Sedative-analgesic medications in critically ill adults: Selection, initiation, maintenance, and withdrawal

Authors: Barry Fuchs, MD, Cassandra Bellamy, PharmD, BCPS
Section Editors: Polly E Parsons, MD, Michael F O'Connor, MD, FCCM **Deputy Editor:** Geraldine Finlay, MD

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: Mar 2023. | **This topic last updated:** Aug 26, 2022.

INTRODUCTION

Distress generally presents as agitation. It is common among critically ill patients, especially those who are intubated or having difficulty communicating with their caregivers [1]. Distress needs to be treated for patient comfort and because it increases sympathetic tone, which may have untoward physiological effects [2]. Barring few exceptions (eg, neuromuscular paralysis, procedures) the administration of sedativeanalgesic medications should not be based on anticipated distress but rather on that which is observed; otherwise, there will be an increased risk of over sedation which has been shown to worsen clinical outcomes.

The management of agitation in critically ill adults is reviewed here, including the initiation, maintenance, and withdrawal of pharmacological sedation. Common sedative-analgesic medications, the treatment of pain, and the use of neuromuscular blocking medications in critically ill patients are discussed elsewhere. (See "Sedative-analgesic medications in critically ill adults: Properties, dose regimens, and adverse effects" and "Pain control in the critically ill adult patient" and "Neuromuscular blocking agents in critically ill patients: Use, agent selection, administration, and adverse effects".)

PRE-INITIATION

Before a sedative-analgesic agent is initiated to manage agitation, the cause of the distress should be identified and treated. Nonpharmacological strategies are preferred and should be implemented prior to the use of pharmacologic treatment.

Identify the cause of distress — Common causes of distress in critically ill patients include anxiety, pain, delirium, dyspnea, and neuromuscular paralysis. These etiologies may occur separately or in combination.

- Anxiety – Anxiety is defined as a sustained state of apprehension and autonomic arousal in response to real or perceived threats [1]. Fear of suffering, fear of death, loss of control, and frustration due to the inability to effectively communicate are typical causes of anxiety in critically ill patients. Symptoms and signs include headache, nausea, insomnia, anorexia, dyspnea, palpitations, dizziness, dry mouth, chest pain, diaphoresis, hyperventilation, pallor, tachycardia, tremulousness, and/or hypervigilance.

  Identifying and treating the proximate cause of anxiety is always ideal as it may ameliorate both problems. Dyspnea, for example, is a common underlying cause of anxiety among critically-ill patients. Thus, if inadequate ventilator flow is causing dyspnea with resultant anxiety, the ultimate treatment for the anxiety (and underlying dyspnea) may be adjustment of ventilator settings. Alternatively, the abrupt onset of anxiety may prompt further work-up for a cardiopulmonary source.

- Pain – Routine patient care (eg, suctioning, repositioning, physical therapy), immobility, trauma, surgery, endotracheal tubes, and other monitoring devices can all produce pain. Evidence of pain may include grimacing, withdrawal, combativeness, diaphoresis, hyperventilation, and/or tachycardia. While self-report is preferred over behavioral pain scales, pain scales are superior to vital signs alone for assessment of pain [3]. The assessment and treatment of pain should be viewed as a priority in patients regardless of ability to communicate as pain is likely under reported during intensive care unit (ICU) stay. Upon ICU discharge, a significant proportion of patients report experiencing moderate to severe pain during ICU care [4]. (See "Pain control in the critically ill adult patient", section on 'Assessment for pain'.)

- Delirium – Delirium is an organic mental syndrome. It is defined as an acute and potentially reversible impairment of consciousness and cognitive function that fluctuates in severity [1]. Delirium occurs in up to 80 percent of ICU patients, but it is frequently unrecognized in older individuals and in patients with hypoactive delirium [5,6]. Delirium may be associated with an underlying cause such as infection, iatrogenic such as medications, or environmental. Prior to treatment, patients should be evaluated for a precipitating factor. In the acute phase, delirious patients have impaired short-term memory, abnormal perception, and intermittent disorientation, which is usually worse at night. Electroencephalography may display diffuse slowing. Delirium due to drug or alcohol withdrawal typically presents as a hyperactive delirium [7]. (See "Management of moderate and severe alcohol withdrawal syndromes", section on 'Delirium tremens' and "Diagnosis of delirium and confusional states", section on 'Evaluation'.)

Delirium is a risk factor for prolonged hospitalization and mortality in critically ill patients [8-10]. Risk factors for delirium include electrolyte imbalances (hypocalcemia, hyponatremia), hyperamylasemia, hyperglycemia, azotemia, hepatic disease (hyperbilirubinemia, elevated hepatic enzymes), infections, drug withdrawal, alcohol withdrawal, malnutrition, cancer, cerebrovascular disease, cardiopulmonary disease, advanced age, and some medications (benzodiazepines, corticosteroids, antihistamines, beta blockers, antiarrhythmics, digitalis glycosides, atropine) [11]. It has been suggested that "hypoactive delirium" be renamed "acute apathy syndrome" because it has a different constellation of causes than "hyperactive delirium" [12]. (See "Acute toxic-metabolic encephalopathy in adults".)

Society guidelines promote the regular assessment of critically ill patients with a delirium assessment tool such as the CAM-ICU or the Intensive Care Delirium Screening Checklist (ICDSC) [13], understanding that the level of arousal may affect the assessment [3], which is discussed separately. (See "Diagnosis of delirium and confusional states", section on 'Recognizing the disorder'.)

- Dyspnea – Dyspnea is a sensation of air hunger or a feeling of suffocation [1]. Evidence of dyspnea may include tachypnea, shallow breathing, diaphoresis, tachycardia, use of the accessory muscles of respiration, hypoxemia, and/or hypercapnia. Dyspnea may exist despite acceptable blood gas parameters. Strategies to alleviate hypoxia or dyspnea such as adjustment of ventilator settings, if possible, should be explored prior to the use of medications.

- Neuromuscular paralysis – All patients undergoing neuromuscular blockade require pharmacological sedation, since neuromuscular paralysis without sedation or adequate pain control is an extremely frightening and unpleasant sensation. Identifying distress in patients undergoing neuromuscular blockade is difficult because the typical physiological responses associated with stress (eg, increased heart rate and blood pressure with stimulation) may not correlate with patient discomfort in this setting. (See "Neuromuscular blocking agents in critically ill patients: Use, agent selection, administration, and adverse effects".)

Treat the cause of distress — Initial treatment of agitation should target the presumed cause of the underlying distress. As an example, a patient who is agitated due to hypoxemia should receive supplemental oxygen.

Nonpharmacological strategies — Nonpharmacological strategies for managing agitation should begin simultaneously with therapy targeting the cause of distress (since the cause of the distress is rarely quickly reversible). Nonpharmacological strategies include reassurance, frequent communication with the patient, regular caregiver visits, establishment of normal sleep cycles, and cognitive-behavioral therapies [14]. Examples of cognitive-behavioral therapies include music therapy, guided imagery, and relaxation therapy.

This strategy of using nonpharmacological interventions to prevent or control agitation, rather than immediately initiating pharmacological sedation, is supported by evidence:

- One trial randomly assigned 140 mechanically ventilated patients to receive either a strategy of no sedation followed by continuous verbal comforting and reassurance or continuous sedation with daily interruption [15]. Only when nonpharmacologic interventions failed were patients treated with a continuous sedative infusion with daily interruption. The trial found that patients managed with a strategy of no sedation had more ventilator-free days and a decreased length of ICU stay, length of hospital stay, and incidence of delirium. There was no difference in posttraumatic stress disorder, quality of life, depression, or recall of the ICU experience in survivors approximately two years after randomization [16].

- Another randomized multicenter trial of 373 mechanically ventilated patients reported that, compared to usual care (UC) or noise-cancelling headphones (NCH), patient directed self-initiated music (PDM; with preferred selections tailored by a music therapist) was associated with a reduction in the visual analog scale for anxiety (52 versus 33) throughout the study period (up to 5.7 days) [17]. In addition, by the fifth day, PDM was associated with a reduction in sedation intensity (sedation intensity score 4.4 versus 2.8) and frequency (5 doses versus 3 doses of study-approved sedative). These findings were confirmed in a meta-analysis of 14 trials examining the impact of music in mechanically ventilated patients [18] and reductions in patients' distress was also reported in ICU patients in the ICU who were receiving noninvasive ventilation [19].

While physical restraints are used by some ICUs, they should never be the sole method employed for managing patients in the ICU. Their use should be supplementary to other more acceptable methods of sedation and use should be transient. When employed, efforts should be made to reduce the use of physical restraints in the ICU.

INITIATION

Sedative-analgesic medication is indicated when treatment of the cause of the distress and nonpharmacological interventions cannot sufficiently control the agitation. The Society of Critical Care Medicine has published guidelines regarding the selection and initiation of sedative-analgesic medications in critically ill patients [3].

Available agents — Sedative-analgesic medications that are commonly used in the intensive care unit (ICU) include benzodiazepines (eg, diazepam, lorazepam, midazolam), opioid analgesics (eg, fentanyl, hydromorphone, morphine, remifentanil), propofol, dexmedetomidine, ketamine, and antipsychotics (eg, haloperidol, quetiapine, ziprasidone) (table 1) [7,20]. Agents such as acetaminophen, nonsteroidal antiinflammatory drugs (ketorolac), gabapentin or pregabalin, and antiepileptics can be used as adjunctive therapy when indicated. All these agents differ in their amount of anxiolysis, analgesia, amnesia, and hypnosis (table 2). Their

mechanisms, properties, dosage regimens, and potential adverse effects are reviewed separately (table 3). (See "Sedative-analgesic medications in critically ill adults: Properties, dose regimens, and adverse effects".)

