# Delirium in the Intensive Care Unit: A Review

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**KEYWORDS**

• Delirium • Intensive care unit • Risk factors • Sedation
• Prevention • Multicomponent treatment
• Pharmacologic treatment • Antipsychotics

This article provides an overview of the literature currently available concerning the epidemiology, definition, diagnosis, pathophysiology, and the management of delirium, with a specific focus on delirium in the intensive care unit (ICU), though the literature and principles described herein generally apply to non-ICU settings and will be relevant to clinicians and researchers working in medical settings outside of critical care. Delirium is a complex and multifaceted syndrome, and though it has a long history in the annals of medicine, key questions pertaining to delirium remain unanswered. Answers to these questions, however, are increasingly being pursued, as reflected in a sharp spike in the number of articles published on delirium in the last decade.

## EPIDEMIOLOGY OF DELIRIUM

Delirium is highly prevalent in medical populations, with rates of up to 80% reported in the highest risk groups (eg, medical ICU cohorts). As with most conditions, rates vary depending on illness severity and diagnostic methods including, and notably, the tools that are used.[1–3] Delirium is associated with adverse outcomes generally, but in ICU

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settings it is particularly concerning due in part to the breadth of untoward consequences to which it is linked. These factors include, but are not limited to, self-extubation and removal of catheters,[4] greater duration of hospitalization,[5–7] increased cost,[8] higher 6-month mortality,[9–11] and long-term cognitive impairment.[12,13] Many of these outcomes appear to be associated with delirium duration as opposed to simply the presence versus absence of delirium, suggesting a possible "dose-response" relationship. For reasons that remain unclear, delirium continues to be significantly unrecognized.

## DEFINITION OF DELIRIUM

The definitive reference for delirium is the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revised) (DSM-IV-TR).[14] According to the DSM-IV-TR, delirium is a condition characterized by: (1) a disturbance of consciousness with inattention, accompanied by (2) acute change in cognition (ie, memory deficits, disorientation, language disturbances, and perceptual disturbances) not accounted for by preexisting, established, or evolving dementia (though cognitive changes can take various forms in delirium, changes in attention are most typically observed); (3) development over a short period of time (hours to days) with fluctuation over time; (4) evidence that the disturbance is caused by the direct physiologic consequences of a general medical condition. Although a consensus about the technical definition of delirium exists, it is described variously and often with imprecision (eg, acute confusional state, ICU psychosis, acute brain dysfunction, encephalopathy, and so forth). Delirium symptoms are frequently similar to and often strongly mimic symptoms of other neuropsychiatric or frankly neurologic disorders. As such, the ability to make a proper diagnosis of delirium is often predicated on information about the baseline cognitive status from the family, caregivers, or other informants. In some cases depression and delirium can be difficult to differentiate, particularly among those with a hypoactive presentation. Farrell and Ganzini[15] showed that 42% of the patients referred to a psychiatric service for evaluation or treatment of a depressive disorder were found to be delirious. In some cases, acute psychosis in schizophrenia and delirium tremens can also be misidentified as delirium. In the case of schizophrenia, individuals are generally not disoriented and do not characteristically have the classic attentional derailments displayed in delirium, while often demonstrating paranoia—a condition rare among hospitalized delirious patients. Delirium tremens (due to alcohol withdrawal) (1) usually presents 48 to 96 hours after cessation of drinking; (2) can last up to 2 weeks; (3) can be worse overnight; (4) level of consciousness and disorientation are impaired and fluctuating; (5) reduced attention and global amnesia are present; (6) cognition and speech are impaired; and (7) hallucinations (usually tactile, visual) and delusions (persecutory) can be present.

## DELIRIUM SUBTYPES

Delirium can be expressed in the context of distinct subtypes, typically referred to as hypoactive, hyperactive, and mixed.[16–18] Hypoactive delirium, often unrecognized, is characterized by symptoms of lethargy and minimal psychomotor activity. Hyperactive delirium, by contrast, is marked by significant agitation. Individuals with mixed expressions fluctuate between the hypoactive and hyperactive expressions. For example, Peterson and colleagues[19] reported that in a cohort of elderly medical ICU patients 43.5% were hypoactive, 54.9% were hyperactive, and fewer than 2% were mixed.

