

CONGRESS REVIEW



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DELIRIUM: SHOULD “NEVER” OCCUR, BUT IF IT DOES ...

With increasing evidence linking delirium to serious sequelae, many intensive care units (ICUs) are adopting delirium screening in daily practice. In addition, government officials are wondering whether delirium should be deemed a “never” event in the hospital, prompting a close look at the identification, treatment and prevention of delirium among critically ill patients.

Delirium as the Next “Never” Event: Is That Realistic? Pratik P. Pandharipande, MD, MSCl

In 2009, the Centers for Medicare & Medicaid Services (CMS) considered proposing delirium in the hospital as the next “never” event (i.e., a medical care error that has serious consequences but is identifiable and preventable). “Can delirium realistically be a ‘never’ event in the ICU?” asked Pratik P. Pandharipande, MS, MSCl, from Vanderbilt University School of Medicine in Nashville, Tennessee, USA. “Perhaps not yet, but there are measures we can take to reduce the burden of this brain dysfunction.”

Regardless of whether delirium becomes a “never” event, one thing is clear: the problem of delirium in the hospital has been gaining attention. “Delirium is no longer the organ dysfunction that nobody cares about,” said Pandharipande, noting that the past 10 years has witnessed a significant rise in delirium research.

Delirium is a brain organ dysfunction characterized by a disturbance of consciousness. It has a rapid onset and fluctuating course and is marked by inattention and disorganized thinking (impaired ability to receive, process, store and recall information). Perceptual disturbances such as illusions and hallucinations can be present. The hypoactive or mixed forms of delirium are most common, while the hyperactive form (e.g., patients pulling out tubes or trying to get out of bed) is rare.

“There’s a wide range of prevalence rates for delirium in the ICU, depending on the diagnostic instrument used and the patient type,” reported Pandharipande. Delirium has been reported to occur in 60% to 80% of mechanically ventilated patients and 20% to 50% of ICU patients with lower severity of illness. “Research suggests that unless the ICU performs routine monitoring for mental status, the majority of delirium cases will go undiagnosed,” Pandharipande said.

The medical community should be concerned about delirium because it has serious consequences. It is associated with adverse outcomes: higher hospital costs, longer hospital stays, a threefold higher risk of mortality within six months, and prolonged neuropsychological dysfunction (Milbrandt EB, et al. *Crit Care Med.* 2004;32:955; Ely EW, et al. *JAMA.* 2004;291:1753; Ouimet S, et al. *Intensive Care Med.* 2007;33:66; Lin SM, et al. *Crit Care Med.* 2004;32:2254). In addition to trying to prevent delirium, it is also important to reduce its duration, because longer duration has been linked to worse neuropsychological outcomes and higher mortality risk (Pisani MA, et al. *Am J Respir Crit Care Med.* 2009;180:1092).

“Delirium represents a spectrum of brain organ dysfunction, with delirium on one end, normal on the other, and subsyndromal delirium in the middle,” explained Pandharipande. “Patients with subsyndromal delirium present with some symptoms of delirium but do not fulfill all diagnostic criteria. Higher mortality and longer length of stay occur more with clinical delirium than subsyndromal delirium, which in turn is associated with worse outcomes than in patients with normal mental status. So we need to realize that delirium is similar to other organ dysfunctions, in which severity of the disease impacts the outcomes.”

In determining whether delirium is identifiable (an essential feature of a “never” event), Pandharipande said progress has been made but more is needed. To ascertain whether delirium is preventable (another feature of a “never” event), it is important to understand the pathogenesis and risk factors. “We need to elucidate the mechanisms and identify risk factors,” said Pandharipande. “Delirium pathogenesis research is in its infancy, but some data suggest that inflammation may play a role, as well as disturbances of neurotransmitters, especially serotonin, dopamine, acetylcholine and norepinephrine.”

Prevention of delirium can be facilitated by avoiding risk factors. Although most of the known risk factors are not modifiable (aging, baseline dementia, psychiatric disorders, underlying inflammation or coagulation, metabolic disturbances, hypoxemia, and perhaps genetic predisposition), two potentially modifiable risk factors have been identified: psychoactive medications and sleep deprivation. Research reveals a temporal relationship between the administration of lorazepam and the occurrence of delirium, with the risk of transitioning to delirium being nearly 100% after a 24-hour period of receiving 20 mg lorazepam (1 mg/h), as shown in Figure 1 (Pandharipande P, et al. *Anesthesiology.* 2006;104:21).