Although barbiturates (eg, thiopental, methohexital) can be used to manage agitation during critical illness in patients not tolerating or responding to other agents, it is not ideal. This is because barbiturates are not potent sedatives and can cause profound cardiovascular and respiratory depression, as well as diminished cerebral blood flow. Phenobarbital may be useful in patients with alcohol withdrawal. Sevoflurane (a polyfluorinated methyl-isopropyl volatile anesthetic) is a newer agent for which safety and efficacy data are limited, prohibiting its routine use as a sedative in the ICU [21-23]. Fospropofol is not available worldwide and thiopental is no longer manufactured in United States or Canada.

Selection of an agent — No sedative-analgesic agent is sufficiently superior to other agents to warrant its use in all clinical situations. The Society of Critical Care Medicine guidelines favor nonbenzodiazepine agents due to evidence of shorter duration of mechanical ventilation, but the optimal agent for short-term or long-term therapy is not known [3]. Selection of an agent must be individualized according to patient characteristics and the clinical situation [24]. Important considerations when selecting a sedative-analgesic agent include the etiology of the distress, expected duration of therapy, clinical status of the patient, and potential interactions with other drugs:

- Etiology of the distress – The appropriate initial pharmacological agent for managing agitation due to distress depends upon the cause of the distress [3]:
  - For distress due to dyspnea or pain, opioids are the agents of choice. (See "Pain control in the critically ill adult patient".)
  - For distress due to delirium, antipsychotics (eg, haloperidol, quetiapine, ziprasidone) should not be routinely used but may be used in cases of significant distress induced by delirium. Although weak evidence suggests that dexmedetomidine may decrease the risk of delirium [25], an Intensive Care Medicine Rapid Practice Guideline (ICM-RPG) has suggested that dexmedetomidine be used when clinicians feel that a reduction in delirium risk outweighs the risk of adverse effects of hypotension and bradycardia [26]. To date there are no agents that prevent delirium. Therapies that do **not** work include statins and bright light. (See "Sedative-analgesic medications in critically ill adults: Properties, dose regimens, and adverse effects", section on 'Antipsychotics'.)
  - For agitation due to stress or anxiety, the Society of Critical Care Medicine endorses the use of propofol rather than benzodiazepines in cardiac surgery patients and propofol or dexmedetomidine rather than benzodiazepines in other surgical and medical patients [3]. (See "Sedative-analgesic medications in critically ill adults: Properties, dose regimens, and adverse effects", section on 'Propofol' and "Sedative-analgesic medications in critically ill adults: Properties, dose regimens, and adverse effects", section on 'Dexmedetomidine' and "Sedative-analgesic medications in critically ill adults: Properties, dose regimens, and adverse effects", section on 'Benzodiazepines'.)

  However, combination therapy is common in the ICU since many patients have more than one cause of distress. As an example, a benzodiazepine plus an opioid is appropriate for a patient whose agitation is due to anxiety and pain. For patients who are intubated and mechanically ventilated and not able to clearly communicate the source of agitation, analgesia should always be provided first [3]. (See "Pain control in the critically ill adult patient".)

- Pharmacokinetic modifying variables (eg, age, body weight, renal and hepatic function) and the desired depth of sedation should also be considered whenever a sedative-analgesic agent is selected. Abnormal pharmacokinetic modifying variables can magnify differences among the sedative-analgesic agents (eg, onset, peak, duration of sedation), especially during deep or long-term sedation.

Initial dose — The initial dose of a sedative-analgesic agent should account for the desired level of sedation ability to tolerate the drug including hemodynamic and respiratory status as well as factors that may affect drug metabolism (ie, patient age, body weight, renal function, hepatic function, drug interactions, history of alcoholism, history of drug abuse). Higher doses are appropriate for deeper sedation and larger patients, while lower doses are appropriate for lighter sedation, smaller patients, patients with advanced age, diminished renal function, or decreased hepatic function. Patients with a history of alcohol or abuse may require higher doses of benzodiazepines or opioids, respectively, to achieve a given effect. (See "Sedative-analgesic medications in critically ill adults: Properties, dose regimens, and adverse effects".)

Administration — The evidence indicates that continuous infusion of a sedative-analgesic prolongs the duration of mechanical ventilation [27]. As a result, current practice favors intermittent bolus doses, daily interruption or dose minimization titrated to light level of sedation (RASS -2 to 0) of continuous infusions [3]. Clinical practice guidelines for the sustained use of sedatives and analgesics in critically ill adults endorse the initial use of intermittent bolus dose, with the initiation of continuous infusions with daily interruption or dose minimization titrated to light level of sedation in patients who require intermittent infusions more often than every two hours [7].

Sedation goal — The ideal sedation goal is for the patient to be awake and comfortable with minimal to no distress (eg, 0 on the RASS scale) (table 4), although some patients may require a deeper level of sedation for optimal management. In general, light levels of sedation are promoted because they decrease mechanical ventilation days and tracheostomy rates, although no effect on mortality has been demonstrated [3]. The sedation goal should be ascertained at the bedside for each patient; while the Society of Critical Care Medicine (SCCM) promotes light sedation rather than heavy sedation, they recognize that no universally accepted definition of light sedation exists. We also agree with the 2018 SCCM [3] guidelines which stated that targeting a RASS level of -2 (previously promoted by 2013 guidelines [7]) is too deep and could lead to the over sedation and delayed recovery of many patients (eg, by eliminating the opportunity for daily physical therapy). In contrast, a proportion of critically-ill, mechanically-ventilated patients require a very deep level of sedation-analgesia to control agitation or pain. A patient-centered approach,

derived by the bedside clinician, is best and should be used to determine the appropriate goal for the depth of sedation. This goal should be determined prior to beginning or escalating sedative-analgesic medications, since this is the target to which initial therapy is titrated. As examples, lighter sedation may be desired when serial neurological exams are required, while deeper sedation may be desired during severe hypoxemic respiratory failure.

The goal depth of sedation should be frequently reassessed and adjusted as the patient's sedation requirement becomes more apparent. Some patients require no sedation, while others require deep sedation to be mechanically ventilated without discomfort, agitation, or asynchrony.

The depth of sedation is typically assessed during the initiation of pharmacological sedation using criteria such as spontaneous movement and response to verbal and tactile stimuli. Scoring systems have been developed to make evaluation of the depth of sedation more rigorous and quantitative, but these systems are more commonly used during the maintenance of sedative-analgesic therapy, as described below. (See 'Monitoring' below.)

MAINTENANCE

Once the initiation of the sedative-analgesic agent achieves a calm state, attention should be directed toward monitoring and avoiding excess sedation. This involves frequent reassessment of pain and sedative requirements to achieve simultaneous patient comfort in an awake and alert patient.

Monitoring — The maintenance of pharmacological sedation requires that patients be reassessed frequently to determine whether their agitation and underlying distress are being adequately managed. Scoring systems have been developed to facilitate this evaluation.

There are scoring systems (ie, scales) to assess pain, sedation, and delirium. The scale appropriate for the presumed cause of distress should be employed. As an example, if the distress was felt to be due to pain and an opioid was initiated, then assessment using a pain scale is appropriate. If the goal of therapy is sedation, then a scale assessing level of sedation should be used.

Once the appropriate scoring system has been used to determine whether the agitation and/or underlying distress is sufficiently controlled, the sedative-analgesic medication should be titrated or tapered to meet the therapeutic goals.

Scoring systems — Scoring systems use multiple criteria to determine the amount of pain, depth of sedation, or presence or severity of delirium. An important limitation of the scoring systems is that reference standards do not exist [28]:

- Pain scales – There exist unidimensional scales (ie, verbal rating scale, visual analogue scale, numeric rating scale) and multidimensional scales (ie, McGill Pain Questionnaire, Wisconsin Brief Pain Questionnaire) to assess a patient's level of pain. The unidimensional scales can be quickly and easily applied in the intensive care unit if the patient is communicative. As an example, the numeric rating scale is a zero to ten point scale on which ten represents the worst pain. Patients choose the number that best describes their pain. The multidimensional scales are more complex and take longer to administer; thus, they may not be appropriate for the intensive care unit. The Behavioral Pain Scale and the Critical-Care Pain Observation Tool are simple, valid, and reliable pain scales for pain assessment in critically ill patients and are recommended as scales of choice by current guidelines [7].

- Sedation scales – There are numerous scoring systems to assess the depth of sedation that are valid and reliable in adults who are mechanically ventilated and critically ill [29-33]. Current guidelines support the use of the Richmond Agitation-Sedation Scale (RASS) (table 4) and the Riker Sedation-Agitation Scale (SAS) [7]. Alternative scoring systems include the Motor Activity Assessment Scale (MAAS), Minnesota Sedation Assessment Tool (MSAT), Ramsay Sedation Scale (table 5), Bizek Agitation Scale, Sheffield Scale, and COMFORT Scale [34-37]. The COMFORT scale is a valid and reliable system for children [35].

- Delirium scales – Many scales and diagnostic instruments have been developed to identify and evaluate delirium, but most exclude critically ill patients due to difficulty communicating with them [3]. However, a rapid bedside instrument that can identify delirium in critically ill patients is the Confusion Assessment Method for the ICU (CAM-ICU) [38]. The Intensive Care Delirium Screening Checklist (ICDSC) is also a simple and valid tool for bedside assessment of delirium. Both scales assess patients for acute mental status changes or fluctuating mental status changes, inattention, disorganized thinking, and/or an altered level of consciousness. Both the CAM-ICU and the ICDSC can identify new or persistent delirium, but neither quantify the severity of the delirium. (See "Diagnosis of delirium and confusional states", section on 'Recognizing the disorder'.)

Bispectral index — For patients who are pharmacologically paralyzed, monitoring is challenging because the scoring systems cannot determine the level of pain, depth of sedation, or presence of delirium. Heart rate and blood pressure have historically been used as indicators of distress in this situation, but these vital signs are neither sensitive nor specific. We believe that there are two reasonable approaches. Pharmacologically paralyzed patients can be given higher than usual doses of both an anxiolytic/amnestic and an analgesic to ensure deep sedation. Alternatively, bispectral index (BIS), auditory evoked potentials, or other objective monitoring systems can be used (table 6) [3]. The latter approach may limit drug accumulation.