### *Subsyndromal Delirium*

Questions persist about a condition existing between the boundaries of "normal" and "delirious." Popularly referred to as subsyndromal delirium (SSD),[20–23] this phenomenon is one in which symptoms never progress to meet the DSM-IV-TR requirements. Though relatively little studied, a recent investigation[24] showed that individuals with syndromal symptoms have worse outcomes than their "normal" counterparts. This finding suggests a continuum of severity[20,23] across a spectrum from "normal" to "frank" delirium.

## ISSUES IN THE DIAGNOSIS OF DELIRIUM

Diagnosis of delirium is done in various ways, with diagnoses often made in the context of clinical interviews (eg, psychiatric or geriatric consultations). Less commonly, formal neuropsychological tests are used. Debate exists regarding the appropriateness of this approach, because attention—widely thought to be the key feature of delirium—influences other domains of cognition (eg, memory, executive functioning, processing speed) so powerfully. In some contexts, notably the ICU, several brief screening tools are used, such as the Intensive Care Delirium Screening Check List (ICDSC)[2] and the confusion assessment method for the ICU (CAM-ICU).[1,3] These tools can be used by nonspecialists and can be used to quickly identify delirium in ICU patients. Descriptions of the CAM-ICU and ICDSC can be found at www.icudelirium.org.

The ICDSC was originally validated in medical and surgical ICU patients against a consulting psychiatrist who served as the standard reference rater.[2] The ICDSC is a highly sensitive tool, with a specificity of 64%. It has a total score ranging from 0 to 8, with delirium defined as a score of 4 or more.

The CAM-ICU, a variant of the Confusion Assessment Method (CAM),[25] from which it was adapted, was designed to be used with intubated patients and validated against content experts who based their delirium diagnoses on the DSM-IV. Psychometric properties are strong,[1,3] with high sensitivity (93%–100%), specificity (89%–100%), and interrater reliability ($\kappa$ = 0.96, 95% confidence interval [CI] 0.92–0.99). The CAM-ICU is used via a 2-step approach (**Fig. 1**), with level of consciousness typically assessed via the Richmond Agitation Sedation Scale (RASS),[26,27] a 10-point scale ranging from −5 (no response to voice or physical evaluation) to +4 (overtly combative, violent, immediate danger for staff). Scores of 0 reflect normal mental status. Patients with RASS scores of −4 or −5 cannot be assessed as, by definition, they are comatose. The CAM-ICU consists of 4 features, each of which parallel DSM-related criteria, with an acute change or fluctuation in mental status (Feature 1), accompanied by inattention (Feature 2), and either disorganized thinking (Feature 3) or altered level of consciousness (Feature 4).

## PATHOPHYSIOLOGY

The pathophysiology of delirium remains a subject of much debate, with many theories and perspectives having been proposed.[28–33]

Studies of pathophysiology to date have involved brain modifications via neuroimaging, inflammation and sepsis, genetics, and the role of biomarkers and neurotransmitters.

### *Neuroimaging*

Little work has been done on the neuroimaging of delirium, though early evidence suggests that delirium may be caused by diffused brain dysfunction rather than

