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To cite this article: Amir Hadanny & Shai Efrati (2016): Treatment of persistent post-concussion syndrome due to mild traumatic brain injury: current status and future directions, Expert Review of Neurotherapeutics, DOI: [10.1080/14737175.2016.1205487](https://doi.org/10.1080/14737175.2016.1205487)

To link to this article: <http://dx.doi.org/10.1080/14737175.2016.1205487>



Accepted author version posted online: 23 Jun 2016.  
Published online: 04 Jul 2016.



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PERSPECTIVE

## Treatment of persistent post-concussion syndrome due to mild traumatic brain injury: current status and future directions

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### ABSTRACT

Persistent post-concussion syndrome caused by mild traumatic brain injury has become a major cause of morbidity and poor quality of life. Unlike the acute care of concussion, there is no consensus for treatment of chronic symptoms. Moreover, most of the pharmacologic and non-pharmacologic treatments have failed to demonstrate significant efficacy on both the clinical symptoms as well as the pathophysiologic cascade responsible for the permanent brain injury. This article reviews the pathophysiology of PCS, the diagnostic tools and criteria, the current available treatments including pharmacotherapy and different cognitive rehabilitation programs, and promising new treatment directions. A most promising new direction is the use of hyperbaric oxygen therapy, which targets the basic pathological processes responsible for post-concussion symptoms; it is discussed here in depth.

### ARTICLE HISTORY

Received 7 February 2016  
Accepted 21 June 2016  
Published online 4 July 2016

### KEYWORDS

Post-concussion; concussion; hyperbaric oxygen; mTBI; traumatic brain injury; HBOT; post-traumatic; blast; treatment; pathophysiology; diagnosis

### 1. The challenge

Traumatic brain injury (TBI) has become a major public health concern worldwide for both civilian and military populations [1]. Although most of these injuries are considered mild, they may initiate a chain of metabolic reactions which propagate to persistent brain injury/post-concussion syndrome (PCS). Today, there is no agreed-upon effective standard of care treatment/intervention for PCS. Experts agree that novel neurotherapeutic methods to repair brain damage are needed more than ever before. The purpose of this paper is to discuss the pathophysiology of PCS, the current available treatments, and promising future directions. Although pediatric mild TBI (mTBI) and its consequence, PCS, are an important issue, the data on children is relatively scarce; thus, this review focuses on adult TBI.

### 2. Epidemiology

Each year, an estimated 10 million cases of TBI arise globally, 1.7–3.8 million occurring in the United States alone, with 75–90% of TBI cases defined as mTBI [2,3]. There are several classifications of the severity of TBI. The most common classification is that of the American Congress of Rehabilitation Medicine (ACRM) and the Centers of Disease Control (CDC), where mTBI is defined as the alteration of brain function caused by external forces with one or more of the following: loss of consciousness for a duration of 0–30 minutes, posttraumatic amnesia for a duration of less than 24 hours, and Glasgow Coma Scale grade of 13–15 [4].

The most common causes for mTBI are motor vehicle accidents, falls, sports, and blast injuries in the military setting. Sports-related concussions are traumatic events that affect up to 3.8 million athletes per year [5]. mTBI has been labeled as the ‘signature injury’ of the wars in Iraq and Afghanistan. It is estimated that 23% of the military service members who have served in Iraq and/or Afghanistan had mTBI [6,7]. Interestingly, 77% of soldiers who sustained any type of TBI were wearing their helmets at the time of injury. At present, no existing helmet is able to fully protect against all threats faced on the battlefield [8].

The cost of care for TBI in the US military population has risen exponentially to approximately \$646 million in 2010 [9], with mTBI accounting for 30–45% of the costs [10]. Very little research has been published on the economic burden that mTBI imposes on patients, their families, employers, and society as a whole [11].

### 3. The march of injury

Most mTBI patients develop a set of symptoms that includes headache, dizziness, fatigue, vertigo, neuropsychiatric symptoms (including behavioral and mood changes, confusion), difficulty in balancing, changes in sleep patterns, and cognitive impairments (including memory, attention, concentration, and executive function disorders) [12]. In most cases of mTBI, 80–90%, symptoms are resolved in days (7–10 days) [13] (Figure 1). However, in 10–20% of the cases, post-concussion symptoms may continue for weeks or months due to metabolic and structural brain damages. Of those patients, 25–33%

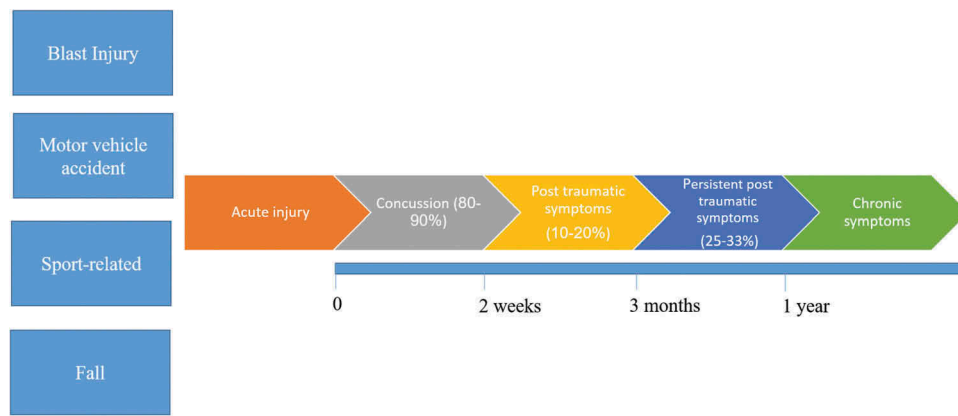


Figure 1. mTBI marching injury.

