

# Clinical Practice Guidelines for the Sustained Use of Sedatives and Analgesics in the Critically Ill Adult

Maintaining an optimal level of comfort and safety for critically ill patients is a universal goal for critical care practitioners. The American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine's (SCCM's) practice parameters for the optimal use of sedatives and analgesics was published in 1995 and recommended a tiered approach to the use of sedatives and analgesics, largely on the basis of expert opinion.<sup>1</sup> These clinical practice guidelines replace the previously published parameters and include an evaluation of the literature published since 1994 comparing the use of these agents. The reader should refer to the accompanying introduction for a description of the methodology used to develop these guidelines.<sup>2</sup>

This document is limited to a discussion of prolonged sedation and analgesia. Consistent with the previous practice guidelines, this document pertains to patients older than 12 years. The majority of the discussion focuses on the care of patients during mechanical ventilation. A discussion of regional techniques is not included. Appendix A summarizes the recommendations made herein.

## Analgesia

In these guidelines, "analgesia" is defined as the blunting or absence of sensation of pain or noxious stimuli. Intensive care unit (ICU) patients commonly have pain and physical discomfort from obvious factors, such as preexisting diseases, invasive procedures, or trauma. Patient pain and discomfort can also be caused by monitoring and therapeutic devices (such as catheters, drains, noninvasive ventilating devices, and endotracheal tubes), routine nursing care (such as airway suctioning, physical therapy, dressing changes, and patient mobilization), and prolonged immobility.<sup>3,4</sup> Unrelieved pain may contribute to inadequate sleep, possibly causing exhaustion and disorientation. Agitation in an ICU patient may result from inadequate pain relief. Unrelieved pain evokes a stress response characterized by tachycardia, increased myocardial oxygen consumption, hypercoagulability, immunosuppression, and persistent catabolism.<sup>5,6</sup> The combined use of analgesics and sedatives may ameliorate the stress response in critically ill patients.<sup>7,8</sup> Pain may also contribute to pulmonary dysfunction through localized guarding of muscles around the area of pain and a generalized muscle rigidity or spasm that restricts movement of the chest wall and diaphragm.<sup>9</sup> Effective analgesia may diminish pulmonary complications in postoperative patients.<sup>10</sup>

Some patients recall unrelieved pain when interviewed about their ICU stays.<sup>3,11,12</sup> The perception of pain can be influenced by several factors, such as the expectation of pain, prior pain experiences, a patient's emotional state, and the cognitive processes of the patient.<sup>11</sup> Patients should be educated about the potential for pain and instructed to communicate their needs in an appropriate manner (such as using an assessment tool or other communication techniques). The goals of therapy should also be communicated to the patient and family. In many cases, pain will be managed but not completely eliminated. Fear of potent analgesics and

misconceptions about pain and analgesics should be addressed. Similarly, practitioner bias against the adequate use of opioids or misplaced fears of adverse effects or addiction may produce inadequate prescribing or administration.<sup>13,14</sup> Educating practitioners and assessing the quality of a pain management program may improve analgesia therapy, but such programs have not been universally successful.<sup>4,15</sup> The importance of appropriate pain management programs has been reinforced by the Joint Commission on Accreditation of Healthcare Organizations's (JCAHO's) establishment of standards on pain assessment and management.

*Recommendation: All critically ill patients have the right to adequate analgesia and management of their pain. (Grade of recommendation = C)*

**Pain Assessment.** There is a limited amount of literature that directly addresses pain assessment in the critical care unit. The articles reviewed in this report include descriptions of pain assessment tools used for critically ill patients, even if these tools were not validated in this population. Studies of pain in the critically ill indicate the importance of systematic and consistent assessment and documentation.<sup>16</sup> The most reliable and valid indicator of pain is the patient's self-report.<sup>17</sup> The location, characteristics, aggravating and alleviating factors, and intensity of pain should be evaluated. Assessment of pain intensity may be performed with unidimensional tools, such as a verbal rating scale (VRS), visual analogue scale (VAS), and numeric rating scale (NRS). VAS comprises a 10-cm horizontal line with descriptive phrases at either end, from "no pain" to "severe pain" or "worst pain ever." Variations include vertical divisions or numeric markings. VAS is reliable and valid for many patient populations.<sup>18</sup> Though not specifically tested in the ICU, VAS is frequently used there<sup>19-22</sup> Elderly patients may have difficulty with VAS.<sup>20</sup> NRS is a zero to ten point scale and patients choose a number that describes the pain, with ten representing the worst pain. NRS is also valid, correlates with VAS, and has been used to assess pain in cardiac surgical patients.<sup>21</sup> Because patients can complete the NRS by writing or speaking, and because it is applicable to patients in many age groups, NRS may be preferable to VAS in critically ill patients.

Multidimensional tools, such as the McGill Pain Questionnaire (MPQ) and the Wisconsin Brief Pain Questionnaire (BPQ), measure pain intensity and the sensory, affective, and behavioral components of that pain but take longer to administer and may not be practical for the ICU environment.<sup>18,22</sup> The MPQ and BPQ are reliable and valid tools but have not been tested or used in the ICU.

Although the most reliable indicator of pain intensity is what the patient reports, critically ill patients are often unable to communicate their level of pain if sedated, anesthetized, or receiving neuromuscular blockade. Neither the VAS nor the NRS will resolve this problem as they rely on the patient's ability to communicate with the care provider. Behavioral-physiological scales may be useful in assessing pain in these patients. Moderate agreement was found

between the VAS and the observer-reported Faces scale for all observations, but less agreement was noted as the pain intensity increased.<sup>19</sup> The verbal descriptive scale (VDS) used in another trial showed moderate correlation ( $r > 0.60$ ) with a behavioral pain scale in assessing pain in postanesthesia patients.<sup>23</sup> A behavioral–physiological scale was compared with an NRS and a moderate-to-strong correlation was observed between the scales.<sup>24</sup> The behavioral–physiological scale also assessed pain-related behaviors (movement, facial expression, and posturing) and physiological indicators (heart rate, blood pressure, and respiratory rate). However, such nonspecific parameters might be misinterpreted or affected by observer bias, leading to an underestimation of the degree of pain experienced by the patient.<sup>12,24–27</sup>

Family members or other surrogates have been evaluated for their ability to assess the amount of pain experienced by noncommunicative ICU patients. While surrogates could estimate the presence or absence of pain in 73.5% of patients, they less accurately described the degree of pain (53%).<sup>28</sup>

The most appropriate pain assessment tool will depend on the patient involved, his/her ability to communicate, and the caregiver's skill in interpreting pain behaviors or physiological indicators.

*Recommendations: Pain assessment and response to therapy should be performed regularly by using a scale appropriate to the patient population and systematically documented. (Grade of recommendation = C)*

*The level of pain reported by the patient must be considered the current standard for assessment of pain and response to analgesia whenever possible. Use of the NRS is recommended to assess pain. (Grade of recommendation = B)*

*Patients who cannot communicate should be assessed through subjective observation of pain-related behaviors (movement, facial expression, and posturing) and physiological indicators (heart rate, blood pressure, and respiratory rate) and the change in these parameters following analgesic therapy. (Grade of recommendation = B)*

**Analgesia Therapy.** Nonpharmacologic interventions including attention to proper positioning of patients, stabilization of fractures, and elimination of irritating physical stimulation (e.g., proper positioning of ventilator tubing to avoid traction on the endotracheal tube) are important to maintain patient comfort. Application of heat or cold therapy may be useful. Other nonpharmacologic techniques to promote patient comfort are discussed later in this document.

Pharmacologic therapies include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and acetaminophen. Opioids mediate analgesia by interacting with a variety of central and peripheral opioid receptors. The opioids currently available have activity at a variety of these receptors, although the  $\mu$ - and  $\kappa$ -receptors are most important for analgesia. Interaction at other receptors may contribute to adverse effects. The analgesic agents most commonly used in ICU patients (fentanyl, morphine, and hydromorphone) are addressed later.<sup>29</sup> Although alfentanil has previously been reported as an analgesic with sedative effects, it will not be extensively discussed because it is not commonly used in North America.<sup>29</sup>

Comparative trials of opioids have not been performed in critically ill patients. The selection of an agent depends on its pharmacology and potential for adverse effects. The characteristics of commonly used opioids and nonopioids are reviewed in Table 1.<sup>30–32</sup> Desirable attributes of an opioid include rapid onset, ease of titration, lack of accumulation of the parent drug or its metabolites, and low cost. Fentanyl has the most rapid onset and shortest duration, but repeated dosing may cause accumulation and prolonged effects. Morphine has a longer duration of action, so intermittent doses may be given. However, hypotension may result from vasodilation and an active metabolite may cause prolonged sedation in the presence of renal insufficiency. Hydromorphone's duration of action is similar to morphine's, but hydromorphone lacks a clinically significant active metabolite or histamine release. Meperidine has an active metabolite that causes neuroexcitation (apprehension, tremors, delirium, and seizures) and may interact with antidepressants (contraindicated with monoamine oxidase inhibitors) and best avoided with selective serotonin-reuptake inhibitors), so it is not recommended for repetitive use.<sup>17,33,34</sup> Because codeine lacks analgesic potency, it is not useful for most patients. Remifentanyl has not been widely studied in ICU patients and requires the use of a continuous infusion because of its very short duration of action.<sup>35</sup> The short duration of action could be beneficial in selected patients requiring interruptions for neurologic examination.<sup>35</sup>

Disease states, such as renal or hepatic insufficiency may alter opioid and metabolite elimination. Titration to the desired response and assessment of the drug's prolonged effect are necessary in all patients. The elderly may have reduced opioid requirements.<sup>30,31,36–39</sup>

Adverse effects of opioid analgesics are common and occur frequently in ICU patients. Of greatest concern are respiratory, hemodynamic, central nervous system, and gastrointestinal effects. Respiratory depression is a concern in spontaneously breathing patients or those receiving partial ventilatory support. Hypotension can occur in hemodynamically unstable patients, hypovolemic patients, or those with elevated sympathetic tone.<sup>40</sup> Opioid-mediated hypotension in euvolemic patients is a result of the combination of sympatholysis, vagally mediated bradycardia, and histamine release (when using codeine, morphine, or meperidine).<sup>41,42</sup> Opioid-induced depression of the level of consciousness may cloud the clinical assessment of critically ill patients, and hallucinations may increase agitation in some patients. Gastric retention and ileus are common in critically ill patients, and intestinal hypomotility is enhanced by opioids.<sup>43,44</sup> Routine prophylactic use of a stimulant laxative may minimize constipation. Small-bowel intubation may be needed for enteral nutrition because of gastric hypomotility.<sup>45</sup> Opioids may increase intra-cranial pressure with traumatic brain injury, although the data are inconsistent and the clinical significance is unknown.<sup>46–48</sup>

**Opioid administration techniques.** Preventing pain is more effective than treating established pain. When patients are administered drugs on an "as needed" basis, they may receive less than the prescribed dose and encounter significant delays in treatment, although the impact on patient outcome has not been well documented.<sup>49</sup> Analgesics should be administered on a continuous or scheduled intermittent basis, with supplemental bolus doses as required.<sup>17</sup> Intravenous administration usually requires lower and more frequent doses than intramuscular administration to titrate to patient comfort. Intramuscular administration is not recommended in hemodynamically unstable

