Promoting Sleep in the ICU - Melatonin and More

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Disclaimer

• No financial disclosures
• PI for feasibility RCT on melatonin vs. placebo for prevention of ICU delirium
Sleep

- Everyone “knows” sleep is an essential physiologic process influenced by biologic and environmental factors.

- Conventional wisdom = sleep needed to maintain health & promoting healing.
  - We tell patients (and family) “Get a good night’s rest”.
• Compared to healthy volunteers, polysomnography studies have demonstrated
  • prolonged sleep latency
  • severely fragmented sleep
  • ↓ sleep efficiency
  • ↑ arousals & awakenings
  • ↑ NREM stage 1 & 2
  • ↓/0 NREM stage 3 (deep) & REM sleep

• Findings remarkably consistent in varying ICU settings.
Sleep in the ICU – poor quantity & quality

Results: Patients’ median total sleep time was 05:00 (IQR: 02:52 to 07:14). The majority of sleep was stage 1 and 2 (medians: 19 and 73%) with scant slow wave and REM sleep. The median duration of sleep without waking was 00:03. Sound levels were high (mean Leq 53.95 dB(A) during the day and 50.20 dB(A) at night) and illuminance levels were appropriate at night (median <2 lux) but low during the day (median: 74.20 lux). There was a median 1.7 care events/h. Patients’ mean self-reported sleep quality was poor. Interrater reliability of sleep staging was highest for slow wave sleep and lowest for stage 1 sleep.
Factors that adversely affect sleep in the ICU

Environmental Factors
- Patient Care Activities
- Diagnostic Procedures
- Sedatives Analgesics
- Lighting Practices
- Noise
- Stress
- Organ Dysfunction
- Inflammatory Response
- Pain
- Psychosis

Pathophysiologica Factors

Figure 1. Factors related to sleep deprivation in critically ill patients.
ICU patient perceptions

- This Δ sleep pattern may explain why 38-51% of patients recall
  - “not being able to sleep”
  - “repeated awakenings in the middle of the night”
- Reported reasons for insufficient sleep: noise or loud voices, traffic (e.g. people walking in/out room), and bright lights.
- 3/4 of SLEAP survivors experience delusional memories (e.g. nightmares, hallucinations).
- Vast majority of patients are either moderately or extremely “bothered” by sleep problems.

Burry LD, Crit Care Med 2015;43(10):2180-90
Sleep promoting interventions in the ICU

“Shhh... He’s almost asleep.”
30 trials N = 1569 participants
Trials = ventilator mode/type, earplugs, eye masks or both, massage, relaxation interventions, foot baths, music, acupressure, aromatherapy, sound masking

Non-pharmacological interventions for sleep promotion in the intensive care unit (Review)

Hu RF, Jiang XY, Chen J, Zeng Z, Chen XY, Li Y, Huining X, Evans DJW
## Interventions for sleep

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Environmental control</td>
<td>Not well studied in ICU. Conflicting benefit.</td>
</tr>
<tr>
<td>- control noise (e.g. earplugs, music therapy)</td>
<td>- Ear plugs - Some trials showed fewer arousals &amp; ↑ REM, others studies show increased sleep quantity but no change in architecture or arousal index.</td>
</tr>
<tr>
<td>- control light (e.g. open blinds during the day; closed at night)</td>
<td>- Relaxation techniques (massage/music/ocean sounds - Small non-randomized trials showing subjective improvement (RCSQ).</td>
</tr>
<tr>
<td></td>
<td>- Quiet time – pre-post QI project - ↓ delirium, ↑ staff/family/patient satisfaction</td>
</tr>
</tbody>
</table>

Scotto CJ. Nurs Crit Care 2009;14:180-184
Hu RF. Crit Care 2010;14:R66
Richards KC. Am J Crit Care 1998;7:288-299
Kamdar BB. Crit Care Med 2013;41:800-809
Interventions for sleep

Non-pharmacologic measures

- ↓unnecessary interruptions at night
- Limit daytime naps
- Physical activity
- Patient history for symptoms suggestive of preexisting sleep disorder
- Review ventilation settings re dysynchrony/central apneas)
- Medication review (ADRs & withdrawal rxn)
Drug withdrawal

Abrupt cessation of:

- sedatives & alcohol will worsen of sleep fragmentation.
- Nicotine, barbiturates, & short-acting benzodiazepines can lead to withdrawal insomnia.
- Beta-blockers increase sympathetic activity.
- Antidepressants have profound withdrawal effects.

