ashp MIDYEAR 2018
Clinical Meeting & Exhibition

Updates in the Management of Pain, Agitation, and Delirium in the ICU

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Disclosures

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Learning Objectives

- Compare the substantial changes to the 2018 Society of Critical Care Medicine (SCCM) guidelines to the 2013 guidelines and their impact on patient assessment and pharmacotherapy.

- Given a patient case, discuss the assessment of pain, agitation, and delirium (PAD), as well as the evidence-based goals for medication titration in a critically ill patient.

- Given a patient case, evaluate pharmacotherapy options and sedation strategies for the prevention and management of PAD in a critically ill patient.

Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the intensive care unit

Devlin JW, Skrobik Y, Gelinas C, Pandharipande P, Slooter A, Watson P, Weinhouse G, Nunnally M, Rochwerg B, Balas MC, van den Boorgaard M, Bosma KJ, Brummel NE, Chanques G, Denehy L, Drouot X, Fraser GL, Harris JE, Joffe AM, Kho ME, Kress JP, Lanphere JA, McKinley S, Neufeld KJ, Pisani MA, Payen JF, Pun BT, Puntillo KA, Riker RR, Robinson BRH, Shehabi Y, Szumita PM, Winkelman, Centofani J, Price, C, Nikayin S, Misak CJ, Flood PD, Kiedrowski K, Alhazzani W.

- 6 different professions; 8 different MD subspecialties
- 6 different countries represented
- 3 ICU survivors
- 4 methodologists
- 5 groups – immobility and sleep disruption new from PAD 2013

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)

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.

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.

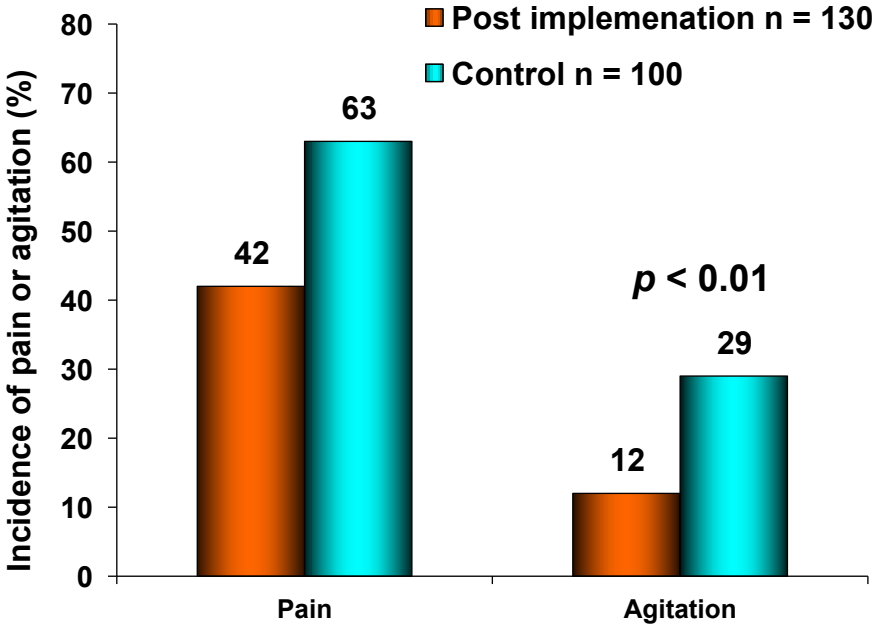
Pain Assessment Recommendations

- 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.

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.

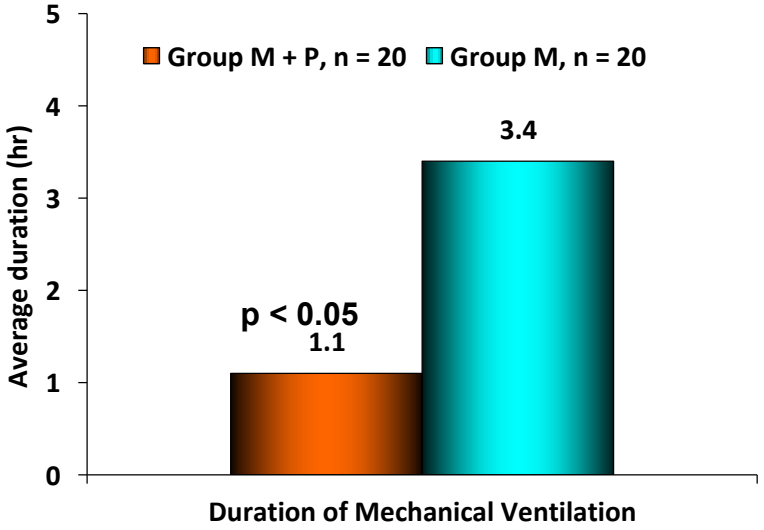
Paracetamol as Adjunctive Treatment for Postoperative Pain After Cardiac Surgery

	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 days$^{\beta}$	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.

Adjunctive Paracetamol with Meperidine vs. Meperidine Alone



Single center, prospective, randomized, placebo-controlled trial of 40 surgical ICU patients after major abdominal or pelvic surgery who were expected to require 24 hours of post-operative sedation and ventilation.

Significant patient characteristics/metrics/outcomes			
	M (n=20)	M + P (n=20)	P value
Meperidine consumption, mg*	198 ± 66	77 ± 18	< 0.05
BPS until extubated*	5.7 ± 2.1	3.7 ± 0.8	< 0.01
VAS after extubation*	2.6 ± 0.3	2.4 ± 0.6	< 0.01
BPS at extubation*	3.6 ± 1.2	2.5 ± 0.8	< 0.05
N/V†	8	1	< 0.05
N/V requiring treatment†	7	1	< 0.05
ICU admission pain score*	0 ± 0	0 ± 0	NS

*Data presented as mean ± SD; †Data presented as n

VAS: Visual Analog Scale; BPS: Behavioral Pain Scale

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

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

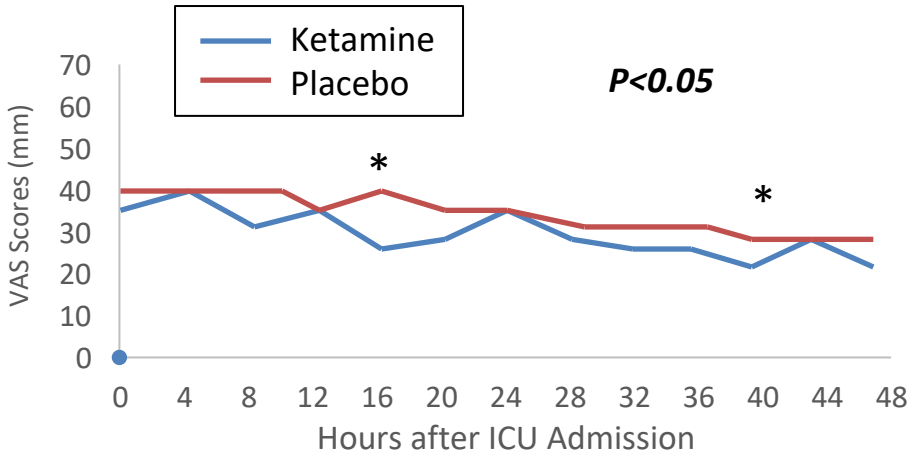
Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

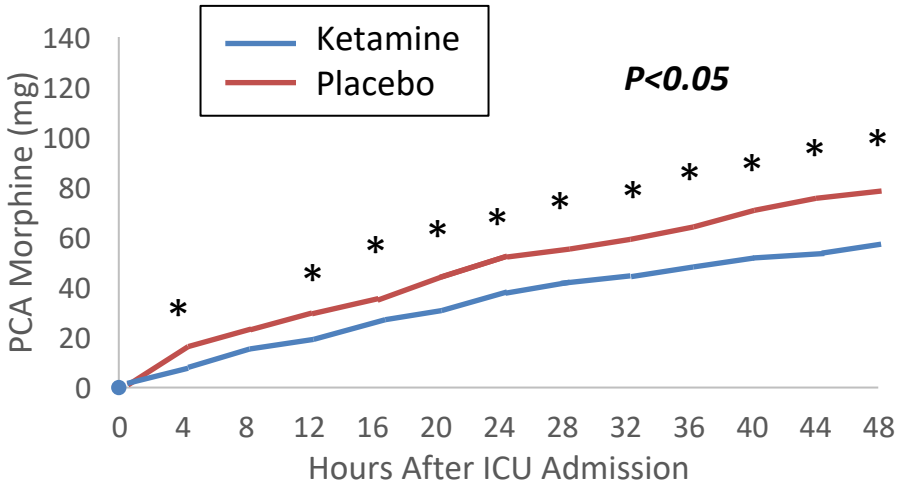
Case Question #1

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/hr continuous infusion

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.

Adjunctive Ketamine

- The 2018 SCCM PADIS guidelines suggest using low-dose ketamine (1 -2 mcg/kg/hr) 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 Lidocaine

- 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 NSAIDs

- 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.

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

- 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.

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

Procedural Pain: NSAIDs

- 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

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

Other Procedural Pain Group Recommendations

- The 2018 SCCM PADIS guidelines
  - 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
  - We suggest offering cold therapy for procedural pain management in critically ill adults
    - Conditional recommendation, low quality of evidence
  - We suggest offering relaxation techniques for procedural 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.

Multimodal Pharmacotherapy: *A LOT* to Choose From but Limited ICU Data

- Acetaminophen
- NSAIDs
- COX-2 inhibitors
- Opioids/mu-receptor agonists
- Local Anesthetics
  - Regional & local techniques
- NMDA receptor antagonists
  - Ketamine
- α-2 agonists
  - Clonidine & Dexmedetomidine
- Anticonvulsants
  - Gabapentin/Pregabalin
- Corticosteroids

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

Buvanendran A, et al. *Curr Opin Anaesthesiol*. 2009 Oct;22(5):588-93.

Other Pain Group Recommendations

- The 2018 SCCM PADIS guidelines
  - 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

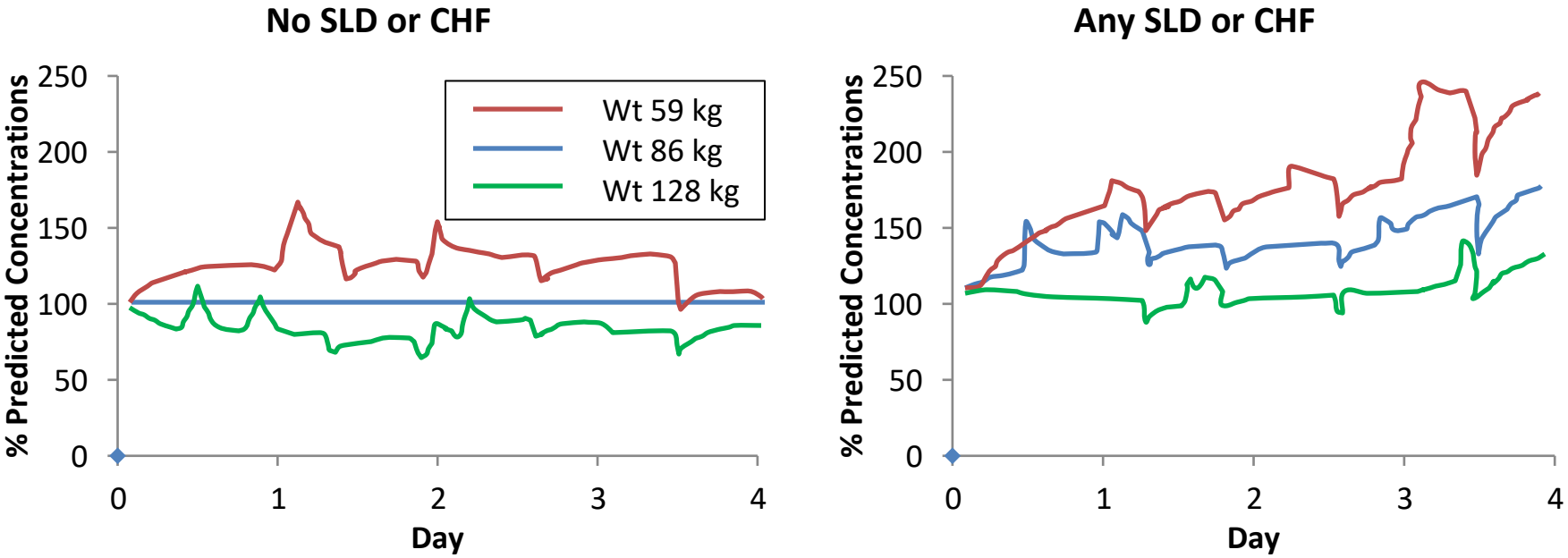
Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Guideline-Recommended Opioid Therapy

- The same opioids (i.e., fentanyl, hydromorphone, morphine, and remifentanil) that were recommended in the 2013 guidelines to manage pain should also be considered when an opioid is deemed to be the most appropriate pharmacologic intervention
  - 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.

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.

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"
  - 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.