Table 1.  
**Pharmacology of Selected Analgesics**<sup>1,17,30-32</sup>

Agent	Equianalgesic Dose (i.v.)	Half-life	Metabolic Pathway	Active Metabolites (Effect)	Adverse Effects	Intermittent Dose <sup>a</sup>	Infusion Dose Range (Usual)	Infusion Cost per day 70 kg <sup>b</sup>
Fentanyl	200 µg	1.5-6 hr	Oxidation	No metabolite, parent accumulates	Rigidity with high doses	0.35-1.5 µg/kg i.v. q 0.5-1 hr	0.7-10 µg/kg/hr	100 µg/hr: \$26.00
Hydromorphone	1.5 mg	2-3 hr	Glucuronidation	None	...	10-30 µg/kg i.v. q 1-2 hr	7-15 µg/kg/hr	0.75 mg/hr: \$5.00-11.00
Morphine	10 mg	3-7 hr	Glucuronidation	Yes (sedation, especially in renal insufficiency)	Histamine release	0.01-0.15 mg/kg i.v. q 1-2 hr	0.07-0.5 mg/kg/hr	5 mg/hr: \$3.50-12.00
Meperidine	75-100 mg	3-4 hr	Demethylation and hydroxylation	Yes (neuroexcitation, especially in renal insufficiency or high doses)	Avoid with MAOIs <sup>c</sup> and SSRIs <sup>d</sup>	Not recommended	Not recommended	...
Codeine	120 mg	3 hr	Demethylation and glucuronidation	Yes (analgesia, sedation)	Lacks potency, histamine release	Not recommended	Not recommended	...
Remifentanyl	...	3-10 min	Plasma esterase	None	...	...	0.6-15 µg/kg/hr	10 µg/kg/hr: \$170.00
Ketorolac	...	2.4-8.6 hr	Renal	None	Risk of bleeding, GI and renal adverse effects	15-30 mg i.v. q 6hr, decrease if age > 65 yr or wt < 50 kg or renal impairment, avoid > 5 days use	...	...
Ibuprofen	...	1.8-2.5 hr	Oxidation	None	Risk of bleeding, GI and renal adverse effects	400 mg p.o. q 4-6 hr	...	...
Acetaminophen	...	2 hr	Conjugation	...	...	325-650 mg p.o. q 4-6 hr, avoid > 4 g/day	...	...

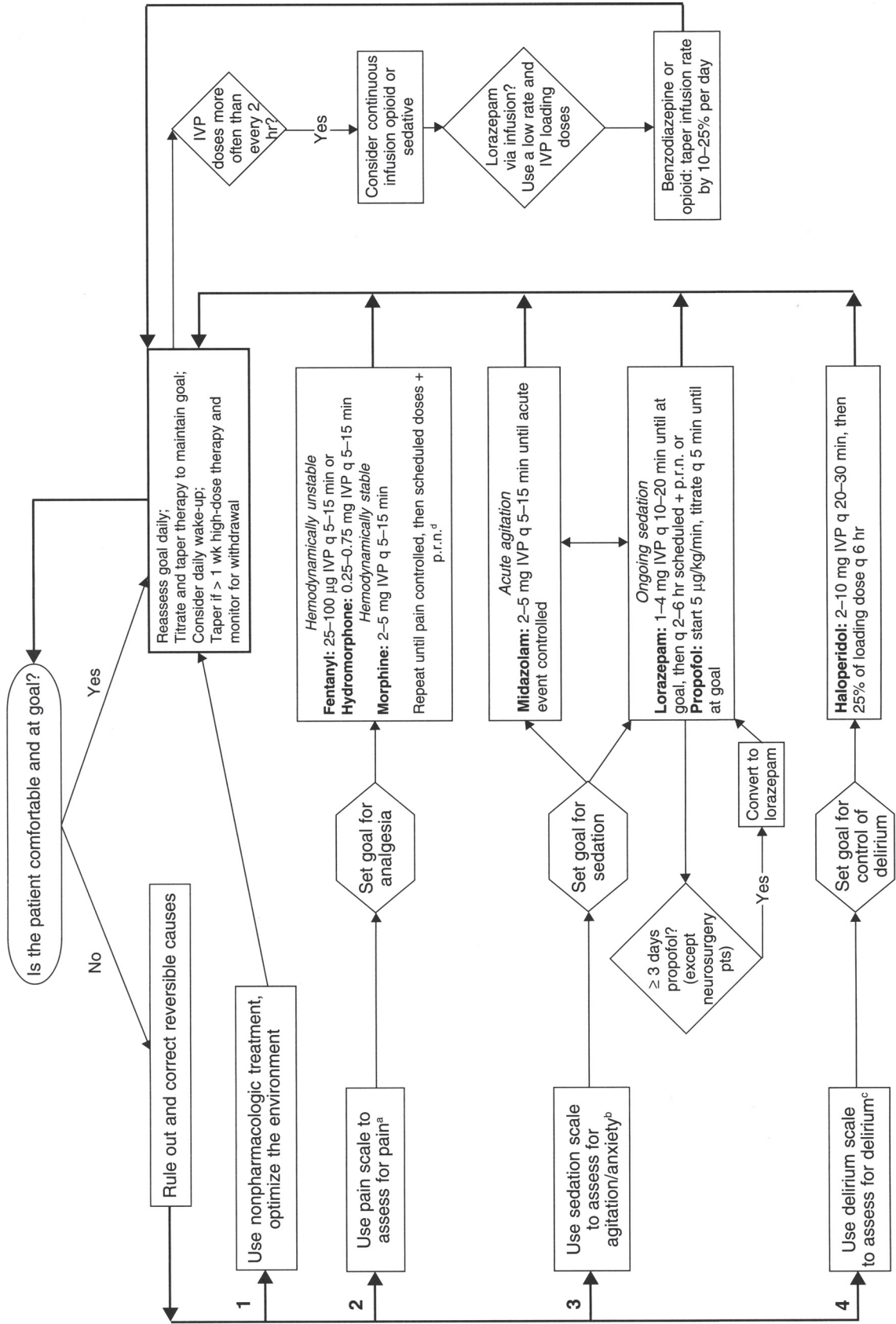
<sup>a</sup>More frequent doses may be needed for acute pain management in mechanically ventilated patients.

<sup>b</sup>Cost based on 2001 average wholesale price.

<sup>c</sup>MAOIs = monoamine oxidase inhibitors.

<sup>d</sup>SSRIs = selective serotonin-reuptake inhibitors.

**Figure 1.** Algorithm for the sedation and analgesia of mechanically ventilated patients. This algorithm is a general guideline for the use of analgesics and sedatives. Refer to the text for clinical and pharmacologic issues that dictate optimal drug selection, recommended assessment scales, and precautions for patient monitoring. Doses are approximate for a 70-kg adult. IVP = intravenous push.



<sup>a</sup>Numeric rating scale or other pain scale.<sup>18</sup>  
<sup>b</sup>Riker Sedation-Agitation Scale or other sedation scale.<sup>82</sup>  
<sup>c</sup>Confusion Assessment Method for the ICU.<sup>165</sup>  
<sup>d</sup>See Table 1 for intermittent dosing for specific agents.

patients because of altered perfusion and variable absorption. When a continuous infusion was used, a protocol incorporating daily awakening from analgesia and sedation allowed more effective analgesic titration and a lower total dose of morphine.<sup>50</sup> Daily awakening was associated with a shorter duration of ventilation and ICU stay.<sup>50</sup> A pain management plan and therapy goal should be established for each patient and reevaluated as the clinical condition changes. An algorithm that illustrates the potential use of opioid analgesics for mechanically ventilated patients is shown in Figure 1. Analgesic orders should be written to allow titration to achieve the analgesic goal and to balance the potential impact of adverse effects.

In noncritically ill patients, patient-controlled analgesia (PCA) has been reported to result in stable drug concentrations, a good quality of analgesia, less sedation, less opioid consumption, and potentially fewer adverse effects, including respiratory complications.<sup>10,51</sup> In addition, a basal rate or continuous infusion mode can be used for consistent analgesia during sleep. Patient selection is important when PCA is used, and particular attention should be paid to the patient's cognition, hemodynamic reserve, and previous opioid exposure. PCA devices can also be used for nurse-controlled analgesia. The elimination of paperwork can improve the timeliness of analgesic administration.

Fentanyl may also be administered via a transdermal patch in hemodynamically stable patients with more chronic analgesic needs. The patch provides consistent drug delivery, but the extent of absorption varies depending on the permeability, temperature, perfusion, and thickness of the skin. There is a large interpatient variability in peak plasma concentrations. Fentanyl patches are not a recommended modality for acute analgesia because of their 12–24-hour delay to peak effect and similar lag time to complete offset once the patch is removed. Breakthrough pain should be treated with rapid-acting agents.

The use of a reversal agent, such as naloxone, is not recommended after prolonged analgesia, because it can induce withdrawal and may cause nausea, cardiac stress, and arrhythmias. Analgesics with agonist–antagonist action, such as nalbuphine, butorphanol, and buprenorphine, can also elicit withdrawal symptoms and should be avoided during prolonged opioid use.

*Recommendations: A therapeutic plan and goal of analgesia should be established for each patient and communicated to all caregivers to ensure consistent analgesic therapy. (Grade of recommendation = C)*

*If intravenous doses of an opioid analgesic are required, fentanyl, hydromorphone, and morphine are the recommended agents. (Grade of recommendation = C)*

*Scheduled opioid doses or a continuous infusion is preferred over an “as needed” regimen to ensure consistent analgesia. A PCA device may be utilized to deliver opioids if the patient is able to understand and operate the device. (Grade of recommendation = B)*

*Fentanyl is preferred for a rapid onset of analgesia in acutely distressed patients. (Grade of recommendation = C)*

*Fentanyl or hydromorphone are preferred for patients with hemodynamic instability or renal insufficiency. (Grade of recommendation = C)*

*Morphine and hydromorphone are preferred for intermittent therapy because of their longer duration of effect. (Grade of recommendation = C)*

**Nonopioid analgesics.** NSAIDs provide analgesia via the nonselective, competitive inhibition of cyclooxygenase (COX), a critical enzyme in the inflammatory cascade. NSAIDs have the potential to cause significant adverse effects, including gastrointestinal bleeding, bleeding secondary to platelet inhibition, and the development of renal insufficiency. Patients with hypovolemia or hypoperfusion, the elderly, and those with preexisting renal impairment may be more susceptible to NSAID-induced renal injury.<sup>52,53</sup> Prolonged use (more than five days) of ketorolac has been associated with a twofold increase in the risk of renal failure and an increased risk of gastrointestinal and operative-site bleeding.<sup>54,55</sup> NSAIDs should not be administered to patients with asthma and aspirin sensitivity.

Administration of NSAIDs may reduce opioid requirements, although the analgesic benefit of NSAIDs has not been systematically studied in critically ill patients. Many oral agents are available, and ibuprofen and naproxen are available in liquid form. Ketorolac is currently the only parenteral NSAID. The safety of ketorolac administration in patients with severe renal insufficiency or those undergoing dialysis has not been determined.

The role, if any, of the more selective COX-2 inhibitors in the critically ill remains unknown. Selective COX-2 inhibiting agents cause less gastrointestinal irritation with long-term use than traditional NSAIDs.<sup>56</sup> The slow onset of action of some agents may decrease their utility for acute pain management.

