REVIEW ARTICLE

CRITICAL CARE MEDICINE

Sedation and Delirium in the Intensive Care Unit

Michael C. Reade, M.B., B.S., D.Phil., and Simon Finfer, M.D.

From the Burns, Trauma and Critical Care Research Centre, University of Queensland, and Joint Health Command, Australian Defence Force, Brisbane (M.C.R.); and the George Institute for Global Health, and Royal North Shore Hospital, University of Sydney, Sydney (S.F.) — all in Australia. Address reprint requests to Dr. Reade at Level 9, University of Queensland Health Sciences Building, Royal Brisbane and Women's Hospital, Brisbane, QLD 4029, Australia, or at m.reade@uq.edu.au.

N Engl J Med 2014;370:444-54.
DOI: 10.1056/NEJMra1208705

Patients in intensive care units (ICUs) are treated with many interventions (most notably endotracheal intubation and invasive mechanical ventilation) that are observed or perceived to be distressing. Pain is the most common memory patients have of their ICU stay.[1] Agitation can precipitate accidental removal of endotracheal tubes or of intravascular catheters used for monitoring or administration of life-sustaining medications. Consequently, sedatives and analgesics are among the most commonly administered drugs in ICUs.

Early intensive care practice evolved from intraoperative anesthetic care at a time when mechanical ventilation was delivered by rudimentary machines that were not capable of synchronizing with patients' respiratory efforts. As a result, deep sedation was commonly used until a patient was able to breathe without assistance. Developments over the past 30 years, including microprocessor-controlled ventilators that synchronize with patients' own respiratory efforts and new, shorter-acting sedative and analgesic medications, have dramatically changed this approach. Equally important has been the recognition that pain, oversedation, and delirium are issues that if undetected and untreated are distressing to patients and associated with increased morbidity and mortality.

Just as the concept of the "triad of anesthesia" underscores the pharmacodynamic interactions among hypnotics, analgesics, and muscle relaxants and the recognition that the simultaneous administration of agents of each class permits the use of lower doses of drugs of all classes, the concept of the "ICU triad" recognizes that pain, agitation, and delirium — and therefore approaches to their management — are inextricably linked (Fig. 1). According to the principle that it is better to treat disease than to mask it, sedatives should be used only when pain and delirium have been addressed with the use of specific pharmacologic and nonpharmacologic strategies.

Pain, Analgesia, and Sedation in the ICU

Prospective studies confirm that the majority of patients who are treated in ICUs have pain,[1] which makes the assessment of pain and provision of adequate analgesia essential components of ICU care. The short-term consequences of untreated pain include higher energy expenditure and immunomodulation.[2,3] Longer-term, untreated pain increases the risk of post-traumatic stress disorder.[4] Assessing whether a patient in the ICU is in pain may be difficult. The reference standard for the assessment of pain is self-reporting by the patient, but patients in the ICU may not be sufficiently interactive to give valid responses. Physiological indicators such as hypertension and tachycardia correlate poorly with more intuitively valid measures of pain,[5] but pain scales such as the Behavioral Pain Scale[6] and the Critical

