Title

Melatonin and Sleep in Preventing Hospitalized Delirium: A Randomized Clinical Trial

Journal

The American Journal of Medicine, 131(9)

ISSN

0002-9343

Authors

Jaiswal, Stuti J
McCarthy, Thomas J
Wineinger, Nathan E
et al.

Publication Date

2018-09-01

DOI

10.1016/j.amjmed.2018.04.009

Peer reviewed

HHS Public Access

Author manuscript

Am J Med. Author manuscript; available in PMC 2019 September 01.

Published in final edited form as:

Am J Med. 2018 September ; 131(9): 1110–1117.e4. doi:10.1016/j.amjmed.2018.04.009.

Melatonin and sleep in preventing hospitalized delirium: A randomized clinical trial

Stuti J. Jaiswal, MD PhD[1,2], **Thomas J. McCarthy, MD**[2], **Nathan E. Wineinger, PhD**[1], **Dae Y. Kang, PhD**[3], **Janet Song**[1], **Solana Garcia**[1], **Christoffel J. van Niekerk, MD**[2], **Cathy Y. Lu**[1], **Melissa Loeks, MPH**[4], and **Robert L. Owens, MD**[3]

[1]The Scripps Research Institute, La Jolla, CA 92037

[2]Department of Internal Medicine, Scripps Clinic/Scripps Green Hospital, La Jolla CA 92037

[3]Division of Pulmonary, Critical Care & Sleep Medicine, University of California San Diego School of Medicine, La Jolla, CA 92037

[4]Respironics, Inc., a Philips Healthcare company

Abstract

Purpose: Studies suggest that melatonin may prevent delirium, a condition of acute brain dysfunction occurring in 20–30% of hospitalized older adults that is associated with increased morbidity and mortality. We examined the effect of melatonin on delirium prevention in hospitalized older adults while measuring sleep parameters as a possible underlying mechanism.

Methods: This was a randomized clinical trial measuring the impact of 3 mg of melatonin nightly on incident delirium and both objective and subjective sleep in inpatients age ≥ 65, admitted to Internal Medicine wards (non-ICU). Delirium incidence was measured by bedside nurses using the confusion assessment method (CAM). Objective sleep measurements (nighttime sleep duration, total sleep time per 24 hours, and sleep fragmentation as determined by average sleep bout length) were obtained via actigraphy. Subjective sleep quality was measured using the Richards Campbell Sleep Questionnaire.

Results: Delirium occurred in 22.2% (8/36) of subjects who received melatonin vs. in 9.1% (3/33) who received placebo (p=0.19). Melatonin did not significantly change objective or subjective sleep measurements. Nighttime sleep duration and total sleep time did not differ

[1.] Stuti J. Jaiswal (corresponding author), The Scripps Research Institute, Scripps Translational Science Institute, 3344 N. Torrey Pines Ct., Suite 300, La Jolla, CA 92037, jaiswal.stuti@scrippshealth.org, Phone: 520-901-0575. [2.] Robert L. Owens (secondary contact), UC San Diego Division of Pulmonary, Critical Care & Sleep Medicine, 9300 Campus Point Drive, #7381, La Jolla, CA 92037, rowens@ucsd.edu.

Author Statement: All of the above authors contributed to this article by participation in the research and preparation of the manuscript. Additionally, all authors had access to the data and a role in writing the manuscript.

Statement of conflict of interests: None of the above listed authors claim any conflict of interest, financial or otherwise, in the preparation of this article. **Although Ms. Loeks is employed by Philips Respironics, the study design and interpretation of all data was done by the investigators.**

Data Statement: The de-identified data for this study is available upon reasonable request to the authors via email to Jaiswal.stuti@scrippshealth.org

Trial Registration: REGISTERED at CLINICALTRIALS.GOV: NCT02597231

between subjects who became delirious vs. those who did not, but delirious subjects had more sleep fragmentation (sleep bout length 7.0±3.0 vs. 9.5±5.3 min; p=0.03).

Conclusions: Melatonin given as a nightly dose of 3mg did not prevent delirium in non-ICU hospitalized patients, or improve subjective or objective sleep.

Keywords

delirium; sleep; melatonin

INTRODUCTION:

Delirium occurs in an estimated 20–30% of elderly patients admitted to hospital wards.[1] Individuals 65 and older, especially those with dementia, evidence of prior cognitive decline, or prior neurologic insult such as stroke, are at increased risk. Major consequences of delirium include increased in-hospital[2] and one-year mortality rates[3], as well as worsened neurocognitive outcomes.[4–6] Delirious patients stay hospitalized longer[7, 8], and are more likely to discharge to a facility instead of home.[9] No FDA-approved therapies exist for the treatment or prevention of delirium, although clinicians frequently prescribe antipsychotics and anxiolytics to control associated agitation, despite data clearly demonstrating their lack of efficacy and risk of serious side effects.[10] Sleep deprivation has been hypothesized as a cause of hospital delirium, and non-pharmacological sleep promotion efforts are part of successful delirium prevention strategies.[11, 12]

Melatonin is naturally secreted by the pineal gland and serves as an important marker of the circadian-rhythm, the body's internal clock; levels are highest during sleep and low during wakefulness. Commercially available melatonin is sold as a non-prescription supplement, has a relatively safe side-effect profile and is generally considered well tolerated. Recent evidence suggests that melatonin, given at doses ranging from 0.5 to 5 mg, and melatonin-receptor agonists may prevent delirium.[13–15] Al-Aama et al. used melatonin at a dose of 0.5 mg daily vs. placebo and reduced delirium rates substantially in elderly (age ≥ 65) inpatients, from 30% to 11%, respectively, as measured by the Confusion Assessment Method (CAM).[14] The mechanism of its action in delirium prevention remains unknown. We hypothesized that the effect of melatonin on delirium prevention was due to increased sleep duration, and we accordingly designed a randomized, double blind, placebo-controlled trial. Specifically, our study examined the incidence of delirium using CAM in elderly ward patients who were randomly assigned to receive either melatonin 3 mg or matching placebo while concurrently measuring sleep duration using a wireless actigraphy device.

