Management of Pain, Agitation, Delirium, and Neuromuscular Blockade in Adult Intensive Care Unit Patients

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Learning Objectives

1. Develop a management strategy for the prevention, treatment, and monitoring of pain, agitation, and delirium (PAD) in an intensive care unit (ICU) patient with various comorbidities.
2. Discuss relevant pharmacokinetic and pharmaco-dynamic considerations of analgesics and sedatives as they pertain to disturbances in critical care physiology.
3. Identify relevant adverse effects, drug interactions, and medication withdrawal syndromes during the management of PAD.
4. Construct a monitoring plan for critically ill patients receiving neuromuscular blockade.
5. Evaluate both verbal and non-verbal ICU patients for pain, agitation, and delirium using a validated screening tool.
6. Recognize the long-term effects of severe respiratory distress and sepsis on cognitive function in adult patients after discharge from a surgical or medical ICU.
7. Identify nonpharmacologic and pharmacologic methods for the prevention and treatment of delirium.
8. Understand the potential role of neuromuscular blocking agents during early acute respiratory distress syndrome.
9. Create a plan for any PAD-related medication that is continued beyond ICU discharge.

Abbreviations in This Chapter

ARDS	Acute respiratory distress syndrome
BPS	Behavioral Pain Scale
CAM-ICU	Confusion assessment method for the intensive care unit
CPOT	Critical-Care Pain Observation Tool
CRRT	Continuous renal replacement therapy
GABA	γ-Aminobutyric acid
ICDSC	Intensive Care Delirium Screening Checklist
ICP	Intracranial pressure
ICU	Intensive care unit
NMBA	Neuromuscular blocking agent
PAD	Pain, agitation, and delirium
PRIS	Propofol-related infusion syndrome
PTSD	Posttraumatic stress disorder
RASS	Richmond Agitation Sedation Scale
SAT	Spontaneous awakening trial
SBT	Spontaneous breathing trial
SCCM	Society of Critical Care Medicine
TOF	Train of four [monitoring]

Self-Assessment Questions
Answers and explanations to these questions may be found at the end of this chapter.

1. S.V. is a 70-year-old woman (weight 50 kg, decreased from 70 kg 2 months ago) admitted to the intensive care unit (ICU) in acute respiratory distress syndrome (ARDS). She has a history of cirrhosis and is currently fluid overloaded (net positive 5 L). She has been on a continuous infusion of fentanyl and propofol for 5 days. Which pharmacologic factor would best be considered with respect to her analgesics or sedatives?

   A. Increased risk of propofol-related infusion syndrome (PRIS) in patients with ARDS.
   B. Unpredictable clearance of fentanyl because of liver disease and volume-overload state.
   C. Faster clearance of fentanyl through cytochrome P450 (CYP) 3A4 enzymatic induction by propofol.
   D. Increased propofol sensitivity because of its low protein binding.

2. A physician in your ICU wants to update the ICU sedation protocol at your institution and include a delirium assessment tool. Which validated tool is best recommended by the Society of Critical Care Medicine (SCCM) for assessing delirium in the ICU?

   A. NEECHAM Confusion Scale.
   B. Intensive Care Delirium Screening Checklist (ICDSC).
   C. Delirium Rating Scale.
   D. Memorial Delirium Assessment Scale.

3. K.T., who has been intubated for 4 days, is receiving infusions of fentanyl at 100 mcg/hour and midazolam at 1 mg/hour to meet analgesic and sedative needs. During the previous 24 hours, her pain score has consistently been rated as "no pain" and her sedation score as "alert and calm." Gastric feeding goals have been reached; however, K.T. has not had a bowel movement in 4 days, and her gastric residuals have increased from 50 to 150 mL. Which recommendation is most clinically indicated?

   A. Discontinue nutrition until K.T. has had a bowel movement and residuals have decreased less than 100 mL.
   B. Place a small bowel feeding tube.
   C. Decrease fentanyl to 75 mcg/hour, and initiate a bowel regimen.
   D. Initiate metoclopramide 5 mg intravenously every 8 hours.

4. E.H. is a 35-year-old man without a significant medical history admitted to the ICU after a motor vehicle accident secondary to alcohol intoxication. His social history includes daily alcohol use (1 six-pack of beer per day). He has been on a fentanyl infusion 125 mcg/hour for pain and a lorazepam infusion 4–6 mg/hour for active alcohol withdrawal. On day 4, his blood pressure (BP) is 146/65 mm Hg, and his urine output is 140 mL/hour; pertinent laboratory values include serum creatinine (SCr) 1.4 mg/dL, blood urea nitrogen (BUN) 15 mg/dL, and new anion gap metabolic acidosis. According to these laboratory values, which is the next best step in therapy?

   A. Calculate an osmolar gap to investigate for propylene glycol toxicity.
   B. Obtain a serum lactate level to rule out septic shock–related anaerobic metabolism.
   C. Obtain a serum ammonia level to rule out encephalopathy.
   D. Consult a nephrologist to rule out acute renal azotemia.

5. L.V. is a 68-year-old man admitted to the ICU for a chronic obstructive pulmonary disease exacerbation requiring intubation. He is receiving a fentanyl infusion at 50 mcg/hour. His home medications include albuterol four times daily, ipratropium four times daily, lisinopril 10 mg daily, and clonazepam 2 mg twice daily. He has no major organ dysfunction, and the medical team wants to avoid reinitiating any home medications at this time. The nurse reports that the "patient is very agitated" 72 hours after intubation. Which is the most appropriate medication to initiate for this patient?

   A. Dexmedetomidine drip.
   B. Scheduled haloperidol.
   C. Propofol drip.
   D. Scheduled quetiapine.

6. H.F. has been sedated and paralyzed while on mechanical ventilation for 3 days, and efforts to discontinue the paralytic agent have failed. She is taking amlodipine and hydrochlorothiazide at home, and her BP has steadily been increasing to systolic pressures of 160–170 mm Hg, with heart rates (HRs) in the 80s while in the ICU. Her laboratory values are as follows: sodium 140 mEq/L, potassium 4.5 mEq/L, chloride 111 mEq/L, bicarbonate 18 mEq/L, BUN 38 mg/dL, and SCr 2.8 mg/dL; she has become anuric. Which is the most appropriate medication for treatment of her high BP while she is on a neuromuscular blocking agent (NMBA)?

   A. Hydrochlorothiazide.
   B. Metoprolol.
   C. Amlodipine.
   D. Hydralazine.

7. A previously discharged patient has come to visit the ICU staff and discuss his recovery from ARDS. You recall that he received high doses of sedatives and analgesics and that he was paralyzed during his ICU stay. Which outpatient complications are most likely to occur in these patients?

   A. Depression and acute mania.
   B. Hearing loss and attention deficit disorder.
   C. Protracted muscular weakness and PTSD.
   D. Muscle hypertrophy and hypothyroidism.

8. R.B. is a 25-year-old man admitted to the ICU after a motor vehicle accident with multiple injuries. He developed severe ARDS from bilateral pulmonary contusions within 24 hours of admission and is receiving hydromorphone 2 mg/hour and midazolam 6 mg/hour to maintain comfort. He is intermittently agitated (Richmond Agitation Sedation Scale [RASS] score of +3) and is not oxygenating adequately after several adjustments of his ventilator settings; the physician would like to initiate paralysis. Which is the next best step in the management of this patient?

    A. Initiate a cisatracurium bolus; then initiate a drip and dose to adequate oxygenation parameters.
    B. Initiate intermittent vecuronium boluses to adequate oxygenation parameters.
    C. Do a spontaneous awakening trial (SAT) because of the patient's high midazolam doses.
    D. Sedate the patient to a "nonagitated" RASS score before initiating neuromuscular blockade.

9. Your ICU team is initiating a delirium prevention protocol and is asking for pharmacy input regarding a list of "medications to consider avoiding" in patients who are at risk of delirium or who screen positive for delirium. Which medication would be best to include on this list?

    A. Ziprasidone.
    B. Methylprednisone.
    C. Ciprofloxacin.
    D. Clonidine.

I. **PAIN, AGITATION, AND DELIRIUM IN THE INTENSIVE CARE UNIT**

A. Background
1. Providing optimal patient comfort in an intensive care unit setting can be extremely challenging. There is often the formidable task of avoiding either under-sedation or over-sedation, while maintaining focus on optimizing clinical outcomes. To assist clinicians in this critical task, the SCCM published updated guidelines in January 2013 for the management of pain, agitation, and delirium (PAD) in intubated and nonintubated adult medical, surgical, and trauma patients in the ICU. SCCM assembled a 20-member multidisciplinary, multi-institutional task force, each with extensive expertise in the overall management and associated outcomes of PAD. Rigorous research has been completed over the past two decades to better our understanding of the assessment tools and medications used for PAD, the prevention and treatment methods used for PAD, and the long-term effects of the ICU environment on patients and caregivers. This research has significantly advanced our knowledge and, together with the 2013 SCCM guidelines, has given clinicians a foundation on which they can consistently provide quality ICU care as it pertains to individual patient needs. Recommendations specific to other patient populations such as burn, neurologic, neurosurgical (including traumatic brain injury), and cardiac populations may need specialized consideration.
2. The PAD guidelines have a renewed focus on the assessment and control of pain in the ICU. Patients continue to report inadequate pain control as their primary complaint during their ICU stay. The guidelines also advocate targeting a lighter level of sedation and stress the importance of routine monitoring for delirium and initiating daily delirium-prevention methods. An additional focus is on the use of routine monitoring tools to assist in the use and titration of nonpharmacologic and pharmacologic therapies.
3. The 2013 PAD guidelines used the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method to develop each recommendation for both descriptive and actionable questions. Only important or critical outcomes were considered when reviewing the evidence, and only critical outcomes were assessed for each recommendation.
    a. Each guideline statement and recommendation was ranked according to the quality and strength of the evidence and was denoted "A" (high quality; randomized controlled trials), "B" (moderate-quality; randomized controlled trials with significant limitations or high-quality observational studies), or "C" (low quality; observational studies).
    b. A *strong* recommendation is worded as "we recommend" and is denoted with a "1," showing that most task force members believed the benefits of the intervention significantly outweighed the risks and would likely pursue the action.
    c. A *weak* recommendation is worded as "we suggest" and is denoted with a "2," showing that most task force members believed the benefits of the intervention likely outweighed the risks, but the task members were not confident about the tradeoff.
    d. A *no recommendation* could also be stated because of either lack of evidence or lack of consensus among the reviewers and would be denoted with a zero.

B. Pharmacy Intervention
1. Pharmacists can provide unique and valuable insight into the management of PAD in the ICU. Much of the management for PAD involves medications with complex pharmacologic profiles and challenging dosing strategies, allowing tremendous opportunity and need for pharmacy expertise on the critical care team. As the management of PAD in the ICU continues to evolve, pharmacists should seek avenues for contributing to the critical care community such as hospital protocol development; provision education for medical, pharmacy, and nursing colleagues; and/or research on pertinent questions surrounding the management of PAD in the ICU.

II. PAIN IN THE INTENSIVE CARE UNIT

A. Introduction
1. More than half of ICU survivors report severe pain as the most traumatic memory of their ICU stay.
2. Uncontrolled pain in the ICU is associated with negative long-term physical and psychological effects such as chronic pain, PTSD, and lower health-related quality of life.
3. Assessing pain in the ICU is challenging, particularly in non-verbal patients. If patients are unable to adequately communicate their degree of pain, medications should be titrated according to validated non-verbal pain scales.

B. Incidence and Causes of Pain
1. Pain may occur in any type of ICU patient, including trauma surgery, cardiac surgery, burn, cardiac, and medical patients. Procedural pain in the ICU has been a focus of ongoing research, and the PAD guidelines discuss giving preprocedural analgesia for patients when pain is anticipated.
    a. Recent data show that 50%–80% of ICU patients report pain as "uncontrolled" during their ICU stay, similar to research from 2 decades ago. This suggests that the routine assessment and treatment of pain should be a renewed and ongoing focus for ICU clinicians.
    b. Pain related to the initial traumatic insult, underlying disease states such as burns or cancer, and post-cardiac surgery pain are common causes of severe pain reported by patients.
    c. ICU survivors also report iatrogenic and procedural-based causes of significant pain: Pain associated with presence of an endotracheal tube and suctioning through the endotracheal tube, patient repositioning to avoid decubitus ulcer formation, wound care procedures, intravenous line insertion, and chest tube management. Preprocedural pain management should be strongly considered for these clinical scenarios. One study reported that up to 60% of patients did not receive preprocedural systemic pain medication for common procedures and wound care in the ICU, although 89% of patients received a topical anesthetic for central venous catheter placement (Am J Crit Care 2002;11:415-29).
    d. A recent international, multicenter study investigated the determinants of procedural pain intensity in the ICU. The procedures found to double the patient's pain intensity score (from preprocedure to during-procedure scoring) were chest tube removal, wound drain removal, and arterial line insertion. This study found that higher-intensity pain and pain distress before the procedure were associated with a high risk of increased pain during the procedure (Am J Respir Crit Care Med 2014;189:39-47).

C. Short- and Long-term Consequences of Pain in the ICU
1. Acute pain can invoke a stress response, resulting in a hypercatabolic state, decreased tissue perfusion, and impaired wound healing. Uncontrolled pain decreases a patient's immune response to infection by suppressing natural killer cell activity and neutrophil function.
2. Long-term studies (12 months post-ICU stay) report detrimental physiologic and psychological function in patients who recall significant pain during their hospitalization, particularly in patients admitted with a traumatic injury.
    a. Health-related quality of life decreased in up to 20% of patients.
    b. Chronic pain was reported in up to 40% of patients.
    c. PTSD was reported in 5%–20% of patients.

D. Assessment of Pain
   1. The gold standard for assessing pain remains the patient's self-report of pain. Many scenarios in the ICU can make the self-reporting of pain challenging for nurses and physicians (e.g., mechanical ventilation and the presence of sedation and/or delirium). Two validated non-verbal pain scales are currently recommended by SCCM to be done in a repetitive and routine manner: the Behavioral Pain Scale (BPS) (Table 1) and the Critical-Care Pain Observation Tool (CPOT) (Table 2).

Table 1. Behavioral Pain Scale

Item	Description	Score
Facial expression	Relaxed	1
	Partially tightened (e.g., brow lowering)	2
	Fully tightened (e.g., eyelid closing)	3
	Grimacing	4
Upper limbs	No movement	1
	Partially bent	2
	Fully bent with finger flexion	3
	Permanently retracted	4
Compliance with ventilation	Tolerating movement	1
	Coughing but tolerating ventilation for most of the time	2
	Fighting ventilator	3
	Unable to control ventilation	4

A BPS score > 5 indicates significant pain.

Adapted with permission from: Lippincott Williams & Wilkins/Wolters Kluwer Health. Payen J, Bru O, Bosson J, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29:2258-63.

