) | 53 (15-94) | 0.50 |
| Fentanyl use* | 22 (56.4) | 16 (50.0) | 0.59 |
| Fentanyl dose** | 310 (210 - 680) | 1543 (335-6629) | 0.03 |

*N (%) **Median (IQR)



Reade MC, et al. JAMA. 2016 Apr 12;315(14):1460-8.

# Clonidine after Non-Cardiac Surgery




- 0.2 mg x 1 or placebo followed by patch
- No reduction in pain scores in the 48 hours following surgery
- No reduction in opioid consumption

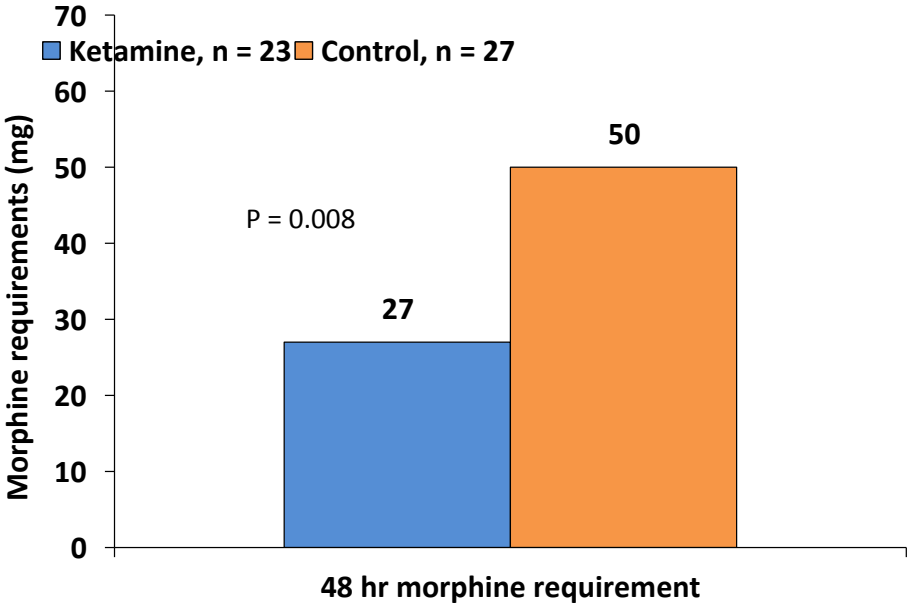
Turan A, et al. Anesth Analg. 2016; 123: 749-57

# Ketamine

- Traditionally used for post-operative analgesia, but increasingly described as adjuncts for analgesia in critical illness (and several other proposed indications)
- Can provide opioid sparing effects while maintaining hemodynamic stability and respiratory drive
- Further prospective comparative research needs to be done to further elucidate its role in analgesia in the ICU setting

- Dosing
  - Sub-anesthetic doses
- Monitoring
  - Hemodynamic changes
  - Mental Status changes
  - ICP Considerations

# Pre-emptive and postoperative Ketamine plus MSO4 vs. MSO4 alone




| | Ketamine (n=23) | Control (n=27) | P value |
|---|---|---|---|
| Intra-op sufentantil, mcg† | 100 [55] | 100 [60] | 0.77 |
| Duration of surgery, min† | 150 [75] | 150 [57] | 0.53 |
| Incidence N/V* | 1 (4) | 10 (37) | 0.01 |
| Awake at hr 48* | 18 (67) | 12 (44) | 0.09 |

† Median [IQR]; * number (%); N/V = Nausea and vomiting

Zakine J, et al. Anesth Analg 2008;106:1856-1861

# Low Dose Ketamine Impact on Opioid Use in Mechanically Ventilated SICU Patients

- Single center, retrospective, N= 40
- Median dosing 5 mcg/kg/min
- Time from ketamine to extubation 1.44 days (0.58-2.66)
- No significant changes in SBP, DBP, HR or RR in six hours post initiation

| Parameter | 1 Hr pre | 6 Hrs post | P Value |
|---|---|---|---|
| MSO4, mg/hr* | 6.66 (4.8-10) | 5 (0-6.66) | 0.004 |
| Phenylephrine equivalent, mg/hr* | 70 (25-90) | 40 (0-80) | 0.019 |
| Propofol, mg/h* | 180 (100-250) | 150 (12.75-200) | 0.014 |
| RASS outside of goal, n | 22 | 20 | 0.476 |
| RASS >0, n | 4 | 10 | <0.001 |
| RASS <-1, n | 18 | 10 | <0.001 |
| *Median (IQR) | | | |

Buchheit JL, J Intensive Care Med. 2017 Jan 1. (epub ahead of print)