METHODS:

Study Design & Setting:

This was a double-blinded, randomized, placebo-controlled trial at a single, tertiary-care, teaching hospital in La Jolla, California, conducted from November 2015 until December 2016. The Scripps Institutional Review Board (IRB) approved the study protocol prior to initiation.

Recruitment and Enrollment:

Eligible patients were aged 65 to 99, newly admitted to an Internal Medicine service (non-ICU) with an expected stay of at least 48 hours beyond enrollment (determined by "inpatient," rather than "observation," admission status). As we examined incident delirium, we excluded individuals already altered or confused at admission (Specific exclusion criteria in Supplemental Methods). Written consent was obtained from eligible subjects or their designated power of attorney within 24–36 hours of admission.

Randomization and Intervention:

Concealed randomization utilized a four-factor randomized block design generated by a staff statistician and was available only to the investigational drug pharmacist. All patients, investigators, clinicians, etc. remained blinded to the intervention assignments until trial completion and after primary data analysis. Subjects received melatonin 3 mg (chosen to promote increased nighttime sleep duration) or a matching, lactose-containing placebo once daily, administered by nurses at 9 pm for a maximum of 14 consecutive nights during hospitalization. Both the melatonin and matching placebo pills were obtained from a local compounding pharmacy.

Measurements and Outcomes:

Wrist-worn actigraphy devices (Philips Actiwatch Spectrum Plus; Philips Respironics, Murrysville, PA) were placed on each subject at enrollment. We used the Montreal Cognitive Assessment (MoCA) and Charlson Comorbidity Index (CCI) and Age-Adjusted CCI (ACCI) to assess baseline cognitive function and illness, respectively.

Our primary outcome was incident delirium, measured by CAM assessments administered twice daily by the subjects' floor nurses (Supplemental Methods contain training details). CAM assessment requires the presence of at least three features -- altered mentation, inattention and either disorganized thinking or altered level of consciousness -- to be considered positive (CAM+). Because the sensitivity of CAM[16, 17] has been questioned, and because delirium may wax and wane, we additionally considered patients who were CAM negative (CAM-) but who developed evidence of Altered Mental Status (AMS) during admission. We defined AMS as CAM- subjects who were either 1) CAM Feature 1 (mentation altered from baseline) positive, or 2) documented to become delirious or altered during admission. This determination was based on physician (SJJ) review of all notes from the medical record.

The secondary outcomes were objective and subjective measurements of sleep obtained via actigraphy and the Richards Campbell Sleep Questionnaire (RCSQ),[18] respectively.

Objective sleep assessment – Actigraphy (Figure 1): Details on actigraphy scoring are reported in Supplemental Methods. Actigraphy-based outcomes were as follows (details in Supplemental Methods): 1) Average nighttime sleep (AvNS) – averaged total sleep time within the nighttime rest interval, 2) Average Total sleep time (AvTST) – average of NS + daytime naps in a calendar day, and 3) Sleep fragmentation – assessed using the average

length of the sleep bout during the NS, with shorter sleep bout length suggesting more sleep fragmentation.

Subjective sleep assessment – questionnaire.—The RCSQ was offered to subjects every morning during study participation. Each item is scored from 0–100 mm (higher numbers indicate better sleep responses) on a visual scale, summed and then divided by 5 to obtain a total score.[18]

Power Calculations:

A power analysis was conducted using existing literature which suggested melatonin and MRAs reduce absolute rates of delirium by 20%.[13–15] Assuming a baseline rate of delirium of 20%, in order to have greater than 80% power (with alpha = 0.05) to detect this reported reduction, 43 patients were required in each group after considering a 20% overall dropout rate (leaving approximately 34 patients per group) based on 10,000 simulations.

Data Analysis and Statistics:

Four analyses were conducted to fully examine the primary outcome. 1) Intention-to-treat (ITT) analysis for all randomized subjects. Missing delirium data for the ITT analysis was filled in using our definition of AMS, as assessed via chart review. 2) An analysis of the per-protocol group (PPG), which excluded individuals who did not receive the study drug after randomization, who withdrew consent, or who were transferred to the ICU and did not continue to receive delirium assessments. 3) Since short hospitalization decreases both the risk for delirium and the opportunity to measure its occurrence, we completed an analysis in PPG subjects who completed at least two nights on the study before discharge. We performed these first three analyses using CAM as the outcome measure. 4), Given the reported low sensitivity of CAM and the results of the first 3 pre-specified analyses, we conducted a *post hoc* analysis using a broader definition of delirium by combining those who were CAM+ with those who were AMS positive (CAM- but AMS+).

Lastly, we compared the characteristics and secondary sleep outcomes in the two groups that became delirious (the first group included only the CAM+ subjects and the second group included the CAM+ subjects as well as those who were CAM- but AMS+) vs. those who did not.

For details on statistical testing, please see Supplemental Methods.

RESULTS:

Recruitment (Figure 2):

We assessed 636 patients for eligibility. Eighty-seven patients were randomized and included in the ITT analysis, with 43 and 44 allocated to the melatonin and placebo groups, respectively. Eighteen patients did not complete the protocol and were excluded from PPG analysis: 12 patients did not receive their allocated intervention on the first night of the study and were withdrawn from the intervention; 2 transferred to the ICU; 3 withdrew consent; 1 patient became CAM+ after enrollment but prior to receiving the intervention. The PPG

cohort therefore contained 69 patients with 36 in the melatonin group and 33 in the placebo group.

