COURSE #90180 — 5 CONTACT HOURS/CREDITS Release Date: 02/01/24 Expiration Date: 01/31/27

Agitation, Sedation, and Delirium in Adult ICU Patients

HOW TO RECEIVE CREDIT

- Read the enclosed course.
- Complete the questions at the end of the course.
- Return your completed Evaluation to NetCE by mail or fax, or complete online at www.NetCE.com. (If you are a physician or Florida nurse, please return the included Answer Sheet/Evaluation.) Your postmark or facsimile date will be used as your completion date.
- Receive your Certificate(s) of Completion by mail, fax, or email.

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Faculty Disclosure
Contributing faculty, Beth Johnston, PharmD, BCPS, has disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

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Division Planners/Director Disclosure
The division planners and director have disclosed no relevant financial relationship with any product manufacturer or service provider mentioned.

Audience
This course is designed for physicians, physician assistants, and nurses involved in the care of patients in intensive care units.

Accreditations & Approvals

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A complete Works Cited list begins on page 22.

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Disclosure Statement

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Course Objective

The purpose of this course is to provide prescribers and other healthcare professionals with the knowledge and skills necessary to identify and act to avoid or address agitation, inappropriate sedation, and delirium in ICU patients.

Learning Objectives

Upon completion of this course, you should be able to:

1. State the principles of analgesia and sedation in ICU patients.
2. Describe appropriate care of ICU patients receiving opioids.
3. Compare sedatives commonly used in ICU patients.
4. Review monitoring requirements in ICU patients receiving sedatives.
5. Discuss the prevention and management of delirium in ICU patients.

EVIDENCE-BASED PRACTICE RECOMMENDATION

Sections marked with this symbol include evidence-based practice recommendations. The level of evidence and/or strength of recommendation, as provided by the evidence-based source, are also included so you may determine the validity or relevance of the information. These sections may be used in conjunction with the course material for better application to your daily practice.

INTRODUCTION

Agitation (characterized by excessive motor activity) is common in critically ill patients, with an incidence of between 16% and 71% [1; 2]. It is reported as severe in 16% to 46% of these patients [1; 2]. Appropriately preventing and treating pain, anxiety, delirium, immobility, and sleep disruption can improve outcomes for these patients [2; 3]. Treatment goals should include both physical and psychological comfort while also keeping patients safe and allowing them to receive needed care [2; 3]. It has been established that minimal sedation that results in comfortable wakefulness improves clinical outcomes [1].

There can be many reasons for a critically ill patient to be agitated. Pain, anxiety, and delirium are three of the most common causes. Other causes can include [1]:

- Drug withdrawal (e.g., nicotine, alcohol)
- Endotracheal tube
- Fear
- Infection (central nervous system, sepsis)
- Ischemia (myocardial, intestinal, cerebral)
- Metabolic (acidosis, hypoglycemia)
- Respiratory failure (hypoxemia, hypercarbia)
- Sleep-wake-cycle disruption
- Tension pneumothorax
- Uncomfortable physical position/immobility

Some of the overarching principles of the Society of Critical Care Medicine (SCCM) guidelines for the management of pain, agitation/sedation, delirium, immobility, and sleep disruption (PADIS) in adult intensive care unit (ICU) patients are [3]:

- Pain, depth of sedation, and delirium should be routinely monitored.
- Pain should be addressed first and treated adequately and pre-emptively.
- Sedation should be provided only if it is needed.
- Light sedation is preferred so that patients are aware and responsive.

Mobilization and/or rehabilitation (in- or out-of-bed) of patients in the ICU may be effective in reducing ICU-acquired muscle weakness as well as a tool for delirium prevention. Sleep disruption, common to ICU patients, may contribute to delirium, prolonged mechanical ventilation, altered immune function, and neurocognitive dysfunction [3].

The SCCM, through the ICU Liberation Collaborative, has developed the evidence-based ABCDEF (also known as the ICU Liberation bundle or A2F bundle) care bundle as a quality improvement initiative [4]. The components of this bundle are:

- A = Assess, prevent, and manage pain
- B = Both spontaneous awakening trials (SAT) and spontaneous breathing trials (SBT)
- C = Choice of analgesia and sedation
- D = Delirium (assess, prevent, manage)
- E = Early mobility and exercise
- F = Family engagement and empowerment

The goal is to use this methodology, so patients are awake, engaged, and mobile. In this model, the ICU team works with patients and family members as partners [4].

Both sedative and analgesic agents are commonly administered to critically ill patients [5]. The following questions can be addressed to help optimize the management of these patients and to prevent the inappropriate use of analgesics and sedatives in critically ill patients [5]:

- Are both sedative and analgesic drugs needed?
- Does the patient have one or more factors that could cause drug accumulation (e.g., kidney or liver impairment)?
- If analgesic and sedative drugs were required and started, are these drugs still needed and are the doses still appropriate?

Patients who receive optimal analgesia and sedation have less pain and anxiety, which allows for invasive procedures, reduces stress and oxygen consumption, and improves synchrony with mechanical ventilation [2; 6; 7]. Providing an appropriate level of analgesia and sedation to ICU patients in particular can improve patient outcomes, including duration of ICU stay and duration of mechanical ventilation [2; 6]. However, a large number of critically ill patients do not receive optimal analgesia and sedation.

ANALGESIA IN ADULT ICU PATIENTS

REFLECTION

How do your patients define pain? What tools can be used to assess pain in critically ill ICU patients who may not be cognitively responsive? What are the goals of pain therapy? What strategies do you use to optimize pain control while minimizing the adverse effects of pain medications?

The International Association for the Study of Pain defines pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" [8]. This definition emphasizes the fact that pain is subjective and that it can exist solely because the person experiencing pain reports it [9].

Pain in adult patients in the ICU has been identified as a great source of stress [1; 3]. The resultant catecholamines that are released into the circulation can negatively impact the patient's condition. Patients may experience arterial vasoconstriction, impaired perfusion to tissues, and reduced tissue-oxygen partial pressure. In addition, pain can cause catabolic hypermetabolism (e.g., hyperglycemia, lipolysis, breakdown of muscle). These effects can impair wound healing and increase the risk of wound infection. Acute pain is an important risk factor for the development of debilitating chronic pain (often neuropathic pain) [3].

Inadequate pain control is often reported by patients discharged from an ICU [3]. Both medical and surgical patients with memories of pain and trauma years after an ICU stay are at increased risk for chronic pain and developing post-traumatic stress disorder (PTSD) [9].

CAUSES OF PAIN IN THE ICU SETTING

Patients in an ICU are likely to experience pain regardless of their diagnosis. It is not uncommon for some pain to go unrecognized and/or untreated. Critically ill patients can experience pain at rest, from common things such as a nasogastric tube, intravenous (IV) lines, or lying in the same position for too long. An endotracheal tube is an important cause of discomfort and pain in ICU patients. An ICU patient's pain may be secondary to surgery, trauma, burns, or cancer [2; 3]. Procedural pain is also common in these patients.

DETERMINING IF A CRITICALLY ILL PATIENT IS IN PAIN

The potential inability of adult ICU patients to communicate verbally cannot be interpreted to mean that they are not in pain. Proper assessment, and subsequent treatment, of pain is crucial due to the negative physical and psychological consequences that can be seen during a patient's hospital stay and after discharge. Identifying pain and treating it early is preferred and more effective than delaying treatment until the pain becomes severe. In fact, preemptive analgesia is recommended for potentially painful procedures such as chest tube removal and wound care [3].

All patients in the ICU setting should be evaluated for pain. Vital signs, such as heart rate and blood pressure, can suggest that a patient is in pain. However, vital signs alone should not be used for pain assessment in adult ICU patients, as these can be confounded by underlying conditions or medications (e.g., vasopressors, inotropes) [10]. Although a patient's own report of pain is the best evaluation, critically ill patients are often not able to communicate [3]. The Critical-Care Pain Observation Tool (CPOT) is one tool that is recommended for

medical, postoperative, and trauma patients who are not able to self-report [3]. This tool includes four categories: facial expressions, body movements, muscle tension, and ventilator compliance or vocalizations for extubated patients [11; 12]. The Behavioral Pain Scale (BPS) is another tool that is recommended for adult ICU patients who are unable to communicate verbally. This scale has three items of assessment: facial expression, upper limb movements, and compliance with mechanical ventilation [12; 13]. This tool is available for both intubated and non-intubated patients [3].

Other examples of pain scales used in the ICU include [1]:

- Numeric Rating Scale (NRS): patient-reported pain, range 1 to 10, target <4
- Critical Care Observational Tool (CPOT): observational, range 0 to 8, target <3

DRUGS OF CHOICE FOR TREATING PAIN IN CRITICAL ILLNESS

The benefits of analgesic agents for pain control in critically ill patients must be balanced with the risks associated with the medications themselves (e.g., respiratory depression, hemodynamic compromise, addiction potential) [6]. In addition, too much or too little analgesia can increase risks such as nosocomial infections, delirium, prolonged duration of mechanical ventilation, and increased duration of ICU and hospital stay [2].

Patients in the ICU have less predictable pharmacokinetics and pharmacodynamics than non-critically ill patients due to hemodynamic instability, altered protein binding, drug interactions, and impaired organ function [6].