Table 2. Critical-Care Pain Observation Tool (CPOT)[a]

Indicator	Description	Score	
Facial expression	No muscular tension observed	Relaxed, neutral	0
	Presence of frowning, brow lowering, orbit tightening, and levator contraction	Tense	1
		Grimacing	2
	All of the above facial movements plus eyelid tightly closed		
Body movements	Does not move at all (does not necessarily mean absence of pain)	Absence of movements	0
	Slow, cautious movements, touching or rubbing the pain site, seeking attention through movements	Protection	1
	Pulling tube, attempting to sit up, moving limbs/thrashing, not following commands, striking at staff, trying to climb out of bed	Restlessness	2
Muscle tension	No resistance to passive movements	Relaxed	0
Evaluation by passive	Resistance to passive movements	Tense, rigid	1
flexion and extention of upper extremities	Strong resistance to passive movements, inability to complete them	Very tense or rigid	2

Table 2. Critical-Care Pain Observation Tool (CPOT)[a] *(continued)*

Indicator	Description	Score	
Compliance with the ventilator (intubated patients)	Alarms not activated, easy ventilation	Tolerating ventilator or movement	0
	Alarms stop spontaneously	Coughing but tolerating	1
	Asynchrony: blocking ventilation, alarms frequently activated	Fighting ventilator	2
OR			
Vocalization (extubated patients)	Talking in normal tone or no sound	Talking in normal tone or no sound	0
	Sighing, moaning	Sighing, moaning	1
	Crying out, sobbing	Crying out, sobbing	2
Total, range			**0–8**

[a]A CPOT score of ≥ 3 indicates significant pain.

Adapted with permission from: Lippincott Williams and Wilkins/Wolters Kluwer Health. Gelinas C, Fillion L, Puntillo K, et al. Validation of the Critical-Care Pain Observation Tool in adult patients. Am J Crit Care 2006;15:420-7.

      a. Assessment scales should be used routinely in all ICU patients (+1B recommendation).
      b. Pain scores should be documented in the medical chart and then used to help formulate daily titrations in pain medications.
      c. The PAD guidelines recommend that patients be treated within 30 minutes of a "significant pain" score (e.g., BPS greater than 5; CPOT score of 3 or greater).
   2. Use of vital signs alone is not recommended for assessing pain in the ICU patient. Abnormal vital signs such as tachycardia and hypertension are appropriate for use as a prompt to further investigate the need for pain control.
   3. Further research is needed to determine the effectiveness of a preprocedural pain assessment tool and the ways in which this assessment will affect analgesic administration. The recent study by Puntillo et al. in 2014 suggests that assessment of pain before a procedure can include current pain intensity, pain distress, and the degree of "worst pain" on the day of the procedure.

  E. Treatment of Pain in the ICU
   1. For an agitated patient whose pain assessment scale shows inadequate pain control, the PAD guidelines recommend treatment with intravenous opioids for nonneuropathic pain before initiating other sedatives in patients on mechanical ventilation in the ICU.
   2. Preprocedural pain medications should be considered in all ICU patients.
      a. Preemptive analgesia for chest tube removal is a "strong" recommendation by SCCM, together with nonpharmacologic relaxation techniques (+1C recommendation).
      b. Preprocedural pain medications should be considered for all other ICU procedures that may potentially cause pain (+2C recommendation). The timing of administration should be appropriate to the onset of the specific analgesic medication chosen.
   3. Postoperative thoracic epidural anesthesia/analgesia is recommended for patients undergoing abdominal aortic aneurysm treatment. Thoracic epidural anesthesia is "suggested" for traumatic rib fractures in the ICU.

4. Pharmacotherapy for pain
    a. Intravenous opioids on an as-needed, scheduled, or continuous-infusion basis are recommended as first-line agents for preventing or treating nonneuropathic pain. The pharmacokinetics of different opioids may vary; thus, opioids should be chosen according to patient comorbidities and individual needs (Table 3). Fentanyl is the most commonly used intravenous opiate in American adult ICUs.

Table 3. Opiates Commonly Used in the ICU

Drug	Metabolic/Drug Interaction Considerations	Usual CI Starting Dose[a]	Drug-Specific Adverse Effects[b]	Drug Accumulation Factors
Fentanyl	3A4 major substrate	12.5–25 mcg/hour; 0.35-0.5 mcg/kg	Muscle rigidity	Hepatic failure; high volume of distribution; high lipophilicity; unpredictable clearance (long context-sensitive half-time) with prolonged infusion
Morphine	Glucuronidation	1–2 mg/hour	Hypotension, bradycardia from histamine release	Hepatic failure; active metabolite (3-morphine glucuronide) accumulates in renal failure
Hydromorphone	Glucuronidation	0.25–0.5 mg/hour	Overdose effects from dosing errors (high-potency opiate)	Hepatic failure
Methadone	3A4 and 2B6 major substrates		QTc prolongation, serotonin syndrome	Long half-life; hepatic and renal failure will delay clearance
Remifentanil	Blood and tissue esterases	Loading dose: 1.5 mcg/kg CI: 0.5–15 mcg/kg/hour	Chest wall rigidity; rebound pain on discontinuing	

[a]Usual starting dose in the ICU for pain management in an opiate-naive patient.

[b]Other common significant adverse effects for all opiates to be considered: Constipation, respiratory depression, bradycardia, hypotension, altered mental status.

CI = continuous infusion.

i. General mechanism of action of opiates: Binds to mu-opioid receptors in the central nervous system (CNS)
ii. Commonly used intravenous opioids in the ICU: Fentanyl, morphine, hydromorphone, remifentanil, and methadone
iii. Tolerance: May quickly develop to all opiates, particularly when given as a continuous infusion. On switching to a different intravenous or oral opiate, equianalgesic dosing may be difficult to estimate, and low starting doses should be considered.
iv. Significant adverse effects: Decreased respiratory drive: this may be desired effect in some ICU scenarios, however, a depressed respiratory drive is a critical negative implication during the ventilatory weaning process; decreased BP and HR, constipation, gastrointestinal (GI) intolerance, altered sensorium

     v.   Gastrointestinal intolerance and constipation: this may be a significant concern with opiates. A bowel regimen should be initiated on day 1 unless contraindicated, with assessment for adequacy every 24-48 hours. Gastrointestinal intolerance in the ICU can result in increased time on mechanical ventilation, delayed time to obtaining nutritional goals, and prolonged ICU stay. Constipation may also contribute to agitation in some patients.

     vi.   Altered mental status: Opiates may induce a sedative effect, as well as an altered sensorium in some patients. Unless contraindicated, clinicians should consider titrating the opiate dose downward in an altered patient who has adequate pain control.

     vii.   Patient-controlled analgesia: In alert and clinically stable patients, use of patient-controlled anesthesia may be considered to titrate to the patient's perceived level of pain.

  b. Fentanyl

     i.   Pharmacokinetics: Hepatic metabolism, CYP3A4 substrate, weak inhibitor of CYP34A. Quick onset and short duration of action; lacks a pharmacologically active metabolite. Highly lipophilic, with a high volume of distribution and high protein binding; maintains a three-compartment model, therefore, continuous-infusion dosing may lead to prolonged and unpredictable clearance (context-sensitive half-time)

     ii.   Many dosage forms: Injectable (intravenous, intramuscular, intrathecal, epidural), transdermal, transmucosal, nasal spray. Different dosage forms should not be converted on a 1:1 mcg basis; use specific manufacturer recommendations if converting. The injectable form of fentanyl is the most commonly used form in the ICU setting; most other formulations of fentanyl are not practical for use in the ICU. The fentanyl patch is not generally appropriate for use in the ICU because of its latent onset (about 12 hours) and erratic/increased absorption in a febrile patient.

     iii.   Adverse effects: Respiratory depression, bradycardia, hypotension, CNS depression, constipation, ileus, risk of serotonin syndrome when used with other serotonergic agents.

  c. Morphine

     i.   Pharmacokinetics: Hepatic metabolism by glucuronidation to two major active metabolites, morphine-3-glucuronide (45%–55%) and morphine-6-glucuronide (10%–15%). The glucuronide metabolites of morphine are both renally eliminated; they may accumulate with either chronic use of morphine or in patients with decreased renal function. Morphine-3-glucuronide does not have analgesic activity, but adverse effects may include seizure activity or agitation. Morphine-6-glucuronide does have analgesic activity by the mu-receptor and may cause additive sedation and respiratory depression if accumulation occurs. Continuous morphine infusions are rarely used for analgesia in the ICU setting because of these concerns with the active metabolites.

     ii.   Dosage forms: Injectable (intravenous, subcutaneous, intrathecal, epidural), and oral. Intravenous-to-oral conversion is not a 1:1 mg ratio.

     iii.   Adverse effects: Histamine release may cause hypotension, bradycardia, respiratory depression, CNS depression, constipation, ileus.

  d. Hydromorphone (Dilaudid)

     i.   Pharmacokinetics: Hepatic metabolism by glucuronidation to inactive metabolite. Low volume of distribution, highly water soluble, and relatively low protein binding.

     ii.   Dosage forms: Injectable (intravenous, subcutaneous) and oral; intravenous-to-oral conversion is not a 1:1 mg ratio.

     iii.   Adverse effects: CNS alterations (e.g. abnormal dreams, aggressive behavior, altered thinking), respiratory depression, hypotension, constipation.

  e. Remifentanil (Ultiva)

     i.   Research primarily done in Europe; limited reported use in U.S. adult ICUs for ongoing analgesic use.

     ii.   Dosage form: Injectable only

       iii. Pharmacokinetics: Clearance by blood and tissue esterases; clearance not dependent on organ function. Fast onset and short duration of action with little to no accumulation. High volume of distribution, high protein binding.

       iv. Adverse effects: Respiratory depression, hypotension, bradycardia, constipation.

       v. Rebound pain: Quick offset (5–10 minutes) may lead to rebound pain and withdrawal symptoms, and ongoing pain medication orders may be needed if remifentanil is interrupted or discontinued.

       vi. Benefits in adult ICUs (e.g. decreased time on mechanical ventilation) have been shown with short-term use (72 hours or less).

       vii. Cost (AWP): 1 mg = $55.16; 5 mg = $234.74.

   f. Methadone

       i. Pharmacokinetics: Phase I hepatic metabolism to inactive metabolites. Major substrate of CYP 34A, 2B6, and therefore may have many drug interactions. Moderate inhibitor of CYP 2D6, weak inhibitor of CYP 3A4. Longer-acting opiate with variable duration of action (12–48 hours); can accumulate quickly in patients with hepatic failure or patients receiving hemodialysis. Animal studies have found that the D-isomer of methadone works as both a partial mu-agonist and an *N*-methyl D-aspartate receptor antagonist (the L-isomer is a full mu-agonist). These properties of the D-isomer are thought to decrease the tolerance effect to other opioids. Methadone is currently marketed as the racemic mixture. Upon initiation of oral methadone, steady state and peak analgesic effect may not be reached for 3-5 days.

       ii. Dosage forms: Injectable (intravenous, intramuscular, subcutaneous), and oral. Not a milligram-per-milligram conversion

       iii. Adverse effects: Corrected QT (QTc) prolongation, altered mental status, respiratory depression, confusion, dizziness, arrhythmias, constipation, risk of serotonin syndrome when used with other serotonergic agents.

5. Non-opioid adjunctive pain medications should be considered in combination with opioids to reduce opioid requirements. Clinically stable patients may tolerate a conversion from opiates to non-opiate medications.

   a. Local and regional anesthetics such as bupivacaine

   b. Acetaminophen (Tylenol)

       i. Total daily acetaminophen doses should be considered from all acetaminophen combination products, with a total recommended daily dose of 4 g. Lower dosing should be noted for liver disease.

       ii. Intravenous acetaminophen: Dose reduction recommended if the creatinine clearance (CrCl) is 30 mL/minute or less or with continuous renal replacement therapy (CRRT) (every 8 hours); contraindicated in severe hepatic disease. Because of limited data for the use of intravenous acetaminophen in the critically ill population and its considerable cost compared with other formulations of acetaminophen, its use in the ICU has become very controversial.

   c. Intravenous or oral nonsteroidal anti-inflammatory medications: Ibuprofen, ketorolac. Use with caution in critically ill patients with renal or hepatic dysfunction. May increase the risk of acute renal failure, bleeding, or GI adverse effects.

   d. Ketamine (Ketalar) has been used for analgesia and sedation primarily in the pediatric population. Published data for the sustained use of ketamine in adults for analgesia and/or sedation are scarce, and the long-term cognitive effects of ketamine are not currently known. Data from animal studies suggest a significant decline in cognitive function after continued use of ketamine.

       i. Called a "dissociative anesthetic," providing analgesic activity at subanesthetic doses. It is a schedule III controlled substance and works primarily as an *N*-methyl-d-aspartate receptor antagonist.

ii. May decrease doses of concurrently used opioids

iii. Off-label uses include refractory pain syndromes, cancer pain, neuropathic pain, asthma (bronchodilatory effects), and refractory seizure activity.

iv. Dosing range is broad; may start at from 0.1 mg/kg/hour up to 0.8 mg/kg/hour

v. Significant adverse effects: Mild to severe emergence reactions (e.g. confusion, excitement, irrational behavior, hallucinations, delirium) in around 12% of patients, enhanced skeletal muscle tone, hypertension, arrhythmias.

6. Specific anticonvulsants are recommended by SCCM for confirmed neuropathic pain. These drugs have not been studied extensively in the ICU population and should be used with caution. Significant adverse effects and drug interactions require low starting doses and close follow-up of anticonvulsants. If the patient is discharged home on an anticonvulsant for pain, follow-up should be documented and the primary care provider notified.

a. Gabapentin (Neurontin)

i. Suggested starting dose range: 300–600 mg/day divided two or three times daily; requires renal adjustment.

ii. Pharmacokinetics: Renally excreted, dose adjusted for reduced CrCl

iii. Adverse effects: May be severe, including CNS depression, paresthesias, and asthenias

b. Carbamazepine (Tegretol)

i. Suggested starting dose range: 50–100 mg twice daily; use with caution in patients with hepatic impairment, and adjust for a CrCl less than 10 or with hemodialysis.

ii. Pharmacokinetics: Strong inducer of many CYP enzymes, substrate of CYP3A4. Closely monitor for drug interactions.

iii. Adverse effects: Somnolence, severe skin reactions (e.g., Stevens-Johnson syndrome, toxic epidermal necrolysis)

F. Analgosedation Recommendation: The PAD guidelines give the analgosedation method of sedation a "weak" +2B level of recommendation, and dosing/titration values are not well defined. The guidelines recognize that current data are primarily limited to open-labeled trials, with most studies using remifentanil and all conducted in Europe where critical care staffing and management practices are different from those in the United States. There is no question that a patient who is in pain or who is agitated secondary to pain should first be treated with analgesia over other types of medication. However, the analgosedation method may become less certain when the patient has a negative pain score but remains persistently agitated. Using analgosedation, clinicians may opt to use opioids instead of non-opioids for "general" agitation (not secondary to pain) and titrate to a sedation score versus a pain score. The guidelines recommend that the short- and long-term adverse effects of opiates be closely monitored in this scenario (e.g. GI intolerance, confusion, opioid dependence). Current analgosedation studies use primarily remifentanil and show a difference in ventilatory days only when used short term. Fentanyl is the most commonly used opioid in the United States for pain control in the ICU. Extrapolation of short-term data with remifentanil to medium or long-term use of fentanyl may be difficult because remifentanil maintains a pharmacokinetic profile very different from that of fentanyl. Given these limitations, it is still notable that the studies using the analgosedation method found a significant decrease in benzodiazepine dosage requirements when opiates were the primary medications used for discomfort and agitation. This is a positive step in decreasing the untoward adverse effects of the benzodiazepine class of sedatives. Clinicians should remain focused on treating pain when indicated; if agitation is ongoing, identifying the source of agitation is of paramount importance in finding the appropriate pharmacologic or nonpharmacologic treatment.