Adverse events:

One subject withdrew after experiencing nausea attributed to the study drug, which post-trial un-blinding revealed to be melatonin.

Baseline characteristics:

Population characteristics and admission diagnoses of the ITT and PPG groups are shown Table 1, with admission diagnoses for the ITT group reported in Supplemental Table 1. There were no significant differences in the reported characteristics between the melatonin and placebo groups.

Melatonin in delirium prevention:

Results for the four analyses conducted for the primary outcome are shown in Table 2. 1) ITT analysis showed an incident CAM+ rate of 15%, with 13 subjects out of 87 becoming CAM+. Four subjects (9.1%) who received placebo became delirious vs. nine (20.9%) who received melatonin (95% CI −5.2% to 28.6%, p = 0.14). Although not significant, this trend was unexpected. 2) PPG analysis was similar - three patients (9.1%) in the placebo group vs. eight (22.2%) in the melatonin group became CAM+ (Table 2, p = 0.19). 3) Further analysis of the PPG excluded 19 patients with an unanticipated short stay of one night; the remaining 51 patients also did not demonstrate a difference in the incidence of CAM+ between groups (Table 2). 4) Finally, there were eight subjects who were CAM- but who were AMS+ (CAM-/AMS+). Considering all CAM+ plus all CAM-/AMS+ subjects, there were 12 (33.3%) in the melatonin vs. 7 (21.2%) in the placebo group (P= 0.29).

Consistent with prior literature, age, length of stay, and a lower MoCA score were associated with developing delirium [19, 20] (STable 2); however, even when controlling for these variables in a conditional analysis, melatonin did not protect against delirium (STable 3).

Melatonin and sleep in the hospital – Objective measurements:

PPG subjects (Table 3) who received melatonin had an AvNS of 539.8 min compared to 492.3 min in the placebo group (95% CI, −40.5 to 135.5; p = 0.28). AvTST was 577.0 min in the melatonin group and 536.5 min in the placebo group (95% CI, −58.2 to 139.2; p=0.41). Subjects had very fragmented sleep during the night, with average sleep bout duration of 8.7 minutes for the entire cohort and 8.8 min in the melatonin group vs. 8.6 in the placebo group (95% CI, −2.8 to 2.4; p=0.89).

Melatonin and sleep in the hospital – Subjective assessments:

RCSQ results were not significantly different between groups (Table 3).

Sleep and delirium:

A complete analysis of the objective and subjective sleep factors associated with developing delirium is reported in Supplemental Table 2. Although the data tended to support decreased

sleep duration in those who became delirious, only sleep fragmentation was significantly associated with developing delirium. When combining the CAM+ with the CAM-/AMS+ population (as done in analysis #4 above), a shorter average sleep bout length was associated delirium (95%CI, 0.3 to 4.7, p=0.03), with an average sleep bout length of 7.0±3.0 minutes in those who became delirious and 9.5±5.3 minutes in those who did not. When this sleep fragmentation finding was carried forward in a multivariable analysis that included age and length of stay, the results were not significant (STable 4; p=0.17).

DISCUSSION:

Our study tested the efficacy of melatonin in an elderly, hospitalized population while also examining inpatient sleep in the context of incident delirium. We did not find that 3 mg of melatonin reduced incident delirium in non-ICU elderly patients, nor did it significantly improve sleep duration or subjective sleep quality. While our results did not allow for an evaluation of sleep as the underlying mechanism of melatonin in delirium prevention, we did observe severe sleep fragmentation in the hospital.

There was not a significant difference in delirium between groups despite analyses accounting for the 1) traditional ITT group, 2) completion of the protocol, 3) short length of stay, and 4) a liberalized definition of delirium. Our findings differ from some,[13, 14] but not all,[21] prior studies of prophylactic melatonin for delirium prevention. Multiple possible reasons exist for these differences and similarities. First, the dose, duration of use, and timing relative to the endogenous circadian rhythm are likely important. Based on our hypothesis of the mechanism of action of melatonin – improved sleep duration – we chose a dose intended to improve sleep duration, rather than a smaller dose (e.g., 0.5 mg) that might be sufficient to improve circadian rhythm entrainment.[22, 23] Our negative findings are similar to de Jonghe et al.[21], who also used 3 mg. Studies using a dose of 0.5 mg [14] may have prevented delirium via circadian effects, although personalized timing relative to the endogenous circadian rhythm, if necessary to improve efficacy or prevent harm, is difficult. Some studies that have shown benefit, such as Hatta et al.,[15] administered medication for seven days (comparatively, our patients had shorter LOS), suggesting melatonin or melatonin agonists may prevent delirium in those hospitalized for longer periods of time. For example, others have shown a benefit of melatonin or MRAs on delirium incidence in critically ill patients who have longer LOS, or in other populations such as those undergoing elective surgeryery.[13, 15] Thus, the findings in our study may not apply to all patient populations.

