ICU Pain Management and Opioid Stewardship

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Disclosure

- Presenter has no financial or intellectual relationships relevant to this activity

Objectives

- Interpret guideline recommendations regarding multimodal analgesia in critically ill adults
- Describe a plan for the application of a multimodal analgesia strategy in critically ill adults
- Discuss opportunities for opioid stewardship from critically ill patients

Case Question #1

RA is a 37 year-old-male admitted to the surgical ICU after end ileostomy for Crohn's disease. The remainder of his past medical history is unremarkable. He is admitted to the ICU on mechanical ventilation and is currently sedated with propofol 35 mcg/kg/min and fentanyl 250 mcg/hr. His RASS is -1 and BPS is 7. Which of the following may be recommended to improve pain control and decrease opioid requirements based on the 2018 SCCM pain, agitation, delirium, immobility, and sleep disturbances (PADIS) guidelines for adult critically ill patients?

A. Oral gabapentin 300 mg twice daily
B. IV lidocaine 30 mcg/kg/min continuous infusion
C. IV ketorolac 30 mg every 6 hours x 72 hr
D. IV ketamine 2 mcg/kg/min continuous infusion

Case Question #2

LR is a 73-year-old female who is on postop day 2 after a four vessel CABG for coronary artery disease. She currently has 1 mediastinal and 1 pleural chest tube that are ordered to be removed by the surgical fellow. According to the 2018 SCCM PADIS guidelines for adult critically ill patients, which intervention may be suggested to reduce pain associated with this procedure?

A. Diclofenac gel applied surrounding chest tube site prior to removal
B. Ketorolac 30 mg IV x1 with chest tube removal
C. Bupivacaine 0.25% 20 mL subcutaneous infiltration surrounding chest tube site prior to removal
D. 50% nitrous oxide and oxygen inhalation administered during chest tube removal

Background

- Up to 80% of ICU patients experience moderate to severe pain
  - Varies among diverse ICU subgroups (medical, surgical, trauma)
  - At rest, with routine ICU care, and for procedures
- Inadequate pain management is associated with increased morbidity and cost
- Chronic Intensive-Care Related Pain (CIRP) is common
  - Development of chronic pain is reported in up to 50% of ICU survivors
  - Can be as high as 80% after certain surgical procedures
- Consider the therapeutic goal on individual patient often
  - Examples:
    - Post operative ICU patient
    - Patient with ARDS May require higher doses of medications to support respiratory system compliance due to inflammation

Karamchandani K, et al. Ann Am Thorac Soc Vol 15, No 9, pp 1016–1023, Sep 2018.

Valsø Å, etal . *Nurs Crit Care.* 2021 Aug 12. doi: 10.1111/nicc.12701. Epub ahead of print.

Bhatraju, et al. *N Engl J Med* 2020 May 21;382(21):2012-22.

Fine PG, et al. *J Pain Symptom Manage* 2009; 38(3): 418-25.

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

Schelling G, et al. *Crit Care Med*. 1998 Apr;26(4):651-9.

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

Choi J,et al. *J Pain Symptom Manage*. 2014 Feb;47(2):257-70.

Hanidziar D, et al. *Anesth Analg.* 2020 Jul;131(1):e40-e41.

Martyn JAJ, et al. *N Engl J Med* 2019; 380(4):365-378.

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

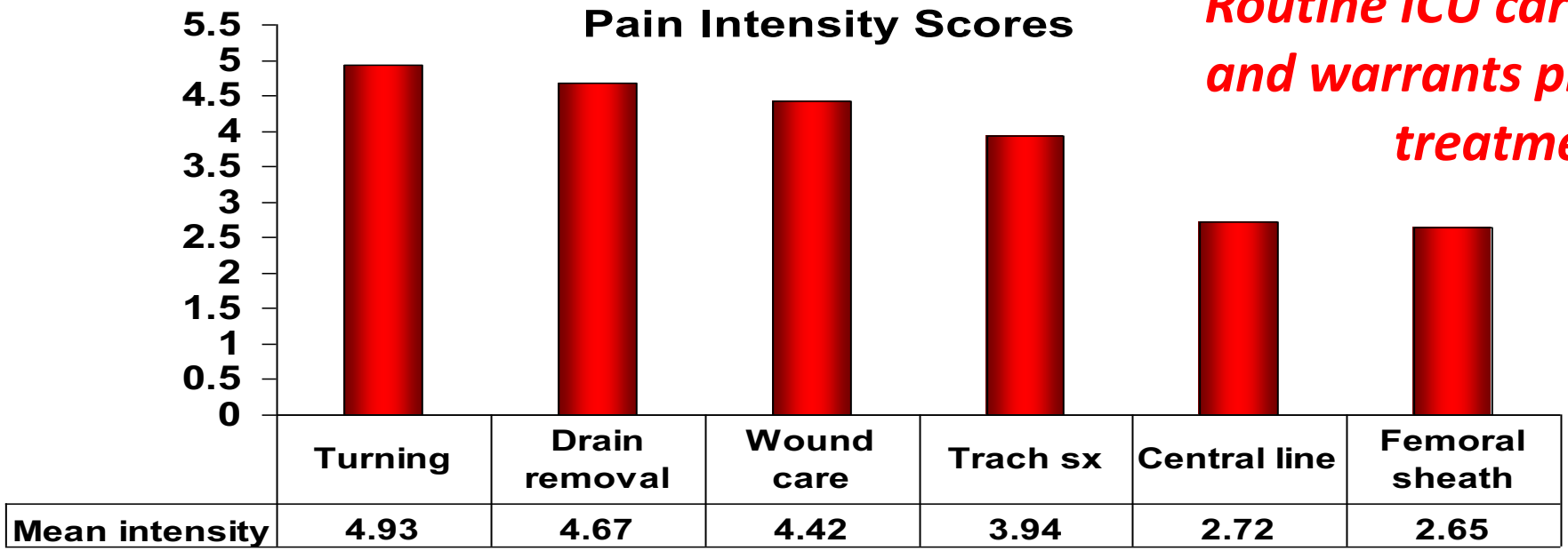
Barr J, et al. *Crit Care Med*. 2013 Jan;41(1):263-306.

Macrae WA. *Br J Anaesth*. 2008 Jul;101(1):77-86.

Sinatra R. *Pain Med*. 2010 Dec;11(12):1859-71.

Chanques G, et al. *Anesthesiology*. 2007;107:858-60.

Pain in the ICU is Common and Influences Patient Outcome



	Turning	Drain removal	Wound care	Trach sx	Central line	Femoral sheath
Mean intensity	4.93	4.67	4.42	3.94	2.72	2.65

Routine ICU care is painful and warrants pre-emptive treatment

N=6201 critically ill adults

- Inadequate pain management is associated with increased morbidities, chronic pain, and cost

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

Schelling G, et al. *Crit Care Med*. 1998 Apr;26(4):651-9.

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

Macrae WA. *Br J Anaesth*. 2008 Jul;101(1):77-86.

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The role of analgesia in the pathway to recovery

Ideal Pathway

Acute illness/Surgery

↓

Optimal Pain Control

↓

Supportive Care

↓

Rehabilitation

↓

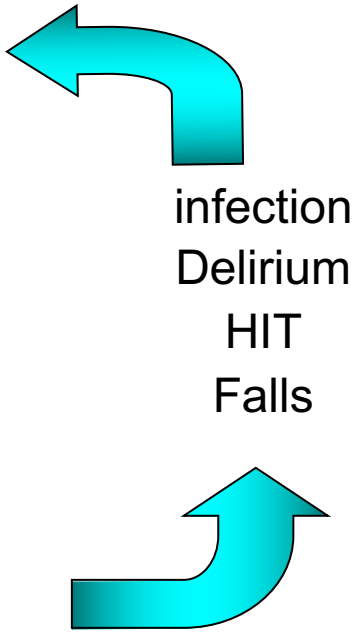
Discharge

Undesired Pathway

Acute illness/Surgery

Inadequate Pain Control

Poor recovery and rehabilitation



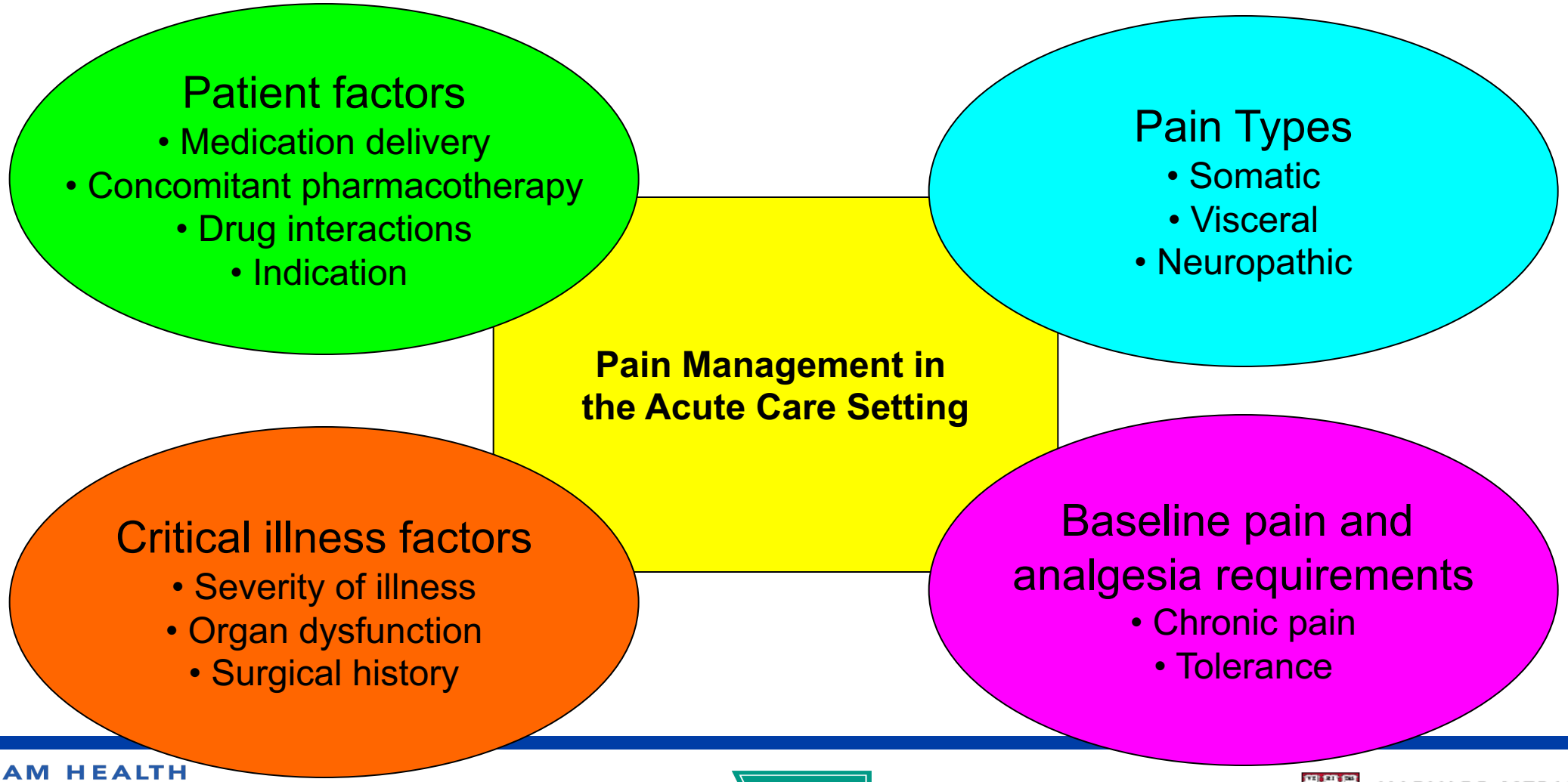
infection
Delirium
HIT
Falls

"Wheel of misfortune"

↕

Chronic pain, prolonged length of stay, post-discharge follow-up and readmissions

Pain Management: One size does not fit all…



Difference in Hard Endpoint = Non-Medication Specific

Strategies:

No one drug is right for all (or most)

1. Set a goal and continually discuss goal
2. Assessment, Assessment, Assessment; and discussion of assessment
3. Non-pharmacologic strategies (ventilator adjustments, etc.)
4. Default: Awake and alert (RASS 0) whenever possible
5. Symptom triggered/preemptive bolus only
6. Sedation/NMBA Holiday
7. Analgosedation or no sedation
8. Patient specific pharmacotherapy (Multimodal)
9. Rotation of medications (avoid accumulation)

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.
Payen JF et al. *Anesthesiology.* 2009;111:1308-1316
Payen JF, et al. *Anesthesiology.* 2007;106:687-695.
Chanques G, et al. *Crit Care Med*. 2006;34(6):1691–9.
Gélinas C, et al. *Int J Nurs Stud*. 2011 Dec;48(12):1495-504.
Erdek M, et al.. *Int J Qual Health Care*. 2004 Feb;16(1):59-64.
van Gulik L, et al. *Eur J Anaesthesiol*. 2010 Oct;27(10):900-5.

