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Curtis N. Sessler and Kimberly Varney

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A M E R I C A N C O L L E G E O F



P H Y S I C I A N S[®]



Patient-Focused Sedation and Analgesia in the ICU*

Curtis N. Sessler, MD, FCCP; and Kimberly Varney, PharmD

Patient-focused sedation and analgesia in the ICU encompasses a strategy of comprehensive structured management that matches initial evaluation, monitoring, medication selection, and the use of protocols with patient characteristics and needs. This is best accomplished through interdisciplinary management by physicians, nurses, and pharmacists. An early consideration is that of the potential predisposing and precipitating factors, as well as prior sedative or analgesic use, factors that may influence pharmacologic and supportive therapy. Frequent monitoring with validated tools improves communication among clinicians and plays an important role in detecting and treating pain and agitation while avoiding excessive or prolonged sedation. Patient-focused management encompasses selecting medications best suited to patient characteristics, including the presence of organ dysfunction that may influence drug metabolism or excessive risk for side effects. The use of protocols to optimize drug therapy has emerged as a key component of management, resulting in reductions in the duration of sedation, mechanical ventilation, and ICU length of stay demonstrated with strategies to titrate medications to specific targets, daily interruption of sedation, intermittent rather than continuous therapy, and analgesia-based therapy. While much attention is paid to the initiation and maintenance of therapy, greater emphasis must be placed on careful de-escalation of therapy in order to avoid analgesic or sedative withdrawal. Finally, more work is needed to explore the relationship of critical illness and sedation management with long-term psychological outcomes.

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Key words: analgesia; delirium; medications; protocols; sedation

Abbreviations: ATICE = Adaptation to the Intensive Care Environment; BIS = bispectral index; DIS = daily interruption of sedation; EMG = electromyography; ICDSC = Intensive Care Delirium Screening Checklist; LOS = length of stay; MSAT = Minnesota Sedation Assessment Tool; MV = mechanical ventilation; NMB = neuromuscular blockade; PTSD = posttraumatic stress disorder; RASS = Richmond Agitation-Sedation Scale; RCT = randomized controlled trial; SCCM = Society of Critical Care Medicine

Critically ill patients, particularly those who are receiving mechanical ventilation (MV), often have pain, anxiety, dyspnea, and other forms of distress.¹ Core principles of ICU care are to provide comfort, to improve tolerance of the harsh ICU environment, and to provide relief from distress. This is often accomplished through identifying and correcting predisposing and precipitating factors, applying non-pharmacologic measures to enhance comfort, and administering sedative and analgesic medications, as depicted in a conceptual framework in Figure 1.² Patients report that the greatest stressors they encounter include pain, sleep deprivation, and the presence of tubes in the nose and mouth, factors that are exceedingly common in the ICU setting.^{1,3,4} Accordingly, it is not surprising that the majority of

ICU patients require IV sedative and analgesic medications.⁵ It is important to recognize that these underlying conditions, including delirium and delusional memories, as well as therapeutic interventions may influence the likelihood of patients having long-term psychological effects.⁶

INTERDISCIPLINARY MANAGEMENT

It is noteworthy that effective sedation management is best accomplished through intradisciplinary planning and practice. By combining nurses' bedside experience, skills, and continuous management of sedation,⁷ pharmacists' knowledge of medications, their interactions and proper role in critically ill patients,⁸ and physicians' integration of sedation

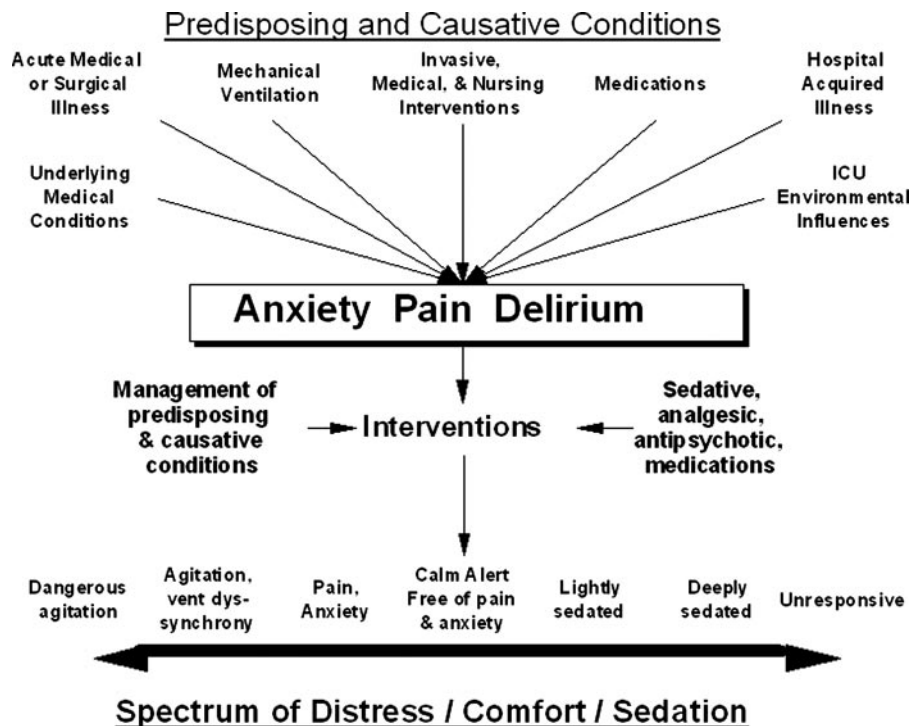


FIGURE 1. Conceptual framework for the interactions among underlying and causative factors, the sensations of pain, anxiety, and delirium, pharmacologic and nonpharmacologic interventions, and the state of a patient along the continuum from deep sedation to overt agitation. Reproduced with permission from Sessler et al.²

issues into medical management,^{2,9} a comprehensive plan can be implemented on a consistent basis. An overview of the principles of the management of sedation and analgesia is displayed in Table 1. Effective management is patient focused, encompassing medication selection to avoid adverse effects or prolonged effects from the parent drug or its active metabolite(s), and titrating sedative and analgesic medications to specific targets for effectiveness (*ie*, tolerance of ICU environment, pain and anxiety control, patient/ventilator synchrony) while avoiding excessive or unnecessarily prolonged sedation that might lead to longer ICU length of stay and the accompanying complications of chronic critical illness.

