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Abstract

Background: Despite strong indications that fatigue is the most common and debilitating symptom after traumatic brain injury, little is known about its frequency, natural history, or relationship with other factors. The current protocol outlines a strategy for systematic review that will identify, assess, and critically appraise studies that assessed predictors for fatigue and the consequences of fatigue on at least two separate time points following traumatic brain injury.

Methods: MEDLINE, EMBASE, COCHRANE Database of Systematic Reviews, CINAHL, and PsycINFO were systematically searched for relevant peer-reviewed studies. Reference lists of eligible papers will also be searched. Inclusion criteria: all English language studies with a longitudinal design that focus on fatigue in adults with primary-impact traumatic brain injury. Exclusion criteria: studies about fatigue following brain injury due to secondary pathological processes (intracranial complications, edema, ischemia/infarction, and systemic intracranial conditions). Excluded studies, along with the reason(s) for exclusion will be reported. Two independent reviewers will conduct all levels of screening, data abstraction, and quality appraisal. Randomized control trial data will be treated as a cohort. Quality will be assessed using the criteria defined by Hayden and colleagues. The review will be conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Conclusions: The review will summarize the current knowledge in the field with the aim of increasing understanding and guiding future research on the associations between fatigue and clinically important factors, as well as the consequences of fatigue in traumatic brain injury. PROSPERO registry number: CRD42013004262.
Keywords: Post-traumatic fatigue, Traumatic brain injury, Rehabilitation, Protocol, Systematic review
Background

Traumatic brain injury (TBI), defined as “an alteration in brain function, or other evidence of brain pathology, caused by an external force,” [1] is a major global health problem. According to the World Health Organization, TBI is predicted to surpass many diseases as a major cause of death and disability by the year 2020 [2]. The incidence of TBI is highest among young people [3], and hence, any adverse long-term effects will impact that person’s ability to return to their previous social roles, including pre-disability employment. Fatigue is commonly reported to be one of the most disabling symptoms in patients following TBI [4], and occurs in 21 to 73% of affected individuals. Fatigue is a symptom, rather than a diagnosis, which is extremely difficult to clarify and operationalize. A generally accepted universal definition of fatigue does not exist, nor is there any conceptual framework for studying fatigue in TBI. Nevertheless, discussions in the literature make a distinction between central fatigue (due to the dysfunction of supramentorial structures involved in mentation) and peripheral fatigue (of physical, metabolic, or muscular origin) [5]. The number of studies including post-TBI fatigue as an outcome measure has rapidly increased over the past decade. Fatigue is reported to be significantly greater in persons who have sustained TBI than in those who have not [6-8]. Higher levels of post-TBI fatigue have been reported to lead to a poorer quality of life [8].

There are several published narrative reviews of fatigue after TBI [9-11]. Systematic reviews are scientifically more robust than narrative reviews and are therefore a more valid source of information and less prone to bias [12]. Thus, our current aim was to identify, appraise, and synthesize all available longitudinal studies on post-traumatic fatigue in an attempt to (1) determine prognostic factors for fatigue onset in patients with TBI; (2) determine the course of
fatigue in patients with TBI; and (3) determine the health consequences of fatigue in patients with TBI. The current protocol outlines a strategy for this systematic review.

**Methods**

The review will be conducted and reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13]. In accordance with these guidelines, our systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) [14] on April 25, 2013 (registration number, CRD42013004262).

*Search methods for the identification of studies*

MEDLINE, CINAHL, and PsycINFO were systematically searched from 1946, 1980, and 1806, respectively; EMBASE was searched from 1974, and COCHRANE Database of Systematic Reviews from 2005 to middle April 2013. The complete search strategy can be found in Additional file 1.

Search terms for fatigue were developed by reviewing the literature found in a previous systematic review of fatigue [15-16], and by consulting an information specialist at the Toronto Rehabilitation Institute. Three categories of search terms will be used (Table 1). We will limit our search to the English language, and to adults aged 18 years and over (with no upper age limit). We will include all articles with the exception of papers assessing fatigue due to secondary pathological processes after brain injury (e.g., edema, intracranial hemorrhages, ischemia/infarction, and systemic intracranial conditions).
In addition to the electronic databases, a manual search of the reference lists of reviews from relevant journals published between 1990 and 2013 (e.g., Journal of Head Trauma Rehabilitation and Neurorehabilitation) will be conducted to ensure a complete search.

