PSAP

Central Nervous System Syndromes in Critically Ill Adults

Gilles L. Fraser, Pharm.D., FCCM; and Richard R. Riker, M.D.

Reviewed by Linda Gore Martin, Pharm.D., M.B.A., BCPS; and Paul Szumita, Pharm.D., BCPS

Learning Objectives

1. Interpret factors affecting the acute and long-term psychological well-being of the critically ill.
2. Design initiatives to prevent agitation, pain, and delirium and the development of post-traumatic stress disorder in intensive care unit (ICU) patients.
3. Design effective strategies to optimize pharmacologically based ICU patient comfort while avoiding therapeutic misadventures.
4. Appraise mechanisms for caregiver evaluation of pain, agitation, and delirium in verbal and nonverbal critically ill patients.
5. Justify the use of "analgesia-first" sedation for most critically ill patients.
6. Argue successfully for and design a program that avoids drug-induced coma for most patients through the provision of protocol-driven and goal-directed sedation and analgesia using validated assessment tools.
7. Develop a mechanism for the application of daily sedative interruption in the ICU.

Introduction

In the past, intensive care unit (ICU) clinicians defined success by the resolution of disease and patient survival resulting in hospital discharge. With time—and the generation of compelling data—there has been a growing appreciation of the influential role of critical illness and its treatment on patient satisfaction and quality of life. The ICU is an incredibly inhumane environment where patient restlessness, discomfort, agitation, and delirium are arguably the most common patient issues challenging clinicians on a daily basis. In addition, neuropsychological dysfunction associated with critical illness is now recognized as a primary contributor to long-term functional and occupational limitations.

The past decade has witnessed the evolution of validated tools to assess major central nervous system (CNS) syndromes (pain, agitation, and delirium), resulting in more rigorous evaluations of their causes and treatments. These efforts have helped identify factors that may lead to development of another important CNS syndrome, post-traumatic stress disorder (PTSD). We now understand that the method of drug administration affects patient outcomes as much as drug choice. This module will review newer findings for detection, prevention, and treatment of ICU CNS syndromes with a focus on strategies designed to make the ICU a more humane and healing environment for adult patients.

Causes of ICU Pain and the Frequency of Undertreatment

Clinicians easily accept and anticipate that patients experiencing prototypical noxious stimuli and disease states such as surgery, trauma, pancreatitis, invasive procedures, or device insertion will likely suffer pain. These patients are routinely offered analgesia. Less well appreciated is the high occurrence of discomfort associated with mundane and routine ICU care: prolonged immobility, repositioning in bed, central line insertion, wound-dressing changes, endotracheal suctioning, and drain removal. Data suggest that only 20% of patients are offered opiate analgesia before the initiation of these potentially painful events. This unfortunate reality has been documented by postdischarge surveys suggesting that more than 40% of ICU patients felt their pain was underestimated and their analgesic needs were unmet.

The Importance and Unique Aspects of ICU Pain

Pain is defined as an unpleasant sensory experience or an emotional experience associated with the introduction of noxious stimuli that typically leads to some evasive action. In the ICU, this avoidance response to pain is often not possible; therefore, the provision of analgesia is often required. Unrelieved pain has a multitude of physiological and psychological consequences. Pain can initiate the stress response leading to increased oxygen consumption,

Abbreviations in This Chapter

BZD	Benzodiazepine
CAM-ICU	Confusion Assessment Method for the Intensive Care Unit
CNS	Central nervous system
CYP	Cytochrome P450
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive care unit
PTSD	Post-traumatic stress disorder

hemodynamic derangement, hyperglycemia, and altered immune system function. It can also lead to anxiety and increase the risk for PTSD after ICU discharge. Providing comfort in the ICU is complicated, however, because many patients are unable to communicate their analgesic needs. This renders traditional pain assessment tools that use direct patient feedback (e.g., the numeric rating scale, visual analog scale) ineffective.

Monitoring Patient Analgesia Needs in the ICU

The high occurrence of inadequate pain control reported by patients supports an aggressive stance toward the provision of analgesia in the ICU. When patient self-report is impossible or unreliable, nurses, other caregivers, and even family members are recruited to make surrogate pain assessments. Clinical practice recommendations for pain evaluation in these patients have been developed by the American Society for Pain Management Nursing. These recommendations include the following. First, serially assess for the ability to self-report, recognizing the value of direct patient feedback and that cognitive function can vary over time. Second, identify potential causes of pain and discomfort (especially those caused by routine ICU care) and acknowledge that nonverbal patients likely experience the sensation. Third, closely observe patient behaviors that are associated with pain (see below). These recommendations discourage the simple use of changes in vital signs because, without corroborative support, they can be misleading indicators of pain. Lastly, if there is any reason to suspect pain, this group recommends an analgesic trial. Patient response to this intervention has the potential to be diagnostic as well as therapeutic.

Behavioral indicators of pain have traditionally been used to assess analgesic needs and response to therapy in nonverbal ICU patients. Two reliable and valid pain assessment tools based on these behaviors—in conjunction with other patient features including compliance with mechanical ventilation—have been developed. Although the Behavioral Pain Scale and the Critical-Care Pain Observation Tool represent a significant step forward in pain evaluation, we await data linking these assessed scores with patient self-report of pain severity.

It is probable that the choice of pain assessment tool is less important than simply incorporating regular pain evaluations into the nursing care plan. Systematic use of pain assessment tools as a means of quickly identifying and communicating patient analgesia needs to prescribers has been shown to reduce the instance of significant pain by two-thirds.

Management of ICU Pain or Discomfort

Identification of the source of discomfort can guide the approach to relief. Non-pharmacological strategies such as relocating misplaced or migrating endotracheal tubes, adjusting the mode of ventilation, or stabilizing fractures are appropriate, as is repositioning the patient to avoid discomfort from any source including decubitus wounds, back pain, or pain from a chest tube. If these and other maneuvers are not adequate or if pain assessment is difficult or impossible, it is reasonable to assume that pain or discomfort is a likely contributor to agitation. Feedback from survivors of critical illness supports this contention, making provision of analgesia a reasonable first step in the pharmacological provision of comfort.

Opiate Therapy

The opiates are the most commonly used analgesics in the critically ill. All opiates share similar pharmacology by interacting with various opiate receptors in the body. Although the relief of pain is generally the most desired pharmacological effect of the agents, well-known adverse events should be anticipated and prevented whenever possible—such as constipation, by the routine administration of stool softeners and stimulant cathartics, and withdrawal symptoms, by gradually tapering doses (10% to 25% per day) for patients receiving therapy longer than 7 days.

Distinctions among the opiates can help guide drug choice for a particular patient. The liver metabolizes all except remifentanil; some have active metabolites that can accumulate in the setting of renal disease, leading to adverse events. For instance, the accumulation of the 6-glucuronide salt of morphine causes excessive narcotic effects, whereas the metabolite of hydromorphone is potentially neurotoxic. The choice of opiates in the presence of renal disease should be determined by the need for rapid onset (fentanyl) or prolonged activity (hydromorphone or remifentanil infusion). Another pharmacological distinction between opiates is the tendency of morphine to cause histamine release. Resultant venodilation may represent a therapeutic advantage when preload reduction is desirable, but it could be counterproductive in hemodynamically unstable patients. For these patients, fentanyl, remifentanil, or hydromorphone may represent better opiate options.

