



## Sleep and Delirium in Older Adults

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### Abstract

**Purpose of Review** Poor sleep and delirium are common in older patients but recognition and management are challenging, particularly in the intensive care unit (ICU) setting. The purpose of this review is to highlight current research on these conditions, their inter-relationship, modes of measurement, and current approaches to management.

**Recent Findings** Sleep deprivation and delirium are closely linked, with shared clinical characteristics, risk factors, and neurochemical abnormalities. Acetylcholine and dopamine are important neurochemicals in the regulation of sleep and wakefulness and their dysregulation has been implicated in development of delirium. In the hospital setting, poor sleep and delirium are associated with adverse outcomes; non-pharmacological interventions are recommended, but tend to be resource intensive and hindered by a lack of reliable sleep measurement tools. Delirium is easier to identify, with validated tools available in both ICU and non-ICU settings; however, an optimal treatment approach remains unclear. Antipsychotics are used widely to prevent and treat delirium, although the efficacy data are equivocal. Bundled non-pharmacologic approaches represent a promising framework for prevention and management.

**Summary** Poor sleep and delirium are common problems in older patients. While these phenomena appear linked, a causal relationship is not clearly established. At present, there are no established sleep-focused guidelines for preventing or treating delirium. Novel interventions are needed that address poor sleep and delirium, particularly in older adults.

**Keywords** Sleep · Delirium · Intensive care · Acetylcholine · Dopamine · Aging

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## Introduction

Over the past two decades, delirium, in particular in older adults ( $\geq 65$  years old) hospitalized in intensive care units (ICUs), has gained substantial attention as a common and major health problem. This attention has been driven, in part, by the rise in the older adult population, combined with an explosion in research highlighting numerous adverse consequences of delirium, including long-term cognitive, physical and mental health impairments, and early death. This knowledge has motivated efforts to better understand and to prevent delirium, highlighting poor sleep, and more specifically sleep/wake disruption, as a common and potentially modifiable risk factor for delirium. Interest is growing in the delirium-sleep/wake relationship, in particular their shared characteristics and mechanisms, bidirectional effects, and impact on outcomes in older adults. This review aims to provide an in-depth overview on this topic, focusing specifically on (1) delirium and (2) poor sleep in older adults; (3) the sleep-delirium connection; (4) tools to evaluate delirium and sleep; and (5) prevention and management of poor sleep and delirium. We conclude by highlighting areas for future research.

## Delirium

### Epidemiology and Consequences

Delirium, an acute, severe neuropsychiatric syndrome characterized by waxing and waning levels of consciousness and periods of inattention and confusion, has gained attention over the past 20 years as a major health problem. A sequela of illness, hospitalization, or post-surgical states, delirium complicates up to 11% of emergency department visits [1], 33% of hospitalizations [2], and 70% of intensive care unit stays among older adults [3]. While predisposing factors such as advanced age, medical comorbidities, and baseline cognitive impairment can predispose patients to delirium, many modifiable precipitating factors also contribute to delirium, including uncontrolled pain, dehydration, and polypharmacy [4, 5]. In hospitalized patients, delirium leads to prolonged length of stay, increased hospital costs [6], long-term cognitive impairments, prolonged institutionalization [7, 8], and early death [9, 10]. Delirium is also costly, accounting for up to \$152 billion in annual US health care expenditures [11]. Due to its short- and long-term consequences and costs, delirium has been identified as a research priority by the American Geriatrics Society (AGS) and National Institute on Aging [12], and a quality-of-care predictor of survival in the Assessing Care of Vulnerable Elders Study (ACOVE) [13].