*From the Virginia Commonwealth University Health System, Medical College of Virginia Hospitals, Richmond, VA.

Dr Sessler is the Orhan Muren Professor of Medicine, Virginia Commonwealth University Health System.

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Correspondence to: Curtis N. Sessler, MD, FCCP, Division of Pulmonary and Critical Care Medicine, Box 980050, Virginia Commonwealth University Health System, Richmond, VA 23298; e-mail: csessler@vcu.edu

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INITIAL EVALUATION AND MANAGEMENT

An important starting place is to consider the possible predisposing and precipitating factors for various forms of distress, plus issues that influence management, as depicted in Figure 1. Underlying medical conditions such as chronic pain or arthritis, acute illness or injury, history of alcohol or substance abuse, and psychiatric illness can influence medication selection. Other issues such as postoperative factors, ICU interventions such as MV, medications, and simple maneuvers like turning and suctioning, as well as sleep deprivation related to excessive noise and light, can all play a role.² Recognition and management of these factors are crucial. Medication reconciliation (*ie*, continuing a patient's chronic home medication regimen) is frequently forgotten in hospitalized patients. Antidepressants, anxiolytics, and antipsychotics are medications of particular concern if not restarted. Severe withdrawal or rebound of chronic symptoms can occur if these medications are withheld for too long, and can lead to serious comorbid issues. For example, patients who appear delirious or severely agitated in the ICU may become overmedicated with sedative drugs because their home medications have been temporarily discontinued. Recognition and management of all of these factors early in their ICU stay are crucial to optimal management of sedation.

Table 1—Key Concepts for Management of Sedation and Analgesia

1. Develop an interdisciplinary, structured approach for managing sedation and analgesia in the ICU
2. Perform patient assessment and optimize the ICU environment
 - A. Identify predisposing and precipitating factors; manage treatable factors
 - B. Identify outpatient medications (medication reconciliation), particularly psychiatric and pain medications; restart medications as appropriate
 - C. Optimize patient comfort and tolerance of the ICU environment
 - D. Optimize MV settings for patient/ventilator synchrony
3. Regularly perform and document structured patient evaluation and monitoring
 - A. Establish and communicate treatment goals
 - B. Assess presence and severity of pain, as well as response to therapy
 - C. Assess level of sedation using a validated sedation scale, as well as response to therapy
 - D. Assess presence and severity of agitation using a validated agitation scale
 - E. Identify delirium, and consider regular assessment of delirium, using a validated delirium assessment instrument
4. Implement a structured patient-focused management strategy
 - A. Select analgesic and sedative drugs based upon patient needs, drug allergies, organ dysfunction (particularly renal or hepatic dysfunction), need for rapid onset and/or offset of action, anticipated duration of therapy, and prior response to therapy
 - B. Focus first on analgesia, then sedation
 - C. Titrate analgesic and sedative drugs to a defined target, using the lowest effective dose
 - D. Implement a structured strategy to avoid accumulation of medications/metabolites: utilize scheduled interruption, or intermittent dosing of analgesic and sedative drugs
 - E. Evaluate and manage severe agitation, including search for causative factors, and perform rapid tranquilization
 - F. Identify delirium, correct precipitating factors, and treat with haloperidol or other neuroleptic drugs
 - G. Avoid potential adverse effects of analgesic and sedative drugs; quickly identify and manage adverse effects that occur
5. Recognize and take steps to ameliorate analgesic and sedative drug withdrawal during de-escalation of therapy

Delirium, an acute reversible disorder of attention and cognition, is a common occurrence among critically ill patients, and may be a marker for worse outcomes, including increased incidence of posttraumatic stress disorder (PTSD) and increased long-term mortality.^{10,11} While classical hyperactive delirium is easily recognized by manifestations of intermittent agitation, hallucinations, and disruptive behavior, a hypoactive form appears to be more common in the ICU setting.¹² A wide variety of medical conditions (including CNS disorders, infections, hypoxia, pain, withdrawal syndromes, electrolyte and metabolic disorders, and various organ dysfunctions) as well as a long list of medications can precipitate delirium.^{2,11,13,14} There is emerging evi-

dence that many cases of hypoactive or mixed delirium in the ICU are related to the sedative effects of anxiolytic and analgesic drugs, particularly lorazepam, that ICU caregivers administer¹⁵; thus, strategies that emphasize using the lowest effective sedative drug dose may help avoid delirium.

Patient-focused sedation incorporates the concept that need for sedation and analgesia differs among patients and varies over time for individual patients. For example, patients who receive unusual forms of ventilatory support such as high-frequency oscillatory ventilation or prone positioning may require deep sedation, or even neuromuscular blockade (NMB), to achieve ventilator synchrony.^{16–18} Patients who are receiving NMB require adequate sedation and analgesia, and periodic cessation of the NMB agent to assess adequacy of sedation and analgesia.¹⁹ In contrast, low tidal volume ventilation *per se* does not require increased sedative drug therapy in comparison to conventional ventilation for the ARDS.^{20–22} Converting the artificial airway from an endotracheal tube to a tracheostomy tube has been associated with use of less sedative and analgesic medication and correspondingly fewer hours of deep sedation.²³ Alcohol and substance abuse is associated with greater sedative drug requirements.²⁴ Importantly, requirements for sedation are dynamic, generally declining as illness improves, and thus must be reassessed frequently.