Similar findings suggest that another benzodiazepine – midazolam – is also a risk factor for delirium, but the data on opiates are mixed (Pandharipande P, et al. *J Trauma.* 2008;65:34). Some findings suggest that reducing pain adequately with morphine is associated with lower rates

of delirium although this may not be true when fentanyl is used for the added benefit of sedation (Pandharipande P, et al. *J Trauma.* 2008;65:34). “In the trauma ICU, morphine looked protective versus fentanyl,” reported Pandharipande. “Additionally, among burn ICU patients, benzodiazepines were associated with delirium, whereas adequate control of pain with opiate administration seemed to reduce the risk of developing delirium on the following day (Pandharipande P, et al. American Society of Anesthesiologists Annual Meeting; 2009).”

In light of this and other data, clinicians can take the following measures to try to reduce delirium in the ICU: monitor patients for delirium, consider evidence-based nonpharmacologic interventions, and reduce or modify exposure to sedatives.

Monitoring for delirium begins with discussions of the patient’s status during daily rounds. “We want to know where our patient’s brain is going, where the brain is now and how it got there,” explained Pandharipande. “We need to have a grasp of the patient’s state of arousal and the content of this arousal.” Arousal status can be detected using validated sedation scale and the content of the arousal with delirium-measuring instruments. Two such tools have been implemented on a large scale: the Confusion Assessment Method-Intensive Care Unit (CAM-ICU) and the Intensive Care Delirium Screening Checklist (ICDSC).

Risk can be reduced through the use of delirium prevention protocols involving nonpharmacologic interventions. One non-ICU study evaluating a multicomponent intervention for geriatric patients found that delirium incidence decreased when protocols were implemented that addressed reorientation and continuity of caregivers, sleep architecture improvement, reduction of deliriogenic medication exposure, cognition stimulation, and geriatrician/trained neuropsychologic personnel visits (Inouye SK, et al. *N Engl J Med.* 1999;340:669). In addition, a study of mechanically ventilated patients demonstrated that early physical and occupational therapy resulted in reduced duration of both delirium and ICU stay (Schweickert WD, et al. *Lancet.* 2009;373:1874).

Implementation of sedation protocols that reduce sedative exposure may be effective in reducing delirium in the ICU, but more evidence is needed. “There is some suggestion that if you reduce benzodiazepine exposure, at least in the sickest of your patients – those with sepsis – you will reduce the duration of delirium,” Pandharipande said.

To decrease or avoid use of benzodiazepines, agents with different mechanisms should be considered. Results from the Maximizing Efficacy of Targeted Sedation and Reducing Neurological Dysfunction (MENDS) trial revealed that administration of dexmedetomidine (an α_2 -agonist) resulted in more days alive without delirium or coma and more time at the targeted level of sedation compared with lorazepam (Pandharipande PP, et al. *JAMA.* 2007;298:2644). Similar results have been demonstrated with dexmedetomidine versus midazolam. The recent Safety and Efficacy of Dexmedetomidine Compared to Midazolam (SEDCOM) trial showed lower prevalence of delirium in the dexmedetomidine group when

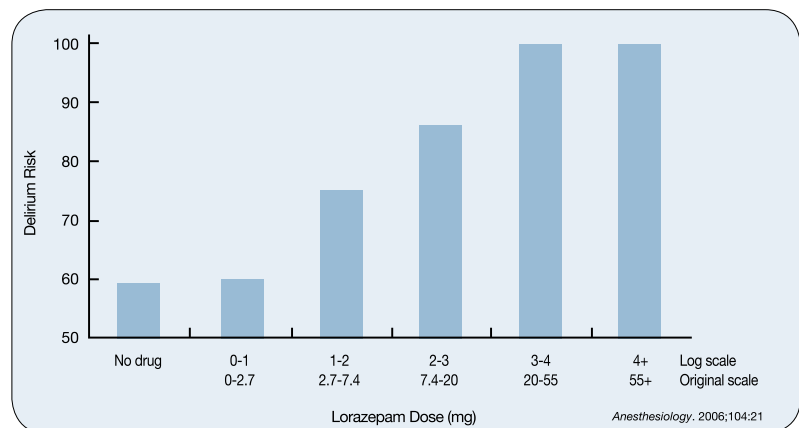


Figure 1. Lorazepam and Delirium

compared to midazolam (Riker RR, et al. *JAMA*. 2009;301:489).

