

## Review

# Bench-to-bedside review: Delirium in ICU patients - importance of sleep deprivation

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## Abstract

Delirium occurs frequently in critically ill patients and has been associated with both short-term and long-term consequences. Efforts to decrease delirium prevalence have been directed at identifying and modifying its risk factors. One potentially modifiable risk factor is sleep deprivation. Critically ill patients are known to experience poor sleep quality with severe sleep fragmentation and disruption of sleep architecture. Poor sleep while in the intensive care unit is one of the most common complaints of patients who survive critical illness. The relationship between delirium and sleep deprivation remains controversial. However, studies have demonstrated many similarities between the clinical and physiologic profiles of patients with delirium and sleep deprivation. This article aims to review the literature, the clinical and neurobiologic consequences of sleep deprivation, and the potential relationship between sleep deprivation and delirium in intensive care unit patients. Sleep deprivation may prove to be a modifiable risk factor for the development of delirium with important implications for the acute and long-term outcome of critically ill patients.

## Introduction

Delirium is common in critical care units, particularly in older people. It is a clinical syndrome characterized by acute onset of fluctuating disturbance in consciousness, inattention, and cognitive dysfunction. Patients may be agitated (hyperactive delirium), may be withdrawn (hypoactive or quiet delirium), or may have features of both agitation and withdrawal at times [1]. Delirium has been shown to occur in up to 80% of critically ill patients and to be an independent predictor of

adverse intensive care unit (ICU) outcomes, including increased risk of death, longer hospital stay, and higher costs [2-7].

Epidemiologic studies have identified numerous risk factors for the development of delirium. Advanced age, pre-existing cognitive impairment, electrolyte disturbance, and many frequently used ICU medications such as benzodiazepines are among the usually cited factors associated with delirium. Sleep deprivation, common in ICU patients, may also be a contributing factor.

Hospitalized patients, particularly those who are critically ill, are known to have severe sleep fragmentation and disturbed sleep. The sleep typical of a critically ill patient is characterized by a predominance of wakefulness and light sleep (sleep stages I and II), and a relative lack of rapid eye movement (REM) and deep sleep (delta sleep, formerly referred to as non-REM sleep stages III/IV) [8-11]. Sleep deprivation is known to lead to several clinical and physiologic manifestations also found in delirium; however, its role in the development of ICU delirium is controversial.

This article will review the clinical and neurophysiologic similarities between delirium and sleep deprivation. The importance of this association lies in its potential as another target for intervention to prevent acute ICU delirium.

ICU = intensive care unit; PSG = polysomnography; REM = rapid eye movement.

## Clinical similarities between delirium and sleep deprivation

The central components of delirium – that is, inattention, fluctuating mental status, and cognitive dysfunction – are also characteristic of patients with sleep deprivation [12,13]. Studies of the effects of sleep loss have mostly included healthy volunteers, and the studies apply models of sleep loss that may not be directly applicable to the critically ill patient; regardless, these sleep-deprived individuals have shown all of the clinical manifestations of hypoactive (quiet) delirium. Sleepiness is the most consistent behavioral consequence of sleep deprivation, with drowsiness and pressure to fall asleep (microsleeps) increasing with sleep loss. Negative effects on mood, loss of vigor, fatigue, and impaired cognition have also been observed after all forms of experimental sleep deprivation [14]. A tendency toward psychotic behavior with associated paranoia occurred in a few subjects deprived of sleep for 112 hours [15]. It was noted that the psychotic behavior increased during the night and abated during the day, as is also typical of ICU delirium. Attention and memory impairment, two key elements in the diagnosis of delirium, have also been found after periods of total and partial sleep deprivation [16,17].