Although our data conflict with other trials that suggest benefit from melatonin, the validity of our results is bolstered by our findings that age, LOS, and the presence of MCI or dementia were clear predictors of delirium, consistent with prior studies.[19, 20] The non-significant trend we observed of increased delirium in the melatonin group must be interpreted with caution. In theory, exogenous melatonin administered at inappropriate times relative to endogenous melatonin release might be harmful. However, the overall rate of delirium in our population is consistent with previously reported rates, and we know of no other studies that have suggested harm. Overall, our study adds to the somewhat mixed

results regarding melatonin in delirium prevention,[24] and supports the notion that non-pharmacological therapies remain the cornerstone of delirium prevention efforts.[25, 26]

While melatonin did not significantly improve sleep duration, we noted the melatonin group averaged approximately 40 minutes more nighttime sleep vs. placebo, which is similar to what was seen in healthy subjects given 1mg of melatonin and exposed to a simulated ICU environment.[27] We observed substantial sleep fragmentation in this population, based on an average nighttime sleep bout length of only ~8.7 minutes. Increased sleep fragmentation was also associated with delirium development in the CAM+ plus CAM-/AMS+ group in a post-hoc, univariate analysis. While others have shown severe sleep fragmentation in the ICU (median sleep duration ~3 minutes),[28–30] this has not been well-described in non-ICU patients. Sleep fragmentation likely occurs due to multiple non-modifiable factors, including the individual, acute illness, unfamiliar environment, etc. However, staff-initiated interruptions probably contribute as well. Although repeated patient interactions are required in the management of acutely ill patients, evidence suggests that clustering nursing and laboratory interventions can improve perceived quality without compromising care.[31, 32]

We acknowledge that we did not use gold-standard polysomnography in this study given that PSG is disruptive, technically difficult and expensive. Wrist-worn actigraphy uses an accelerometer to determine rest and activity patterns, cannot offer sleep staging information or diagnose many sleep disorders, but can provide measures of basic sleep metrics such as sleep duration (generally slightly overestimated) and fragmentation.[33–35] It has been used in clinical research contexts such as Alzheimer's dementia, CHF, cancer survivors, traumatic brain injury, and limited use in the inpatient setting.[36–42]

While the RCSQ has not been validated in those with MCI or dementia, which are frequently encountered in hospitalized older patients, it is one of the few validated assessments measuring overnight sleep (not baseline sleep health), and has been used by others in delirium-related studies.[12] Subjects reported subjectively poor sleep (average score range 49–76 mm, lower scores suggesting decreased perceived sleep quality), but scores were slightly better than those obtained from ICU patients (reported averages 45–55 mm).[12, 28, 43] The melatonin group had non-significantly higher scores on all RCSQ items when compared to the placebo group, but again, with no improvement in delirium which is consistent with results from Kamdar et al.[12] Our data reinforce the need for objective sleep measurements in the hospital.

Limitations in this study include a single-center site and a number of patients who did not receive the allocated intervention. Nevertheless, we remain adequately powered for our primary outcome based on pre-specified power analysis. We did not use gold-standard neuropsychiatric assessments of delirium, but rather relied on CAM administered by bedside clinicians trained in its use.[44] Although we did not assess for inter-rater reliability or assessment timing, we undertook substantial training and provided information in written form to support bedside assessments, which may not be feasible in a non-research setting. There are concerns about sensitivity with use of CAM,[17, 45, 46] which is why we performed a rigorous chart review to assess for evidence of altered mental status despite CAM-

measurements. Regardless, this did not impact the study results, and delirium prevalence in our cohort matched other published data.

In conclusion, melatonin 3 mg administered to newly admitted elderly patients did not prevent delirium, nor did it improve subjective or objective measures of sleep. Sleep fragmentation was substantial in this population and requires further study to determine if important in delirium pathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Sources of support: This research was funded in part by a NIH/NCATS flagship Clinical and Translational Science Award Grant (KL2 TR001112 and UL1 TR001114), and a Scripps Clinic Medical Group Research and Education Grant

REFERENCES

1. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: asystematic literature review. Age and ageing. 2006;35:350–364. [PubMed: 16648149]
2. Avelino-Silva TJ, Campora F, Curiati JA, Jacob-Filho W. Association between delirium superimposed on dementia and mortality in hospitalized older adults: A prospective cohort study. PLoS Med. 2017;14:e1002264. [PubMed: 28350792]
3. McCusker J, Cole M, Abrahamowicz M, Primeau F, Belzile E. Delirium predicts 12-month mortality. Archives of internal medicine. 2002;162:457–463. [PubMed: 11863480]
4. Basinski JR, Alfano CM, Katon WJ, Syrjala KL, Fann JR. Impact of delirium on distress, health-related quality of life, and cognition 6 months and 1 year after hematopoietic cell transplant. Biol Blood Marrow Transplant. 2010;16:824–831. [PubMed: 20100587]
5. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. Lancet. 2014;383:911–922. [PubMed: 23992774]
6. Salluh JI, Wang H, Schneider EB, et al. Outcome of delirium in critically ill patients: systematic review and meta-analysis. BMJ. 2015;350:h2538. [PubMed: 26041151]
7. McCusker J, Cole MG, Dendukuri N, Belzile E. Does delirium increase hospital stay? Journal of the American Geriatrics Society. 2003;51:1539–1546. [PubMed: 14687382]
8. Chen CC, Li HC, Liang JT, et al. Effect of a Modified Hospital Elder Life Program on Delirium and Length of Hospital Stay in Patients Undergoing Abdominal Surgery: A Cluster Randomized Clinical Trial. JAMA Surg. 2017;152:827–834. [PubMed: 28538964]
9. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. JAMA. 2010;304:443–451. [PubMed: 20664045]
10. Neufeld KJ, Yue J, Robinson TN, Inouye SK, Needham DM. Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis. Journal of the American Geriatrics Society. 2016;64:705–714. [PubMed: 27004732]
11. Inouye SK. Prevention of delirium in hospitalized older patients: risk factors and targeted intervention strategies. Annals of medicine. 2000;32:257–263. [PubMed: 10852142]
12. Kamdar BB, King LM, Collop NA, et al. The effect of a quality improvement intervention on perceived sleep quality and cognition in a medical ICU. Critical care medicine. 2013;41:800–809. [PubMed: 23314584]
13. Sultan SS. Assessment of role of perioperative melatonin in prevention and treatment of postoperative delirium after hip arthroplasty under spinal anesthesia in the elderly. Saudi J Anaesth. 2010;4:169–173. [PubMed: 21189854]

