Sleep and Postoperative Delirium—New Avenues

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- Edward Life Sciences (Investigator initiated research, Consultant)
Postoperative Delirium

- Current Postoperative Delirium Burden
- Sleep and Delirium- What is the connection
- Enhancing Natural Sleep- Current work

Topic Outline

- Current Postoperative Delirium Burden
- Sleep and Delirium- What is the connection
- Enhancing Natural Sleep- Current work
Association of any Adverse Hospital Outcomes by Complication and Delirium Status

Table 5. Association of any Adverse Hospital Outcomes by Complication and Delirium Status

<table>
<thead>
<tr>
<th>Status</th>
<th>Any Adverse Outcome</th>
<th>Adjusted RR (95% CI)</th>
<th>PAR, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No complications or delirium (n = 404)</td>
<td>252 (62.4)</td>
<td>1 [Reference]</td>
<td>1 [Reference]</td>
</tr>
<tr>
<td>Complications only (n = 27)</td>
<td>22 (81.5)</td>
<td>1.2 (1.0-1.6)</td>
<td>0.8 (0.0-1.5)</td>
</tr>
<tr>
<td>Delirium only (n = 115)</td>
<td>105 (91.3)</td>
<td>1.4 (1.3-1.5)</td>
<td>5.8 (4.7-6.8)</td>
</tr>
<tr>
<td>Complications and delirium (n = 20)</td>
<td>20 (100)</td>
<td>1.6 (1.4-1.8)</td>
<td>1.3 (1.0-1.6)</td>
</tr>
</tbody>
</table>

Abbreviations: PAR, population attributable risk; RR, relative risk.

*Adjusted for age, sex, race, Charlson Comorbidity Index score, surgery type (orthopedic vs all others), and anesthesia type (general vs spinal).

Relative risks were calculated with a generalized linear model, Poisson error term, log-link, and robust error variance.

Effect of Delirium and Other Major Complications on Outcomes After Elective Surgery in Older Adults. JAMA Surg. 2015;150(12):1134-1140.

Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

Crit Care Med. 2018 Sep;46(9):e825-e873.
Complete consensus for delirium treatment

We suggest using a multicomponent, non-pharmacological intervention* that is focused (but not limited to) reducing modifiable risk factors for delirium, improving cognition, and optimizing sleep, mobility, hearing/visions in critically ill adults. (Conditional recommendation, Low quality of evidence) *These multicomponent interventions include (but are not limited to) strategies to improve cognition (e.g., re-orientation, cognitive stimulation, music, use of clocks), improve sleep (e.g., minimizing light and noise), improve wakefulness (i.e., reduced sedation), reduce immobility (e.g., early mobilization), and reduce hearing and/or visual impairment (e.g. use of hearing aids, glasses).

Intervenable causes

- Sleep, Pain and Cognition

Conclusions and Relevance—Major postoperative complications and delirium are separately associated with adverse events and demonstrate a strong combined effect. Delirium occurs more frequently, and has greater impact at the population level than other major complications.
Abnormal Sleep patterns in ICU

**TABLE 2. List of Factors That Patients Report as Disruptive to Sleep**

<table>
<thead>
<tr>
<th>Environmental</th>
<th>Physiologic and Pathophysiologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Light (421, 453, 454, 480, 482–484, 486–488)</td>
<td>Discomfort (454, 483, 486, 488, 490)</td>
</tr>
<tr>
<td>Comfort of bed (483, 486–488)</td>
<td>Feeling too hot or too cold (484, 486, 488)</td>
</tr>
<tr>
<td>Activities at other bedside (483, 486, 487)</td>
<td>Breathing difficulty (484, 491)</td>
</tr>
<tr>
<td>Visitors (clinician or family) (483)</td>
<td>Coughing (484, 491)</td>
</tr>
<tr>
<td>Room ventilation system (483)</td>
<td>Thirst (484, 486) and hunger (489, 488)</td>
</tr>
<tr>
<td>Hand washing by clinicians (483)</td>
<td>Nausea (484, 488)</td>
</tr>
<tr>
<td>Bad odor (486, 488)</td>
<td>Needing to use bedpan/urinal (488, 488)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Care Related</th>
<th>Psychologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nursing care (447, 453, 480, 482–484, 486, 488, 491)</td>
<td>Anxiety/worry/stress (480, 484, 486, 489–491)</td>
</tr>
<tr>
<td>Patient procedures (447, 453, 480, 482, 483, 485, 488)</td>
<td>Fear (485, 486, 489)</td>
</tr>
<tr>
<td>Vital sign measurement (442, 448, 471, 477, 481, 483)</td>
<td>Unfamiliar environment (485, 488, 491)</td>
</tr>
<tr>
<td>Diagnostic tests (447, 453, 480, 483)</td>
<td>Disorientation to time (454, 486)</td>
</tr>
<tr>
<td>Medication administration (447, 453, 480, 482)</td>
<td>Loneliness (488, 491)</td>
</tr>
<tr>
<td>Restricted mobility from lines/catheters (454, 486, 488)</td>
<td>Lack of privacy (485, 488)</td>
</tr>
<tr>
<td>Monitoring equipment (454, 486, 488)</td>
<td>Hospital attire (486, 488)</td>
</tr>
<tr>
<td>Oxygen mask (486, 488)</td>
<td>Missing bedtime routine (483)</td>
</tr>
<tr>
<td>Endotracheal tube (491)</td>
<td>Not knowing nurses’ names (486)</td>
</tr>
<tr>
<td>Urinary catheters (489)</td>
<td>Not understanding medical terms (486)</td>
</tr>
</tbody>
</table>
ICU Sleep- Key features