Remifentanil is an ultra–short-acting, easily titrated opiate that is degraded by nonspecific plasma and tissue esterases to a metabolite that has 0.02% the activity of the parent drug. It does not accumulate with prolonged use, and its metabolism and clearance are independent of liver or kidney function. Offset of activity occurs reliably within 10 minutes of infusion interruption even with long-term use, making this an attractive opiate option for patients requiring frequent neurologic assessments and for those with multiple organ failure. Chest wall rigidity is generally not seen at the doses used in the ICU (0.1–0.4 mcg/kg/minute based on ideal body weight). Dosing titration increments of 0.025 mcg/kg/minute at 5- to 10-minute intervals have been recommended. Because of its rapid offset of action, the potential for patients to experience pain on termination of remifentanil

therapy should be anticipated. Appropriate caregiver advice would include careful stepwise downward dose titration or consideration of changing to a long-acting alternative analgesic. Caregivers should be further advised to clear intravenous tubing of all remifentanil on discontinuance of therapy to prevent the inadvertent administration of this opiate later.

Remifentanil contains glycine as an excipient and is not to be administered in the epidural or intrathecal spaces. In addition, there is concern about the accumulation of glycine and its metabolic product, ammonia, and associated neurologic and cardiac complications. Preliminary data in patients treated for 72 hours suggest that remifentanil is safe, but because glycine concentrations correlate directly with the dose of remifentanil as well as inversely with creatinine clearance, caution is advised, especially in the patient with impaired renal function.

Analgesia-Based "Sedation"

Analgesia-based "sedation" is commonly employed in European ICUs. The concept of providing analgesia first with subsequent sedation supplementation is supported by the frequency of pain and discomfort as primary causes of agitation. This strategy has been compared favorably with more traditional propofol- and benzodiazepine (BZD)-based regimens. Patients receiving "analgesia-first" approaches consistently achieve comfort goals; less than half of these patients require sedation supplementation with other traditional sedative agents. Tested opiates have included remifentanil, fentanyl, and morphine. There are no overwhelming data to support one opiate over another, but remifentanil may offer an advantage in selected patients because its extremely short half-life permits frequent neurologic evaluations. Alternatively, fentanyl represents a reasonable choice because it is inexpensive and relatively short acting. Support for the analgesia-first approach is becoming stronger in light of recent data describing the deliriogenic potential of the BZDs and the recognition of potentially fatal reactions with propofol.

Agitation and Its Consequences in the Critically Ill

Agitation is a very common problem in the ICU, affecting about half of adult patients. It is described as excess motor activity that can be either nonpurposeful (flailing in bed) or purposeful and counterproductive (removing medical devices or attempting to escape). Agitation leads to undesirable acute and long-term sequelae and may adversely affect humanistic and economic outcomes. Acute adverse events associated with ICU agitation include disruption of anastomotic sutures, resulting in surgical reintervention, and removal of medical devices such as endotracheal, vascular, feeding, and drainage tubes, all with varying morbidity and costs. Other acute consequences of agitation are heightened risk for nosocomial infections, trauma resulting from falls, and caregiver injury from violent patient behaviors. Long-term sequelae of agitation are just beginning to be appreciated. Up to 80% of patients remember unpleasant experiences (anxiety, fear, agony, respiratory distress, pain, and nightmares) that can lead to development of PTSD and other cognitive disorders.

Table 1-1. Improvement in Patient Outcomes Associated with the Use of Protocolized Sedation and Analgesia and Validated Assessment Tools[a]

28% to 57% reduction in mechanical ventilation time
30% to 47% reduction in ICU length of stay
53% reduction in the need for tracheostomy
33% reduction in the occurrence of significant pain
59% reduction in the occurrence of significant agitation
67% reduction in the need for neurodiagnostic testing for unexplained mental status changes
50% reduction in ICU complications: ventilator-associated pneumonia, bacteremia, barotrauma, venous thromboembolic disorders, cholestasis, pressure sore, and sinusitis
Elimination of PTSD (0% vs. 31%, p=0.06) versus usual care without daily sedation interruption

[a]$p \leq 0.05$, except where noted.
ICU = intensive care unit; PTSD = post-traumatic stress disorder.

Risk Factors and Frequency of ICU Agitation

Unrelieved pain, sedation use, hyperthermia, hypo- and hypernatremia, acidemia, hypoxemia, history of alcohol abuse or psychiatric disorders, and sepsis have all been identified as risk factors for ICU agitation. Of interest, a cause for agitation cannot be found in one-third of the cases; most cases are likely multifactorial. The complex and enigmatic nature of ICU agitation is well illustrated by literature referencing more than 40 potential etiologies, making the task of providing directed therapy difficult. This issue is even more complicated because many ICUs do not systematically evaluate patient mental status with validated assessment tools. The result is that extreme behaviors are often the first recognized sign of sedative need.

Assessment of ICU Agitation and Its Impact on Outcomes

More than a dozen assessment tools have been developed since the Ramsay scale was introduced in 1974. Advances have included rigorous evaluations of reliability and validity together with provision of very specific behavioral descriptors to guide scoring for both sedation and agitation. The specific sedation/agitation scale used for assessment is less important than its incorporation into daily clinical practice. Data suggest that nurses who include systematic evaluations of agitation and sedation prompt more timely remedial interventions, and their patients experience a 33% reduction in the occurrence of dangerous agitation. Furthermore, use of sedation protocols that incorporate assessment tools to guide sedation titration while allowing daily assessment of wakefulness dramatically improves patient outcomes (Table 1-1). These benefits may be caused in part by consistent provision of sedation that results in patients who are sleepy, but capable of being aroused, while avoiding drug-induced coma. Oversedation is associated

with prolonged mechanical ventilatory requirements and ICU stay; perhaps still more worrisome is its relationship to the development of delirium. Exposure to even brief periods of drug-induced coma imparts a significant risk. Even more troubling is evidence suggesting that patients who experience delirium and drug-induced coma have a worse prognosis than if they experience delirium alone.

Clinicians face a daunting challenge: provision of comfort while finding the balance between agitation and coma. This sedation goal is extremely complex because it is a dynamic issue evolving as patient condition and treatments change. For example, it is reasonable to offer sustained deep sedation for patients who are receiving neuromuscular blocking agents or for those with elevated intracranial pressures, tenuous respiratory function, and complex surgical wounds. For most patients, use of sedative titration goals in conjunction with a daily interruption method should promote formation of factual memories while maintaining comfort. Even though data are supportive of this approach, the implementation of this strategy at the bedside has been problematic.

It is discouraging to note that less than 60% of ICUs use a sedation-scoring tool and that even fewer employ a daily sedation interruption strategy. Without proper monitoring in place, it is easy to understand why more than 40% of patients are more deeply sedated than desired and that drug-induced coma may be a feature of ICU care nearly one-third of the time. Identification of potential reasons for this may be helpful when designing strategies to optimize sedation.

A pervasive belief among caregivers is that patient awareness and the formation of factual memories of the ICU experience are cruel and may lead to long-lasting psychological sequelae such as PTSD. They also believe that light sedation could result in increased oxygen consumption and myocardial ischemia in patients at risk. On investigation, none of these concerns has been borne out. Families also influence the depth of sedation offered to patients. It is quite common for them to voice concerns that patients look uncomfortable or too awake and that they would prefer to see their loved ones sleeping and not moving.

