The Royal Melbourne Hospital

**Dr Laurie Showler**
**Intensive Care Physician**

**t:** +61 416 958 489
**e:** laurie.showler@mh.org.au

**Intensive Care Unit**

11th February 2023

Professor Hua-Dong Wang

Editor-in-chief, World Journal of Critical Care Medicine

Dear Professor Wang

**Re: Sleep during and following critical illness: A Narrative Review**
Manuscript No: 82787

Many thanks for your email dated 31st January 2023.

On behalf of my co-authors, we thank all the editors and reviewers for their assessments and constructive comments. We believe that we have addressed all of the issues raised, which has enhanced the quality of the manuscript.

All additions to the manuscript have been included in this letter using red font. New or tables and figures have been collected in an appendix.

**Reviewer 1**

**R1 Q1.** The emphasis on longitudinal effects of critical illness on sleep is more in abstract with manuscript describing the effects of sleep deprivation on critical illness. Both these inter-related effects can thus be emphasised in the abstract considering it's a stand-alone document.

*Response*
We agree (page 2). Please see joint response below for R1 Q2.

**R1 Q2.** It is suggested that a sentence pertaining to the conclusion of the review can be included in the abstract.

*Response*

We agree (page 2). The initial abstract did not adequately address the two elements highlighted above. Therefore, the whole abstract has been significantly rewritten and restructured to reference the longitudinal aspect of sleep deprivation in critical illness, as well as key points of conclusion.

**R1 Q3.** The manuscript is very well written covering all aspects pertaining to the topic, however, due to its extensive nature, its suggested that some topics can be comprehensively covered as images/tables. Eg: Measurement of sleep in the critically ill.

*Response*

We agree. The addition of further tables and figures would enhance the article and permit the text to be significantly reduced.

The following tables have been added or amended to achieve this aim:

| | |
|---|---|
| **Table 1:** (pages 4 & 46) | Simplified polysomnographic features of the American Academy of Sleep Medicine phases of sleep. (New) |
| **Table 2:** (pages 8 & 47) | Comparison of studies assessing the effects of ventilator mode on sleep quantity and quality. (Minor amendment) |
| **Table 3:** (pages 12 & 49) | Additional sleep stages for atypical sleep in critically ill patients proposed by Watson et al. (New) |
| **Table 4:** (pages 12 & 49) | Comparison of AASM and Rechtschaffen and Kales criteria sleep stage nomenclature. (New) |
| **Table 5:** (pages 15 & 50) | Summary of objective methods of sleep measurement in the critically ill. (New) |
| **Table 6:** (pages 24 & 51) | Summary of randomised clinical trials assessing nocturnal melatonin as a pharmacological sleep aid. (New) |
| **Supplemental table 1:** (pages 22 & 53) | Comparison of studies assessing the efficacy of ear plugs and eye masks to improve sleep quality and quantity. (Minor amendments) |
| **Figure 1:** (pages 16 & 52) | Patient completed Richards-Campbell Sleep Questionnaire (RCSQ). (New) |

The associated sections of text have been edited to remove information that is covered in table or graphical form.

**R1 Q4.** The antipsychotic medication Haloperidol has not been explicitly mentioned in the antidepressant section of the manuscript and in my opinion its worthy of a mention considering the extensive use in recent times.

*Response*

We agree (page 10). The frequent use of haloperidol for sedation and management of delirium in the ICU makes it a pharmacological agent of interest for its effect on sleep. While there is no direct research to describe haloperidol's effects on sleep quantity or archictecture in the ICU population, there are studies of its effect on EEG waveforms and sleep parameters in other settings. We have amended the section on 'Pharmacological Causes of Sleep Disturbance' to include reference to haloperidol.

> 'Antipsychotic medications are of particular interest due to their use in the management of delirium and have been observed to have variable effects on sleep architecture. Haloperidol has been shown to increase sleep efficiency, whereas the atypical agents, olanzapine and risperidone, have the additional effect of promoting slow wave sleep.'

**R1 Q5.** The 2018 PADIS (Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU) pertaining to sleep can be referenced to emphasize the most recent evidence related to the topic.