PADIS – Pain Recommendations

- Key 2018 SCCM PADIS guidelines recommends
  - Management of pain for adult ICU patients should be guided by routine pain assessment and pain should be treated before a sedative agent is considered
    - Good practice statement
  - Among critically ill adults who are able to self-report pain, the 0–10 Numeric Rating Scale (NRS) administered either verbally or visually is a valid and feasible pain scale.
    - Ungraded
  - Among critically ill adults unable to self-report pain and in whom behaviors are observable, the Behavioral Pain Scale in intubated (BPS) and nonintubated (BPS-NI) patients and the Critical-Care Pain Observation Tool (CPOT) demonstrate the greatest validity and reliability for monitoring pain.
    - Ungraded

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Hierarchy of Pain Assessment

1. Self-reporting is preferred
2. Search for Potential Causes of Pain
3. Observe Patient Behaviors
4. Proxy Reporting (family members, parents, unlicensed caregivers, professional caregivers) of Pain and Behavior/Activity Changes
5. Attempt an Analgesic Trial

Herr K, et al. *Pain Manag Nurs*. 2011 Dec;12(4):230-50.

Pain Assessment Scales: Self-Reporting Patient

- Able to communicate and self reporting
  - Numerical rating scales (NRS or NRS 11)
  - Visual analogue scales (VAS)
- Thresholds/Acceptable pain
  - Typically, < 3 to 5 (scale 0-10)
  - Not all pain is avoidable, making individualized goal-oriented therapy vital
- Limitations
  - Patient unable to communicate

American Society of Anesthesiologists. *Anesthesiology.* Feb 2012;116(2):248-273.
Barr J, et.al. *Crit Care Med*. 2013 Jan;41(1):263-306.
The Joint Commission. Safe use of opioids in hospitals. *Sentinel Event Alert. August* , 2012.

Pain Assessment Scales: Unable to Communicate

- Behavioral pain assessment tools
  - Facial expression, movement, ventilator interaction
- Consensus Guideline- recommended scales
  - Critical-Care Pain Observation Tool (CPOT) (Range 0-8)
    - —Score > 2
  - Behavioral Pain Scale (BPS) (Range 3-12)
    - —Score > 5
- Limitations:
  - Validation still needed:
    - —Diverse languages/cultures
    - —Traumatic brain Injury
  - Paralysis

Gélinas C, et al. *Am J Crit Care.* 2006;15:420-427.
Arbour C, et al. *Pain Manag Nurs*. 2014 Jun;15(2):506-18.
Barr J, et al. *Crit Care Med*. 2013 Jan;41(1):263-306.
Herr K, et al. *Pain Manag Nurs*. 2011 Dec;12(4):230-50.
Arbour C, et al. *Crit Care Nurse*. 2011 Dec;31(6):66-8.

Protocol-based Pain First/Analgosedation

- The 2018 SCCM PADIS guidelines recommend
  - Using an assessment-driven, protocol-based (analgesia/analgosedation), stepwise approach for pain and sedation management in critically ill adults
    - Conditional recommendation, moderate quality of evidence

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Impact of Pain Assessment on Outcomes in the ICU

- A higher degree of pain assessment with a validated tool via protocol or education is associated with:
  - Improved pain scores
  - Reductions in length of ventilation and ICU/hospital stay
  - Reduced mortality
  - ↑↓ prescription and consumption of opioids
  - Reduced consumption of sedatives
  - Reduced need for bolus analgesics in non-communicative
  - Increased use of nonopioid analgesics
  - No effect on opioid related adverse drug events (ORADE)

Gélinas C, et al. *Int J Nurs Stud*. 2011 Dec;48(12):1495-504.
Erdek M, et al.. *Int J Qual Health Care*. 2004 Feb;16(1):59-64.
van Gulik L, et al. *Eur J Anaesthesiol*. 2010 Oct;27(10):900-5.
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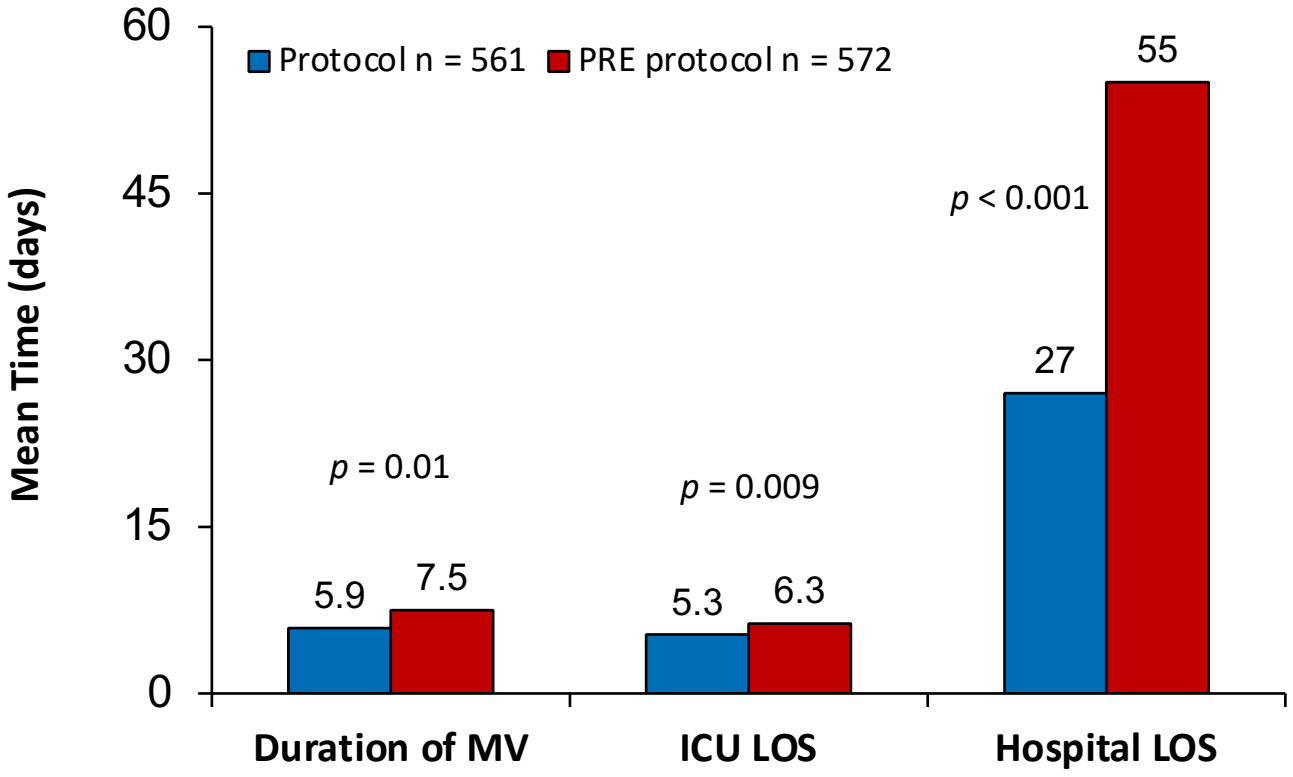
Payen JF, et al. *Anesthesiology*. 2007;106:687-695.
Chanques G, et al. *Crit Care Med*. 2006;34(6):1691–9.

Impact of Pain-Sedation-Delirium Protocol



Significant patient characteristics/metrics/outcomes

	Protocol	PRE	P value
Delirium†	34.2	34.7	0.9
Subsyndromal Delirium†	24.6	33	0.009
Lorazepam equivalents, mg*	2.75 ± 7.94	5.79 ± 31.78	0.02
MSO4 equivalents, mg*	22.3 ± 40.1	103.5 ± 239.2	<0.001

*Data presented as mean ± SD †Data presented as %

Subsyndromal delirium; max ICDSC 1-2 in ICU

Single center, observational trial of 1,133 adult ICU patients requiring > 24hr of ICU care before (PRE) (n = 572) and after (n = 561) implementation of a protocol for pain, sedation, and delirium management at Hospital Maisonneuve-Rosemont from 8/2003 to 11/2005. Protocol used goal-oriented sedation to target RASS and numeric rating scale (NRS).

Skrobik Y et al. *Anesth Analg*. 2010 Aug; 111(2):451-63.

Implementation of a Pain Management Algorithm

Outcome measure	Control (N = 252)	Intervention (n = 398)	P – value
Ventilation time, hr	79 (26-205)	46 (17-153)	0.01
Length of ICU stay, d	3.0 (1.7-6.9)	2.6 (1.7-5.4)	0.04
Length of hospital stay, d	13 (7-24)	13 (7-24)	0.79
Sedation level			
MAAS	2 (0-3)	2 (1-3)	0.28
RASS	-1 (-3 to 0)	0 (-2 to 0)	0.09
Agitation event, n (%)	14 (6)	9 (3)	0.02

Data presented as median (IQR) unless otherwise noted
MAAS: Motor Activity Assessment Scale

Olsen BF, et al. *J Crit Care*. 2016; 36: 207-211.