Investigators also have evaluated the effects of antipsychotic agents on delirium risk among ICU patients. One double-blind randomized controlled trial found that following cardiac surgery, a single dose of 1 mg risperidone administered upon arrival to the ICU reduced the delirium incidence rate from 31.7% to 11.1% (Prakanrattana U, et al. *Anaesth Intensive Care*. 2007;35:714). In one of the first placebo-controlled studies of antipsychotics in critically ill patients, there was no difference in resolution of delirium and coma with the use of a typical (haloperidol) versus atypical (ziprasidone) antipsychotic agent (Girard TD, et al. *Crit Care Med*.

2010;38:428). Another recent study showed that in patients with delirium, there was faster time to resolution of the first episode of delirium with quetiapine versus placebo (Devlin JW, et al. *Crit Care Med*. 2010;38:419). This will be discussed later in this article.

Pandharipande summarized his remarks by noting that progress has been made in making delirium identifiable and emphasizing some of the risk factors that can drive the targeting of therapies and improve outcomes. "We're focusing more on trying to reduce the duration of delirium, as has been seen in many studies, while still trying to clarify the best way to reduce delirium incidence and make it a 'never' event in the future."

Typical Versus Atypical Antipsychotics: Which Is the Better Option? John W. Devlin, PharmD, FCCM

Haloperidol currently may be the drug of choice for delirium in many ICUs, but are atypical antipsychotic agents a better option? "The mechanisms for delirium in the critically ill patient are numerous and complex, and one of the common pathways by which delirium occurs is neurotransmitter imbalance, including a decrease in acetylcholine and an increase in dopamine," stated John W. Devlin, PharmD, FCCM, from Northeastern University School of Pharmacy in Boston, Massachusetts, USA. "This creates a compelling area for focusing treatment interventions, particularly considering the availability of many different antipsychotic agents that modulate these neurotransmitters."

Devlin noted that pharmacologic therapy should be considered only after the underlying causes of delirium have been treated, and it should usually be reserved for severe agitation that puts at risk the safety of the patient or caregiver. In general, the positive signs of delirium (e.g., agitation, hallucinations) are more likely to respond to antipsychotic therapy than the negative signs (e.g., hypoactivity, inattention, disordered cognition, depressed level of consciousness). The number of causes of delirium is substantially greater among ICU versus non-ICU patients. "Therefore, we have to be careful about extrapolating the results of non-ICU studies," Devlin said.

The receptor adherence properties differ widely among antipsychotic agents. For example, haloperidol is predominantly D₂ dopaminergic; ziprasidone is almost entirely serotonergic; olanzapine and risperidone are predominantly serotonergic; and quetiapine is predominantly adrenergic and histaminic. All antipsychotics appear to be equally efficacious in psychosis, but are they also similar in delirium, considering their differing pharmacologic properties? "A 2 to 20 mg/day dose of haloperidol is adequate to achieve the 60% binding to D₂ receptors necessary for an antipsychotic effect, but we're not sure of the exact dose needed in delirium treatment," said Devlin.

Clinical practice guidelines released by the American Psychiatric Association suggested that 1 mg to 2 mg of haloperidol be administered every two to four hours and be titrated to higher doses if agitation continues; some physicians also reported using atypical antipsychotics at that time. In 2002, the Society of Critical Care Medicine sedation guidelines (*Crit Care Med*. 2002;30:119) included a grade C recommendation stating that haloperidol is the preferred agent for delirium treatment in critically ill patients. Most recently, the United Kingdom Delirium Guidelines have offered more conservative recommendations, recognizing the paucity of studies regarding anti-delirium therapy.