Thorough review of Rx & medication history useful to prevent withdrawal /manage ICU patients with difficulty sleeping
# Effect of Medications on Sleep

## Table 20.1 The Effects of Common Medications on Sleep in Hospitalized Patients

<table>
<thead>
<tr>
<th>Medications (Examples)</th>
<th>Sleep Alterations</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Analgesics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioids (M.S., Codeine, Demerol)</td>
<td>↓TST, REM, SWS; ↑W</td>
<td>Sedating properties may worsen SDB</td>
</tr>
<tr>
<td>NSAIDs (Ibuprofen)</td>
<td>↓TST, SE</td>
<td></td>
</tr>
<tr>
<td><strong>Antidepressants</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tricyclics (Amitriptyline, doxepine)</td>
<td>↓W, REM; ↑TST</td>
<td>Drowsiness; CNS depression enhanced by alcohol intake</td>
</tr>
<tr>
<td>SSRIs (Paroxetine, fluoxetine)</td>
<td>↓TST, SE, REM; ↑W</td>
<td>Insomnia, agitation; extensive drug interactions</td>
</tr>
<tr>
<td><strong>Antiepileptics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>↓SL; ↑SWS, TST</td>
<td>CNS effects; extensive drug interactions</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>↓W, SL, REM; ↑TST</td>
<td>Sedating effects common</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>↓LS, REM; ↑SWS</td>
<td>Drowsiness, fatigue</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>↓W; ↑TST, REM, SWS</td>
<td>Dream disturbances, emotional lability, dizziness, drowsiness</td>
</tr>
</tbody>
</table>

*Abbreviations: NA, not available; REM, rapid eye movement sleep; SDB, sleep-disordered breathing; SE, sleep efficiency; SL, sleep latency; SWS, slow-wave sleep; W, wakefulness; TST, total sleep time.*

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<td><strong>Anti-Parkinsonian drugs</strong></td>
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<td></td>
</tr>
<tr>
<td>levodopa</td>
<td>↓SWS; nightmares</td>
<td>Disturbing dreams, mood changes, malaise</td>
</tr>
<tr>
<td>methyldopa</td>
<td></td>
<td>Drowsiness, nightmares</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>haloperidol</td>
<td>↓W, SL; ↑SE</td>
<td>Insomnia, restlessness</td>
</tr>
<tr>
<td><strong>Cardiovascular agents</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>β3 antagonist (propranolol, metoprolol)</td>
<td>↑W, SL; ↑REM</td>
<td>Drowsiness, fatigue</td>
</tr>
<tr>
<td>Calcium channel blockers (Nifedipine, verapamil)</td>
<td>NA</td>
<td>Drowsiness, weakness</td>
</tr>
<tr>
<td>ACE inhibitors (lisinopril)</td>
<td>No known sleep effects</td>
<td>Fatigue, syncope</td>
</tr>
<tr>
<td>diuretics (HCTZ, furosemide)</td>
<td>NA</td>
<td>Insomnia, weakness, nocturia</td>
</tr>
</tbody>
</table>

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Redeker, NS, et al. Sleep Disorders and Sleep Promotion in Nursing Practice: Springer Publishing Company; 2011.
## Effect of Medications on Sleep