Pharmacists need to become involved in the effort to implement protocols for sedation and analgesia together with daily sedation interruption. Caregivers and family members must understand that drug-induced comas may result in patient behaviors suggestive of comfort but that this degree of sedation has serious consequences including prolonged ICU stay, greater mortality, and diminished long-term quality of life.

Treatment and Prevention of ICU Agitation

Identification and correction of factors contributing to agitation represent essential first steps in the prevention and treatment of ICU agitation. Concurrent non-pharmacological approaches include the provision of comfortable positioning in bed, music and massage therapy, verbal assurances, establishment of sleep-wake cycles, frequent family visits, and removal of all nonessential invasive medical devices and tubes. Most ICU patients, however, require some pharmacological support to maintain comfort.

Benzodiazepines

The 2002 Society of Critical Care Medicine guidelines for sedation and analgesia suggest that lorazepam represents a preferred option for patients requiring long-term and sustained sedation, but only after analgesic needs have been addressed. The rationale for choosing this BZD includes its simple metabolic pathway (glucuronidation) that does not produce active metabolites and does not involve cytochrome P450 (CYP) enzyme systems, thus limiting its pharmacokinetic-based drug interaction potential.

Midazolam is quicker in onset and offset and is recommended for patients needing more rapid sedation and for those with short-term or intermittent sedative needs. It is not a recommended choice for sustained sedation because it follows context-specific pharmacokinetics—prolonged treatment results in extended pharmacological activity caused by an accumulation of the parent drug. Midazolam may also exhibit prolonged sedation in patients with impaired renal function because of the accumulation of an active metabolite, 1-hydroxymidazolam. In addition, because it is metabolized by CYP 3A4, this drug is subject to significant interactions with a number of inhibitors and substrates of this enzyme system including fluconazole, fentanyl, and propofol.

The BZDs remain primary sedatives in the critical care environment because of their valuable amnestic, anxiolytic, and antiseizure properties. The importance of drug-mediated amnesia in the ICU patient is not certain, however, except in the setting of pharmacological-induced paralysis. Data suggest that the development of factual memory is protective, and partial amnesia with associated delusional memories may lead to development of PTSD.

Anxiety is another indication for the use of BZDs. Thirty percent of the critically ill report anxiety, which is commonly associated with the uncertainty of their condition and surroundings, the plethora of exposure to uncomfortable experiences, and the inability to communicate and their resultant sense of isolation. Despite many good reasons to choose BZDs as the mainstay of sedation in the critically ill, this strategy may be re-evaluated with the upcoming revision of the Society of Critical Care Medicine guidelines for sedation and analgesia. Recent studies suggest that the very agents commonly used for patient comfort often result in significant adverse outcomes.

The BZDs commonly result in excessive sedation over time, because of an accumulation of either the parent drug or active metabolites. This may interfere with liberation from mechanical ventilation and extend exposure to associated risks such as ventilator-associated pneumonia, stress ulcers, and deep venous thrombosis. Close monitoring with sedation assessment tools and titration to desired goals are essential to avoid inadvertent prolonged sedation with these agents. Even with these safeguards in place, alternative sedatives should be considered. Trials indicate that patients remain ventilator dependent longer when they are administered intermittent BZDs compared with propofol, despite use of identical sedation titration goals and daily sedation interruption.

It has long been appreciated that BZD use is associated with delirium, but the nature of this association has been unclear because these agents are commonly used to treat delirious patients. Recent data evaluating 11 covariates identified lorazepam as an independent risk factor for the development of delirium. Nearly all patients who received more than 20 mg of lorazepam for 24 hours subsequently

developed this diagnosis; however, drug amount may not be as important as drug effect. A recent study of risk factors for delirium confirmed previous observations and found no association with BZD use unless these drugs resulted in even brief periods of coma. It may be prudent to limit indications for BZD sedation in patients with anxiety, seizures, and alcohol or sedative withdrawal and avoid deep sedation for most.

Lastly, the issue of potential propylene glycol toxicity is becoming more widely appreciated. This low-molecular-weight diluent found in parenteral formulations of lorazepam can lead to hyperosmolality, metabolic acidosis, and acute tubular necrosis. Risk factors include the duration and dose of lorazepam, concurrent use of other drugs also containing this diluent, and renal and hepatic dysfunction. Because most hospitals are not able to assay propylene glycol, a readily available surrogate, serum osmolality, has been used to detect accumulation of this product. Twice-weekly serum osmolality determinations with identification of an osmol gap of 10–15 may help recognize at-risk patients who should change to another sedative regimen. Midazolam is an appropriate BZD alternative because it does not contain propylene glycol.

Propofol

Data suggest that propofol represents an excellent choice for short-term sedation, and a growing body of literature suggests that it is a viable option for long-term sedation, especially for patients requiring frequent neurologic evaluations, but more safety data are needed. This γ-aminobutyric acid receptor agonist is easily titratable and offers consistency in both onset and offset. Compared with other sedatives, the pharmacodynamics of propofol are not appreciably altered by organ dysfunction, but this agent is a known substrate of hepatic CYP 3A4 and may alter the clearance of other drugs such as midazolam. Propofol has no analgesic activity and produces a similar degree of amnesia as the BZDs when given in equi-sedative doses. Caution is advised when offering daily sedation interruption for patients treated with this agent. The infusion should be reduced incrementally, and not abruptly discontinued, to avoid rapid awakening, anxiety, and agitation.

Most adverse events associated with propofol therapy are predictable and well recognized and include respiratory depression and decreases in vascular tone. Twice-weekly triglyceride serum determinations are recommended to detect lipemia that may be related to (but is not necessary for) propofol-induced pancreatitis; it may also be a hallmark of propofol infusion syndrome.

Propofol infusion syndrome is a rare, but extremely lethal, aspect of propofol therapy. Initially recognized in the pediatric population, it is characterized by hemodynamic collapse, bradycardia that transitions to asystole, metabolic acidosis, rhabdomyolysis, and lipemia. The pathophysiology of propofol infusion syndrome is not well understood, but it may involve impaired fatty acid oxidation and direct effects on oxidative phosphorylation through mitochondrial toxicity. It appears to be related to dose (greater than 80 mcg/kg/minute) and duration (longer than 48 hours), although several recent reports have described it in patients treated with usual doses and within hours of drug initiation. Patient-specific risk factors for developing propofol infusion syndrome include acute neurologic illnesses, sepsis and the systemic inflammatory response syndrome, vasopressor dependence, and corticosteroid treatment. Other data have also implicated a genetic defect in acylcarnitine metabolism or in β-oxidation, both resulting in deranged fatty acid function. Because there is no known effective treatment for patients with propofol infusion syndrome, it is recommended that propofol be immediately stopped when it is suspected. Some have advocated hemodialysis or hemofiltration, but the acuity of the syndrome with its rapidly fatal course often precludes such intervention. Carbohydrate administration has also been recommended to suppress fat metabolism and limit resultant accumulation of free fatty acids.

