Health care practitioners must provide effective sedation and analgesia management for patients in the intensive care unit (ICU). These patients require adequate sedation and analgesia because many factors in the ICU can cause them to experience stress, anxiety, and pain, including underlying medical conditions, acute medical or surgical illness, invasive interventions, and environmental influences. Practitioners can mitigate these factors with appropriate sedation and analgesia therapy.

Clinicians should first assess and control patients’ pain and then assess and control their anxiety through appropriate sedation therapy. Although assessment of pain control has improved in health care, the incidence of pain is still considered to be as high as 50% in medical and surgical ICU patients. After initiating an analgesia and sedation regimen, clinicians should assess the effectiveness of these regimens using validated scales. Patient-focused scales are designed to achieve adequate sedation and pain control without oversedating or undersedating patients. Adverse effects of oversedation include hemodynamic instability and prolongation of treatment with mechanical ventilation. However, undersedation can lead to stress and unwanted memories of the ICU stay for patients. In addition, disruptive or restless behavior may interfere with patients’ care and healing.

Some patients are able to articulate their level of pain; however, some critically ill patients may not be able to report their own pain as a result of treatment with mechanical ventilation, altered levels of consciousness, and use of sedative agents or neuromuscular blockers. Use of patient-focused information to health care providers about a patient’s level of consciousness and allows for patient-focused therapy.

Requirements for sedation and analgesia are dynamic during a patient’s course in the ICU. Implementing an interdisciplinary approach can help provide patients with the best possible sedation and analgesia management throughout their ICU stay. Clinicians need to become familiar with the available sedation and analgesia scales. Flow charts and sedation scales are successful when used, but a recent survey showed that only about 50% of hospitals actually use them.

Guidelines on the management of pain, agitation, and delirium recently have been updated by the Society of Critical Care Medicine (SCCM). This article

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reviews the benefits of objective monitoring and titration recommendations based on patient-focused scales. In addition, this article discusses medication selection on the basis of patient factors for the adult population.

Benefits of Objective Monitoring of Analgesia and Sedation Therapy

Objective monitoring of analgesia and sedation therapy allows for patient-tailored regimens. Appropriately using patient-centered scales can help practitioners achieve effective sedation and analgesia management. These scales should be thoroughly validated by several health care practitioners and in different intensive care settings. Another important characteristic of scales is interrater reliability, which means that the same scale score can be achieved by multiple disciplines of practitioners.

Pain Assessment

The most reliable way to assess a patient’s level of pain is through self-reporting. Patients who are being treated with mechanical ventilation, however, may not be able to verbalize their pain. In these patients, pain assessment still may be possible using voice commands asking the patient to blink or squeeze his or her eyes tightly to indicate that he or she is experiencing pain.4 Other signs, such as body movement, ventilator synchrony, and changes in vital signs, also can be closely monitored in patients who are unable to communicate.5

Monitoring vital signs is important for assessing whether deeply sedated patients are experiencing pain; however, an increase in heart rate or blood pressure should not be used alone in the decision to administer pain medication.2 Changes in vital signs can be an indicator to prompt health care professionals to further assess pain control and can be used in conjunction with validated pain assessment scales. The 2 most reliable and validated pain scales recommended by the SCCM 2013 guidelines are the Behavioral Pain Scale (BPS) and the Critical-Care Pain Observation Tool (CPOT).2

The BPS is based on 3 behavioral categories: facial expression, body movement, muscle tension, and compliance with ventilation. Each of these categories includes 4 subcategories, allowing the score to range from 3 to 12, or from no pain to maximum pain.4,6

The CPOT is another scale clinicians can use to assess pain levels in patients who are deeply sedated as well as in patients who can verbally communicate.7 The CPOT scale is based on 4 behavioral categories: facial expression, body movement, muscle tension, and compliance with ventilation (for patients who are intubated) or vocalization (for patients who are not intubated). The score for the CPOT scale can range from 0 to 8, indicating no pain to the most pain, respectively.

Clinicians also need to be aware of some other factors when using these scales. At times, a patient’s upper extremity range of motion is limited by the equipment and catheters in the ICU room. This limited range of motion may affect the score in the domain of upper extremity movement on the BPS scale, potentially resulting in a lower pain score, which could then result in the patient not receiving essential pain medication. In addition, both the BPS and CPOT scales are based on patients’ behaviors. Once a patient becomes unresponsive to external stimuli, these scales will no longer be useful.