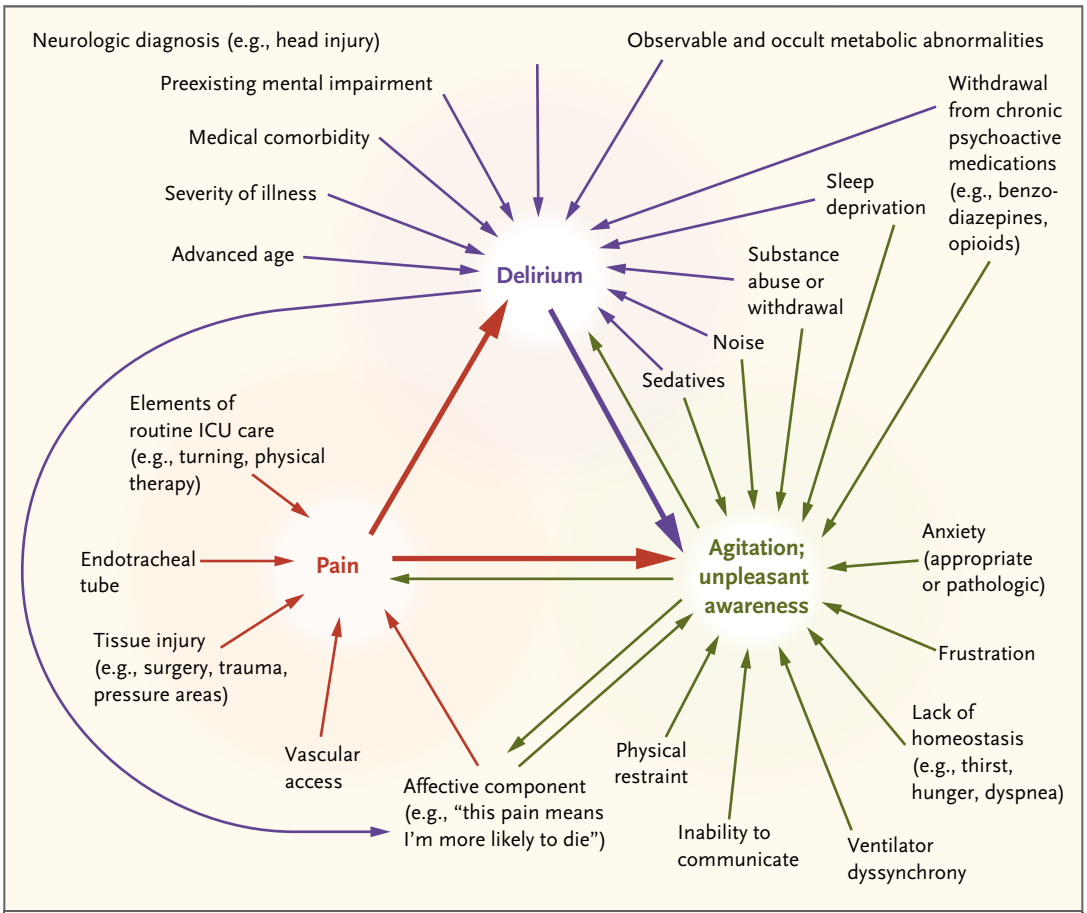

Figure 1. Causes and Interactions of Pain, Agitation, and Delirium.

Drugs and other treatments for pain, agitation, and delirium form an "ICU triad" cognitive management analogous to the "triad of anesthesia," which highlights interactions among hypnotics, analgesics, and muscle relaxants to encourage balanced anesthesia. The "ICU triad" concept highlights that changing one element is unlikely to be as effective as a coordinated approach.

Care Pain Observation Tool[7] provide structured and repeatable assessments and are currently the best available methods for assessing pain.

A minority of ICU patients have an indication for continuous deep sedation, for reasons such as the treatment of intracranial hypertension, severe respiratory failure, refractory status epilepticus, and prevention of awareness in patients treated with neuromuscular blocking agents. This review will focus on the remaining overwhelming majority of patients undergoing mechanical ventilation for whom the use of sedatives and analgesics should be minimized, with the goal that they be calm, lucid, pain-free, interactive, and cooperative with their care.

Evidence from randomized, controlled trials consistently supports the use of the minimum possible level of sedation. In a landmark trial that compared routine daily interruption of sedative infusions with discretionary interruption by treating clinicians, patients whose sedation was routinely interrupted received less sedation overall and spent fewer days undergoing mechanical ventilation and fewer days in the ICU.[8] Although the trial was too small to assess differences in mortality or discharge destination, the observed reductions in the duration of mechanical ventilation and length of stay in the ICU were associated with a nonsignificant reduction in mortality and a nonsignificant increase in the proportion of pa-

tients who were discharged to their own homes.[8] A subsequent larger multicenter trial combined the daily interruption of sedation with daily spontaneous breathing trials.[9] Daily interruption of sedation was associated with reduced administration of a benzodiazepine sedative, reduced duration of mechanical ventilation, reduced length of stay in the ICU, and significantly increased survival. In contrast, when daily interruption of sedation was added to a protocol for sedation practice that already sought to minimize the level of sedation, the total sedative dose was increased and there was no clinical benefit.[10]

These conflicting results are open to a number of interpretations, including that daily interruption is beneficial only when it results in a reduction in the total dose of sedative administered. The conflicting findings also highlight that the results of daily interruption of sedation may be context-specific and will depend on the population being studied, protocol adherence, and management of the control group. A randomized, controlled trial in which all patients undergoing mechanical ventilation received morphine for the treatment of pain in an "analgesia first" approach compared a protocol of no sedation with the routine use of sedation with daily interruption.[11] Patients who were assigned to the protocol of no sedation had shorter stays in the ICU and the hospital and more days without mechanical ventilation.

The consistent message from all these sedation-interruption trials is that minimizing sedation among patients in the ICU provides clinical benefit. Further support comes from a prospective, multicenter, longitudinal cohort study showing that the depth of sedation was independently associated with the duration of mechanical ventilation, in-hospital mortality, and rates of death within 180 days.[12] In a randomized, controlled trial, the use of lighter sedation resulted in more ventilator-free and ICU-free days.[13] In comparison with deep sedation, the use of lighter sedation did not increase the rate of short-term adverse events, and long-term psychiatric outcomes were either unaffected or improved.[13-16]

CHOICE OF SEDATIVE AGENT

Despite at least 90 trials comparing sedative regimens,[17] in general, no sedative drug is clearly superior to all others. Sedatives that are commonly used in the ICU are the benzodiazepines midazolam and lorazepam (and to a lesser extent, diazepam), the short-acting intravenous anesthetic agent propofol, and dexmedetomidine.[12] Remifentanil, an opioid, is also used as a sole agent because of its sedative effects. Benzodiazepines act through γ-aminobutyric acid type A ($GABA_A$) receptors, as in part does propofol, whereas dexmedetomidine is an α_2-adrenoceptor agonist, and remifentanil is a μ-opioid receptor agonist (Table 1). Marked differences in prescribing patterns among countries suggest that the choice of agent is determined more by tradition and familiarity than by evidence-based practice.