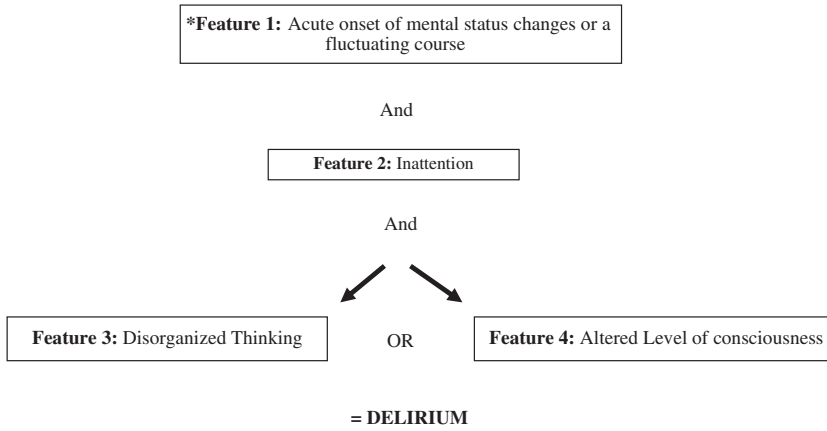


**Fig. 1.** The Confusion Assessment Method for the ICU (CAM-ICU). The diagnosis of delirium requires the presence of acute onset of changes or fluctuations in the course of mental status (Feature 1) and inattention (Feature 2), plus either disorganized thinking (Feature 3) or an altered level of consciousness. * The level of consciousness (arousal) is first evaluated with the Richmond Agitation Sedation Scale (RASS). The RASS is a10-point scale ranging from −5 (no response to voice or physical evaluation) to +4 (overtly combative, violent, immediate danger for staff), with RASS score of 0 denoting a calm and alert patient. The patient comatose (RASS −5 or −4) cannot be assessed for delirium. The patient with a RASS score of −3 or greater (−2 to +4) can be assessed by the CAM-ICU. (*Adapted with permission from* Dr. E. Wesley Ely, http://www.icudelirium.org/).

localized disruption.[34,35] Two studies have demonstrated decreased cerebral blood flow in multiple areas of the brain in studies of delirious patients.[36,37] Other investigations have reported structural abnormalities in those experiencing delirium (eg, cerebral ventricles, gross white and gray matter atrophy, cortical and subcortical lesions, or ventricular enlargement).[36–40]

### *Inflammation and Sepsis*

Sepsis-related inflammation likely contributes to the development of delirium in the ICU. Numerous mechanisms underlying this contribution have been proposed, with one prominent suggestion being that the inflammatory cascade occurring in sepsis may decrease essential oxygen delivery and nutrient to cells by impairing capillary flow.[41–43] Inflammatory mediators (ie, tumor necrosis factor $\alpha$, interleukin-1, and other cytokines and chemokines) can result in disseminated intravascular coagulation, with leukocyte-vascular endothelium adhesion and induced endothelial damage. Sepsis-induced encephalopathy has been thought to be attributable to the degradation of the blood-brain barrier,[44] and the prolonged exposure to the lipopolysaccharide[45] may impair the synaptic transmission and neuronal excitability in the hippocampus. While these investigations suggest a link between delirium and sepsis, clearly more studies are needed to better evaluate the role of the inflammatory process and the coagulopathy related to sepsis and delirium.

### *Biomarkers, Neurotransmitters, Sedatives, and Analgesic Medications*

The correlation between delirium, biomarkers, and different neurotransmitters is very poorly understood although data exist regarding potential interactions of delirium with

acetylcholine, amino acids, and neurotransmitters such as monoamines and γ-aminobutyric acid (GABA). A comprehensive discussion of these interactions is beyond the scope of this review, although the authors offer several brief observations in the context of an overview. With regard to acetylcholine, it has been suggested that greater anticholinergic activity due to overuse of anticholinergic medications is associated with a subsequent increase in delirium symptom severity,[46] though the specific nature of this association needs to be further investigated. Similarly, limited evidence supports a possible association between amino acid precursors, and some investigators have proposed that the alteration of the availability of large neutral amino acids (LNAA) may be involved in the development of delirium.[47–49] Multiple neurotransmitters are also thought to be involved in delirium, including monoamines (eg, serotonin, dopamine, norepinephrine), imbalances in acetylcholine, glutamate, and GABA, with monoamines, in particular, modulating neurotransmission and thereby affecting behavior, cognitive functioning, and mood.[50] With regard to GABA, the primary inhibitory neurotransmitter in the central nervous system (CNS), its release has been hypothesized to be linked with delirium. As several agents widely used in the ICU (eg, benzodiazepines and propofol) have high affinity for GABAergic receptors, their relationship with delirium in the ICU is of significant interest. Recently, Pandharipande and colleagues[51] evaluated the relationship between administration of sedatives and analgesics and delirium in an ICU cohort, demonstrating that lorazepam is an independent risk factor for daily transition to delirium (odds ratio = 1.2, 95% CI 1.2–1.4). While sedative agents such as benzodiazepines and propofol act on the GABA receptor and are implicated in the genesis of delirium, novel GABA receptor-sparing agents (ie, dexmedetomidine) may be an alternative for sedation of ICU patients. Pandharipande and colleagues[52] reported that medical and surgical ICU patients sedated with dexmedetomidine have 4 more days alive without delirium or coma (median days, 7 vs 3.0; $P = .01$) than patients sedated with lorazepam. With regard to opiates data remain unclear, as findings to date have been inconsistent.[53,54]