BIS monitoring uses Fourier transform analysis of electroencephalographic data to estimate the depth of sedation. It is used primarily during operative anesthesia in patients without underlying neurologic disease. BIS monitoring is not used routinely in the ICU because there are conflicting data regarding its benefit and electromyelographic activity from the scalp muscles creates artifact [39-45]. We and others believe BIS monitoring is a reasonable approach to assessing depth of

sedation in ICU patients receiving deep levels of sedation or neuromuscular paralysis [3]; however, we agree that BIS monitoring should not replace the clinical assessment of sedation in the routine management of ICU patients until more favorable data are reported. Also, clinicians should recognize the potential for misinterpretation of the BIS algorithm in patients with electromyographic activity [46].

Avoid excess sedation — Sedative-analgesic medications should not be overused because excess sedation may unnecessarily prolong the duration of mechanical ventilation [27,47,48]. Two strategies have been shown in randomized trials to reduce duration of mechanical ventilation and complications related to prolonged mechanical ventilation: intermittent boluses of medication (including analgesia without sedatives, sometimes referred to as "no" sedation) [27,49] and the daily interruption of continuous infusions [50-53]. Both of these approaches have been protocolized in many ICUs in an attempt to avoid excess sedation; however, the value of protocols in this regard remains unproven [54,55]. We believe there is sufficient evidence to justify efforts to minimize sedative-analgesic infusions, although the optimal method (eg, protocol-driven intermittent infusions, daily interruption, or a combination) is not known. Additional studies focusing on efficacy, feasibility, and safety are needed to determine the optimal approach.

Intermittent bolus — An observational study of 242 patients compared the duration of mechanical ventilation among patients who received a continuous sedative-analgesic infusion to those who received either intermittent sedative-analgesic infusions or no sedative-analgesics based on a nursing protocol [49]. The group that received intermittent infusions or no medication had a shorter duration of mechanical ventilation (median of 56 hours) than the group that received a continuous infusion (median of 185 hours). Data that compared no sedation to light sedation with daily interruption of sedative infusions are discussed below. (See 'Daily interruption and nursing protocolized sedation' below.)

Daily interruption and nursing protocolized sedation — Daily interruption of sedation (DSI) refers to discontinuing the continuous sedativeanalgesic infusion until the patient is awake and following instructions, or until the patient is uncomfortable or agitated, and deemed to require the resumption of sedation. The rationale DSI is that they facilitate assessment of the patient's underlying neurologic status, as well as the patient's need for ongoing sedation. Nursing-protocolized (NP)-sedation is defined as an established sedation protocol implemented by nurses at the bedside to sedative choices and medication titration to achieve prescription-targeted sedations scores. Several studies have compared these mechanisms and no consistent robust difference has been reported [51,56-58]. The SCCM state that light sedation can be achieved in most patients most of the time using either method. Thus, many ICUs practice one or both of these methods.

Randomized trials and meta-analyses report possible benefit from DSI or NP-sedation with regard to reducing duration of mechanical ventilation and length of stay. However, there is considerable heterogeneity among trials which limits interpretation of the analysis. As examples:

- In a trial of 128 patients who were receiving mechanical ventilation and a continuous sedative-analgesic infusion, patients were randomly assigned to continue conventional management or to undergo daily spontaneous awakening trials [50]. The spontaneous awakening trials consisted of interruption of the continuous infusion until the patient was awake. The group whose continuous infusion was interrupted daily had a shorter duration of mechanical ventilation (4.9 versus 7.3 days) and length of ICU stay (6.4 versus 9.9 days), as well as fewer neurodiagnostic tests. Limitations of the trial include that it was performed in a single center, ventilator weaning was not standardized, and the spontaneous awakening trials were monitored closely by study personnel, which is not feasible in most ICUs.

- A similar trial randomly assigned 336 patients to a daily spontaneous breathing trial and either a daily spontaneous awakening trial or conventional sedation management [59]. The daily spontaneous awakening trial group had decreased one-year mortality (but not 28-day mortality), an increased number of ventilator-free days, a decreased length of ICU stay, and a decreased length of hospital stay. The group also had less cognitive impairment at three months (absolute risk reduction of 20 percent), although there was no difference at 12 months [60].

- A meta-analysis of nine trials demonstrated only marginal reductions in the duration of mechanical ventilation (13 percent), ICU and hospital length of stay (10 and 6 percent, respectively) when compared with strategies that do not utilize daily sedative interruption [61]. There was

  no difference in risk of death, rate of accidental endotracheal tube removal, incidence of new onset delirium, or in the doses of sedative administered. The confidence intervals were wide which indicates imprecision and limits interpretation of the analysis.

- A meta-analysis of six randomized trials of mechanically ventilated patients in closed nonspecialty ICUs reported that, compared with usual care, protocolized sedation (algorithm and/or daily interruption) was associated with a rate reduction in overall mortality (15 percent), length of hospital stay (3.5 days), and tracheostomy (31 percent) [62]. There was no difference on the duration of mechanical ventilation and rate of self-extubation or re-intubation.

While these trials indicate that daily interruption of continuous sedative-analgesic infusions are beneficial, compliance to protocols can be challenging, and the benefit may be less or absent if a sedation protocol is also being concurrently used [63-65]. This was illustrated by a multicenter trial in which 430 mechanically-ventilated patients were randomly assigned to receive protocolized sedation (PS) alone or protocolized sedation plus daily interruption (PS+DI) of their continuous sedative-analgesic infusion [56]. The median time to successful extubation, the primary outcome, was seven days in both groups. The PS+DI group had higher mean doses of infusions of midazolam and fentanyl as well as a greater number of boluses of benzodiazepines and opiates, than the PS group. No differences were noted in the rates of unintentional removal of medical devices, ICU delirium, diagnostic neuroimaging, or tracheostomy. Of note, the average daily dose of midazolam was higher in both groups in this study than in the daily interruption trial described above [50]. The seemingly disparate results from the two clinical trials may be reconciled by the notion that protocolized weaning of sedation by the bedside nurse (as in the control group of the PS versus PS+DI study [56]) can effectively achieve the minimal effective sedative dose requirement for patients. This would explain the lack of any further benefit, when the minimal effective dose is interrupted.

Daily interruption of light sedation has been compared with "no sedation." In a single-center randomized trial of 710 mechanically ventilated patients, light sedation, defined as a score of -2 to -3 on the Richmond Agitation and Sedation Scale (RASS; this scale ranges from -5 [unresponsive] to +4 [combative]) with daily interruption, was compared with "no sedation" [66]. Patients in the sedation group received a propofol infusion followed by midazolam while patients in the "no sedation" group were allowed to receive intermittent analgesia with intravenous morphine and sedated only if necessary and if nonpharmacologic methods and analgesia with morphine had failed. By day 7, the mean RASS score was -0.8 in the nonsedation group and -1.8 in the sedation group. Although the 90-day mortality was lower in the sedation group, it was not statistically significant (37 versus 42 percent). The number of ICU- and ventilator-free days and days free from coma or delirium was also no different. Although the thromboembolic event rate was higher in the sedation group, the total event rate was low (11 of 710 patients [1.5] percent). However, the inclusion criteria were very specific (among 2300 screened only 710 underwent randomization) suggesting that the approach of "no sedation" is not generalizable to all mechanically ventilated patients. In addition, one-third of patients in the nonsedation group received sedation in the first 24 hours after randomization and continued to receive intermittent morphine during the trial. Furthermore, the trial may have been underpowered to detect a difference in mortality. Further studies are required before the practice of "no sedation" can be routinely applied to mechanically ventilated patients in the ICU.

Concerns related to patient safety have been a significant obstacle to implementation of daily interruption of continuous sedative-analgesic infusions [67,68]. These concerns include the possibility of long-term psychological sequelae (eg, posttraumatic stress disorder [PTSD]) and myocardial ischemia. There is little evidence to support these concerns, as demonstrated by the following studies:

- An observational study performed using patients from the first randomized trial described above plus contemporaneous patients that were not enrolled in that trial found that patients who received daily interruption of their continuous sedative-analgesic infusion did not experience adverse psychological outcomes and were less likely to have symptoms of PTSD than those who received conventional management [69].

- In the trial described above that randomly assigned 336 patients to a daily spontaneous breathing trial and either a daily spontaneous awakening trial or conventional sedation management [59], there was no difference in the frequency of PTSD at 3 or 12 months [60].

- A prospective cohort study evaluated 74 patients with risk factors for coronary artery disease who were receiving mechanical ventilation [70]. Electrocardiographic monitoring was performed during the continuous sedative-analgesic infusion and during interruption of the continuous infusion. Myocardial ischemia (defined as ST segment elevation or depression >0.1 mV from baseline lasting 10 minutes or longer) was identified in 24 percent of the patients at some time during the study. Myocardial ischemia was not more common during interruption of the continuous infusion, although heart rate, blood pressure, respiratory rate, and catecholamines increased significantly. The study did not address the cumulative effects of multiple days of interrupting the continuous infusion.

WITHDRAWAL

When pharmacological sedation is no longer necessary, the sequence and rate of discontinuing the sedative-analgesic agents must be determined:

- For patients receiving more than one sedative-analgesic medication (eg, a sedative and an opioid), the opioid should be tapered last so that the patient does not awake in pain.

- The rate of the reduction should be individualized. Generally speaking, discontinuation over a short period of time (eg, hours) is acceptable if the sedative-analgesic agent has been administered for a short duration (≤7 days). In addition, abrupt discontinuation may be appropriate in patients who have received sedation for greater than seven days who are deeply sedated from prolonged accumulation of medication. However, a gradual reduction (~10 to 25 percent per day) may be necessary if the sedative-analgesic agent has been administered for >7 days and the patient exhibits evidence of tachyphylaxis, with increasing dosage required over time to achieve the same level of sedation.

