

Update on the Management of Pain, Agitation, and Delirium in the ICU

Kevin E. Anger, Pharm.D., BCPS
Manager Investigational Drug
Service Brigham and Women's
Hospital
Boston, Massachusetts

Gilles Fraser, Pharm.D., MCCM
Clinical Pharmacist in Critical
Care
Maine Medical Center
Portland, Maine

**Paul M. Szumita, Pharm.D., BCCCP,
BCPS, FCCM**
Clinical Pharmacy Practice Manager
Brigham and Women's Hospital
Boston, Massachusetts



Disclosures

- Faculty have nothing to disclose.

Objectives

- Describe recent literature on management of pain, agitation, and delirium (PAD) in the intensive care unit (ICU).
- Apply key concepts in the selection of sedatives, analgesics, and antipsychotic agents in critically ill patients.
- Recommend methods to overcome key barriers to optimizing pain, sedation, and delirium pharmacotherapy in critically ill patients.

Case-Based Approach to Pain Management in the ICU

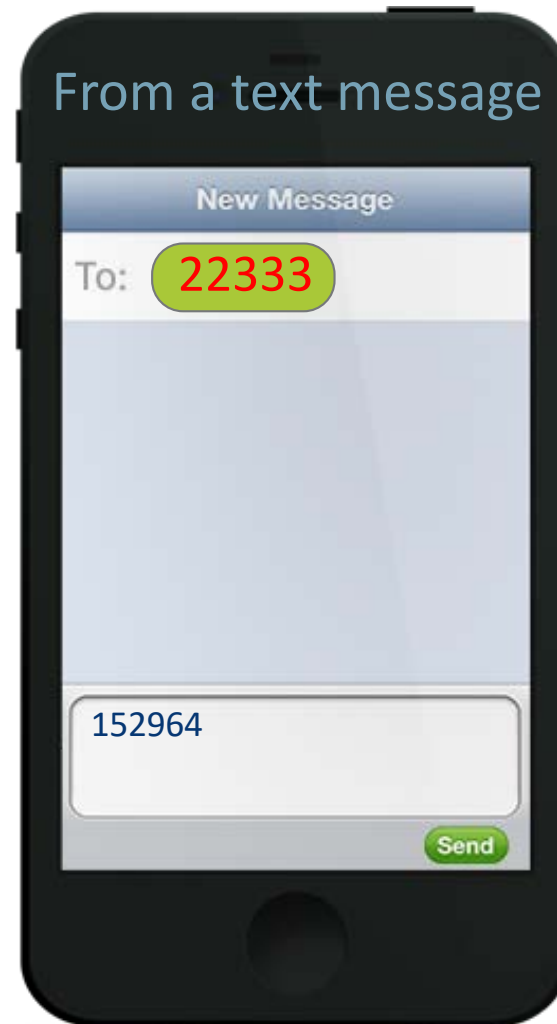
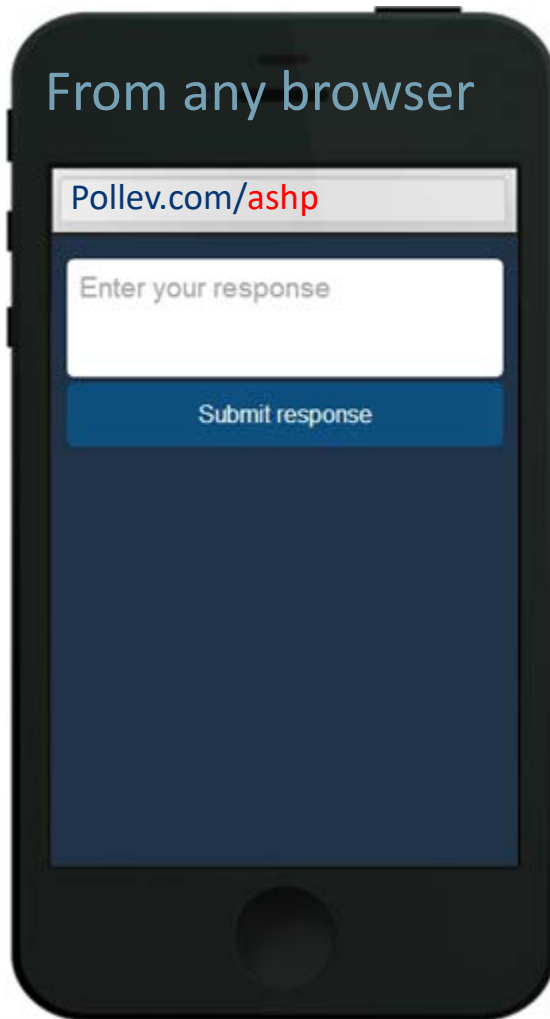
Kevin E. Anger, Pharm.D., BCPS

Manager Investigational Drug Service Brigham
and Women's Hospital
Boston, Massachusetts



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It's incredibly amazing! **152965**

It's aw-right. **152968**

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Question #1

DT is a 70 yo male w/ COPD, S/P XRT for NSC lung CA, now admitted to the medical ICU for respiratory failure secondary to pneumonia meeting ARDS criteria. Significant home medications include oxycodone sustained release 40mg TID, oxycodone 10-20mg Q4hrs PRN pain, Advair 500/50mcg BID, ASA 81mg QD, and albuterol neb Q4hrs PRN. DT is intubated is currently very agitated (RASS +3), on “ARDS net ventilation settings.”

Which of the following is the best to further assess DT’s agitated state?

- A** Serum cortisol
- B** Behavioral pain scale (BPS)
- C** Urine toxicology screen
- D** Confusion Assessment Method ICU (CAM-ICU)



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Etiology of Agitation in Critically Ill Patients

- Gas exchange
 - Hypoxemia
 - Hypercarbia
- Metabolic
 - Hypoglycemia
 - Acidosis
- Ventilator-related
 - Endotracheal tube malposition
 - Tension pneumothorax
- Patient-ventilator dyssynchrony
 - Inadequate flow rates
 - High or low tidal volumes
 - Ventilator Inspiratory/Expiratory times
- Pain
 - Surgical/Trauma/Procedural
 - Baseline pain
 - Routine care/mobilization
- Drug and alcohol related
 - Intoxication
 - Withdrawal
- Infection
 - Central nervous system infection
 - Sepsis
- Ischemia
 - Myocardial
 - Intestinal
 - Cerebral
- Patient positioning in bed
- Fear and Anxiety
 - Inability to communicate
- Sleep deprivation
- Full bladder and or colon
- Drug side effects
 - Anticholinergic
 - Paradoxical response to benzodiazepines

Epidemiology and Outcomes of Pain in the ICU

- 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
- Development of chronic pain is reported in up to 50% of ICU survivors
 - Can be as high as 80% after certain surgical procedures

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.

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

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

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

“Difficult” analgesia management patients

Patient subpopulation	Barriers to management
Chronic opioid users	Intrathecal pumps Buprenorphine – requires switch to full agonist Tolerance, sensitization, and hyperalgesia
Extracorporeal membrane oxygenation (ECMO)	Altered pharmacokinetics Mobilization requirements for lung transplant
Severe burns	Altered pharmacokinetics Complex pain physiology
Severe brain injury (trauma, anoxic)	Assessment of pain symptoms
Obesity	Altered pharmacokinetics
Obstructive sleep apnea	Respiratory depression susceptibility
Dementia/Cognitive impairment	Assessment of pain symptoms
Pediatrics	Altered pharmacokinetics Assessment of pain symptoms

Consensus Guidelines in Adults

- **American College of Critical Care Medicine (ACCM) Pain, Agitation, Delirium Guidelines**
 - Pain should be routinely monitored in all adult ICU patients (LOE +1B)
 - Use of validated pain assessment tools
 - Vital signs
 - Should not be used alone for pain assessment in adult ICU patients (LOE –2C)
 - Can serve as cue for further assessment of pain (LOE +2C)
 - Behavioral pain scales in non-communicative patients
 - medical, postoperative, or trauma (except for brain injury) adult ICU patients who are unable to self-report and in whom motor function is intact and behaviors are observable.
- **American Society of Anesthesiologists (ASA) Perioperative Pain Guidelines**
 - Use standardized, validated instruments to facilitate the regular evaluation and documentation of pain intensity, the effects of pain therapy, and side effects caused by the therapy

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

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 1-10)
 - Not all pain is avoidable, making individualized goal-oriented therapy vital
- Limitations
 - Patient unable to communicate

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

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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 stay
 - Reduced mortality
 - ↑↓ prescription and consumption of opioids
 - Reduced consumption of sedatives
 - Reduced need for bolus analgesic in non communicative
 - Increased use of nonopioid analgesics
 - Opioid related adverse drug events (ORADE) neutral

Key Concepts of ICU Pain Assessment

- Pain should be routinely assessed **AND** documented using validated pain assessment tools
- Self-reporting and non communicative scales are essential
- Therapeutic goal of analgesia is established and is patient-specific
 - Thresholds for treatment established as raw value or delta value
- Pain assessment tools have limitations
- Analgesic trial may be an effective form of assessment

Question #2

DT is on propofol @ 5mg/kg/hr due to agitation (RASS +2) and ventilator dyssynchrony. DT is on assist control ventilation with tidal volumes ~6ml/kg, positive-end expiratory pressure of EEP 12 cmH₂O , FiO₂ 0.8 and is tachycardic (heart rate 110 beats/minute). DT currently has a RASS fluctuating from (+2 to -3), CAM-ICU is unable to assess, and CPOT of 6.

Which of the following interventions would you make to DT's PAD regimen?

- A** Standing acetaminophen 500mg IV every 6hr
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- C** Dexmedetomidine infusion 0.2-0.7mcg/kg/hr titrated to RASS +2 to -3 & CPOT < 2
- D** Hydromorphone infusion 1-3mg/hr titrated to goal RASS and CPOT with 1-3mg every hour as IV bolus for pain by CPOT



Question #2

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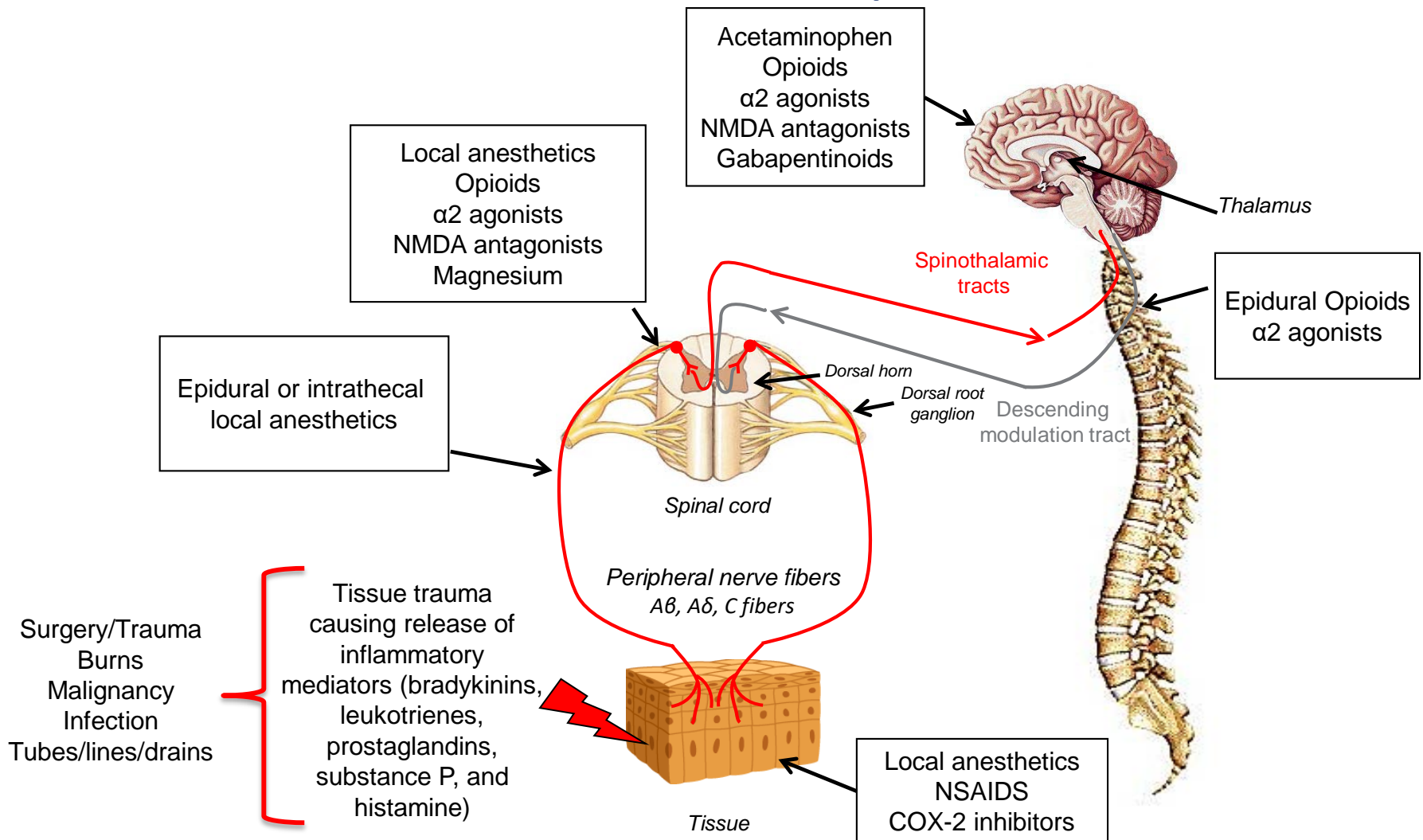
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Mechanisms of pain and analgesics: Not all about opioids



Patient-Specific Factors for Selection of Analgesic Regimens

- Pain physiology/severity/duration
 - Surgical site/type, malignancy, neuropathic
- Age
- Body habitus: Obesity and cachexia (Volume of distribution)
- Allergies and “sensitivities”
- Medication administration access (IV, IM, enteral)
- Chronic pain: medication tolerance and pain sensitization/hyperalgesia mechanisms
- Organ function/clearance mechanisms (Renal, hepatic, plasma esterase, drug Interactions)
- Hemodynamic status (stable vs. unstable)
- Respiratory status (Obstructive sleep apnea, mechanically ventilated)
- Coagulopathy/hematological derangements
- Institutional resources