Patient Cases

1. Your patient in the medical ICU is taking the following pain medications at home and is reportedly stable on the documented doses: methadone 20 mg twice daily, gabapentin 900 mg three times daily, and oxycodone 10 mg three times daily. He has no other significant medical history. The team initiated his home medication regimen on admission. His laboratory values on day 4 are as follows: sodium 140 mEq/L, potassium 4.7 mEq/L, chloride 107 mEq/L, bicarbonate 17 mEq/L, BUN 35 mg/dL, SCr 3.2 mg/dL, and glucose 120 mg/dL. The nurse reports increased confusion and drowsiness during the past 48 hours. Which are the most significant pharmacologic concerns?

    A. Oversedation from drug accumulation with new-onset renal failure.
    B. Hyperammonemic encephalopathy from gabapentin accumulation.
    C. Increased methadone sensitivity from metabolic acidosis.
    D. Preexisting drug interactions from dual-opiate therapy.

Questions 2 and 3 pertain to the following case.

2. R.L. is a 26-year-old man intubated and admitted to the trauma ICU for several injuries, including bilateral femur fractures and penetrating lung and abdominal injuries after a motor vehicle accident. He is hypertensive and tachycardic after intubation, and the resident wants to order medications for patient comfort. His alcohol screen was positive, but his other basic laboratory values were within normal limits. His family is not available to provide his medical and social history. Which medications for PAD are most appropriate for this patient?

    A. Dexmedetomidine infusion and propofol.
    B. Oral acetaminophen every 6 hours and lorazepam.
    C. Fentanyl infusion and midazolam.
    D. Fentanyl patch and lorazepam.

3. After 2 weeks, R.L. is being prepared for chest tube removal. Which is the best pain management regimen during chest tube removal?

    A. Give oral acetaminophen 325 mg administered 5–10 minutes before chest tube removal.
    B. Make no change in pain treatment because his current pain regimen is adequate.
    C. Increase his pain medication dose by 50% on the morning of chest tube removal.
    D. Give fentanyl 50 mcg injectable 15 minutes before chest tube removal.

III. AGITATION IN THE INTENSIVE CARE UNIT

A. Agitation in the ICU – Maintaining patient comfort for the duration of the ICU stay can be challenging. Both the under-treatment and over-treatment of pain or agitation can lead to negative consequences. Treatment of an agitated patient should begin with attempts to identify and correct the etiology of the agitation. Common causes of agitation in the ICU include pain, delirium, hypoxia, hypoglycemia, dehydration, and drug or alcohol withdrawal. Close inspection of significant patient variables will also help determine the appropriate sedative:
    1. Ongoing pain control
    2. Substance abuse and smoking history
    3. Baseline neurologic function, including history of seizure activity
    4. Anticipated time on mechanical ventilation
    5. Home medication use, including any medications from which a patient could experience withdrawal symptoms: Benzodiazepines, opioids, antidepressants, antipsychotics, antiepileptics, other γ-aminobutyric acid (GABA) receptor agonists
    6. Hemodynamic values (BP, HR)

    7.   Comorbidities, including renal, hepatic, and pancreatic function

B. Primary Medications for the Treatment of Agitation – Include propofol, dexmedetomidine, and benzodiazepines (usually lorazepam and midazolam) (Table 4). Benzodiazepines are first-line agents for status epilepticus, alcohol withdrawal, benzodiazepine dependence or withdrawal, need for deep sedation or amnesia, and with the use of neuromuscular blockade. Other indications for benzodiazepines may exist, which must be scrutinized throughout the ICU stay.

Table 4. Sedatives for Patients on Mechanical Ventilation in the ICU

Drug	Onset and Duration	Precautions for Use	CYP Substrate (major)	Usual Dose	Significant Adverse Effects
Propofol	Onset: 1 min Duration: short term: 0.5–1 hr; long term > 7 days: variable; 25–50 hr has been observed (depends on depth and time on sedation)	Hypotension, bradycardia, hepatic/ renal failure, pancreatitis	2B6	5–50 mcg/kg/ min; 0.3–3 mg/kg/hr	Hypotension, respiratory depression, bradycardia, PRIS
Dexmedetomidine	Onset: 5–10 min (with LD) 1–2 hr (without LD) Duration: 1–2 hr	Hepatic failure; symptomatic bradycardia	2A6	LD: 0.5–1 mcg/kg (optional) MD: .2–0.7 mcg/kg/hr	Hypo-/ hyper- tension, bradycardia
Lorazepam	Onset: 5–20 min Duration: 4-8 hrs; prolonged with CI	Delirium, renal failure	N/A	Intermittent: 1–4 mg IV every 4–6 hr	Oversedation, propylene glycol toxicity, delirium
Midazolam	Onset: 3–5 min Duration: 2–6 hr, prolonged with CI	Hepatic failure, end-stage renal failure or dialysis, delirium	3A4 (active metabolite)	0.02–0.1 mg/ kg/hr	Oversedation, delirium

CI = continuous infusion; hr = hour(s); IV = intravenously; LD = loading dose; MD = maintenance dose; min = minute(s); N/A = not applicable; PRIS = propofol-related infusion syndrome.

C. SCCM provides the following statement in the PAD guidelines regarding sedation in the ICU: "We suggest that sedation strategies using non-benzodiazepine sedatives (either propofol or dexmedetomidine) may be preferred to sedation with benzodiazepines (either midazolam or lorazepam) to improve clinical outcomes in mechanically ventilated adult ICU patients" (+2B weak recommendation). SCCM further states that "benzodiazepine use may be a risk factor for the development of delirium in adult ICU patient" (level B quality of evidence). Two randomized studies evaluated the differences in clinical outcomes while adult ICU patients were receiving sedation with either a benzodiazepine or a non-benzodiazepine strategy. Heterogeneity occurred among the findings of these two studies (see No. 1 and No. 2 below), which may be partly because of differences in study method. Clinicians should be aware that several complex factors are present in the ICU that can affect clinical outcomes and the prevalence of delirium. More research is needed to further elucidate the direct impact of specific medications on these outcomes.

1. The MENDS study compared the sedative effects of lorazepam and dexmedetomidine in medical and surgical adult ICU patients (n=103) (JAMA 2007;298:2644-53.). This study found no difference in the prevalence of "delirium without coma" (lorazepam 82%; dexmedetomidine 79%, p=0.65) or in the duration of delirium (lorazepam 4 days; dexmedetomidine 2.5 days, p=0.71). Dexmedetomidine had more "delirium free + coma free" days compared with lorazepam (7 vs. 3 days, p=0.01), and the prevalence of "delirium or coma" was lower in the dexmedetomidine group (87 vs. 98%, p=0.03). There was no difference in mechanical ventilator–free days, ICU length of stay, or 28-day mortality, but more patients were within 1 point of their RASS goal when receiving dexmedetomidine (67%) compared with lorazepam (55%), p=0.008.

2. The SEDCOM study compared the sedative effects of midazolam with those of dexmedetomidine in medical and surgical adult ICU patients, n=366. The prevalence of delirium was lower in the dexmedetomidine group (54%) than in the midazolam group (76.6%), p<0.001 (JAMA 2009;301:489-99). Median time to extubation was shorter in the dexmedetomidine group (3.7 days) compared with the midazolam group (5.6 days), p<0.01; however, the time in target sedation range, ICU length of stay, and mortality were no different between the two groups.

D. A recent meta-analysis was published that assessed the differences in ICU outcomes among sedative agents: "Benzodiazepine versus Non-benzodiazepine based sedation for mechanically ventilated, critically ill adults." This meta-analysis reviewed trials from 1996 to 2013 (Crit Care Med Sept 2013;41:S30-38):

1. Study inclusion criteria: (1) randomized controlled parallel-group design; (2) medical and surgical adult ICU patients on mechanical ventilation receiving intravenous sedation; (3) received a non-benzodiazepine (either propofol 1% or dexmedetomidine) compared with a benzodiazepine (either lorazepam or midazolam); and (4) had predefined outcomes: ICU length of stay, duration of mechanical ventilation, delirium prevalence, and all-cause short term mortality (45 days of study enrollment or during hospitalization). Excluded cardiac surgery and obstetric patients because this population has distinct clinical practices and outcomes that may differ from medical and surgical populations

2. Data from six randomized trials were included in the review (1235 patients), describing four primary outcomes:

    a. ICU length of stay (all six studies reported): ICU length of stay was longer in a benzodiazepine strategy compared with a non–benzodiazepine-based strategy (mean difference 1.6 days; 95% confidence interal (CI), 0.72–2.5; p=0.0005).

    b. Duration of mechanical ventilation (four of six studies reported): Longer duration of mechanical ventilation in a benzodiazepine strategy compared with a non-benzodiazepine-based strategy (mean difference 1.9 days; 95% CI, 1.7–2.09; p=0.00001)

    c. Delirium prevalence (two of six studies reported): No difference in delirium prevalence between a benzodiazepine and a non-benzodiazepine-based strategy (relative risk (RR) 0.98; 95% CI, 0.76–1.27; p=0.94)

    d. Short-term (45 days or less) all-cause mortality (four of six studies reported): No difference in risk of death between a benzodiazepine and a non–benzodiazepine-based strategy (RR 0.98; 95% CI, 0.76–1.27, p=0.94)

E. Lorazepam (Ativan)

1. Pharmacokinetics: A benzodiazepine that binds to the postsynaptic $GABA_A$ receptor, undergoes hepatic clearance by conjugation to inactive compounds, has a moderate to high volume of distribution and high protein binding. Onset of action is 15–30 minutes, slower than that of benzodiazepines that are more lipophilic (e.g., midazolam). Duration of action of intermittent dosing is 4–8 hours. As a continuous infusion, clearance of lorazepam decreases in an unpredictable fashion, and prolonged sedation may occur.

2. Effects: Anxiolysis/sedation, anticonvulsant, muscle relaxant. Maintains anterograde amnesia properties; however, studies report that delusional memories have occurred in patients receiving benzodiazepines in the ICU.

3. Dosing range: 1–4 mg every 4–6 hours intermittent dosing is recommended before using continuous infusion, as rapid accumulation with prolonged duration of action of lorazepam commonly occurs with continuous infusion.

4. Data: Carson et al. studied the number of days on mechanical ventilation in medical ICU patients receiving intermittent lorazepam (n=64) compared with continuous-infusion propofol (n=68); each group underwent daily interruption of sedation if the fraction of inspired oxygen (F_{IO_2}) was less than 80%. Median time on mechanical ventilation was 9 days in the lorazepam group versus 4.4 days in the propofol group, p=0.006; ICU length of stay was 12.7 days in the lorazepam group versus 8.6 days in the propofol group (p=0.05); no difference in hospital mortality. Delirium was not assessed in this study (Crit Care Med 2006;34:1326-32).

5. Propylene glycol toxicity: Because of its insolubility, injectable lorazepam is diluted in propylene glycol. Propylene glycol toxicity can occur with lorazepam infusions for more than 48 hours, particularly at doses of 6–8 mg/hour or greater: Presence of an osmolar gap, metabolic acidosis, unexplained new onset renal failure, and respiratory failure should prompt concern for propylene glycol toxicity, and lorazepam should be discontinued.

6. Other adverse effects: Paradoxical agitation, oversedation, confusion, and prolonged duration of sedative action, respiratory depression, hypotension.

F. Midazolam (Versed)
1. Pharmacokinetics: Benzodiazepine that binds to the postsynaptic $GABA_A$ receptor; undergoes phase I hepatic metabolism to an active glucuronidated metabolite, α_1-hydroxymidazolam, which is then renally excreted. A short- to medium-acting benzodiazepine in patients with normal renal and hepatic function. CYP3A4 substrate. Midazolam is highly lipophilic, has a high volume of distribution, and is highly protein-bound.

2. Clearance: Clearance of midazolam or its metabolite is significantly altered if either hepatic (primary drug accumulation) or renal (active metabolite α-hydroxymidazolam accumulation) functions are significantly impaired. CRRT partially clears the active metabolite, but does not effectively clear the parent compound, and therefore is not recommended as a method for definitive midazolam clearance (Am J Kidney Dis Feb 2005;45:360-71). High lipophilicity and high volume of distribution may lead to significant drug accumulation and a depot effect in the ICU patient. In general, clearance of midazolam when infused continuously becomes very unpredictable in the critically ill population, and emergence times may be significantly prolonged.

3. Effects: Anxiolysis/sedation, anticonvulsant, muscle relaxant. Maintains anterograde amnesia properties; however, studies report that delusional memories have occurred in patients receiving benzodiazepines in the ICU.

4. Dosing range: 1–4 mg every 2–4 hours intermittently or as needed should be considered before initiating continuous infusion. Elderly patients may tolerate only 1–2 mg per dose.

5. Data: In a multicenter European trial (MIDEX), Jakob et al. compared midazolam (n=251) with dexmedetomidine (n=249) with daily interruption and spontaneous breathing trials (SBTs); patients received fentanyl boluses for pain (JAMA 2012;307:1151-60). There was no difference in the primary outcome: proportion of time in target RASS (0, -3) without rescue therapy in midazolam (56%) versus dexmedetomidine (60%) groups. Median time on mechanical ventilation was lower in dexmedetomidine group (5 days) than in midazolam group (6.8 days), p=0.03. Patients' ability to communicate discomfort or pain to clinical staff was better in the dexmedetomidine group. There was significantly more bradycardia and hypotension in the dexmedetomidine versus midazolam groups, and more patients in the dexmedetomidine group had a drug discontinued because of its lack of efficacy.