It is important for clinicians to realize that there may be a delay (ie, days) between the moment that reduction of the sedative-analgesic agent begins and the patient begins to awaken, particularly following long-term therapy. This is because lipophilic drugs accumulate in tissue stores and must be mobilized for elimination.

During the reduction of the sedative-analgesic medication, the patient should be closely observed for withdrawal symptoms. Acute withdrawal symptoms in this setting appear to be common. In an observational study of 28 mechanically ventilated patients who had been in the ICU for greater than one week, nine patients (32 percent) developed acute withdrawal symptoms when their sedative-analgesic medication was reduced [71]. Higher doses of benzodiazepines and opiates conferred a higher risk of withdrawal.

Benzodiazepine withdrawal symptoms include agitation, confusion, anxiety, tremors, tachycardia, hypertension, and fever. Seizures may also occur. The administration of intermittent intravenous or oral lorazepam (0.5 to 1 mg every 6 to 12 hours) may help protect the patient from developing withdrawal symptoms as the continuous benzodiazepine infusion reduced.

Opiate withdrawal symptoms include agitation, anxiety, confusion, rhinorrhea, lacrimation, diaphoresis, mydriasis, piloerection, stomach cramps, diarrhea, tremor, nausea, vomiting, chills, tachycardia, hypertension, and fever. Several strategies have been proposed for preventing opioid withdrawal, including de-escalating the dose, converting to a longer acting oral equivalent, converting to a long-acting barbiturate (eg, phenobarbital), and adding an alpha-2-agonist (clonidine, dexmedetomidine)

[72,73]. However, there are no controlled trials of any strategy and there is no consensus as to the best strategy. Data are limited to case reports, including two reports in which dexmedetomidine was initiated at a dose of 0.7 mcg/kg/hour (with or without a loading dose) and successfully facilitated opioid withdrawal [74,75].

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Nonprocedural sedation".)

SUMMARY AND RECOMMENDATIONS

- **Rationale** – Distress is common in critically ill patients, particularly among those who are intubated or have difficulty communicating with their caregivers. However, many patients may be comfortable without requiring a depressed level of consciousness. (See 'Introduction' above.)

- **Assessment** – Before a sedative-analgesic agent is initiated to treat agitation due to distress, the cause of the distress should be identified and treated. Nonpharmacological strategies should be implemented simultaneously. (See 'Pre-initiation' above.)

- **Initiation** – Pharmacological sedation is indicated when treatment of the cause of the distress and the nonpharmacological interventions cannot sufficiently control the agitation. (See 'Initiation' above.)

  - **Agent selection** – Available agents are listed in the table (table 1). The sedative-analgesic agent and its initial dose are selected on the basis of several factors: the etiology of the distress, the expected duration of therapy, potential drug interactions, the desired depth of sedation, and pharmacokinetic-modifying variables (table 3). (See 'Available agents' above and 'Selection of an agent' above and 'Initial dose' above.)

  - **Administration** – We recommend **not** routinely using uninterrupted sedative-analgesic infusions to sedate critically ill patients (**Grade 1B**). Intermittent boluses, continuous infusions directed by a sedation protocol, or daily interruption of continuous infusions are preferable. (See 'Administration' above and 'Avoid excess sedation' above.)

- **Monitoring** – All patients should be frequently reassessed to determine whether their agitation and underlying distress are being adequately managed (table 4 and table 5). The sedative-analgesic medication should then be titrated or tapered accordingly. Scoring systems have been developed to facilitate the evaluation. (See 'Monitoring' above.)

- **Withdrawal** – Once comfort is achieved initially, the goal depth of sedation should be frequently reassessed and adjusted. As the respiratory failure or other critical illness is treated, the sedative requirement should fall. Thus, daily attempts should be made to reduce the level of sedation, although the rate of the reduction must be individualized. For patients receiving more than one sedative-analgesic medication, we taper the opioid last, so that the patient does not awake in pain. During the reduction of sedation, the patient should be closely observed for withdrawal symptoms. (See 'Withdrawal' above.)

REFERENCES

1. Hansen-Flaschen J. Improving patient tolerance of mechanical ventilation. Challenges ahead. Crit Care Clin 1994; 10:659.
2. Lewis KS, Whipple JK, Michael KA, Quebbeman EJ. Effect of analgesic treatment on the physiological consequences of acute pain. Am J Hosp Pharm 1994; 51:1539.
3. Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018; 46:e825.
4. Griffiths J, Hatch RA, Bishop J, et al. An exploration of social and economic outcome and associated health-related quality of life after critical illness in general intensive care unit survivors: a 12-month follow-up study. Crit Care 2013; 17:R100.
5. Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004; 32:955.
6. McNicoll L, Pisani MA, Zhang Y, et al. Delirium in the intensive care unit: occurrence and clinical course in older patients. J Am Geriatr Soc 2003; 51:591.
7. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013; 41:263.
8. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004; 291:1753.
9. Klein Klouwenberg PM, Zaal IJ, Spitoni C, et al. The attributable mortality of delirium in critically ill patients: prospective cohort study. BMJ 2014; 349:g6652.
10. Mehta S, Cook D, Devlin JW, et al. Prevalence, risk factors, and outcomes of delirium in mechanically ventilated adults. Crit Care Med 2015; 43:557.

11. Aldemir M, Ozen S, Kara IH, et al. Predisposing factors for delirium in the surgical intensive care unit. Crit Care 2001; 5:265.
12. Schieveld JNM, Strik JJMH. Hypoactive Delirium Is More Appropriately Named as "Acute Apathy Syndrome". Crit Care Med 2018; 46:1561.
13. Krewulak KD, Rosgen BK, Ely EW, et al. The CAM-ICU-7 and ICDSC as measures of delirium severity in critically ill adult patients. PLoS One 2020; 15:e0242378.
14. Fontaine DK. Nonpharmacologic management of patient distress during mechanical ventilation. Crit Care Clin 1994; 10:695.
15. Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 2010; 375:475.
16. Strøm T, Stylsvig M, Toft P. Long-term psychological effects of a no-sedation protocol in critically ill patients. Crit Care 2011; 15:R293.
17. Chlan LL, Weinert CR, Heiderscheit A, et al. Effects of patient-directed music intervention on anxiety and sedative exposure in critically ill patients receiving mechanical ventilatory support: a randomized clinical trial. JAMA 2013; 309:2335.
18. Bradt J, Dileo C. Music interventions for mechanically ventilated patients. Cochrane Database Syst Rev 2014; :CD006902.
19. Messika J, Martin Y, Maquigneau N, et al. A musical intervention for respiratory comfort during noninvasive ventilation in the ICU. Eur Respir J 2019; 53.
20. Wunsch H, Kahn JM, Kramer AA, Rubenfeld GD. Use of intravenous infusion sedation among mechanically ventilated patients in the United States. Crit Care Med 2009; 37:3031.
21. Soro M, Gallego L, Silva V, et al. Cardioprotective effect of sevoflurane and propofol during anaesthesia and the postoperative period in coronary bypass graft surgery: a double-blind randomised study. Eur J Anaesthesiol 2012; 29:561.
22. Gagnon DJ, Fontaine GV, Riker RR, Fraser GL. Repurposing Valproate, Enteral Clonidine, and Phenobarbital for Comfort in Adult ICU Patients: A Literature Review with Practical Considerations. Pharmacotherapy 2017; 37:1309.
23. Hammond DA, Rowe JM, Wong A, et al. Patient Outcomes Associated With Phenobarbital Use With or Without Benzodiazepines for Alcohol Withdrawal Syndrome: A Systematic Review. Hosp Pharm 2017; 52:607.
24. Roberts DJ, Haroon B, Hall RI. Sedation for critically ill or injured adults in the intensive care unit: a shifting paradigm. Drugs 2012; 72:1881.
25. Lewis K, Alshamsi F, Carayannopoulos KL, et al. Dexmedetomidine vs other sedatives in critically ill mechanically ventilated adults: a systematic review and meta-analysis of randomized trials. Intensive Care Med 2022; 48:811.
26. Møller MH, Alhazzani W, Lewis K, et al. Use of dexmedetomidine for sedation in mechanically ventilated adult ICU patients: a rapid practice guideline. Intensive Care Med 2022; 48:801.
27. Kollef MH, Levy NT, Ahrens TS, et al. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. Chest 1998; 114:541.
28. Wittbrodt ET. The ideal sedation assessment tool: an elusive instrument. Crit Care Med 1999; 27:1384.
29. Devlin JW, Boleski G, Mlynarek M, et al. Motor Activity Assessment Scale: a valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit. Crit Care Med 1999; 27:1271.
30. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med 1999; 27:1325.
31. Weinert C, McFarland L. The state of intubated ICU patients: development of a two-dimensional sedation rating scale for critically ill adults. Chest 2004; 126:1883.
32. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002; 166:1338.
33. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond AgitationSedation Scale (RASS). JAMA 2003; 289:2983.
34. Bizek KS. Optimizing sedation in critically ill, mechanically ventilated patients. Crit Care Nurs Clin North Am 1995; 7:315.
35. Ambuel B, Hamlett KW, Marx CM, Blumer JL. Assessing distress in pediatric intensive care environments: the COMFORT scale. J Pediatr Psychol 1992; 17:95.
36. Olleveant N, Humphris G, Roe B. A reliability study of the modified new Sheffield Sedation Scale. Nurs Crit Care 1998; 3:83.
37. Ramsay MA, Savege TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. Br Med J 1974; 2:656.
38. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Crit Care Med 2001; 29:1370.
39. Simmons LE, Riker RR, Prato BS, Fraser GL. Assessing sedation during intensive care unit mechanical ventilation with the Bispectral Index and the Sedation-Agitation Scale. Crit Care Med 1999; 27:1499.
40. Deogaonkar A, Gupta R, DeGeorgia M, et al. Bispectral Index monitoring correlates with sedation scales in brain-injured patients. Crit Care Med 2004; 32:2403.
41. Mondello E, Siliotti R, Noto G, et al. Bispectral Index in ICU: correlation with Ramsay Score on assessment of sedation level. J Clin Monit Comput 2002; 17:271.
42. Frenzel D, Greim CA, Sommer C, et al. Is the bispectral index appropriate for monitoring the sedation level of mechanically ventilated surgical ICU patients? Intensive Care Med 2002; 28:178.
43. Ely EW, Truman B, Manzi DJ, et al. Consciousness monitoring in ventilated patients: bispectral EEG monitors arousal not delirium. Intensive Care Med 2004; 30:1537.
44. De Deyne C, Struys M, Decruyenaere J, et al. Use of continuous bispectral EEG monitoring to assess depth of sedation in ICU patients. Intensive Care Med 1998; 24:1294.