Criteria for considering studies for this review

Types of studies:

• Peer-reviewed published longitudinal studies (i.e., studies that have assessed fatigue* on at least two separate occasions) in English, conducted in adults with a clinical diagnosis of TBI**.
• Studies that were primarily designed to investigate the predictors and consequences of fatigue in the TBI population.
• Types of participants:
  • Men and women aged 18 years or older, with TBI defined by clinical criteria**.
  • Any means of diagnosis or assessment of fatigue.

*Fatigue: any measures of fatigue will be accepted (e.g., the presence or absence of fatigue determined using a single question, a case definition on a fatigue scale, or fatigue scores reported as a continuous variable). For the purpose of this review, we will define “human fatigue” as “the undesirable state produced by effort - the physical or mental effort of doing work” [17].

**For the purpose of this review, we will focus on TBI cases of primary-impact injury only. The operational definitions for the clinical identification of primary-impact TBI include: (i)
concussion: “a trauma-induced alteration in mental status that may or may not involve loss of consciousness” [18]; (ii) coup and contrecoup (damage at the site or opposite to the site of blow); (iii) contusion (hemorrhagic); and (iv) diffuse axonal injury.

**Exclusion criteria**

- Studies that focus on a different but parallel topic to fatigue (e.g., sleepiness***, impaired alertness, or vigilance).
- Studies about fatigue after brain injury due to secondary pathological processes (e.g., edema, intracranial hemorrhages, ischemia/infarction, and systemic intracranial conditions).
- Letters to editors and reviews without data, case reports; conference abstracts and unpublished manuscripts****.

*** The cause of a patient’s symptoms can be hard to determine on a single item scale as patients with TBI may use vague words to describe their state (e.g. sleepiness vs. fatigue). Sleepiness is a basic physiological state, the presence and intensity of which can be inferred by how readily sleep onset occurs, how easily sleep is disrupted, and how long sleep endures [18]. The utilized measures, and items within them, can guide in distinguishing the fatigue phenomena from sleepiness. For example, the symptom related to sleepiness may be presented as unintended episodes of falling asleep during the daytime or elevated numbers on standardized sleepiness scales; symptoms related to fatigue will manifest as muscular weakness or lack or energy. We recognize that some fatigue scales may include items related to sleepiness. As part of our review, we will report whether utilized fatigue scales were uni- or multi-dimensional.
To reduce the publication bias, we will use the following approaches to find unpublished studies: 1) will search in the Cochrane Handbook (through the Cochrane Library CD) for registries with completed and ongoing studies registered in the area of TBI and through the website www.controlled-trials.com which provides online access to a listing of ongoing and completed control trials; and 2) will contact the principal investigators of relevant studies directly, asking whether they know of additional studies. We will also screen for the conference abstracts bearing in mind to contact the study authors to obtain full study details.

Types of study design

Criteria for considering studies for this review

All experimental (intervention and effectiveness studies with prospective longitudinal design), and non-experimental (observational studies, i.e., cohort and case control) will be considered for this review.

Selection of studies

All hits will be saved in EndNote and duplicates removed. For the first level of screening, two reviewers (TM and TK) will read the titles and abstracts of all the citations from the electronic database searches and remove all citations not related to primary-impact TBI. For the second level of screening, each reviewer will individually assess the full article, if the title or abstract suggests that the study might meet the inclusion criteria; any conflicting views will be resolved by consultation between reviewers, or by seeking advice from other experts (AC, CS, and JDC).
Studies failing to meet the inclusion criteria will be excluded, and the reason listed in the “Characteristics of excluded studies” (Additional file 2).

**Data extraction**

For studies fulfilling the inclusion criteria, the two independent reviewers (TM and TK) will independently extract data into data collection forms grouped according to their design.

Randomized control trial (RCT) studies will be treated as cohorts: we will utilize the control (e.g. untreated group) data from RCT studies to address the second research objective (e.g. to determine the course of fatigue) if the intervention had an effect. If the trial is negative, both intervention and control groups will be used.

The abstracted data will include (1) study characteristics (author names, publication year, country of study, study setting, study design, sample size, methods of measuring fatigue and other variables [e.g., factors], number of participants assessed for fatigue at each time point, time between assessments, and time since injury for each follow-up); (2) participant characteristics (mean age, sex, definition of TBI, localization of injury, and injury severity); and (3) results (reported frequencies of fatigue and other factors, and reported associations between fatigue and other variables)(Tables 2 and 3).