Acetaminophen is an analgesic used to treat mild to moderate pain. In combination with an opioid, acetaminophen produces a greater analgesic effect than higher doses of the opioid alone.<sup>57</sup> The role of acetaminophen in critical care is limited to relieving mild pain or discomfort, such as that associated with prolonged bed rest or use as an antipyretic. Care must be taken to avoid excessive and potentially hepatotoxic doses, especially in patients with depleted glutathione stores resulting from hepatic dysfunction or malnutrition. Acetaminophen should be maintained at less than 2 g per day for patients with a significant history of alcohol intake or poor nutritional status and less than 4 g per day for others (Table 1).<sup>58</sup>

*Recommendations: NSAIDs or acetaminophen may be used as adjuncts to opioids in selected patients. (Grade of recommendation = B)*

*Ketorolac therapy should be limited to a maximum of five days, with close monitoring for the development of renal insufficiency or gastrointestinal bleeding. Other NSAIDs may be used via the enteral route in appropriate patients. (Grade of recommendation = B)*

## Sedation

The indications for sedative agents are not well defined. Sedatives are common adjuncts for the treatment of anxiety

and agitation. The causes of anxiety in critically ill patients are multifactorial and are likely secondary to an inability to communicate amid continuous noise (alarms, personnel, and equipment), continuous ambient lighting, and excessive stimulation (inadequate analgesia, frequent vital signs, repositioning, lack of mobility, and room temperature). Sleep deprivation and the circumstances that led to an ICU admission may increase patient anxiety, affecting up to 50% of ICU patients.<sup>38,59</sup> Efforts to reduce anxiety, including frequent reorientation, maintenance of patient comfort, provision of adequate analgesia, and optimization of the environment, may be supplemented with sedatives. Some patients with respiratory failure require sedation to facilitate mechanical ventilation, although sedation should not be used in lieu of appropriate ventilation strategies.

Agitation is common in ICU patients of all ages, occurring at least once in 71% of patients in a medical-surgical ICU.<sup>38</sup> Agitation can be caused by multiple factors, such as extreme anxiety, delirium, adverse drug effects, and pain.<sup>38</sup> However, not all patients with anxiety will exhibit agitation; some patients may be fearful, anxious, and withdrawn. When patients exhibit signs of anxiety or agitation, the first priority is to identify and treat any underlying physiological disturbances, such as hypoxemia, hypoglycemia, hypotension, pain, and withdrawal from alcohol and other drugs. The prevalence of drug and alcohol abuse in the general population is high, and these substances are commonly associated with traumatic injury.<sup>60–62</sup> Patients in the ICU should be assessed for symptoms of intoxication or withdrawal upon admission and for several weeks thereafter.<sup>60–62</sup> When possible, patients should be questioned about the use of herbal medicines because these products may contribute to significant drug interactions and adverse effects.<sup>63</sup>

Recent studies have confirmed that agitation may have a deleterious effect on patients by contributing to ventilator dyssynchrony, an increase in oxygen consumption, and inadvertent removal of devices and catheters.<sup>38,64–67</sup> Sedatives reduce the stress response and improve the tolerance of routine ICU procedures.<sup>68</sup> The use of sedatives to maintain patient safety and comfort is often essential to the ICU therapeutic care plan. The sedation of mechanically ventilated patients is often medically necessary and should be based on an individualized assessment and the patient's needs. Sedatives should be administered intermittently or on an "as needed" basis to determine the dose that will achieve the sedation goal. Sedatives, as outlined in this guideline, are not intended to be used as a method of restraint and are not to be "used as a means of coercion, discipline, convenience, or retaliation by staff" (Federal regulation 42 CFR 482.13). It is important to consider this principle in order to follow the intent of the Centers for Medicare and Medicaid Services regulation regarding restraints.

An analgesic may be the appropriate initial therapy when pain is the suspected cause of acute agitation. Although opioids may produce sedating effects, they do not diminish awareness or provide amnesia for stressful events. Sedative-amnestic therapy is required to reliably attain amnesia.<sup>69–72</sup> Without amnesia, many patients who recall their ICU stay report unpleasant or frightening memories, which may contribute to post-traumatic stress disorder (PTSD) symptoms.<sup>21,73</sup> However, some patients have vivid hypnagogic hallucinations (dreams just before loss of consciousness) with sedative-amnestic therapy.<sup>74</sup> As sedation blunts explicit memory, these hallucinations may be patients' only memory of the ICU experience.<sup>75</sup> Recalling

delusions, without memory of real events, may also contribute to acute PTSD-related symptoms.<sup>75</sup> Other data suggest that PTSD may be experienced by 4–15% of ICU survivors.<sup>76,77</sup> Amnestic sedatives may paradoxically contribute to agitation and disorientation because patients may not remember where they are or why they are in the ICU.

*Recommendation: Sedation of agitated critically ill patients should be started only after providing adequate analgesia and treating reversible physiological causes. (Grade of recommendation = C)*

**Sedation Assessment.** *Subjective assessment of sedation and agitation.* Frequent assessment of the degree of sedation or agitation may facilitate the titration of sedatives to predetermined endpoints.<sup>78–80</sup> An ideal sedation scale should provide data that are simple to compute and record, accurately describe the degree of sedation or agitation within well-defined categories, guide the titration of therapy, and have validity and reliability in ICU patients. Many scales are available, but a true gold-standard scale has not been established.<sup>79</sup> Several scales have construct validity with good correlation between the scales' measures and other measures of sedation. None of the scales have been tested for their ability to detect a patient's response to changes in sedative therapy, dosage, or withdrawal. However, a defined sedation goal, using the Ramsay scale and a protocol-driven sedation plan, was shown to reduce the duration of mechanical ventilation and length of stay.<sup>80</sup> The authors did not report other patient outcome measures relative to the adequacy of analgesia or sedation.

The Riker Sedation–Agitation Scale (SAS) was the first scale proven to be reliable and valid in critically ill adults.<sup>81,82</sup> SAS scores a patient's level of consciousness and agitation from a seven-item list describing patient behavior (Table 2). Excellent inter-rater reliability has been demonstrated and validity has been shown with two other scales. The Motor Activity Assessment Scale (MAAS), adapted from the SAS, has also been validated and shown reliable for use in critically ill patients.<sup>83</sup> The MAAS has seven categories to describe patient behaviors in response to stimulation (Table 2). The Ramsay scale measures three levels of awake states and three levels of asleep states (Table 2).<sup>84</sup> It has been shown to have an acceptable interrater reliability compared with the SAS, but has been criticized for its lack of clear discrimination and specific descriptors to differentiate between the various levels.<sup>82,85</sup> Nevertheless, the Ramsay scale has been used in many comparative sedation trials and is widely used clinically. The Vancouver Interaction and Calmness Scale (VICS) has also been validated for the assessment of sedation in adult critically ill patients.<sup>86</sup> With the VICS scoring system, patients are assessed independently for the ability to interact and communicate and for their level of activity or restlessness. The VICS has not been tested to identify optimal sedation endpoints. Another scale, the Observer's Assessment of Alertness/Sedation Scale, is often used in the operating room but lacks the ability to assess agitation and has never been tested in the ICU.<sup>87</sup> The COMFORT scale has been extensively tested and applied in the ICU environment, but only in children.<sup>88</sup>

The appropriate target level of sedation will primarily depend on a patient's acute disease process and any therapeutic and supportive interventions required. A common target level of sedation in the ICU is a calm patient that can be easily aroused with maintenance of the normal

Table 2.  
Scales Used to Measure Sedation and Agitation

Score	Description	Definition
Riker Sedation–Agitation Scale (SAS) <sup>82</sup>		
7	Dangerous agitation	Pulling at endotracheal tube (ETT), trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, biting ETT
5	Agitated	Anxious or mildly agitated, attempting to sit up, calms down to verbal instructions
4	Calm and cooperative	Calm, awakens easily, follows commands
3	Sedated	Difficult to arouse, awakens to verbal stimuli or gentle shaking but drifts off again, follows simple commands
2	Very sedated	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Minimal or no response to noxious stimuli, does not communicate or follow commands
Motor Activity Assessment Scale (MAAS) <sup>83</sup>		
6	Dangerously agitated	No external stimulus is required to elicit movement and patient is uncooperative pulling at tubes or catheters or thrashing side to side or striking at staff or trying to climb out of bed and does not calm down when asked
5	Agitated	No external stimulus is required to elicit movement and attempting to sit up or moves limbs out of bed and does not consistently follow commands (e.g., will lie down when asked but soon reverts back to attempts to sit up or move limbs out of bed)
4	Restless and cooperative	No external stimulus is required to elicit movement and patient is picking at sheets or tubes or uncovering self and follows commands
3	Calm and cooperative	No external stimulus is required to elicit movement and patient is adjusting sheets or clothes purposefully and follows commands
2	Responsive to touch or name	Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs when touched or name is loudly spoken
1	Responsive only to noxious stimulus <sup>a</sup>	Opens eyes or raises eyebrows or turns head toward stimulus or moves limbs with noxious stimulus
0	Unresponsive	Does not move with noxious stimulus
Ramsay Scale <sup>84</sup>		
1	Awake	Patient anxious and agitated or restless or both
2		Patient cooperative, oriented and tranquil
3		Patient responds to commands only
4	Asleep	A brisk response to a light glabellar tap or loud auditory stimulus
5		A sluggish response to a light glabellar tap or loud auditory stimulus
6		No response to a light glabellar tap or loud auditory stimulus

<sup>a</sup>Noxious stimulus = suctioning or 5 seconds of vigorous orbital, sternal, or nail bed pressure.

sleep–wake cycle, but some may require deep levels of sedation to facilitate mechanical ventilation. The desired level of sedation should be defined at the start of therapy and re-evaluated on a regular basis as the clinical condition of the patient changes. Regimens should be written with the appropriate flexibility to allow titration to the desired endpoint, anticipating fluctuations in sedation requirements throughout the day.

**Objective assessment of sedation.** Objective testing of a patient's level of sedation may be helpful during very deep sedation or when therapeutic neuromuscular blockade masks observable behavior. Vital signs, such as blood pressure and heart rate, are not specific or sensitive markers of the level of sedation among critically ill patients. Tools utilized in objective assessment include heart rate variability and lower-esophageal contractility, but most are based on a patient's electroencephalogram (EEG). The raw EEG signal has been manipulated in several devices to simplify bedside interpretation and improve reliability. For example, the bispectral index (BIS) uses a digital scale from 100 (completely awake) to 0 (isoelectric EEG).<sup>89</sup> Most of the literature about the use of BIS in the operating room supports strong agreement between BIS and patient recall or level of hypnosis.<sup>90</sup> Elective

surgery patients receiving sedatives have shown a strong inverse correlation between hypnotic drug effect and BIS.<sup>91,92</sup>

Although the BIS may be a promising tool for the objective assessment of sedation or hypnotic drug effect, it has limitations in the ICU environment.<sup>93–95</sup> BIS scores may vary between patients at the same subjective level of sedation, and subjective scales may be more reproducible during light sedation.<sup>93,94</sup> Muscle-based electrical activity may artificially elevate BIS scores if the patient has not received neuromuscular blockade.<sup>94</sup> A new version of BIS software is being tested for improved applicability in measuring ICU sedation. BIS has not been tested in patients with metabolic impairments or structural abnormalities of the brain. Studies have not compared the patient outcomes of using BIS versus subjective scales. Although BIS is likely to be useful when patients are deeply comatose or under neuromuscular blockade, routine use of this device cannot be recommended until the value and validity are confirmed.