PADIS via ABCDEF Bundle

- Goal to increase the following:
  - Liberation from ventilator
  - Early ICU and hospital discharge
  - Return to normal brain function
  - Independent functional status
  - Survival
- Awakening and Breathing trial coordination
- Choice of sedative and analgesics
- Daily delirium monitoring
- Early mobility exercise
- Family involvement

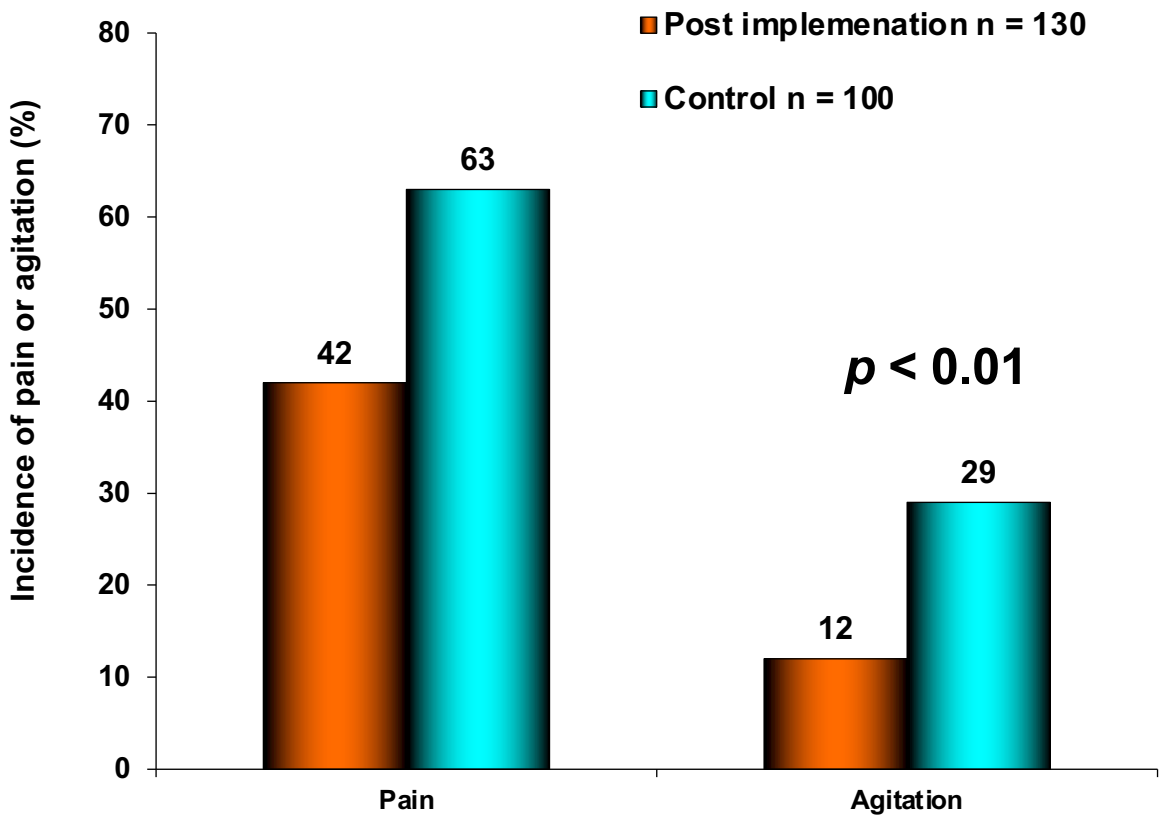
Balas MC, et al. *Crit Care Med*. 2014 May;42(5):1024-36.
Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

ABCDEF Bundle Via PADIS

- For every 10% increase in total bundle compliance, patients had a 15% higher hospital survival

Barnes-Daly MA, et al. Crit Care Med. 2017 Feb;45(2):171-178.

Systematic Implementation of Pain and Sedation Tools



Significant patient characteristics/metrics/outcomes

	Pre	Post	P value
Other analgesics administered**	**1.0 (0.6-1.8)**	**2.0 (1.2-3.8)**	**0.002**
Mechanical Ventilation, hr*	120	65	0.01
Duration CIVS, hr*	84	48	0.03
Duration CIVI Opioid, hr*	96	60	0.02
Nosocomial infection†	17 (17)	11 (8)	<0.05

*Data presented in median hrs; †Data presented as n (%); **Data presented as median (25-75 percentiles); CIVS; Continuous intravenous infusion sedation; CIVI: continuous intravenous infusion

Single center, prospective, two phase, controlled study of 230 ICU patients requiring > 24-hr stay before (n = 100) and after (n = 130) implementation of a pain and sedation guideline at Montpellier University hospital in France. Education and encouragement of use of pain scale and sedation assessment tools.

Chanques G, et al. *Crit Care Med*. 2006;34(6):1691–9.

Chemical Mechanism of Pain

- Many chemical mediators interact with nociceptive neurons
  - Pro-inflammatory cytokines, chemokines, neurotrophins:
    - Vanilloid type 1 receptor, 5-hydroxytryptamine receptors, Histamine type 1 , Protaglandin E2, Prostanoid receptors EP subtype, bradykinin receptors, interleukin-1 beta, inteleukin-1 receptor, nerve growth factor, tyrosine kinase A receptor, adenosine triphosphate, purinergic receptor subtype, hydrogen ion, calcium, protein tetrodotoxin-resistant voltage-gated sodium channel, substance P, acid-sensing channel.
- Result
  - Activating intracellular signaling cascade leading the activation of protein kinase A (PKA) or protein kinase C (PKC)

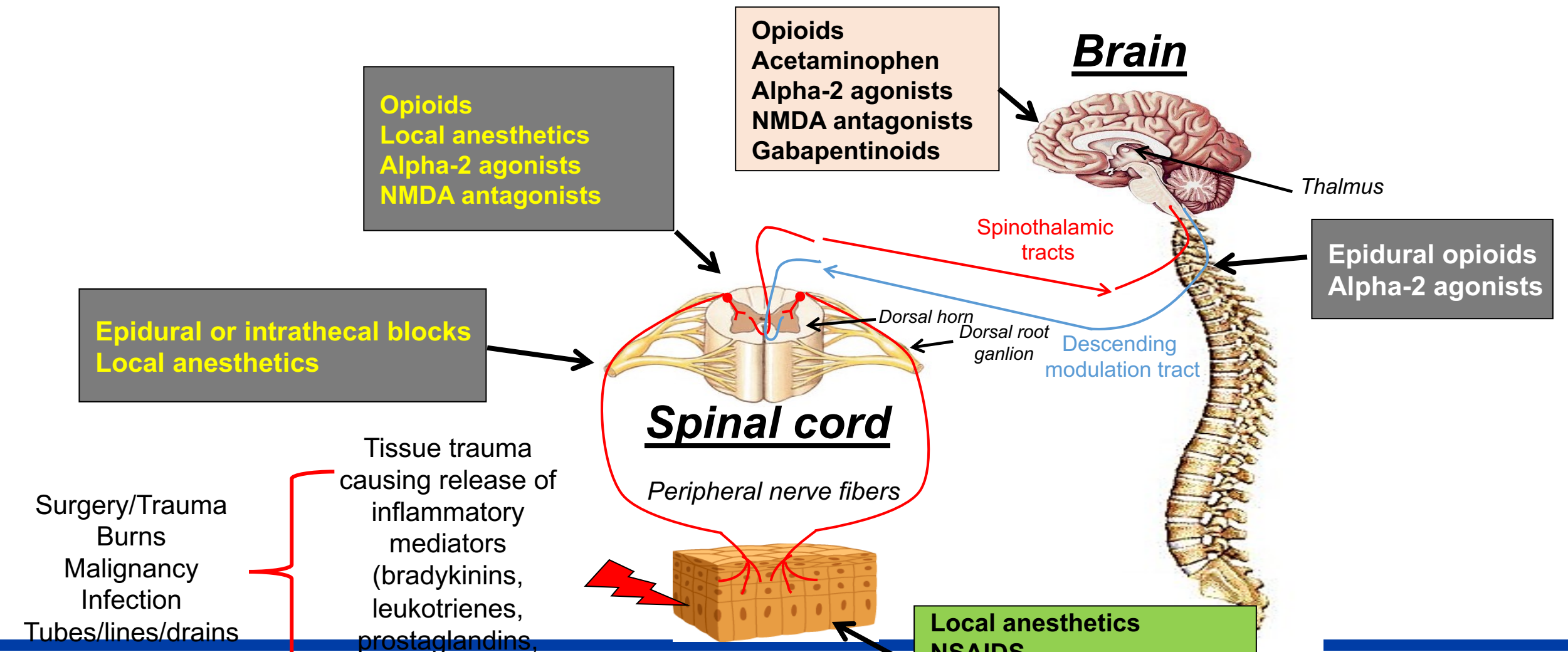
Cesare P, et al. Neuron 1999; 23: 617-24.
Aley KO, et al. J Neurosci 1999; 19:2181-6

Multimodal Analgesia

- Definition
  - Combining different analgesics that act by different mechanisms and at different sites in the nervous system, resulting in additive or synergistic analgesia with lowered adverse effects compared to sole administration of individual analgesics
- Also known as “balanced analgesia”
- Established 1993
- Recommended by perioperative practice guidelines
- A standard part of all Enhanced Recovery after Surgery (ERA) pathways
- <u>Limited focused ICU literature</u>

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.
Kehlet H. *Anesth Analg*. 1993 Nov;77(5):1048-56.
Young A, et al. *Anesthesiol Clin*. 2012 Mar;30(1):91-100.
American Society of Anesthesiologists. *Anesthesiology.* 2012 Feb;116(2):248-73.
Buvanendran A, et al. *Curr Opin Anaesthesiol*. 2009 Oct;22(5):588-93.

Effective ICU Pain Control: Not Just Opioids



Multimodal Analgesia: 2018 SCCM PADIS guidelines

PICO Question	
P	Critically ill adult patients in an ICU
I	Adjunctive: • Acetaminophen (IV/PO/PR) • Nefopam • Ketamine • Neuropathic analgesia • IV lidocaine • NSAID (IV/PO)
C	No adjunctive use of XX
O	• VAS score at 24 hours postoperatively (in cm) • Mean BPS pain scores until patient extubated • Pain score at extubation • Time to extubation (minutes) • Rescue opioid doses • Opioid consumption (in morphine equivalents)

Paracetamol as Adjunctive Treatment for Postoperative Pain After Cardiac Surgery

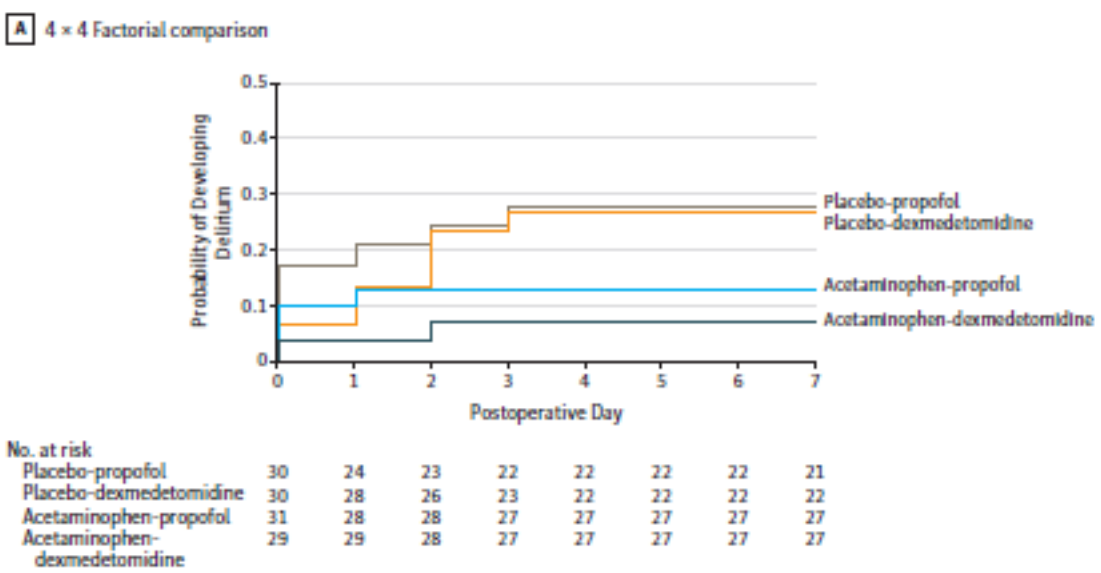
	Paracetamol (n = 56)	Placebo (n=57)	p value
Pain at 12 hr*	1 [0-6)	2 [1-10]	0.0041
Pain at 18 hr*	1 [0-5]	2 [0-8]	0.0039
Pain at 24 hr*	1 [0-5]	2 [0-8]	0.0044
Morphine total dose 1st 3 daysβ	48 mg	97 mg	NS
Morphine total dose 1st 3 days^	5 mg [2-10]	5 mg [5-15]	NS
Rescue dose of morphine@	8 mg (14.2)	14 mg (24)	NS

