Chapter e27: Critical Care: Pain, Agitation, and Delirium

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CHAPTER SUMMARY FROM THE PHARMACOTHERAPY HANDBOOK

For the Chapter in the Schwinghammer Handbook, please go to Appendix 3, Critical Care: Patient Assessment and Pharmacotherapy.

KEY CONCEPTS

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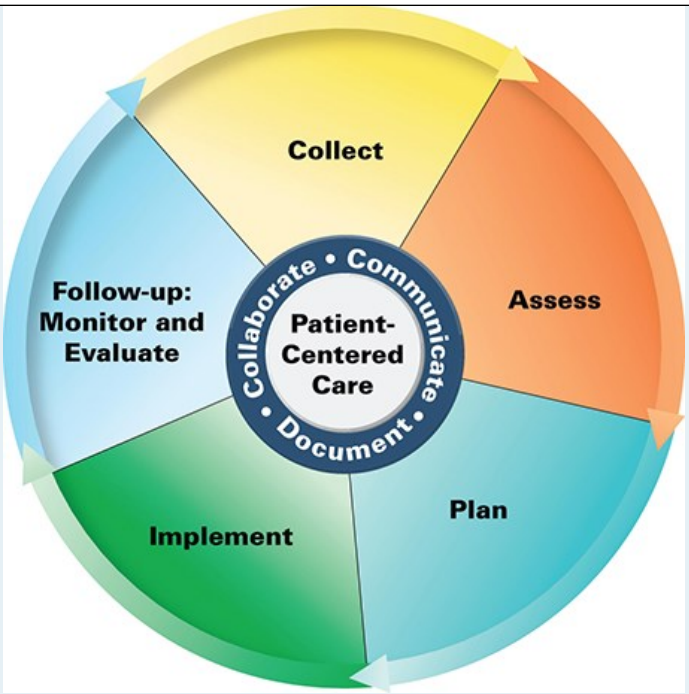
1. The primary goal of pain, agitation, and delirium (PAD) management is to provide patient comfort and safety with secondary goals to prevent immediate and long-term adverse physical and psychological outcomes.
2. PAD are interrelated and can confound efforts to provide intensive care including mobility, sleep, participation in care, and in shared patient/caregiver decisions about appropriate levels of care.
3. It is important to systematically evaluate PAD with validated tools for timely identification and correction of inciting clinical issues.
4. Preventative measures and nonpharmacologic strategies for PAD management should be initiated as early as possible.
5. A multifaceted, interprofessional approach to PAD management impacts care and clinical outcomes.
6. Pain is an important cause of agitation in the intensive care unit (ICU) and should be assessed and treated before administration of sedatives.
7. No proven pharmacologic strategies limit the severity and duration of ICU delirium.
8. Sedative choice (dexmedetomidine or propofol) and depth of sedation may have an important impact on patient assessments and outcomes.

PATIENT CARE PROCESS

Patient Care Process* for the Management of Critically Ill Adults with Pain, Agitation, and Delirium



Collect

- Patient-specific characteristics, co-morbidities, allergies, and intolerance to medications
- Psychosocial history (eg, chronic pain, substance misuse, psychiatric diagnoses)
- Symptom specific history (eg, onset, location, duration, chronicity, severity, consequences, and inciting/remediating factors)
- Documented response to interventions for PAD management (efficacy and intolerance)
- Current and past medication use with attention to those associated with agitation or delirium (see Table e27-2)
- Objective data including vital signs, pertinent labs, physical and neurologic evaluations, pertinent imaging studies, short and long-term goals of care including the need for palliative care

Assess

- Presence of PAD symptoms (see Table e27-1)
- Presence of risk factors for PAD (see Table e27-3)
- Symptom resolution using validated PAD assessment tools (see Table e27-4)
- Presence of co-occuring psychological conditions that may confound treatment plan
- Adverse medication reactions or intolerance associated with the use of pharmacologic management of PAD (see Table e27-6)

Plan (collaborate with patient, family, and health professionals)

- Before using medications for symptom relief, ensure that preemptive/preventative strategies are in place, that inciting/prescipitating factor(s) are identified and reversed if possible, and employ nonpharmacologic management strategies (see Table e27-1)
- If necessary, offer pharmacologic management options with identification of treatment goals and a plan to safely terminate therapy when the clinical issue resolves (see Tables e27-1 and e27-5)

- Contingencies should be identified if the initial plan is not successful or not tolerated

Implement

- Educate patient/family and treating team about all elements of the therapeutic plan
- Identify proper starting and incremental dose adjustments along with reasonable assessment durations when using tiratable medications.

Follow-up: Monitor and Evaluate

- Resolution of PAD
- Presence of adverse medication reactions
- Monitor withdrawal and resurgence of clinical issues upon discontinuance of medications for PAD management. Implement a dose tapering strategy if appropriate.
- Evaluate the continued need for medications initated in the ICU for PAD management upon discharge from the ICU and hospital and discontinue unwarranted medications

* **Collaborate with patient, caregivers, and other healthcare professionals.**

BEYOND THE BOOK

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Watch the video entitled "CAM-ICU Delirium Test" at the following link: <https://www.youtube.com/watch?v=6WyJ0zL7VkI>. This brief 3-minute video is an overview of a common and valid method of screening for delirium in critically ill adults who are unable to verbalize. This activity is useful to enhance student understanding of the COLLECT and ASSESS steps in the patient care process.

INTRODUCTION

Pain, agitation, and delirium are considered the most common clinical conditions confronting critically ill patients and their caregivers. These issues are stressful for patients as well as families and are often precipitated by factors that are frequently seen in the critically ill such as hemodynamic instability, inadequate oxygenation, metabolic derangements, pain, the inability to communicate, immobility, sleep deprivation, the need for invasive instrumentation, and loss of autonomy all occurring in an unfamiliar and threatening environment.

1 Short-term patient goals for PAD management include the provision of comfort and safety. It is also important to consider newly recognized long-term outcomes in critical care survivors that affect their quality of life such as the inability to return to baseline physiologic and cognitive function and a high frequency (50%) of unemployment for a year or longer after discharge from the hospital.[1-3] In addition, post-discharge post-traumatic stress disorder (PTSD) and depression are experienced by 7% and 20% to 30% of ICU survivors respectively at 1 year.[4,5]

All of these outcomes are impacted by our choice of therapeutics for PAD management. For example, the provision of inadequate pain relief can be regarded as inhumane, but conversely, overaggressive opioid therapy continued in the outpatient setting represents an obvious and avoidable risk factor in this era of opioid misuse.[6] The complexity of the pharmacologic and nonpharmacologic management of PAD requires knowledge of the risks and benefits of each option and necessitates a standardized, but flexible evidence-based approach[7] (Table e27-1).

TABLE e27-1

Management of PAD

Assess for presence of PAD	
Pain	≥4 times per nursing shift and as needed with NRS, BPS, CPOT
Agitation/sedation	≥4 times per nursing shift and as needed with RASS and SAS
Delirium	Once per nursing shift and as needed with CAM-ICU and ICDSC
Identify and correct inciting factors when possible	
Establish patient-specific treatment goals	
Nonpharmacologic management	
Pain	Massage therapy; relaxation techniques; cold packs; manipulative medicine
Agitation	Manage pain and discomfort; provide reassurance, support, and empathetic explanations for procedures, diagnostic tests, and diagnoses; avoid excessive noise, immobility, constipation, and physical restraints
Delirium	Correct modifiable risk factors; promote diurnal sleep patterns, and orientation to person, place, circumstance; encourage family visitation; provide cognitive stimulation, mobility efforts; limit sedation
Pharmacologic management	
Pain	Opioids and non-opioids for non-neuropathic; gabapentinoids for neuropathic and post-operative pain; multimodal options
Agitation	Analgosedation; propofol or dexmedetomidine for most patients; reserve benzodiazepines for specific indications
Delirium	Dexmedetomidine for agitated delirium that interferes with weaning from mechanical ventilation; antipsychotics not routinely recommended
Assess response to therapy; if not adequate, consider alternative approach	
Determine plan for withdrawal of pharmacotherapy and transition of care	

BPS, behavioral pain scale; CAM-ICU, confusion assessment method for the ICU; CPOT, critical care pain observational tool; ICDSC, intensive care delirium screening checklist; NRS, Numeric rating scale; RASS, Richmond agitation sedation scale; SAS, sedation agitation scale.

Data from References 7,8.

Although we will be discussing PAD in this chapter as discrete clinical issues, the reader should appreciate that they are inter-related.[9] The interwoven nature of PAD is well demonstrated by a patient with unrelieved pain (a risk factor for delirium) who develops agitation. Dangerous agitation can result in patient harm or injury, but attempts to control these behaviors with sedatives can inadvertently precipitate delirium without addressing the inciting problem of pain.

DEFINITIONS AND CONSEQUENCES OF PAD

Pain

Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage."[7] Healthcare providers readily accept and anticipate that ICU patients will have pain associated with surgery, trauma, pancreatitis, or with invasive procedures, but less frequently recognize that pain is provoked by routine ICU care such as repositioning, endotracheal suctioning, and arterial gas determinations.[10,11] Furthermore, it should be appreciated that 50% of patients experience considerable pain at rest, with surgical patients complaining of pain at the site of injury, while medical patients cite back or limb pain.[12] Unrelieved pain is the most common unpleasant memory of ICU survivors and is associated with an acute stress response resulting in hypercatabolic states, increased oxygen demand and the potential for tissue ischemia, impaired wound healing and hyperglycemia.[13–16] Acute pain can also interfere with sleep, mobility and physiotherapy efforts, and pulmonary therapy such as coughing and deep breathing—all impeding the healing process. Longer term issues such as chronic pain syndromes and PTSD have been associated with inadequate analgesia.[13,17]

Agitation

Agitation is described as excess motor and psychological activity that is out of proportion to the evoking stimuli. Resulting behaviors can be either nonpurposeful such as thrashing movements in bed or purposeful and counterproductive such as attempting to dislodge an endotracheal tube or trying to escape the ICU. The most common adverse outcome resulting from uncontrolled agitation is the removal of medical devices.[18,19] Most often this is a mere nuisance such as the removal of a pulse oximeter, but sometimes this represents a legitimate safety risk such as dislodgement of an endotracheal tube, a surgical drain, or vascular access. Uncontrolled agitation in a violent patient may also result in trauma to self and to caregivers. In addition, the excessive sympathetic drive associated with agitation may lead to myocardial ischemia in patients with coronary disease, while blood pressure elevations may be catastrophic in patients with intracerebral hemorrhage or aortic dissection. Disruption of anastomotic sutures is another potential morbid consequence of ICU agitation. Furthermore, agitation may result in longer time in the ICU and on the ventilator exposing patients to a number of iatrogenic risks including nosocomial infections and thromboembolic events.