Dexmedetomidine

Dexmedetomidine is an α_2-adrenergic receptor agonist introduced in 1999 for short-term sedation initiated in mechanically ventilated critically ill patients. It is a unique sedative agent because it has little or no clinically significant effect on respiratory drive. This property suggests that dexmedetomidine is theoretically a very useful agent in agitated patients to avoid mechanical ventilatory support or to facilitate its withdrawal. A recent double-blind, randomized, controlled trial compared continuous infusions of dexmedetomidine with lorazepam in 106 mechanically ventilated medical and surgical ICU patients. Primary outcome measures—days alive without delirium or coma and time spent at the identified sedation goal—favored the dexmedetomidine group. There were no differences seen between the groups in 28-day mortality, mechanical ventilator free–days, ICU lengths of stay, cost of care, or post-ICU neuropsychological testing scores. In terms of safety outcomes, there were no differences between groups except that the dexmedetomidine patients experienced more sinus bradycardia (17% vs. 4%, p=0.03). This study allowed dexmedetomidine and lorazepam infusions as high as 1.5 mcg/kg/hour and 10 mg/hour, respectively, and for as long as 5 days. Bolus drug administration was not permitted. It is interesting to note that in contrast to other comparative trials, patients treated with dexmedetomidine required more fentanyl for analgesia than those treated with lorazepam. These data should be considered preliminary as we await the results of a recently completed comparative trial of long-term dexmedetomidine versus midazolam. Dexmedetomidine is a hemodynamically active agent commonly resulting in hypotension and bradycardia and sometimes requiring critical intervention or stabilization. Dexmedetomidine is hepatically cleared, dictating dose adjustments in patients with liver disease. Because it permits patient awareness on stimulation and does not offer amnesia, it is not an appropriate sedative choice for those requiring deep sedation or those undergoing therapeutic paralysis.

Approved dosing guidelines for dexmedetomidine allow use for no more than 24 hours at infusions of up to 0.7 mcg/kg/hour. Preliminary reports have documented that as many as 20% of patients require a higher dose, and longer infusion durations may be safe. Potential risks associated with long-term use—rebound hypertension and tachycardia on discontinuance and adrenal insufficiency—have not been well described but should be anticipated.

Preliminary data portend the possibility of a greatly expanded role for dexmedetomidine in the critically ill.

Data published in several abstracts suggest that because dexmedetomidine does not affect γ-aminobutyric acid receptors or have anticholinergic properties, it is helpful in preventing or even treating delirium. This hypothesis is currently being tested in a prospective fashion. Furthermore, meta-analyses indicate that α_2-adrenergic agonists such as clonidine and dexmedetomidine prevent perioperative cardiovascular complications by attenuating the stress response; this is accomplished through the inhibition of central sympathetic outflow and reduced peripheral norepinephrine release. Large, controlled, clinical trials are needed to establish the potential cardioprotective role of this agent. Finally, there is a growing body of literature suggesting that noradrenergic hyperactivity leads to the development of PTSD. Preliminary data suggest a protective role for agents such as dexmedetomidine, which modulate this response.

Neuromuscular Blockade

Although neuromuscular blockade is used in as many as 98% of ICUs, reports of prolonged paralysis or weakness have dampened enthusiasm for its routine use. It is estimated that less than 10% of ICU patients receive neuromuscular blockade for longer than 24 hours. The most common indications for these drugs are to optimize patient tolerance of mechanical ventilation when all other remedial options have been exhausted, to maintain a motionless state to protect surgical wounds or the placement of life-preserving medical devices, or to help limit oxygen consumption. Concerns for patient awareness of therapeutic paralysis dictate careful attention to the adjunctive delivery of adequate sedating, amnestic, and analgesic medications.

Table 1-2. ICU Delirium

Consequences:
A 3-fold increase in 6-month mortality
An extra 5 days of dependency on mechanical ventilation
A 4-fold increase in frequency of medical device removal
An average increased hospital length of stay of 8–10 days with an associated increase in per-patient cost of care by at least $15,000
A 9-fold increase in the incidence of cognitive impairment at hospital discharge
Preventive strategies:
Patient reorientation with clocks and calendars
Continual provision of cognitive stimulation
Encouragement of normal sleep/wake cycles by allowing uninterrupted sleep with lowered nighttime light and noise levels while avoiding drug-based sleeping aids
Normalization of metabolic indices
Facilitation of patient mobility by limiting tethering by catheters and restraints
Restoration of eyeglasses and hearing aids, if appropriate
Critical examination of administered drugs with considered cessation of all nonessential or deliriogenic drugs
Anticipation of substance or drug withdrawal
Reservation of benzodiazepine therapy for the treatment of anxiety or CNS sedative withdrawal and for those receiving neuromuscular blocking agents

CNS = central nervous system.

ICU Delirium

Delirium is an acute change in cognitive function that typically exhibits waxing and waning during the course of the day. Central to the diagnosis are features of disorganized thought together with an altered level of consciousness and inattentiveness. Critical illness delirium is related to a variety of causes including metabolic disorders, infections, CNS diseases, brain injury, and drug or substance use and withdrawal. It is, therefore, not surprising to find that the frequency of occurrence varies from 15% to 80% among patient populations. There are at least three subtypes of delirium: hyperactive, hypoactive, and mixed. The hyperactive variety is easily identified by patient behaviors such as restlessness, agitation, aggression, and paranoia; it consists of less than 2% of delirious episodes. More than 40% of delirium can be characterized as hypoactive, identified by patients who exhibit withdrawn, quiet, and paranoid behaviors. More than 50% of delirious episodes are of the mixed variety. Furthermore, delirium may represent a spectrum with as many as 33% of patients falling short of the threshold for diagnostic criteria. This has been described as subsyndromal delirium and is associated with a parallel, but less severe range of adverse outcomes than seen with full-blown clinical delirium.

Recent data associate delirium with a longer duration of mechanical ventilation and ICU stay, greater 6-month mortality, and higher hospital costs (Table 1-2). Neuropsychological insults associated with delirium lead to cognitive disorders—difficulties with memory, psychomotor speed, spatial abilities, attention, and verbal fluency—and possibly to the development of PTSD. All contribute significantly to quality-of-life issues long after patient discharge.

Pathogenesis of Delirium

The neurobiology of delirium has yet to be fully described but is probably associated with many factors including disruption of the delicate balance of various neurotransmitter and receptor functions, the release of inflammatory cytokines increasing blood-brain barrier permeability and altering neurotransmission, and diffuse brain injury. Encephalopathy, hypoxemia, acidosis, infections, and metabolic and hemodynamic instability are some of the physiologic conditions associated with delirium.

About 30% of cases of delirium have a pharmacological basis. More than 100 drugs have been characterized as deliriogenic, and most have been shown to affect CNS neurotransmitter or receptor function. Prototypically, these agents have overt anticholinergic activity (e.g., diphenhydramine), but many affect choline receptors in a subclinical, yet measurable, fashion. The potential for additive anticholinergic burden with multiple drugs and the subsequent development of delirium has been demonstrated. Furthermore, withdrawal from various substances such

as ethanol, BZDs, opiates, selective serotonin reuptake inhibitors, and tobacco is associated with delirium. These data underscore the importance of regular scrutiny of prescribed drugs and discontinuance of all nonessential drugs when delirium becomes evident. Prehospital drug and substance use and abuse should be carefully documented by interviewing the patient, friends, caregivers, and family members and having all drugs available for inspection. If delirium is related to home drug withdrawal, careful consideration of reinstitution of therapy is indicated.

Delirium Assessment in the ICU

Intensive care unit delirium is a commonly undetected and clinically relevant issue affecting as many as 80% of the critically ill. The most likely reason for missed diagnoses in 60% of patients is that fewer than 1 in 10 ICUs routinely tests for this disorder. Another reason for missed diagnoses is that one of the most common variants, hypoactive delirium, is clinically subtle, especially in the nonverbal patient. Two assessment tools were published in 2001 to facilitate recognition of delirium in the ICU patient population: the Confusion Assessment Method for the ICU (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC). Despite these advances in identification of ICU delirium, it remains uncertain if routine bedside application of these assessment tools improves patient outcomes.

