



Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Lange, PW;Turbic, A;Soh, CH;Clayton-Chubb, D;Lim, WK;Conyers, R;Watson, R;Maier, AB

Title:

Melatonin does not reduce delirium severity in hospitalized older adults: Results of a randomized placebo-controlled trial

Date:

2024-06

Citation:

Lange, P. W., Turbic, A., Soh, C. H., Clayton-Chubb, D., Lim, W. K., Conyers, R., Watson, R. & Maier, A. B. (2024). Melatonin does not reduce delirium severity in hospitalized older adults: Results of a randomized placebo-controlled trial. *Journal of The American Geriatrics Society*, 72 (6), pp.1802-1809. <https://doi.org/10.1111/jgs.18825>.




Persistent Link:

<https://hdl.handle.net/11343/351414>

License:

[CC BY-NC](#)

BRIEF REPORT**Melatonin does not reduce delirium severity
in hospitalized older adults: Results of a randomized
placebo-controlled trial**

Peter W. Lange MBBS^{1,2}  | **Alisa Turbić BSc³** | **Cheng Hwee Soh PhD¹** |
Daniel Clayton-Chubb MD^{4,5,6}  | **Wen Kwang Lim MD¹** |
Rachel Conyers PhD^{7,8} | **Rosie Watson PhD^{1,9}** | **Andrea B. Maier PhD^{10,11,12}** 

¹Department of Aged Care and Medicine, The Royal Melbourne Hospital, Melbourne Medical School, The University of Melbourne, Parkville, Victoria, Australia

²Department of Geriatrics and General Medicine, Werribee Mercy Hospital, Werribee, Victoria, Australia

³Bone and Fractures Research Program, Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Victoria, Australia

⁴Department of Gastroenterology, Alfred Health, Prahran, Victoria, Australia

⁵Department of Gastroenterology, Eastern Health, Box Hill, Victoria, Australia

⁶Department of Medicine, Central Clinical School, Monash University, Victoria, Australia

⁷Department of Paediatrics, The University of Melbourne, Parkville, Victoria, Australia

⁸Heart Disease, Stem Cell Biology, Murdoch Children's Research Institute, Parkville, Victoria, Australia

⁹Population Health and Immunity Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Australia

¹⁰Department of Human Movement Sciences, @AgeAmsterdam, Faculty of Behavioural and Movement Sciences, Vrije Universiteit Amsterdam, Amsterdam Movement Sciences, Amsterdam, The Netherlands

¹¹Healthy Longevity Translational Research Program, Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Singapore

¹²Centre for Healthy Longevity, @AgeSingapore, National University Health System, Singapore, Singapore

Correspondence

Peter W. Lange, Werribee Mercy Hospital,
300 Princes Highway, Werribee,
VIC 3031, Australia.
Email: peterwlangecorrespondence@gmail.com

Funding information

Royal Melbourne Hospital

Abstract

Background: Delirium is common in older inpatients, causing distress, cognitive decline, and death. Current therapies are unsatisfactory, limited by lack of efficacy and adverse effects. There is an urgent need for effective delirium treatment. Sleep wake cycle is disturbed in delirium; endogenous Melatonin is perturbed, and exogenous Melatonin is a safe and effective medication for sleep disorders.

This study aims to determine the effect of oral Melatonin 5 mg immediate release (IR) nightly for five nights on the severity of delirium in older (≥ 65 years) medical inpatients.

Methods: This was a double-blinded, randomized controlled trial in general internal medicine units of a tertiary teaching hospital.

Older inpatients with Confusion Assessment Method positive, hyperactive or mixed delirium within 48 h of admission or onset of in-hospital delirium were

Andrea Maier and Rosie Watson are joint final authors.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial](https://creativecommons.org/licenses/by-nc/4.0/) License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes.

© 2024 The Authors. *Journal of the American Geriatrics Society* published by Wiley Periodicals LLC on behalf of The American Geriatrics Society.

included. The primary outcome was change in delirium severity measured with the Memorial Delirium Assessment Scale (MDAS).