The role of gene predisposition has also been investigated in the pathogenesis of delirium. Indeed the gene encoding for apolipoprotein E (APO-E) is a gene that has been evaluated for a possible relationship with ICU delirium. APO-E is known to be implicated with a higher susceptibility of Alzheimer disease as well as poorer cognitive outcomes after cardiac surgery, though results in this regard are somewhat equivocal.[55] Ely and colleagues[56] evaluated the relationship between APO-E genotypes and delirium in medical ICU patients, showing that the APO-E4 carriers were delirious for 2 more days than those without APO-E polymorphisms (median [interquartile range]: 4 [3–4.5] days versus 2 [1–4 days]; $P = .05$). Alternatively, one recent investigation found that among elderly medical patients, APO-E4 carriers were not found to have a higher risk of delirium.[57]

## MANAGEMENT OF DELIRIUM: PREVENTION AND TREATMENT

Most studies conducted in the last several years evaluating preventative and treatment protocols for delirium have included non-ICU patients. ICU patients present a higher incidence of delirium, and a multifactorial approach should be considered to identify the presence of risk factors. The authors first describe the risk factors for delirium and available preventive and treatment protocols.

### *Risk Factors*

Risk factors are typically considered to be in one of two categories: predisposing and precipitating. Though studied extensively in general medical populations, risk factors

for delirium have been relatively little investigated in critically ill medical, surgical, and trauma patients.[4,6,56,58] As such, ICU clinicians and researchers should rely on evidence from the broader risk-factor literature, as appropriate. In a study by Dubois and colleagues[4] hypertension and history of smoking emerged as strong predictors of delirium in medical and surgical ICU cohorts. Elsewhere, Ouimet and colleagues[6] demonstrated that percentage of days with abnormal bilirubin level, exposure to morphine, and the epidural route of analgesia were also associated with delirium. Aldemir and colleagues[58] have reported a link between delirium and laboratory abnormalities such as hypocalcemia (<8 mg/mL), hyponatremia (<130 mmol/L), elevated levels of serum urea nitrogen (>100 mg/dL), hyperbilirubinemia (>10 mg/dL total bilirubin), and anemia (hematocrit <25%) in surgical ICU patients. Multiple other risk factors have been reported including age (>65 years), the presence of dementia at baseline, severity of illness, fever (38°C), infections, respiratory diseases, hypotension (symptomatic, or systolic blood pressure <80 mm Hg), and metabolic acidosis.[51,58,59]

Other risk factors have been elucidated in non-ICU cohorts but have not yet been shown to be associated with ICU delirium. These factors include use of physical restraints, use of bladder catheter, malnutrition (serum albumin level <30 g/L), impairment of vision (visual acuity <20/70), more than 3 medications added (during the 24–48-hour period before delirium onset), fracture on admission, and any iatrogenic event (eg, any diagnostic procedure or therapeutic intervention or any harmful occurrence that was not a natural consequence of the patient's illness).[60–62]

### *Analgesics and sedatives*

ICU patients often receive analgesics and sedatives for the treatment of pain, the provision of comfort, and for anxiety reduction (particularly in the context of mechanical ventilation).[63] Some of these medications can have a detrimental effect and are risk factors for delirium. In particular, a strong association has been demonstrated between delirium and exposure to certain medications such as lorazepam, midazolam, and meperidine.[4,6,51,53,54] These studies highlight the importance of evaluating and treating pain, and suggest there could be potential advantages to the use of alternative sedatives such as $\alpha$2-agonists for patients in the ICU.[52]

### *Sleep*

Adequate sleep is critically important to ICU patients, though it is well known that sleep deprivation is common. Some evidence suggests that ICU patients "sleep" only 2 hours per day.[64] Although the link between sleep and delirium is unclear, evidence indicates that mechanical ventilation and sedative and analgesic exposure likely contribute to sleep-cycle alteration.[65] As sedatives common in the ICU such as lorazepam and midazolam are delirium risk factors and may act via sleep disruption, greater attention should be given to this association as a site of future intervention.