EVALUATION OF PAIN, SEDATION, AGITATION, AND DELIRIUM

Bedside evaluation of the level of consciousness or arousability, cognitive function, presence and intensity of pain, and presence and intensity of agitation is an integral component of daily patient care.^{2,9,25} The detection and quantification of pain or agitation is useful to prompt the initiation or escalation of therapy as well as the reevaluation for reversible causes.²⁶ The routine determination of the level of consciousness, which often incorporates the domains of arousal and cognition, helps guide sedative drug dosing and avoidance of excessively deep sedation. Thus, utilization of tools—sedation scales and pain evaluation instruments—is important for patient-focused therapy, typically by establishing a target level of sedation to which medications are titrated to achieve, and to minimize pain.

Pain Evaluation

Evaluation of pain is relatively straightforward for patients who are alert enough to “self-report” by speaking, nodding, or pointing in response to questions about severity of pain. This is often performed

using an instrument such as a 10-cm visual analog scale, or a scale with extremes of measurement anchored by numerical (0 to 10), descriptive (“no pain” to “worst pain ever”), or diagrammatic (smiling face to crying face) variables, the patient indicating their level of pain.²⁷ Asking about pain should be performed frequently, particularly prior to administering sedatives or when these agents are stopped temporarily. Assessment of pain is less reliable and less valid when inferred through observation of patient behaviors, although recent instruments such as the Critical Care Pain Observation Tool²⁸ show promise. The components of Critical Care Pain Observation Tool and other similar tools^{29–31} are based on recognition of common behaviors, such as facial grimacing, restless body movement, rigid limbs, and patient/ventilator asynchrony observed during painful procedures and validated against self-report.^{32,33} While hypertension, tachycardia, and tachypnea are also commonly observed during painful stimuli, their lack of specificity for pain³⁴ has dampened enthusiasm for routine use. These symptoms may be more telling if combined with a positive history of chronic or acute pain, or use of chronic pain medications.

Sedation Evaluation

The level of sedation is assessed in many ICUs using a sedation scale; however, surveys indicate they are used by fewer than one half of practitioners,³⁵ ICUs,³⁶ and consecutive patients receiving MV.³⁷ Useful features of a sedation scale include rigorous multidisciplinary development; ease of administration, recall, and interpretation; well-defined discrete criteria for each level; sufficiency sedation levels for effective drug titration; assessment of agitation; demonstration of interrater reliability for relevant patient populations; and evidence of validity.²⁵ Although a number of sedation scales have been developed for ICU use, the following sedation scales satisfy many of these characteristics and have been tested for interrater reliability in multiple patient populations at multiple hospitals and validated against numerous measures: the Ramsay Sedation Scale,³⁸ the Sedation Agitation Scale,³⁹ the Motor Activity Assessment Scale,⁴⁰ the Richmond Agitation-Sedation Scale (RASS),⁴¹ the Adaptation to the Intensive Care Environment (ATICE) instrument,⁴² and the Minnesota Sedation Assessment Tool (MSAT).⁴³ A common approach to testing level of consciousness is to observe the patient to see if they are awake, and if not, then to stimulate the patient using auditory stimulation (speaking to the patient), followed by more intensive (physical) stimulation if there is no response to auditory stimuli. The patient’s response to increasing levels of stimulation is noted and a score assigned, as

with the Ramsay Sedation Scale, RASS, ATICE, and MSAT. In some scales, cognition—as the ability to follow a command (*ie*, RASS, ATICE)—and sustainability (*ie*, RASS) are included in the testing.^{41,42} Additionally, agitation is identified and graded in severity in Sedation Agitation Scale, Motor Activity Assessment Scale, RASS, and ATICE.^{39–42} Finally, widespread integration into ICU practice has been documented for RASS, MSAT, and ATICE.^{41,44–47} Implementation of sedation evaluation with a scale is an integral component of many treatment algorithms, and has been documented to result in more precise dosing, reduced sedative and analgesic drug use, shorter duration of MV, and reduced need for vasopressor therapy,⁴⁸ as well as reduced incidence of oversedation.⁴⁹

Objective Measurement of Brain Activity

Objective assessment of brain activity can be performed using EEG signals processed by proprietary algorithms such as with the bispectral index (BIS),⁵⁰ patient state index,⁵¹ cerebral state index,⁵² and Narcotrend index⁵³ systems to yield a single numerical value from 0 (complete EEG suppression) to 100 (awake). These monitors offer advantages of using objective physiologic parameters, a simplified numerical display, and near-continuous measurement, yet are rarely utilized in the clinical ICU setting today.⁵⁰ Factors such as electromyography (EMG) or electrical current-related artifact, which are less problematic in the operating room setting, increase variability of BIS in the critically ill patient. In fact, the administration of a NMB agent to sedated ICU patients led to remarkable decreases in BIS, averaging 24 U and 35 U in two studies,^{54,55} demonstrating the potential importance of EMG interference. While EMG artifact may account in part for the wide variability in correlation ($r^2 = 0.21$ to 0.93) between BIS and level of sedation as judged by various sedation scales,⁵⁰ the use of newer algorithms designed to reduce EMG influence may not eliminate BIS variability.⁵⁶ Experts recommend using BIS for selected cases, such as monitoring the level of consciousness of patients treated with NMB agents and for deep (pentobarbital-induced) coma⁵⁷; however, routine use must await studies that demonstrate added value from better outcomes and/or cost savings. Additional approaches to brain monitoring in the ICU include response entropy and state entropy,⁵⁸ and auditory-evoked potentials.^{59,60}