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

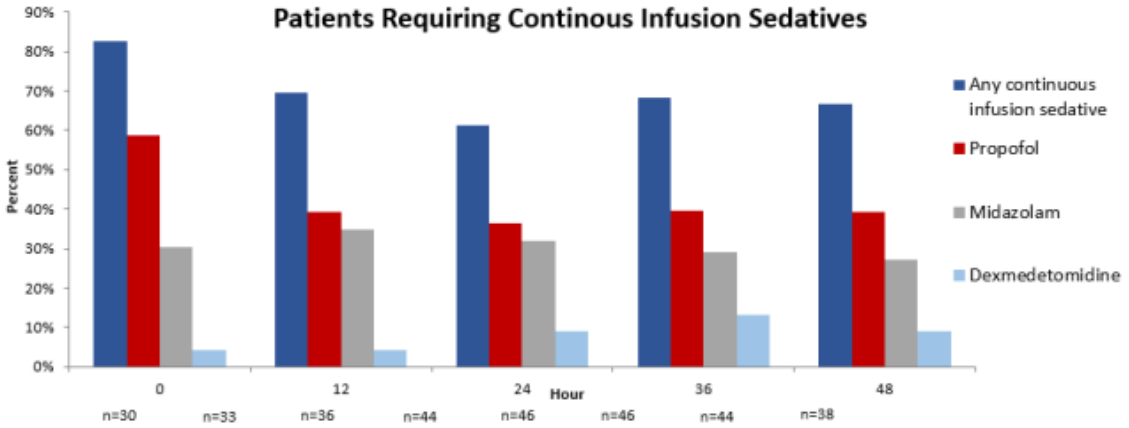
- Wanzuita et al.:
  - Trend toward increased ventilator-free days
  - Higher probability of being mechanical ventilation-free at day 5
  - Among patients able to be weaned from mechanical ventilation:
    - Decreased time to extubation

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

IV Fentanyl to IV Hydromorphone Rotation

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 M, et al. *J Pharm Pract.* 2018; Epub ahead of print.

Protocol-Based Pain First/Analgosedation

PICO	
P	Critically ill adult patients in an ICU
I	Protocol-based (analgesia/analgosedation) pain assessment and management program
C	Usual care
O	• Pain intensity • Medication exposure (opioids and sedatives) • Adverse events • Duration of mechanical ventilation • ICU Length of stay

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

Analgosedation

- The 2018 SCCM PADIS guidelines suggest
  - Analgesia-first sedation (analgesic [usually an opioid] is used before a sedative to reach the sedative goal)

  -or-

  - Analgesia-based sedation (analgesic [usually an opioid] is used instead of a sedative to reach the sedative goal)

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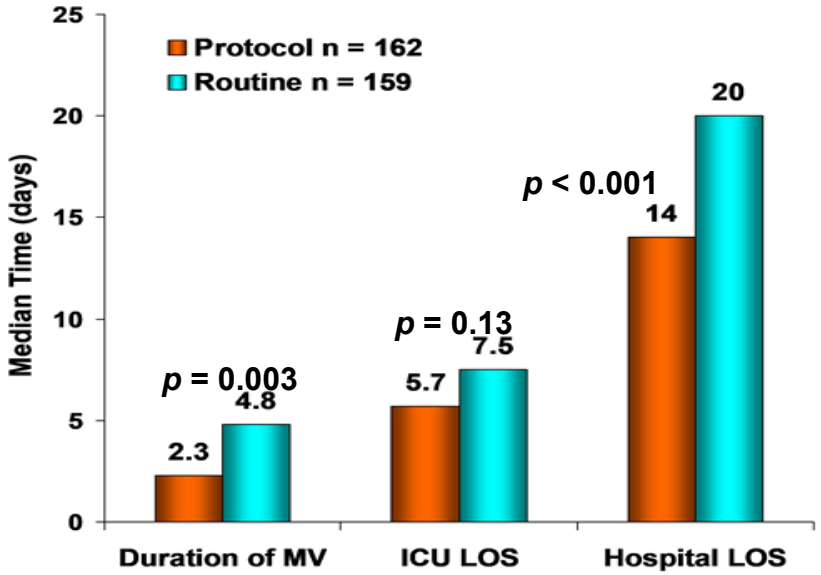
Key Concepts of Analgosedation

- Takes advantage of certain opioid properties
  - Reduces/eliminates sedative requirements and their associated ADRs
  - Improves sedation-agitation scores
  - Dyspnea & respiratory depressant properties
- May accentuate opioid-related ADRs
  - Gastric dysmotilty, 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.

Nursing-Implemented Sedation Protocol: Barnes Jewish Pilot United States



Significant patient characteristics/metrics/outcomes

	Protocol	Routine	P value
CIVS†	66 (40)	66 (42)	0.9
Duration CIVS, hrs*	3.5 ± 4	5.6 ± 6.4	0.003
Bolus†	118 (72)	127 (80)	0.14
Reintubated†	14 (8.6)	21 (13)	0.2
Trached†	10 (6.2)	21 (13.2)	0.04

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

CIVS; Continuous intravenous infusion sedation

Single center, prospective trial of 332 consecutive ICU patients requiring mechanical ventilation randomized to protocolized sedation (n = 162) or routine care (n = 159). Protocol used goal-directed sedation to target Ramsey with bolus requirements before initiation of continuous infusion and up titration of opioids and benzodiazepines.

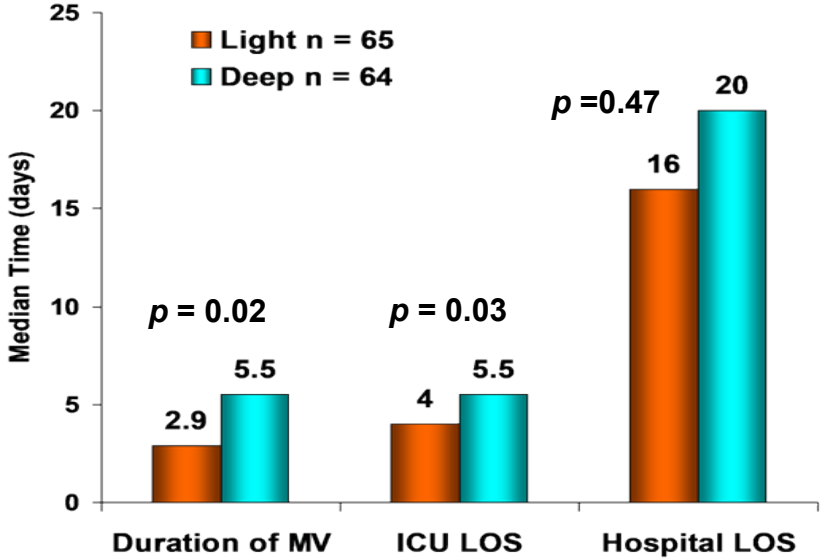
Brook AD, et al. *Crit Care Med*. 1999;27(12): 2609–15.

Protocol-based Pain First/Analgosedation

- The 2018 SCCM PADIS guidelines recommend
  - 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
  - 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.

Depth of Sedation and Clinical Outcomes and Mental Health After Critical Illness



Significant patient characteristics/metrics/outcomes

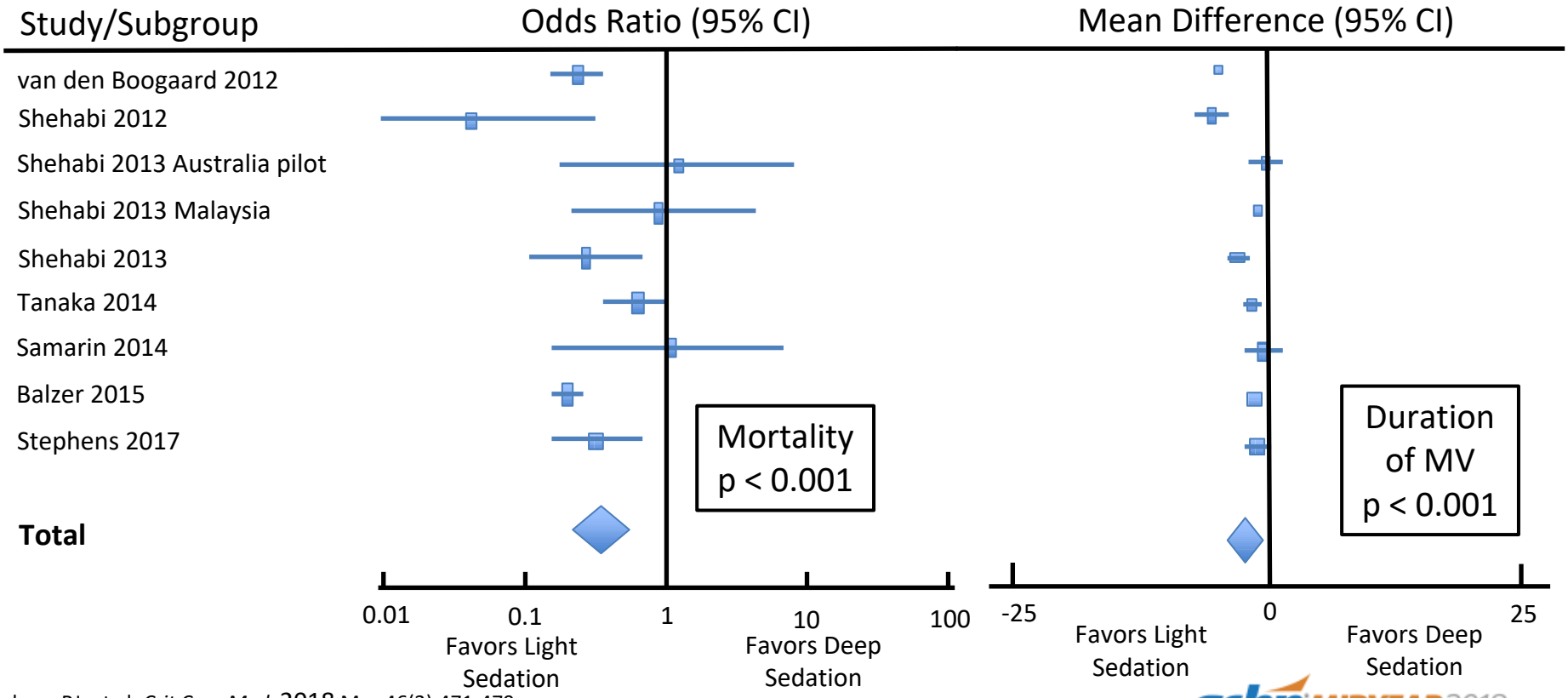
	Light	Deep	P value
PTSD score ICU discharge*	52	57	0.39
PTSD score 4 wk post ICU*	46	56	0.07

*Data presented in mean of Impact of Event Scale-Revised post-traumatic stress disorder (PTSD)

Single center, prospective, open label trial of 137 ICU patients requiring mechanical ventilation randomized to light (Ramsey 1-2) or deep (Ramsey 3-4) sedation at Geneva Hospital Switzerland. Extensive exclusion criteria, removing high-risk patients and those with baseline cognitive dysfunction.

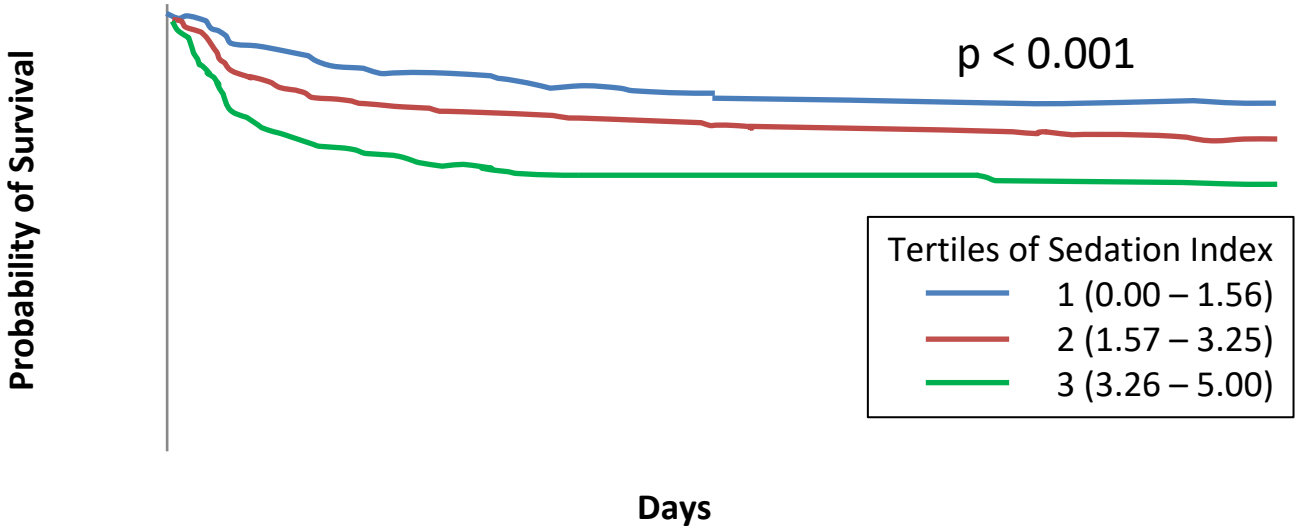
Treggiari MM, et al. *Crit Care Med*. 2009 Sep;37(9):2527-34.