A previous pilot trial showed 120 participants randomized 1:1 to Melatonin or Placebo would provide 90% power to demonstrate a 3-point reduction in the MDAS.

Results: One hundred and twenty participants were randomized, 61 to Melatonin 5 mg and 59 to Placebo. The medication was well tolerated. The mean MDAS improvement was 4.9 (SD 7.6) in the Melatonin group and 5.4 (SD 7.2) in the Placebo group, p -value 0.42, a non-significant difference. A post-hoc analysis showed length of stay (LOS) was shorter in the intervention group (median 9 days [Interquartile Range (IQR) 4, 12] vs. Placebo group 10 [IQR 6, 16] p -value = 0.033, Wilcoxon Rank Sum test).

Conclusions: This trial does not support the hypothesis that Melatonin reduces the severity of delirium. This may be due to no effect of Melatonin, a smaller effect than anticipated, an effect not captured on a multidimensional delirium assessment scale, or a type II statistical error. Melatonin may improve LOS; this hypothesis should be studied.

KEYWORDS

aged neurocognitive disorders, delirium, inpatients, melatonin, sepsis-associated encephalopathy, sleep wake disorders

INTRODUCTION

Delirium is a geriatric syndrome frequently found in older adults in hospitals often undiagnosed.¹⁻³ Delirium can cause irreversible cognitive impairment (CI), functional decline, long-term care transition, health care costs, and death.⁴⁻⁸ Delirium is characterized by disturbance of attention, consciousness, hallucinations, delusions, and/or motor activity (hyperactive, hypoactive, normal, and mixed types), following a fluctuating course with acute onset.⁹ Changes in circadian rhythm affecting sleep are frequent, and a potential mechanism links delirium and sleep.^{10,11} There are currently no effective treatments available for delirium, antipsychotics have modest efficacy for severe symptoms of delirium but are associated with significant adverse effects and are not recommended for routine use.¹²⁻¹⁴

Melatonin is a neurotransmitter and hormone from the pineal gland that regulates circadian rhythm. Melatonin secretion is perturbed in delirium: low levels of urinary metabolites in hyperactive delirium, and high levels in hypoactive motor states.¹⁵⁻¹⁷ There have been multiple studies evaluating the potential role of Melatonin (or Melatonin receptor agonists) in preventing delirium in hospitalized adults, though results have been mixed.¹⁸ There is little study on the use of Melatonin for established delirium. We conducted a pilot that found a

Key points

- Participants were older medical inpatients with hyperactive or mixed delirium who were not planned for surgery.
- Adherence to the study medication was good and the therapy was safe.
- Melatonin 5 mg nightly for five nights in older medical inpatients did not reduce the severity of delirium.
- Sleep improved.

Why does this paper matter?

There are no known non-pharmacological or pharmacological therapies that improve the history of delirium; this trial shows that while Melatonin has many promising properties given the frequent disturbance of circadian rhythm and Melatonin's beneficial influence on that, in the treatment of delirium in this setting it did not reduce delirium severity. Multicomponent non-pharmacological interventions remain the mainstay of prevention and treatment of delirium.

definitive study of the hypothesis that 5 mg immediate release melatonin nightly for five nights would reduce the severity of delirium in older medical inpatients would be feasible, and 120 participants (anticipating a 30% drop-out rate) would have 90% power to demonstrate a statistically significant outcome.¹⁹

This study aims to determine if 5 mg immediate release of Melatonin nightly for five nights reduces the severity of delirium in older medical inpatients with delirium.