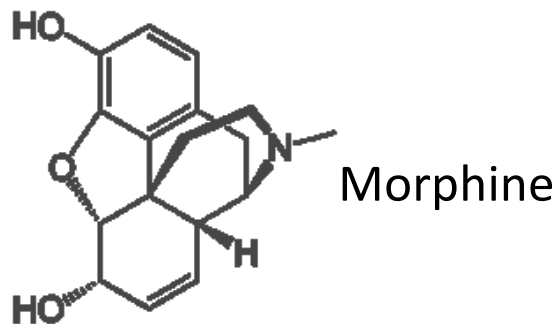
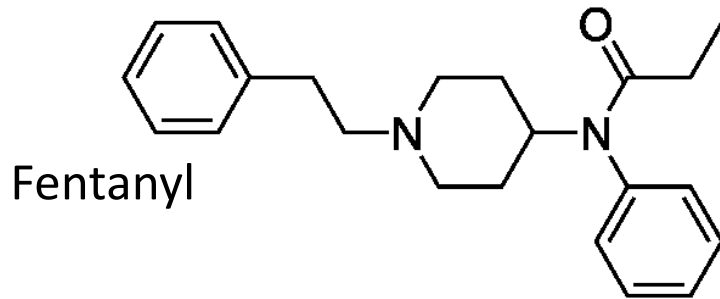
ACCM Pain, Agitation, Delirium Guidelines in Adults

- IV opioids are the first-line treatment for non-neuropathic pain (LOE +1C)
 - All available IV opioids, when titrated to similar pain intensity endpoints, are equally effective (LOE C)
- Analgesia-first sedation should be used in mechanically ventilated ICU patients (LOE +2B)
- Preemptive analgesic therapy and/or nonpharmacologic therapy for invasive and potentially painful procedures (+2C), chest tube removal (+1C)

Opioid Pharmacology

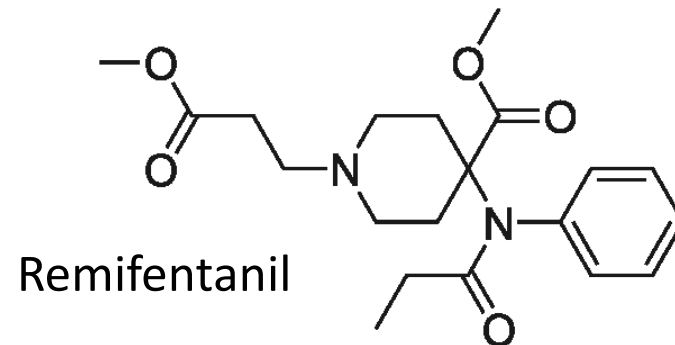
Four Opioid Subclasses

- Phenanthrenes
- Benzomorphans
- Phenylpiperidines
- Diphenylheptanes



Clinical Effects

- Analgesia
- Sedation
- Respiratory depression/anti dyspnea
- Anti-shivering



Guiding Principles for Opioid Selection in the ICU

- Route (IV often needed)
 - Onset for procedure/routine care
- Use in hemodynamic instability
 - Sedation +/- histamine release
- Duration of therapy & volume of distribution
 - Accumulation capacity
- Dosing/efficacy
 - Chronic tolerance
 - Acute tolerance and sensitization mechanisms
 - Acute opioid tolerance (AOT) or OIH opioid-induced hyperalgesia
- Clearance mechanisms/organ function
- Tolerance to side effects
 - Hypotension, pruritus, CV effects

Pharmacology of “The Big Four” Opioid Analgesics

Variable	Fentanyl	Hydromorphone	Morphine	Remifentanyl
Onset (min)	1-2	5-10	5-10	1-3
Elimination T _{1/2}	2-4 hr*	2-3 hr	3-4 hr	3 - 10 min
Organ failure prolongation	Hepatic	Hepatic	Renal/Hep	None
Metabolic pathway	N-dealkylation CYP3A4/5	Glucuronidation	Glucuronidation	Plasma esterases
Active Metabolite	Yes	No	Yes	No

*Context-sensitive half-life

Erstad BL, et al. *Chest*. 2009 Apr;135(4):1075-86.

Pasero C, et al. *Chest*. 2009 Jun;135(6):1665-72.

Rozendaal FW, et al. *Intensive Care Med*. 2009 Feb;35(2):291-8.

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

Devlin JW, et al. *Anesthesiol Clin*. 2011 Dec;29(4):567-85.

Non workhorse and transition opioids in the ICU

- Methadone
 - Antihyperalgesic profile (NMDA antagonist)
 - Potential for transition from short-acting agents to facilitate weaning from the ventilator
 - Caution with initiation/transition
- Oxycodone
 - Limited to oral route
- Meperidine
 - Weak analgesic with a high frequency and severe ADR profile*
 - Delirium, serotonin syndrome, seizures
 - Neurotoxic normeperidine metabolite → Accumulation in elderly/renal dysfunction
 - Use should be limited to low dose for rigors/shivering

Opioid adverse drug effects

- **Class effects**
 - Respiratory depression
 - Constipation
 - N/V
 - Pruritus
 - Withdrawal
 - Myoclonus
 - Hypotension
 - Delirium
 - Post traumatic stress disorder
 - Immunomodulation
- **Specific agents**
 - Fentanyl
 - Chest wall rigidity
 - Transdermal toxicity
 - Morphine
 - Cholecystitis
 - Remifentanyl
 - ↑ ammonia levels
 - Meperidine
 - Tremors/seizures
 - Methadone
 - QTC prolongation

Erstad BL, et al. *Chest*. 2009 Apr;135(4):1075-86.

Benyamin R, et al. *Pain Physician*. 2008 Mar;11(2 Suppl):S105-20.

Pisani MA, et al. *Crit Care Med*. 2009 Jan;37(1):177-83.

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.

Key Concepts in Opioid therapy for Pain in the ICU

- Choice of agent, route, dosing, and monitoring is often patient-specific
- Acute/Chronic opioid tolerance or suspected hyperalgesia
 - Opioid rotation, multimodal, anti-hyperalgesia agents
- Institutional level
 - Institutional guidelines
 - Opioid equianalgesic dosing tables
 - Information systems and smart pumps
 - Specialist consultation for patients with complex chronic pain or opioid withdrawal

Pasero C, et al. *Chest*. 2009 Jun;135(6):1665-72.

American Society of Anesthesiologists.. *Anesthesiology*. Feb 2012;116(2):248-273.

Shaheen PE, et al. *J Pain Symptom Manage*. 2009 Sep;38(3):409-17.

Hofbauer R, et al. *Eur J Anaesthesiol*. 1999 Oct;16(10):702-7.

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Question #3

PS is 55 yo male s/p ex lap with whipple procedure. PS is admitted to the SICU postoperatively due to intraoperative bleeding and respiratory failure secondary to transfusion related acute lung injury (TRALI). PS is on assist control ventilation with TV ~6ml/kg, positive end expiratory pressure 10 cmH₂O, FiO₂ 0.6 and is tachycardic (heart rate 100 beats/minute). PS currently has a RASS fluctuating from +1 to -1 and CPOT of 6.

Which of the following interventions would you make to initiate PS's PAD regimen?

- A** Ibuprofen 400mg IV Q6hrs
- B** Dexmedetomidine IV infusion 0.2-0.7mcg/kg/hr titrated to RASS +2 to -3 & CPOT < 2
- C** Fentanyl IV infusion 0-200 mcg/hr and Fentanyl 25-50mcg every 20mins PRN titrated to Goal RASS and CPOT
- D** Ketamine IV infusion 0.3mg/kg/hr titrated to Goal RASS and CPOT



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“Analgo-sedation”

- Also known as analgesia-based or analgesia-first sedation
- Principles based on findings that pain and discomfort may cause agitation
- Address pain and discomfort first, and then add a hypnotic agent if necessary
- Fairly extensive research on the concept going back over a decade, mostly European data
- Typically opioid-based sedation therapy with short-acting agents, however case for dexmedetomidine-based therapy could be made

Key Concepts of Analgosedation

- Takes advantage of certain opioid properties
 - Reduces/eliminates sedative requirements and their associated ADRs
 - Improves sedation-agitation scores
 - Dyspnea & respiratory depressant properties
- Can accentuate opioid-related ADR's
 - Gastric dysmotility, delirium, hypotension, myoclonus, chest wall rigidity
- May not be appropriate in patients with GABA agonist/sedative needs:
 - Alcohol/drug withdrawal & drug intoxication
 - Neuromuscular blockade
 - Elevated intracranial pressure & status epilepticus

Park G, et al. *Br J Anaesth*. 2007;98:76-82.

Rozendaal FW, et al. *Intensive Care Med*. 2009;35:291-298.

Devabhakthuni S, et al. *Ann Pharmacother*. 2012 Apr;46(4):530-40.

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Analgesic administration: Technique is as important as agent selection

- Preemptive analgesia
 - Initiated before and is operational during procedures in-order to reduce the physiological consequences of nociceptive pain transmission
 - More effective than the same treatment administered during or after the procedure to reduce pain and analgesic needs
 - **Pharmacologic & Non pharmacologic**
 - Upgraded in the surgical realm to the concepts of preventative and protective analgesia

ACCM Pain, Agitation, Delirium Guidelines in Adults

- Enteral gabapentin or carbamazepine in addition to IV opioids should be considered for treatment of neuropathic pain (LOE +1A)
- Nonopioid analgesics should be used to decrease the amount of opioids administered (or to eliminate the need for IV opioids altogether) and to decrease opioid-related side effects (LOE +2C)
- Neuraxial techniques:
 - Thoracic epidural anesthesia/ analgesia should be considered for abdominal aortic aneurysm surgery, (LOE +1B) traumatic rib fractures(LOE +2B)
 - No recommendation
 - Lumbar epidural over parenteral opioids for postoperative abdominal aortic aneurysm surgery
 - Intrathoracic or nonvascular abdominal surgical procedures
 - Medical ICU patients (0, No Evidence)

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 consensus guidelines
- Limited focused ICU literature

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.

Multimodal Agents: A *LOT* to choose from but not much ICU data

“Workhorse agents”

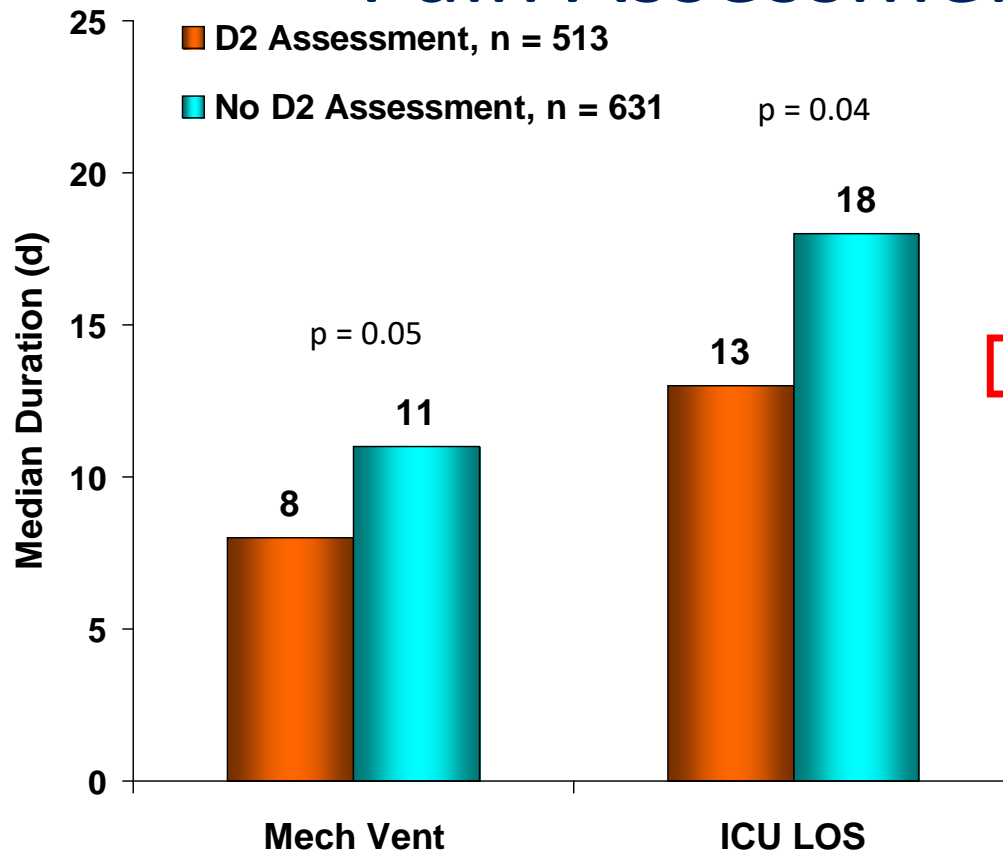
- Anti-inflammatory
 - Acetaminophen
 - NSAIDs
 - Cox-2 inhibitors
- Opioids/mu-receptor agonists
- Local Anesthetics
 - Regional & local techniques

“Secondary agents”

- NMDA receptor antagonists
 - Ketamine
- α -2 agonists
 - Clonidine & Dexmedetomidine
- Anticonvulsants
 - Gabapentin/Pregabalin
- Corticosteroids
- TRPV1 agonist: Capsaicin
- Cannabinoids

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

Improved Outcomes Associated with Pain Assessment in the ICU



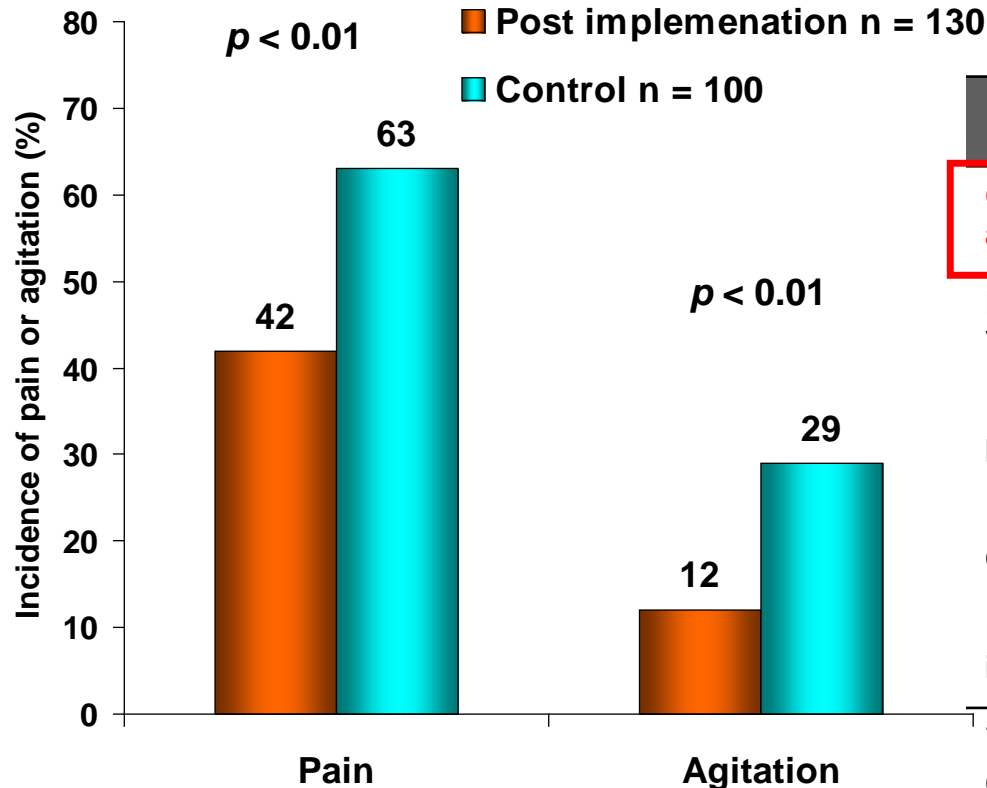
Significant medication-related outcomes

	No D2	D2	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 (%)

Post-hoc analysis of the DOLOREA prospective, observational analysis in 14 European ICUs from January 2004 to January 2005. 1,144 patients were divided into those assessed for pain on day 2 (n=513) and those not assessed for pain on day 2 (n=631). Various pain scales were used among different institutions.

