

# Delirium in the Intensive Care Unit: Is Dexmedetomidine Effective?

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Delirium in the intensive care unit affects approximately 30% of patients despite vigorous efforts to encourage the use of effective screening tools and preventive strategies. The success of pharmacological treatment of delirium remains equivocal; moreover, a paucity of research supports the use of atypical antipsychotic medications. However, dexmedetomidine appears to have a promising role in delirium management. This review includes an overview of the pathophysiology and types of delirium and describes 2 established tools used to screen for delirium. Published research related to the use of dexmedetomidine in the management of delirium is also discussed. The authors make recommendations for critical care nurses on dexmedetomidine use in the context of providing evidence-based nursing care to intensive care unit patients with delirium. (*Critical Care Nurse*. 2019;39[4]:e8-e21)

**D**elirium is a form of acute brain dysfunction and is characterized by an acute onset of confusion that is transient and reversible. Delirium is associated with increased mortality and morbidity.<sup>1-4</sup> Delirium may occur at any age but more commonly presents in older patients whose mental status has previously been affected by conditions such as fever, electrolyte imbalance, or dehydration. Delirium is a common phenomenon in the intensive care unit (ICU) environment. Some of the detrimental effects experienced by critically ill patients include increased risk of hospital-acquired infection, long-term memory impairment, prolonged hospital stays, and an increased risk of mortality.<sup>3,5</sup>

Despite strategies that have been instituted to prevent delirium, such as daily sedation awakening protocols, early mobilization, and the use of screening tools, delirium continues to be an important patient care issue.<sup>6</sup> For example, in a Canadian prospective cohort study of consecutive patients admitted to the ICU, Ouimet et al<sup>3</sup> found that delirium occurred in at least 243 of 764 patients (31.8%).

Delirium has short- and long-term consequences including prolonged mechanical ventilation, self-extubation, use of physical restraints, longer ICU and hospital stays, long-term memory and physical impairments, and increased mortality at 6 months.<sup>5,7</sup>

Dexmedetomidine (Precedex, Pfizer Inc) was approved in 1999 by the Food and Drug Administration (FDA) for short-term ( $\leq 24$ -hour) sedation in patients receiving mechanical ventilation.<sup>6,8,9</sup> Dexmedetomidine is a selective  $\alpha_2$ -adrenoreceptor agonist that produces anxiolytic and analgesic effects with minimal respiratory depression. The drug appears to be a desirable choice for managing delirium in the ICU.<sup>10,11</sup> Compared with clonidine, another  $\alpha_2$ -adrenoreceptor agonist, dexmedetomidine has 8 times more affinity for  $\alpha_2$ -adrenoreceptors. In addition, dexmedetomidine has more effective sedative and analgesic properties.<sup>2,12</sup>

Registered nurses (RNs) in ICUs play a critical role in the nursing management of delirious patients. Nurses should have a thorough understanding of pharmacological therapies, such as dexmedetomidine, in the treatment of delirium. The purpose of this article is to provide an overview of delirium and its pathophysiology, manifestations, complications, and nonpharmacological treatments; discuss current pharmacological approaches to delirium; review the pharmacology of dexmedetomidine; and compare dexmedetomidine with current pharmacological management strategies for delirium. We also review the research related to dexmedetomidine and make recommendations for ICU RNs in the context of nursing care considerations when administering the drug.

## Delirium

Delirium presents as acute onset of confusion characterized by a change or fluctuation in baseline mental

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status or attention, disorganized thinking, or an altered level of consciousness. It is difficult to obtain a precise incidence rate for delirium in the ICU because of variance in screening tools used, types of ICU, and patients sampled. Two tools have been used to assess patients at risk for developing delirium. The Intensive Care Delirium Screening Checklist (ICDSC), based on *Diagnostic and Statistical Manual of Mental Disorders* criteria,<sup>13</sup> is a simple 8-item checklist. An ICDSC score greater than 4 indicates the patient is at risk for developing delirium. The ICDSC tool and scoring is further described in Figure 1.<sup>14</sup> The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) is based on the original Confusion Assessment Method and was adapted by Ely et al<sup>15</sup> for use in nonverbal patients receiving mechanical ventilation. The CAM-ICU tool is summarized in Figure 2.<sup>14</sup>

Roberts et al<sup>16</sup> completed a 6-month multisite, prospective epidemiological study in Australia. They used the ICDSC to determine the incidence of delirium in 185 ICU patients, 142 of whom (76.7%) received mechanical ventilation. Eighty-four patients (45%) were at risk for developing delirium, on the basis of ICDSC scores of greater than 4.<sup>16</sup> The Delirium Epidemiology in Critical Care study, a 1-day point-prevalence multicenter assessment, was completed in 104 ICUs in 11 countries in North and South America and Spain.<sup>4</sup> A total of 975 patients were

screened with the CAM-ICU tool.

Patients who were deeply sedated, as defined by the Richmond

Consequences of delirium include prolonged mechanical ventilation, self-extubation, use of physical restraints, longer hospital stays, and increased mortality.

Agitation-Sedation Scale, were not included in the study because their sedation level did not allow for accurate assessment of delirium. A final sample of 232 patients who did not require mechanical ventilation were enrolled, and 75 (32.3%) were identified with delirium on the basis of their CAM-ICU scores.<sup>4</sup> As illustrated by these 2 studies, the incidence of delirium varies. However, according to the literature reviewed, an estimated 30% of ICU patients experience delirium.<sup>3,4,7</sup>

### Etiology, Pathophysiology, and Risk Factors

The reticular formation is a complex network of interconnected nuclei situated in the brainstem. Part of the function of the reticular formation is to maintain wakefulness and regulate vital reflexes, such as cardiovascular

## Intensive Care Delirium Screening Checklist Worksheet (ICDSC)

- Score your patient over the entire shift. Components don't all need to be present at the same time.
- Components #1 through #4 require a focused bedside patient assessment. This cannot be completed when the patient is deeply sedated or comatose (ie, SAS = 1 or 2; RASS = -4 or -5).
- Components #5 through #8 are based on observations throughout the entire shift. Information from the prior 24 hrs (ie, from prior 1-2 nursing shifts) should be obtained for components #7 and #8.