6. Adverse effects: Paradoxical agitation, oversedation, and prolonged duration of sedative action; respiratory depression, hypotension

G. Propofol (Diprivan)
   1. SCCM suggests using a non-benzodiazepine (propofol or dexmedetomidine) for sedation to improve clinical outcomes in mechanically ventilated patients (+2B weak recommendation). Further evidence is required to substantiate potential differences in the incidence of delirium between non-benzodiazepine sedatives and benzodiazepines. The guidelines state "there is insufficient data to determine the relationship between propofol use and the development of delirium in adult ICU patients" (level C quality of evidence).
   2. Mechanism of action: General anesthetic by potentiation of the $GABA_A$ receptor; may inhibit *N*-methyl D-aspartate receptor activity at high doses. Propofol decreases cardiac β-adrenergic responsiveness and attenuates β-adrenergic signal transduction in cardiac myocytes, resulting in direct cardiac depressive effects.
   3. Pharmacokinetics: Hepatic conjugation; clearance may be prolonged (from minutes to hours) in patients with severe hepatic impairment or cirrhosis or with long-term infusions as it redistributes from fat and muscle to plasma. Highly lipophilic and large volume of distribution leads to extensive tissue distribution of propofol. Propofol maintains a three-compartment linear model: plasma, rapidly equilibrating tissues (e.g. major organs), slowly equilibrating tissues (e.g. fat deposits). Propofol is a substrate of several CYP enzymes, including CYP 2B6, 2C9, 2C19, and 3A4; pharmacokinetic studies of healthy volunteers show a 25% increase in propofol plasma levels when given with midazolam, a weak CYP3A4 and 2C9 inhibitor.
   4. Formulation: Standard propofol is a 1% (10 mg/mL) lipid emulsion containing 1.1 kcal/mL (0.1 g of fat per 1 mL of propofol), which must be considered when calculating nutritional intake (e.g., propofol dosed at 50 mcg/kg/minute in a patient weighing 70 kg would provide approximately 500 calories per day contributed by fat). Propofol contains 0.005% disodium edetate (EDTA) to decrease the rate of microorganism growth, which is known to chelate trace metals, including zinc. Zinc supplementation may be considered in patients at high risk of zinc deficiency (sepsis, burns, large-volume diarrhea) if propofol is used for more than 5 days. Strict aseptic technique must be followed when handling propofol; manufacturers recommend discarding propofol bottles and changing intravenous tubing every 12 hours to decrease the risk of contamination.
   5. Dosing range for ICU sedation: Propofol should be initiated at a low dose (approximately equal to 5 mcg/kg/minute) and titrated every 5–10 minutes to goal sedative effect; most patients in the ICU will be maintained at a dose of 5–50 mcg/kg/minute. Abrupt discontinuation of propofol is not recommended because of its rapid clearance (5–10 minutes).
   6. Data: In a multicenter European trial (PRODEX), Jakob et al. compared propofol (n=249) with dexmedetomidine (n=251) in patients managed with daily sedation interruption and SBTs and when pain was optimized using fentanyl boluses (JAMA 2012;307:1151-60). There was no difference in the primary outcome: proportion of time in target RASS (0, -3) without rescue therapy in propofol (65%) versus dexmedetomidine (65%) groups. No difference in median time on mechanical ventilation in propofol (5 days) versus dexmedetomidine (4 days), p=0.24. Patients' ability to communicate discomfort or pain to the clinical staff was better in the dexmedetomidine group. Critical illness polyneuropathy was more common in propofol (n=11) than in dexmedetomidine (n=2), p<0.02.
   7. Adverse effects: Bradycardia and hypotension (may be more common or severe in patients with cardiac dysfunction, intravascular volume depletion, or low systemic vascular resistance); respiratory depression, hypertriglyceridemia, pancreatitis with or without hypertriglyceridemia, symptoms related to PRIS.

8. Propofol Related Infusion Syndrome: This syndrome is a rare but life-threatening complication of propofol, generally occurring at doses exceeding 50 mcg/kg/minute for 48 hours or more. The mechanism of PRIS is complex and not completely understood, but it may include alterations in liver metabolism of the lipid emulsion, leading to the accumulation of ketone bodies and lactate and/or disruptions in the mitochondrial respiratory chain and inhibition of oxidative phosphorylation. Patients with urea cycle disorders may experience alterations in propofol metabolism within 24–48 hours of propofol use. Consider avoiding in patients with acute liver failure, or pancreatitis, because the symptoms of PRIS may be difficult to distinguish from the underlying disease state abnormalities. PRIS can be life threatening, and propofol should be discontinued immediately if symptoms are present.

   a. Clinical characteristics of PRIS may include metabolic acidosis, acute renal failure, cardiac failure, rhabdomyolysis, myoglobinemia, myoglobinuria, hyperkalemia, hypertriglyceridemia, and elevated creatine kinase levels.

   b. Risk factors for PRIS or other adverse effects of propofol may include decreased oxygen delivery to tissues, neurologic injury, sepsis, use of vasoactive medications, high-dose propofol, acute liver failure, and a history of hypertriglyceridemia and/or pancreatitis.

H. Dexmedetomidine (Precedex)

   1. Mechanism of action: α2-Adrenoceptor agonist in brain stem, resulting in inhibition of norepinephrine release. Dexmedetomidine maintains sedative, and weak analgesic or opiate-sparing properties. Its pain-relieving effects remain poorly quantified and are likely variable. Intubation is not required with the use of dexmedetomidine, given its lack of effect on the respiratory center. In general, dexmedetomidine is considered a weak sedative and would not be appropriate for use when deep sedation is required
   (e.g., in a patient requiring neuromuscular blockade).

   2. Pharmacokinetics: Hepatic by glucuronidation and renal excretion. Onset with loading dose 15–20 minutes; onset without loading dose greater than 20 minutes; duration of action 1–2 hours (may be significantly prolonged in hepatic impairment and when infused for prolonged periods of time). High protein binding 94%.

   3. Clinical effects: Sedation, analgesia (decreases opioid doses when used concomitantly). Unlike benzodiazepines, dexmedetomidine shows an increase in slow-wave sleep activity and improved sleep architecture in a small series of ICU patients; however, the clinical significance of these effects remains unclear.

   4. Dosing for ICU sedation: Optional loading dose 0.5–1 mcg/kg intravenously over 10 minutes, followed by 0.2–0.7 mcg/kg/hour. The loading dose may cause severe tachycardia and hypertension because of receptor oversaturation, which may then result in significant bradycardia and/or hypotension. Because of these untoward hemodynamic effects, the loading dose is rarely administered in clinical ICU practice on initiation of dexmedetomidine, and the drip is generally initiated at 0.2 mcg/kg/hour. If a loading dose is desired, a reduced infusion rate should be considered. For the maintenance infusion dose, randomized trials have safely used dexmedetomidine at higher-than-manufacturer recommended doses (up to 1.5 mcg/kg/hour).

   5. Duration of use: Although the package insert recommends a therapy of 24 hours or less, longer use for up to 7 days has been found safe in large randomized trials; thus, ICU clinicians often administer dexmedetomidine for longer than 24 hours.

   6. Cardiac surgery population: Short-term use of α2-agonists may decrease the inflammatory and stress response during and after cardiac surgery. Retrospective and randomized trials have shown decreased cardiac events (e.g., arrhythmias, myocardial infarction), decreased mortality, decreased time on mechanical ventilation, less acute kidney injury, less delirium, and lower opiate and benzodiazepine needs with dexmedetomidine use.

7. Adverse effects: Tachycardia, bradycardia, hypertension, hypotension, dry mouth. Should generally be avoided in patients with acute decompensated heart failure or advanced heart block.

8. Withdrawal symptoms: Case reports have been published describing the symptoms of dexmedetomidine withdrawal when used beyond 7 days at higher-than-recommended doses (e.g., tachycardia, hypertension, anxiety, general discomfort). A slow taper of dexmedetomidine may be necessary, or the addition of clonidine has been used in some cases to help decrease withdrawal symptoms and taper off the dexmedetomidine infusion. A tapering plan for clonidine should be documented if a patient is discharged from the ICU on clonidine for dexmedetomidine withdrawal.

9. Other ICU uses: Procedural sedation, palliative care pain and anxiety control, adjunct to opiates for sickle cell crisis, adjunct to benzodiazepines or propofol for alcohol withdrawal, bridge to extubation while tapering off longer-acting sedatives and/or opiates.

I. Amnestic Effects of Sedatives: Lorazepam, midazolam, and propofol all produce anterograde amnesia. This may be a beneficial effect of these drugs in certain ICU settings.

J. Delusional Memories and Nightmares: Patients who have received benzodiazepines in the ICU have reported frightening memories and confusion about what was actually happening to them during routine ICU care (e.g., thoughts of being stabbed with a knife during intravenous line placement). Concerns for PTSD, anxiety, depression, and delayed cognitive recovery may be associated with the prolonged use of benzodiazepines, obviating the patient's ability to form factual memories. The analgosedation method of sedation is a recent recommendation; therefore, adequate long-term studies on cognitive effects of analgosedation have not been done.

K. Level of Sedation in the ICU
1. Titrating medications to a goal sedation level via a sedation algorithm has been shown to decrease time on mechanical ventilation, ICU length of stay, and rates of tracheostomy. To assist in reaching and maintaining a goal level of sedation, the SCCM currently recommends either daily interruption of sedation, or titrating to a lighter versus deeper level of sedation, unless clinically contraindicated (+1B strong recommendation). The goal level of sedation will change throughout a patient's ICU stay, as the patient may require a deeper level in the first 24-48 hrs, then a lighter level of sedation as their condition improves. The guidelines recognize the challenges in defining "light" versus "deep" sedation and encourage clinicians to remain focused on the patient's safety and comfort while minimizing the short- and long-term complications of either under- or oversedating their ICU patients. To better define "light" sedation, the PAD guidelines offer specific practice principles to help clinicians in their daily sedation management: (1) patients should receive sedation only if required and (2) sedatives should be titrated to allow patient responsiveness and awareness, as shown by their ability to purposefully respond to a combination of any three of the following actions on request: open eyes, maintain eye contact, squeeze hand, stick out tongue, and wiggle toes. These assessments are critical in the complete evaluation of PAD and in motivating early mobility efforts. The two validated sedation scales currently recommended by the PAD guidelines are the RASS (Table 5) and the Riker Sedation-Agitation Scale (Table 6).

2. The PAD guidelines suggest using objective measures of brain function (e.g. Auditory evoked potentials, Bispectral index) as an adjunct to subjective sedation assessments in adult ICU patients concomitantly receiving a NMBA (+2B); the guidelines also recommend that "electroencephalogram monitoring be used to monitor nonconvulsive seizure activity in adult ICU patients with either known or suspected seizures or to titrate electrosuppressive medication to achieve burst suppression in adult ICU patients with elevated intracranial pressure (+1A)".

Table 5. Richmond Agitation Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violet; immediate danger to staff
+3	Very agitated	Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff
+2	Agitated	Frequently 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

Precedure

1. Observe patient. Is patient aleart and calm (score 0)?

    Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under *description*)?

2. If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.

    Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score -1).

    Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score -2).

    Patient has any movement in response to voice, excluding eye contact (score -3).

3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is not response to shaking shoulder.

    Patient has any movement to physical stimulation (score -4).

    Patient has no response to voice or physical stimulation (score -5).

Table 6. Riker Sedation-Agitation Scale

7	Dangerous agitation	Pulling at ETT, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side to side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting ETT
5	Agitated	Anxious or mildly agitated, attemting 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 again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands

ETT, endotracheal tube

3. As patients are kept more awake in the ICU, close attention must be paid to describing each part of their daily ICU care to facilitate factual memories. Patients who recall factual versus delusional memories may have less long-term PTSD, depression, and anxiety.

4. Sedation goals may change daily depending on the patient's health status. These goals should be addressed each day on patient care rounds and documented in the patient chart, and medications should be titrated to the goal sedation score.

5. Sedation scores should be done every 2–4 hours throughout the day and evening. Consider assessing every 4 hours during nighttime sleeping hours to minimize sleep interruption.

L. Acute Withdrawal Syndrome of Long-term Analgesia and/or Sedation in the ICU
    1. Patients who have been receiving high doses of continuous-infusion sedation and/or analgesia in the ICU for an extended period may be at risk of symptoms of sedative or analgesia withdrawal as dose tapering begins. In a retrospective review of adult trauma/surgical ICU patients, 32% of patients experienced either sedative or opiate withdrawal soon after discontinuing these medications. The patients in this study had been in the ICU for 20 days or more and were receiving higher mean daily analgesic and sedative doses compared with the non-withdrawal patients (fentanyl 6.4 mg vs. 1.4 mg; lorazepam 38 mg vs. 11 mg). The withdrawal patients in this study were also more likely to have received a NMBA (Crit Care Med 1998;26:676-84).

    2. The risk factors for and incidence of sedation or analgesia withdrawal in adult ICU patients have not been well characterized; however, these are important monitoring parameters in the long-term ICU patient receiving high doses of these medications. Use of longer-acting agents given orally or by feeding tube has been described to assist in the transition off long-term continuous infusions. The medical indication and dosing plan for using oral medications to taper off continuous infusions should be clearly documented in the medical chart on patient discharge from the ICU.

Patient Cases

4. D.L. is a 44-year-old woman with a history of smoking and chronic pancreatitis (triglyceride level 100 mg/dL on admission) who and has been on mechanical ventilation for 4 days. She is on hydromorphone 2 mg/hour and propofol 50 mcg/kg/minute for pain and sedation. Her pain and sedation scores are at goal, but her delirium score is "positive." Laboratory values show high triglyceride levels (630 mg/dL), elevation in liver function tests 3 times her baseline, and increasing lactate (5.0 mmol/L); other laboratory values and hemodynamic values are within normal limits. Which changes to this patient's sedation regimen would be most appropriate?

    A. Discontinue hydromorphone and initiate fentanyl drip.
    B. Decrease propofol drip and add haloperidol as needed for delirium.
    C. Add quetiapine 25 mg every 12 hours for delirium.
    D. Discontinue propofol and initiate dexmedetomidine drip.

5. A new attending physician has joined your cardiac surgery ICU team. The ICU routinely sedates with midazolam for a postoperative coronary bypass; however, the new attending would like to switch to dexmedetomidine, a non-formulary medication for your hospital. Which determinant is most appropriate to consider when completing a cost-benefit analysis of a more expensive sedative in the ICU?

    A. Nursing satisfaction score.
    B. Physician experience and preference.
    C. Days on mechanical ventilation.
    D. Pharmacy intravenous administration costs.

Patient Cases (*continued*)

6. P.S. has been on mechanical ventilation for 2 weeks and is now ready for extubation. Her sedating medications have included fentanyl infusion 50 mcg/hour and dexmedetomidine 1.5 mcg/kg/hour for 12 days. Which adverse event(s) would best be monitored after the withdrawal of these medications?

    A. Tachycardia/hypertension secondary to dexmedetomidine withdrawal.
    B. Increased gastric residuals secondary to fentanyl withdrawal.
    C. Dry mouth and urinary retention secondary to dexmedetomidine withdrawal.
    D. Bradypnea/bradycardia secondary to fentanyl withdrawal.

7. T.R. is admitted to the ICU for complications after a failed liver transplant 3 months prior. He has been sedated with fentanyl 25 mcg/hour and midazolam 3 mg/hour for the past 3 days. On rounds, the nurse tells the team that she could not assess his pain score during the past 12 hours because he is unresponsive, and she rates him "deeply sedated" (RASS -4, -5). Which is the most appropriate consideration with respect to his analgesic or sedation management?