Sedation Assessment

According to Schweickert and Kress,8 2 main features of patient-focused sedation protocols are assessment of the patient and titration parameters based on this assessment. The appropriate use of these scoring tools allows patients to benefit from these therapies without experiencing adverse effects. These adverse effects may include oversedation or undersedation, uncontrolled pain, disruptive behavior, stress, and decreased respiratory drive. The goal is to keep patients comfortable while allowing them to cooperate with their care.9 The use of protocol-directed sedation scales is associated with a shorter duration of treatment with mechanical ventilation and shortened ICU and hospital lengths of stay. Patients with protocol-directed sedation therapy also receive continuous infusions of sedative agents for a shorter period of time and have a lower tracheostomy rate.8

The Richmond Agitation Sedation Scale (RASS) and the Riker Sedation-Agitation Scale (SAS) are considered the most reliable and valid sedation scales, according to the 2013 SCCM guidelines for use in adult patients in the ICU setting.2 The 2 scales are highly correlated in evaluating arousal states among all ICU populations.10

The RASS was developed as a collaboration between several different health care professionals, including physicians, nurses, and pharmacists; it is an assessment of arousal, cognition, and sustainability using eye opening, eye
contact, and physical movement as domains. This 10-point scale ranges from −5 to +4, with levels of sedation ranging from unarousable to combative, respectively. The 3 different behavioral categories within this scale are as follows: +1 to +4 are levels of anxiety or agitation, 0 is the level to denote a calm and alert state, and −1 to −5 are levels of sedation. A brief procedure is used by practitioners to assign an RASS score based on the descriptions associated with each level of sedation. The goal sedation level for most patients is light sedation; practitioners often aim for a score between 0 and −2 after titrating the dose to achieve a particular sedation level. The use of light sedation is associated with better clinical outcomes, including shorter length of stay in the ICU and fewer days of treatment with mechanical ventilation.

The Riker SAS is scored from 1 (unarousable) to 7 (dangerous agitation), with each score or level of sedation associated with a descriptor. The 3 different behavioral categories within the SAS are as follows: 1 to 3 are levels of sedation, 4 is the level to denote a calm and cooperative state, and 5 to 7 are levels of agitation. Again, the practitioner assesses the patient’s score using a brief procedure that involves evaluating the patient’s level of arousal and assigning a score using the descriptors associated with each level of sedation. A score between 3 and 4 is indicative of a goal of light sedation in the SAS.

Medication Selection

When selecting a therapeutic regimen to address patients’ pain and anxiety levels, practitioners must consider several medication-specific factors, including duration, onset and offset of effect, presence of active metabolites, adverse effects, and duration of analgesia and sedation. Most patients initially require administration of sedative or analgesic agents by continuous intravenous (IV) infusion; as the patient’s condition improves, the transition to intermittent IV or oral therapy should be done as tolerated. Recognition of patient-specific factors, such as medication history, alcohol abuse, or substance abuse, also can help determine the initial regimen. Alcohol and substance abuse can increase the analgesic and sedative drug requirements of the patient. Medication reconciliation should be performed, as the abrupt discontinuation of certain medications, such as antidepressants, anxiolytics, and antipsychotics, may contribute to a patient’s anxiety and pain level.

Pain Medications

Pain can be experienced by patients in the ICU for various reasons, including surgery, trauma, treatment with mechanical ventilation, and routine care in the unit. As mentioned previously, clinicians should assess a patient’s pain level before initiating analgesia and sedation management, if possible. Pain control may affect hemodynamic status, including better control of the patient’s stress level, blood pressure, and heart rate. Stress is associated with poor patient outcomes because of an increase in catecholamine release that results in arteriolar vasoconstriction and impaired tissue perfusion.

Opioids remain the mainstay of therapy for pain management in critically ill patients. Some of the desirable pharmacological characteristics of opioid therapy include rapid onset, ease of titration, limited drug or active metabolite accumulation, and relatively low cost. The appropriate choice of agent will depend on pharmacokinetic parameters and patient-specific factors. Many adverse effects are associated with the use of opioids in the ICU setting, including respiratory, hemodynamic, central nervous system, and gastrointestinal effects. Some of the most commonly used analgesic agents, including morphine, fentanyl, remifentanil, hydromorphone, and meperidine, are discussed further (see Table 1).

Morphine is a naturally occurring opioid and a μ-receptor agonist. Morphine is more hydrophilic than other opioids, resulting in a comparatively slower onset of action, approximately 15 minutes. Compared with the other opioids, the half-life of morphine is long, approximately 3 to 7 hours, allowing for intermittent bolus intravenous (IV) dosing. Caution should be used in patients who are hemodynamically unstable because of the histamine release associated with IV administration of morphine, which causes vasodilation and hypotension. Renal dose adjustment is necessary in patients with decreased renal function because of the accumulation of morphine’s metabolite; therefore, initial doses should be decreased in patients with renal insufficiency.

