



Management of agitation in the intensive care unit

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Agitation is a frequent, challenging problem in intensive care units (ICUs) and affects at least 71% of patients, both young and old [1–3]. Contributing factors include underlying illness, pain, anxiety, and delirium. Dangerous consequences range from poorly tolerated invasive therapy to self-destructive behavior, leading to widespread, sometimes heavy-handed, sedation [4,5].

Patients in the ICU are often too sedated. A recent study found that fewer than 5% were agitated when assessed; this suggested that some sedation is excessive or unnecessary [6]. Used inappropriately, sedatives can impair cognition and depress consciousness and lead to secondary complications, such as failure to wean from mechanical ventilation, prolonged ICU stays, and increased cost of care [7–10]. Conscientious clinicians must strike a balance between treating agitation and avoiding oversedation. This article outlines a systematic, practical approach to evaluating agitation and suggests recommendations for safe, effective treatment.

Characteristics and causes of agitation in the intensive care unit

Agitation is characterized by excess motor activity and is driven by internal factors, such as disease, pain, anxiety, and delirium [11,12]. Activity may be purposeless or, more dangerously, self-destructive. Consequences include removing or disconnecting

catheters, self-extubation, ventilator dysynchrony, and increased oxygen consumption [13–18]. Agitation may also lead to detrimental long-term outcomes that range from unpleasant memories to posttraumatic stress disorder, although some investigators have suggested an association with treatment, rather than agitation itself [19–24].

It is tempting, but dangerous, to consider agitation the natural consequence of critical illness. Similarly, it would be wrong to sedate patients indiscriminately without considering causes that require specific treatment (Box 1) [1,25]. Many patients need sedation, particularly those who require mechanical ventilation, but inappropriate or excess sedation can have unintended consequences [7,8]. In addition to increased length of stay and failure to wean from the ventilator, excessively sedated patients can develop prolonged cognitive impairment and delirium. Important problems, such as chest pain, dyspnea, and neurologic changes, can be missed because patients are difficult to assess.

Agitated patients need the same type of systematic evaluation applied to problems such as hypotension and hypoxia. Finding a specific cause may allow directed, effective treatment (see Box 1). Potentially life-threatening problems such as hypoxia, hypercarbia, hypoglycemia, and sepsis should be considered. Problems that can be easily corrected, but are often missed because patients cannot communicate, should be sought. Examples include uncomfortable bed position and dry mouth.

The problem of patient-ventilator dysynchrony merits special attention [15–17]. Potential causes include inadequate or excessive inspiratory flow rates, tidal volumes that are too high or too low, and ineffective effort. Inadequate ventilator flow rates can

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Box 1. Causes of agitation that require specific interventions

Potentially life threatening

- Gas exchange
 - Hypoxemia
 - Hypercarbia
- Metabolic
 - Hypoglycemia
 - Acidosis
- Ventilator related
 - Endotracheal tube malposition
 - Tension pneumothorax
- Infection
 - Central nervous system infection
 - Sepsis
- Drug and alcohol related
 - Intoxication
 - Withdrawal
- Ischemia
 - Myocardial
 - Intestinal
 - Cerebral

Miscellaneous

- Patient-ventilator dyssynchrony
 - Inadequate flow rates
 - Excessive tidal volumes
- Uncomfortable bed position
- Fear
- Inability to communicate
- Sleep deprivation
- Full bladder
- Nausea
- Need to defecate
- Nicotine withdrawal
- Drug side effects
 - Anticholinergic
 - Paradoxical response to benzodiazepines

be readily detected by examining ventilator graphics. In some patients, simple maneuvers, such as changing the inspiratory flow rate or tidal volume or using pressure control, may improve tolerance of mechanical ventilation. Occasionally, however, heavy sedation may be required for poorly-tolerated mechanical ventilation techniques, such as inverse ration ventilation or permissive hypercapnia. Still, medication should never substitute for effective ventilator adjustments.

Treatment of agitation

Compared with life-threatening problems, such as shock and respiratory failure, the treatment of agitation receives little attention. A recent systematic review found only 15 prospective, randomized studies that investigated successful sedation as a primary outcome in mechanically-ventilated patients [26]. Effective management, however, in addition to providing comfort, is indispensable in helping patients tolerate sometimes noxious treatments and procedures.