    A. Sedative medications are appropriate, but you are concerned about encephalopathy.
    B. Sedated state is likely from the protracted use of midazolam and fentanyl in hepatic failure.
    C. Hydrophilic properties of fentanyl may delay clearance and increase sedative effects.
    D. Fentanyl and midazolam doses are too high and should be decreased by 25%.

IV. DELIRIUM IN THE INTENSIVE CARE UNIT

A. Delirium is a disturbance in consciousness resulting in the inability to receive, process, store, or recall information. In the ICU, delirium may present as hyperactive (agitated), hypoactive (calm but confused; lethargic), or, most commonly, mixed hyper/hypoactive states. Distinguishing characteristics include:
    1. Acute onset or fluctuating course
    2. Inattention and disorganized thinking
    3. Altered level of consciousness

B. Incidence of Delirium in the ICU and Association with Long-term Cognitive Impairment– Incidence of delirium in the ICU may be very high: 30%–80%. Development of delirium in the ICU is associated with up to a 3-fold increase in mortality and an increase in cognitive decline, longer hospital stay, and increased likelihood of discharge to nursing home. Two recent studies found a longer duration of delirium was independently associated with worse activity of daily living scores and worse cognitive impairment scores at 3 and 12 months post-ICU discharge (Crit Care Med 2014;42(2):369-77; N Engl J Med 2013;369:1306-16).
    1. The underlying pathophysiology of delirium is not well understood; however, it may involve a complex set of factors, including inflammation, hypoxemia, altered cerebral perfusion and metabolism, and an imbalance in central neurotransmitters (e.g., dopamine, norepinephrine, acetylcholine, GABA, glutamate). It is commonly called "acute brain failure" to liken it to other major organ failures needing incisive attention.
    2. Risk Factors for Delirium: a recent systematic review of studies from 2001 to 2013 described 11 variables identified as risk factors for developing delirium in the ICU, extracting from only strong or moderate level of evidence (Crit Care Med 2015;43:40-47):
        a. Age
        b. Preexisting dementia
        c. History of baseline hypertension
        d. Sedative-associated coma

      e.   APACHE II (Acute Physiology and Chronic Health Evaluation II) score

      f.   Delirium on the previous day

      g.   Emergency surgery

      h.   Mechanical ventilation

      i.   Organ failure

      j.   (Poly)trauma

      k.   Metabolic acidosis

3. Medication Induced Delirium: several classes of medications are well known to cause altered mental status or cognitive impairment, in or out of the intensive care unit. These may include anticholinergics, benzodiazepines, opiates, antipsychotics, antispasmodics, and anticonvulsants. If these medications are used in a critically ill patient who also has, or is at risk for, critical illness-related delirium, the degree of confusion or delirium could clearly worsen. The precise impact of these and other medications on the onset, duration, or severity of delirium in the ICU is still not well characterized in randomized controlled trials using the appropriate methodology for a fluctuating illness such as delirium (e.g. Markov modeling). Given the multifactorial nature of delirium in the ICU, clinicians should be leery of solely assigning blame to medications if a patient presents with symptoms of delirium. Despite this limitation, certain medications should invoke caution when used in an ICU patient who is at risk for delirium or who has developed delirium:

      a.   Benzodiazepines and Opiates (inconclusive evidence): PAD guidelines state that "benzodiazepine use may be a risk factor for the development of delirium in adult ICU patients (B)." However, recent research including a meta-analysis, systematic review, and randomized trial did not find a direct association between use of benzodiazepines and the development of delirium in the ICU (Crit Care Med 41:S30-8; Crit Care Med 43:40-7; Crit Care Med 43:557-66). Further research is needed to clarify the independent relationship between benzodiazepines and delirium in the ICU. Exercising caution with use, dosing, and titration of these medications continues to be warranted.

      b.   Anticholinergics: known for their sedating and altered mentation adverse effects and should be used with caution in the ICU setting.

      c.   Systemic corticosteroids in patients with acute lung injury: In a secondary analysis of a multicenter observational study of adult medical and surgical ICU patients with acute lung injury (n=330), Schreiber et al. found a significant and independent association between the use of systemic corticosteroids and transition to delirium from a non-comatose, non-delirious state within 24 hours of corticosteroid administration (odds ratio [OR] 1.52 [1.05–2.21], p=0.03). Delirium was documented on one or more days in 83% of patients, with a median of 7 days' duration. There was no significant association in prednisone-equivalent dose and transition to delirium. The authors recognize that a direct causal relationship cannot be determined between corticosteroid use and delirium from this observational study; however, they believe that the study adds valuable data toward our understanding of risk factors for delirium in the ICU (Crit Care Med 2014;42:1480-6).

4. Outcomes of Sedation-related versus Illness-related Delirium: There is ongoing research investigating differences in outcomes between sedation-related delirium and non-sedation-related or persistent delirium (e.g. delirium related to an underlying illness). A recent single center study using propofol and fentanyl uniquely timed their CAM-ICU assessments before and after a daily sedation interruption protocol. They found that patients were 10.5 times more likely to screen positive for delirium when assessed before daily sedation interruption, versus after daily sedation interruption. Patients who had "no delirium" or "reversible sedation-related delirium", had significantly shorter days on mechanical ventilation, ICU days, hospital days, and decreased 1-year mortality compared to the "persistent delirium" group. These authors suggest the timing of delirium assessment with sedation interruption is crucial to better defining the type of ICU delirium; and that patients with "reversible sedation-related delirium" may have better outcomes than those with "non-sedation-related persistent delirium" (Am J Resp Crit Care Med 2014;189:658-665).

Patients could have both sedation-related and illness-related delirium, and additional research in this area is needed to clarify differences in short and long-term outcomes.

5. Iatrogenic precipitants may include, but not be limited to:
   a. Presence of new infection
   b. Dehydration and malnutrition
   c. Use of physical restraints and catheters

C. Monitoring for Delirium: SCCM provides a grade 1B strong recommendation for routine monitoring in all ICU patients for delirium, using either the CAM-ICU or the ICDSC. The PAD guidelines summarized their review of five delirium assessment scales used for adult ICU patients. The two scales with the highest psychometric (e.g., validity and reliability) scores were the CAM-ICU and the ICDSC. Both of these scales were designed for patients in the ICU either on or off mechanical ventilation, and both showed high sensitivity and specificity when tested against the American Psychiatric Association's criteria for delirium. The CAM-ICU and ICDSC are the delirium assessment scales currently recommended in the PAD guidelines for use in adult ICU patients.

1. Delirium assessment should be done every 8–12 hours and documented in the medical chart; results should be discussed with the medical team. Recent data suggests delirium assessments should ideally be performed only after a decrease or interruption in sedative doses, with appropriate time allowed for drug clearance (Am J Resp Crit Care Med 2014;189:658-665).

2. If delirium is detected, the medical team should correct possible etiologies, decrease ongoing risk factors, and try nonpharmacologic treatment and preventive measures when appropriate.

D. Prevention of Delirium: There are currently no data to support using pharmacologic therapy to prevent the onset of delirium in the general adult ICU patient. Postoperative patients represent a high-risk subset of patients for the development of delirium, particularly patients 65 years and older. Delirium has been reported in 15%–53% of postoperative patients and is as high as 80% when patients are admitted to the ICU. Studies using antipsychotics for the prophylaxis of delirium in this subset of patients have yielded mixed results. One study by Kees J et al. of elderly patients undergoing hip surgery were randomized to haloperidol versus placebo beginning preoperatively and for 3 days postoperatively. No difference in the incidence of postoperative delirium was detected between the groups; however, the duration of delirium was shorter in the haloperidol group. A separate study by Wang et al. randomized postoperative patients 65 years or older (n=457) undergoing non-cardiac surgery to haloperidol (0.5-mg bolus, followed by 0.1 mg/hour for 12 hours) or placebo. The haloperidol prophylaxis group was less likely to develop delirium during the 7-day study period compared with placebo (15% vs. 23%, p=0.031). Outside this specific subset of high-risk patients, data are still scarce from which to draw conclusions regarding pharmacologic prophylaxis for delirium in the general critically ill population, and more research is needed. At this point, nonpharmacologic measures for preventing delirium should remain a focus for all ICU patients when such measures are considered safe and feasible. These may prevent 30%–40% of new-onset delirium cases, particularly in the elderly:

1. Early mobilization (+1B recommendation)
2. Sleep interventions to decrease nighttime disturbances: Cluster patient care activities and medication administration to daytime and evening to help normalize sleep patterns; control light and noise; consider earplugs at night in patients without delirium (+1C recommendation).
3. Decrease the use of benzodiazepines and anticholinergics in patients at risk of delirium; use the lowest effective doses of any sedating medication (e.g., opiates, antipsychotics).

E. Sleep in the ICU: Uninterrupted sleep (ideally 4 hours or more) is vital for an adequate immune response to illness, to maintain normal metabolic and hormonal balance, and possibly to decrease delirium and/or agitation. Several disturbances in the ICU such as alarms, general noise, and frequent physical interruptions (e.g., examination, turning, laboratory tests, medication administration) make it challenging for patients to reach and maintain the slow-wave sleep cycle needed for optimal immune function. Sleep research in the ICU is ongoing, and more information will be forthcoming regarding its effects in the critically ill patient. Currently the PAD guidelines recommend promoting sleep in adult ICU patients by optimizing patients' sleep environments (+1C recommendation):

1. To avoid waking patients at night, pharmacists should ensure that medications are scheduled during the daytime and evening hours, if possible—particularly orally or subcutaneously administered medications.

2. Sleep protocols should seek to cluster patient care activities (e.g., vital sign checks, radiology tests, laboratory checks, sedation assessments) around nighttime sleeping hours unless clinically indicated in a specific patient population.

F. Treatment of Delirium: Realizing that the cause of delirium may be multifactorial, clinicians should remain vigilant in identifying and correcting the underlying etiology of delirium as their first step in management. Common iatrogenic precipitants that are often undetected include new-onset infection (e.g., urinary tract infection, pneumonia), dehydration, and malnutrition. Additionally, patients could present or progress to alcohol withdrawal or withdrawal from other chronic medications / substances, and present as hyperactive delirium. If suspected, this withdrawal syndrome must be addressed and treated accordingly. All of these concerns should be ruled out and treated as indicated if there is concern for delirium. The SCCM states "treatment with atypical antipsychotics may decrease the duration of delirium" (grade C level of evidence); however, the PAD guidelines also state there is "no evidence to support use of haloperidol to prevent or decrease duration of delirium." Limited data exist for using antipsychotics to treat delirium in the ICU; therefore, the initial focus should be on nonpharmacologic treatment measures. If an antipsychotic is initiated, a strategy for discontinuation or outpatient follow-up should be documented to help avoid inadvertent continuation beyond the hospital environment (Table 7). Serious adverse effects are associated with the use of any antipsychotic; effects such as arrhythmias, serotonergic syndrome, neuroleptic malignant syndrome, extrapyramidal symptoms, and oversedation should be monitored on a daily basis. Initial and maximum doses for atypical antipsychotics for ICU delirium are not well described.

Table 7. Antipsychotics[a]

Drug	CYP Substrate (major)	Usual Starting Dose	Significant Adverse Effects[b]	Formulations
Haloperidol	3A4, 2D6	1–2 mg elderly; 2–4 mg if history of psychiatric disorders	Anticholinergic: * Sedation: * EPS: ** NMS: *	PO, IM, IV (non-FDA approved)
Olanzapine	1A2	5 mg	Anticholinergic: ** Sedation: ** EPS: * NMS: * neuromuscular weakness	PO, disintegrating tablet, IM
Quetiapine	3A4	12.5–25 mg	Anticholinergic: ** Sedation: ** NMS: * Orthostatic hypotension: **	PO
Risperidone	2D6	0.5–1 mg	Anticholinergic: * Sedation* EPS: ** NMS: * Orthostatic hypotension: ** cardiac conduction abnormalities	PO, disintegrating tablet
Ziprasidone	1A2 (minor) 3A4 (minor)	20 mg PO; 10 mg IM	Anticholinergic: * Sedation: * EPS: * NMS: *	Oral, IM

NOTE: * = lower risk; ** medium-higher risk.

[a]Not all medications listed are FDA label approved for use in delirium; not all are recommended by SCCM for the treatment of delirium in the ICU.

[b]Adverse effects other than QTc prolongation. Documented QTc prolongation incidence: IV haloperidol = ziprasidone > risperidone > olanzapine = quetiapine.

EPS = extrapyramidal symptoms; IM = intramuscular(ly); IV = intravenous(ly); NMS = neuroleptic malignant syndrome; PO = oral(ly).

1. Quetiapine (Seroquel): Studied by Devlin et al. in a randomized, placebo-controlled pilot trial to compare the efficacy and safety of scheduled quetiapine with placebo for the treatment of delirium in ICU patients during a 10-day study period (Crit Care Med 2010;38:419-27). Significant exclusions were as follows: patients with end-stage liver disease, those with alcohol withdrawal, those with a QTc greater than 500, and those on concomitant QTc-prolonging agents. This very small pilot study (n=36), in which the placebo group was administered as-needed intravenous haloperidol, found that quetiapine was associated with a shorter time to first resolution of delirium, reduced duration of delirium, and less agitation compared with placebo. Mortality and ICU length of stay were not different from placebo. Quetiapine is available in immediate- or extended-release oral dosage forms.
   a. Pharmacokinetics: Hepatically metabolized to one active and two inactive metabolites. Metabolites renally cleared. Many drug interactions, CYP3A4 (major) and CYP2D6 (minor) substrates. Peak plasma levels for oral about 1½ hours (immediate release).
   b. Initial dose range for ICU delirium: 50 mg once to three times daily. Consider lower starting doses for elderly patients because of sedating effects. The Devlin study initiated 50 mg every 12 hours and titrated to a maximum dose of 200 mg every 12 hours.

    c. Adverse effects (early onset): Sedation, orthostatic hypotension, extrapyramidal symptoms, QTc prolongation.

2. Olanzapine (Zyprexa): Available in oral, orally disintegrating, and intramuscular (immediate and extended release) dosage forms. Intramuscular administration may result in plasma concentrations 5 times those of oral administration. The U.S. Food and Drug Administration (FDA) warns that the use of intramuscular olanzapine has resulted in unexplained deaths; use of intramuscular olanzapine with benzodiazepines may result in significant oxygen desaturation.

    a. Pharmacokinetics: Metabolized by glucuronidation and CYP 1A2, 2D6 oxidation. Clearance is significantly increased (around 40%) in smokers and decreased in females (around 30%). Many drug interactions, CYP1A2 (major) and CYP2D6 (minor) substrates. Weak inhibitor of several CYP isoenzymes. Peak plasma levels for oral: About 6 hours.

    b. Suggested starting dose for ICU delirium: 5 mg orally once daily.

    c. Adverse effects (early onset): Drowsiness, extrapyramidal symptoms, neuromuscular weakness, serotonin syndrome. High doses may cause cardiac arrhythmias, cardiopulmonary arrest, and extreme sedation to coma-like states.