Nonpharmacologic methods, such as relaxation, massage, music therapy, lumbar support, injury stabilization, application of cold, and repositioning, can help improve patient comfort and decrease pain [2; 3; 6]. However, these methods are considered complementary in critically ill patients and are unlikely to completely control pain [6].

Non-Opioid Analgesics

Non-opioid analgesics, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) (e.g., ibuprofen, ketorolac), may be used in adult ICU patients as part of multimodal pharmacotherapy [3]. These can be considered adjuncts and most appropriate for the treatment of less severe pain. They are recommended for use in addition to opioids to help reduce opioid requirements (i.e., opioid-sparing) and opioid-related side effects, improve pain control, and improve patient-centered outcomes [3; 6].

Acetaminophen should be avoided in patients with significant liver dysfunction. Further, clinicians should exercise caution with NSAIDs in patients with kidney dysfunction, heart failure, cirrhosis, gastrointestinal bleeding, or platelet abnormalities [14].

Various medications (e.g., tricyclic antidepressants, gabapentin) are recommended for the treatment of neuropathic pain [3]. Monotherapy with IV opioids is not recommended in the treatment of neuropathic pain [3]. In some cases, gabapentin, pregabalin, and carbamazepine are used as opioid-sparing agents in critically ill adults.

The Society of Critical Care Medicine suggests using nefopam (if feasible) either as an adjunct or replacement for an opioid to reduce opioid use and their safety concerns for pain management in critically ill adults.

(https://www.sccm.org/Clinical-Resources/Guidelines/Guidelines/Guidelines-for-the-Prevention-and-Management-of-Pa. Last accessed January 25, 2024.)

Level of Evidence: Very low

Ketamine

Ketamine may be a safe and effective option in select ICU patients [14]. Ketamine seems to work as well as opioids for acute pain. (Note that pain doses are much lower than those used for sedation/anesthesia.) However, there are still potential side effects, such as nausea, mild hallucinations, and confusion.

In addition, limited safety data exist for higher-risk patients, including those with schizophrenia or with decompensated heart failure, as ketamine may increase heart rate or blood pressure. Clinicians may consider using ketamine to reduce opioid needs or to consider ketamine as an alternative if opioid use may not be safe [15; 16].

It is important to adhere to hospital protocols for ketamine use, including contraindications, as these may vary among facilities. Examples of contraindications include:

- Risk for psychotic behavior, such as schizophrenia or alcohol withdrawal
- History of severe allergic reaction to ketamine
- Increased intracranial or intraocular pressure
- Hypertensive emergency
- Decompensate heart failure
- Cardiac ischemia
- Uncontrolled cardiovascular disease (e.g., heart failure [during acute decompensation], acute coronary syndrome)

Emergence reactions with ketamine appear to be rare, especially with the lower doses used for pain. Reactions may involve anxiety, delirium, dream-like states, nightmares, illusions, or visual hallucinations [15; 16].

Clinicians should consider warning patients about the potential for emergence reactions; this may improve acceptance [15; 16]. Emergence reactions may not be as common with lower doses or in those older than 65 years of age, but caution is still warranted. Patients who are given ketamine should be provided with an appropriate environment and minimal stimuli during recovery to minimize emergence reactions. This may include dim lighting, limited noise, and have a comforting person present.

Lidocaine

Intravenous lidocaine is also sometimes an option for refractory acute and chronic pain syndromes, such as renal colic, neuropathic pain, and headaches. In addition, lidocaine is used perioperatively to limit opioids and hasten recovery [17].

However, lidocaine is not appropriate in all patients. For example, IV lidocaine should not be combined with regional anesthesia due to the increased risk for local anesthetic systemic toxicity [17]. IV lidocaine is contraindicated in patients with cardiac conduction abnormalities (including Adams-Stokes or Wolff-Parkinson-White syndromes) and severe sinoatrial, atrioventricular, or intraventricular block [17]. It should also be avoided in patients with seizure disorders, due to seizure risk with supratherapeutic blood levels of lidocaine [17].

Opioid Analgesics

Opioids are recommended as first-line agents for treating non-neuropathic pain in adult ICU patients due to their combined analgesic and sedative properties [2; 3; 6]. Respiratory depression from opioids is common, as well as hypotension secondary to a decrease in sympathetic tone or vasodilation from histamine release. Opioids can also cause decreased gastrointestinal mobility, pruritus, flushing, urinary retention, and delirium [6]. The adverse effects of opioids can increase a patient's length of stay in the ICU and worsen post-ICU outcomes. Efforts should be made to use non-opioid analgesics as well as nonpharmacologic methods to reduce opioids to the lowest effective dose for the shortest period of time [3].

All IV opioids are considered equally effective when titrated to achieve similar pain intensity endpoints [3]. The appropriate agent should be chosen based on its pharmacokinetics, metabolism, and adverse effect profile. Also consider if the patient is opioid tolerant.

COMPARISON OF OPIOIDS COMMONLY USED IN CRITICALLY ILL PATIENTS			
Drug	**Onset (IV)**	**Half-Life**	**Comments**
Fentanyl	1 to 2 minutes	2 to 4 hours	Less hypotension compared with morphine Accumulates in liver impairment
Hydromorphone	5 to 10 minutes	2 to 3 hours	Accumulates in kidney and liver impairment
Morphine	5 to 10 minutes	3 to 4 or 5 hours	Accumulates in kidney and liver impairment

Source: [20] *Table 1*

Potential adverse effects to consider when using opioids in patients in an ICU include:

- Depressed consciousness
- Hallucinations
- Hyperalgesia
- Hypotension
- Ileus and constipation
- Increased intracranial pressure
- Nausea and vomiting
- Peripheral vasodilation
- Pruritus
- Respiratory depression
- Urinary retention
- Withdrawal

The primary opioids used in critically ill adult patients are fentanyl, morphine, and hydromorphone (***Table 1***) [3; 6]. Meperidine is not generally recommended due to the risk for neurologic toxicity (e.g., reduction of seizure threshold) [9].

Continuous opioid infusions may be used for ongoing pain, as well as for moderate or severe pain that is not relieved by intermittent injections. Intermittent, or bolus, injections are also useful for moderate pain and for preprocedure analgesia prior to and during painful procedures such as dressing changes. If a patient is conscious, they may be able to use patient-controlled analgesia (PCA) to control their pain by self-administering bolus injections as needed, with or without an underlying continuous infusion. All infusions and doses should be monitored closely and titrated as needed to give optimal pain relief while avoiding oversedation and unwanted adverse effects.

Fentanyl is commonly used for continuous pain control. It has a relatively short half-life (two to four hours), which makes it easily titrated when given as a continuous infusion [6]. Fentanyl is metabolized in the liver, has no active metabolites, and may accumulate in patients with liver impairment [9]. Fentanyl is lipophilic and may accumulate in fat and muscle with prolonged infusions, increasing the half-life in patients with obesity [6]. The accumulated drug may be released after the infusion is stopped, leading to prolonged activity. However, fentanyl is often preferred because it does not undergo elimination via the kidney. Fentanyl also causes less hypotension than morphine.

Morphine and hydromorphone can be used as continuous infusions but may be chosen for intermittent IV injections because their half-lives are longer than fentanyl [6]. Morphine and hydromorphone are metabolized by the liver, and the metabolites are excreted by the kidneys. Their effects can be prolonged in patients with liver or kidney impairment [6; 9].

Morphine has a half-life of 3 to 5 hours, with an onset of analgesia of 5 to 10 minutes. It has a moderate volume of distribution, and its effects can be prolonged in obese patients [6]. Morphine causes histamine release, which can result in hypotension, itching, flushing, and bronchospasm [6; 7; 19].

Hydromorphone is much more potent than morphine. It has an inactive metabolite that may cause neuroexcitatory symptoms, especially for patients with kidney impairment, in which there can be accumulation with repeated doses [18].

Remifentanil is a derivative of fentanyl. It is metabolized by blood and tissue esterases and does not accumulate in patients with kidney or liver impairment. Remifentanil has a very short half-life (shorter than fentanyl) of 3 to 10 minutes and should not be used for bolus dosing alone [6]. It may be preferred for patients who need prompt reversal of action (e.g., requirement for frequent neurologic assessments). Remifentanil should be dosed on ideal body weight, or adjusted body weight in obese patients [3; 6]. Fentanyl and remifentanil are equal in terms of achieving sedation goals with no difference found in a patient's duration of mechanical ventilation [6]. However, the use of remifentanil in the ICU setting seems limited by its high cost and its association with hyperalgesia following discontinuation of infusions [6; 7]. Despite the theoretical advantages of remifentanil, more evidence is needed to solidify its place in therapy for analgesia and sedation in critically ill patients [2].

Sufentanil has a quick onset of one to three minutes, similar to fentanyl. It should not be used for bolus dosing alone. Sufentanil has no active metabolites, and its clearance is not affected in patients mild or moderate kidney impairment [9]. The dose should be based on ideal body weight if the patient's actual weight is more than 120% of ideal body weight [21]. For patients without IV access, sufentanil is also available in a sublingual formulation that is administered by trained staff. However, it is more expensive than other opioids and there are not data to prove it is more effective. For patients without IV access, hospital protocols should be followed for other opioid administration routes; for example, fentanyl injection can be given intranasally.