## Mechanism and Presentation

While delirium is a multifactorial phenomenon, with several proposed pathophysiological mechanisms, mechanistic research has been slow in part due a lack of well-established animal models and an absence of easily obtainable biomarkers [14]. Among the neurological pathways hypothesized to precipitate delirium, one involves the prefrontal cortex, anterior cingulate, and basal ganglia, and another involves the parietal lobes, superior colliculus, and thalamic pulvinar nucleus [15]. More recently, a functional network comprised of several interconnected brain structures has been implicated in delirium [16]. Disturbances in these pathways lead to decreased cholinergic activity and dopaminergic excess, contributing to delirium [17]. The depressed cholinergic activity pathway is supported by the observation that anticholinergic medications precipitate delirium [18, 19], and dopaminergic excess based on the possible therapeutic effect on delirium of haloperidol, a potent dopamine antagonist [20]. Recently, the dopaminergic pathway has been a common target for pharmaceutical trials for delirium treatment and prevention [21]. Besides acetylcholine and dopamine, neurotransmitters serotonin, gamma-aminobutyric-acid (GABA), glutamate, histamine, and norepinephrine are also implicated in delirium, but their mechanisms are not well established [20, 22].

A pro-inflammatory pathway may also contribute to delirium [14], particularly in acutely ill patients with higher levels of inflammatory biomarkers (e.g., cytokines) [23]. Theoretically, this pro-inflammatory state disrupts the blood-brain barrier, leading to tissue edema, neurotransmitter imbalance, and apoptosis leading to cognitive dysfunction [24].

Oxidative stress, another potential mechanism behind delirium, occurs when chronic hypoperfusion leads to a mismatch between oxygen delivery and consumption, leading to a rise in non-oxidative metabolism and accumulation of reactive and potentially toxic oxygen and nitrogen species [14]. Accumulation of these products can damage cerebral tissue, contributing to cerebral dysfunction and manifesting as delirium [25].

Once delirious, patients can exhibit either hyperactive, hypoactive, or mixed motoric subtypes [26]. In the ICU, hypoactive delirium predominates, characterized by reduced psychomotor activity, lethargy, and augmented GABA and melatonin activity [27]. In contrast, depressed GABA and melatonin often occur with hyperactive delirium, characterized by increased psychomotor activity, agitation, disruptive behavior, sleep-wake disruption, and hallucinations [28]. Patients with mixed delirium fluctuate between the hypo- and hyperactive states. Recent research suggests that the hypoactive subtype portends a poor prognosis compared to the hyperactive form [29].

## Delirium in Older Adults

The majority of delirium occurs in older ( $\geq 65$  years old) hospitalized adults, affecting up to 50% [30] and 70% [3] of older non-ICU and ICU patients, respectively. Delirium also commonly affects older patients in non-hospital nursing units and post-acute care facilities [31]. Advanced age is independently associated with delirium in the acute care setting [32], as dementia and mild cognitive impairment are often clinically unrecognized [33]. While the mechanism for increased risk of delirium in older adults is unclear, age-related neurodegeneration and associated alterations in acetylcholine, catecholamine, and serotonin may play a role.

As compared to their younger counterparts, older patients are at risk for worse delirium-associated outcomes [34]. Incident delirium predisposes patients to new and persistent cognitive deficits and can accelerate the development of dementia for those with pre-existing cognitive impairment [35]. In older adults, hospital-associated delirium increases the risk of accidental disruption of life-sustaining therapy (e.g., self-extubation) and longer duration of mechanical ventilation and ICU and hospital length of stay [9, 36, 37]. Decreased ability to perform activities of daily living and loss of functional independence is a common outcome of delirium lasting 5 or more days [8]. Incident delirium also increases the risk of mental health impairments including posttraumatic stress and depression [38]. As a consequence, delirium in older adults, and its associated cognitive, physical, mental health, and quality of life impairments, increases the risk of rehospitalization and early death [39, 40].

## Poor Sleep in Older Adults

The remainder of this review will focus on the relationship of poor sleep, sleep/wake disruption, and delirium in older adults. Under normal circumstances, total sleep time declines until age 60 years, plateauing at 6 to 7 h a night [41]. However, with age, sleep becomes more fragmented, with a rise in N1 and N2 (“light”) sleep and a corresponding decline in slow wave sleep (SWS) and rapid eye movement (REM), stages considered vital for rest and repair [42]. More N1/N2 and less SWS render older adults more susceptible to arousals and awakenings from noxious stimuli such as light, sound, and physical discomforts such as pain or urge to micturate. Hence, up to 50% of older adults experience poor sleep quality [43]. Moreover, approximately 5% of older adults have clinically significant insomnia and 20% have sleep apnea syndromes [44], further contributing to sleep disruption [45]. Finally, older patients with dementia exhibit greater N1 sleep, altered N2 architecture, and decreased SWS and REM compared to non-demented counterparts [44].