14. Al-Aama T, Brymer C, Gutmanis I, Woolmore-Goodwin SM, Esbaugh J, Dasgupta M. Melatonin decreases delirium in elderly patients: a randomized, placebo-controlled trial. International journal of geriatric psychiatry. 2011;26:687–694. [PubMed: 20845391]
15. Hatta K, Kishi Y, Wada K, et al. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. JAMA psychiatry. 2014;71:397–403. [PubMed: 24554232]
16. van Eijk MM, van den Boogaard M, van Marum RJ, et al. Routine use of the confusion assessment method for the intensive care unit: a multicenter study. American journal of respiratory and critical care medicine. 2011;184:340–344. [PubMed: 21562131]
17. Kuczmarska A, Ngo LH, Guess J, et al. Detection of Delirium in Hospitalized Older General Medicine Patients: A Comparison of the 3D-CAM and CAM-ICU. J Gen Intern Med. 2016;31:297–303. [PubMed: 26443577]
18. Richards KC, O'Sullivan PS, Phillips RL. Measurement of sleep in critically ill patients. J Nurs Meas. 2000;8:131–144. [PubMed: 11227580]
19. Ranhoff AH, Rozzini R, Sabatini T, Cassinadri A, Boffelli S, Trabucchi M. Delirium in a sub-intensive care unit for the elderly: occurrence and risk factors. Aging Clin Exp Res. 2006;18:440–445. [PubMed: 17167309]
20. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: a systematic review and meta-analysis. Age and ageing. 2014;43:326–333. [PubMed: 24610863]
21. de Jonghe A, van Munster BC, Goslings JC, et al. Effect of melatonin on incidence of delirium among patients with hip fracture: a multicentre, double-blind randomized controlled trial. CMAJ. 2014;186:E547–556. [PubMed: 25183726]
22. Lewy AJ, Ahmed S, Jackson JM, Sack RL. Melatonin shifts human circadian rhythms according to a phase-response curve. Chronobiol Int. 1992;9:380–392. [PubMed: 1394610]
23. Deacon S, Arendt J. Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. Brain research. 1995;688:77–85. [PubMed: 8542325]
24. Chen S, Shi L, Liang F, et al. Exogenous Melatonin for Delirium Prevention: a Meta-analysis of Randomized Controlled Trials. Mol Neurobiol. 2015.
25. Inouye SK, Bogardus ST, Jr., Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. N Engl J Med. 1999;340:669–676. [PubMed: 10053175]
26. Inouye SK, Bogardus ST, Jr., Williams CS, Leo-Summers L, Agostini JV. The role of adherence on the effectiveness of nonpharmacologic interventions: evidence from the delirium prevention trial. Archives of internal medicine. 2003;163:958–964. [PubMed: 12719206]
27. Huang HW, Zheng BL, Jiang L, et al. Effect of oral melatonin and wearing earplugs and eye masks on nocturnal sleep in healthy subjects in a simulated intensive care unit environment: which might be a more promising strategy for ICU sleep deprivation? Critical care. 2015;19:124. [PubMed: 25887528]
28. Elliott R, McKinley S, Cistulli P, Fien M. Characterisation of sleep in intensive care using 24-hour polysomnography: an observational study. Critical care (London, England). 2013;17:R46.
29. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. American journal of respiratory and critical care medicine. 2001;163:451–457. [PubMed: 11179121]
30. Drouot X, Bridoux A, Thille AW, et al. Sleep continuity: a new metric to quantify disrupted hypnograms in non-sedated intensive care unit patients. Critical care. 2014;18:628. [PubMed: 25420997]
31. Bartick MC, Thai X, Schmidt T, Altaye A, Solet JM. Decrease in as-needed sedative use by limiting nighttime sleep disruptions from hospital staff. Journal of hospital medicine : an official publication of the Society of Hospital Medicine. 2010;5:E20–24.
32. Yoder JC, Yuen TC, Churpek MM, Arora VM, Edelson DP. A prospective study of nighttime vital sign monitoring frequency and risk of clinical deterioration. JAMA Intern Med. 2013;173:1554–1555. [PubMed: 23817602]
33. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep. 2003;26:342–392. [PubMed: 12749557]

34. Marino M, Li Y, Rueschman MN, et al. Measuring sleep: accuracy, sensitivity, and specificity of wrist actigraphy compared to polysomnography. Sleep. 2013;36:1747–1755. [PubMed: 24179309]
35. Sadeh A, Hauri PJ, Kripke DF, Lavie P. The role of actigraphy in the evaluation of sleep disorders. Sleep. 1995;18:288–302. [PubMed: 7618029]
36. Ancoli-Israel S, Clopton P, Klauber MR, Fell R, Mason W. Use of wrist activity for monitoring sleep/wake in demented nursing-home patients. Sleep. 1997;20:24–27. [PubMed: 9130330]
37. Fetveit A, Bjorvatn B. Sleep disturbances among nursing home residents. International journal of geriatric psychiatry. 2002;17:604–609. [PubMed: 12112156]
38. Redeker NS, Muench U, Zucker MJ, et al. Sleep disordered breathing, daytime symptoms, and functional performance in stable heart failure. Sleep. 2010;33:551–560. [PubMed: 20394325]
39. Alexander S, Minton O, Andrews P, Stone P. A comparison of the characteristics of disease-free breast cancer survivors with or without cancer-related fatigue syndrome. Eur J Cancer. 2009;45:384–392. [PubMed: 18977131]
40. Duclos C, Dumont M, Blais H, et al. Rest-Activity Cycle Disturbances in the Acute Phase of Moderate to Severe Traumatic Brain Injury. Neurorehabil Neural Repair. 2014;28:472–482. [PubMed: 24379082]
41. Grossman MN, Anderson SL, Worku A, et al. Awakenings? Patient and Hospital Staff Perceptions of Nighttime Disruptions and Their Effect on Patient Sleep. J Clin Sleep Med. 2017;13:301–306. [PubMed: 27923432]
42. Missildine K, Bergstrom N, Meininger J, Richards K, Foreman MD. Sleep in hospitalized elders: a pilot study. Geriatr Nurs. 2010;31:263–271. [PubMed: 20682404]
43. Kamdar BB, Shah PA, King LM, et al. Patient-nurse interrater reliability and agreement of the Richards-Campbell sleep questionnaire. Am J Crit Care. 2012;21:261–269. [PubMed: 22751369]
44. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Critical care medicine. 2001;29:1370–1379. [PubMed: 11445689]
45. Neufeld KJ, Hayat MJ, Coughlin JM, et al. Evaluation of two intensive care delirium screening tools for non-critically ill hospitalized patients. Psychosomatics. 2011;52:133–140. [PubMed: 21397105]
46. Han JH, Wilson A, Graves AJ, et al. Validation of the Confusion Assessment Method for the Intensive Care Unit in older emergency department patients. Acad Emerg Med. 2014;21:180–187. [PubMed: 24673674]