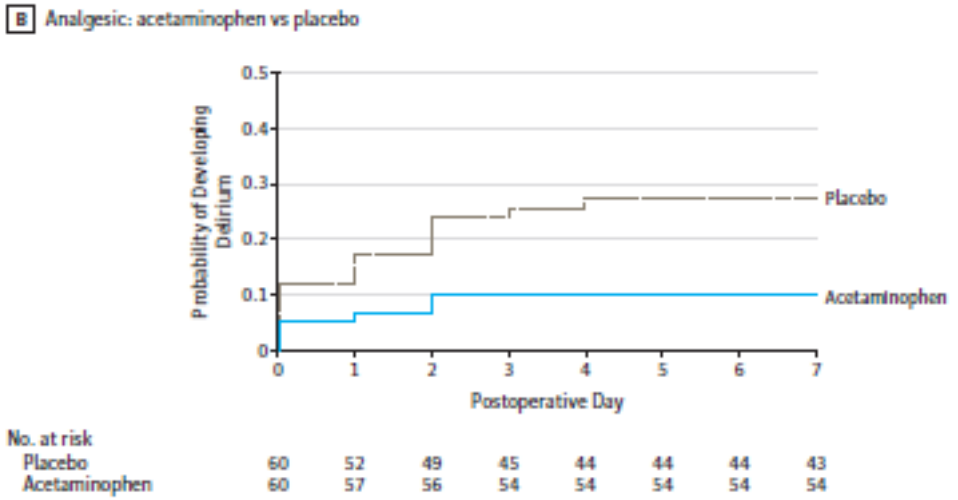
*visual analog scale mean [range]
β Mean
^ Median [range]
@ n (%)

- Paracetamol 1 g every 6 hr for 72 hr vs. placebo
- Standard analgesia was tramadol with morphine as needed

Cattabriga I, et al. *Eur J Cardiothorac Surg*. 2007 Sep: 32(3): 527-31.

DEXACET RCT





- Single-center RCT (BIDMC, Boston, MA): post-op cardiac surgery. 4 groups: placebo-propofol (30), placebo-dexmed (30), IV acetaminophen-propofol (31), IV acetaminophen-dexmed (29).

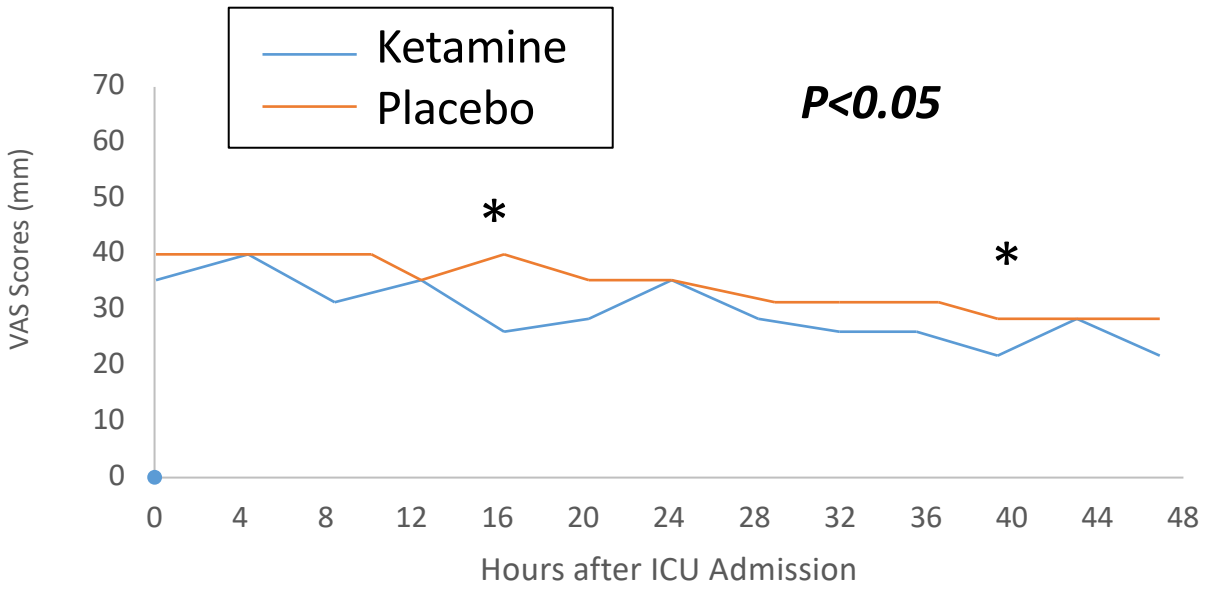
Subramaniam B, et al. JAMA. 2019 Feb 19;321(7):686-696.

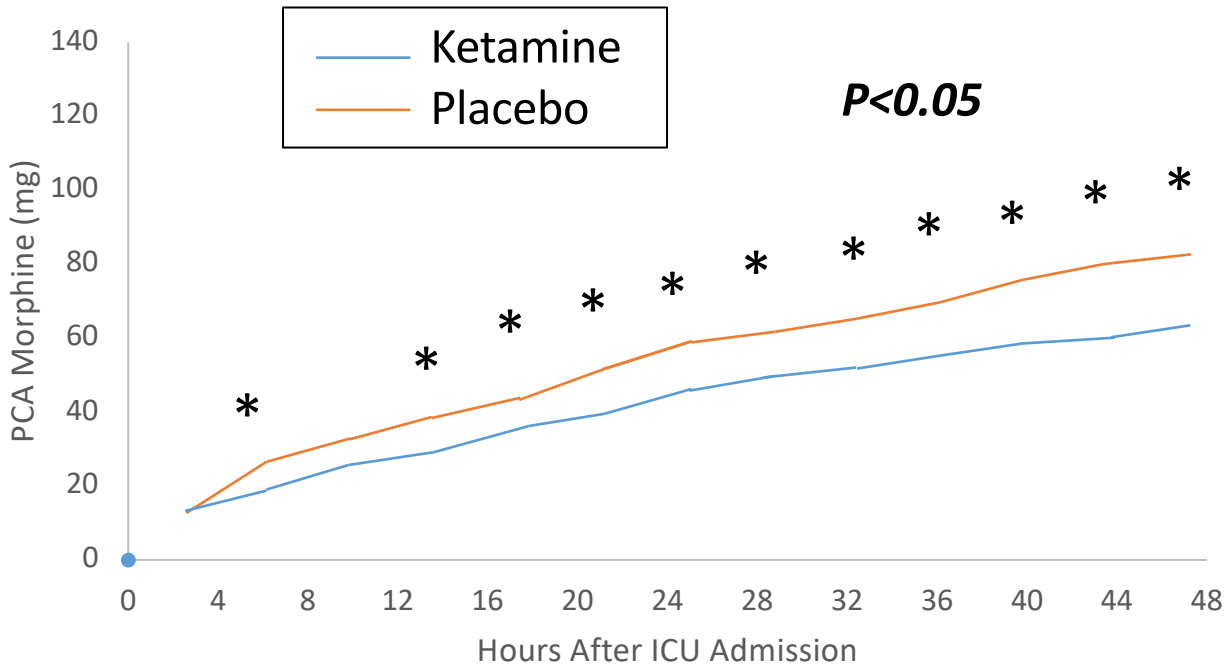
Adjunctive Acetaminophen

- The 2018 SCCM PADIS guidelines suggest using acetaminophen as an adjunct to an opioid to decrease pain intensity and opioid consumption for pain management in critically ill adults
  - Conditional recommendation, very low quality of evidence

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Adjunctive Low-Dose Ketamine in Surgical ICU Patients





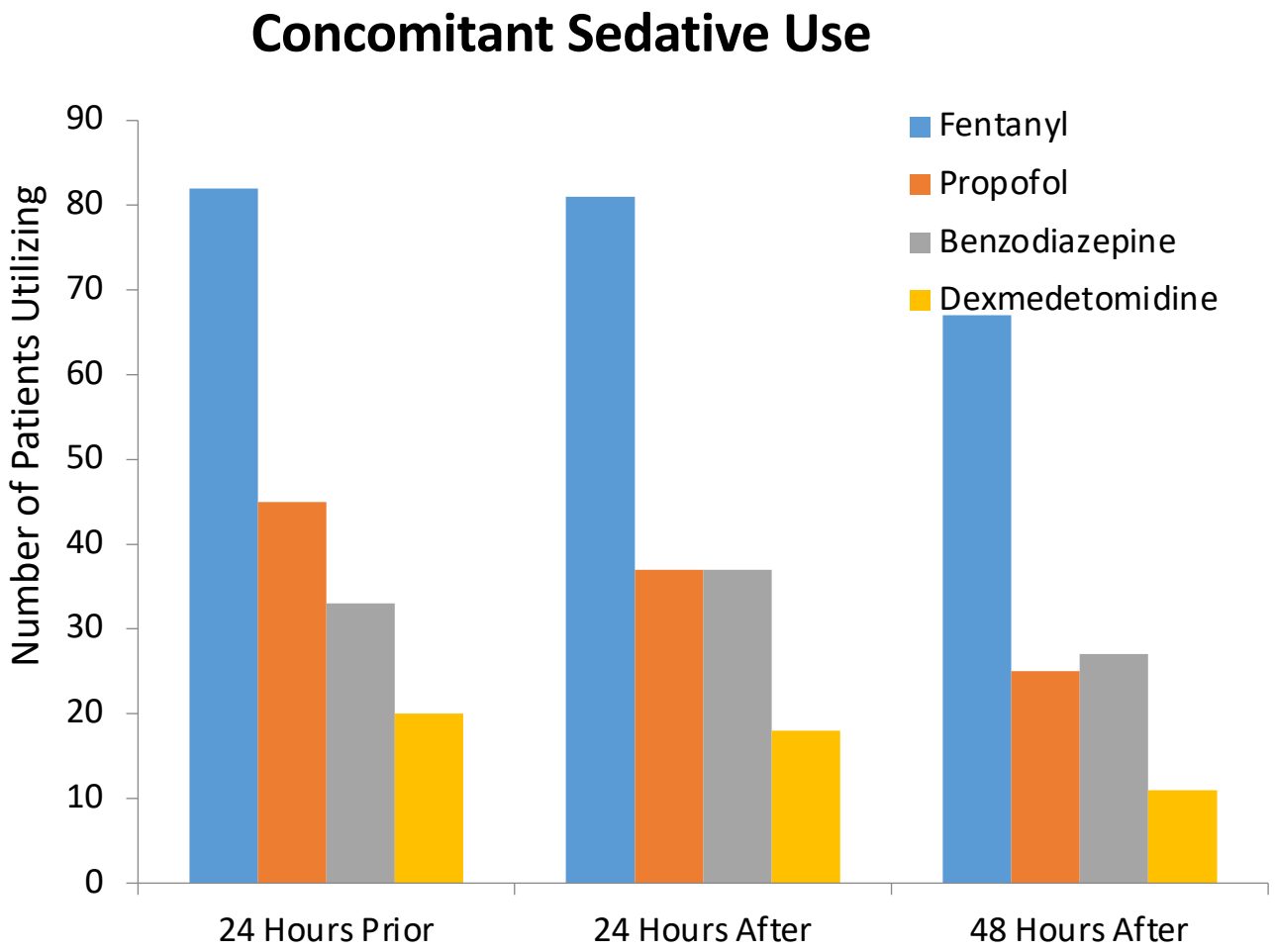
Single-center, prospective, randomized, double-blind trial including 93 patients scheduled to have major abdominal surgery and post-op management and ventilation in the SICU. Patients were randomized to receive morphine by patient-controlled analgesia with either placebo or ketamine (for 48 hours). Both groups were allowed as-needed morphine boluses.