The ICDSC evaluates the presence of eight different diagnostic characteristics of delirium: altered level of consciousness; inattention; disorientation; hallucinations, delusions, or psychosis; agitation or psychomotor retardation; inappropriate speech or mood; sleep/wake cycle disturbances; and symptom fluctuation observed during the course of one nursing shift. An ICDSC score of four or more symptoms correlates well with delirium as diagnosed by formal psychiatric evaluation. Patients with coma or stupor caused by pharmacological or physiologic causes during most of the observational period are not scored.

To confirm the diagnosis of delirium with the CAM-ICU, acute onset of mental status changes or a fluctuating course, as well as inattention, must be present together with disorganized thinking, altered level of consciousness or both. The CAM-ICU evaluation requires focused interactions with patients and takes about 2 minutes to perform. Note that, in contrast to the ICDSC, the altered level of consciousness caused by sedative and analgesic therapy can be used to characterize a patient as delirious with CAM-ICU. There is no nursing standard for the frequency of CAM-ICU assessment, although it is commonly performed once or twice daily.

Management of ICU Delirium

Three components of delirium management in the ICU include prevention, treatment of the underlying disorder, and pharmacological and non-pharmacological behavioral therapy.

Delirium Prevention Strategies

Because it is possible to lower the incidence of delirium in non-ICU settings by at least 40%, preventive strategies should be offered routinely (Table 1-2). A potential preventive pharmacological approach has been described for the "prophylactic" use of haloperidol in high-risk patients. Although therapy did not affect the incidence of postoperative delirium in non-ICU elderly hip-surgery patients receiving low-dose perioperative haloperidol (1.5 mg/day), these patients experienced reductions in the severity and duration of delirium that translated to a shortened hospital stay.

Delirium Treatment

Once delirium has been identified, the mainstay of treatment is simultaneous identification and correction of potential physiologic causes (e.g., hypoxia, hyperthermia, hypercarbia, pain, acidosis, hemodynamic instability, infection) and control of potentially dangerous behavioral disturbances. Physical restraints should be considered the intervention of last resort because they may actually worsen agitation and increase morbidity. Constant observation by family or caregivers such as doulas (assistants similar to those used in childbirth) may represent a humane, holistic, and less-toxic approach.

Because delirium is thought to be predominantly an issue of an imbalance of CNS dopamine and choline, these neurotransmitters and others (γ-aminobutyric acid and norepinephrine) are prime targets for pharmacotherapy. There are no data in the critical care literature to guide treatment of hypoactive delirium; in fact, literature on ICU delirium treatment is wholly limited to a variety of case and observational reports and one small comparative trial. Furthermore, there are no prospective ICU data suggesting that therapy reduces the duration and severity of symptoms or improves any other clinically relevant outcome. Despite this, intensive care practitioners commonly prescribe some sort of drug for these patients, ranging from typical antipsychotic agents (e.g., haloperidol) to atypical agents (e.g., quetiapine), and some (18%) even use BZDs—agents known to be deliriogenic.

Haloperidol is the dopamine antagonist most commonly used to treat symptoms of ICU delirium. It has no significant effect on respiratory drive or hemodynamic function in euvolemic patients, but onset of activity may be delayed for 15–20 minutes, even when administered intravenously. Many variations of dose escalation protocols exist, including multiple small intermittent doses, rapidly escalating doses, and administration of continuous infusions. It is unclear which strategy is optimal, but recent data citing the relationship between haloperidol dosages greater than 35 mg daily and torsades de pointes suggest a conservative approach. The odds of developing this ventricular dysrhythmia are highest when the QTc interval exceeds 521 milliseconds. This highlights the potential risk for concurrent therapy with other agents also affecting repolarization such as amiodarone, azole antifungals, fluoroquinolones, and macrolides. It is prudent to ensure adequate potassium, magnesium, and electrocardiographic monitoring for haloperidol-treated patients and perhaps avoidance of this agent altogether in patients with a history of heart disease. Because they have little effect on repolarization, olanzapine, quetiapine, and risperidone represent reasonable antipsychotic alternatives for patients who develop or are at risk for haloperidol-induced QTc prolongation.

In an effort to avoid drug-induced movement disorders, many clinicians have adopted use of second-generation antipsychotics as haloperidol alternatives despite very limited data supporting this practice. A single randomized

comparative trial in delirious, critically ill patients found that 5 mg daily of enteral olanzapine was as effective in symptom control as 2.5–5 mg of enteral haloperidol given three times daily, and it caused fewer movement disorders.

Second-generation antipsychotics share many of the side effects of haloperidol, including neuroleptic malignant syndrome. They have agent-specific adverse event profiles as well: hyperglycemia, bradycardia, pancreatitis, and hypotension with olanzapine; prolongation of QTc with ziprasidone; agranulocytosis with clozapine; and sedation with quetiapine. Although elderly patients with dementia have a greater risk for cardiovascular and infectious sequelae when treated with second-generation antipsychotics, it is unclear if this risk extends to short-term treatment in similar patients with ICU delirium.

It is difficult to define an appropriate role for second-generation antipsychotics in patients with ICU delirium, but they may have utility when parenteral access is lacking. For patients unable to swallow tablets (but with accessible and functional gastrointestinal tracts), olanzapine, risperidone, and aripiprazole are available as orally dissolving tablets. Ziprasidone and olanzapine are available as immediate-release intramuscular injections, although dose-related side effects (QTc prolongation and hypotension, respectively) limit the ability to titrate these drugs to effect.

Although BZDs are commonly used to treat agitation in the setting of delirium, they should be reserved for patients withdrawing from ethanol or sedative drug use or for those requiring rapid tranquilization because they pose a danger to themselves or to their caregivers. Under these circumstances, control over violent or dangerous behaviors outweighs the deliriogenic potential of these drugs.

Post-traumatic Stress Disorder After Critical Illness

Post-traumatic stress disorder has only recently been recognized as a common long-term psychological consequence of the ICU experience. That almost 15% of ICU survivors develop PTSD should come as no surprise. These patients have lived through life-threatening experiences as traumatic as any natural disaster or violent act. To compound the issue, as many as 73% of ICU patients suffer from very troubling delusional memories that serve as triggers for this psychiatric disorder.

Post-traumatic stress disorder is characterized by an assortment of persistent symptoms shortly after exposure to a real or imagined extreme traumatic stressor. Three categories of symptoms are typically present: (1) reexperiencing the traumatic event in a vivid and frightening fashion; (2) avoidance of stimuli associated with that trauma; and (3) hyperarousal resulting in hypervigilance for threats, exaggerated startle responses, and sleep disturbances. The onset of PTSD generally occurs within 1 month, and resolution usually occurs within 1 year. Unfortunately, as many as 30% of these patients will remain symptomatic for more than 3 years after the traumatic event. Quality-of-life issues are predominant for patients with PTSD. They often cannot hold jobs, and financial and interpersonal relationships suffer. Sexual dysfunction occurs in most patients, and substance abuse often serves as self-medication for symptom relief.

