Author’s response to reviews

Title: Efficacy of Melatonin for Sleep Disturbance Following Traumatic Brain Injury: A Randomized Controlled Trial

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Thank you for the positive feedback. We have addressed all of the reviewer comments point by point as detailed below. The reviewers have asked us to include additional analysis and comment on the study design in the discussion. In making these changes, our manuscript length has increased. We hope you will approve of our revised submission.

Comments from Reviewer 1:

This double blind crossover study reports on the effect of melatonin supplementation (2mg/d; 2 weeks) on sleep quality in patients with traumatic brain injury (TBI), reporting sleep disturbance. This is an important study because sleep disturbances are commonly reported following TBI. Although the sleep problems contribute to ongoing cognitive dysfunction, poorer rehabilitation outcomes, lower productivity and poorer functional status in these patients, they are often overlooked.
Previous findings from the same group demonstrated that TBI is associated with attenuated and delayed melatonin profiles; specifically, reduced evening and overnight melatonin production as compared to age and sex matched controls. When nocturnal melatonin production/secretion is inappropriately timed or impaired in relation to the environment, timed melatonin replacement therapy may be beneficial.

The aims are clear and well defined, with a few secondary endpoints only. The study design and patient population are well described.

This study included 33 patients with TBI and insomnia and had 82% power to detect a small effect size (f = .20). The statistical methods are clearly described and concise.

The paper shows that melatonin supplementation improves sleep quality as measured by questionnaires and sleep efficiency as measured in an objective manner (actigraphy) with minimal side effects. Importantly, melatonin improved vitality and mental health and decreased anxiety and fatigue compared to placebo.

Based on the current findings, the authors were able to propose that melatonin affords TBI patients an alternative treatment to alleviate sleep disturbance with minimal side-effects.

Response: Thank you for your glowing review regarding our study. We hope that our findings will influence the way physicians prescribe and implement melatonin supplementation in patients with TBI.

Comments from Reviewer 2:

Comment (1). The study concludes that long-acting melatonin helps to improve sleep quality and its consequences for daily functioning. However these conclusions are based on statistically found differences. They are not supported by clinical impression of the patients. Especially only 28 - 47 % correctly guessed their treatment. In placebo-controlled melatonin studies about 95 % of the participants correctly guess their treatment!. Furthermore Clinical Global impression was not assessed. These items s should be commented in the discussion.

Response: Most of the positive outcomes were based on self-report by the participants, namely improved sleep quality on the PSQI, less impact of fatigue on their daily activities on the FSS, less anxiety symptoms on the HADS and increased vitality and mental health on the SF-36. Therefore we would argue that although no Clinical Global Impression rating was made, the findings do reflect significant changes that were perceived by the participants themselves. We have no included the following in the discussion in the sixth paragraph on page 13: Although no clinical global impression was obtained in the current study, a large majority of the outcome
measures were based on self-report by the participants, and thus the current findings are clinically meaningful because changes were perceived by the participants themselves.

Comment (2). Melatonin is a chronobiotic drug with some hypnotic properties. This study mainly concerns the hypnotic properties, without placing these in the general perspective of melatonin. Timing of melatonin administration is crucial for its effects, i.e. 5-6 hours before (delayed) Dim Light Melatonin Onset(1). This is important because several studies suggest that DLMO is delayed in TBI(2-4). In the present study DLMO was hardly not measured. Maybe the lack of effect of circadin at sleep onset could be caused because circadin was not timed adequately. This is also the explanation for the finding that a meta-analysis with melatonin administered at a time related to DLMO showed that melatonin improved sleep(5), while a meta-analysis with melatonin, administered before bedtime ( just like in the present study) did not improve sleep(6). The discussion should mention that circadian rhythmicity should be studied in TBI preferentially by measuring DLMO, eventually by estimating DLMO.