## Sleep in Hospitalized Older Adults

For all hospitalized patients, sleep is generally poor quality, with sleep disorders, pain, anxiety, and acute illness representing predisposing factors, and hospital- and care-related disruptions representing precipitating factors [46, 47]. Among modifiable disruptions, hospitalized patients have identified noise (59%), nursing interruptions (30%), uncomfortable beds (18%), bright lights (16%), and unfamiliar surroundings (14%) as common reasons for poor sleep in the hospital [48, 49].

In older hospitalized adults, sleep quality is particularly poor, averaging 2.5 fewer hours than home [50]. Sleep quality is even worse in older patients hospitalized in ICUs, characterized by fragmentation, decreased or absent REM and SWS, preponderance of N1, and predominance during daytime hours [44, 51, 52]. In the ICU environment, frequent loud sounds, patient-care interactions, sleep-altering medications (i.e., sedative infusions), and mechanical ventilation contribute to disrupted sleep [53–56].

While the mechanism is not understood, poor sleep quality during hospitalization has been associated with adverse outcomes in older adults [57]. For example, poor hospital sleep quality is believed to hinder participation in self-care and rehabilitation activities during post-illness recovery [58], increasing older adults’ risk of falls, functional impairment, institutionalization, and early death.

## The Sleep-Delirium Connection

Though causal pathways remain elusive, sleep/wake disruption and delirium are believed to be tightly associated, with a bidirectional relationship that is accentuated with aging. Parallel symptoms have been noted in both sleep-deprived and delirious states, including fluctuating periods of inattention, mental status, and cognitive dysfunction [59, 60]. Attention and memory impairment, two key features of delirium, are also common after partial and total sleep deprivation [61, 62]. Additionally, poor sleep and delirium share many common risk factors, such as uncontrolled pain, stress, prolonged immobility, and acute illness [63]. Among medications, benzodiazepines are independently associated with delirium and disrupt sleep architecture by suppressing SWS and REM [64], with a dose-dependent effect [65]. Anticholinergic medications are also associated with delirium and REM suppression [66].

Despite overlapping factors, strong evidence regarding the association between poor sleep and delirium is lacking, particularly in hospitalized patients. Conflicting findings have been found in critically ill patients; however, studies have been limited substantially by unmeasured confounders and challenges in accurate, large-scale measurement (see Sleep

and Delirium Measurement below) [67]. Perhaps the most compelling ICU study in 27 mechanically ventilated patients demonstrated a significant adjusted association between shorter versus longer REM duration, as measured using polysomnography, and incident delirium [55].

Several studies have evaluated the relationship between the pre-existing sleep disorders syndromes and postoperative delirium (POD). For example, two studies evaluating patients undergoing elective knee [68] and/or hip replacement surgery [69] showed that those with obstructive sleep apnea (OSA), versus those without, were more likely to develop delirium. Similarly, following cardiac surgery, sleep-disordered breathing has been associated with a 6-fold increase in delirium risk [70]. These data were synthesized in a recent systematic review and meta-analysis involving 12 studies, which suggested a pooled odds ratio of POD of 4.75 for patients with OSA, and 5.60 for unspecified sleep disorders [71]. While prior studies on POD were limited by lack of sleep measurement, a recent pilot study involving EEG recordings suggested an association of lower sleep time and higher sleep latency on postoperative day 1 and higher prevalence and severity of POD [72]. The underlying POD-sleep mechanism remains unclear and may involve factors such as hypoxia and stress. Some have speculated that that severe OSA may be associated with reduced cholinergic activity, a known delirium risk factor [19].

Although little mechanistic data exist on poor sleep precipitating delirium, several plausible pathways have been proposed. Sleep deprivation involves various specific areas of the brain, many of which are involved in the pathogenesis of delirium. In healthy volunteers undergoing 24-h sleep deprivation and PET imaging, decreased cerebral metabolism was noted in the prefrontal cortex, thalamus, and posterior parietal cortex, key brain areas involved in delirium [73]. Another study involving EEG demonstrated involvement of the frontal and parietal cortical areas in sleep-deprived subjects [74]. Similarly, from a neurohormonal standpoint, imbalances seen in delirium have been observed during sleep deprivation, including those involving acetylcholine and dopamine [75]. Dopaminergic activity rises after periods of sleep deprivation and is similarly upregulated in delirium [17].

