

Article details: 2019-0137	
Title	Circadian rhythm – a neglected aspect of the post-concussion insomnia assessment: a cross-sectional, observational study
Authors	Dora M. Zalai MD PhD, Todd A. Girard PhD, Michael D. Cusimano MD PhD, Colin M. Shapiro MBCh PhD
Reviewer 1	Name withheld
Institution	Withheld
General comments (author response in bold)	Withheld
Reviewer 2	Name withheld
Institution	Toronto, Ont.
General comments (author response in bold)	<p>My comments will be made in the order they arise in the paper, with the exception of editorial issues, which I will add at the end. Where possible, I will give page and line numbers(s) to identify the text of concern.</p> <p>Table 2: The median and IQR are preferred measures of a statistical distribution that may not be symmetrical. However, I prefer specifying the 25th and 75th percentiles, rather than giving merely the distance between them as IQR; with this information, any lack of symmetry is easy to see.</p> <p>Page 5, line 44 and Table 2: If the mTBI must have occurred 3-24 months before the screening assessment, why is the maximum time since injury in Table 2 as high as 27 months? The footnote is not clear, and the explanation would be more appropriate in the inclusion criteria.</p> <p>Page 6, line 49 - page 7, line 5: What does the Actiwatch actually measure? It is not a device that is familiar to me, and perhaps not to other readers. Should a reference be given for readers who would like more information? Or can they just visit the internet to get what they need?</p> <p>Page 8, line 52: Given that the objectives of the research refer to CRSWD almost exclusively, the rationale for comparing only subjects with DSWPD with controls (i.e., those with no CRSWD) is not clear, and should be so.</p> <p>Page 10, lines 8-12: Drowsiness has been shown in many circumstances (e.g., traffic crashes) to increase the risk of accident and injury. Did these injuries occur predominantly in the morning? This seems likely if the theory in this paragraph is correct, but I can find no information in Table 2 or elsewhere in this point.</p> <p>Page 11, lines 12-15: This is the only reference I have seen to the preponderance of young people among this with CRSWD among the mTBI cases studied. There is no information about sex in the results shown; the proportion of women in the study is relatively high, given that men typically have higher incidence rates of injury. Is the proportion with sleep problems the same in each sex?</p> <p>I said that I would raise any editorial or proof-reading issues at the end, but I found none; this paper seems to be free of such errors.</p>
Author initial response	We thank you for the thorough evaluation of the manuscript and for the opportunity to receive questions and comments from peer reviewers. We appreciate the insightful questions raised and have addressed each of them in a separate letter attached to the re-submission (Please see the attached document "Letter to the Editor_Revision [THIS HAS BEEN ARCHIVED and is not available].
Additional author responses to	a. <i>Comment 3: you provided a lengthy response to this comment, and it seems that</i>

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this information will appear in a separate paper. That being the case, perhaps these details should not appear in this paper.

Response: This comment (Reviewer 1- Comment 3 for Additional Analysis) requested calculation of the phase angles between the reported sleep timing and DLMO measures reported in the original Table 4 (Table 5 of last submission). We responded in detail to the Reviewers related queries. However, in short, we felt that this analysis was beyond the scope of the current paper and are preparing these data as part of a separate manuscript. As discussed above, and in line with the board's recommendation here, we have now removed this Table and these details from the current manuscript.

b. Some of the responses to point 5 should be included within the limitations section of the manuscript, with appropriate reasoning.

Response: We fully agreed that it would be highly desirable to replicate the study with a matched control group and to assess rates of CRSWD accompanying insomnia patients without mTBI. We had included a comment on this in the Discussion, "...this study did not include an age and sex-matched comparison group of patients with chronic insomnia who did not have a history of TBI. Future replication of this study will benefit from an inclusion of such groups to allow for more direct comparison of rates and on the sleep-wake measures. Given that research on CRSWDs among patients with insomnia alone is limited, these studies will add valuable information not only for those with TBI, but also to the general insomnia and CRSWD literature." (p. 13).

As requested, we have now integrated our prior response points into the manuscript to elaborate on the issues:

"Although preliminary, the observed proportion... Estimates for adolescents are 3-7% in the general population, rising to 7-16% in clinical samples with psychiatric conditions of this age group (11, 24-26). The particularly high rates in the younger mTBI participants in the current study bolster need for more studies to determine the rates of CRSWDs across demographic and clinical samples" (p.10)

With respect to Reviewers 1 and 2, we re-address here comments that may not have been fully addressed or only discussed in our response and not explicitly in the manuscript:

a. Reviewer 1 sought clarification (Point 1) regarding the term "consecutive" sample in the objectives statement. We noted in our response, "This simply implies that we screened (and if they were eligible, included) all patients in succession who expressed interest in participating in and met eligibility criteria for the study. There was no other screening that may have inflated the number of participants with circadian problems." We have now rephrased the objectives statement in the manuscript, **"The objective was to determine the rate of CRSWDs according to standard diagnostic criteria using evidence-based comprehensive assessment – including actigraphy and dim light melatonin onset – in a treatment-seeking sample of individuals with chronic insomnia following mTBI"** (p.5). The specific recruitment details are described in the Methods.

b. Reviewer 1 (Clarification Point 4) also asked for more details regarding the actigraphy data. These are now detailed in the **Appendix**. Regarding the manual scoring, which involved setting the "rest period" (the period between bedtime and rise time, we add, **"inter-rater agreement was always within a minute"** (p.31). This difference is negligible with respect to the scope of hours in bed and does not impact the diagnosis of CRSWDs.

c. Reviewer 1 (Clarification Point 7) queried who performed the CRSWD diagnoses. As per our prior response, we now add to the paper, **"CRSWDs were diagnosed according to International Classification of Sleep Disorders (ICSD 3) criteria (11) based on**

agreement between physician and clinical psychologist diagnoses, both with specialization in sleep medicine” (p.8).

d. Reflecting our response to Reviewer 1 (Clarification Point 8), we also detail, “**As reported during the interviews and verified by family when present**, three quarters of the sample denied having subjective sleep problems or sleep disorders prior to their injury. 100% reported moderate or significant worsening of their sleep since the injury” (p.8).

e. Reviewer 1 (Additional Analyses Point 1), asked about light exposure data and potential subgroup differences in exposure patterns. We had provided a lengthy response, but had not integrated much into the paper as we didn’t see it sufficiently relevant to elaborate there. We will report on these relations in a separate paper. Regardless, as discussed above, we have also now removed the subgroup level comparisons from the current manuscript.

f. Reviewer 1 (Additional Analyses Point 2) asked, “Was there a correlation between circadian phase and symptom severity (e.g., ISI scores).” We have now added our prior response to the manuscript, “**There was no meaningful difference between the average ISI scores among people who were normally entrained (ISI = 19.8), who had delayed phase sleep-wake disorder (ISI = 20.7) or advanced phase sleep-wake disorder (ISI = 20.5). The ISI score of the single person with an irregular rhythm was 24.**” (p.9)

g. Reviewer 1 (Additional Analyses Point 4) requested, “Please provide demographic comparison for the “No CRSWD (n = 37)” and the “DSWPD (n = 10)” groups including age, sex, employment status. Are the differences in sleep timing and circadian phase different between the groups after adjusting for these 3 covariates?” In response we had discussed these relations and added Table 4 to the last submission. As per the Board’s recommendation and our above responses, however, these subgroup comparisons and this table have now been removed.