Although haloperidol has been shown to reduce mortality rates in critically ill patients, it is unclear whether its use in delirium improves outcome (Milbrandt EB, et al. *Crit Care Med*. 2005;33:226). In fact, haloperidol use has been identified as an independent predictor for prolonged delirium (Pisani MA et al. *Crit Care Med*. 2009;37:177). Additionally, intravenous (IV) haloperidol and higher-than-recommended doses of haloperidol have been linked to QT prolongation and torsades de pointes.

Atypical antipsychotic agents offer several potential advantages compared with haloperidol and other conventional antipsychotics. These include decreased incidence of extrapyramidal symptoms (EPS), little effect on the QTc interval (with the exception of ziprasidone), decreased hypotension and fewer orthostatic effects (compared with IV haloperidol), lower risk of neuroleptic malignant syndrome, low chance of causing laryngeal dystonia, and lower mortality rates (when administered to elderly patients with dementia to control behavioral symptoms). "Thus, there are compelling reasons suggesting safety advantages with atypical antipsychotics compared with haloperidol," remarked Devlin. "Certainly, the use of atypical antipsychotics is increasing." In 2001 only 4% of clinicians used antipsychotics to treat delirium in the ICU compared with 40% in 2007 (Ely EW, et al. *Crit Care Med*. 2004;32:106; Patel RP, et al. *Crit Care Med*. 2009;37:825).

Few prospective randomized placebo-controlled trials on antipsychotic therapy for delirium in the ICU have been reported. The Modifying the Incidence of Delirium (MIND) trial compared the use of haloperidol

5 mg, ziprasidone 40 mg, and placebo for up to 14 days in mechanically ventilated adults with an abnormal level of consciousness or who were receiving sedative or analgesic therapy (Girard TD, et al. *Crit Care Med*. 2010;38:428). Drug titration was allowed. Primary outcome of the study was the number of days alive without delirium or coma during the 21-day study period. Exclusion criteria were extensive; of the 3,297 patients screened, 103 met eligibility requirements. Not all of the patients had delirium at baseline.

The results showed that, while the number of patients alive without delirium or coma increased over 21 days, no differences occurred among the three groups (i.e., haloperidol, ziprasidone or placebo) with respect to the number of delirium-free and coma-free days, number of days on the study drug, or number of doses of additional haloperidol. "Based on this randomized double-blind, placebo-controlled evidence, we can conclude that there isn't necessarily a role for haloperidol in treatment of delirium in ICU patients," said Devlin.

Another double-blind, placebo-controlled, randomized study investigated the efficacy and safety of quetiapine in critically ill patients with delirium (Devlin, JW, et al. *Crit Care Med*. 2010;38:419). The use of quetiapine 50 mg twice daily, which could be titrated up to 200 mg twice daily, was compared with placebo. The protocol included haloperidol as needed, usual sedation, and analgesia at the discretion of the physician. Oversedation was managed by withholding the study drug when the sedation-agitation scale score was less than 2. Primary outcome for the study was time to first resolution of delirium, defined as an Intensive Care Delirium Screening Checklist Score (ICDSC) score of 3 or less. Exclusion criteria were extensive, permitting enrollment of only 36 of 258 patients with delirium who tolerated enteral nutrition. At study entry, most patients were intubated and both groups had an average ICDSC of 5.

The findings revealed that over the 10-day study period, the quetiapine group experienced greater delirium resolution than the placebo group (see Figure 2). The time spent in delirium was nearly four times longer in the placebo group. The number of patients receiving quetiapine who had delirium recurrence after initial resolution was half that of patients receiving placebo. Hours spent agitated were substantially lower with quetiapine, but there was no difference between groups in the hours spent deeply sedated. Quetiapine also did not differ from placebo in mechanical ventilation duration, ICU and hospital duration, or hospital mortality. No safety concerns led to discontinuation of quetiapine.

