Reviewer’s report

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

Version: 0 Date: 22 Aug 2017

Reviewer: Nava Zisapel

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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.

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes
Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes

Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

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I am the founder of Neurim Pharmaceuticals, the company that developed Circadin, the medicinal product that has been used in this project. Neither I nor the company were involved in any way in the study, or informed on this study, or aware of it in any manner. Circadin is not indicated for the use described in the paper and apparently used as a blinded experimental drug with locally produced placebo control.

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