Aside from acetylcholine and dopamine, melatonin and its precursors and breakdown products have received considerable attention in the context of the sleep-delirium relationship. Under normal circumstances, the amino acid tryptophan undergoes conversion to melatonin, and melatonin is subsequently released by the pineal gland in a circadian pattern. Melatonin release is strongly influenced by sleep-wake rhythms and zeitgebers such as ambient light, feeding schedules and social interactions, and tightly intertwines with other vital circadian processes, including rest-activity rhythms and transcription of genes necessary for cell repair, regeneration, and death. In the hospital setting, circadian misalignment is common and is considered a predisposing factor for delirium.

This theory is supported by several studies, including those linking lower tryptophan levels with incident delirium following cardiac surgery [76], and others demonstrating higher delirium incidence in patients with abolished circadian melatonin secretion [77, 78]. Studies evaluating urinary 6-sulphatoxymelatonin (6-SMT), a melatonin breakdown product, demonstrated lower 6-SMT levels in patients with hyperactive delirium and higher levels in hypoactive delirium, suggesting a relationship of melatonin and circadian misalignment with motoric subtypes of delirium [28].

## Tools to Evaluate Sleep and Delirium

Feasible, large-scale modes of evaluation are vital for efforts aimed at better detecting, preventing, and treating poor sleep and delirium, and for future research focusing on the sleep-delirium relationship and associated outcomes. However, as delirium predominantly occurs in the inpatient setting, in particular the ICU, measurement of both delirium and sleep is extremely complicated, hindered by logistical and confounding factors inherent to the busy hospital environment. The primary modes of measurement are summarized below and in Tables 1 and 2.

### Polysomnography

The gold standard for measuring sleep in non-critically ill populations is polysomnography (PSG), which involves electroencephalography, electrooculography, electromyography, respiratory, oxygen saturation, and electrocardiography. Despite its utility, PSG is costly, cumbersome, resource intensive, and prone to electrode dislodgement, particularly in hospitalized or critically ill patients [79]. Additionally, in critically ill patients, the presence of severe sleep fragmentation [80], daytime sleep [53, 81], and atypical EEG patterns [82] makes PSG vulnerable to misinterpretation using traditional scoring criteria. For example, sleep spindles, which characterize N2 sleep, commonly occur with administration of benzodiazepines, while delta wave activity (as seen in SWS (N3)) can be seen in the setting of encephalopathy (i.e., secondary to toxic-metabolic disturbances or hepatic dysfunction). Hence, traditional sleep staging should be applied cautiously in ICU patients. An ICU-specific PSG scoring algorithm has been proposed but has yet to gain widespread use [82, 83].

### Electroencephalography and Odds Ratio Product

Electroencephalography (EEG) utilizes scalp electrodes to measure brain activity, without EMG, EOG, and other monitors, and is therefore less cumbersome than PSG [84]. In non-critically ill patients, EEG and PSG are highly sensitive and specific for delineating wake versus sleep, with EEG lacking