METHODS

This was a double-blinded, randomized, placebo-controlled trial of Melatonin immediate release 5 mg nightly for five nights versus placebo, conducted at a 550 bed university teaching hospital that provides free healthcare to an

ethnically and socio-economically diverse area of Melbourne, Australia. The Royal Melbourne Hospital has an extensive residential care Inreach and Hospital-In-The-Home service, but these patients were not eligible. The protocol and power calculation were based on a pilot study by the same group, with the addition of an inclusion criteria that enrollment was within 2 days of admission or onset of delirium.¹⁹ Participants were identified via the institution's screening procedure with 4AT, confirmed with the Confusion Assessment Method (CAM), and enrolled if they met inclusion (>65 years, not for surgery and others) and not exclusion criteria. Primary outcome was a change in the Memorial Delirium Assessment Scale (MDAS), measured daily by trained research staff for 5 days of intervention and followed for a further 2 days. Six-month follow-up for cognition and other outcomes was planned. The study was approved (MHHREC2019.043) by our institute Human Research Ethics Committee (HREC) and conducted in

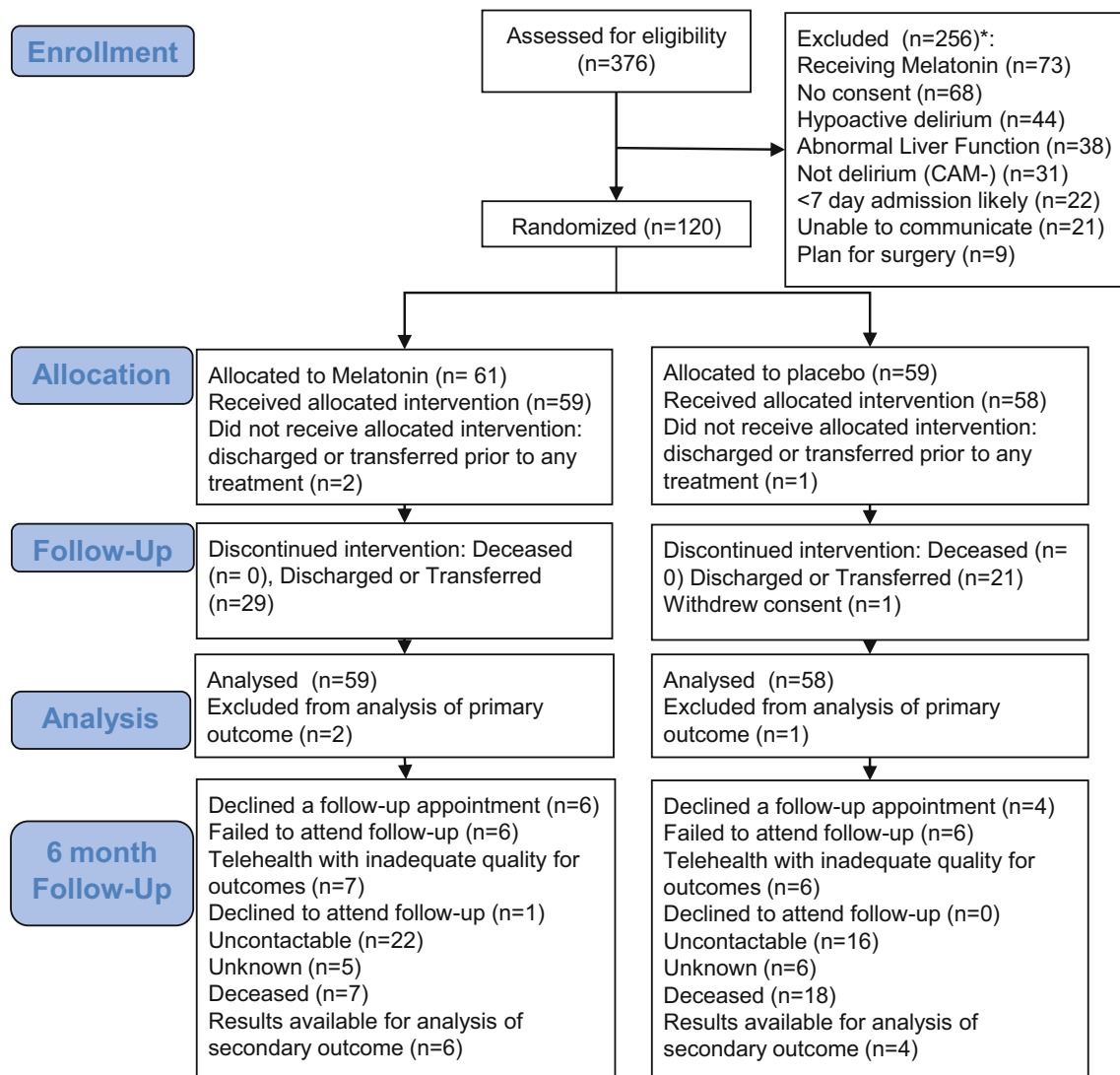


FIGURE 1 CONSORT diagram.