*Recommendations: A sedation goal or endpoint should be established and regularly redefined for each patient. Regular assessment and response to therapy should be systematically documented. (Grade of recommendation = C)*

The use of a validated sedation assessment scale (SAS, MAAS, or VICS) is recommended. (Grade of recommendation = B)

Objective measures of sedation, such as BIS, have not been completely evaluated and are not yet proven useful in the ICU. (Grade of recommendation = C)

**Sedation Therapy. Benzodiazepines.** Benzodiazepines are sedatives and hypnotics that block the acquisition and encoding of new information and potentially unpleasant experiences (anterograde amnesia) but do not induce retrograde amnesia. Although they lack any analgesic properties, they have an opioid-sparing effect by moderating the anticipatory pain response.<sup>96,97</sup> Benzodiazepines vary in their potency, onset and duration of action, uptake, distribution, metabolism, and presence or absence of active metabolites (Table 3). Patient-specific factors, such as age, concurrent pathology, prior alcohol abuse, and concurrent drug therapy, affect the intensity and duration of activity of benzodiazepines, requiring individualized titration. Elderly patients exhibit slower clearance of benzodiazepines or their active metabolites and have a larger volume of drug distribution, contributing to a marked prolongation of elimination.<sup>111</sup> Compromised hepatic or renal function may slow the clearance of benzodiazepines or their active metabolites. Induction or inhibition of hepatic or intestinal enzyme activity can alter the oxidative metabolism of most benzodiazepines.<sup>112</sup>

Benzodiazepine therapy should be titrated to a predefined endpoint, often requiring a series of loading doses. Hemodynamically unstable patients may experience hypotension with the initiation of sedation. Maintenance of sedation with intermittent or “as needed” doses of diazepam, lorazepam, or midazolam may be adequate to accomplish the goal of sedation.<sup>78</sup> However, patients requiring frequent doses to maintain the desired effect may benefit from a continuous infusion by using the lowest effective infusion dose. Continuous infusions must be used cautiously, as accumulation of the parent drug or its active metabolites may produce inadvertent oversedation. Frequent reassessment of a patient’s sedation requirements and active tapering of the infusion rate can prevent prolonged sedative effects.<sup>80</sup> However, awakening times after several days of sedation may be quite unpredictable in clinical use. In contrast, tolerance to benzodiazepines may occur within hours to several days of therapy, and escalating doses of midazolam have been reported.<sup>113,114</sup> While not well described in the literature, paradoxical agitation has also been observed during light sedation and may be the result of drug-induced amnesia or disorientation.

Diazepam has been shown to provide rapid onset and awakening after single doses (Table 3).<sup>78,115</sup> Because of its long-acting metabolites, a prolonged duration of sedative effect may occur with repeated doses, but this may be acceptable for long-term sedation.<sup>78</sup> Lorazepam has a slower onset but fewer potential drug interactions because of its metabolism via glucuronidation (Table 3).<sup>98,112</sup> The slow onset makes lorazepam less useful for the treatment of acute agitation. Maintenance of sedation can be accomplished with intermittent or continuous intravenous administration. Lorazepam has an elimination half-life of 12–15 hours, so an infusion is not readily titratable. Loading doses given by i.v. push should be used initially with relatively fixed infu-

Table 3. Pharmacology of Selected Sedatives<sup>1,30-32,98-110</sup>

Agent	Onset After i.v. Dose	Half-life of Parent Compound	Metabolic Pathway	Active Metabolite	Unique Adverse Effects	Intermittent i.v. Dose <sup>a</sup>	Infusion Dose Range (Usual)	Cost per day 70 kg patient <sup>b</sup>
Diazepam	2–5 min	20–120 hr	Desmethylation and hydroxylation	Yes (prolonged sedation)	Phlebitis	0.03–0.1 mg/kg q 0.5–6 hr	...	20 mg q 4 hr: \$5.00–20.50
Lorazepam	5–20 min	8–15 hr	Glucuronidation	None	Solvent-related acidosis/renal failure in high doses	0.02–0.06 mg/kg q 2–6 hr	0.01–0.1 mg/kg/hr	48 mg/day: \$55.00
Midazolam	2–5 min	3–11 hr	Oxidation	Yes (prolonged sedation, especially with renal failure)	...	0.02–0.08 mg/kg q 0.5–2 hr	0.04–0.2 mg/kg/hr	6 mg/hr: \$65.00–309.00
Propofol	1–2 min	26–32 hr	Oxidation	None	Elevated triglycerides, pain on injection	...	5–80 µg/kg/min	50 µg/kg/min: \$235.00–375.00
Haloperidol	3–20 min	18–54 hr	Oxidation	Yes (EPS) <sup>c</sup>	QT interval prolongation	0.03–0.15 mg/kg q 0.5–6 hr	0.04–0.15 mg/kg/hr	10 mg q 6 h: \$62.00–65.00

<sup>a</sup>More frequent doses may be needed for management of acute agitation in mechanically ventilated patients.

<sup>b</sup>Cost based on 2001 average wholesale price.

<sup>c</sup>EPS = extrapyramidal symptoms.

sion rates. Lorazepam infusions should be prepared using the 2 mg/mL injection and diluted to a concentration of 1 mg/mL or less and mixed in a glass bottle.<sup>116,117</sup> Despite these precautions, precipitation may develop.<sup>118</sup> An alternative is to administer undiluted lorazepam as an infusion using a PCA device.<sup>78</sup> The lorazepam solvents polyethylene glycol (PEG) and propylene glycol (PG) have been implicated as the cause of reversible acute tubular necrosis, lactic acidosis, and hyperosmolar states after prolonged high-dose infusions. The dosing threshold for this effect has not been prospectively defined, but these case reports described doses that exceeded 18 mg/hr and continued for longer than four weeks and higher doses (>25 mg/hr) continuing for hours to days.<sup>119–121</sup> It seems prudent to avoid doses of this magnitude. Alternatively, lorazepam and diazepam may be administered via the enteral route in tablet or liquid form.<sup>122</sup> Large doses of liquid lorazepam (i.e., 60 mg of 2 mg/mL every six hours) may lead to diarrhea because of the high PEG and PG content.<sup>123</sup>

Midazolam has a rapid onset and short duration with single doses, similar to diazepam (Table 3).<sup>115</sup> The rapid onset of midazolam makes it preferable for treating acutely agitated patients. Accumulation and prolonged sedative effects have been reported in critically ill patients using midazolam who are obese or have a low albumin level or renal failure.<sup>99–103</sup> Prolonged sedative effects may also be caused by the accumulation of an active metabolite, alpha-hydroxymidazolam, or its conjugated salt, especially in patients with renal insufficiency.<sup>101–105</sup> Significant inhibition of midazolam metabolism has been reported with propofol, diltiazem, macrolide antibiotics, and other inhibitors of cytochrome P450 isoenzyme 3A4, which could influence the duration of effect.<sup>107,108,112</sup> Daily discontinuation of midazolam infusions (wake up) with retitration to a Ramsay scale endpoint reduced midazolam requirements and was associated with a reduction in the duration of mechanical ventilation and length of ICU stay.<sup>50</sup> However, the patients in this trial were off of midazolam for an average of 5.3 hours per day, so this research technique may be difficult to implement. Patients should be closely monitored for self-extubation or the removal of other monitoring devices during the daily awakening sessions.

The routine use of a benzodiazepine antagonist, such as flumazenil, is not recommended after prolonged benzodiazepine therapy because of the risks of inducing withdrawal symptoms and increasing myocardial oxygen consumption with as little as 0.5 mg of flumazenil.<sup>124</sup> An i.v. dose of flumazenil 0.15 mg is associated with few withdrawal symptoms when administered to patients receiving midazolam infusions.<sup>125</sup> If flumazenil is used to test for prolonged sedation after several days of benzodiazepine therapy, a single low dose is recommended.

**Propofol.** Propofol is an intravenous, general anesthetic agent. However, sedative and hypnotic properties can be demonstrated at lower doses. Compared with benzodiazepines, propofol produces a similar degree of amnesia at equisedative doses in volunteers.<sup>69</sup> In a clinical trial of ICU patients, propofol did not produce amnesia as often as midazolam.<sup>70</sup> Like the benzodiazepines, propofol has no analgesic properties.

Propofol has a rapid onset and short duration of sedation once discontinued (Table 3). While most of the early literature documents the comparatively rapid resolution of sedation after propofol infusions, a slightly longer recovery has been reported after more than 12 hours of infusion.<sup>110,126</sup>

No changes in kinetic parameters have been reported in patients with renal or hepatic dysfunction.

Propofol is available as an emulsion in a phospholipid vehicle, which provides 1.1 kcal/mL from fat and should be counted as a caloric source. Long-term or high-dose infusions may result in hypertriglyceridemia.<sup>127–129</sup> Other adverse effects most commonly seen with propofol include hypotension, bradycardia, and pain upon peripheral venous injection. The hypotension is dose related and more frequent after bolus dose administration. Elevation of pancreatic enzymes has been reported during prolonged infusions of propofol.<sup>130,131</sup> Pancreatitis has been reported following anesthesia with propofol, although a causal relationship has not been established.<sup>132</sup> Prolonged use (>48 hours) of high doses of propofol (>66 µg/kg/min infusion) has been associated with lactic acidosis, bradycardia, and lipidemia in pediatric patients and doses >83 µg/kg/min have been associated with an increased risk of cardiac arrest in adults.<sup>133,134</sup> The adults at highest risk for cardiac complications received > 100 µg/kg/min infusion of a 2% propofol solution to achieve deep sedation after neurologic injury.<sup>134</sup> FDA has specifically recommended against the use of propofol for the prolonged sedation of pediatric patients. Patients receiving propofol should be monitored for unexplained metabolic acidosis or arrhythmias.

Alternative sedative agents should be considered for patients with escalating vasopressor or inotrope requirements or cardiac failure during high-dose propofol infusions.

Propofol requires a dedicated i.v. catheter when administered as a continuous infusion because of the potential for drug incompatibility and infection. Improper aseptic technique with propofol in the operating room has led to nosocomial postoperative infection.<sup>135</sup> However, a clinically relevant incidence of infectious complications has not been reported with ICU use.<sup>136</sup> The manufacturers suggest that propofol infusion bottles and tubing should hang no more than 12 hours and solutions transferred from the original container should be discarded every 6 hours. A preservative has been added to propofol to decrease the potential for bacterial overgrowth in case the vial would become contaminated. One of the propofol formulations contains edetic acid (Diprivan, AstraZeneca) and the manufacturer recommends a drug holiday after more than seven days of infusion to minimize the risk of trace element abnormalities. Another product (propofol, Gensia Sisor) contains sodium metabisulfite, which may produce allergic reactions in susceptible patients. Sulfite sensitivity occurs more frequently in patients with asthma.

While propofol appears to possess anticonvulsant activity, excitatory phenomena, such as myoclonus, have been observed. There are several case reports and small, uncontrolled studies describing the efficacy of propofol in refractory status epilepticus (after traditional treatment regimens have failed or are not tolerated) and electroconvulsive shock therapy.<sup>137,138</sup> Case reports have also described roles for propofol in delirium tremens refractory to high-dose benzodiazepine therapy.<sup>139</sup>

Propofol has been used to sedate neurosurgical patients to reduce elevated intracranial pressure (ICP).<sup>140,141</sup> The rapid awakening from propofol allows interruption of the infusion for neurologic assessment. Propofol may also decrease cerebral blood flow and metabolism. Propofol and morphine produced improved control of ICP compared with morphine alone in the treatment of severe traumatic brain injury (TBI).<sup>141</sup> Propofol reduced elevated ICP more effectively than fentanyl following severe TBI.<sup>142</sup> High doses of propofol should be used cautiously in this setting.<sup>134</sup>

Propofol infusions used to reduce elevated ICP may need to be continued longer than usually recommended for routine sedation.<sup>141</sup>

**Central  $\alpha$ -agonists.** Clonidine has been used to augment the effects of general anesthetics and narcotics and to treat drug withdrawal syndromes in the ICU.<sup>143–148</sup> The more selective  $\alpha$ -2 agonist, dexmedetomidine, was recently approved for use as a sedative with analgesic-sparing activity for short-term use (<24 hours) in patients who are initially receiving mechanical ventilation. Patients remain sedated when undisturbed, but arouse readily with gentle stimulation. Dexmedetomidine reduces concurrent analgesic and sedative requirements and produces anxiolytic effects comparable to benzodiazepines.<sup>145–148</sup> Rapid administration of dexmedetomidine may produce transient elevations in blood pressure. Patients maintained on dexmedetomidine may develop bradycardia and hypotension, especially in the presence of intravascular volume depletion or high sympathetic tone. The role of this new agent in the sedation of ICU patients remains to be determined.