Devlin emphasized that there are a number of important methodological differences between MIND study and the quetiapine study that should

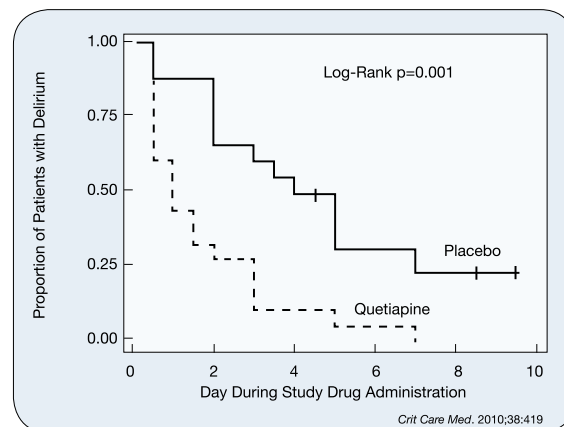


Figure 2. Proportion of Patients With Delirium

be considered before making conclusions about the role of antipsychotic therapy in the ICU for patients with delirium:

- Compared to the MIND study, where approximately half the patients had delirium and one-third had coma at study entry, all of the patients in the quetiapine study had delirium and none had coma at baseline.
- The MIND study included patients undergoing active withdrawal, while the quetiapine study did not.
- The MIND study randomized all patients within 72 hours of ICU admission, whereas the quetiapine enrolled patients far later.
- The primary efficacy outcome was days without delirium or coma, whereas the quetiapine study outcome was time to first resolution of delirium.
- The receptor activity of the antipsychotics studies in each study differ substantially.

“As another limitation, there is also the question of whether the placebo was truly used in either study, given that a substantial number of patients allocated to placebo in each study received haloperidol on many days as needed,” Devlin said.

A third randomized trial, which was not placebo-controlled, compared the use of olanzapine 5 mg daily (decreased by 50% in elderly patients) and halo-

peridol 2.5 mg to 5 mg three times daily to treat delirium in critically ill patients (Skrobik YK, et al. *Intensive Care Med.* 2004;30:444). The olanzapine dose was not titrated. As-needed intravenous (IV) haloperidol and benzodiazepines were allowed for agitation. The primary outcome was severity of delirium. Eligibility criteria included delirium at study entry; exclusion criteria were extensive and similar to the aforementioned trials. The results showed no difference between olanzapine and haloperidol in reducing delirium severity. However, no patients in the olanzapine group, compared with six patients in the haloperidol group, developed possible extrapyramidal systems (EPS). “It is important to note that only oral haloperidol was used in the study, and this is associated with a much lower incidence of EPS than IV haloperidol,” said Devlin.

“We can conclude from the literature that there are no high-quality data to support the use of haloperidol alone to treat delirium in the ICU, despite guideline recommendations,” Devlin stated. “While there are pilot data suggesting that quetiapine added to as-needed haloperidol may improve delirium resolution and patient outcomes, many methodological issues need to be addressed in future studies surrounding this area before firm conclusions surrounding the efficacy and safety of antipsychotic therapy for delirium in the ICU can be made.”

Haloperidol as the “Go-To” Drug: Is Dexmedetomidine a Better Option? Richard R. Riker, MD

“I think dexmedetomidine should be the ‘go-to’ drug to both prevent the development of delirium and clear delirium once it occurs,” stated Richard R. Riker, from the University of Vermont College of Medicine and Maine Medical Center in Portland, Maine, USA. Before discussing evidence supporting the use of dexmedetomidine to treat and prevent delirium in critically ill patients, Riker summarized the serious implications of delirium, while emphasizing the need to pay attention to coma (especially the drug-induced form), which is associated with an even lower survival rate than delirium (Oiumet S, et al. *Intensive Care Med.* 2007;33:66). “We really need to consider both coma and delirium when trying to optimize our practice of sedation in the ICU,” Riker stressed.

Dexmedetomidine is an α_2 agonist that provides both sedation and analgesia without causing significant respiratory depression. It reduces shivering and also exerts anxiolytic and sympatholytic (i.e., antihypertensive, antitachycardiac) activity. Potential adverse effects associated with dexmedetomidine include bradycardia, hypotension and vasoconstriction with rapid infusion or at high doses.

Riker presented six reasons why dexmedetomidine should be the drug of choice for delirium in the ICU:

- Increased delirium has been observed with γ -aminobutyric acid (GABA) agonists, the most commonly used sedatives for ICU patients.
- Improved outcomes for ICU patients have been associated with dexmedetomidine compared with GABA agonists.
- Delirium incidence has been reduced with dexmedetomidine.
- Delirium clearing is facilitated by use of dexmedetomidine.
- Cost savings have been achieved with dexmedetomidine compared with GABA antagonists.
- Evidence suggests that dexmedetomidine may be better than haloperidol.