**Table 1** Sleep assessment methods

Sleep assessment tool	Validated against PSG	Description	Ratings done by	Advantages	Disadvantages
May also have utility in evaluating sleep during delirium Polysomnography (PSG) [53, 79, 80, 82, 83]		Multimodal tool involving electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), respiratory effort, oxygen saturation, and electrocardiography	Data analyzed by computers in real time, confirmed by non-critically ill patients experts	Gold standard to sleep/wake and sleep stage evaluation in non-critically ill patients Objective Can aid in diagnosis of sleep disorders	Cumbersome, costly, resource intensive, and prone to dislodgement in hospitalized or critically ill patients Vulnerable to misinterpretation in hospitalized patients
EEG [84, 85]	Yes	Utilizes numerous scalp leads to measure brain activity; does not include EMG, EOG	Data analyzed by computers in real time, confirmed by experts	High sensitivity and specificity for sleep-wake determination Objective Validated in ambulatory patients	Interpretation in critically ill patients challenging due to factors (i.e., sedatives) which can affect the EEG pattern Lacks specificity in sleep stage differentiation Same interpretation challenges of EEG interpretation
Odds ratio product (ORP) [86, 87] Actigraphy [89–93]	Yes Yes	EEG-derived continuous estimate of sleep depth, ranging from 0 (deep sleep) to 2.5 (fully awake) Accelerometer-based device (often a wristwatch) which measures patient activity	Activity data analyzed by computer algorithm, used to determine sleep-wake	Surrogate for sleep-wake measurement in community settings Noninvasive	Overestimation of “sleep” in mostly inactive hospitalized and/or critically ill patients
Do not have utility in evaluating sleep during delirium Richards-Campbell Sleep Questionnaire (RCSQ) [94–97]	Yes	Subjective assessment involving 100 mm visual analogue scale to assess 5 domains of sleep: depth, latency, efficiency, quality, and number of awakenings	Proxies can complete if patients are unable	Brief Easy to administer Inexpensive Can be administered repeatedly	Infeasible in cognitively impaired (e.g., delirious) patients Nurse proxies may overestimate patients’ sleep quality
Leeds Sleep Evaluation Questionnaire (LSEQ) [99] Verran/Snyder-Halpern Sleep Scale [98]	No No	Subjective assessment involving 10,100 mm visual analogue scales related to falling asleep, sleep quality, awakenings, daytime alertness, feelings, and balance Subjective assessment of sleep over the previous three nights, two visual analogue scales evaluating sleep: disturbance and effectiveness	Completed by patients Completed by patients	Brief Easy to administer Inexpensive Takes longer time to complete than RCSQ	Infeasible in cognitively impaired (e.g., delirious) patients Not validated against PSG Infeasible in cognitively impaired (e.g., delirious) patients Validated for ages 20–78 years with no history of sleep difficulties
Sleep in Intensive Care Unit Questionnaire (SICUQ) [54]	No	Subjective 27-item evaluation of sleep quality at home and the ICU environment, on Likert scales of 1–10, with questions about disruptiveness of ICU activities and noises	Completed by patients	Compares subjective assessment of sleep in ICU and at home	Infeasible in cognitively impaired (e.g., delirious) patients Does not account for severity of illness or medication use
Saint Mary’s Hospital Sleep Questionnaires (SMHSQ) [100]	No	Subjective 14-item evaluation of sleep in the hospital	Completed by patients	Designed for repeated use	Takes longer to complete Low internal consistency

PSG polysomnography, EEG electroencephalography, EOG electrooculography, EMG electromyography, ORP odds ratio product, RCSQ Richards-Campbell Sleep Questionnaire, LSEQ Leeds Sleep Evaluation Questionnaire, VSH Verran/Snyder-Halpern Sleep Scale, SICUQ Sleep in Intensive Care Unit Questionnaire, SMHSQ Saint Mary’s Hospital Sleep Questionnaires

**Table 2** Delirium assessment methods

Delirium screening tool	Criteria on which Scale was based	Number of items	Time to complete (minutes)	Ratings done by
CAM-ICU [102]	DSM-IV	9	≤ 2	Trained health professional
ICDSC [103]	DSM-IV	8	7–10	Non-specialist staff
DRS-R-98 (106)	DSM-IV	16	10	Psychiatrists
NEECHAM Confusion Scale [107]	Research	9	10	Nurses
Delirium Observation Screening Scale [108]	DSM-IV	25	5–10	Research Assistant
Nursing Delirium Screening Scale [109]	Research	5	1	Nurses

*CAM-ICU* Confusion Assessment Method for the ICU, *DSM* Diagnostic and Statistical Manual for Mental Disorders, *ICDSC* Intensive Care Delirium Screening Checklist, *DRS-R-98* Delirium Rating Scale-Revised 98, *NEECHAM* Neelon-Champagne

specificity for differentiating sleep stages [85]. In critically ill patients, EEG interpretation is especially challenging, due to marked sleep-wave fragmentation, artifact, and alteration of normal signals by common ICU issues such as sedation and illness itself.