<b>1. Altered level of consciousness</b>	<b>NO</b>	<b>0</b>	<b>1 Yes</b>
Deep sedation/coma over entire shift [SAS = 1, 2; RASS = -4,-5]			= Not assessable
Agitation [SAS = 5, 6, or 7; RASS = 1-4] at any point			= 1 point
Normal wakefulness [SAS = 4; RASS = 0] over the entire shift			= 0 points
Light sedation [SAS = 3; RASS = -1, -2, -3]:			= 1 point (if no recent sedatives)
			= 0 points (if recent sedatives)
<b>2. Inattention</b>	<b>NO</b>	<b>0</b>	<b>1 Yes</b>
Difficulty following instructions or conversation, patient easily distracted by external stimuli.			
Will not reliably squeeze hands to spoken letter A: <b>SAVE A H A A R T</b>			
<b>3. Disorientation</b>	<b>NO</b>	<b>0</b>	<b>1 Yes</b>
In addition to name, place, and date, does the patient recognize ICU caregivers?			
Does patient know what kind of place they are in? (list examples: dentist's office, home, work, hospital)			
<b>4. Hallucination, delusion, or psychosis</b>	<b>NO</b>	<b>0</b>	<b>1 Yes</b>
Ask the patient if they are having hallucinations or delusions. (eg, trying to catch an object that isn't there).			
Are they afraid of the people or things around them?			
<b>5. Psychomotor agitation or retardation</b>	<b>NO</b>	<b>0</b>	<b>1 Yes</b>
Either (a) Hyperactivity requiring the use of sedative drugs or restraints in order to control potentially dangerous behavior (eg, pulling IV lines out or hitting staff) OR (b) Hypoactive or clinically noticeable psychomotor slowing or retardation			
<b>6. Inappropriate speech or mood</b>	<b>NO</b>	<b>0</b>	<b>1 Yes</b>
Patient displays: inappropriate emotion; disorganized or incoherent speech; sexual or inappropriate interactions; is either apathetic or overly demanding			
<b>7. Sleep-wake cycle disturbance</b>	<b>NO</b>	<b>0</b>	<b>1 Yes</b>
Either: frequent awakening/< 4 hours sleep at night OR sleeping during much of the day			
<b>8. Symptom fluctuation</b>	<b>NO</b>	<b>0</b>	<b>1 Yes</b>
Fluctuation of any of the above symptoms over a 24 hr period.			

**TOTAL SHIFT SCORE:** \_\_\_\_\_  
(0 – 8)

<u>Score</u>	<u>Classification</u>
0	Normal
1-3	Subsyndromal delirium
4-8	Delirium

**Figure 1** Intensive Care Delirium Screening Checklist worksheet.<sup>14</sup>

Abbreviations: ICU, intensive care unit; IV, intravenous; RASS, Richmond Agitation-Sedation Scale; SAS, sedation-agitation scale. Adapted from Bergeron et al (*Intensive Care Med.* 2001;27(5):859-864) and Ouimet et al (*Intensive Care Med.* 2007;33(6):1007-1013).

function and respiration. The reticular formation projects into the thalamus, basal ganglia, and specific areas of the cerebral cortex and limbic system. The projections of the reticular formation into the cerebral cortex and limbic areas are referred to as the reticular activating system. The precise cause of delirium is unknown, but neurotransmitter imbalance, increased levels of inflammatory

mediators, and impaired oxidative metabolism may disrupt the reticular activating system.<sup>17</sup>

Imbalances in neurotransmitters result in neuronal instability and unpredictable neurotransmissions, which are manifested as acute confusion.<sup>17,18</sup> Inflammatory cytokines are thought to contribute to the development of delirium by altering blood-brain barrier permeability

## CAM-ICU Worksheet

Feature 1: Acute Onset or Fluctuating Course	Score	Check here if present
Is the patient different than his/her baseline mental status? OR Has the patient had any fluctuation in mental status in the past 24 hours as evidenced by fluctuation on a sedation/level of consciousness scale (i.e., RASS/SAS), GCS, or previous delirium assessment?	Either question Yes →	<input type="checkbox"/>
<b>Feature 2: Inattention</b>		
<b>Letters Attention Test</b> (See training manual for alternate <b>Pictures</b> ) <b>Directions:</b> Say to the patient, "I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand." Read letters from the following letter list in a normal tone 3 seconds apart. <b>S A V E A H A A R T</b> or <b>C A S A B L A N C A</b> or <b>A B A D B A D A A Y</b> <b>Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."</b>	Number of errors >2 →	<input type="checkbox"/>
<b>Feature 3: Altered Level of Consciousness</b>		
Present if the Actual RASS score is anything other than alert and calm (zero)	RASS anything other than zero →	<input type="checkbox"/>
<b>Feature 4: Disorganized Thinking</b>		
<b>Yes/No Questions</b> (See training manual for alternate set of questions) <ol style="list-style-type: none"> <li>1. Will a stone float on water?</li> <li>2. Are there fish in the sea?</li> <li>3. Does one pound weigh more than two pounds?</li> <li>4. Can you use a hammer to pound a nail?</li> </ol> <b>Errors are counted when the patient incorrectly answers a question.</b> <b>Command</b> Say to patient: "Hold up this many fingers" (Hold 2 fingers in front of patient) "Now do the same thing with the other hand" (Do not repeat number of fingers) *If the patient is unable to move both arms, for 2 <sup>nd</sup> part of command ask patient to "Add one more finger." <b>An error is counted if patient is unable to complete the entire command.</b>	Combined number of errors >1 →	<input type="checkbox"/>
<b>Overall CAM-ICU.</b>  <b>Feature 1 plus 2 and either 3 or 4 present = CAM-ICU positive</b>	Criteria Met →	<input type="checkbox"/> <b>CAM-ICU Positive (Delirium Present)</b>
	Criteria Not Met →	<input type="checkbox"/> <b>CAM-ICU Negative (No Delirium)</b>

**Figure 2** Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) worksheet.<sup>14</sup>

Abbreviations: GCS, Glasgow Coma Scale; RASS, Richmond Agitation-Sedation Scale; SAS, Sedation Agitation Scale. Reprinted with permission from www.ICUDelirium.org. Copyright E. Wesley Ely, MD, MPH.

and further affecting neurotransmission.<sup>1</sup> Thus, delirium is caused by alterations in neurotransmitter production and activity.<sup>18,19</sup>

A recent study of neuroimaging with computed tomography has provided a better understanding of the effects of delirium on the brain.<sup>20</sup> The investigators compared computed tomography scans of patients during

and after episodes of delirium and found a reduction in overall cerebral blood flow during delirium. The blood flow was less in subcortical and occipital regions, suggesting that delirium is a widespread, rather than a localized, dysfunction.<sup>20</sup>

Several factors contribute to the increased risk of developing delirium among all hospitalized patients.

