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SCIENTIFIC INVESTIGATIONS

Poorer sleep quality predicts melatonin response in patients with traumatic brain injury: findings from a randomized controlled trial

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Study Objectives: A recent clinical trial demonstrated that melatonin treatment was effective in improving self-perceived sleep quality in patients with traumatic brain injury (TBI); however, it remains unclear which patients benefited from melatonin treatment. To that end, findings from the clinical trial were re-examined to identify possible predictors of treatment response.

Methods: Hierarchical multiple regression was used to identify patient characteristics, TBI injury characteristics, and self-report measures assessing sleep, fatigue, mood, and anxiety symptomatology that may uniquely explain a change in self-reported sleep quality scores (follow-up minus baseline score) as assessed by the Pittsburgh Sleep Quality Index (PSQI).

Results: After controlling for patient demographic and TBI injury-related variables, baseline self-report measures of sleep, fatigue, mood, and anxiety explained an additional 32% of the variance in change in PSQI scores. However, only baseline PSQI score made a unique and statistically significant contribution ($\beta = -0.56$, $P = .006$). After controlling for patient and TBI characteristics, baseline PSQI scores further explained 27% of the variance in change in PSQI scores (R^2 change = .27, $F_{1, 27}$ change = 11.79, $P = .002$). The standardized β for baseline PSQI score revealed a statistically significant negative relationship with change in PSQI score ($\beta = -0.54$, $P = .002$), revealing that higher PSQI score at baseline was associated with better sleep outcomes.

Conclusions: In a sample comprising predominantly severe TBI and comorbid insomnia, participants who report poorer sleep quality have the most to gain from melatonin treatment irrespective of time since injury, demographics, fatigue, daytimes sleepiness, mood, and anxiety symptomology.

Clinical Trial Registration: Registry: Australian New Zealand Clinical Trials Registry; Name: Efficacy of Melatonin for Sleep Disturbance Following Traumatic Brain Injury; URL: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=343083&showOriginal=true&isReview=true; Identifier: ACTRN12611000734965.

Keywords: sleep disturbance, insomnia, traumatic brain injury, acquired brain injury, melatonin

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BRIEF SUMMARY

Current Knowledge/Study Rationale: Melatonin treatment is therapeutic in improving sleep quality and sleep efficiency in patients with traumatic brain injury with minimal to no adverse events.

Study Impact: The current study suggests that patients with traumatic brain injury reporting poorer sleep quality have the most gain from melatonin treatment, irrespective of injury characteristics and pretreatment mood, anxiety, fatigue, and daytime sleepiness.

INTRODUCTION

Sleep disturbances such as insomnia and hypersomnia are highly prevalent after traumatic brain injury (TBI).[1,2] Despite the high prevalence of these sleep conditions in the TBI population, evidence-based treatments for such conditions, such as melatonin and cognitive-behavioral therapy, have only recently been shown to be efficacious.

Of relevance to the current study, findings from our own randomized controlled trial demonstrated that 4 weeks of melatonin treatment was efficacious in improving self-reported sleep quality. Although these findings were the first to validate the therapeutic use of melatonin in the TBI population, it remains unclear which patients benefited from melatonin treatment. To that end, candidate predictors such as levels of self-reported fatigue, daytime somnolence, sleep quality (before melatonin treatment), and mood and anxiety symptomatology were selected a priori. The aim of the present study was to examine the association of patient characteristics and self-reported symptoms before treatment with improvement in self-reported sleep quality after 4 weeks of melatonin treatment.

METHODS

Trial design

This study is a secondary analysis obtained from a phase 3 randomized, placebo-controlled, double-blind, 2-period, 2-treatment crossover clinical trial evaluating the efficacy of melatonin (2 mg, prolonged release) treatment for sleep disturbances in patients with

TBI. A crossover design was used so that participants served as their own control. The study was approved by the Monash University (CF11/1900-2011001061), Epworth HealthCare (52111), and Austin Health (H2013/04950) Human Research Ethics Committees. Participants consented before participating. Enrolled participants completed assessments before and after the 2-week baseline assessment and after each 4-week treatment period. Participants received melatonin or placebo for 4 weeks, followed by a crossover with the remaining treatment. Treatments were separated by a 48-hour washout period. The study protocol and results are outlined elsewhere.[3]