The risks of transitioning to delirium with the use of sedative-analgesics have been reported, indicating a strong association between relatively low doses of lorazepam and development of delirium (Pandharipande P, et al. *Anesthesiology.* 2006;104:21). “In contrast, we now have a number of studies indicating that dexmedetomidine appears to reduce the incidence of delirium,” Riker said. When patients receiving mechanical ventilation received sedation with infusions of either lorazepam or dexmedetomidine (the MENDS study), the incidence of delirium was significantly lower with dexmedetomidine than lorazepam. Moreover, the dexmedetomidine group had a significant increase in delirium-free and coma-free days compared with those treated with lorazepam (Pandharipande PP, et al. *JAMA.* 2007;298:2644).

Midazolam, another benzodiazepine agent, also has been implicated in the development of delirium and has been associated with poorer outcomes than dexmedetomidine. The Safety and Efficacy of Dexmedetomidine Compared with Midazolam (SEDCOM) study (Riker RR, et al. *JAMA.* 2009;301:489) showed a higher prevalence of delirium among intubated ICU patients treated with midazolam compared with dexmedetomidine. Other findings revealed that time to extubation was reduced with dexmedetomidine versus midazolam, and that patients receiving dexmedetomidine were more communicative, more cooperative, and had a trend towards better ventilator tolerance, as rated by nurses caring for them.

“We can’t talk about GABA agents without talking about propofol,” said Riker. “As we consider the desirable rapid onset and offset of this

drug, we must also keep in mind that propofol infusion syndrome – a life-threatening complication – occurs not just with high doses given for a long duration. We’re also seeing increased case reports of this syndrome occurring with reasonable doses over hours, rather than days. This is definitely something we want to monitor.”

Dexmedetomidine was compared with propofol and midazolam in a randomized, open-label study involving cardiac surgical ICU patients, with dexmedetomidine demonstrating favorable results (Maldonado JR, et al. *Psychosomatics.* 2009;50:206). A significant reduction in delirium incidence was observed with dexmedetomidine compared with either propofol or midazolam.

Discussing the beneficial effects of dexmedetomidine in facilitating the clearance of delirium, Riker returned to data from the SEDOM trial (Riker RR, et al. *JAMA.* 2009;301:489). The investigators found that among patients who had delirium at baseline, delirium persisted during study drug therapy in only 68.7% of dexmedetomidine-treated patients, compared to 95.5% of midazolam-treated patients.

Pharmacoeconomic data suggest financial benefits for using dexmedetomidine in the ICU. A 12-month retrospective database analysis examined billing claims from 2003 for more than 10,000 patients who received midazolam plus propofol with or without dexmedetomidine (Dasta JF, et al. *Pharmacotherapy.* 2006;26:798). Results showed a significant reduction in mean total treatment charges with the addition of dexmedetomidine compared to the two-drug combination of midazolam and propofol. The SEDCOM trial yielded similar cost-saving data for dexmedetomidine compared with midazolam (Dasta JF, et al. *Crit Care Med.* 2010;38:497).

Riker’s final reason for advocating the use of dexmedetomidine in the ICU relates to evidence that the agent may be better than haloperidol. “In addition to the data we have comparing the atypical antipsychotics to haloperidol, a recent small pilot study from Australia reported favorable results for dexmedetomidine in comparison to haloperidol. Dexmedetomidine was associated with significantly shorter hours to extubation and significantly decreased ICU length of stay (Reade MC, et al. *Crit Care.* 2009;13:R75).”

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Continuing Education Self-Assessment

DELIRIUM: SHOULD IT BE A “NEVER” EVENT IN THE ICU?

3. Which one of the following statements is true regarding evidence on the use of pharmacologic agents in critically ill patients with delirium?
 - a. Dexmedetomidine reduced time to extubation compared with midazolam.
 - b. Quetiapine reduced days on mechanical ventilation compared with placebo.
 - c. Robust evidence supports the use of haloperidol alone in the treatment of delirium.
 - d. Ziprasidone was associated with more delirium-free days than haloperidol.
4. Early physical and occupational therapy appears to have no effect on reducing delirium duration in critically ill patients.
 - a. True
 - b. False