In the ICU, sedative medications or poorly managed pain can predispose patients to developing delirium. In a prospective cohort study, Inouye and Charpentier<sup>21</sup> examined risk factors for delirium in 196 patients aged 70 years and older who were admitted to general medicine wards in Yale New Haven Hospital, Connecticut. The investigators found an increased risk of delirium due to physical restraints, addition of more than 3 medications in a 24-hour period, presence of a urinary catheter, and any iatrogenic event.<sup>21</sup> The study did not include critically ill patients, but many of the same risk factors are frequently encountered in the ICU environment (see Table 1).<sup>21,22</sup>

### Manifestations and Complications of Delirium

Delirium has 3 presentations: hyperactive, hypoactive, and mixed delirium. Hyperactive delirium is associated with general disruptive behaviors such as shouting, hitting, and self-removal of catheters in association with extreme levels of agitation, emotional lability, and anxiety.<sup>18,23</sup> Peterson et al<sup>23</sup> found that 6 of 614 patients (1%) had hyperactive delirium and all cases occurred in patients younger than 65 years.

Hypoactive delirium is characterized by withdrawal, lethargy, apathy, and lack of responsiveness. Peterson et al<sup>23</sup> observed that the hypoactive type occurred in 267 of 614 ICU patients (43.5%) and more commonly presented in the

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older patients (51.8%; odds ratio, 3.0; 95% CI, 1.7-5.3).

Hypoactive

delirium is associated with a worse prognosis because it is less easily recognized and is often undertreated.<sup>7,18</sup>

In mixed delirium, patients fluctuate between hyperactive and hypoactive symptoms.<sup>19</sup> Peterson et al<sup>23</sup> found that mixed delirium was the most common type of presentation in patients aged 65 years or older.

Short- and long-term consequences of delirium include prolonged mechanical ventilation, self-extubation, use of physical restraints, longer ICU and hospital stays, long-term memory and physical impairments, and increased mortality at 6 months.<sup>18,22,24</sup> Long-term memory impairment caused by delirium is a type of long-term cognitive impairment, a syndrome of significant and persistent cognitive deficits following a critical illness. The syndrome involves

**Table 1** Delirium risk factors<sup>21,22</sup>

Predisposing factors (patient factors)	Precipitating factors (events that may occur during the course of the critical illness)
Older age	Restraints and catheters
Alcoholism	Prolonged pain
Smoking	Psychoactive medications
Hypertension	Sleep deprivation
Respiratory disease	Iatrogenic events
Cognitive impairment	Severity of illness
Depression	Respiratory disease
Vision and hearing impairment	Hypoxemia
Apolipoprotein E4 polymorphism	Severe sepsis
	Dehydration or hypotension
	Laboratory test abnormalities
	Anemia

impairment of executive functioning, which includes planning, problem solving, inhibition, and control of behavior.<sup>22</sup>

### Delirium Prevention and Treatment

The management of delirium begins with identifying patients at risk by using the CAM-ICU and ICDSC screening tools. Using the tools does not prevent the development of delirium, but ICU RNs can use these tools as part of routine nursing care to identify patients at risk.<sup>22,24</sup>

Ideally, patients at risk of delirium would be identified early and strategies to prevent the onset of delirium would be instituted. The ABCDEFS of delirium, summarized in Table 2, provide clinicians with simple preventive strategies to help reduce the likelihood that a patient will develop delirium.<sup>1,6,19,22,25</sup>

According to the Society of Critical Care Medicine (SCCM) clinical practice guidelines, using drug protocols to prevent delirium is not recommended because compelling evidence indicates that such protocols do not reduce the development or duration of delirium.<sup>19</sup> Initial management of delirium is aimed at treating the underlying cause, reducing the duration of delirium, and preventing complications.<sup>22</sup> Management includes nonpharmacological and pharmacological approaches. Nonpharmacological management strategies for delirium are outlined in Table 3.<sup>14,22,24</sup>

### Current Pharmacological Management of Delirium

No pharmacological interventions are currently approved by the FDA for the treatment of delirium.

**Table 2** The ABCDEFS of delirium<sup>1,6,14,19,22,25</sup>

<b>A</b> ssess and manage pain	Inadequate pain management increases catecholamine levels, leading to arteriolar vasoconstriction, impaired tissue perfusion, and suppression of the immune system. <sup>18</sup>
<b>B</b> oth spontaneous awakening trial (SAT) and spontaneous breathing trial (SBT)	The SAT and SBT assess the patient's level of sedation and readiness for extubation.
<b>C</b> hoice of sedative and analgesic	SCCM 2013 guidelines recommend sedation with nonbenzodiazepine medications (eg, propofol or dexmedetomidine). Use sedation scale and tailor sedative needs to the patient's needs, and reduce risk of oversedation.
<b>D</b> elirium assessment and management	Assess the patient regularly with the CAM-ICU or ICDSC to identify early delirium development.
<b>E</b> arly mobility	Early mobility is the only intervention resulting in decreased delirium days. Patients can safely mobilize within 48 hours of initiation of mechanical ventilation. Early mobilization reduces duration of ICU and hospital stay and increases return to functional independence on discharge.
<b>F</b> amily engagement	Provide the family information about delirium (eg, causes, manifestations, treatment, expected course, and consequences).
<b>S</b> leep	Promote sleep by optimizing environments (eg, control light and noise, cluster care activities). Decrease stimuli at night and protect sleep cycle.