**Analysis**

*Methodological quality and risk of bias assessment*
Study quality will be assessed independently by two reviewers (TK and TM) using the guidelines developed by Hayden et al. (2006) for assessing prognostic studies [19]. The appraisal will consist of two steps. The first step will assess the items related to six potential sources of bias (study participation and attrition, prognostic factors and outcome measurements, confounding measurement and account, and analyses). The second step will judge the presence of potential biases as “Yes,” “Partly,” “No,” or “Unsure.” Then the reviewers will decide if a study has a fatal flaw or bias. If so, that study will fall into the category of “high risk of bias.” In order to ensure the explicit basis for bias assessment, we will record the reasons for our judgment of “high risk of bias,” including the main reasons why the decision of exclusion was made. For the “low risk of bias” studies, we will abstract data on the relationships between fatigue and other variables. Any statistical measure of association (e.g., odds ratio, hazard ratio, or relative risk) will be reported (see Additional file 4).

To summarize the level of evidence, we will utilize a system similar to the Scottish Intercollegiate Guidelines Network Methodology [19]: (i) “++” when all, or most of the quality criteria proposed by Hayden (2006) are fulfilled (allowing one “Partly” while appraising all potential sources of bias); (ii) “+” when some of the criteria are fulfilled; and (iii) “-” when few or none of the criteria are fulfilled (at least one “Yes”). We will refer to group (i) as “high-quality studies” and group (ii) as “moderate-quality studies” (see Additional table 3).

**Data synthesis and analysis**

Given the diversity in definitions of fatigue, populations of interest, and the statistical methodology used to express association, a meta-analysis will be not conducted. The findings of studies with sufficient quality will be synthesized by means of tabulation and qualitative
description. Only brief summary results will be provided for studies that do not meet our quality criteria.

Dealing with missing data

Primary authors will be contacted in the case of missing data. Where possible, the proportion of missing data will be stated, along with possible reasons. In the case of duplicate publications and companion papers of a primary study, we will try to maximize the yield of information by the simultaneous evaluation of all available data. In any cases of doubt, the original publication (usually the oldest version) will take priority.

Discussion

To the best of our knowledge, this is the first systematic review of fatigue in TBI, and has the potential to significantly improve methodological understanding of its frequency, natural history, and associated factors. Our systematic review has a number of strengths. First, we used extensive search strategies, making it unlikely that we will miss relevant studies. Second, our strategies are intentionally sensitive, rather than specific. Third, two authors will extract the data independently, thus reducing the chance of errors occurring in data extraction. Furthermore, we will use a rigorously developed protocol, with clearly defined inclusion and exclusion criteria, which were decided upon in advance of performing the searches. Finally, expanded synonyms of the word “fatigue” and “brain injuries” were used in the search. A potential weakness of this review is that we pre-specified only studies published in the English language to be included, and therefore, any relevant studies published in other languages have been omitted. An attempt will be made to identify non-English language papers (e.g. usually titles and abstracts are translated
to English in many databases) and document their existence and reason for exclusion as
“language” will be recorded.

In addition, all of the articles to be included in this review were peer-reviewed and, as such, there is some publication bias.

**Dissemination plans**

An extensive knowledge translation strategy will be implemented at the conclusion of this review. The target audience is rehabilitation practitioners and other professionals (e.g., TBI specialists, sleep specialists, and psychiatrists) who work with the TBI population. The results of this systematic review will be presented at relevant meetings locally (e.g., Rehabilitation Research Day, Southern Ontario Neuroscience Association Annual Meeting), nationally (e.g., ABI Canadian Conference and Canadian Sleep Society National Meeting), and internationally (Brain Injury World Congress and Sleep Society World Conference). The results will be published in a peer-reviewed journal to be made available to the appropriate academic and clinical audience.

**Implications**

Fatigue is a common post-TBI symptom, and is likely to be long lasting. This systematic review and best-evidence synthesis has been planned to inform clinical practice and future research by formulating new questions, and encouraging scientists and clinicians to examine certain
relationships in greater detail, and to discover how disease-specific processes can contribute to fatigue in TBI.

**List of abbreviations**

TBI, traumatic brain injury; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews; RCT, randomized control trial.

**Competing interests**

The authors have no conflicts of interest to declare pertaining to this review.