Consideration of nonpharmacologic approaches and treatment of specific medical disorders always takes precedence. Life-threatening problems, such as hypoxia and hypoglycemia, and pain from acute diseases, such as myocardial infarction, require prompt attention. Non-life-threatening problems, such as fear, inability to communicate, and uncomfortable bed position, may respond to simple interventions, such as reassurance, a writing board, and repositioning. General approaches that may promote comfort include music therapy and hypnosis, although the effectiveness of these interventions requires further study [27,28]. Even when medication is required, nonpharmacologic interventions can be useful adjuncts to allow lower dosages of medication.

Pain, anxiety, and delirium are the most common causes of agitation that require medication [1]. It is critical to distinguish among them because each requires specific treatment with analgesics, anxiolytics, or antipsychotics, alone or in combination. The failure to identify these problems, particularly pain and delirium, can result in missed opportunities for effective treatment. Some patients become withdrawn rather than agitated but still need treatment. Medication should be used judiciously and thoughtfully and never as a nonspecific chemical “restraint.”

Pharmacotherapy in the critically ill poses unique challenges, particularly because the most commonly used agents have been studied primarily in other populations, such as otherwise healthy people who are undergoing surgery. Findings from these studies may not extrapolate well to the ICU. Factors that may alter response to sedatives and analgesics are outlined in Box 2.

Drugs for pain, anxiety, and delirium are largely lipid soluble. Variations in lipid solubility determine many pharmacokinetic properties. More highly soluble agents, such as fentanyl and midazolam, have a more rapid onset than less soluble ones, such as morphine and lorazepam (Table 1). Similarly, after a single dose, the effects of highly soluble medications diminish more quickly with diffusion into adipose tissue. In contrast, when given repetitively or continu-

Box 2. Factors in the critically ill that alter response to sedative and analgesic agents

Advanced age
 Malnutrition
 Decreased protein binding
 High total body water
 Increased volume of distribution
 Decreased fat and lean mass
 Altered liver and renal function
 Slowed metabolism
 Obesity
 The effects of underlying disease
 Polypharmacy

ously, lipid stores build and the effects of otherwise short-acting drugs become prolonged and more dependent on liver and renal metabolism and excretion. When given in combination (eg, benzodiazepines and narcotics), many agents become synergistic and potentially increase efficacy but also toxicity.

Analgesia (management of pain)

There are few reliable estimates of the prevalence of pain in patients in the ICU. Pain and discomfort are common, for example, in those with cancer [29]. It is likely, however, that pain is widely prevalent, given the nature of critical illness, treatments, and related procedures. Unrelieved pain causes a variety of untoward responses, including tachycardia, increased oxygen consumption, hypercoagulability, immunosuppression, and persistent catabolism [1].

Pain is inherently subjective and therefore, detection and assessment depend upon a patient's ability to communicate, the most reliable indicator being self report. Visual analog, numerical rating, or verbal rating scales may help patients describe symptoms and severity. For those who cannot communicate, recently

introduced techniques that focus on factors, such as physiologic changes, movement, and facial expressions, may help clinicians assess pain. Two recently described scales, the P.A.I.N. and BPS, are examples [30,31].

Narcotics are the main agents used to treat pain; they work primarily by binding to specific receptors in the central nervous system (CNS) [32]. At low doses, they provide analgesia. Sedation occurs as doses increase. Narcotics can be given by several routes: intravenous (IV), intramuscular, enteral, intrathecal, transcutaneous, inhaled, and epidural. IV is used most commonly in the ICU for predictable delivery. Unlike benzodiazepines and propofol, narcotics provide no anxiolysis or amnesia. All are specifically antagonized by naloxone.

The narcotics that are recommended for the ICU are morphine, fentanyl, and hydromorphone [1]. Meperidine should be avoided because active metabolites that can cause seizures may accumulate, particularly in renal failure. Newer, rapidly-acting agents, such as alfentanil, sufentanil, and remifentanil, have no clear role at present [33].

Morphine and meperidine are metabolized by the liver to active metabolites that depend on the kidney for excretion. Dosage adjustments are required with renal dysfunction [34]. In contrast, fentanyl has no active metabolites and dosage modifications are probably unnecessary. All narcotics require adjustment in the elderly, those who have hepatic dysfunction, and with previous use.