Constipation Management

All patients receiving opioids should be on an effective bowel regimen. It is important to initiate bowel regimens when the opioid is started instead of waiting for symptoms to develop. Bowel regimens typically include a scheduled osmotic (e.g., polyethylene glycol [PEG] 3350) or stimulant laxative (e.g., bisacodyl). These two can be combined if necessary. Other medications, such as magnesium citrate, glycerin suppositories, or enemas, can be added on if these are not effective. Although adding a stool softener (e.g., docusate) to a stimulant laxative is widely recommended, small studies show that this approach is not beneficial [59; 60].

The bowel regimen should be individualized based on patient characteristics and special considerations. Unique considerations include [22]:

- Avoid bulk laxatives in patients who are immobile, on fluid restriction, or have difficulty swallowing.
- Avoid oral laxatives in patients with an intestinal obstruction.
- Use enemas or suppositories for patients with fecal impaction.
- Use an osmotic laxative (e.g., PEG 3350) for patients who should avoid straining, such as after surgery or myocardial infarction.
- Avoid saline laxatives (e.g., magnesium-containing, oral sodium phosphate) in patients at risk for electrolyte abnormalities (e.g., concomitant diuretics, elderly, heart or kidney failure).

Addressing Opioid Tolerance

Treating acute pain in patients taking chronic opioids can be challenging. For example, postsurgical or trauma patients often need large doses to control pain, which can be outside of some clinician's comfort zone [23]. When selecting or evaluating pain regimens, ensure surgical patients continue their

OPIOIDS BY STRUCTURAL CLASS	
Structural Opioid Class	**Specific Opioids**
Morphine group	Buprenorphine Butorphanol Codeine Hydrocodone Hydromorphone Levorphanol Morphine Nalbuphine Oxymorphone Oxycodone Pentazocine
Phenylpiperidines	Fentanyl Meperidine Remifentanil Sufentanil
Phenylpropylamines	Tapentadol Tramadol
Diphenylheptanes	Methadone
Source: [27]	*Table 2*

usual maintenance regimen before surgery to prevent withdrawal and uncontrolled pain and verify that as-needed doses are adequate based on the scheduled regimen [23]. The oral route is preferred, but if the patient cannot take their usual maintenance regimen (e.g., post-operatively), consider converting it to basal rate PCA. It is important to avoid escalating the patient's long-acting opioid regimen and to avoid long-acting opioids or fentanyl patch for acute pain. When selecting doses, consider potency differences among opioids [23].

Opioid-Induced Hyperalgesia

Opioid-induced hyperalgesia is defined as "a state of nociceptive sensitization caused by exposure to opioids" [24]. Patients with opioid-induced hyperalgesia experience a sensitivity to pain that could be the same as their original, underlying pain or could originate from a different source [25]. Opioid-induced hyperalgesia can present in a way that is often mistaken for opioid tolerance. Tolerance to the analgesic effects of opioids can develop and requires escalating doses of opioids to maintain the same level of pain control. If a patient has tolerance to an opioid, pain will decrease when the opioid dose is increased. If the patient has opioid-induced hyperalgesia, increasing the opioid makes the pain even worse and a decrease in the opioid dose relieves the pain [24]. Switching opioids can also help relieve hyperalgesia [26]. Opioid-induced hyperalgesia should be considered in the differential diagnosis when opioid therapy fails [25].

Opioid Allergy

Opioid allergy is a common patient complaint. However, less than 2% of opioid reactions are "true allergies" and may be more appropriately categorized as pseudoallergies. A pseudoallergy is a side effect of opioids that can resemble an allergy but is usually caused by histamine release from mast cells. Symptoms of a pseudoallergy often include flushing, itching, rash, or hives. Opioids most associated with pseudoallergies include codeine, morphine, and meperidine. True allergies are more likely with symptoms such as severe hypotension; breathing, speaking, or swallowing difficulties; or swelling of the face, lips, mouth, tongue, pharynx, or larynx. Patients allergic to one opioid are thought to be less likely to react to an opioid in a different structural class (***Table 2***). Because true allergy is rare, there is not enough information to assess the chance of cross-reactivity. In addition, several opioids' product labeling contraindicates their use in patients with true allergies to any opioid.

Opioid Stewardship Considerations

Long-term opioid use, which is associated with the development of opioid use disorder, overdose, and other risks, often begins with opioid use for acute pain [28]. Clinicians and facilities should take steps to ensure prescribers and patients are on the same page regarding opioid risks and benefits. For example, before surgery, educate patients about postoperative pain. Tolerable pain and improved function are goals; complete pain relief is not always realistic.

Organizational strategies to reduce unnecessary or unsafe opioid prescribing include [28]:

- Avoid storing long-acting opioids in acute pain areas.
- Remove long-acting opioids from preoperative order sets.
- Have opioid orders default to starting doses.

Opioid safety is also a consideration at transitions of care. Patients taking medications for opioid dependence should be identified on admission, as there are special considerations for managing acute pain in these patients. Inpatient opioid use should be reviewed to help assess the need for a discharge opioid prescription. In all cases, caution should be exercised when switching patients between opioids to ensure equianalgesic doses are properly considered [28].

SEDATION IN ADULT ICU PATIENTS

WHEN IS SEDATION NEEDED IN CRITICALLY ILL PATIENTS?

Sedation should only be considered after a patient's pain is adequately controlled. The analgesia-based sedation model (also called analgosedation or analgesia-first sedation) first addresses pain and discomfort, then adds sedative agents if necessary. Analgesia-first sedation is suggested in treatment guidelines for adult ICU patients [3]. The advantages of analgesia-based sedation include a reduced need for sedatives, shorter duration of mechanical ventilation, and shorter duration of ICU stay. Disadvantages of analgesia-based sedation may include an increased risk of delirium. However, sedation titration (e.g., titrating to awake yet calm according to the Richmond Agitation-Sedation Scale [RASS]) can be used to minimize this risk [29].

Heavy or deep sedation, once much more common in ICUs, is now often referred to as oversedation. Deep sedation has been associated with increased morbidity and mortality, and more recent sedation protocols for patients in the ICU emphasize the importance of analgesia-based sedation; early mobility and physical therapy; spontaneous awakening and breathing trials, and the use of the enteral route, when appropriate [2]. The goals of light sedation (as opposed to deep sedation) are to keep a patient able to tolerate mechanical ventilation and other procedures required for care, calm and comfortable, and easily arousable [2].

Inappropriate levels of sedation (too high or too low) are not uncommon in patients in the ICU [7]. It is important to assess a patient's level of sedation by using objective assessment tools. In one study, nurses found 32% of patients to be oversedated using objective measures, while only 3% were considered oversedated by subjective measures [7]. As such, the use of scales (e.g., RASS, Riker Sedation-Agitation Scale [SAS], Motor Activity Assessment Scale [MAAS]) is preferred for objectively measuring quality and depth of sedation in adult ICU patients [3; 6]. These scales assess where a patient lies on a continuum between "combative" or "dangerously agitated" and "unarousable." Appropriate use of these scales can lead to lower doses of sedative agents and reduced duration of mechanical ventilation [3]. The RASS rates patients based on behavior, verbal stimulation, and physical stimulation. Scores range from +4 (indicating combative, violent, immediate danger to staff) to -5 (for patients who are unarousable, with no response to verbal or physical stimulation). The Riker SAS assesses level of sedation based on behavior, verbal stimuli, and physical stimuli. The scale ranges from 7 (dangerous agitation) to 1 (unarousable).

Appropriate levels of sedation will vary based on patient specific situations. For example, light sedation is not appropriate for patients receiving neuromuscular blocking agents. In these patients, ensure that analgesics and sedatives are titrated to deep sedation before starting a neuromuscular blocker. If patients are paralyzed with neuromuscular blocking agents, an objective measure of brain function, such as the bispectral index monitor (BIS), a quantitative electroencephalograph (EEG) to assess the depth of anesthesia, could be used to assess sedation status [3]. Deeper sedation may also be needed in patients with severe respiratory distress in order to ensure optimal ventilation (i.e., ventilator synchrony).

EVIDENCE-BASED PRACTICE RECOMMENDATION

The Society of Critical Care Medicine suggest using light sedation (versus deep sedation) in critically ill, mechanically ventilated adults.

(https://www.sccm.org/Clinical-Resources/Guidelines/Guidelines/Guidelines-for-the-Prevention-and-Management-of-Pa. Last accessed January 25, 2024.)

Level of Evidence: Low

To reduce drug accumulation and oversedation, the following strategies may be helpful:

- Daily sedation interruption
- Giving a bolus before increasing the infusion rate
- If using benzodiazepines, giving intermittent bolus doses of benzodiazepines instead of continuous infusions
- Use of integrated sedation protocols
- Use of agents with ultra-short half-lives

Daily interruption of sedation or targeting a light level of sedation is a conditional recommendation in the pain and sedation treatment guidelines for mechanically ventilated ICU patients, due to the low quality of evidence available [3]. Daily interruption of sedation in mechanically ventilated ICU patients has been shown to reduce mortality, duration of stay, and the risk of adverse events [5; 30]. However, this strategy is often not used or optimized in these patients [5; 31].

Daily sedation interruption, defined as short-term discontinuation of IV sedatives and sometimes analgesics, and nursing-protocolized-targeted sedation are both options to achieve and maintain appropriate light sedation (but are not appropriate for patients requiring deep sedation due to use of neuromuscular blocking agents) [3]. Goals include limiting drug accumulation, promoting wakefulness, allowing for neurological assessments, increasing tolerance for drug discontinuation, and preparing patients for extubation [31]. The medications are adjusted or stopped, then the patient is observed until they are awake, uncomfortable, or agitated. If the patient is awake and comfortable, sedative infusions are not recommended to be restarted. However, if the patient is agitated or uncomfortable, medications are restarted, typically at 50% of the previous dose and titrated to desired sedation score [32]. Both options are considered safe ways to assess and maintain appropriate light sedation [3].