Participants

Participants with TBI were community-dwelling individuals who had a documented history of mild to severe TBI. Participants were recruited from rehabilitation centers and community agencies via referrals from medical and allied health. All participants had novel sleep complaints after TBI, corroborated by Pittsburgh Sleep Quality Index (PSQI) scores ≥ 8, and a diagnosis of insomnia diagnosed by a board-certified sleep physician (D.M.). Inclusion and exclusion criteria are reported elsewhere.[3] In summary, eligible participants were ages 18–65 years with a verified TBI and a period of unconsciousness indicated by a Glasgow Coma Scale score of 3–14 and/or posttraumatic amnesia (PTA). Patients with a TBI were not eligible if they reported sleep, fatigue, or neurologic problems before head injury; if they were working the night shift; if they had recently undertaken travel across more than 1 time zone; if they had untreated sleep apnea; or if they had recently used sleep medication. Throughout the study, participants were not permitted to start new pharmacologic/psychological/behavioral interventions with the intent to remedy sleep. Medical examination, as well as blood and urine toxicology screening, indicated that all participants were in good health. Urine was screened to rule out illicit substance use, and blood tests determined that female participants were not pregnant.

Treatment

Participants were randomly allocated to a 4-week supply of melatonin or placebo treatment. Participants consumed capsules orally at the same time every night, approximately 2 hours before their habitual bedtime. Melatonin was a prolonged-release formula (2 mg, Circadin, Neurim Pharmaceuticals, Tel-Aviv, Israel). Placebo treatment was identical in appearance consisting of mannitol (106 mg), acacia (11 mg), and pure icing sugar (106 mg). Melatonin and placebo treatments were encapsulated in identical 2-piece gelatin capsules. The melatonin preparation was selected based on previous research[4–7] and was the only prescription formulation available in Australia at the time of study conception.

Randomization and blinding

Participants were randomized by an independent researcher, with randomization occurring after the baseline data collection, as previously described.[3] Treatments were prepared and allocated by a pharmacist not affiliated with the study. The pharmacist did not interact with the researchers or participants. Participants received 1 container at the start of each treatment period. All parties were blinded to medication assignment, with unblinding occurring after the last evaluation.

Primary outcome

In light of our findings that demonstrated that melatonin was effective in improving self-perceived sleep quality,[3] the current analysis focused on self-perceived sleep quality as measured by global PSQI scores. The PSQI comprises 19 questions evaluating self-perceived sleep quality in the previous month. Global PSQI scores reflect a composite of self-perceived sleep duration, sleep disturbance, sleep latency, sleep efficiency, daytime dysfunction, and sleep quality. Higher values indicate poorer sleep quality (score range, 0–21). The PSQI was completed at the start of the baseline intervention before randomization and treatment.

Predictor variables

A range of demographic and TBI characteristics were obtained from hospital records. Because of the small sample size, TBI characteristics were limited to time since injury (expressed in months) and TBI severity, given that both these factors have been associated with sleep disturbance and sleep quality.[8–10] Time since injury was included on the basis that patients receiving treatment at a later time point since injury may be associated with greater impairments in sleep. TBI severity, as measured by PTA, was selected over Glasgow Coma Scale, given that PTA is associated with TBI pathology, and PTA has consistently been demonstrated to be a stronger predictor of longer-term cognition, functional, occupational, and psychosocial outcomes in survivors of TBI compared with Glasgow Coma Scale and loss of consciousness.[11–17] Anxiety, depression, and fatigue were included, given that these factors are consistently associated with sleep disturbance after TBI,[8,18,19] whereas daytime somnolence is frequently reported in patients with a TBI.[2,20] Age and sex were also included, given the well-known differences in sleep.[21,22] Self-reported questionnaires assessing fatigue, anxiety, and depressive symptomatology were obtained before participants embarked on the 2-week baseline assessment (ie, before receiving treatment). All the scales selected have been previously validated in the TBI population. Daytime somnolence was assessed using the Epworth Sleepiness Scale.[23] Fatigue was assessed with the Fatigue Severity Scale.[24] Self-reported anxiety and depressive symptomology were assessed with the Hospital Anxiety and Depression Scale.[25] Self-report predictor variables were selected a priori given the known influence of these variables on sleep. PSQI scores obtained at baseline were included in the model given that worse sleepers may be more amenable to intervention. All predictor variables were obtained before randomization and before the start of treatment.