Delirium Evaluation

Delirium is associated with worse outcomes^{10,11} and has been frequently found in ICU patients when using some^{10,61,62} but not all assessment tools^{11,63–65}

and depending on the patient population. Detection of delirium in the critically ill patient has been challenging because inability to speak and often to write impairs testing, yet tools for use in ICU patients have been developed.⁶⁶ Many validated tools are interventional, such as the Confusion Assessment Method for the ICU,⁶¹ or the Cognitive Test for Delirium⁶⁷ (or its abbreviated version),⁶⁸ in which a rater directly tests state of consciousness, comprehension, memory, attention, and vigilance. Other validated instruments use observation with a checklist of behaviors such as level of consciousness, inattention, disorientation, hallucinations, agitation, inappropriate mood, sleep-wake cycle disturbance, and symptom fluctuation as in the Intensive Care Delirium Screening Checklist (ICDSC)⁶³ or the Nursing Rating Scale for ICU Delirium.⁶⁷ The Confusion Assessment Method for the ICU and ICDSC are more recently developed and have been extensively validated. The ICDSC also allows identification of “subsyndromal” delirium that may progress to overt delirium.⁶⁹ Although routine screening for the presence of delirium is recommended in the 2002 Society of Critical Care Medicine (SCCM) guidelines for sedative and analgesic therapy,⁹ surveys indicate that delirium testing of ICU patients with a validated tool is rarely performed.^{35,70}

Other components of sedation-related monitoring of the ICU patient include detection and quantification of conditions that influence sedation management decisions, including agitation,^{39–42} patient movement as a surrogate for agitation,^{43,71,72} and patient/ventilator asynchrony.^{73,74} Future approaches will likely integrate multiple measurements in order to optimize patient comfort and tolerance of the ICU setting.

MANAGING SEDATION AND ANALGESIA

Pharmacologic therapy is required in the majority of ICU patients, particularly those who are receiving MV.⁵ Medications are often administered by continuous infusion for ease of use and to provide a smooth course; however, continuous infusion has been linked to prolonged sedation and longer length of ICU stay.⁷⁵ Accordingly, intermittent therapy or provision of schedule daily interruption of sedation (DIS) is often employed to avoid excessive and prolonged effects.^{76–78} Often, multiple medications are administered in order to treat both pain and anxiety, or to provide synergy, thus allowing reduced dosing of medications.^{5,79,80} Several studies suggest that focusing first on providing analgesia rather than initially on anxiolysis may provide more effective⁷⁹ and shorter duration of MV.⁸¹ In most cases, IV administration is desirable since absorption from the GI

tract or following subcutaneous or IM injection is less reliable, and precise titration to the target effect is more accurate. However, administration of transdermal or enteral medications may have a role in some patients, particularly those who require longer-term sedation and analgesia management, resulting in elimination or reduction in IV dosages.⁸² Measures must be taken to avoid long-term sedative or opioid medication dependence after ICU discharge; explicit plans for cessation or scheduled tapering of these drugs are necessary as the patient leaves the ICU, particularly for patients with a history of alcohol or substance dependency.

MEDICATIONS FOR SEDATION AND ANALGESIA

The two major classes of medications used to promote comfort and tolerance of the ICU environment are the sedative-hypnotic agents and opioid analgesics, which provide anxiolysis, sedation, amnesia, and analgesia to the patient. General considerations for medication selection include effectiveness; factors related to duration, onset, and offset of effect; presence of active metabolites; adverse effects; costs related to drug acquisition as well as to duration of sedation; and any recent history of opioid or benzodiazepine use. Characteristics of commonly used IV administered sedative and analgesic drugs are displayed in Table 2.

Sedative Medications

The benzodiazepines, midazolam and lorazepam, are commonly administered by continuous infusion or intermittent injection in the North American ICUs,^{35,83} whereas lorazepam is rarely used and midazolam enjoys widespread use in Europe.^{37,84} Lorazepam given by intermittent boluses or continuous IV infusion was recommended in the 2002 SCCM consensus guidelines as the preferred sedative drug for ICU patients who require prolonged therapy, whereas midazolam was recommended only for short-term (< 48 h) sedation because of concerns for unpredictable awakening observed after prolonged infusion.⁹ Some of the delayed emergence with midazolam may be attributable to accumulation of the parent compound in hepatic failure, or an active metabolite, α -hydroxymidazolam, which is cleared by the kidney and may lead to prolonged sedation in patients with renal insufficiency.^{85,86} In a series of consecutive patients with prolonged sedation after cessation of midazolam infusion, many patients had elevated serum levels of α -hydroxymidazolam (all patients had serum creatinine > 1.5 mg/dL), or detectable levels of midazolam many hours after infusion discontinuation.⁸⁶ There are relative few

