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Title: Management of unfavorable outcome after mild Traumatic Brain Injury: review of physical and cognitive rehabilitation and of psychological care in post-concussive syndrome

Titre : Prise en charge des évolutions défavorables dans les suites d'un traumatisme crânio-cérébral léger

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Highlights:

- No current recommendation for the specific management of post-concussive syndrome after mTBI
- Efficacy of some pharmacological drugs and rehabilitation on headache and vertigo
- Efficacy of classical rehabilitation and brain-stimulation techniques on cognition
- Efficacy of Cognitive and Behavioral Therapy and psychoeducational interventions
- If PTSD is associated, its management is crucial for recovery

Management of unfavorable outcome after mild Traumatic Brain Injury: review of physical and cognitive rehabilitation and of psychological care in post-concussive syndrome

Prise en charge des évolutions défavorables dans les suites d'un traumatisme crânio-cérébral léger

Abstract

Introduction: Mild Traumatic Brain Injury (mTBI) is a public health issue with approximately 42 million people worldwide affected yearly. Most patients have a favorable short-term recovery but 10-20% are likely to develop post-concussive syndrome (association of physical, cognitive, and psychological difficulties after injury). Post-concussive syndrome can be associated with Post-Traumatic Stress Disorder (PTSD). There is to date no recommendation on the interventions that could be done to reduce post-concussive syndrome. The present review aims at summarizing the effect of therapeutic education, physical and cognitive rehabilitation and of psychological care in mTBI patients with post-concussive syndrome.

Methods: In the current international literature, we investigated the effects of therapeutic education, physical and cognitive rehabilitation and of psychological care in this population using the Medline database and we discussed the results of these studies.

Results: The application of a therapeutic education intervention within 3 months after mTBI has been found appropriate and effective to prevent post-concussion syndrome in several studies but the timeline of this intervention differs among the existing studies. Concerning physical disabilities, several pharmacological, rehabilitative and non-pharmacological techniques have shown some efficacy in reducing headache and vertigo; rTMS seems also promising in this context. The management of fatigue is also crucial and requires a multidisciplinary approach. We did not find any intervention in mTBI patients with post-concussive syndrome suffering from dysosmia and/or dysgueusia. No pharmacological treatment is currently recommended to reduce the cognitive symptoms of post-concussive syndrome after mTBI. Rehabilitation and brain-stimulation techniques have already proven their efficacy to reduce the cognitive impairment in this population. Even if the use of Virtual Reality software seems well tolerated in this population, its efficacy and additional value needs to be demonstrated in larger studies. Concerning the psychological care after mTBI, Cognitive and Behavioral Therapy interventions are the most frequently reported in this population, followed by psychoeducational interventions. PTSD management seems crucial in overall recovery of patients with post-concussive syndrome.

Conclusion: Many studies have sought to demonstrate the effectiveness of various rehabilitation techniques, including different cognitive rehabilitation programs, technology-assisted rehabilitation, different types of brain stimulation and some pharmacological treatments. However, most of these studies are of a low level of scientific evidence and it would be necessary to carry out well-conducted prospective randomized trials in order to offer an appropriate and effective multidisciplinary management for patients with post-concussive syndrome after mTBI.

Keywords: mTBI, post-concussive syndrome, rehabilitation, therapeutic education, cognition, psychological care

Résumé

Introduction : Le traumatisme crânio-cérébral léger (TCCL) est un problème de santé publique avec environ 42 millions de personnes touchées chaque année dans le monde. La grande majorité des patients ont une évolution favorable à court terme, mais 10 à 20 % d'entre eux vont développer un syndrome post-commotionnel (défini par l'association de symptômes physiques, cognitifs et psychologiques dans les suites du TCCL). Un trouble de stress post-traumatique (TSPT) peut également s'associer au syndrome post-commotionnel. Il n'existe pas à ce jour de recommandations de bonne pratique sur la prise en charge du syndrome post-commotionnel dans les suites d'un TCCL. La présente revue vise à synthétiser les effets de l'éducation thérapeutique, de la réadaptation physique et cognitive et de la prise en charge psychologique décrites dans la littérature internationale dans cette population.

Méthodes : A l'aide de la base de données Medline, nous avons identifié et sélectionné dans la littérature internationale actuelle les articles relatant de l'éducation thérapeutique, de la réadaptation physique et cognitive et de la prise en charge psychologique des patients TCCL présentant un syndrome post-commotionnel et nous avons discuté des résultats de ces études afin de dégager les axes majeurs de prise en charge.