Systematic Implementation of Pain and Sedation tools: Montpellier France



Significant patient characteristics/metrics/outcomes

	Pre	Post	P value
Other analgesics**	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 (%) CIVS; Continuous intravenous infusion sedation; **Data presented as median (25-75 percentiles)

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

Acetaminophen & NSAIDs: Often forgotten

- Surgical populations: Basal +/- preemptive acetaminophen and NSAIDs
 - Improved pain control
 - Reduced opioid utilization and opioid-related ADRs
 - Potential for reduced LOS
- Cons
 - Platelet dysfunction and bleeding risk (NSAIDs)
 - Black box in cardiac surgery
 - Organ dysfunction (Renal: NSAIDs, Hepatic: Acetaminophen)
 - Fever suppression
 - Cost of certain agents

Retsky M, et al. *Curr Med Chem*. 2013;20(33):4163-76.

Bayouth L, et al. *Am Surg*. 2013 Nov;79(11):1207-12.

Ender, et al. *Anesthesiology*. 2008; 109:61-66.

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

Smith HS. *Pain Med*. 2011 Jun;12(6):961-81.

Local Anesthetics: It's about technique

Variable	Regional Neuraxial	Regional peripheral continuous/ single shot	Local/ Wound Infiltration
Pros	<ul style="list-style-type: none"> • Potent analgesia • Can combine with opioid/α-2 agonist 	<ul style="list-style-type: none"> • Potent analgesia • Opioid sparing 	<ul style="list-style-type: none"> • Ease of Admin • No specialist • Can discharge patient
Limitations	<ul style="list-style-type: none"> • Antithrombotic therapy • Coagulopathy/ thrombocytopenia • Specialist needed • ADRs/Toxicity 	<ul style="list-style-type: none"> • Specialist needed • Reduced limitations/ADR's compared to neuraxial 	<ul style="list-style-type: none"> • Technology limits on duration of effect • \$\$\$

Evolving role of local anesthetic analgesia in the ICU

- Advancement in the efficacy and safety of single shot and nerve catheter placement
 - Peripheral nerve catheters for continuous infusion
 - Local/wound infiltration analgesia
 - Thoracotomy/sternotomy, major abdominal, plastics, orthopedic
- Fast track surgical protocols using multimodal analgesia with local anesthetic backbones
 - Improved pain control
 - Reduced opioid consumption and ADR's
 - Reduced rehabilitation time
 - Reduced length of stay
 - Reduced mortality (thoracics)

White PF, et al. *Anesthesiology*. 2003;99(4):918-23.

Dowling R, et al. *J Thorac Cardiovasc Surg*. 2003 Nov;126(5):1271-8.

Chiu KM, et al. *J Thorac Cardiovasc Surg*. 2008 Jun;135(6):1348-52.

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Pöpping DM, et al. *Ann Surg*. 2014 Jun;259(6):1056-67.

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Merritt CK, et al. *Best Pract Res Clin Anaesthesiol*. 2014 Mar;28(1):41-57.

Ketty and DExCLoN: Adjuncts not backbones of multimodal regimen

Ketamine

- Primary analgesic mechanism: NMDA antagonism
 - Anti sensitization
 - Opioid sparing
- Dose related analgesia effects → Low dose
- Combo with opioids/Locals
 - Burn dressing changes
 - Hyperalgesia/AOT
- Cons
 - Slow recovery time
 - ADR's
 - Specialist often required

Dexmedetomidine & Clonidine

- Primary analgesic mechanism: α -2 agonism descending pain modulating
 - +/- Opioid consumption
- Multimodal with opioids
 - Hyperalgesia/AOT
- Cons
 - CV ADR's
 - Bolus can be dangerous
 - \$\$\$

Gregoretti C, et al. *Drugs*. 2008;68(17):2427-43.

Suzuki M. *Curr Opin Anaesthesiol*. 2009 Oct;22(5):618-22.

Persson J. *CNS Neurosci Ther*. 2013 Jun;19(6):396-402.

Erstad BL, et al. *J Crit Care*. 2016 Oct;35:145-9.

Blaudszun G, et al. *Anesthesiology*. 2012 Jun;116(6):1312-22.

Giovannoni MP, et al. *Med Res Rev*. 2009 Mar;29(2):339-68.

Reardon DP, et al. *Am J Health Syst Pharm*. 2013 May 1;70(9):767-77.

Analgesia and Early Mobilization

- Pain, agitation, and delirium are key barriers to mobilization in the ICU
- Pharmacotherapy selection may be limited by adverse effects
 - Local anesthetics (by administration location)
 - Opioids
 - α 2 agonists
 - Ketamine
- Multimodal therapy
 - Acetaminophen/NSAIDs
 - Local infiltration analgesia (LIA) in selected surgical populations

Local Protocols and guidelines for PAD in the ICU

- Predominantly multicomponent analysis with interventions for pain, agitation, and delirium
- Address core components of management
 - Assessment tool and goal directed
 - Multimodal pharmacotherapy
 - Order sets/Algorithms/Information systems implementation
- Impact on outcomes
 - ↑ Adherence to best practices
 - Improved pain control
 - Reduced morbidities and adverse effects
 - Cost savings

Key Takeaways

1. Perform and document pain assessments
 - Communicative and non-communicative
2. Structured patient-focused management strategy
 - Incorporate key patient considerations into drug therapy
 - Goal directed multimodal approach
3. Systematic ICU/Institutional approach
 - Guideline or protocol
 - Educational, specialist resources
 - IS implementation

Adult ICU Sedation

Gilles Fraser, Pharm.D., MCCM

Clinical Pharmacist in Critical Care

Maine Medical Center

Portland, Maine



ICU Agitation

- Frequent (up to 86%) and complex
- Management is context/patient specific
 - Probable reason(s) for agitation
 - Pain, substance withdrawal, anxiety, delirium, ventilator asynchrony
 - Other modifiers
 - Intubated vs. not, hemodynamic stability, short vs. long-term sedation, light vs. deep sedation, organ dysfunction
 - Potential neurotoxicity
- Caregiver responsibilities
 - Appreciate the short- AND long-term ICU patient consequences of therapeutic choice and method of administration

What We've Learned: Goals for Our ICU Patients

- **THEN:** Survival and discharge
- **NOW:** Don't fix patients and break them at the same time
 - **Short-term issues** = pain, anxiety, fear, coma, prolonged mechanical ventilation and ICU stay, delirium, delusions, trauma, disruption of anastomotic sutures, and medical device removal
 - **Complications after hospital discharge**
 - Persistent delirium = 10%
 - Long-term cognitive impairment \approx 30% at one year
 - Similar to traumatic brain injury or Alzheimer's disease
 - New unemployment \sim 50%
 - Posttraumatic stress disorder (PTSD) \approx 7–15%
- **FUTURE:** Modifiable risk factors?

Question #4

The ACCM PAD guidelines suggest that comfort and wakefulness should be sedation goals for most ICU patients. This is represented by :

- A** RASS -2 (opens eyes and tracks for <10 seconds)
- B** Sedation Agitation Score (SAS) 3 to 4 (obeys commands)
- C** Arousal with any stimulus
- D** Arousal with verbal stimulus



Question #4

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Goal: Titrate Sedatives to Wakefulness

“respond to commands (i.e., a combination of any three of the following actions upon request: open eyes, maintain eye contact, squeeze hand, stick out tongue, and wiggle toes). This degree of responsiveness and awareness goes beyond patients being merely “sleepy but arousable” and is essential for the evaluation of pain through patient self-report, for assessing patients’ readiness to wean and extubate, for performing delirium assessments, and for implementing early mobility efforts.”

Validated Tools for Sedation/Agitation Assessment

- Sedation Agitation Scale (SAS)
 - Please note word order
- Richmond Agitation Sedation Scale (RASS)





Sedation-Agitation Scale (SAS) 1994

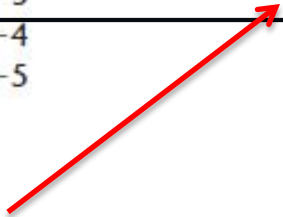
Score	State	Behaviors
7	Dangerous Agitation	Pulling at ET tube, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very Agitated	Does not calm despite frequent verbal reminding, requires physical restraints
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
4	Calm and Cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off, follows commands
2	Very Sedated	Arouses to physical stimuli but does not communicate or follow commands
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

Riker. Crit Care Med 1999; 27:1325-9

Richmond Agitation-Sedation Scale (RASS)

RICHMOND AGITATION-SEDATION SCALE

Score	Term		Description
+4	Combative		Overtly combative or violent; immediate danger to staff
+3	Very agitated		Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated		Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless		Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm		
-1	Drowsy		Not fully alert, but has sustained (more than 10 seconds) awakening, with eye contact, to voice
-2	Light sedation		Briefly (less than 10 seconds) awakens with eye contact to voice
-3	Moderate sedation		Any movement (but no eye contact) to voice
-4	Deep sedation		No response to voice, but any movement to physical stimulation
-5	Unarousable		No response to voice or physical stimulation



Question #4

The ACCM PAD guidelines suggest that comfort and wakefulness should be sedation goals for most ICU patients. This is represented by :

- A** RASS -2 (opens eyes and tracks for <10 seconds)
- B** **SAS 3 to 4 (obeys commands)**
- C** Arousal with any stimulus
- D** Arousal with verbal stimulus



Question #5

Patient has been kept at a RASS of -3 as a sedation goal (moves to verbal stimulus). Can delirium be evaluated?

- A** Yes, because that is what icudelirium.org suggests
- B** Yes, because the level of sedation does not influence delirium assessment
- C** No, because icudelirium.org suggests that patients should be able to respond to queries
- D** No, because RASS -3 can influence delirium assessments





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Does RASS -3 = Moderate Sedation?

- Any movement but no eye contact to verbal stimuli
- Vanderbilt authors and others
 - Coma
 - Severe brain dysfunction
 - Deep sedation
- And why is this important?

Andresen JM. *Crit Care Med.* 2014; 42:2244-51.

Page VJ. *Lancet Respir.* 2013;1:515-23.

Vasilevskis EE. *Crit Care. Med* 2016; 44:138-46.

Barr J. *Crit Care Med.* 2013; 41:263-306.

Shehabi Y. *Intensive Care Med.* 2013; 39:910-8.

We All Agree---Avoid Sedation-Induced Coma for Most Patients

- Reduces
 - Mechanical ventilation time (28-57%)
 - ICU length of stay (30-47%)
 - Neurodiagnostic testing (67%)
- Limits the post-intensive care syndrome (PICS)?
 - Delirium?
 - PTSD?
 - Long-term cognitive impairment?

RASS and CAM-ICU ASSESSMENTS

N = 12,875

Study	RASS -2 to -3			RASS 0 to -1		
	# Assessments	# CAM ICU positive	Frequency (%)	# Assessments	# CAM ICU positive	Frequency (%)
1	588	387	66	9441	2065	22
2	92	90	98	71	22	31
3	50	40	80	896	146	16
4	218	212	97	1019	259	25
Total	948	729	77	11427	2492	22

Timing of CAM-ICU vs Sedation Depth

Should I do a CAM-ICU assessment before, during, or after a Spontaneous Awakening Trial (SAT)?

“The best picture of the patient’s mental status will come from assessing delirium serially throughout the day. Thus, we recommend that you assess patients for delirium both before and after daily sedative interruption (SAT).”

icudelirium.org accessed 8.15.16

“Drug induced sedation does not, in our opinion, constitute delirium” Ouimet ICM 2007

Question #5

Patient has been kept at a RASS of -3 as a sedation goal (moves to verbal stimulus). Can delirium be evaluated?

- A** Yes, because that is what icudelirium.org suggests
- B** Yes, because the level of sedation does not influence delirium assessment
- C** No, because icudelirium.org suggests that patients should be able to respond to queries
- D** No, because **RASS -3 can influence delirium assessments**



Sedation Management

- Light sedation for most patients (B)
 - Allow wakefulness: respond purposefully to at least three commands
 - RASS and SAS for sedation assessment
- Use protocol with daily sedation interruption (SAT) or that targets light level of sedation (1B)

Question #6

Which of the following is true regarding protocolization of sedation using SAT or titration to wakefulness?

- A** SAT is best since there are mortality benefits
- B** Titration is best since patients experience less time on mechanical ventilation
- C** Either SAT or titration is fine since they result in shorter ICU stays
- D** Either SAT or titration is fine since they have associated mortality benefits



Question #6

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Daily Sedation Interruption (SAT) vs Light Sedation Titration Lumpers Versus Splitters

- Lumpers prevail = 2013 ACCM PAD, 2016 CHEST/American Thoracic Society guidelines and the Mayo Clinic Proceedings meta-analysis
 - No apparent advantage of one approach over the other
- No advantage of sedation interruption when patients are also receiving light sedation

Protocolized Sedation and Clinical Outcomes in Ventilated ICU Patients

ACCP/ATS 2016 (in press)

- **Duration of ventilation**
 - Shortened by 1 day ($p = 0.11$)
 - $I^2 = 63\%$
- **ICU LOS**
 - Shortened by 1.8 days ($p = 0.03$)
 - $I^2 = 71\%$
- **Mortality (hospital)**
 - Relative risk = 0.88 ($p = 0.3$)
 - $I^2 = 0\%$

Meta-analysis 2015 Mayo Clin Proc

- **Duration of ventilation**
 - Shortened by 1 day ($p = 0.18$)
 - $I^2 = 74\%$
- **ICU LOS**
 - Shortened by 1.7 days ($p = 0.03$)
 - $I^2 = 60\%$
- **Mortality (hospital)**
 - Relative risk = 0.89 ($p = 0.27$)
 - $I^2 = 0\%$

Protocolized PAD Management Seems Worthwhile!

- Decreases time in the ICU and perhaps requiring mechanical ventilation
- Facilitates Early Mobility, which decreases delirium burden and allows independent functioning
- Perceived vs. Actual Practice
 - Survey 85 ICUs = 24-hr practice snapshot
 - Sedation protocols used in 50% ICUs
 - Sedation interruption reported in 66% ICUs
 - *Performed in 36% patients*
 - Delirium monitoring reported in 25% ICUs
 - *Performed in 10% of patients*

Question #6

Which of the following is true regarding protocolization of sedation using SAT or titration to wakefulness?