- Total sleep time (TST) and sleep efficiency are often normal
- Sleep fragmentation, the proportion of time spent in light sleep (stages N1 + N2), and time spent sleeping during the day (vs. night) are higher
- The proportion of time spent in deep sleep (stage N3 sleep and REM) is lower
- Subjective sleep quality is reduced
- NO CAUSE AND EFFECT between sleep and delirium
- Sleep measurements in ICU is challenging
- Is sleep different in critically ill adults if delirium is present?
  - Greater disruption of circadian rhythm; REM sleep is lower

Postoperative Delirium

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- Sleep and Delirium- What is the connection
- Enhancing Natural Sleep- Current work
A Systematic Review and Meta-Analysis Examining the Impact of Sleep Disturbance on Postoperative Delirium

Fadayomi, Ayotunde B.; Ibala, Reine; Bilotta, Federico; Westover, Michael B.; Akeju, Oluwaseun. Critical Care Medicine46(12):e1204-e1212, December 2018.

Forest plot for all studies and subgroup analyses by study characteristics. A, Forest plot showing pooled analysis of studies categorized into obstructive sleep apnea and unspecified types of sleep disturbance. B, Forest plot showing pooled analysis of studies categorized into preoperative sleep disturbance and postoperative sleep prospective.
A Systematic Review and Meta-Analysis Examining the Impact of Sleep Disturbance on Postoperative Delirium

Fadayomi, Ayòtúndé B.; Ibala, Reine; Bilotta, Federico; Westover, Michael B.; Akeju, Oluwaseun
Critical Care Medicine46(12):e1204-e1212, December 2018.

Forest plot for all studies and subgroup analyses by study characteristics. A. Forest plot showing pooled analysis of studies categorized into prospective and retrospective study design. B. Forest plot showing pooled analysis of studies categorized into studies with median/mean age less than 65 yr and greater than or equal to 65 yr.

A Systematic Review and Meta-Analysis Examining the Impact of Sleep Disturbance on Postoperative Delirium

Fadayomi, Ayòtúndé B.; Ibala, Reine; Bilotta, Federico; Westover, Michael B.; Akeju, Oluwaseun
Critical Care Medicine46(12):e1204-e1212, December 2018.

Forest plot for all studies and subgroup analyses by study characteristics. A. Forest plot showing pooled analysis of studies with crude odds ratio. B. Forest plot showing pooled analysis after restricting to those with sleep disturbance before onset of delirium.
Sleep Restriction on Circadian secretory pattern

The Journal of Clinical Endocrinology & Metabolism, Volume 89, Issue 5, 1 May 2004, Pages 2119–2126,

Neuroinflammation and Perioperative NeuroCognitive Disorders

Novel risk markers and long-term outcomes of delirium: The Successful Aging after Elective Surgery (SAGES) Study Design and Methods

**Postoperative Delirium**
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Brain age from the electroencephalogram of sleep

Haoqi Sun, Luis Paixao, Jefferson T. Oliva, Balaji Goparaju, Diego Z. Carvalho.

Apart shows an average of 5.4 years increase in BA. Participants with significant neurological or psychiatric disease exhibit a mean excess BA, or “brain age index” (BAI = BA-CA) of 4 years relative to healthy controls. Participants with hypertension and diabetes have a mean excess BA of 3.5 years. The findings raise the prospect of using the sleep EEG as a potential biomarker for healthy brain aging.