Delirium

Delirium is an acute onset psychiatric syndrome (caused by an underlying medical condition) characterized by inattention, disorganized thinking, and changes in baseline mental status occurring in a fluctuating manner. Other symptoms of delirium including hallucinations, fear associated with incomprehensible experiences, and extreme emotional feelings can be stressful to patients, families and caregivers.

Three variants of delirium have been identified: hyperactive delirium where patients exhibit motor activity associated with agitation, hypoactive delirium which is associated with a calm demeanor or lethargy, mixed delirium when patients fluctuate between the other two subtypes.[20] Specific definitions and criteria for these subtypes vary, and others have further characterized delirium subtypes by level of arousal (decreased, normal, or increased).[21] The clinical significance and prognostic value of these different delirium subtypes have yet to be defined.

Delirium is strongly *associated* with prolonged hospital stay as well as long-term cognitive impairment similar to that seen in patients with mild Alzheimer's disease or traumatic brain injury, but whether delirium *causes* these worse outcomes is unclear.[2] The effect of delirium on other important clinical outcomes such as ICU length of stay, discharge disposition to a place other than home, dependence on others for activities of daily living, depression, and mortality is unclear. ICU delirium does not seem to be a risk factor for PTSD.[7] It should be emphasized that emotional or psychological distress are the only features of delirium that most agree are causally related.

EPIDEMIOLOGY OF PAD

Pain

1 2 3 There are many reasons why significant pain is experienced by the majority of patients in the ICU setting, and why unrelieved pain is experienced by more than 40%. Pain is associated with a number of factors, including acute and chronic illness, surgery, trauma, burn injuries, pancreatitis, cancer, comorbidities (arthritis, spinal column issues, chronic pain syndromes), immobility, invasive medical and monitoring devices. Pain also is associated with several routine ICU procedures, including repositioning in bed, catheter and drain insertion and removal (especially chest

tube removal and arterial line insertion), endotracheal and tracheal suctioning, and wound care.[8,22] Ineffective pain management is often related to clinician underestimation of its frequency and consequences. Without systematic evaluations, pain may be unrecognized especially in patients who are unable to convey their analgesic needs because of the presence of an endotracheal tube or altered mental status due to their acute illness or sedative regimen.[23,24] Furthermore, the personal and cultural bias of caregivers may serve as barriers to adequate pain relief if they believe that analgesia with opioids may lead to or sustain addiction and misuse. Patients may also play a direct role in inadequate pain relief by not communicating their analgesic needs. They may stoically tolerate pain because of cultural beliefs or because they are concerned about the side effect profile of medications. Interestingly, some patients under-report pain fearing that healthcare provider bias against opioid use will reduce their sense of empathy and alter their care.[13,24]

Agitation

2 Some degree of agitation occurs frequently in ICU patients and is a source of discomfort and concern for patients, families, and clinicians.[8] While the most common causes of agitation are pain, delirium, anxiety or substance/prescription withdrawal or intoxication, some patients do not have an obvious reason for their behavior.[25] The multifactorial etiology of agitation along with the potential presence of an unrecognized or undiagnosed baseline psychiatric illness, confounds the ability to provide directed therapy. This is exacerbated by the fact that many patients cannot articulate their needs or concerns because of the presence of an endotracheal tube, depth of sedation, or the presence of encephalopathy.

2 Pain must always be considered the primary reason for agitation until it is ruled out. This is best evaluated by patient self-report and with validated behavioral pain scales if self-report is not possible.[7] Psychiatric illness, psychoactive drug use (prescription and other substances including alcohol), cognitive impairment, metabolic derangements, along with kidney and liver failure predispose patients to ICU agitation.[26] Many medications and nonprescription substances are associated with agitation as a result of withdrawal or acute toxicity (Table e27-2). Extreme anxiety can lead to agitation especially if it is provoked by unexpected or unexplained therapeutic or diagnostic interventions. The apprehension of not knowing the outcomes of an acute illness can be an important cause of anxiety and agitation in susceptible patients and reinforces the need to continually inform patients about their health status and planned interventions.

TABLE e27-2

Common ICU Medications Associated with Agitation and Delirium

Category	Medication	Agitation	Delirium	With Use	With Withdrawal
Antibiotic					
	Cefepime[27,28]	x	x	x	
	Macrolide[29]	x		x	
	Quinolones[29–31]	x	x	x	
	Voriconazole[29]		x	x	
Anticholinergic					
	Diphenhydramine[32]		x	x	
Anticonvulsant					
	Gabapentin[33]	x			x
	Levetiracetam[34]	x		x	
	Pregabalin[35]	x			x
Antidepressant					
	Amitriptyline[36]	x	x		x
	SSRI[36,37]	x	x	x	x
	SNRI[36,37]	x	x	x	x
Gabaminergic					
	Benzodiazepines[7,36]	x	x	x	x
Miscellaneous					
	Corticosteroids[38]	x	x	x	
	Digoxin[39]	x	x	x	
	Ketamine[36]	x	x	x	x
	Psychoactive medications[7,36]	x	x	x	x

SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor.

Illness related factors contributing to ICU agitation include acute respiratory failure, fever, acidosis, hypoxemia, sepsis, other infectious diagnoses, and hyperactive or mixed delirium from a number of causes. In addition, neurologic insults resulting from strokes or traumatic brain injury, malignancies, and seizures can provoke agitation.

Possible environmental factors leading to agitation include sleep deprivation, excessive noise or light, mechanical or noninvasive ventilation, the inability to communicate, loss of control over body functions, thirst, and the presence of intravascular and drainage catheters and feeding tubes. Use of restraints is often necessary to ensure patient safety, but these devices also contribute to agitation.[26] Systematically assessing and addressing these causes of agitation is the first step in providing comfort in the ICU and should proceed prior to or contemporaneously with medication use.

Delirium

Delirium is common in ICU patients, occurring with an estimated frequency between 20% and 90%.[40] The actual incidence of ICU acquired delirium may be lower than previously reported in part related to changes in critical care practices that avoid deep sedation and facilitate physiotherapy and mobility interventions.

Evaluating risk factors for delirium in the ICU is complex due to heterogeneity in the underlying diseases and their severity prior to delirium onset, competing events that may preclude delirium detection, the high frequency of multiple delirium risk factors being present, and varying detection rules for delirium and risk factors. Delirium risk factors have been categorized in different ways, but perhaps the most helpful approach is to identify those that are correctable (eg, medication selection, depth of sedation) and should be the focus of our interventions, compared to those that cannot be altered (eg, age, severity of underlying disease).[41] Table e27-3 lists these risk factors, identifying a small number of correctable or preventable factors, including infections, metabolic derangements such as hypoglycemia, hyponatremia, hyperammonemia, acidemia, and benzodiazepine administration.[41] Besides benzodiazepines, many other medications may increase the risk for delirium. It is also important to emphasize that intentional or inadvertent discontinuance of some medications or substances may contribute to delirium (Table e27-3).

TABLE e27-3

Risk Factors for ICU Delirium

Predisposing Risk Factors[a]	Quality	Level of Evidence
Age	High	Strong
Dementia	High	Strong
Hypertension	High	Strong
Acute Physiologic Assessment and Chronic Health Evaluation (APACHE) score	High	Strong
Emergency surgery	High	Strong
Organ system failure	Positive	Moderate
Polytrauma	Mixed	Strong
Potentially Correctable Factors		
Coma	High	Strong
Delirium previous day	High	Strong
Mechanical ventilation	Mixed	Strong
Metabolic acidosis	High	Strong

[a]Additional reported factors which were inconclusive or with only weak evidence on systematic review: gender, alcohol or nicotine use, American Society of Anesthesiologists physical status, cardiac disease, acute respiratory disease, impaired kidney function, admission to medical team, fever, anemia, bilirubin or urea elevation, hyper-/hyponatremia, room without daylight.

Data from Reference 42.

4 Environmental risk factors are also potentially correctable risk factors for delirium, including forced immobility, restraint use, the presence of invasive catheters, excessive noise and lighting, omission of common orientation aids such as clocks, calendars, eyeglasses, hearing devices, and natural circadian light. It is uncertain if sleep deprivation is a cause or consequence of delirium, but this common ICU issue should be addressed.[7]

Identifying specific patients at high risk for delirium may provide an opportunity to focus on preventative strategies and assessment plans. Two delirium prediction tools, E-PRE-DERILIC and PRE-DERILIC have been developed and tested for validity. They assess age, acuity of illness indicators, urgency of admission, infection, coma, sedation, morphine use, urea or blood urea nitrogen, metabolic acidosis, alcohol use, mean arterial blood pressure, use of corticosteroids, respiratory failure, and other risk factors. E-PRE-DERILIC is administered at the time of ICU admission, whereas PRE-DERILIC is assessed within 24 hours of ICU admission. E-PRE-DERILIC is preferred by clinicians because it is easier to use, but PRE-DERILIC may have better predictive capabilities.[43]

PATHOPHYSIOLOGY OF PAD

Pain

Pain is a complex symptom and can be classified as acute, chronic, or acute on chronic.