DRUGS OF CHOICE FOR SEDATION IN CRITICALLY ILL PATIENTS

Experts point out qualities of the ideal sedative medication: inexpensive, minimal risk of respiratory depression, elimination independent of kidney or liver function, short half-life, and no active metabolites. However, no currently available agent meets all these criteria [6].

Sedative agents commonly used in the adult ICU setting include propofol, dexmedetomidine, ketamine, and benzodiazepines (e.g., lorazepam, midazolam) (***Table 3***) [3; 6]. Some critically ill patients receive propofol plus additional agents for sedation; however, as discussed, there is a trend toward the use of lighter sedation [7]. Note that this parallels the trend to keep patients comfortable while awake, interactive, and oriented.

COMPARISON OF COMMONLY USED NON-BENZODIAZEPINE SEDATIVES		
Properties	**Propofol**	**Dexmedetomidine**
Mechanism	GABA agonist	Alpha-2 receptor agonist
Onset	1 to 2 minutes	5 to 10 minutes
Common side effects	Bradycardia Hypotension Respiratory depression Neuroexcitatory effects Pancreatitis Hypertriglyceridemia	Bradycardia Hypotension
Comments	Use for more than 48 hours can lead to a prolonged duration of action Anticonvulsant effects, but no analgesic effects	Analgesic effects, but no anticonvulsant effects Ideal for non-mechanically ventilated patients as it lacks respiratory depression effects Not appropriate for use in patients requiring deep sedation (e.g., mechanically ventilated patients)
Source: [2; 3; 6; 7; 9; 33; 36]		*Table 3*

Potential consequences of undersedation include [7]:

- Hypoxemia
- Increased stress
- Severe anxiety and/or agitation
- Unplanned extubation

Conversely, potential consequences of oversedation are [7]:

- Cognitive impairment
- Depressed respiratory drive
- Increased duration of ICU stays
- Increased duration of mechanical ventilation
- Increased risk of infection

Propofol

Propofol is an anesthetic and gamma-aminobutyric acid (GABA) agonist [6; 7]. It has sedative, hypnotic, anxiolytic, amnestic, antiemetic, and anticonvulsant properties; it does not have analgesic properties [2; 3]. Its amnestic properties are less than with benzodiazepines in adult ICU patients at light levels of sedation [9]. Propofol has a rapid onset of action (one to two minutes) and a short duration (as short as three minutes with short-term use) [6; 9]. This is an advantage for rapid sedation as well as rapid awakening [7]. However, long-term administration of propofol (more than 48 hours) can lead to a prolonged duration of action [9].

Propofol is given as a continuous infusion, not by intermittent dosing, due to its short half-life and dose-dependent hypotension. It is metabolized mainly in the liver to inactive metabolites that are excreted in urine [18].

Side effects of propofol include hypotension (occurring in up to 25% of patients), bradycardia, respiratory depression, neuroexcitatory effects, pancreatitis, and hypertriglyceridemia [2; 6; 7]. Propofol is supplied as a lipid emulsion. Triglycerides should be monitored in patients at risk for hypertriglyceridemia and during prolonged therapy. In addition, calories from propofol should be counted toward a patient's caloric goals [2]. The 10% lipid emulsion of many propofol formulations has approximately 1.1 kcal (0.1 g of fat) per mL of propofol [32].

It is important to be careful about look-alike errors with propofol. Propofol has a similar milky-white appearance to liposomal bupivacaine or clevidipine.

The inactive ingredients in these emulsion formulations can vary and may affect their appropriateness for different patients. For example, the emulsion formulations contain soybean oil and egg lecithin. Other formulations contain sulfites or benzyl alcohol. These are all ingredients that may cause allergic reactions in some patients [18].

High doses of propofol (more than 65–80 mcg/kg/minute) as well as prolonged infusions (more than 48 hours) are associated with propofol-related infusion syndrome (PRIS) [34]. This is a serious side effect that may involve arrhythmias, hypotension, hypertriglyceridemia, kidney dysfunction, severe metabolic acidosis, and rhabdomyolysis [7; 9]. The incidence of propofol infusion syndrome is about 1% and mortality is up to 33% [9]. The minimally effective dose of propofol should always be used. Monitoring should include serum creatine kinase, serum triglycerides, and observation for any unexplained anion gap metabolic acidosis. Supportive care, including early recognition and prompt discontinuation of propofol, is essential, as there are no effective treatments available for propofol infusion syndrome [6].

Some patients may require higher sedative doses than expected even to achieve light sedation, such as those with COVID-19. There are no hard and fast rules when treating these patients, but certain strategies should be considered to ensure safe and appropriate use [3; 21; 33; 34]. Generally, use propofol first. All patients should be monitored for hypotension and symptoms of the rare but fatal PRIS, unexplained metabolic acidosis, rhabdomyolysis, and bradycardia. There is no consensus on a maximum propofol dose, but PRIS risk goes up with higher doses and longer durations. Clinicians should consider allowing short-term use above the standard, such as up to 80 mcg/kg/min for a few days. With higher doses, triglycerides should be checked more frequently (e.g., a few times per week). Propofol is often stopped for triglyceride levels greater than 500 mg/dL, but a higher threshold should be considered, because pancreatitis is rare when triglyceride levels are less than 1,000 mg/dL. If giving high propofol doses for multiple days, other sedatives may be added; using lower doses of each medication may limit side effects.

Alternatives should be available when propofol is not an option due to issues such as shortages. Dexmedetomidine may be considered for light sedation. Patients administered dexmedetomidine should be monitored for bradycardia and hypotension. This agent does not provide deep-enough sedation to use with a paralytic. If deep sedation is needed, add or switch to a midazolam drip. It is important to limit use of midazolam when able, because benzodiazepines are linked to delirium risk. A ketamine drip may be considered as an add-on option, especially with hypotensive patients, because it can raise blood pressure, and those requiring additional analgesia. Ketamine use should be avoided in patients with decompensated heart failure, and all patients should be monitored for tachycardia and increased secretions.

Dexmedetomidine

Dexmedetomidine is a relatively selective, alpha-2 receptor agonist [35]. It has analgesic, anxiolytic, sedative, and opioid-sparing properties. Dexmedetomidine has no anticonvulsant activity and should never be used alone in alcohol withdrawal [2]. It can be used for sedation in non-mechanically ventilated patients due to its lack of significant respiratory depression [3; 6; 7]. Patients are easily arousable with dexmedetomidine but can remain sedated when undisturbed [2]. The use of dexmedetomidine is associated with reduced duration of mechanical ventilation and possibly a lower incidence of delirium in comparison with benzodiazepines [3; 7].

Dexmedetomidine has an onset of action of 5 to 10 minutes, a peak effect at about 1 hour, and a short duration of action (with a half-life of 2 to 3 hours). It is administered as a continuous infusion, rarely with a bolus dose [3].

COMPARISON OF BENZODIAZEPINES COMMONLY USED IN CRITICALLY ILL PATIENTS			
Characteristics	**Lorazepam**	**Midazolam**	**Diazepam**
Onset	15 to 20 minutes	2 to 5 minutes	2 to 5 minutes
Duration of effect[a]	6 to 8 hours	30 to 60 min	2 to 4 hours
Frequency	Intermittent or continuous	Intermittent or continuous	Only intermittent
Drug interactions	Low risk	Metabolized by CYP3A4	Metabolized by CYP2C19 and 3A4
Active metabolites	No	Yes	Yes
Dose adjustment	Not if mild or moderate kidney or liver impairment	Kidney, liver	Kidney, liver
Administration	Contains propylene glycol IV incompatibilities Risk of precipitation	No propylene glycol	Contains propylene glycol
Risks	Delirium Can accumulate in peripheral tissues	Delirium	Delirium Injection site pain and phlebitis
[a]When used intermittently for less than 48 hours			
Source: [2; 38]			*Table 4*

Bradycardia and hypotension are common side effects with continuous infusions of dexmedetomidine [6]. Hypotension can be significant and adverse effects are not always quickly reversed when the infusion is stopped. Hypertension can occur after the infusion is stopped and with bolus injections. The rapid administration of a bolus dose can cause cardiovascular instability, tachycardia, bradycardia, or heart block. For this reason, the initial bolus may be avoided in most patients [6; 7].

Dexmedetomidine is metabolized in the liver. Lower doses should be used initially in patients with severe liver disease and titrated to effect [36]. Product labeling of dexmedetomidine warns of tolerance, tachyphylaxis, and increased adverse effects when used for more than 24 hours' duration [36]. However, several studies have shown safety and efficacy with longer durations [9].

Benzodiazepines

Historically, benzodiazepines have been the most commonly used agents for sedation in the ICU setting [2]. However, guidelines now recommend benzodiazepines as second-line therapy, with dexmedetomidine, propofol, and analgesia-based sedation regimens being preferred [3; 6]. Benzodiazepines seem to be associated with poorer patient outcomes, such as development of delirium, longer duration of mechanical ventilation, and longer duration of ICU stay in medical, surgical, trauma, and burn patients [2; 6; 7]. Still, the use of benzodiazepines remains important in critically ill patients for treatment of seizures and alcohol withdrawal. They also have a role in deep sedation (when indicated) or to reduce doses of other sedatives [3].