Abbreviations: CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; ICDSC, Intensive Care Delirium Screening Checklist; ICU, intensive care unit; SCCM, Society of Critical Care Medicine.

**Table 3** Nonpharmacological interventions for treating delirium<sup>14,22,24</sup>

Visual and hearing aids  
Repeated reorientation  
Cognitively stimulating activities multiple times a day  
Familiar objects from patient's home  
Lights off at night, on during the day  
Nonpharmacological sleep interventions  
Early and frequent mobilization  
Timely removal of catheters and physical restraints  
Early correction of dehydration  
Use of a scheduled pain management protocol  
Minimization of unnecessary noise/stimuli  
Avoidance or minimization of physical restraints

Medications used to treat delirium are haloperidol and atypical antipsychotics such as olanzapine, quetiapine, and risperidone.<sup>2,22,26</sup>

### Antipsychotics

Antipsychotics are used to treat acute and chronic psychotic disorders, acute agitation, and bipolar disorder. First-generation antipsychotics are also referred to as neuroleptics, conventional antipsychotics, or typical antipsychotics. All first-generation antipsychotics are dopamine receptor antagonists that block the D<sub>2</sub> receptor. However the drugs have varied effects on α<sub>1</sub>, histamine, and muscarinic receptors, resulting in different adverse effect profiles.<sup>26,27</sup> First-generation antipsychotics

are subject to extensive metabolism through the cytochrome P450 enzyme system.

In the setting of liver impairment or drug interactions, the clearance of antipsychotics is reduced. The most common adverse effects associated with first-generation antipsychotics include extrapyramidal symptoms, tardive dyskinesia, neuroleptic malignant syndrome, QT prolongation and torsades de pointes, sudden death, and an increased risk of mortality when used to treat psychiatric symptoms associated with dementia in older patients.<sup>22,26</sup>

Haloperidol is a first-generation antipsychotic that gained popularity in the 1990s for treatment of agitated patients in the ICU.<sup>27</sup> Since then, haloperidol has been used to manage delirium, but to date no evidence has shown that it reduces the duration of delirium.<sup>2,19</sup> Additionally, haloperidol is not FDA approved for the management of delirium.<sup>27</sup>

Despite the lack of evidence and FDA approval, haloperidol continues to be used to treat delirium in patients in the ICU.<sup>19,28</sup> In a survey completed through Vanderbilt University in 2006, physicians, nurse practitioners, and physician assistants were asked about their behaviors and attitudes regarding sedation practices for patients in the ICU with delirium. A total of 1384 health care providers completed the survey, with 1190 respondents (86%) identifying haloperidol as the medication used for the management of delirium.<sup>28</sup>

Haloperidol continues to be used to treat delirium in ICUs despite the lack of evidence for its use. The SCCM guidelines for managing pain, agitation, and delirium do not support the use of haloperidol to prevent or treat delirium.<sup>19</sup> Wang and colleagues<sup>29</sup> suggested that haloperidol is the preferred agent for treating delirium because of its desirable characteristics for delirium management. For example, haloperidol has a rapid onset of action, has no active metabolites, does not require dosing adjustments for organ dysfunction, and can be given orally and parenterally.<sup>29</sup>

Because of the lack of evidence, the efficacy of haloperidol and the optimal haloperidol regimen for treating delirium are unknown.<sup>30</sup> For patients with hyperactive delirium who do not have cardiac or electrolyte abnormalities, Maldonado<sup>17</sup> recommended low-dose haloperidol (<20 mg/24 h). To help monitor therapy and allow for dose reductions in case of adverse effects, Maldonado<sup>17</sup> suggested obtaining a baseline electrocardiogram and electrolyte levels and reviewing current medications before administering haloperidol. If the QTc interval increases to greater than 25% of baseline or greater than 500 milliseconds, the therapy should be stopped and an atypical antipsychotic, such as risperidone or quetiapine, should be administered.<sup>17</sup> For patients with hypoactive delirium, Maldonado<sup>22</sup> recommended very low-dose haloperidol (0.25-1 mg/24 h).

### Atypical Antipsychotics

Practitioners may have apprehension and concerns about using antipsychotic agents, given their established adverse effect profile.<sup>22</sup> Therefore, the rate of atypical antipsychotic use in the symptomatic management of delirium has been increasing.<sup>17,22</sup> Compared with antipsychotics such as haloperidol, atypical antipsychotics have reduced affinity for dopamine receptors but have a range of affinities for serotonin, acetylcholine, and norepinephrine receptors in the central nervous system.<sup>26</sup>

There is weak evidence that atypical antipsychotics reduce the duration of delirium, as demonstrated by a small prospective, randomized, double-blind, placebo-controlled study.<sup>31</sup> In the study, 36 patients with delirium in 3 adult ICUs in Boston, Massachusetts; Portland, Maine; and Montreal, Quebec, Canada, were randomized to receive quetiapine 50 mg (n = 18) or placebo (n = 18) every 12 hours. Any patient could also receive haloperidol as required. The median duration for resolution of delirium in the quetiapine group was 1 day, which was significantly less

than the 4.5 days in the placebo group ( $P = .001$ ).<sup>31</sup> However, the study had a small sample size, and further research is needed before the definitive use of quetiapine can be advocated.

Lonergan et al<sup>32</sup> completed a Cochrane review comparing haloperidol with the second-generation antipsychotics risperidone, olanzapine, and quetiapine for the treatment of delirium. Three studies met the selection criteria. The review found no significant differences between low-dose haloperidol (<3 mg/d) and olanzapine and risperidone for the management of delirium (odds ratio, 0.63; 95% CI, 0.29-1.38;  $P = .25$ ). The review did not find a higher incidence of adverse effects with low-dose haloperidol. Compared with placebo, haloperidol did not reduce the incidence of delirium but did decrease the severity and duration of delirium in postoperative patients.<sup>32</sup> The conclusions should be considered within the context of the small sample sizes and limited scope of the included studies.