**Sedative Selection.** Acute agitation arises from a variety of etiologies, including pain. A short-acting opioid analgesic, such as fentanyl, may provide immediate sedation and patient comfort; however, fentanyl has not been compared with other sedatives in a controlled trial. Midazolam and diazepam also have a rapid onset of sedation.<sup>115</sup> Propofol has a rapid onset, but hypotension and infusion-site pain can result from bolus dose administration. Cautious use of sedatives is recommended for patients not yet intubated because of the risk of respiratory depression.

Comparative trials of prolonged sedation have been performed in a variety of critical care settings. Many were supported by pharmaceutical industry research grants; as a result, newer products have been evaluated more frequently. Outcome is usually described in terms of the speed of onset, ability to maintain the target level of sedation, adverse effects, time required for awakening, and ability to wean from mechanical ventilation. Most of the prospective, randomized trials are experimentally flawed because they are unblinded, use uncontrolled amounts of opioids, and exclude patients with obesity or renal or hepatic insufficiency. This limits their general applicability. There is a need for more large, high-quality, randomized trials of the effectiveness of different sedative agents.<sup>149</sup> Most of the trials used a Ramsay scale for assessment, so the depth of sedation can generally be compared among the trials. The trials are summarized in Tables 4–6.

**Duration of therapy.** Short-term (<24 hours), randomized, open-label trials of sedation have compared propofol and midazolam most often (eight of nine trials) (Table 4). An opioid was available to all patients. Awakening times for patients taking propofol ranged from 1 to 105 minutes versus 1 to 405 minutes for patients receiving midazolam.<sup>128,150–157</sup> Time to extubation has also been compared, but other variables may influence this outcome measure. Clinically, these agents produced similar outcomes following <24 hours of infusion (Table 4).

An intermediate duration of sedation (one to three days) was reported in three randomized open-label trials (Table 5). Propofol and midazolam were compared for sedation of medical ICU patients and a mixed medical–surgical ICU population with respiratory failure.<sup>157,158</sup> Patients receiving propofol had statistically more predictable awakening times than patients receiving midazolam in both trials. Clinically, this time difference was not as significant and did not produce more

rapid discharge from the ICU.<sup>157</sup> In a three-way comparison of midazolam, lorazepam, and propofol infusions for sedation of surgical ICU patients, the authors concluded that lorazepam was the preferred agent in this population.<sup>118</sup> Overall, these agents were similar in the levels of sedation provided, the time required to achieve adequate sedation, and the number of dose adjustments per day. However, midazolam produced adequate sedation during a greater percentage of time while propofol was associated with more undersedation and lorazepam with more oversedation. Morphine was provided on an as needed basis and the average dose was similar in all three groups. Awakening times were not reported. Precipitation of lorazepam infusions was reported.<sup>118</sup>

Nine open-label, randomized trials comparing long-term sedation (more than three days) were reviewed in these guidelines (Table 6).<sup>70,127–129,157,159–163</sup> Most of the trials compared propofol with midazolam. All trials included opioid therapy, although administration was not controlled. Most studies used a Ramsay scale for patient assessment. In these trials, propofol consistently produced more rapid awakening than midazolam with a statistical and, probably, a clinical difference.<sup>70,127–129,160,161</sup> Propofol patients awakened and were extubated in 0.25–4 hours while midazolam patients required 2.8–10 hours to awaken and up to 49 hours for extubation (Table 6).<sup>157</sup> The greatest difference in time to awakening was seen when a deep level of sedation was the goal of therapy (Ramsay level 4–5). Patients receiving propofol awakened from deep sedation significantly faster than those receiving midazolam.<sup>127–129</sup> Lorazepam and midazolam were also compared for long-term sedation.<sup>159,162</sup> One of these studies used a double-blind study design.<sup>162</sup> There was no statistically significant difference in awakening time between these agents when titrated to similar levels of sedation, although the awakening times associated with lorazepam appeared to be more predictable.

**Sedative comparison.** Four trials compared lorazepam with midazolam.<sup>118,154,159,162</sup> Intermittent lorazepam doses produced sedation comparable to a midazolam infusion during an eight-hour observation period.<sup>154</sup> Both lorazepam and midazolam have the potential to cause accumulation and prolonged drug effects or oversedation if administered excessively via continuous infusion, especially when deep levels of sedation are attempted.<sup>118,159</sup> However, a rigorous protocol of assessment and titration of lorazepam infusions to moderate levels of sedation produced a less variable awakening time with lorazepam than with midazolam, although the absolute difference in awakening time was not statistically significant.<sup>159</sup> A nurse-managed sedation protocol, which included the active titration of lorazepam infusions to a defined endpoint, avoided a prolonged sedative effect compared with physician management of infusion rates.<sup>80</sup> A blinded trial of lorazepam versus midazolam found that the lorazepam infusions were easier to manage than midazolam infusions because fewer dose adjustments were required to maintain the desired level of sedation.<sup>162</sup> In this trial, wide inter- and inpatient variability was noted between sedative plasma concentrations and the Ramsay score. No difference was noted in patient recovery when patients were evaluated for 24 hours after the end of the infusion. Awakening times were not reported in two of the other trials.<sup>118,154</sup>

When titrated to a standard endpoint, midazolam and propofol provide comparable levels of sedation with a similar onset of effect.<sup>128,150–153,155–157</sup> As shown in Table 4,

Table 4. Clinical Trials with Less Than 24 Hours of Sedation<sup>a</sup>

Level of Evidence (Reference)	Population Type (No. Patients)	Exclusion Criteria	Trial Design	Drugs	Mean Dosage	Actual Duration	Sedation Endpoint or Goal	Outcome Measure	Significance or Conclusion
1 (150)	MICU/SICU (100)	Obese, head injury, NMBA use	Multicenter, open-label	Propofol Midazolam Morphine: to all patients	Propofol: 1.77 mg/kg/hr Midazolam: 0.1 mg/kg/hr	Propofol: 20.2 hr Midazolam: 21.3 hr	Ramsay level 2-4	Awakening time: most awake at end of infusion, longest: Propofol: 105 min, Midazolam: 405 min	No statistical analysis reported
2 (128)	MICU/SICU (88 total, 40 short-term sedation)	Neurologic injury, ongoing NMBA use	Open-label	Propofol Midazolam Morphine: to all patients	Propofol: 2.3 mg/kg/hr Midazolam: 0.17 mg/kg/hr	Propofol: 11.9 hr Midazolam: 11.9 hr	Ramsay level 2-5 and modified GCS	Time to extubation: Propofol: 0.3 hr Midazolam: 2.5 ± 0.9 hr	$p < 0.05$ , Propofol more rapid extubation
2 (151)	CABG (30)	Obese, renal or hepatic insufficiency	Open-label	Propofol Midazolam Sufentanil: to all patients	Propofol: 2.71 ± 1.13 mg/kg/hr Midazolam: 0.09 ± 0.03 mg/kg/hr	Propofol: 9.5 hr Midazolam: 9.8 hr	Ramsay level 5	Time to extubation: Propofol: 250 ± 135 min Midazolam: 391 ± 128 min	$p < 0.01$ , Propofol more rapid extubation
1 (152)	CABG (84)	Renal or hepatic insufficiency	Open-label	Propofol Midazolam Morphine: p.r.n.	Propofol: 0.7 ± 0.09 mg/kg/hr Midazolam: 0.018 ± 0.001 mg/kg/hr	Propofol: 9.2 hr Midazolam: 9.4 hr	Ramsay level 3	Time to extubation: Propofol: 4.3 hr Midazolam: 3.5 hr	Not statistically significant
1 (153)	SICU (60)	None	Open-label, consecutive patients	Propofol Midazolam Morphine: p.r.n.	Propofol: 114.8 mg/hr (80.1 ± 21.1 kg) Midazolam: 2.1 ± 1.3 mg/hr (74.2 ± 24 kg)	16 hr observation, total sedation duration not defined	Ramsay level 3 and response to stimulation	Postsedation score at 5, 30, 60, and 90 min: Propofol scores lower at 5 and 30 min	$p < 0.05$ , Midazolam more heavily sedated
1 (154)	MICU/SICU (61% trauma)	Cardiac insufficiency, neurosurgical or unstable	Multicenter, open-label	Lorazepam Midazolam Morphine: p.r.n.	Lorazepam: 1.6 ± 0.1 mg i.v. push Midazolam: 14.4 ± 1.2 mg infusion over 8 hr	8 hr	Multiple scales: anxiety, amnesia, pain, GCS, Ramsay level 3	Adequacy of sedation	Comparable sedation scores

(Continued on next page)

Table 4. (Continued)

Level of Evidence (Reference)	Population Type (No. Patients)	Exclusion Criteria	Trial Design	Drugs	Mean Dosage	Actual Duration	Sedation Endpoint or Goal	Outcome Measure	Significance or Conclusion
1 (155)	Cardiac surgery (41)	Renal, hepatic, or cardiac failure	Double-blind	Propofol Midazolam Morphine: p.r.n.	Propofol: 0.64 ± 0.17 mg/kg/hr Midazolam: 0.015 ± 0.001 mg/kg/hr	Propofol: 4 hr Midazolam: 4 hr	Ramsay level 2-4	Awakening time: Propofol: 88.6 ± 51 min Midazolam: 93.8 ± 59.4 min	Not statistically significant
1 (156)	CABG (75)	Renal failure, neurologic history, hepatic failure, cardiovascular dysfunction	Double-blind	Propofol Midazolam Both Propofol and Midazolam Morphine: to all patients	Propofol: 1.2 ± 0.03 mg/kg/hr Midazolam: 0.08 ± 0.01 mg/kg/hr Propofol: and Midazolam: Propofol: 0.22 ± 0.33 mg/kg/hr, Midazolam: 0.02 mg/kg/hr	Propofol: 14.4 hr Midazolam: 14.1 hr Propofol and Midazolam: 14.7 hr	Modified GCS	Time to extubation: Propofol: 0.9 ± 0.3 hr Midazolam: 2.3 ± 0.8 hr Propofol and Midazolam: 1.2 ± 0.6 hr	p = 0.01, Midazolam vs. Propofol or Propofol and Midazolam
2 (157)	MICU/SICU (99)	Neurosurgery, coma, seizures	Multicenter, open-label, intention-to-treat analysis	Propofol Midazolam Opiates: p.r.n.	Actual doses not specified	≤24 hr - post hoc stratum Propofol: n = 21 Midazolam: n = 26	Ramsay scale, level was specified daily	Time to extubation: Propofol: 5.6 hr Midazolam: 11.9 hr	p = 0.029 Overall: Propofol: 60.2% of time at target Ramsay score Midazolam: 44% of time at target Ramsay score, p < 0.05

<sup>a</sup>MICU = medical intensive care unit, SICU = surgical intensive care unit, NMBA = neuromuscular blocking agent, GCS = Glasgow Coma Score, CABG = coronary artery bypass graft.

there is generally no statistical or clinical difference in awakening times between propofol and midazolam when used for short-term sedation. Data from longer trials of sedation (more than 72 hours) suggest that propofol is associated with more reliable and rapid awakening, both statistically and clinically, than midazolam.<sup>106,127,128,156,158,160</sup>

