

# Does improving sleep for the critically ill reduce the incidence and duration of delirium? An evidence-based review

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## Abstract

Delirium is associated with poor patient outcome. Critical-care nurses maintain that patients with disrupted sleep appear to develop delirium. We sought to explore whether improving sleep in the critically ill patients reduced the incidence and duration of delirium. Our review of five relevant studies suggests that there is low-quality evidence that improving sleep may reduce the incidence of delirium. The bidirectional association between delirium and sleep stymies research in this area, and thus, establishing cause and effect, is difficult. Research exploring other patient-centred outcomes, such as pain intensity, suggests that enhancing sleep may improve these outcomes.

## KEYWORDS

critical illness, delirium, sleep

## 1 | BACKGROUND AND CLINICAL QUESTION

Delirium, regardless of type, is associated with poor patient outcomes including increased long-term morbidity and mortality.<sup>1</sup> The behavioural manifestations of hyperactive delirium variants, such as agitation and unintentional self-harm, can also be challenging, often requiring the continuous presence of nurses to maintain safety. In addition, there is evidence that atypical sleep, that is, polysomnography data containing the absence of the characteristics of healthy sleep, for example, no K complexes or sleep spindles, is associated with an increased risk of mortality in critically ill patients.<sup>2</sup>

Critically ill patients frequently experience disruption and poor sleep quality.<sup>3</sup> Anecdotally, critical care nurses maintain that patients with disrupted sleep appear to be more likely to develop delirium. Furthermore, nurses recognize that their efforts to promote night-time sleep appears to prevent delirium.<sup>4</sup> This theory has biological plausibility and provide

clinical evidence. For example, sleep disturbance due to increased sleep pressure often results in features of hypoactive delirium, such as daytime somnolence, which is characterized by inattention and altered mood and circadian rhythm. The postulated neurotransmitter pathways and brain centres affected by delirium are central to sleep homeostasis and circadian rhythmicity.<sup>5,6</sup> However, it should be noted that this effect is likely bidirectional. Delirium adversely affects sleep homeostasis and circadian rhythms, and disrupted sleep/circadian rhythms contribute to the risk of developing delirium. Clinical evidence of this association in critically ill patients was highlighted in a small study conducted in a medical ICU ( $n = 23$ ).<sup>7</sup> Patients without stage 2 non-rapid eye movement sleep had clinical evidence of delirium. In addition, a meta-analysis revealed a strong association between preoperative sleep disturbance and postoperative delirium; patients were more likely to have postoperative delirium if they had preoperative sleep disturbance.<sup>8</sup> Thus, we strove to explore whether improving sleep quality for the critically ill reduces the incidence and duration of delirium.

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## 2 | SEARCH STRATEGY

Prior to conducting the search, keywords and medical subject heading (MESH) terms were identified with the assistance of a health librarian. Three electronic databases were searched, Embase, Medline and PsychINFO, using the following keywords: critical ill, circadian rhythm, sleep wake cycle, sleep intervention, sleep habit, diurnal rhythm and sleep wake disorder. The MESH terms were critical illness, critical care, intensive care, delirium, sleep hygiene and sleep disorders. The search included any papers that would help address the review question and potentially provide insights into cause and effect; thus, interventional study reports were included. We did not include studies reporting observational studies or reviews as these were less likely to shed light on the effect of improving sleep on the incidence of delirium.

We included four other papers obtained from a manual search that were not revealed in the database search. There were 114 relevant records including more than 20 conference abstracts. After examining the titles and abstracts, five relevant and recently published papers were found to be suitable for addressing our review question. Therefore, this review is based on five papers. Details are presented in Table 1.

## 3 | REVIEW OF THE EVIDENCE

Four papers reported prospective before-after studies, and one reported a randomized controlled trial (RCT) of the effectiveness of melatonin on delirium and sleep. All studies were conducted using subjective sleep assessments, including the Richard Campbell Sleep Questionnaire (RCSQ).<sup>11</sup> Delirium was identified in four studies using the Confusion Assessment Method-ICU (CAM-ICU)<sup>14</sup> and the Intensive Care Delirium Screening Checklist (ICDSC)<sup>15</sup> in one study.