Response: Previous research from our group has revealed that circadian rhythms are sometimes (although not always) misaligned in TBI patients (see Grima et al., 2016, Neurorehabilitation and Neural Repair versus Shekleton et al., 2010, Neurology). We agree that phenotyping (DLMO) would be an important step in future studies, to inform treatment approach and time of administration. We have added this as a suggestion for future research. We did not have the resources to do this in the current study. We designed the study to exploit the sleep-promoting effects of melatonin, which have been well described (see Rajaratnam et al., 2004 J Physiol), using a prolonged release preparation that mimics the endogenous profile and targets sleep maintenance problems. As such, timing of treatment was selected to exploit the sleep promoting effects based on the recommendations for Circadin. We were concerned about administering melatonin several hours before sleep time due to the risk of increased sleepiness during the evening hours. To address your comments, we have included the following in the second paragraph in the discussion:

The current study was designed to exploit the sleep-promoting effects of melatonin, which have been previously characterized [22], utilizing a prolonged release preparation that mimics the endogenous profile and targets sleep maintenance problems. Therefore, timing of treatment was selected to harness the sleep prompting effects, with time of administration consistent with directions for use as indicated by the manufacture. Although additional information regarding endogenous melatonin profiles would have been useful, melatonin supplementation was found to be therapeutic. Phenotyping circadian phase (e.g., DLMO) would be an important step for future studies, to inform treatment approach by targeting underlying circadian misalignment for maximal benefit.
Comment (3). In sleep literature there is a firm discussion going on about the usefulness of long acting melatonin compared to fast release melatonin(7). This should be mentioned in the discussion. Further it should be recommended that comparative studies between long-acting en fast release melatonin are needed.

Response: Thank you for your suggestion. We agree that comparison studies are needed to explore the therapeutic efficacy of alternative melatonin preparations. At the time the current study was conceptualized, the only available melatonin preparation approved by the regulatory body in Australia (i.e., the Therapeutic Goods Administration which is equivalent to the U.S. Food and Drug Administration) was Circadian. The goal of the current study was to utilize a melatonin preparation that would enable clinicians to implement this treatment at the conclusion of the study. To address your comment, we have encouraged researchers to utilize other preparations to determine which melatonin preparations would yield the best results in the TBI population.

To address your comment, we have included the following in the second paragraph in the discussion: Furthermore, recent discussions regarding the therapeutic outcomes between short versus long-acting melatonin preparations [23], suggest comparative studies are needed for evidence-based recommendations.

Comment (4). Now adays the basic treatment for insomnia is Cognitive Behavour Therapy for insomnia (CBT-I). This also applies for insomnia in TBI. This should be mentioned placing drug treatment in a broad treatment perspective for insomnia in TBI.

Response: We acknowledge the multi-factorial nature of sleep disturbances, which are caused by both biological and psychological factors. You rightly point out that CBT-I has now been established as the gold standard treatment for insomnia in non-TBI individuals. Recent work by our group has built on previous findings (Nguyen et al., 2017 Cognitive Behaviour Therapy to Treat Sleep Disturbance and Fatigue After Traumatic Brain Injury: A Pilot Randomized Controlled Trial) now establishing CBT as another potentially effective treatment for sleep disturbances. Nevertheless there are some individuals with TBI who are not inclined towards or by virtue of their cognitive impairments are unable to benefit from psychological therapies, for whom melatonin supplementation may be more beneficial. In light of these findings from our group and others, the use of melatonin supplementation should be considered as one of a number of potential treatments for sleep disturbance following TBI. We have now included the following paragraph in the discussion.

While melatonin was found to be effective in alleviating sleep disturbance, it is acknowledged the mechanisms underpinning sleep disturbances in TBI involve multiple biological and psychological systems such as alterations in monoaminergic neurons [44, 45] and wake-promoting hypocretin-1 neurons [46], and alterations in melatonin levels [8, 9], as well as pain
and mood disturbance. This suggests that while melatonin supplementation may alleviate sleep disturbance in individuals with TBI, melatonin is unlikely to address all sleep problems. Cognitive behavioral therapy for insomnia (CBT-I) has been shown efficacious in TBI populations. Due to the multi-factorial nature of sleep disturbances following TBI, complementing melatonin supplementation with CBT-I may prove beneficial.