Table 2—IV Sedative and Opioid Analgesic Medications Used in Adult ICU Patients*

Drug/Class	Elimination	Onset/Duration	Dosing (IV)	Concentration	Advantages	Disadvantages	Relative Daily Cost
Lorazepam/ benzodiazepine	Hepatic conjugation to inactive metabolite	5–20 min/6–8 h; up to 24–72 h in elderly/cirrhosis/ESRD	LD: 2–4 mg IV push MD: 2–6 mg IV q4h–q6h; infusion: 1–10 mg/h; start low in elderly	100 mg/100 mL D5W only	Inexpensive, longer half-life	Propylene glycol toxicity at high doses (anion gap metabolic acidosis, renal insufficiency)	\$\$
Midazolam/ benzodiazepine	Cytochrome P450 3A4; active metabolite excreted renally	5–10 min/1–4 h (longer in ESRD/CHF/liver failure)	LD: 2–5 mg IV push MD: 1–20 mg/h; start low in elderly	100 mg/100 mL NS or D5W	Shorter acting if preserved organ function; fast onset	Many drug interactions, may increase midazolam levels, active metabolite accumulates in renal failure	\$\$\$
Propofol	Conjugation	30–50 s/ approximately 3–10 min (dose dependent)	MD: 5–150 µg/kg/min	Premixed (10 mg/mL)	Short acting	↓ BP, increase serum triglyceride, pancreatitis, propofol infusion syndrome, zinc depletion	\$\$\$\$
Dexmedetomidine	Hepatic Cytochrome P450 and glucuronidation	Immediate/ approximately 6 min (longer in liver failure)	LD: 0.5–1 µg/kg over 10 min; MD: 0.2–0.7 µg/kg/h for 24 h	100 µg/50 mL NS only	Very short duration; has some analgesic properties	↓ BP, ↓ HR; not approved for use > 24 h, some studies use longer	\$\$\$\$\$
Morphine sulfate/opioid analgesic	Conjugation; active metabolite excreted renally	5–10 min/2–4 h	LD: 2–4 mg IV push MD: 2–30 mg/h for ventilated patients	100 mg/100 mL NS or D5W	Reduces tachypnea	↓ BP, respiratory depression, accumulation in hepatic/renal failure	\$
Fentanyl/opioid analgesic	Cytochrome P450 3A4	1–2 min/2–4 h (longer in liver failure)	LD: 25–50 µg IV push MD: 0.7–10 µg/kg/h for ventilated patients	1.25 or 2.5 mg/250 mL NS or D5W	Less hypotension than morphine	3A4 inhibitors may increase fentanyl; fever will increase patch fentanyl levels by 30%	\$\$
Hydromorphone/opioid analgesic	Hepatic	5–10 min/2–4 h	LD: 0.2–0.6 mg IV push MD: 0.5–3 mg/h	100 mg/100 mL NS or D5W	May work if patients are tolerant to morphine/fentanyl	Respiratory depression, caution in nonventilated patient; highly addictive	\$
Alfentanil/opioid analgesic	Hepatic; active metabolites excreted renally	1 min/30–60 min (dose dependent)	LD: 50–75 µg/kg slowly over 3–5 min; MD: 0.5–3 µg/kg/min (usual 1–1.5 µg/kg/min)	10 mg/250 mL NS or D5W	Very short-acting agent	↓ HR, ↓ BP, ↑ ICP; 3A4 inhibitors may increase levels of alfentanil	\$\$
Remifentanyl/opioid analgesic	Tissue esterases	1–3 min/10–20 min	LD: 1 µg/kg over 1 min MD: 0.6–15 µg/kg/h for MV (unlabeled use); use ideal body weight	5 mg/250 mL NS or D5W	No accumulation in hepatic or renal failure	↓ HR, ↓ BP, ↑ ICP	\$\$\$
Sufentanil/opioid analgesic	Hepatic	1–3 min/dose-dependent duration	LD: 1–2 µg/kg slowly over 3–5 min; MD: 8–50 µg as needed	250 µg/250 mL D5W; variable stability in NS		↓ HR, ↓ BP, ↑ ICP	\$

*ESRD = end-stage renal disease; LD = loading dose; MD = maintenance dose; D5W = 5% dextrose in water; CHF = congestive heart failure; NS = normal saline solution; ↓ BP = hypotension; ↓ HR = bradycardia; ↑ ICP = increased intracranial pressure.

†Dollar signs represent arbitrary scale of medication costs, ranging from \$ = very low cost, to \$\$\$\$\$ = very high cost.

randomized controlled trials (RCTs) in which lorazepam and midazolam are compared for long-term (> 72 h) infusion. No significant difference in time to awakening was noted in two studies,^{87,88} whereas Barr and coworkers⁸⁹ found significantly shorter emergence time and time to extubation for midazolam vs lorazepam infusion in a double-blinded RCT of postoperative patients without significant renal, hepatic, or neurologic impairment. Additionally, prolonged high-dose administration of lorazepam can result in accumulation of the vehicle, propylene glycol, resulting in worsening renal function, metabolic acidosis, and altered mental status.⁹⁰ Toxicity is typically observed after prolonged (> 7 d), high-dose (average of 14 mg/h), continuous lorazepam infusion, and can be recognized by measuring an increased osmolal gap.⁹⁰ Lorazepam infusion was identified as an independent risk factor for transition to delirium among ICU patients receiving MV¹⁵; however, examination of the odds ratios for other sedative and opioid analgesics agents used less frequently in the study suggests it may occur with other agents. In light of drug accumulation with continuous infusion, and concerns for propylene glycol toxicity, long-term high-dose lorazepam should be used with caution. Midazolam may be a better alternative if hepatic and renal function is normal.

Despite consensus recommendations that administration of propofol be limited to < 24 to 48 h,⁹ it remains widely used worldwide.^{5,35,83,84} Propofol infusion has been compared to midazolam infusion for sedation in the ICU in many RCTs. Walder and colleagues⁹¹ demonstrated more effective sedation (higher percentage of time) and shorter weaning time for short-term (< 36 h) infusion but higher adverse event rates with propofol compared to midazolam in a systematic review of 27 RCTs. Duration of MV was similar for propofol and midazolam infusions, however, when DIS was routinely used with both drugs.⁷⁷ In contrast, duration of MV was significantly shorter with propofol infusion and DIS compared to intermittent lorazepam in a recent RCT.⁷⁸ Propofol infusion has been linked to a number of adverse effects,⁹² including hypertriglyceridemia,⁹³ dose-dependent hypotension,⁹⁴ and the propofol infusion syndrome, a rare clinical syndrome of rhabdomyolysis, metabolic acidosis, renal failure, and cardiac failure after high doses of propofol.⁹⁵