3. Risperidone (Risperdal): Available in oral and oral dispersible tablets (M-tabs) and intramuscular injection dosage forms.

    a. Pharmacokinetics: Hepatically metabolized to active metabolites, renally cleared. Many drug interactions, CYP2D6 (major) and CYP3A4 (minor) substrates and P-glycoprotein. Peak plasma levels for oral about 1 hour.

    b. Suggested starting dose for ICU delirium: 0.25–0.5 mg once or twice daily.

    c. Adverse effects (early onset): Cardiac arrhythmias, anticholinergic effects, extrapyramidal symptoms.

4. Ziprasidone (Geodon): Studied in a multicenter, randomized, placebo-controlled pilot trial of mechanically ventilated patients to test the hypothesis that antipsychotics would improve days alive without delirium or coma in the ICU (MIND trial). Medical and surgical adult ICU patients (n=101) from six tertiary care centers in the United States on mechanical ventilation who had an abnormal level of consciousness or were on analgesia/sedative medications were randomly assigned to receive haloperidol, ziprasidone, or placebo every 6 hours for up to 14 days during a 21-day study. During the study, no difference was found in median days alive without delirium or coma between the haloperidol (14 days), ziprasidone (15 days), and placebo (12.5 days) groups, p=0.66. They also found no difference in ventilator-free days, hospital length of stay, or mortality among the three groups. (Crit Care Med 2010;38:428-37). Ziprasidone is available in oral and intramuscular dosage forms.

    a. Pharmacokinetics: Hepatic by glutathione and aldehyde oxidase. Minor substrates of CYP 1A2, 3A4. Peak plasma levels for oral about 6 hours; intramuscular about 1 hour.

    b. Suggested starting dose for ICU delirium: 20 mg twice daily (oral).

    c. Adverse effects (early onset): Somnolence, extrapyramidal symptoms, dizziness, orthostatic hypotension.

V. "ABCDE BUNDLE": SEDATION MANAGEMENT, VENTILATOR WEANING, AND EARLY MOBILITY

A. Incorporating several concomitant patient care interventions has been shown to improve care; incorporating such interventions into one consolidated bundle is an effective implementation strategy. The ABCDE bundle has been shown to reduce sedative needs, potentially prevent or decrease the duration of delirium, and decrease the time on mechanical ventilation. This research is still ongoing; therefore, some controversy may exist regarding the necessity of all of these steps.

B. The purpose of the bundle is to provide a daily structured and coordinated effort of decreasing sedative doses, together with weaning of mechanical ventilation, and early mobility. This bundle may need to be modified to best fit a specific ICU environment and requires a multidisciplinary approach (e.g., physician, nursing, pharmacy, respiratory therapy, and physical and occupational therapy). Many challenges with the bundle have been recognized and published, notably the lack of adequate staff to fully perform the bundle on a consistent basis (e.g., 1 respiratory therapist for 8–10 patients; lack of physical therapists and nursing care partners), and nursing concerns with having two patients undergoing an awakening trial or breathing trial at the same time.

C. Using a stepwise approach, the ABCDE bundle coordinates patient safety screens with the SAT and the SBT. The initial awakening and breathing ("AB") steps start the bundle; safety screen criteria may vary among institutions, as may the time to wait if a patient does not pass the initial screens (e.g. 8 hours vs. 12 hours vs. 24 hours). The ABC (Lancet 2008;371:126-34) and ABCDE (Crit Care Med 2014;42:1024-36) study protocols were to wait 24 hours before rescreening patients for the SAT or SBT if these protocols failed.

1. SAT safety screen (criteria may vary, published trial protocols have had variations): If any are present, discontinue the protocol and repeat in 12–24 hours or according to hospital protocol:
    a. Current RASS greater than 2; or goal for deeper sedation (e.g. RASS -3 to -5)
    b. Active seizures
    c. Alcohol withdrawal
    d. F_{IO_2} of 60% or greater (these criteria are not consistently present among published trial protocols)
    e. Neuromuscular blockade
    f. Myocardial ischemia in previous 24 hours or ongoing myocardial ischemia
    g. Intracranial pressure (ICP) less than 20 mm Hg or need for control of ICP
    h. Receiving extracorporeal membrane oxygenation

2. If pass SAT safety screen, begin SAT: Hold continuous benzodiazepine infusions and/or sedative boluses; for shorter-acting agents (e.g., propofol), gradually decrease dose every 20–30 minutes to point of awareness. Bolus opioids allowed for breakthrough pain. Continuous opioid infusions allowed if presence of active pain. If the patient "passes" the SAT, continue to the SBT safety screen.

3. SAT failure (if any are present, discontinue the protocol and repeat in 12–24 hours or according to hospital protocol):
    a. Anxiety/agitation/pain present (e.g., RASS greater than +1 for 5 minutes or more)
    b. Respiratory rate greater than 35 breaths/minute for 5 minutes or more
    c. Oxygen saturation less than 88% for 5 minutes or more
    d. ICP greater than 20 mm Hg
    e. Acute cardiac ischemia or arrhythmia
    f. Respiratory or cardiac distress (e.g., HR increase of 20 beats/minute or greater, HR less than 55 beats/minute, use of accessory muscles, abdominal paradox, diaphoresis, or dyspnea)

4. If SAT fails: Reinitiate sedation, if necessary, at half the previous dose and titrate to goal. Determine reasons for SAT failure. Repeat SAT steps in 12–24 hours or according to hospital protocol.

5. SBT safety screen (if any are present, discontinue the protocol, and reinitiate the previous sedative dose; repeat in 12–24 hours or according to hospital protocol):
    a. Agitation
    b. Oxygen saturation less than 88%, F_{IO_2} greater than 50%
    c. PEEP (positive end expiratory pressure) greater than 7.0 cm H2O
    d. Myocardial ischemia in previous 24 hours
    e. Increasing vasopressor requirements
    f. Lack of inspiratory efforts

6. SBT: If a patient tolerates the SBT for more than 2 hours, consider extubation.

7. SBT failure:
    a. Respiratory rate greater than 35 breaths/minute (for more than 5 minutes) or less than 8 breaths/minute
    b. Oxygen saturation less than 88% for more than 5 minutes
    c. ICP greater than 20 mm Hg, mental status change
    d. Acute cardiac ischemia or arrhythmia
    e. Respiratory distress (use of accessory muscles, abdominal paradox, diaphoresis, and dyspnea)
8. If SBT fails: Reinitiate sedation, if necessary, at half the previous dose and titrate to goal. Repeat bundle in 12–24 hours or according to hospital protocol.
9. Choose the right sedative ("C"): Use a multidisciplinary approach, including focused pharmacy input, to choose a sedative according to individual patient needs, hemodynamic stability, and organ function (e.g., hepatic, renal, cardiac, pulmonary, pancreatic).

D. Delirium Monitoring and Management ("D"): Monitor sedation to titrate toward a daily goal, and assess for delirium using the CAM-ICU or ICDSC when patients are wakeful on a routine basis (every 8–12 hours).

E. Early Mobility ("E"): Perform a mobility safety screen, and use a daily mobility protocol.

F. Spontaneous Awakening Trials vs. Lighter Sedation vs. the ABCDE Bundle
    1. Studies comparing these methods of managing sedation have not shown convincing differences in time on mechanical ventilation. However, these studies did not use safety screens to identify patients for the SAT, and used frequent nursing dosing titrations (e.g. every 15-30 minutes) when patients were oversedated; thus, they may not be applicable to some hospital protocols (JAMA 2012;308:1985-92).
    2. Two studies by Girard et al. and Balas et al. that did coordinate the SAT with the SBT both showed decreased time on mechanical ventilation. SCCM now discusses the benefits of this coordination on its Web site.

Patient Cases

8. P.V. is a 70-year-old woman with diabetes and hypertension admitted to the ICU in respiratory failure (F_{IO_2} 80%) secondary to MRSA (methicillin-resistant *Staphylococcus aureus*) pneumonia and refractory shock, for which she was administered norepinephrine and hydrocortisone. She is day 4 of mechanical ventilation (F_{IO_2} 45%), is off norepinephrine for 48 hours, and has been afebrile for 48 hours. The nurse describes new confusion and she is concerned for delirium on examination, but the patient denies pain. Her medications include vancomycin 1000 mg daily, heparin 5000 units subcutaneously every 12 hours, hydrocortisone 50 mg every 6 hours, famotidine 20 mg daily, NPH (neutral protamine Hagedorn) insulin 20 units daily, and fentanyl 75 mcg/hour. Which is the most appropriate recommendation at this time?

    A. Decrease fentanyl and add lorazepam.
    B. Decrease fentanyl and stop hydrocortisone.
    C. Decrease fentanyl and add quetiapine.
    D. Decrease fentanyl and stop famotidine.

Patient Cases (*continued*)

9. D.B. is a 45-year-old man admitted to the ICU after a motor vehicle accident. On day 2, he develops atrial fibrillation, and the team initiates an amiodarone infusion. Other medications include metoprolol 50 mg twice daily, levofloxacin 500 mg daily, fluconazole 400 mg daily, quetiapine 75 mg every 8 hours, and docusate. Which are the most relevant adverse events to consider from this combination of medications?

    A. QTc prolongation and SCr elevation.
    B. QTc prolongation and liver enzyme elevation.
    C. QTc prolongation and rhabdomyolysis.
    D. QTc prolongation and hypokalemia.

10. G.D., a 59-year-old man with no significant medical history, is admitted to the neurosurgery ICU after a subarachnoid hemorrhage and needs intubation. He is hemodynamically stable; however, ICPs have ranged from 25 to 30 mm Hg. Sedatives include a fentanyl drip and propofol 30 mcg/kg/minute. His sedation score is "deeply sedated," and the intensivist asks about doing the SAT. Which clinical value would exclude this patient from undergoing the SAT?

    A. Patient needs ongoing pain medication.
    B. Patient is younger than 60 years.
    C. Propofol needs no SAT because it is a short-acting agent.
    D. Patient has an ICP greater than 20 mm Hg.

11. Nursing staff members have asked you to give an in-service on SATs for their ICU. They express concern because they have heard that patients often do not tolerate turning off or tapering sedatives each day. Which would best address these concerns within the lecture?

    A. Focus on the data stating that SATs are safe for any type of patient population.
    B. Focus on using the confusion assessment method for the intensive care unit (CAM-ICU) to determine whether the patient is appropriate for the SAT.
    C. Focus on the safety screens for both the SAT and the SBT.
    D. Focus on the improved outcomes associated with daily SATs versus targeting lighter sedation.

VI. NEUROMUSCULAR BLOCKADE IN THE INTENSIVE CARE UNIT

A. The most recent SCCM guidelines for the sustained use of neuromuscular blockade in the ICU were published in 2002. Surveys have reported a dramatic decrease in the use of NMBAs during the past 20 years, from around 80% to 15% in patients on mechanical ventilation. This change in practice may be secondary to a better understanding of the serious adverse effects of prolonged paralysis, together with accepted standards of care for modes of mechanical ventilation in patients with ARDS.

B. Clinical Scenarios for the Use of NMBAs in the ICU May Include:
    1. Rapid sequence intubation
    2. ARDS
    3. Status asthmaticus
    4. Elevated ICP
    5. Elevated intra-abdominal pressure
    6. Therapeutic hypothermia after cardiac arrest

C. Acute Respiratory Distress Syndrome
1. Cisatracurium has been the most-studied NMBA for ARDS since 2000, primarily as short-term treatment and in severe cases of ARDS. In 2010, a randomized placebo-controlled trial (n=340) found that short-term cisatracurium (48 hours) significantly improved 90-day survival, increased ventilator-free days, increased organ dysfunction–free days, and decreased barotrauma in patients with severe ARDS (Pao_2/Fio_2 less than 120 mm Hg). The investigators did not find a difference in neuromuscular weakness compared with placebo. Other cisatracurium studies have shown improvements in oxygenation and a reduction in inflammatory mediators.
2. In retrospective studies, the use of NMBAs in ARDS was associated with a prolonged duration of mechanical ventilation, prolonged ICU length of stay, and increased mortality.
3. Use of NMBAs in ARDS remains extremely controversial, and their exact role for this indication needs further investigation. Short-term use of cisatracurium (48 hours or less) when used early may be beneficial for severe ARDS (Pao_2/Fio_2 less than 120 mm Hg). It is imperative to understand that the use of NMBAs in ARDS should be considered a last resort and that they are to be used only after aggressive sedation maneuvers and appropriate ventilatory changes have been tried.

D. Therapeutic Hypothermia After Cardiac Arrest
1. The American Heart Association guidelines for "post-cardiac arrest care" (Circulation 2010;122:S768) provide the following summary statements regarding therapeutic hypothermia: "We recommend that comatose (e.g., lack of meaning response to verbal commands) adult patients with return of spontaneous circulation (ROSC) after out-of-hospital ventricular fibrillation cardiac arrest should be cooled to 32°C–34°C for 12–24 hours (Class I, level of evidence B). Induced hypothermia also may be considered for comatose adult patients with ROSC after in-hospital cardiac arrest of any initial rhythm or after out-of-hospital cardiac arrest with an initial rhythm of pulseless electrical activity or asystole (Class IIb, level of evidence B)."
2. NMBAs have been used to prevent or treat shivering during therapeutic hypothermia.
3. The optimal combination and dosing of sedatives and paralytics have not been well established because the metabolism of these drugs is significantly slowed during hypothermia, and potency may be decreased. NMBAs have been used in both a bolus and continuous-infusion fashion during therapeutic hypothermia.

E. Sedation During NMBA: It is critical that patients are in a sedated, nonagitated state, and pain-free state with a benzodiazepine and opioid before initiating a NMBA. Additional agents such as propofol may also be necessary to achieve patient comfort before beginning paralysis.