- A** SAT is best since there are mortality benefits
- B** Titration is best since patients experience less time on mechanical ventilation
- C** **Either SAT or titration is fine since they result in shorter ICU stays**
- D** Either SAT or titration is fine since they have associated mortality benefits



Make It Easy To Do The Right Thing!

Summary
Chart Review
Results Review
Notes
MAR
Medications
Flowsheets

Order Sets

Order Sets

Multiple Versions of User Order Sets
You can now save multiple versions of user order sets. Click the Manage My Version link below to begin. [Learn More](#) Do Not Show This Again

▼ Pulm/Crit Care ICU Sedation/Analgesia/Delirium [Manage My Version](#) Add Order

Please remember that the most common cause of agitation in the ICU is pain and/or discomfort and that an "analgesia first" approach for appropriate patients is recommended.
MMC Guidelines for the Evaluation and Management of Delirium in the Adult ICU Patient
MMC Analgesia/Sedation Protocol for Mechanically Ventilated Patients

Medications

▶ Intermittent Agitation/Discomfort	0 of 8 selected
▶ Sustained Agitation/Discomfort with a Goal of Light Sedation in a Mechanically Ventilated Patient	0 of 22 selected
▶ Sustained Agitation/Discomfort with Goal of Light Sedation in Mechanically-Ventilated Patients Requiring High-Dose Vasopressors	0 of 15 selected
▶ Sustained Agitation/Discomfort with a Goal of Light Sedation in a Patient Without Mechanical Ventilator Requirements	0 of 16 selected
▶ Delirium (not related to substance withdrawal)	0 of 13 selected
▶ Deep Sedation in Patients Receiving Mechanical Ventilation	0 of 16 selected

Labs

Chemistry - Other
Based on the selection of some medications, certain laboratory tests should also be ordered:
- If Propofol is ordered, also select Triglyceride lab orders.
- If Valproate Sodium or Valproic acid is ordered, also select the Ammonia lab order.

- Ammonia
- Lipid Panel Non-Fasting
- Lipid Panel

Ad-hoc Orders Add Order

Click the Add Order button to add an order in this section

Close F9 Previous F7 Next F8

Sedating agents

- “Analgo-sedation”
- Benzodiazepines
 - Selected patients
- Propofol
- Dexmedetomidine

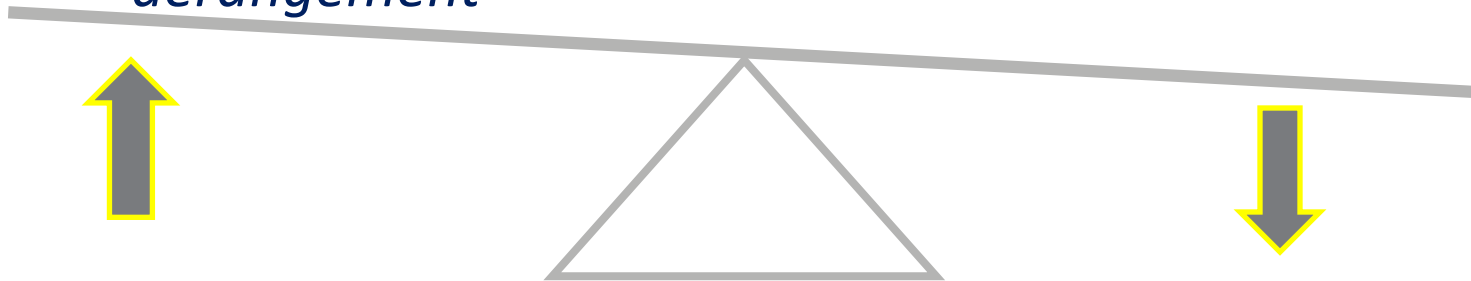
Introducing Analgesia-Based “Sedation,” a Tough Sell!

- Analgosedation or analgesia-first (A-1) sedation
- Discomfort is a common cause of agitation
- Any opioid useful... typically rapid onset and offset
- ~ 50% will require additional sedative agents

Clinical Practice Pearl: This is one way to limit avoidable serious adverse reactions from sedatives (death, delirium, immunomodulation, metabolic acidosis, hemodynamic derangement, etc).

Finding the Balance with Analgosedation

- Pain and discomfort are common causes for agitation
- Avoid potential sedative-related adverse events:
 - *Immunomodulation*
 - *Death (e.g., PRIS)*
 - *Delirium*
 - *Metabolic acidosis*
 - *Hemodynamic derangement*
- *ICU LOS, ventilator time, delirium, VAP, mortality, and cost of care NOT consistently reduced*
- May interfere with respiratory drive, gastric motility, nutrition
- Potential for withdrawal
- Rigorously evaluated mostly in European ICUs



Potential Benefits

PRIS = propofol related infusion syndrome

Potential Limitations

Benzodiazepines: Good and Bad

- Useful for
 - GABA agonist withdrawal
 - Anxiety
 - Intermittent agitation
 - Agitation in the setting of hemodynamic instability?
 - Seizures
 - Deep sedation and when amnesia is beneficial
- And sometimes they are indeed the devil's handiwork

Sedation Management: Benzodiazepines NOT Optimal

- Sedation strategies with non-benzodiazepines may be preferred because they are associated with improved clinical outcomes (2B)
 - Ventilator time
 - ICU time
 - Delirium?
- No effect on mortality

Comparative Hypotensive Effects

- Midazolam = Dexmedetomidine (27%)
 - SEDCOM Riker RR. JAMA 2009; 301:489-99
- Midazolam (12%) < Dexmedetomidine (21%)
 - MIDEX Trial Jakob SM. JAMA 2012;307:1151-60
- Propofol = Dexmedetomidine
 - PRODEX trial (13% each) Jacob SM. JAMA 2012;307:1151-60
 - Neurocritical Care Patients; ~25% each Erdman MJ. Crit Care Med 2014; 42:1696-702

Propofol: Indications and Pharmacodynamics

- Pharmacology: GABA agonist
- Preferred over the benzodiazepines (2B)
- Benefits
 - Rapid onset & offset
 - Allows easy dose titration to goal and facilitates daily sedation evaluation
 - Shorter time on mechanical ventilation and in the ICU vs benzodiazepines Carson SS. *Crit Care Med.* 2006; 34:1326-32
 - Has not been linked to delirium

Propofol: Concerns

- Not reliably amnestic, especially at low doses
- NO analgesia!
- Hypotension, hypertriglyceridemia, respiratory depression
 - Limits patient through-put to non-ICU setting
- Propofol Infusion Syndrome (PRIS)--rare, but often fatal

Dexmedetomidine

- Pharmacology: α -2 agonist
 - Has sedating, anxiolytic, and opiate-sparing properties
 - Permits patient awareness and responsiveness on stimulation
- Comparative data vs propofol are few

Dexmedetomidine

Competing Concerns

Use Dex

- Less time on the ventilator (2B)
- No interference with respiratory drive
- Less delirium (2B)
- Sympatholysis can be helpful

Don't Use Dex

- Econotoxicity; need ICU for administration
- Hemodynamic derangement
- Not for deep sedation
 - No amnestic properties

Helpful Hints

- If you wouldn't treat a patient with a beta-blocker, don't use dex
- Withdrawal tachycardia and hypertension unusual

Pearls For The Use of Dexmedetomidine

- Do not use loading dose
- Expand dosing range to 1.4mcg/kg/hr
- Expand permissible treatment duration >24hr
- Combination with other sedatives or analgesics OK
- Transition to clonidine (may facilitate transfer to non-ICU setting)

Alternative Agents

- Clonidine
- Ketamine
- Valproate
- Quetiapine (for its sedative effects)
- Phenobarbital
- Volatile anesthetics

Key Takeaways

- Sedation goal = comfort and wakefulness for most
 - Example: When RASS is used, offer additional evaluations to include assessments of wakefulness.
- Protocolization of sedation shortens ICU stay by about 2 days
 - Either daily SAT or simple titration to wakefulness may be used
- Analgosedation is effective and often avoids the need for standard sedatives
 - Example: Start with an opioid for those patients requiring sedation

Always
remember....



“Caution should be exercised, however, when guiding patients in selecting their music.

Chaotic music, such as hip-hop and heavy metal, is not healing to human cells.”

!!!!!!!!!!!!

Courtesy of Lauren Payne, Pharm.D.

Updates on Delirium in Critically ill Patients

Paul M. Szumita, Pharm.D., BCCCP, BCPS, FCCM
Clinical Pharmacy Practice Manager
Brigham and Women's Hospital
Boston, Massachusetts



2013 ACCM Guidelines: Delirium in Adult ICU Patients

- Outcomes associated with delirium
 - Delirium is associated with increased mortality and increased ICU and hospital LOS: (LOE A)
 - Delirium is associated with the development of post-ICU cognitive impairment in adult ICU patients: (LOE B)

Associated outcomes from ICU delirium

- During ICU and hospitalization
 - Increased mortality
 - Increased re-intubation rates
 - Increased length of stay
 - Higher cost of care
 - Increased need for tracheotomy
 - Increase restraint use
- Post hospital discharge
 - Increased mortality
 - Decreased functional status at 6 months
 - Increased risk of long-term cognitive impairment
 - Increased risk of dementia
 - Increase reliance on chronic care facilities
- Key Term – “Associated” = Not implying causation
- Is medication-related delirium = to toxic-metabolic delirium?

Mehta S .et al. *Crit Care Med.* 2015 Mar;43(3):557-66.

Salluh JI, et al. *BMJ.* 2015 Jun 3;350:h2538.

Dolan MM et al. *J Gerontol A Biol Sci Med.* 2000 Sep;55(9):M527-34.

Nelson JE et al. *Arch Intern Med.* 2006; 166;1993-1999.

Ely EW, et al. *JAMA.* 2004; 291:1753-1762.

Milbrant EB et al. *Crit Care Med.* 2004;32:955-62.

Jackson JC, et al. *Neuropsych Rev.* 2004;14:14:87-98.

Question #7

Compared to persistent delirium, rapidly reversible delirium (sedation related) is associated with:

- A** Increased mortality
- B** Decreased mortality
- C** The same mortality
- D** Increase discharge to hospice

Question #7

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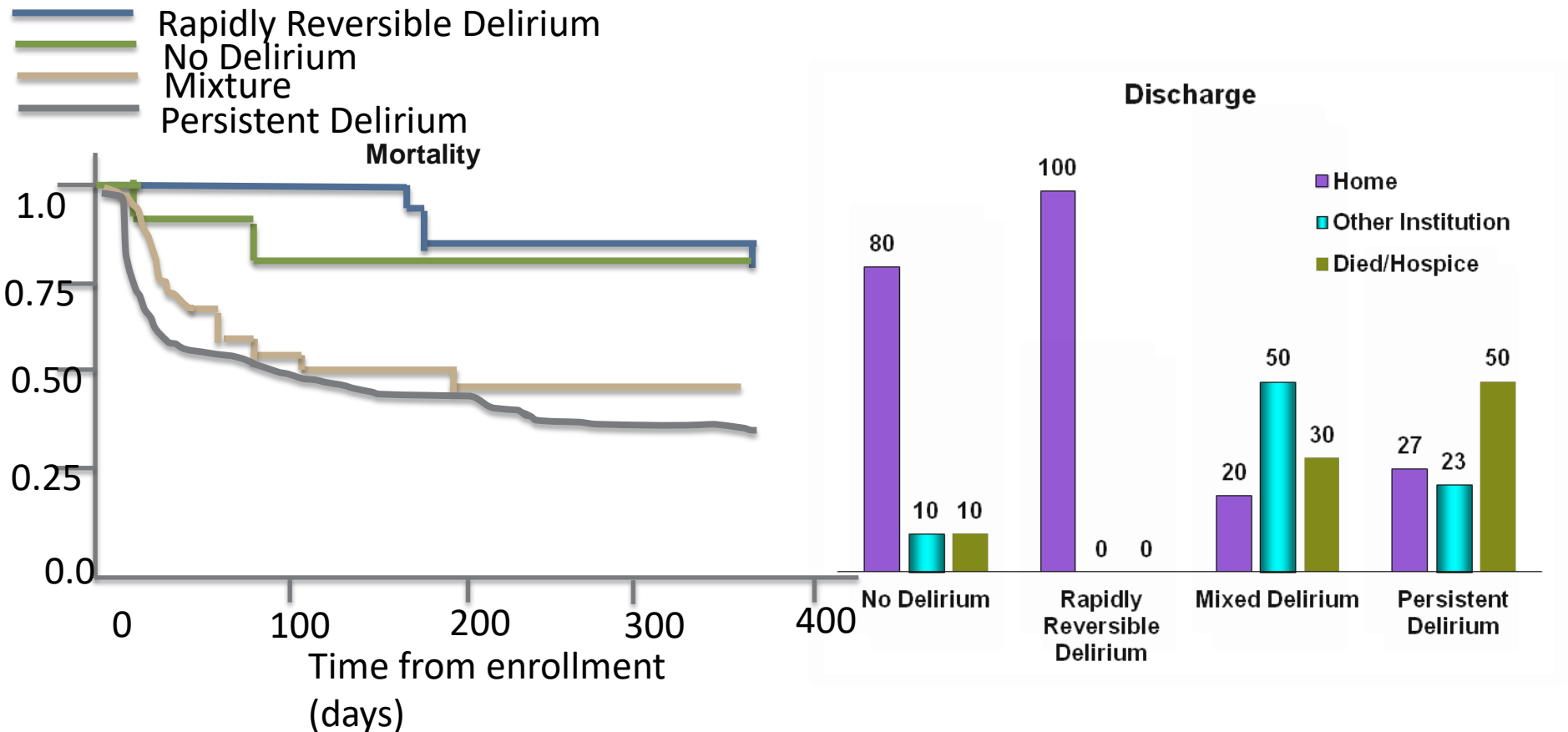
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Rapidly Reversible, Sedation-Related Delirium



Single center, prospective, cohort of 102 intubated adult medical ICU patients at the University of Chicago. CAM-ICU assessed before and after SAT daily. Rapidly reversible delirium defined by CAM-ICU assessment abated within 2 hours of an SAT.

Question #7

Compared to persistent delirium, rapidly reversible delirium (sedation related) is associated with:

- A Increased mortality
- B Decreased mortality**
- C The same mortality
- D Increase discharge to hospice

Delirium Outcomes Summary

- Avoiding delirium would be best
- Likely different classification of delirium based on cause (beyond the classic hypoactive, hyperactive, mixed)
 - Toxic metabolic
- Different classifications of delirium based on cause probably are associated with different outcomes (prime area for research)
 - e.g., Delirium from liver failure likely is not the same as delirium from hypoxia

2013 ACCM Guidelines: Delirium in Adult ICU Patients

- **Detecting and monitoring delirium**
 - Routine monitoring of delirium is recommended in adult ICU patients (LOE +1B)
 - Confusion Assessment Method- ICU (CAM-ICU) and Intensive Care Delirium Screening Checklist (ICDSC) are most reliable (LOE A)
 - Delirium monitoring is feasible in clinical practice (LOE B)

What is the prevalence/Incidence of delirium?