concordance with the Declaration of Helsinki. The trial is registered with the Australia New Zealand Clinical Trials Registry (ACTRN12619000034134). Reporting conforms to CONSORT 2010 guidelines. Full details of methods are available in the supplementary file.

RESULTS

Participants and adherence to the protocol

During the study period, 376 potential participants were assessed for eligibility, 256 were excluded for reasons illustrated in Figure 1. Of the 256 patients excluded, 68 patients' surrogate decision-makers declined to consent to participation (39% of otherwise suitable potential participants). Forty-four (17%) exclusions were due to hypoactive delirium. Therefore, 120 participants met inclusion criteria, consented, and were randomized according to the study methodology. Table 1 shows the baseline characteristics of the participants. Participants were recruited between March 2021 and March 2022 when planned recruitment was achieved. More patients in the Melatonin group lived in residential care (18% vs. 8.5%), and few overall. Both randomization arms were otherwise well-balanced.

TABLE 1 Baseline characteristics of the study participants.

Characteristic	Melatonin (n = 59)	Placebo (n = 58)
Age-years	87.1 ± 6.6	87.1 ± 6.9
Female sex	30 (51%)	32 (52%)
sMMSE at study entry	12.1 ± 7.3	13.3 ± 5.8
Baseline MDAS (0–30)	14.2 ± 4.1	14.7 ± 4.4
Alcohol standard units/day >0	11 (18%)	13 (22%)
IQCODE ≥3.45 and/or Dementia Diagnosis	33 (56%)	34 (59%)
Delirium at admission	45 (76%)	45 (78%)
History of depression	15 (25%)	14 (24%)
Age Adjusted CCI (0–40)	2.0 (1.8)	1.9 (2.1)
Katz index of ADLs (0–6)	4.1 (1.9)	4.3 (2.0)
Years of education	8.4 ± 3.3	8.2 ± 3.5
Living in supported accommodation	11 (18%)	5 (9%)
Receiving home supports	36 (59%)	35 (59%)

Note: Values are presented as mean ± SD unless indicated otherwise. Abbreviations: CCI, Charlson Comorbidity Scale; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly, range 0–5; Katz index of ADLs, Katz index of activities of daily living; MDAS, Memorial Delirium Assessment Scale;

Two patients in the Melatonin group and one in the Placebo group were discharged or transferred out of the study site before receiving any intervention, so were not included in the analysis. No participants deceased during the study period, 29 were discharged or transferred out of the study site prior to completion of the study period in the Melatonin group, and 21 in the Placebo group. One participant in the Placebo group had surrogate consent withdrawn prior to the completion of the study period.

There was one protocol violation due to an error in the dispensing instructions through the electronic medical record where three participants were ordered eight capsules per night. No adverse effect resulted. Further details are available in the supplementary file. Results were analyzed with and without these participant's results without substantial difference; the results presented include these participants.

Primary and secondary outcome analysis

The mean improvement (reduction) in MDAS from baseline score during treatment was 4.9 (SD 7.6) in the Melatonin group and 5.4 (SD 7.3) in the Placebo group, difference of differences 0.5 (95% C.I. –3.2, 2.2) *p*-value 0.43 (Student's *t*-test), a non-significant difference. In a pre-specified subgroup analysis by pre-morbid CI, there was a suggestion of less improvement with melatonin treatment in the group without CI: Placebo group mean MDAS improvement 7.1 (8.4) versus Melatonin group mean MDAS improvement 4.9 (SD 8.2); *p*-value 0.040. In exploratory analyses of secondary outcomes there was a suggestion of improved sleep in the group with CI (Placebo median 0, IQR [0,2]) Melatonin 0, [0,2] *p* = 0.045 Wilcoxon Rank-Sum test). Safety-related outcomes were not significantly different. No adverse events related to Melatonin use occurred. Further results are displayed in Table 2.