Benzodiazepines have anxiolytic, amnestic, sedative, hypnotic, and anticonvulsant effects, but no analgesic activity (***Table 4***) [3]. Adverse effects include respiratory depression and hypotension. These effects are more pronounced with concomitant cardiopulmonary depressants, especially opioids [3].

Lorazepam and midazolam are commonly used in the ICU setting [6]. They are given either by intermittent or, less commonly, by continuous infusion. Diazepam is also used occasionally and is given by intermittent infusions, not continuously [9]. Diazepam and midazolam have a quicker onset of action (2 to 5 minutes) than lorazepam (15 to 20 minutes).

Repeated dosing of benzodiazepines causes accumulation in adipose tissue [36]. This accumulation increases the duration of effect after they are stopped, particularly in obese patients. Both diazepam and midazolam are metabolized by the liver to active metabolites [2; 6]. These active metabolites are eliminated via the kidneys, so the effects of diazepam and midazolam may be prolonged in patients with impaired kidney function [2; 6; 7]. Lorazepam is metabolized by the liver but does not have active metabolites [6]. Diazepam can cause phlebitis when injected into peripheral veins [9].

Note that injectable lorazepam and diazepam are formulated with a propylene glycol solvent, and some patients have allergies to this solvent. There have also been reports of toxicity (e.g., metabolic acidosis, hypotension) with higher-than-recommended doses of lorazepam. Patients with kidney impairment or using high doses of lorazepam (1 mg/kg/day or more) for prolonged periods of time may be at increased risk of toxicity [2; 37].

Neuromuscular Blockers

Neuromuscular blocking agents (e.g., atracurium, vecuronium, cisatracurium) paralyze skeletal muscles but do not have sedative or analgesic properties. The use of paralysis via neuromuscular blockers in mechanically ventilated adult ICU patients has decreased considerably due to the potential for worse patient outcomes with this deep sedation. Within the ICU, neuromuscular blockade is still useful in certain mechanically ventilated patients, such as to facilitate breathing synchronization, to reduce the severity of muscle spasms associated with tetanus, and to decrease oxygen consumption [6; 38; 39].

In the ICU, the most commonly used neuromuscular blockers are succinylcholine and rocuronium, with rocuronium considered the preferred agent, particularly for rapid sequence intubation [57]. Rocuronium is the most recently developed neuromuscular blocking agent, introduced in 1992, and developed as a short- to intermediate-acting nondepolarizing agent with an extremely rapid, dose-based onset [64; 65; 66]. The usual intubating dose is 0.6–1.2 mg/kg. Its rapid onset (45 to 90 seconds) has placed it as a nondepolarizing alternative to succinylcholine; however, doses sufficient to speed onset to this degree come with long durations of action (60 to 90 minutes). In the patient whose airway is difficult and in whom the chance of failure to rapidly intubate may lead to a comorbid or mortal event, succinylcholine has been the criterion standard. This circumstance, however, has changed with the introduction of sugammadex to clinical practice in the United States. This novel reversal agent works by surrounding the molecules of rocuronium, precluding it from binding to the nicotinic acetylcholine receptor [67]. Following an intubating dose of rocuronium, administration of sugammadex allows the complete recovery of neuromuscular function in a shorter time than an equipotent dose of succinylcholine.

Succinylcholine is an older agent, but it is still used in some facilities. Upon injection, succinylcholine rapidly distributes throughout the body, binding to the acetylcholine receptors on the postsynaptic muscle tissue. Instead of preventing muscular contraction, it causes a random and uncoordinated firing of these receptors, resulting in the physical manifestation of anything from minor twitching to tonic contraction of major muscle groups. These fasciculations are an indicator that the drug is working. After the muscle groups tighten, they relax, but the presence of the drug on the receptors does not allow the muscle tissue to immediately repolarize [65].The effective dose is 0.5–0.6 mg/kg, and the usual intubating dose is 1.0–1.5 mg/kg. Doses in excess of 5 mg/kg are associated with a phase II block, which unpredictably prolongs the action of succinylcholine. The onset of action is 1 minute, with a return to normal typically seen after 9 to 13 minutes.

Atracurium and cisatracurium are generally the preferred agents in patients with kidney or liver impairment, patients receiving systemic corticosteroids, and patients with acute respiratory distress syndrome, targeted temperature management, or traumatic brain injury [6; 40]. Both undergo Hoffman elimination (independent of the liver or kidneys) to inactive metabolites. When neuromuscular

blockade is used in mechanically ventilated ICU patients, attempts should be made to limit drug dose as well as duration of use [2].

Neuromuscular blockers are considered high-alert medications. It is important to develop and follow preparation and administration policies to ensure safety (e.g., application of auxiliary labels to IV bags, pharmacy and nursing double checks, specific placement on delivery to patient care units). Other ways to focus on safe use of neuromuscular blocking agents are to ensure the lowest doses for the shortest duration to minimize complications, such as myopathy, and to use clinical endpoints (e.g., ventilator synchrony) and train-of-four to monitor. Auxiliary medications (e.g., eye lubricants, venous thromboembolism prophylaxis) are necessary in many patients.

While mechanical ventilation is possible without the co-administration of neuromuscular blocking drugs, some forms of mechanical ventilation will be difficult for the patient to tolerate. For example, as the mechanical ventilator inflates the lungs, a volume will be reached that triggers the Hering-Breuer response [68]. This reflex ordinarily stops negative pressure inspiration in the normally breathing adult; however, in the mechanically ventilated patient, it may cause the patient to violently attempt to cough, more commonly known as "bucking" on the ventilator. This phenomenon may be attenuated by either sedation or narcotic analgesia, but the doses of such medications may result in prolonged inhibition of normal respiration and delay extubation. Further, in patients with either acute lung injury or acute respiratory distress syndrome (sometimes referred to as noncardiogenic pulmonary edema), the administration of neuromuscular blockade can decrease oxygen consumption [69]. In one study of 340 patients requiring mechanical ventilation secondary to acute respiratory distress syndrome, a group that received a 15-mg bolus dose of cisatracurium followed by an infusion of 37.5 mg/hour for 48 hours resulted in a 90-day mortality rate of 31.6%, compared with a mortality rate of 40.7% in those not receiving the protocol [70]. While the importance of the judicious use of neuromuscular blockers in the critically ill cannot be understated, one study provides clear and convincing evidence of the importance of a sufficient level of sedation that should also be given to these patients. In their study, patients were more likely to develop delirium in the absence of or inadequacy of sedation [71]. In their research, 64.4% of mechanically ventilated patients experienced delirium and had a 30-day mortality rate of 30.3%, compared with a rate of 11.9% in those not experiencing delirium [71]. Clinicians should always keep in mind the concept that neuromuscular blockers offer no diminution of central nervous system function whatsoever, and there can be few things as terrifying as being paralyzed and wide awake.

With the use of a peripheral nerve stimulator and the co-administration of sedation, the ICU staff can closely monitor a patient's degree of neuromuscular blockade [72]. Patients requiring prolonged neuromuscular blockade in the ICU are best treated with intravenous infusions of intermediate-acting agents. As with all hospitalized patients, the goal is to treat the underlying disease or injury as quickly as possible, and then wean the patient from the ventilator in a quick and efficient manner. While intermittent boluses of neuromuscular blockers will prevent patient movement, they may impede the reversal and weaning process. A large loading dose of neuromuscular blocking drug, given to ensure quick onset, has the disadvantage of exceeding the therapeutic dose levels and extinguishing the train-of-four response (no twitches). Until the dose begins to degrade, there is no way to determine the extent of neuromuscular blockade. Indeed, there may be a supramaximal dose, resulting in prolonged blockade. The infusion dose, though taking a bit longer to set up, stops at the desired point. The lack of peaks and nadirs ensures the correct dose throughout the administration of the drug, easing recovery from neuromuscular blockade.

Finally, the administration of large bolus doses of neuromuscular blocking agents in the ICU has been associated with prolonged blockade [72]. This is attributed primarily to those agents degraded by the liver and eliminated by the kidney. During the

peak stages of the patient's illness or injury, hepatic and/or renal function may decrease. Agents such as pancuronium and vecuronium, with significant hepatic breakdown, active metabolites, and diminished renal excretion, have been associated with prolonged neuromuscular blockade lasting days or weeks after the cessation of administration [72]. This phenomenon appears especially linked to those patients presenting with sepsis. One group of researchers speculated the aggravating effects of neuromuscular blockers in these patients may also be due to degraded renal function [73].

WITHDRAWAL OF THERAPY

Withdrawal from analgesics and sedatives is linked to longer time on the ventilator and in the ICU. Several strategies have been identified to help prevent withdrawal when stopping high doses of ICU analgesics and sedatives, including identifying patients at risk for withdrawal, such as:

- Patients receiving five more days of analgesics and sedatives
- Patients receiving high doses
- Younger patients
- Obese patients
- Patients with a history of chronic opioid, alcohol, or benzodiazepine use

Taking proactive steps to minimize withdrawal is also recommended. This involves weaning doses, instead of stopping abruptly, and using a multimodal approach to sedation and analgesia. Safely tapering agents may consist of reducing opioid or benzodiazepine infusion by 10% to 30% each day or reducing the opioid infusion by 20% to 40% initially, with additional reductions of 10% every 12 to 24 hours. Alternatively, patients may be switched to an oral substitute, with the infusion tapered by 10% to 30% with each oral dose, then taper oral agent by 10% to 30% each day once stable off infusion. If a more conservative oral dose is started, a slower infusion taper may be needed. The tapering plan should be clearly communicated at transitions of care to minimize the risk of patients ending up on unneeded opioids or benzodiazepines long-term.