The association of sleep deprivation and hyperactive delirium is more controversial. Sleep deprivation, as studied in healthy volunteers, has not been shown to lead to the overt agitation or hallucinations present with this delirium subtype. In 1959 a New York disc jockey stayed awake for 200 hours [18,19]. Toward the end of the 200 hours he developed paranoid delusions and auditory and visual hallucinations, and these problems were initially attributed to sleep deprivation. Later, it was suspected that the large doses of methylphenidate that the disc jockey took to stay awake were the actual cause of his paranoia and hallucinations.

Dement and Vaughan studied the effects of prolonged wakefulness, and observed that healthy volunteers who were sleep deprived would become confused, ill-tempered, and extremely sleepy; however, they never became either psychotic or hyperactively delirious [20]. The longest observed case of sleep deprivation involved an 18 year old who stayed awake for 264 hours. At times during his long-term sleep deprivation, he would become angry that he was not being allowed to fall asleep. He was not, however, reported to experience symptomatology consistent with hyperactive delirium or hallucinations [21].

Sleep loss, as with delirium, has been shown to result in demonstrable neurocognitive dysfunction. Sleep deprivation leads to decrements in psychomotor vigilance (the ability to sustain attention and respond in an appropriate amount of time), working memory, and response inhibition (subjects respond when no stimulus is present or respond to the wrong stimulus) [22]. Problems with verbal fluency, creative thinking, nonverbal planning, and temporal memory, as may be

observed in delirium, may also develop as a result of sleep deprivation [13]. Even one night of total sleep deprivation reduces the alertness of healthy volunteers and their performance on serial addition/subtraction tasks [23].

The persistence of these adverse changes in cognitive performance is often underestimated. Mood disturbance and subjective sleepiness return to baseline quickly once recovery sleep begins; however, some performance tasks are slower to recover [24]. Healthy volunteers sleep deprived for up to 48 hours, for example, have a continued abnormality in psychomotor vigilance even after 5 nights of recovery sleep [25]. A similar delay in psychomotor recovery occurs with delirium. Patients who were delirious in the hospital are observed to recover to their baseline mental status prior to discharge and may even return to work, but with demonstrable impairments in task performance and thought processing when tested months later [26].

## Exploring the mechanistic relationship between delirium and sleep deprivation

Delirium is believed to be due to a malfunction of specific regions of the cerebral cortex and related structures of the brainstem. This malfunction may be due to vulnerability of distinct neural circuits to a variety of insults leading to cellular dysfunction. Two interconnecting neural circuits – one involving the prefrontal cortex, anterior cingulate, and basal ganglia; and the other circuit involving the parietal lobes, superior colliculus, and thalamic pulvinar – have been proposed as important pathways for attention and working memory [14]. When these neural circuits are compromised, the resulting imbalance of the involved neurotransmitters is thought to lead to the clinical manifestations of delirium [27]. Although multiple neurotransmitter systems are probably involved, it is thought that a deficiency in cholinergic innervation and excess of dopaminergic stimulation are the final common pathways for the development of clinical signs and symptoms of delirium [28]. Once thought to be just temporary, the cognitive manifestations of this neuronal dysfunction have been shown to last from months to years in survivors of critical illness [29,30].

Evidence of the importance of the prefrontal cortex and non-dominant posterior parietal cortex comes from neurophysiologic studies and is supported by functional imaging and lesion studies. Mesulam and colleagues and Koponen and colleagues both identified lesions with a prefrontal and a posterior parietal focus in patients with delirium [31,32]. Other investigators have identified lesions of the caudate or thalamus, areas that directly interact with the prefrontal cortex or posterior parietal cortex, in delirious patients [33]. Consistent with these findings are positron emission tomography and single-photon emission computerized tomography studies of some delirious patients demonstrating changes of cerebral perfusion and metabolism in these same regions of the central nervous system [34,35].