The RCSQ is a subjective sleep assessment instrument widely used in acute care settings. It was originally validated in a population of male veterans using PSG.<sup>11</sup> The original RCSQ contained five visual analogue scales [VAS] (0–100 mm, where 100 mm is the best sleep possible) representing sleep domains, sleep depth, ability to go to sleep, ability to return to sleep after waking, sleep disturbance and overall quality of sleep. Global sleep quality is the average of the VAS scores. Cut-off scores for healthy sleep (population norms) have not yet been established, but there is beginning evidence that a score of 63 mm is a reliable cut-off score for good-quality sleep.<sup>16</sup>

Darby et al.<sup>9</sup> reported a prospective quality improvement study in which data were collected for delirium-free days (1 [IQR 0–2.5] vs. 1 [0–2]) and RCSQ (59.4 [IQR 43.2–71.6] vs. 61.2 [49.9–75.5] mm) before and after the implementation of a multicomponent staged sleep protocol revealed no change in delirium and sleep outcomes. In this study, confounding factors were not controlled for in the analysis; the intervention was incremental (only patients who continued to experience poor sleep received interventions included in the additional stages, such as eye masks and melatonin) and stage 3 interventions included the administration of antipsychotics.

### What is known about the topic

- Anecdotally nurses have always acknowledged that disrupted sleep was a potential delirium risk factor. This is not surprising since postulated neurotransmitter pathways and brain centres affected during delirium are central to sleep homeostasis and circadian rhythmicity.

### What this paper adds

- Studies suggest a need to greatly improve practice focused on creating the conditions for nocturnal rest, sleep and healthy circadian rhythms, and thus reduce the risk of delirium.
- Delirium experts agree that measures to promote and maintain sleep may reduce the likelihood of delirium, and have other beneficial outcomes such as reduced pain intensity and stress and increased patient satisfaction.

After the implementation of a not dissimilar study by Patel et al.<sup>10</sup> patients reported an increase in sleep quality (pre:  $60.8 \pm 3.5$  vs. post:  $75.9 \pm 2.24$  mm) and the incidence of delirium was lower (pre: 33 % [ $n = 55/167$ ] vs. post: 14 % [ $n = 24/171$ ]). In this study the difference between nocturnal mean light and sound levels and compliance measured before and after the implementation of the intervention indicated that clinicians adopted many components (sound pre:  $68.8 \pm 4.2$  dB vs. post:  $61.8 \pm 9.1$  dB; light levels pre:  $594 \pm 88.2$  lux vs. post:  $301 \pm 53.5$  lux). However, the study pre- and post-phases were relatively short (4 weeks), and it is unclear if this change was sustained. The analyses were not longitudinal, and RCSQ data for each patient was only included for one night.

The prospective before-after study by Tonna et al.,<sup>12</sup> in which a multicomponent intervention was tested, revealed a reduced prevalence of delirium (mean proportion of positive CAM-ICU assessments over the first 14 days in the ICU ( $20 \pm 31\%$  vs.  $15 \pm 28\%$ ) and time to first CAM-ICU positive assessment). However, there was no difference in the overall median sleep quality-adjusted difference (3.4 [95CI:  $-5.2$  to  $11.5$ ] mm). The compliance rates with most components of the intervention were close to 100%, except for eye mask use, which was only 2%.

There was a significant reduction in the incidence of delirium between the pre- and post-intervention periods ( $-3.7\%$ ,  $p = 0.02$ ) but no difference in the incidence of delirium ( $22\%$ – $36\%$  vs.  $12\%$ – $43\%$ ) in the prospective before-after study conducted by van de Pol et al.<sup>17</sup> In this study, a nocturnal-sound reduction protocol was implemented to reduce the incidence of delirium and improve the sleep quality of intensive care patients. Despite the reduced trend in delirium incidence, there was no difference in mean sleep quality over time ( $-2.89$  mm) and no difference in mean sleep quality between the pre- and post-intervention time periods ( $48$ – $59$  mm vs.  $49$ – $70$  mm).

TABLE 1 Evidence table.