Résultats : Une intervention d'éducation thérapeutique dans les 3 mois suivant le TCCL a été décrite comme efficace pour prévenir le syndrome post-commotionnel dans plusieurs études, mais le moment préférentiel de cette intervention diffère selon les études existantes. En ce qui concerne les symptômes physiques du syndrome post-commotionnel, plusieurs moyens médicamenteux, non pharmacologiques et notamment de rééducation ont démontré une certaine efficacité dans les études existantes pour réduire les céphalées et les vertiges fréquents dans cette pathologie ; l'utilisation de la rTMS semble également prometteuse dans ce contexte. La gestion de la fatigue est également cruciale et nécessite une approche multidisciplinaire. Nous n'avons pas trouvé d'intervention décrite chez les patients avec syndrome post-commotionnel présentant une dysosmie et/ou une dysgueusie, pourtant fréquentes et souvent sous-estimées. Aucun traitement pharmacologique n'est actuellement recommandé pour réduire les symptômes cognitifs du syndrome post-commotionnel. Les techniques de rééducation cognitive classique et de stimulation cérébrale non invasive ont déjà montré leur efficacité pour réduire les troubles cognitifs dans cette population. Même si l'utilisation d'outils de Réalité Virtuelle est décrite comme bien tolérée dans cette population, son efficacité et sa valeur ajoutée doivent être prouvées dans des études de plus grande ampleur. En ce qui concerne l'accompagnement psychologique de ces patients, les thérapies cognitives et comportementales sont les plus décrites pour cette population, suivies par les interventions de psycho-éducation, et semblent efficaces. La prise en charge du TSPT semble crucial pour le rétablissement des patients.

Conclusion : De nombreuses études ont retrouvé une efficacité de diverses techniques de réadaptation, y compris de différents programmes de rééducation cognitive, de rééducation assistée par la technologie, de différents types de stimulation cérébrale et de certains traitements pharmacologiques. Cependant, la plupart de ces études n'ont qu'un faible niveau de preuve et il semble nécessaire de mener des essais prospectifs randomisés de plus grande

ampleur afin de valider une prise en charge multidisciplinaire appropriée pour les patients atteints d'un syndrome post-commotionnel dans les suites d'un TCCL.

Mots clés : TCCL, syndrome post-commotionnel, rééducation, éducation thérapeutique, cognition, soutien psychologique

Introduction

Mild Traumatic Brain Injury (mTBI) is an important public health issue because of its high occurrence in the general population. While the medium- and long-term prognosis is very favorable in the vast majority of cases, between 10 and 20% of the brain-injured people are going to develop an unfavorable outcome with persistent physical, cognitive and psychological complaints, sometimes in the long term, which will negatively impact their social and professional future. Concerning the existing recommendations and guidelines about the management of mTBI, the Pediatric Mild Traumatic Brain Injury Guideline Workgroup outlined specific recommendations concerning the management mTBI among children, based on 4 articles, in 2016. Unfortunately, concerning the low confidence level of the included studies, no conclusions could be reached. Furthermore, the department of Veterans Affairs/Department of Defense of the United States wrote recommendations concerning the management of physical and cognitive symptoms after mTBI. Concerning headache and sleep disturbance, these authors recommended and described treatment including education, non-pharmacological and pharmacological interventions; for dizziness and disequilibrium, they recommended specific vestibular, visual and proprioceptive exercises with a trained care provider; no recommendation was given concerning the care of tinnitus nor for visual symptoms. These authors also recommended that the presence of psychological or behavioral symptoms “should be evaluated and managed according to existing evidence-based clinical practice guidelines, and based upon individual factors and the nature and severity of symptoms”. For patients with cognitive symptoms that did not resolve 30-90 days after mTBI, these authors recommended a short cognitive rehabilitation, but no medication, supplements, nutraceuticals, herbal medicines nor a prolonged course of therapy in the absence of patient improvement. Unfortunately, the rehabilitation techniques for cognitive symptoms were not detailed in the manuscript. The authors also concluded that there was insufficient evidence to recommend for or against the use of interdisciplinary or multidisciplinary teams in the management of patients with chronic symptoms attributed to mTBI. Concerning the prevention of PCS after mTBI, Ellemberg established a “commotion gestion protocole” for athletes in 2016. This author recommended a sensibilization plan, a surveillance system for commotions, a procedure for withdrawing from sport activity, an oral and written communication with the athletes, their relatives and their general practitioner, a medical follow-up and a specific procedure for return-to-school and return-to-physical activity. The Health and Social Services Ministry of Canada and the Motor Accidents Authority of New South Wales (Australia) issued similar recommendations respectively for the period 2005-2010 and in 2008 for the care of mTBI, regarding information, reassuring, and the need for a follow-up if high morbidity risks exist. Despite these guidelines, neither document detailed entirely the content of patients’ education and information.

The main objective of this article is to review the therapeutic education that can be offered to patients who suffer from a post-concussive syndrome, the physical and cognitive rehabilitation modalities already reported as efficient in the existing literature and the recommended psychological management of this population. We differentiate between studies focusing on preventing PCS and on studies focusing on treating PCS.

Methods

We completed the literature review regarding rehabilitation and mTBI in July 2019, using the Medline database. We used the following keywords: “mild traumatic brain injury” AND (“rehabilitation”, “treatment”, “post concussion”, “post commotional” OR “post concussive”); then we subsequently added the following keywords: “therapeutic education”, “attention”, “memory”, “dysexecutive”, “executive”, “neglect”, “social cognition”, “concentration”, “anxiety”, “mood”, “affect”, “phobia”, “phobic”, “PTSD”, “sleep”, “insomnia”, “irritability”, “headache”, “fatigue”, “dizziness”, “vertigo”, “balance” and “vestibular syndrome”. We first screened the funding articles on the basis of their titles and abstracts, and then selected the articles that 2 authors found pertinent in order to answer to the practical question of managing and care PCS after mTBI, and divided the articles between these 2 aspects.

Results

- **Preventing PCS after mTBI**

According to King et al. (2013) [1], psychoeducational treatment consists of “the early provision of information related to diagnosis and possible symptoms, normalization of these symptoms, reassurance of positive expectation of recovery, and education on coping strategies”. Indeed, a brief therapeutic education intervention within 3 months after mTBI has been described as appropriate and effective to prevent post-concussive syndrome in several studies [2] [3]. Moreover, Mittenberg et al. (1996; 2001) [4] [5] demonstrated that a single psychoeducation session of approximately one hour allowed patients to express significantly fewer symptoms and of a shorter duration than the control group, 6 months after mTBI. In this last study, psychoeducation consisted of the distribution of a guide manual of about 10 pages and an interview with a psychotherapist. The computer modality without the intervention of a therapist also seems quite effective, the protocol proposed by King et al. (2013) [1] lasting approximately 20-30 minutes. Brunger et al. (2014) proposed a brief initial psychoeducation, then patients with persistent disorders were offered 2 weeks of intensive psychoeducation and cognitive behavioral re-education; semi-directed interviews were then performed. Patients included in this study reported that the psychoeducation had allowed them to accept the rehabilitation path, and to appreciate its benefits [6]. Nevertheless, in the existing literature, the use of a psychoeducation program and its beneficial effects on mTBI symptoms are still debated.

The Zurich Consensus statement on concussion in sport recommends that patients have to rest 24-48 hours after concussion [7]. Indeed, some recent studies showed that an excessive cognitive recovery soon after concussion may worsen symptoms and delay recovery. However, Leddy et al. (2016) [8] highlighted that “recent research, however, suggests that prolonged rest beyond the first couple of days after concussion might hinder rather than aid recovery and that a more active approach to concussion management should be considered.” More precisely, the 2017 International Concussion in Sport Group’s systematic review concluded that “patients should be encouraged to gradually increase activity after a brief period (24–48 hours) of cognitive and physical rest and that interventions including cervical and vestibular rehabilitation, cognitive behavioral therapy, multifaceted collaborative care, and closely monitored sub-symptom threshold exercise may be of benefit.” (Leddy et al., 2016; 2018 [9] [10]).

- **The management of PCS after mTBI**

- a) Therapeutic education**

Belanger et al. (2015) [11] discussed the relevance of intervention timelines. The proposed intervention of these authors was online and no significant differences were found regarding the persistence of symptoms between patients who received treatment and the control group. However, there was a significant difference between groups concerning the chronic patients (i.e. patients who suffered from a mTBI for more than a year before intervention). Matuskeviciene et al. (2013) [12] did not find any positive effect on chronic patients of their psychoeducational intervention compared to usual care. Another point discussed in the literature is the target of the psychoeducation done. Belanger et al. (2019) [11] found a significant relationship between the perception of self-effectiveness and the response to cognitive rehabilitation. The authors did not find any significant difference concerning cognition, daily functioning and behavior between patients who received the treatment and those who did not. This study did not include any control group and all patients included benefited from a psychoeducation before the other proposed interventions. Finally, the plural modalities of care are to be taken into consideration. Indeed, Cooper et al. (2015; 2017) [13] [14] found that the association of a psychoeducation with multidisciplinary care (speech therapist, occupational therapist and psychotherapist) was more effective than psychoeducation and medical support alone. However, this study did not include a control group either.

- b) Physical rehabilitation**

Headache is one of the most common post-concussion symptom. Pharmacological and non-pharmacological management of headache after mTBI have been described in the international literature. Recently, Cushman et al. (2018) [15] evaluated retrospectively the effect of gabapentin and tricyclic antidepressants on reducing headache in 277 mTBI patients. These authors described a significant decrease of the headache score in all groups regardless of the medication status. However, the 2 groups with medication (60 patients with gabapentin and 94 patients with tricyclic antidepressants) and the group without medication (123 patients) had the same longitudinal change in headache score. Furthermore, Yerry et al. (2015) [16], in a retrospective consecutive case series of 64 mTBI service members, found a subjective improvement of headache in 64% of them after botulinum toxin injections. Janak et al. (2015) [17] retrospectively evaluated the effects of both pharmacological and musculoskeletal therapy on persistent headache in 257 mTBI veterans and found a significant decrease (46.7% versus 67.3%) of headache evaluated using the Neurobehavioral Symptom Inventory. Unfortunately, the description of the treatments provided was not listed in the article. Repetitive Transcranial Magnetic Stimulation (rTMS) seems also a promising technique, with a significant reduction of persistent headache intensity and of debilitating headache exacerbation in the treatment group as shown by Leung et al. (2016) [18] in 12 mTBI patients compared to 12 others receiving a sham stimulation.

Vertigo, in particular benign paroxysmal vertigo (BPPV), dizziness and imbalance are also very common in mTBI patients with post-concussive syndrome. Vertigo has been shown to be related with a vestibular dysfunction [19], in particular with a secondary utricular

dysfunction [20]. BPPV has been effectively treated with canalith repositioning therapy [21]. Treatments for non-BPPV vestibular dysfunction are mainly focused on vestibular rehabilitation associated with additional rehabilitation methods and medication [22]. Vestibular rehabilitation includes gaze stability exercises, gait and balance training, as well as general reconditioning, which has already shown its efficacy [23]. Some other rehabilitation techniques have been proposed, like the use of a Virtual Reality environment task [24] or cervical spine physiotherapy combined with vestibular rehabilitation [25]. Finally, some authors (Naguib et al., 2014 [26] and Hoffer et al., 2013 [27], respectively) showed the efficacy of pharmacological drugs, such as betahistine dihydrochloride or N-acetyl cysteine, to enhance vestibular rehabilitation and reduce vestibular post-concussive symptoms.

Fatigue is a common symptom after mTBI. Even if its frequency tends to decrease over time, fatigue can persist years after the injury. Mollayeva et al. (2014) [28], in a systematic literature review, showed that fatigue after mTBI is a nonhomogeneous entity, with several factors influencing the course of chronic fatigue, such as initial fatigue at the acute phase and its management. The occurrence of a hypopituitarism should be also considered in case of prolonged fatigue [29]. Even if a reduction of fatigue is usually observed in most studies, some of these reported fluctuations over the course of patients' follow-up, which can also be explained by the diversity of the tools used for evaluating fatigue, of the study protocols and of the presence of confounding factors such as apathy, sleep disorders, depression, anxiety, lack of motivation, litigation, cognitive dysfunction or medication or drug effects (in particular alcohol or antidepressants). Management of fatigue is often proposed in rehabilitation programs but consists of non-specific rehabilitation including mainly exercise training in patients who often present deconditioning [30] [31] [32], or in specialized interdisciplinary rehabilitation associating neuropsychological care, exercise therapy, therapeutic education and physiotherapeutic coaching [33], but fatigue is often a secondary judgment criterion in these studies. Pharmacological treatments such as methylphenidate have been shown efficient for reducing fatigue at 6 months in 30 mTBI patients with post-concussive syndrome including fatigue [34], but this study was not placebo-controlled.

Two particular symptoms sometimes reported by mTBI patients with post-concussive syndrome are dysosmia and dysgueusia. Ciofalo et al. (2018) [35] reported that 33.5% of their mTBI study population had an olfactory dysfunction (87% of them had an anosmia and 13% an hyposmia). Their prevalence is probably underestimated but they have a high impact on feeding and on mood, because of the disinterest or even the disgust of food that they cause. In Drummond et al.'s longitudinal follow-up of 37 patients (2018) [36], 87.7% of them demonstrated persisting olfactory impairment at 12 months. If the symptoms are present, a consultation in otolaryngology is often needed to ensure that a local cause cannot explain the symptoms. The morphological imaging done to evaluate the integrity of the olfactory neuronal network is not always conclusive. The specific rehabilitation of dysosmia and dysgueusia is sometimes proposed by therapists specialized in olfactory functions, but we did not find any publication in this population assessing the efficacy of this treatment.

c) Cognitive rehabilitation

First, some pharmacological treatments have been tried to reduce cognitive symptoms of post-concussive syndrome after mTBI. Although some of them, like alpha2-antagonists (McAllister et al., 2011) [37] or a cerebrolysin therapy [38] (Chen et al., 2013) improved cognitive functions (in particular working and long-term memory) in some studies, no pharmacological

treatment is currently recommended to reduce the cognitive symptoms of post-concussive syndrome after mTBI. Furthermore, the impact of some pharmacological treatments such as antidepressant is still controversial in the literature, with an improvement of cognitive functions by reducing depression reported by some studies [39] (Fann et al, 2001), while some others found an increase of fatigue and of cognitive dysfunction after the use of antidepressants. The use of antidepressant drugs in mTBI patients with post-concussive syndrome should also be dictated by the psychological symptoms and not the cognitive ones.

Other non-pharmacological treatments have already been tried in this population, such as brain stimulation techniques. Among them, high-frequency repetitive transcranial magnetic stimulation (rTMS) [40] over the left dorso-lateral prefrontal cortex (DLPFC) enhanced cognitive functions such as working memory, executive function, processing speed, and attention. Moreover, a task-related functional magnetic resonance imaging showed that this cognitive improvement was related to a stronger activation in the DLPFC and a deactivation in the anterior cingulate cortex (ACC) during a verbal and nonverbal working memory task. rTMS techniques seem promising to improve cognitive functions of mTBI patients with post-concussive syndrome. Other studies also found a positive effect of transcranial red/near-infrared light emitting diodes therapy (LED) on cognitive functions in mTBI patients with post-concussive syndrome [41] [42]. Several studies also evaluated the effect of hyperbaric oxygen treatment on cognitive functions in mTBI patients with post-concussive syndrome and showed contradictory results. Four of them [43] [44] [45] [46] were positive, whereas four others [47] [48] [49] [50] did not find any significant effect on cognition. But few of them [44] [51] were randomized controlled trials and used an appropriate sham treatment as control condition, which limits the scope of the results.

Furthermore, various cognitive rehabilitation programs have been already experimented in this population. Some of them are quite similar to other rehabilitation techniques already used in patients with moderate or severe TBI, like Goal Management Training or a specific attentional training, and improved as well the cognitive functions (here the executive and attentional functions respectively) of the mTBI participants [52] [53]. Similarly, the association of several well-known cognitive rehabilitation techniques, named compensatory cognitive training, associating interactive didactic presentations, in-class discussions, cognitive strategies learning (like time management, internal memory strategies, self-monitoring or goal setting), and external aids showed some efficacy on several cognitive functions (attention, memory, executive ones) in mTBI veterans with post-concussive syndrome [54]. Other authors, like Kontos et al. (2018) [55], by associating several interventions on sleep, vestibular and oculomotor systems, cognitive functions and psychological state based specifically on the impairments of each patient, showed an improvement of several functions, notably the cognitive ones. Other authors evaluated the effect of a cognitive rehabilitation assisted by technology. A Virtual Reality-based rehabilitation program seemed efficient on executive and attentional functions of one patient with mTBI [56], as well as a computerized attentional training [57]. Even if the use of Virtual Reality software seemed well tolerated [58], their efficacy and their additional value need to be proven in larger studies. Furthermore, Cooper et al. (2017) [59] showed in a randomized controlled trial including 126 mTBI participants that both therapist-directed cognitive rehabilitation and integrated therapist-directed cognitive rehabilitation combined with cognitive-behavioural psychotherapy reduced functional cognitive symptoms beyond psychoeducation and medical management alone. Overall, cognitive rehabilitation techniques focused on precise neuropsychological impairments seem efficient and recommended for mTBI patients who suffer from post-concussive syndrome which includes cognitive troubles.

Because no predictive factor until now has been found to predict the superiority of one rehabilitation technique over another [60], the cognitive rehabilitation program used should be personalized and adapted to the impairments found during the neuropsychological assessment of each mTBI patients.

Finally, some non-cognitive rehabilitation techniques have also showed to reduce cognitive impairments of mTBI patients with post-concussive syndrome. For example, Vik et al. (2018) [61] showed that a 8-week music-supported intervention by playing the piano improved cognitive functions and functional neuroimaging scans in 11 mTBI patients with attentional, mnemonic and social interaction problems. The use of other rehabilitation techniques improving balance, like Yoga or Qigong [62], or psychological care [63], like mindfulness-based stress reduction therapy, seem also promising to improve the cognitive functioning and the well-being of the participants, but the level of evidence of the studies found in the current literature is quite low and larger randomized controlled studies are still needed.

d) Psychological care of post-concussive syndrome

Psychological symptoms after a mTBI are frequent, especially in case of unfavorable outcome. Their assessment and their care are necessary, because of the worsening of the physical and cognitive symptoms that they can induce and because of the daily-life repercussions. The most common symptoms are anxiety and mood disorders, more rarely phobia, compulsive troubles, sleeping and feeding disorders. A Post-Traumatic Stress Disorder (PTSD), although it does not belong to the post-commotional syndrome, is often associated to it, and worsens the psychological outcome of this population. As explained previously in the therapeutic education intervention part, an early intervention has already been shown as efficient for preventing post-concussive symptoms. Scheenen et al. (2017) [64] evaluated the effectiveness of an early Cognitive Behavioral Therapy Intervention (CBTi) compared to telephone counselling (TC) in at risk 91 mTBI patients and did not find any significant difference concerning anxiety and depression levels at 3, 6 and 12 months. Patients in the TC group presented a better favorable outcome at 12 months, and fewer complaints at 3 and 12 months using a questionnaire (Head Injury Symptom Checklist) derived from the Rivermead Post-Concussion Symptoms Questionnaire. The use of telephone counselling, which seems easier to set up than classical and repetitive physical appointments, seems also a promising possibility to prevent psychological symptoms of post-concussive syndrome in mTBI patients. Furthermore, Gil-Jardiné et al. (2018) [65] showed that a single eye movement desensitization and reprocessing intervention in patients with high risk of PTSD decreased significantly the outcome of post-concussion-like symptoms and PTSD at 3 months compared to a short reassurance session and usual care, but all patients were not brain-injured in this study.

During clinical interviews made with mTBI patients with post-concussive syndrome, the disruption of basic needs is often mentioned. Patients often relate a global slowdown, an important fatigability, an irritability which is also reported by their family, as well as a loss of self-confidence. Furthermore, toxic substances consumption or abuse, such as tobacco or cannabis, is often increased, while some others like alcohol or coffee are reduced. When sleeping and fatigue problems are reported, it can consist on a constant desire to sleep, sometimes over 10 to 12 hours by night, associated with more than 1 hour of rest time during the day. Contrarily, for mTBI patients with anxiety disorders and/or PTSD, common complaints are falling asleep difficulty, frequent awakenings during the night, and restless

nights because of nightmares and anxious ruminations. In both cases, patients report non-recuperative sleep. In total, 4 categories of sleep disorders have been reported in patients with mTBI: insufficiency of sleep duration or continuity, alterations in sleep changes (i.e. changes in sleep architecture), pathologies in sleep (sleep disorders), and abnormalities of the timing of sleeping (circadian rhythm disorders). Subjective complaints of sleep–wake disturbances occur in 30–70% of those with TBI of all severity [66]. The Defense and Veterans Brain Injury Center warned against the use of caffeine during the chronic phase of mTBI because of the worsening of sleep fragmentation and insomnia (2015) [67]. The benefits of near infrared light for intracellular healing have also been associated with improved sleep quality over a 2-month period among 10 patients with persistent TBI symptoms [68]. The use of pharmacological treatment should be adapted to the category of sleep disorder of the patient. Melatonin is often used in clinical practice in case of circadian rhythm disorders, but its efficacy in mTBI patients has not been studied specifically until now. The use of classical pharmacological drugs inducing sleep should be considered with caution, because of the possible cognitive and psychological side effects. Finally, one study [69] evaluated the effect of therapeutic education (using brochures) associating with telephone-based problem-solving (PST) treatment on sleep quality in a large number of active duty post deployment service members with mTBI and found that this PST treatment improved significantly the sleep quality of mTBI at 6 months, but the difference with a control group receiving education only was not significant anymore at 12 months.

Psychological support offers are mainly based on Cognitive and Behavioral Therapy (CBT). Patients' needs and expectations are first discussed and evaluated, and therapeutic goals are then set together with them. That includes gradual resumption in everyday life activities and exposure to anxiogenic stimuli, and also off-session exercises. Each patient has to follow an individualized program adapted to their psychological difficulties and needs. In a recent review of literature about psychological intervention in TBI patients (all severity), Gomez-de-Regil et al. (2019) [70] found that 42% of the studies found (n=26) used CBT for treating psychological symptoms of TBI, versus 26% using psychoeducation (n=16) and 5% neuropsychological interventions (n=3). The use of CBT has showed promising positive results at reducing anger, depression, anxiety and PTSD symptoms and at improving coping in TBI patients [71] [72].

Another therapy often proposed for mTBI patients is based on the patient's psychoeducation in different fields: PTSD, panic attacks (if concerned), emotions regulation, sleeping and fatigue management, assertiveness, relaxation etc. A good knowledge of the patient's attitude towards these topics is required. The patient's own involvement in their internal and external resources is also interesting. The therapist has to rely on the patient's skills and to help them to readjust themselves if necessary by using other strategies when theirs do not work anymore. A work based on patient's reassurance, using motivational interviews and self-directed exercises will allow the mobilization of forgotten resources and reinforce their feeling of self-efficacy. Another part of the psychological support is based on the functional analysis of problematic situations, and therefore learning and using different tools from CBT, such as Beck's columns. During this therapy, the patient has to observe and to take a step back from a problematic situation. This focus exercise contributes to decrease their hyper-reactivity and their irritability. It improves awareness, adjustment and prevents the patient from moving forward. Sometimes, it even allows the patient to use efficient and unaltered abilities that had not been exploited until now.

If PTSD is associated with post-concussive syndrome after mTBI, it worsens the recovery prognosis of the patient and should be managed specifically, additionally to the management of the post-concussive symptoms. Some studies showed the efficacy of some techniques to reduce PTSD in mTBI patients: mindfulness-based stress reduction therapy [73] [63] (Cole et al., 2015; Azulay et al., 2013), multidisciplinary care including cognitive rehabilitation, vestibular intervention, headache management and integrated behavioral healthcare [74] etc.

Finally, mTBI patient with post-concussive syndrome and therapist have to create a strong therapeutic alliance/partnership in order to decrease patient's psychological symptoms and to improve their autonomy. The necessity of empowerment of the patient during this therapy implies to decrease progressively the avoidance behaviors and to expose gradually the patient to several emotions, body-guided sensations and thoughts. Rather than freezing and reinforcing their post-concussive symptoms, the patient will re-engage themselves in a more flexible dynamic, will activate compensation means that will allow them to achieve realistic goals until their recovery.

Conclusion

Many studies have sought to demonstrate the effectiveness of various rehabilitation techniques in mTBI patients with post-concussive syndrome, including different cognitive rehabilitation programs, technology-assisted rehabilitation, different types of brain stimulation and pharmacological treatments. The combination of several care including therapeutic education, classical cognitive rehabilitation techniques, management of physical symptoms like fatigue, vertigo and headache and psychological care using Cognitive and Behavioural Therapy and psycho-education seems an interesting lead to reduce the symptoms of post-concussive syndrome after mTBI. The early start of care seems also a crucial point to prevent the chronicity of the symptoms, with repercussion on daily-life and professional activities and on quality of life. However, most of the studies found and presented here are of a low level of scientific evidence and it would be necessary to carry out well-conducted prospective controlled randomized trials in order to offer an appropriate and effective management for patients with post-concussion syndrome after mTBI.

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| First author and date of publication | Goal of the intervention | Effect |
|--------------------------------------|---------------------------------------------------|--------|
| Preventing PCS after mTBI | | |
| Paniak, 1998 | Therapeutic education | + |
| Paniak, 2000 | Therapeutic education | + |
| Mittenberg, 1996 | Therapeutic education | + |
| Brunger, 2014 | Therapeutic education | + |
| Leddy, 2016 | Rest beyond the first couple of days | - |
| Management of PCS after mTBI | | |
| <i>Therapeutic education</i> | | |
| Belanger, 2015 | Therapeutic education | + |
| Matuseviciene, 2013 | Therapeutic education | - |
| <i>Physical rehabilitation</i> | | |
| Cushman, 2018 | Reducing headache with pharmacological treatment | - |
| Yerry, 2015 | Reducing headache with botulinum toxin injections | + |

| | | |
|---------------------------------|--------------------------------------------------------------------------------------------------------|---|
| Janak, 2015 | Reducing headache with pharmacological and musculoskeletal therapy | + |
| Leung, 2016 | Reducing headache with rTMS | + |
| Józefowicz-Korczyńska, 2018 | Treating benign paroxysmal vertigo with canalith repositioning therapy | + |
| Weightman, 2010 | Treating vertigo with vestibular rehabilitation | + |
| Naguib, 2014 | Treating balance disorders with Betahistine dihydrochloride | + |
| Hoffer, 2013 | Treating vertigo with n-acetyl cysteine | + |
| Jankowski, 1990 | Treating fatigue with a circuit training program | + |
| Giordon, 1998 | Treating fatigue with exercise | + |
| Rytter, 2018 | Treating fatigue with neuropsychological treatment and physiotherapeutic coaching | + |
| Johansson, 2016 | Treating fatigue with methylphenidate | + |
| <i>Cognitive rehabilitation</i> | | |
| Mcallister, 2011 | Improving cognitive functions using alpha2-antagonists | + |
| Chen, 2013 | Improving cognitive functions using a cerebrolysin therapy | + |
| Fann, 2001 | Improving cognitive functions using an antidepressant | + |
| Koski, 2014 | Improving cognitive functions using rTMS | + |
| Naeser, 2014 | Improving cognitive functions using transcranial red/near-infrared light emitting diodes therapy (LED) | + |
| Hipskind, 2019 | Improving cognitive functions using transcranial red/near-infrared light emitting diodes therapy (LED) | + |
| Harch, 2017 | Improving cognitive functions using hyperbaric oxygen | + |
| Boussi-Gross, 2013 | Improving cognitive functions using hyperbaric oxygen | + |
| Weaver, 2018 | Improving cognitive functions using hyperbaric oxygen | + |
| Mozayeni, 2019 | Improving cognitive functions using hyperbaric oxygen | + |
| Walker, 2014 | Improving cognitive functions using hyperbaric oxygen | - |
| Wolf, 2012 | Improving cognitive functions using hyperbaric oxygen | - |
| Cifu, 2014 | Improving cognitive functions using hyperbaric oxygen | - |
| Cifu, 2014 | Improving cognitive functions using hyperbaric oxygen | - |

| | | |
|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------|
| Waid-Ebbs, 2014 | Improving executive functions using Goal Management Training | + |
| Palmese, 2000 | Improving attentional functions using a specific attentional training | + |
| Storzbach, 2017 | Improving attentional, mnemonic, executive functions using an association of several rehabilitation techniques (compensatory cognitive training, associating interactive didactic presentations, in-class discussions, cognitive strategies learning (like time management, internal memory strategies, self-monitoring or goal setting), and external aids) | + |
| Kontos, 2018 | Improving cognitive functions using several interventions on sleep, vestibular and oculomotor systems, cognitive functions and psychological state | + |
| Rábago, 2011 | Improving attentional and executive functions using Virtual Reality | + |
| Van Vleet, 2015 | Improving attentional functions using a computerized attentional training | + |
| Cooper, 2017 | Improving functional cognitive symptoms using therapist-directed cognitive rehabilitation and integrated therapist-directed cognitive rehabilitation combined with cognitive-behavioural psychotherapy | + |
| Vik, 2018 | Improving cognitive functions using music playing | + |
| Yost, 2013 | Improving cognitive functions using Yoga or Qigong | + |
| Azulay, 2013 | Improving cognitive functions using mindfulness-based stress reduction therapy | + |
| <i>Psychological care</i> | | |
| Scheenen, 2017 | Reducing anxiety and depression using an early Cognitive Behavioral Therapy Intervention (CBTi) compared to telephone counselling | - |
| Gil-Jardine, 2018 | Reducing the risk of PTSD and PCS at 3 months using a single eye movement desensitization and reprocessing intervention in patients with high risk of PTSD | + |
| Morries, 2015 | Improving sleep quality using near infrared light | + |
| Vuletic, 2016 | Improving sleep quality using therapeutic education (using brochures) associating with telephone-based problem-solving (PST) treatment | + at 6 months, - at 12 months |
| Waldron, 2013 | Reducing anger, depression, anxiety and PTSD using Cognitive and Behavioral Therapy | + |
| Block, 2013 | Reducing psychological troubles using Cognitive and Behavioral Therapy | + |
| Cole, 2015 | Reducing PTSD using mindfulness-based stress reduction therapy | + |
| Janak, 2017 | Reducing PTSD using multidisciplinary care including cognitive rehabilitation, vestibular intervention, headache management and integrated behavioral healthcare | + |

Table 1. Studies focusing on preventing and caring post-concussion symptoms after mild Traumatic Brain Injury: presentation of the goal of the intervention and of the effect (+=positive, -=negative) of each intervention detailed.