### Table 20.1  The Effects of Common Medications on Sleep in Hospitalized Patients (Continued)

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<th>Medications (Examples)</th>
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</thead>
<tbody>
<tr>
<td>Corticosteroids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prednisone; cortisone</td>
<td>↓REM, SWS; ↑W</td>
<td>Insomnia, restlessness, behavior changes</td>
</tr>
<tr>
<td>H2 Antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cimetidine</td>
<td>↑SWS</td>
<td>Hallucinations, somnolence</td>
</tr>
<tr>
<td>Mood Stabilizers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>↑TST, SWS; ↓REM</td>
<td>Drowsiness, lethargy</td>
</tr>
<tr>
<td>Respiratory</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Theophylline</td>
<td>↓TST, SE, REM, SWS; ↑W</td>
<td>Agitation, insomnia</td>
</tr>
<tr>
<td>Sedatives/Hypnotics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines (Midazolam)</td>
<td>↓W, REM, SWS, SL; ↑TST</td>
<td>Delirium, dreaming, insomnia, nightmares</td>
</tr>
<tr>
<td>Propofol</td>
<td>↓W, SL; ↑TST</td>
<td>CNS depressant; hypnotic</td>
</tr>
</tbody>
</table>

Abbreviations: NA, not available; REM, rapid eye movement sleep; SDB, sleep-disordered breathing; SE, sleep efficiency; SL, sleep latency; SWS, slow-wave sleep; W, wakefulness; TST, total sleep time.

Redeker, NS, et al. Sleep Disorders and Sleep Promotion in Nursing Practice: Springer Publishing Company; 2011.
Saving drugs for last...

BMJ Open Pharmacological interventions to improve sleep in hospitalised adults: a systematic review

Salmaan Kanji,1,2 Alexandru Mera,3 Brian Hutton,2,4 Lisa Burry,5 Erin Rosenberg,6 Erika MacDonald,2,7 Vanessa Luks8

ABSTRACT
Objectives: Patients often suffer from disturbed sleep in hospital. Poor-quality sleep in hospitalised patients has been associated with significant morbidity and pharmacological sleep aids are often prescribed. The objective of this systematic review is to evaluate the comparative efficacy and safety of pharmacological interventions used for sleep in hospitalised patients.

Setting/participants: We searched MEDLINE, Embase, the Cochrane database and grey literature for prospective studies that evaluated sleep in hospitalised adults after a pharmacological intervention.

Primary and secondary outcome measures: Two reviewers assessed studies for inclusion and extracted data for efficacy outcomes, including sleep efficiency, sleep latency, sleep fragmentation and objectively measured sleep stage distribution. Risk of bias was assessed and meta-analyses were planned contingent on data availability.

Strengths and limitations of this study

- The use of a validated systematic search strategy of multiple databases to identify relevant studies.
- Article screening and data extracted independently by two investigators.
- The research team consisted of physicians, pharmacists, an epidemiologist/methodologist, a sleep expert and pharmacotherapy specialists.
- The studies included were typically small, outcomes were often measured subjectively and most studies did not have a standard approach to the evaluation of safety.
- Not all drugs currently being used in clinical settings were identified in clinical trials and comparative trials were identified without placebo controls for many drugs.
Drug interventions for sleep

• 15 studies, 861 participants
• Medications = benzodiazepines, non-benzodiazepine sedatives, melatonin, propofol and dexmedetomidine.
• Heterogeneity & variable outcome reporting precluded meta-analysis in most cases.
• Insufficient evidence to suggest Rx improves the quality or quantity of sleep.
• No Rx class or specific drug was identified as superior to placebo or no treatment.
Melatonin for the promotion of sleep in adults in the intensive care unit (Review)

Lewis SR, Pritchard MW, Schofield-Robinson OJ, Alderson P, Smith AF
“Ever notice how your cat licks her feet, then goes to sleep? This new sleep aid is made from synthetic cat feet!”
Take home points

- Sleep abnormalities are common in the ICU.
- It is distressing to patients and still bothersome post-discharge.
- Sleep-promoting interventions have been poorly studied in ICU patients. We will likely need a multipronged approach that heavily relies on non-pharmacological therapies.