Side effects include those that are characteristic to the class and those that are related to specific agents. All narcotics cause respiratory depression, dysphoria, decreased gastrointestinal motility, nausea, and emesis, which can interfere with enteral feeding [35]. All can cause hypotension, particularly when patients are volume-depleted. Hypotension is more common with morphine than fentanyl, particularly when given as a bolus [33]. Factors that contribute to hypotension in euvoletic patients include sympatholysis, vagally-

Table 1
 Pharmacology of commonly used sedatives and analgesics

Drug	Initial dose	Maintenance dosage	Peak (min)	Duration after bolus (min)
Fentanyl	25–100 µg	0.5–2 µg/kg/h	2–5	30–45
Morphine	2–5 mg	2–10 mg/h	30	120–240
Midazolam	0.5–2 mg	0.01–0.2 mg/kg/h	2–5	30–120
Lorazepam	0.5–2 mg	0.01–0.1 mg/kg/h	15–30	360–480
Propofol	0.5 mg/kg ^a	5–75 µg/kg/min	<1 +	5–10
Haloperidol	2–10 mg ^b	25% of load q6 hrs ^b	30	Variable (hours)

^a Propofol boluses commonly cause hypotension. Sedation generally occurs within 10 minutes without a bolus.

^b Can repeat every 20 to 30 minutes until adequate sedation achieved.

mediated bradycardia, and, in agents such as morphine, histamine release. Histamine release also causes pruritus, bronchospasm, and vasodilation. Fentanyl can cause vagotonia as well as muscle rigidity [36].

The threshold for treating patients in the ICU with narcotics should be low, particularly considering the high prevalence of pain. Fentanyl is preferred over morphine when rapid onset or short duration is required [37]. Either agent is effective for continued treatment. Because fentanyl is short acting, it is best given by continuous infusion when repeated dosing is needed. Careful monitoring and control of the airway is mandatory with IV fentanyl because of the potential for rapid respiratory depression. Morphine can be given either by intermittent dosing or continuous infusion. Dosing is highly variable and generally requires titration to effect (see Table 1). Care should be taken to avoid excess accumulation, particularly in elderly patients and those who have liver failure. In patients who are treated with significant dosages for prolonged periods (eg, more than 5 days), gradual downward titration may be required to avoid withdrawal symptoms.

Anxiolysis (management of anxiety)

The prevalence of anxiety in the ICU is unknown, but is likely common given multiple contributing factors, including the effects of illness (eg, respiratory distress), fear, inability to communicate, underlying psychiatric disorders, and personality traits. For this reason, anxiolytics and powerful sedatives, such as the benzodiazepines and propofol, are among the most commonly used agents in the ICU. Neither the benzodiazepines nor propofol provide analgesia, which makes it essential to consider and treat pain before turning to these medications.

Benzodiazepines

Benzodiazepines, particularly lorazepam and midazolam, are the agents that are used most commonly for anxiety (see references [1,32,38,39]). Other uses include promoting sleep, treating seizures and delirium tremens, and fostering amnesia, particularly during procedures. Benzodiazepines bind to CNS γ -aminobutyric acid (GABA) receptors, which promote chloride transduction [32]. They synergize with narcotics and potentiate beneficial effects and toxicities, such as respiratory depression. Used alone, benzodiazepines depress respiration, but less than narcotics. Benzodiazepines are less likely to cause hypotension than narcotics, although it can occur, particularly with high-dose midazolam [40,41]. In susceptible individuals, particularly the elderly who have delirium,

benzodiazepines can increase agitation and confusion; neuroleptics, such as haloperidol, are preferred [1,3]. Accumulation following prolonged use of benzodiazepines may cause cognitive impairment and delirium even after treatment is discontinued. Dosing generally needs to be decreased well before drugs are stopped. All benzodiazepines are reversible with flumazenil, which should be used judiciously and in low doses (eg, 0.2 mg) to avoid withdrawal and seizures [42].