2018 Light vs. Deep Sedation: Systematic Review and Meta-Analysis



Stephens RJ, et al. *Crit Care Med*. 2018 Mar;46(3):471-479.

Depth of Sedation and Long-Term Outcomes



Prospective observational trial of patients expected to be intubated for >24 hours in Australia, New Zealand, Malaysia, and Singapore. Depth of sedation in the first 48 hours predicted increased risk of death, delirium, and delayed time to extubation.

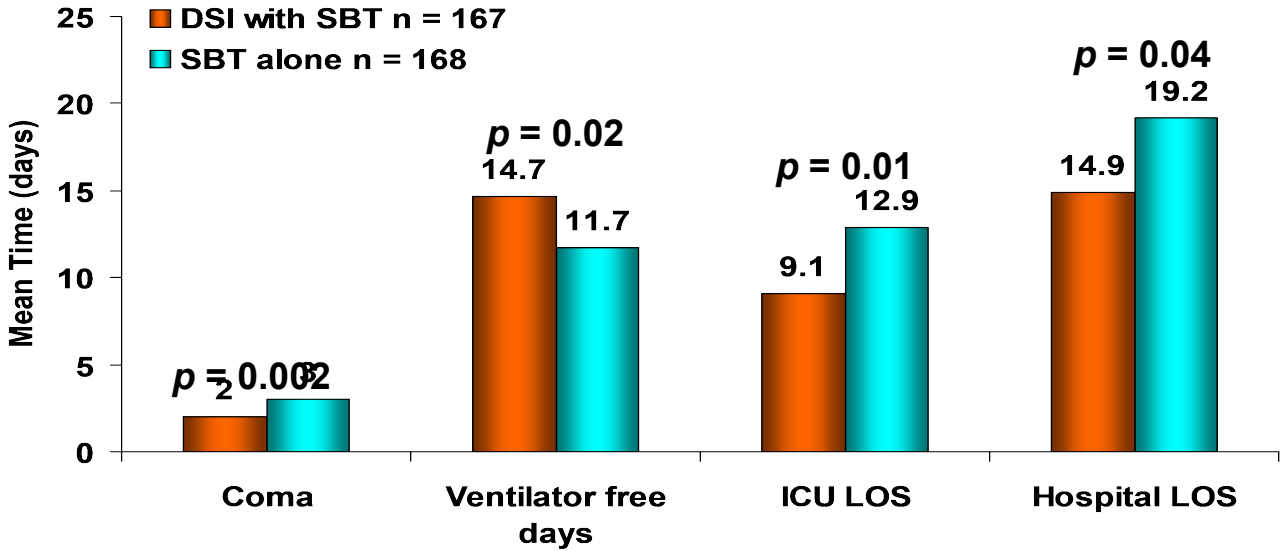
Shehabi Y, et al. *Crit Care Med*. 2018; 46: 850-859.

Light vs. Deep Sedation

- The 2018 SCCM PADIS guidelines suggest using light sedation (versus deep sedation) in critically ill, mechanically ventilated adults
  - Conditional recommendation, low quality of evidence

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

Paired Sedation and Ventilator Weaning Protocol: *ABC Trial*



Four center trial of 336 mechanically ventilated patients randomized to management with a daily sedative interruption (DSI) followed by a spontaneous breathing trial (SBT) or with sedation per usual care plus a daily SBT.

Girard TD, et al. *Lancet*. 2008 Jan 12;371(9607):126-34.

Daily Interruptions or Nursing-Protocolized Targeted Sedation

- The 2018 SCCM PADIS guidelines suggest
  - In critically ill intubated adults, daily sedative interruption (DSI) protocols and nursing- protocolized- (NP) targeted sedation can achieve and maintain a light level of sedation.
    - Ungraded

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

Case Question #3

TM is a 28-year-old male admitted to the medical ICU with a diagnosis of pancreatitis. Notable laboratory results include amylase 570 U/L, lipase 804 U/L, and triglycerides 726 mg/dL. After initial fluid resuscitation, he develop hypoxemic respiratory failure requiring intubation. He is currently sedated with propofol 50 mcg/kg/min and fentanyl 150 mcg/hr. His Riker score is 2 and CPOT is 1. Despite mechanical ventilation, he remains hypoxemic with a P:F ratio of 90 and the decision is made to initiate an atracurium infusion. Which of the following would be the most appropriate recommendation for management of TM's pain and sedation prior to initiation of atracurium?

A. Increase propofol to 60 mcg/kg/min and titrate to goal Riker score 1
B. Add midazolam 4 mg IV x1, then 1-10 mg/hr and titrate to goal Riker score 1
C. Discontinue propofol and initiate midazolam 4 mg IV x1, then 1-10 mg/hr and titrate to goal Riker score 1
D. Discontinue fentanyl 150 mcg/hour and initiate hydromorphone 2mg IV x1, then 0.5-4 mg/hr and titrate to goal Riker score 1

Separation of Cardiac Surgery vs. Non-Cardiac Surgery

PICO (Cardiac)	
P	Critically ill adult patients in a cardiac surgery ICU
I	Propofol
C	Benzodiazepines

O	• Time to light sedation
	  • 30 minutes
	• Duration of mechanical ventilation
	  • 1 hour
	• ICU Length of stay
	• Adverse events

PICO (Non-cardiac)	
P	Critically ill adult patients in a non-cardiac surgery ICU
I	Propofol or dexmedetomidine
C	Benzodiazepines

O	• Time to light sedation
	  • 4 hours
	• Duration of mechanical ventilation
	  • 8-12 hours
	• ICU Length of stay
	• Adverse events

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

Propofol Versus Benzodiazepines in Cardiac Surgery

- The 2018 SCCM PADIS guidelines suggest using propofol over a benzodiazepine for sedation in mechanically ventilated, post-cardiac surgery patients
  - Conditional recommendation, low quality of evidence

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

Choice of Sedative: Non-Cardiac Surgery ICUs

- General takeaway points from MENDS, SEDCOM, MIDEX, PRODEX studies:
  - Benzodiazepine sedation strategies may:
    - Increase likelihood of coma
    - Increase duration of mechanical ventilation
    - Increase percentage of patients with delirium at specific time points
  - Benzodiazepine sedation strategies have not been shown to:
    - Increase ICU length of stay
    - Increase overall incidence of delirium
    - Significantly change time spent in goal sedation range
  - No significant differences between propofol and dexmedetomidine:
    - Time spent in goal sedation range
    - Duration of mechanical ventilation
    - Hospital and ICU length of stay
    - Mortality

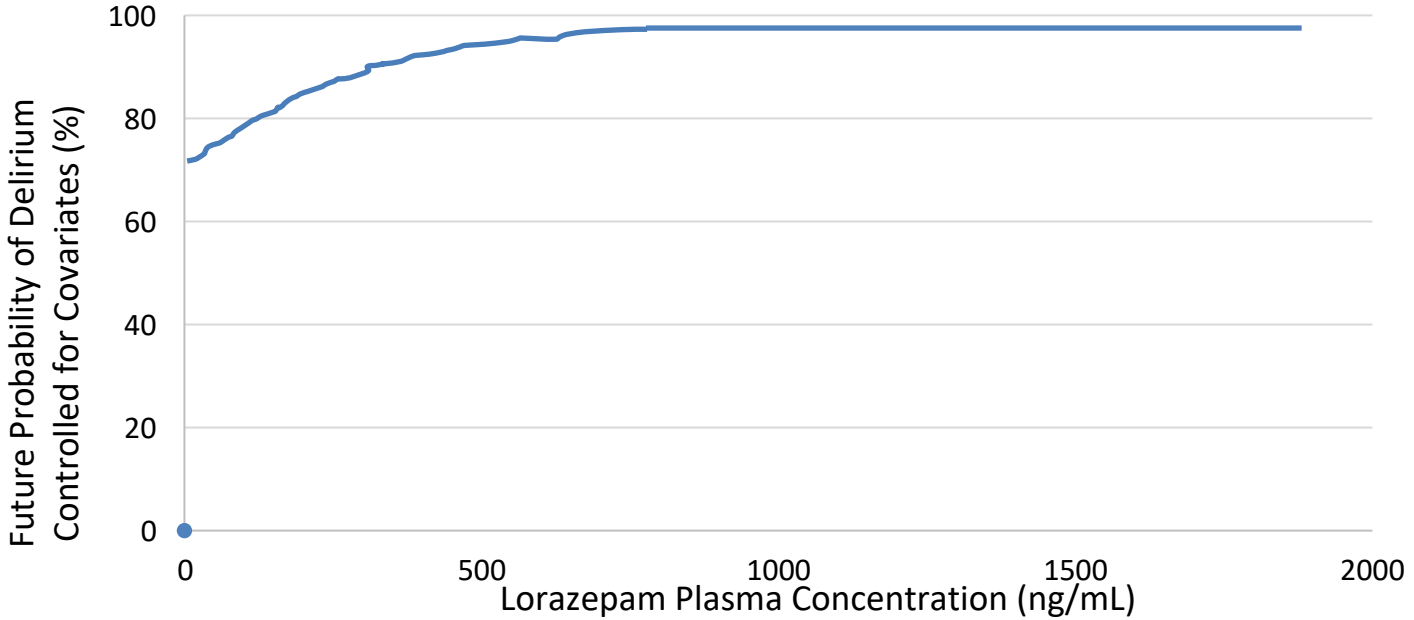
Pandharipande PP, et al. *JAMA.* 2007;298:2644-2653.
Riker RR, et al. *JAMA*. 2009 Feb 4;301(5):489-99.
Jakob SM, et al. JAMA. 2012 Mar 21;307(11):1151-60.

Choice of Sedative in Non-Cardiac Surgery ICUs

- The 2018 SCCM PADIS guidelines suggest using either propofol or dexmedetomidine over benzodiazepines for sedation in critically ill mechanically ventilated patients
  - Conditional recommendation, low quality of evidence

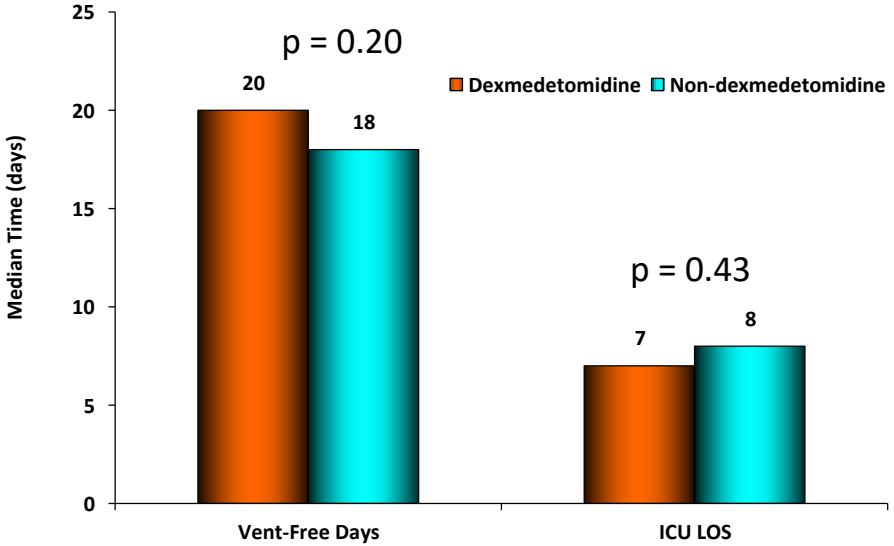
Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Lorazepam Plasma Concentration Associated with Delirium



Stollings JL, et al. *Ann Pharmacother* 2018;52(6):513-21.

Dexmedetomidine for Sedation in Patients with Sepsis



Significant patient characteristics/metrics/outcomes			
	Dex	Non-Dex	P value
28-day mortality*	19 (19)	28 (28)	0.14
Well-controlled sedation†	17-58	20-39	0.01
Delirium- and coma-free days	NR	NR	0.17

*n (%)

†Range, %

Multicenter (8 ICUs in Japan), open-label randomized trial comparing dexmedetomidine versus non-dexmedetomidine sedation in patients with sepsis.

Kawazoe Y, et al. *JAMA*. 2017; 317(13): 1321-1328.