Meditation and Sleep

- ↓GABA and inflammatory markers - Streeter CC. J Altern Complement Med, 2010
- Higher Melatonin levels
- Mimic Natural Sleep
- ↑ sleep quality, efficiency Khalsa S. Appl Psychophysiol Biofeedback, 2004 (Yoga)
- Cancer patients (Mindfulness)
  - Reduce total wake time
  - Improve Sleep Quality
- ↑Sleep Quality in old (Tai Chi)
- Cognitive Based Therapy-Insomnia
Sleep stages have distinct EEG signatures that result from differences in the neural circuits that are involved in their generation and maintenance. The spectrogram, which is the decomposition of the EEG signal by frequency as a function of time, makes these differences clear. These signatures are also visible in the raw EEG signal (black traces represent first 10 s of data shown in spectrogram). (a) EEG slowing and the loss of the wake state alpha oscillations are distinguishing features of N1 sleep. (b) Slow-delta (0.1–4 Hz) and alpha (8–12 Hz) oscillations are the predominant EEG signatures of propofol-general anesthesia. This finding is consistent with the EEG signatures of other intravenous GABA\(_{A}\) receptor targeting anesthetics (i.e., benzodiazepines, etomidate) during general anesthesia. (c) Slow-delta oscillations, theta (4–8 Hz), and alpha oscillations are the predominant EEG signatures of sevoflurane-general anesthesia. This finding is consistent with the EEG signatures of other modern day derivatives of ether during general anesthesia (desflurane, isoflurane). The close similarities between the EEG signatures of propofol and modern day derivatives of ether anesthesia has been suggested to result from enhancement of GABA\(_{A}\) receptor IPSCs. (d) Isoelectricity is observed when high doses of anesthetics such as sevoflurane and propofol are administered. Significantly enhancement of IPSCs in cortical circuits is a mechanism to explain isoelectricity. (e) Gamma oscillations (>30–45 Hz) that are interspersed with slow-delta (black arrow on spectrogram and raw EEG) oscillations are the predominant EEG signatures of general anesthesia maintained with the NMDA receptor antagonist ketamine.

db, decibels; EEG, electroencephalogram; Hz, Hertz; N1, non-rapid eye movement stage 1 sleep; N2, non-rapid eye movement stage 2 sleep; N3, non-rapid eye movement stage 3 sleep; REM, rapid eye movement.
Sedation states. Each anesthetic drug has a different EEG signature that results from differences in the neural circuits that are involved in state generation and maintenance. The spectrogram, which is the decomposition of the EEG signal by frequency as a function of time, makes these differences clear. These signatures are also visible in the raw EEG signal (black traces represent first 10 s of data shown in spectrogram). (a) Beta (~13–30 Hz) oscillations are the predominant EEG signature of sedation maintained by propofol and other medications that enhance GABA<sub>G</sub> receptor IPSCs (i.e., ether anesthetics, benzodiazepines, zolpidem). (b) Slow-delta and spindle (12–16 Hz; red arrow on spectrogram and raw EEG) oscillations are the predominant EEG signatures of dexmedetomidine-sedation. These dexmedetomidine-induced EEG signatures very closely approximate the EEG signatures of N2 sleep (Figure 1b).

dB, decibels; EEG, electroencephalogram; GABA<sub>G</sub>, gamma amino butyric acid A; Hz, Hertz; IPSCs, inhibitory post synaptic currents.
Low-dose nocturnal dexmedetomidine prevents ICU delirium. A Randomized, Placebo-controlled Trial. Am J Respir Crit Care Med 2018

Figure 2. Kaplan-Meier curve for the time to the first occurrence of delirium between dexmedetomidine (blocks wake state) and placebo groups during the ICU stay for those patients still at risk for developing delirium each day for the first time (log rank P value = 0.006). Patients with persistant coma on any given day were deemed not to have delirium.

Suvorexant and Sleep/Delirium in ICU Patients Eikermann M et al.
Orexin receptor antagonist -blocks awake state
Melatonin and Sleep in Preventing Hospitalized Delirium: A Randomized Clinical Trial

Stuti J. Jaiswal, MD, PhD, Nathan E. Wineinger, PhD, Robert L. Owens, MD, Janet Song, Robert L. Owens, MD, Nathan E. Wineinger, PhD, Solana Garcia, Christoffel J. van Niekerk, MD, Cathy Y. Liu, Melissa Looks, NPPC, Robert L. Owens, MD

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Impact of Melatonin on Sleep and Pain After Total Knee Arthroplasty Under Regional Anesthesia With Sedation: A Double-Blind, Randomized, Placebo-Controlled Pilot Study

Meghan A. Kirksey, MD, PhD, Nathan E. Wineinger, PhD, Robert L. Owens, MD, Nathan E. Wineinger, PhD, Solana Garcia, Christoffel J. van Niekerk, MD, Cathy Y. Liu, Melissa Looks, NPPC, Robert L. Owens, MD

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Step count on Postoperative Delirium Following Cardiac Surgery

Enrolling... from Clinicaltrials.gov

Thank you