*Response*

We agree (page 20). As the only professional society guideline directly addressing sleep disturbance in ICU, this is a vital addition. I have added a reference to this in the section on Sleep Optimisation Strategies.

‘In 2018, the Society of Critical Care Medicine published its clinical practice guidelines for the prevention and management of pain, agitation, delirium, immobility and sleep disruption (PADIS) to summarise the contemporary evidence on this subject.’

**R1 Q6.** Due to the recent publication of a similar review (PMCID: PMC8200142 PMID: 34135650 titled ‘Updated Perspectives on the Management of Sleep Disorders in the Intensive Care Unit’), it is recommended that the authors highlight the unique findings of their review in abstract, core-tip and conclusions.

*Response*

Many thanks for highlighting the excellent article, which we have now referenced in the sections Measuring Sleep in the Critically Ill (page 12) and Causes of Sleep Disturbance in the Critically Ill (page 5). We hope that the changes to the rewritten abstract (page 2) allow readers to identify our unique findings and perspective.

**Reviewer 2**

No questions were raised, or corrections requested by reviewer 2.

**Reviewer 3**

**R3 Q1.** Please include a figure that summarizes the periods of sleep.

*Response*

We agree (pages 22 and 45). The addition of a more graphical representation of the phases of sleep will provide greater clarity to the reader. In response, we have added table 1 to describe the simplified polysomnographic features of the American Academy of Sleep Medicines phases of sleep.

**R3 Q2.** Please, describe the criteria developed by Watson et al in a table.

*Response*

We agree (pages 12 and 49). Given the clarity with which Watson *et al*. have described their 7 additional criteria, we have included this in table 3. We feel this works very well alongside your suggestion to add a description of normal sleep phases.

**R3 Q3.** Usually, this type of article started with an epidemiology section. Please, your section “Epidemiology of Sleep Disturbance during and after critical Illness” could be described first, before “Overview of Normal Sleep”.

*Response*
Given the complexities of the topic and many readers’ lack of background knowledge on this subject, we feel that leaving the overview of normal sleep as the first heading to follow the methods will help contextualise the subsequent sections on sleep in the critically ill.

**R3 Q4.** Please, describe in a table the two systems for scoring polysomnographic sleep data. This allows the reader a better understanding.

*Response*
We agree (pages 12 and 49). We have included a table comparing the American Association of Sleep Medicine’s and the Rechtschaffen and Kales’ sleep phases in table 4. While this is a simplification, we hope this will provide adequate information for the reader to understand the similarities and differences of the 2 systems.

**R3 Q5.** Please, include a table that stated the RCSQ score.

*Response*
We agree (pages 15 and 52). Given the common use of the Richards-Campbell Sleep Questionnaire (RCSQ), elaboration on its components and scoring would certainly be of interest to the reader. We have included an example of the RCSQ and its scoring in figure 1.

**R3 Q6.** I believe that the causes of sleep disturbance could be described after epidemiology, this is a logical order.

*Response*

We agree (page 5). The section ‘Causes of Sleep Disturbance in the Critically Ill’ has been moved to follow the section ‘Epidemiology of Sleep Disturbance During and After Critical Illness’, as suggested.

**R3 Q7.** What are zeitgebers? Page 2.

*Response*

We agree (page 6). The term zeitgeber was poorly defined and an esoteric choice. Zeitgebers are external cues that entrain or synchronise the body’s circadian clock. In response, we have opted to remove the term zeitgeber and amend the text as follows:

> ‘Critically ill patients have been shown to have temporally disorganized circadian rhythmicity, likely due to the absence or disruption of normal external entraining cues, such as light exposure, changes in ambient temperature and eating patterns.’

**R3 Q8.** This statement “Sleep is a pro-inflammatory state characterized by immune cell proliferation and production of pro-inflammatory cytokines” must be corrected.

*Response*

We agree (page 19). This statement may be misleading outside of the referenced article’s context (Besedovsky, et al. 2012). We have reworded this sentence to avoid causing confusion and emphasise the immune upregulation that occurs during sleep.

> ‘Immune upregulation, including immune cell proliferation and production of pro-inflammatory cytokines, is typical during the early phases of sleep.’