In the pilot trial, the standard deviation for the primary outcome was 5.0 for melatonin and placebo 4.1, smaller than in this trial. The median duration of admission to enrolment was 6 days (IQR 4, 9) versus this trial: 1 day (IQR 1, 3) that may explain this difference. In keeping with this, drop-out rates were higher in this trial (43%) than pilot (28%), but most in the pilot dropped out due to death (five deaths out of eight dropped out), whereas in this trial due to discharge (zero deaths of 53 dropped out).

At the planned 6-month follow-up, 10 participants (8%) had results available for analysis. 25 (21%) had decreased, one (0.8%) declined to attend for follow-up, 12 (10%) failed to attend a scheduled appointment,

TABLE 2 Primary and secondary outcomes.

Outcome	Melatonin (n = 59)	Placebo (n = 58)	p-value*
Primary			
Improvement in Baseline MDAS days 1–5 (mean ± SD)	4.9 (7.6)	5.4 (7.2)	0.42
Difference	0.5 (95% CI –3.2, 2.2)		
With CI	4.8 (6.9) (n = 33)	4.2 (6.0) (n = 34)	0.40
Without CI	4.9 (8.2) (n = 26)	7.1 (8.4) (n = 24)	0.04
Secondary			
Improvement in MDAS days 6–7 (mean ± SD)	2.1 (5.4)	2.2 (5.1)	0.97
With CI	2.5 (5.4)	1.9 (5.0)	0.65
Without CI	1.7 (5.3)	2.6 (5.4)	0.57
Arousal: Proportion of mRASS = 0 (mean ± SD)	0.55 (0.39)	0.68 (0.33)	0.08
With CI	0.47 (0.41)	0.71 (0.36)	0.06
Without CI	0.64 (0.35)	0.64 (0.36)	0.47
Duration: Days CAM+	1 (1, 4)	3 (1, 4)	0.35
With CI	2 (1, 5)	1 (0, 4)	0.40
Without CI	1 (0, 3)	3 (1, 5)	0.92
Received any rescue medications	23 (39%)	24 (41%)	0.82
With CI	13 (39%)	13 (38%)	0.89
Without CI	10 (38%)	11 (46%)	0.95
Sleep quality: Nights MDAS item 10 > 0	116 (39%)	126 (43%)	0.098
With CI	32 (19%)	69 (43%)	0.045
Without CI	55 (42%)	47 (39%)	0.098

Note: Values are presented as Median inter-quartile range unless indicated otherwise.

Abbreviations: CAM, Confusion Assessment Method; CI, Premorbid cognitive impairment; MDAS, Memorial Delirium Assessment Scale range 0–30; mRASS, Richmond Agitation and Sedation Scale (–5, +4).

*Continuous, normally distributed variables assessed using Student's *t*-test, non-normally distributed Wilcoxon Rank-Sum test, categorical Fisher's Exact Test, (all values 2 sided).

13 (11%) had an appointment scheduled for telehealth but were unable to complete outcomes due to sensory or CI, 10 (8%) declined to be referred for follow-up on discharge from hospital, 38 (32%) had changed address (most often into residential care) and could not be offered an appointment and reasons for non-attendance for 11 (9%) participants could not be determined. The planned six-month outcomes and biomarker analysis were not performed because of limited data.

In a post-hoc analysis length of stay in the acute hospital was analyzed. Median length of stay for the Placebo group was 10 days (IQR 6, 16) and for the intervention 9 days (4, 12) (Wilcoxon Ranksum $p = 0.033$).

DISCUSSION

This RCT provided no evidence to support the hypothesis that Melatonin 5 mg immediate release nightly for five

nights reduces the severity of delirium by three or more points on the MDAS. This may be due to (i) no effect of Melatonin immediate release on the severity of delirium; (ii) a smaller effect than anticipated; (iii) an effect not captured on a multidimensional delirium assessment scale; (iv) an effect on a subset of the study population or (v) a type II statistical error.