Dexmedetomidine is a selective α_2 -adrenergic receptor agonist with a short half-life of approximately 2.3 h, and has sedative, analgesic, anxiolytic, and sympatholytic effects without depressing respiratory drive. Dexmedetomidine currently has limited approval by the US Food and Drug Administration for sedation in postoperative patients of < 24 h duration, although other ICU settings are being investi-

gated. In small studies of short-term use in the postoperative or trauma patients, dexmedetomidine has been shown to decrease opiate use, and to facilitate extubation in patients who have failed previous ventilator weaning attempts due to severe agitation.⁹⁶ Case reports have also documented success in preventing alcohol withdrawal in patients in the perioperative period.⁹⁷ Drug-related adverse effects are primarily cardiovascular including hypotension and bradycardia,⁹⁸ particularly when loading doses are used. Tolerance to the drug has been seen and there are concerns for a rebound effect when used beyond 24 to 48 h. Most studies find that higher-than-recommended doses are needed for efficacy but that a ceiling dose effect is reported at a dose approximately 1.5 $\mu\text{g}/\text{kg}/\text{h}$.⁹⁹ Dystonia has been reported and may be due to its effect on acetylcholine release.⁹⁹ Acquisition cost is higher than for other sedative agents, although one retrospective outcomes study¹⁰⁰ of > 10,000 cardiac surgery patients suggests favorable clinical and economic outcomes when dexmedetomidine is added to midazolam and propofol for sedation. Publication of additional research will help to clarify new roles for this drug.

Opioid Analgesic Medications

A variety of opioids used by IV administration in adults are available for use in ICUs throughout the world; many of these are compared in Table 2. Surveys and prospective surveillance studies^{35-37,83,84} indicate widespread use of fentanyl and morphine sulfate, although sufentanil enjoys considerable use in Europe.^{37,84} The 2002 SCCM guidelines recommend the use of fentanyl, hydromorphone, or morphine if an IV opioid analgesic is required.⁹ Opioids function through stimulation of receptors, principally via the μ_1 and μ_2 opioid receptors. All opioids produce a dose-dependent respiratory depression; other common side effects include muscle rigidity, hypotension, delayed GI transit, nausea, pruritus, and urinary retention.²⁷ There are important differences in regards to lipid solubility, volume of distribution, and metabolism that are reflected in data displayed in Table 2. Particularly noteworthy is that morphine is metabolized to several active metabolites, including morphine-6-glucuronide that is more active than the parent compound, and accumulates in renal failure potentially resulting in prolonged sedation and respiratory depression.¹⁰¹ Morphine should be avoided in patients who have renal insufficiency. Fentanyl has a rapid onset of action as a result of high lipophilicity and a short duration of action from redistribution.²⁷ Elimination is delayed,

however, with prolonged administration as a result of its large volume of distribution.

Often analgesic medications are added to a sedative infusion, so-called “co-sedation” or “analgesosedation,” with reduced doses of both agents and in some cases more effective therapy.⁷⁹ European studies demonstrate shorter duration of MV with an analgesic-based vs sedative-based protocol.⁸¹ Remifentanyl, a drug that has organ-independent metabolism, was successfully used in this trial⁸¹; however, other clinical trials demonstrate similar results between remifentanyl and fentanyl, except for a greater incidence of pain during drug de-escalation with remifentanyl.¹⁰²

Antipsychotic Agents

Therapy with antipsychotic agents such as haloperidol may be necessary for effective management of delirium and agitation. For treatment of acute agitation, the butyrophenone haloperidol can be administered in escalating doses from 1 mg to as much as 20 mg by IV injection, often in combinations with a benzodiazepine, until calmness is achieved.¹⁰³ Haloperidol has been associated with extrapyramidal effects, and cardiac conduction abnormalities, specifically prolonged QTc-associated *torsades de pointes* arrhythmia.¹⁰⁴ These tend to be dose-related adverse effects. A baseline ECG should be documented and periodically repeated with continued use of the drug. In addition to maintaining normal magnesium, potassium, and calcium levels, it is important to consult with a pharmacist regarding drug interactions that could potentiate cardiac arrhythmias (*ie*, amiodarone and other antiarrhythmics, antifungal azoles, quinolones, macrolides, etc.). Haloperidol may be administered as a scheduled medication for management of delirium. Interestingly, in a retrospective study, use of haloperidol in ICU patients receiving MV was associated with a lower mortality rate in a dose-response fashion than nonuse, although the explanation(s) for this is not clear.¹⁰⁵ While there is interest in examining newer antipsychotic agents for management of delirium, only olanzapine has been directly compared to haloperidol thus far. Olanzapine was found to be of similar efficacy to haloperidol in controlling delirium, but with fewer extrapyramidal side effects in a small prospective trial.¹⁰⁶

PROTOCOLS AND ALGORITHMS TO IMPROVE SEDATION MANAGEMENT

Structured approaches to the management of sedation and analgesia have been demonstrated in prospective studies^{26,47,76–79,81,107–109} to reduce side effects of medications, decrease unnecessary testing, reduce the duration of MV and the frequency of

tracheostomy, shorten the ICU and hospital length of stay, decrease the likelihood of having ICU-related medical complications, and reduce costs of hospitalization. A variety of strategies have been employed, including using medications with a shorter half-life, titrating medications to end-points identified by sedation scales, mandating temporary cessation of sedative drug infusion, use of intermittent sedative therapy, and employing algorithms that proactively identify pain, agitation, and/or patient/ventilator asynchrony. Several studies that tested strategies using a prospective controlled study design deserve further comment (Table 3).

Following demonstration that continuous infusion of sedatives and analgesics was associated with prolonged ventilator time and with longer ICU and hospital LOS,⁷⁵ Brook and colleagues⁷⁶ conducted a single-center RCT comparing a nursing-implemented algorithm with conventional practice. This algorithm emphasized the following: (1) early detection of pain, (2) use of intermittent therapy with fentanyl or lorazepam, reserving continuous infusions for patients who had inadequate response to intermittent therapy, and (3) de-escalation of continuous infusions to intermittent therapy. They demonstrated shorter duration of MV, shorter ICU and hospital LOS, and lower rates of tracheostomy.