Sleep deprivation has been shown to affect the same regions of the central nervous system. Thomas and colleagues, for example, measured the regional cerebral metabolic rate by positron emission tomography scan in healthy volunteers deprived of sleep for 24 hours [23]. These subjects had a global decrease in glucose metabolism but with focally accentuated decreases in glucose uptake in the prefrontal cortex, thalamus, and posterior parietal cortex in response to cognitive tasks. Interestingly, blood oxygen level-dependent functional magnetic resonance imaging studies of healthy subjects deprived of sleep for 35 hours demonstrated an activation of the prefrontal and parietal cortices during a specific learning task [36]. The authors postulate that this phenomenon represents compensation for the failure of normal neural systems when challenged with specific learning tasks. Electroencephalography studies of sleep-deprived subjects similarly support the theory that frontal and parietal cortical areas may be susceptible to sleep deprivation [37].

Sleep deprivation, as is observed in ICU patients, also shares some of the neurohormonal changes observed in delirium. It has long been known that the cholinergic system is integral to the generation of REM sleep. Evidence for a relationship between REM sleep deprivation and cholinergic dysregulation derives mostly from animal models that suggest acetylcholine levels would decrease in the brain after REM sleep deprivation, as may occur in delirium [38,39].

Dopamine is believed to be important to attention, motor activity, mood, motivation, and memory [28]. Dopamine and acetylcholine interact closely, often reciprocally, in the central nervous system [27]. Dopamine levels are increased under conditions known to cause delirium; that is, intoxication with 3,4-dihydroxy-L-phenylalanine and opiates, cocaine binges, and hypoxia [40]. Activation of the dopaminergic system is also observed after periods of sleep deprivation [41].

The mechanism of delirium and the consequences of sleep deprivation continue to be studied. Although a direct relationship has not been established, it seems probable that these two conditions that share so many epidemiologic, biochemical, and anatomic similarities would be clinically related. Table 1 summarizes the similarities between delirium and sleep deprivation.

**Sleep deprivation as a risk factor for delirium**

Patients are at higher risk for developing delirium if they are older and have pre-existing cognitive impairment, sensory impairment, poor functional status, immobility, multiple comorbid medical problems, alcohol abuse, depression, and cancer. The risk of developing delirium is further enhanced by the addition of precipitating factors imposed both as part of the underlying illness and of treatment. A common precipitating factor in ICU patients is the administration of certain medications such as benzodiazepines [42]; even routine practices such as bladder catheterization and restraints,

**Table 1**

**Clinical and physiologic similarities shared by delirium and sleep disruption**

Clinical features	
	Inattention
	Fluctuating mental status
	Impaired cognition, specifically those relating to executive function (memory, planning, creative thinking, judgment)
	Delayed recovery after the insult is removed
Risk factors	
	Intensive care unit admission
	Mechanical ventilation
	Pain
	Stress
	Pre-existing cognitive impairment
	Advanced age
	Alcoholism
	Depression
	Sepsis
	Head trauma
	Medications
	Sedatives, especially $\gamma$ -aminobutyric acid agonists such as benzodiazepines
	Anticholinergics
	Sympathomimetics
	Corticosteroids
	Anticonvulsants
Pathophysiology	
	Cholinergic deficiency
	Dopaminergic excess
	Altered metabolism at specific regions of the central nervous system
	Prefrontal cortex
	Posterior parietal cortex

however, may be enough to lead to clinically apparent delirium.

Is sleep deprivation a risk factor for delirium? Few clinical studies have been designed with the primary intent of answering this question. Helton and colleagues studied 62 critically ill medical and surgical patients during their first 5 days in the ICU with the intention of correlating patients' sleep deprivation with the development of mental status changes [43]. The authors did attempt to control for medications and conditions that would affect mental status. Sleep

deprivation was determined by the number of uninterrupted sleep cycles – that is, 75-minute periods of time without interruption – compared with what would be normal for the patient at home. The authors were therefore measuring potential sleep cycles. They found that mental status changes were more likely in patients with greater sleep deprivation. To fully establish this relationship, however, more rigorous investigation utilizing polysomnography and objective measures of delirium in critically ill patients are needed.