This study adds to the literature regarding Melatonin and delirium. Case reports of treatment of delirium with Melatonin have been published.¹⁵ There have been three studies of melatonin prophylaxis for delirium that indicate the effect of melatonin on delirium. In a trial of 0.5 mg Melatonin in medical inpatients, Melatonin prophylaxis was successful but Melatonin did not change delirium severity.²⁰ Sultan et al. compared open label 5 mg melatonin versus clonidine, no treatment, or midazolam in older adults undergoing emergency and elective hip arthroplasty and reported reduced delirium incidence and decreased severity though this was not evaluated with a validated

scale.²¹ However, 3 mg for prophylaxis of delirium with fractured neck of femur repair improved neither frequency or severity, though the length of stay was shorter.²² One RCT of 1 mg Melatonin pre-elective hip arthroplasty and for 5 days post-operatively suggested a reduction in post-operative cognitive decline, though delirium was not diagnosed using any validated tools.²³ A RCT of 8 mg of ramelteon (a Melatonin-receptor agonist) for 7 days was also effective in reducing the incidence of delirium by DSM-IV criteria, though it had no impact on delirium severity if developed.²⁴ Thus, prior to this study, the literature held no definitive evidence of the effect of Melatonergic agents in reducing pre-existing delirium severity.

This trial does not provide evidence to refute the null hypothesis that Melatonin does not reduce delirium severity on the MDAS by three or more points in older inpatients with delirium. Our pilot trial found 120 participants would have 90% power to demonstrate a statistically significant outcome. In this trial, recruitment was achieved, and dropout as expected, suggesting against a Type 2 error as a cause of our observation of no difference in the groups, however, the variance of the outcome was larger in this trial than the pilot, that may have contributed to a Type 2 error. The margin of three points on the MDAS was derived from studies of antipsychotic agents in delirium.²⁵ It may be that Melatonin has an effect on delirium severity that is less than three points on average. This study does not provide evidence against that hypothesis and that should be studied in future studies.

The MDAS is a multi-dimensional delirium assessment scale with elements of cognition, psychomotor arousal, psychiatric symptoms, and sleep. The effect of Melatonin may be on some or one of these components resulting in no significant effect overall. On exploratory analysis, we found sleep subscales were improved and length of stay suggested an improvement in the intervention group. These findings align with previous studies reporting an effect of Melatonin on length of stay in delirious patients in different clinical settings, (e.g., cardiac and intensive care units).^{26,27} These should be regarded as hypothesis-generating.

We hypothesized that if Melatonin changed the course of delirium, it may also ameliorate late consequences such as CI. Due to frequent loss to follow-up at the 6-month follow-up appointment, we were unable to examine these outcomes. This highlights the difficulties in studying this population, and the malign and serious sequelae of the presentation. This should encourage further study to intervene on these late consequences.

Strengths of this trial include enrollment in an ethnically, culturally, and economically diverse community, rigorous randomization and blinding, pragmatic inclusion and exclusion criteria, well-matched intervention groups including cognitively impaired participants, prompt recruitment

with an acceptable ratio of enrollment to exclusion, infrequent drop-outs due to adverse events, and the use of well-validated study outcomes. Of note, exclusion due to surrogate decision maker declining consent was low: 39%.

Limitations of the trial include; single site enrollment; no selection for acute precipitants or underlying predispositions; participants unable to communicate excluded; the hypothesized effect was large; surgical patients were excluded, and the intervention was brief. Few participants lived in residential care. Physiological Melatonin secretion has a large peak after dusk then a slow reduction to dawn.²⁸ Melatonin immediate release preparations are rapidly absorbed, producing higher than physiological levels for a shorter period, with metabolism highly variable and influenced by sex.^{29,30} Therefore this study may have been limited by the non-physiological levels of Melatonin.