Statistical analyses

An intention-to-treat analysis was used. Hierarchical multiple regression[26,27] was used to examine TBI injury characteristics and self-report measures predicting change in PSQI score. All residuals were inspected for normality, with all assumptions met. Results were considered statistically significant if 2-tailed $P < .05$. The primary outcome variable, change in PSQI score,

was calculated by subtracting PSQI scores at follow-up from PSQI scores at baseline. Negative values on this outcome indicated a favorable treatment response, whereas positive values indicated lesser improvements in sleep quality. Statistical analysis was performed using IBM SPSS Statistics 26 (IBM Corporation, New York, NY).

RESULTS

Participant flow

A total of 107 individuals with TBI were referred to the study, with 38 participants consenting.[3] Thirty-five participants underwent assessment before and after a 2-week baseline run-in phase, after which participants were randomized to treatment. However, of the 35 participants randomized, 3 participants withdrew during the placebo intervention, bringing the total to 32 participants. No participants withdrew when assigned melatonin first. Of the 3 participants who withdrew during the placebo, 1 participant agreed to complete questionnaires after placebo and melatonin treatment, which was included in the current analysis. Therefore, the final intention-to-treat analysis included 33 participants.

Baseline characteristics

Participant demographics are presented in **Table 1.** All participants with TBI were diagnosed with chronic insomnia according to the American Academy of Sleep Medicine criteria by a board-certified respiratory and sleep physician (D.M.). The sample comprised participants with severe TBI (PTA > 7 days predominantly; 85%), with males comprising 67% of the sample. TBI from vehicular accidents was the most frequently reported mechanism of injury (n = 23; 70%).

Analysis samples and treatment compliance

Self-report data were obtained for all 33 participants, except for the Hospital Anxiety and Depression Scale (n = 32). Most participants took 28/28 of their allocated treatments, with the median (50th percentile) treatment compliance at 100% for both melatonin (25th–75th percentile = 97%–100%) and placebo (25th–75th percentile = 96%–100%) treatments.

Associations between baseline and TBI characteristics and change in PSQI score

Pearson's product-moment correlational analysis is presented in **Table 2.** The correlational analysis revealed that there was a statistically significant negative association between baseline PSQI scores and change in PSQI score ($r[33] = -.54$, $P < .001$). No other TBI-related injury or demographic or self-report measures were significantly correlated with the dependent variable. Inspection of the histogram and Q-Q plots of the dependent variable, the change in the PSQI score, revealed that the distribution appeared normally distributed. The mean score for change in PSQI was −2.76, with a standard deviation of 4.10 (median = −2.00; 25th to 75th percentile = −4.50 to −1.00).

Hierarchical multiple regression analysis is featured in **Table 3.** Patient demographics and TBI injury characteristics only explained 12% of the variance in PSQI change scores, and the overall model was not statistically significant ($F_{4, 28} = 0.95$, $P = .45$; **Table 3**). None of the above individual predictors were statistically significant ($P > .05$). To determine the contribution of self-report measures on PSQI scores, participant characteristics were entered into the first block of variables in the regression model, followed by self-report questionnaires in the second block. After controlling for demographic and TBI injury–related variables, the total variance explained by model 2 (R^2) as a whole was 44%. In model 2, the addition of self-report measures explained an additional 32% of the variance in PSQI change scores, although the increase in R^2 narrowly failed to achieve statistical significance (R^2 change = .3230; $F_{5, 21}$ change = 2.4315; $P = .06910$). Inspection of the individual predictors revealed that only baseline PSQI score was a statistically significant predictor ($\beta = -0.56$, $P = .006$).