Daily Interruption of Sedation

Kress and colleagues⁷⁷ tested a strategy of DIS compared to usual practice in an RCT, also comparing midazolam to propofol infusions in a 2 × 2 factorial design. All DIS patients had sedative and analgesic (morphine sulfate) infusions discontinued each morning until the patient was able to follow three or more of four simple commands or became agitated. Infusions were restarted at one half the original rate. They demonstrated significant reductions in duration of MV and shorter ICU LOS, as well as fewer diagnostic studies for unexplained altered mental status. There was no difference in any outcomes between the midazolam and propofol groups, although DIS resulted in significantly lower daily doses of midazolam and morphine but not propofol. This observation implies that more rapid extubation and ICU discharge may be related to a combination of reduced drug accumulation, and additional opportunities for initiating weaning from MV.¹¹⁰ This strategy has also been linked to a reduction in ICU complications, largely as a result of a shorter ICU LOS.¹¹¹

In a two-center RCT, Carson et al⁷⁸ compared propofol infusion vs intermittent therapy with lorazepam; both groups received DIS and morphine sulfate for analgesia. The continuous infusion propo-

Table 3—Prospective Trials of Sedation Protocols in Adult ICU Patients*

Source	Patients and Setting	Study Design	Key Components of Protocol	Major Findings	Comments
Brook et al ⁷⁶	321 MV medical ICU patients, US university hospital	RCT: protocol-directed sedation vs non-protocol-directed sedation (control)	Nursing-directed protocol that emphasizes using intermittent therapy; fentanyl, lorazepam	Protocol group had shorter duration of MV (56 h vs 117 h, $p = 0.008$); shorter ICU LOS (5.7 d vs 7.5d, $p = 0.013$); shorter hospital LOS (14.0 d vs 19.9 d, $p = 0.003$); lower tracheostomy rate (6.2% vs 13.2%, $p = 0.038$)	2×2 factorial design; patients also randomized to receive midazolam or propofol
Kress et al ⁷⁷	128 MV medical ICU patients; US university hospital	RCT: intervention vs control	Intervention group received DIS	Intervention group had shorter duration of MV (4.9 d vs 7.3 d, $p = 0.004$); shorter ICU LOS (6.4 d vs 9.9 d, $p = 0.02$); and fewer diagnostic tests for changes in mental status (9% vs 27%, $p = 0.02$)	Protocol adherence = 83.7%
MacLaren et al ¹⁰⁷	158 MV patients in medical-surgical-neurologic Canadian ICU	Prospective two-phase study: empiric before/protocol after	Evidence-based sedation and analgesia protocol	Protocol group had less "discomfort" (11% vs 22.0.4%, $p < 0.001$); less pain (5.9% vs 9.6%, $p < 0.05$); lower hourly sedation cost (Canadian \$5.68 vs Canadian \$7.69, $p < 0.01$); trend for longer sedation duration (122.7 h vs 88.0 h, $p < 0.1$); trend for longer duration of MV (61.6 h vs 39.1 h, $p = 0.13$)	
Mascia et al ¹⁰⁸	158 MV medical and surgical ICU patients, US tertiary care university hospital	Prospective two-phase study: baseline before/guidelines after	Guidelines based upon "rational cost-effective use of drugs"	Guideline group had lower direct drug costs; shorter duration of MV (167 h vs 317 h)†; shorter ICU LOS (9.2 d vs 19.1d)†; shorter hospital LOS (19.1 d vs 34.3 d)†	
Brattebo et al ¹⁰⁹	285 MV surgical ICU patients, Norwegian university hospital	Prospective two-phase study: baseline before/guideline after	Small-scale rapid-cycle improvement model; protocol, sedation scale	Protocol group had shorter duration of MV (5.3 d vs 7.4 d)†; trend for shorter ICU LOS (8.3 d vs 9.3 d)†	
De Jonghe et al ⁴⁷	102 MV medical ICU patients, French university-affiliated hospital	Prospective two-phase study: control before/algorithm after	Algorithm: regular assessment of consciousness and tolerance to ICU environment with goal of tolerance and high LOC	Algorithm group had shorter time to arousal (2 d vs 4 d, $p = 0.006$); shorter duration of MV (4.4 d vs 10.3 d, $p = 0.014$)	
Breen et al ⁸¹	105 MV medical-surgical ICU patients, 10 European countries	15-center RCT: analgesic (remifentanyl based) or sedative (midazolam based)	Titration of analgesic (remifentanyl, fentanyl, or morphine) and sedative (midazolam) drugs to targets	Analgesic-based group had shorter time from weaning to extubation (0.9 h vs 27.5 h, $p < 0.001$); shorter duration of MV (94 h vs 147.5 h, $p = 0.033$)	
Carson et al ⁷⁸	132 MV, sedated medical ICU patients, two US university hospitals	RCT: lorazepam by intermittent bolus, or propofol by continuous infusion	Daily interruption of sedation was performed in both groups	Continuous infusion propofol group had shorter duration of MV (5.8 d vs 8.4 d, $p = 0.04$); trend for more ventilator-free survival (18.5 d vs 10.2 d, $p = 0.06$)	

(Continued)

Table 3—Continued

Source	Patients and Setting	Study Design	Key Components of Protocol	Major Findings	Comments
Chanques et al ²⁶	230 MV medical-surgical ICU patients, French university hospital	Prospective two phase study: control before/protocol after	Protocol emphasis on systematic evaluation of pain and agitation	Protocol group had lower incidence of pain (42% vs 63%, p = 0.002); lower incidence of agitation (12% vs 29%, p = 0.002); shorter duration of MV (65 h vs 120 h, p < 0.05); fewer nosocomial infections (8% vs 17%, p < 0.05)	
Richman et al ⁷⁹	30 MV medical ICU patients, US university hospital	RCT: sedation with benzodiazepine, or co-sedation with benzodiazepine plus opiate	Nurse-implemented protocol; midazolam, fentanyl†	Co-sedation group had fewer hour with “off-target” sedation (4.2 h vs 9.1 h, p < 0.002); fewer episodes of patient/ventilator asynchrony (0.4/h vs 1.0/h, p < 0.05)	Small sample size; trend for more ileus with co-sedation; duration of MV not reported

*LOC = level of consciousness.