Comment (5). In this cross over trial the wash out period was only 48-h. It could be possible that melatonin improves sleep (wake rhythm) and that this improvement remains after stopping melatonin treatment. Consequently when the participant is first treated with melatonin and later with placebo, the effect of placebo treatment could be identical with that of melatonin. This should be mentioned in the discussion. Therefore parallel studies should be recommended in stead of cross over studies…

Response: The 48 hour washout period was chosen to minimize carryover of treatment and to provide time to recharge the actiwatch and provide participants with the alternative treatment. Previous studies have demonstrated that melatonin rhythms revert back to their original rhythms when exogenous melatonin is ceased (Lockley et al., (2000) Journal of Endocrinology; Sack et al., (2000) NEJM; Hack et al., (2003) J Biol Rhythms). We do acknowledge that in the absence of circadian profiling we cannot rule out carryover of melatonin treatment (for those individuals that received melatonin first); however, most of our treatment outcomes (with the exception of actiwatch and sleep diary) were collected four weeks and two days (including the washout) after melatonin ceased when circadian phase would have re-established.

In light of the known heterogeneity in the TBI population, we opted for a cross over design as opposed to a parallel design given that the design minimized confounding covariates (e.g., TBI characteristics and secondary factors such as mood, anxiety and pain), which were controlled by each participant serving as their control.

We have now included this comment in the discussion as follows:

We implemented a 48-hour washout period between consecutive treatments. Although the terminal half-life for melatonin is relative short (3.5-4 hours) [23], it is possible that melatonin administered in the first treatment period could have induced a circadian phase advance, which could have persisted for up to several days in the following (placebo) treatment period [10-12]. We confirmed that there were no treatment order effects across all outcome measures, and we limited most of the assessment treatment outcomes (except sleep diary and actigraphy) to the end of each treatment condition, when circadian phase would have re-established after melatonin treatment had ceased.
Comment (6). Time of administration of circadin should be mentioned, more than: 2 hours before initiating sleep. If not known this should be commented in the discussion.

Response: Data regarding treatment consumption was obtained and we have included the following information regarding consumption of treatment in the ‘Numbers Analyzed and treatment Compliance’ section featured on Page 9. Circadin was consumed on average at 21:16hrs (Q1-Q3 = 21:18 – 21:57), while placebo treatment was consumed at 20:45hrs (Q1-Q3 = 20:04 – 21:45).

Comment (7). It could be possible that severity of the TBI correlates with the effect of treatment. This should be studied and commented in the discussion.

Response: We investigated the association between each of our primary outcome measures (i.e., Pittsburgh Sleep Quality Index: PSQI; Sleep Onset Latency: Sol) and TBI severity. For both PSQI and SOL, TBI severity was not correlated with PTA and GCS scores, respectively. We have now included the following sentence in the results section on page 9 under the ‘Primary outcomes’ subheading in the results section. Correlational analysis did not reveal any significant association between TBI severity (as measured by PTA or GCS respectively) and effect of treatment for both PSQI or sleep onset latency (p > .05 for all).

Comment (8). The time at which the diary is completed each day should be mentioned.

Response: Participants were not asked to record the time of day they completed the diary, but were given instructions throughout the study via text messages to complete the diary as soon as possible after awakening each day. We have now included the following statement in the second paragraph of the ‘Primary End Point’ subheading. To facilitate compliance, participants were sent daily text messages in the morning reminding them to complete the sleep diary.

Comment (9). How many days the participants wore the actigraph?

Response: Information regarding the number of days participants wore actigraphy is now featured in the ‘Numbers Analyzed and Treatment Compliance’ section on page 9. Participants wore actigraphy on average 25 days (Q1-Q3 = 24 – 28 days) when receiving melatonin, and 24 days during placebo (Q1-Q3 = 23 – 28 days). Paired sample t-tests (2-tailed) revealed no differences in the number of days of actigraphy between melatonin and placebo (t (31) = 1.19, p = .244).
Comment (10). Both in the results section and in the methods section duration of the study (August 2011 - August 2016) is mentioned. One is sufficient.