45. Vivien B, Di Maria S, Ouattara A, et al. Overestimation of Bispectral Index in sedated intensive care unit patients revealed by administration of muscle relaxant. Anesthesiology 2003; 99:9.
46. Dahaba AA. Different conditions that could result in the bispectral index indicating an incorrect hypnotic state. Anesth Analg 2005; 101:765.
47. Shehabi Y, Chan L, Kadiman S, et al. Sedation depth and long-term mortality in mechanically ventilated critically ill adults: a prospective longitudinal multicentre cohort study. Intensive Care Med 2013; 39:910.
48. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med 2012; 186:724.
49. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. Crit Care Med 1999; 27:2609.
50. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000; 342:1471.
51. Carson SS, Kress JP, Rodgers JE, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Crit Care Med 2006; 34:1326.
52. Schweickert WD, Gehlbach BK, Pohlman AS, et al. Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. Crit Care Med 2004; 32:1272.
53. Balas MC, Vasilevskis EE, Olsen KM, et al. Effectiveness and safety of the awakening and breathing coordination, delirium monitoring/management, and early exercise/mobility bundle. Crit Care Med 2014; 42:1024.
54. Aitken LM, Bucknall T, Kent B, et al. Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients. Cochrane Database Syst Rev 2015; 1:CD009771.
55. Collinsworth AW, Priest EL, Campbell CR, et al. A Review of Multifaceted Care Approaches for the Prevention and Mitigation of Delirium in Intensive Care Units. J Intensive Care Med 2016; 31:127.
56. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012; 308:1985.
57. de Wit M, Gennings C, Jenvey WI, Epstein SK. Randomized trial comparing daily interruption of sedation and nursing-implemented sedation algorithm in medical intensive care unit patients. Crit Care 2008; 12:R70.
58. Nassar Junior AP, Park M. Daily sedative interruption versus intermittent sedation in mechanically ventilated critically ill patients: a randomized trial. Ann Intensive Care 2014; 4:14.
59. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008; 371:126.
60. Jackson JC, Girard TD, Gordon SM, et al. Long-term cognitive and psychological outcomes in the awakening and breathing controlled trial. Am J Respir Crit Care Med 2010; 182:183.
61. Burry L, Rose L, McCullagh IJ, et al. Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation. Cochrane Database Syst Rev 2014; :CD009176.
62. Minhas MA, Velasquez AG, Kaul A, et al. Effect of Protocolized Sedation on Clinical Outcomes in Mechanically Ventilated Intensive Care Unit Patients: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Mayo Clin Proc 2015; 90:613.
63. Mehta S, Burry L, Martinez-Motta JC, et al. A randomized trial of daily awakening in critically ill patients managed with a sedation protocol: a pilot trial. Crit Care Med 2008; 36:2092.
64. Kher S, Roberts RJ, Garpestad E, et al. Development, implementation, and evaluation of an institutional daily awakening and spontaneous breathing trial protocol: a quality improvement project. J Intensive Care Med 2013; 28:189.
65. Hager DN, Dinglas VD, Subhas S, et al. Reducing deep sedation and delirium in acute lung injury patients: a quality improvement project. Crit Care Med 2013; 41:1435.
66. Olsen HT, Nedergaard HK, Strøm T, et al. Nonsedation or Light Sedation in Critically Ill, Mechanically Ventilated Patients. N Engl J Med 2020; 382:1103.
67. Devlin JW, Tanios MA, Epstein SK. Intensive care unit sedation: waking up clinicians to the gap between research and practice. Crit Care Med 2006; 34:556.
68. Mehta S, Burry L, Fischer S, et al. Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. Crit Care Med 2006; 34:374.
69. Kress JP, Gehlbach B, Lacy M, et al. The long-term psychological effects of daily sedative interruption on critically ill patients. Am J Respir Crit Care Med 2003; 168:1457.
70. Kress JP, Vinayak AG, Levitt J, et al. Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. Crit Care Med 2007; 35:365.
71. Cammarano WB, Pittet JF, Weitz S, et al. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. Crit Care Med 1998; 26:676.

72. Honey BL, Benefield RJ, Miller JL, Johnson PN. Alpha2-receptor agonists for treatment and prevention of iatrogenic opioid abstinence syndrome in critically ill patients. Ann Pharmacother 2009; 43:1506.

73. Al-Qadheeb NS, Roberts RJ, Griffin R, et al. Impact of enteral methadone on the ability to wean off continuously infused opioids in critically ill, mechanically ventilated adults: a case-control study. Ann Pharmacother 2012; 46:1160.

74. Maccioli GA. Dexmedetomidine to facilitate drug withdrawal. Anesthesiology 2003; 98:575.

75. Multz AS. Prolonged dexmedetomidine infusion as an adjunct in treating sedation-induced withdrawal. Anesth Analg 2003; 96:1054.

Topic 1606 Version 54.0

GRAPHICS

Drugs used to sedate critically-ill patients

Analgesics
Fentanyl
Hydromorphone
Morphine sulfate
Remifentanil
Sedative-hypnotics
Benzodiazepines
Diazepam
Lorazepam
Midazolam
Anesthetic-sedatives
Propofol
Alpha-2 agonists
Dexmedetomidine
Neuroleptics
Haloperidol
Olanzapine
Quetiapine
Risperidone
Barbiturates*
Methohexital
Thiopental

* Not recommended as usual agents for ICU sedation. See Text.

Graphic 69394 Version 1.0

Effects of sedative drugs

Drug	Anxiolysis	Hypnosis	Amnesia	Analgesia
Benzodiazepines	+	+	+	–
Dexmedetomidine	+	–	–	+
Haloperidol	+	+*	+*	–
Opioid analgesics	–	–	–	+

Propofol	+¶	+	+*	–

* Minimal effect.

¶ Only at low doses.

Graphic 51282 Version 2.0

Intravenous* sedative and analgesic dosing regimens for managing pain, agitation, and delirium in the intensive care unit

Drug	Loading dose	Maintenance dose range	Onset (minutes)	Duration of intermittent dose (minutes)	Characteristics and role
Opioid analgesics¶					
Fentanyl¶	1 to 2 mcg/kg$^{\Delta}$ (25 to 100 mcg)¶	0.35 to 0.5 mcg/kg every 0.5 to 1 hour intermittent (25 to 50 mcg)¶ **and/or** 0.7 to 10 mcg/kg/hour infusion[1] For most patients, 1 to 3 mcg/kg/hour infusion (50 to 300 mcg/hour)¶ with asneeded intermittent bolus doses is sufficient	<1 to 2	30 to 60$^{\diamond}$	**Advantages:** Potent analgesic-sedative with immediate onset and less hypotension than other opioid analgesic choices due to relative lack of histamine release. Metabolized hepatically by CYP3A4 to inactive metabolites. **Disadvantages:** Highly lipophilic parent drug accumulates in adipose and other tissue with repeated or prolonged administration. Chest wall rigidity may occur with higher dosing§. **Role:** A good choice for analgesia for most critically ill patients.
Hydromorphone	0.5 to 2 mg$^{\Delta}$	0.2 to 0.6 mg every 1 to 2 hours intermittent **and/or** 0.5 to 3 mg/hour infusion	5 to 10	240 to 300	**Advantages:** IV administration requires small volumes relative to other opioids. Non-CYP metabolism (glucuronidation) may be an advantage for patients receiving drugs that significantly alter CYP3A4 metabolism and thereby interact with fentanyl. **Disadvantages:** Potentially neurotoxic (excitatory) metabolite(s) may accumulate in hepatic and/or renal dysfunction§. **Role:** Analgesic option alternative to fentanyl or morphine. Dose adjustment and gradual titration needed for patients with renal and/or hepatic impairment.
Morphine sulfate	2 to 10 mg$^{\Delta}$	2 to 4 mg every 1 to 2 hours intermittent **and/or** 2 to 30 mg/hour infusion	5 to 10	240 to 300	**Advantage:** Non-CYP metabolism (glucuronidation) may be an advantage for selected patients receiving drugs that significantly alter CYP3A4 metabolism and thereby interact with fentanyl. **Disadvantages:** Can accumulate in hepatic or renal dysfunction and prolong effects. Histamine release and vagally mediated venodilation, hypotension, and bradycardia can be significant§. **Role:** Analgesic alternative to fentanyl or hydromorphone where preload reduction and myocardial depressive effects are desirable or tolerable. Dose adjustment and gradual titration needed for patients with renal and/or hepatic impairment. Avoid in patients with advanced or decompensated liver disease with renal impairment due to risk of accumulation of neurotoxic metabolite. Infusions are not generally used for sedation or analgesia in the ICU but are more commonly used for palliative purposes.