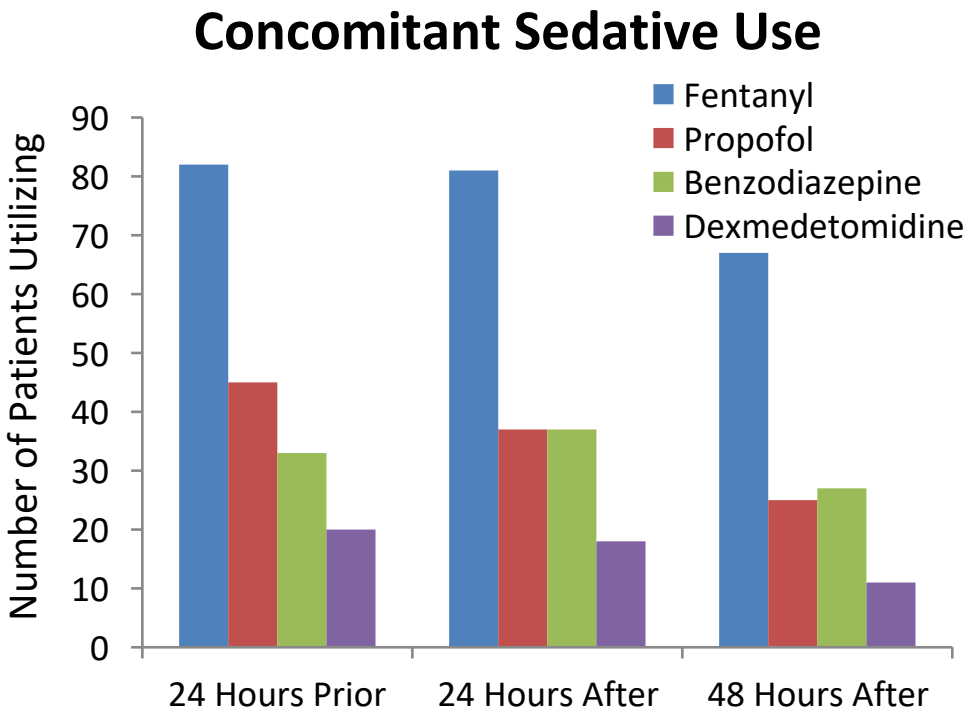
Benzodiazepines: Limited Use in 2018 but Still Useful in Several Populations

- Useful for
  - Deep sedation and when amnesia is the goal (i.e. neuromuscular blockade)
  - Sedation in the setting of hemodynamic instability
  - Ethanol withdrawal (with or without other agents)
  - Anxiety/agitation with as needed bolus
  - Neurologic indications
    - Seizures
    - Elevated intracranial pressure

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.

Antipsychotics as Sedatives

	Quetiapine (n = 18)	Placebo (n = 18)	*p - value*
Sedative			
Midazolam equivalents per day, mg	5.3 (0 – 42)	26.5 (0.3 – 74)	0.32
Days when ≥1 dose given	1 (0 – 4)	4 (1 – 9)	0.09
Fentanyl			
Amount per day, mcg	0 (0 – 65)	170 (14 – 1089)	0.02
Days when ≥1 dose given	0 (0 – 3)	4 (1 – 9)	0.03

Prospective, randomized, double-blind placebo-controlled trial comparing quetiapine and placebo for treatment of delirium

Devlin JW, et al. *Crit Care Med.* 2010; 38: 419-427.

Antipsychotics as Sedatives

	Haloperidol (n = 71)	Placebo (n = 70)	*p - value*
Fentanyl			
Total dose, mg	8.62 (10.93)	14.24 (22.29)	0.06
Number of days	4.48 (3.40-5.56)	5.50 (4.11-6.89)	0.25
Propofol			
Total dose, mg	5308 (7663)	8170 (10,343)	0.06
Number of days	3.89 (4.35)	5.19 (4.38)	0.08
Midazolam			
Total dose, mg	8.37 (28.92)	48.74 (195.02)	0.09
Number of days	0.35 (0.81)	0.76 (2.16)	0.14
Data reported as mean (SD) or median (IQR)			

Prospective, randomized, double-blind placebo-controlled trial comparing the effect haloperidol with placebo on the duration of delirium or coma

Page VJ, et al. *Lancet Respir Med.* 2013;1:515-23.

Antipsychotics as Sedatives

Al-Qadheeb et al:

- Randomized, double-blind, placebo-controlled trial of haloperidol versus placebo to prevent conversion of subsyndromal delirium to delirium
  - No significant difference in days where a continuous sedative was administered
  - Haloperidol decreased the number of hours per study day spent agitated (0 vs. 2, p = 0.008)

Al-Qadheeb NS, et al. *Crit Care Med*. 2016; 44: 583-591.

ashp MIDYEAR 2018
Clinical Meeting & Exhibition

Updates in the Management of Pain, Agitation, and Delirium in the ICU

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Case Question #4

CS is a 71-year-old female in the cardiac surgery ICU following coronary artery bypass surgery. Her preoperative American Society of Anesthesiology (ASA) score was 4. She is on as needed fentanyl boluses and a propofol infusion with visual analog scale of 1, RASS of -1, and an Intensive Care Delirium Screening Checklist score of 5. She has received several blood transfusions for a hemoglobin of less than 9.5 g/dL of in the ICU. Per the 2018 SCCM PADIS guidelines for adult critically ill patients, which modifiable risk factors for delirium does CS have?

A. Propofol infusion
B. Advanced age
C. Blood transfusions
D. Preoperative ASA score of 4

Pathophysiology of Delirium in Critically Ill Patients

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

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

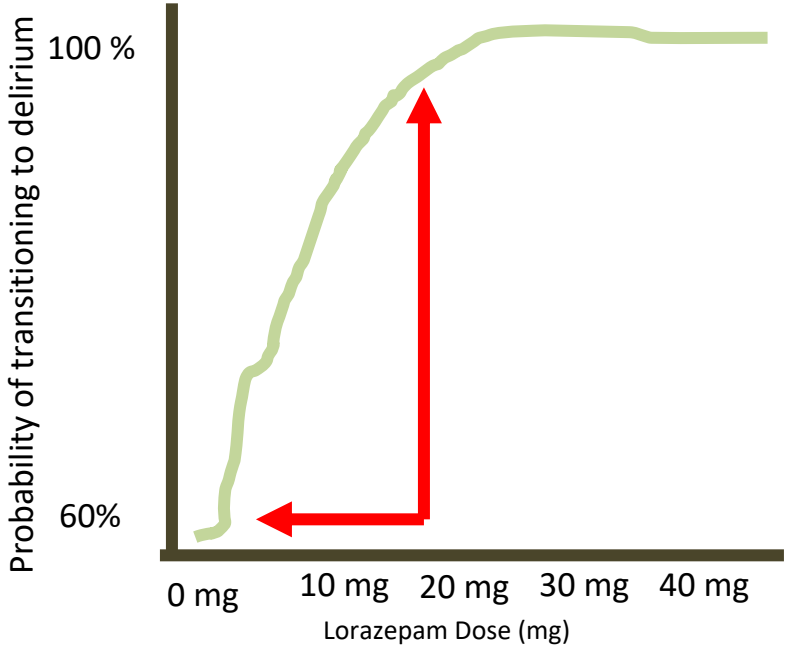
Bongard FS, Sue DY (Eds): *Current Critical Care Diagnosis & Treatment*. 2nd edition. 2002.

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

Zaal IJ et al. *Crit Care Med.* 2015 Jan;43(1):40-7.

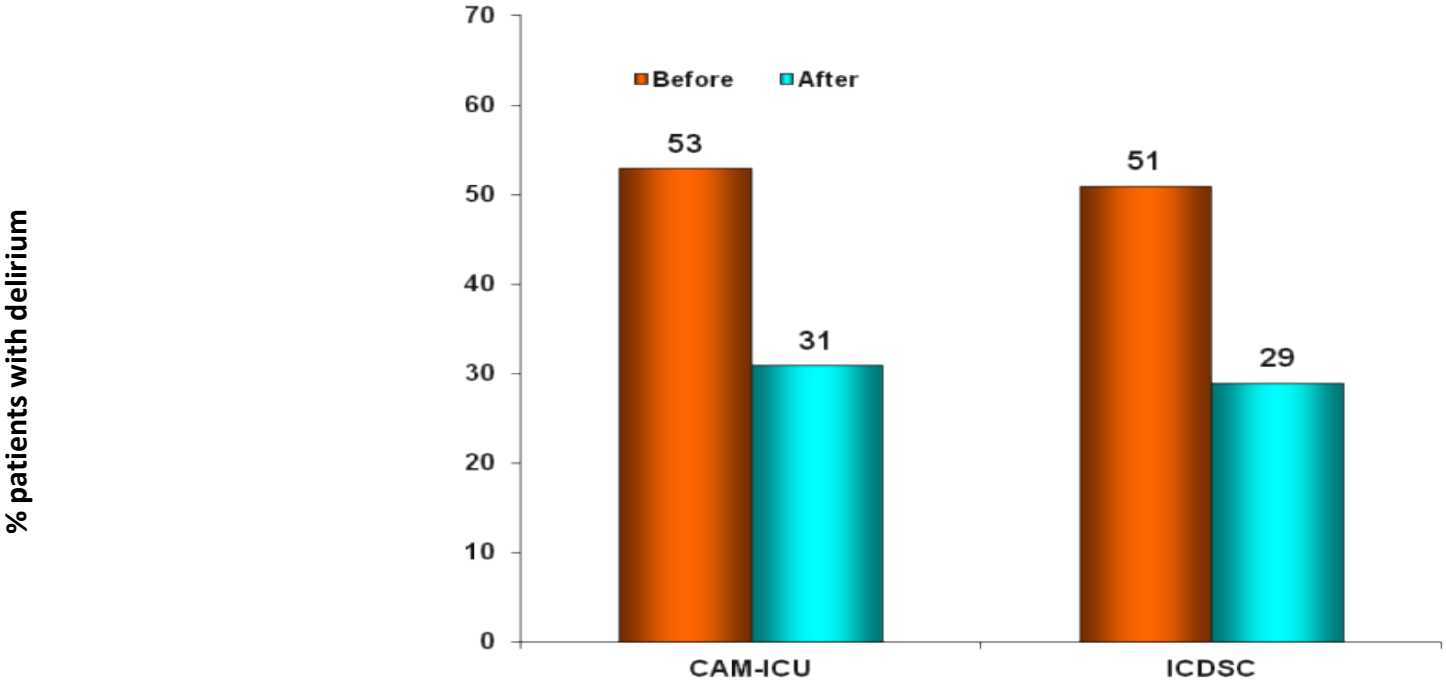
Probability of Transitioning to Delirium in Mechanically Ventilated Patients



Pandharipande P, et al. *Anesthesiology*. 2006 Jan;104(1):21-6.

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 Intensive Care Delirium Screening Checklist (ICDSC) and Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) during Spontaneous Awakening Trial (SAT).

Haenggi M, et al. *Intensive Care Med*. 2013 Dec;39(12):2171-9.

Sedative Plasma Concentration and Delirium

- Prospective cohort of the MENDS trial
- Assessed the plasma concentrations of selected sedative and the risk of next-day delirium
  - Lorazepam plasma concentrations
    - Associated with a nonlinear increased risk of delirium
  - Dexmedetomidine plasma concentrations
    - Associated with neither an increased nor decreased risk of delirium
- Fentanyl
  - DOSE – was nonlinearly associated with the risk of delirium up to 2500 mcg/day then the risk fell
    - Reminder the median fentanyl dose
      - 575 mcg/day dexmedetomidine group
      - 150 mcg/day lorazepam group
- Interpretation:
      - Exposure to sedatives capable of deeply sedating, likely leads to increase delirium

Stollings JL, et al. *Ann Pharmacother*. 2018 Jun;52(6):513-521.

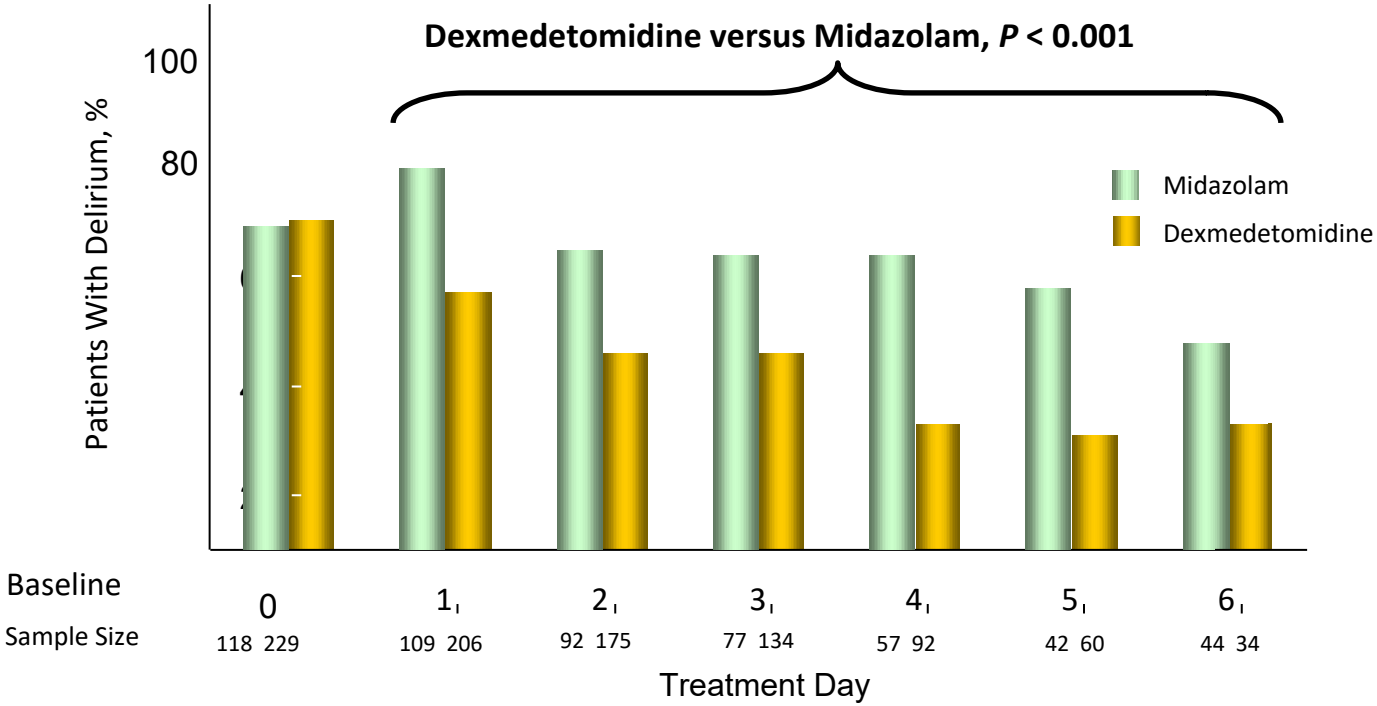
Dexmedetomidine vs. Lorazepam: *MENDS TRIAL*