Given that baseline PSQI score was a statistically significant predictor of the dependent variable, patient demographic and TBI injury characteristics were entered into the first block of variables in the multiple regression model, with baseline PSQI scores entered in the second block. Consistent with previous analysis,[3] further analyses revealed no statistical interaction effects between treatment (ie, melatonin first, melatonin second) and baseline PSQI scores ($P = .39$), suggesting that the relationship between baseline and change scores did not differ as a result of the treatment group. After controlling for participant and TBI injury characteristics, the third model now explained 39% of the variance in change in PSQI scores ($F_{5, 27} = 3.41$, $P = .016$) overall. After adjusting for age, sex, TBI severity, and time since injury, baseline PSQI scores explained an

Table 1—Baseline characteristics.

TBI Characteristics	Overall (n = 33)
Age, mean (SD), y	36.6 (10.6)
Body mass index, mean (SD), kg/m^2	25.7 (3.8)
Male, n (%)	22 (66.7)
Months post-injury, mean, (IQR Q1; Q3), raw value	44 (12–99)
Lowest GCS, median (IQR Q1; Q3), raw value	6 (3–12)
PTA duration, median (IQR Q1; Q3), d	33 (13–47)
Mild TBI, n (%), PTA 0 to ≤ 1 d	2 (6)
Moderate TBI, n (%), PTA > 1 to ≤ 7 d	3 (9)
Severe TBI, n (%), PTA > 7 d	28 (85)
PSQI, global score[a]	10.6 (4.2)
ESS, score[a]	7.8 (5.7)
HADS-anxiety[a]	9.2 (4.9)
HADS-depression[a]	9.3 (4.8)
FSS, score[a]	46.6 (11.9)

TBI participants injury characteristics, demographics and self-reported sleep quality, fatigue, anxiety, and mood scores before melatonin treatment. [a]Reflects data before the commencement of baseline intervention. ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, GCS = Glasgow Coma Scale, HADS = Hospital Anxiety Depression Scale, IQR = interquartile range, PSQI = Pittsburgh Sleep Quality Index, PTA = post-traumatic amnesia, SD = standard deviation; TBI = traumatic brain injury.

Table 2—Intercorrelations among the variables with the dependent variable: PSQI change score.

	PSQI Change Score	Time Since Injury	Sex	Age	PTA Days	HADS-Depression	HADS-Anxiety	ESS	FSS	PSQI Baseline
PSQI change score	1.00									
Time since injury	−0.17	1.00								
Sex	−0.26	−0.10	1.00							
Age	−0.01	0.01	0.36*	1.00						
PTA days	−0.08	0.14	−0.11	−0.31*	1.00					
HADS-depression	−0.17	−0.02	0.31	0.01	−0.12	1.00				
HADS-anxiety	−0.16	−0.05	0.14	−0.31*	−0.01	.060**	1.00			
ESS	−0.29	0.13	0.18	0.26	−0.30*	0.43*	0.52**	1.00		
FSS	−0.16	0.19	−0.13	−0.17	−0.07	0.42*	0.40*	0.43*	1.00	
PSQI baseline	−0.54**	−0.06	0.21	0.04	−0.18	0.26	0.29	0.27	0.35*	1.00

Correlational analysis of PSQI scores (dependent variable) with predictor variables. ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, GCS = Glasgow Coma Scale, HADS = Hospital Anxiety Depression Scale, PSQI = Pittsburgh Sleep Quality Index, PTA = posttraumatic amnesia. *P < .05; ** P < .01.

additional 27% of the variance in PSQI scores after melatonin treatment (R^2 change = .27; $F_{1,\ 27}$ change = 11.79; P = .002). Inspection of the standardized beta for baseline PSQI score revealed a statistically significant negative relationship between baseline PSQI score with the outcome variable, the change in the PSQI score (β = −0.54, P = .002). This finding indicates that higher PSQI scores at baseline were associated with negative difference scores (better outcomes) at follow-up, which is indicative of improved sleep quality. Possible curvilinear relationships (quadratic and cubic) between baseline PSQI and change in PSQI scores were examined but did not lead to statistically significant improvements in R^2 compared with a linear model (R^2 for linear = .29, P = .001; R^2 change for quadratic = .03, P = .263; R^2 change for cubic = .02, P = .372).