### *Impact of risk factors*

Both predisposing and precipitating factors may interact to increase the risk of the development of delirium in individual patients. This notion has been articulated by Inouye and Charpentier,[60] who have posited that delirium develops in the context of the interplay between "vulnerability" and the severity of a given "insult." Put simply, individuals are admitted to the hospital with a set of predisposing factors that may make them particularly susceptible to developing delirium. In such patients, typically those who are both elderly and suffering from mild or moderate cognitive impairment, a single insult (eg, use of restraint) could be the factor contributing to delirium. Alternatively, patients resistant to the development of delirium could still experience this syndrome because of precipitating factors such as severity of illness, administration

of sedatives, and immobilization, which could be seen as the precipitating cause of delirium. Clinicians could count also on the acronym ICUDELIRIUM(S) (**Table 1**) to easily remember the main risk factors and conditions linked to delirium and then create a risk stratification, as indicated by Inouye,[66] in which one point is given to each risk factor present at admission and a patient is classified as being at low (no risk factors), intermediate (1 or 2 risk factors), and high risk (3 or 4 risk factors) of developing delirium.

### *Prevention Protocols: Multicomponent and Pharmacologic Interventions*

#### *Multicomponent prevention protocols*

Delirium is usually a multifactorial syndrome, often driven by various risk factors. Therefore, a multicomponent intervention approach designed to address primary risk factors may be the most effective. To date, no interventions have been conducted for this specific purpose in an ICU setting, but information may be gleaned from studies of general hospital and surgical patients (**Table 2**).

The Hospital Elder Life Program (HELP)[67] is a well-known study conducted with a focus on assessing the efficacy of a multicomponent approach to delirium treatment

**Table 1**
**Mnemonic for risk factors and causes of ICUDELIRIUM(S)**

| | |
|---|---|
| **I**atrogenic exposure | • Consider any diagnostic procedure or therapeutic intervention or any harmful occurrence that was not a natural consequence of the patient's illness |
| **C**ognitive impairment | • Preexisting dementia, or MCI or depression |
| **U**se of restraints and catheters | • Reevaluate the use of restraints and bladder catheters daily |
| **D**rugs | • Evaluate the use of sedatives (eg, benzodiazepines or opiates) and medications with anticholinergic activity<br>• Consider the abrupt cessation of smoking or alcohol<br>• Consider withdrawal from chronically used sedatives |
| **E**lderly | • Evaluate patients older than 65 years with greater attention |
| **L**aboratory abnormalities | • Especially hyponatremia, azotemia, hyperbilirubinemia, hypocalcemia, and metabolic acidosis |
| **I**nfection | • Sepsis and severe sepsis<br>• Especially urinary, respiratory tract infections |
| **R**espiratory | • Consider respiratory failure ($Pco_2$ >45 mm Hg or $Po_2$ <55 mm Hg or oxygen saturation <88%)<br>• Consider causes such as COPD, ARDS, PE |
| **I**ntracranial perfusion | • Consider presence of hypertension or hypotension<br>• Consider hemorrhage, stroke, tumor |
| **U**rinary/fecal retention | • Consider urinary retention or fecal impaction, especially in elderly and postoperative patients |
| **M**yocardial | • Consider myocardial causes: myocardial infarction, acute heart failure, arrhythmia |
| **S**leep and sensory deprivation | • Consider the alterations of the sleep cycle and sleep deprivation<br>• Consider the nonavailability of glasses (poor vision)<br>• Consider the nonavailability of hearing devices (poor hearing) |

*Abbreviations:* ARDS, acute respiratory distress syndrome; COPD, chronic obstructive pulmonary disease; MCI, mild cognitive impairment; PE, pulmonary embolism.