Remifentanil¶	Optional: 1.5 mcg/kg¶ [1] Most ICU patients can be managed without bolus doses; if required, a bolus of 0.5 mcg/kg is	0.5 to 15 mcg/kg/hour infusion Use ideal body weight to determine dose for obese patients¶	1 to 3	5 to 10 (after cessation of infusion)	**Advantages:** Ultra-short-acting. Cleared by nonspecific plasma esterases to inactive metabolites. Does not accumulate in renal or hepatic impairment. Prompt reversal of analgesia and sedation upon discontinuation. **Disadvantages:** Anticipate pain and discomfort upon abrupt cessation. Glycine excipient may accumulate
	usually sufficient; larger boluses are associated with significant reductions in HR and MAP				in renal impairment§. **Role:** An alternative to fentanyl for patients requiring frequent neurologic assessments or those with multiorgan failure.
Nonopioid analgesics (adjunctive or opioid sparing)					
Acetaminophen (paracetamol)	None	Oral, rectal: 325 to 1000 mg every 4 to 6 hours IV: 650 mg IV every 4 hours to 1000 mg IV every 6 hours, or 15 mg/kg IV every 6 hours for patients weighing <50 kg Maximum ≤4 g/day	Oral: 30 to 60 Rectal: Variable IV: 5 to 10	240 to 360	**Advantages:** Lacks dependence and tolerance of opioids. Lacks antiplatelet effect and gastrointestinal toxicity of NSAIDs. **Disadvantages:** Lacks significant anti-inflammatory effect. IV preparation requires administration over 15 minutes. Can cause hepatotoxicity in chronic or acute overdose. Avoid or use a lower daily dose in older adults and patients at risk for hepatotoxicity (eg, heavy alcohol use or malnourished). Interacts with warfarin (may prolong INR) and CYP-inducing drugs (elevated risk of hepatic inflammation). **Role:** First choice for treatment of mild to moderate acute pain and febrile conditions. Adjunctive analgesic that may reduce opioid requirements. When hepatic dysfunction is significant, consider avoiding or reducing dose (eg, ≤2 g/day total).
Ketorolac	Optional: 30 mg once	Age <65 years and weight ≥50 kg: 15 to 30 mg every 6 hours; maximum 120 mg/day for up to 5 days Age ≥65 years or weight <50 kg: 15 mg every 6 hours; maximum 60 mg/day for up to 5 days	IV: ~30	360 to 480	**Advantages:** Lacks dependence and tolerance of opioids. Effective anti-inflammatory. **Disadvantages:** Can cause or worsen renal insufficiency. Dose-related risk of gastropathy. Reversibly inhibits platelet functioning. May alter cardioprotective effect of aspirin. **Role:** Adjunctive analgesic that may reduce opioid requirements. Avoid in renal impairment, gastrointestinal bleeding, platelet dysfunction, ischemic heart disease, heart failure, reduced cardiac output, hypovolemic state, asthma, or cirrhosis. Contraindicated in treatment of perioperative pain in coronary artery bypass graft surgery. Patients should be well hydrated.
Ibuprofen	None	Oral: 400 mg orally every 4 hours (maximum 2.4 g/day chronic) IV: 400 to 800 mg IV every 6 hours (maximum 3.2 g/day acute)	Oral: 30 IV: ~30	240 to 360	**Advantages:** Lacks dependence and tolerance of opioids. Effective anti-inflammatory. **Disadvantages:** Can cause or worsen renal insufficiency. Dose-related risk of gastropathy. Reversibly inhibits platelet functioning. Can alter cardioprotective effect of aspirin. **Role:** Short-term treatment of moderate acute pain and febrile conditions. Adjunctive analgesic that may reduce opioid requirements. Avoid in renal impairment, gastrointestinal bleeding, platelet dysfunction, ischemic heart disease, heart failure, reduced cardiac output, hypovolemic state, asthma, or cirrhosis. Contraindicated in treatment of perioperative pain in coronary artery bypass graft surgery. Patients should be well hydrated.

Gabapentin	None	Oral: Initially 100 mg 3 times per day Oral: Maintenance 900 to 3600 mg per day in 3 divided doses	Variable	--	**Advantages:** Effective for treatment of neuropathic pain. Low risk of drug interactions. **Disadvantages:** Requires enteral administration, scheduled dosing, and individualized titration over days to weeks. Oral bioavailability is variable (27 to 60%) and inversely proportional to dose. Adverse effects include sedation, dizziness, and ataxia, which may be intensified in renal impairment, requiring dose adjustment. Should not be abruptly stopped, due to risk of discontinuation symptoms. **Role:** Useful adjunct to other analgesics for treatment of neuropathic and postoperative pain or dysesthesias in patients who can be treated with enteral medication. Dose adjustment needed for renal impairment.
Pregabalin	None	Oral: Initially 75 mg once or twice per day Oral: Maintenance 150 to 300 mg twice per day	Variable (hours to days)	--	**Advantages:** Effective for treatment of neuropathic pain. Oral bioavailability (>90%) is more reliable than gabapentin and may provide for more rapid onset of analgesia with a shorter amount of time needed to titrate to full dose. Low risk of drug interactions. **Disadvantages:** Requires enteral administration, scheduled dosing, and titration over days to weeks. Adverse effects include sedation, blurred vision, dry mouth, dizziness, and ataxia, which may be intensified in renal impairment, requiring dose adjustment. Should not be abruptly stopped, due to risk of discontinuation symptoms. **Role:** Useful adjunct to other analgesics for treatment of neuropathic and postoperative pain or dysesthesias in patients who can be treated with enteral medication. Dose adjustment needed for renal impairment.
Anesthetic-sedative					

Propofol[¶]	Bolus doses are usually not given in the ICU	5 to 50 mcg/kg/**minute**[¶] Titrate every 5 to 10 minutes in increments of 5 to 10 mcg/kg/**minute** Some patients require up to 70 mcg/kg/minute, which can increase risk of propofol infusion syndrome (refer to UpToDate topics on sedativeanalgesic medications in critically ill patients: properties, dose regimens, and adverse effects)	<1 to 2	3 to 10[◇]	**Advantages:** Potent sedative-hypnotic associated with an immediate onset and rapid awakening upon discontinuation when administered for short-term use. Metabolism is reportedly unaltered in hepatic or renal impairment and subject to few significant drug interactions. Infusion is readily titratable to desired depth of sedation, minimizing risk of oversedation. Propofol effectively decreases intracranial pressure, lowers cerebral metabolism, controls intractable seizures, and may reduce shivering in the rewarming phase of induced hypothermia following resuscitation from cardiac arrest. **Disadvantages:** Adverse effects include hypotension, bradycardia, respiratory depression, decreased myocardial contractility, elevated triglycerides, peripheral injection site pain, and rarely propofol infusion syndrome (refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects). Specific product presentations may include potential allergens (egg, soy, peanut, others). Consult product label information. No analgesic effects. **Role:** A good choice in conjunction with appropriate analgesia for short-term sedation of patients in whom rapid awakening is advantageous. Also a good choice to decrease elevated intracranial pressure or for short-term sedation in a general critical care population that is likely to be ready soon for ventilator weaning trials.
Ketamine	0.25 to 0.5 mg/kg bolus IV Bolus doses may be given prior to sedation with an infusion of ketamine or as a single bolus (eg, patients with burns prior to dress changes or for procedural sedation) Bolus dosing may be repeated if necessary during the procedure (maximum dose 2 mg/kg in a 30 minute period)	0.05 to 0.4 mg/kg/hour	≤1	10 to 15 (single dose)	**Advantages:** A potent dissociative sedativeanesthetic with marked analgesia that maintains cardiac output and mean arterial pressure without inhibition of respiratory drive. Does not inhibit protective reflexes. May reduce acute opioid tolerance. **Disadvantages:** Sympathetic stimulation (ie, increased heart rate and myocardial oxygen demand, elevated intracranial pressure and systemic blood pressure) may be intolerable depending upon clinical setting. Rarely, cardiorespiratory depression associated with rapid administration or higher doses. Adverse effects may include hallucinations, delirium upon withdrawal, tonic-clonic movements, dissociative experiences, unpleasant recall, hypersalivation, nausea, and vomiting. Complex metabolism includes CYP3A4, 2C9, 2B6, and non-CYP hepatic transformations and an active metabolite (norketamine), which may accumulate in renal and/or hepatic impairment or due to drug interactions. **Role:** An alternate choice for postsurgical pain management, severe agitation, or as an adjunctive analgesic in patients with severe refractory pain in clinical settings where increased myocardial oxygen demand and sympathetic tone are tolerable.
Central alpha$_2$ agonist					