DISCUSSION

The current investigation revealed that baseline self-perceived sleep quality, as measured by PSQI scores, was the only statistically significant predictor of change in PSQI scores after 4 weeks of melatonin treatment. In a sample predominantly comprising participants with severe TBI, after controlling for patient demographics and TBI injury characteristics, baseline PSQI scores uniquely explained 27% of the variance in change in PSQI score after 4 weeks of melatonin treatment in a TBI cohort diagnosed with insomnia. This analysis revealed that poorer sleep quality pretreatment was associated with greater gains in sleep quality in response to melatonin treatment. Aside from baseline PSQI scores, no other patient demographic, TBI injury characteristics, or self-reported fatigue, daytime sleepiness, mood, or anxiety symptomology was found to be significantly predictive of change in PSQI scores after melatonin treatment.

The current findings suggest that patients with TBI with severe head injury are likely to benefit from melatonin treatment, irrespective of their age, sex, or time since sustaining their head injury. Although 4 weeks of melatonin treatment have been shown to reduce fatigue and anxiety in patients with TBI,[3] baseline fatigue and anxiety symptomology (before melatonin treatment) had no significant bearing on PSQI scores after melatonin treatment.

The fact that age was not predictive of PSQI scores is an interesting finding given that the randomized controlled trial administered a melatonin preparation (2 mg; prolonged release) to a younger cohort with an average age of 37 years. Although this medication is only approved for insomnia in those older than age 55 years, the current study is consistent with other findings that show that the medication is efficacious in improving sleep quality in younger individuals (ie, ages 18–55 years).[28] The current analysis suggests that age is no barrier in improving sleep quality in patients with a TBI that are younger than age 55 years. TBI severity was not significantly associated with PSQI scores after melatonin treatment, and, again, this finding is encouraging because it suggests that all patients with a TBI, regardless of head injury severity, could benefit from treatment.

The improvements in sleep quality after 4 weeks of melatonin treatment may be underpinned by synergistic physiologic and psychological processes. The well-known soporific (ie, sleep prompting) effects of exogenous melatonin[29] via attenuation of the wake-promoting signals of the suprachiasmatic nucleus at the level of the MT1 receptor,[30] together with the hypothermic response,[31] may have helped patients improve their sleep experience. Improvements in sleep quality may have also been driven by changes to circadian timing. However, given that the randomized controlled trial was focused on exploiting the sleep-promoting effects of melatonin regardless of circadian phase and amplitude,[3] we cannot capture the extent to which circadian phase contributed to improvements in sleep quality. However, irrespective of a patient's circadian phase, exogenous melatonin was found to be effective in improving sleep quality, which is in keeping with other trials using the same melatonin preparation.[5–7] Melatonin's muscle relaxant[32] and anxiolytic properties[33] may have improved sleep quality by assisting participants with a TBI to transition into a quieter psychological

Table 3—Summary of hierarchical regression analysis for variables predicting response to melatonin treatment.

Variable	Model 1			Model 2			Model 3		
	β	*B*	*SE B*	β	*B*	*SE B*	β	*B*	*SE B*
Participant variables									
Age	0.08	−0.03	0.08	0.17	0.07	0.08	0.03	0.01	0.07
Sex	−0.32	−2.71	1.63	−0.19	−1.60	1.68	−0.20	−1.71	1.41
PTA duration (d)	−0.06	−0.01	0.02	−0.22	−0.03	0.02	−0.16	−0.02	0.02
Time since injury (mo)	−0.19	−0.01	0.01	−0.16	−0.01	0.01	−0.19	−0.01	0.01
Self-report measures									
PSQI[a]				−0.56*	−0.54	0.18	−0.54*	−0.52	0.15
HADS-depressiona				−0.04	−0.04	0.19			
HADS-anxiety[a]				0.22	0.18	0.22			
ESS, daytime somnolence[a]				−0.34	−0.24	0.17			
FSS, daytime fatigue[a]				0.13	0.05	0.07			
R^2		0.12			0.44			0.39	
R^2 change		0.12			0.32			0.27	
F change for R^2		0.95			2.43			11.79*	