# Ketamine BWH analysis

- Single center, retrospective chart review of all ketamine CI at doses <0.9 mg/kg/hr from 9/1/10-8/31/13 N=396
- 69.9% surgical, 30.1% non-surgical (23.9% ICU level care)
- Median duration 35.69 hrs (19.18-66.82)
- Pain scores PRE v POST: 7.1 + 2.63 vs. 6.42 + 2.01 ($p < 0.001$)
- Hypertension: 21.4%, hypotension: 15.1%

Kator S, et al. Am J Health-Syst Pharm. 2016; 73(suppl 1):S22-9

# Regional Analgesia

- Regional analgesia such as epidural analgesia allows targeting of therapy and potentially denser analgesia
- Limited in ICU applicability due to risks of
  - Hemodynamic Instability
  - Epidural Hematoma

# Transversus Abdominus Plane (TAP) Block

- Ultrasound guided single shot or placement of a continuous catheter of local anesthetic
- Useful in critically ill patients with abdominal pain entirely above or entirely below the T10 dermatome, potential to serve as the backbone of analgesia in some patients
- 2012 Meta analysis: single shot TAP blocks decrease cumulative morphine utilization at 24–48 h after abdominal surgery, reduce incidence of PONV
- Complications: bowel perforations, liver lacerations during placement

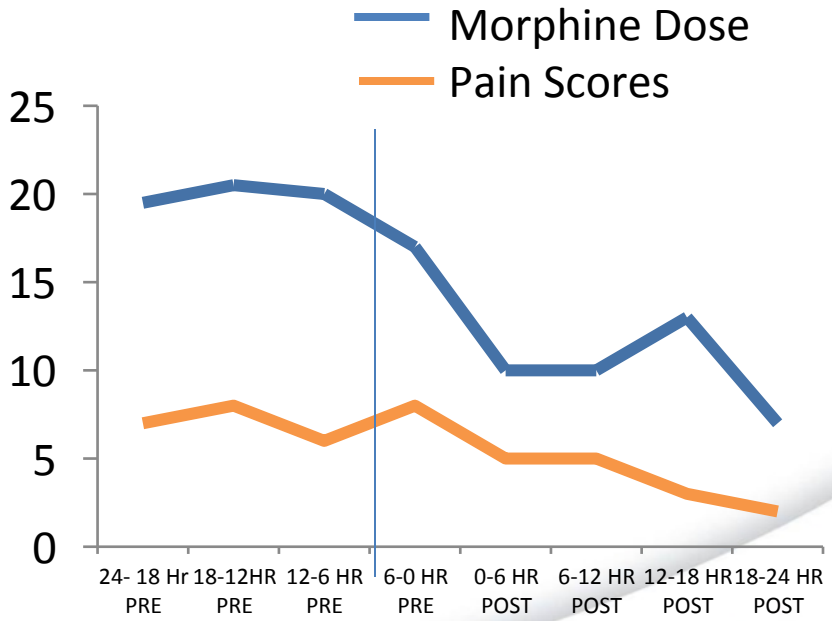
# Lidocaine Infusion for Pain

- Largely extrapolating from non-ICU data
- RCT in lumbar surgery preincision bolus of (1.5 mg/kg) and infusion (2 mg/kg/h) until the end of surgery
  - Decreased VAS scores at 2–24 h after surgery
  - Decreased total fentanyl consumption
  - Decreased length of hospital stay
  - Increased satisfaction scores
- 2015 Cochrane review found when compared with placebo
  - reduced postoperative pain up to 24 h in patients after open or laparoscopic abdominal surgeries

- Dosing
  - Bolus: 1-1.5 mg/kg
  - Maintenance: 0.5-2 mg/kg/hr (**Ideal Body Weight**)
- Monitoring
  - Mental Status changes
  - Local anesthetic toxicity
  - Drug-Drug Interactions
- TDM
  - Target lidocaine level < 4

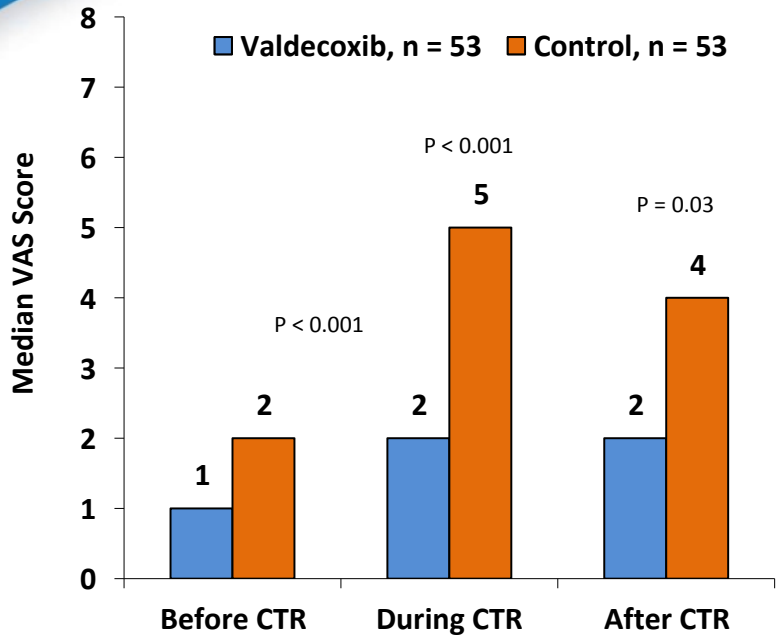
# Lidocaine Infusion for Pain in the ICU