Risk Factors for Developing Post-ICU PTSD

Preliminary data suggest that recall of two or more traumatic memories, even nonfactual delusional ones (e.g., feelings of panic or suffocation, severe pain, nightmares) is strongly related to the development of PTSD. Although it is reasonable to presume that pharmacologically mediated amnesia is protective against this risk, the opposite may be true. The intensity of ICU sedation may be an important determinant of the formation of delusional memories, the development of delirium, and, ultimately, the occurrence of PTSD. Furthermore, sustained sedation without daily interruption is associated with more symptoms of PTSD. Understanding why ICU patients are at risk for this disorder is important because it may permit timely preventive strategies, preemptive psychological interventions, and identification of patients who should be monitored after discharge.

ICU Strategies to Avoid PTSD Development

It appears that prevention of PTSD should focus on provision of sedation adequate to avoid traumatic memories while preserving patient awareness and ability to form factual memories. Daily sedation interruption strategies have facilitated achievement of this goal. Patients need to be provided an accurate but humane understanding of the realities of their critical illness. The risk for developing PTSD is highest in those who retain only delusional memories of their ICU stay. A simple intervention, keeping a diary containing pictures and text describing patient status over time, has been successful. It allows patients to come to terms with their illness and to remember real events; for the bereaved, it can be a source of comfort.

Table 1-3. Topics Requiring Local Consensus for ICU Sedation and Analgesia Protocolization

Choice of drugs as well as assessment tools and protocols for use
Location and frequency of nursing documentation of pain, delirium, agitation, sedation assessments, and treatment
Suggest mechanism similar to that currently used for recording vital signs
Mandate use of identified titration goals incorporated within each sedative and analgesic order
Identification of follow-up strategies to evaluate compliance and outcomes with the effort
Protocolization of daily sedation interruption
Procedures for discontinuing or tapering specific sedatives
Criteria describing patient contraindications and parameters for termination of the effort
Guidelines for reinstatement of sedation and for the provision of rescue sedatives if needed
Identification of the timing of the effort

ICU = intensive care unit.

Preliminary data suggest the potentially protective role of some drugs in the setting of PTSD. Stress hormones such as epinephrine, cortisol, and vasopressin have been shown to facilitate memory in animal trials. Exogenous administration of these substances leads to learning and memories that are robust and long lasting. Pharmacological blockers of these hormones lead to the opposite effect. This helps explain preliminary findings that administration of propranolol shortly after a traumatic event may prevent the emergence of PTSD. This same rationale can be used to explain the potential value of agents that act presynaptically to block norepinephrine release, such as clonidine and dexmedetomidine. Although cortisol has been shown to enhance memory consolidation, in higher doses, it may actually impair memory retrieval by blunting the stress response and resulting catecholamine release. Two trials have demonstrated lower rates of PTSD after administration of stress-dose hydrocortisone in hemodynamically unstable ICU patients. Data in this area of post-ICU psychological disorders remain in the descriptive and hypothesis-generating phase, and clinical recommendations based on rigorous data cannot be made.

The Role of the Pharmacist in Optimizing the Provision of Comfort

The administration of analgesics and sedatives is an essential part of ICU care, and more than 90% of patients receive these drugs. Although cost of these therapies varies tremendously, they account for less than 10% of total expenditures associated with critical illness. These data emphasize that the pharmacists' role in optimizing the provision of comfort should focus on the impact of these drugs on relevant patient outcomes and not on direct costs.

There is clearly a gap between published evidence and actual ICU practice. Surveys indicate that less than 50% of ICUs interrupt sedation on a daily basis, use protocols or guidelines for sedation or analgesia use, or employ validated sedation scoring systems for patient evaluation. This issue needs to be addressed locally, and caregiver behaviors need to change. The most effective means of altering clinical practice involves a multifactorial, multidisciplinary approach using education, thought leaders, point-of-use reminders, and caregiver-specific practice feedback together with continuous protocol evaluation and modification (if needed). Essentially, the pharmacist's role is to provide relevant data and facilitate its bedside application in a fashion that is easy to implement and sustain and that is as automated as possible. Specific issues needing local consensus are discussed in Table 1-3.

Conclusion

The past decade has witnessed remarkable advances in our understanding of how to provide comfort for ICU patients. The foundation of these advances has been development and validity testing of assessment tools to identify and quantitate pain, sedation, agitation, and delirium, enabling the evaluation of outcomes resulting from various clinical initiatives. We now know, for example, that simply providing systematic evaluations of pain and agitation significantly reduces occurrence rates. Our ability to quantify sedation levels and identify delirium has led to the discovery that, for most, a safe sedation strategy is one that allows a sleepy, comfortable patient who is capable of being aroused and that unnecessary drug-induced coma may lead to life-threatening complications. Lastly, development of these tools has helped to identify risk factors for long-term and potentially devastating psychological disturbances such as delirium and PTSD. Although no new treatments have recently been introduced, we have learned much about adverse event potentials of existing drugs. Many of these toxic effects mimic diseases of the critically ill (metabolic acidosis, hemodynamic collapse, coma, and delirium) and require heightened sensitivity for their identification. The combination of all of these advances has contributed to an increased understanding of complex relationships between critical illness, CNS disorders, and drugs used to treat them. Currently, the greatest challenge facing critical care practitioners is application of these findings to routine patient care.

Annotated Bibliography

1. Aissaoui Y, Zeggwagh AA, Zekraoui A, Abidi K, Abouqal R. Validation of a behavioral pain scale in critically ill, sedated, and mechanically ventilated patients. Anesth Analg 2005;101:1470–6.

   Caring for critically ill patients who cannot verbalize their analgesic needs remains an important clinical challenge. There were no validated assessment tools until a behavioral-based scale in surgical ICU patients was tested in 2001. The current study evaluated the validity and reliability of the Behavioral Pain Scale in 30 mechanically ventilated and deeply sedated medical ICU patients. Because there is no "gold standard" for pain evaluation in the critically ill, these investigators relied on construct validity and validated the scale against known logical consequences (or constructs) associated with painful stimuli from tracheal suctioning and peripheral venous cannulation—an increase in heart rate and blood pressure. They also confirmed that the pain score after the painful procedures was higher (another construct). They then evaluated component responsiveness to the introduction of noxious stimuli, noting that all three components of the scale (facial expression, upper limb movement, and compliance with mechanical ventilation) responded in concert. As expected, there was no significant correlation between the pain scores and hemodynamic variability. Reliability was confirmed by comparing the rated pain assessments of 12 physicians and 16 nurses. The Behavioral Pain Scale is simple to use and takes about 4 minutes to perform. It is important to emphasize that this and other behavioral-based pain assessment tools can only be performed in patients who are able to respond in all categories of rated behavior, not in those who are paralyzed, flaccid, or undergoing deep sedation. To date, there is no firm association between the score using these behavioral-based tools and severity of pain.

2. Chanques G, Jaber S, Barbotte E, Violet S, Sebbane M, Perrigault P, et al. Impact of systematic evaluation of pain

and agitation in an intensive care unit. Crit Care Med 2006;34:1691–9.