**R3 Q9.** Please, since it is a complex subject. The authors must describe in the introduction how they will present the article and how it was divided.

*Response*

We agree. We have rewritten the abstract to give an overview of how the ensuing article will be presented.

Once again, we would like to thank all editors and reviewers for their time and insights.

Yours sincerely,

Laurie Showler

## Tables and Figures

Table 1. Simplified polysomnographic features of the AASM phases of sleep

| Sleep Stage | Electroencephalogram | Electrooculogram | Chin electromyogram |
|---|---|---|---|
| Wake | Alpha activity (sinusoidal 8-13 Hz) | Rapid eye movements<br>Reading eye movements<br>Slow eye movements<br>Blinks | Normal or high tone |
| N1 | < 50% alpha activity<br>> 50% low amplitude mixed frequency activity (4-7 Hz) | Slow eye movements | Variable, usually lower than wake |
| N2 | Sleep spindles<br>K-complexes | None | Variable tone |
| N3 | Slow (delta) wave (0.5-2Hz) $\geq$ 20%<br>Sleep spindles may occur | None | Variable tone |
| REM | Low amplitude mixed frequency activity<br>No sleep spindles or K-complexes | Rapid eye movements | Low tone |

Table 3**.** Additional sleep stages for atypical sleep in critically ill patients proposed by Watson et al.

| **Sleep Stage** | **EEG Waveform Description** |
|---|---|
| Pathologic wakefulness | Any EEG frequency other than alpha or beta with behavioural characteristics of wakefulness. |
| Atypical 1 ($A_t1$) | Alpha and/or theta waves present for > 10% of the epoch, without sleep spindles or K-complexes in the preceding 3 minutes. Polymorphic delta waves, frontal intermittent rhythmic delta (FIRDA), or triphasic activity may be present. |
| Atypical 2 ($A_t2$) | Polymorphic delta waves, frontal intermittent rhythmic delta, or triphasic activity with alpha or beta activity superimposed on delta waves without sleep spindles or K-complexes in the preceding 3 minutes |
| Atypical 3 ($A_t3$) | Polymorphic delta waves, frontal intermittent rhythmic delta, or triphasic activity without alpha or beta activity superimposed on delta waves. |
| Atypical 4 ($A_t4$) | Burst-suppression pattern with EEG amplitude < 5 microvolts for > 0.5 seconds |
| Atypical 5 ($A_t5$) | Suppressed pattern with EEG amplitude < 20 microvolts |
| Atypical 6 ($A_t6$) | Isoelectric activity throughout epoch |

EEG: Electroencephalogram

Table 4. Comparison of AASM and Rechtschaffen and Kales criteria sleep stage nomenclature

| | **AASM** | **R&K** |
|---|---|---|
| Wake | Stage W | Stage W |
| NREM Sleep | Stage N1 | Stage 1 |
| | Stage N2 | Stage 2 |
| | Stage N3 | Stage 3<br>Stage 4 |
| REM Sleep | Stage R | Stage REM |

AASM: American Academy of Sleep Medicine
R&K: Rechtschaffen and Kales criteria

Table 5: Summary of objective methods of sleep measurement in the critically ill

| Method | Benefits | Limitations |
|---|---|---|
| Full polysomnography (PSG) | • Gold standard technique<br>• Provides polygraphic data on EEG, eye movements and chin tone<br>• Established guidelines for interpreting data for normal sleep | • Complex set up<br>• Relatively expensive<br>• Poorly tolerated in 25% of patients<br>• Interferes with nursing care<br>• May interfere with patient sleep<br>• Interpretation requires sleep specialist<br>• No validated criteria for atypical EEG found commonly in critically ill |
| Bispectral index (BIS) monitor | • Small anatomic footprint<br>• Simplified set up compared to PSG<br>• Does not require sleep specialist for interpretation<br>• Less affected by atypical EEG common in critically ill | • Inaccurate differentiation of REM from N1/N2 sleep<br>• Correlates weakly with RCSQ<br>• No validated criteria for interpretation of results<br>• Primarily designed to monitor depth of sedation |
| Limited lead EEG | • Small anatomic footprint<br>• Simplified set up compared to PSG<br>• May not require sleep specialist for interpretation | • Accuracy dependent on device and auto-staging software<br>• Interpretation dependent on sleep specialist if not using auto-staging |
| Actigraphy | • Minimally invasive<br>• Simple set up<br>• Easy to perform serial measures<br>• Established use in outpatient setting | • Poor accuracy compared to PSG and nurse observation, including over-estimation of total sleep time and sleep efficiency<br>• Confounded by immobility, weakness, sedation, and neurological injury. |
| Under mattress sensor | • Non-invasive modality<br>• Simple set up | • Moderate agreement, but poor specificity compared to PSG<br>• No correlation with RCSQ |