A complex physiologic cascade results in the detection, transmission, and perception of pain initiated by stimulating nerve transmission and release of inflammatory substances (substance P, bradykinin, histamine, prostaglandins, serotonin). These nerve impulses travel to the spinal cord where both excitatory (glutamine and aspartate) and inhibitory γ- aminobutyric acid (GABA) neurotransmitters help define the individual's perception of the stimuli. Ultimately, endogenous substances within the brain such as endorphins and enkephalins modulate the pain signal.[44] The complexity of these pathways help explain the great variability in an individual patient's perception and tolerance of painful events (see Chapter 79).

Agitation

There are no established pathophysiologic pathways to explain adverse behavioral changes associated with agitation, but excessive sympathetic activity, changes in pain sensation or hypothalamic-pituitary-adrenal axis dysfunction have been implicated.[45]

Delirium

The underlying pathophysiology of delirium is incompletely understood. Though classically described as an imbalance of brain neurotransmitters (particularly choline, dopamine, and serotonin), this represents an oversimplification. Other proposed pathways for delirium include a direct neurotoxic effect of inflammatory cytokines, derangement of the blood brain barrier, and neuronal dysfunction, ultimately leading to the behavioral and cognitive symptoms common to this disorder.[46]

ASSESSMENT TOOLS AND THERAPEUTIC GOALS

Pain

3 Pain management begins with a careful assessment of its source, duration and severity, but this may be difficult in ICU patients. ICU patients are often unable to communicate their analgesic needs; however, despite these barriers, all ICU patients should have their pain assessed with a validated scoring tool at least four times during a nursing shift, as well as, before and after the administration of an analgesic medication.[8] Online sources for selected PAD assessment tools are provided in Table e27-4. The systematic assessment of pain decreases significant pain by nearly 50%, and since pain is more readily identified as the reason for agitation, inappropriate sedative use is decreased by 30%.[23,47] Reductions in the duration of ventilation and length of ICU stay have also been associated with pain management strategies that include embedded pain assessment protocols.[47,48]

TABLE e27-4

Online Sources for Selected PAD Assessment Tools

Tool	Website
Pain (CPOT, BPS)	http://www.icudelirium.org/pain.html
Agitation/sedation (RASS, SAS)	http://www.icudelirium.org/sedation.html
Delirium (CAM-ICU, ICDSC)	http://www.icudelirium.org/delirium/monitoring.html
Delirium risk factors/causes	http://www.icudelirium.org/terminology.html

BPS, behavioral pain scale; CAM-ICU, confusion assessment method for the ICU; CPOT, critical care pain observational tool; ICDSC, intensive care delirium screening checklist; RASS, Richmond agitation sedation scale; SAS, sedation agitation scale.

Patient self-report is regarded as the gold standard to evaluate pain with the numeric rating scale (NRS 0-10) representing the most commonly used metric. A score greater than 3 (on an 11 point scale) represents significant pain. For patients unable to communicate, but who retain motor activity (ie,

no neuromuscular blockade or neuromuscular disease), validated behavioral pain scales such as the Critical Care Pain Observation Tool (CPOT) or the Behavioral Pain Scale (BPS) should be used.[7] Though these two pain scales are similar (they evaluate facial expression, body movement, muscle tension, and compliance with the ventilator), they are scored differently and thresholds to determine significant pain reflect these differences. It should be noted that patient behaviors such as facial expression, eye closure, and muscle rigidity are blunted with increasing levels of sedation emphasizing the importance of maintaining light sedation to accurately assess pain.[49,50]

Surrogate pain assessments by family members may provide additional information for patients unable to self-report. Pain is correctly identified in most cases, but the severity of that pain is often overestimated by families. Nurses correctly identify pain with a similar accuracy as family members, but interestingly, they tend to underestimate its severity.[51] This highlights the importance of providing light sedation to facilitate more accurate estimates of analgesic need directly from patients, and when self-report is not possible, to utilize several sources of information.

Vital signs are commonly used as a measure of pain or discomfort, but this practice should be discouraged since elevations in heart rate, respiratory rate, and blood pressure can occur in response to non-pain-related stimuli such as fear, anxiety, and other stressors in the ICU. Furthermore, they can be modulated by many therapeutic interventions including beta-blockers, calcium channel blockers, and sympathomimetic agents. Increased vital signs should primarily serve as cues for further pain evaluation using validated scoring tools, and normal vital signs should not preclude the possibility of pain.[8]

Agitation/Sedation

4 Similar to pain, the first step to limit agitation is through systematic assessments with validated scoring tools performed at least four times during a nursing shift.[8] This practice may result in a 33% reduction in potentially dangerous agitation through early identification and correction of stressful patient conditions.[23] If agitation persists and requires the administration of sedative medications, these same assessment tools can be used to monitor the response to therapy and to serve as a means of identifying and communicating sedation goals to all caregivers.

At least 11 sedation scales have been proposed for use in the ICU, but 2 are recommended by the SCCM 2018 PADIS guidelines based on a psychometric analysis of their reliability, validity, feasibility, and utility; RASS and SAS (Table e27-4).[52] For most patients, a light level of sedation provides comfort, allows wakefulness, and enables patient self-report of pain and participation in delirium assessment. A SAS score of 4 and RASS of −1 have been shown to best predict light sedation.[53] Treatment goals should include the ability for patients to comfortably and safely participate in their care as well as in decisions about that care. This degree of sedation also facilitates effective pulmonary toilet, liberation from mechanical ventilation, participation in physiotherapy and mobility, repositioning, and other nursing interventions. Furthermore, avoiding deep sedation decreases mortality, ICU and hospital lengths of stay, and the need for tracheostomy and diagnostic testing for unexplained mental status changes.[44] In fact, the provision of light sedation administered within the first 48 hours of mechanical ventilation may have a favorable impact on mortality, delirium frequency, and ease of extubation.[45]

It should be recognized that deep sedation (RASS −3 to −5 or SAS 1-2) may be necessary for specific subsets of ICU patients; such as those with status epilepticus, receiving neuromuscular blockade, having elevated intracranial pressure, experiencing tenuous respiratory function despite mechanical ventilation, and to protect complex surgical wounds. Since the clinical exam is likely not helpful to guide deep sedation titration once patients are unresponsive, the PADIS guidelines recommend that therapy be monitored with processed EEG-based technology such as the bispectral index (BIS).[7] Appreciation of the potential influence of electromyographic (EMG) artifact is critical to the interpretation of the BIS findings.[54]

Two different sedation strategies for mechanically ventilated ICU patients are promoted by SCCM, ACCP and the ATS.[7,55] The first approach is to consistently provide light sedation, defined as the ability of patients to attend to 3 of 5 commands such as wiggle toes, display two fingers, open eyes.[8,56] Another approach allows deeper sedation coupled with a daily “wake up” when sedation is interrupted at least once daily in order to assess mental status and is often linked with a spontaneous breathing trial. Both of these approaches appear effective, but the first allows patients to communicate and participate in their care throughout the day rather than on an intermittent basis.

Delirium

3 The PADIS guidelines suggest that best practice includes systematic delirium assessments with validated tools at least twice daily.[7] Theoretical

benefits include identification of hypoactive delirium (which is often missed clinically), timely recognition and correction of inciting factors for delirium (potentially leading to improved outcomes), and the opportunity to discuss delirium's distressful symptoms with patients and their families.

At least five delirium assessment tools are available for the ICU. However, the CAM-ICU and ICDSC are recommended based on favorable psychometric testing (validity, reliability, feasibility, impact on patient outcomes; Table e27-4).[8] Despite improvements in delirium identification with these tools, their effect on clinical outcomes remains unclear. This may relate to the fact that currently available tools to detect delirium confound these assessments since they cannot discriminate between physiologic and pharmacologic changes in mental status.[7] It is important to note that patients with initial positive delirium assessments that resolve after interrupting sedation have clinical outcomes similar to those who never test positive for delirium. In fact, rapidly-reversible sedation-related delirium may represent sedation and not delirium,[57,58] and it emphasizes the value of performing delirium assessments when patients are as wakeful as possible and certainly after sedation interruption.

TREATMENT

The primary pharmacotherapy recommendations for PAD and the corresponding PADIS guidelines are presented in Table e27-5.

TABLE e27-5

Selected Pharmacotherapy Recommendations from the 2018 PADIS Guidelines

Recommendation	Recommendation Grade[a]
Pain	
Use multimodal approach to decrease opioid exposure	Conditional
Use enteral gabapentin, pregabalin, or carbamazepine with opioids for neuropathic pain	Strong
Use enteral gabapentin, pregabalin, or carbamazepine with opioids for pain after cardiovascular surgery	Conditional
Use an opioid, at the lowest effective dose or NSAID as an opioid alternative for procedural pain along with nonpharmacologic interventions	Conditional
Use an assessment-driven, protocol-based stepwise approach for pain management	Conditional
Agitation/sedation	
Use with an assessment-driven, protocol-base, stepwise approach for sedation management	Conditional
Titrate sedatives to light (vs deep) sedation	Conditional
Propofol or dexmedetomidine are preferred over benzodiazepines for sedation	Conditional
Delirium	
Do not use haloperidol or atypical antipsychotics to prevent delirium	Conditional
Do not routinely use haloperidol or atypical antipsychotics to treat delirium	Conditional
Use dexmedetomidine for delirium in ventilated patients where agitation is precluding weaning or extubation	Conditional

[a]Strong recommendation: applies to almost all patients, is based on moderate to high quality data where the benefits clearly outweigh the burdens;

Conditional recommendation: applies to most patients but with significant exceptions based on context using data that are conflicting, low quality, insufficient or involve limited patient populations where there may be a close balance between benefits and burdens.

Data from Reference 7.