If minimizing the depth and duration of sedation is accepted as a desirable goal, then the use of a short-acting agent with an effect that can be rapidly adjusted such as propofol or remifentanil should offer advantages over longer-acting agents or agents with active metabolites. As compared with benzodiazepines, propofol has not been shown to reduce mortality but may result in a reduction in the length of stay in the ICU.[18] Dexmedetomidine may also have advantages over benzodiazepines, since it produces analgesia, causes less respiratory depression, and seemingly provides a qualitatively different type of sedation in which patients are more interactive and so potentially better able to communicate their needs.[19] As compared with lorazepam and midazolam, dexmedetomidine resulted in less delirium and a shorter duration of mechanical ventilation but not reduced stays in the ICU or hospital.[19-21] When two short-acting and titratable drugs such as propofol and dexmedetomidine were compared, there was no significant difference in the time spent at the target sedation level and no difference in either the duration of mechanical ventilation or ICU stay.[19]

Remifentanil has a half-life of 3 to 4 minutes that is independent of the infusion duration or organ function. It has been investigated as a sedative agent in ICUs predominantly among surgical patients. It has been compared with midazolam alone, midazolam with fentanyl, fentanyl alone, and morphine.[22-25] Although remifentanil has been associated with a reduced duration of mechanical ventilation and ICU stay in these small trials, it has not yet been evaluated in a large, heterogeneous population of critically ill patients and is currently not a common choice in most ICUs.

Table 1. Sedatives and Analgesics in Common Use in the ICU.*

Drug (Brand Name)	Mechanism of Action	Typical Adult Dose	Pharmacokinetic Properties	Adverse Effects
Midazolam (Versed)	$GABA_A$ agonist	Bolus, 1 to 5 mg; infusion, 1 to 5 mg/hr	Half-life, 3 to 11 hr; active metabolite accumulates with prolonged infusion; metabolized by hepatic oxidation, with renal excretion of active metabolite	Possibly a higher risk of delirium and tolerance than with certain other sedatives
Lorazepam (Ativan)	$GABA_A$ agonist	Bolus, 1 to 4 mg; infusion, 1 to 5 mg/hr	Slower onset (5 to 20 min) than that of midazolam or diazepam (2 to 5 min); half-life, 8 to 15 hr; metabolized by hepatic glucuronidation, with no active metabolites, so offset may be more predictable than that of midazolam in critical illness	Possibly a higher risk of delirium and tolerance than with certain other sedatives
Diazepam (Valium; Diazemuls)	$GABA_A$ agonist	Bolus, 1 to 5 mg	Half-life, 20 to 120 hr; metabolized by hepatic desmethylation and hydroxylation; active metabolite accumulates in renal failure	Poorly soluble in water, so prolonged peripheral intravenous infusion may cause phlebitis; possibly a higher risk of delirium and tolerance than certain other sedatives
Propofol (Diprivan)	$GABA_A$ agonist, with other effects, including on glutamate and cannabinoid receptors	50 to 200 mg/hr or 1 to 3 mg/kg/hr	Half-life, 30 to 60 min after infusion; longer after prolonged infusion because of redistribution from fat stores; metabolized by hepatic glucuronidation and hydroxylation	Vasodilatation or negative inotropy causing hypotension or bradycardia; propofol infusion syndrome (lactic acidosis, arrhythmia, and cardiac arrest), mostly associated with prolonged infusion rates of >4 to 5 mg/kg/hr; hypertriglyceridemia; pancreatitis
Dexmedetomidine (Precedex)	α_2-Agonist	0.2 to 1.5 μg/kg/hr	Half-life, 2 hr; does not accumulate with prolonged infusion; metabolized by hepatic glucuronidation and oxidation, with no active metabolites	Transient hypertension, then hypotension; bradycardia, dry mouth, nausea
Remifentanil (Ultiva)	μ-Opioid agonist (also with κ-opioid agonist effects)	0.5 to 2 μg/kg/min; loading dose of 0.4 to 0.8 μg/kg may be considered	Half-life, 3 to 4 min; does not accumulate with prolonged infusion; metabolized by plasma esterases and so is unaffected by organ function	Nausea, constipation, respiratory depression, bradycardia
Fentanyl (Sublimaze)	μ-Opioid agonist (also with κ-opioid agonist effects)	20 to 100 μg/hr; loading dose of 50 to 100 μg may be considered	Half-life, 1.5 to 6 hr; highly fat soluble, so rapid onset but accumulates with prolonged infusion; metabolized by hepatic oxidation; no active metabolites	Nausea, constipation, respiratory depression, skeletal-muscle rigidity with high bolus doses
Morphine (Roxanol; Duramorph)	μ-Opioid agonist (also with κ-opioid and δ-opioid agonist effects)	1 to 5 mg/hr; loading dose of 2 to 5 mg may be considered	Half-life, 3 to 7 hr; more water soluble, so slower onset than fentanyl with less accumulation; metabolized by hepatic glucuronidation to morphine-6-glucuronide (10%) (20 times as active as parent drug) and morphine-3-glucuronide (90%) (inactive as an analgesic but causes neuroexcitation, at least in animal models), both with renal excretion	Nausea, constipation, respiratory depression, histamine release and consequent vasodilatation and hypotension, itch
Hydromorphone (Dilaudid)	μ-Opioid agonist (also with κ-opioid and δ-opioid agonist effects)	0.5 to 2 mg/hr; loading dose of 0.4 to 1.5 mg may be considered	Half-life, 1.5 to 3.5 hr; 7 to 11 times as potent as morphine; metabolized by hepatic glucuronidation to hydromorphone-3-glucuronide, with effects similar to those of morphine-3-glucuronide	Nausea, constipation, respiratory depression

* $GABA_A$ denotes γ-aminobutyric acid type A.