	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

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

Dexmedetomidine vs. Midazolam: *SEDCOM TRIAL*



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

Dexmedetomidine vs. Midazolam: *SEDCOM TRIAL*

	Dexmedetomidine (n = 244)	Midazolam (n = 122)	*p* Value
Time in target sedation range*	77.3	75.1	*p* = 0.18
Mean Dose	0.83 mg/kg/hr	0.056 mg/kg/hr	
Extubation time, days**	3.7 (3.1-4.0)	5.6 (4.6-5.9)	*p* = 0.01
ICU LOS, days**	5.9 (5.7-7.0)	7.6 (6.7-8.6)	*p* = 0.24

***Value expressed as mean %**

**** Value expressed as median (IQR)**

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

Dexmedetomidine vs. Propofol/Midazolam for Long-term Sedation in ICU (PRODEX MIDEX Pilot Analysis)

	Dexmedetomidine (n = 41)	Propofol/Midazolam (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, days*	6.6 (2.2–20.7)	6.8 (2.6–30.8)	*p* = 0.28
ICU LOS from randomization, days*	5.5 (1.7–19.5)	5.7 (1.7–29.0)	*p* = 0.82
ICU LOS MICU, days*	5.0 (1.7 –19.5)	4.9 (1.8 –29.0)	*p* = 0.43
ICU LOS SICU, days*	5.7 (2.0 –16.7)	5.9 (1.7–16.8)	*p* = 0.06

***Value expressed as median (IQR)**

Trial stopped early

Ruokonen E, et al. *Intensive Care Med*. 2009 Feb;35(2):282-90.

Evaluation of Unable-to-Assess CAM-ICU Documentation

- Convenience sample of 3 months in MICU and SICU at a single center
  - 116 CAM-ICU documented as *unable to assess (UTA)*
  - 103 CAM-ICU documented as *positive*
  - 220 CAM-ICU documented as *negative*
- UTA 36 % of all assessments
  - Inappropriate UTA documentations ~30%
- Rates of assessments inappropriately documented as “UTA” may be higher than previously reported in literature

Terry KJ, Anger KE, Szumita PM. *J Intensive Care*. 2015 Nov 26;3:52.

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
- Blinded continuous infusion
- No antipsychotic use data

- 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

Jakob SM, et al. *JAMA.* 2012 Mar 21;307(11):1151-60.

Drug/Dose Minimization Strategies = Outcomes

1. Assessment, Assessment, Assessment; and discussion of assessment
2. Awake and alert (RASS 0)
3. Ventilator changes
4. Symptom-triggered bolus only
5. Sedation Holiday (if in the unfortunate situation of being on continuous infusion)
6. Analagosedation or no sedation
7. Patient-specific pharmacotherapy
8. Rotation of medication (avoid accumulation)

Six-Month Outcomes after Restrictive or Liberal Transfusion for Cardiac Surgery- TRICS III Trial

- Multicenter open-label, non-inferiority trial to compare restrictive with liberal strategies in adult cardiac surgery patients
  - 4664 patients
    - Restrictive: transfuse for < 7.5 g/dL
    - Liberal: transfuse for < 9.5 g/dL
  - No significant difference in any outcomes

Mazer CD, et al. *N Engl J Med*. 2018 Aug 26. doi: 10.1056/NEJMoa1808561. Epub ahead of print

2018 SCCM PADIS Guidelines: Delirium

- Modifiable risk factors (ungraded)
  - Benzodiazepine use
  - Blood transfusion
- Non-modifiable risk factors (ungraded)
  - Age, dementia, prior coma, pre-ICU emergency surgery or trauma, increasing Acute Physiology and Chronic Health Evaluation (APACHE) score and American Society of Anesthesiology (ASA) score
- Delirium may be able to be predicted through modeling (ungraded)
- Critically ill adults should be regularly assessed for delirium (good practice statement)
- Level of arousal may influence delirium (ungraded)

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

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 (adherence to local guideline)
  - Assessment tool
  - Surgical/medical
  - Type of surgery
  - Study design
  - Metric
  - Mechanical ventilation

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.

Case Question #5

Per the 2018 SCCM PADIS guidelines for adult critically ill patients, which is an outcome strongly associated with ICU delirium?

A. Mortality
B. Increased ICU Length of Stay
C. Post-Traumatic Stress Disorder
D. Cognitive impairment at 3 and 12 months

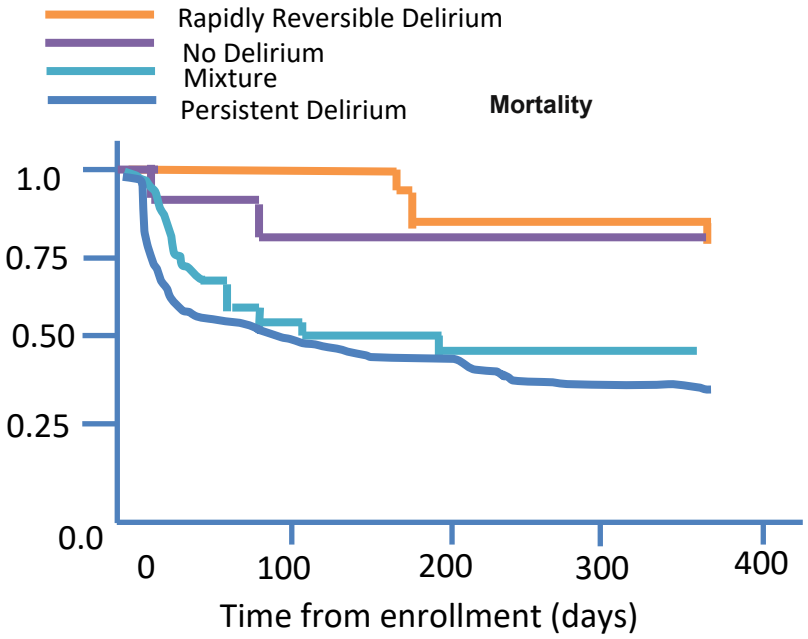
Outcomes Associated with ICU Delirium

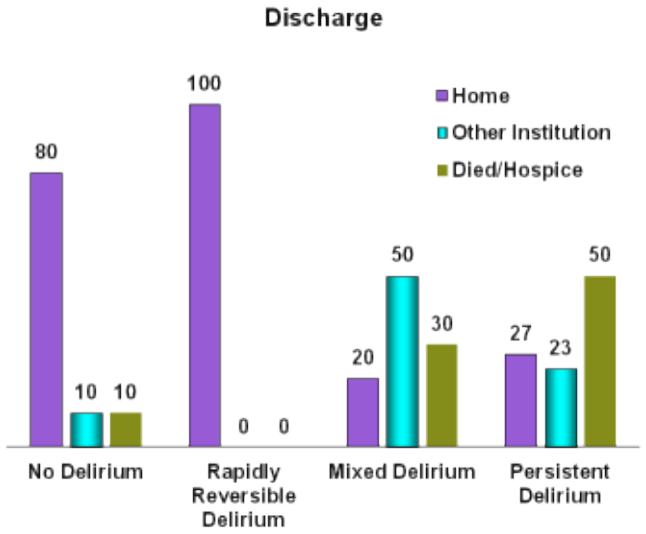
- During ICU and hospitalization
  - Increased mortality
  - Increased re-intubation rates
  - Increased length of stay
  - Higher cost of care
  - Increased need for tracheotomy
  - Increased restraint use

- Post hospital discharge
  - Increased mortality
  - Decreased functional status at 6 months
  - Increased risk of long-term cognitive impairment
  - Increased risk of dementia
  - Increased reliance on chronic care facilities
- Key Term – "Associated" does not imply causation
- Is medication-related delirium the same as 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.
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.
Dolan MM et al. *J Gerontol A Biol Sci Med.* 2000 Sep;55(9):M527-34.

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.

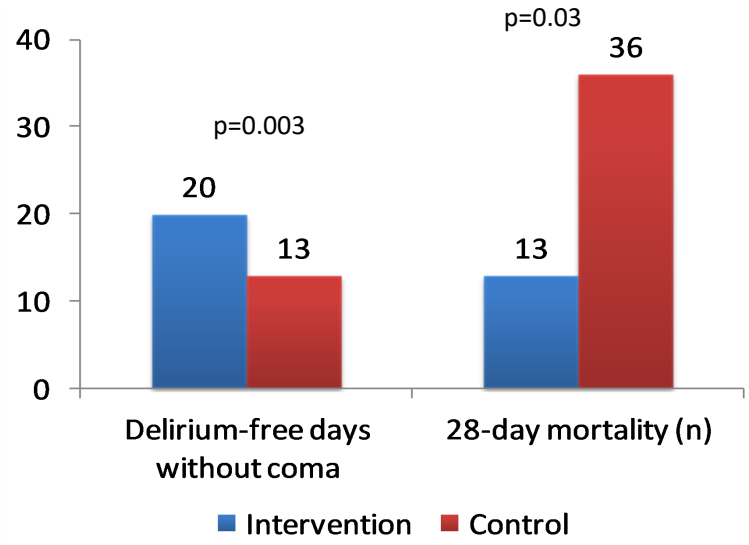
Patel SB, et al. *Am J Respir Crit Care Med.* 2014;189(6):658-665.

2018 SCCM PADIS Guidelines: Delirium

- Delirium is associated with (ungraded)
  - Strongly: Cognitive impairment at 3 and 12 months
  - MAY be: Longer ICU length of stay
- Delirium is NOT associated with (ungraded)
  - Post-traumatic stress disorder or post-ICU distress
- Delirium is NOT consistently associated with (ungraded)
  - ICU length of stay
  - Discharge disposition to place other than home
  - Depression
  - Functionality dependence
  - Mortality
- Rapidly reversible delirium is associated with outcomes that are similar to patients who never experience delirium (Ungraded)

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

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

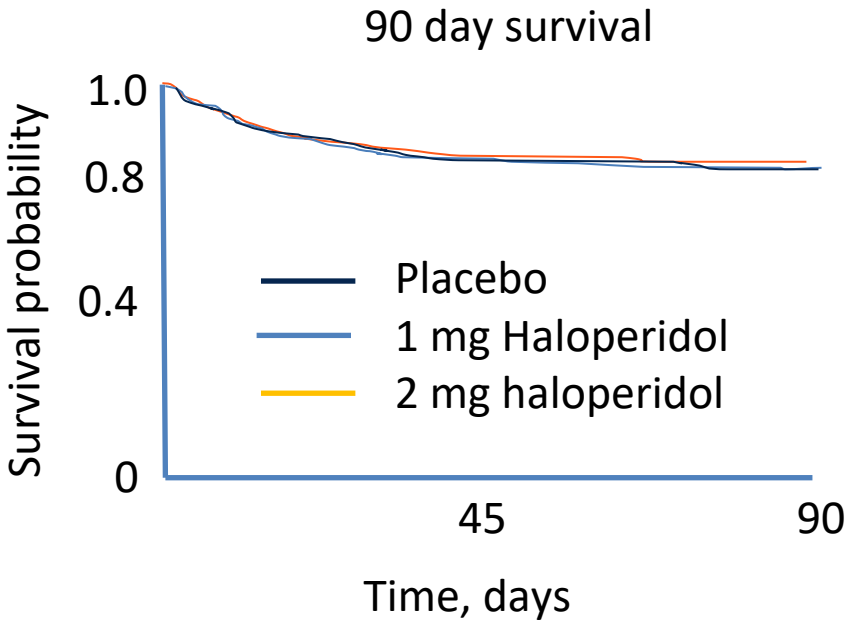
Data presented in median

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.

Van den Boogaard M, et al. *Critical Care*. 2013 Jan; 17(1):R9.