General Concepts

Pain

4 and 5 Many *nonpharmacologic* interventions have been proposed to reduce pain with varying results, but few have been studied rigorously. Nonpharmacologic approaches are generally safe, not expensive to implement, and may complement pharmacologic management options.[7] The higher degree of pain that most ICU patients experience will, however, often require additional pharmacologic treatment.

The choice of *pharmacologic* agent(s) for pain relief is complex. A number of patient factors must be considered including the type of pain (nociceptive vs neuropathic, chronic vs acute), its intensity (mild to severe), precipitating factors (present at rest or only with specific events such as suctioning, repositioning, inserting or removing medical devices), its duration (prolonged vs limited), prior patient response to interventions, the status of organs responsible for medication metabolism and clearance, pulmonary function, hemodynamic stability, required onset and offset for pain relief, evidence for tolerance to analgesic choice, the need for IV administration, consideration of potential drug interactions and adverse medication reactions, and whether the patient requires continuous ventilator support.

Analgesic agents can be administered in a variety of ways. IV administration as a continuous infusion is useful for sustained analgesia, while intermittent injections are appropriate for procedural, predictable, or short-lived pain. Enteral administration should be reserved for patients not requiring analgesic dose titration. Opioid transdermal patch formulations may be helpful in stable patients once analgesic requirements are established, but because their onset is delayed they are not recommended in critically ill patients. For patients with intact motor function who are sufficiently wakeful, patient-controlled analgesia represents another viable option for analgesic delivery. Nonintravenous regional or neuraxial strategies may be useful in a variety of pain syndromes and are usually the domain of anesthesiologists.

6 An analgesia-first (the administration of an analgesic agent *before* sedation administration) or analgesia-based (the administration of an analgesic agent *instead* of a sedative) strategy has been suggested in the 2013 PAD and 2018 PADIS guidelines.[7,8] This approach is based on the fact that pain is common in ICU patients, is a major reason for agitation, and that a step-wise protocol-based intervention improves pain relief, limits sedation requirements, decreases dependency on mechanical ventilation, and may shorten ICU length of stay.[59] An analgesia-first approach is not appropriate for agitation due to substance withdrawal (except if opioid related), any medication-induced condition such as serotonin syndrome, neuroleptic malignant syndrome or encephalopathy, status epilepticus, or any other condition with a clear and reversible etiology best treated with a directed management strategy.

Because the opioids are associated with a number of important adverse medication reactions as well as the perceived risk of addiction and misuse,[60] a multimodal approach is suggested.[7] A multimodal approach (concurrent medication options with different mechanisms of action) offers the promise of improving analgesic response while limiting exposure to the opioids and their complications.

Sedation/Agitation

2 As discussed above, management strategies must consider and address pain as the most common cause for ICU agitation while simultaneously seeking to identify and treat other underlying reasons for agitation. If pain or discomfort is not present or if the provision of analgosedation is not adequate, traditional sedative agents may be required. Therapeutic choices for agitation must be driven by patient context. Clinicians should consider previous patient response to interventions, the status of organs responsible for medication metabolism and clearance, hemodynamic stability, neurologic function, respiratory status, home medication and substance use, prior or acquired psychiatric diagnoses, the required onset and offset for behavioral control, the need for IV administration, the degree of ventilator support, and consideration of potential drug interactions and adverse medication reactions. Commonly used analgesics and sedative agents that are administered as infusions are presented in Table e27-6.

TABLE e27-6

Common ICU Analgesics and Sedatives Administered as Infusions

Drug	MOA	Dosing Range[a]	PK/PD properties	ADR and Special Populations	Useful Information
Analgesics					
Fentanyl	μ agonist	25-200 mcg/h; LD = 50-100 mcg	1-2 min onset; 2-4 h half-life; CYP3A metabolism; no active metabolites	Serotonin syndrome; caution with SSRI and SNRI	Rapid onset and offset; useful in kidney disease; less hypotension vs morphine; interaction with CYP3A metabolized drugs (midazolam)
Hydromorphone	μ agonist	0.5-4 mg/h; LD = 0.5-2 mg	5-10 min onset; 2-3 h half-life; glucuronidation; neurotoxic metabolite	Rare neurotoxicity due to metabolite accumulation in kidney disease	Slower onset than fentanyl, but longer duration; no CYP interactions and no serotonin syndrome
Morphine	μ agonist	2-30 mg/h; LD = 2-5 mg	5-10 min onset; 3-4 h half-life; demethylation and glucuronidation; active metabolites	Hypotension; accumulation of active metabolites in kidney disease	Venodilation from histamine release
Remifentanil	μ agonist	0.5-15 mcg/kg/h; LD = 1.5 mcg/kg	1-3 min onset; 3-4 min half-life; esterase metabolism; no active metabolites	Allows frequent evaluations of neurologic function	Drug clearance unaffected by organ dysfunction; use IBW to dose obese patients; costly
Ketamine	NMDA receptor antagonist	0.05-0.4 mg/kg/h; LD: 0.1-0.5 mg/kg	1 min onset; 2-3 h half-life; demethylation; active metabolite	Possible hypertension; psychological disturbances	Does not interfere with respiratory function; useful for opioid tolerant patients
Sedatives					
Dexmedetomidine	Central α2 agonist	0.2-1.4 mcg/kg/h	5-10 min onset; 3 h half-life; CYP2A6 metabolism and glucuronidation; no active metabolites	Bradycardia and hypotension	Does not interfere with respiratory function; allows “cooperative sedation;” opioid sparing properties; less delirium than midazolam
Midazolam	GABA agonist	1-5 mg/h; LD = 1-5 mg	2-3 min onset; 3-11 h half-life; CYP3A metabolism; active metabolites	Delirium; context-sensitive half-life	Less hypotension than propofol or dexmedetomidine; allows deep sedation and amnesia; CYP3A interactions
Propofol	GABA agonist	5-50 mcg/kg/min	1-2 min onset; 3-12 h half-life; CYP2B6 and CYP3A metabolism; no active metabolites	Hypotension; PRIS; hypertriglyceridemia; pancreatitis	Allows easy goal titration and neurologic evaluations; can provide deep sedation with amnesia; no analgesia; interacts with midazolam

ADR, adverse drug reaction; cooperative sedation, ability to participate in care and follow commands; CYP, cytochrome P450; GABA, γ- aminobutyric acid; h, hour; IBW, ideal body weight; LD, loading dose; MOA, mechanism of action; min, minute; NMDA, N-methyl-d-aspartate; PK/PD, pharmacokinetic/pharmacodynamic; PRIS,

propofol related infusion syndrome; SSRI, selective serotonin reuptake inhibitor; SNRI, serotonin norepinephrine re-uptake inhibitor.

[a]Typical dosing range for adult ICU patients; analgesic dosing requirements for pain relief may exceed these recommendations as will sedative dosing requirements to produce deep sedation

Data from Reference 8.

Sedative agents can be administered in a variety of ways. IV administration as a continuous infusion is useful for sustained agitation while intermittent injections are appropriate for procedures or acute control of agitation. Some medications, such as lorazepam and clonidine may be given via enteral feeding tubes using available enteral formulations or administered sublingually. It should be appreciated and emphasized that not all ICU patients require sedation.

Delirium

7 The mainstay of delirium management is to identify and correct contributing factors. These risk factors are generally grouped according to the ability to be corrected or treated (Table e27-3). There is no evidence supporting pharmacological interventions to prevent ICU delirium, even in high risk patients.[61,62] Furthermore, there is little evidence demonstrating clinical improvement with pharmacological treatment of delirium (except perhaps related to alcohol withdrawal).[63] Symptom control with antipsychotics or dexmedetomidine for agitated patients may be reasonable.[7]

Nonpharmacologic Management

Pain

4 Initial pain management strategies should be directed at the source of the discomfort and may include nonpharmacologic strategies such as repositioning in bed, adjustment of endotracheal or chest tube placement, or stabilization of fractures. In addition, nontraditional medical approaches such as manipulative medicine may be helpful. Other beneficial nonpharmacologic strategies include massage therapy, music (with particular attention to patient preference), relaxation techniques, and cold packs (the latter two are helpful in the setting of procedural pain management).[7] If these strategies are not adequate, pharmacologic options should be employed.

Agitation

2 4 Since stress is a primary reason for agitation, its source should be identified as quickly as possible. It is reasonable to assume that pain and discomfort are often present and nonpharmacologic strategies to limit these conditions should be the first considered. Survivors of the ICU experience have reported that loss of control over basic activities of daily living is both frightening and stressful. Caregiver reassurance, support, and an empathetic explanation for tests, procedures, and care plans, along with frequent family visits represent personal approaches that can reduce the psychological stress associated with being critically ill. Other modifiable stressors that should be addressed include dyspnea, excessive noise, constipation or distended bladder, and immobility. The low risk, low cost features of nonpharmacologic interventions for ICU agitation support their use even in the absence of supporting evidence.[7]

Despite the lack of evidence supporting any clinical benefit, physical restraints have been traditionally been used in combative patients to prevent medical device removal, avoid falls, and to protect staff. However, restraints may paradoxically increase the risk for all of these issues and may contribute to delirium. Routine placement of restraints should be discouraged.[7]

Delirium

5 7 The initial management of delirium should involve a thorough evaluation and correction of modifiable risk factors including metabolic derangements, infections, medication use and withdrawal syndromes, and brain injury.[64] A multicomponent nonpharmacological approach for delirium prevention and treatment centers on consistent patient orientation to time, place, person and circumstance by caregivers and family. These approaches may include access to calendars, clocks, family photos, and daylight, the provision of eyeglasses and hearing devices, promotion of diurnal sleep patterns along with limiting napping during daylight periods, cognitive stimulation, mobility efforts, and the limitation of sedation. When used in a multicomponent, bundled fashion, these interventions reduce the incidence and duration of delirium and are recommended by the PADIS

guidelines.[7]

Pharmacologic Management

Pain

Opioids

Opioids are the most frequently used medications for pain relief in the ICU because of their potency, ease of administration through a variety of routes (eg, enteral, rectal, transdermal, IV, epidural), caregiver familiarity, and because they have some sedative properties. Opioids typically serve as the foundation for analgosedation.