- 3%?
- 15%?
- 50%?
- 80%?
- Highly dependent on:
 - Systematic screening (all patients every shift?)
 - Underestimating if not done (if you're not looking you, won't find it)
 - Frequency of assessment (and adherence)
 - Assessment tool
 - Surgical/medical
 - Type of surgery
 - Study design
 - Metric
 - Mechanically vented

Mehta S, et al. *Crit Care Med*. 2015 Mar;43(3):557-66.
Ely EW, et al. *JAMA*. 2004;291:1753-1762.
Maldonado JR, et al. *Psychosomatics*. 2009;50(3):206-17.
Mariscalco G, et al. *Ann Thorac Surg*. 2012;93:1439-47.
Bakker RC, et al. *Eur J Cardiothorac Surg*. 2012;41:544-9.
Gamberini M, et al. *Crit Care Med*. 2009;37:1762-8.
Spronk PE, et al. *Intensive Care Med*. 2009 Jul;35(7):1276-80.

Evaluation of unable-to-assess CAM-ICU documentation

- Convenience sample of 3 months in MICU and SICU at a single center
 - 116 unable to assess (UTA)
 - 103 positive
 - 220 negative
- UTA 36 % of all assessments
 - Inappropriate UTA documentations ~30%
- Rates of inappropriate UTA assessments may be higher than previously reported in literature
- Additional research may be warranted to identify acceptable rates of inappropriate UTA CAM-ICU assessments

MICU-3C Unit Safety Dashboard

	Vent											PPX			Devices		
	SAT	SBT	Oral Care	HOB	V _t	Delirium Mgmt	Sedation Mgmt	Early Mobility	Family Mtg	Glucose Control	Nutrition	Pharm VTE	Mech VTE	GI	CVC	A-line	Foley
	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Guideline Compliant	Guideline Compliant	Risky State	Action Needed	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Not Applicable	Not Applicable	Risky State
	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Guideline Compliant	Guideline Compliant	Risky State	Action Needed	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Not Applicable	Not Applicable	Risky State
en	Risky State	Risky State	Guideline Compliant	Guideline Compliant	Guideline Compliant	Risky State	Action Needed	Not Applicable	Action Needed	Action Needed	Guideline Compliant	Guideline Compliant	Risky State	Guideline Compliant	Risky State	Not Applicable	Not Applicable
	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Guideline Compliant	Guideline Compliant	Risky State	Action Needed	Guideline Compliant	Action Needed	Guideline Compliant	Guideline Compliant	Guideline Compliant	Not Applicable	Not Applicable	Risky State
	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Action Needed	Guideline Compliant	Not Applicable	Not Applicable	Guideline Compliant	Action Needed	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Not Applicable	Risky State
	Guideline Compliant	Not Applicable	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Not Applicable	Guideline Compliant	Guideline Compliant	Action Needed	Risky State	Guideline Compliant	Risky State	Not Applicable	Not Applicable	Risky State
	Not Applicable	Risky State	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Action Needed	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Guideline Compliant	Not Applicable	Not Applicable	Risky State

Not Applicable



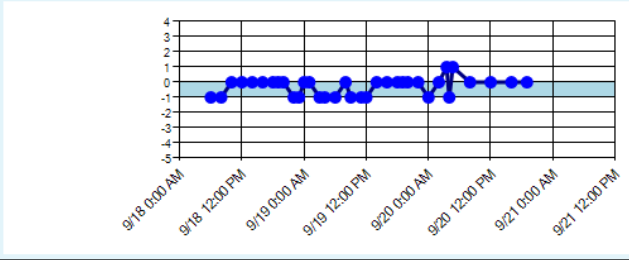
Guideline Compliant



Risky State



Action Needed

Sedation	<p>RN has had the opportunity to provide input to team from patient and family regarding goals and plan of care.</p> <p><input type="radio"/> Yes <input type="radio"/> No</p>	
Delirium	<p>Coordination of Sedation</p> <p>RASS Current 24-hr Average: 0</p> 	
PPX		
Mobility		
Restraints		
Nutrition		
Glucose		
Communication		
Disposition		
Code Status		
RN Summary		
Delirium Management		<p>CAM-ICU-(M)</p> <p>CAM results in last 24h: 9/20 08:00 Negative 9/20 04:00 Negative 9/20 08:00 Negative</p> <p>Last QTc: 449 msec (9/19/16 15:42) Antipsychotics:</p> <p>We have discussed a plan to optimize delirium management.</p> <p><input type="radio"/> Yes <input type="radio"/> No</p>
Mobility		<p>Pressure Ulcers Braden Score: 15 (high risk) Pressure Ulcer:</p> <p>We have discussed the patient's pressure ulcer prophylaxis and passive mobilization.</p> <p><input type="radio"/> Yes <input type="radio"/> No</p> <p>Active Mobilization Consult Placed: 9/10/16 5:54</p> <p>It is appropriate for the patient to participate in active mobility efforts</p> <p><input type="radio"/> Yes <input type="radio"/> No, due to the following reason:</p> <ul style="list-style-type: none"> <input type="radio"/> Hemodynamic instability (frequent titration of pressors) <input type="radio"/> Unsafe to perform SAT <input type="radio"/> Paralysis <input type="radio"/> Post-surgical concerns <input type="radio"/> Comfort measures only status <p>The patient has a new mobility or strength impairment requiring a PT consult.</p> <p><input type="radio"/> Yes <input type="radio"/> No</p>

Detection and Monitoring Summary

- Prevalence is highly patient population dependent
- CAM-ICU or ICDSC should routinely be used
- Each institution should have a standard and quality improvement method

Question #8

According to the 2013 ACCM PAD Guidelines, what are the baseline risk factors significantly associated with the development of delirium in the ICU in addition to preexisting dementia and high severity of illness?

- A** Benzodiazepine consumption and history of alcoholism
- B** History of hypertension and history of alcoholism
- C** Hyperglycemia and history of diabetes
- D** Preexisting pain, history of opioid dependence



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2013 SCCM Guidelines: Delirium in Adult ICU Patients

- **Delirium risk factors**

- Four baseline risk factors are positively and significantly associated with the development of delirium in the ICU: preexisting dementia, history of hypertension and/or alcoholism, and a high severity of illness at admission (B)
- Coma is an independent risk factor for the development of delirium in ICU patients (B)
- Conflicting data surround the relationship between opioid use and the development of delirium in adult ICU patients (B)
- Benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients (B)
- There are insufficient data to determine the relationship between propofol use and the development of delirium (C)
- In mechanically ventilated adult ICU patients at risk of developing delirium, dexmedetomidine infusions administered for sedation may be associated with a lower prevalence of delirium compared to benzodiazepine infusions (B).

Question #8

According to the 2013 ACCM PAD Guidelines, what are the baseline risk factors significantly associated with the development of delirium in the ICU in addition to preexisting dementia and high severity of illness?

- A** Benzodiazepine consumption and history of alcoholism
- B** **History of hypertension and history of alcoholism**
- C** Hyperglycemia and history of diabetes
- D** Preexisting pain, history of opioid dependence



Pathophysiology of Delirium in Critically ill Patients

Subtype	Mechanism	Etiologies
Toxic Metabolic	Hypercarbia	Respiratory Failure
	Hypoxia	Cardiopulmonary bypass
	Encephalopathies	Organ failure: Liver, renal, heart
	Elevated Ammonia	Overdose
	Elevated BUN	Toxin Ingestion
	Hyperthermia	Intoxification of alcohols (ethanol, ethylene glycol, methanol)
	Electrolyte abnormalities	Sepsis
	Toxin mediated Infection/Inflammation	
Alteration of neurotransmitters	GABA and Glutamate	Ethanol abuse
	Dopamine	Excessive or inappropriate tapering of benzodiazepines/ barbiturates/ opioids
	Norepinephrine	Sleep deprivation and circadian rhythm alteration
	Serotonin	
	NMDA	
	Acetylcholine	Pain

Most cases are multifactorial!! = Treatment is multimodal!!

Question #9

JM currently is receiving IV norepinephrine 20 mcg/min, vasopressin 0.04 units/min, epinephrine 5 mcg/min, and propofol 75 mcg/kg/min, with fentanyl IV bolus doses prn. JM is noted to have a MAP = 66 mmHg, HR = 91 bpm, CPOT 0, RASS -3, CAM-ICU positive. Which of the following would be the best initial management recommendation based on assessments, current medication therapy, hemodynamics and vital signs?

- A** Replace propofol with a dexmedetomidine infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU
- B** Replace propofol with a midazolam infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU
- C** Continue propofol to achieve a goal RASS of 0 to -1 and negative CAM-ICU
- D** Add quetiapine 50 mg NG every 12 hr to achieve a goal of negative CAM-ICU



Question #9



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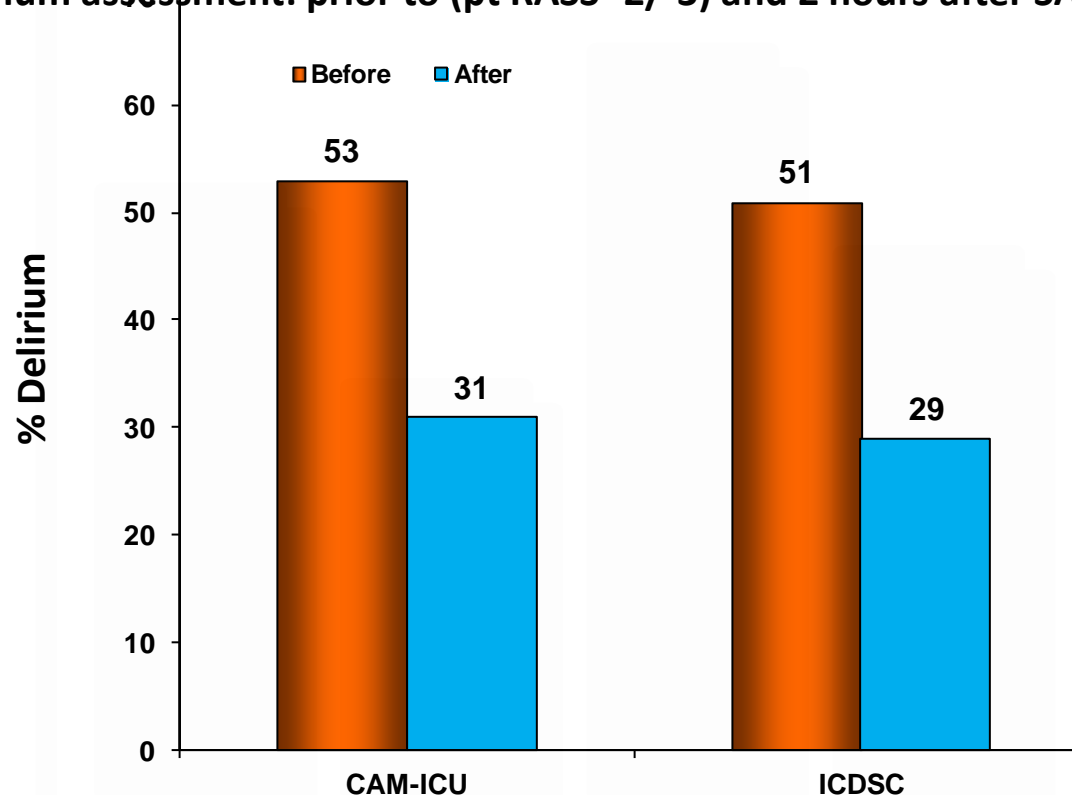
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Effect of Sedation Level on the Prevalence of Delirium

Delirium assessment: prior to (pt RASS -2/-3) and 2 hours after SAT



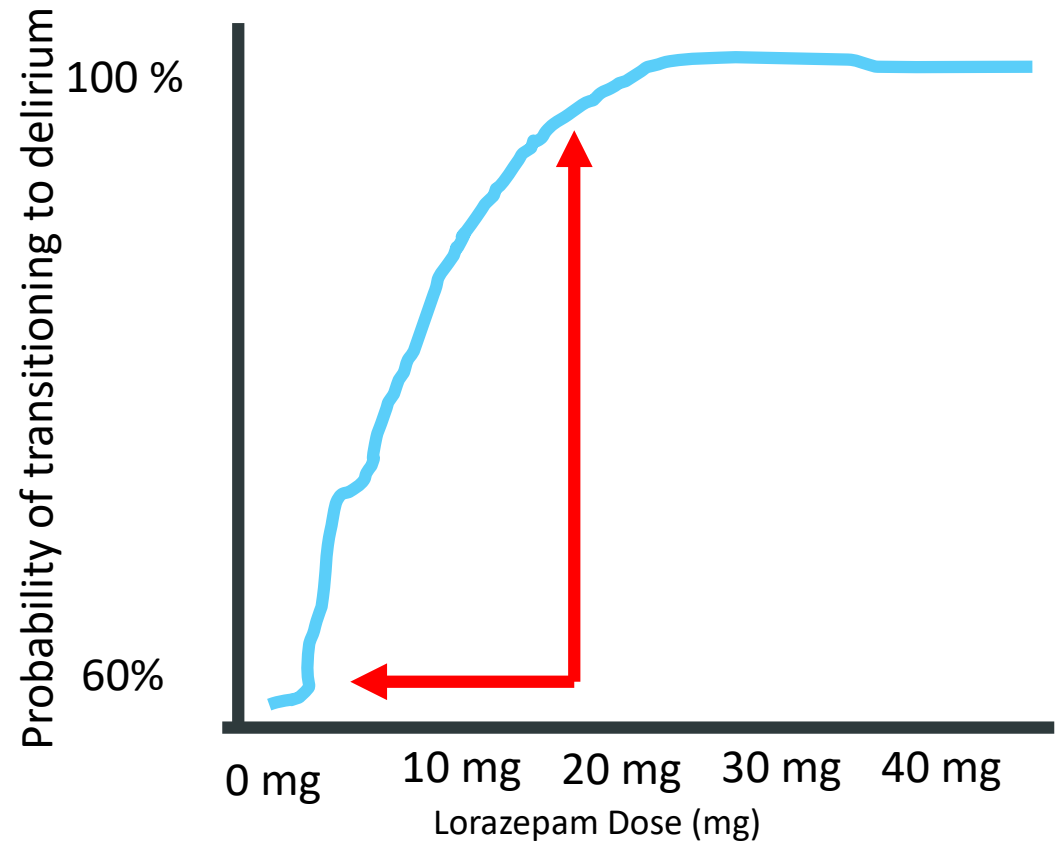
Single center in Switzerland, prospective, double-blind trial of 104 mixed medical/surgical ICU. 80 patients enrolled (467 patient days) and delirium assessed via the ICDSC and CAM-ICU during SAT.