DELIRIUM IN ICU PATIENTS: PREVENTION AND TREATMENT

Delirium is an acute change in mental status characterized by inattention and disorganized thinking or altered level of consciousness [6; 9]. Up to 8 out of 10 mechanically ventilated ICU patients may have delirium, but it can occur whether a patient is mechanically ventilated or not [6; 9].

General risk factors for delirium are [41; 42; 43; 44]:

- Age older than 65 years
- Alcohol misuse
- Cognitive impairment or dementia
- Depression
- Poor vision or hearing
- Poor functional status
- Post-surgery
- Severe or critical illness

Risk factors with the strongest association for the development of delirium in ICU patients are [3]:

- Advanced age
- Benzodiazepine use
- Blood transfusion
- History of coma
- More severe illness
- Pre-existing dementia

Patients with delirium have an impaired ability to receive, process, and store information [2]. These patients may be hyperactive and are often described as combative or agitated, with delusions, hallucinations, and psychomotor agitation; others will be hypoactive, with depression, confusion, decreased mental activity, and withdrawal [2; 9].

In general, symptoms of delirium are [9]:

- Change in cognition such as memory deficit, disorientation, or language disturbance, or a perceptual disturbance (such as hallucinations or delusions)

- Reduced ability to focus, sustain, or shift attention
- Reduced clarity of awareness of the environment

Other common symptoms may include [9]:

- Abnormal psychomotor activity
- Emotional disturbances such as fear, anxiety, anger, depression, apathy, or euphoria
- Sleep disturbances

The onset of symptoms is typically acute (i.e., over one to two days). Delirium has been described as "acute brain failure." The course of symptoms is typically fluctuating.

Delirium in ICU patients is associated with long-term cognitive impairment, increased mortality, increased duration of mechanical ventilation, and increased duration of ICU and hospital stay [2; 3; 7]. The cause of delirium is not clear, although it has been associated with the use of sedative medications, such as benzodiazepines, and patient factors, such as cognitive impairment, sleep deprivation, immobility, visual and hearing impairment, and dehydration [2; 6]. Oversedation and undersedation are also risk factors for the development of delirium [45]. Strategies to reduce these factors, which may help decrease the risk of delirium, include [2]:

- Early mobilization (strongly recommended)
- Regulation of sleep-wake cycles
- Creating an environment conducive to uninterrupted sleep (e.g., clustering patient care activities such as bathing and lab tests)
- Provision of eyeglasses and hearing aids
- Noise reduction
- Controlling light to mimic a normal day and night schedule

In some cases, delirium may also be disease-induced (e.g., severe sepsis). In these cases, treatment of the underlying cause can reduce the incidence, severity, and duration of delirium. Delirium is also associated with drug or alcohol withdrawal after abrupt discontinuation, typically manifesting as hyperactive delirium [3].

When present, clinicians should work to ensure that the underlying causes of delirium are addressed. This assessment is guided by the mnemonic THINK:

- T: Toxic situations (e.g., medications, dehydration, organ failure), or use tight titration of medications that can cause delirium (i.e., use low doses)
- H: Hypoxemia
- I: Infection or immobilization
- N: Nonpharmacologic interventions (e.g., hearing aids, glasses, orientation, environment conducive to sleep)
- K: K+ (potassium) or other electrolyte problems

In addition, withdrawal of alcohol, tobacco, or benzodiazepines should be considered as a potential cause. The patient's home medications list should be reviewed to identify less well-known potential causes of withdrawal delirium. For example, there are published case reports of delirium in patients withdrawn from selective serotonin reuptake inhibitors (SSRIs), serotonin norepinephrine reuptake inhibitors (SNRIs), baclofen, gabapentin, pregabalin, and antipsychotics [61; 62; 63].

Validated assessment tools, such as the Confusion Assessment Method for ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC), can be used to detect delirium in adult ICU patients [2; 3]. The CAM-ICU requires patient interaction and results in either a positive or negative outcomes; the target is negative. The ICDSC also relies on patient interaction. It is scored on a range from 0 to 8, with a score of 3 of greater indicating delirium.

According to the Society of Critical Care Medicine, critically ill adults should be regularly assessed for delirium using a valid tool.

(https://www.sccm.org/Clinical-Resources/Guidelines/Guidelines/Guidelines-for-the-Prevention-and-Management-of-Pa. Last accessed January 25, 2024.)

Level of Evidence: Ungraded

Medications should be reviewed and recommendations made to reduce the risk of delirium. The total number of medications should be reduced, with a particular focus on minimizing the use of anticholinergics (e.g., diphenhydramine, promethazine), benzodiazepines, and opioids (especially meperidine) [44; 46; 47]. If possible, the doses of medications that could cause delirium should be reduced, and use of psychoactive medications in general should be minimized [48; 50]. If feasible, administration schedules should be modified to maintain a normal sleep-wake cycle [43]. Any sedatives used should have a specific indication, targeting a light level of sedation [3].

Pharmacologic prevention of delirium is not recommended [3]. The potential benefit of cholinesterase inhibitors (e.g., rivastigmine, donepezil), antipsychotics, gabapentin, and melatonin have all been studied, but there is no consistent evidence to support their use.

Further, clinicians should refrain from routinely using medications to treat delirium, as high-quality evidence to support medications to treat delirium is generally lacking [3]. The first step is to address the underlying cause when possible, as discussed. Antipsychotics should be reserved for treatment of severe distress (e.g., due to hallucinations or delusions) or for agitated patients that may pose a risk of harm to self or others despite nondrug interventions [3; 45; 49].

If use of an antipsychotic is necessary, start with a low dose and titrate to symptom control [43; 50]. For example, haloperidol may be administered at a dosage of 1–5 mg IV every 12 hours, as needed, with consideration to reducing starting dose by 50% in older adult patients [51]. IV haloperidol can be given every four to eight hours if needed, but the total daily dose should not exceed 20 mg. Because of the age-related, gradual decline in glomerular filtration rate, patients older than 50 years of age may have a lower renal clearance and longer elimination half-life of haloperidol; caution is therefore required when using haloperidol for treatment of acute delirium in elderly patients and others with reduced renal and hepatic function [50]. Elderly patients are also more susceptible to extrapyramidal side effects of haloperidol, such as acute dystonia, parkinsonism, or tardive dyskinesia, each of which may impair the ability to swallow and increase the risk for aspiration pneumonia.

Patients who are being administered antipsychotics should be monitored for QT prolongation. It seems rare when using low antipsychotic doses, but a 12-lead electrocardiogram (ECG) may be indicated to monitor high-risk patients, such as those with a baseline QT greater than 450 ms in men or 460 ms in women, or those taking amiodarone or other medications likely to prolong QT. Generally, the antipsychotic should be halted if the QT rises more than 60 ms from baseline or to greater than 500 ms [52; 53].

Best practice is to consider discontinuing antipsychotics when patients are transferred to the floor if at all possible. An estimated one in five patients receiving an antipsychotic for the first time in the hospital will be discharged with a likely unnecessary prescription [54].

CONSIDERATIONS FOR CULTURALLY AND LINGUISTICALLY COMPETENT CARE

The assessment of agitation, sedation, and delirium in the ICU is dependent on evaluation of the patient's responses to screenings and/or stimuli. In addition, patient and family education can be essential to ensuring optimal patient-centered care.

A study of culturally competent care among physicians and nurses in Australian ICUs found that deficits in the consideration and documentation of cultural sensitive care, particularly end-of-life care [58]. The author presented three recommendations to improve care for critically ill patients [58]:

- Comprehensive documentation is required of how clinicians assess patient and family member cultural wishes and preferences, in conjunction with how clinicians attempt to address these cultural needs. It is recommended that social care, inclusive of cultural needs, is also routinely documented.
- It is recommended that social workers are more routinely involved in patient care commencing from admission to the ICU. The roles and expectations of clinicians and social workers in assessing and documenting cultural wishes and preferences should be acknowledged by the whole healthcare team and documented in the policies and procedures to reduce the risk of omission and role ambiguity.
- Clinicians should aim to use interpreters in all family meetings in which language barriers exist to reduce potential conflict and enhance communication.

Depending upon the patient's language, an interpreter may be difficult to locate. Or, an organization may not have the funds to bring in an interpreter. Also, bringing in an interpreter creates a triangular relationship with a host of communication dynamics that must be negotiated [74]. Many view interpreters merely as neutral individuals who communicate information back and forth. However, another perspective is that the interpreter is an active agent, negotiating between two cultures and assisting in promoting culturally competent communication and practice [75; 76]. In this more active role, the interpreter's behavior is also influenced by a host of cultural variables such as gender, class, religion, educational differences, and power/authority perceptions of the patient [75; 76]. Consequently, an intricate, triangular relationship develops between all three parties. Another factor affecting the communication process is the fact that many interpreters are not adequately trained in the art of interpretation in mental health and general health settings, as there are many technical and unfamiliar terms. An ideal interpreter goes beyond being merely proficient in the needed language/dialect [77]. Interpreters who are professionally trained have covered aspects of ethics, impartiality, accuracy, and completeness [78]. They are also well-versed in interpreting both the overt and latent content of information without changing any meanings and without interjecting their own biases and opinions [78]. Furthermore, knowledge about cross-cultural communication and all the subtle nuances of the dynamics of communicating in a mental health or general health setting is vital [76; 77].