All opioids share similar pharmacologic properties and interact with μ-opioid receptors to inhibit the release of inflammatory and excitatory mediators resulting in disruption of nerve signal propagation and diminished activity of nociceptors. Most opioids also have N-methyl-d-aspartate (NMDA) receptor agonist properties which paradoxically increase nociceptor stimulation and may result in the development of tolerance to their analgesic activity. Distinctions between the opioid medications are largely (though not entirely) related to their pharmacokinetics, pharmacodynamics, and expected adverse medication reactions (Table e27-6). These differences can help guide the optimal choice of opioid for a specific patient. For example, if rapidity of action is desired, IV fentanyl with its high degree of lipophilicity would be preferred whereas hydromorphone might be a better choice if a longer duration of action required. Morphine administration should be avoided for patients with kidney disease because of accumulation of its renally-cleared active metabolites.[8]

Opioid-Associated Adverse Medication Reactions

Opioid therapy is associated with diverse and significant adverse medication reactions. Constipation is common to all opioids and results from stimulation of gastrointestinal μ receptors leading to inhibition of gastric emptying and delays in gastrointestinal transit times in both small and large intestines. As many as 80% of opioid treated patients will experience constipation.[65] This is often associated with discomfort and delays achievement of nutritional goals. Opioid-induced constipation is also associated with inadequate oxygenation, hypotension, prolonged ICU length of stay and even mortality.[66] Pre-emptive management with routine administration of stool softeners and stimulant cathartics may be effective, but if they are not sufficient, a step-wise introduction of other modalities such as lactulose, polyethylene glycol, stimulant suppositories or enemas is recommended. Methylnaltrexone, a peripherally acting μ receptor antagonist is often effective when initial strategies fail.[64] Dosing is weight based and dependent on kidney function, and since methylnaltrexone does not cross the blood-brain barrier, opioid-mediated pain control is maintained. Methylnaltrexone is contraindicated in patients with bowel obstruction because of the risk for intestinal perforation.[67]

Respiratory depression is also common to all opioid medications and can interfere with efforts to wean from mechanical ventilation. Risk factors for opioid-induced respiratory depression include age over 60 years, opioid naivety, pulmonary or cardiac dysfunction, pre-existing impairment of ventilator drive (sleep apnea or obesity hypoventilation syndrome), the use of other sedative agents, and conditions that interfere with diaphragmatic function such as thoracic surgery. Careful titration of opioids is important for all patients but especially for this high-risk group and for those with tenuous respiratory function.[68]

Opioid-induced hyperalgesia is defined as an increase in pain response related to opioid exposure after minimal or even no exposure to noxious stimuli.[69] The clinical impact of opioid-induced hyperalgesia ranges from an acute loss of pain relief to the development of chronic pain syndrome. The proposed mechanism for opioid-induced hyperalgesia, sensitization of pro-nociceptive pathways through activation of NMDA receptors resulting in an influx of intracellular calcium which in turn heightens the response to pain, provides the rationale for using NMDA receptor antagonists, such as ketamine and methadone. Other management approaches include multimodal analgesic strategies, careful opioid dose titration, opioid rotation, and the use of regional anesthetic techniques.

Given the opioid epidemic, there is growing concern with the use of opioids in the ICU and the misuse potential after discharge. Approximately 20% to 40% of ICU patients are prescribed opioids at discharge, with only 3% continuing to persistent use; however, more research is needed to understand the impact of opioids in the ICU and chronic opioid use and misuse.[6,70]

Fentanyl

Fentanyl is a widely used opioid in United States ICUs because of its rapid onset of action and ease of titration. It is largely metabolized by CYP3A4 and may interact with commonly used ICU medications including, but not limited to, midazolam, the azole antifungals, macrolides, protease inhibitors, barbiturates, rifampin. Only 10% of fentanyl is excreted unchanged by the kidney, and no renally excreted active metabolites are formed.[8] Therefore, fentanyl dosing requirements are unchanged in patients with impaired kidney function though they may be reduced in patients with hepatic disease or heart failure.[71]

Fentanyl has 5-hydroxytryptamine 1A agonist properties and may occasionally be associated with serotonin syndrome in patients receiving other serotonergic medications.[72,73]

Hydromorphone

Hydromorphone is a potent semisynthetic opioid with a relatively long duration of action (~3 hours) which may be beneficial if prolonged pain relief is required, but this same feature interferes with dose titration.[8] It is hepatically cleared and is safe to use in patients with kidney disease though accumulation of the neurotoxic 3-glucuronide metabolite is possible in this setting. Important differences in opioid dosing equivalents should be appreciated when using hydromorphone since the IV formulation is approximately seven times more potent than IV morphine.

Morphine

Contemporary use of morphine is traditionally limited for the treatment of dyspnea, myocardial infarction (histamine releasing properties result in venodilation and a reduction in preload), and as a part of palliative care for the terminally ill. Use of this opioid is complicated by its relatively slow onset of action, potential for bronchospasm, and the accumulation of active metabolites. The 3 and 6 glucuronide salts are associated with neurotoxicity which may lead to seizures and oversedation respectively in patients with impaired kidney function.[8]

Methadone

Methadone is a unique synthetic opioid since it is a μ receptor agonist as well as an NMDA receptor antagonist. This latter pharmacologic property may restore analgesic responsiveness in chronic pain patients who have exhibited tolerance to high doses of standard opioids. This opioid has a complex pharmacokinetic profile with a half-life that varies from 15 to 60 hours depending on hepatic and CYPs 3A4 and 2B6 enzyme function and the presence of drug-drug interactions. Methadone can facilitate extubation and discontinuance of opioid infusions,[74,75] but is associated with a number of clinically important issues. There are no reliable dose equivalents when transitioning from standard opioids to methadone so conservative initial dosing and careful titration is necessary with rescue doses of another opioid in place until an adequate methadone regimen is determined.[76] When converting from IV to oral methadone the oral availability is greater than 75% and a 1:1.3 ratio should be used.[77] Another concern involves QTc prolongation and the potential for ventricular dysrhythmias such as torsades de pointes. Risk factors for torsades include the administration of more than 30 mg per day, concurrent use of other QTc prolonging medications, electrolyte imbalances, and the presence of structural or arrhythmogenic heart disease. Baseline and follow-up ECG monitoring is recommended for patients with these risk factors along with maintenance of serum potassium and magnesium in normal ranges.[78] And lastly, like fentanyl, methadone induces serotonin syndrome when used concurrently with other serotonergic medications.[79,80]

Remifentanil

Remifentanil is an ultra-short acting opioid administered as an infusion. Remifentanil is advantageous in patients with organ dysfunction and in those who require frequent neurologic evaluations since it is degraded by plasma esterases resulting in a 3 minute half-life. This short half-life can also pose a risk for patients if the infusion is inadvertently interrupted exposing patients to a loss of analgesia as well as the potential for acute opioid withdrawal. Healthcare professionals should be informed of these risks and be prepared to administer longer acting opioids if this occurs. Lastly, the risk of opioid induced hyperalgesia may be greater with remifentanil compared to other opioids.[81,82]

Buprenorphine

Buprenorphine is a partial μ-opioid receptor agonist with kappa opioid receptor antagonist properties. Buprenorphine's use in the ICU is usually reserved for continuation of pre-ICU admission treatment for opioid dependence or chronic pain. Because of its opioid antagonist properties, patients who have a history of recent buprenorphine administration will often require much higher doses of standard opioids for their ICU care.[83]

Tramadol

Tramadol is an oral synthetic opioid that modulates the pain response in a number of ways including weak μ opioid receptor activity, serotonin release, inhibition of norepinephrine reuptake and by acting as an NMDA antagonist. While tramadol may produce less respiratory depression than standard opioids, its use in the ICU is limited by its low potency, medication interactions (CYP metabolism), epileptogenic properties, and the potential to induce serotonin syndrome.[84]

Nonopioid Analgesic Agents

Adjunctive, nonopioid medications such as acetaminophen, ketamine, nonsteroidal anti-inflammatory drugs, and neuropathic agents such as pregabalin and gabapentin are used with the intention of sparing opioid use and attendant adverse medication reactions (ileus, respiratory depression) and improving pain management. These potential benefits must be weighed against their adverse medication reactions, for example, liver toxicity with acetaminophen, risk of bleeding with NSAIDs, neurotoxicity and behavioral issues with ketamine, and altered mental status with gabapentin.[85]

Acetaminophen

Acetaminophen, a central cyclooxygenase inhibitor, consistently decreases opioid dosing requirements by as much as 20% in non-ICU trials. Unfortunately, there are very few supportive ICU-specific studies. The PADIS guidelines suggest that acetaminophen should be considered for pain relief especially in patients at high risk for opioid-associated side effects (eg, patients recovering from abdominal surgery or at risk for ileus or nausea or vomiting).[7] It should be appreciated that the IV formulation of acetaminophen has been associated with hypotension with a reduction in mean arterial pressure of greater than 15 mm Hg in as many as 50% of patients. The reasons for this remain unclear.[86] Daily dosing of acetaminophen for acute short-term use should be limited to less than 4 gm in those with cirrhosis or a history of alcohol use disorder and for longer term use, a maximum of 2 to 3 gm daily is recommended.[85]

Gabapentinoids

Gabapentin and pregabalin modulate pain response by interfering with the influx of intracellular calcium which reduces glutamate and substance P release. Since gabapentinoids provide opioid sparing properties, the PADIS guidelines recommend the use of these medications for the treatment of pain.[7] No difference in time to extubation or ICU length of stay is apparent in patients receiving gabapentinoids versus those who do not.