**Authors' contributions**

TM, TK, SM, CS, JDC and AC contributed to the conception and design of the review. TM developed the idea and designed the protocol. TK co-developed the idea and supported TM in the development of search strategy; SM was responsible for building the graphic data representation (e.g. table, figures, etc.) and helped to draft the proposal. JDC provided expertise at each level and also reviewed the protocol. CS and AC inspired the idea and critically reviewed the protocol. TM wrote the first draft, which was revised by TK, AC, CS, and JDC. TM and TK registered the protocol. All authors read and approve the final manuscript.
Acknowledgements

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References


Mollayeva T, Kendzerska T, Mollayeva S, Shapiro MC, Colantonio A, Cassidy JD. 
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14. PROSPERO- International Prospective Register of Systematic Reviews. [http://www.crd.york.ac.uk/prospero/].


Table 1: Terms Used in Search

<table>
<thead>
<tr>
<th>Brain Injuries</th>
<th>Fatigue</th>
<th>Models</th>
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<tbody>
<tr>
<td>- exp Brain Injuries/</td>
<td>- fatigue/or fatigue syndrome, chronic/or asthenia/or mental fatigue/or muscle fatigue/or lethargy/listlessness or letarg$ or apath$ or malaise).tw</td>
<td>- (“Models, Theoretical”[Mesh] OR “Causality”[Mesh] OR “Etiology”[Subheading])</td>
</tr>
<tr>
<td>- craniocerebral trauma/ or exp brain injuries/ or coma, post-head injury/ or head injuries, closed/ or head injuries, penetrating/ or exp intracranial hemorrhage, traumatic/ or exp skull fractures/</td>
<td>- ((low or lack) adj5 energy).tw</td>
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Table 2: Studies assessing fatigue at two or more time points after TBI

<table>
<thead>
<tr>
<th>First author, date, country, study setting</th>
<th>Sample (N), injury severity/definition (% of total), time of assessment post-TBI and number of participants that completed assessment at each point of,</th>
<th>Study design, follow-up time if applicable</th>
<th>Main statistical method</th>
<th>Measure of fatigue</th>
<th>Results</th>
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<tr>
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<td>Frequency of fatigue at each time point (95% CI)</td>
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</table>
Table 3: Longitudinal studies reporting associations between fatigue and other variables after TBI*

<table>
<thead>
<tr>
<th>First author, date, country, study setting</th>
<th>Sample (N), injury severity/definition (% of total), time since injury (TSI), mean age (or age ±SD), gender (M, %)</th>
<th>Study design, follow-up time if applicable</th>
<th>Main statistical method</th>
<th>Measure of fatigue</th>
<th>Results</th>
</tr>
</thead>
</table>

*Only results from the multivariable analysis will be reported. Univariate associations will be reported only in a case when adjustment was not performed. Where possible, 95% confidence intervals will be reported.

Table 4. The most common significant predictors of post-traumatic fatigue reported

<table>
<thead>
<tr>
<th>Study, author and year</th>
<th>Factor1</th>
<th>Factor2</th>
<th>Factor3</th>
<th>Factor4</th>
<th>Factor5</th>
<th>Factor…</th>
</tr>
</thead>
</table>

* - no correlation was reported in fully adjusted model between Fatigue post-TBI and Factor (1, 2, etc.)

● - positive significant association; ○ - negative significant association; ○ - no significant association was reported in multivariable model; “—“ - was not included in the model.

Additional material

**Additional file 1:** Search strategies. This file provides the list of search terms used to search MEDLINE, EMBASE, COCHRANE Database of Systematic Reviews, CINAHL and PsycINFO.

**Additional file 2:** Characteristics of Excluded Studies. This file contains table for excluded studies.

**Additional file 3:** Quality assessment of studies using guidelines developed by Hayden et al., 2006. This file contains items that will aid reviewers in completing the quality assessment.
Additional files provided with this submission:

Additional file 1: Additional file 2.docx, 13K  
http://www.systematicreviewsjournal.com/imedia/1306711318996886/supp1.docx
Additional file 2: Additional file 3.docx, 14K  
http://www.systematicreviewsjournal.com/imedia/1854175789996886/supp2.docx
Additional file 3: Additional file 1.docx, 32K  
Additional file 4: SystematicReviewTable 1May16_2013.docx, 16K  
http://www.systematicreviewsjournal.com/imedia/1224678110996886/supp4.docx