Guillou N, et al. *Anesth Analg* 2003; 97:843-847.

Ketamine for Sedation

Introduction of low-dose ketamine (median dose 0.41 mg/kg/hr) for adjunctive sedation:

- Improved time at goal Sedation-Agitation Scale in the first 24 hours
- Decreased frequency of agitation
- Allowed for reduction or discontinuation of concomitant sedatives (63% of patients)
- Relatively well tolerated (7.7% discontinuation rate)



Groetzinger LM, et al. Pharmacotherapy. 2018; 32(2): 181-188.

Ketamine in the ICU: A tale of caution

Table 1 Quantification of opioid and sedative use

	Protocol group ($n = 10$)	Control group ($n = 10$)	p value
Cumulative fentanyl equivalents from ECMO initiation to decision to achieve wakefulness, mg	15,200 (5488 to 26,981)	8275 (1363 to 20,194)	0.12
Cumulative midazolam equivalents from ECMO initiation to decision to achieve wakefulness, mg	1420 (474 to 3424)	324 (172 to 2454)	0.08
Cumulative fentanyl equivalents during duration of ICU, mg/day	6 (4 to 9)	5 (2 to 10)	0.58
Cumulative midazolam equivalents during duration of ICU, mg/day	8 (6 to 12)	6 (3 to 10)	0.32

- Indication for use is key
  - Routine surgical vs. ARDS

Dzierba AL, et al. *Intensive Care Med.* 2016 Nov;42(11):1822-1823.

Adjunctive Ketamine

- The 2018 SCCM PADIS guidelines suggest using low-dose ketamine (1 -2 mcg/kg/min) as an adjunct to opioid therapy when seeking to reduce opioid consumption in post-surgical adults admitted to the ICU
  - Conditional recommendation, very low quality of evidence

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Adjunctive Neuropathic Pain Medications

- Two post-cardiac surgery trials
  - 40 pregabalin (150 mg prior to surgery then 150 mg daily)
  - 60 placebo patients

- Pooled data show
  - Reduction in opioid consumption
  - No other differences

Pesonen A, et al. *Br J Anaesth* 2011; 106:873–881.

Joshi SS, et al. *Ann Card Anaesth* 2013; 16:180–185.

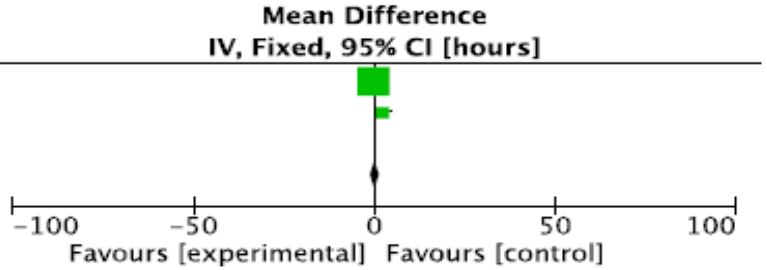
Adjunctive Neuropathic Pain Medications

Adjuvant Treatment – Neuropathic medication

Time to Extubation (hours)

Study or Subgroup	Neuropathic Pain Agent Mean [hours]	SD [hours]	Total	Control Mean [hours]	SD [hours]	Total	Weight	Mean Difference IV, Fixed, 95% CI [hours]
Joshi 2013	7.45	1.95	20	7.68	1.98	20	76.6%	-0.23 [-1.45, 0.99]
Pesonen 2011	10.63	4.75	29	8.33	3.88	31	23.4%	2.30 [0.10, 4.50]
Total (95% CI)			**49**			**51**	**100.0%**	**0.36 [-0.70, 1.43]**

Heterogeneity: $Chi^2 = 3.88$, df = 1 (P = 0.05); $I^2 = 74\%$
Test for overall effect: Z = 0.67 (P = 0.51)



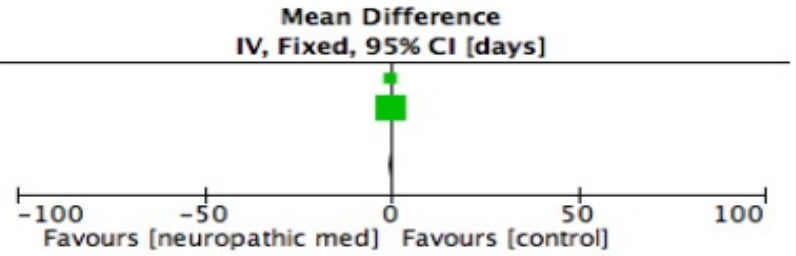
No difference

Adjuvant Treatment – Neuropathic medication

ICU Length of Stay (Days)

Study or Subgroup	Neuropathic Pain Agent Mean [days]	SD [days]	Total	Control Mean [days]	SD [days]	Total	Weight	Mean Difference IV, Fixed, 95% CI [days]
Joshi 2013	3.05	0.68	20	3.2	1.77	20	25.4%	-0.15 [-0.98, 0.68]
Pesonen 2011	1.5	0.8	29	1.5	1.1	31	74.6%	0.00 [-0.48, 0.48]
Total (95% CI)			**49**			**51**	**100.0%**	**-0.04 [-0.46, 0.38]**

Heterogeneity: $Chi^2 = 0.09$, df = 1 (P = 0.76); $I^2 = 0\%$
Test for overall effect: Z = 0.18 (P = 0.86)



No difference

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Adjunctive Neuropathic Pain Medications

- The 2018 SCCM PADIS guidelines
  - Recommend using a neuropathic pain medication (e.g., gabapentin, carbamazepine, pregabalin) with opioids for neuropathic pain management in critically ill adults
    - Strong recommendation, moderate quality of evidence
  - Suggest using a neuropathic pain medication (e.g., gabapentin, carbamazepine, pregabalin) with opioids for pain management in ICU adults after cardiovascular surgery
    - Conditional recommendation, low quality of evidence

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Adjunctive IV Lidocaine

- One single-center RCT of 100 cardiac surgery patients requiring post-operative ICU stay found that lidocaine (1.5 mg/kg IV bolus over 10 min during surgery followed by 10 ug/kg/min continuous infusion x 48 hrs) vs. placebo did not affect self-reported pain, fentanyl or sedative consumption, time to extubation or ICU LOS

- Meta-analysis of non-ICU, abdominal surgery, lidocaine vs placebo RCTs found low-moderate effect on reduced pain intensity scores but no decrease in opioid use or other relevant clinical outcomes

- Neurologic and cardiac safety concerns may be greater in ICU patients

Insler DR et al. *Can J Anesth.* 2000; 47:1192.
Kranke P et al. *Coch Database Syst Rev.* 2015.
Schuler BR, et al. *Clin J Pain.* 2021 Sep 1;37(9):657-663.

IV Lidocaine: Abdominal Surgery Meta-Analysis

- Intravenous lidocaine administration
  - Decreased the duration of ileus
  - Length of hospital stay
  - Postoperative pain intensity at 24 h after operation
  - Incidence of nausea and vomiting

Marret E, et al. *Br J Surg.* 2008 Nov;95(11):1331-8.

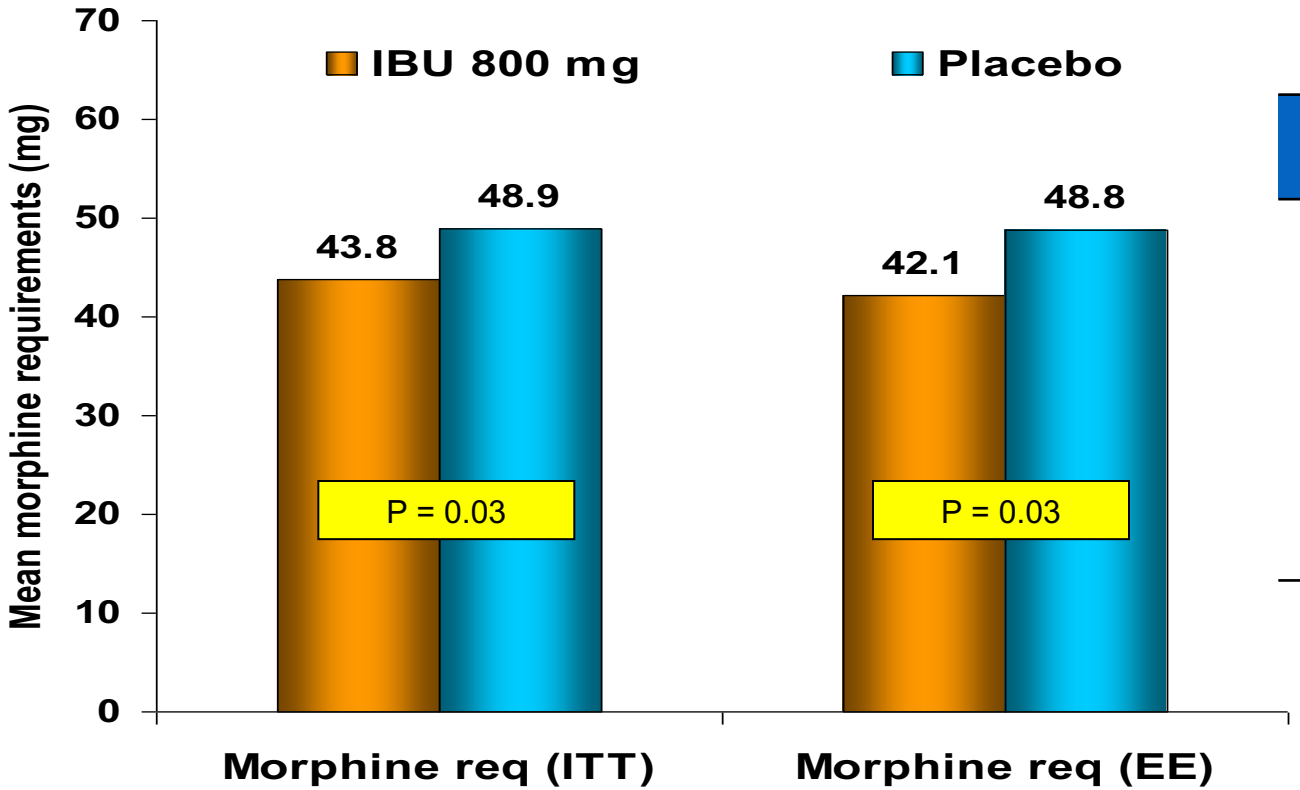
Adjunctive Lidocaine in ICU

- ICU Data
  - No significant differences:
    - Self reported pain
    - Opioid requirements
    - ICU LOS
    - Hospital LOS

- Recommendation
  - The 2018 SCCM PADIS guidelines suggest not routinely using IV lidocaine as an adjunct to opioid therapy for pain management in critically ill adults
    - Conditional recommendation, low quality of evidence

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Adjunctive ibuprofen following orthopedic or abdominal surgery



Significant patient characteristics/metrics/outcomes

	IBU 800 (n=138)	Placebo (n=134)	P value
Pain at rest (1-24hr), VAS-AUC†	73.9 ± 39	91 ± 46	0.001
Pain w/moving (1-24hr), VAS-AUC†	106.3 ± 43.9	123.3 ± 46	0.002
ADE total*	124 (90)	126 (94)	NS
Nausea*	82 (59)	94 (70)	NS
Pyrexia*	10 (7)	23 (17)	0.015

*Data presented in n (%); †Data presented as mean ± SD

Multicenter, multinational, randomized, double-blind, placebo-controlled trial that enrolled patients undergoing elective orthopedic or abdominal surgery and were expected to require post-op analgesia for at least 24 hours. All patients received morphine and were randomized to receive placebo, ibuprofen 400 mg or 800 mg every 6 hours for 2 days (max 5 days). First dose was administered at wound closure.