As a class, benzodiazepines are highly protein bound and lipid soluble, although to different degrees. Midazolam is more lipid soluble than lorazepam; thus it has a more brisk onset and offset, making it the drug of choice for rapid or temporary sedation (see Table 1). After prolonged use, however, the duration of midazolam increases significantly as a result of accumulation in adipose stores, decreased metabolism, an increased volume of distribution, obesity, advanced age, and liver and renal dysfunction [32,37,40,43–45]. Unlike lorazepam, midazolam is oxidized in the liver by the cytochrome P450 system, and potentially causes prolonged effects in patients who have liver dysfunction and those who receive drugs that require competitive metabolism, such as erythromycin and fluconazole [46,47]. Tolerance and tachyphylaxis can occur with prolonged use, particularly after 3 or more days [40]. Midazolam is metabolized to an active, but probably not clinically significant, metabolite, α -hydroxymidazolam [41,47].

In contrast to midazolam, lorazepam has a slower onset, is longer acting, and is preferred for continuous sedation (see Table 1) (see references [39,47,48]). Unlike midazolam, lorazepam undergoes glucuronidation and is not metabolized by the P450 system, and, therefore, is less subject to hepatic dysfunction and drug interactions [47]. It has no active metabolites. Lorazepam is generally less expensive than propofol and midazolam [47,49]. Like midazolam, lorazepam accumulates after extended use, which leads to prolonged effects following treatment. High doses can cause acute tubular necrosis and metabolic acidosis with increased anion and osmolar gaps that are due to accumulation of propylene glycol or polyethylene glycol in the carrying solution [50–52].

Lorazepam and midazolam are useful for appropriate indications (see references [47,48,53]). Both can be given by continuous infusion. In a randomized, double-blind study, patients who were treated with lorazepam achieved a desirable level of sedation 87% of the time, compared with 66% of the time in those who received midazolam [47]. In another study, patients who were given a continuous infusion of midazolam took longer to recover their baseline mental status, 1815 minutes compared with 261 minutes with lora-

zepam [53]. In contrast, other investigators found longer recovery times with lorazepam or no difference [47,54].

Because its onset is rapid and its acute duration is limited, midazolam is preferred for short procedures and when the need for sedation is urgent. In contrast, for prolonged sedation, lorazepam is preferred because of lower cost, more consistent efficacy, fewer drug interactions, and less dependence on hepatic metabolism. Both agents require careful monitoring for withdrawal phenomena when discontinued, particularly after several days of use [55].

Propofol

Propofol is a sedative-hypnotic with mild anxiolytic and amnestic properties [56,57]. Key benefits include rapid onset and offset, easy titration, and metabolism that is independent of hepatic and renal function (see Table 1). Clinical effects correlate closely with serum levels [58]. Even after several days, most patients awaken within minutes to hours of stopping infusions, although more time is needed with deeper and longer sedation [58,59]. Potential advantages include earlier discontinuation of mechanical ventilation and the ability to perform serial neurologic assessments [60–63]. Like the benzodiazepines, propofol interacts with GABA receptors in the CNS, although the mechanism is less clear.

Propofol has secondary properties of uncertain significance, including antiepileptic, antiemetic, antipruritic, muscle relaxing, bronchodilating, and antioxidant effects [33,57]. Propofol can treat delirium tremens [64]. Amnesia is not as consistent as with benzodiazepines [65]. Propofol provides no analgesia and concurrent narcotics are needed for pain. Although patients awaken quickly when the drug is stopped, more studies are needed to assess cognitive recovery. Withdrawal phenomena can occur when propofol is discontinued abruptly [65].

Propofol is associated with several side effects and toxicities, some theoretical, others predictable and significant. The most important is hypotension, which is common in patients who are volume depleted or already hemodynamically unstable [56,57]. The risk of hypotension can be decreased, but not avoided completely, by foregoing bolus dosing. Hypertriglyceridemia is common, particularly in patients who were treated for several days at high doses, although the frequency may be less with the 2%, than with the 1%, formulation [66]. Propofol-related lipid loads must be considered when calculating calorie intake and prescribing tube feeds. Sepsis that is due to contamination of propofol has been described, but should be unusual with good practice, which requires infusing the med-

icine directly from the glass container and regularly changing IV sets [67]. Other potential side effects include pancreatitis, metabolic acidosis, adrenal insufficiency, and immune suppression.