Although weak evidence supports the use of atypical antipsychotic agents in the management of delirium, one hindrance to their use is that no intravenous formulations are available.<sup>26</sup> Additionally, the adverse effects of atypical antipsychotics, specifically sedation, tachycardia, and orthostatic hypotension, may be detrimental to critically ill patients and may limit their use in this population.<sup>26</sup>

### Benzodiazepines

Benzodiazepines contribute to the development of delirium through the mechanisms outlined in Table 4. In instances of delirium tremens and withdrawal syndromes, benzodiazepines are the preferred treatment of choice.<sup>1</sup> More recently, delirium development has been associated with the use of benzodiazepines in patients with alcohol withdrawal. Maldonado<sup>33</sup> completed a literature review to develop a benzodiazepine-sparing treatment protocol for patients with alcohol withdrawal and suggested that the use of benzodiazepines is an independent risk factor for the development of delirium. At this time, the SCCM guidelines still recommend the use of benzodiazepines for alcohol withdrawal; however, the results of the Maldonado review<sup>33</sup> may change clinical practice in the future.

### Propofol

The 2013 SCCM guidelines recommend using nonbenzodiazepine sedation strategies including agents such as

**Table 4** Role of benzodiazepines in delirium<sup>22</sup>

Effect (mediated by $\gamma$ -aminobutyric acid)	Contribution to delirium
Interference with physiologic sleep patterns	This effect does not produce natural sleep. Sleep disruption leads to memory deficits.
Centrally mediated acetylcholine deficit	The cholinergic system is involved in arousal, attention, memory, and rapid eye movement sleep. A cholinergic deficit leads to alteration in mental function.
Disruption of circadian rhythm of melatonin release	Melatonin regulates the sleep-wake cycle. Impaired melatonin release leads to changes in sleep patterns.
Disruption of alamic gating function	Thalamic filtering of relevant information to the cortex is impaired. Sensory overload results with hyperarousal.

propofol over sedation with benzodiazepines. Propofol is an intravenous sedative that binds to multiple central nervous system receptors, including  $\gamma$ -aminobutyric acid, muscarinic, and nicotinic receptors.<sup>19</sup> Therefore, propofol has a similar mechanism of action as benzodiazepines, but there are certainly differences between the 2 agents.

Propofol is a highly lipid-soluble drug that is distributed into peripheral tissues and can rapidly cross the blood-brain barrier. It has a rapid onset (40 seconds to 3 minutes) and has anxiolytic and amnesic effects.<sup>34</sup> Propofol has high hepatic clearance and is rapidly cleared with short-term infusions. With increased duration of propofol infusions, steady-state volume of distribution increases, which leads to a longer half-life. Propofol commonly causes respiratory depression and hypotension. Rarely, hypertriglyceridemia, acute pancreatitis, myoclonus, and propofol infusion syndrome can occur.<sup>19,34</sup>

Propofol has been associated with fewer delirious effects than benzodiazepines.<sup>22</sup> However, in 2 of 3 studies comparing propofol with dexmedetomidine, propofol was associated with a higher incidence of delirium.<sup>5,35,36</sup> Propofol may be a more appropriate agent than benzodiazepines, but dexmedetomidine may be preferable to propofol.<sup>22</sup>

### Other Pharmacological Management Strategies

Pharmacological management of delirium also involves reviewing medications that may be causing or potentiating the delirium. Maldonado<sup>22</sup> recommended conducting a medication review. Medications known to cause delirium or have a high anticholinergic potential should be discontinued, and a suitable alternative should be used.

In summary, research findings are equivocal with respect to the use of medications to prevent delirium,

partly because of heterogeneous and small sample sizes. The ideal clinical situation is the prevention or at least the early detection of delirium and the use of nonpharmacological management strategies.<sup>22</sup> When pharmacological therapy is necessary, the ideal drug would relieve symptoms without causing excessive sedation, would have fewer adverse effects than haloperidol, and would not interact with other drugs. In addition, the ideal drug would have an analgesic effect, thereby sparing the need for opioids.<sup>37</sup> Dexmedetomidine has a medication profile with these characteristics.

### Dexmedetomidine

Dexmedetomidine is an  $\alpha_2$ -adrenoreceptor agonist that has sedative, analgesic, and anxiolytic properties.<sup>11,38</sup>  $\alpha_2$ -Adrenoreceptors are found throughout the body in the central nervous system, peripheral nervous system, liver, pancreas, kidney, and eye.<sup>2,38</sup>

In the brainstem, the locus coeruleus contains many  $\alpha_2$ -adrenoreceptors and plays a key role in wakefulness and regulation of nociceptive neurotransmission.<sup>38</sup> Stimulation of  $\alpha_2$ -adrenoreceptors in the brain and spinal cord has inhibitory effects leading to sedation, analgesia, hypotension, and bradycardia.<sup>38</sup> Dexmedetomidine acts as an agonist in the locus coeruleus and inhibits norepinephrine release, resulting in depression of alertness and sympathetic activity that manifests as sedation, hypotension, and bradycardia.<sup>11</sup>

### Pharmacokinetics and Administration

Dexmedetomidine is administered intravenously, has an onset of action of approximately 15 minutes, and

**Pharmacological management of delirium also involves reviewing medications that may be causing or potentiating the delirium.**



reaches peak concentration after 1 hour of continuous infusion.<sup>11</sup> Dexmedetomidine has a half-life of 2 hours and follows first-order linear kinetics. It is metabolized almost completely in the liver to inactive metabolites. Patients with hepatic dysfunction may require lower doses, but renal dosing is not required.<sup>39</sup>

The recommended loading dose of dexmedetomidine is 1 µg/kg over 10 minutes, followed by a continuous infusion of 0.2 to 0.7 µg/kg per hour, titrated to the desired level of sedation.<sup>12</sup> A higher dose of dexmedetomidine (1.5 µg/kg per hour) has been administered without clinically significant adverse effects.<sup>11</sup> When dexmedetomidine is given to replace another sedative, a loading dose is generally not required.<sup>8</sup> Bolus therapy and rapid dosage adjustment to achieve the desired level of sedation have been associated with more adverse drug events.<sup>39,40</sup> It is recommended that dexmedetomidine be infused for 24 hours.<sup>16</sup> However, infusions of greater than 24 hours have not shown any adverse effects.<sup>39</sup>

Dexmedetomidine can be administered safely in conjunction with anesthetics, sedatives, hypnotics,