Systematic Review of Risk Factors for Delirium in Critically Ill Adults

- Strong evidence
 - ↑Age
 - Dementia
 - Hypertension
 - Pre-ICU surgery or trauma
 - ↑APACHE II score
 - Mechanical ventilation
 - Metabolic acidosis
 - Delirium on the prior day
 - Sedation-associated coma

Probability of Transitioning to Delirium in Mechanically Ventilated Patients

- 198 mechanically ventilated patients admitted to the MICU or CCU at Vanderbilt University Medical Center from February 2000 to May 2001
- APACHE II: 25.7 ± 8.4
- Sepsis/ARDS: 47%



Question #9

JM currently is receiving IV norepinephrine 20 mcg/min, vasopressin 0.04 units/min, epinephrine 5 mcg/min, and propofol 75 mcg/kg/min, with fentanyl IV bolus doses prn. JM is noted to have a MAP = 66 mmHg, HR = 91 bpm, CPOT 0, RASS -3, CAM-ICU positive. Which of the following would be the best initial management recommendation based on assessments, current medication therapy, hemodynamics and vital signs?

- A** Replace propofol with a dexmedetomidine infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU
- B** Replace propofol with a midazolam infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU
- C** **Continue propofol to achieve a goal RASS of 0 to -1 and negative CAM-ICU**
- D** Add quetiapine 50 mg NG every 12 hr to achieve a goal of negative CAM-ICU



Extremely controversial question

- Is it the sedative drug or the level of sedation?
 - Glass of wine or a bottle of tequila

Risk Factors Summary

- Many risk factors
 - Often non-modifiable
- Modify as many of the risk factors as possible in a systematic way

2013 ACCM Guidelines: Delirium in Adult ICU Patients

- Delirium prevention
 - Early mobilization to prevent delirium is recommended (LOE +1B)
 - Conflicting data surround the relationship between opioid use and delirium in adult ICU patients (LOE B).
 - Benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients (LOE B).
 - Inconclusive relationship between propofol use and delirium in adult ICU patients (LOE C)
 - In mechanically ventilated adult ICU patients at risk of developing delirium, dexmedetomidine infusions administered for sedation may be associated with a lower prevalence of delirium compared with benzodiazepine infusions (LOE B)
 - Antipsychotics should not be given to prevent delirium (LOE -2C)
 - No recommendation for the use of dexmedetomidine to prevent delirium in adult ICU patients (LOE 0,C)

Preventive Strategies

- Largely nonpharmacologic and involves multidisciplinary action
 - Correct any known precipitating cause
 - Toxic metabolic, hypoxia, infection, organ dysfunction, shock
 - Early mobilization
 - Use of scheduled pain management protocols and pain scales
 - Target awake and alert via the use of sedation scales
 - Provide light, signs, calendars, clocks
 - Reorient, hearing aids, eyeglasses
 - Encourage family visits
 - Timely removal of catheters and restraints
 - Bowel, hydration, nutrition issues
 - Minimizing unnecessary stimuli
 - Adjusting ventilator settings
 - Promote sleep-wake pattern
 - Medication review

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

Collinsworth AW, et al. *J Intensive Care Med*. 2016 Feb;31(2):127-41.

O'Mahony R, et al. *Ann Intern Med*. 2011; 154: 746–751.

Schwartz AC, et al. *Int J Psychiatry Med*. 2016;51(2):160-70.

Nelson S, et al. *Biomed Res Int*. 2015; ePub Oct 19, 2015: 1-7.

<http://www.nice.org.uk/guidance/cg103/chapter/1-recommendations>
(accessed 5 September 2016).

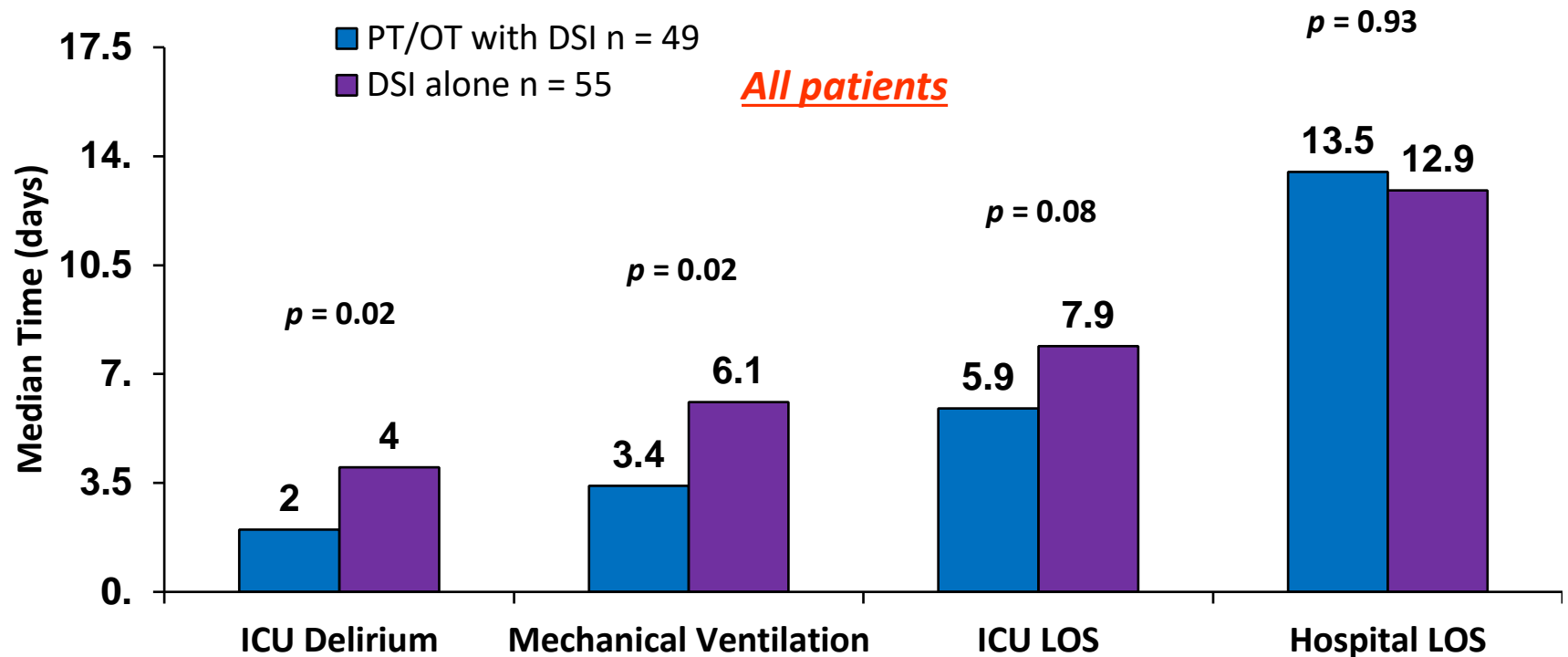
Caution

- Dot phrase world
 - Early mobilization
 - Minimize deep sedation
 - Maximize day/night cycle
 - Frequent orientation
 - Post reminders of friends and family - Photos

Collaborative Approach

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

Early PT and OT in Mechanically Ventilated ICU Patients



Two-center trial of 104 adult patients on mechanical ventilation for less than 72 hr, randomized to early exercise and mobilization (PT and OT) during periods of daily interruption of sedation or to daily interruption (DSI) of sedation with therapy as ordered by the primary care team.

Question #10

JM currently is receiving IV norepinephrine 20 mcg/min, vasopressin 0.04 units/min, amiodarone 0.5 mg/min, and propofol 20 mcg/kg/min. JM is noted to have a MAP = 66 mmHg, HR = 91 bpm, CPOT 4, RASS +1, CAM-ICU positive . Which of the following would be the best initial management recommendation based on assessments, current medication therapy, hemodynamics and vitals?

- A** Replace propofol with a dexmedetomidine infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU
- B** Replace propofol with a midazolam infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU
- C** Add fentanyl bolus 25-50 mcg PRN CPOT >2 to achieve a goal CPOT < 3, goal RASS of 0 to -1 and negative CAM-ICU
- D** Add quetiapine 50 mg NG every 12 hr to achieve a goal of negative CAM-ICU





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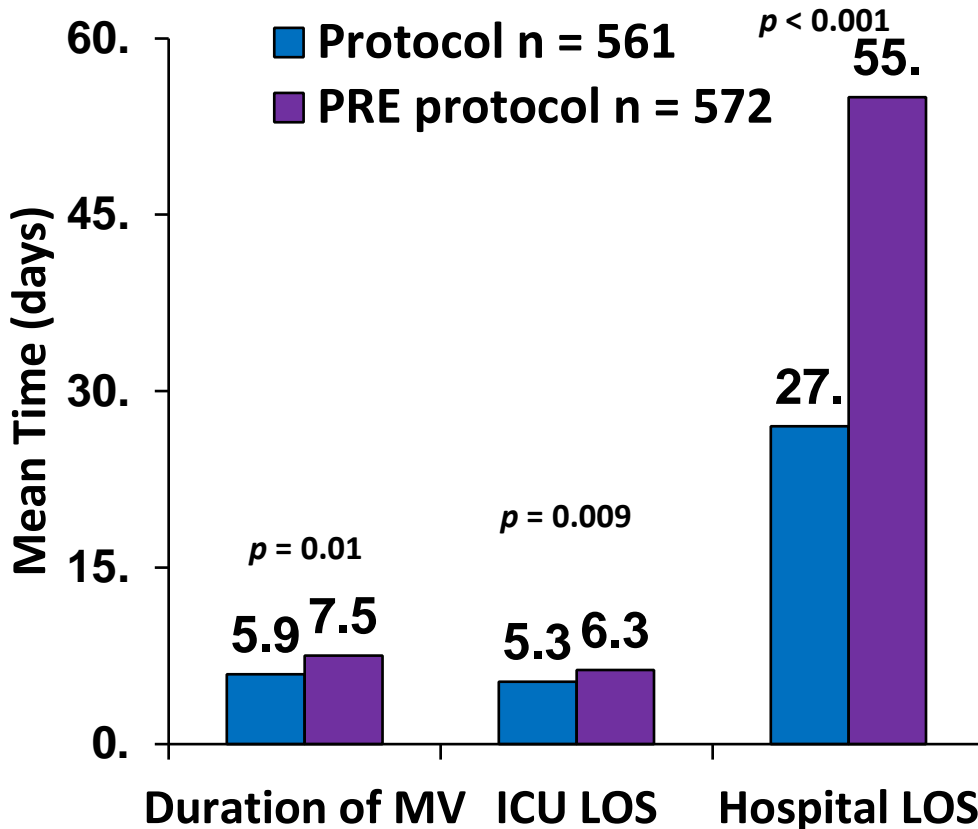
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Impact of Pain-Sedation-Delirium Protocol on Subsyndromal Delirium



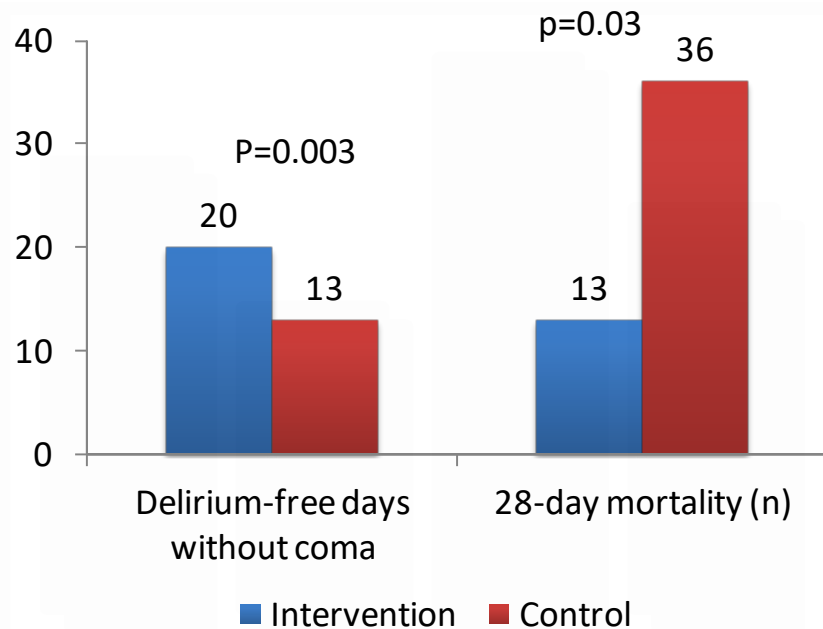
Significant patient characteristics/metrics/outcomes

	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 †Data presented as n (%)
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 8/03 to 11/05. Protocol used goal oriented sedation to target RASS and numeric rating scale (NRS).

Haloperidol Prophylaxis in Critically Ill Patients



	Intervention (n=177)	Control (n= 299)	p-value
Haloperidol dose administered, mg/day (IQR)	2 (2-3)	6 (3-10)	<0.0001
RASS, (IQR)	-1 (-3-0)	-1 (-3-0)	0.84
Observed delirium incidence; N (%)	115 (65%)	225 (75%)	0.01
LOS-ICU (days)	6	7	0.65
LOS-Hospital (days)	20	21	0.16
Duration MV (hr)	90	118	0.24
Unplanned tube/line removal (%)	21 (12%)	58 (19%)	0.02

Data presented in median

Single center, before/ after evaluation of ICU delirium prevention protocol carried out in 476 critically ill patients at high risk for delirium in mixed (primarily medical/ surgical) 33 bed ICU in the Netherlands. High-risk patients, defined as having predicted delirium risk > 50% using PREDELIRIC scoring, diagnosis of dementia or alcohol abuse, were prophylactically dosed with haloperidol 1mg IV every 8 hr from ICU admission to 24 hours after ICU admission. Patients screened for delirium using CAM-ICU.