develop permanent brain injury and experience persistent PCS (formerly referred to as prolonged PCS – PPCS), in which the symptoms become chronic and last for over 6 months [14–18] (Figure 1). Once symptoms after mTBI become persistent, prognosis for full resolution is guarded. Although patients may improve or fluctuate in the level of complaints, if symptoms are present at 3 months, symptoms are also likely to be present at 12 months post-injury [19]. Patients with PCS have been referred to as ‘the walking wounded’ and ‘the miserable minority’, because many of them struggle with lasting neuropsychiatric sequelae that last for years or even a lifetime [20]. Some of PPCS patients develop chronic traumatic encephalopathy (CTE), which is a progressive neurodegenerative syndrome including mood disorders, behavioral and cognitive impairment, with or without sensorimotor impairment [21].

#### 4. Risk factors

Several factors increase the risk for development of PCS after brain injury. Meares et al. [22] found that pre-injury mental disorders such as depression or anxiety and acute posttraumatic stress (at 5 days post-injury) were predictive of post-concussive symptoms at 3 months. Ponsford et al. added that premorbid psychiatric and physical history, concurrent anxiety and trauma-related symptoms, life stressors, and pain were predictive of post-concussive symptoms at follow-up [23]. Moreover, stress exacerbates PCS. Other studies found that age over 40 [24,25], being female [25,26], sustaining previous head injuries [25], and substance misuse [27] also increase the risk for PCS.

Other potential factors may include pituitary dysfunction and decreased release of growth hormone [28], vestibular dysfunction [29], sleep disturbances [30], and chronic pain syndrome [31].

In addition, it is important to appreciate the fact that each patient enters the mTBI insult with a diverse range of individualized genetic, developmental, social, psychological, and biological resilience and vulnerability factors that contribute to both good and poor outcome [32].

#### 5. The pathophysiologic cascade

Concussion is the result of rapid acceleration and deceleration of the brain within the skull, leading to rotational and shear-strain forces. Due to different viscosities and densities, the gray matter–white matter junctions in the frontal and temporal lobes are the most vulnerable sites [33–35]. The shearing of axons, usually referred to as diffuse axonal injury (DAI), is the predominant injury in mTBI leading to cognitive dysfunction [36,37]. As will be discussed below, new advances in noninvasive neuroimaging have provided the evidence in humans for white matter damage [38]. The following pathophysiology cascade suggested by the authors is mainly based on years of animal studies. Most of the studies did not undertake helmet wearing into consideration. The sudden stretching of the neuronal and axonal membranes initiates an indiscriminate flux of ions through previously regulated ion channels and transient physical membrane defects [39,40]. This process is followed by a widespread release of a multitude of neurotransmitters, particularly excitatory amino acids (EAAs) such as glutamate and aspartate [40,41], resulting in further changes of neuronal ionic homeostasis. This posttraumatic ionic cellular derangement leads to mitochondrial calcium overloading [41,42], which is responsible for inducing changes of inner membrane permeability with consequent malfunctioning, uncoupling of oxidative phosphorylation, overproduction of reactive oxygen species (ROS), and, finally, mitochondrial swelling and dysfunction [43] (Figure 2).

EAAs released in the process activate microglia, the first line of active immune defense in the central nervous system (CNS). When activated, microglia release a series of immune factors, including ROS, reactive nitrogen species, inflammatory cytokines, and additional excitatory neurotransmitters [44]. This ‘immunoexcitotoxicity’ response further disrupts mitochondrial function. The overall function is to remove the inciting pathogens and damaged brain tissue, yet if the excitatory environment persists, a chronic low-grade inflammation may continue [45].

In addition to the axons, vascular elements in the gray–white matter junctions are sheared and damaged [46]. As the microvascular injury propagates, the regional cerebral blood flow (CBF)/perfusion decreases and the injured brain suffers