**Table 2**
**Delirium management in the ICU[a]**

| | Interventions | Setting and Study Design |
|---|---|---|
| Step 1: Prevention | | |
| 1. Evaluation of risk factors | | |
| 2. Multicomponent protocols | | |
| Multicomponent strategy[67] | Targeted intervention on cognitive impairment, sleep deprivation, immobilization, psychoactive medications, vision impairment, hearing impairment, dehydration | Non-ICU clinical trial |
| Proactive geriatric consultation[68] | Daily visits with geriatrics for entire hospital duration, with target recommendations used | Non-ICU clinical trial |
| Nursing-led model[95] | (1) Nursing detection of delirium with validated tools. (2) Nursing evaluation of potential causes of delirium when delirium is diagnosed. (3) Proactive plan for preventing and managing the common risk factors involving nurses and physicians. (4) Create an environment that enhances reintegration and help the patient to reduce confusion and agitation | Non-ICU clinical trial |
| 3. Pharmacologic protocols | | |
| Haloperidol[71] | Haloperidol 0.5 mg 3 times a day, started at admission and continued until 3 days after surgery | Non-ICU (hip surgery patients) randomized, placebo-controlled trial |
| Risperidone[72] | Risperidone 1 mg after surgery | Non-ICU (postcardiac surgery) double-blind, placebo-controlled randomized trial |
| Sedation with dexmedetomidine[52] | Dexmedetomidine to a maximum dose of 1.5 μg/kg per hour | ICU randomized trial |
| Step 2: Treatment | | |
| Pharmacologic treatment | | |
| Haloperidol[63] | Haloperidol 2–5 mg (0.5–2 mg in the elderly) intravenously, followed by double repeated doses every 15–20 min if agitation persists up to a maximum of 20 mg/d | SCCM Guidelines[63] |
| Olanzapine[86] | Olanzapine, starting dose 5 mg (2.5 mg over 65 years) and titrated on clinical judgment | ICU randomized trial, no placebo group |
| Risperidone[87] | Risperidone, starting dose 0.5 mg twice a day, up to a maximum of 2.5 mg/d | ICU and non-ICU, blind clinical trial. No placebo group |

*Abbreviation:* SCCM, Society of Critical Care Medicine.
[a] The data included in this table are obtained combining ICU and non-ICU studies.

and management. The study consisted of an intervention aimed at 6 delirium risk factors (ie, cognitive impairment, sleep deprivation, immobilization, psychoactive medications, vision impairment, hearing impairment, and dehydration). Delirium incidence was reduced in the intervention group in comparison with the usual care group (9.9% vs 15%). No differences were noted between groups with regard to delirium severity of recurrence rates, however. In a similar vein, Marcantonio and colleagues[68] studied the effects of randomizing hip surgery patients to proactive geriatric consultation versus usual care, finding that those receiving geriatric consultation (a very comprehensive array of assessments and/or interventions) experienced a 36% relative risk reduction in incident delirium but no benefits with regard to abbreviated delirium duration or delirium severity. Other studies[69,70] have demonstrated that multifactorial interventions are effective in reducing the duration, but not the incidence, of delirium.

### *Pharmacologic prevention protocols*

To date two studies[71,72] have evaluated the efficacy of antipsychotics for delirium prevention. Data are unclear regarding the use of anticholinergic drugs (ie, rivastigmine and donepezil) for delirium prevention and treatment.[73,74]

Kaslivaart and colleagues[71] conducted a randomized, double-blind, placebo-controlled trial in hip surgery patients and showed that that low-dose prophylactic haloperidol (0.5 mg 3 times a day, started at admission and continued until 3 days after surgery) was ineffective compared with placebo in reducing the incidence of postoperative delirium, though it reduced delirium severity (as measured by the DRS-R-98, with a mean difference of 4.0; 95% CI 2.0–5.8; $P = .001$).

Prakanrattana and Prapaitrakool[72] concluded, in a double-blind, placebo-controlled randomized trial, that a single dose (1 mg) of risperidone following coronary artery bypass surgery reduced postoperative delirium incidence (11.1% vs 31.7%, respectively; $P = .009$, relative risk = 0.35, 95% CI 0.16–0.77).

The chronic use of rivastigmine in patients affected by dementia may help prevent delirium in high-risk elderly patients admitted to a medical ward.[74] Donepezil was shown to be ineffective in delirium prevention and treatment in a randomized controlled trial including a cohort of an older population without dementia undergoing elective total joint replacement surgery.[73]

Of interest is that benzodiazepines are frequently used as sedatives in the ICU although they themselves have been shown to be deliriogenic.[6,51,53,54] Pandharipande and colleagues[52] piloted an approach using a new sedation protocol with dexmedetomidine, a highly selective $\alpha$2-agonist, versus lorazepam in medical and surgical ICU patients. Individuals treated with dexmedetomidine spent fewer days in coma and more time neurologically "normal" (defined as without coma or delirium) than their counterparts sedated via lorazepam. This preliminary work suggests a need for larger trials aiming to prove $\alpha$2-receptor agonists (eg, dexmedetomidine, clonidine) to be alternative sedative agents less likely to cause delirium than the benzodiazepines.