Haloperidol Prophylaxis Among ICU Adults with High Risk of Delirium

- Multicenter RCT on haloperidol 1 mg, 2 mg, or placebo
- 1789 patients
- No significant differences in:
  - Mortality
  - delirium incidence
  - delirium-free and coma-free days
  - duration of mechanical ventilation
  - duration of ICU length of stay
  - hospital length of stay



Van den Boogaard M. et al. *JAMA.* 2018 Feb 20;319(7):680-690.

Preventing ICU Subsyndromal Delirium Conversion to Delirium with Low-dose IV Haloperidol

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

Al-Qadheeb NS, et al. *Crit Care Med.* 2016 Mar;44(3):583-91.

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

- Randomized, double blind, placebo- controlled RCT at 2 medical centers 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

Su X, et al. *Lancet.* 2016;388:1893-902.

2018 SCCM PADIS Guidelines: Delirium Recommendations

- Medications should not be used to prevent delirium
  - Haloperidol, atypical antipsychotics, dexmedetomidine, statins, ketamine
  - Conditional recommendation, vey low to low quality of evidence

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

Preventive Strategies

- Largely nonpharmacologic and involves interprofessional 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;2015:635737.
http://www.nice.org.uk/guidance/cg103/chapter/1-recommendation (accessed 5 September 2016).

Case Question #6

JD is an 82-year-old woman in the cardiac surgery intensive care unit who is mechanically ventilated status post coronary artery bypass graft surgery. She is receiving an intravenous (IV) propofol infusion at 20 mcg/kg/min.

- Critical-Care Pain Observation Tool (CPOT) score is 2,
- Richmond Agitation and Sedation Scale (RASS) score is +2
- Confusion Assessment Method for the ICU (CAM-ICU) is positive.
- She is ready for extubation from a pulmonary point of view; however, her agitation precludes extubation.

Based on her assessment scores, and the 2018 SCCM PADIS guidelines, which of the following would be the most reasonable addition?

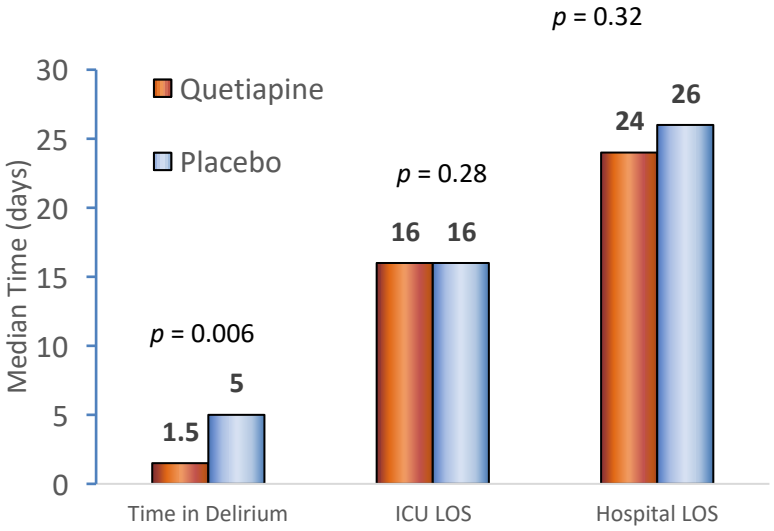
A. Dexmedetomidine IV infusion
B. Fentanyl IV infusion with a goal CPOT score of 0
C. Quetiapine enterally every 12 hours
D. Haloperidol IV as needed for delirium

Pharmacologic Agent to Treat Delirium in all Critically Ill Adults with Delirium

PICO	
P	Critically ill adult patients in an ICU with delirium
I	Pharmacologic agent
C	No use of pharmacologic agent
O	• Delirium duration • Duration of mechanical ventilation • ICU length of stay • Mortality

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

Quetiapine for the Treatment of Delirium in Mixed ICU Patients



	Quetiapine	Placebo	P value
SAS ≥5, hr*	6	36	0.02
SAS ≤2, hr*	0	0	0.54
Haloperidol mg/day*	1.9	4.3	0.26
Midazolam equiva-lents mg/day*	5.3	26	0.32

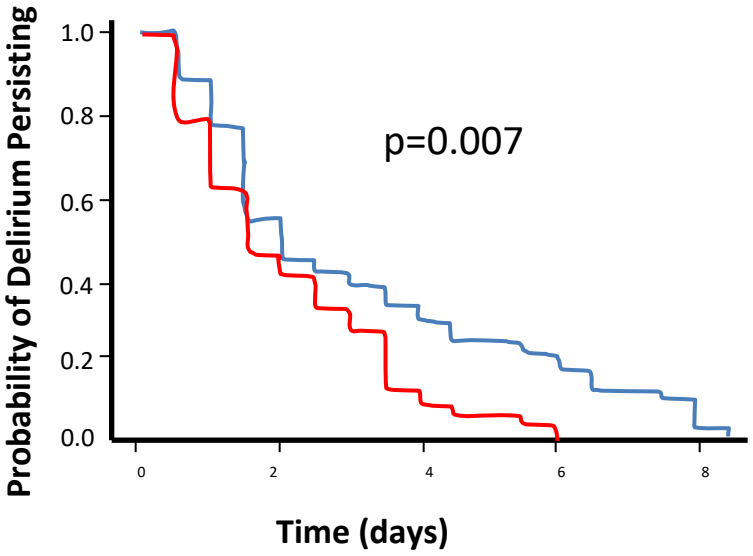
*Data presented in median

†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 twice daily (titrated up to 200mg twice daily) or placebo with open label IV haloperidol in both groups. 258 screened, 36 enrolled.

Devlin JW, et al. *Crit Care Med*. 2010 Feb;38(2):1-9.

Quetiapine for the Treatment of Hypoactive Delirium



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

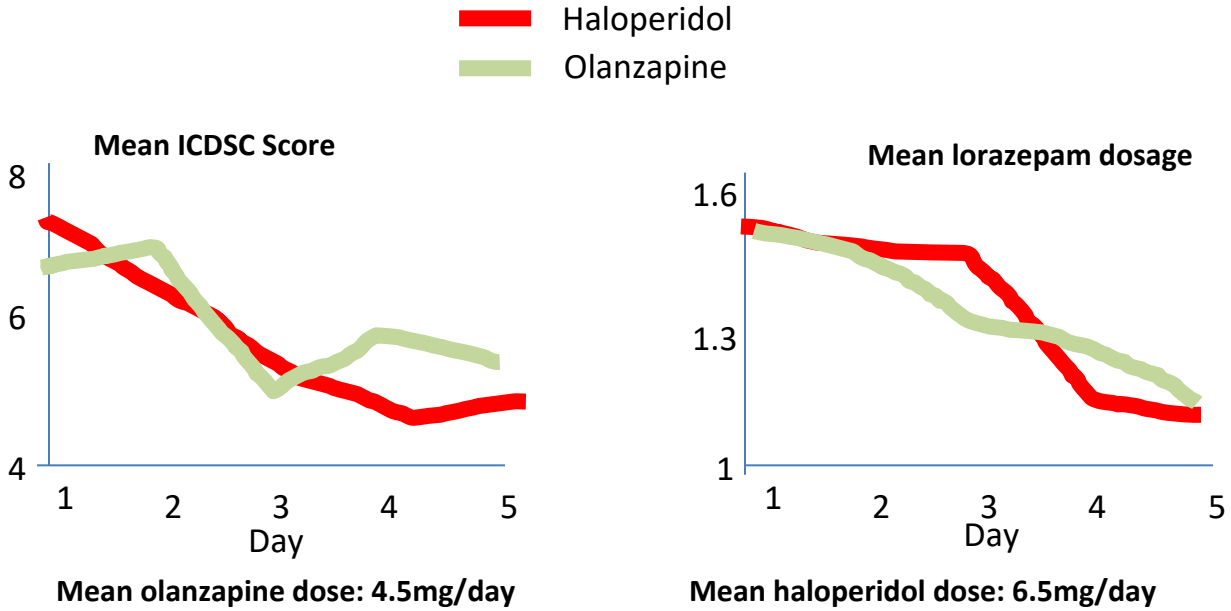
*Data presented in median AP: antipsychotic

†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

Michaud CJ, et al. *Pharmacotherapy.* 2015 Aug;35(8):731-9.

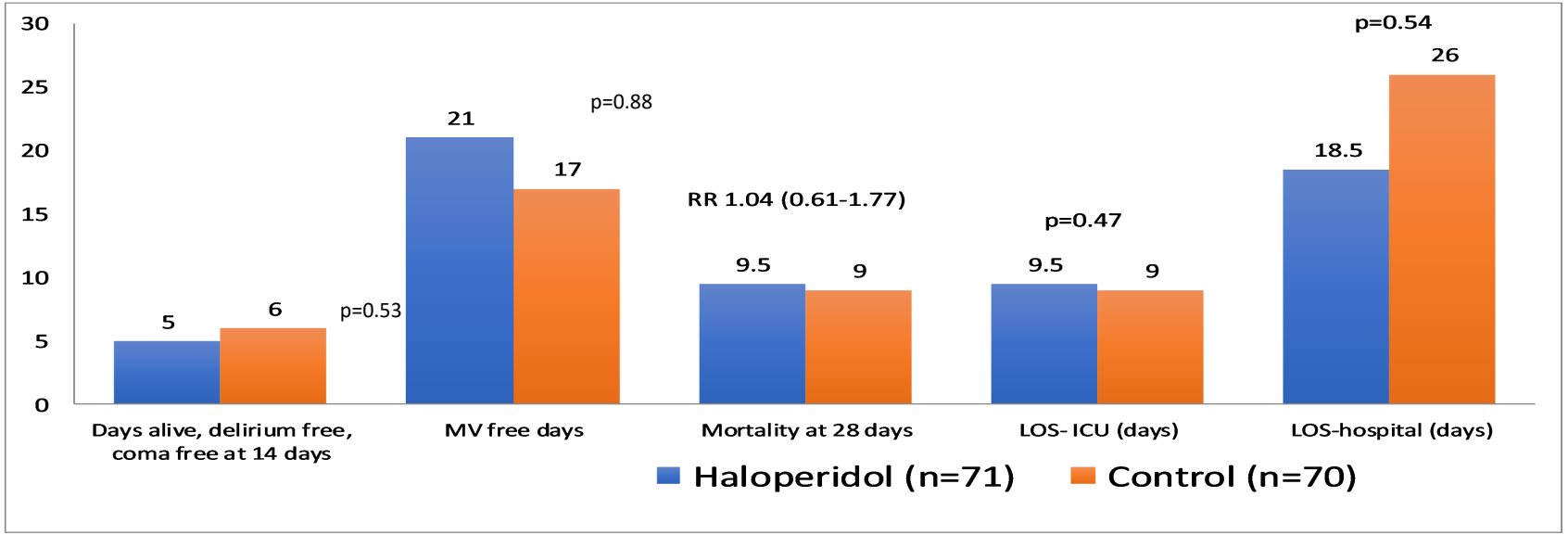
Olanzapine vs. Haloperidol for the Treatment of Delirium in SICU Patients



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 daily or haloperidol 2.5–5 mg every 8 hr "titrated per response," with rescue haloperidol. Patients > 60 yr received a lower initial dosage (haloperidol 0.5–1 mg, or olanzapine 2.5 mg).

Skrobik YK, et al. *Intensive Care Med*. 2004;30:444–9.

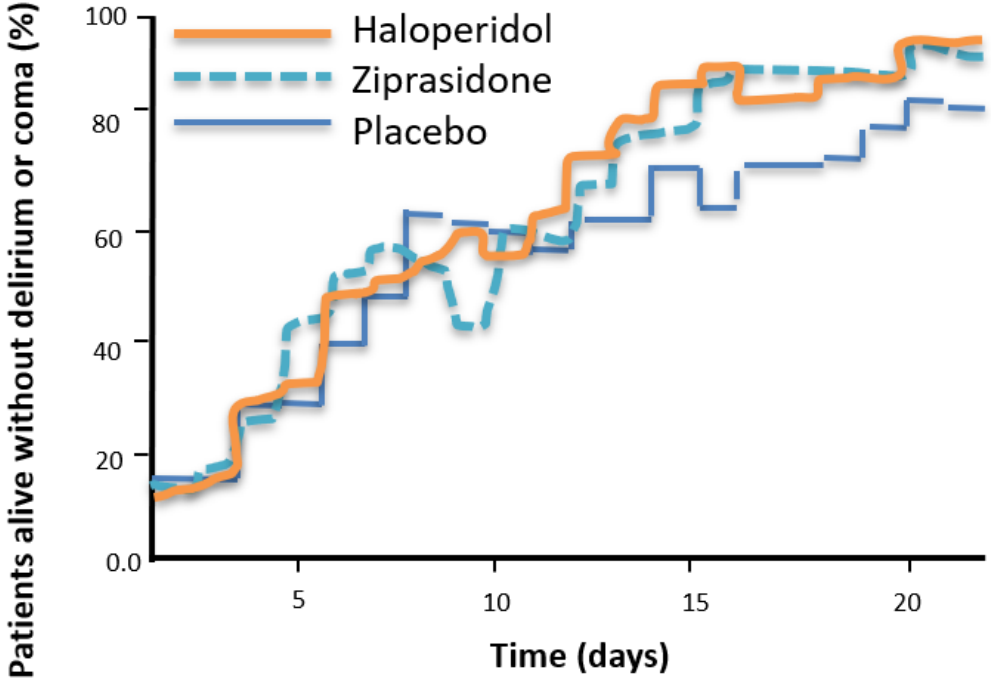
HOPE ICU- Effect of Early Treatment with IV Haloperidol on Duration of Delirium



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 every 8 hr within 72 hr of ICU admission regardless of their delirium or coma status.