Fentanyl is a synthetic opioid that targets μ receptors to exert analgesic effects. Fentanyl is the preferred analgesic agent when rapid pain control is needed, as it has an onset of action of approximately 1 to 3 minutes. The quick onset is due to fentanyl’s highly lipophilic properties. Fentanyl also has a short duration of action as a result of its rapid distribution into the peripheral tissues. However, prolonged...
administration of fentanyl has been associated with accumulation of the drug in the peripheral tissues, resulting in an increased elimination half-life and increased duration of action. No histamine release is associated with fentanyl administration as is seen with morphine; therefore, fentanyl is a good choice for patients with hemodynamic instability. Although fentanyl has no active metabolites, lower dosing should be considered in patients with severe hepatic insufficiency. However, it is a more appropriate agent for patients with renal insufficiency. A potential rare adverse effect is chest wall rigidity, which is associated with difficulty in breathing for the patient.

Remifentanil is newly recommended by the 2013 SCCM guidelines as a preferred analgesic agent. This medication has Food and Drug Administration approval not only for use as a general anesthetic agent but also for postoperative pain management in patients who are being treated with mechanical ventilation. Remifentanil is also a synthetic \( \mu \) receptor agonist with an ultra-fast onset of approximately 1 minute and a half-life of about 3 to 10 minutes. Because of the ultra-short duration of action, patients will require a continuous infusion for pain control. This drug should be tapered on discontinuation, or a long-acting opioid should be initiated to prevent withdrawal symptoms or pain. Also, because remifentanil has a fast onset of action, syringes should be changed promptly to avoid interruptions in analgesia therapy. In addition to its analgesic properties, remifentanil also has sedative properties. Patients still experiencing anxiety at a dose of 0.2 mcg/kg per minute of remifentanil should receive a second sedative agent.

Like fentanyl, remifentanil does not have any active metabolites. Two clinical scenarios where remifentanil may accumulate as a result of decreased metabolism are hypothermia and severe acidosis. The metabolism and elimination of this drug do not depend on any organ system; therefore, it can be used in patients with hepatic and/or renal dysfunction. Although remifentanil is an agent that is recommended by the 2013 SCCM guidelines, the increased cost associated with the use of this agent should be considered. Clinicians also should be aware of the similarity in spelling and pronunciation of fentanyl and remifentanil. This similarity increases the risk for a medication error that could lead to detrimental effects, especially for an opioid-naive patient.

Hydromorphone is a semisynthetic \( \mu \) receptor agonist with a similar duration of action to morphine, allowing for intermittent bolus IV dosing. However, hydromorphone is approximately 7.5 times more potent than morphine. Hydromorphone does not have an active metabolite and is not associated with the release of histamine when compared with morphine. Because it does not cause histamine release, this agent is a good choice for patients with hemodynamic instability and is considered the drug of choice for patients with renal insufficiency.

Meperidine is a weak \( \mu \) agonist that is metabolized to a clinically active metabolite, normeperidine, that causes neuroexcitability

### Table 1: Usual Doses of Analgesic Agents

<table>
<thead>
<tr>
<th></th>
<th>Infusion Rates</th>
<th>Intermittent Dosing</th>
<th>Onset After IV Loading Dose, min</th>
<th>Elimination Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine</td>
<td>5-35 mg/h IV</td>
<td>2-4 mg IV every 1-2 h</td>
<td>5-10</td>
<td>3-7 h</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>25-30 mcg/h IV</td>
<td>50-100 mcg IV every 1-2 h</td>
<td>1-3</td>
<td>~3.5 h</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>Loading dose: 0.5-1 mcg/kg per minute</td>
<td>Not recommended</td>
<td>1-3</td>
<td>3-10 min</td>
</tr>
<tr>
<td></td>
<td>Maintenance dose: 2.5-20 mcg/kg per hour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>0.5-2 mg/h IV</td>
<td>0.7-4 mg IV every 4 hours</td>
<td>5-10</td>
<td>2-3 h</td>
</tr>
<tr>
<td>Meperidine</td>
<td>50-150 mg every 3 to 4 hours IM or SQ</td>
<td></td>
<td>10-15</td>
<td>2-4 h</td>
</tr>
</tbody>
</table>

**Abbreviations:** IM, intramuscular; IV, intravenous; SQ, subcutaneous.

*Based on data from references 2, 11, 20, and 21.
and accumulates in patients with renal failure, potentially causing seizures. Similar to morphine, meperidine also releases histamine. Because of its histamine release, this agent is not a good choice for patients who are hemodynamically unstable. The use of meperidine is contraindicated in patients taking monoamine oxidase inhibitors, such as selegiline. Use also should be cautioned in combination with serotonin-reuptake inhibitors, such as citalopram and fluoxetine, as a result of the potential for serotonin syndrome. Because of the adverse effect profile of meperidine, this agent is not recommended as a first-line analgesic agent. However, note that meperidine has a role in the treatment of postoperative shivering.