- Two center, retrospective review, N=21
- Mean dose 0.93mg/min + 0.61 duration 48 hrs + 33
- Significant reductions in pain scores and opioid requirements
- 3 patients (11%) d/c'd therapy due to high level or suspected adverse effects




Mo Y, et al. J Clin Pharmacol. 2017 Jul;57(7):830-836.

# Adjunctive topical valdecoxib gel improves pain scores after CT removal




Enrolled consecutive cardiac surgery patients from March to May 2004. All patients (n = 53) received both valdecoxib gel and paraffin gel on either of the two chest tubes. All patients received both study drug and control. No systemic analgesics had been administered for at least four hours. Valdecoxib or paraffin gel was applied at least 30 minutes prior to CT removal.

Singh M, et al. J Cardiothorac Vasc Anesth 2005;19(6):719-722

# What About the SCCM PAD Guidelines

- Updated version expected soon
- Multimodal therapy changes likely to be limited from a quality of evidence standpoint
- Acetaminophen, ketamine in surgical patients, valdecoxib gel?
- Opportunity to highlight gaps in the literature

# What Should We Target in our Analyses?

- Patient-reported outcomes
  - pain intensity, interference with function, adverse effects, quality of life, satisfaction, quality of recovery, development of chronic pain
- Clinical outcomes
  - complications, analgesic consumption, mortality
- Health economic outcomes
  - costs of resource utilization and interventions (manpower, equipment, and disposables) in private versus state-run health-care systems

# The Road Forward

| Research Target | Specific Focus | Research Design |
|---|---|---|
| Characterization of opioid withdrawal and OIH | Patients on CI opiates for ≥ 72 hours | Descriptive |
| Side-by-side comparison of analgesics | Opioids vs. non-opioids vs. both opioids and non-opioids | Prospective, comparative Research |
| Impact of a multimodal analgesia regimen on ICU patient outcomes | Patient ICU-related outcomes such as duration of MV, LoS, pain scores, adverse events + Post ICU outcomes such as PTSD, chronic pain syndrome, opioid dependence | Longitudinal descriptive research; experimental research |

Puntillo K. et al. Intensive Care Med (2017) 43:1386–1388

# Patient Case- WK

- 69 y.o. male s/p gastrectomy with Roux-en-Y reconstruction & jejunal tube placement complicated by code blue for suspected TRALI reaction
- Intubated secondary to hypoxemic respiratory failure and transferred to the ICU
- Immediate post-operative analgesia was bupivacaine PCEA + fentanyl PCA, standing rectal acetaminophen
  - When being turned this morning, MD discovers patient's epidural catheter has become dislodged
- POD 3: This morning complaining 8/10 pain localized at site of jejunal tube, shouting whenever his abdomen is touched
  - Patient reports fentanyl PCA makes him sleepy
- Surgical team strict declaration for nothing via mouth or via J-tube

Notable labs:

Creatinine: 1.8 mg/dL (baseline 0.93 mg/dL)

INR 1.7

# Which of the following interventions is most appropriate to treat this patient's pain

A. Apply lidocaine 5% patches around the patient's abdomen
B. Initiate lidocaine infusion at rate of 1 mg/kg/hr
C. Initiate ultrasound guided placement of transverse abdominus plane block catheter with bupivicaine 0.125% at 8mL/ hr
D. Add ketorolac 30 mg IV q6h

**WK Is initiated on a lidocaine infusion at 1 mg/kg/ hr. Patient reports pain control is adequate with the infusion and fentanyl PCA, however the next morning he is CAM-ICU (+) and according to his RN experiencing hallucinations. What is the appropriate next therapeutic step?**

A. Increase lidocaine infusion to 1.5 mg/kg/hr
B. Add a continuous infusion to the patient's fentanyl PCA
C. Send a STAT lidocaine level
D. Start quetiapine 25 mg q8h

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# Key Takeaways

- Key Takeaway #1
  - 2009 Consensus Guidelines for multimodal analgesia still not being followed
- Key Takeaway #2
  - ERAS's foundation lies in standardization, pharmacists can help direct and develop non opioid based perioperative pain guidelines
- Key Takeaway #3
  - While high quality literature on multimodal in the critically ill is lacking, pharmacists have the opportunity to be a part of multimodal initiatives and evaluate their impact