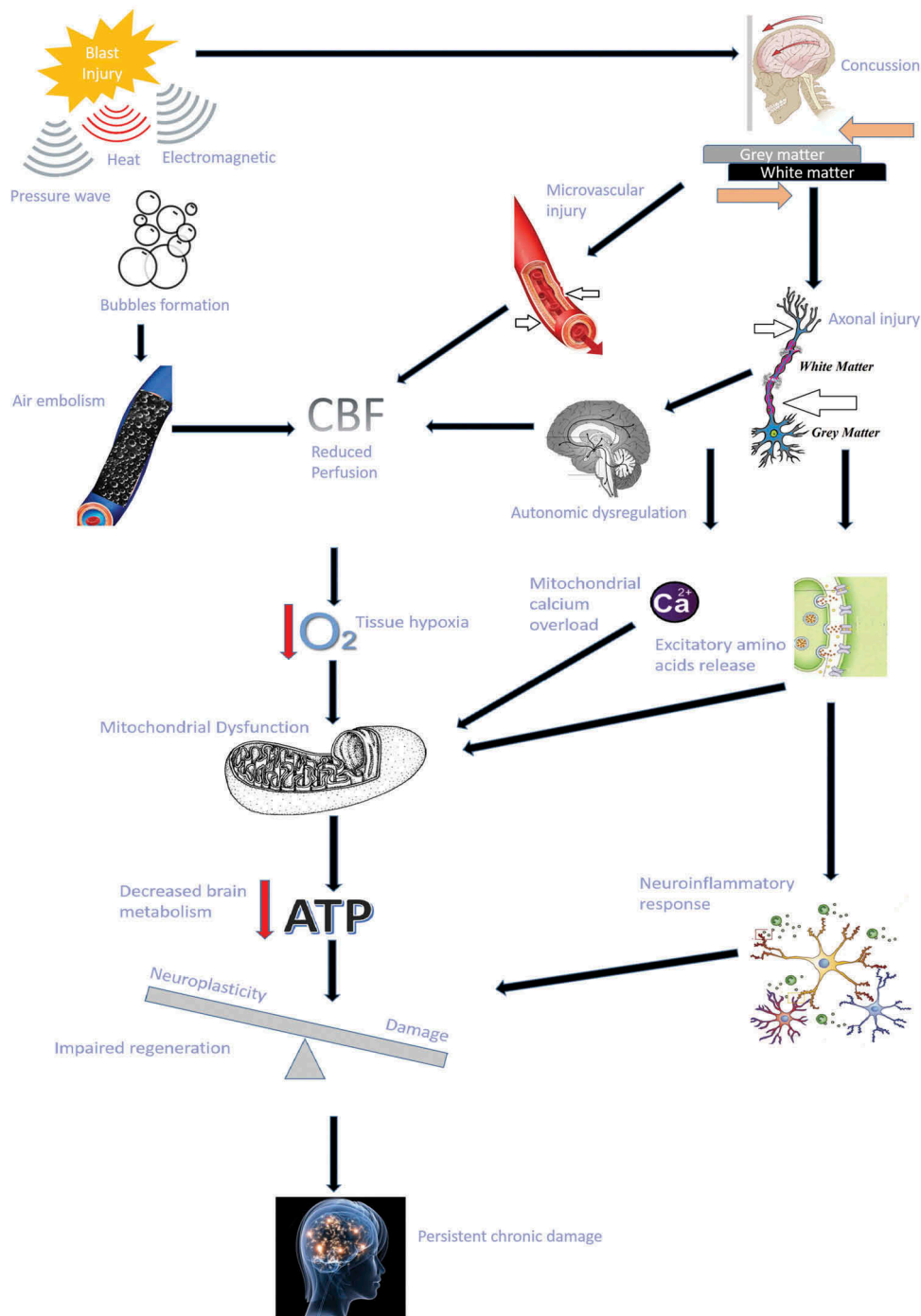


Figure 2. The theoretical pathophysiology of PCS.

from hypoxia. In turn, mitochondrial function, which is directly dependent on the partial pressure of oxygen, is further significantly decreased [47,48] (Figure 2).

Even though further data from human clinical trials are needed, the diffuse neuronal injury may damage the primary autonomic nervous system, which has been shown to be distributed in high cortical regions in addition to the brainstem [49]. Thus, autoregulation, the maintenance of CBF at appropriate levels during changes in systemic blood pressure, and global CBF can be disturbed [46,50–54]. Impairment of the CBF sensitizes the brain to secondary insults, such as hypotension, intracranial hypertension, and dehydration [52,55]. The

reduced CBF further increases the brain tissue hypoxia described above (Figure 2).

In the case of blast injury, there are complex and multifactorial mechanisms involved due to the blast wave transmission to the brain. Light, acoustic, thermal, and electromagnetic energy is also released, some of which damages the CNS in addition to the effects of the pressure wave [56]. Each tissue type has a characteristic acoustic impedance when ultrasound waves pass through. An acoustic impedance mismatch develops when shock waves pass through tissues of different density, resulting in mechanical disruption (spallation) of axons and microvasculature [57] (Figure 2). The blast wave induces

sudden changes in intracranial pressure that result in bubble formation, particularly at the interfaces between the cerebrospinal fluid (CSF) and the brain. The bubbles formed can cause cavitation of brain tissue, disruption of axonal pathways, damage to capillaries as well as lodging in blood vessels, and reduction of regional blood flow [57]. In addition, animal studies showed that air embolism after blast-related lung injury and a blood surge from the torso via the blood vessels to the head, caused by the blast wave, can transmit high pressure to the vasculature in the brain, damaging small blood vessels and the blood–brain barrier [58].