†Indicates p values not reported.

fol with DIS group had significantly shorter duration of MV. Thus, DIS is emerging as a useful technique to shorten duration of MV, and this “sedation vacation” has been widely embraced.¹¹²

Questions arose regarding the neuropsychiatric impact of repeated abrupt awakening on critically ill patients,¹¹³ yet subsequent research has demonstrated that patients randomized to DIS have fewer symptoms of PTSD compared to control subjects.¹¹⁴ Interruption of sedation is associated with a surge in circulating catecholamines; however, patients with coronary artery disease subjected to DIS had no increase in cardiac ischemia when taken off sedation.¹¹⁵ These studies are encouraging for the safety of widespread use of DIS, although caution for selected patients, such as those with hypertensive crisis or status asthmaticus, who might have significant consequences from the resulting stress response or patient/ventilator asynchrony, should be exercised.¹¹⁰ Finally, there are theoretical concerns with regards to the use of DIS in patients who have a history of alcohol abuse because precipitation of withdrawal could occur if the patient is not otherwise receiving medications that protect for alcohol withdrawal.

Other protocol-based approaches to sedation management have been demonstrated in a sequential study design with comparison to an earlier control period, to reduce duration of MV,^{47,81,108,109} improve the quality of sedation,¹⁰⁷ reduce patient/ventilator asynchrony,⁷⁹ and reduce drug costs,⁷⁹ although one protocol that increased use of lorazepam was associated with a trend for longer ventilator duration.¹⁰⁷ Common themes for effective protocols include targeting pain, agitation, and intolerance of the ICU environment,^{26,47} and focusing more on analgesic therapy than sedation.^{79,81}

SEDATIVE AND ANALGESIC DRUG WITHDRAWAL

Development of signs and symptoms of acute opioid and sedative drug withdrawal syndrome can follow long-term administration of these medications in ICU patients. This phenomenon has been particularly well studied in critically ill children.^{116–118} Cammarano et al¹¹⁹ reported that one third of adult trauma patients who received > 1 week of ICU hospitalization had clear evidence of acute withdrawal once drugs were discontinued. Longer duration and higher doses of opioids, benzodiazepines, and propofol were associated with withdrawal, as was less haloperidol administration. Recently, withdrawal was detected in 13.2% of ICU patients and linked to delirium in the ICU.⁶ Research suggests that CNS and sympathetic nervous system markers for withdrawal can peak with 6 h of cessation of sedative (midazolam, propo-

fol) and opioid (sufentanil) drug infusion,¹²⁰ having potential implications for interruption of sedation in susceptible patients. Importantly, clinicians must maintain a high index of suspicion for sedative and analgesic drug withdrawal as a patient recovers from critical illness because many of the symptoms, such as restlessness, insomnia, delirium, nausea, hypertension, tachycardia, diaphoresis, and fever, are non-specific and may be easily overlooked. Strategies for gradual weaning of sedative and analgesic agents and/or substitution with orally or subcutaneously administered drugs in high-risk patients may be useful.^{117,118,121}

SEDATIVE AND ANALGESIC THERAPY AND LONG-TERM PSYCHOLOGICAL OUTCOMES

The impact of sedative and analgesic medications on neuropsychological health after recovery from critical illness is a complex issue because of many confounding factors, such as interruption of sedation, withdrawal from these agents or other substances, critical illness and organ dysfunction, preexisting neuropsychological disorders, physical restraint and immobilization, pain, delirium, memory formation, and amnesia. Nevertheless, the influence of sedation on subsequent recall of real or imagined events as well as the development of PTSD and depression is an important, yet underrecognized issue. Nelson and colleagues¹²² observed a positive association between duration of sedation and depression-related and PTSD-related symptoms 6 to 41 months after acute lung injury. No difference in PTSD was noted, however, between high and low sedative drug doses.¹²² Samuelson and coworkers¹²³ found that patients who had no recall for ICU events were more likely to have had heavy sedation with fewer periods of wakefulness. Patients who subsequently had delusional memories had longer ICU LOS, received higher doses of sedative drugs, and had more periods of being alert or agitated.¹²³ Interestingly, DIS was associated with less frequent PTSD and a trend for better psychosocial adjustment to illness when tested months later.¹¹⁴ These DIS patients had shorter duration of MV and sedation, yet had more episodes of being alert or agitated, than control patients. Some experts¹²⁴ postulate that recall for factual events, rather than internally generated images such as hallucinations and nightmares, may be protective for developing subsequent PTSD. In recent work,⁶ these authors found associations between prolonged sedation but also physical restraint with little or no sedation and development of PTSD. Although further research is needed, clinicians should be aware that sedative and analgesia

drugs may play a role in subsequent psychological impairment in the ICU setting. Further, they should be alert for signs of emotional trauma and the possible need for psychological interventions during recovery from critical illness.

SUMMARY AND CONCLUSIONS

The majority of critically ill patients receive sedative and/or analgesic medications to combat pain and anxiety and to improve tolerance of the ICU environment. Patient-focused care related to these issues includes assessment of predisposing and precipitating factors, frequent monitoring, careful medication selection, and use of strategies to precisely target therapy to defined end points and avoid sedation that is excessive or prolonged.

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