Hierarchical regression analysis for each of the 3 models with change in PSQI (ie, follow-up minus baseline) entered as the dependent variable. Model 1 is limited to demographic and injury characteristics. Model 2 evaluates self-reported data while controlling for demographic and injury characteristics. Model 3 evaluates baseline PSQI scores (before melatonin treatment) after controlling for demographic and injury characteristics. [a]Reflects self-report data collected before the commencement of baseline intervention. *P < .05. β = standardized coefficients, *B* = unstandardized coefficients, ESS = Epworth Sleepiness Scale, FSS = Fatigue Severity Scale, HADS = Hospital Anxiety Depression Scale, PSQI = Pittsburgh Sleep Quality Index, PTA = posttraumatic amnesia (d), *SE B* = standard error for unstandardized coefficients.

and physiologic state of arousal to promote sleep. Although melatonin has gained popularity as a treatment of choice given its favorable adverse effect profile and is marketed as a natural remedy for the treatment of sleep disorders, melatonin is proving an effective treatment option for patients with TBI and comorbid sleep disturbance. Although the research is in its infancy and more trials are required to replicate our findings, to date, administration of melatonin in adult individuals with TBI has revealed improvements in self-perceived sleep quality, actigraphy sleep efficiency, reduced fatigue and anxiety symptomology,[3] and actigraphy-derived total sleep time and reduced sleep onset,[34] whereas in another study it has not.[35]

Although 50% of patients with TBI with sleep complaints experience insomnia,[2] there is no consensus for the treatment of insomnia in this neurologic population. Although patients with TBI and comorbid insomnia present with a range of sleep complaints (eg, sleep-onset insomnia, sleep-maintenance insomnia, sleep-state misperception), our study demonstrates that regardless of the insomnia presentation in this cohort, melatonin is effective in alleviating insomnia symptomatology by improving self-reported sleep quality. Although peak sleep organizations all recommend cognitive-behavioral therapy for insomnia as the first-line treatment for insomnia,[36–39] the findings from 2 randomized controlled trials[3,34] and the finding that patients with TBI with comorbid insomnia have attenuated endogenous melatonin concentrations[18,40] suggest that melatonin treatment should be complemented with psychological therapy in this neurologic population for maximal potency.

Although the present study is the first to identify factors associated with treatment response to melatonin in a TBI population, the current findings need to be considered in the context of some methodologic shortcomings. First, given the small sample size, the number of variables for inclusion in the current analysis was limited. In light of this, variables were selected a priori based on theoretical grounds,[26,41] and the current findings need to be replicated in a separate and larger sample. Although the current study included patients across the TBI severity spectrum, the majority had severe TBI, and as such, it is unclear if the current findings would translate to people with mild TBI. Future studies investigating the efficacy of melatonin in larger groups with mild or moderate TBI are needed to confirm the efficacy of melatonin for sleep disturbance in these groups. Although the current study focused on variables easily available in clinical practice, it was unable to take into account additional predictors such as genetic factors,[42] dysfunctional beliefs regarding the impact melatonin would have on their sleep, baseline endogenous melatonin profiles, circadian timing, sleep architecture, or sleep-wake schedules. Based on previous work by the current group,[18,40] it is hypothesized that individuals with reduced endogenous melatonin concentrations at baseline may be more likely to benefit from melatonin treatment. Last, given that melatonin was only administered for 4 weeks, it is unclear whether baseline PSQI scores would predict PSQI scores for melatonin administration longer than 4 weeks or with different melatonin preparations or dosages. As such, the association of baseline PSQI scores with treatment response may not be generalizable to other melatonin preparations.

In a sample predominantly comprising individuals with severe TBIs, the single best predictor of change in PSQI score after 4 weeks of melatonin treatment is self-perceived sleep

quality before treatment. It remains to be seen whether the same findings hold for patients with milder head injuries, different melatonin preparations, dosages and longer treatments periods; however, the current findings provide justification to incorporate melatonin treatment when treating patients with severe TBI with comorbid insomnia who present with poor self perceived sleep quality.

ABBREVIATIONS

PSQI, Pittsburgh Sleep Quality Index
PTA, posttraumatic amnesia
TBI, traumatic brain injury

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