Propofol is expensive. In one ICU, it accounted for 6.8% to 13.2% of total drug costs [68]. Combining propofol with midazolam may lower costs [69]. Some investigators suggested that propofol can yield cost savings by decreasing the duration of mechanical ventilation [63]. Savings are quickly negated, however, when extubation is not pending. Therefore, it is difficult to justify propofol for prolonged sedation. Whether it offers any advantages when benzodiazepines are used carefully remains to be seen. Ultimately, propofol is best reserved for patients in whom benzodiazepines fail and in patients whose sedation requires rapid titration [1].

Treatment of delirium

Several recent publications that emphasize new diagnostic techniques have established that delirium is frequent in the ICU, particularly among the elderly, demented, and those who are undergoing mechanical ventilation [70,71]. In the latter population, one study found delirium in 83% that lasted a mean of 2.4 days [70]. Agitation related to delirium, although limited to the minority, can be dangerous, particularly if patients try to harm themselves by removing IV lines or endotracheal tubes. Delirium is an independent risk factor for increased length of stay and is associated with subsequent development of posttraumatic stress disorder [22,72]. It can be easily identified using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), that was recently described by Ely and colleagues [70,73]. Simple and quickly performed (average 2 minutes), the CAM-ICU reliably identifies delirium, even when mechanical ventilation prevents verbal communication.

No formal trials have prospectively compared treatments for delirium. Antipsychotic medications, such as haloperidol, are the drugs of choice [1]. A butyrophenone, haloperidol, is underused in the ICU [74,75]. Dosing is generally higher than outside of the ICU (see Table 1). Although 1 to 2 mg IV every 4 to 6 hours may be adequate, up to 5 to 10 mg every 4 to 6 hours may be needed. Continuous infusions of up to 25 mg/hour have been described [75]. In addition to treating delirium, haloperidol is also useful in patients who cannot tolerate respiratory depression and in those who have paradoxical responses to benzodiazepines, particularly the elderly.

The most important side effect of haloperidol is Torsades de Pointes, which occurs in patients who

have a QT interval corrected (QTc) that is greater than 500 milliseconds and those who receive high dosages (eg, more than 35 mg in 24 hours) [75–77]. Haloperidol should be used carefully, if at all, in patients who have prolonged QTc. Because haloperidol can lower the seizure threshold, it should be used cautiously in those who are at risk for seizures [78].

Dexmedetomidine

Dexmedetomidine, an α_2 agonist, is playing an increasing role in the ICU, particularly in postoperative patients [79,80]. Potential advantages include maintenance of the respiratory drive, rapid awakening (even as infusions continue), analgesia, amnesic properties, good hemodynamic tolerance when given as continuous infusions, and decreased requirements for other medications, such as midazolam and morphine [80,81]. Hypotension can occur during loads because of sympatholytic effects [80]. Until further data accumulate in patients in medical ICUs, routine use is not recommended.

Treatment goals (objective measurements of sedation and agitation)

Sedation goals should meet individual patient needs. Most patients should be kept comfortably awake or lightly asleep but easily arousable. A few patients need deeper sedation, particularly those who require neuromuscular blockade or those who are undergoing difficult-to-tolerate mechanical ventilation, such as inverse ratio or permissive hypercapnia.

Since the 1970s, several investigators designed scales to allow clinicians to objectively measure and describe agitation and to guide therapy [82–88]. Features of a good scale include: (1) the ability to document and measure agitation or calm, (2) clearly defined end points for adjusting treatment, (3) mea-

surements that are easily learned and recorded, and (4) good interrater and intrarater reliability [89].

The most commonly used scale, the Ramsay Sedation Scale, was introduced in the 1970s for surgical procedures [82]. It includes six levels of behavior, ranging from 1 (agitated) to 2 (alert and calm), to 3 through 6 (increasing degrees of sedation from easily arousable to unarousable) (Box 3). Recent work has confirmed acceptable interrater reliability [83]. Although simple, the Ramsay Sedation Scale has shortcomings, most importantly using a single number to describe agitation, which makes it impossible to distinguish between mild and severe distress. More descriptive scales should take its place soon.

The Sedation Agitation Scale (SAS), which was developed by Riker and colleagues [83], is simple and validated and provides a more detailed description of agitation and sedation (Table 2). Useful descriptions accompany the scale to guide scoring. The SAS correlates well with the Bispectral Index (BIS), which is an electroencephalogram (EEG)-based scale [88].