## *Pharmacologic Treatment*

The use of medications in the treatment of delirium is common, and should be considered following a thorough assessment of relevant predisposing and precipitating risk factors. At present, haloperidol is the drug of choice for the treatment of delirium as indicated by the Guidelines of the Society of Critical Care Medicine[63] and of the American Psychiatry Association (APA),[75] though its efficacy has not been tested in a placebo-controlled trial. Several open trials[76–85] have evaluated the efficacy of typical and atypical antipsychotic delirium treatment, but only two have included a cohort of ICU patients.[86,87]

Skrobik and colleagues[86] studied the safety and clinical utility of olanzapine (starting dose 5 mg daily) versus haloperidol (starting dose 2.5–5 mg every 8 hours) for the treatment of ICU delirium. Olanzapine and haloperidol were associated with reduction in delirium symptoms over time. However, recommendation for it and other atypical antipsychotics as a treatment for delirium in the critical care setting is limited by the current trial and absence of placebo-controlled data. Han and Kim[87] evaluated, in a double-blind trial, the efficacy of risperidone (starting dose 0.5 mg twice a day) versus haloperidol (starting dose 0.75 mg twice a day) for treatment of delirium in 24 medical, oncology, and ICU patients, concluding that no significant differences existed between groups on outcome measures including delirium severity scores. More recently two randomized clinical trials including placebo in their design, have investigated the role of typical and atypical antipsychotics for the treatment of delirium in critically ill patients.[88,89]

Devlin and colleagues[88] compared the efficacy of the addition of a regimen of as needed haloperidol plus quetiapine (50 mg every 12 hours and titrated on a daily basis by increments of 50 mg every 12 hours to a maximum dose of 200 mg every 12 hours) vs as needed haloperidol plus placebo in the treatment of 36 ICU delirious patients. Medications were titrated to effect, such that if a patient required open-label haloperidol for agitation in the last 24-hours the dose of the study drug was increased. Patients treated with quetiapine had faster resolution of delirium compared to the placebo (Median [IQR] 1.0 [0.5–3.0] days for quetiapine vs 4.5 [2.0–7.0] days for placebo, $P = .001$).

In a second trial Girard and colleagues[89] conducted the Modifying the Incidence of Delirium (MIND) Trial, which randomized 103 medical and surgical mechanically ventilated ICU patients to treatment with haloperidol (5 mg), ziprasidone (40 mg) or placebo. Duration of delirium was similar between groups (haloperidol: 14.0 vs ziprasidone 15.0 vs placebo 12.5, $P = .66$). This trial was conducted as a pilot, feasibility, study and therefore was not powered to answer to determine the efficacy of antipsychotics in the treatment of delirium. A larger scale trial is now being performed (NCT01211522).

From the data currently available, atypical (eg, olanzapine, risperidone, quetiapine, ziprasidone) and typical antipsychotics (eg, haloperidol) may or may not be helpful in the treatment of delirium. Typical and atypical antipsychotics, especially in elderly patients with dementia, have been associated with increased mortality[90–93] and confer potential side effects more generally. To date the studies that have evaluated the short-term used of antipsychotics for the treatment of delirium have not shown an increased risk of death. However, these studies did not focus on the side effects of these drugs in geriatric ICU patients with dementia. As such, future studies of antipsychotics should include this particular aspect as an outcome measure.

## SUMMARY

Delirium is recognized as a common form of acute brain dysfunction in medically ill patients in general and critically ill patients in particular, leading researchers to view it as the "sixth vital sign."[94] Mechanisms implicated in the pathophysiology of delirium are still elusive. Intriguing data are available with respect to the interaction between sepsis, acetylcholine levels, the interaction between drugs that altering GABA levels, and delirium. Several risk factors are thought to be associated with delirium, including specific medications for sedation or pain management, widely used in an ICU setting; their use should therefore be carefully evaluated. Current multicomponent protocols and pharmacologic interventions designed for the non-ICU setting can potentially

be adapted for a critical-care setting. Future studies in the ICU setting should build on current work, to (1) assess the efficacy of multicomponent protocols to prevent delirium and (2) assess the safety and efficacy of antipsychotics versus placebo in the prevention and treatment of delirium, while carefully evaluating the outcomes in elderly patients with dementia.

**Key Points**

1. Medically ill patients, particularly populations at high risk (eg, ICU patients) should receive a complete evaluation of predisposing and precipitating risk factors, giving particular attention to the exposure to pain medications and sedatives
2. It is mandatory to assess and diagnose delirium in the ICU with the use of available tools such as the ICDSC and the CAM-ICU

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