EEG: Electroencephalogram; N1: Non-REM sleep stage 1; N2: Non-REM sleep stage 2; PSG: Polysomnography; REM: Rapid eye movement sleep; RCSQ: Richards Campbell Sleep Questionnaire

Table 6. Summary of randomised clinical trials assessing nocturnal melatonin as a pharmacological sleep aid

| Authors | Design | Patients | Intervention & control | Sedation | Outcome |
|---|---|---|---|---|---|
| Ibrahim *et al.*[159] 2006 | Single centre, double-blind, randomised trial | 32 pts | I: Melatonin 4 mg<br>C: placebo<br>For ≥ 48 hours | Infusions ceased for ≥ 12 hours | No significant difference in total sleep time by modified SOT |
| Bourne *et al.*[137] 2008 | Single centre, double-blind, randomised trial | 24 pts | I: Melatonin 10 mg<br>C: Placebo<br>For 4 nights | Ceased for ≥ 30 hours | No significant difference in total RCSQ or sleep efficiency by BIS |
| Foreman *et al.*[223] 2015 | Single centre, pilot, randomised trial | 12 pts | I: Melatonin 3 mg plus eye masks and headphones<br>C: Standard care<br>For 1-7 days | Propofol allowed. Opiates ceased > 24 hours | Primary outcome not determined in 65% due to uninterpretable PSG |
| Mistraletti *et al.*[222] 2015 | Single centre, double-blind, randomised trial | 82 pts | I: Melatonin 3+3 mg<br>C: Placebo<br>From day 3 of ICU until ICU discharge | Enteral hydroxyzine and lorazepam allowed | No significant difference in total sleep time by nurse observation |
| Gandolfi *et al.*[225] 2020 | Double centre, double-blind, randomised trial | 203 pts | I: Melatonin 10 mg<br>C: Placebo<br>For 7 days or until hospital discharge | As per treating clinician | Statistically improved total RCSQ, *mean (SD):*<br>I: 61 (26)<br>C: 70 (21) (p=0.03)<br><br>No significant difference in total sleep time by nurse observation |
| Wibrow *et al.* 2021 | Multicentre (12), double blind, randomised, trial | 841 pts | I: Melatonin 4 mg<br>C: Placebo<br>For 14 days or until ICU discharge | As per treating clinician | No significant difference in total RCSQ |

BIS: Bispectral index; ICU: Intensive care unit; PSG: Polysomnography; RCSQ: Richards Campbell Sleep Questionnaire; SOT: Sleep observation tool.

Figure 1. Patient completed Richards-Campbell Sleep Questionnaire (RCSQ)

Place your "X" anywhere on the answer line that you fell best describes your sleep last night:

**Question 1**: My sleep last night was:

Deep Sleep _____ Light Sleep

**Question 2**: Last night, the first time I got to sleep, I:

Feel asleep almost immediately _____ Just never could fall asleep

**Question 3**: Last night, I was:

Awake very little _____ Awake all night long

**Question 4:** Last night, when I woke up or was awakened, I:

Got back to sleep immediately _____ Couldn't get back to sleep

**Question 5**: I would describe my sleep last night as:

A good night's sleep _____ A bad night's sleep

A score for each question is given based on the length of the line in millimetres from the 0 point (right end of the line) to the cross of the patient's "X".
Scores may range from 0 (worst possible sleep) to 100 (best possible sleep).
Total Sleep Score is derived by adding the individual scores for each question and dividing by 5.