**Dexmedetomidine can be administered safely in conjunction with anesthetics, sedatives, hypnotics, neuromuscular blockade agents, and opioids.**

neuromuscular blockade agents, and opioids.<sup>12</sup> Most patients

treated with dexmedetomidine require additional sedative or analgesic agents.<sup>38,41</sup> Concurrent use of dexmedetomidine and other sedatives may enhance the effects of dexmedetomidine and may require dose reductions to reduce the risk of pharmacodynamic interactions.<sup>12</sup> Interactions have been seen specifically with sevoflurane, isoflurane, propofol, alfentanil, and midazolam. Dexmedetomidine can be infused before, during, and after extubation of mechanically intubated patients.<sup>8</sup>

### Adverse Effects

Because of inhibition of norepinephrine release, most of the significant adverse effects of dexmedetomidine are related to sympatholytic activity and are often dose related. Martin et al<sup>42</sup> compared dexmedetomidine with placebo in 401 postsurgical patients in an ICU in a double-blind, randomized, multicenter, controlled trial. The most commonly reported adverse effects with dexmedetomidine were hypotension (61 of 203 patients [30%],  $P < .001$ ), hypertension (24 of 203 patients [12%],

$P = .005$ ), and bradycardia (18 of 203 patients [18%],  $P = .003$ ).<sup>42</sup> Riker et al<sup>43</sup> found a greater incidence of bradycardia in patients receiving dexmedetomidine (103 of 244 patients [42.2%]) than in those receiving midazolam (23 of 122 patients [18.9%],  $P < .001$ ).

Increased episodes of hypotension and bradycardia are associated with higher or rapid dose increases of dexmedetomidine.<sup>41</sup> The loading dose of dexmedetomidine may cause temporary hypertension because of the initial activation of vascular  $\alpha_2$ -adrenoreceptors. Persistent hypertension may be corrected by decreasing the rate of infusion.<sup>12</sup>

### Nursing Vigilance and Drug Withdrawal

Dexmedetomidine should be administered with caution to patients with advanced heart block, severe ventricular dysfunction, hypovolemia, preexisting diabetes mellitus, or chronic hypertension because the drug may cause more pronounced hypotension and bradycardia in this patient population.<sup>8</sup> Caution should be used when administering dexmedetomidine along with medications that may also cause bradycardia or have sympatholytic effects.<sup>8</sup> Medications that have negative chronotropic effects should be used with care because they may increase the risk of hypotension by causing an additive pharmacodynamic effect.<sup>12</sup> Nurses in cardiovascular ICUs need to be particularly vigilant because patients are at increased risk of cardiovascular adverse effects with the concomitant use of chronotropic drugs.

The dexmedetomidine drug monograph indicates an increased risk of adverse effects with abrupt discontinuation. These adverse effects include tachycardia, hypertension, anxiety, agitation, headache, tremor, nausea, and vomiting.<sup>8</sup> The adverse effects of withdrawal are due to a rebound effect. However, in a prospective, double-blind, randomized, multicenter trial of 244 patients, Riker et al<sup>43</sup> did not report adverse events or drug-related withdrawal effects with abrupt discontinuation of dexmedetomidine infusions.

### Dexmedetomidine Effects on Delirium

We reviewed studies that examined the role of dexmedetomidine in the management of delirium (summarized in Table 5). We did not include studies in which dexmedetomidine was part of a preventive strategy. Overall, dexmedetomidine seems to have a

favorable effect on reducing the incidence and duration of delirium.<sup>5,35,43,44,47,49</sup>

The Dexmedetomidine Compared to Morphine study and the Dexmedetomidine for Sepsis in ICU Randomized Evaluation trial did not show statistically significant results that dexmedetomidine reduced delirium.<sup>36,48</sup> However, the end point of delirium was not a primary outcome of the latter study, and the result should be considered within this context.<sup>36</sup> The results are supported by a recent meta-analysis of 8 studies by Lui et al<sup>50</sup> comparing dexmedetomidine with propofol in patients who underwent cardiac surgery. Of the 8 studies reviewed, 4 reported the incidence of delirium, with sample sizes ranging from 55 to 295 patients. Among these 4 studies, 18 of 193 patients (9.3%) in the dexmedetomidine group and 47 of 200 patients (23.5%) in the propofol group had delirium.<sup>50</sup>

Lui et al<sup>50</sup> demonstrated that dexmedetomidine sedation significantly reduced postoperative delirium (risk ratio, 0.40; 95% CI, 0.24-0.64;  $P = .0002$ ). They recommended that the results be viewed with caution because the number of patients was limited and the effect may have been overestimated. The primary outcomes, selection of patients, study periods, sedation levels, and outcome definitions varied. The methods of assessments differed across trials, which may have affected the precision and reliability of outcome comparisons.<sup>50</sup>

At face value, the results of the review demonstrated a reduction in delirium with dexmedetomidine administration. However, generalizing the results should be done with caution because the studies used different inclusion and exclusion criteria, sampling methods, and medication protocols. In some studies, delirium was a secondary outcome. Given the heterogeneity of the studies, it is difficult for us to make a consensus statement on the use of dexmedetomidine for delirium.

### Advantages of Dexmedetomidine Over Current Management Strategies

As with antipsychotic and atypical antipsychotic agents in patients with delirium, the use of dexmedetomidine requires further investigation in adequately powered, double-blind, randomized, controlled trials. However, in comparison with current pharmacological management strategies, dexmedetomidine does appear to have some advantages. A comparison of the clinical effects of dexmedetomidine and other pharmacological agents is presented in Table 6.<sup>51</sup>

In comparison with the most common adverse effects of antipsychotics (QTc prolongation, extrapyramidal effects, and sedation), the adverse effect profile of dexmedetomidine may be less detrimental to critically ill patients.<sup>52</sup> Additionally, haloperidol is metabolized in the liver by the cytochrome P450 enzymes, resulting in more drug interactions and potentiating the drug's effect.<sup>8</sup> Clinicians must be aware of interactions and be diligent in ensuring that patients do not receive medications that have known interactions.