F. Two Classes of NMBAs According to Mechanism of Action: Depolarizing and nondepolarizing:
1. Depolarizing NMBAs: Bind and activate acetylcholine receptors, causing persistent depolarization, which then renders muscle fibers resistant to further cholinergic stimulation. Succinylcholine is the only available depolarizing NMBA. Because of its quick onset and short duration, it is commonly the drug of choice for urgent or emergency intubation.
    a. Pharmacokinetics: Hydrolyzed by plasma pseudocholinesterase
    b. Usual dose: .05–1.5 mg/kg intravenously or intramuscularly
    c. Onset intravenously: 30–60 seconds; intramuscularly: 2–3 minutes
    d. Duration intravenously: 4–6 minutes; intramuscularly: 10–30 minutes
    e. Should not be used in patients with a history of malignant hyperthermia, hyperkalemia, stroke, paralysis, glaucoma, penetrating eye injuries, or spinal, crush, or burn injuries after 24 hours
    f. Adverse effects: Arrhythmias, bradycardia or tachycardia, hyperkalemia, rhabdomyolysis

2. Nondepolarizing NMBAs: Nicotinic receptor antagonists (competitive), blocking the action of acetylcholine at the neuromuscular junction. Divided into aminosteroid group (pancuronium, vecuronium, and rocuronium), and benzyl isoquinolinium group (atracurium, cisatracurium, doxacurium, and mivacurium)

    a. Pancuronium: Long-acting aminosteroid; intermittent or scheduled bolus may be preferred to continuous infusion because of accumulation and variable clearance. Older NMBA, not used much in the United States

        i. Pharmacokinetics: Hepatically metabolized (30%–50%) and renally cleared as unchanged drug (50%–70%). Accumulation and prolonged duration of paralysis will occur with varying degrees of hepatic and/or renal dysfunction. Duration of about 60–120 minutes

        ii. Adverse effects: Vagolytic activity, sympathetic stimulation, bradycardia, prolonged effect

    b. Vecuronium (Norcuron): Intermediate-acting aminosteroid; often used as continuous infusion

        i. Pharmacokinetics: Hepatically metabolized (30%–50%); cleared renally (20%–30%), with fecal excretion. Has an active metabolite, around half the activity of parent compound. Duration 30 minutes after bolus intubation dose

        ii. Adverse effects: Vagolytic activity at higher doses, prolonged weakness

    c. Rocuronium (Zemuron): An intermediate-acting aminosteroid; considered a suitable alterative to succinylcholine for rapid sequence intubation (dose: 0.6–1.0 mg/kg) because of its rapid onset of action (60–90 seconds). Duration 30–40 minutes

        i. Pharmacokinetics: Primarily hepatically metabolized, minimal renal excretion. No active metabolite. Prolonged effects have been observed in patients with hepatic or renal failure.

        ii. Adverse effects: Vagolytic activity at higher doses, bradycardia

    d. Atracurium: Intermediate-acting benzyl isoquinolinium; a mixture of 10 stereoisomers (contains 15% cisatracurium)

        i. Pharmacokinetics: Undergoes Hofmann elimination to form the toxic metabolite laudanosine at high levels. Laudanosine is a cerebral stimulant that may precipitate seizure activity, clearance dependent on liver and kidney function. Duration of atracurium 20–40 minutes

        ii. Adverse effects: Histamine release may cause cardiovascular adverse effects and bronchospasm; laudanosine accumulation may cause seizure activity.

    e. Cisatracurium (Nimbex): An intermediate-acting benzyl isoquinolinium. Differences compared with atracurium: It is only one isomer, has a slower onset at normal bolus doses, no histamine release

        i. Pharmacokinetics: Undergoes Hofmann elimination, forms laudanosine but at much lower levels than atracurium. Renal and hepatic dysfunction do not alter cisatracurium clearance. Duration 30–60 minutes

        ii. Adverse effects: Prolonged weakness with continued use

G. Drug Interactions with NMBAs: Certain medications may decrease the activity of NMBAs, whereas others can enhance or prolong the paralytic action.

    1. Drugs decreasing the activity of NMBAs:

        a. Calcium: Antagonizes the effect of magnesium on neuromuscular blockade

        b. Carbamazepine: Competitor of acetylcholine receptor

        c. Phenytoin: depressed post-synaptic response to acetylcholine

        d. Ranitidine: Unknown mechanism

        e. Theophylline: Unknown mechanism

2. Drugs prolonging the activity of NMBAs:
   a. Antibiotics: Aminoglycosides, clindamycin, tetracyclines, vancomycin. Decreases pre-junctional acetylcholine release with decreased postjunctional acetylcholine receptor sensitivity; blocks acetylcholine receptor
   b. Cardiac medications: β-Blockers, calcium channel blockers, procainamide, quinidine, and furosemide. Decreases pre-junctional acetylcholine release
   c. Immunosuppressants: Steroids (decrease end plate sensitivity to acetylcholine), cyclosporine (inhibits metabolism of certain NMBAs)

H. Choice of NMBA: Intermediate- to longer-acting agents such as vecuronium may be tried in bolus fashion initially before continuous infusion, particularly if organ dysfunction is present. The duration of paralysis for NMBAs cleared by Hofmann degradation may be more reliable when used as a continuous infusion because their clearance is not dependent on renal or hepatic function.

I. Train-of-Four (TOF) Monitoring and Dose Titration
   1. Typically, the goal of using a NMBA is to improve patient-ventilator synchrony and increase oxygenation. This may be achieved with varying degrees of paralysis and may not necessitate 100% block.
   2. Monitoring the depth of neuromuscular blockade by peripheral nerve stimulators (e.g., TOF), together with measured oxygenation parameters, helps find the "lowest effective paralytic dose" and allows quicker recovery of spontaneous neuromuscular transmission once the NMBA is discontinued. Some clinicians do not believe that TOF monitoring is necessary and believe that using the clinical values alone is sufficient to determine NMBA dosing.
   3. TOF delivers four supramaximal electrical impulses every 0.5 second to the ulnar, facial, or posterior tibial nerve. Response to the impulse is then measured by muscle twitches visualized from the associated innervated muscles (thumb or eye). Goals of paralysis can usually be reached with 2 or 3 of 4 twitches; 0 of 4 twitches indicates complete neuromuscular blockade, usually necessitating a decrease in NMBA dose. Oxygenation goals may be reached even with 4 of 4 twitches, indicating the NMBA dose is effective and an increase is not warranted.
   4. A baseline electrical current should be established before initiating a NMBA to determine how much electrical current is needed to produce a twitch. Usually 10–20 mA (amperage) is sufficient. The conduction of the electrical impulse may be dampened because of peripheral edema, loss of electrode adhesion, incorrect electrode placement, and hypothermia, which can lead to inaccurate readings. These factors should be reassessed with each use of the TOF.

J. Complications of NMBAs
   1. Prolonged weakness: Several case reports associate the use of NMBAs and prolonged weakness, which could include myopathy, polyneuropathy, or neuromyopathy. Other risk factors may include concomitant use of corticosteroids, persistent hyperglycemia, and type of NMBA used. However, data are inconsistent and not controlled, and further studies are needed to clarify specific risk factors for prolonged weakness associated with NMBAs. Following a trend in creatine kinase level every 48–72 hours may help assess the presence of myopathy secondary to paralysis and prolonged immobilization. A creatine kinase level should not be solely relied on for the presence of myopathy, and daily determination of need for the NMBA should still be considered, even with a normal creatine kinase.
   2. Corneal abrasions: Paralysis eliminates the ability of the eyes to close and blink, increasing the risk of corneal ulcerations and infection. Prophylactic eye protection must be used in all patients on NMBAs (e.g., lubricating eye ointments or eye covers).

3. Thrombosis: Caused partly by immobility, patients receiving a NMBA may be up to 8 times more likely to have a deep venous thrombosis (DVT) than those not on a NMBA. Prophylaxis for a DVT must be provided for all patients on a NMBA.

4. Awareness: Recent case reports document patient awareness during paralysis in the ICU. These patients report weird dreams, fear, resistance of restraints, thoughts of life and death, and pain. It is critical that patients be deeply sedated before initiating a NMBA.

5. Resistance to paralysis and/or potentiation: Certain disease states may produce an up-regulation in acetylcholine skeletal muscle receptors, leading to higher-than-normal doses of the NMBA (e.g., muscle trauma, muscle atrophy, burns). Acid-base disorders, electrolyte imbalances, and adrenal insufficiency may also cause unpredictable alterations in dosing requirements.

6. Anaphylaxis: Allergic reactions can occur after the first dose of a NMBA because the ammonium ions in NMBAs are commonly found in the household environment and in household products. If an allergic reaction is suspected, skin prick testing for the NMBA against a control can be done within 6 weeks of the reaction.

Patient Cases

12. You are rounding with the ICU team on a patient who is paralyzed and sedated for severe ARDS. On chart review, you notice that the documented TOF has been at an amplitude of 10 mA during the past 24 hours and is 2 of 4 twitches. Arterial blood gas is pH 7.36, P_{CO_2} 50, P_{O_2} 91, and bicarbonate 24 mEq/L on 50% inspired oxygen; the patient is synchronous with the ventilator, and other clinical markers are stable. Which would be the best change to make in the management of this patient's paralysis?

    A. Increase the dose until the TOF is 1 of 4 twitches.
    B. Decrease the dose because the patient tolerates it, according to laboratory values and ventilator synchrony.
    C. Increase the stimulator amplitude until the TOF is 4 of 4 twitches.
    D. Decrease the stimulator amplitude to avoid pain from excessive electrical stimulation.

13. O.N. comes to the emergency department altered and agitated. An emergency laboratory panel returns: sodium 137 mEq/L, potassium 5.5 mEq/L, chloride 103 mEq/L, bicarbonate 10 mEq/L, BUN 66 mg/dL, SCr 2.5 mg/dL, pH 7.20, P_{CO_2} 45, Pa_{O_2} 66, and bicarbonate 13 mEq/L. For the next 20 minutes, the patient becomes hypotensive and unresponsive, and the first-year resident physician wants to intubate the patient. Which is the most appropriate paralytic, given the clinical scenario?

    A. Pancuronium.
    B. Succinylcholine.
    C. Atracurium.
    D. Rocuronium.

VII. POST–INTENSIVE CARE SYNDROME

Post-intensive care syndrome has become a recognized set of medical complications that can start in the ICU and continue for weeks to months after ICU discharge. SCCM has taken progressive steps in helping clinicians recognize the prolonged post-ICU complications, which may significantly affect patients and their families over the long term. The SCCM Web site includes information for providers and families as well as other supportive care Web sites and video links to educate all involved.

A. ICU-Acquired Weakness: Muscle weakness that begins to develop during the ICU stay because of prolonged immobility and critical illness. Can affect normal daily activity levels and the ability to return to a working environment.

B. Cognitive Dysfunction: Problems with recall, problem solving, organizational skills, and attention deficits.

C. Mental Health: Anxiety, depression, and PTSD have been well described in the post-ICU recovery period. Patients may need long-term psychological follow-up and medications, depending on the severity of compromise.

D. Family Involvement: The importance of family input in care, motivation, and understanding cannot be overstated. Providers should educate families and make them well aware of the potential challenges in front of them and the resources that are available, as well as stress their own personal health hygiene. If the family is physically and emotionally strong, the patient's recovery is likely to be a more rapid and successful process.

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ANSWERS AND EXPLANATIONS TO PATIENT CASES

1. Answer: A

Methadone, gabapentin, and oxycodone will all have significant drug accumulation in the presence of renal failure. This is clinically relevant, particularly in new-onset renal failure and in "home" doses, given that the sedative effects of drug accumulation can occur and must be considered. In this case, holding or significantly decreasing the doses of all three medications should be considered to rule out a drug-induced cause of confusion or drowsiness (Answer A is correct). Unlike valproic acid, gabapentin has not been shown to produce hyperammonemia (Answer B is incorrect). There are no known properties of methadone that should cause increased sensitivity during metabolic acidosis (Answer C is incorrect). Since the case states that the patient was stable on those home medications at the stated doses, concern for preexisting drug interactions prior to the ICU would not be relevant (Answer D is incorrect).

2. Answer: C

This patient has a clear indication for intravenous pain medication because of his multiple traumas and abdominal injury, as well as an indication for a drug that will prevent or treat alcohol withdrawal until a thorough social history can be verified. Although all of the answers would treat pain and alcohol withdrawal, only a fentanyl infusion would be adequate for quick onset and dose titration in a patient with significant pain (Answer C is correct). Dexmedetomidine is considered "opiate sparing" but is not indicated for use as a single analgesic agent to treat significant pain in the ICU (Answer A is incorrect). Oral acetaminophen, which has a delayed onset, is not considered a potent analgesic for multiple traumatic injuries; additionally, it may not be absorbed if given orally, given this patient's abdominal injury (Answer B is incorrect). A fentanyl patch has a delayed onset of 12–24 hours and is not easily titratable; moreover, absorption is not dependable in a critically ill patient (Answer D is incorrect).

3. Answer: D

The PAD guidelines specifically cite chest tube removal as an indication for both preemptive analgesia and nonpharmacologic relaxation techniques. This is given a "strong" recommendation, determining that the benefits outweigh the risks of preemptive therapy (Answer D

is correct). The low dose of acetaminophen given right before the procedure will most likely not cover for the pain associated with chest tube removal (Answer A is incorrect). Increasing the patient's ongoing pain regimen on the morning of the procedure could cause excessive drug exposure and adverse effects for several hours (Answer C is incorrect). Extensive studies of appropriate preemptive analgesia for chest tube removal have not been completed; however, administering an opiate appropriately timed before manipulation of a chest tube is an accepted standard of therapy (Answer B is incorrect).

4. Answer: D

This patient's abnormal laboratory values are potentially secondary to propofol use. She has been on a moderately high dose of propofol for 4 days and has a history of pancreatitis. The differential for her increasing triglyceride level and her elevation in hepatic enzymes and lactate level should include PRIS. Given the severity of PRIS, propofol should be discontinued and alternative methods of sedation used (Answer D is correct). One of the primary concerns based on her abnormal laboratory values should be PRIS, and therefore replacing the opiate with a different opiate would not change her clinical scenario (Answer A is incorrect). Since PRIS is a potential life-threatening adverse event, propofol should be completely discontinued; additionally, haloperidol is not recommended in the ICU for a positive delirium score (Answer B is incorrect). Although the PAD guidelines state that quetiapine has been shown in a small pilot study to reduce the duration of delirium, it would not be the only intervention to make at this time due to the concern of PRIS in this patient (answer C is incorrect).

5. Answer: C

When evaluating the cost-benefit of a sedative in the ICU, it is appropriate to consider days on mechanical ventilation because this is a direct measurement of the minimum number of days in the ICU. Each day spent in an adult ICU on mechanical ventilation costs an average of $1500 per day. When medication costs per day are considerably less than the cost per day in the ICU and medication has been shown to decrease days on mechanical ventilation compared with less expensive alternatives, it is reasonable to consider adding the medication to formulary. Use of the drug should then be

followed up with an assessment of appropriate practice, as recommended by the manufacturer or established guidelines (Answer C is correct). Although nursing satisfaction and physician preference will play a partial role in the evaluation of medications, they should not be the primary determinants for the addition of a medication to a hospital formulary (Answers A and B are incorrect). Pharmacy intravenous administration costs are generally standardized for similar medications administered intravenously, and therefore would not determine differences in the overall cost of these medications (Answer D is incorrect).

6.   Answer: A

Dexmedetomidine is FDA label approved for short-term sedation in the ICU (not to exceed 24 hours), with a dosing range of 0.2–0.7 mcg/kg/hour. Postmarketing clinical studies have used the drug for up to 7 days, and at doses of up to 1.2 mcg/kg/hour, without report of withdrawal symptoms. Since these controlled trials were published, there have been case reports of withdrawal symptoms when dexmedetomidine was used for greater than 7 days and at doses exceeding 1 mcg/kg/hour; symptoms have included tachycardia, hypertension, sweating, and severe anxiety. Although the incidence of and risk factors for experiencing dexmedetomidine withdrawal are still unknown, clinicians should be aware of this effect if dexmedetomidine has been used for more than 7 days and should monitor for 12–24 hours after discontinuation. If withdrawal occurs, reinitiating dexmedetomidine and then decreasing it with a slower taper should be considered, or initiating a taper of clonidine may assist the patient through the withdrawal period (Answer A is correct). Decreasing or discontinuing an opiate should facilitate gastric motility (Answer B is incorrect). Anticholinergic effects such as dry mouth or urinary retention have not been reported with discontinuation of dexmedetomidine (Answer C incorrect). Opiate withdrawal symptoms do not include bradypnea or bradycardia; however, tachycardia may be seen (Answer D is incorrect).