### **Investigation of the relationship between sleep deprivation and delirium**

To carefully study the effect of sleep deprivation on the development of ICU delirium, polysomnography (PSG) needs to be performed over a 24-hour period. Sleep in critically ill patients is distributed irregularly throughout the day and night [8,10,11]. To fully evaluate the effects of sleep on clinical outcomes such as delirium, PSG cannot be limited to the nocturnal time period and should include as much time during the patient's ICU stay as possible. In addition, vasoactive medications, sedatives, and analgesics all have profound effects on sleep architecture [44]. As these medications are weaned, patients' sleep patterns will also change.

Moreover, the interpretation of PSG in the ICU is challenging and is a new frontier in critical care. In fact, the traditional, manual scoring system for PSG may not be as reproducible as spectral analysis of electroencephalography in mechanically ventilated critically ill patients [45]. Encephalopathy is common in the ICU and can cause electroencephalography patterns similar to slow-wave sleep [10]. Sedatives can also cause profound effects on the electroencephalography, producing a decrease in electroencephalography amplitude and an increase in frequency – which may be erroneously scored as wakefulness if using standard Rechtschaffen and Kales criteria. Short periods of electroencephalography burst suppression may also occur secondary to benzodiazepines and propofol administration on PSG epochs otherwise scored as stage I or stage II sleep. It is important to take into account these electroencephalography findings in addition to standard sleep staging when interpreting PSG in ICU patients.

Independent of PSG data, risk factors for the development of sleep deprivation in critically ill patients overlap with those of delirium (Table 2). Admission to an ICU alone, mechanical ventilation, pain, and stress are risk factors for the development of both delirium and sleep deprivation. Patients with pre-existing cognitive impairment (that is, dementia) are both at high risk for developing delirium and are also known to have sleep problems at baseline with features similar to those of the critically ill. Patients with dementia have an increased percentage of stage I sleep, decreased slow-wave sleep, loss of the defining features of stage II sleep (sleep spindles and K complexes), and decreased REM percentage – all of which are features of the poor sleep of many critically ill patients.

In addition, many of the commonly used medications associated with delirium – benzodiazepines and opiates, for example – adversely affect sleep architecture by suppressing both slow-wave sleep and REM sleep [44]. Those medications with an anticholinergic effect, if they cross the blood–brain barrier, are highly associated with delirium; and these medications may also have characteristic effects on sleep [46]. Medications with a significant anticholinergic effect, such as tricyclic antidepressants and antihistamines, suppress REM sleep. Other medications commonly used in the ICU and associated with delirium – such as corticosteroids, sympathomimetics, and anticonvulsants – also disrupt sleep [44].

In conclusion, delirium may be caused by numerous and protean insults to peripheral, systemic, and central nervous system function leading to the same final common pathway. It is in this context that sleep deprivation is plausible as a contributing factor in the onset of delirium even in the absence of data definitively establishing it as an independent risk factor (Figure 1).

### **Outcomes of delirium**

The importance of diagnosing and treating delirium is related to its association with adverse outcomes. Numerous studies have confirmed that the development of delirium during a hospital course is associated with increased length of stay in the hospital [7], worse physical and cognitive status upon discharge and for at least 12 months thereafter [26], and a higher mortality [2,4,47]. All clinical delirium variants (that is, hyperactive and hypoactive) have been associated with poorer outcomes relative to those who do not develop delirium [47]. Delirium has also been demonstrated to cause distress among family members and caretakers as well as among those patients with recall of their experience. Patients who developed delirium while in the hospital were more likely to require institutional care following their acute illness, to suffer a decline in their prehospitalization performance status, and to have higher 1-year mortality than a comparable group who did not develop delirium during hospitalization.

Poor neurocognitive outcomes of patients who developed delirium but survived their critical illness have also been demonstrated [29,30]. Some of these patients have demonstrable, long-lasting, possibly permanent deficits after discharge from the hospital. Several investigators have found a higher incidence of dementia in follow-up of patients who became delirious while in the hospital [48]. It is not known, however, whether the delirium itself was the cause, whether delirium exposed a pre-existing tendency toward cognitive impairment, or whether other variables such as medications were responsible for this phenomenon.