### Sedative Medications
When patients first experience anxiety, clinicians should determine the underlying cause. After identifying the stimuli and attempting to reduce the patients’ anxiety, clinicians can then begin sedation therapy. Current guidelines recommend a goal of light sedation for patients being treated with mechanical ventilation, because it is associated with better clinical outcomes. The most common medications used for sedation in the ICU setting are midazolam, lorazepam, propofol, and dexmedetomidine. Please see Table 2 for dosing recommendations.

Midazolam is frequently used as a sedative agent in the ICU because of its pharmacokinetic properties, including rapid onset and short duration of action. Midazolam is a short-acting benzodiazepine. Its clinical effects result from agonist activity on γ-aminobutyric acid receptors, which produces anxiolysis, hypnosis, amnesia, muscular relaxation, and anticonvulsant activity. Midazolam is more lipid soluble than the other benzodiazepines causing faster onset of action and quicker recovery time. These properties make midazolam an ideal agent for patients requiring routine neurological assessment and for analgesia associated with routine procedures in the ICU setting.

Certain patient populations are prone to oversedation with midazolam usage. Midazolam is very lipid soluble and will accumulate in obese patients because of their increased adipose tissue. All benzodiazepines are primarily metabolized through the liver. Patients with any type of liver dysfunction can have increased plasma levels and effects of benzodiazepines. Specifically, patients with cirrhosis have an increase in volume of distribution, and as a result, the half-life of midazolam increases significantly.

### Table 2: Usual Doses of Sedative Agents

<table>
<thead>
<tr>
<th>Sedative Medication</th>
<th>Usual Dose and Titration</th>
<th>Onset After IV Loading Dose, min</th>
<th>Half-life, h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>Intermittent IV infusion: 0.02-0.06 mg/kg every 2-6 h</td>
<td>15-20</td>
<td>8-15</td>
</tr>
<tr>
<td></td>
<td>Continuous IV infusion: 0.01-0.1 mg/kg per hour</td>
<td>Titrate by: 1 mg every hour</td>
<td></td>
</tr>
<tr>
<td>Midazolam</td>
<td>Intermittent IV infusion: 0.04-0.2 mg/kg every 0.5 to 2 h</td>
<td>3-5</td>
<td>2-6</td>
</tr>
<tr>
<td></td>
<td>Continuous IV infusion: 0.02-0.1 mg/kg per hour</td>
<td>Titrate by 1-2 mg every hour</td>
<td></td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>Loading dose: 1 mcg/kg over 10 min</td>
<td>-6</td>
<td>-2</td>
</tr>
<tr>
<td></td>
<td>Continuous IV infusion: 0.2-0.7 mcg/kg per hour</td>
<td>Titrate by 0.2-1 mcg/kg per hour</td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>Loading dose: 5 mcg/kg per minute</td>
<td>1-2</td>
<td>4-7</td>
</tr>
<tr>
<td></td>
<td>Continuous IV infusion: 5-50 mcg/kg per minute</td>
<td>Titrate by 5-10 mcg/kg per minute every 5-10 min</td>
<td></td>
</tr>
</tbody>
</table>

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*Based on data from references 2, 13, 20, 22, and 23. Abbreviation: IV, intravenous.
In addition, patients with renal dysfunction may accumulate the metabolite of midazolam, which may result in prolonged sedation.\(^9\) The same sedative effect can be achieved with lower doses of midazolam in elderly patients because of the drug’s prolonged half-life as a result of age-related pharmacokinetics. Clinicians should start with lower doses and titrate the dose at a slower rate for this patient population.