At a standard healthy condition, the brain utilizes almost all the oxygen/energy delivered. As oxygen supply decreases by any of the above mechanisms, the mitochondria fail, oxidative phosphorylation is halted, and the amount of energy in the form of adenosine triphosphate (ATP) is dramatically reduced. In order to initiate the repair processes of the damaged brain tissue, there is increased energy demand. For example, to reestablish ionic hemostasis, Na/K ATP-dependent pumps must work at their maximal capacities. Under normal aerobic conditions and correct mitochondrial functioning, glucose consumption is coupled to oxygen consumption, thus optimizing ATP generation [59]. However, due to mitochondrial dysfunction described above, during the time of maximum energy request, the neurons need to work overtime via the more rapid, but less efficient, oxygen-independent glycolysis, which is unable to fulfill the energy requirements [59,60]. These suggest that even mTBI may cause biochemical changes which lead to depressed brain energy generation and accordingly decreased brain metabolism [61]. Hypometabolism is likely to influence brain activation [62,63], reduce long-term potentiation and learning, and decrease neural plasticity [64]. Since neurotrophins, such as brain-derived neurotrophic factor (BDNF), are regulated by neural activity, reduced metabolism decreases the synaptic facilitation and neurotransmitter release enhancement [65,66]. Changes in brain activation can also have an effect on the regulation of the hypothalamic–pituitary–adrenal axis, culminating in profound effects on synaptic plasticity as well as cognitive and affective well-being [67].

Several magnetic resonance spectroscopy studies conducted in humans support the evidence of decreased brain metabolism in TBI [68–70]. Functional magnetic resonance imaging (fMRI) study of individuals with mild to moderate brain injury found neural activity alterations even a year after the acute injury [71].

When the microenvironment of the injury is intact, including restored global and regional CBF and collateral flow, brain metabolism recovers and initiates tissue repair processes. This will culminate in the recovery of the neurological dysfunction within days to weeks. However, when the microvasculature is injured, the hypoxic environment of the damaged tissue would persist and can culminate in either cell death or chronic neuroinflammation, persistent mitochondrial dysfunction, and decreased brain metabolism. Chronic malfunctioning brain metabolism leads to decreased neuronal activity, loss of synapses, and hampered neuronal connectivity [72], theoretically resulting in permanent brain injury and persistent PCS.

Moreover, mTBI-induced pathophysiologic cascade makes the brain more susceptible to severe and irreversible cellular injury by a second impact of even a very modest injury [73]. If, after a first mild injury, a second concussion finds the cells in the condition of recovering from the initial one and still in perfectly reversible energetic failure, it may lead to further mitochondrial malfunctioning, culminating in the same irreversible energetic failure described above. In addition, the second impact causes a much higher level of neuroinflammatory response due to the activated microglia [45]. Thus, a second mTBI occurring proximately to the first event may have synergistic deleterious effects resulting in persistent brain damage. Brain damage is progressive and often accelerated by the number of brain injuries that occur in an individual [74].

## 6. Diagnosis

Currently, the clinical diagnosis is based on self-reported symptoms and questionnaire evaluations. PCS is a broad term used to describe a complex disorder with a variable combination of post-concussion symptoms. The International Classification of Diseases (10th edition) [75] requires the presence of three symptoms for 4 weeks following a head injury. The Diagnostic and Statistical Manual of Mental Disorders – 4th edition (DSM-IV) [76] requires neuropsychological evaluation or quantified cognitive assessment in addition to three symptoms for at least 3 months, which interfere with social/occupational functioning. Due to controversy regarding the term ‘syndrome’, post-concussional disorder in the DSM-5 was replaced by ‘Neurocognitive symptoms associated with traumatic brain injury’ [77].

PCS symptoms include three clinical domains: cognitive complaints (decreased memory, attention, and concentration), somatic complaints (headache, fatigue, insomnia, dizziness, tinnitus, sensitivity to noise or light), and affective complaints (depression, irritability, and anxiety). Posttraumatic vertigo and/or dizziness after concussion may be attributable to a variety of conditions. It may result from any combination of labyrinthopathy or vestibular migraine dysfunction, chronic subjective dizziness or anxiety, or the direct neurological effect of mTBI [78]. Different patients may have symptoms primarily from one or another domain, although in general these domains are not mutually exclusive and can interact and feed on each other [79].

In most cases, classic anatomical brain imaging, such as computed tomography (CT) and MRI, has poor sensitivity for the pathophysiologic effects of mTBI. Novel techniques have been developed and are increasingly used for objective evaluation of the brain damage: Diffuse tensor imaging can demonstrate the combination of axonal injury and secondary gliosis with local microvascular injury [80]. Perfusion/dynamic susceptibility contrast MRI can demonstrate reduced global and regional CBF as well as cerebral blood volume (CBV)[81]. fMRI can demonstrate abnormalities in the activation and allocation of working memory resources with increased activation of working memory networks and recruitment of areas outside the working memory network [71,82] as well as decreased functional connectivity in specific networks [83]. Quantitative electroencephalogram can identify physiological



dysfunction and persisting neuronal dysfunction [84]. Positron emission tomography (PET) can measure regional brain metabolism [85], demonstrating both hypo- and hypermetabolism areas. Single photon emission CT (SPECT) can grossly evaluate regional CBF and demonstrate hypoperfusion areas in mTBI patients. In addition to brain imaging, biomarkers in the blood, saliva, urine, and CSF are under investigation for mTBI diagnosis. The most widely studied blood biomarkers are glial fibrillary acidic protein (GFAP) and ubiquitin C-terminal hydrolase-L1 (UCH-L1).

## 7. Current management of PCS

### 7.1. Pharmacotherapy

Patients treated for PCS receive various off-label pharmacologic and psychotherapeutic interventions to address comorbidities or PCS-related symptoms such as depression, but no medication has been approved by the US FDA for the treatment of any neuropsychiatric consequences of TBI (Table 1) [86]. The proposed mechanism of action of the medications involves inhibiting the EAA glutamate and aspartate release and/or interfering with their attachment to receptors, blocking their excitotoxic effects. Nonsteroidal anti-inflammatory drugs (NSAIDs) may affect chronic neuroinflammation and have shown efficacy in reducing headaches (Figure 3) [45,87].

The most common medications prescribed are antidepressants [88]. Several small, non-randomized, uncontrolled studies and case reports suggest that selective serotonin reuptake inhibitors (SSRIs) are efficacious in reducing depression and cognitive impairments [89,90]. The new antidepressants that affect norepinephrine, serotonin, and dopamine have not been evaluated scientifically.

Anticholinergic drugs may have shown short-term effects on cognitive function (mainly memory) in several open-label controlled trials on TBI patients. However, significant adverse events limit their use [91–93].

One randomized controlled trial (RCT) on desmopressin showed minimal improvement in cognitive functions. Methylphenidate has shown beneficial effects on attention, especially processing speed, and on general cognitive functioning in

non-randomized small studies on patients with more severe TBI. However, in mTBI its use has not been evaluated properly [94].

Antimigraine medications have shown some benefit on headaches as well as memory dysfunction and dizziness [95].

### 7.2. Vestibular physical therapy

Vestibular physical therapy (VPT) is a sub-specialization within physical therapy that requires patients with dizziness and balance disorders to perform challenging postural, gait, and gaze stability tasks [96]. Most VPT programs prescribe exercises needed to be done multiple times at home, presuming the patient is compliant and can do the exercises safely. In a retrospective analysis, it showed some efficacy in reducing dizziness and imbalance symptoms mainly when initiated several days after injury [97]. Unfortunately, VPT was not evaluated in the delayed phase in PPCS patients.

### 7.3. Cognitive rehabilitation

In principle, cognitive rehabilitation aims at direct remediation of specific processes such as attention, memory, or executive functioning and focuses on strategies that compensate for impaired function in these areas. Cognitive rehabilitation can be performed in the context of real-world activities or using cognitive exercises with workbooks or computers. The mechanism of action is unknown – it may be symptomatic alone or may assist in generating new neurons (neuroplasticity) and synapses (synaptogenesis).

The evidence to support the benefit of formal cognitive rehabilitation in this population is lacking. Research has demonstrated limited effectiveness of cognitive rehabilitation on cognitive functioning – mainly on attention and activities of daily living using single-group design studies [98,99]. In a recent small RCT, cognitive rehabilitation had small improvement in memory and some PCS symptoms without any significant change in other cognitive domains [100].

In two large RCTs, individual interventions by a qualified rehabilitation team did not appear to impact the long-term outcome and no improvements were seen after 1–10 years [101,102].

Table 1. PCS treatment efficacy and evidence level.

	Evidence level	Physical symptoms	Emotional Symptoms	Cognitive Symptoms
Cognitive behavioral therapy (in acute setting)	Moderate	Mild improvement	Improvement	None
Cognitive rehabilitation	Weak	None	None	Mild improvement in memory and attention
Education	Moderate-strong	Mild improvement	None	None
Exercise	Weak	Improvement	None	None
Hyperbaric oxygen therapy	Moderate-strong	Improvement	Improvement	Improvement
Mindful-based stress reduction	Moderate	None	None	None
Pharmacotherapy	Weak	Improvement with antimigraine drugs	Mild improvement in depression with SSRI	Mild benefit with SSRI, desmopressin, and amantadine
Rehabilitation program	Moderate	None	None	None
Repetitive transcranial magnetic stimulation	Weak	Mild improvement	None	None
Rest	Strong	None	None	None

Weak = non-RCTs, flawed methodology, Moderate = RCTs, flawed methodology, Strong = RCTs with acceptable methodology. RCT = randomized controlled trial.

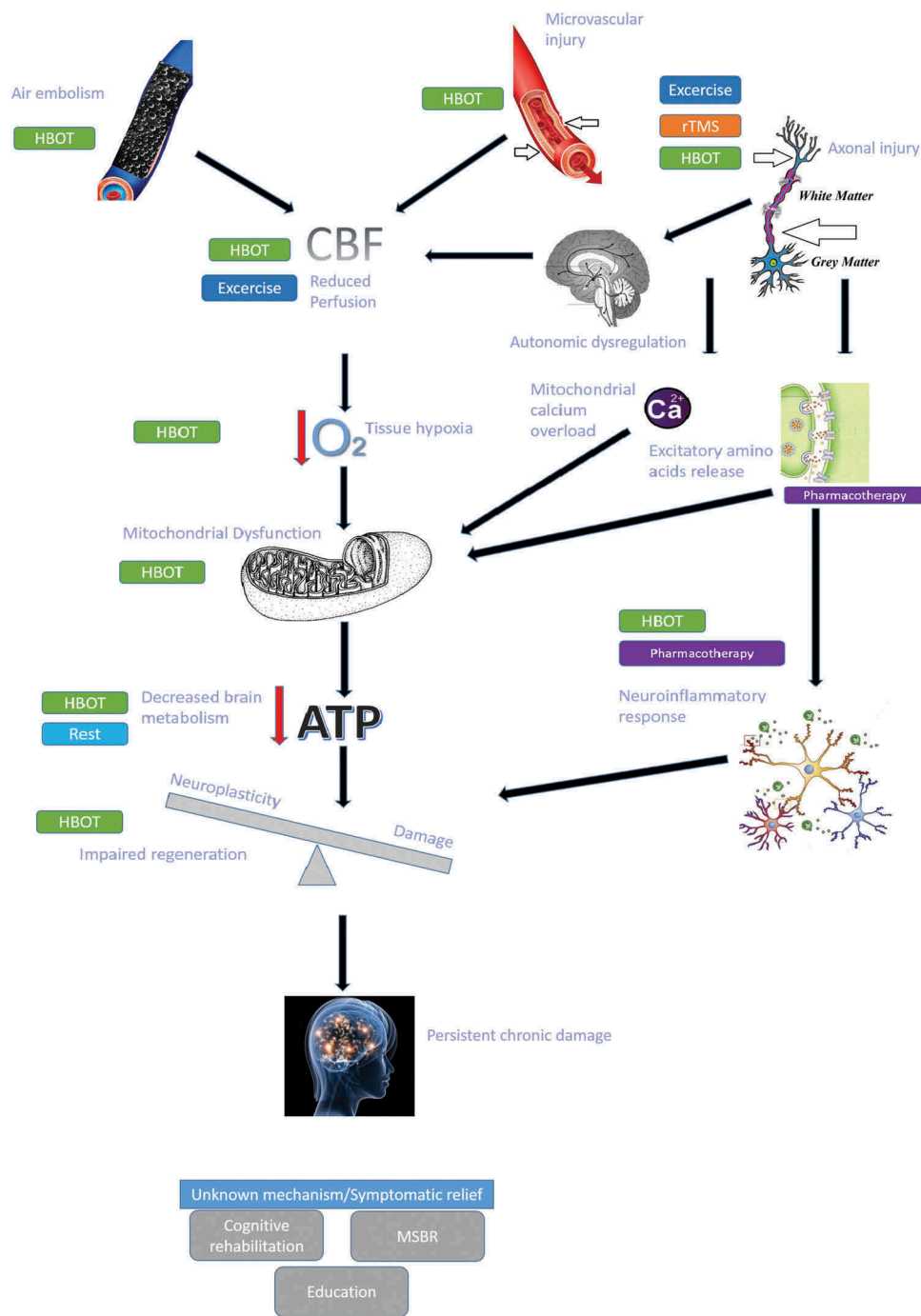


Figure 3. Treatments' theoretical mechanism of action.

#### 7.4. Cognitive behavioral therapy

Cognitive behavioral therapy (CBT) is a mode of therapy that focuses on examining the relationship between thoughts, feelings, and behaviors. By helping to challenge certain patterns of thoughts that tend to lead to maladaptive behaviors, patients begin to develop new ways of approaching how they relate to themselves, others, and the environment. A recent review of 42 studies, including 17 RCTs, on CBT for post-concussive symptoms provided evidence that when applied early, it may have some efficacy in reducing PCS somatic symptoms, anxiety, and depression

but no cognitive improvement [103]. A small pilot RCT of CBT early after mTBI (within 6 weeks post-injury) found that CBT seemed to facilitate recovery and prevent longer-term symptoms [104]. The mechanism of intervention on PCS pathology is unknown.

#### 7.5. Education

Generally, this involves the early provision of information about diagnosis and possible PCS symptoms, reassurance about prognosis, education on ways of coping and

resumption of activities. One RCT reported benefit of education when provided immediately after injury – improved sleep and anxiety, reduced distress but with no difference in neuropsychological measures [105]. There were six RCTs with varied qualities in this category that concluded no benefit or reported inconclusive findings [103]. The most recent meta-analysis of the best evidence studies concluded that applying education intervention early for an unselected group of patients with mTBI is not effective. However, patients with posttraumatic amnesia of 1 hour or longer do benefit from routine follow-up contact to receive information and advice [106,107]. Accordingly, based on the data available today, education may be effective in preventing PPCS; however, there are no data that demonstrate their efficacy in PPCS patients. The possible mechanism of intervention on PCS pathology is unknown.

### 7.6. Rehabilitation programs

Rehabilitation includes a multidisciplinary approach that may include psychotherapy, physiotherapy, speech and language therapy, cognitive rehabilitation therapy, medications, and others [106,107]. However, several systematic reviews found limited evidence to support the efficacy of rehabilitation programs. There were four RCTs that examined the efficacy of rehabilitation programs that included psychotherapy. Three concluded no difference between groups following the addition of a problem-solving intervention [101,108,109]. The fourth one reported mixed findings following the addition of individual and group support [110]. Thirteen uncontrolled, non-randomized, small sample sized studies with different psychological interventions on the entire spectrum of TBI (severe TBI included) reported different results [103]; functional improvements in family interactions and daily living [111], self-awareness [111] and productivity [103,112].

### 7.7. Mindfulness-based interventions and relaxations (MSBR)

The practice of mindfulness involves learning attention control and cultivating moment-to-moment awareness of thoughts, feelings, and bodily sensations. The focus is to enhance self-efficacy and reduce the self-perception of helplessness in the face of residual symptoms. Two controlled studies using relaxation found no difference or even increased PCS [113,114].