In summary, this study does not support the clinical use of Melatonin in older inpatients to reduce delirium severity. There were several limitations that might have affected the potential to demonstrate a benefit; these should be the focus of future research. Promising future avenues include different doses and/or release preparations, individualized dosing, larger trials to detect smaller effects, and focus on specific outcomes within delirium. Further study to define the potential role of Melatonin in the treatment of delirium is required before suggesting adoption or abandoning this approach.

AUTHOR CONTRIBUTIONS

PL initiated, developed, supervised, completed measures, analysed and wrote the final paper. AT supervised, completed measures, analysed and wrote the final paper. CS completed measures, analysed and wrote the final paper. DC, WL, RC, RW and AM developed, supervised, analysed and wrote the final paper. All authors listed above have contributed substantially to the conception or design of the work or to the acquisition, analysis, or interpretation of data for the work and have participated in drafting the work or revising it critically for important intellectual content. Additionally, each author has given their approval to the final version of the manuscript and has agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

ACKNOWLEDGMENTS

Role of the Sponsor: The study was sponsored by the Royal Melbourne Hospital, which had no role in the design, methods, subject recruitment, data collections, analysis and preparation of paper. Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

FUNDING INFORMATION

The Royal Melbourne Hospital supported the study through project funding. Protocol available from the corresponding author on request. Trial Registration: ACTRN12619000034134.

CONFLICT OF INTEREST STATEMENT

The authors have no conflicts. Description of authors' roles: PWL designed the trial, conducted the trial, collected data, statistical analysis, and wrote the paper. AT and CS conducted the trial, collected data, and contributed to writing the paper. RC, KL, and DC designed and planned the trial and wrote the paper. RW and ABM designed the trial, assisted in conducting the trial, statistical analysis, and writing the paper. We wish to thank Professor Brian Le for acting as an independent safety monitor.

SPONSOR'S ROLE

None.