Southworth S, et al. Clin Ther 2009;31(9):1922-1935

Adjunctive NSAIDs in ICU

- Data
  - 2 small RCTs in ICU
    - Cardiac surgery
    - Abdominal surgery
  - No significant difference in pain scores at 24 hours
  - Small reduction in opioid consumption
  - No significant difference in ADRs

- Recommendation
  - The 2018 SCCM PADIS guidelines suggest not routinely using a COX-1 selective NSAID as an adjunct to opioid therapy for pain management in critically ill adults
    - Conditional recommendation, low quality of evidence

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Procedural Pain in ICU

- The 2018 SCCM PADIS guidelines
  - Suggest using an NSAID administered intravenously, orally, or rectally as an alternative to opioids for pain management during discrete and infrequent procedures in critically ill adults
    - Conditional Recommendation, low quality of evidence
  - Suggest not using an NSAID topical gel for procedural pain management in critically ill adults
    - Conditional recommendation, low quality of evidence
  - Suggest not using either local analgesia or nitrous oxide for pain management during chest tube removal in critically ill adults
    - Conditional recommendation, low quality of evidence

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Is dexmedetomidine opioid sparing?

- Depends
  - Pure surgical trials = maybe
  - Mixed medical/surgical = likely not
    - No difference in SEDCOM, PRO/DEX, MID/DEX
    - In fact,… MENDS = more than opioid consumption is 3X in the dex arm

Venn MR, et al. *Crit Care.* 2000, 4:302-308.

Martin E, et al. J Intensive Care Med. 2003 Jan-Feb;18(1):29-41.

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

Pandharipande PP, et al. *JAMA.* 2007 Dec 12; 298(22) :2644-53.

Riker RR, et al. *JAMA.* 2009 Feb 4;301(5):489-99.

Dexmedetomidine vs Lorazepam: MENDS TRIAL; Key Critiques

	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	*p* Value
Lorazepam mg/hr (mean)		**3**	
Fentanyl mcg/day (mean)	575	150	$p = 0.006$
Sedated deeper than nurse goal RASS score, Days %	15	33	$p = 0.01$

Pandharipande PP, et al. *JAMA*. 2007 Dec 12; 298(22) :2644-53.

Multimodal Pain Management: A LOT to Choose From but Limited ICU Data

- 2018 PADIS endorsed
  - Acetaminophen
  - NMDA receptor antagonists
    - Ketamine
  - Anticonvulsants
    - Gabapentin/Pregabalin
  - Non-pharmacological
- Other Options
  - NSAIDs
  - COX-2 inhibitors
  - α-2 agonists
    - Clonidine & Dexmedetomidine
  - Corticosteroids
  - Local Anesthetics
    - Systemic, regional & local techniques

Choice of agent, route, dosing, and monitoring is often patient-specific and limited by resources available

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.
Buvanendran A, et al. *Curr Opin Anaesthesiol*. 2009 Oct;22(5):588-93.
Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Adverse Drug Reactions for Select "Multimodals"

APAP	NSAIDS/COX II	Local anesthetics	Alpha-2 agonists	NMDA antagonists	Anticonvulsants
Liver toxicity/failure	GI toxicity	Hypotension	Hypotension	Hallucinations	Hallucinations
Nausea and Vomiting	Renal failure	Bradycardia	Bradycardia	Tachycardia	Withdrawal
Hypotension (IV)	Bleeding	Urinary retention*	Tachycardia		Seizures
	CV events	Epidural hematomas*			Excess sedation
	Nausea and Vomiting	Neurotoxicity			

Anticonvulsants: gabapentin/pregabalin

*Associated with epidural administration

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):S251-43.
Devlin JW, et al. Crit Care Med. 2018 Sep;46(9):e825-e873.
Schuler BR, et al. *Clin J Pain*. 2021 Sep 1;37(9):657-663.

Multimodal is more than medications

- The 2018 SCCM PADIS guidelines
  - Suggest cold therapy for procedural pain management in critically ill adults
    - Conditional recommendation, low quality of evidence
  - Suggest offering relaxation techniques for procedural pain management in critically ill adults
    - Conditional recommendation, very low quality of evidence
  - Suggest offering massage for pain management in critically ill adults
    - Conditional recommendation, low quality of evidence
  - Suggest offering music therapy to relieve both non-procedural and procedural pain in critically ill adults
    - Conditional recommendation, low quality of evidence

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Case Question #1

RA is a 37 year-old-male admitted to the surgical ICU after end ileostomy for Crohn's disease. The remainder of his past medical history is unremarkable. He is admitted to the ICU on mechanical ventilation and is currently sedated with propofol 35 mcg/kg/min and fentanyl 250 mcg/hr. His RASS is -1 and BPS is 7. Which of the following may be recommended to improve pain control and decrease opioid requirements based on the 2018 SCCM pain, agitation, delirium, immobility, and sleep disturbances (PADIS) guidelines for adult critically ill patients?

A. Oral gabapentin 300 mg twice daily
B. IV lidocaine 30 mcg/kg/min continuous infusion
C. IV ketorolac 30 mg every 6 hours x 72 hr
D. IV ketamine 2 mcg/kg/min continuous infusion

Case Question #2

LR is a 73-year-old female who is on postop day 2 after a four vessel CABG for coronary artery disease. She currently has 1 mediastinal and 1 pleural chest tube that are ordered to be removed by the surgical fellow. According to the 2018 SCCM PADIS guidelines for adult critically ill patients, which intervention may be suggested to reduce pain associated with this procedure?

A. Diclofenac gel applied surrounding chest tube site prior to removal
B. Ketorolac 30 mg IV x1 with chest tube removal
C. Bupivacaine 0.25% 20 mL subcutaneous infiltration surrounding chest tube site prior to removal
D. 50% nitrous oxide and oxygen inhalation administered during chest tube removal

2018 PADIS - Guideline-Recommended Opioid Therapy

- The optimal choice of opioid and the dosing regimen used for an individual patient depends on many factors, including the drug's pharmacokinetic and pharmacodynamic properties

- The use of meperidine is generally avoided in ICU patients because of its potential for neurologic toxicity

Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

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

Comparison of Opioids

Medication	Time to Onset, min	Half-life	Prolonged Clinical Effect Due to Context-Sensitive Half-life	Primary Metabolic Pathway	Prolonged Clinical Effect Due to Organ Failure	Practical Considerations
Fentanyl	1	2-4 h	Yes: significant	N-dealkylation CYP450 3A4/5	Hepatic	• Requires phase 1 metabolism; therefore, a prolonged clinical effect with inhibitors of CYP450 3A4/5 • Accumulation risk in obese patients • Rare, potentially life-threatening increased risk of serotonin syndrome and chest wall rigidity
Hydromorphone	5-10	2-3 h	Not applicable	Glucuronidation	Hepatic	• Therapeutic substitute for fentanyl or morphine in patients with hepatic or renal dysfunction
Morphine	5-10	3-4 h	Not applicable	Glucuronidation	Renal and hepatic	• Histamine release—leading to hypotension • Metabolite accumulation in renal dysfunction leading to central nervous system toxicity • Cholecystitis
Remifentanil	1-3	3-10 min	Yes: minor	Hydrolysis by plasma and tissue esterases	Renal: minimal	• High risk of opioid-induced tachyphylaxis • High risk of opioid-induced hyperalgesia • May increase ammonia levels • Accumulation in obese patients, suggest ideal body weight dosing

Posa P, Singh J, Stollings J. ICU Liberation. 2020. Second Edition. Mount Prospect, IL. Society of Critical Care Medicine.

Opioids – Many Potential "Unwanted" Effects

- Class effects
  - Respiratory depression
  - Sedation
  - Constipation
  - N/V
  - Pruritis
  - Withdrawal
  - Hypotension
  - Delirium
  - PTSD
  - Immunomodulation
  - hyperalgesia
  - Opioid use disorder (post-ICU)
- Specific agent effects
  - Fentanyl/sufentanil
    - Chest wall rigidity (perhaps masked as ARDS)
    - Serotonin Syndrome
    - Unpredictable pharmacokinetics
    - Growing context-sensitive half-life
  - Remifentanil
    - ↑ Ammonia levels
    - Tachyphylaxis
  - Morphine
    - Cholecystitis
    - Neurotoxicity
  - Meperidine
    - Tremors/seizures
  - Methadone
    - QTC prolongation

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.
Chen A, et al. *Pain Med* 2015;16 Suppl 1:S27-S31.
Hammond DA, et al. *Pharmacotherapy*. In press.
Peng PW, et al. *Anesthesiology* 1999; 90(2):576-99.
Richardson S, et al. *JAMA* 2020 Apr 22;323(20):2052-9.
Alhazzani W, et al. *Intensive Care Med* 2020 May;46(5):854-87.

Opioid Rotation

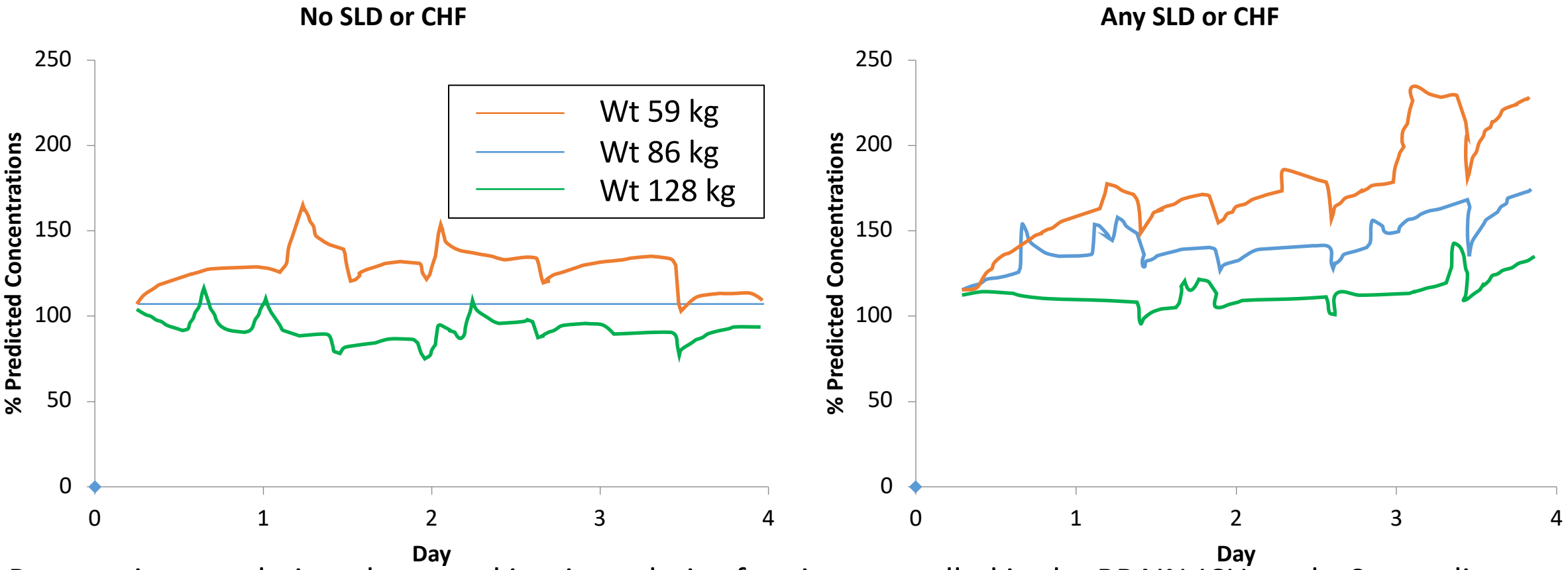
- Defined as a change in opioid drug or route of administration with the goal of improving outcomes

- Goals of opioid rotation are to establish an opioid regimen that is more effective than the prior therapy
  - Improved analgesic efficacy
  - Reduced adverse effects
  - Improved treatment-related outcomes

- "Indications" for rotation (or simply a better fit from the beginning?)
  - Occurrence of intolerable adverse effects during dose titration
  - Poor analgesic efficacy despite aggressive dose titration
  - Problematic drug-drug interactions
  - Change in clinical status that suggests benefit from an opioid with different pharmacokinetic properties

Fine PG, et al. *J Pain Symptom Manage*. 2009; 38(3): 418-425.