7.   Answer: B

Midazolam is metabolized by CYP3A4 enzymes, and clearance can be strongly affected by alterations in liver function, particularly end-stage liver disease or cirrhosis. Midazolam accumulation can occur very quickly when used as continuous infusion in liver disease and can lead to a coma-like state (Answer B is correct). Fentanyl is also cleared in part by CYP3A4 enzymes, and clearance may be affected by severe liver dysfunction; therefore the clearance of midazolam and fentanyl both will likely be a problem in this patient who has fulminant hepatic failure (Answer A is incorrect). The prolonged action of fentanyl from a continuous infusion may also occur because of its high volume of distribution and lipophilic properties (Answer C is incorrect). This patient is "deeply sedated" on the sedation score and unresponsive while receiving sedative and analgesic infusions for 3 days. The most appropriate option is to turn off these infusions to allow for drug clearance in order to assess mental status. There is not a concern for abrupt discontinuation or withdrawal of midazolam or fentanyl in this patient, as severe hepatic dysfunction will allow a slow decrease in systemic levels (Answer D is incorrect).

8.   Answer: B

One of the first responses when a patient presents who is newly altered or with concern for delirium is to rule out a drug-induced cause. For this patient, who has had resolution of shock, there is no longer an indication for hydrocortisone, and it should be discontinued. In an observational study of patients with acute lung injury, steroids were independently associated with the transition to delirium from a non-delirious, non-comatose state. Steroids are also associated with other complications when used in the ICU (e.g., hyperglycemia, muscle weakness, increased infection risk) and should be decreased or discontinued as soon as indications for use have resolved (Answer B is correct). Histamine-1 or histamine-2 receptor blockers are associated with altered mental status if not dosed appropriately for renal function and/or age. Famotidine is a histamine-2 blocker with low potential for anticholinergic adverse effects (compared with ranitidine or cimetidine) and is appropriately dosed in this patient; therefore, it should not be causing altered mental status (Answer D is incorrect). According the PAD guidelines, lorazepam would not be an appropriate medication to administer if there is a concern for delirium, particularly in an elderly patient (Answer A is incorrect). The first step of assessment for new onset confusion or delirium is to identify and/or avoid the cause for delirium; adding quetiepine at this stage would not be the next step (Answer C is incorrect). If no improvement is seen after treating or removing the cause, then consideration for quetiapine may be appropriate.

9. Answer: B

Drug interactions and adverse drug effects are common and may be severe in the ICU, where multiple medications are administered in a complex environment to patients who may have varying degrees of organ dysfunction. Common classes of drugs used in the ICU (antipsychotics, azole anti-fungals, quinolones, antarrhythmics, etc..) are well known to cause numerous adverse effects. If these medications are used in combination, patients may be at considerable risk of more severe adverse effects, notably QTc prolongation and acute liver enzyme elevation (Answer B is correct). Elevation in serum creatinine or hypokalemia should not be common with these medications (Answers A and D are incorrect). None of the medications from the case should commonly cause rhabdomyolysis (Answer C is incorrect). Adverse effects of all medications should be monitored closely in the ICU, particularly if high-risk medications are used in combination.

10. Answer: D

When evaluating for the SAT, a safety screen is currently recommended to help identify patients who may not tolerate the discontinuation of sedative medication(s). Different safety screens are currently being used; however, they all consistently state an elevated ICP of greater than 20 mm Hg as exclusion criteria to performing the SAT. Sedatives are often used as standard of care to help control elevated ICPs; therefore, turning them off abruptly could have serious adverse consequences on the ICP (Answer D is correct). Using propofol would not exclude a patient from undergoing the SAT; however, because propofol is short acting, the dose should gradually be decreased, and not abruptly discontinued (Answer C is incorrect). Patient age has no impact on the safety or efficacy of the SAT, and therefore is not a consideration (Answer B is incorrect). If a patient needs ongoing pain medication, they are able to continue the analgesia per current SAT protocols, and still perform the other aspects of the SAT. If the analgesia medication is causing excessive drowsiness, the clinician could choose to decrease the dose as indicated (Answer A is incorrect).

11. Answer: C

Studies comparing the SAT (or daily interruption of sedation) with a standard sedation protocol targeting light sedation have not shown differences in time on mechanical ventilation (Answer D is incorrect). These studies did not, however, coordinate the SAT with the SBT. The PAD guidelines give a "strong" recommendation for either strategy (spontaneous awakening or targeted light sedation) as appropriate during sedation management. In 2008, Girard et al. found that coordinating the SAT, followed by the SBT, decreased time on mechanical ventilation compared with standard care (Wake Up and Breathe, or "ABC," trial). After the 2013 PAD guidelines were published, Balas et al. followed up the ABC trial with the ABCDE trial, coordinating the SAT, SBT, delirium assessment, and early mobility, and showed significantly fewer days on mechanical ventilation compared with standard care. Due to earlier studies demonstrating possible withdrawal complications in certain ICU populations when undergoing daily interruption of sedation, these studies effectively used an extensive safety screen before doing the SAT or the SBT (Answer A is incorrect). A safety screen is now recommended before doing any type of SAT to help prevent complications of turning off sedation (Answer C is correct). The CAM-ICU is not currently part of the spontaneous awakening trial procedure, and should not impact whether or not a patient undergoes the SAT (Answer B is incorrect).

12. Answer: B

The TOF method of assessment is primarily used to help determine the degree of neuromuscular blockade and should not be used to titrate a NMBA dose. The patient's clinical status and laboratory values are the true determinants for dosing a NMBA. Patients may be at their clinical goal with a TOF of 2 or 3 twitches of 4. This is the ideal scenario, and it will predict a faster recovery of muscular use and strength (Answer B is correct). A TOF of 0 or 1 of 4 twitches predicts a much slower recovery time, and clinicians should try to decrease the NMBA as soon as the patient is clinically stable by laboratory values and ventilator management (Answer A is incorrect). A baseline electrical current intensity (amperage) should be established before the onset of neuromuscular blockade and should not be changed through the duration of paralysis, unless a new baseline is indicated (Answer D is incorrect). As the electrical intensity (amperage) is established, an increase in the amperage is not indicated during infusion of the NMBA in order to increase the number of twitches. A decrease in the dose of NMBA would be indicated if an increase in the number of twitches is the clinical goal (Answer C is incorrect).

13. Answer: D

Because of its rapid onset and short duration of action, succinylcholine is usually the drug of choice for rapid sequence intubation. However, succinylcholine also has important exclusions and warnings for use, including malignant hyperthermia, elevated creatine phosphokinase, hyperkalemia, stroke, paralysis, glaucoma, penetrating eye injuries, and spinal, crush, or burn injuries after 24 hours. Succinylcholine would not be a good choice for this patient, whose potassium level is 5.5 mEq/L, because it can further elevate potassium levels (Answer B is incorrect). Rocuronium is considered an acceptable alternative for rapid sequence intubation with a rapid onset of action (Answer D is correct). Pancuronium has a slow and unpredictable onset and is therefore not a good choice for rapid sequence intubation (Answer A is incorrect). Atracurium is known to release histamine into the systemic circulation, particularly when given as a bolus dose. This could further exacerbate this patient's hemodynamic instability and complicate the clinical scenario (Answer C is incorrect).

ANSWERS AND EXPLANATIONS TO SELF-ASSESSMENT QUESTIONS

1.   Answer: B

The pharmacokinetics/pharmacodynamics of fentanyl infusions have not been well studied in the critically ill adult population, particularly when used as a continuous infusion for prolonged periods. Most data for fentanyl are derived from short-term infusions or boluses in healthy volunteers as well as from animal models. Fentanyl is hepatically metabolized primarily by the CYP3A4 enzyme, and decreased clearance of fentanyl has been described in patients with significant liver disease. Other properties of fentanyl, including high volume of distribution, high protein binding, and high lipophilicity, may contribute to unpredictable clearance and a prolonged context-sensitive half-time in a critically ill patient (Answer B is correct). Propofol clearance may also be altered in various patient populations, including ICU patients, with prolonged use. Propofol is a CYP3A4 inhibitor; a crossover study of healthy volunteers showed a 27% increase in midazolam plasma concentrations when midazolam was given with propofol (Answer C is incorrect). Pharmacokinetic properties of propofol include a large volume of distribution and high protein binding (Answer D is incorrect). Disease states identified as risk factors for PRIS may include sepsis, acute liver failure, and history of pancreatitis; ARDS is not currently a documented risk factor (Answer A is incorrect).

2.   Answer: B

Authors of the PAD guidelines summarized their review of five delirium assessment scales used for adult ICU patients. The two scales with the highest psychometric (e.g., validity and reliability) scores were the CAM-ICU and the ICDSC (Answer B is correct). The NEECHAM scale, Delirium rating scale, and Memorial delirium scale have been used in various patient care settings, however, these were not included in the PAD guideline review and are not currently recommended by SCCM (Answers A, C, and D are incorrect).

3.   Answer: C

Constipation and gastric intolerance caused by a slow-moving GI system are extremely common with opiate use. These adverse effects can delay time to nutritional goals, increase time on mechanical ventilation, and increase ICU length of stay. As ICU clinicians continue to focus on pain control and use of opiates as the initial drug for analgesia and sedative needs, gastric intolerance must be closely monitored from day 1. Ensuring the appropriate dose and using an effective bowel regimen will be necessary to help maintain a functional GI tract (Answer C is correct). A small bowel feeding tube may be a reasonable option in this case, but treating the cause by decreasing the opiate dose and initiating bowel medications should be tried before an invasive procedure (Answer B is incorrect). The American Society of Parenteral and Enteral Nutritional 2009 guidelines for critically ill patients recommend implementing measures to reduce the risk of aspiration once residuals are greater than 200 mL and do not recommend holding enteral nutrition until residuals have reached greater than 500 mL (Answer A is incorrect). Because of its adverse effects, metoclopramide should be considered only if safer options are ineffective (Answer D is incorrect).

4.   Answer: A

This patient is at risk of experiencing propylene glycol toxicity after being on a lorazepam drip for more than 48 hours. Lorazepam must be dissolved in propylene glycol, an alcohol that can cause an osmolar gap and metabolic acidosis from lactate, particularly in patients with significant hepatic and/or renal failure. Not all hospitals can measure quantitative propylene glycol levels; therefore, surrogate markers such as abnormal osmolar gap and elevated lactate levels may indicate propylene glycol toxicity and a need to discontinue lorazepam. Although lorazepam drips are not routinely used for general sedation in adult ICUs, they may be used for other indications (e.g., severe EtOH [ethyl alcohol] or benzodiazepine withdrawal), and clinicians should remain aware of this serious complication (Answer A is correct). Although elevated lactate levels can cause a metabolic acidosis, this patient is hemodynamically stable with no symptoms of shock (Answer B is incorrect). Encephalopathy will not cause a metabolic acidosis, therefore an ammonia level would not be helpful at this stage (Answer C is incorrect). His labs and urine output do not indicate acute renal failure, and therefore a nephrology consult would not be indicated (Answer D is incorrect).

5.   Answer: C

This is a common scenario in the ICU when a patient is admitted and intubated, and home psychiatric medications are not initially given. Holding medications from which a patient may withdrawal (benzodiazepines, antidepressants, antipsychotics, tramadol, other GABA receptor agonists) could result in severe agitation secondary to withdrawal, and a perceived need for additional medications to treat these "agitated" symptoms (e.g., antipsychotics). Patients receiving only analgesia for comfort during intubation would be at risk for this complication. In this patient case, the patient may be withdrawing from his home clonazepam. If reinitiating the drug is not feasible, a sedative that would treat benzodiazepine withdrawal should be used. Propofol is the only option from the available answers that would cover for benzodiazepine withdrawal (Answer C is correct). None of the other medication options would cover this patient for benzodiazepine withdrawal (Answers A, B, and D are incorrect).

6.   Answer: D

Certain medications can prolong the paralytic effects of NMBA, usually by decreasing the pre-junctional release of acetylcholine, decreasing acetylcholine receptor sensitivity, or blocking the acetylcholine receptor. Both β-blockers and calcium channel blockers can decrease the release of acetylcholine and cause a delayed recovery of neuromuscular blockade, even once the paralytic has been discontinued (Answers B and C are incorrect). Hydrochlorothiazide would not be an effective agent for an anuric patient (Answer A is incorrect). Hydralazine would be the safest and most effective agent in this patient who is on a NMBA (Answer D is correct). Once the patient has recovered their extremity movement and strength, it is reasonable to consider reinitiating a β-blocker or calcium channel blocker.

7.   Answer: C

Of the listed combinations, both protracted muscular weakness and PTSD have been well-documented complications in the post-ARDS literature. Patients taking these combinations may require extensive physical rehabilitation for protracted neuromuscular weakness as well as long-term cognitive rehabilitation to return to a functional baseline. The critical care community, which is becoming more aware of these post-ICU complications, is focusing on education and research for critical care providers and families of ICU survivors (Answer C is correct). The prolonged immobility and duration of use of analgesics and sedatives in the ICU can lead muscle breakdown and atrophy (Answer D is incorrect). Psychiatric complications such as anxiety and depression are well documented in survivors of ARDS, however, acute mania has not been a described complication (Answer A is incorrect). Hearing loss is a toxicity of certain medications used in the ICU (e.g. aminoglycosides), however, this has not been found to be a complication in ARDS survivors (Answer B is incorrect).

8.   Answer: D

It is inappropriate to initiate a NMBA in a patient who has a sedation scale score that is rated "agitated." This implies that the patient may potentially detect pain or discomfort while paralyzed (Answers A and B are incorrect). The goal should be to achieve a deeply sedated and/or nonagitated state before initiating a NMBA in an effort to avoid any patient discomfort that may be undetected during paralysis (Answer D is correct). The SAT would be inappropriate in someone who is rated "agitated" on the sedation scale or in a patient requiring escalating doses of sedation (Answer C is incorrect).

9.   Answer: B

In the general population, systemic corticosteroids are known to cause hyperactivity and agitation; in a recent study by Schreiber et al. of adult ICU patients, only age and use of systemic corticosteroids in the preceding 24 hours were independently associated with the transition to delirium from a non-delirious state (Answer B is correct). Clonidine is known for causing sedative effects, but there is no data associating clonidine with delirium (Answer D is incorrect). Antipsychotics and antibiotics are not currently recognized as risk factors for the development of delirium (Answers A and C are incorrect).