The Richmond Agitation Sedation Scale (RASS), which was created by Sessler and colleagues [84], is becoming increasingly popular (Table 3) [6]. It uses 10 points that range from –5 (unarousable) through 0 (calm, alert) to +4 (combative) that are based on observing the patient's response to verbal and physical stimuli. Clear, easily followed instructions accompany the RASS, which is easily taught to staff. The RASS correlates with administered doses of sedatives and analgesics [6]. It has been validated in several populations (medical, surgical, ventilated, non-ventilated, sedated, non-sedated) and well received by nursing staff [6,84]. It correlates well with the Glasgow Coma Scale, the BIS, and the development of delirium.

Sedation scales that require observation of behavior have inherent shortcomings. First, they require clinical judgment, extensive teaching, and institutional validation to ensure reliability. Second, they are of little value in patients who have severe cognitive disorders and are useless in patients who require neuromuscular blockade. Finally, they cannot measure depth of sedation when patients are unarousable.

Under specific circumstances (eg, with neuromuscular blockade or deep sedation), measures, such as the BIS and auditory evoked responses (AER) or median nerve somatosensory evoked responses (MnSSER), could provide useful alternatives (see references [88,90–93]). In one study, auditory evoked potentials correlated well with Ramsay scores [92]. In another, changes in AER and MnSSER correlated well with nursing interventions [91].

The BIS scores sedation by transforming EEG recordings into a number that ranges from 0 to 100

Box 3. The Ramsay Sedation Scale

1. Anxious and agitated or restless, or both
2. Cooperative, oriented, and tranquil
3. Response to commands only
4. Brisk response to light glabellar tap or loud auditory stimulus
5. Sluggish response to light glabellar tap or loud auditory stimulus
6. No response to light glabellar tap or loud auditory stimulus

Table 2
The Sedation Agitation Scale

Score	Classification	Description
7	Dangerously agitated	Pulls at ETT, tries to remove catheters, climbs over bed rail, strikes at staff, thrashes side to side
6	Very agitated	Does not calm despite frequent verbal reminding of limits, requires physical restraints, bites ETT
5	Agitated	Anxious or mildly agitated, attempts to sit up, calms down to verbal instructions
4	Calm, 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

Abbreviation: ETT, Endotracheal tube.

[88,94]. Zero indicates complete cessation of brain activity, whereas 100 indicates complete wakefulness. As a guide, scores in the mid to upper 90s indicate that the patient is awake; scores in the 70s to 80s correlate with conscious sedation; scores from 40 to 60 occur with general anesthesia [88]. The BIS correlates with SAS and RASS and the ability to respond to commands (see references [6,88,95]). Thus far, BIS has

shown value in surgical settings and has promise in the ICU, particularly for deeply sedated patients and those who require neuromuscular blockade (see references [88,95–97]).

Recent work suggests important limitations to the BIS. In patients who are not receiving neuromuscular blockade, electromyogram (EMG) interference may prevent accurate recordings [90]. A recent study of surgical and medical patients, for example, showed poor correlation between the BIS and SAS, which was at least partially attributable to artifact that was caused by muscle movement [98]. Newer devices, that filter EMG signals, may obviate this problem. In a recent Emergency Department study, the BIS discriminated well between heavy (ie, general anesthesia) and light sedation, but was less reliable in grading lesser degrees of sedation [99]. In a surgical-anesthesia ICU, the BIS did not correlate with clinical sedation measures in 42% of patients and was less reliable with deeper sedation [100].

Clearly, further research is required to determine in which populations, if any, the BIS should be used. In contrast, clinical agitation sedation scales, particularly the RASS or SAS, can be recommended for general use, even while further research continues to determine whether use improves outcomes [1].

Protocols and guidelines

There is growing concern that many patients in the ICU are too sedated, which leads to complications, such as prolonged mechanical ventilation, increased length of stay, delirium, and cognitive impairment. In one study, the use of continuous IV sedation correlated with an increased duration of mechanical ventilation