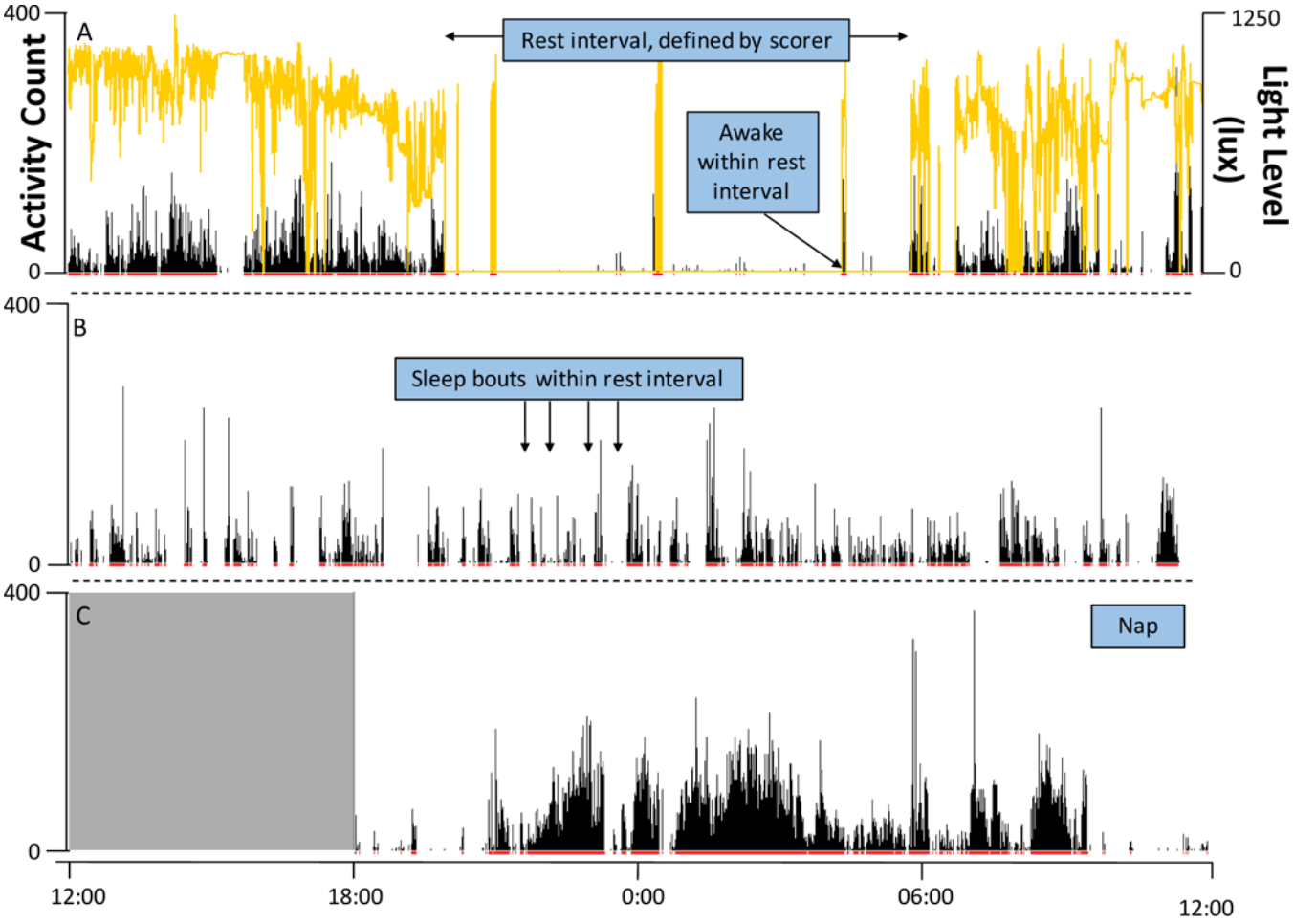

Figure 1. Actigraphy analysis methods and terms.