This important study demonstrates that the simple process of evaluating pain and agitation within the nursing care plan allows an appropriate and timely remedial response to patient distress. Using a before-after methodology, this study measured the impact of three (or more) daily evaluations of pain, with the Behavioral Pain Scale and the Numeric Rating Scale, and sedation, using the Richmond Agitation Sedation Scale, on the incidence of pain and agitation. Nurses were encouraged to notify physicians with the discovery of any pain or agitation event. Protocols were not used to administer sedatives and analgesic agents. This simple intervention resulted in patients experiencing one-third less agitation and one-half less pain. The duration of mechanical ventilation was reduced by almost 3 days, and a 50% reduction in nosocomial infections was seen. There was no significant difference in ICU length of stay or ICU mortality. This study can be used to encourage practitioners to incorporate validated analgesia and assessment tools into routine patient care, if not already in place.

3. Breen D, Karabinis A, Malbrain M, Morais R, Albrecht S, Jarnvig IL, et al. Decreased duration of mechanical ventilation when comparing analgesia-based sedation using remifentanil with standard hypnotic-based sedation for up to 10 days in intensive care unit patients: a randomized trial. Crit Care 2005;9:R200–10.

The concept of analgesia-based sedation is easily understood within the context of the occurrence of discomfort that is associated with critical illness. Unrelieved pain is an issue consistently voiced by ICU survivors. In addition, recent data implicating standard hypnotic-based sedative regimens with negative clinical and quality-of-life outcomes have spurred explorations of alternative strategies to provide patient comfort. The present study compared a remifentanil-based regimen with rescue midazolam (if needed) versus midazolam-based sedation with morphine or fentanyl analgesia in 105 long-term mechanically ventilated patients in a randomized, open-label, multicenter trial. All had their sedative and analgesic drugs titrated to allow the patient to be sleepy but capable of being aroused, without experiencing discomfort. Medical and surgical ICU patients were included, but those requiring deep sedation were not. Remifentanil was begun as a 0.1-mcg/kg/minute to 0.15-mcg/kg/minute infusion titrated at 5-minute to 10-minute intervals in increments of 0.025 mcg/kg/minute. Once a dose of 0.3 mcg/kg/minute was reached, midazolam boluses (2 mg or less) were used. There was no dosing protocol for the comparator group; midazolam and morphine or fentanyl were offered in accordance with routine clinical practice to achieve therapeutic goals. Remifentanil-treated patients required 2 days less with mechanical ventilation than the comparator group. Both groups spent 97% of the time at the dual therapeutic goals of adequate sedation and comfort. Of the remifentanil group, 74% received midazolam during the study, but exposure to this agent was four or nine times less than in the midazolam/morphine and midazolam/fentanyl groups, respectively. In terms of safety, rigidity was not observed with remifentanil; one patient experienced significant hypotension with hypnotic-based sedation. Unfortunately, delirium was not assessed at all. This study adds to an expanding list of trials that demonstrate the safety and efficacy of analgesia-based sedation.

4. Jaber S, Chanques G, Altairac C, Sebbane M, Vergne C, Perrigault P, et al. A prospective study of agitation in a medical-surgical ICU: incidence, risk factors, and outcomes. Chest 2005;128:2749–57.

This is a prospective observational study of the incidence, risk factors, and outcomes of agitation in 182 ICU patients. A clinical pharmacist assessed agitation with a modified Ramsay score by direct observation and by obtaining feedback from nurses and physicians on a daily basis. Delirium was not assessed, and protocols for sedation and analgesia administration were not used. Agitation developed in 52% of patients. This study adds to the literature by identifying seven independent risk factors for developing agitation and by quantifying the adverse sequelae with this condition—a higher rate of removal of medical devices, a higher rate of nosocomial infections, and a longer ICU stay. The importance of having analgesia and sedation protocols in place is suggested by comparing agitation rates (16%) in ICUs that actively monitor these issues.

5. Kam PCA, Cardone D. Propofol infusion syndrome. Anaesthesia 2007;62:690–70.

This represents the most up-to-date, complete, and independent review of this syndrome currently available. Potential biochemical mechanisms (impaired mitochondrial respiratory chain function) and potential contribution of genetics (very long-chain acyl-coenzyme A dehydrogenase deficiency) are used to explain the pathophysiologic features of the propofol infusion syndrome: cardiovascular collapse, metabolic acidosis, rhabdomyolysis, and lipemia. The successful management of this often-fatal adverse drug reaction requires a high index of suspicion together with prompt recognition of its development. A potential early marker for propofol cardiac instability may be the development of right bundle branch block with "coved" or convex-curved ST-elevations in the right precordial leads (V1–V3).

6. Gerlach AT, Dasta JF. Dexmedetomidine: an updated review. Ann Pharmacother 2007;41:245–52.

Dexmedetomidine offers a unique activity as an opiate-sparing sedative. The purported clinical advantages of allowing patient evaluations on stimulation and its minimal effect on respiratory function have yet to be demonstrated in clinical trials. The rigidity of labeled dosing guidelines—24-hour limit for treatment at a dose that many consider too low—may be partly to blame. This review is well organized and discusses dexmedetomidine use in several patient populations and for various indications. The authors briefly describe clinical studies that have used higher doses at longer durations than currently recommended by the U.S. Food and Drug Administration. The role of this agent to prevent delirium in adults—using data available in abstract form—is included, but it should be noted that additional data supporting the use of dexmedetomidine to treat delirium were recently presented at the 2007 Society of Critical Care Medicine meeting. Lastly, the authors comment that any pharmacoeconomic evaluation must include collateral expenditures such as length of stay and costs of adverse drug reactions; then, they include a recent retrospective evaluation of a large administrative database showing that higher drug acquisition costs for dexmedetomidine translated to lower total hospital charges. The major criticism of this review is that it did not critically evaluate dexmedetomidine data within the context of the risks and benefits of alternative treatment strategies that interact with central μ-aminobutyric and γ-aminobutyric acid receptors.

7. Weinert CR, Calvin AD. Epidemiology of sedation and sedation adequacy for mechanically ventilated patients in a medical and surgical intensive care unit. Crit Care Med 2007;35:393–401.

This study extensively evaluated sedative use patterns, patient behaviors, and nursing bedside evaluations in an oncology and transplant critical care service. The most startling and insightful finding in this study was that although patients were either in a coma or nearly unarousable 30% of the time, they were characterized as "oversedated" during only 2.6% of evaluations. Given what is known about the importance of sedative dose titration and the avoidance of drug-induced coma, this study helps to shed light on the difficulties translating clinical data to bedside application. The authors argue that adequacy of sedation has never been defined and that a wide range of sedation levels has been used in clinical studies. This is true, but it should not dissuade the application of rigorously developed data indicating that most patients benefit from meaningful interactions with their environment and caregivers at least once daily.

8. De Jonghe B, Bastuji-Garin S, Fangio P, Lacherade JC, Jabot J, Appéré-De-Vecchi C, et al. Sedation algorithm in critically ill patients without acute brain injury. Crit Care Med 2005;33:120–7.

This before-after prospective trial evaluated the effect of the introduction of a sedation algorithm designed to maintain a high level of consciousness in 102 mechanically ventilated patients. All patients received midazolam for sedation and fentanyl for analgesia during both phases of the study. The omission of brain-injured patients removed a significant confounder and allowed better assessment of the effect of sedation pharmacology on mental status. The introduction of the algorithm was associated with a 57% decrease in the duration of mechanical ventilation and nearly a 50% reduction in ICU length of stay that seemed to be related to more rapid awakening. The results of this trial are consistent with seven other studies that have demonstrated important improvements in clinical outcomes with use of protocols for sedation and analgesia.