ORCID

Peter W. Lange  <https://orcid.org/0000-0002-0162-1664>

Daniel Clayton-Chubb  <https://orcid.org/0000-0001-7479-9669>

Andrea B. Maier  <https://orcid.org/0000-0001-7206-1724>

REFERENCES

- Travers C, Byrne G, Pachana N, Klein K, Gray L. Prospective observational study of dementia and delirium in the acute hospital setting. *Intern Med J.* 2013;43:262-269.
- Bellelli G, Morandi A, Di Santo SG, et al. "delirium day": a nationwide point prevalence study of delirium in older hospitalized patients using an easy standardized diagnostic tool. *BMC Med.* 2016;14:106.
- Lange PW, Lamanna M, Watson R, Maier AB. Undiagnosed delirium is frequent and difficult to predict: results from a prevalence survey of a tertiary hospital. *J Clin Nurs.* 2019;28:2537-2542.
- Fong TG, Jones RN, Shi P, et al. Delirium accelerates cognitive decline in Alzheimer disease. *Neurology.* 2009;72:1570-1575.
- Vochteloo AJ, Moerman S, Tuinebreijer WE, et al. More than half of hip fracture patients do not regain mobility in the first postoperative year. *Geriatr Gerontol Int.* 2013;13:334-341.
- Krogseth M, Wyller TB, Engedal K, Juliebo V. Delirium is a risk factor for institutionalization and functional decline in older hip fracture patients. *J Psychosom Res.* 2014;76:68-74.
- Igarashi M, Okuyama K, Ueda N, et al. Incremental medical cost of delirium in elderly patients with cognitive impairment: analysis of a nationwide administrative database in Japan. *BMJ Open.* 2022;12:e062141.
- Kiely DK, Marcantonio ER, Inouye SK, et al. Persistent delirium predicts greater mortality. *J Am Geriatr Soc.* 2009;57(1):55-61.
- Wilson JE, Mart MF, Cunningham C, et al. Delirium. *Nat Rev Dis Prim.* 2020;6:90.
- FitzGerald JM, O'Regan N, Adamis D, et al. Sleep-wake cycle disturbances in elderly acute general medical inpatients: longitudinal relationship to delirium and dementia. *Alzheimers Dement (Amst).* 2017;7:61-68.
- Kyeong S, Choi SH, Eun Shin J, et al. Functional connectivity of the circadian clock and neural substrates of sleep-wake disturbance in delirium. *Psychiatry Res Neuroimag.* 2017;264:10-12.
- Thom RP, Mock CK, Teslyar P. Delirium in hospitalized patients: risks and benefits of antipsychotics. *Cleve Clin J Med.* 2017;84:616-622.
- Schrijver EJ, de Graaf K, de Vries OJ, Maier AB, Nanayakkara PW. Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: a systematic review of current evidence. *Eur J Intern Med.* 2016;27:14-23.
- Lonergan E, Luxenberg J, Areosa SA. Benzodiazepines for delirium. *Cochrane Database Syst Rev.* 2009;2009:CD006379.
- Hanania M, Kitain E. Melatonin for treatment and prevention of postoperative delirium. *Anesth Analg.* 2002;94:338-339. table of contents.
- Angeles-Castellanos M, Ramirez-Gonzalez F, Ubaldio-Reyes L, Rodriguez-Mayoral O, Escobar C. Loss of melatonin daily rhythmicity is associated with delirium development in hospitalized older adults. *Sleep Sci.* 2016;9:285-288.
- Balan S, Leibovitz A, Zila SO, et al. The relation between the clinical subtypes of delirium and the urinary level of 6-SMT. *J Neuropsychiatry Clin Neurosci.* 2003;15:363-366.
- Khaing K, Nair BR. Melatonin for delirium prevention in hospitalized patients: a systematic review and meta-analysis. *J Psychiatr Res.* 2021;133:181-190.
- Lange PW, Clayton-Chubb DI, Watson R, Maier AB. Results from a double blinded, randomized, placebo-controlled, feasibility trial of melatonin for the treatment of delirium in older medical inpatients. *Intern Med J.* 2020;51:33-41.
- 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. *Int J Geriatr Psychiatry.* 2011;26:687-694.
- 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.
- 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-E556.
- Fan Y, Yuan L, Ji M, Yang J, Gao D. The effect of melatonin on early postoperative cognitive decline in elderly patients undergoing hip arthroplasty: a randomized controlled trial. *J Clin Anesth.* 2017;39:77-81.
- 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.
- Tahir TA, Eeles E, Karapareddy V, et al. A randomized controlled trial of quetiapine versus placebo in the treatment of delirium. *J Psychosom Res.* 2010;69:485-490.
- Shi Y. Effects of melatonin on postoperative delirium after PCI in elderly patients: a randomized, single-center, double-blind, placebo-controlled trial. *Heart Surg Forum.* 2021;24:E893-E897.
- Nishikimi M, Numaguchi A, Takahashi K, et al. Effect of Administration of Ramelteon, a melatonin receptor agonist, on the duration of stay in the ICU: a single-center randomized placebo-controlled trial. *Crit Care Med.* 2018;46:1099-1105.

28. Claustrat B, Brun J, Chazot G. The basic physiology and pathophysiology of melatonin. *Sleep Med Rev.* 2005;9:11-24.
29. Harpoe NG, Andersen LP, Gogenur I, Rosenberg J. Clinical pharmacokinetics of melatonin: a systematic review. *Eur J Clin Pharmacol.* 2015;71:901-909.
30. Markantonis SL, Tsakalozou E, Paraskeva A, Staikou C, Fassoulaki A. Melatonin pharmacokinetics in premenopausal and postmenopausal healthy female volunteers. *J Clin Pharmacol.* 2008;48:240-245.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Supplementary Text S1. Trial design

Supplementary Figure S1. Schedule of procedures: Assessments and medication administration

Supplementary Table S1. Schedule of procedures

Supplementary Figure S2. CONSORT checklist

How to cite this article: Lange PW, Turbić A, Soh CH, et al. Melatonin does not reduce delirium severity in hospitalized older adults: Results of a randomized placebo-controlled trial. *J Am Geriatr Soc.* 2024;72(6):1802-1809. doi:[10.1111/jgs.18825](https://doi.org/10.1111/jgs.18825)