Vertical lines represent the activity count in a 15 second epoch. Red markers at base of actigraphy bars represent epochs scored as awake by the software/algorithm. Light channel (yellow) removed from panels B and C in order to demonstrate activity patterns. **A. Hospitalized adult with long sleep bouts.** Rest intervals (light blue background) are determined by the scorer, using decreased activity levels and light level changes, as periods where the subject is likely to be sleeping/trying to sleep. Sleep bouts within the rest interval are determined by the software's algorithm which scores sleep or wake based on activity count thresholds in a particular epoch and multiple surrounding epochs; the sum total of these sleep bouts give the total duration of sleep within a particular interval. Please note the clear changes in activity level between daytime and nighttime, and also the minimal amount of wrist activity during sleep for this individual. **B. Hospitalized adult with short sleep bouts.** Here, sleep within the rest interval is characterized by multiple short sleep bouts (examples shown with arrows in this panel), suggesting substantial sleep fragmentation. **C. Acutely ill, hospitalized adult with CAM+ delirium.** This individual was noted to become delirious overnight. Note the increased and prolonged activity during the night as well as the lack of sleep. Daytime rest periods ≥ 30 minutes were designated as naptime rest intervals; naps were summed together with the NS to determine the total sleep time (TST) for a 24-hour period. Gray area in this panel is time prior to the start of the device's recording.

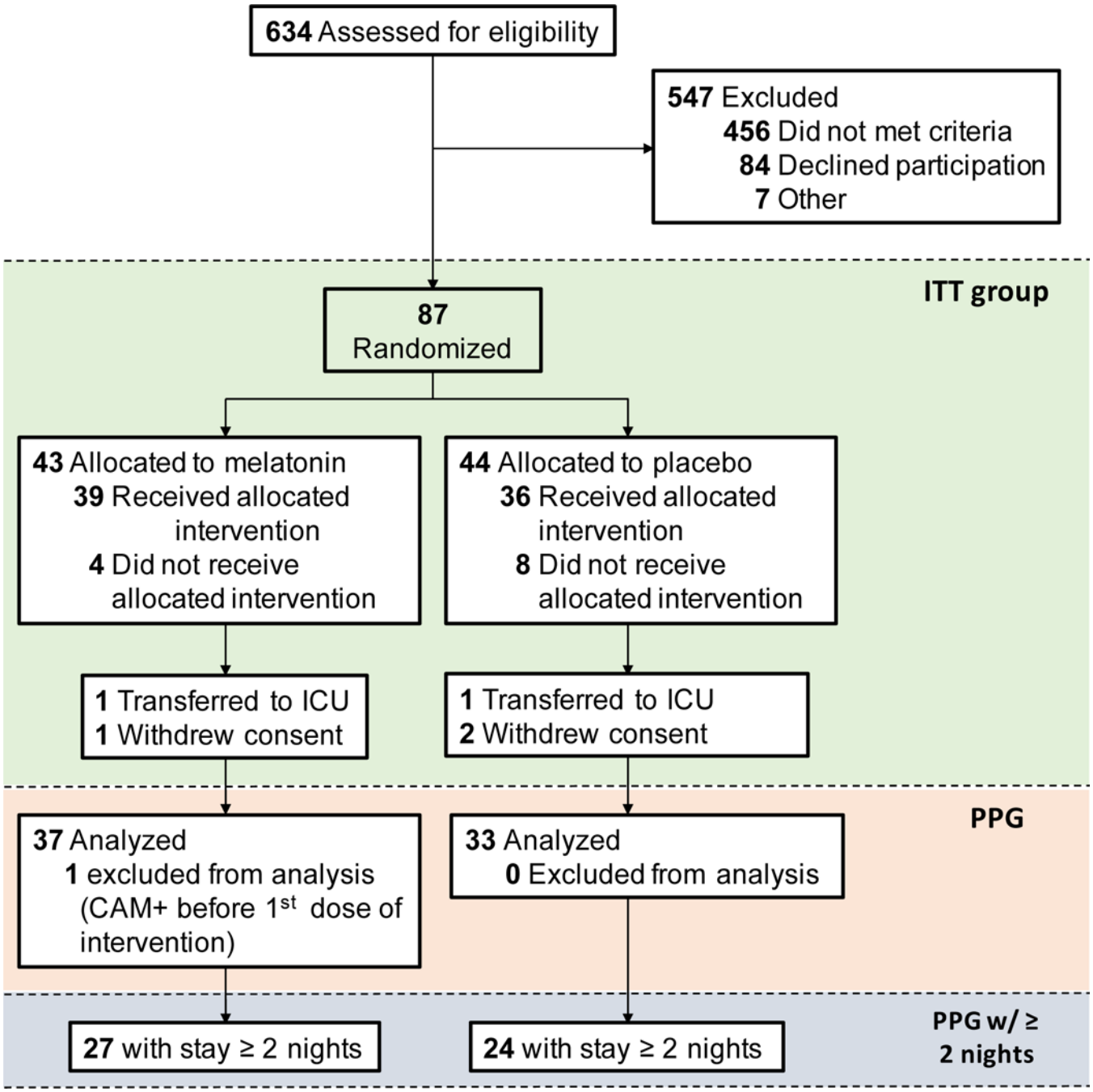

Figure 2. Participant Flow Diagram.

Of the 634 patients for eligibility, 456 individuals met exclusion criteria: 46.5% of patients were not expected to stay more than 2 nights, 15.1% had AMS on admission or prior to enrollment, 6.1% were NPO/unable to swallow, 5.0% were already on a scheduled antipsychotic medication, 4.1% could not consent due to a language barrier, 4.1% were excluded based on the request of the attending physician, 3.7% had cirrhosis, 2.8% had an existing seizure disorder, and the remaining patients were excluded for other reasons (e.g. known brain tumors, transfer to a different service, last 48 hours of life, etc.). 84 patients

declined participation after investigators discussed the study with them. There were 7 patients who enrolled but were not assigned to receive medication due to pharmacy error, unexpected discharge, or transfer to the ICU before the subject could be randomized. 87 patients were randomized; however, 12 subjects did not receive the allocated intervention due to the following: 2 individuals had difficulty with swallowing at time of medication administration, 1 patient wanted a stronger sleeping medication, 3 withdrew consent, there were 1 nursing errors in giving the patient medication, 2 consulting surgeons did not want the patient to receive the medication, and the remaining 3 were pharmacy errors related to dispensing the medication. 69 subjects were included in the final per-protocol group (PPG). ITT = intention-to-treat. CAM = Confusion Assessment Method.