Dexmedetomidine	Optional: 1 mcg/kg over 10 minutes if hemodynamically stable Usually not given	0.2 to 1.5 mcg/kg/hour Initiate at 0.2 mcg/kg/hour and titrate every 30 minutes**	5 to 10 (optional loading dose) 15 (without loading dose)	60 to 120	**Advantages:** Effective sedative sympatholytic (central alpha$_2$ agonist) with moderate anxiolysis and analgesia. Character and depth of sedation may permit critically ill, mechanically ventilated patients to be interactive or easily awakened, yet comfortable. Can be used in non-mechanically ventilated ICU patients and continued as needed following extubation. Reduces shivering in the rewarming phase of induced hypothermia following resuscitation from cardiac arrest. May be less likely to cause delirium than other sedative choices. **Disadvantages:** Potentially significant hypotension and bradycardia or hypertension that do not resolve quickly upon abrupt discontinuation. Metabolized hepatically by glucuronidation and CYP2A6. Dose reduction recommended with renal and/or hepatic impairment. Rapid administration of loading dose may be associated with cardiovascular instability, tachycardia, bradycardia, or heart block. Does not induce the deep sedation needed for neuromuscular blockade. **Role:** A good choice for short- and long-term sedation in critically ill patients without relevant cardiac conditions. May be useful for sedation of patients with or at high risk of developing delirium, although this has not been well established.
Benzodiazepines¶					
Midazolam¶	0.01 to 0.05 mg/kg$^{\Delta}$ (0.5 to 4 mg)¶	0.02 to 0.1 mg/kg/hour infusion (2 to 8 mg/hour)¶ with intermittent bolus dose(s) if needed. While the patient is on a continuous infusion, periodic re-bolus may be needed to maintain the sedation goal. This approach may help prevent unnecessary dose creep of the infusion.	2 to 5	30$^{\diamond}$	**Advantages:** A potent amnestic and anxiolytic agent with an immediate onset of action and a short duration of effect when administered short term (<48 hours). It is the only IV benzodiazepine that is not delivered in propylene glycol. **Disadvantages:** Hepatically metabolized by CYP3A4 to active metabolites that may accumulate and cause prolonged sedation if delivered long term. Half-life may be prolonged in critically ill patients with hepatic or renal impairment. Risk of delirium. Also, it interacts with drugs used in the ICU (eg, some antiretrovirals, azole antifungals) that alter CYP metabolism such that excess sedation can occur with concomitant use of midazolam and drugs metabolized by CYP3A4. **Role:** A good choice for short-term anxiolysis and treatment of acute agitation. Dose adjustment and gradual titration are needed for patients with renal and/or hepatic impairment.
Lorazepam¶	0.02 to 0.04 mg/kg$^{\Delta}$ (1 to 2 mg)¶	0.02 to 0.06 mg/kg every 2 to 6 hours intermittent (1 to 4 mg)¶ **and/or**	15 to 20	360 to 480$^{\diamond}$	**Advantages:** Sedative, amnestic, potent anxiolysis with anticonvulsant properties. Hepatically metabolized by glucuronidation to inactive metabolites. Relatively low risk of drug interactions and safety in mild to moderate hepatic and renal impairment.

		0.01 to 0.1 mg/kg/hour infusion (0.5 to 10 mg/hour)¶			**Disadvantages:** Relatively slow onset. Risk of oversedation when titrating due to delayed response and accumulation in peripheral tissues. Risk of delirium. IV incompatibilities and risk of line precipitate. Propylene glycol solvent may accumulate with prolonged use or high dosing causing metabolic acidosis and end-organ dysfunction (refer to UpToDate topics on sedative-analgesic medications in critically ill patients: properties, dose regimens, and adverse effects). Long half-life, with significant risk of accumulation in older adults or in patients with significant renal or hepatic impairment. **Role:** A good choice for sedation and anxiolysis for most patients, including those who may require long-term ongoing sedation. Although intermittent bolus dosing may be preferred, a continuous infusion may be initiated for patients requiring frequently repeated higher dosing.
Diazepam¶	0.05 to 0.2 mg/kg$^{\Delta}$ (5 to 10 mg)¶	0.03 to 0.1 mg/kg every 0.5 to 6 hours intermittent (1 to 7 mg)¶ Continuous infusion is not recommended	2 to 5	20 to 60$^{\diamond}$	**Advantages:** Rapid onset with potent sedative and muscle-relaxant effects. **Disadvantages:** Hepatically metabolized by CYP2C19 and 3A4 to active metabolites that may accumulate and cause prolonged sedation if delivered long term. Half-life may be prolonged in critically ill patients with hepatic and/or renal impairment. Risk of delirium. Also, it interacts with drugs used in the ICU that alter CYP metabolism. Injection solution contains propylene glycol solvent and cannot be delivered as a continuous infusion. Injection site pain and risk of phlebitis limit usefulness of IV injections. **Role:** Seldom used for sedation of critically ill patients. May be useful for critically ill patients at risk of alcohol withdrawal or seizures due to drug overdose or poisoning.
Antipsychotics					
Haloperidol¥	0.03 to 0.15 mg/kg$^{\Delta}$ Variable doses; refer to UpToDate topics on sedativeanalgesic medications in critically ill patients: properties, dose regimens, and adverse effects	0.03 to 0.15 mg/kg every 30 minutes to 6 hours Various regimens; refer to UpToDate topics on sedativeanalgesic medications in critically ill patients: properties, dose regimens, and adverse effects	5 to 20 minutes (IV)	30 to 360$^{\diamond}$	**Advantages:** Moderately sedating dopamine$_2$ antagonist for control of positive symptoms of delirium and ICU psychoses. Minimal cardiorespiratory effects in euvolemic, hemodynamically stable patients. **Disadvantages:** Complex hepatic metabolism includes CYP3A4 and 2D6 transformations. Some experts consider certain metabolites to be active or potentially neurotoxic. Half-life becomes prolonged with repeated administration. Adverse effects include dose-dependent QT interval prolongation and hypotension. Interacts with some common ICU drugs by interference with metabolism and/or by having an additive effect, prolonging the QTc. Extrapyramidal symptoms and neuroleptic malignant syndrome are rare in critical care use. **Role:** Potential treatment for agitation and/or delirium in critically ill patients.

Olanzapine‡	Optional: 5 to 10 mg IM May repeat every two to four hours if needed (maximum total 30 mg)	Oral: Initially 5 to 10 mg once daily; increase every 24 hours as needed by 5-mg increments up to 20 mg/day	IM: 15 to 45	IM: ≥120	**Advantages:** Availability of short-acting IM formulation; less risk of extrapyramidal symptoms and QT prolongation than haloperidol. **Disadvantages:** Adverse effects include orthostatic hypotension, hyperglycemia, somnolence, QT interval prolongation, and anticholinergic effects. Undergoes extensive hepatic metabolism including non-CYP (ie, glucuronidation) and CYP1A2 transformations. Half-life may be prolonged (ie, ≥50 hours) with increased risk of accumulation in patients who are older, female, nonsmoking, and/or in the setting of hepatic or renal impairment. **Role:** Potential alternative or add-on to as-needed IV haloperidol for treatment of acute agitation and/or delirium in the ICU. Use lowest starting dose and titrate more gradually in patients with renal and/or hepatic impairment and/or other factors that predispose for slowed metabolism (see "Disadvantages" above).
Quetiapine‡	None	Oral: Initially 50 mg every 12 hours; increase every 24 hours as needed up to 400 mg/day	Oral: 60 (initial effect); ≥24 hours (full effect)	Oral: 6 to 12 hours	**Advantages:** Less risk of extrapyramidal symptoms and possibly less risk of QT prolongation than haloperidol. **Disadvantages:** Requires enteral route of administration and scheduled dosing due to slow onset of action and relatively gradual titration schedule. Adverse effects may include sedation or orthostatic hypotension, and risk of QT interval prolongation remains. Hepatically metabolized by CYP3A4 to active and inactive metabolites. **Role:** A potential choice as adjunct to as-needed IV haloperidol for treatment of agitation and/or delirium. In advanced hepatic impairment, initiate with reduced dose and titrate in lower increments.
Ziprasidone†	Optional: 10 mg IM May repeat every two hours if needed (maximum 40 mg total) **or** 20 mg IM May repeat once after 4 hours if needed (maximum 40 mg total)	Oral: 20 to 40 mg orally every 12 hours	IM: 30	IM: ≥90	**Advantages:** Availability of short-acting IM formulation; less risk of extrapyramidal symptoms than haloperidol. **Disadvantages:** Orthostatic hypotension, hyperglycemia, QT prolongation; undergoes extensive hepatic metabolism by hepatic non-CYP and CYP3A4 transformations to active and inactive metabolites; IM formulation contains cyclodextrin (a potential nephrotoxin), which can accumulate in renal impairment; an IV formulation is not available. Oral formulation needs to be taken in a fed state (≥500 calories) for reliable absorption. **Role:** A potential alternative or add-on to as-needed IV haloperidol for treatment of acute agitation in the ICU†. Dose reduction is needed in advanced hepatic impairment. Specific recommendations are not available. Avoid prolonged use of IM preparation in patients with renal impairment due to risk of accumulation of cyclodextrin additive.

Dosing information in this table is for critically ill adults and includes indications, dosing, duration of use, and routes of administration not listed in the US Food & Drug Administration approved product labeling. Refer to UpToDate content on managing pain, agitation, and delirium in critically ill adults, the Lexicomp drug monographs[2], and most recent product labeling for additional information.

Data provided in "Characteristics and role" on drug metabolism and the presence of active metabolite(s) are included and may be useful for assessing the potential for drug interactions and risk of drug accumulation in renal and/or hepatic organ impairment.

CYP: cytochrome P-450 metabolism; IV: intravenous; ICU: intensive care unit; HR: heart rate; MAP: mean arterial pressure; NSAIDs: nonsteroidal antiinflammatory drugs; INR: international normalized ratio; QT: QT interval on the electrocardiogram; QTc: corrected QT interval; IM: intramuscularly.

* All doses shown are for IV administration except where otherwise noted (eg, oral or rectal acetaminophen, IM olanzapine optional initial dose).

¶ In patients who are **obese**, standard, non-weight-based initial dosing is preferred. Standard adult doses, ie, scaled to ideal body weight, are shown in parentheses following weight-based doses. A separate calculator to determine ideal body weight is available in UpToDate. For additional information, refer to UpToDate topic reviews on ICU management of the complicated postoperative bariatric surgery patient.

Δ One or more loading doses may be needed. See onset of action data for minimum time between re-dosing. Loading dose should be reduced or omitted in patients who are older, hypovolemic, having increasing vasopressor requirements, or at-risk for hemodynamic compromise.

◇ Duration of action shown is for initial dosing. Duration becomes significantly prolonged after repeated dosing or with administration as a continuous infusion due to accumulation of drug in adipose tissue.

§ As with all opioids, tolerance may require dose escalation, and withdrawal syndrome may be precipitated upon abrupt discontinuation.

¥ Dosing of haloperidol in agitated schizophrenia differs from the recommendations listed in this table for agitated delirium in the ICU and is reviewed separately. Refer to UpToDate topic reviews of emergency management of the acutely agitated or violent patient and pharmacotherapy for acute schizophrenia.