Fentanyl Pharmacokinetics in Critically Ill Patients



Prospective population pharmacokinetic analysis of patients enrolled in the BRAIN-ICU study. Severe liver disease (SLD) and congestive heart failure (CHF) were found to significantly increase % of predicted fentanyl concentrations.

Choi L, et al. *Crit Care Med*. 2016; 44(1): 64-72.

Fentanyl vs. Hydromorphone – a signal?

Patients requiring ECMO on either fentanyl or hydromorphone for at least 6 hours.

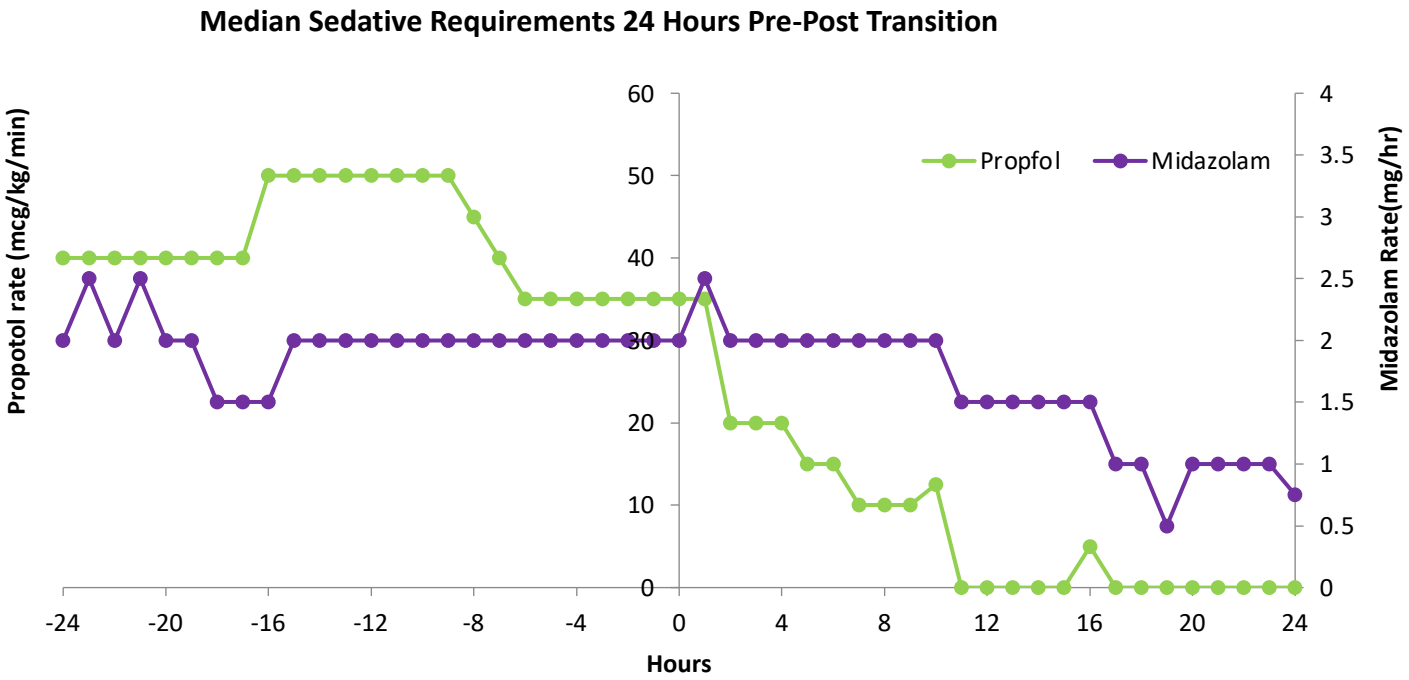
After matching in ECMO patients			
	Hydromorphone n =54	Fentanyl N = 54	
Delirium free coma free - 7 days; days n (%)	125 (53.2)	85 (42.1)	P= 0.006
ICU LOS, days; median [IQR]	17.4 [10.6-33]	20 [9.9-44.1]	SD= 0.002
CRRT, n (%)	24 (44.4)	22 (40.7)	SD= 0.02
Fentanyl equivalents, mcg; median [IQR]	554.8 [286.7-905.1]	2291.1 [1052.5-4022.7]	P< 0.005
Midazolam equivalents, mg; median [IQR]	1.1 [0.5-25]	1.4 [0.7-3.7]	P= 0.35
Propofol equivalents, mg; median [IQR]	281.9 [109.2-806.8]	405.7 [150.4-888.2]	P= 0.50

Landolf KM, et al. *Pharmacotherapy.* 2020 May;40(5):389-397.

Fentanyl vs. Hydromorphone – a signal?

Rationale for Rotation (N = 46)	N (%)
Improved ventilatory compliance	13 (28)
Tachyphylaxis/pain control	9 (20)
Opioid rotation	7 (15)
Reduction in sedatives	6 (13)
Liver impairment	5 (11)
ECMO	2 (4)

ECMO: Extracorporeal membrane oxygenation



Kovacevic MP, Szumita PM, et al. *J Pharm Pract.* 2020 Apr;33(2):129-135.

IV Fentanyl to Enteral Methadone Rotation

- Al-Qadheeb et al.:
  - Decreased fentanyl dose requirements
  - Decreased time to fentanyl infusion discontinuation
  - Increased likelihood of fentanyl discontinuation

- Wanzuita et al.:
  - Trend toward increased ventilator-free days
  - Higher probability of being mechanical ventilation-free at day 5
  - Among patients able to be weaned from mechanical ventilation:
    - Decreased time to extubation

Wanzuita R, et al. *Crit Care.* 2012; 16: 49-57.
Al-Qadheeb NS, et al. *Ann Pharmacother.* 2012; 46: 1160-1166.

Need more robust data on the following (and more)

- Will certain patient populations benefit from different strategies?
  - What mediation for what type of patient?
- Multimodal pain management outcomes trials
  - Combination of therapies
- What outcomes in the PICO questions should be prioritized?
- Will multimodal pain management lead to less chronic pain?
- Data/recommendations for regional/neuraxial techniques

Opioid Use in the United States

- 4x increase in opioid prescriptions between 1997-2002
  - Fewer restrictions among states on opioid prescribing
  - New JCAHO pain management standards
    - Pain = the 5th vital sign
  - Aggressive marketing by opioid manufacturers
- US accounts for 5% of world's population but consumes 88% of the world's prescription opioids
  - In 2010, each American, on average, consumed 710 mg morphine equivalents

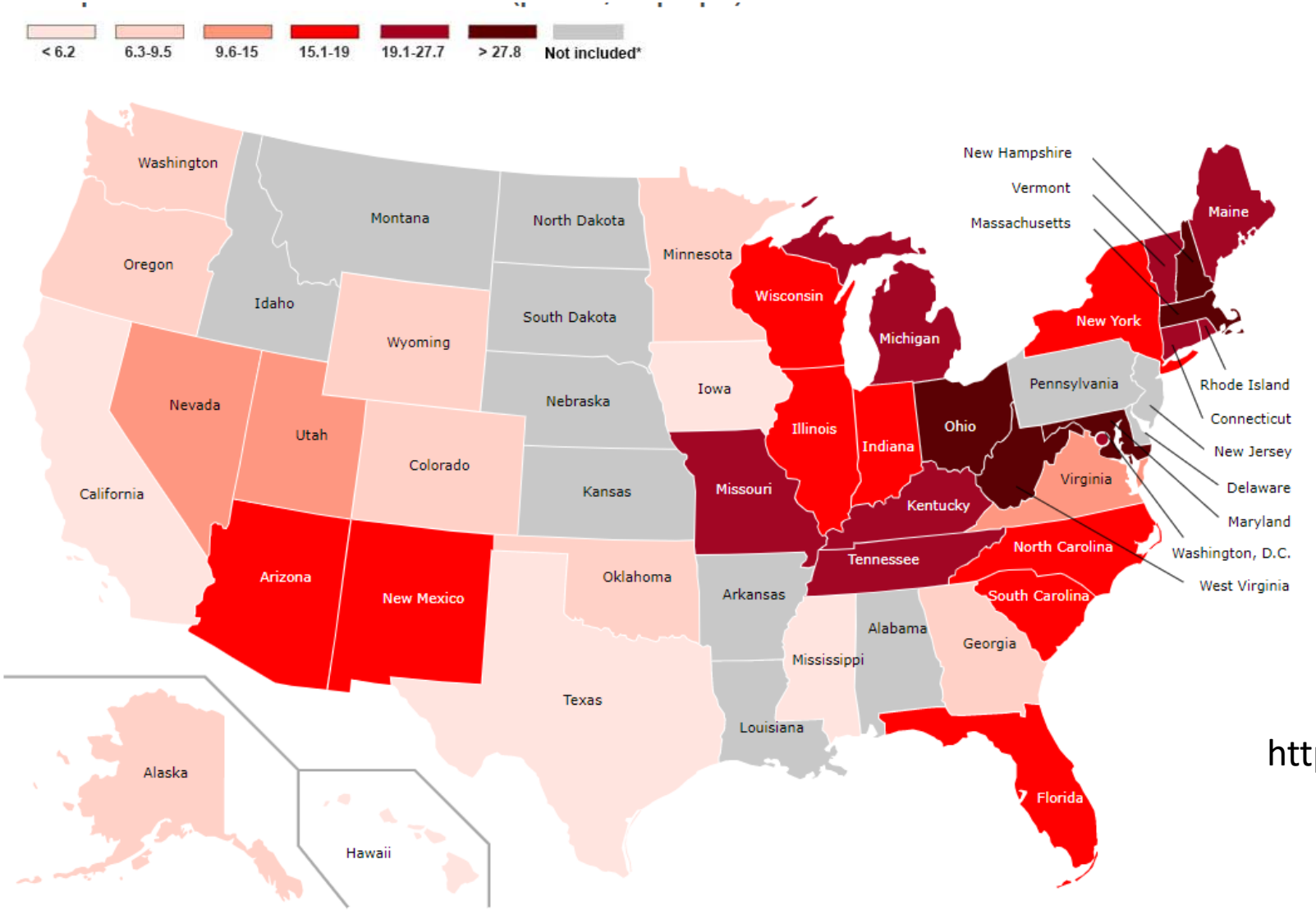
Wick EC et al. JAMA Surgery 2017; 152:691.