Preventing ICU subsyndromal delirium conversion to delirium with low-dose IV haloperidol

- Double-blinded, placebo controlled pilot study. 68 mixed medical/surgical ICU received 1 mg every 6 hours until delirium occurred:
 - 34 patients in each arm
 - Developed delirium = no difference
 - Haloperidol reduced time agitated

Melatonin Receptor Agonists

- Help promote sleep
 - Very little evidence in ICU patients
- One small Japanese study (67 patients – of which 24 were in ICU)
 - prevalence of delirium 3% in ramelteon group vs 32% placebo in medically ill patients
- Much more literature is needed to support routine use of ramelteon in the ICU

Dexmedetomidine for prevention of delirium in elderly patients after non-cardiac surgery: a randomized, double-blind, placebo-controlled trial

- Randomized, double blinded, placebo- controlled RCT at 2 medical centers is in Beijing, China
- Dexmedetomidine 0.1 mcg/kg/hr or placebo
- APACHE II score ~ 10; surgical ICUs (non-CV surg)
- Primary endpoint incidence of delirium during the first 7 postoperative days
 - Dex 32/350 (9%), placebo 79/350 (23%), $p < 0.0001$

Prevention Summary

- Clearly would like to eliminate delirium
 - Not feasible
- Non-pharmacologic interventions in all patients when feasible
 - Early mobilization best evidence
 - Goal awake and alert
- Pharmacologic prophylaxis
 - Often not helpful and potentially harmful
 - Needs further research

Question #10

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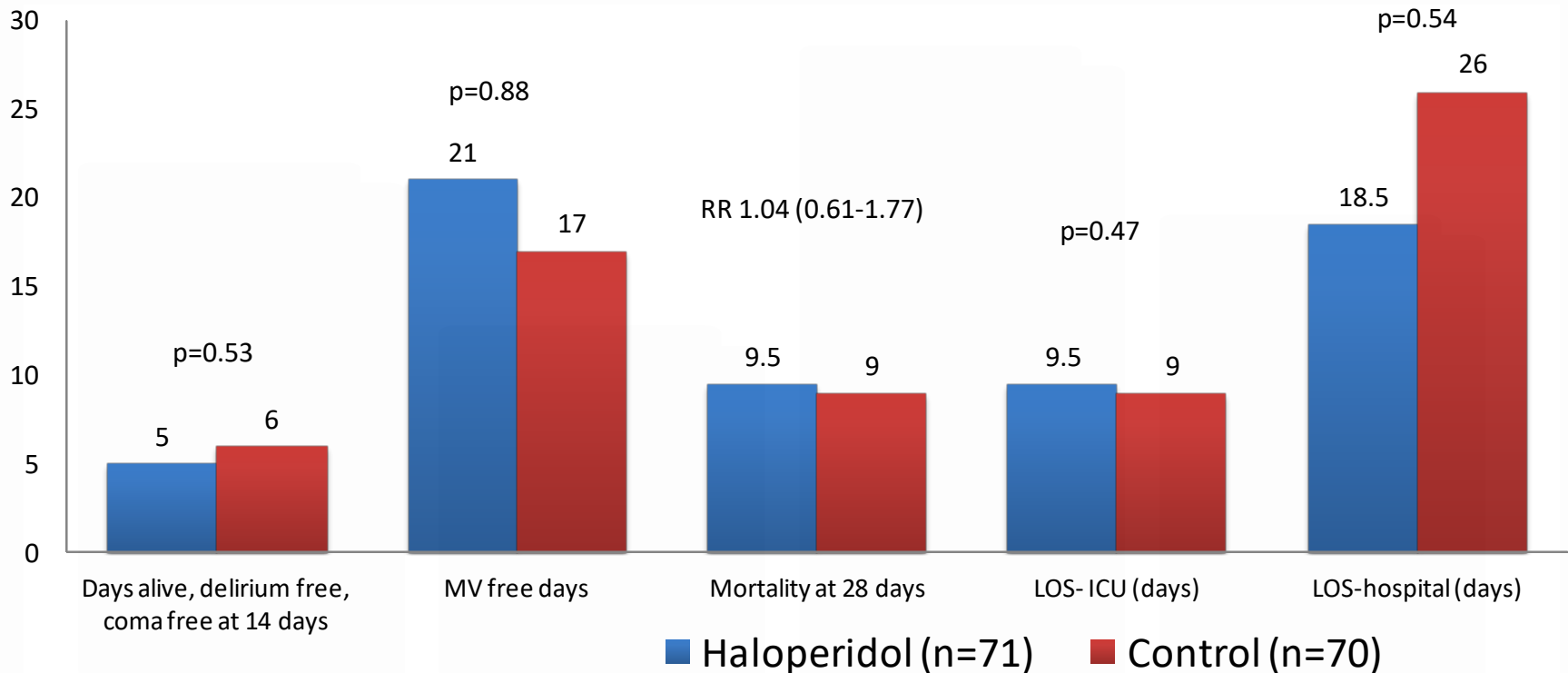
- A** Replace propofol with a dexmedetomidine infusion titrated to achieve a goal RASS of 0 to -1 and negative CAM-ICU
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- D** Add quetiapine 50 mg NG every 12 hr to achieve a goal of negative CAM-ICU



2013 SCCM Guidelines: Delirium in Adult ICU Patients

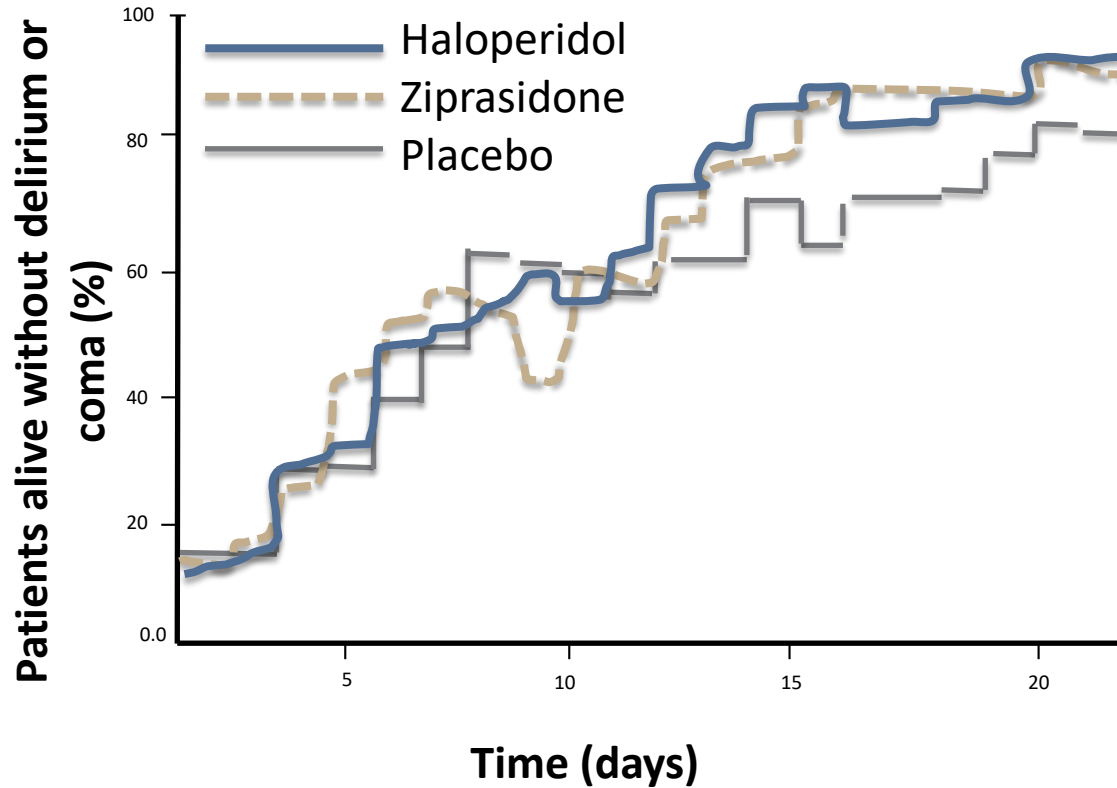
- Delirium treatment
 - Haloperidol treatment of delirium (no recommendation)
 - Atypical antipsychotics may reduce duration of delirium (LOE C)
 - We do not recommend administering rivastigmine to reduce the duration of delirium in ICU patients (LOE –1B).
 - We do not suggest using antipsychotics in patients at significant risk for torsades de pointes (i.e., patients with baseline prolongation of QTc interval, patients receiving concomitant medications known to prolong the QTc interval, or patients with a history of this arrhythmia) (LOE –2C)
 - In ICU patients with delirium unrelated to alcohol or benzodiazepine withdrawal, continuous IV infusions of dexmedetomidine rather than benzodiazepine infusions may be preferred for sedation to reduce the duration of delirium (LOE +2B)

HOPE ICU- Effect of Early Treatment with IV Haloperidol on Duration of Delirium



Single center, randomized, double-blind, placebo controlled trial in mixed medical/ surgical ICU. Early treatment of critically ill MV patients with IV haloperidol for duration of ICU stay or until delirium-free and coma-free for 48 hours. Patients were included if mechanically ventilated within 72 hr of ICU admission. Patients in intervention arm were administered haloperidol 2.5 mg IV q 8hr within 72 hours of ICU admission to the ICU regardless of their delirium or coma status.

MIND Feasibility Trial

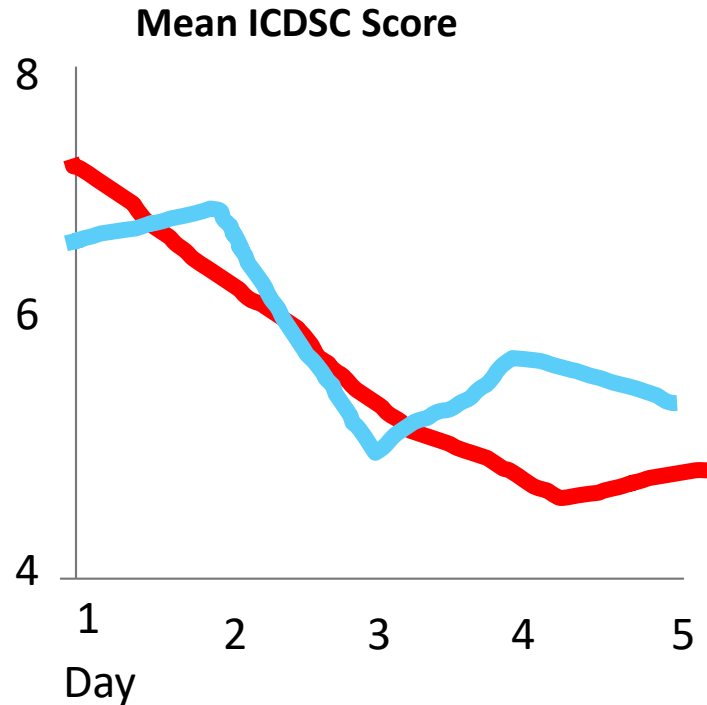


Randomized, double-blind, placebo-controlled trial. Six centers in USA. 101 Mechanically ventilated mixed medical/surgical ICU patients with delirium diagnosed by positive CAM-ICU. Haloperidol, ziprasidone or placebo every 6 hours for up to 14 days. Number of days alive without delirium or coma at day 21 primary endpoint.

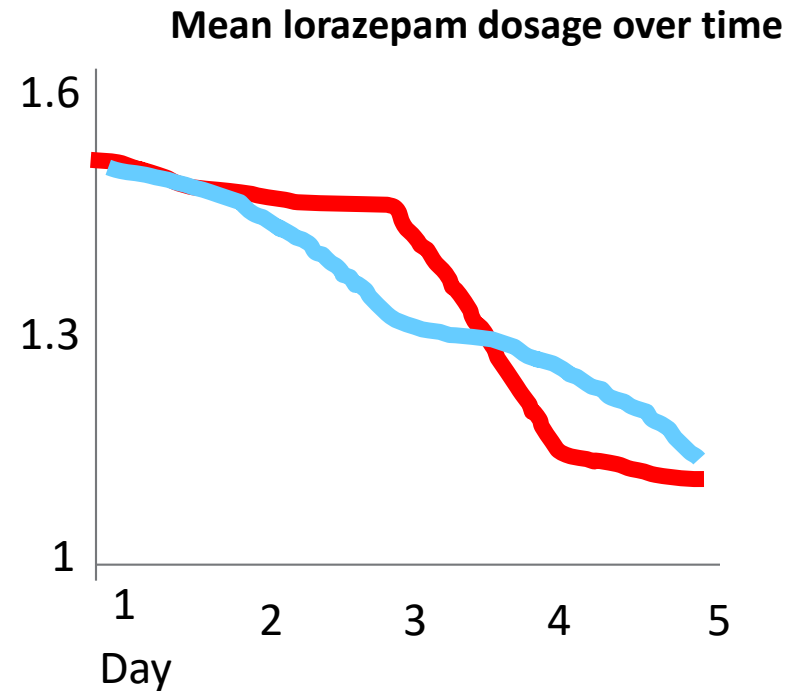
Olanzapine vs. Haloperidol for the Treatment of Delirium in SICU Patients

— Haloperidol

— Olanzapine



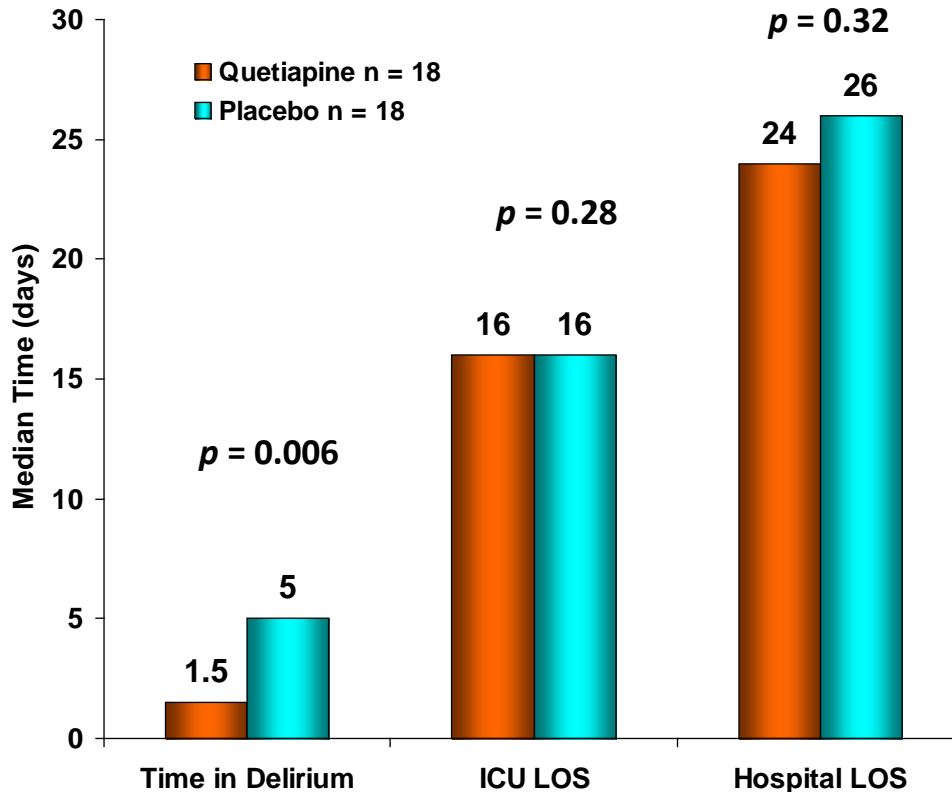
Mean olanzapine dose: 4.5mg/day



Mean haloperidol dose: 6.5mg/day

Single center, prospective, open label trial of 73 mixed medical/surgical ICU patients with delirium via ICDSC scale tolerating tube feeds, randomized to olanzapine 5mg QD or haloperidol 2.5–5 mg every 8hr “titrated per response,” with rescue haloperidol. Patients > 60 yr received a lower initial dosage (haloperidol 0.5–1 mg, or olanzapine 2.5 mg).

