

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

# Nutritional Supplements for Mild Traumatic Brain Injury: Clinical Effectiveness

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## Research Questions

1. What is the clinical effectiveness of nutritional supplementation as a prophylactic treatment for mild traumatic brain injury?
2. What is the clinical effectiveness of nutritional supplementation as treatment for mild traumatic brain injury?

## Key Findings

One systematic review and one randomized controlled trial were identified regarding the clinical effectiveness of nutritional supplementation as treatment for mild traumatic brain injury.

## Methods

A limited literature search was conducted by an information specialist on key resources including Medline, Embase, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were mTBI and melatonin, nicotinamide or sulforaphane. No filters were applied to limit the retrieval by study type. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and March 9, 2020. Internet links were provided, where available.

## Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

**Table 1: Selection Criteria**

<b>Population</b>	Q1: People of all ages, at risk for mild traumatic brain injury Q2: People of all ages, with suspected or diagnosed mild traumatic brain injury
<b>Intervention</b>	The following nutritional supplements, either as single ingredients or in combination preparations: <ul style="list-style-type: none"> <li>- Nicotinamide mononucleotide</li> <li>- Melatonin</li> <li>- Sulforaphane</li> </ul>

<b>Comparator</b>	Q1,2: Placebo or usual diet
<b>Outcomes</b>	Q1,2: Clinical effectiveness (e.g., severity of signs and symptoms [e.g., nausea, headache, dizziness], duration of hospitalization, mental status [e.g., level of consciousness, memory], sleep quality, structural brain lesions, neurologic disability, performance measures) and harms (e.g., morbidity, mortality, adverse drug reactions, side effects)
<b>Study Designs</b>	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies

## Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports and systematic reviews are presented first followed by randomized controlled trials and non-randomized studies.

One systematic review with meta-analysis<sup>1</sup> and one randomized controlled trial<sup>2</sup> were identified regarding the clinical effectiveness of nutritional supplementation as treatment for mild traumatic brain injury. No relevant health technology assessments or non-randomized studies were identified regarding the use of nutritional supplements as a treatment or prophylactic treatment for mild traumatic brain injury.

Additional references of potential interest are provided in the appendix.

## Overall Summary of Findings

One systematic review with meta-analysis<sup>1</sup> and one randomized controlled trial<sup>2</sup> were identified regarding the clinical effectiveness of nutritional supplementation as treatment for mild traumatic brain injury. The authors of the systematic review found two clinical studies regarding the effectiveness of melatonin in improving outcomes after traumatic brain injury (TBI), although both of these studies were of low quality and of uncertain significance.<sup>1</sup> The authors of the randomized controlled trial<sup>2</sup> aimed to determine the efficacy of melatonin supplementation for sleep disturbances in patients with TBI. Compared to placebo, melatonin supplementation for four weeks significantly reduced sleep quality index scores, thus improving sleep quality.<sup>2</sup> Melatonin supplementation also increased vitality, sleep efficiency (monitored by actigraphy) and mental health and decreased anxiety and fatigue of patients. However, there was no effect on sleep onset latency and no significant effect on daytime sleepiness.<sup>2</sup>

## References Summarized

### Health Technology Assessments

No literature identified.

### Systematic Reviews and Meta-analyses

1. Barlow KM, Esser MJ, Veidt M, Boyd R. Melatonin as a Treatment after Traumatic brain injury: A Systematic Review and Meta-Analysis of the Pre-Clinical and Clinical Literature. *J Neurotrauma*. 2019 Feb 15;36(4):523-537.  
[PubMed: PM29901413](#)

## Randomized Controlled Trials

2. Grima NA, Rajaratnam SMW, Mansfield D, Sletten TL, Spitz G, Ponsford JL. Efficacy of melatonin for sleep disturbance following traumatic brain injury: a randomised controlled trial. *BMC Med.* 2018 01 19;16(1):8.  
[PubMed: PM29347988](#)

## Non-Randomized Studies

No literature identified.

## Appendix — Further Information

### Previous CADTH Reports

3. Amino Acids and Related Supplements for Mild Traumatic Brain Injury: Clinical Effectiveness. (*CADTH Rapid response report: summary of abstracts*). Ottawa (ON): CADTH; 2020: <https://www.cadth.ca/amino-acids-and-related-supplements-mild-traumatic-brain-injury-clinical-effectiveness>
4. Lipids and Related Supplements for Mild Traumatic Brain Injury: Clinical Effectiveness. (*CADTH Rapid response report: summary of abstracts*). Ottawa (ON): CADTH; 2020: <https://www.cadth.ca/lipids-and-related-supplements-mild-traumatic-brain-injury-clinical-effectiveness-0>

### Randomized Controlled Trials – Upcoming Trials

5. University of Calgary. NCT01874847: PLAY GAME: Post-concussion Syndrome in Youth - Assessing the GABAergic Effects of Melatonin (PLAYGAME). *ClinicalTrials.gov*. Bethesda (MD): U.S. National Library of Medicine. 2017: <https://clinicaltrials.gov/ct2/show/NCT01874847?term=melatonin&cond=traumatic+brain+injury&draw=2&rank=2>

### Review Articles

6. Osier N, McGreevy E, Pham L, et al. Melatonin as a Therapy for Traumatic brain injury: A Review of Published Evidence. *Int J Mol Sci*. 2018 May 22;19(5):22. [PubMed: PM29786658](#)
7. Trojian TH, Wang DH, Leddy JJ. Nutritional supplements for the Treatment and Prevention of Sports-Related Concussion-Evidence Still Lacking. *Curr Sports Med Rep*. 2017 Jul/Aug;16(4):247-255. [PubMed: PM28696987](#)
8. Ashbaugh A, McGrew C. The Role of Nutritional supplements in Sports Concussion Treatment. *Curr Sports Med Rep*. 2016 Jan-Feb;15(1):16-19. [PubMed: PM26745164](#)
9. Fernandez-Gajardo R, Matamala JM, Carrasco R, Gutierrez R, Melo R, Rodrigo R. Novel therapeutic strategies for traumatic brain injury: acute antioxidant reinforcement. *CNS Drugs*. 2014 Mar;28(3):229-248. [PubMed: PM24532027](#)
10. Mendes Arent A, Souza LFD, Walz R, Dafre AL. Perspectives on molecular biomarkers of oxidative stress and antioxidant strategies in traumatic brain injury. *BioMed Res Int*. 2014;2014 (no pagination). [PubMed: PM372615126](#)
11. Haar CV, Peterson TC, Martens KM, Hoane MR. The Use of Nicotinamide as a Treatment for Experimental Traumatic Brain Injury and Stroke: A Review and Evaluation. *Clin Pharmacol Biopharm*. 2013;S1:005. <https://www.omicsonline.org/open-access/the-use-of-nicotinamide-as-a-treatment-for->

[experimental-traumatic-brain-injury-and-stroke-a-review-and-evaluation-2167-065X.S1-005.pdf](#)

12. Samantaray S, Das A, Thakore NP, et al. Therapeutic potential of melatonin in traumatic central nervous system injury. *J Pineal Res.* 2009 Sep;47(2):134-142. [PubMed: PM19627458](#)