‡ The precise role of second-generation antipsychotics in the treatment or prevention of agitated delirium in ICU is not established. Quetiapine and olanzapine recommendations and data are based on limited experience and small trial results.[1,2] Some experts start at one-quarter to one-half of doses shown and titrate gradually based upon response particularly in older adults and patients with organ dysfunction.

† Ziprasidone recommendations and data are based on limited experience and small trial results in treatment of undifferentiated agitation without symptoms of delirium in non-critically ill emergency department patients.[3,4] Small trial results failed to demonstrate a benefit for scheduled oral ziprasidone in prevention of delirium in a general ICU population.[5]

** Dosing of dexmedetomidine in obese patients is typically performed according to the ideal body weight.

References:

1. *Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med 2010; 38:419.*
2. *Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med 2004; 30:444.*
3. *Martel M, Sterzinger A, Miner J, et al. Management of acute undifferentiated agitation in the emergency department: a randomized double-blind trial of droperidol, ziprasidone, and midazolam. Acad Emerg Med 2005; 12:1167.*
4. *Mantovani C, Labate CM, Sponholz A Jr, et al. Are low doses of antipsychotics effective in the management of psychomotor agitation? A randomized, rated-blind trial of 4 intramuscular interventions. J Clin Psychopharmacol 2013; 33:306.*
5. *Girard TD, Pandharipande PP, Carson SS, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med 2010; 38:428.*

Adapted from:

1. *Barr J, Fraser GL, Puntillo K, et al. Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit. Crit Care Med, 2013; 41:263.*
2. *Lexicomp Online. Copyright © 1978-2023 Lexicomp, Inc. All Rights Reserved.*
3. *Devlin JW, Skrobik Y, Gélinas C, et al. Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU. Crit Care Med 2018; 46:e825.*

Graphic 79667 Version 42.0

Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent, immediate danger to staff
+3	Very agitated	Pulls on or removes tubes or catheters, aggressive behavior toward staff
+2	Agitated	Frequent nonpurposeful movement or patient-ventilator dyssynchrony
+1	Restless	Anxious or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, sustained (>10 seconds) awakening, eye contact to voice
-2	Light sedation	Briefly (<10 seconds) awakens with eye contact to voice
-3	Moderate sedation	Any movement (but no eye contact) to voice
-4	Deep sedation	No response to voice, any movement to physical stimulation
-5	Unarousable	No response to voice or physical stimulation
Procedure		
1.	Observe patient. Is patient alert and calm (score 0)?	
2.	Does patient have behavior that is consistent with restlessness or agitation?	
	Assign score +1 to +4 using the criteria listed above.	
3.	If patient is not alert, in a loud speaking voice state patient's name and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker.	
	Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score -1).	
	Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score -2).	
	Patient has any movement in response to voice, excluding eye contact (score -3).	
4.	If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response.	
	Patient has any movement to physical stimulation (score -4).	
	Patient has no response to voice or physical stimulation (score -5).	

Reproduced with permission from: Sessler C, Gosnell M, Grap MJ, et al. The Richmond agitation-sedation scale. Validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002; 166:1338. Copyright © 2002 American Thoracic Society.

Graphic 57874 Version 2.0

The Ramsay sedation scale

Clinical score	Patient characteristics
1	Awake; agitated or restless or both
2	Awake; cooperative, oriented, and tranquil
3	Awake but responds to commands only
4	Asleep; brisk response to light glabellar tap or loud auditory stimulus
5	Asleep; sluggish response to light glabellar tap or loud auditory stimulus
6	Asleep; no response to glabellar tap or loud auditory stimulus

Redrawn from Ramsay, MA, Savage, TM, Simpson, BR, Goodwin, R, Br Med J 1974; 2:656.

Graphic 65842 Version 4.0

Processed EEG brain monitors

Monitor*	Manufacturer¶	Parameters	Monitoring range	Notes
Unprocessed electroencephalogram (EEG)	Non-proprietary	Alpha, beta, gamma, delta, theta waves, sleep spindles; K complexes, spectral edge frequency, burst suppression; isoelectricity.	No specific index Permutation entropy can be derived	Advantages: Rapid response time, cheap, non-proprietary. Disadvantages: No index or value, requires attention, requires training.
			High frequency, low amplitude (gamma and beta dominance)	Wakefulness common.
			Alpha oscillations	Drowsiness/sedation common.
			Spindles, K complexes, some delta waves	Explicit recall rare.
			Slow delta waves, spectral edge <12	Surgical anesthesia common.
			Burst suppression and isoelectricity	Deep anesthesia common.
Bispectral index (BIS)	Covidien Medical	Bispectral index (proprietary algorithm) based upon beta power, bispectral coherence (synchfastslow), and burst suppression ratio.	0 to 100	Raw EEG and parameters such as spectral edge frequency can and should be displayed. Advantages: Index value can be used to guide anesthesia. May improve outcomes. Disadvantages: Slow response time, costly, proprietary.
			80 to 100	Wakefulness common.
			60 to 80	Drowsiness/sedation common.
			50 to 60	Explicit recall rare.
			30 to 50	Surgical anesthesia common.
			0 to 30	Deep anesthesia common.
Entropy	GE Healthcare	State entropy (SE) and response entropy (RE) indices; burst suppression ratio; entropy of EEG signal decreases with sleep and anesthesia.	RE: (0 to 100) SE: (0 to 91)	SE of EEG signal calculated up to 32 Hz. RE includes additional frequencies up to 47 Hz. SE is always ≤RE. Raw EEG can and should be displayed.
			80 to 100	Wakefulness common.
			Sudden drop in entropy	May be associated with loss of responsiveness.
			40 to 60	Explicit recall rare. Surgical anesthesia common.
			Sudden rise in RE	May indicate pain or muscle activity.
			Lower entropy numbers and burst suppression	Deep anesthesia common.
A-line AEP Monitor/2 (Adds EEG parameters)	Danmeter a/s	Middle latency auditory evoked potentials (MLAEPs); ARX Auditory Index (AAI); middle latency (20 to 80 msec); Composite AAI Index (Proprietary - combines EEG and MLAEP information).	0 to 100	Full range.
			60 to 100	Wakefulness common.
			40 to 60	Drowsiness/sedation common.
			25 to 40	Light anesthesia common.
			15 to 25	Surgical anesthesia common.
			0 to 15	Deep anesthesia common.
Cerebral State Hand-held device Wireless connection to anesthesia monitor	Danmeter a/s	Cerebral State Index (CSI) (Proprietary); burst suppression electromyography and signal quality are indicated; index derived mainly from alpha and beta EEG ratios, burst suppression.	0 to 100	Full range.
			90 to 100	Wakefulness common.
			80 to 90	Drowsiness common.
			60 to 80	Light anesthesia common.

Narcotrend	MT MonitorTechnik GmbH & Co. KG	Cerebrogram (Proprietary); Raw EEG waveform displayed; median and spectral edge frequencies; power in EEG frequency bands is shown.	40 to 60	Surgical anesthesia common.
			10 to 40	Deep anesthesia common.
			0 to 10	Burst suppression or isoelectric EEG.
			A to F	Full range.
			A	Wakefulness common.
			B	Drowsiness common.
			C	Light anesthesia common.
NeuroSense monitor	NeuroWave systems Inc.	The index is calculated via analysis of the EEG signals in the gamma frequency band; uses bilateral frontal EEG channels for derivation of index.	D	Surgical anesthesia common.
			E	Deep anesthesia common.
			F	Burst suppression or isoelectric EEG.
			1 to 100	Conceptualized for use in closedloop anesthesia. Promoted as having a rapid response time.
qCON 2000 monitor	Quantum Medical	The qCON index (proprietary) is a measure of hypnosis that is derived from spectral analysis and burst suppression rate. The qNOX reference scale (proprietary) is derived through EEG signals in patients moving in response to nailbed pressure, and is the component designed for noxiousness. The proprietary algorithm of this device, based on "Adaptive Neuro Fuzzy Inference System" (proprietary), assumes that the EEG signal contains dissociable information on hypnosis and nociception.	0 to 99	Theoretically provides information on both hypnosis and nociception. Promoted as having a rapid response time.
SEDline	Hospira	Patient state index (PSI) (proprietary); raw EEG waveform displayed; density spectral array (DSA) shown; converts EEG acquired from four active, ground and reference electrodes into a proprietary index; anteriorization of EEG power; loss of coherence.	0 to 100	Full range.
			90 to 100	Wakefulness common.
			50 to 90	Drowsiness/sedation common.
			25 to 50	Surgical anesthesia common.
			10 to 25	Deep anesthesia common.
			0 to 10	Burst suppression or isoelectric EEG.
SNAP II	Stryker	SNAP index (Proprietary); spectral analysis of low (0 to 18 Hz) and high (>80 Hz) frequency EEG components; PDA portable device; raw EEG waveform displayed.	0 to 100	Full range.
			90 to 100	Wakefulness common.
			65 to 90	Drowsiness/sedation common.
			50 to 65	Surgical anesthesia common.
			0 to 50	Deep anesthesia common.

* All brain monitors are not specific for the anesthetic state. Patient morbidity, drugs and even natural sleep can confound anesthetic depth monitoring.

¶ Specific manufacturer guidelines for use may vary.

Graphic 81084 Version 8.0

Contributor Disclosures

Barry Fuchs, MD No relevant financial relationship(s) with ineligible companies to disclose. **Cassandra Bellamy, PharmD, BCPS** No relevant financial relationship(s) with ineligible companies to disclose. **Polly E Parsons, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Michael F O'Connor, MD, FCCM** Consultant/Advisory Boards: Intensix/CLEW [Predictive analytics in medicine]. All of the relevant financial relationships listed have been mitigated. **Geraldine Finlay, MD** No relevant financial relationship(s) with ineligible companies to disclose. Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy