Fatigue after traumatic brain injury: a systematic review.

Ali, A.; Morfin, J.; Mills, J.; Pasipanodya, E.C.; Maas, Y.J.; Huang, E.; ... ; Zedlitz, A.M.E.E.

J Head Trauma Rehabil
Vol. 37, No. 4, pp. E249–E257

OPEN

Fatigue After Traumatic Brain Injury: A Systematic Review

Arshad Ali, MHA; Jussely Morfin, BS; Judith Mills, AHIP, MLIS, NCMA; Elizabeth C. Pasipanodya, PhD; Yvonne J. Maas, MSc; Emily Huang, MD; Benjamin Dirlikov, MA; Jeffrey Englander, MD; Aglaia Zedlitz, PhD

Objective: To provide a systematic review of published interventions for posttraumatic brain injury fatigue (PTBIF). **Methods:** PubMed and OneSearch were systematically searched for PTBIF interventions published between January 1, 1989, and March 31, 2019. Search results were evaluated for inclusion based on an abstract and full-text review. Inclusion criteria were (1) an investigation of an intervention, (2) participant sample including individuals with traumatic brain injury (TBI), (3) report of fatigue outcome data among individuals with TBI, and (4) articles available in English, Spanish, French, German, Afrikaans, or Dutch. A risk of bias assessment was conducted on all included publications. **Results:** The search resulted in 2343 publications, with 37 meeting inclusion criteria for this review. Categories of PTBIF interventions were pharmacological ($n = 13$), psychological ($n = 9$), exercise-based ($n = 4$), complementary alternative medicine ($n = 5$), electrotherapeutic ($n = 3$), and multimodal ($n = 3$). Only methylphenidate, modafinil, and cognitive behavioral therapy interventions included multiple cohorts. Pharmacological and psychological interventions represented the groups with the lowest risk of bias. **Conclusions:** This review includes 37 studies, with 21 studies published after 2014. Methylphenidate and melatonin were the only pharmacological agents found to reduce fatigue in randomized controlled trials. Creatine given to children prospectively at onset of injury reduced fatigue at follow-up. Walking and water aerobics were effective exercise interventions in isolated randomized controlled studies. One multimodal study of children after concussion was more effective at reducing fatigue and postconcussion symptoms than community standard of care. Other interventions had equivocal results. Overall, more work remains to understand and develop treatments for PTBIF.
Key words: *brain injuries*, *fatigue*, *intervention*, *mental fatigue*, *TBI*, *traumatic*, *traumatic brain injury*

TRAUMATIC BRAIN INJURY (TBI) is caused by external force to the cranium and intracranial contents and can result in profound consequences.[1] Approximately 2.5 million individuals sustain TBIs in the United States each year, resulting in approximately 50 000 deaths, over 80 000 permanent disabilities, and an estimated $60 billion in direct and indirect costs.[2] The chronic consequences of TBI vary in type and severity but can include epilepsy, sleep disorders, cognitive and motor dysfunction, neuroendocrine dysregulation, and psychiatric problems.[3–7] Post-TBI fatigue (PTBIF) is a ubiquitous sequela of TBI, with estimates suggesting a prevalence range of 21% to 70% among individuals who experienced a TBI.[8] PTBIF may simultaneously interfere with, and be exacerbated by, engagement in physical and cognitive activities, subsequently restricting participation in activities of daily living, social engagement, and occupational functioning.[9–12] Thus, the chronic experience of PTBIF has significant consequences on adjustment and recovery following TBI.

Although PTBIF is typically conceptualized to be a multidimensional construct, encapsulating physical (eg, tiredness and exhaustion), psychological (eg, lack of motivation), and cognitive (eg, difficulty with concentration, focus, and mental flexibility) components, a standard holistic definition of PTBIF has not been adopted in research or medicine.[13] Many common scales utilized in PTBIF research tend to assess discrete

Author Affiliations: *Rehabilitation Research Center, Santa Clara Valley Medical Center, San Jose, California (Messrs Ali and Dirlikov, Ms Morfin, and Dr Pasipanodya); Medical Library, Santa Clara Valley Medical Center, San Jose, California (Ms Mills); SeneCure, GGZ-Breburg, Tilburg, the Netherlands (Ms Maas); Physical Medicine and Rehabilitation Department, Santa Clara Valley Medical Center, San Jose, California (Drs Huang and Englander); Department of Orthopedic Surgery, Stanford University School of Medicine, Palo Alto, California (Dr Englander); and Institute of Psychology, Health, Medical and Neuropsychology Unit, Leiden University, Leiden, the Netherlands (Dr Zedlitz).*

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are provided in the HTML and PDF versions of this article on the journal's Web site (www.headtraumarehab.com).

The authors declare no conflicts of interest.

Corresponding Author: *Arshad Ali, MHA, Rehabilitation Research Center, Santa Clara Valley Medical Center, San Jose, CA 95128 (arshad.ali@hhs.sccgov.org).*

DOI: 10.1097/HTR.0000000000000710

aspects of fatigue. For instance, the widely used Fatigue Severity Scale largely assesses the impact, but not severity, of fatigue and has few items assessing psychological and cognitive facets of PTBIF.[14] Furthermore, the vast majority of fatigue measures used in PTBIF research were validated among individuals without TBI or neurological conditions.[15,16] Consequently, the various scales commonly used to measure fatigue may not characterize PTBIF adequately and may contribute to the wide range in observed PTBIF prevalence estimates (21%-70%).[8]

Despite variability in the definition and measurement of PTBIF, investigating treatments that may ameliorate PTBIF is important. A 2014 review identified 19 articles published in English that investigated PTBIF interventions.[8] A substantial proportion of identified articles (8/19) evaluated pharmacological interventions and the majority of the remaining studies (8/11) investigated the efficacy of cognitive behavioral and physical activity interventions. However, few studies in the review investigated PTBIF as the primary outcome, most interventions had a high risk of bias, and interventions were rarely investigated in multiple cohorts. Therefore, the authors were unable to suggest specific interventions for clinical practice.[8] A more recent review including studies from 2014-2016 as well as a 2017 review targeting randomized controlled trials on complementary and alternative interventions provided an update on PTBIF treatments, yet noted similar shortcomings, such as a need for larger sample sizes, replicating results, and clearer definition of PTBIF.[17,18]

Given equivocal findings of efficacy in past reviews, this article was motivated to provide a comprehensive review of PTBIF intervention research to date. The current systematic review provides a broad review of PTBIF treatments that expands upon previous work by including (1) PTBIF intervention research published in 6 languages, (2) peer-reviewed and non-peer-reviewed (gray) literature, and (3) studies that include TBI-specific fatigue data, regardless of the percentage of individuals with TBI included in the study.

METHODS

Search strategy, data extraction, and database preparation

The initial aim of the study was to provide a meta-analysis of published PTBIF treatments, yet due to variability in treatment types, study design, and outcome measures the study was amended to provide a review of published treatments instead (see Appendix III for Supplemental PRISMA checklist, available at: http://links.lww.com/JHTR/A462). The search strategy followed the Population Intervention Control Outcome (PICO) question: "In patients who have experienced TBI, what treatments, compared to usual care, no treatment/placebo, or alternate treatment, alleviate PTBIF symptoms?" This PICO question was supplemented by searches of interventional studies without a control condition to capture all studies investigating treatments for PTBIF. Cuijpers' (2016) guide was utilized as a reference for constructing this broad list of search terms (see Supplemental Appendixes I and II, available at: http://links.lww.com/JHTR/A457 and http://links.lww.com/JHTR/A458) that included physical, psychological, and cognitive aspects of fatigue. A medical librarian queried OneSearch and PubMed search engines in May 2019 to find relevant publications (eg, scientific manuscripts, abstracts, dissertations, and non-peer-reviewed publications). When queried, OneSearch and PubMed included 22 and 3 databases, respectively (see Supplemental Appendixes I and II, available at: http://links.lww.com/JHTR/A457 and http://links.lww.com/JHTR/A458). The search results were exported from PubMed and OneSearch as text files in MEDLINE format and generic bibliographic management format, respectively. A MATLAB script converted the long-format bibliographic information into an easy-to-read wide-format excel. All articles were assigned an identification number and columns were added to track the independent reviewers' decisions and notes.

Review process

A 2-stage review process, consisting of an abstract review followed by a full-text review, was carried out such that each abstract and full-text article were reviewed by 2 independent reviewers. Inclusion criteria were (1) an investigation of an intervention, (2) participant sample including individuals with TBI, (3) report of fatigue outcome data among individuals with TBI, and (4) articles available in English, Spanish, French, German, Afrikaans, or Dutch. Duplicate search results were removed. If information within abstracts was unclear, a full-text review was carried out to determine inclusion. Articles with conflicting reviews were discussed among the study team, and a consensus decision was reached.

Data abstraction

A subset of the included manuscripts was assigned to each author for data abstraction and risk of bias assessment. The following data were abstracted, when reported in the articles: (1) year published, (2) country where the research was conducted, (3) study design, (4) intervention information, (5) inclusion/exclusion criteria, (6) basic demographics (ie, sample size, sex, race/ethnicity, and age), (7) percentage of sample with TBI, (8) outcome measure(s) used, and (9) TBI-specific results (eg, pre- to postintervention statistics). Based on the type of intervention included, 6 intervention

categories (pharmacological, psychological, exercise-based, complementary and alternative medicine [CAM], electrotherapeutic, and multimodal) were created to summarize the results.

Risk of bias assessment

For randomized studies, risk of bias was assessed using the revised Cochrane risk-of-bias tool (version 2).[19] This tool provides preset questions and an algorithm to assess the level of bias in the following categories: randomization process, deviations from the intended intervention, missing outcome data, measurement of the outcome, and selection of reporting results. Ratings of overall bias are suggested at the end of the questionnaire and confirmed or modified by the user. For studies without randomization, criteria from Cuijper's guidelines were used.[20] Similar to the Cochrane risk-of-bias tool, this assessment includes selection bias, performance bias, detection bias, attrition bias, reporting bias, other bias, and overall risk of bias assessments. A lack of randomization, blinding, preset analysis plan, and statistical reporting for either assessment tool yields a greater risk of bias score. Results from the risk of bias rating are summarized graphically in Figure 1.

RESULTS

OneSearchy and PubMed queries identified 2343 publications from March 1, 1989, to March 31, 2019 (1394 and 949, respectively; see Figure 2.[21]). Out of the 2343 publications, 790 were removed as duplicate entries and the remaining 1553 went through the abstract review process. Based on inclusion criteria, 1402 publications were excluded during the abstract review, leaving 151 publications eligible for full-text review. The full-text review excluded an additional 114 publications, resulting in 37 publications for inclusion in this review.

The 37 publications included in this study were categorized into pharmacological ($n = 13$; see Supplemental Table 1a, available at: http://links.lww.com/JHTR/A459), psychological ($n = 9$; see Supplemental Table 1b, available at: http://links.lww.com/JHTR/A459), exercise-based ($n = 4$; see Supplemental Table 1c, available at: http://links.lww.com/JHTR/A459), complementary alternative medicine ($n = 5$; see Supplemental Table 1d, available at: http://links.lww.com/JHTR/A459), electrotherapeutic ($n = 3$; see Supplemental Table 1e, available at: http://links.lww.com/JHTR/A459), and multimodal interventions ($n = 3$; see Supplemental Table 1f, available at:

Randomized Trials

Author(s)/Publication Year	Intervention Category	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
Johansson et al. 2014	Pharmacological	?	+	+	+	+	?
Johansson et al. 2015	Pharmacological	+	+	?	+	+	+
Zhang & Wang 2017	Pharmacological	+	+	+	+	+	+
Grima et al. 2018	Pharmacological	+	+	+	+	+	+
Sakellaris et al. 2007	Pharmacological	+	?	+	+	+	?
Berginstrom et al. 2017	Pharmacological	+	+	+	+	+	+
Jha et al. 2008	Pharmacological	+	+	+	+	+	+
Kaiser et al. 2010	Pharmacological	+	+	–	+	+	?
Theadom et al. 2018	Pharmacological	+	+	+	+	+	+
Lequerica et al. 2015	Pharmacological	+	+	+	+	+	+
Potter et al. 2016	Psychological	+	+	+	+	+	+
Nguyen et al. 2017	Psychological	+	+	?	+	+	+
D'antonio et al. 2013	Psychological	+	+	+	+	?	?
Leonard 2002	Psychological	+	+	–	?	+	?
Raina et al. 2016	Psychological	+	+	?	+	?	+
Liebenberg 1997	Psychological	+	–	–	–	–	–
Kalokowsky–Hayner et al. 2017	Exercise–based	+	+	+	+	+	+
Driver & Ede 2009	Exercise–based	?	+	+	+	+	?
Gemmel & Leathem 2006	Exercise–based	?	–	+	+	+	–
Miller et al. 2015	CAM	+	+	?	+	+	?
Sinclair et al. 2014	CAM	+	+	+	+	+	+
Smith et al. 1994	Electrotherapy	+	+	+	+	+	+
Rytter et al. 2019	Multimodal	+	+	?	+	+	+

Non–Randomized Trials

Author(s)/Publication Year	Intervention Category	Selection Bias	Performance Bias	Detection Bias	Attrition Bias	Reporting Bias	Other Bias	Overall Bias
Mossburg et al. 2016	Pharmacological	–	–	–	+	?	+	?
Khateb 2005	Pharmacological	–	–	–	–	?	–	–
Lu et al. 2016	Psychological	–	–	–	–	–	–	–
Ouellet et al. 2004	Psychological	–	–	–	+	?	?	–
Howe et al. 2019	Psychological	–	–	–	–	?	?	–
Chin et al. 2015	Exercise–Based	–	–	–	?	+	?	?
Lagos et al. 2013	CAM	–	–	–	+	+	–	–
Qin 2017	CAM	–	–	–	+	+	?	–
Baker & Wigram 2004	CAM	–	–	–	+	?	?	?
Nelson & Etsy 2015	Electrotherapy	–	–	–	?	?	?	?
Nelson & Etsy 2010	Electrotherapy	–	–	–	?	+	–	–
Gagon et al. 2016	Multimodal	–	–	–	+	+	+	–
Gauvin–Lepage et al. 2018	Multimodal	–	–	–	+	?	?	–

+ Low risk
? Some concerns
– High risk

Figure 1. Randomized trial risk of bias was assessed using the Cochrane risk–of–bias tool Version 2. Non–randomized trials were assessed using guidelines from the Cuijper's 2019 Practical Guide. The Johannson 2017 article was not included in the risk of bias assessment since it was a follow–up study and not an intervention.

Figure 1. Risk of bias assessment.

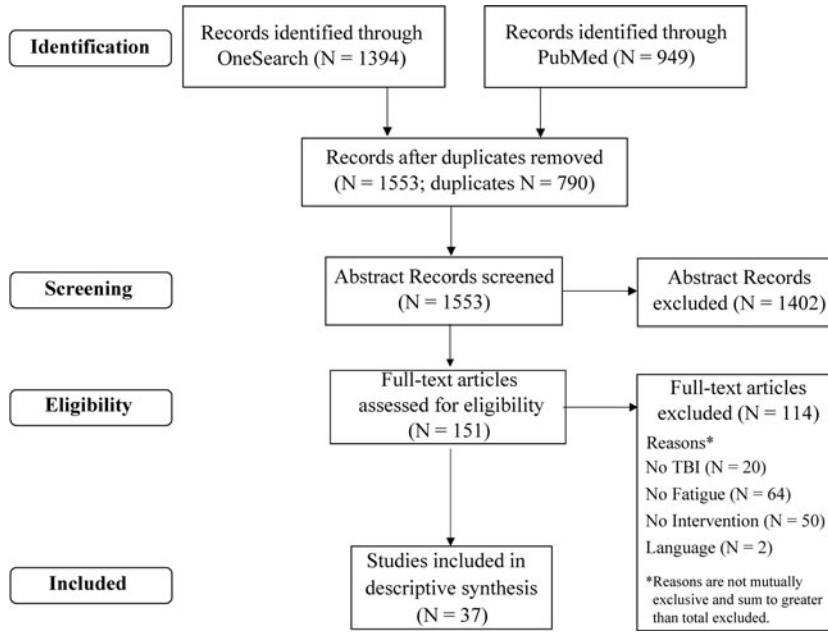

Figure 2. PRISMA diagram.

http://links.lww.com/JHTR/A459). Only 9 out of 37 studies targeted fatigue as the primary outcome. The risk of bias assessment revealed 2 high-risk, 14 low-risk, and 7 randomized studies with some concern, while the nonrandomized studies showed 9 high-risk, 0 low-risk, and 4 studies with some concern (see Figure 1). One study was not assessed for bias since it was a nonintervention follow-up study.

Pharmacological interventions

Thirteen publications on pharmacological interventions were identified in this study (see Supplemental Table 1a, available at: http://links.lww.com/JHTR/A459). These interventions included 9 different pharmacological agents, with methylphenidate being the most investigated treatment (4/13 publications). Six studies specifically mentioned fatigue as a target of the pharmacological intervention, while other studies included broader targets, such as cognitive sequelae after TBI, or sleep. Ten of the 13 studies were randomized controlled studies, 2 used a single-arm design, and 1 study presented follow-up data. Due to the higher incidence of controlled studies, this category of studies presented generally a low risk of bias (see Figure 1).

Methylphenidate was one of the most studied treatments (4 publications, including 1 follow-up study), which include studies with multiple cohorts and significant reductions in PTBIF symptoms across studies (an 8- to 12-point reduction in the Mental Fatigue Scale [MFS] post-treatment).[22–25] Two studies investigated modafinil[26,27] with mixed results, while the remaining interventions used unique pharmacological agents (herbal supplement MLC901,[28] monoaminergic stabilizer ((−)-OSU6162),[29] melatonin,[30] creatine,[31] human growth hormone (HGH),[32] ramelteon,[33] and donepezil.[34] Melatonin and creatine showed significant improvements in PTBIF compared to controls, and HGH showed improvements although no control was included. The monoaminergic stabilizer, ramelteon, and herbal supplement did not show improvements in PTBIF compared with the placebo control, and donepezil did not show PTBIF improvements in their single-arm design.

Psychological interventions

Nine studies, utilizing a range of therapeutic interventions (cognitive behavioral therapy [CBT], client-centered therapy, psychoeducation, behavioral activation, and pacing), were identified (see Supplemental Table 1b, available at: http://links.lww.com/JHTR/A459). Of these interventions, only one primarily targeted fatigue[35] (see Supplemental Table 1b, available at: http://links.lww.com/JHTR/A459). Although most studies were randomized controlled (6/9), all studies were characterized by small sample sizes comprised of fewer than 50 participants (range 1-46) and short postintervention follow-up periods (0-4 months). The 3 uncontrolled studies were either a case series ($n = 3$),[36] case study ($n = 1$),[37] or single group study ($n = 6$).[38] The studies included in the psychological intervention category all used different PTBIF measurements, except for 2 studies[35,39] that both used the Fatigue Severity Scale. Evidence of the efficacy of psychological intervention in improving fatigue was mixed, with only 2 studies[39,40] reporting unequivocal findings of improvement in fatigue after intervention.

Exercise-based interventions

Four interventions included in this study utilized exercise-based interventions[41–44] (see Supplemental Table 1c, available at: http://links.lww.com/JHTR/A459). Of the 4 exercise-based interventions, 3 interventions (walking, aerobic exercise, and aquatic program) showed positive effects on fatigue assessments, with 1 intervention (walking) specifically targeting fatigue symptoms. The walking-based intervention[44] included a large, randomized cohort ($n = 123$), crossover design, and multiple fatigue assessments (Global Fatigue Index, Barrow Neurologic Institute Fatigue Scale Overall Severity Index Score, and Multidimensional Fatigue Inventory). All measurements showed significant reductions in PTBIF post-intervention, which were sustained at follow-up 12 weeks after the intervention was completed. Both the aerobic and aquatic interventions showed within treatment group reductions in PTBIF; yet the aquatic intervention study, which included a control, did not find between-group differences. The tai chi intervention[43] did not observe significant reductions in PTBIF.

Complementary and alternative medicine

Only 1 of the 5 CAM interventions included in this study targeted fatigue specifically (blue light therapy)[45] (see Supplemental Table 1d, available at: http://links.lww.com/JHTR/A459). Two studies used a randomized controlled design (blue light therapy and hyperbaric oxygen), while the other 3 interventions (heart rate variability feedback,[46] hand self-shiatsu,[47] and singing[48]) did not include a control group. Only the blue light therapy intervention observed significant improvements in PTBIF compared with both control groups (yellow light and no treatment), while the singing and hand self-shiatsu studies showed within treatment group improvements.

Electrotherapeutic interventions

This review identified 2 articles and 1 abstract that included electrotherapeutic interventions (see Supplemental Table 1e, available at: http://links.lww.com/JHTR/A459). These publications used 2 interventions, electroencephalographic biofeedback[49,50] and cranial electrostimulation (CES); however, only the CES study[51] included control groups (sham and placebo). All 3 studies showed decreases in PTBIF symptom ratings, with the CES study also showing significant reductions in post-TBI symptoms post-intervention for the intervention group but not the control group.

Multimodal interventions

This review identified 3 multimodal studies,[52–54] only 1 of which was a randomized control trial[54] (see Supplemental Table 1f, available at: http://links.lww.com/JHTR/A459). All 3 studies focused on ameliorating postconcussion symptoms primarily and not fatigue specifically. However, all 3 studies reported positive findings of some fatigue diminishment after the often-extensive treatments. All studies included a combination of psychoeducational, psychotherapeutic, and exercise-based interventions, although each was distinct.

DISCUSSION

Our systematic review of the literature identified 37 studies that investigated the impact of interventions on PTBIF. Approximately 50% of the interventions included in this study were not included in earlier PTBIF treatment reviews.[8,17,18] Pharmacological, psychological, and exercise-based studies were more frequently randomized controlled trials and, therefore, showed a lower overall risk of bias compared with the other types of interventions (see Figure 1).

Pharmacological interventions

Pharmacological interventions represented the group of publications with the lowest risk of bias, with 10 out of 13 publications being randomized controlled trials. Although this group of interventions showed the greatest scientific rigor, challenges remain in translating interventions into available treatments. For instance, methylphenidate was one of the most-studied treatments with the greatest effects on PTBIF, and it is already commonly prescribed for PTBIF symptoms in the United States. However, treatment with methylphenidate involves a complicated prescribing process, as it is a controlled substance with a potential for abuse and adverse side effects. Despite this, for the experienced prescriber and reliable patient, methylphenidate can be an effective option that can be quickly titrated because of its short half-life.[55] Modafinil, another commonly prescribed PTBIF medication in the United States, had mixed results showing potential within treatment group improvements but significant group differences (treatment compared with control) were less clear. Recombinant human growth hormone (RHGH) is typically prescribed to individuals with diagnosed growth hormone deficiency; however, it requires daily injection, is expensive with likely a lifelong treatment, and requires frequent monitoring. Potential side effects of RHGH include fluid retention, hyperglycemia, and tumor growth. In some studies, the withdrawal of treatment resulted in worsening of cognitive symptoms.[56,57] Thus, an experienced prescriber, usually an endocrinologist, is necessary when considering this treatment for indicated conditions. An investigational medication used primarily for alcohol dependence, monoaminergic stabilizer (−)-OSU6162,

was also included in this review and showed within-group improvements, but no statistically significant between-group differences were observed. As it carries a hazard warning of toxicity[58] and is not yet indicated for clinical use for any condition, further investigation is required. Taken together, although some of these pharmacological interventions showed preliminary promise in alleviating PTBIF symptoms, translation into clinical use has some challenges.

On the other hand, melatonin, prescribed primarily for help with sleep regulation, is inexpensive, available over-the-counter, has minimal side effects, and low abuse or overdose potential. The effect on PTBIF may be secondary to improved sleep and may only improve sleep-related fatigue. In addition, one study of creatine administration to children within 4 hours of injury to prevent some of the most common post-TBI symptoms, including fatigue, suggests that a simple amino acid supplement may have significant impact with minimal morbidity.[31,59] As this was the only medication study that attempted to prevent post-TBI symptoms, replication is necessary among both children and adults to support these favorable findings. Given that creatine and melatonin are supplements and come in multiple formulations, finding the most effective formulation and dose may pose the biggest challenge. Also, complication may arise due to different drug interactions as well as variability in quality control since supplements are not FDA-approved. Despite this, of the pharmacological interventions, melatonin and creatine were considered easier and safer to use. Moreover, evaluation of medications prescribed for other medical problems may have fatigue as side effects, so modifying the dosage or type of those medications may be just as effective in pharmacological management of fatigue as adding an additional medication.[60]

Psychological interventions

Despite the preliminary state of research on psychological interventions for PTBIF, CBT has been proven to ameliorate fatigue in many other populations suffering from fatigue (eg, chronic fatigue syndrome, cancer, and multiple sclerosis).[61–63] In Europe and the United States, psychosocial interventions are generally used to address fatigue, yet a standard treatment protocol is not established. Since CBT focuses on thoughts, behavior, and emotional aspects, it might tap into several aspects of the multidimensional nature of PTBIF. Furthermore, CBT may include pacing and physical activity and the principles of CBT can be adapted easily to patients with TBI. It is thus plausible that CBT is also effective for patients suffering from PTBIF,[64–66] yet the evidence so far is thus scarce; more research focusing on fatigue and utilizing larger sample sizes is needed.

Exercise-based interventions

Physical activity has been promoted for improving general health for decades in healthy individuals[67] and represents a treatment modality that is low risk and relatively easy to implement, once deemed safe for the individual with TBI. It has also been promoted in the scientific literature and popular press for slowing the progress of Alzheimer's disease and other dementias and in mitigating the fatigue associated with chronic systemic conditions such as Parkinson's disease, multiple sclerosis, congestive heart failure, obesity, systemic lupus erythematosus, and chronic fatigue syndrome.[68] With the increase in availability and adoption of wearable fitness devices (eg, pedometers, GPS trackers, and heart rate monitors), individuals with TBI can get immediate and reliable feedback, set independent goals, and/or work with a treating physician, therapist, or trainer/coach to reach activity and fitness goals. Often the biggest barrier to increasing physical activity in managing fatigue is finding the activity that a given individual is eager to perform on a regular basis. In sum, exercise as simple as walking 3 times per week can be beneficial to ameliorate fatigue and should be a component of fatigue management.[69,70]

Complementary and alternative medicine

Growing research in CAM treatments suggests they may improve quality of life and symptoms for individuals with TBI. A 2016 review by Hernández and colleagues[71] provided an overview of the use, opportunities, and challenges associated with adopting CAM interventions for individuals with TBI, which are echoed in this review. CAM treatments provide safe, effective, nonpharmacological, and often inexpensive therapies that may alleviate a variety of symptoms, including fatigue. Although further validation is required, the ability for individuals with TBI to self-administer and adopt these practices into their routine provides a promising avenue for investigating PTBIF treatments.

Electrotherapeutic interventions

Noninvasive neural stimulations, such as cranial electrotherapy stimulation (CES) and electroencephalographic biofeedback, are treatments that have been associated with promoting neuroplasticity and/or normalizing neurotransmitter homeostasis.[72,73] Due to potential risk factors, such as seizures and acute amnesia, more work will be needed before translation into general clinical use is feasible.[72,73] The publications included in this review provide only minimal evidence for treatment efficacy.[49–51]

Multimodal interventions

Evidence for efficacy of multimodal interventions in the treatment of PTBIF seems somewhat promising. This is in line with the multimodal concept of fatigue, as it includes physical, emotional, and cognitive components, and treatment of these different foci might thus aid these patients. Moreover, in individuals post-stroke, multi-modal treatment, including both graded activity and CBT, has been found effective,[74] thus warranting further research in patients with TBI.

Limitations and future directions

This systematic review cast a broad net to cover 30 years of research investigating PTBIF interventions published in multiple languages. However, due to variability in study methodologies, including in primary interventional outcomes and measures, we were unable to conduct quantitative meta-analyses of the research studies.

Articles identified in this review used several validated scales to measure PTBIF; however, few of the included studies utilized TBI-specific measures. Although a significant amount of historical fatigue data has been collected using measures like the MFS, Fatigue Severity Scale, Post-Concussion Symptom Scale, and Beck's Depression Inventory, a transition to a TBI-specific scale is recommended. The Traumatic Brain Injury Quality-of-Life (TBI-QOL) is a recently validated scale using input from individuals with TBI and their caregivers, clinicians, and researchers; it is available in computerized and short-form versions.[75] Although there are multiple validated scales for fatigue, future works should utilize TBI-specific measures like the TBI-QOL Fatigue Item Bank[75,76] to help standardize results.

Post-TBI symptoms, including PTBIF, vary in presentation, severity, and duration, and this interindividual variability poses a challenge for research and for standardization of treatment. Given the heterogeneity in the presentation of PTBIF, statistical approaches that investigate individual variability (eg, factor analysis) and identify responder/nonresponder groups and their corresponding characteristics following intervention (eg, mixture models) may further elucidate the nature of PTBIF and identify treatment moderators.

Lastly, strong evidence to support recommendations for specific clinical treatments for PTBIF is nascent. For instance, this systematic review identified many studies with small sample sizes and only 2 treatments (methylphenidate and modafinil) that were investigated using different cohorts. Thus, future work should aim to investigate potential interventions using larger sample sizes, more robust methods, and strive for replication to bolster preliminary findings of efficacy. Additionally, due to a lengthy review process, our review explored studies up to March 2019 and the inclusion of publications after that time point is recommended for future reviews.

CONCLUSION

More research is required to further our understanding of PTBIF and effective interventions to ameliorate it. As a result of limited high-quality research investigating PTBIF, there is a paucity of unequivocal evidence to support specific treatments. Although methylphenidate can be effective, prescription should be in consideration of patient reliability characteristics. However, exercise and over-the-counter treatments to address PTBIF related to sleep disturbances, such as melatonin, represent low-risk options with several studies reporting efficacy. As PTBIF is multifaceted, multimodal clinical treatment approaches that include sustainable levels of exercise, judicious medication prescription, and/or behavioral therapy provided by a multidisciplinary rehabilitation team is recommended until more specific fatigue-related mechanisms/treatments are identified.

REFERENCES

1. National Institute of Neurological Disorders and Stroke. Traumatic Brain Injury Information Page. Published March 27, 2019. Accessed July 17, 2020. https://www.ninds.nih.gov/Disorders/All-Disorders/Traumatic-Brain-Injury-Information-Page
2. Centers for Disease Control and Prevention. Report to Congress: Traumatic Brain Injury in the United States. Published January 31, 2019. Accessed July 18, 2020. https://www.cdc.gov/traumaticbraininjury/pubs/tbi_report_to_congress.html
3. Bramlett HM, Dietrich WD. Long-term consequences of traumatic brain injury: current status of potential mechanisms of injury and neurological outcomes. *J Neurotrauma*. 2015;32(23):1834–1848. doi:10.1089/neu.2014.3352
4. Najafi MR, Tabesh H, Hosseini H, Akbari M, Najafi MA. Early and late posttraumatic seizures following traumatic brain injury: a five-year follow-up survival study. *Adv Biomed Res*. 2015;4:82. doi:10.4103/2277-9175.156640
5. Scheid R, von Cramon DY. Clinical findings in the chronic phase of traumatic brain injury. *Dtsch Arzteblatt Int*. 2010;107(12):199–205. doi:10.3238/arztebl.2010.0199
6. Vaaramo K, Puljula J, Tetri S, Juvela S, Hillbom M. Predictors of new-onset seizures: a 10-year follow-up of head trauma subjects with and without traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2014;85(6):598–602. doi:10.1136/jnnp-2012-304457
7. Wilson L, Stewart W, Dams-O'Connor K, et al. The chronic and evolving neurological consequences of traumatic brain injury. *Lancet Neurol*. 2017;16(10):813–825. doi:10.1016/S1474-4422(17)30279-X

8. Cantor JB, Ashman T, Bushnik T, et al. Systematic review of interventions for fatigue after traumatic brain injury: A NIDRR Traumatic Brain Injury Model Systems Study. *J Head Trauma Rehabil*. 2014;29(6):490–497. doi:10.1097/HTR.0000000000000102
9. Cantor JB, Ashman T, Gordon W, et al. Fatigue after traumatic brain injury and its impact on participation and quality of life: *J Head Trauma Rehabil*. 2008;23(1):41–51. doi:10.1097/01.HTR.0000308720.70288.af
10. Ezekiel L, Field L, Collett J, Dawes H, Boulton M. Experiences of fatigue in daily life of people with acquired brain injury: a qualitative study. *Disabil Rehabil*. 2020:1–9. doi:10.1080/09638288.2020.1720318
11. Palm S, Rönnbäck L, Johansson B. Long-term mental fatigue after traumatic brain injury and impact on employment status. *J Rehabil Med*. 2017;49(3):228–233. doi:10.2340/16501977-2190
12. Stulemeijer M, van der Werf S, Bleijenberg G, Biert J, Brauer J, E.Vos P. Recovery from mild traumatic brain injury. *J Neurol*. 2006;253(8):1041–1047. doi:10.1007/s00415-006-0156-5
13. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses. *Neurology*. 2013;80(4):409–416. doi:10.1212/WNL.0b013e31827f07be
14. Krupp LB, LaRocca NG, Muir-Nash J, Steinberg AD. The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus. *Arch Neurol*. 1989;46(10):1121–1123. doi:10.1001/archneur.1989.00520460115022
15. Tyson SF, Brown P. How to measure fatigue in neurological conditions? A systematic review of psychometric properties and clinical utility of measures used so far. *Clin Rehabil*. 2014;28(8):804–816. doi:10.1177/0269215514521043
16. Visser-Keizer AC, Hogenkamp A, Westerhof-Evers HJ, Egberink IJL, Spikman JM. Dutch Multifactor Fatigue Scale: a new scale to measure the different aspects of fatigue after acquired brain injury. *Arch Phys Med Rehabil*. 2015;96(6):1056–1063. doi:10.1016/j.apmr.2014.12.010
17. Shuman-Paretsky M, Gumber S, Dams-O'Connor K. Interventions for posttraumatic brain injury fatigue: an updated review. *Curr Phys Med Rehabil Rep*. 2017;5(1):12–21. doi:10.1007/s40141-017-0147-8
18. Xu G-Z, Li Y-F, Wang M-D, Cao D-Y. Complementary and alternative interventions for fatigue management after traumatic brain injury: a systematic review. *Ther Adv Neurol Disord*. 2017;10(5):229–239. doi:10.1177/1756285616682675
19. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;366:l4898. doi:10.1136/bmj.l4898
20. Cuijpers P. *Meta-Analysis in Mental Health: A Practical Guide*. VU University; 2016. Accessed July 18, 2020. https://indd.adobe.com/view/5fc8f9a0-bf1e-49d3-bf5f-a40bfe5409e0
21. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;339:b2535. doi:10.1136/bmj.b2535
22. Johansson B, Wentzel A-P, Andréll P, Odenstedt J, Mannheimer C, Rönnbäck L. Evaluation of dosage, safety and effects of methylphenidate on posttraumatic brain injury symptoms with a focus on mental fatigue and pain. *Brain Inj*. 2014;28(3):304–310. doi:10.3109/02699052.2013.865267
23. Johansson B, Wentzel A-P, Andréll P, Mannheimer C, Rönnbäck L. Methylphenidate reduces mental fatigue and improves processing speed in persons suffered a traumatic brain injury. *Brain Inj*. 2015;29(6):758–765. doi:10.3109/02699052.2015.1004747
24. Johansson B, Wentzel A-P, Andréll P, Rönnbäck L, Mannheimer C. Long-term treatment with methylphenidate for fatigue after traumatic brain injury. *Acta Neurol Scand*. 2017;135(1):100–107. doi:10.1111/ane.12587
25. Zhang W-T, Wang Y-F. Efficacy of methylphenidate for the treatment of mental sequelae after traumatic brain injury. *Medicine (Baltimore)*. 2017;96(25):e6960. doi:10.1097/MD.0000000000006960
26. Jha A, Weintraub A, Allshouse A, et al. A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury: *J Head Trauma Rehabil*. 2008;23(1):52–63. doi:10.1097/01.HTR.0000308721.77911.ea
27. Kaiser PR, Valko PO, Werth E, et al. Modafinil ameliorates excessive daytime sleepiness after traumatic brain injury. *Neurology*. 2010;75(20):1780–1785. doi:10.1212/WNL.0b013e3181fd62a2
28. Theadom A, Barker-Collo S, Jones KM, Parmar P, Bhattacharjee R, Feigin VL. MLC901 (NeuroAiD II^{TM}) for cognition after traumatic brain injury: a pilot randomized clinical trial. *Eur J Neurol*. 2018;25(8):1055–e1082. doi:10.1111/ene.13653
29. Berginström N, Nordström P, Schuit R, Nordström A. The effects of (−)-OSU6162 on chronic fatigue in patients with traumatic brain injury: a randomized controlled trial. *J Head Trauma Rehabil*. 2017;32(2):E46–E54. doi:10.1097/HTR.0000000000000236
30. 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;16(1):8. doi:10.1186/s12916-017-0995-1
31. Sakellaris G, Nasis G, Kotsiou M, Tamiolaki M, Charissis G, Evangeliou A. Prevention of traumatic headache, dizziness and fatigue with creatine administration. A pilot study. *Acta Paediatr*. 2008;97(1):31–34. doi:10.1111/j.1651-2227.2007.00529.x
32. Mossberg KA, Durham WJ, Zgaljardic DJ, et al. Functional changes after recombinant human growth hormone replacement in patients with chronic traumatic brain injury and abnormal growth hormone secretion. *J Neurotrauma*. 2017;34(4):845–852. doi:10.1089/neu.2016.4552
33. Lequerica A, Jasey N, Portelli Tremont JN, Chiaravalloti ND. Pilot study on the effect of ramelteon on sleep disturbance after traumatic brain injury: preliminary evidence from a clinical trial. *Arch Phys Med Rehabil*. 2015;96(10):1802–1809. doi:10.1016/j.apmr.2015.05.011
34. Khateb A, Ammann J, Annoni J-M, Diserens K. Cognition-enhancing effects of donepezil in traumatic brain injury. *Eur Neurol*. 2005;54(1):39–45. doi:10.1159/000087718
35. Raina KD, Morse JQ, Chisholm D, Leibold ML, Shen J, Whyte E. Feasibility of a cognitive behavioral intervention to manage fatigue in individuals with traumatic brain injury: a pilot study. *J Head Trauma Rehabil*. 2016;31(5):E41–E49. doi:10.1097/HTR.0000000000000196/bib>
36. Lu W, Krellman JW, Dijkers MP. Can Cognitive behavioral therapy for insomnia also treat fatigue, pain, and mood symptoms in individuals with traumatic brain injury? A multiple case report. *NeuroRehabilitation*. 2016;38(1):59–69. doi:10.3233/NRE-151296
37. Ouellet M-C, Morin CM. Cognitive behavioral therapy for insomnia associated with traumatic brain injury: a single-case study. *Arch Phys Med Rehabil*. 2004;85(8):1298–1302. doi:10.1016/j.apmr.2003.11.036
38. Howe EI, Løvstad M, Langlo K-PS, et al. Feasibility of a cognitive rehabilitation program for individuals with mild-to-moderate traumatic brain injury: participants' engagement and satisfaction. *Cogent Med*. 2019;6(1). doi:10.1080/2331205X.2019.1565614
39. Nguyen S, McKay A, Wong D, et al. Cognitive behavior therapy to treat sleep disturbance and fatigue after traumatic brain injury: a pilot randomized controlled trial. *Arch Phys Med Rehabil*. 2017;98(8):1508–1517.e2. doi:10.1016/j.apmr.2017.02.031
40. Potter SDS, Brown RG, Fleminger S. Randomised, waiting list controlled trial of cognitive–behavioural therapy for persistent postconcussional symptoms after predominantly mild–moderate traumatic brain injury. *J Neurol Neurosurg Psychiatry*. 2016;87(10):1075–1083. doi:10.1136/jnnp-2015-312838