PREVENTION AND TREATMENT OF DELIRIUM

The *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV),[26] lists four domains of delirium: disturbance of consciousness, change in cognition, development over a short period, and fluctuation. Delirium is defined by the National Institutes of Health as "sudden severe confusion and rapid changes in brain function that occur with physical or mental illness." The most common feature of delirium, thought by many to be its cardinal sign, is inattention. Delirium is a nonspecific but generally reversible manifestation of acute illness that appears to have many causes, including recovery from a sedated or oversedated state.

The pathophysiology of delirium that is associated with critical illness remains largely uncharacterized and may vary depending on the cause. The increased risk associated with the use of $GABA_A$ agonists and anticholinergic drugs led to the suggestion that the GABAergic and cholinergic neurotransmitter systems play a contributory role. In particular, central cholinergic deficiency may be a final common pathway. Alternative hypotheses include excess dopaminergic activity and direct neurotoxic effects of inflammatory cytokines. Currently, these hypotheses are unproven, making pharmacologic management strategies largely empirical.

Studies using magnetic resonance imaging have shown a positive association between the duration of delirium in the ICU and both cerebral atrophy and cerebral white-matter disruption.[27,28] These preliminary investigations indicate either that delirium in the ICU gives rise to alterations in brain structure or that the presence of such cerebral atrophy and white-matter disruption renders patients more susceptible to delirium.

Regardless of the cause and the underlying pathophysiology, delirium is now recognized as a frequent and serious event in critically ill patients. There is no diagnostic blood, electrophysiological, or imaging test for delirium, which therefore remains a clinical diagnosis. Estimates for the incidence of delirium in the ICU range from 16%[29] to 89%,[30] with the reported incidence affected both by the characteristics of the population being studied and by the diagnostic criteria used. Risk factors that have been identified include an advanced age and the presence of more than one condition associated with coma, followed by treatment with sedative medications, a neurologic diagnosis, and increased severity of illness.[31] A diagnosis of delirium is associated with increased mortality (estimated as a 10% increase in the relative risk of death for each day of delirium[32]) and decreased long-term cognitive function.[33]

There are two distinct forms of delirium, hypoactive and agitated (or hyperactive). When individual patients intermittently have both forms, it is termed mixed delirium. The hypoactive form is characterized by inattention, disordered thinking, and a decreased level of consciousness without agitation. Pure agitated delirium affects less than 2% of patients with delirium in the ICU.[34] Patients with hypoactive delirium are the least likely to survive, but those who do survive may have better long-term function than those with agitated or mixed delirium.[33] Separating the effects of delirium status from those of illness severity with respect to the risk of death is difficult, since patients with more serious illnesses are at increased risk for both delirium and death. Association studies typically adjust for illness severity on admission to the ICU rather than at the time that delirium is diagnosed. Although the association between delirium and a worse outcome is clear, a causal relationship has not been established. Currently, the evidence that specific treatment of delirium may improve outcomes is tenuous.

ASSESSMENT AND MONITORING OF SEDATION AND DELIRIUM

Although ICU practice is characterized by close monitoring of carefully administered care, surveys that have been conducted in various countries have shown that the depth of sedation frequently goes unmonitored.[35] This finding is surprising and unacceptable, since evidence suggests that the routine monitoring of sedation may improve patients' outcomes.[36]

SEDATION SCALES

Of the sedation scales described, the Riker Sedation–Agitation Scale[37] and the Richmond Agitation–Sedation Scale[38] are the most commonly reported, but in head-to-head comparison,

neither is demonstrably superior[39] (Table 2). For the majority of patients undergoing mechanical ventilation in an ICU, an appropriate target is a score of 3 to 4 on the Riker Sedation–Agitation Scale (which ranges from 1 to 7, with scores of <4 indicating deeper sedation, a score of 4 indicating an appearance of calm and cooperativeness, and scores of ≥5 indicating increasing agitation) or a score of –2 to 0 on the Richmond Agitation–Sedation Scale (which ranges from –5 to +4, with more negative scores indicating deeper sedation and more positive scores indicating increasing agitation, and with 0 representing the appearance of calm and normal alertness).

IDENTIFYING DELIRIUM

In routine practice, ICU staff members typically do not diagnose delirium in almost three quarters of their patients who have the condition, whereas active screening by research nurses identified delirium in up to 64% of patients who were considered to be delirious by a psychiatrist, a geriatrician, or a neurologist.[40] Scales with respect to delirium in the ICU apply the four DSM-IV domains defining delirium in general medical and psychiatric patients to those in the ICU whose severity of illness can rapidly fluctuate, who receive multiple analgesics and sedatives, and who are unable to speak owing to endotracheal intubation. Two scales are in common use, the Confusion Assessment Method for the ICU (CAM-ICU)[41] and the Intensive Care Delirium Screening Checklist (ICDSC)[29] (Table 3). The CAM-ICU reports a dichotomous assessment at a single time point, whereas the ICDSC lists signs that can be observed over a period of time. Although such

Table 2. Sedation Scales for Patients in the ICU.

Scale and Scoring Method	Description
Riker Sedation–Agitation Scale (SAS)*	
Dangerous agitation (score of 7)	Pulling at endotracheal tube, trying to remove catheters, climbing over bed rail, striking at staff, thrashing from side to side
Very agitated (score of 6)	Requiring restraint and frequent verbal reminding of limits, biting endotracheal tube
Agitated (score of 5)	Anxious or physically agitated, calming at verbal instruction
Calm and cooperative (score of 4)	Calm, easily rousable, follows commands
Sedated (score of 3)	Difficult to arouse but awakens to verbal stimuli or gentle shaking; follows simple commands but drifts off again
Very sedated (score of 2)	Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
Cannot be aroused (score of 1)	Minimal or no response to noxious stimuli, does not communicate or follow commands
Richmond Agitation–Sedation Scale (RASS)†	
Combative (score of 4)	Overtly combative, violent, immediate danger to staff
Very agitated (score of 3)	Pulls or removes tubes or catheters; aggressive
Agitated (score of 2)	Frequent nonpurposeful movement, fights ventilator
Restless (score of 1)	Anxious but movements not aggressive or vigorous
Alert and calm (score of 0)	Alert and calm
Drowsy (score of –1)	Not fully alert but has sustained awakening (eye opening or eye contact) to voice (≥10 sec)
Light sedation (score of –2)	Briefly awakens with eye contact to voice (<10 sec)
Moderate sedation (score of –3)	Movement or eye opening to voice but no eye contact
Deep sedation (score of –4)	No response to voice but movement or eye opening to physical stimulation
Cannot be aroused (score of –5)	No response to voice or physical stimulation

* Data are from Riker et al.[37]
† Data are from Sessler et al.[38]

Table 3. Scoring Systems for the Diagnosis of Delirium in Critically Ill Patients.*

System, Scoring Method, and Criteria
Confusion Assessment Method for the ICU (CAM-ICU)†
Scoring is positive or negative according to the presence or absence of criteria listed
Patient must be sufficiently awake (RASS score, –3 or more) for assessment according to the following criteria:
An acute change from mental status at baseline or fluctuating mental status during the past 24 hr (must be true to be positive)
More than 2 errors on a 10-point test of attention to voice or pictures (must be true to be positive)
If the RASS is not 0 and the above two criteria are positive, the patient is delirious
If the RASS is 0 and the above two criteria are positive, test for disorganized thinking using 4 yes/no questions and a 2-step command; >1 error means the patient is delirious; ≤1 error excludes delirium
Intensive Care Delirium Screening Checklist (ICDSC)‡
A score of ≥4 is positive for delirium (with scores of 1 to 3 termed "subsyndromal delirium")
Patient must show at least a response to mild or moderate stimulation. Then score 1 point for each of the following features, as assessed in the manner thought appropriate by the clinician:
Anything other than "normal wakefulness"
Inattention
Disorientation
Hallucination
Psychomotor agitation
Inappropriate speech or mood
Disturbance in sleep or wake cycle
Fluctuation in symptoms

* RASS denotes Richmond Agitation–Sedation Scale.
† Data are from Ely et al.[41]
‡ Data are from Bergeron et al.[29]

scales are essential in objectively diagnosing delirium for research purposes, it is not clear that the use of these scales is more sensitive than unstructured assessments made by trained bedside nurses who are prompted to look for delirium. Some studies have shown a high sensitivity when such assessments are performed by bedside nurses,[42] whereas other studies have shown conflicting results.[43] Used alone (without an accompanying sedation scale), none of the published scales distinguish hyperactive from hypoactive delirium, and none of the published scales quantify the relative importance of individual elements of the scales despite recognition that specific treatments may shorten the duration of some elements and prolong the duration of others. All the scales dichotomize delirium as being either present or absent, although it would seem to be intuitive that delirium has different degrees of severity. The CAM-ICU and ICDSC are currently the two accepted methods for identifying a condition that otherwise frequently goes undiagnosed.[44]

PREVENTION AND TREATMENT OF DELIRIUM

PREVENTION

There is some evidence that delirium can be prevented. Outside the ICU, repeated reorientation, noise reduction, cognitive stimulation, vision and hearing aids, adequate hydration, and early mobilization can reduce the incidence of delirium in hospitalized patients.[45] Haloperidol prophylaxis in patients undergoing hip surgery reduced the severity and duration of delirium.[46] Among patients in the ICU, the duration of delirium was cut in half with early mobilization during interruptions in sedation.[47]

Pharmacologic studies of delirium prevention include trials comparing one sedative–analgesic regimen with another and studies of antipsychotic drugs administered with the specific intent of preventing delirium. Four placebo-controlled trials have evaluated pharmacologic prophylaxis of delirium; low-dose haloperidol[48] and low-dose risperidone[49] both reduced the incidence of delirium, as did a single low dose of ketamine during the induction of anesthesia.[50] However, these trials were conducted among patients undergoing elective surgical procedures, and it is not clear whether their results can be extrapolated to the general ICU population. In contrast, the cholinesterase inhibitor rivastigmine was ineffective in preventing delirium.[51]

Sedation with dexmedetomidine rather than benzodiazepines appears to reduce the incidence of delirium in the ICU. In a multicenter, randomized trial predominantly involving medical patients in the ICU, the administration of dexmedetomidine or midazolam resulted in similar proportions of time within the target range of –2 to +1 on the Richmond Agitation–Sedation Scale among patients, but those assigned to receive dexmedetomidine had a reduced risk of delirium and spent less time undergoing mechanical ventilation.[21] As compared with a lorazepam infusion, sedation with dexmedetomidine

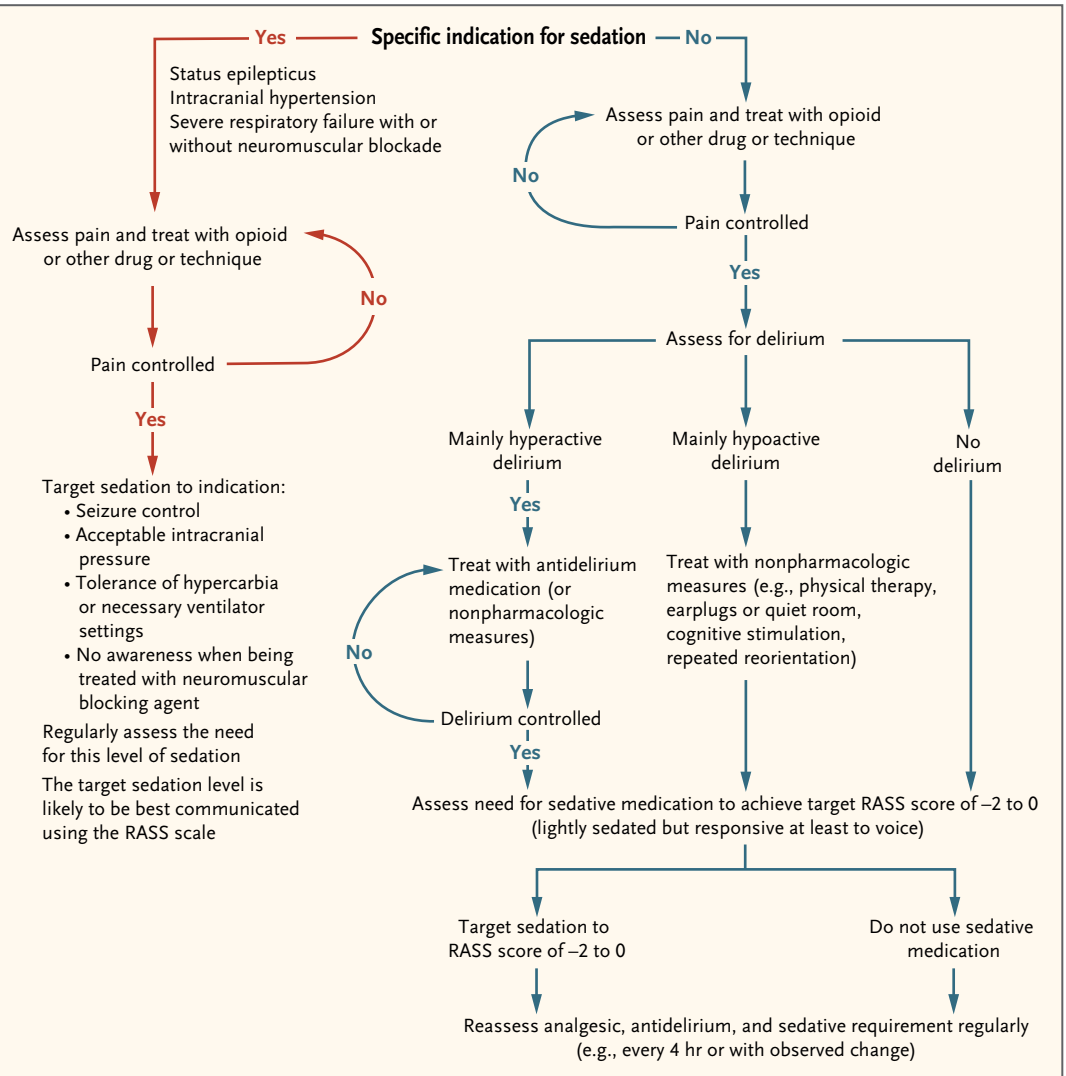

Figure 2. Algorithm for the Coordinated Management of Pain, Agitation, and Delirium.

The application of this algorithm — which combines the use of analgesics, antidelirium agents, sedatives, and nonpharmacologic techniques — will depend on the individual situation for each patient. For example, patients undergoing surgery who are suitable candidates for rapid extubation and who have little risk of delirium may be treated only with analgesia and rapidly diminishing sedation. RASS denotes Richmond Agitation–Sedation Scale, which ranges from –5 to +4, with more negative scores indicating deeper sedation and more positive scores indicating increasing agitation, and with 0 representing the appearance of calm and normal alertness.

resulted in more time at the target level of sedation and longer survival without delirium or coma.[20] In a multicenter European trial, patients were randomly assigned to continue treatment with their current sedative (midazolam or propofol) or to switch to sedation with up to 1.4 μg of dexmedetomidine per kilogram of body weight per hour.[19] There were no between-group differences in the proportion of time at the target level of sedation. The rates of the composite end point of agitation, anxiety, or delirium were lower with dexmedetomidine than with propofol, but the rates with dexmedetomidine were equivalent to those with midazolam. When delirium was assessed with the use of the CAM-ICU 48 hours after sedation was discontinued, there were no significant differences among the groups.

TREATMENT

There is very little evidence to guide the management of established delirium, and most existing trials were categorized by the investigators as pilot studies. Only one small placebo-controlled trial supports the efficacy of a drug treatment for established delirium in patients in the ICU. In a study of 36 patients who were randomly assigned to treatment with quetiapine or placebo, delirium resolved faster in patients who received quetiapine. The use of quetiapine also increased the number of patients who were discharged to their own home or to rehabilitation.[52] A study of 103 patients who were randomly assigned to receive regular haloperidol, ziprasidone, or placebo showed no significant differences in the number of days that patients survived without delirium or coma.[53] The single study comparing haloperidol with an atypical antipsychotic (olanzapine) showed equivalent efficacy.[54] None of these trials distinguished between hyperactive and hypoactive delirium.

In a pilot study comparing dexmedetomidine with haloperidol in patients with hyperactive delirium, dexmedetomidine was associated with a shorter time to extubation and shorter length of stay in the ICU.[55] This finding is supported by a randomized trial of dexmedetomidine versus midazolam in which patients with delirium at the time of enrollment had a more rapid resolution of delirium if they were assigned to receive dexmedetomidine than if they were assigned to receive midazolam.[21] However, definitive evidence supporting the use of dexmedetomidine for the treatment of delirium is not currently available.

QUALITY IMPROVEMENT TECHNIQUES

Frameworks that facilitate the aforementioned approaches have been developed. These include the "pain, agitation, and delirium" (PAD) guidelines[44] and the "spontaneous awakening and breathing coordination, attention to the choice of sedation, delirium monitoring, and early mobility and exercise" (ABCDE) bundle.[56] These guidelines emphasize improving team communication in the ICU, standardizing care processes, and prioritizing methods to lighten sedation and facilitate early mobilization and extubation. Each guideline recognizes the conceptual evolution from spontaneous-breathing trials and interruption of sedation to a comprehensive approach to monitoring and managing pain, agitation, and delirium.

CONCLUSIONS

Accumulating evidence suggests that the management of sedation and delirium can have an important effect on the outcomes of patients who are treated in ICUs. Currently available data suggest that the best outcomes are achieved with the use of a protocol in which the depth of sedation and the presence of pain and delirium are routinely monitored, pain is treated promptly and effectively, the administration of sedatives is kept to the minimum necessary for the comfort and safety of the patient, and early mobilization is achieved whenever possible (Fig. 2).

Dr. Reade reports receiving grant support through his institution from Hospira. Dr. Finfer reports receiving grant support through his institution from Fresenius Kabi; being a member of the International Sepsis Forum (ISF) council, which has received funding from Eisai, Siemens, Agennix, AstraZeneca, BD Diagnostics, bioMérieux, BRAHMS/Thermo Fisher, Eli Lilly, Roche, Spectral, Toray, Philips, Apex, Ferring, BioCritica, and Plasma Protein Therapeutics Association during his membership; and receiving consulting fees from Edwards (paid to ISF), lecture fees from Eli Lilly and PPTA (donated to ISF), and travel support from the ISF. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. Stein-Parbury J, McKinley S. Patients' experiences of being in an intensive care unit: a select literature review. Am J Crit Care 2000;9:20-7.
2. Swinamer DL, Phang PT, Jones RL, Grace M, King EG. Effect of routine administration of analgesia on energy expenditure in critically ill patients. Chest 1988;93:4-10.
3. Page GG, Blakely WP, Ben-Eliyahu S. Evidence that postoperative pain is a mediator of the tumor-promoting effects of surgery in rats. Pain 2001;90:191-9.
4. Myhren H, Ekeberg O, Toien K, Karlsson S, Stokland O. Posttraumatic stress, anxiety and depression symptoms in patients during the first year post intensive care unit discharge. Crit Care 2010;14(1):R14.
5. Gélinas C, Tousignant-Laflamme Y, Tanguay A, Bourgault P. Exploring the validity of the bispectral index, the Critical-Care Pain Observation Tool and vital signs for the detection of pain in sedated and mechanically ventilated critically ill adults: a pilot study. Intensive Crit Care Nurs 2011;27:46-52.
6. Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29:2258-63.
7. Gélinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care