Page V, et al. *Lancet Respir Med.* 2013 Aug; 1:515-523.

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 was the primary endpoint.

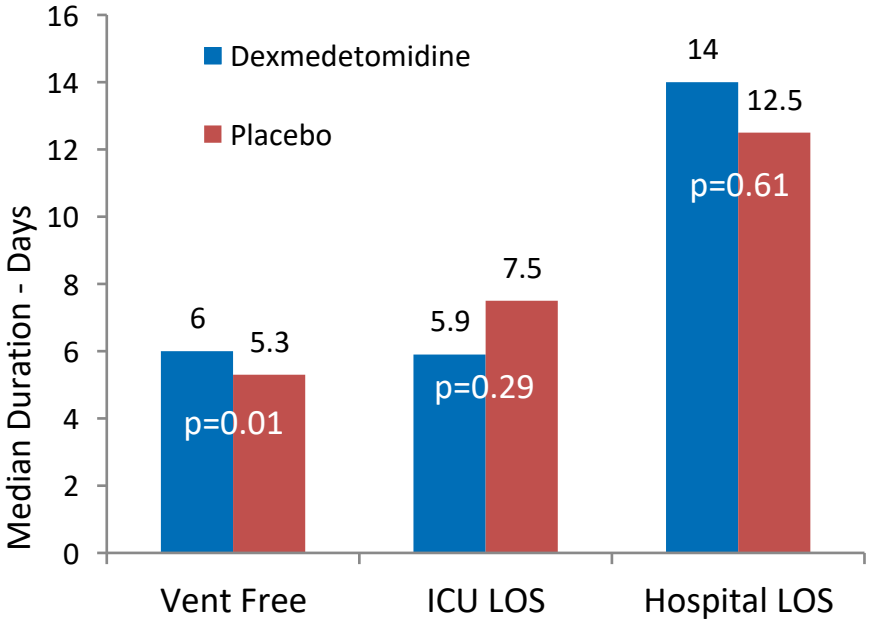
Girard TD, et al. *Crit Care Med*. 2010 Feb;38(2):428-37.

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

Carrasco G, et al. *Crit Care Med*. 2016 Jul;44(7):1295-306.

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.

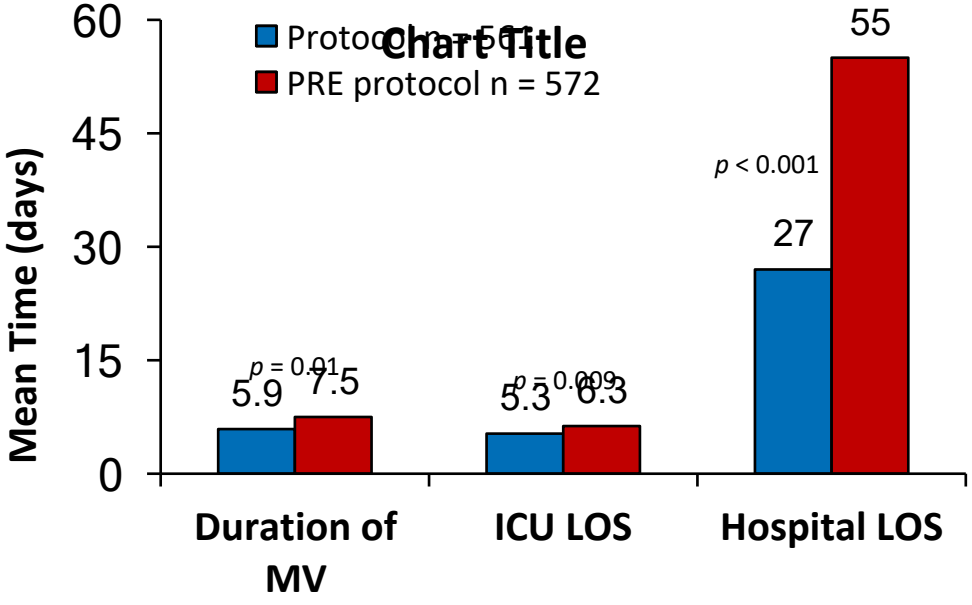
Reade MC, et al. *JAMA.* 2016 Apr 12;315(14):1460-8.

2018 SCCM PADIS Guidelines: Delirium

- Not routinely using haloperidol, an atypical antipsychotic, or HMG-CoA reductase inhibitor (i.e. statin) to treat delirium
  - Conditional recommendation, low quality of evidence
- Medications should not be used to treat subsyndromal delirium
  - Conditional recommendation, vey low to low quality of evidence
- Utilization of dexmedetomidine for the treatment of agitated delirium for mechanically vented patients where agitation is precluding weaning/extubation
  - Conditional recommendation, low quality of evidence
- Not using bright light therapy to reduce delirium
  - Conditional recommendation, low quality of evidence

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

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 ± 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).

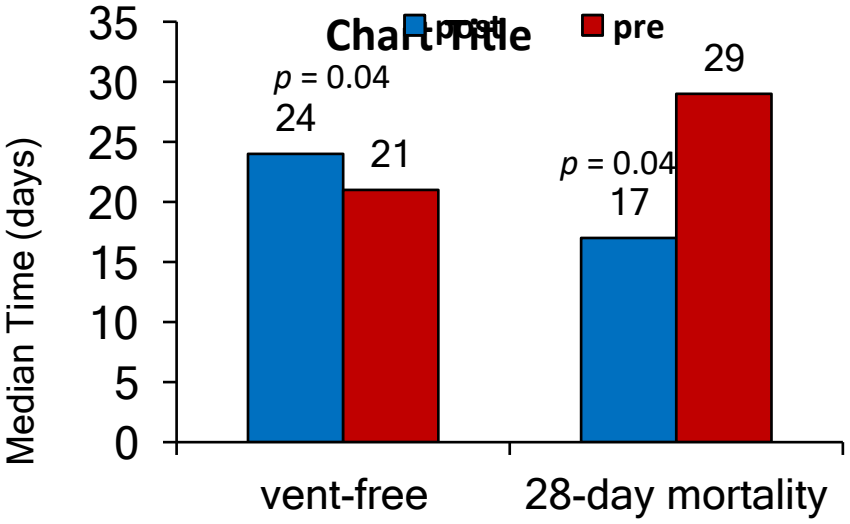
Skrobik Y et al. *Anesth Analg*. 2010 Aug; 111(2):451-63.

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.

Prospective pre-post ABCDE bundle implementation



Important patient metrics/outcomes			
	Protocol	Routine	P value
Delirium anytime; n(%)	73 (48.7)	91 (62.3)	0.02
ICU days delirious; median(IQR)	33.3(18.8-50)	50(30-64.3)	0.003
Out of bed in ICU; n(%)	99 (66.0)	70(48)	0.002
Unplanned extubation; n(%)	7 (7.5)	7(7.5)	0.98
Re-intubation; n(%)	11 (11.7)	16 (17.2)	0.28

Single center, prospective, pre-post ABCDE bundle implementation study at Nebraska Medical Center. 296 ICU patients (medical/surgical) , pre (n = 146) Feb-Oct 2011 and post (n = 150) Oct 2011 to April 2012 .

Balas MC, et al. *Crit Care Med*. 2014 May;42(5):1024-36.

Prevention/Management of Delirium

- Nonpharmacologic
  - Correct any known precipitating cause (toxic metabolic)
  - Early mobilization
  - Use of sedation scales
  - Use of scheduled pain management protocols and pain scales
  - Reorientation of patients
  - Timely removal of catheters and restraints
  - Early correction of dehydration
  - Minimizing unnecessary stimuli
  - Adjusting ventilator settings

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;2015:635737.
http://www.nice.org.uk/guidance/cg103/chapter/1-recommendations

2018 SCCM PADIS Guidelines: Delirium Recommendations

- Suggest using a multicomponent, nonpharmacologic intervention that is focused on (but not limited to) reducing modifiable risk factors for delirium, improving cognition, and optimizing sleep, mobility, hearing, and vision in critically ill adults
  - conditional recommendation, low quality of evidence

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

Need more robust data on the following questions (and more)

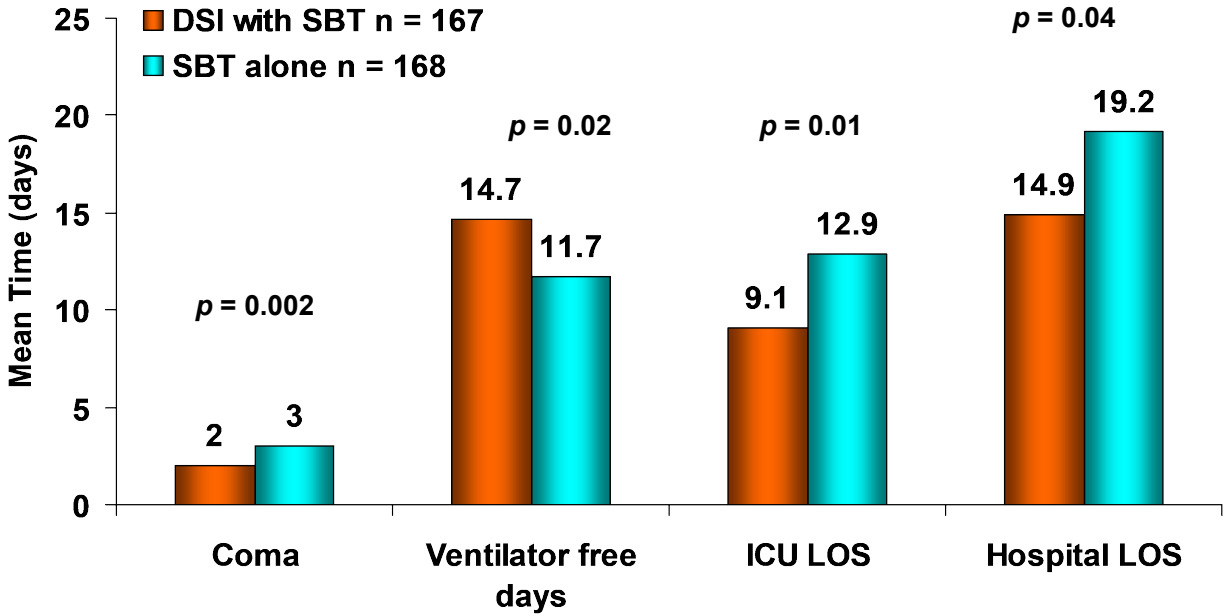
- Will certain patient populations benefit from different strategies?
  - Dexmedetomidine in fast-track cardiac surgery
- Is ketamine-based sedation associated with less delirium?
- Is analgesia-based sedation associated with less delirium?
- Should ABCDEF Bundle implementation be considered best practice?

Transitions of Care Considerations in the ICU

- Medications initiated during ICU stay are often continued post-ICU
  - Antipsychotics
  - 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

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.