Following long-term sedation, propofol awakening times ranged from 0.25 to 2.5 hours and midazolam awakening times ranged from 2.8 to 30 hours (Table 6). One center's comparison of two concentrations of propofol (1% and 2%) versus midazolam used in trauma patients has shown that midazolam provides deep levels of sedation more reliably than propofol, but the awakening times were much longer with midazolam.<sup>127,163</sup>

More patients receiving 1% propofol experienced failure because of elevated triglycerides, but the 2% propofol group experienced failure because of inadequate sedation. Failure of propofol to provide adequate sedation of trauma patients was reported elsewhere, although an explanation was not apparent.<sup>118</sup>

*Economic comparison.* Several of these studies presented limited pharmacoeconomic data. In most reports, the sedative costs were the only costs considered (cost minimization).<sup>118,154-156,162</sup> Some studies included a portion of the costs for ICU patient care.<sup>128,161</sup> A sedative with a low acquisition cost may be cited as the least expensive agent for prolonged sedation (e.g., lorazepam).<sup>1,32,118</sup> A complete economic analysis should consider costs associated with the evaluation and treatment of sedation-induced adverse effects (e.g., prolonged sedation, infection, and hypertriglyceridemia), therapy failures (additional agents or high doses required), and drug preparation and administration costs (precipitation and tubing changes) to determine the total cost of therapy. The cost of sedation-induced prolongation of ventilation or length of ICU stay is likely to reduce the potential difference in acquisition costs between benzodiazepines and propofol.<sup>164</sup> Institutional variables

Table 5. Clinical Trials with One to Three Days of Sedation<sup>a</sup>

Level of Evidence (Reference)	Population (No. Patients)	Exclusion Criteria	Design	Drugs	Mean Dosage	Actual Duration	Sedation Endpoint/Goal	Outcome Measure	Significance/Conclusion
1 (158)	MICU with respiratory failure (73)	...	Open-label	Propofol Midazolam Morphine: p.r.n.	Propofol: 1.25 ± 0.87 mg/kg/hr Midazolam: 3.1 ± 3.2 mg/hr	Up to 3 days	Behavior scale	Awakening: defined by eye opening ability to follow with eyes, hand grasp, and tongue protrusion	Many awake during infusion, Propofol: smaller range of awakening times. Used daily wake-up to reassess patients
2 (118)	Surgical or Trauma ICU (31)	Alcohol abuse, head injury, dialysis	Open-label	Propofol Midazolam Lorazepam Morphine: p.r.n.	Propofol: 2 ± 1.5 mg/kg/hr Midazolam: 0.04 ± 0.03 mg/kg/hr Lorazepam: 0.02 ± 0.01 mg/kg/hr	Propofol: 86.4 ± 72 hr Midazolam: 60 ± 72 hr Lorazepam: 72 ± 52.8 hr	Ramsay level 2–4	Time with adequate sedation: Midazolam: 79% Propofol: 62% Lorazepam: 68%	Lorazepam vs. midazolam $p = 0.03$ Midazolam vs. Propofol $p = 0.01$ Propofol: more undersedation Lorazepam: 31% more over-sedation 14% and precipitation 18%
2 (157)	MICU or SICU (99)	Neurosurgery, coma, seizures	Multicenter, Open-label, intention-to-treat analysis	Propofol Midazolam Opioids: p.r.n.	Actual doses not specified	24–72 hr = post hoc stratum Propofol: $n = 21$ Midazolam: $n = 17$	Ramsay scale, level was specified daily	Time to extubation Propofol: 7.4 hr Midazolam: 31.3 hr	$p = 0.068$ , Enrollment ended early, insufficient power. Overall: Propofol: 60.2% of time at target Ramsay score Midazolam: 44% of time at target Ramsay score, $p < 0.05$

<sup>a</sup>MICU = medical intensive care unit, ICU = intensive care unit, SICU = surgical intensive care unit.

Table 6. Clinical Trials of More Than Three Days of Sedation

Level of Evidence (Reference)	Population (No. Patients)	Exclusion Criteria	Design	Drugs	Mean Dosage	Actual Duration	Sedation Endpoint/Goal	Outcome Measure	Significance/Conclusion
2 (128)	MICU/SICU <sup>a</sup> (88 total, 28 medium-term, 20 long-term sedation)	Neurologic injury, ongoing NMBA use	Open-label	Propofol Midazolam Morphine: to all patients	Propofol 2.3 mg/kg/hr Midazolam 0.17 mg/kg/hr	Medium: Propofol: 116 hr Midazolam: 113 hr Long Propofol: 312 hr Midazolam: 342 hr	Ramsay level 2-5 and modified GCS	Time to extubation: Medium: Propofol: 0.4 ± 0.1 hr Midazolam: 13.5 ± 4 hr Long: Propofol: 0.8 ± 0.3 hr Midazolam: 36.6 ± 6.8 hr	Medium: $p < 0.05$ Long: $p < 0.05$
1 (159)	MICU (20)	CNS abnormal	Open-label	Lorazepam Midazolam Morphine: to all patients	Lorazepam: 0.06 ± 0.04 mg/kg/hr Midazolam: 0.24 ± 0.16 mg/kg/hr	Lorazepam: 77 hr Midazolam: 108 hr	Ramsay level 2-3	Return to baseline mental status: Lorazepam: 261 ± 189 min, Midazolam: 1815 ± 2322 min	Not statistically significant
1 (160)	MICU/SICU (98)	Renal, hepatic, or cardiac failure, ongoing NMBA use	Open-label, multicenter	Propofol Midazolam Morphine: p.r.n.	Propofol: 2.8 ± 1.1 mg/kg/hr Midazolam: 0.14 ± 0.1 mg/kg/hr	Propofol: 81 hr Midazolam: 88 hr	Own sedation scale	Awakening lightly sedated: Propofol: 14 ± 0.8 min Midazolam: 64 ± 20 min Deep sedation: Propofol: 27 ± 16 min Midazolam: 237 ± 222 min	Light: $p < 0.05$ Heavy: $p < 0.01$
1 (129)	MICU/SICU (108 consecutive)	Chronic liver disease, head injury, ongoing NMBA use	Open-label	Propofol Midazolam Morphine: to all patients	Propofol: 3.07-5.7 mg/kg/hr Midazolam: 14 ± 0.1 mg/kg/hr	Propofol: 139 hr Midazolam: 141 hr	Ramsay level 4-5	Time to t-tube Propofol: 4 ± 3.9 hr Midazolam: 48.9 ± 47.2 hr	$p = 0.0001$ Propofol: high triglycerides 12% men, 50% women

(Continued on next page)

Table 6 (continued)

Level of Evidence (Reference)	Population (No. Patients)	Exclusion Criteria	Design	Drugs	Mean Dosage	Actual Duration	Sedation Endpoint/Goal	Outcome Measure	Significance/Conclusion
2 (70)	MICU/SICU (68 consecutive)	None	Open-label	Propofol Midazolam Morphine: p.r.n.	Propofol: 1.8 ± 0.08 mg/kg/hr Midazolam: 0.07 ± 0.003 mg/kg/hr	Propofol: 99 hr Midazolam: 141 hr	Ramsay level 2–3 also rated amnesia	Awakening: Propofol: 1.8 ± 0.4 hr Midazolam: 2.8 ± 0.4 hr Amnesia: Propofol: 29% Midazolam: 100%	$p < 0.02$ More propofol patients with agitation upon awakening
2 (161)	MICU/SICU (26)	Hepatic or renal insufficiency, head injury, ongoing NMBA use	Open-label	Propofol + alfentanil Midazolam + morphine	Alfentanil: 0.5–2 µg/kg/hr Propofol: 1–4 mg/kg/hr Morphine: 17–70 µg/kg/hr Midazolam: 0.03–0.2 mg/kg/hr	...	Own scale, goal: moderate-heavy sedation	Time to extubation: Propofol: 3 hr (1–13 hr) Midazolam: 50 hr (1–121 hr)	$p = 0.006$
1 (127)	Trauma ICU (100 consecutive)	Renal or hepatic failure	Open-label	Propofol Midazolam Propofol + midazolam Morphine: p.r.n.	Propofol: 2.12 ± 1.2 mg/kg/hr Midazolam: 0.19 ± 0.09 mg/kg/hr Propofol and Midazolam: Propofol: 1.6 ± 0.05 mg/kg/hr, Midazolam: 0.14 ± 0.08 mg/kg/hr	Propofol: 5.2 days Midazolam: 6.6 days Propofol and Midazolam: 7.2 days	Own scale, goal: moderate to heavy sedation	Awakening (excluding head trauma): Propofol: 110 ± 50 min Midazolam: 660 ± 400 min Propofol and Midazolam: 190 ± 200 min	Midazolam vs Propofol or Propofol and Midazolam: $p < 0.01$ ; Propofol: high triglyceride levels
1 (162)	MICU (64)	Head injury, ongoing NMBA use	Blinded	Lorazepam Midazolam Fentanyl p.r.n.	Lorazepam: 23.1 ± 14.4 mg/day Midazolam: 372 ± 256 mg/day	Lorazepam: 141 hr Midazolam: 141 hr	Addenbrooke sedation scale, initial moderate to heavy sedation, tapering to	Awakening similar, times not reported	Satisfactory sedation: Lorazepam: 87 ± 10.5%, Midazolam: 66.2 ± 23.1%

Table 6 (continued)

2 (163)	Trauma ICU (63 consecutive)	Renal or hepatic failure	Open-label	Propofol 2% Midazolam Morphine: to all patients	Propofol: 6400 ± 1797 mg/day Midazolam: 297.8 ± 103.8 mg/day	Propofol: 6.5 hr Midazolam 11.1 hr	Own scale, goal: moderate to heavy sedation	Awakening (no head trauma) Propofol: 145 ± 50 min Midazolam: 372 ± 491 min	Awakening: not statistically significant Less triglyceride elevation than historical control (reference 117)
2 (157)	MICU/SICU (99)	Neurosurgery, coma, seizures	Multicenter, open-label, intention-to-treat analysis	Propofol Midazolam Opioids: p.r.n.	Actual doses not specified	24–72 hr - post hoc stratum Propofol: n = 4 Midazolam: n = 10	Ramsay scale, level was specified daily	Time to extubation: Propofol: 8.4 hr Midazolam: 46.8 hr	p = 0.03, enrollment ended early, insufficient power limits conclusion Overall: Propofol: 60.2% of time at target Ramsay score Midazolam: 44% of time at target Ramsay score, p < 0.05

<sup>a</sup>MICU = medical intensive care unit, ICU = intensive care unit, NMBA = neuromuscular blocking agent, GCS = Glasgow Coma Score, SICU = surgical intensive care unit.

(bed availability) or patient-specific factors (other injuries and the need for observation) may impact a patient's length of stay more than the sedation regimen. More rapid extubation with propofol was not associated with a shorter length of stay in a multicenter Canadian trial.<sup>157</sup> Research that considers all of these cost factors is needed to estimate the overall cost of sedative regimens. Since the frequency of sedation-induced adverse effects has not been well described, there are insufficient data to create pharmacoeconomic models comparing the potential costs of sedative regimens. The acquisition costs of sedatives vary widely among institutions, and costs may decline with the availability of generic products (Table 3).

Multidisciplinary development and implementation of sedation guidelines have been shown to reduce direct drug costs (from \$81.54 to \$18.12 per patient per day), ventilator time (317 to 167 hours), and the lengths of ICU stay (19.1 to 9.9 days) and total stay without a change in mortality.<sup>165</sup> Although an economic analysis was not performed, a nursing-implemented sedation protocol using lorazepam reduced the duration of sedation and mechanical ventilation and the tracheostomy rate.<sup>80</sup> A systematic multi-disciplinary team approach to sedation and analgesia will produce clinical and economic benefits.