Lorazepam is a long-acting benzodiazepine with the same mechanism of action as midazolam but with a longer half-life of 8 to 15 hours. In comparison with midazolam, lorazepam does not have any active metabolites and is cleared by glucuronide conjugation in the liver.\(^2\) The clinical effect of lorazepam is increased in patients with renal failure and elderly patients; again these patients require less drug to achieve the same sedation levels. Intravenous lorazepam is soluble only in propylene glycol, and the accumulation of propylene glycol toxicity. Adverse effects associated with the accumulation of propylene glycol include metabolic disturbances, lactic acidosis, acute tubular necrosis, and hyperosmolarity. Treatment of propylene glycol toxicity includes discontinuation of the lorazepam infusion, supportive care, and hemodialysis.\(^3\) The use of long-acting benzodiazepines, such as lorazepam, is associated with deeper sedation levels and longer duration of treatment with mechanical ventilation. These effects are mainly due to lorazepam’s relatively long half-life, making it difficult to easily titrate this drug to desired sedation levels without oversedating the patient and increasing emergence time.\(^2\) In addition, the risk of delirium is increased with the use of lorazepam. For these reasons, the 2013 SCCM guidelines recommend that in patients being treated with mechanical ventilation, nonbenzodiazepine sedative agents should be used when possible rather than benzodiazepines because they are associated with improved clinical outcomes.\(^2\)

Propofol is an anesthetic agent with hypnotic, anxiolytic, and amnestic properties. Propofol has a very rapid onset because it is lipid soluble and readily crosses the blood-brain barrier.\(^2\) High hepatic and extra hepatic clearance results in a short duration of action. Because of the drug’s fast onset and short duration of action, it is considered a first-line agent for the sedation of patients requiring regular assessment of neurological function. In addition, propofol is considered neuroprotective and has antiepileptic properties because of its activity on N-methyl-D-aspartate receptors, which lowers intracranial pressure. Propofol is also a good sedative choice for patients who are anticipated to be treated with mechanical ventilation for a short period of time. Several dose-dependent adverse effects, including hypotension, respiratory depression, hypertriglyceridemia, and acute pancreatitis, are associated with the use of propofol.

Propofol infusion syndrome is associated with the use of propofol for more than 48 hours and at doses greater than 75 mcg/kg per minute; although this syndrome occurs rarely, it is a serious adverse effect.\(^16\) Hyperkalemia, tachyarrhythmia, bradycardia, and hypertriglyceridemia are associated signs. Propofol infusion syndrome may result in myocardial failure, metabolic acidosis, rhabdomyolysis, dysrhythmias, and renal failure. Practitioners should monitor patients for these signs to prevent serious adverse effects.\(^17\)

Dexmedetomidine is a selective \(\alpha_2\) receptor agonist with sedative, analgesic, and sympatholytic properties.\(^18\) It is rapidly redistributed into tissues and metabolized by the liver. The 2 most common adverse effects associated with dexmedetomidine are bradycardia and hypotension as a result of its agonist activity on \(\alpha_2\) receptors. Bradycardia, however, is typically associated with bolus dosing. Currently, dexmedetomidine is approved by the Food and Drug Administration for short-term use in patients undergoing procedural sedation or being treated with mechanical ventilation. Recent studies demonstrate that dexmedetomidine is safe for use for a period longer than 24 hours, and the use of dexmedetomidine for more than 24 hours is a commonly accepted practice across the country.\(^19\) This agent does not produce respiratory depression, as do other sedative agents.\(^19\) Some of the benefits of this agent include a decreased incidence of delirium, shorter length of treatment with mechanical ventilation, and the ability to assess cognitive function.\(^16\) In addition, dexmedetomidine has an analgesic sparing effect as a result of its analgesic properties.

**New Recommendations**

In 2013, the SCCM updated the 2002 guidelines on sedation, analgesia, and delirium.\(^2\) Some of the key changes in these guidelines include recommending the use of 2 different analgesia and sedation scales.

Recommendations were also made specifically for analgesia management. For procedures...
such as chest tube removal that are typically associated with pain, pain medication should be administered before the procedure. Preemptive pain management is more effective than treating pain after it occurs.

Key recommendations for sedation therapy include maintaining light levels of sedation. Recent literature shows that light levels of sedation are associated with improved clinical outcomes, including shorter length of stay in the ICU and treatment with mechanical ventilation for fewer days. Recommendations on selection of medication include nonbenzodiazepine therapy over benzodiazepine therapy when possible. Patients who require higher doses of sedative agents and long-term treatment with mechanical ventilation, however, may require combination therapy with benzodiazepines to provide appropriate sedation therapy.

The 2013 SCCM guidelines stress the importance of patient-focused monitoring scales and medication selection. Clinicians must optimize pain control and then initiate sedation therapy. In addition, pain control with opioids leads to lower sedative requirements to achieve light sedation levels and fewer adverse effects.

REFERENCES