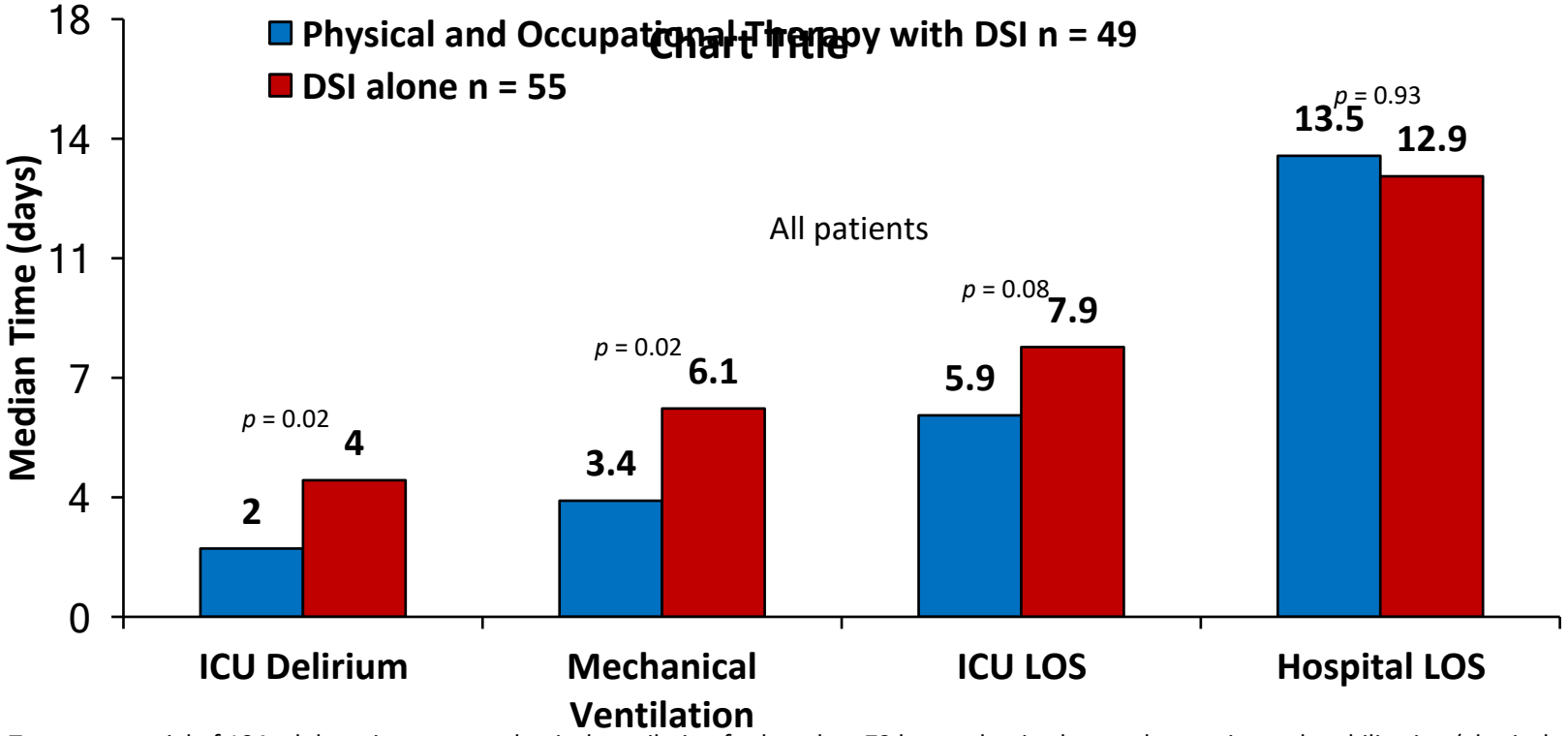
Paired Sedation and Ventilator Weaning Protocol: *ABC Trial*



Four center trial of 336 mechanically ventilated patients randomized to management with a DSI followed by an SBT or with sedation per usual care plus a daily SBT.

Girard TD, et al. *Lancet*. 2008 Jan 12;371(9607):126-34.

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 (physical and occupational therapy) during periods of daily sedation interruption (DSI) or to DSI with therapy as ordered by the primary care team.

Schweickert WD et al. *Lancet*. 2009 May 30; 373(9678):1874-82.

Mobilization Safety Parameters

System	Starting mobility session	Stopping mobility session
Cardiovascular	HR: 60-130 BPM SBP: 90-180 mm Hg or MAP: 60-100 mm Hg	HR: decrease below 60 or increase above 130 BPM SBP: decrease below 90 or increase above 180 mm Hg MAP: decrease below 60 or increase above 100 mm Hg
Respiratory	RR: 5-40 breaths/min SPO_2: ≥ 88% FIO_2: < 0.6 and PEEP < 10 Airway is adequately secured	RR: decreases below 5 or increases above 40 breaths/min SPO_2: decreases below 88% Concerns regarding adequate securement of the airway
Neurologic	Able to open eyes to voice Absent of: • New or symptomatic arrhythmias • Chest pain with concern for MI • Unstable spinal injury • Unstable fracture • Active gastrointestinal bleed	Changes in consciousness "Clinically relevant event" • New/symptomatic arrhythmia • Chest pain with concern for MI • Ventilator asynchrony • Fall/Bleeding/Medical device removal or malfunction • Distress reported by patient or observed by clinician
Other	Mobilization may be performed with the following: • Femoral vascular access devices (with some exceptions) • During continuous renal replacement therapy • Infusion of vasoactive medications	

Abbreviations: HR = Heart rate, BPM = beats per minute, SBP = systolic blood pressure, MAP = mean arterial pressure, RR = respiratory rate, SPO_2 = oxygen saturation, FIO_2 = fraction of inhaled oxygen, PEEP = peak end expiratory pressure, MI = myocardial infarction

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

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.

2018 SCCM PADIS Guidelines: Mobilization

- Performing rehabilitation or mobilization in ICU
  - Conditional recommendation, low quality of evidence
- Serious safety events or harms do not occur commonly during physical rehabilitation or mobilization
  - Ungraded
- Major indicators for safely initiating rehabilitation/mobilization include stability in cardiovascular, respiratory, and neurologic status
  - Vasoactive infusions and mechanical ventilation are not barriers to initiating rehabilitation/mobilization, assuming patients are otherwise stable with use of these therapies.
  - Ungraded
- Major indicators for stopping rehabilitation/mobilization include development of new cardiovascular, respiratory, or neurologic instability
  - Other events, such as a fall or medical device removal/malfunction, and patient distress
  - Ungraded

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

Case Question #7

KL is 56-year-old man on day 3 of admission to the SICU, intubated, and mechanically ventilated for Acute Respiratory Distress Syndrome. He is receiving an IV fentanyl infusion at 75 mcg/hr with a VAS of 1, his RASS score ranges from 0 to -1, his CAM-ICU status is positive, and he is sleeping for no more than 2 hours at night. In addition to using a sleep-promoting, multicomponent protocol, which of the following is most appropriate for KL's sleep disturbance, per the 2018 SCCM PADIS guidelines for adult critically ill patients?

A. Medication to promote sleep is not warranted
B. Add melatonin in the evening
C. Initiate a low-dose dexmedetomidine infusion from 11 pm to 6 am
D. Initiate a low-dose propofol infusion from 11 pm to 6 am

2018 SCCM PADIS Guidelines: Sleep Disturbances – Ungraded Statements

- Subjective sleep quality is reduced in critically ill vs. healthy
- Sleep fragmentation, the proportion of time spent in light sleep (stages N1+N2), and time spent sleeping during the day (versus night) are higher
- The proportion of time spent in deep sleep (N3 sleep and rapid eye movement [REM] stage) is lower
- The presence of delirium may not affect total sleep time, sleep efficiency, or sleep fragmentation
- The influence of delirium on the proportion of time spent in light (N1 + N2) versus deeper (N3) sleep is unknown
- REM sleep is lower if delirium is present

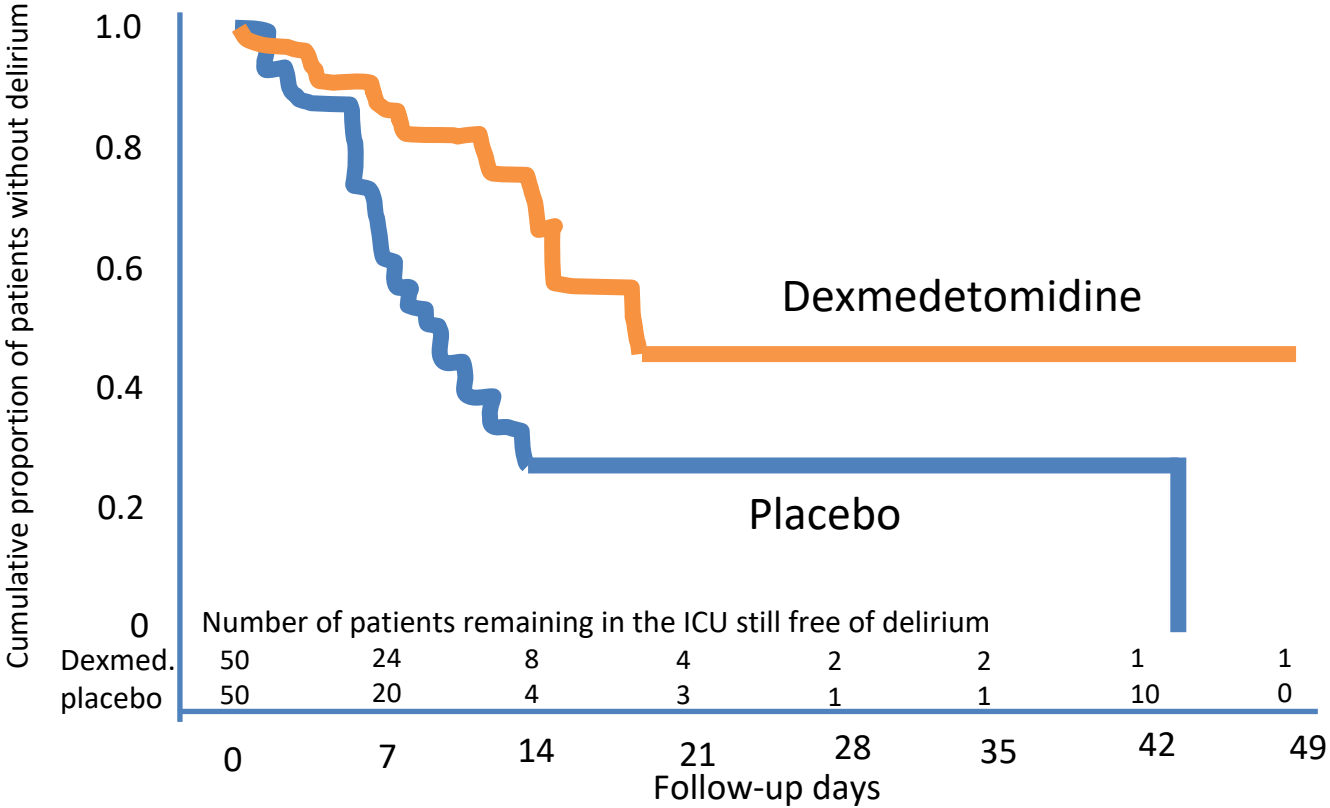
Devlin JW, et al. *Crit Care Med*. 2018 Sep;46(9):e825-e873.

Disruptive Sleep in the ICU

- Environmental
  - Noise, light, bed, activities in room, odor, handwashing, visitors
- Physiologic and pathophysiologic
  - Pain, discomfort, too hot, too cold, breathing difficulty, cough, thirst/hunger, nausea, needing to void
- Care-related
  - Nursing care (e.g. medication administration, vital sign measurements), procedures, diagnostic tests, lines/catheters/equipment, endotracheal tube
- Psychologic
  - Anxiety/worry/stress/fear, unfamiliar environment, disorientation to time, loneliness, lack of privacy, hospital attire, missing bedtime routine

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

Low-dose Nocturnal Dexmedetomidine



Two-center RCT general medical/surgical critically ill adults. Dexmedetomidine initiated at 0.2 mcg/kg/hr, titrated by 0.1 mcg/kg/hr every 15 min to goal RASS score of -1 or maximum rate of 0.7 mcg/kg/hr

Skrobik Y, et al. *Am J Respir Crit Care Med.* 2018 May 1;197(9):1147-1156.

Melatonin and Melatonin Receptor Agonists

- May help promote sleep
  - Very little evidence in ICU patients
- Pilot study of ramelteon (melatonin receptor agonist)
  - 67 patients (24 ICU patients)
  - Prevalence of delirium 3% in ramelteon group vs. 32% in placebo group in medically ill patients
- More evidence is needed to support routine use of melatonin or ramelteon in the ICU

Hatta K, et al. *JAMA Psychiatry*. 2014:71(4);397-403.
Mo, Y et al. *J Intensive Care Med*. 2016 Aug;31(7):451-5.

Ramelteon

- Single-center RCT in Japanese medical ICU

Variables	Ramelteon (n = 45)	Control (n = 43)	p
ICU length of stay, median (range), days*	4.56 (2.1-7.07)	5.86 (2.97-14.16)	NS
Hospital mortality, n (%)	3 (6.7)	3 (7.5)	NS
Occurrence of delirium, n (%)	11 (24.4)	20 (46.5)	0.044
Length of delirium, mean (SD), days	0.78 (1.81)	1.40 (2.30)	0.048

*primary endpoint

Nishikimi M, et al. *Crit Care Med.* 2018 Jul;46(7):1099-1105.

2018 SCCM PADIS Guidelines: Sleep Disturbances Recommendations

- No recommendation regarding the use of melatonin to improve sleep in critically ill adults
  - no recommendation, very low quality of evidence
- No recommendation regarding the use of dexmedetomidine at night to improve sleep
  - no recommendation, low quality of evidence
- Suggest not using propofol to improve sleep in critically ill adults
  - conditional recommendation, low quality of evidence
- Suggest using a sleep-promoting multicomponent protocol in critically ill adults
  - conditional recommendation, very low quality of evidence
- Suggest using noise and light reduction strategies to improve sleep in critically ill adults
  - conditional recommendation, low quality of evidence

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

Delirium, Immobility, and Sleep Disturbances: KEY TAKEAWAYS

1) **KEY TAKEAWAYS: Delirium**
   - Preventive strategies are mostly nonpharmacologic
   - Collaborative approach is necessary
   - Less than favorable recommendations for antipsychotics for management of delirium
   - Dexmedetomidine may be effective, probably by avoiding the adverse effects from alternative agents

2) **KEY TAKEAWAYS: Immobility**
   - Extensive guidance available on safety parameters for mobility

3) **KEY TAKEAWAYS: Sleep Disruption**
   - Guidance provided to optimize sleep environment

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Questions?