Study	Aim and method	Sample and key results	Strengths	Limitations
Darby et al. <sup>9</sup>	To quantify the effect of a multicomponent sleep protocol on delirium-free days, RCSQ score, "optimal sleep nights", duration of mechanical ventilation, ICU and hospital length of stay and in-hospital mortality. Prospective before-after quality improvement project. The unit-wide protocol comprised three incremental stages "optimize sleep hygiene", "non-pharmacologic interventions" and 'pharmacologic interventions' including melatonin. Measures included RCSQ and CAM-ICU	Pre = 78 Post = 84, >50% male, median age 59 years, 1/3rd respiratory diagnoses. No difference in the median number of delirium-free days (1 [IQR 0–2.5] vs. 1 [0–2]) or median RCSQ score (59.4 [IQR 43.2–71.6] vs. 61.2 [49.9–75.5] mm) after the implementation of the protocol. Clinically and statistically significant decreases in median duration of mechanical ventilation and hospital length of stay.	Study conducted in the real-world. Included large number of sleep protocol days (Pre = 308 days Post = 295 days). Compliance with intervention measured. Collected data for administration of medications: melatonin, benzodiazepines, opioids, antipsychotics, dexmedetomidine and propofol.	Quality improvement methodology so potential confounding factors were not controlled. Protocol included administration of anti-psychotics for delirium (no evidence for effectiveness) and administration of these was not different after the sleep protocol was implemented (i.e., did not decline).
Patel et al. <sup>10</sup>	To reduce the incidence of sleep deprivation and delirium using a non-pharmacological intervention. Prospective before-after quality improvement project. The intervention comprised environmental control measures such as dimming light at night and minimizing unnecessary sound and clustering care, offering eye masks and mobilizing. Measures included RCSQ and CAM-ICU. SICQ administered when patients left ICU.	Pre = 167 Post = 171 RCSQ completed for 30 pre and 29 post-intervention. 50% male, mean age 60 years, 30%–40% of completed RCSQ patients with surgical diagnoses. Mean RCSQ in the Pre = 60.8 ± 3.5 vs. Post = 75.9 ± 2.24, ( $p < 0.001$ ) and number of nights with 3-h periods of uninterrupted sleep was higher post intervention (32% vs. 39%, $p = 0.029$ ). Incidence of delirium lower post intervention (33% [ $n = 55/167$ ] vs. 14% [ $n = 24/171$ ], $p = 0.001$ ).	Compliance with intervention measured. Measured light and sound levels.	Data collected for 4 weeks before and 4 weeks after implementation of the intervention. Data for one RCSQ for each patient randomly selected (completed at different times during their ICU stay). Simplistic analysis. Analyses did not control for changes over time. Used the RCSQ mean score to estimate sleep efficiency (Richards <sup>11</sup> used a formula that is, $= 46.88 + [0.39 \times \text{RCSCQ}]$ )
Tonna et al. <sup>12</sup>	To improve delirium and sleep-wake disruption. Prospective before-after quality improvement project. Intervention included encouraging circadian activity, optimizing conditions conducive to nocturnal sleep, minimizing administration of medications to induce sleep and maximize environmental conditions. Measures included RCSQ and CAM-ICU	Pre = 332 Post = 314, >60% male, median age 61 years, >70% surgical (cardiovascular). No difference in median number of days CAM-ICU positive, (3 [IQR, 2–5] days pre intervention vs. 3 [IQR: 2–6 days] days post intervention; $p = 0.22$ ). Reduced prevalence of delirium, that is, mean proportion of positive CAM-ICU assessments (20 ± 31% vs. 15 ± 28%; $p = 0.02$ ) and time to first CAM-ICU positive assessment. No difference in overall median sleep quality (52 [IQR: 37–69]	Compliance with intervention measured. Sleep medication administration including melatonin collected in the postintervention period. Extensive analyses controlled for many factors including time.	Nurses completed RCSQ on behalf of patients if they were delirious (69% of the RCSQ data).

TABLE 1 (Continued)

Study	Aim and method	Sample and key results	Strengths	Limitations
		mm vs. 55 [IQR: 41–69] mm; adjusted difference, 3.4 [95CI: –5.2 to 11.5] mm; $p = 0.43$ ). Sensitivity analyses revealed that the intervention was associated with a reduced hazard of delirium especially for operative patients.		
van de Pol et al. <sup>17</sup>	To measure the effect of a nocturnal sound-reduction protocol on the incidence of delirium and the quality of sleep in critically-ill patients admitted to ICU. Prospective before-after improvement project including interrupted time series analysis. Intervention included limiting staff conversations, shutting doors, clustering care and providing ear plugs. Measures included RCSQ and ICDSC	Pre = 211 Post = 210 >50% male, >70% surgical and median age 68–69 years Significant reduced trend in delirium between pre- and post-intervention periods ( $-3.7\%$ , $p = 0.02$ ) but no difference in the incidence of delirium (22%–36% vs. 12%–43%). No difference in trend means sleep quality over time ( $-2.89$ , $p = 0.64$ ) and no difference in mean sleep quality between pre and post intervention time periods (48–59 mm vs. 49–70 mm). Perception of nocturnal noise was lower after the intervention (70, IQR: 60–80, $p = 60$ –80 vs. 65 IQR: 50–80, $p = 0.01$ ).	Interrupted time series analysis controlled for changes in the variables of interest over time. Measured sound levels after the intervention, collected data for perceived noise, and sleep-inducing and delirium-treating medication administrations.	Sample size not explained (method of estimating not included). Cohorts taken from short time frame and thus variation in characteristics such as type of admission and related variables.
Wibrow et al. <sup>13</sup>	To determine the effect of melatonin when given early on delirium prevalence in critically ill patients and indirect benefits of melatonin on sleep. Multicentre, RCT, double-blind trial. Intervention 4 mg melatonin or placebo enterally for 14 nights in ICU or until discharge. Measures included RCSQ, Little's questionnaire, "observed sleep" and the CAM-ICU.	Melatonin = 419 placebo = 422 60% male, 50% respiratory/cardiac diagnoses, mean age 62 years. No difference between groups for mean number of delirium positive assessments (melatonin $79.4 \pm 33.6\%$ vs. placebo $80.0 \pm 33.5\%$ , $p = 0.547$ ). Longitudinal analyses revealed no significant differences between groups for delirium outcomes either. No difference in sleep quality and quantity	Randomisation to treatment conducted centrally. Allocation concealment and masking maintained for clinicians, investigators and statisticians. Intent to treat analysis. Few missing doses of melatonin.	79% of RCSQs administered by nurses. The reliability of sleep quality assessed by proxy is known to be poor. "Observed sleep" not defined and therefore reliability of "estimated sleep hours" uncertain.