In a small sample with dropouts as controls, no follow-up, and high attrition rates, a 10-week MSBR program improved performance on measures associated with improved quality of life and self-efficacy [115]. The possible mechanism of intervention on PCS pathology is unknown.

### 7.8. Rest

Current guidelines recommend a period of cognitive and physical rest in the early post-injury period, because symptoms can increase with cognitive and physical exertion [116,117]. However, prolonged rest can lead to physical deconditioning, metabolic disturbances, and secondary symptoms such as

fatigue and reactive depression [118,119]. There is no scientific evidence that prolonged rest for more than several weeks in concussed patients is beneficial [120].

Due to the decreased metabolism state, rest in the early state could reduce the demand for energy and reduce symptoms (Figure 3). However, in later phases, rest would not increase the supply of energy needed for repair processes.

## 8. Promising new directions

The above-mentioned interventions have been used for several decades with limited success. The reason may lie in the fact that none of those treatments is targeting the baseline pathophysiology cascade described above, which is responsible for the syndrome. We present three new future directions for PCS treatment.

### 8.1. Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) includes the inhalation of 100% oxygen at pressures exceeding 1 atmosphere absolute (ATA) in order to enhance the amount of oxygen dissolved in the body tissues. During HBOT treatment, the arterial O<sub>2</sub> tension typically exceeds 2000 mmHg, and levels of 200–400 mmHg occur in tissues [121]. The most common clinical uses of HBOT are for nonhealing wounds and radiation-related injuries.

There are many preclinical, basic science studies evaluating the different pathophysiological effects of HBOT on TBI-induced damage. There are also several clinical trials but only one prospective RCT [122] was performed on a population without any potential secondary gain (such as obtaining financial compensation, avoiding work/army duty...), which evaluated both PCS symptoms (subjective clinical measure) and brain SPECT (objective measure of brain pathology). In this trial, HBOT induced significant improvements in cognitive functions compared to the control group. Moreover, using a crossover design, patients in the control group were switched to HBOT after the control period. After the cross to HBOT, there was comparable significant cognitive improvement, as in the treated group. The cognitive function improvements included memory, executive functions, information processing speed, and attention. In addition to the objective change in brain perfusion/metabolism, HBOT induced significant improvement in the quality of life and cognitive functions. The significant improvement in brain metabolism, noticeable in brain SPECT after HBOT, correlated with the improvement in the cognitive functions.

Four other RCTs [123–127] had significant methodological flaws, including an invalid control group, meaning a population with potential secondary gain from reporting sick without any objective evaluation of brain functions, and a control group that was treated with 'low dose' of pressure. From these studies, one can conclude that even a low dosage of pressure (1.3 ATA) may have significant beneficial effects.

Three other prospective studies [128–130] as well as several cohort studies [81,131–133] reported improvement in PCS and cognitive functions, including memory, attention, and executive



functions. In one of these studies, perfusion MRI was used as part of the evaluation of post-TBI patients treated with HBOT 10.3 ± 3.2 years after their injury: Whole-brain perfusion analysis showed significantly increased CBF and CBV, correlating with the significant improvement in the cognitive scores [81].

In addition to the previous limitations mentioned above, the main limitation of any HBOT clinical study is related to proper handling of the control groups. The only way to administer appropriate 'placebo' of HBOT is to bring the patients to the hyperbaric chamber and to increase the environmental pressure to an extent that the patients will feel it in their ears. The minimal pressure needed to gain such a feeling should be 1.3 ATA. However, compressed air at 1.3 ATA (significant by means of CNS environment), in addition to the pressure effect, increases the plasma oxygen tension by more than 50%, which makes it a low-dose treatment rather than sham/placebo intervention [134]. This limitation can be overcome by cross-over design with clear objective end points (such as brain imaging).

HBOT has several mechanisms of action (Figure 3):

- **Oxygenation of hypoxic tissue** – HBOT can significantly increase brain tissue oxygenation. The effect lasts for at least 6 hours after the HBOT session. Moreover, the tissue oxygenation results in a higher cerebral metabolism rate [135].
- **Neuroplasticity** – The elevated oxygen concentration in the blood and injured tissue during treatment [136–138] can supply the energy needed for neuroplasticity (regeneration of the damaged brain tissue). HBOT induces neuroplasticity by stimulating cell proliferation [139], promotes neurogenesis of endogenous neural stem cells [140], regenerates axonal white matter [141], improves maturation and myelination of injured peripheral and cranial neural fibers [142,143], and stimulates axonal growth, thus increasing the ability of the neurons to function and communicate with each other [144,145]. The common denominator to all repair and regeneration mechanisms is that they are all oxygen-dependent.
- **Restoration of mitochondrial function** – At the cellular level, HBOT can improve cellular metabolism, reduce apoptosis, alleviate oxidative stress, and increase levels of neurotrophins and nitric oxide through enhancement of mitochondrial function (in both neurons and glial cells) [138,140,146]. HBOT can restore normal mitochondrial function, which is a critical pillar of recovery after TBI [147].
- **Angiogenesis** – HBOT was also found to have a significant role in the initiation and facilitation of angiogenesis, which is required for axonal regeneration [148–151]. By inducing angiogenesis, HBOT improves the regional cerebral vascular flow necessary for neurogenesis and synaptogenesis [81,152,153].
- **Improves global and regional CBF** – In addition to increased regional CBF by angiogenesis, HBOT improves the global cerebral vascular flow [154–157].
- **Anti-inflammatory** – HBOT can reduce inflammatory reactions [158], reduce both microgliosis and astrogliosis reactions [159,160], and promote blood–brain barrier integrity.
- **Increased brain metabolism** – Due to increased blood flow and oxygenation, brain metabolism increases significantly, as seen in PET and SPECT scans [122].