Gabapentinoid medications have limitations, primarily involving their sedative potential and their lack of IV availability. Since they are renally eliminated, dosing needs to be adjusted in patients with impaired kidney function.

Ketamine

Ketamine is noncompetitive NMDA receptor antagonist blocking the effects of glutamate release. Its use is associated with dissociative, sedative, analgesic, and amnestic effects.[87] Other properties of ketamine include the release of endogenous catecholamines (helpful in patients with hypotension and hazardous in those with hypertension), bronchodilation (helpful in asthma exacerbations), and lack of interference with respiratory drive (helpful in patients with tenuous pulmonary function) and gastrointestinal motility (helpful in patients with ileus or constipation). Low dose ketamine infusions are adjunctive to opioid therapy in the post-surgical ICU setting due to a reduction in morphine consumption.[7,88] Adverse medication reactions of ketamine include neuropsychiatric effects (emergence phenomenon, confusion, nightmares, hallucinations, which are rarely seen on medication discontinuance with doses less than 0.5 mg/kg/hour), hypertension, diplopia, nystagmus, and nausea and vomiting. Relative contraindications for ketamine with subdissociative dosing are not well established, but a recent consensus guideline includes poorly controlled cardiovascular disease or hypertension, pregnancy, active psychosis, and severe liver disease.[89] Though popular, additional research to define ICU-specific risks, benefits, and dosing schemes with ketamine are needed.

Nonsteroidal Anti-Inflammatory Drugs

NSAIDs inhibit prostaglandin synthesis in response to noxious stimuli and interfere with the acute inflammatory response. In the setting of postoperative ICU pain, short-term NSAIDs may decrease opioid requirements without effecting the frequency of nausea/vomiting and without increasing the risk for bleeding or kidney injury. None-the-less, because of their well-established adverse medication reactions, NSAIDs should be avoided in patients with bleeding diathesis and kidney disease.[7]

α2 Agonists

Dexmedetomidine and clonidine are central α2 receptor agonists commonly used in the ICU. They are typically regarded as sedative agents, but they have opioid sparing properties as well. Pain modulation is likely mediated by α2 receptor agonism in the substantia gelatinosa in the dorsal horn of the spinal column.[90] These agents are discussed in detail in the Pharmacologic Management of Agitation section of this chapter.

Agitation

Most ICU patients will require some form of pharmacologic strategy to maintain comfort and safety, but these same interventions may predispose to high morbidity. To maintain the fine balance between efficacy and harm, carefully choosing both an appropriate sedation option and titration goal is required. These choices can affect short- and long-term outcomes including the duration of mechanical ventilation, ICU length of stay, 90-day mortality, the incidence of delirium, and long-term neurocognitive and psychologic function.[91,92]

Benzodiazepines

Benzodiazepines activate γ- aminobutyric acid A (GABA) receptors and have anxiolytic, amnestic, sedative and anticonvulsant activity. These agents can cause respiratory depression, altered sensorium, and hypotension especially with concurrent opioid use. The benzodiazepines are no longer considered first line agents for the treatment of agitation in the ICU since they are associated with prolonged time on the ventilator and in the ICU and may increase the risk for delirium, especially when administered as continuous infusions[7,8,42,93] These outcome differences are likely related to challenges with dose titration arising from benzodiazepine pharmacodynamic and pharmacokinetic properties.

Midazolam is metabolized by CYP3A4 with a half-life of approximately 3 hours after IV bolus administration. This lipid soluble benzodiazepine is often used in the ICU since its onset is very quick and it can be given both as a bolus and infusion. With short-term use, the duration of action of midazolam is brief, but can be dramatically prolonged when administered as an infusion for longer than 48 hours.[8] The lipophilicity of midazolam helps to explain this effect, termed “context sensitive half-life” where the parent drug accumulates as a function of duration of exposure resulting in prolongation of its offset.[94] The extended activity of midazolam resulting from context sensitive half-life issues is compounded by the accumulation of an active metabolite (α1-hydroxymidazolam) in patients with kidney disease.[95]

Lorazepam, a longer acting benzodiazepine with relatively low lipid solubility and associated slower onset of effect, is used less frequently in the ICU. It is generally prescribed for the treatment of alcohol withdrawal and for acute treatment of seizures. Its utility as an infusion is limited by the large amount of the diluent, propylene glycol, present in the IV formulation that can accumulate in a dose dependent fashion to cause metabolic acidosis, renal tubular dysfunction, and hyperosmolarity.[96]

Despite these short-comings, the benzodiazepines remain important sedative options for select patients. They may be preferred as premedications for procedures, to provide deep sedation particularly when amnesia is required (such as when neuromuscular blockade is used), to acutely treat seizures, for the management of alcohol withdrawal, and perhaps in conjunction with opioid-based analgosedation to sedate patients who are hemodynamically compromised since propofol and dexmedetomidine are commonly associated with hypotension.[97,98]

Propofol

Both the 2013 PAD and 2018 PADIS guidelines suggest that either propofol or dexmedetomidine are preferred as sedative agents over the benzodiazepines in critically ill mechanically ventilated ICU patients.[7,8,99] Propofol binds to multiple central nervous system sites including GABA,

glycine, nicotinic and muscarinic receptors to produce sedative, anxiolytic, amnestic, antiemetic and anticonvulsant activity. It is highly lipid soluble with rapid transport through the blood-brain barrier into and out of the brain. The resultant ease of titration makes propofol a desirable agent for many different types of patients and clinical conditions especially when frequent neurologic evaluations are required and to facilitate daily sedation interruption efforts. Its use is also associated with a shorter length of stay and a lower incidence of delirium compared to the benzodiazepines.[100] Propofol and dexmedetomidine have similar outcomes in regard to length of mechanical ventilation, delirium and mortality.[101] The choice between propofol and dexmedetomidine is determined by the need for mechanical ventilation (dexmedetomidine is fine for patients who are not ventilated) and the desired depth of sedation and amnestic effects (propofol use is favored for deep sedation and amnesia).

Propofol does not possess analgesic activity, is associated with hypotension, depresses respiratory drive, interferes with airway protection and is associated with a low frequency, but highly morbid condition called the propofol-related infusion syndrome (PRIS).[102] Risk factors have traditionally focused on exposure (dose exceeding 4mg/kg/hr and duration longer than 48 hours), but some patients may experience PRIS with lower doses and within a short period after infusion initiation. Mitochondrial dysfunction is thought to mediate this often deadly reaction which is characterized by hypotension, bradycardia, Brugada-like arrhythmias, creatine-kinase elevation, metabolic acidosis, and death.[103] Since there is no antidote for this syndrome, early recognition, discontinuance of propofol and supportive measures are required.

Propofol is administered as an infusion containing 10% lipid emulsion with egg lecithin and soybean oil and therefore it should be avoided in patients with allergies to eggs or soybeans. In addition, the caloric load of propofol infusions (1.1 kcal/mL [4.6 kJ/mL]) must be considered when nutritional requirements are calculated. The lipid carrier vehicle may increase the free fraction of other medications such as valproate.[104]

Dexmedetomidine

8 Dexmedetomidine is a selective central α-2 receptor agonist that inhibits synaptic release of norepinephrine in the coeruleus locum and dorsal region of the spinal cord, and other areas, and offers anxiolytic, sympatholytic and opioid sparing activity without significantly impairing respiratory drive.[90] It can be administered to patients who are not supported by mechanical ventilation and offers an option for multimodal analgesia. These attributes are especially useful in treating agitated patients who are in the process of weaning from mechanical ventilation, in nonintubated patients with tenuous respiratory function, and may be helpful in patients with delirium or withdrawing from alcohol or opioids.[105] Dexmedetomidine infusions offer a light sedative state allowing patients to be interactive, and may facilitate pain assessment, mobilization efforts, and accurate delirium screening. The cooperative sedation produced by dexmedetomidine precludes its use for patients requiring deep sedation or amnesia. In addition, dexmedetomidine should be used very cautiously in patients with hemodynamic instability or reduced left ventricular function since its central α-2 receptor agonist properties can result in bradycardia and hypotension.[100,105]

Alternative Sedative Agents

No new sedative agents for ICU use have been FDA approved since dexmedetomidine in 1999, and all existing options are limited by efficacy, which varies by patient characteristics, development of adverse medication reactions, and the need for IV administration in a monitored setting. In an effort to explore alternative approaches, older medications have been repurposed in novel ways to help treat agitation in patients not responding to or intolerant of traditional agents and to help transition patients to non-ICU settings. For example, clonidine may aid in alcohol or opioid withdrawal syndromes, be employed as a part of multimodal pain relief, and used as an enteral alternative to dexmedetomidine. Valproate may be considered for agitation in patients with a history of bipolar disease, traumatic brain injury, or with seizure disorders. Phenobarbital has found utility in the setting of alcohol or benzodiazepine withdrawal. All three of these alternative agents carry some risk; clonidine with its withdrawal syndrome and hemodynamic effects, valproate and its association with hyperammonemia and liver derangement, and phenobarbital with its drug interaction profile and potential for excessive sedation. As is true with all sedative agents, patient-specific features and goals should guide medication choice.[106]

Delirium

2 7 The most important and perhaps the only strategy to effectively treat delirium is to identify and correct or reverse its underlying cause, which may include infections, metabolic derangements, hypoxia, hyperthermia, pain, acidosis, central nervous system diseases, medication/substance use or withdrawal. Traditional pharmacologic treatment options for the symptoms of agitated delirium include haloperidol and the atypical antipsychotics. These agents block dopamine, serotonin, histamine, α adrenergic, and muscarinic receptors resulting in mood stabilizing effects. They do not affect

respiratory drive, but may variably prolong the QTc depending on the agent used. In addition, long-term administration has been associated with cardiovascular events and death especially in older patients with dementia.[107] These agents may not influence the severity or duration of delirium, and may not have a beneficial effect on clinically relevant outcomes such as time on the ventilator, time in the ICU, and mortality.[62] The PADIS guidelines do not recommend routine use of antipsychotic agents for patients with delirium.[7] Whether these medications offer any benefit for the distress associated with delirium such as anxiety, fear, delusional thinking or hallucinations has yet to be determined. It is important to emphasize that as many as 75% of patients initiated on antipsychotic medications in the ICU are discharged from the ICU on these medications, and as many as 55% of patients are discharged from the hospital with prescriptions for these agents either intentionally or inadvertently resulting in exposure to potential adverse medication reaction risks including cardiovascular events and death.[108–110]