Response: Thank you for identifying this duplication. We have now removed the following first sentence from the ‘Participant Flow’ subheading. Eligible participants were screened between August 2011 and August 2016.

Comments from Reviewer 3

Previous studies have shown that melatonin exhibited sleep promoting properties in insomnia and tetraplegia patients. Whether this will also hold in TBI patients is unknown. Hence, this study was conducted to determine the effect of melatonin supplementation on sleep disturbances in patients with TBI. It used a randomized, double-blind, 2x2 cross-over design, with each treatment period (melatonin or placebo) lasting 4 weeks separated by a 48 hour wash-out period to minimize carry-over effects. There were two primary endpoints (sleep quality and sleep onset latency), and several secondary outcomes. The reporting of the trial design, conduct, and results were generally adequate and clear. The CONSORT diagram was detailed enough to help understand study flow, and the mixed-model accounted for between- and within-subject variability. Effect estimates and precision were presented in terms of confidence intervals. However, some aspects of the study need clarification and further consideration:

Comment (1) The manuscript can be improved by following reporting guidelines in the literature (e.g., Li et al. (2015) "Design, analysis, and reporting of cross-over trials for inclusion in a meta-analysis"; and Mills et al. (2009) "Design, analysis, and presentation of crossover trials") including: --- stating the rationale for cross-over design --- justifying the washout period duration, and presenting relevant data to help understand whether or not potential carry-over effects exist.

Response: Thank you for suggesting these improvements. The rationale to use a cross-over design over a parallel design was to minimize confounding covariates such as TBI characteristics and factors underpinning sleep disturbance such as depression, anxiety, and pain, which were inherently controlled by each participant serving as their own control. Additionally, the implementation of a cross-over design reduced the number of participants required. Ethically, we felt obliged to provide all participants with the active treatment given that many patients were in need of assistance. Furthermore, many participants are often discouraged to participate in studies when the active treatment is not offered, so this design ensured all participants were guaranteed melatonin treatment.
To address your comment we have now justified utilization of a cross over design in the ‘Trial Design’ section in the methods section on page 3.

In light of the known heterogeneity between TBI patients and sleep disturbances in this population, the use of a cross over design minimized the influence of confounding covariates such as injury related characteristics and factors contributing to sleep disturbances such as mood, anxiety and pain.

The 48 hour washout period was chosen to minimize carryover of treatment and to provide time to recharge the actiwatch and provide participants with the alternative treatment. Previous studies have clearly demonstrated that melatonin rhythms revert back to their original rhythms when exogenous melatonin is ceased (Lockley et al., (2000) Journal of Endocrinology; Sack et al., (2000) NEJM; Hack et al., (2003) J Biol Rhythms). We do acknowledge that in the absence of circadian profiling we cannot rule out carryover of melatonin treatment (for those individuals that received melatonin first); however, most of our treatment outcomes (with the exception of actiwatch and sleep diary) were collected four weeks and two days (including the washout) after melatonin ceased when circadian phase would have re-established. We have now included this comment in the discussion as follows:

We implemented a 48-hour washout period between consecutive treatments. Although the terminal half-life for melatonin is relative short (3.5-4 hours) [23], it is possible that melatonin administered in the first treatment period could have induced a circadian phase advance, which could have persisted for up to several days in the following (placebo) treatment period [10-12]. We confirmed that there were no treatment order effects across all outcome measures, and we limited most of the assessment treatment outcomes (except sleep diary and actigraphy) to the end of each treatment condition, when circadian phase would have re-established after melatonin treatment had ceased.

Comment (2) In the title and abstract, safety appears to be one of the primary outcomes to evaluate, but the study was not designed to evaluate it. Safety was never discussed in the background section of the main article. Serious adverse events and symptoms were mentioned, but no specific safety outcome measure was defined nor tested.