Dexmedetomidine has advantages over current pharmacological management strategies, considering the pharmacokinetic profile of the drug and the pathophysiology of delirium. Maldonado et al<sup>5</sup> proposed that dexmedetomidine has antidelirium properties for the following reasons:

- Dexmedetomidine has a high specificity and selectivity for  $\alpha_2$ -adrenoreceptors and blocks norepinephrine, disrupting 1 of the neurotransmitter pathways theorized to play a role in delirium.
- Dexmedetomidine produces sedative effects without respiratory depression. Sedatives and analgesics can cause respiratory depression, which can lead to hypoxemia. In the critically ill patient, decreased oxygen supply and increased oxygen demand can lead to decreased oxygen availability to cerebral tissue and the development of delirium.
- Dexmedetomidine has no anticholinergic effects.
- Dexmedetomidine theoretically promotes a more physiologic sleep-wake cycle, reducing the incidence of delirium.<sup>2,5</sup>
- Dexmedetomidine reduces the need for deliriogenic agents such as benzodiazepines.

Hipp and Ely<sup>27</sup> suggested that lower delirium rates associated with dexmedetomidine use resulted from avoidance of deliriogenic agents, such as benzodiazepines and opioids, rather than from a protective effect of dexmedetomidine against delirium.

Dexmedetomidine appears to have superior qualities over the antipsychotic medications in the management of delirium. However, because evidence related to the successful use of the drug is limited, we would strongly caution clinicians to be vigilant when administering dexmedetomidine to ICU patients with delirium.

### Implications for Critical Care Nurses

The critical care nurse plays a fundamental role in implementing strategies to prevent delirium and in

**Table 5** Dexmedetomidine studies included in review

Study	Sample	Research method
Carrasco et al, <sup>44</sup> 2016	Patients (N=132) aged 18-95 years, with agitated delirium as evidenced by ICDSC scores between 4 and 8 and RASS scores of +1 to +4	Nonrandomized controlled trial
Djaiani et al, <sup>35</sup> 2016	Patients (N=183) aged 18-95 years, with agitated delirium as evidenced by ICDSC scores between 4 and 8 and RASS scores of +1 to +4	Single-blind, prospective, randomized controlled trial
Kawazoe et al, <sup>36</sup> 2017	Patients aged 20 years or older (in 8 ICUs in Japan) with sepsis and requiring noninvasive or invasive mechanical ventilation for at least 24 hours	Open-label, multicenter randomized clinical trial
Maldonado et al, <sup>5</sup> 2009	Postoperative patients (N=90) who underwent cardiac surgery with cardiopulmonary bypass, receiving mechanical ventilation	Open-label, prospective, randomized trials
Mirski et al, <sup>45</sup> 2010	Intubated, brain-injured and nonbrain-injured patients (N=64); 33 received at least 1 drug and 30 completed the study	Randomized, prospective, double-blind, crossover trial
Pandharipande et al, <sup>46</sup> 2007	Medical and surgical patients (N=103) receiving mechanical ventilation	Double-blind, randomized controlled trial at 2 tertiary care sites
Reade et al, <sup>47</sup> 2016	Patients (N=71) receiving mechanical ventilation who required mechanical restraint, antipsychotic medication, had positive CAM-ICU score	Double-blind, parallel-group, placebo-controlled, multicenter randomized trial
Reade et al, <sup>37</sup> 2009	Delirious, agitated patients (N=20) receiving mechanical ventilation	Randomized, open-label, parallel-group pilot study
Riker et al, <sup>43</sup> 2009	Intubated patients (N=366) receiving mechanical ventilation	Double-blind, randomized, prospective trial, completed in 5 countries
Shehabi et al, <sup>48</sup> 2009	Patients aged 60 years or older, after cardiovascular surgery, receiving mechanical ventilation	Randomized, double-blind controlled trial
Su et al, <sup>49</sup> 2016	Patients (N=700) aged 65 years or older admitted to ICU after noncardiac surgery in 2 hospitals in China	Randomized, double-blind, parallel-arm placebo-controlled trial

Abbreviations: CAM-ICU, Confusion Assessment Method for the Intensive Care Unit; DSM-IV-TR, *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition, Text Revision) ICDSC, Intensive Care Delirium Screening Checklist; ICU, intensive care unit; IQR, interquartile range; IV, intravenous; OR, odds ratio; PO, primary outcome; RASS, Richmond Agitation-Sedation Scale; RR, relative risk; SO, secondary outcome.