An algorithm was developed to incorporate many of the assessment issues with the therapy options in this document (Figure 1). When using this algorithm, the pharmacology, potential adverse effects, and therapeutic issues discussed in this document should be considered.

*Recommendations: Midazolam or diazepam should be used for rapid sedation of acutely agitated patients. (Grade of recommendation = C)*

*Propofol is the preferred sedative when rapid awakening (e.g., for neurologic assessment or extubation) is important. (Grade of recommendation = B)*

*Midazolam is recommended for short-term use only, as it produces unpredictable awakening and time to extubation when infusions continue longer than 48–72 hours. (Grade of recommendation = A)*

*Lorazepam is recommended for the sedation of most patients via intermittent i.v. administration or continuous infusion. (Grade of recommendation = B)*

*The titration of the sedative dose to a defined endpoint is recommended with systematic tapering of the dose or daily interruption with retitration to minimize prolonged sedative effects. (Grade of recommendation = A)*

*Triglyceride concentrations should be monitored after two days of propofol infusion, and total caloric intake from lipids should be included in the nutrition support prescription. (Grade of recommendation = B)*

*The use of sedation guidelines, an algorithm, or a protocol is recommended. (Grade of recommendation = B)*

## Sedative and Analgesic Withdrawal

Patients exposed to more than one week of high-dose opioid or sedative therapy may develop neuroadaptation or physiological dependence. Rapid discontinuation of these agents could lead to withdrawal symptoms. Opioid withdrawal signs and symptoms include dilation of the pupils, sweating, lacrimation, rhinorrhea, piloerection, tachycardia, vomiting, diarrhea, hypertension, yawning, fever, tachypnea, restlessness, irritability, increased sensitivity to pain, cramps, muscle aches, and anxiety. Benzodiazepine withdrawal signs and symptoms include dysphoria, tremor, headache, nausea, sweating, fatigue, anxiety, agitation, increased sensitivity to light and sound, paresthesias, muscle cramps, myoclonus, sleep disturbances, delirium, and seizures. Propofol withdrawal has not been well described but appears to resemble benzodiazepine withdrawal.

The occurrence of sedative and analgesic withdrawal has been described in both adult and pediatric ICU populations.<sup>166–168</sup> In adults, withdrawal is associated with the length of stay, mechanical ventilation, and the dose and duration of analgesic and sedative therapy. Patients at highest risk include those who stay greater than seven days in the ICU, receive greater than 35 mg/day of lorazepam, or greater than 5 mg/day of fentanyl.<sup>166</sup>

Studies of pediatric patients have found that the rate of medication weaning may be very important in the development of withdrawal syndromes.<sup>167,169</sup> Although not tested prospectively, it has been recommended that daily dose decrements of opioids not exceed 5–10% in high-risk patients.<sup>170</sup> If the drug is administered intermittently, changing the therapy to longer-acting agents may also attenuate withdrawal symptoms.<sup>171</sup> Another recommendation for opioid weaning is to decrease a continuous infusion rate by 20–40% initially and make additional reductions of 10% every 12–24 hours, depending on the patient's response.<sup>172</sup> Conversion to a continuous subcutaneous infusion has also been used for gradual fentanyl and midazolam weaning in children.<sup>173</sup> Patient care costs may be increased unnecessarily if sedatives and analgesics are withdrawn too slowly.

*Recommendation: The potential for opioid, benzodiazepine, and propofol withdrawal should be considered after high doses or more than approximately seven days of continuous therapy. Doses should be tapered systematically to prevent withdrawal symptoms. (Grade of recommendation = B)*

## Delirium

As many as 80% of ICU patients have delirium, characterized by an acutely changing or fluctuating mental status, inattention,

disorganized thinking, and an altered level of consciousness that may or may not be accompanied by agitation. Placing severely ill patients in a stressful environment for prolonged periods exacerbates the clinical symptoms of delirium.<sup>174–177</sup>

Delirium is usually characterized by fluctuating levels of arousal throughout the day, associated with sleep–wake cycle disruption, and hastened by reversed day–night cycles.<sup>178</sup> Delirium may be associated with confusion and different motoric subtypes: hypoactive, hyperactive, or mixed.<sup>179,180</sup> Hypoactive delirium, which is associated with the worst prognosis, is characterized by psychomotor retardation manifested by a calm appearance, inattention, decreased mobility, and obtundation in extreme cases. Hyperactive delirium is easily recognized by agitation, combative behaviors, lack of orientation, and progressive confusion following sedative therapy.

**Assessment of Delirium.** The gold standard criteria used to diagnose delirium is the clinical history and examination as guided by the *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*.<sup>177</sup> Although many scales and diagnostic instruments have been developed to facilitate the recognition and diagnosis of delirium, these scales routinely exclude ICU patients because it is often difficult to communicate with them.<sup>178,181</sup> Several groups of delirium investigators have recently collaborated to develop and validate a rapid bedside instrument to accurately diagnose delirium in ICU patients, who are often nonverbal because they are on mechanical ventilation. This instrument is called the Confusion Assessment Method for the ICU (CAM-ICU).<sup>181,182</sup> The work was begun by Hart and colleagues with their publication of the Cognitive Test for Delirium and a later version called the Abbreviated Cognitive Test for Delirium.<sup>183,184</sup> These two investigations were limited because they included approximately 20 patients each and excluded some of the most severely ill patients who are often cared for in the ICU. These factors led the authors to recommend that additional research with delirium assessment tools be conducted before routine application in mechanically ventilated patients.<sup>184</sup>

Collaboration among specialists in pulmonary and critical care, neurology, psychiatry, neuropsychology, and geriatrics has led to the development of a useful assessment tool.<sup>182,185</sup> It is based on the Confusion Assessment Method (CAM), which was designed specifically for use by health care professionals without formal psychiatric training, and incorporates *DSM-IV* criteria for the diagnosis of delirium.<sup>186</sup> CAM, which is the most widely used delirium assessment instrument for non-psychiatrists, is easy to use and has demonstrated utility in important clinical investigations.<sup>187,188</sup>

Critical care nurses can complete delirium assessments with the CAM-ICU in an average of 2 minutes with an accuracy of 98%, compared with a full *DSM-IV* assessment by a geriatric psychiatric expert, which usually requires at least 30 minutes to complete. The CAM-ICU assessments have a likelihood ratio of over 50 for diagnosing delirium and high inter-rater reliability ( $\kappa = 0.96$ ).<sup>185</sup> In the two subgroups expected to present the greatest challenge to the CAM-ICU (i.e., those over 65 years and those with suspected dementia), the instrument retained excellent inter-rater reliability, sensitivity, and specificity. To complete the CAM-ICU, patients are observed for the presence of an acute onset of mental status change or a fluctuating mental status, inattention, disorganized thinking, or an altered level of consciousness (Table 7). With the CAM-ICU, delirium was diagnosed in

Table 7.  
**The Confusion Assessment Method for the Diagnosis of Delirium in the ICU (CAM-ICU)<sup>182,185</sup>**

Feature	Assessment Variables
1. Acute Onset of mental status changes or Fluctuating Course	<p>Is there evidence of an acute change in mental status from the baseline?                      Did the (abnormal) behavior fluctuate during the past 24 hours, i.e., tend to come and go or increase and decrease in severity?                      Did the sedation scale (e.g., SAS or MAAS) or coma scale (GCS) fluctuate in the past 24 hours?<sup>a</sup>                      Did the patient have difficulty focusing attention?</p>
2. Inattention	<p>Is there a reduced ability to maintain and shift attention?                      How does the patient score on the Attention Screening Examination (ASE)? (i.e., Visual Component ASE tests the patient's ability to pay attention via recall of 10 pictures; auditory component ASE tests attention via having patient squeeze hands or nod whenever the letter "A" is called in a random letter sequence)</p>
3. Disorganized thinking	<p>If the patient is already extubated from the ventilator, determine whether or not the patient's thinking is disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject.                      For those still on the ventilator, can the patient answer the following 4 questions correctly?                      1. Will a stone float on water?                      2. Are there fish in the sea?                      3. Does one pound weigh more than two pounds?                      4. Can you use a hammer to pound a nail?                      Was the patient able to follow questions and commands throughout the assessment?                      1 "Are you having any unclear thinking?"                      2. "Hold up this many fingers." (examiner holds two fingers in front of patient)                      3. "Now do the same thing with the other hand." (not repeating the number of fingers)</p>
4. Altered level of consciousness (any level of consciousness other than alert (e.g., vigilant, lethargic, stupor, or coma))	<p>Alert: normal, spontaneously fully aware of environment, interacts appropriately                      Vigilant: hyperalert                      Lethargic: drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally                      Stupor: difficult to arouse, unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly; can be aroused only by vigorous and repeated stimuli and as soon as the stimulus ceases, stuporous subjects lapse back into the unresponsive state.                      Coma: unarousable, unaware of all elements in the environment, with no spontaneous interaction or awareness of the interviewer, so that the interview is impossible even with maximal prodding</p>

PATIENTS ARE DIAGNOSED WITH DELIRIUM IF THEY HAVE BOTH FEATURES 1 AND 2 AND EITHER FEATURE 3 OR 4.

<sup>a</sup>SAS = Sedation–Analgesia Scale, MAAS = Motor Activity Assessment Scale, GCS = Glasgow Coma Scale.

87% of the ICU patients with an average onset on the second day and a mean duration of 4.2 ± 1.7 days.<sup>185</sup> Ongoing research will assist in understanding the etiology of delirium and the effects of therapeutic interventions.

Another instrument for delirium screening was validated in ICU patients by comparison with a psychiatric evaluation.<sup>189</sup> The use of these tools in prospective trials will delineate the long-term ramifications of delirium on the clinical outcomes of ICU patients. The study of delirium and other forms of cognitive impairment in mechanically ventilated patients and other risk factors for neuropsychological sequelae after ICU care may be an important advancement in the monitoring and treatment of critically ill patients.

*Recommendation: Routine assessment for the presence of delirium is recommended. (The CAM-ICU is a promising tool for the assessment of delirium in ICU patients.) (Grade of recommendation = B)*

**Treatment of Delirium.** Inappropriate drug regimens for sedation or analgesia may exacerbate delirium symptoms. Psychotic or delirious patients may become more obtunded and confused when treated with sedatives, causing a paradoxical increase in agitation.<sup>190</sup>

Neuroleptic agents (chlorpromazine and haloperidol) are the most common drugs used to treat patients with delirium.

They are thought to exert a stabilizing effect on cerebral function by antagonizing dopamine-mediated neurotransmission at the cerebral synapses and basal ganglia. This effect can also enhance extrapyramidal symptoms (EPS). Abnormal symptomatology, such as hallucinations, delusions, and unstructured thought patterns, is inhibited, but the patient's interest in the environment is diminished, producing a characteristic flat cerebral affect. These agents also exert a sedative effect.

Chlorpromazine is not routinely used in critically ill patients because of its strong anticholinergic, sedative, and α-adrenergic antagonist effects. Haloperidol has a lesser sedative effect and a lower risk of inducing hypotension than chlorpromazine. Droperidol, a chemical congener of haloperidol, is reported to be more potent than haloperidol but has been associated with frightening dreams and may have a higher risk of inducing hypotension because of its direct vasodilating and antiadrenergic effects.<sup>191,192</sup> Droperidol has not been studied in ICU patients as extensively as haloperidol.