Response: We did not mean to imply in the title and abstract that a primary outcome of the study was the safety of melatonin. Therefore this has been removed from the title and study aims. We did maintain daily contact with participants, in part to monitor for serious adverse events and participants completed a side effects questionnaire to monitor symptoms experienced throughout the study, which were duly reported. We acknowledge this oversight in describing these methods only for the first time in the results section and have moved this to the methods section as follows:
Comment (3) The operational definition of compliance needs to be stated more precisely. It was not clear what the percentages represent (e.g., 100% median treatment compliance).

Response: We apologize for any confusion. We intend to mean that the majority of participants consumed 28 of their 28 allocated treatments (i.e., 100% compliant with treatment protocol) and this has now been stated in the second paragraph of the ‘Numbers Analyzed and Treatment Compliance’ section:

The majority of participants consumed 28 of their 28 allocated treatments; median treatment compliance was 100% across both treatments (melatonin Q1 - Q3 = 97-100%; placebo Q1 - Q3 = 96-100%).

Comment (4) In the mixed model, was the term "sequence" included in the model the interaction between treatment and period?

Response: Yes, sequence was included in the model as outlined in the statistical analysis section on page 8. For each of the primary and secondary outcome measures, sequence was not significant and because of this data was not presented. We have now included the following sentence in the results section on page 10: Sequence was not significant across primary and secondary outcome measures (data not shown).

Comment (5) On page 5 line 1-2, what does "regularly contacted" mean (daily, weekly?). Also, how frequently did deferring treatment happen? Was this similar between the melatonin and placebo period?

Response: To ensure compliance, participants were sent daily text messages to consume treatment, fill in questionnaires and they were contacted on a weekly basis to monitor for adverse symptoms regularly contacted. The sentence on page 5 now reads: To ensure compliance, participants were sent daily text messages, to consume treatment and fill in daily sleep diary. They were also contacted on a weekly basis to monitor for adverse symptoms.

None of the participants deferred treatment in the study. All participants completed the protocol as intended. We have now included the following sentence in the ‘Participant Flow’ section on page 9.

No participant deferred treatment, with all participants receiving treatments as intended.

Comment (6) There is a distinction between "effectiveness" and "efficacy", but the paper used these terms interchangeably. The article should pick whichever is more appropriate, and should
use that term consistently. Based on the tightly controlled nature of the intervention (eg, within 2-hours of initiating sleep, text reminders, etc), "efficacy" seemed more appropriate.

Response: Thank you for this comment. The term effectiveness has been replaced with efficacy throughout the paper and title. We agree this is a more appropriate term.

Comment (7) The authors should consider proof reading the article as several typographical errors can be found throughout the manuscript: --- page 7 line 41: alpha<0.05 should be alpha=0.05 --- Table 1 footnote on PSQI --- Table 2 treatment effect estimate of sleep efficiency should be positive 0.32, and the confidence interval limits were reversed. Also, it is strange that the 95% CI includes 0, but the p-value was significant (p=0.04). --- Table 2 treatment effect estimate of MH score should be 2.51 --- Figure 1 bottom boxes had "ITI" instead of "ITT"

Response: Thank you for identifying these errors. The following changes have been made.

- Page 7 line 41: alpha<0.05 has been replaced with $\alpha = .05$

- Table 1 footnote regarding PSQI has been resolved. The abbreviation for PSQI now reads PSQI, Pittsburgh Sleep Quality Index;

- Table 2 treatment effect estimate of sleep efficiency should be positive 0.32, and the confidence interval limits were reversed. Also, it is strange that the 95% CI includes 0, but the p-value was significant (p=0.04). Thank you for pointing out this error. The treatment effect should have read 0.32 (0.01 to 0.63). The confidence interval does not cross zero in line with the significant p value.

- Table 2 treatment effect estimate of MH score should be 2.51. This has now been changed.

- Figure 1 bottom boxes had "ITI" instead of "ITT". This has now been changed.