Treatment	Delirium related outcome	Delirium assessment tool	Results
All patients received IV haloperidol initially, but if agitation was not controlled with the maximum dose of haloperidol (30 mg), patients were assigned to the dexmedetomidine group (n=46).	Quality of sedation, defined as percentage of time patient was within RASS score 0, -1, or -2; ICDSC < 4 (PO)	ICDSC	Percentage of time with ICDSC score <4: dexmedetomidine, 52% (95% CI, 37.5-66.4); haloperidol, 29.5% (95% CI, 13-42.3); <i>P</i> =.005
Dexmedetomidine (n=91) bolus 0.4 µg/kg followed by infusion of 0.2-0.7 µg/kg per hour Propofol (n=92) infusion of 25-50 µg/kg per minute	Incidence of delirium (PO)	CAM-ICU	Postoperative delirium occurred in 16 of 91 (17.5%) dexmedetomidine patients and 29 of 92 (31.5%) propofol patients (OR 0.46; 95% CI, 0.23-0.92; <i>P</i> =.03).
Dexmedetomidine (n=100), 0.1-0.7 µg/kg per hour titrated to goal of RASS 0 Sedation without dexmedetomidine (n=101): propofol 0-3 µg/kg per hour, midazolam 0-0.15 mg/kg per hour	CAM-ICU score (SO) with post hoc analysis on delirium-free days	CAM-ICU	CAM-ICU positive scores: dexmedetomidine group, 44 (44%); control group, 45 (45%); <i>P</i> = .94 No significant differences between delirium-free days existed ( <i>P</i> = .17).
Dexmedetomidine (n=30) loading dose of 0.4 µg/kg, then infusion of 0.2-0.7 µg/kg per hour Propofol (n=30) infusion of 25-50 µg/kg per minute Midazolam (n=30) infusion of 0.5-2 mg/h	Proportion of patients that developed delirium in each treatment arm (PO)	DSM-IV-TR criteria by research assistant	Delirium in the study population, 31 of 90 (34%) patients; in dexmedetomidine group, 1 of 30 (3%); in propofol group, 15 of 30 (50%); in midazolam group, 15 of 30 (50%). Mean ICU stays were 1.9 days for dexmedetomidine, 3.0 days for propofol, 3.0 days for midazolam groups.
Dexmedetomidine infusions ranged from 0.2 to 0.7 µg/kg per hour. Propofol infusions ranged from 20 to 70 µg/kg per minute.	Incidence of delirium (SO)	CAM-ICU	Positive CAM-ICU score: 1 patient (3%)
Dexmedetomidine (n=52), no boluses, 0.15-1.5 µg/kg per hour Lorazepam infusion (n=51), 1-10 mg/h	Days alive without delirium or coma during a 12-day evaluation period (PO)	CAM-ICU	Dexmedetomidine patients had more days without delirium or coma (mean, 7 days; IQR 1-10) than did lorazepam patients (mean, 3 days; IQR 1-6); <i>P</i> =.01.
Dexmedetomidine (n=39), 0-1.5 µg/kg per hour Placebo, normal saline infusion (n=32)	Including time to first CAM-ICU score that indicated no delirium (SO)	CAM-ICU	Delirium resolved faster in the dexmedetomidine group (median, 23.3 hours) than in the placebo group (median, 40 hours). Median difference between groups, 16.0 hours (95% CI, 3-28 hours; <i>P</i> = .01).
Dexmedetomidine (n=10), optional loading dose of 1 µg/kg IV, followed by 0.2-0.7 µg/kg per hour Haloperidol (n=10), optional loading dose of 2.5 mg, followed by 0.5-2 mg/h	Proportion of time with a satisfactory ICDSC score (<4) (SO)	ICDSC	Percentage of time with ICDSC score <4: dexmedetomidine, 95.5% (median); haloperidol, 31.5% (median); <i>P</i> =.12)
Dexmedetomidine (n=244), loading dose of 1 µg/kg, infusion of 0.08 µg/kg per hour Midazolam (n=122), optional loading dose of 0.5 mg/kg, then infusion of 0.06 µg/kg per hour	Prevalence and duration of delirium, measured by delirium-free days in a 28-day period (SO)	CAM-ICU	Of patients with positive CAM-ICU scores at the beginning of the study (n=229), dexmedetomidine patients had a 32.2% reduction in delirium (95% CI, 21-43%; <i>P</i> <.001) and more delirium-free days (2.5 vs 1.7 days; <i>P</i> = .002).
Dexmedetomidine (n=152), 0.1-0.7 µg/kg per hour Morphine (n=147), 10-70 µg/kg	Percentage of patients who developed delirium within 5 days of surgery (PO)	CAM-ICU	Delirium, dexmedetomidine, 8.6%; morphine, 15% (RR 0.571, 95% CI 0.256-1.099; <i>P</i> = .09). Duration of delirium: dexmedetomidine, 2 days; morphine, 5 days (95% CI 1.09-6.67; <i>P</i> = .03).
Nonintubated patients (n=159) received dexmedetomidine 0.1 µg/kg per hour; intubated patients (n=191) received dexmedetomidine after being stabilized with propofol or midazolam at 0.1 µg/kg per hour Placebo (n=350), IV normal saline	Incidence of delirium in the first 7 days after surgery (PO)	CAM-ICU	Postoperative delirium occurred in 32 of 350 (9%) patients given dexmedetomidine and 79 of 350 (23%) given placebo (OR 0.35; 95% CI, 0.22-0.54; <i>P</i> <.001).

**Table 6** Clinical effects of dexmedetomidine and other pharmacological agents

Effects	Dexmedetomidine	Benzodiazepines	Propofol	Opioids	Haloperidol
Sedation	X	X	X	X	X
Alleviation of anxiety	X	X			
Analgesic properties	X			X	
No respiratory depression	X				X
Cooperative sedation	X				
Mimicking of natural sleep	X				

Adapted from Short<sup>91</sup> with permission.

assessing the development of delirium. We cannot emphasize enough the importance of using strategies as outlined in Table 3 to prevent delirium and using screening tools to identify delirium. Maldonado<sup>22</sup> recommends identifying the underlying cause of delirium and tailoring the treatment plan according to each patient's situation. However, critical care RNs must assess and manage delirium to resolve the situation effectively and prevent complications.

Pharmacological intervention is likely to be required to treat delirium. For patients who need continuous intravenous infusion of a pharmacologic agent, the SCCM

**Critical care nurses must assess and manage delirium to resolve the situation effectively and prevent complications.**

2013 clinical practice guidelines indicate a “moderate quality of evidence” recommending the use of dexmedetomidine over benzodiazepines.<sup>19</sup> The guidelines do not provide a recommendation for the use of other nonbenzodiazepine drugs or atypical antipsychotics to manage delirium. According to the SCCM guidelines, haloperidol is not recommended for reducing the duration of delirium.<sup>19</sup> However, no other statement is provided regarding the use of haloperidol or atypical antipsychotics to manage delirium.

## Conclusion

We support the SCCM clinical practice guideline recommendations and suggest using dexmedetomidine instead of benzodiazepines to manage delirium.<sup>19</sup> We also recommend using dexmedetomidine for patients who have delirium and no contraindications to dexmedetomidine. When dexmedetomidine is the pharmacological agent used to treat delirium, critical care nurses

must have a comprehensive understanding of the pharmacodynamics of the drug.

The best approach to delirium is to use screening tools for early identification of the condition. However, when delirium does occur and pharmacological management is warranted, considering the patient's characteristics and underlying cause of delirium is crucial for effective management and reduction of adverse effects. Pharmacological management may include dexmedetomidine. **CCN**

Financial Disclosures  
None reported.

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## See also

To learn more about caring for patients with delirium, read “Delirium Monitoring: Yes or No? That Is The Question” by Marra et al in the *American Journal of Critical Care*, March 2019;28:127-135. Available at [www.ajconline.org](http://www.ajconline.org).

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