On the patients' side, they may be wary about utilizing interpreters for a host of reasons. They may find it difficult to express themselves through an interpreter [79]. If an interpreter is from the same community as the patient, the patient may have concerns about sharing private information with an individual who is known in the community and the extent to which the information disclosed would remain confidential. In some cases, raising the issue of obtaining an interpreter causes the patient to feel insulted that their language proficiency has been questioned. Finally, if an interpreter is from a conflicting ethnic group, the patient may refuse having interpreter services [74]. The ideal situation is to have a well-trained interpreter who is familiar with health and mental health concepts.

If an interpreter is required, the practitioner must acknowledge that an interpreter is more than a body serving as a vehicle to transmit information verbatim from one party to another [79]. Instead, the interpreter should be regarded as part of a collaborative team, bringing to the table a specific set of skills and expertise [79]. Several important guidelines should be adhered to in order to foster a beneficial working relationship and a positive atmosphere.

A briefing time between the practitioner and interpreter held prior to the meeting with the patient is crucial. The interpreter should understand the goal of the session, issues that will be discussed, specific terminology that may be used to allow for advance preparation, preferred translation formats, and sensitive topics that might arise [77; 79; 80]. It is important for the patient, interpreter, and practitioner to

be seated in such a way that the practitioner can see both the interpreter and patient. Some experts recommend that the interpreter sit next to the patient, both parties facing the practitioner [78].

The practitioner should always address the patient directly. For example, the practitioner should query the patient, "How do you feel?" versus asking the interpreter, "How does she feel?" [78]. The practitioner should also always refer to the patient as "Mr./Mrs. D" rather than "he" or "she" [79]. This avoids objectifying the patient.

At the start of the session, the practitioner should clearly identify his/her role and the interpreter's role [79]. This will prevent the patient from developing a primary relationship or alliance with the interpreter, turning to the interpreter as the one who sets the intervention [77]. The practitioner should also be attuned to the age, gender, class, and/or ethnic differences between the patient and the interpreter [79]. For example, if the patient is an older Asian male immigrant and the interpreter is a young, Asian female, the practitioner must be sensitive to whether the patient is uncomfortable given the fact he may be more accustomed to patriarchal authority structures. At the conclusion of the session, it is advisable to have a debriefing time between the practitioner and the interpreter to review the session [77; 79; 80].

In this multicultural landscape, interpreters are a valuable resource to help bridge the communication and cultural gap between patients and practitioners. Interpreters are more than passive agents who translate and transmit information back and forth from party to party. When they are enlisted and treated as part of the interdisciplinary clinical team, they serve as cultural brokers, who ultimately enhance the clinical encounter. In any case in which information regarding diagnostic procedures, treatment options and medication/treatment measures are being provided, the use of an interpreter should be considered.

CONCLUSION

Optimizing the management of analgesia, sedation, and delirium in adult ICU patients is important for improving outcomes, such as the duration of mechanical ventilation and the duration of ICU stay. Using validated tools to detect and monitor a patient's level of pain and sedation should be part of the treatment plan. There are several agents that can be used to achieve analgesia and sedation, and having a familiarity with their properties, benefits, and risks can help ensure the best therapy is given for each patient.

Implicit Bias in Health Care

The role of implicit biases on healthcare outcomes has become a concern, as there is some evidence that implicit biases contribute to health disparities, professionals' attitudes toward and interactions with patients, quality of care, diagnoses, and treatment decisions. This may produce differences in help-seeking, diagnoses, and ultimately treatments and interventions. Implicit biases may also unwittingly produce professional behaviors, attitudes, and interactions that reduce patients' trust and comfort with their provider, leading to earlier termination of visits and/or reduced adherence and follow-up. Disadvantaged groups are marginalized in the healthcare system and vulnerable on multiple levels; health professionals' implicit biases can further exacerbate these existing disadvantages.

Interventions or strategies designed to reduce implicit bias may be categorized as change-based or control-based. Change-based interventions focus on reducing or changing cognitive associations underlying implicit biases. These interventions might include challenging stereotypes. Conversely, control-based interventions involve reducing the effects of the implicit bias on the individual's behaviors. These strategies include increasing awareness of biased thoughts and responses. The two types of interventions are not mutually exclusive and may be used synergistically.

Works Cited

1. DeBiasi EM, Akgün KM, Pisani M. Awake or sedated: trends in the evaluation and management of agitation in the intensive care unit. *Semin Respir Crit Care Med*. 2015;36(6):899-913.
2. Bennett S, Hurford WE. When should sedation or neuromuscular blockade be used during mechanical ventilation? *Respir Care*. 2011;56(2):168-176; discussion 176-180.
3. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. 2018;46(9):e825-e873.
4. Ely EW. The ABCDEF bundle: science and philosophy of how ICU liberation serves patients and families. *Crit Care Med*. 2017;45(2):321-330.
5. Brochard L. Less sedation in intensive care: the pendulum swings back. *Lancet*. 2010;375(9713):436-438.
6. Hughes CG, McGrane S, Pandharipande PP. Sedation in the intensive care setting. *Clin Pharmacol*. 2012;4:53-63.
7. Devabhakthuni S, Armahizer MJ, Dasta JF, Kane-Gill SL. Analgosedation: a paradigm shift in intensive care unit sedation practice. *Ann Pharmacother*. 2012;46(4):530-540.
8. International Association for the Study of Pain. IASP Terminology. Available at https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698. Last accessed January 22, 2024.
9. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med*. 2013;41(1):263-306.
10. Rijkenberg S, Stilma W, Endeman H, et al. Pain measurement in mechanically ventilated critically ill patients: behavioral pain scale versus critical-care pain observation tool. *J Crit Care*. 2015;30(1):167-172.
11. Gélinas C, Fillion L, Puntillo KA, et al. Validation of the critical-care pain observation tool in adult patients. *Am J Crit Care*. 2006;15(4):420-427.
12. Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center. Assess, Prevent and Manage Pain. Available at https://www.icudelirium.org/medical-professionals/assess-prevent-and-manage-pain. Last accessed January 22, 2024.
13. Stites M. Observational pain scales in critically ill adults. *Crit Care Nurse*. 2013;33(3):68-78.
14. Guillou N, Tanguy M, Seguin P, et al. The effects of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. *Anesth Analg*. 2003;97(3):843-847.
15. Sheikh S, Hendry P. The expanding role of ketamine in the emergency department. *Drugs*. 2018;78(7):727-735.
16. Pourmand A, Mazer-Amirshahi M, Royall C, et al. Low dose ketamine use in the emergency department, a new direction in pain management. *Am J Emerg Med*. 2017;35(6):918-921.
17. TRC Healthcare. Clinical Resource: Intravenous Lidocaine for Pain Management. Pharmacist's Letter/Prescriber's Letter. January 2018.
18. Elsevier Clinical Key. Available at https://www.clinicalkey.com. Last accessed January 22, 2024.
19. Swart LM, van der Zanden V, Spies PE, et al. The comparative risk of delirium with different opioids: a systematic review. *Drugs Aging*. 2017;34(6):437-443.
20. Society of Critical Care Medicine. Recommendations for alternative analgesic and sedation. *Critical Connections*. 2012;2.
21. Adams CD, Altshuler J, Barlow BL, et al. Analgesia and sedation strategies in mechanically ventilated adults with COVID-19. *Pharmacotherapy*. 2020;40(12):1180-1191.
22. TRC Healthcare. Clinical Resource: Treatment of Constipation in Adults. Pharmacist's Letter/Prescriber's Letter. April 2019.
23. TRC Healthcare. Professional Resource: Stepwise Approach to Acute Pain in Chronic Opioid Patients. Pharmacist's Letter/Prescriber's Letter. December 2016.
24. Carullo V, Fitz-James I, Delphin E. Opioid-induced hyperalgesia: a diagnostic dilemma. *J Pain Palliat Care Pharmacother*. 2015;29(4):378-384.
25. Lee M, Silverman SM, Hansen H, et al. A comprehensive review of opioid-induced hyperalgesia. *Pain Physician*. 2011;14(2):145-161.
26. Silverman SM. Opioid induced hyperalgesia: clinical implications for the pain practitioner. *Pain Physician*. 2009;12(3):679-684.
27. TRC Healthcare. Clinical Resource: Opioid Allergy. Pharmacist's Letter/Prescriber's Letter. December 2022.
28. TRC Healthcare. Clinical Resource: Opioid Stewardship Checklist. Hospital Pharmacist's Letter/Pharmacy Technician's Letter. October 2020.
29. Pandharipande P, Hayhurst CJ. Pain Control in the Critically Ill Adult Patient. Available at https://www.uptodate.com/contents/pain-control-in-the-critically-ill-adult-patient. Last accessed January 22, 2024.
30. Strøm T, Toft P. Sedation and analgesia in mechanical ventilation. *Semin Respir Crit Care Med*. 2014;35(4):441-450.
31. Miller MA, Bosk EA, Iwashyna TJ, Krein SL. Implementation challenges in the intensive care unit: the why, who, and how of daily interruption of sedation. *J Crit Care*. 2012;27(2):218.e1-e7.
32. Burry L, Rose L, McCullagh IJ, et al. Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation. *Cochrane Database Syst Rev*. 2014;2014(7):CD009176.