- **Bubble recompression (blast injury)** – HBOT has been used for decades in recompression of bubbles formed during diving or iatrogenic air embolism. HBOT reduces bubble volume by its pressure effect and hastens inert gas elimination by tissue oxygenation [161].

As explained in detail by [134], the diverse and powerful innate repair mechanisms activated by HBOT are associated both with the elevated level of dissolved oxygen and with the elevated pressure.

HBOT targets the baseline pathophysiology responsible for persistent PCS (Figure 3). Currently, there is not sufficient data to specify the patients who can benefit the most from HBOT in regards to clinical characteristics such as age, time from injury, and type of injury. However, the correlation between metabolic brain imaging and the cognitive/symptom improvement holds the promise for an objective evaluation for patients who are candidates for HBOT. Therefore, patients should have brain metabolic imaging performed, in addition to anatomical imaging as part of the evaluation. Patients should be selected for treatment only if they demonstrate considerable metabolism defects. Further research is needed and should be performed in order to evaluate the efficacy and the optimal candidates and protocol (duration and pressure) of HBOT.

The disadvantages of HBOT include the time consumption of daily sessions for 2–3 months, the cost of the sessions, and the mild side effects that may occur during the sessions. Although the treatment cost may sum to \$5000–\$20,000, it is still cost-effective compared to the standard yearly cost of a PPCS patient, estimated at \$32,000 (without taking into account the loss of work) [162]. HBOT is considered a safe intervention with a complication rate of 2–3%, which is mainly mild and reversible middle ear barotrauma [163].

## 8.2. Exercise

As previously mentioned, uncontrolled activity too soon after concussion is detrimental to recovery [164]. In a small study, controlled aerobic exercise rehabilitation, after first establishing symptom-free exercise capacity via treadmill testing, has helped athletes and nonathletes in PCS recovery [165]. The role of physical exercise in promoting neurocognitive recovery and symptom reduction has been shown in other brain injuries [166].

There are two suggested mechanisms of action: In a small sample, controlled aerobic exercise rehabilitation restored normal CBF regulation, as indicated by fMRI activation, in PCS patients [167].

Recent studies have shown that exercise can induce cognitive improvements in the elderly [168] and poststroke patients [169]. Aerobic exercise upregulated BDNF, which can increase neurogenesis and neuroplasticity [170]. Thus, exercise may have a much more significant effect on PCS, which should be further evaluated.

## 8.3. Repetitive transcranial magnetic stimulation (rTMS)

rTMS is a well-established, validated technique to quantify excitation and inhibition of the primary motor cortex, the spinal nerve roots, and the peripheral motor pathway

(corticospinal) [171,172]. In a single uncontrolled small study, 4-week treatments with rTMS showed mild improvement in PCS but no change in cognitive function [173]. The exact mechanisms behind rTMS-induced plasticity are still unknown. Some have suggested that rTMS may increase neural stem cell proliferation and differentiation or synaptic plasticity [174].

## 9. Expert commentary

PCS has become a growing cause of morbidity, and most of today's treatments have little effect on PCS when challenged scientifically. The main reason is that most interventions are targeting the symptoms and not the actual pathophysiology of PCS. Exercise-based rehabilitation and rTMS provide new directions, but yet again may offer only a partial solution to the basic pathology. Unlike other interventions, HBOT can target the basic pathologic processes responsible for persistent PCS, has solid strong preclinical evidence and growing clinical evidence for its beneficial neuroplasticity effects, and can be considered as a safe new therapeutic option for those patients.

## 10. Five-year view

The number of mTBI victims is expected to grow considerably due to military and terror actions around the globe. In addition, due to higher awareness, the number of reports of civilian accidents and sports-related brain injuries is also expected to grow.

In the authors' perspective, HBOT has the potential to become part of the standard of care for PCS.

## Key issues

- Although most of traumatic brain injuries are considered mild, 10–20% of the patients suffer from post-concussion symptoms for weeks-months and 3–5% of those patients may have persistent post-concussion symptoms for years.
- The pathophysiology of post-concussion syndrome may include axonal injury, microvascular injury, bubbles formation, cerebral blood flow disruption, neuroinflammation and tissue hypoxia which lead to mitochondrial dysfunction and decreased brain metabolism.
- Current treatments include pharmacotherapy, cognitive rehabilitation, mindfulness-based stress reduction and rest. However, these treatment modalities failed to show sufficient efficacy, most probably because they are not targeting the pathophysiological processes responsible for persistent PCS.
- Hyperbaric oxygen therapy, repetitive transcranial magnetic stimulation and exercise are new, future treatment directions.
- Hyperbaric oxygen therapy may offer a solution for the basic pathological processes responsible for post-concussion symptoms.

## Acknowledgments

Mr. Raz Tuval is thanked for editorial assistance.

## Funding

This paper was not funded.

## Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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Reference annotations

• Of interest

•• Of considerable interest

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