Table 3
The Richmond Agitation Sedation Scale

Point	Patient response to verbal and physical stimuli
+4	Combative - combative, violent, immediate danger to staff
+3	Very agitated - Pulls or removes tubes or catheters; aggressive
+2	Agitated - Frequent nonpurposeful movement, fights ventilator
+1	Restless - Anxious, apprehensive but movements not aggressive or vigorous
0	Alert and calm
-1	Drowsy - Not fully alert, but has sustained (>10 seconds) awakening (eye opening/contact) to voice
-2	Light sedation - Drowsy, briefly (<10 seconds) awakens to voice or physical stimulation
-3	Moderate sedation - Movement or eye opening (but not eye contact) to voice
-4	Deep sedation - No response to voice, but movement or eye opening to physical stimulation
-5	Unarousable - No response to voice or physical stimulation

and longer lengths of stay in the ICU and hospital [8]. In a prospective, randomized, controlled study, daily interruption of sedation was associated with decreased duration of mechanical ventilation, shorter length of stay in the ICU, and fewer neurologic evaluations [7]. In both studies, improved outcomes were probably related to decreased medication use.

Mounting evidence supports the use of sedation protocols and guidelines in the ICU (see references [1,7,9,10,62,101]). Potential benefits include more appropriate depth of sedation, more judicious dosing, decreased drug accumulation, shorter duration of mechanical ventilation, less cognitive impairment, decreased need for neuromuscular blockade, fewer neurologic work-ups, and cost savings. Key features of such guidelines include an effort to achieve discrete sedation goals while minimizing the quantity of medication given. A well-considered, easily followed pro-

ocol was recently published by the Society of Critical Care Medicine (Fig. 1) [1].

Special considerations

Several special situations pose unique challenges to the intensivist, particularly patients who are experiencing withdrawal from benzodiazepines and narcotics, those who require treatment with neuromuscular blockade, and those who require palliative care.

Withdrawal from benzodiazepines and narcotics

Withdrawal from benzodiazepines or narcotics occurs in a subset of patients in the ICU. In addition to those who experience withdrawal from medications taken at home (including alcohol), a subgroup may