Haloperidol is commonly given via intermittent i.v. injection.<sup>193</sup> The optimal dose and regimen of haloperidol have not been well defined. Haloperidol has a long half-life (18–54 hours) and loading regimens are used to achieve a rapid response in acutely delirious patients. A loading regimen starting with a 2-mg dose, followed by repeated doses (double the previous dose) every 15–20 minutes while agitation persists, has been described.<sup>193,194</sup> High doses of haloperidol

(>400 mg per day) have been reported, but QT prolongation may result. However, the safety of this regimen has been questioned.<sup>192, 195–200</sup>

Once the delirium is controlled, regularly scheduled doses (every four to six hours) may be continued for a few days; then therapy should be tapered over several days. A continuous infusion of haloperidol (3–25 mg/hr) has been used to achieve more consistent serum concentrations.<sup>81,201</sup> The pharmacokinetics of haloperidol may be affected by other drugs.<sup>202</sup>

Neuroleptic agents can cause a dose-dependent QT-interval prolongation of the electrocardiogram, leading to an increased risk of ventricular dysrhythmias, including torsades de pointes.<sup>195–200</sup> Significant QT prolongation has been reported with cumulative haloperidol doses as low as 35 mg, and dysrhythmias have been reported within minutes of administering i.v. doses of 20 mg or more.<sup>199</sup> A history of cardiac disease appears to predispose patients to this adverse event.<sup>200</sup> The actual incidence of torsades de pointes associated with haloperidol use is unknown, although a historical case-controlled study suggests it may be 3.6%.<sup>199</sup>

EPS can occur with these agents. A slowly eliminated active metabolite of haloperidol appears to cause EPS.<sup>203–208</sup> EPS has been reported less frequently after i.v. versus oral haloperidol administration, but concurrent benzodiazepine use may mask EPS appearance. Self-limited movement disorders can be seen several days after tapering or discontinuing haloperidol and may last for up to two weeks.<sup>209</sup> Treatment of EPS includes discontinuing the neuroleptic agent and a clinical trial of diphenhydramine or benztropine mesylate.

Other adverse effects have also been described. Haloperidol therapy for the control of agitation after a traumatic brain injury may prolong the duration of posttraumatic amnesia, but the effect on functional recovery has not been well demonstrated in humans.<sup>210</sup> Although haloperidol is the most common antipsychotic agent associated with neuroleptic malignant syndrome and has been implicated in approximately 50% of reported episodes (only three cases were reported in critically ill patients receiving intravenous haloperidol), its adverse effects may be underreported.<sup>211–214</sup>

Haloperidol therapy for acutely agitated or delirious patients has not been studied prospectively in agitated ICU patients, but its utility has been suggested in case series.<sup>81,193,201</sup>

*Recommendations: Haloperidol is the preferred agent for the treatment of delirium in critically ill patients. (Grade of recommendation = C)*

*Patients should be monitored for electrocardiographic changes (QT interval prolongation and arrhythmias) when receiving haloperidol. (Grade of recommendation = B)*

## Sleep

Sleep is believed to be important to recover from an illness. Sleep deprivation may impair tissue repair and overall cellular immune function.<sup>215</sup> Sleeplessness induces additional stress in critical care patients.<sup>3,216</sup> Allowing a patient to obtain an adequate amount of sleep may be difficult in a critical care unit. Sleep in the ICU has been characterized by few complete sleep cycles, numerous awakenings, and infrequent rapid-eye-movement (REM) sleep.<sup>217</sup> Atypical sleep patterns were demonstrated in critically ill patients receiving high doses of sedatives.<sup>218</sup>

**Sleep Assessment.** Similar to pain assessment, the patient's own report is the best measure of sleep adequacy, since polysomnography is not a clinically feasible tool in the critical care setting. If self-report is not possible, systematic observation of a patient's sleep time by nurses has been shown to be a valid measure.<sup>219</sup> A VAS or questionnaire can be used to assess sleep for specific patients.<sup>220</sup>

**Nonpharmacologic Strategies.** *Titrating environmental stimulation.* Nonpharmacologic interventions to promote sleep and increase overall patient comfort may include environment modification, relaxation, back massage, and music therapy. Noise in critical care settings is an environmental hazard that disrupts sleep.<sup>221–223</sup> Sources of noise include equipment, alarms, telephones, ventilators, and staff conversations. Noise levels above 80 decibels cause arousal from sleep. Sleep occurs best below 35 decibels.<sup>222</sup> Earplugs effectively decreased noise and increased REM sleep in healthy volunteers in a study that simulated noise heard in an ICU.<sup>224</sup> A creative unit design with single rooms may ameliorate noise and provide lighting that better reflects a day–night orientation.<sup>225</sup> Lighting mimicking the 24-hour day helps patients achieve normal sleep patterns, so bright lights should be avoided at night. In addition, care should be coordinated to minimize frequent interruptions during the night.

*Relaxation.* Head-to-toe relaxation may benefit anxious critically ill patients who can follow directions. Relaxation will lead to a parasympathetic response and a decrease in respiratory rate, heart rate, jaw tension, and blood pressure. Relaxation techniques include deep breathing followed by the sequential relaxation of each muscle group.<sup>226</sup> Relaxation, in combination with music therapy, is effective in patients with myocardial infarction.<sup>227</sup>

*Music therapy.* Music therapy relaxes patients and decreases their pain. Music intervention with cardiac surgery patients, during the first postoperative day, decreased noise annoyance, heart rate, and systolic blood pressure.<sup>228</sup> In mechanically ventilated patients, music therapy decreased anxiety and promoted relaxation.<sup>229</sup> Music therapy is a proven intervention for anxious patients in other critical care settings.<sup>229–231</sup> Music can decrease heart rate, respiratory rate, myocardial oxygen demand, and anxiety scores and improve sleep.<sup>232,233</sup> When selecting music, a patient's personal preference should be considered.

*Massage.* Back massage is an alternative or adjunct to pharmacologic therapy in critically ill patients. Approximately 5–10 minutes of massage initiates the relaxation response and increases a patient's amount of sleep.<sup>234,235</sup>

**Pharmacologic Therapy to Promote Sleep.** Patients may remain sleep-deprived despite nonpharmacologic interventions. Most patients need a combination of analgesics, sedatives, and relaxation techniques to decrease pain and anxiety and promote sleep. Sedative-hypnotics can induce sleep in healthy individuals, but little is known of their use in the critically ill. There was no difference in sleep quality between two groups of nonintubated ICU patients receiving midazolam or propofol.<sup>59</sup> Oral hypnotics, such as benzodiazepines or zolpidem, are used in nonintubated patients to decrease sleep latency while increasing total sleep time without affecting sleep architecture in stages three and four and REM sleep.<sup>215</sup>

*Recommendation: Sleep promotion should include optimization of the environment and nonpharmacologic methods to promote relaxation with adjunctive use of hypnotics. (Grade of recommendation = B)*

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6. If intravenous doses of an opioid analgesic are required, fentanyl, hydromorphone, and morphine are the recommended agents. (Grade of recommendation = C)
7. Scheduled opioid doses or a continuous infusion is preferred over an “as needed” regimen to ensure consistent analgesia. A PCA device may be utilized to deliver opioids if the patient is able to understand and operate the device. (Grade of recommendation = B)
8. Fentanyl is preferred for a rapid onset of analgesia in acutely distressed patients. (Grade of recommendation = C)
9. Fentanyl or hydromorphone are preferred for patients with hemodynamic instability or renal insufficiency. (Grade of recommendation = C)
10. Morphine and hydromorphone are preferred for intermittent therapy because of their longer duration of effect. (Grade of recommendation = C)
11. NSAIDs or acetaminophen may be used as adjuncts to opioids in selected patients. (Grade of recommendation = B)
12. Ketorolac therapy should be limited to a maximum of five days, with close monitoring for the development of renal insufficiency or gastrointestinal bleeding. Other NSAIDs may be used via the enteral route in appropriate patients. (Grade of recommendation = B)
13. Sedation of agitated critically ill patients should be started only after providing adequate analgesia and treating reversible physiological causes. (Grade of recommendation = C)
14. A sedation goal or endpoint should be established and regularly redefined for each patient. Regular assessment and response to therapy should be systematically documented. (Grade of recommendation = C)
15. The use of a validated sedation assessment scale (SAS, MAAS, or VICS) is recommended. (Grade of recommendation = B)
16. Objective measures of sedation, such as BIS, have not been completely evaluated and are not yet proven useful in the ICU. (Grade of recommendation = C)
17. Midazolam or diazepam should be used for rapid sedation of acutely agitated patients. (Grade of recommendation = C)
18. Propofol is the preferred sedative when rapid awakening (e.g., for neurologic assessment or extubation) is important. (Grade of recommendation = B)
19. Midazolam is recommended for short-term use only, as it produces unpredictable awakening and time to extubation when infusions continue longer than 48–72 hours. (Grade of recommendation = A)
20. Lorazepam is recommended for the sedation of most patients via intermittent i.v. administration or continuous infusion. (Grade of recommendation = B)
21. The titration of the sedative dose to a defined endpoint is recommended with systematic tapering of the dose or daily interruption with retitration to minimize prolonged sedative effects. (Grade of recommendation = A)
22. Triglyceride concentrations should be monitored after two days of propofol infusion, and total caloric intake from lipids should be included in the nutrition support prescription. (Grade of recommendation = B)
23. The use of sedation guidelines, an algorithm, or a protocol is recommended. (Grade of recommendation = B)
24. The potential for opioid, benzodiazepine, and propofol withdrawal should be considered after high doses or more than approximately seven days of continuous

## Appendix A—Summary of Recommendations

1. All critically ill patients have the right to adequate analgesia and management of their pain. (Grade of recommendation = C)
2. Pain assessment and response to therapy should be performed regularly by using a scale appropriate to the patient population and systematically documented. (Grade of recommendation = C)
3. The level of pain reported by the patient must be considered the current standard for assessment of pain and response to analgesia whenever possible. Use of the NRS is recommended to assess pain. (Grade of recommendation = B)
4. Patients who cannot communicate should be assessed through subjective observation of pain-related behaviors (movement, facial expression, and posturing) and physiological indicators (heart rate, blood pressure, and respiratory rate) and the change in these parameters following analgesic therapy. (Grade of recommendation = B)
5. A therapeutic plan and goal of analgesia should be established for each patient and communicated to all caregivers to ensure consistent analgesic therapy. (Grade of recommendation = C)

- therapy. Doses should be tapered systematically to prevent withdrawal symptoms. (Grade of recommendation = B)
25. Routine assessment for the presence of delirium is recommended. (The CAM-ICU is a promising tool for the assessment of delirium in ICU patients.) (Grade of recommendation = B)
  26. Haloperidol is the preferred agent for the treatment of delirium in critically ill patients. (Grade of recommendation = C)
  27. Patients should be monitored for electrocardiographic changes (QT interval prolongation and arrhythmias) when receiving haloperidol. (Grade of recommendation = B)
  28. Sleep promotion should include optimization of the environment and nonpharmacologic methods to promote relaxation with adjunctive use of hypnotics. (Grade of recommendation = B)

Developed through the Task Force of the American College of Critical Care Medicine (ACCM) of the Society of Critical Care Medicine (SCCM), in collaboration with the American Society of Health-System Pharmacists (ASHP), and in alliance with the American College of Chest Physicians; and approved by the Board of Regents of ACCM and the Council of SCCM on November 15, 2001, and the ASHP Board of Directors on November 17, 2001.

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The bibliographic citation is as follows: Society of Critical Care Medicine and American Society of Health-System Pharmacists. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Am J Health-Syst Pharm.* 2002; 59:150–78.