EEG recordings have also been used to calculate an odds ratio product (ORP), a continuous estimate of sleep depth validated in ambulatory and ICU patients [86, 87]. The ORP ranges from 0 (deeply asleep) to 2.5 (fully awake), with ORP < 1.0 predicting sleep and > 2.0 predicting wakefulness [87]. ORP can help differentiate sleep and wake, and was used in a recent study to demonstrate that increased wakefulness and right-left hemisphere ORP concordance can predict extubation success in mechanically ventilated patients [87]. However, ORP-based sleep stage determination in hospitalized patients is limited by substantial interrater variability, similar to EEG.

In patients with delirium, EEG tends to demonstrate background slowing and increased spectral variability with periodic discharges such as triphasic waves and polymorphic delta activity [88]. Similar patterns can also be seen in non-convulsive status epilepticus (NCSE), a mimicker of delirium [88].

## Actigraphy

Actigraphy involves an accelerometer, usually housed in a wristwatch-type interface, to measure activity levels. Computer algorithms are then applied to activity data to determine sleep and wake. In community-dwelling adults, actigraphy has been validated to measure sleep [89], but has been shown to overestimate sleep in mostly inactive critically ill patients [90, 91]. However, given its minimal invasiveness, long battery life, and low cost, actigraphy has potential for large-scale, long-term sleep estimation in hospitalized patients [92, 93]. However, similar to PSG, hospital- and ICU-specific

interpretation algorithms are needed before actigraphy can be used widely in the inpatient setting.

## Questionnaires

Unlike objective modes of sleep evaluation, questionnaires, though subjective, are feasible to perform on a large scale. Specifically, the Richards-Campbell Sleep Questionnaire (RCSQ), a 5-item instrument evaluating sleep depth, latency, efficiency, quality, and number of awakenings, has been validated against PSG in critically ill patients [94]. While the RCSQ has been used in several ICU-based studies to evaluate sleep, and the impact of interventions to improve sleep [95, 96], it must be completed by an alert patient, thus limiting its utility in the context of delirium. Bedside staff (i.e., nurses) can complete the RCSQ on their patients' behalf, but have been shown to overestimate patient sleep quality [97]; hence, proxy completion should be performed with caution. Other subjective methods of assessing sleep are available and include the Verran/Snyder-Halpern Sleep Scale [98], Leeds Sleep Evaluation Questionnaire (LSEQ) [99], Sleep in the Intensive Care Unit Questionnaire (SICUQ) [54], and Saint Mary's Hospital Sleep Questionnaires (SMHSQ) [100] (Table 1).

## Delirium Assessment Methods

In the inpatient setting, delirium frequently goes unrecognized. Validated delirium assessment tools are essential for prompt identification and management of delirium. The Society for Critical Care Medicine (SCCM) Pain, Agitation, Delirium, Immobility and Sleep Disruption (PADIS) guidelines recommend routine screening for delirium in the ICU setting [101]. These guidelines recommend two delirium screening tools: Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) [102] and Intensive Care Delirium Screening Checklist (ICDSC) [103]. Both screening

tools involve a consciousness assessment using a standardized scale, such as Richmond Agitation Sedation Scale [104], followed by CAM-ICU or ICDSC items. The CAM-ICU involves 4 domains and takes  $\leq 2$  min to perform at the bedside, while the ICDSC involves 8 domains, 4 for current delirium symptoms and the other 4 comparing present symptoms against the previous nursing shift [105]. For patients not admitted to the ICU, the Confusion Assessment Method (CAM), which laid the foundation for the CAM-ICU, can be utilized. Other less-utilized delirium tools include the Delirium Rating Scale-Revised (DRS-R-98) [106], Neelon-Champagne (NEECHAM) Confusion Scale [107], Delirium Observation Scale [108], and Nursing Delirium Screening Scale (Table 2) [105, 109].