pain observation tool in adult patients. Am J Crit Care 2006;15:420-7.
8. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. N Engl J Med 2000;342:1471-7.
9. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. Lancet 2008;371:126-34.
10. Mehta S, Burry L, Cook D, et al. Daily sedation interruption in mechanically ventilated critically ill patients cared for with a sedation protocol: a randomized controlled trial. JAMA 2012;308:1985-92.
11. Strøm T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. Lancet 2010;375:475-80.
12. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. Am J Respir Crit Care Med 2012; 186:724-31.
13. Treggiari MM, Romand JA, Yanez ND, et al. Randomized trial of light versus deep sedation on mental health after critical illness. Crit Care Med 2009;37:2527-34.
14. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB. The long-term psychological effects of daily sedative interruption on critically ill patients. Am J Respir Crit Care Med 2003;168:1457-61.
15. Strøm T, Stylsvig M, Toft P. Long-term psychological effects of a no-sedation protocol in critically ill patients. Crit Care 2011;15:R293.
16. Jackson DL, Proudfoot CW, Cann KF, Walsh TS. The incidence of sub-optimal sedation in the ICU: a systematic review. Crit Care 2009;13:R204.
17. Roberts DJ, Haroon B, Hall RI. Sedation for critically ill or injured adults in the intensive care unit: a shifting paradigm. Drugs 2012;72:1881-916.
18. Ho KM, Ng JY. The use of propofol for medium and long-term sedation in critically ill adult patients: a meta-analysis. Intensive Care Med 2008;34:1969-79.
19. Jakob SM, Ruokonen E, Grounds RM, et al. Dexmedetomidine vs midazolam or propofol for sedation during prolonged mechanical ventilation: two randomized controlled trials. JAMA 2012;307:1151-60.
20. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. JAMA 2007;298:2644-53.
21. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. JAMA 2009;301:489-99.
22. Muellejans B, Matthey T, Scholpp J, Schill M. Sedation in the intensive care unit with remifentanil/propofol versus midazolam/fentanyl: a randomised, open-label, pharmacoeconomic trial. Crit Care 2006;10:R91.
23. Breen D, Karabinis A, Malbrain M, 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 randomised trial. Crit Care 2005;9:R200-R210.
24. Dahaba AA, Grabner T, Rehak PH, List WF, Metzler H. Remifentanil versus morphine analgesia and sedation for mechanically ventilated critically ill patients: a randomized double blind study. Anesthesiology 2004;101:640-6.
25. Spies C, MacGuill M, Heymann A, et al. A prospective, randomized, double-blind, multicenter study comparing remifentanil with fentanyl in mechanically ventilated patients. Intensive Care Med 2011;37:469-76.
26. Diagnostic and statistical manual of mental disorders, 4th ed. text rev.: DSM-IV-TR. Arlington, VA: American Psychiatric Association, 2011.
27. Gunther ML, Morandi A, Krauskopf E, et al. The association between brain volumes, delirium duration, and cognitive outcomes in intensive care unit survivors: the VISIONS cohort magnetic resonance imaging study. Crit Care Med 2012;40: 2022-32.
28. Morandi A, Rogers BP, Gunther ML, et al. The relationship between delirium duration, white matter integrity, and cognitive impairment in intensive care unit survivors as determined by diffusion tensor imaging: the VISIONS prospective cohort magnetic resonance imaging study. Crit Care Med 2012;40:2182-9.
29. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med 2001; 27:859-64.
30. Ely EW, Girard TD, Shintani AK, et al. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. Crit Care Med 2007;35: 112-7.
31. van den Boogaard M, Pickkers P, Slooter AJ, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. BMJ 2012; 344:e420.
32. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. Am J Respir Crit Care Med 2009; 180:1092-7.
33. van den Boogaard M, Schoonhoven L, Evers AW, van der Hoeven JG, van Achterberg T, Pickkers P. Delirium in critically ill patients: impact on long-term health-related quality of life and cognitive functioning. Crit Care Med 2012;40:112-8.
34. Peterson JF, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. J Am Geriatr Soc 2006;54:479-84.
35. Soliman HM, Melot C, Vincent JL. Sedative and analgesic practice in the intensive care unit: the results of a European survey. Br J Anaesth 2001;87:186-92.
36. De Jonghe B, Bastuji-Garin S, Fangio P, et al. Sedation algorithm in critically ill patients without acute brain injury. Crit Care Med 2005;33:120-7.
37. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. Crit Care Med 1999;27:1325-9.
38. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. Am J Respir Crit Care Med 2002;166:1338-44.
39. Pun BT, Dunn J. The sedation of critically ill adults — part 1: assessment: the first in a two-part series focuses on assessing sedated patients in the ICU. Am J Nurs 2007;107:40-8.
40. van Eijk MM, van Marum RJ, Klijn IA, de Wit N, Kesecioglu J, Slooter AJ. Comparison of delirium assessment tools in a mixed intensive care unit. Crit Care Med 2009;37:1881-5.
41. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). JAMA 2001; 286:2703-10.
42. Vasilevskis EE, Morandi A, Boehm L, et al. Delirium and sedation recognition using validated instruments: reliability of bedside intensive care unit nursing assessments from 2007 to 2010. J Am Geriatr Soc 2011;59:Suppl 2:S249-S255.
43. Reade MC, Eastwood GM, Peck L, Bellomo R, Baldwin I. Routine use of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) by bedside nurses may underdiagnose delirium. Crit Care Resusc 2011;13:217-24.
44. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. Crit Care Med 2013;41:263-306.
45. Vidán MT, Sanchez E, Alonso M, Montero B, Ortiz J, Serra JA. An intervention integrated into daily clinical practice reduces the incidence of delirium during hospitalization in elderly patients. J Am Geriatr Soc 2009;57:2029-36.

46. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. J Am Geriatr Soc 2005;53:1658-66.
47. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. Lancet 2009;373:1874-82.
48. Wang W, Li HL, Wang DX, et al. Haloperidol prophylaxis decreases delirium incidence in elderly patients after noncardiac surgery: a randomized controlled trial. Crit Care Med 2012;40:731-9.
49. Prakanrattana U, Prapaitrakool S. Efficacy of risperidone for prevention of postoperative delirium in cardiac surgery. Anaesth Intensive Care 2007;35:714-9.
50. Hudetz JA, Patterson KM, Iqbal Z, et al. Ketamine attenuates delirium after cardiac surgery with cardiopulmonary bypass. J Cardiothorac Vasc Anesth 2009;23:651-7.
51. Gamberini M, Bolliger D, Lurati Buse GA, et al. Rivastigmine for the prevention of postoperative delirium in elderly patients undergoing elective cardiac surgery — a randomized controlled trial. Crit Care Med 2009;37:1762-8.
52. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. Crit Care Med 2010;38:419-27.
53. Girard TD, Pandharipande PP, Carson SS, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. Crit Care Med 2010;38:428-37.
54. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. Intensive Care Med 2004;30:444-9.
55. Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. Crit Care 2009;13:R75.
56. Vasilevskis EE, Pandharipande PP, Girard TD, Ely EW. A screening, prevention, and restoration model for saving the injured brain in intensive care unit survivors. Crit Care Med 2010;38:Suppl:S683-S691.