Abbreviations: CAM-ICU, confusion assessment method-ICU; ICDSC, intensive care delirium screening checklist; ICU, intensive care unit; RCSQ, richards campbell sleep questionnaire (0–100 mm, the higher the better quality the sleep); SICQ, sleep in intensive care questionnaire.

However, the patient's perception of nocturnal noise was lower after the intervention (70, IQR: 60–80, 60–80 vs. 65 IQR: 50–80 mm).

The only RCT<sup>13</sup> revealed no significant effect of 4 mg melatonin administered enterally on the prevalence of delirium (79% vs. 80%) and secondary outcomes including the quality ( $59 \pm 26$  vs. 58

$\pm 26$  mm) and quantity ( $3.8 \pm 2.9$  vs.  $3.9 \pm 3.4$  h) of sleep in adult patients treated in 12 ICUs. The study design was rigorous, including allocation concealment, computer randomisation, placebo-control and double-blinding. However, up to 79% of all the RCSQs were completed by nurses.

In summary, these five studies provided low-quality evidence that improving sleep for the critically ill reduces the incidence and duration of delirium and highlights the difficulty in researching sleep and delirium. Both sleep and delirium are challenging to measure and their bidirectional relationship complicates the establishment of cause and effect. PSG data are often not interpretable because many critically ill people have atypical sleep, and subjective sleep measures have recognized limitations, such as the need for adequate cognitive acumen. In addition, it is known that reliability is low when subjective assessments are administered by a proxy (e.g., Wibrow et al.<sup>13</sup>). Estimations of sleep duration are notoriously divergent (often underestimated by the participant and overestimated by the observer). Delirium assessment is a challenging task. Delirium is identified from behavioural signs which may fluctuate presenting problems quantifying it, thus “delirium free days” (e.g., Darby et al.<sup>9</sup>) is probably a better metric than others such as the number of positive assessments (e.g., Tonna et al.<sup>12</sup>). In addition, many, often similar, factors impact on both sleep and delirium such as the environmental conditions (sound and light levels), model of care including family/person centredness and diagnosis (case mix). These factors are challenging to control, and thus, there is a need for much larger multicentre cluster RCTs. Research and practice to improve sleep in critical care requires the same priority as research and practice to optimize nutrition. Arguably, the huge improvements in the provision of nutrition in critical care require over the past decades can be largely attributed to the resources invested in performing large multicentre controlled trials.

## 4 | IMPLEMENTATION INTO PRACTICE

This brief examination of research evidence suggests that promoting sleep for the critically ill may reduce the incidence and prevalence of delirium. However, the level of evidence for this is low.

As stated previously, the association between sleep disruption and delirium has been established and is partly attributed to shared brain pathways. The association is bidirectional, and thus, cause and effect are difficult to establish. These studies highlight the difficulties in investigating bidirectionally associated outcomes. The inability to identify cause and effect greatly stymies attempts to develop effective interventions. Of note, all the studies except the RCT tested multicomponent interventions and compliance data were not collected for all studies; thus, even if the interventions were effective, the dose and component of the intervention that was most effective was unclear.

Only subjective sleep measures were used to measure sleep and polysomnography (PSG) was not used in any of the studies. However, the rationale for not using PSG may have been resource limitations and the knowledge that critically ill people often experience atypical sleep patterns. Specifically, EEG does not contain characteristics of healthy sleep, for example, few of the features of stage 2 sleep (no K complexes or sleep spindles) and rapid eye movement sleep.<sup>2,18,19</sup>

Despite the lack of strong research evidence indicating that efforts to improve sleep in critically ill patients reduce the incidence and duration of delirium, experts agree that measures to promote and

maintain sleep may reduce the likelihood of delirium and have other beneficial outcomes such as reduced pain intensity and stress and increased patient satisfaction.<sup>20</sup> In addition, actions taken to reduce the risk of delirium may improve sleep quality. Studies investigating the quality and quantity of sleep in the critically ill suggest a need to greatly improve practice focused on creating the conditions for nocturnal rest, sleep and healthy circadian rhythms, and thus reduce the risk of delirium.

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## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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