## Prevention and Management of Poor Sleep and Delirium

Managing poor sleep in the hospital is challenging, particularly in older adults, but may help with delirium prevention. It is widely believed that any interventions to improve sleep should involve a multifaceted, interdisciplinary approach [110]. In a recent systematic review of sleep-focused ICU interventions to improve delirium, 6 of 10 studies reported statistically significant reductions in delirium incidence, while 3 showed a reduction in delirium duration [111]. Both pharmacologic and non-pharmacologic interventions can be employed, with minimization of sleep-disrupting medications as an important cornerstone of treatment.

Non-pharmacologic interventions to improve sleep include environmental optimization and relaxation techniques. While non-pharmacologic strategies can be resource intensive and require rigorous implementation methods to maintain sustainability, they are generally safe, low cost, and have limited side effects. Buy-in from hospital systems can be difficult, given inherent challenges in measuring improvements in sleep, and a lack of data on sleep interventions leading to improved outcomes. Data are also mixed regarding specific non-pharmacologic sleep promoting interventions in non-ICU hospitalized patients, as noted in a recent systematic review of 13 studies. More specifically, in this systematic review, 8 interventions involving relaxation techniques (4 RCTs) demonstrated a 0–38% improvement in sleep quality, 3 involving daytime bright light a 7–18% improvement, and two involving a sleep hygiene intervention a 0–5% improvement [112]. However, 11 of these 13 studies had a medium to high risk of bias (e.g., were limited by sampling error or selection, detection, and/or performance bias). From an environmental standpoint, noise minimization has been shown to improve subjective sleep quality ratings and includes staff-wide behavioral modification, use of ear plugs with or without eye masks, white noise, and soundproof material [113]. Daytime mobility

interventions may also help with delirium prevention and may also help promote nighttime sleep, though evidence is lacking to support this notion [114, 115].

After non-pharmacological interventions are attempted, pharmacologic strategies to promote sleep can be considered. A key first step in this approach is the discontinuation of sleep-disrupting and/or deliriogenic medications. The American Geriatric Society Beers criteria for inappropriate medications in older adults can help identify many of these medications [116] (Table 3). In the area of delirium prevention, there is substantial interest in the role of antipsychotics; however, efficacy data are equivocal [117]. More specifically, a recent RCT examined the use of haloperidol for delirium prophylaxis showed no decrease in delirium incidence and no improvement in overall mortality [118]. Subsequently, another RCT examining the effect of haloperidol or ziprasidone versus placebo on ICU delirium found no difference in delirium-free days [21]. While recent guidelines make no recommendation regarding antipsychotics for the prevention or treatment of delirium [117], these medications may be reasonable to administer in the setting of agitation with the risk of staff or patient harm.

Aside from antipsychotics, other pharmacologic strategies to improve both sleep and delirium are being investigated. Specifically, a recent study evaluated low-dose nocturnal dexmedetomidine (an  $\alpha$ -2 agonist with sedative, hypnotic and analgesic properties) in mostly mechanically ventilated ICU patients had mixed results, with improvements in delirium incidence but no improvement in sleep quality [119]. Additionally, melatonin and melatonin receptor agonists are gaining attention, in part due to their favorable side-effect profile and role in re-entraining circadian rhythms [120]. Despite this attention, a Cochrane review involving 4 randomized trials and 151 participants found insufficient evidence to conclude that melatonin improves the quality and quantity of sleep in patients hospitalized in ICUs [120]. Regardless of equivocal supporting evidence, pharmacologic strategies remain a compelling area of investigation.

Whether non-pharmacological only, or combined with pharmacological interventions, a multicomponent, bundled approach is recommended for sleep and delirium improvement [95, 96, 110]. Among recent interventions, the ICU-focused “ABCDEF” bundle (Assess, Prevent and Manage Pain; Both Spontaneous Awakening and Breathing Trials; Choice of Analgesia and Sedation; Delirium Assessment, Prevention, and Management; Early Mobility and Exercise; Family Engagement/Empowerment) has gained popularity and has been associated with reductions in delirium, ventilator days, and ICU readmissions [121, 122]. Alternatively, the eCASH (Early Implementation of Comfort and Analgesia using Minimal Sedation and Humane care) concept, derived from the Pain, Agitation and Delirium guidelines, is a new approach to improve outcomes of patients in ICU [123].