Opioid Use in the United States

- Prescription Opioid Misuse
  - Roughly 21 to 29 percent of patients prescribed opioids for chronic pain misuse them.
- Prescription Opioid Misuse Leads to Heroin Use
  - An estimated 4 to 6 percent who misuse prescription opioids transition to heroin.
  - About 80 percent of people who use heroin first misused prescription opioids.
- Opioid Overdose
  - Opioid overdoses increased 30 percent from July 2016 through September 2017 in 52 areas in 45 states.
  - In the Midwest, opioid overdoses increased 70 percent from July 2016 through September 2017.
- Cost is $78.5 billion annually (including health care, lost productivity, addiction treatment and criminal justice involvement)

https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis#one

Opioid-Involved Overdose Death Rate Per 100,000 people - CDC 2018



https://www.cdc.gov/opioids/data/index.html

Opioid use after ICU

- Mean opioid consumptions continuously declined 24 month after ICU stay, but did not return to baseline (pre-ICU)
- Patients with chronic opioid use, mortality was increased 6-18 months after ICU admission
- Chronic opioid use after discharge from ICU is complex and multifactorial

von Oelreich E, et al. *Crit Care Med.* 2021 Mar 1;49(3):462-471.

Transitions of Care Considerations in the ICU (and pre transition)

- Multimodal therapy while in the ICU may be beneficial, including reducing the development of tolerance and dependence on opioids while in the ICU
- Weaning of opioids from patients who have required high doses and/or prolonged durations
- Medications initiated during ICU stay are often continued post-ICU
  - Antipsychotics
  - Opioids
  - Sedatives
  - Stress ulcer prophylaxis and many more
- Efforts to align indications for use of medications with the active problem list at transition of care are warranted
  - ICU to the ward
  - Ward to home/rehabilitation facility

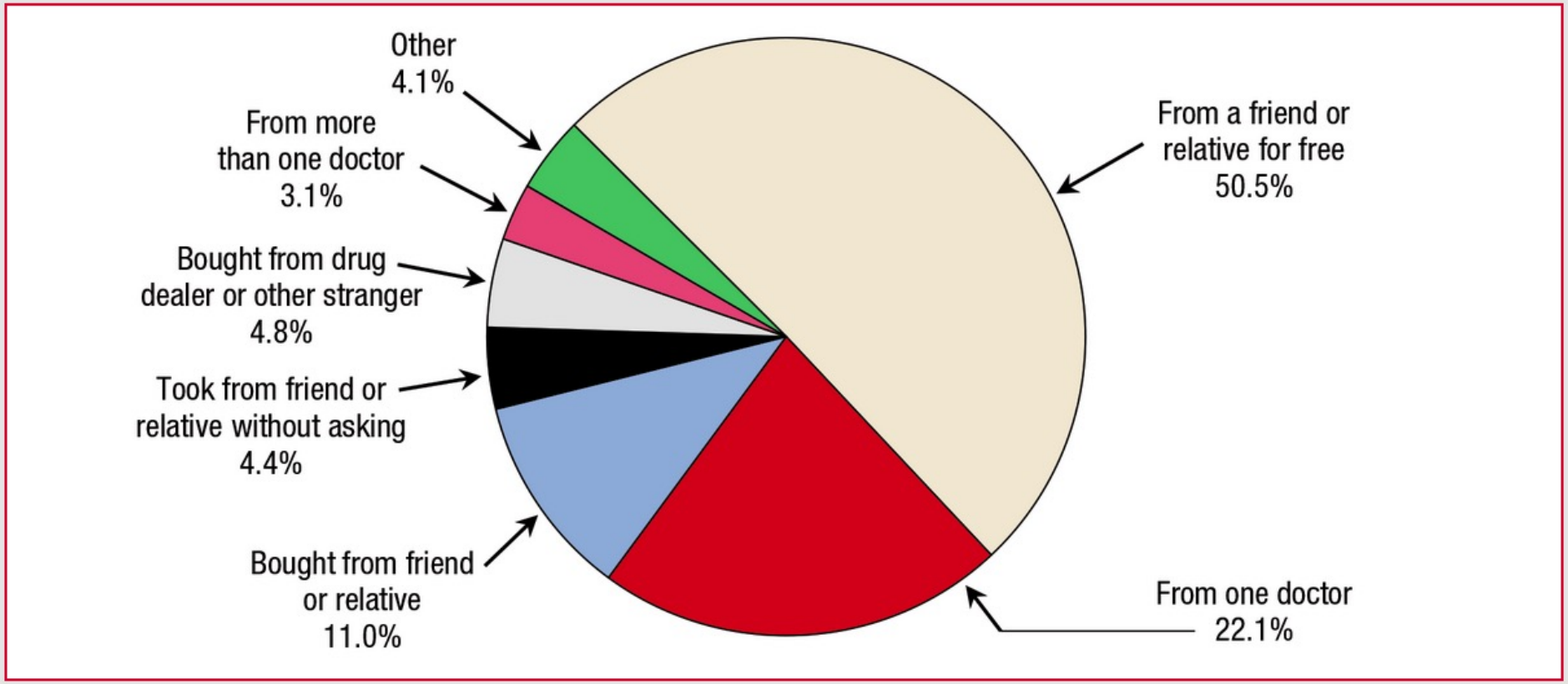
Hanidziar D, et al. *Anesth Analg.* 2020 Jul;131(1):e40-e41.

Terry K, et al. *SAGE Open Med*. 2015;3:32050312115621767.

Farrokh S, et al. *J Pharm Pract*. 2017 Jun;30(3):342-346.

Marshall J, et al. *J Crit Care*. 2016 Jun;33:119-24.

Figure 1. Source of prescription pain relievers for the most recent nonmedical use among past year users aged 12 or older: annual averages, 2013 and 2014



Source: SAMHSA, Center for Behavioral Health Statistics and Quality, National Surveys on Drug Use and Health (NSDUHs), 2013 and 2014.

https://www.samhsa.gov/data/sites/default/files/report_2686/ShortReport-2686.html

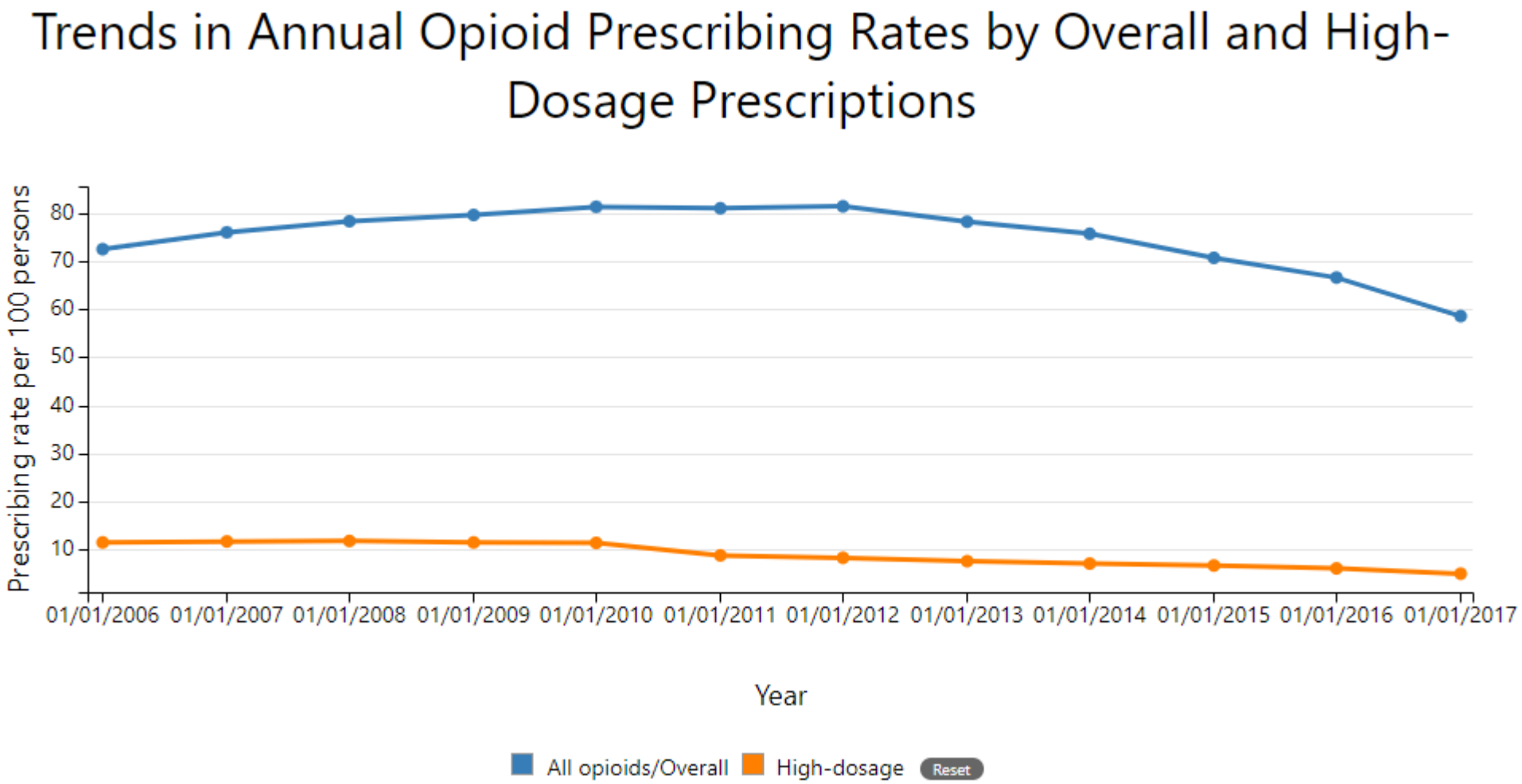
What are HHS and NIH hoping to do about the opioid crisis?

- The U.S. Department of Health and Human Services (HHS) is focusing its efforts on five major priorities:

1. Improving access to treatment and recovery services
2. Promoting use of overdose-reversing drugs
3. Strengthening our understanding of the epidemic through better public health surveillance
4. Providing support for cutting-edge research on pain and addiction
5. Advancing better practices for pain management

https://www.drugabuse.gov/drugs-abuse/opioids/opioid-overdose-crisis#one

The Good News – Overprescribing may be improving



https://www.cdc.gov/drugoverdose/deaths/prescription/practices.html

Collaborative Approach

- Clinicians, Educators, Administrators, Programmers, Physicians
  - Pharmacists
  - Licensed independent practitioners
  - Nurses
  - Information systems personnel
  - Respiratory Therapists
  - Physical Therapists
  - Occupational Therapists
  - Care coordinators

Rivosecchi RM, et al. *J Crit Care*. 2016 Feb;31(1):206-11.

Take Home Points

- Critically ill patients are often in pain
- Several strategies to treat pain in critically ill patients
- Opioids have therapeutic benefit; however, effort should be taken to minimize exposure/overexposure as much possible
  - Opioids have a high addiction potential and incidence of abuse
  - Opioids are a gateway to use of heroin and other illicit drugs
- Focus on re-thinking prior to transitions of care
- Need further research to address how to best optimize prescriptions after ICU discharge

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