9. Pandharipande P, Shintani A, Peterson J, Pun BT, Wilkinson GR, Dittus RS, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. Anesthesiology 2006;104:21–6.

It has been known for decades that BZDs are associated with delirium. The question of whether exposure to these agents resulted in delirium or whether the association was incidental because they are often administered to treat the delirium remained. This study clarified the issue by reanalyzing data (from a previously published trial) collected specifically to identify risk factors contributing to the change to delirium. They found that lorazepam was an independent risk factor after adjusting for 10 different covariates. Two other drugs, midazolam and fentanyl, were not identified as risk factors ($p=0.09$). Further analysis indicated a plateau in the relationship between lorazepam dosage and the development of delirium. Twenty milligrams during the course of a day corresponded to a 100% probability for delirium transition within 24 hours. Other patient factors that predicted the change to delirium included individuals older than 65 years and severity of illness. Of interest is that the administration of anticholinergic drugs was not predictive of delirium development. The most important finding from this study is that the very drugs we use for patient comfort may incur significant psychological risk.

10. Carson SS, Kress JP, Rodgers JE, Vinayak A, Campbell-Bright S, Levitt J, et al. A randomized trial of intermittent lorazepam versus propofol with daily interruption in mechanically ventilated patients. Crit Care Med 2006;34:1326–32.

Mounting evidence supports the use of protocols for sedatives, with dose titration to a sleepy patient but one who is capable of being aroused, together with daily sedative interruption to assess dosing needs. This study found that the choice of agents (propofol or intermittent lorazepam) influenced outcomes. Both treatment groups were sedated to the same degree, received daily sedation holidays, and were offered analgesia based on regular evaluations. Mechanical ventilator dependence was 2.5 days shorter in the propofol-treated patients; this difference was 4.5 days for those who were discharged from the hospital. These patients also stayed in the ICU for 4 days less than the lorazepam-treated survivors. Sedation group assignment did not affect mortality or hospital length of stay. It is unclear why propofol-treated patients can be weaned earlier from mechanical ventilation. Propofol may offer an advantage over lorazepam by allowing easier titration during daily sedation holidays, thus allowing nurses to focus on other aspects of care delivery. Alternatively, it could be a reflection of adverse cognitive outcomes arising from the deliriogenic properties of lorazepam. Propofol is emerging as a preferred hypnotic agent for routine sedation in the ICU.

11. Devlin JW, Fong JJ, Fraser GL, Riker RR. Delirium assessment in the critically ill. Intensive Care Med 2007;33:929–40.

This up-to-date critical review of ICU delirium assessment tools includes all currently available instruments with in-depth descriptions of their components and patient care applications, as well as the practical aspects of use. Advantages and limitations of each are listed. Discussion extends to the identification of barriers to routine delirium assessment and strategies to overcome these hurdles. This paper should be required reading for the discriminating clinician interested in ICU delirium assessment tools.

12. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. Intensive Care Med 2007;33:66–73.

This prospective study involving 764 medical and surgical ICU patients evaluated the incidence of delirium and the risk factors for its occurrence. This report confirms what has been previously reported (delirium occurs in more than 30% of ICU patients, is related to severity of illness and history of alcohol abuse, is associated with prolongation of ICU stay by 7 days, and nearly doubles the ICU mortality). Newer findings include the lack of association of delirium with sedative or analgesia therapy unless these drugs are used to induce even brief periods of coma. Particularly worrisome is the finding that patients with the combination of coma and delirium had a lower 100-day survival than those experiencing delirium alone. It may be that the choice of sedative agent has less influence on outcomes than how it is used.

13. Jones C, Backman C, Capuzzo M, Flaatten H, Rylander C, Griffiths RD. Precipitants of post-traumatic stress disorder following intensive care: a hypothesis generating study of diversity of care. Intensive Care Med 2007;33:978–85.

This prospective observational study from five different European ICUs examined the relationship between memories, sedation practices, and other factors on subsequent development of PTSD in 238 mechanically ventilated patients. Sedation doses and level of sedation were collected, as was the

occurrence of delirium during the ICU stay. Post-traumatic stress disorder symptoms were evaluated at 2 and 3 months post-ICU discharge and were found in 9.2% of patients, with delusional memories serving as the mechanism of the PTSD. Patients receiving high daily doses of BZDs and opiates (but not propofol) were more likely to develop delirium and associated delusional memories; this was identified as a contributor to the development of PTSD. A history of previous psychological problems and the use of physical restraints were also associated with this diagnosis. This is the largest study of its type to identify factors associated with the development of PTSD in ICU patients and confirms the potential negative impact of oversedation on long-term psychological health.

14. Al-Haddad M, Hayward I, Walsh TS. A prospective audit of cost of sedation, analgesia, and neuromuscular blockade in a large British ICU. Anaesthesia 2004;59:1121–5.

    The economic impact of sedative choice has never been adequately evaluated, but this issue remains an important topic because 90% of ICU patients receive sedatives or analgesics at an estimated yearly cost of $0.8 billion to $1.2 billion. Most clinicians sense that the cost of these drugs is important, but relative to the total expenditures incurred during critical illness, they account for a very small proportion of hospital expense. This prospective audit of 155 admissions to a United Kingdom ICU indicates that sedatives and analgesics represent a significant portion of ICU pharmacy costs (81% of the total) but that they account for less than 1% of the total costs associated with critical illness. These data are a bit different from those published elsewhere, in which sedatives and analgesics account for 10% of pharmacy costs, and these costs represent 10% of the total cost of an ICU stay. Health care practices in the United Kingdom versus the United States probably explain these differences. Nonetheless, the importance of this and other studies is that the cost of sedative drugs is insignificant compared with days spent in the ICU. We should focus on collateral expenditures associated with sedative administration practice.

15. Milbrandt EB, Deppen S, Harrison PL. Costs associated with delirium in mechanically ventilated patients. Crit Care Med 2004;32:955–62.

    Delirium is associated with increased morbidity and mortality and has a tremendous effect on long-term quality-of-life issues. Another reason to be concerned about delirium is that it accounts for significant health care resource consumption. A hospital administrative database was used to detect differences in the cost of care of medical ICU patients who did or did not develop delirium. After adjustment for age, severity of illness, comorbidities, and other confounders, delirium was associated with a 39% increase in the cost of ICU care and a 31% increase in the cost of total hospital care. In absolute dollars, this represents $9000 and $14,000 (ICU and hospital costs, respectively) excess in expenditures per patient with this diagnosis. It is insightful to understand this economic toll in terms of locally derived data. For example, if a 42-bed ICU admits 1200 patients yearly and 30% develop delirium, the added attributable yearly expense is more than $5 million.

16. Girard TD, Kress JP, Fuchs BD, Thomason JWW, Schweickert WD, Pun BT, 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 randomized controlled trial. Lancet 2008;371:126–34.

    This randomized multicenter trial of 336 mechanically ventilated medical ICU patients tested the hypothesis that coordination of sedation interruption strategies with spontaneous breathing trials can improve clinical outcomes. Patients randomized to the sedation interruption group had a greater than 20% reduction in days spent on mechanical ventilation, days spent in the ICU, and days spent in the hospital; however, more patients in this group self-extubated (10% vs. 4%, p=0.03). Many clinicians will find that this study can serve as a valuable model for implementing daily evaluations of sedation and mechanical ventilatory support by making use of its criteria for passing (and failing) both the safety screens and the actual sedation interruption and spontaneous breathing trials.