Quetiapine for the Treatment of Delirium in Mixed ICU Patients



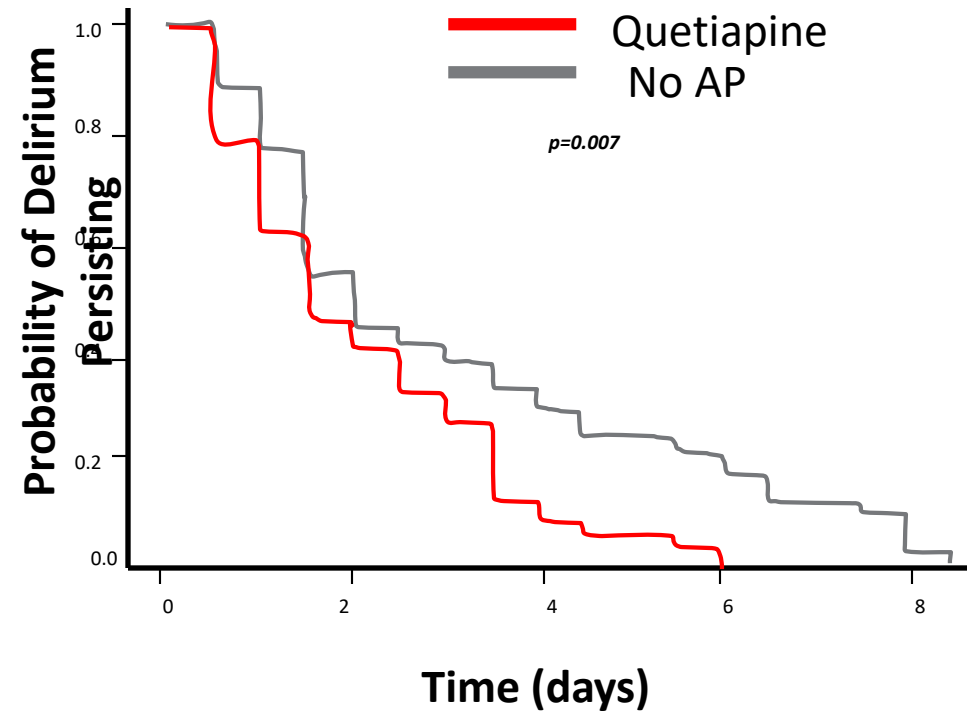
	Quetiapine	Placebo	P value
SAS \geq 5, hrs*	6	36	0.02
SAS \leq 2, hrs*	0	0	0.54
Haloperidol mg/day*	1.9	4.3	0.26
Midazolam equivalents mg/day*	5.3	26	0.32

*Data presented in median

†Data presented as n (%)

Three center, prospective, double-blind trial of 36 mixed medical/surgical ICU patients with delirium via ICDSC scale and tolerating tube feeds, randomized to quetiapine 50mg BID (titrated up to 200mg BID) or placebo with open label IV haloperidol in both groups. 258 screened, 36 enrolled.

Quetiapine for the Treatment of Hypoactive Delirium



	Quetiapine (n=52)	No AP [^] (n=61)	P value
Time to delirium *	4	4	0.55
Duration of delirium *	1.5	2	0.04
Duration of MV *	7	7.5	0.88
Duration MV after CAM+	3	5	0.07
DEX †	14 (27)	14 (23)	0.57

[^] Antipsychotic medication

*Data presented in median

†Data presented as n (%)

Two center, retrospective study of 113 mixed medical/surgical ICU patients with hypoactive delirium diagnosed by positive CAM-ICU and RASS scores between 0 and -3. Resolution of delirium defined as first 24-hour period of consecutive negative CAM-ICU screenings

Quetiapine effect on QTc interval

Multivariable Analysis

Variable	OR (CI)	P - value
CAD	1.12 (0.92 – 1.35)	0.24
CHF	0.92 (0.69 – 1.21)	0.53
Baseline QTc > 400 msec	0.84 (0.65-1.09)	0.19
Baseline QTc > 450 msec	0.88 (0.76 – 1.00)	0.055
TDD > 50 mg	1.09 (0.91 – 1.30)	0.37
TDD > 100 mg	0.87 (0.68 – 1.13)	0.30
TDD > 150 mg	1.22 (0.92 – 1.60)	0.16
1 or more concomitant meds	1.15 (1.00-1.32)	0.046

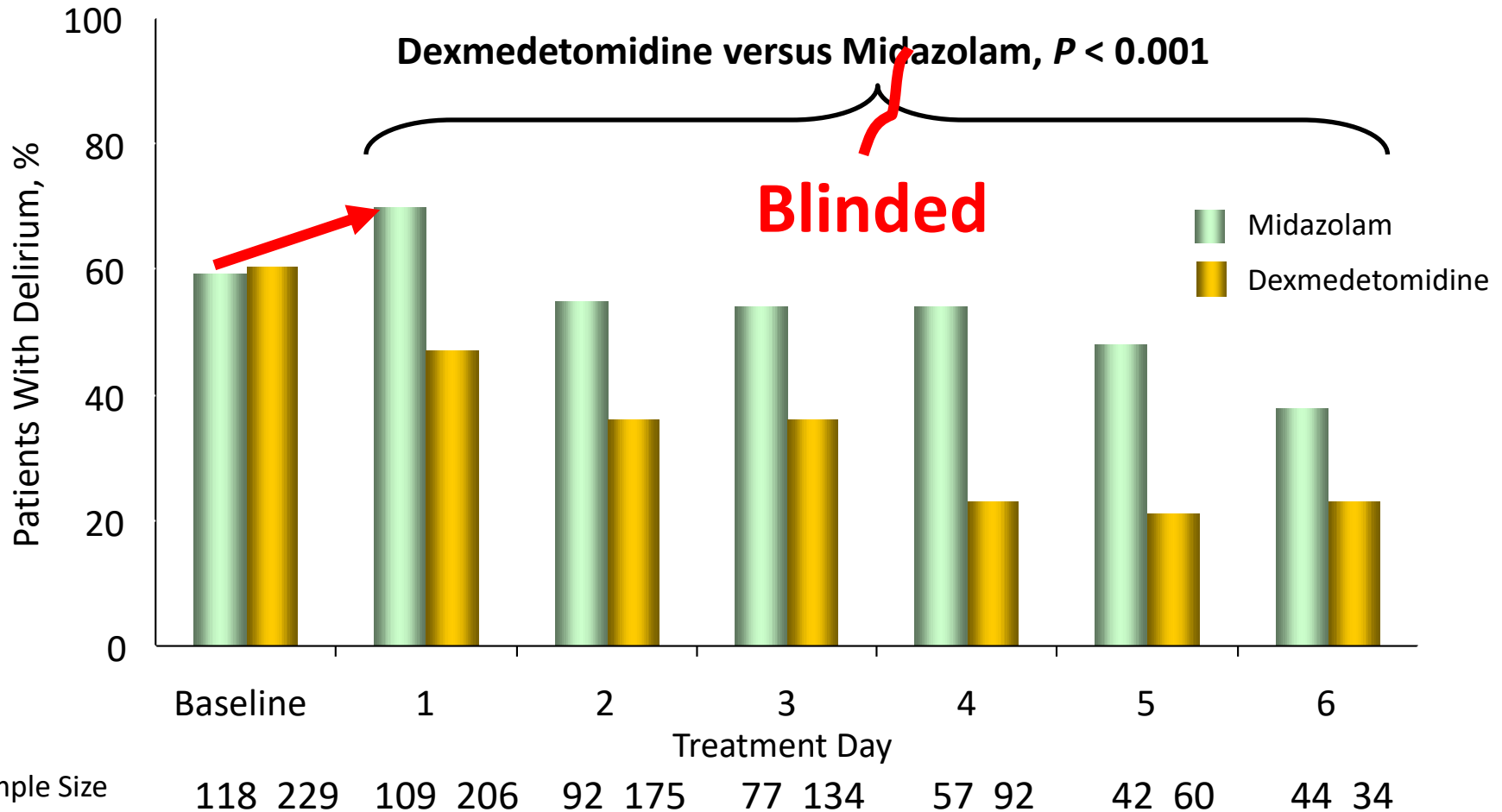
Dexmedetomidine vs Lorazepam: *MENDS TRIAL*

	Dexmedetomidine (n = 52)	Lorazepam (n = 51)	p Value
Delirium, No. (%)	41 (79)	42 (82)	p = 0.65
Duration of Delirium, days	2.5 (1-5)	4 (1-5)	p = 0.71
Ventilator-free, days	22 (0-24)	18 (0-23)	p = 0.22
ICU LOS, days	7.5 (5-19)	9 (6-15)	p = 0.92
28 day all-cause mortality, No. (%)	9 (17)	14 (27)	p = 0.18

Hospital LOS not reported

Dexmedetomidine vs Midazolam: *SEDCOM TRIAL*

Dexmedetomidine versus Midazolam, $P < 0.001$



Dexmedetomidine vs Propofol/Midaz for long-term sedation in ICU (PRODEX MIDEX Pilot Analysis)

	Dexmedetomidine (n = 41)	Midaz/Prop (n = 44)	p Value
Time in target sedation range* (hr)	64	63	NS
CAM ICU Positive	43.9	25.0	p = 0.04
Extubation time, hr*	77.2 (17.5–338.8)	110.6 (20.1–675.0)	p = 0.11
ICU LOS from admit*	6.6 (2.2–20.7)	6.8 (2.6–30.8)	p = 0.28
ICU LOS from randomization*	5.5 (1.7–19.5)	5.7 (1.7–29.0)	p = 0.82
ICU LOS MICU*	5.0 (1.7 –19.5)	4.9 (1.8 –29.0)	p = 0.43
ICU LOS SICU*	5.7 (2.0 –16.7)	5.9 (1.7–16.8)	p = 0.06

*Value expressed as median (IQR)

Trial stopped early

Dexmedetomidine vs Midazolam or Propofol: *MIDEX PRODEX; Key Critiques*

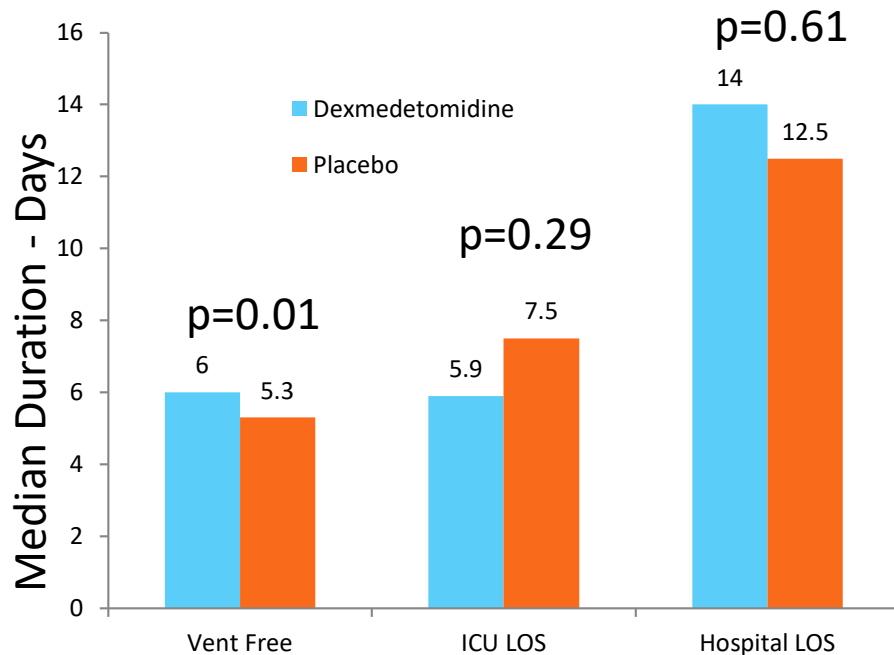
	Dexmedetomidine	Midaz/Prop	p Value
PRODEX CAM ICU Positive: n(%)	22 (9.6)	31 (13.7)	0.231
MIDEX CAM ICU Positive: n(%)	28 (11.9)	33 (13.9)	0.396

- RASS awake and alert
 - 0 to -3
 - (4 to -5)
- Dose equivalence
 - Six dose levels of each study drug covered the full dose range
 - dexmedetomidine, 0.2-1.4 mcg/kg per hour;
 - midazolam, 0.03-0.2 mg/kg per hour;
 - propofol, 0.3-4.0 mg/kg per hour
- Blinded continuous infusion
- No antipsychotic use data

Dexmedetomidine for the Treatment of Hyperactive Delirium Refractory to Haloperidol in Nonintubated ICU Patients: A Nonrandomized Controlled Trial

- Nonrandomized , controlled, single center in Barcelona, Spain
- Agitated delirium
- Dexmedetomidine added for non-responders to haloperidol (n = 47) vs. responders haloperidol (n= 86)
 - Dexmedetomidine patients had a higher percentage of time at satisfactory sedation level 92.7% vs. 59.3% p= 0.0001
- Dexmedetomidine may be useful as a rescue drug for treating agitation due to delirium in patients who fail to respond to haloperidol

Effect of Dexmedetomidine Added to Standard Care for Agitated Delirium



Other Metrics

	Dex n=39	Placebo n=32	P value
Any day antipsychotic %	36.8	65.6	0.02
Study day with any antipsychotic %	26.3	40	0.08
Underwent tracheostomy %	17.9	6.3	0.14
Time to tracheostomy Median hours	41.9	71.1	< 0.01
Any day Propofol Median (mg)	980	5390	<0.001

Multicenter RCT in New Zealand and Australia in mixed medical/surgical ICUs. Dex (39) or placebo (32) added to standard of care in agitated delirious patients.

Treatment Summary

- Very little evidence that any specific medication will provide better outcome than alternatives
- More research is needed
- Patient-specific personalized regimen is important
- Atypical antipsychotics may be helpful in certain patients
- Dexmedetomidine has a role, but needs further investigation

Key Takeaways

- Key Takeaway #1
 - ICU delirium is common and is often associated with poor outcomes
- Key Takeaway #2
 - Preventive strategies are mostly non-pharmacologic
 - Collaborative approach is necessary
- Key Takeaway #3
 - Treatment
 - Atypical antipsychotics may have a role
 - Dexmedetomidine may be effective, probably by avoiding the adverse effects from the alternative agents

Questions?

References and Recommended Readings

Guidelines

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- Practice guidelines for the perioperative management of patients with obstructive sleep apnea: an updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of patients with obstructive sleep apnea. *Anesthesiology*. Feb 2014;120(2):268-286.

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References and Recommended Readings

General Reviews (Cont)

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