41. Chin LMK, Chan L, Woolstenhulme JG, Christensen EJ, Shenouda CN, Keyser RE. Improved cardiorespiratory fitness with aerobic exercise training in individuals with traumatic brain injury. *J Head Trauma Rehabil*. 2015;30(6):382–390. doi:10.1097/HTR.0000000000000062
42. Driver S, Ede A. Impact of physical activity on mood after TBI. *Brain Inj*. 2009;23(3):203–212. doi:10.1080/02699050802695574
43. Gemmell C, Leathem JM. A study investigating the effects of Tai Chi Chuan: individuals with traumatic brain injury compared to controls. *Brain Inj*. 2006;20(2):151–156. doi:10.1080/02699050500442998
44. Kolakowsky-Hayner SA, Bellon K, Toda K, et al. A randomised control trial of walking to ameliorate brain injury fatigue: a NIDRR TBI model system centre-based study. *Neuropsychol Rehabil*. 2017;27(7):1002–1018. doi:10.1080/09602011.2016.1229680
45. Sinclair KL, Ponsford JL, Taffe J, Lockley SW, Rajaratnam SMW. Randomized controlled trial of light therapy for fatigue following traumatic brain injury. *Neurorehabil Neural Repair*. 2014;28(4):303–313. doi:10.1177/1545968313508472
46. Lagos L, Thompson J, Vaschillo E. A Preliminary study: heart rate variability biofeedback for treatment of postconcussion syndrome. *Biofeedback*. 2013;41(3):136–143. doi:10.5298/1081-5937-41.3.02
47. Qin P. *Effectiveness of Hand Self-Shiatsu for Post Sport-Related Concussion Sleep Disturbance in Young Athletes* [thesis]. University of Alberta; 2017. doi:10.7939/R36D5PR3B
48. Baker F, Wigram T. The immediate and long-term effects of singing on the mood states of people with traumatic brain injury. *Br J Music Ther*. 2004;18(2):55–64. doi:10.1177/135945750401800204
49. David VN, Esty ML. Neurotherapy for TBI: a CAM intervention. *Brain Inj*. 2010;24(3):366. doi:10.3109/02699051003648227
50. Nelson DV, Esty ML. Neurotherapy of traumatic brain injury/posttraumatic stress symptoms in vietnam veterans. *Mil Med*. 2015;180(10):e1111–e1114. doi:10.7205/MILMED-D-14-00696
51. Smith RB, Tiberi A, Marshall J. The use of cranial electrotherapy stimulation in the treatment of closed-head injured patients. *Brain Inj*. 1994;8(4):357–361. doi:10.3109/02699059409150986
52. Gagnon I, Grilli L, Friedman D, Iverson GL. A pilot study of active rehabilitation for adolescents who are slow to recover from sport-related concussion: active rehabilitation in concussion. *Scand J Med Sci Sports*. 2016;26(3):299–306. doi:10.1111/sms.12441
53. Gauvin-Lepage J, Friedman D, Grilli L, et al. Effectiveness of an exercise-based active rehabilitation intervention for youth who are slow to recover after concussion. *Clin J Sport Med*. 2020;30(5):423–432. doi:10.1097/JSM.0000000000000634
54. Rytter HM, Westenbaek K, Henriksen H, Christiansen P, Humle F. Specialized interdisciplinary rehabilitation reduces persistent postconcussive symptoms: a randomized clinical trial. *Brain Inj*. 2019;33(3):266–281. doi:10.1080/02699052.2018.1552022
55. Morton WA, Stockton GG. Methylphenidate abuse and psychiatric side effects. *Prim Care Companion J Clin Psychiatry*. 2000;2(5):159–164. doi:10.4088/pcc.v02n0502
56. Slattery M, Bredella MA, Stanley T, Torriani M, Misra M. Effects of recombinant human growth hormone (rhGH) administration on body composition and cardiovascular risk factors in obese adolescent girls. *Int J Pediatr Endocrinol*. 2014;2014(1):22. doi:10.1186/1687-9856-2014-22
57. Souza FM, Collett-Solberg PF. Adverse effects of growth hormone replacement therapy in children. *Arq Bras Endocrinol Amp Metabol*. 2011;55(8):559–565. doi:10.1590/S0004-27302011000800009
58. sigmaaldrich. Millipore Sigma OSU6162 hydrochloride PZ0177. Accessed November 19, 2020. https://www.sigmaaldrich.com/catalog/product/sigma/pz0177
59. Institute of Medicine (US) Committee on Trauma, and the Brain, Erdman J, Oria M, Pillsbury L. Creatine. National Academies Press; 2011. Accessed November 13, 2020. https://www.ncbi.nlm.nih.gov/books/NBK209321/
60. Giap B, Englander J. Fatigue after concussion: epidemiology, causal factors, assessment, and management. In: Bigler ED, Victoroff J, eds. *Concussion and Traumatic Encephalopathy: Causes, Diagnosis and Management*. Cambridge University Press; 2019:743–755. doi:10.1017/9781139696432.026
61. Malouff JM, Thorsteinsson EB, Rooke SE, Bhullar N, Schutte NS. Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: a meta-analysis. *Clin Psychol Rev*. 2008;28(5):736–745. doi:10.1016/j.cpr.2007.10.004
62. van den Akker LE, Beckerman H, Collette EH, et al. Cognitive behavioural therapy for MS-related fatigue explained: a longitudinal mediation analysis. *J Psychosom Res*. 2018;106:13–24. doi:10.1016/j.jpsychores.2017.12.014
63. Wu C, Zheng Y, Duan Y, et al. Nonpharmacological interventions for cancer-related fatigue: a systematic review and Bayesian network meta-analysis. *Worldviews Evid Based Nurs*. 2019;16(2):102–110. doi:10.1111/wvn.12352
64. Price JR, Mitchell E, Tidy E, Hunot V. Cognitive behaviour therapy for chronic fatigue syndrome in adults. *Cochrane Database Syst Rev*. 2008;2008(3). doi:10.1002/14651858.CD001027.pub2
65. Prins JB, Bleijenberg G, Bazelmans E, et al. Cognitive behaviour therapy for chronic fatigue syndrome: a multicentre randomised controlled trial. *Lancet North Am Ed*. 2001;357(9259):841–847. doi:10.1016/S0140-6736(00)04198-2
66. Quarmby L, Rimes KA, Deale A, Wessely S, Chalder T. Cognitive-behaviour therapy for chronic fatigue syndrome: comparison of outcomes within and outside the confines of a randomised controlled trial. *Behav Res Ther*. 2007;45(6):1085–1094. doi:10.1016/j.brat.2006.08.019
67. Warburton DER, Nicol CW, Bredin SSD. Health benefits of physical activity: the evidence. *CMAJ*. 2006;174(6):801–809. doi:10.1503/cmaj.051351
68. Sallis RE. Exercise in the treatment of chronic disease: an underfilled prescription. *Curr Sports Med Rep*. 2017;16(4):225–226. doi:10.1249/JSR.0000000000000378
69. Fogelman D, Zafonte R. Exercise to enhance neurocognitive function after traumatic brain injury. *PM R*. 2012;4(11):908–913. doi:10.1016/j.pmrj.2012.09.028
70. Giap B, Englander J. Fatigue after concussion: epidemiology, causal factors, assessment, and management. In: *Concussion and Traumatic Encephalopathy: Causes, Diagnosis and Management*. Cambridge University Press; 2019. doi:10.1017/9781139696432.026
71. Hernández TD, Brenner LA, Walter KH, Bormann JE, Johansson B. Complementary and alternative medicine (CAM) following traumatic brain injury (TBI): opportunities and challenges. *Brain Res*. 2016;1640:139–151. doi:10.1016/j.brainres.2016.01.025
72. Dhaliwal SK, Meek BP, Modirrousta MM. Non-invasive brain stimulation for the treatment of symptoms following traumatic brain injury. *Front Psychiatry*. 2015;6:119. doi:10.3389/fpsyt.2015.00119
73. Hummel FC, Cohen LG. Non-invasive brain stimulation: a new strategy to improve neurorehabilitation after stroke? *Lancet Neurol*. 2006;5(8):708–712. doi:10.1016/S1474-4422(06)70525-7
74. Zedlitz AMEE, Fasotti L, Geurts ACH. Post-stroke fatigue: a treatment protocol that is being evaluated. *Clin Rehabil*. 2011;25(6):487–500. doi:10.1177/0269215510391285
75. Tulsky DS, Kisala PA, Victorson D, et al. TBI-QOL: development and calibration of item banks to measure patient reported outcomes following traumatic brain injury. *J Head Trauma Rehabil*. 2016;31(1):40–51. doi:10.1097/HTR.0000000000000131
76. Kisala PA, Bushnik T, Boulton AJ, Hanks RA, Kolakowsky-Hayner SA, Tulsky DS. Measuring fatigue in TBI: development of the TBI-QOL Fatigue Item Bank and Short Form. *J Head Trauma Rehabil*. 2019;34(5):289–297. doi:10.1097/HTR.0000000000000530