Table 1.

Baseline Characteristics of the Patients in Per-Protocol Group

	Intention-to-Treat		Per-Protocol	
Characteristic	**Melatonin (N = 43)**	**Placebo (N = 44)**	**Melatonin (N = 36)**	**Placebo (N = 33)**
Female Sex – no. (%)	25 (58.1)	29 (65.9)	21 (58.3)	21 (63.6)
Age (±SD)	81.2±7.3	80.1±8.3	81.5±6.9	79.9±7.9
Race or ethnic group – no. (%)				
White	40 (93.0)	40 (90.9)	33 (91.7)	29 (87.9)
Underwent an Operation – no (%)	8 (18.6)	12 (27.3)	7 (19.4)	8 (24.2)
Median Length of Stay (LOS) – days (IQR)	3.0 (2.0 to 5.0)	3.0 (2.0 to 4.0)	3 (2.0 to 5.0)	3.0 (2.0 to 4.0)
Charlson Comorbidity Index (±SD)	2.7±2.0	2.4±1.9	3.0±2.0	2.4±1.7
Age-Adjusted Charlson Comorbidity Index (±SD)	6.4±2.4	6.0±2.2	6.7±2.3	6.0±2.1
Montreal Cognitive Assessment (±SD)	22.2±6.1	22.1±4.4	22.4±6.3	22.0±4.4

Intention-to-treat and Per-protocol group baseline characteristics. Demographic information included gender, age, race, operative/non-operative reason for admission, and length of stay. Additionally, we examined the baseline comorbidities of the patients, their baseline cognitive function, as well as the presence of insomnia. For context, a Charslon Comorbidity Index of 3 corresponds to a 77% estimated 10-year survival; the age-adjusted Charlson Comorbidity Index adds an additional point for ever decade of life >50. Accordingly, a score of 6 corresponds to a 2% estimated10-year survival. using the Charlson Comorbidity Index and the age-adjusted Charlson Comorbidity Index. A score of ≥ 26 on the Montreal Cognitive Assessment is considered normal, while a score between 22–26 generally indicates mild cognitive impairment. IQR = Interquartile range. SD = standard deviation.

Table 2.

Primary Outcome – Four analyses of delirium incidence

	Group	Delirium Measurement	Melatonin	Placebo	Relative Risk	(95% CI)	P
1	**ITT**	**CAM** CAM+/N in group (%)	9/43 **(22.2)**	4/44 **(9.1)**	2.3	(0.8 to 6.9)	0.14
2	**PPG**	**CAM** CAM+/N in group (%)	8/36 **(22.2)**	3/33 **(9.1)**	2.4	(0.7 to 8.4)	0.16
3	**PPG** – ≥ 2 nts	**CAM** CAM+/N in group (%)	6/27 **(22.2)**	2/24 **(8.3)**	1.6	(0.7 to 3.4)	0.27
4	**PPG**– Expanded delirium	**CAM+ and CAM−/AMS+** CAM+, plus AMS+/N in group (%)	12/36 **(33.3)**	7/33 **(21.2)**	2.7	(0.6 to 12.0)	0.20

Analysis of delirium incidence. Delirium incidence was examined in four separate analyses. In analysis 1–3, the ITT and per-protocol groups were examined for delirium incidence using only the CAM assessments, with the 3rd analysis including only those in the PPG who completed at least 2 nights of the study. The 4th analysis was also completed in the PPG using an expanded definition of delirium which included those who were CAM + as well as those who were CAM− but AMS+. No difference in delirium incidence was found between subjects who received melatonin vs. placebo groups in any method of analysis. Relative risk of < 1.0 suggests benefit of melatonin, while greater than >1.0 suggests harm. ITT = intention-to-treat; PPG = per-protocol group. (those who completed the protocol); CAM = Confusion Assessment Method; AMS = Altered mental status.

Table 3.

Secondary Outcome – Sleep Characteristics in Per-Protocol Group

Variable	Melatonin (N=36)	Placebo (N=33)	(95% CI)	P
Objective sleep – Actigraphy Measurements				
Average Nighttime Sleep - minutes (±SD)	539.8±134.8	492.3±194.4	(−41.9 to 136.8)	0.29
Average Total Sleep Time (minutes)	577.0±169.1	536.5±203.3	(−58.2 to 139.2)	0.41
Average length of nighttime sleep bout (minutes)	8.6±5.6	8.8±3.9	(−2.8 to 2.4)	0.89
Subjective Sleep – RCSQ Answers				
RCSQ – Total (sleep efficiency index)	71.4	63.6	(−3.9 to 19.5)	0.19
Question 1 (sleep depth) – mm (±SD)	57.1±32.5	49.2±30.7	(−8.7 to 24.5)	0.34
Question 2 (falling asleep) – mm (±SD)	72.2±24.9	63.0±20.8	(−5.7 to 24.1)	0.22
Question 3 (number of awakenings) – mm (±SD)	76.2±22.1	62.9±29.5	(−0.5 to 27.1)	0.06
Question 4 (% of time awake) – mm (±SD)	72.9±27.0	57.3±33.4	(−0.3 to 31.6)	0.05
Question 5 (sleep quality) – mm (±SD)	66.1±29.5	62.6±30.6	(−12.4 to 19.5)	0.66

Objective and subjective sleep results. Both objective and subjective sleep characteristics were calculated for the per-protocol group and compared between the two arms.