33. Product information for Diprivan. Fresenius Kabi. Lake Zurich, IL. January 2020.
34. Hemphill S, McMenamin L, Bellamy MC, Hopkins PM. Propofol infusion syndrome: a structured literature review and analysis of published case reports. *Br J Anaesth*. 2019;122(4):448-459.
35. Chanques G, Constantin JM, Devlin JW, et al. Analgesia and sedation in patients with ARDS. *Intensive Care Med*. 2020;46(12):2342-2356.
36. Product information for Precedex. Hospira, Lake Forest, IL. August 2022.
37. Canadian Pharmacists Association. Ottawa: Canadian Pharmacists Association; 2022. Available at http://www.e-therapeutics.ca. Last accessed January 22, 2024.
38. Product information for Ativan injection. Hikma Pharmaceuticals USA. Berkeley Heights, NJ. February 2021.
39. TRC Healthcare. Clinical Resource: Tapering Critical Care Analgesics and Sedatives. Hospital Pharmacist's Letter/Pharmacy Technician's Letter. March 2022.
40. Bouju P, Tadié JM, Barbarot N, et al. Clinical assessment and train-of-four measurements in critically ill patients treated with recommended doses of cisatracurium or atracurium for neuromuscular blockade: a prospective descriptive study. Ann Intensive Care. 2017;7(1):10.
41. TRC Healthcare. Clinical Resource: Neuromuscular Blocking Agents in Adult Patients. Pharmacist's Letter/Prescriber's Letter. June 2022.
42. Szakmany T, Woodhouse T. Use of cisatracurium in critical care: a review of the literature. *Minerva Anestesiol*. 2015;81(4):450-460.
43. National Institute for Health and Care Excellence. Delirium: Prevention, Diagnosis and Management in Hospital and Long-Term Care. Available at https://www.nice.org.uk/guidance/cg103. Last accessed January 22, 2024.
44. Khan BA, Zawahiri M, Campbell NL, et al. Delirium in hospitalized patients: implications of current evidence on clinical practice and future avenues for research: a systematic evidence review. *J Hosp Med*. 2012;7(7):580-589.
45. American Geriatrics Society. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. *J Am Geriatr Soc*. 2015;63(1):142-150.
46. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: a systematic review and meta-analysis. *Age Ageing*. 2014;43(3):326-333.
47. Bassett R, Adams KM, Danesh V, et al. Rethinking critical care: decreasing sedation, increasing delirium monitoring, and increasing patient mobility. *Jt Comm J Qual Patient Saf*. 2015;41(2):62-74.
48. Critical Illness, Brain Dysfunction, and Survivorship (CIBS) Center. Management of Delirium in the ICU. Available at https://www.icudelirium.org/medical-professionals/delirium/management-of-delirium-in-the-icu. Last accessed January 22, 2024.
49. Rothberg MB, Herzig SJ, Pekow PS, et al. Association between sedating medications and delirium in older inpatients. *J Am Geriatr Soc*. 2013;61(6):923-930.
50. Canadian Coalition for Seniors' Mental Health. 2014 Guideline Update: The Assessment and Treatment of Delirium. Available at https://ccsmh.ca/wp-content/uploads/2016/03/2014-ccsmh-Guideline-Update-Delirium.pdf. Last accessed January 22, 2024.
51. Girard TD, Exline MC, Carson SS, et al. Haloperidol and ziprasidone for treatment of delirium in critical illness. *N Engl J Med*. 2018;379(26):2506-2516.
52. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383(9920):911-922.
53. Product information for Haldol. Janssen Pharmaceuticals. Titusville, NJ. November 2020.
54. Grindrod KA, Nagge J. Simplifying QT prolongation for busy clinicians. *Can Fam Physician*. 2019;65(4):268-270.
55. Tisdale JE. Drug-induced QT interval prolongation and torsades de pointes: role of the pharmacist in risk assessment, prevention and management. *Can Pharm J (Ott)*. 2016;149(3):139-152.
56. Marshall J, Herzig SJ, Howell MD, et al. Antipsychotic utilization in the intensive care unit and in transitions of care. *J Crit Care*. 2016;33:119-124.
57. Rodríguez-Blanco J, Rodríguez-Yanez T, Rodríguez-Blanco JD, et al. Neuromuscular blocking agents in the intensive care unit. *J Int Med Res*. 2022;50(9):03000605221128148.
58. Brooks LA, Manias E, Bloomer MJ. How do intensive care clinicians ensure culturally sensitive care for family members at the end of life? A retrospective descriptive study. *Intensive and Critical Care Nursing*. 2022;73:103303.
59. Engle AL, McFee Winans AR. Rethinking docusate's role in opioid-induced constipation: a critical analysis of the evidence. *J Pain Palliat Care Pharmacother*. 2021;35(1):63-72.
60. Yang A, Lam T, Jierjian E, Walden SG, Coulson EE. An evaluation of docusate monotherapy and the prevention of opioid-induced constipation after surgery. *J Pain Palliat Care Pharmacother*. 2022;36(1):18-23.
61. Tsai L-H, Lin J-W. A case report on elderly psychotic-like symptoms caused by antidepressant discontinuation. *Annales Médico-Psychologiques*. 2022;180(7):664-669.
62. Çalışkan AM, İnanlı I, Çalışkan S, Eren I. Delirium after pregabalin withdrawal. *Alpha Psychiatry*. 2021;22(2):118-119.
63. Phu PJJ, Looi JCL, Nair PC, Allison S, Chan SKW, Bastiampillai T. Psychosis related to baclofen withdrawal or overdose: a systematic review. *East Asian Arch Psychiatry*. 2023;33(1):3-14.

64. Martyn JA. Neuromuscular physiology and pharmacology. In: Miller RD (ed). *Miller's Anesthesia*. 8th ed. Philadelphia, PA: Elsevier; 2015: 423-443.
65. Haas RE, Darsey DA, Powell D. Neuromuscular blocking agents, reversal agents, and their monitoring. In: *Nurse Anesthesia*. 6th ed. St. Louis, MO: Elsevier; 2018: 162-195.
66. Lien C, Eikermann M. Neuromuscular blockers and reversal drugs. In: Hemmings HC, Egan TD (eds.) *Physiology and Pharmacology for Anesthesia: Foundations and Clinical Application*. 2nd ed. Philadelphia, PA: Elsevier; 2019: 325-348.
67. Naguib M. Sugammadex: another milestone in clinical neuromuscular pharmacology. *Anesth Analg*. 2007;104(3):575-581.
68. Hall J. Regulation of respiration. In: Hall JE, Guyton AC (eds). *Guyton and Hall's Textbook of Medical Physiology*. 13th ed. Philadelphia, PA: Elsevier, Inc.; 2016; 539-549.
69. Warr J, Thiboutot Z, Rose L, Mehta S, Burry LD. Current therapeutic uses, pharmacology, and clinical considerations of neuromuscular blocking agents for critically ill adults. *Ann Pharmacother*. 2011;45(9):1116-1126.
70. Yegneswaran B, Murugan R. Neuromuscular blockers and ARDS: thou shalt not breathe, move, or die! *Crit Care*. 2011;15(5):311.
71. Shehabi Y, Riker RR, Bokesch PM, et al. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care patients. *Crit Care Med*. 2010;38(12):2311-2318.
72. Pandit L, Agrawal A. Neuromuscular disorders in critical illness. *Clin Neurol Neurosurg*. 2006;108(7):621-627.
73. Schefold JC, Bierbrauer J, Weber-Carstens S. Intensive care unit-acquired weakness (ICUAW) and muscle wasting in critically ill patients with severe sepsis and septic shock. *J Cachexia Sarcopenia Muscle*. 2010;1(2):147-157.
74. Ayonrinde O. Importance of cultural sensitivity in therapeutic transactions: considerations for healthcare providers. *Dis Manage Health Outcomes*. 2003;11(4):233-248.
75. Hwa-Froelich DA, Westby CE. Considerations when working with interpreters. *Commun Disord Q*. 2003;24(2):78-85.
76. National Council on Interpreting in Health Care, Inc. National Standards for Healthcare Interpreter Training Programs. Available at https://www.ncihc.org/assets/documents/publications/National_Standards_5-09-11.pdf. Last accessed January 22, 2024.
77. Lynch EW. Developing cross-cultural competence. In: Lynch EW, Hanson MJ (eds). *A Guide for Working with Children and their Families: Developing Cross-Cultural Competence*. 4th ed. Baltimore, MD: Paul H. Brookes Publishing, Co.; 2011: 41-78.
78. Tribe R. Working with interpreters in mental health. *Int J Cult Ment Health*. 2009;2(2):92-101.
79. Dysart-Gale D. Clinicians and medical interpreters: negotiating culturally appropriate care for patients with limited English ability. *Fam Community Health*. 2007;30(3):237-246.
80. Raval H, Smith J. Therapists' experiences of working with language interpreters. *Int J Ment Health*. 2003;32(2):6-31.

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