**Table 3** Medications commonly used to promote sleep in hospitalized patients [58, 64, 124–126]

Medication	Mechanism of action	Route of administration	Side effects	Sleep effects	Risk of delirium in older adults
<b>Listed under Beers criteria</b>					
Opiates [127–129]	CNS opioid receptor agonist	Oral or intravenous	Dependency, hypotension, respiratory depression, withdrawal	↓N3, ↓REM, ↓TST, ↑W	↑
Atypical antipsychotics [130, 131]	5HT <sub>2</sub> D <sub>2</sub> -receptor antagonist	Oral	Dizziness, extrapyramidal symptoms, neuroleptic malignant syndrome, orthostatic hypotension	↑N3, +/-↑REM, ↑SE, ↓SL, ↑TST, ↓W	No change
Typical antipsychotics [130, 131]	Dopamine receptor antagonist	Oral or intravenous	Anticholinergic effects, extrapyramidal symptoms, neuroleptic malignant syndrome, QT prolongation, tardive dyskinesia	↑N2, ↑N3, ↑SE, ↓SL, ↑TST, ↓W	No change
Trazodone [132, 133]	Serotonin reuptake inhibitor, 5-HT <sub>1A</sub> , 1C <sub>2</sub> ; H <sub>1</sub> receptor antagonist	Oral	Anticholinergic syndrome, arrhythmias, orthostatic hypotension	↑N3, ↑REM, +/-↑SE, ↓SL	+/-↑
Antihistamines [133]	H <sub>1</sub> -receptor antagonist	Oral or intravenous	Anticholinergic syndrome, dizziness, impaired coordination	+/-↑N3, ↓REM, +/-↑SE, ↓SL	↑
Benzodiazepines [3, 134–136]	GABA receptor agonist	Oral or intravenous	Dependency, delirigenic, dizziness, hypotension, withdrawal	↓N3, ↓REM, ↓SL, ↑TST, ↓W	↑
Non-benzodiazepine hypnotics [137]	GABA receptor agonist	Oral	Daytime somnolence, dizziness, confusion	↓N2, ↓N3, ↑REM, ↓SL ↑TST, ↓W	↑
<b>Not listed under Beers criteria</b>					
Dexmedetomidine [136, 138]	α <sub>2</sub> -Agonist	Intravenous	Bradycardia, hypotension	↑N2 with sleep spindles, +/-↑N3/SWS, ↓REM, ↓SE, ↓SL	↓
Propofol [139, 140]	GABA receptor agonist	Intravenous	Bradycardia, hypotension, propofol infusion syndrome, respiratory depression	↓REM, ↓SL, ↑TST, ↓W	↑
Melatonin and melatonin receptor agonists [141–145]	Melatonin 1 and 2 receptor agonist	Oral	Dizziness, hallucinations, nausea, vivid dreams	↑SE, ↓SL, ↑ TST	↓

SWS slow wave sleep, REM rapid eye movement, SE sleep efficiency, SL sleep latency, TST total sleep time, W wake  
 ↓ = decreased; ↑ = increased; ↑↓ = equivocal; +/-↑ = may increase; +/-↓ = may decrease



Sleep promotion is one of many components embedded within these bundles, making them particularly attractive options for intervention efforts aimed at improving sleep and delirium in hospitalized older adults. Implementing and sustaining such bundles is challenging and requires buy-in from staff and leadership, dedicated champions, an interdisciplinary team, and audit-and-feedback methods. Ongoing investigations are needed to evaluate, refine, and reproduce these invention bundles.

## Conclusions

As evidence grows regarding the benefits of multicomponent interventions to improve sleep and delirium in inpatient settings, methods for intervention implementation into routine care will need to be studied. Furthermore, mechanistic research on how poor sleep or sleep/wake disruption, particularly among older adults, may lead to delirium will increase the utility of sleep-related delirium prevention efforts. Finally, larger studies are needed to evaluate the risks and potential benefits of medications and medication deprescribing in hospitalized older patients at risk for poor sleep and delirium.

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## Compliance with Ethical Standards

**Conflict of Interest** None.

**Human and Animal Rights** This article does not contain any studies with human or animal subjects performed by any of the authors.

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