Currently, there is limited evidence to support the use of dexmedetomidine for intubated patients when agitated delirium interferes with extubation.[111] Dexmedetomidine may reduce delirium occurrence, but it is not clear if dexmedetomidine is useful for delirium that is not associated with agitation and for delirious patients where agitation does not preclude extubation efforts.[112]

Medication Withdrawal

Sedative and opioid withdrawal symptoms may be seen in as many as 30% of mechanically ventilated patients.[113,114] Unfortunately, the risks for developing withdrawal and its management are not clear. Withdrawal symptoms appears to be more frequent with the use of high doses for prolonged durations. Symptoms of withdrawal classically include the opposite of the medication's pharmacologic effect, but in general these symptoms can be regarded as nonspecific. The presence of unexplained agitation, tachycardia, hypertension, insomnia, delirium, nausea, diarrhea, diaphoresis and fever should prompt consideration of withdrawal. The 2013 PAD guidelines suggest that medications should be tapered over several days (if possible) when iatrogenic withdrawal is suspected.[8] Alternatively, the use of longer acting agents such as methadone or clonazepam can facilitate gradual discontinuance within a class of these medications. There is much to learn regarding iatrogenic withdrawal in ICU patients.

Transitions of Care Issues

5 As many as 75% of patients have medications initiated in the ICU to manage PAD and their continued need should be assessed with each transition of care, from ICU to floor and again at hospital discharge. The issue is confounded by the fact that nearly 40% of medications used in the ICU are "off-label" resulting in unclear indications for use.[115] Inadvertent or inappropriate continuation of ICU initiated psychoactive medications (antipsychotic agents, valproate, and clonidine) is well documented and occurs with a frequency of up to 75% after ICU discharge and 55% after hospital discharge[109,110,116–118] Some patients will require longer-term medical management with continuation of medications after ICU discharge, but for most, this represents improper prescribing. A number of strategies including electronic handoffs and process improvement efforts have limited efficacy, especially when considering prescriptions provided at hospital discharge.[119] Recommended strategies to prevent these occurrences include mandating inclusion of the indication for use along with a stop date or weaning plan within the medication order, initiating an electronic medical record-based alert system to warn prescribers that an ICU initiated medication is being continued after ICU discharge, and consistently offering medication reconciliation at every step (including transfer out of the ICU and discharge) within transitions of care.[109]

EVALUATION OF THERAPEUTIC OUTCOMES

5 Frequent systematic evaluations of PAD using validated assessment tools per the SCCM guidelines (at least four times per shift for pain and sedation/agitation and at least twice daily for delirium) aids in the timely recognition of these issues.[8] Positive assessments for PAD should prompt a search for inciting factors, initiate corrective action, and encourage preemptive or preventative interventions.

Persistent distressful or dangerous symptoms of PAD often require nonpharmacologic and/or pharmacologic management. These interventions should be evaluated for therapeutic efficacy and for possible adverse medication reactions. A multimodal approach which includes nonpharmacologic and pharmacologic strategies should be in place, and for most patients, goals of therapy include the provision of comfort and safety while allowing participation in their own care.[120,121] Sedation-induced coma should be reserved for specific indications since it adversely affects outcomes.

Medication withdrawal symptoms and resurgence of clinical issues upon discontinuance of medical management of PAD should be monitored, and if

indicated, reinitiation of the medication or a dose tapering strategy should be considered. Continual reevaluation of the need for psychoactive or analgesic medications initiated in the ICU is required since many patients inadvertently or inappropriately remain on these agents even after hospital discharge.

CONCLUSION

Many important short and long-term outcomes in critical care patients are influenced by the management of PAD. Features that are common for the optimal management for PAD include the provision of preventative measures, the systematic assessment PAD, the establishment of appropriate therapeutic goals, the use of nonpharmacologic modalities, and only when these are inadequate, that pharmacologic options be employed. Since PAD in ICU patients is multifactorial, a multimodal interprofessional strategy is generally beneficial. Lastly, pharmacological management choices are driven by patient context, therapeutic goals, and a thorough evaluation of risks and burdens by considering medication pharmacodynamics, pharmacokinetics, and adverse medication reaction profiles.

ABBREVIATIONS

ACCP	American College of Chest Physicians
ATS	American Thoracic Society
BIS	Bispectral Index
BPS	Behavioral Pain Scale
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CPOT	Critical Care Pain Observation Tool
COPD	Chronic Obstructive Pulmonary Disorder
CYP	Cytochrome P450 enzyme
ECG	Electrocardiogram
EEG	Electroencephalogram
E-PRE-DERILIC	Early Prediction of Delirium in ICU Patients
FDA	Food and Drug Administration
GABA	γ- aminobutyric acid
ICU	Intensive Care Unit
IV	Intravenous
NMDA	N-methyl-d-aspartate
NRS	Numeric Rating Scale
NSAID	Nonsteroidal Anti-inflammatory Drug

PAD	Pain, Agitation, Delirium
PADIS	Pain, Agitation, Delirium, Immobility, Sleep Disturbance
PRE-DERILIC	Prediction of Delirium in ICU Patients
PRIS	Propofol Related Infusion Syndrome
QTc	Corrected QT interval
RASS	Richmond Agitation Sedation Scale
RCT	Randomized Controlled Trial
SAS	Sedation Agitation Scale
SCCM	Society of Critical Care Medicine
SNRI	Serotonin Norepinephrine Re-uptake Inhibitor
SSRI	Selective Serotonin Re-uptake Inhibitor

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SELF-ASSESSMENT QUESTIONS

1. A 50-year-old male was involved in a motor vehicle crash and suffered significant chest trauma including multiple rib fractures. He has developed respiratory failure with evidence of pneumonia and a pleural effusion and now requires mechanical ventilation and the placement of a chest tube. Which assessment tool should be utilized to monitor the patient's pain?

   A. Richmond Agitation Sedation Scale (RASS)

   B. Confusion Assessment method for the ICU (CAM-ICU)

   C. Intensive Care Delirium Screening Checklist (ICDSC)

   D. Critical Care Pain Observation Tool (CPOT)

2. An acute respiratory distress syndrome patient is being paralyzed with cisatracurium and deeply sedated with fentanyl and propofol to facilitate mechanical ventilation with a lung protective strategy. The patient's nurse is interested in discontinuing fentanyl drip because the documented CPOT score = 0. The RASS score is −5. Which of the following is the *best* therapeutic option at this time?

   A. Turn off the fentanyl infusion since there is no evidence for pain

   B. Have the nurse monitor vital signs after turning off the fentanyl infusion since these are valid indicators of pain

   C. Retain fentanyl since pain cannot be assessed with CPOT in patients without motor activity

   D. Ask a surrogate to assess the patient's pain before turning off the fentanyl

3. Which of the following is the *most likely* to influence ICU delirium and pain assessments?

   A. Sedation during delirium and pain assessments

   B. Lack of a validated ICU delirium and pain assessment tools

   C. The subjectivity of validated delirium and pain assessment tools

   D. Caregiver inexperience in administering these assessments

4. A non-intubated patient with respiratory distress in the setting of an acute exacerbation of chronic obstructive pulmonary disease develops agitation that seems related to his dyspnea. Aerosolized bronchodilators help his oxygenation, but even after a 2 mg dose of IV midazolam, he remains agitated. His mean arterial blood pressure is 60 mm Hg without vasopressor support. When asked about any discomfort, he rates his pain as 4 on the numeric rating scale. Which of the following is the *best* initial therapeutic option for this patient?

   A. Propofol infusion after intubation

   B. Dexmedetomidine infusion without intubation

   C. Intermittent fentanyl injection without intubation

   D. Midazolam infusion after intubation

5. Which statement is *true* regarding non-pharmacologic strategies for PAD management?

   A. They are most effective when used in a multifaceted approach

   B. They are made more efficient by focusing on one effort

   C. They are generally ineffective, but not likely to cause harm

   D. They do not lend themselves to a bundled approach

6. An 86-year-old woman with a minimal medical history presents with a urinary tract infection and acutely becomes sleepy, withdrawn, and confused. She is unable to follow commands appropriately though she has no history of cognitive dysfunction. Diagnostic screening tests have not yet been performed. Which condition is the *most likely* explanation for her behavior?

   A. Hypoactive or decreased arousal delirium

   B. Post-traumatic stress disorder (PTSD)

   C. Dementia

   D. Depression with dementia

7. An older adult patient (NKDA, no significant past medical history) is determined to have delirium based on a screening assessment tool, the CAM-ICU. The urine grows *E. Coli* susceptible to most antibiotics. What is the *best* treatment for this patient's psychiatric symptoms at this time?

   A. Intravenous haloperidol

   B. Enteral quetiapine

   C. Appropriate antibiotics

   D. Intramuscular olanzapine

8. Most opioid medications confer pain relief by μ-opioid receptor agonist properties. Which of the following may have utility in patients who have experienced tolerance to opioid-induced analgesia?

   A. Morphine because its active metabolites act synergistically with the parent drug

   B. Methadone because of its NMDA receptor agonist properties

   C. Hydromorphone because it is a synthetic opioid and more potent than morphine

   D. Remifentanil because it is easily titratable

9. When compared to infusions of propofol and dexmedetomidine, midazolam infusions are associated with which of the following?