The development of delirium is clearly associated with poor short-term and long-term outcomes relative to those patients who do not develop delirium. It is far less clear how to intercede in such a way as to positively affect outcomes. If

**Table 2****Medications that can cause delirium and their effects on sleep**

Medication	Effect
Analgesics	
Opioids	Decreased REM, decreased SWS
Nonsteroidal anti-inflammatory agents	Decreased total sleep time, decreased sleep efficiency
Anesthetics	
Isoflurane	Decreased SWS
Anticholinergics	
Diphenhydramine	Decreased sleep latency, decreased REM
Benzotropine	Decreased REM
Anticonvulsants	
Phenytoin	Sleep fragmentation, increased SWS
Carbamazepine	Decreased REM, increased SWS
Valproic acid	Decreased nocturnal melatonin blood levels
Anti-Parkinson's agents	
Levodopa	At high doses, hallucinations, nightmares
Amantadine	Confusion, hallucinations
Cardiac drugs	
$\beta$ -Blockers	Decreased total sleep time, REM, SWS (lipophilic > nonlipophilic)
Clonidine	Decreased REM
Digitalis	Insomnia, nightmares
Methyldopa	Decreased SWS, increased REM, nightmares
Corticosteroids	
Decreased REM, decreased SWS	
Psychiatric drugs	
Tricyclic antidepressants	Decreased REM
Selective serotonin reuptake inhibitors	Decreased REM, decreased total sleep time
Sedative/hypnotics	
Benzodiazepines	Decreased REM, decreased SWS

REM, rapid eye movement; SWS, slow-wave sleep (stage III/IV).

sleep deprivation does ultimately prove to be a cause of or a contributor to ICU delirium, it would establish its link with these poor ICU outcomes and would intensify the need to create and study intervention protocols designed to facilitate sleep in the ICU.