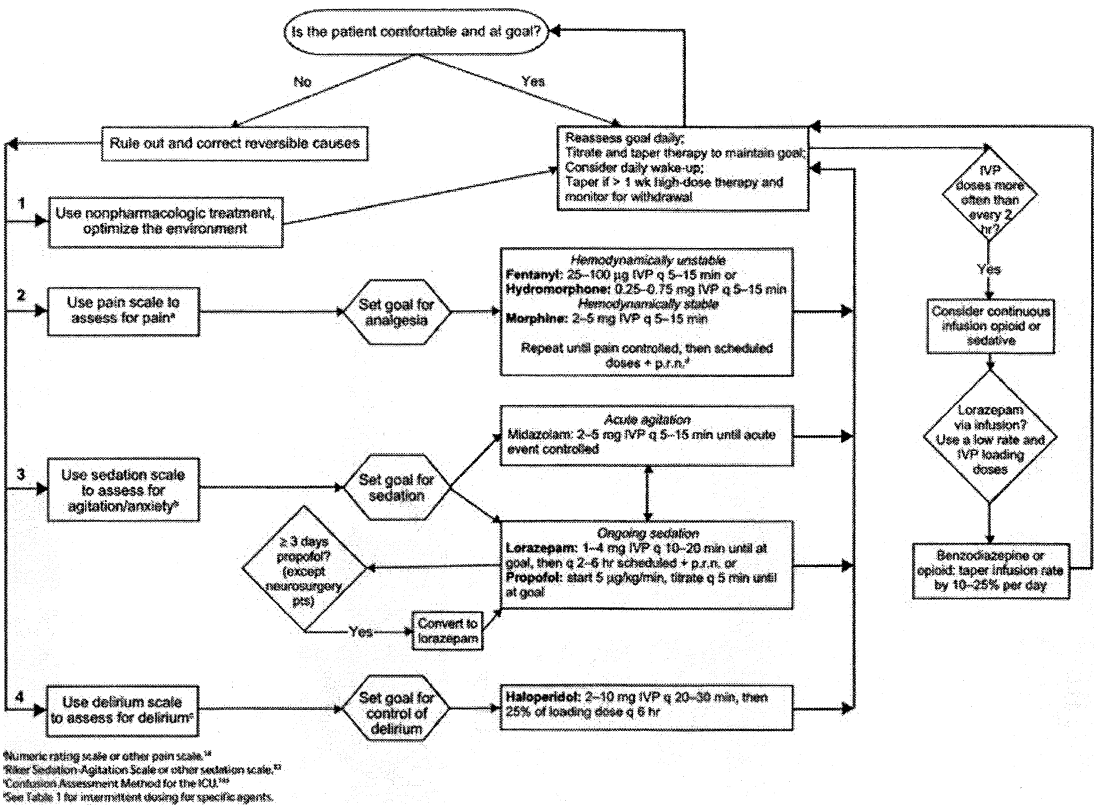


Fig. 1. Society of Critical Care Medicine protocol for assessing and treating agitation in the ICU. (a) Numeric rating scale or other pain scale [31]. (b) Riker Sedation-Agitation Scale or other sedation scale [83]. (c) Confusion Assessment Method for the ICU [70]. (d) See Table 1 for intermittent dosing for specific agents. IVP = intravenous push. (From Jacobi J, Fraser GL, Coursin DB et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002;30(1):124; with permission.)

withdraw from medication that is given in the ICU, particularly those who receive high dosages of benzodiazepines or narcotics over long periods. Symptoms and signs include agitation, hypertension, tachycardia, and diaphoresis, and may easily be missed because of their similarity to other manifestations of critical illness. In one study, 32% of patients experienced withdrawal [55]. Risk factors included treatment with high dosages of narcotics and benzodiazepines, use of neuromuscular blockade, prolonged mechanical ventilation, use of propofol, and not using (or using relatively low doses of) haloperidol. Acute respiratory distress syndrome seemed to be a risk factor, but may have been related to more aggressive sedation. Strategies to prevent withdrawal include judicious dosing of narcotics and benzodiazepines, careful downward titration while monitoring vital signs and symptoms, and providing extra benzodiazepine or narcotics in patients who show signs of withdrawal. A recent study described using propofol as a bridge in patients who were being weaned from midazolam; propofol was also associated with less agitation as midazolam was discontinued [102].

Neuromuscular blockade

Effective sedation generally allows clinicians to avoid more drastic interventions, such as neuromuscular blockade, which should only be used when critical therapy, such as mechanical ventilation, would be otherwise impossible [103]. Even in patients who require poorly-tolerated modes of mechanical ventilation, such as permissive hypercapnia, neuromuscular blockade can generally be avoided. In some cases, however, the drive to breathe, potentiated by hypercapnia, may prevent effective patient-ventilator synchrony, even when patients are nearly comatose. Although increasing sedation may further blunt the respiratory drive, neuromuscular blockade may be necessary for effective oxygenation and ventilation, to prevent complications, and even to limit the accumulation of sedatives. When instituting neuromuscular blockade, it is critical to ensure analgesia and to sedate heavily, generally to the point of coma. Neuromuscular blockade should be stopped immediately when feasible, generally when the medical condition improves. Important complications that are associated with neuromuscular blockade include prolonged weakness that is related to drug accumulation and a severe myopathy, particularly when corticosteroids are administered simultaneously [104]. Because it is impossible to use any of the clinical agitation and sedation scales, intermittent discontinuation of neuro-

muscular blockade to evaluate for agitation or use of a BIS monitor should be strongly considered.

Palliative care

There is significant concern that many patients who are destined to die in the ICU do so with pain and discomfort (see references [29,105,106]). In patients who have terminal illnesses, but are still being treated with curative intent, it may be difficult to balance effective palliation and avoid overmedication, particularly given the complications outlined above. In patients who are having life support withdrawn, treatment of pain and other discomforting symptoms may require aggressive dosing for effective results [107,108]. Although respiratory depression, hypotension, and death are never the goals of therapy, it is often necessary, and ethically acceptable, to give high dosages to ensure adequate palliation, even if such side effects occur. Dosages of morphine and other narcotics that are necessary to alleviate pain and dyspnea may be particularly high in some cases, but thoughtful titration should allow effective treatment in almost all patients.

Summary

Although the effective evaluation and management of agitated patients often receives less attention than other aspects of critical illness, it is among the most important and rewarding challenges that face critical care physicians. Key features of effective management include a thorough, organized search for potentially dangerous and correctable causes; a sound understanding of the pharmacology of analgesics and sedatives; and keeping a steady eye on appropriate management goals. In turn, the reward for excellent care will be shorter lengths of stay, more rapid liberation from mechanical ventilation, improved cognition, cost savings, and, perhaps, improved survival.

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