   A. A longer duration of mechanical ventilation and higher mortality

   B. A longer duration of mechanical ventilation and ICU length of stay

   C. An increased risk for delirium without affecting time on the ventilator and in the ICU

   D. A reduction in ICU costs since its acquisition costs are less than the other two options

10. As a part of a quality assurance program, you find that 25% of patients continue to receive ICU initiated psychoactive medications when they are transferred to a non-ICU nursing unit. Which strategy is *most appropriate* to employ to reduce inappropriate or unintended medication continuation?

    A. Create a policy mandating discontinuance of all psychoactive medications prior to transfer out of the ICU

    B. Allow the practice to continue since the risk of recurrence of adverse or dangerous behaviors is so high

    C. Allow these medications to be continued in a non-ICU setting, but with proactive orders to taper dosing to ensure that they are completely discontinued within 5 days

    D. Ensure that medication reconciliation is in place during all transitions of care to determine if the initial indications remain for psychoactive medication use

11. Ventilatory support of patients with acute respiratory distress syndrome is often prolonged and requires sustained sedation and analgesia for comfort and to facilitate synchrony with the ventilator. Many of these patients also have concomitant kidney injury. Which of the following combinations is *preferred* in this setting?

    A. Fentanyl and midazolam

    B. Fentanyl and propofol

    C. Morphine and propofol

    D. Hydromorphone and midazolam

12. An 80-year-old male who resides in a skilled nursing facility is admitted with septic shock and respiratory failure related to pneumonia. His mean arterial blood pressure is 60 mm Hg and vasopressor therapy is initiated. His urine output is diminished and his serum creatinine has doubled over baseline in the last 24 hours. After intubation, he becomes very agitated and requires pharmacologic management for safety and comfort. Which of the following options is the *best* choice for managing his agitation?

    A. Fentanyl and propofol infusions

    B. Fentanyl infusion and intermittent midazolam

    C. Dexmedetomidine infusion

    D. Morphine infusion and intermittent intravenous haloperidol

13. A 75-year-old male is admitted to the ICU with respiratory distress due to COPD exacerbation. He has a history of atrial fibrillation treated with diltiazem 30 mg every 6 hours for rate control and chronic back pain treated with acetaminophen on an as needed basis. Within 12 hours, he becomes agitated and is provided a dexmedetomidine infusion, but his heart rate is now 45 beats per minute. He is not requiring mechanical ventilation, and the team is interested in an alternative regimen that will provide comfort while preserving his respiratory drive. Which of the following strategies would be *preferred*?

    A. Fentanyl infusion titrated to pain relief

B. Scheduled enteral clonidine with as needed morphine

C. Scheduled enteral quetiapine with as needed fentanyl

D. Scheduled enteral acetaminophen with as needed hydromorphone injection

14. A 35-year-old female suffers extensive thoracic trauma after a motor vehicle crash. Surgical intervention was successful, but she now has an ileus likely due to post-operative use of continuous infusion fentanyl and this interferes with achieving her nutritional goals. Which of the following is *not* a good option for relief of moderate to severe pain in this patient?

A. Add ketamine infusion with scheduled acetaminophen

B. Continue fentanyl infusion with aggressive scheduled bowel preparations and add acetaminophen

C. Transition to methadone for pain relief

D. Substitute dexmedetomidine for fentanyl and add scheduled acetaminophen

15. Which psychoactive medication is *not* associated with withdrawal symptoms with abrupt discontinuance after prolonged high dose exposure?

A. Quetiapine

B. Clonidine

C. Midazolam

D. Fentanyl

SELF-ASSESSMENT QUESTION-ANSWERS

1. **D.** The RASS is used to monitor sedation, and CAM-ICU and ICDSC are used to monitor delirium. CPOT is an option to monitor pain in critically ill patients unable to communicate their pain.

2. **C.** We assume that pain/discomfort is present even in patients at rest and perhaps in particular in patients who are immobile and receiving nonphysiologic respirations. There is no reliable way to assess pain in a patient who is deeply sedated and pharmacologically paralyzed since CPOT requires some motor activity for assessment. Surrogate pain evaluations do not offer any value in unresponsive, paralyzed patients and vital signs are not adequate indicators of pain in the ICU.

3. **A.** ICU delirium and pain assessment tools have been evaluated for reliability, feasibility, validity, and clinical utility in clinical environments, and as such, make selections B, C and D incorrect. Data on the influence of sedation levels or arousal to evaluate pain is limited to one study (Reference 40), while the influence of arousal levels on delirium assessments is well supported with data from over 12,000 patient-specific evaluations. When patients are not able to track with their eyes for 10 seconds after verbal stimuli, the frequency of positive delirium assessments is 75%, but decreases to 22% when they are wakeful (Reference 5).

4. **C.** Pain may be present in a resting patient should always be assessed as a reason for agitation. A numeric rating score of 4 suggests that pain is present in this patient and should be addressed. Propofol would likely control his agitation by masking pain, but would require the insertion of an endotracheal tube and initiation of mechanical ventilator support. It is also associated with many adverse medication reactions such as hemodynamic instability. Dexmedetomidine might be a reasonable choice since it offers opioid sparing properties and does not require mechanical ventilation for use, but it is also associated with hemodynamic instability. Midazolam infusions should be reserved for specific patient populations since they are associated with prolonged time on the ventilator and in the ICU and are also associated with delirium.

5. **A.** The etiology of PAD is often multifactorial and it should be managed using a multifaceted approach; ideally without resorting to pharmacologic strategies. While data supporting efficacy of these nonpharmacologic interventions are sparse, they may be helpful and are not likely to cause harm. Music is a good example of a potentially effective means of influencing analgesic requirements which carries little risk for harm (as long as

patient listening preference is considered). Utilizing these strategies as a part of a bundled approach to ICU care can have a positive impact on outcomes.

6. **A.** Delirium is characterized by acute changes in mental status and arousal associated with inattention that is initiated by a medical issue such as an infection. PTSD is a more chronic condition and usually is apparent weeks after a traumatic event. Dementia can be distinguished from delirium by the chronicity of symptoms. Depression may help to explain her lethargy, but should not cause confusion, and it is generally not a condition that occurs acutely without an inciting factor.

7. **C.** Treatment of delirium should be directed at its cause, and in this case, it is likely the infection. There are no data to support the use of antipsychotics in delirium of any kind, but especially when behaviors are not dangerous to self or to others.

8. **B.** All of the answers contain accurate descriptions of the various opioid options, but opioid choice is best determined by patient context. Morphine has active metabolites, but one of them actually heightens the perception of pain. Hydromorphone is indeed synthetic and the IV formulation is approximately seven times more potent than IV morphine. But opioid tolerance isn't an issue of dosing as much as it is activation of the NMDA receptor site resulting in heightened pain perception. Remifentanil has a half-life of 3 minutes, is administered as an IV infusion, and is associated with rapid onset of opioid hyperalgesia. It would not be a good choice for these reasons. Methadone has NMDA receptor agonist properties and has found utility in restoring analgesia for patients who have become tolerant to standard opioids.

9. **B.** Randomized controlled trials have demonstrated that midazolam use is not associated with an increase in mortality, but it does adversely influence time on the ventilator and in the ICU. In addition, infusions of midazolam are associated with an increased risk for delirium. Acquisition costs for midazolam are lower than for dexmedetomidine and propofol, but these savings are negated when the costs of care (increased time in the ICU and on the ventilator) are considered.

10. **D.** The continued need for all medications, but particularly those initiated in the ICU for an acute indication should be evaluated during all transitions of care. The decision about whether to continue, discontinue, or taper dosing of these medications should consider patient context. This makes protocolization using automatic stop or tapering orders ill-advised from a patient care perspective.

11. **B.** Both of these agents are short acting, are not cleared by the kidneys and do not produce active metabolites. The midazolam component in answers A and D degrades to an active metabolite that has two-thirds the activity of the parent drug and it accumulates in kidney disease. Answer C is incorrect since morphine degrades to two active metabolites that accumulate in kidney disease. Hydromorphone is generally regarded as an appropriate opioid in renal disease, but it carries the small risk of accumulation of a neurotoxic metabolite.

12. **B.** Agitated hemodynamically compromised patients are challenging to manage since many of the sedatives we offer (propofol and dexmedetomidine) can cause or exacerbate hypotension. Morphine is not a good choice since it can cause venodilation related to histamine release and also since its active metabolites will accumulate in kidney disease. Fentanyl does not cause histamine release and has no active metabolites. When analgosedation is offered, additional standard sedation is required in approximately 50% of patients. For breakthrough agitation, intermittent midazolam is often effective and with this mode of administration (vs a continuous infusion), the risk for delirium is low.

13. **D.** His history includes the successful use of acetaminophen, but there may be new onset pain that could be effectively and safely treated with as needed intermittent IV hydromorphone. Infusions of opioids should be avoided due their potential respiratory depression activity. Clonidine is pharmacologically related to dexmedetomidine and can be expected to share in its adverse medication reaction profile including bradycardia. There are no data supporting the benefits of quetiapine in agitated patients.

14. **C.** Multimodal analgesia can result in opioid sparing properties making combinations of ketamine and dexmedetomidine appropriate choices. If an opioid is needed, the provision of bowel preparations should be in place. The use of methadone as a single pain agent would not likely offer an advantage over continuous infusion fentanyl in terms of her gastrointestinal function.

15. **A.** There is no pharmacologic withdrawal that is associated with the antipsychotics, but resurgence of psychiatric symptoms may occur and probably warrant cautious discontinuance or downward dose titration. Withdrawal symptoms from opioids and benzodiazepines can be expected after prolonged exposure. Seizures associated with benzodiazepine withdrawal is potentially life threatening. Clonidine withdrawal syndrome also included potentially life-threatening symptoms including hypertension and tachycardia.