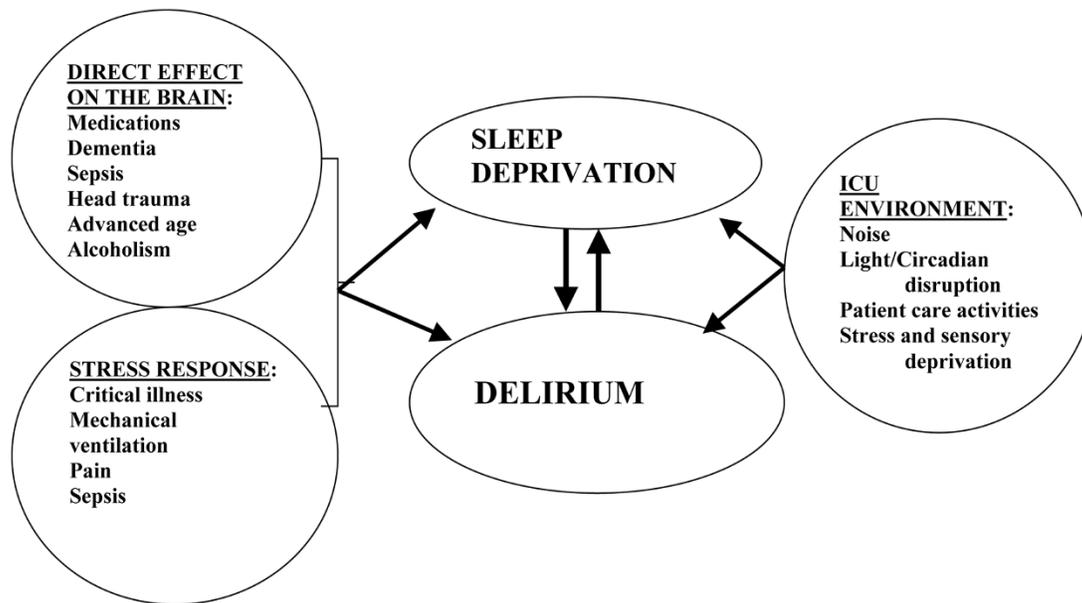
### Management of sleep deprivation

In light of available data, it may be reasonable to conclude that the treatment of sleep deprivation may prevent, shorten, or improve delirium and its medical consequences. Similar to the treatment of delirium, an integrative approach with both pharmacologic and nonpharmacologic strategies should be undertaken to treat sleep deprivation [44]. As with delirium, attention to controlling the patients' environment should include maintaining a quiet, dark room during the night, and

reducing sleep interruptions during the nocturnal hours. During the day, however, light levels should be maintained and patients kept awake if possible as one strategy to consolidate sleep at night.

A review of possible pre-existing sleep disorders and medications that could disrupt sleep should routinely be conducted (Table 2). For patients who require mechanical ventilation, attempts should be made to minimize discomfort, to optimize patient-ventilator synchrony, and to attend to possible central apneas that may occur on pressure support ventilation and proportional assist ventilation as these have also been shown to disrupt sleep [49,50]. For those patients still unable to sleep despite nonpharmacologic means, short-acting hypnotics and sedating antipsychotics and anti-

Figure 1



Delirium and some associated risk factors. A possible relationship between delirium and some of its associated risk factors, including sleep deprivation. ICU, intensive care unit.

depressant medications have been used off-label for this purpose but increase the patients' risk of developing delirium. For those patients who need continuous sedation (that is, those on mechanical ventilation), nocturnal propofol may be a reasonable agent to use – based on some animal studies suggesting that resolution of sleepiness known to occur under natural sleep may also occur under sedation with propofol [51,52]. Studies need to be performed, however, to demonstrate that treating sleep deprivation in ICU patients improves delirium emergence or duration.

**Conclusions**

Delirium is highly prevalent among critically ill patients. Its causes are protean but its manifestations represent dysfunction of specific neurohormonal pathways of the central nervous system. Severe sleep deprivation is an important problem for critically ill patients as it has been shown to have both short-term and long-term effects on patients' quality of life. Sleep deprivation may also be a risk factor for delirium, which would further link it to higher morbidity, mortality, and length of ICU stay. Sleep deprivation research has revealed many similarities, both clinically as well as experimentally, with delirium. These similarities are characterized by poor thought processing, attention and memory deficits, and fluctuating mental status. These findings are consistent with the alterations found on specific regional brain activity both by lesion studies as well as by functional imaging studies that implicate the prefrontal and the nondominant parietal cortices. Animal experiments and some indirect evidence from human

studies suggest a prominent role for the cholinergic and dopaminergic systems, but clearly the neuropathogenesis of delirium and the consequences of sleep deprivation are complicated and probably involve multiple overlapping neurotransmitter circuits and neurohormonal pathways.

The occurrence of delirium has both short-term implications for patients' acute illness as well as long-term implications for patients' recovery and subsequent quality of life. A paucity of sleep for these same critically ill patients denies them an integral homeostatic biologic function essential for life and with putatively restorative function. Sleep deprivation in the ICU is profound and may be a risk factor for delirium. It is important for clinicians to realize, however, that – even without an established link to delirium – sleep deprivation itself is a potentially treatable cause of significant patient discomfort with an established link to adverse ICU quality of life. Accordingly, treatment of sleep deprivation should be considered a comfort measure comparable to pain control and anxiolysis.

It seems likely from the available data, although unproven, that sleep deprivation may play an important role in the pathogenesis of some cases of delirium by affecting those areas of the central nervous system associated with delirium. Prevention or treatment of sleep deprivation may help to prevent or improve ICU delirium and its consequences, but further research is needed to determine the exact role sleep deprivation plays in its pathogenesis.

## Competing interests

The authors declare that they have no competing interests.

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