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Review

Evaluation of current post-concussion protocols

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ABSTRACT

The growing number of concussions and mild traumatic brain injuries (mTBI) with the lack of evidence-based treatment options is a continuous health concern. This creates problems when evaluating and providing efficacious symptom management to patients suffering from post-concussion syndrome (PCS). Numerous pharmacological and non-pharmacological agents have been utilized in an attempt to treat PCS. Some of these approaches include physical therapy, analgesics, antidepressants, and nutraceuticals. Although these treatments have had some success, there has been inconsistent outcomes, with some examples of patients' symptoms worsening. Among pharmaceutical agents, fluoxetine has been a popular choice for the symptom management of PCS. Although some patients have had symptom resolution with the use of fluoxetine, there is still a lack of conclusive data. Of the several biochemical changes that occur in a patient's brain following a concussion, an increase in reactive oxygen species (ROS) is of particular concern. In order to counteract the responses of the brain, antioxidants, such as ascorbic acid, have been utilized to reverse the damaging cellular effects. However, this may inadvertently cause an increase in ROS, rather than a reduction. Although there is a lack of consistency in exactly when each treatment was used in the post-injury interval, it is important that we analyze the strengths and weaknesses of the most commonly used agents due to the lack of a set protocol. The studies were chosen in a non-exhaustive manner and were not consistent in patients' post-injury intervals, in addition to other baseline characteristics. However, over-arching claims that some treatments may benefit more than others can be made. This review evaluates both the pharmaceutical and non-pharmaceutical protocols that are most commonly utilized in post-concussive patients for their efficacy in treatment of post-concussive syndrome (PCS).

1. Introduction

Concussion, also known as mild traumatic brain injury (mTBI), is defined as an alteration of the normal function of the brain caused by a biomechanical force. According to the Centers for Disease Control and Prevention (CDC), 2.87 million TBI-related emergency department visits, hospitalizations, and deaths occurred in the United States in 2014, including over 837,000 of them occurring among children. With rapidly increasing TBI related emergency department visits and no universally established treatment, concussion is a public health crisis and a growing concern [1]. Of the almost 3 million Americans that encounter a traumatic brain injury (TBI) yearly, 290 000 were hospitalized and over 50 000 perished due to their injuries [2]. In late 2018, the first CDC guidelines were established for the diagnosis and management of mTBI among children [3]. However, due to the lack of evidence-based treatment options, post-concussion protocol mainly consist of symptomatic treatment to prevent a recurring concussion and to expedite the recovery process. Patients with a concussion history are three times more likely to have an incidental concussion when compared to those without a concussion history [4].

Acute post-concussion symptoms can be divided into two categories: signs observed and signs reported. The most common signs observed include loss of consciousness, confusion, and not being able to recall events prior to or after the trauma. Among the signs reported from the patient, headache, nausea, dizziness and light sensitivity are the most common [5].

Without proper management, the concussion and the symptoms that come along with the injury can develop into a chronic condition known as post-concussive syndrome (PCS). Between 24%–84% of mTBI patients will develop this chronic condition [6] consisting of headaches, dizziness, fatigue, sensitivity to light or sound, sleep disturbance, and/or concentration difficulties [7]. These long-term effects of a concussion can last up to months post-initial injury, leading to a decreased quality of life. According to the DSM-V criteria, PCS is diagnosed as either mild or major neurocognitive disorder (NCD) due to TBI. In order to have a diagnosed NCD, a patient must have decline in cognitive ability, including memory, concentration, and processing speed. Other specific criteria include: 1) evidence of a traumatic brain injury, 2) NCD

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presents immediately after the TBI or immediately after recovery of consciousness and persists past the acute post-injury period [8].

Of those people who develop PCS, up to 25 % of them will experience prolonged PCS, where the symptoms continue for over six months [9]. In addition, research has shown that 75 % of TBI patients suffer from major depressive disorder (MDD) [10]. According to the National Institute of Mental Health, depression (major depressive disorder or clinical depression) is a mood disorder consisting of persistent symptoms ranging from sad and/or anxious mood to fatigue and restlessness [10]. Of the total TBI patient population that suffer from depression, 35 % of them are classified as mild TBI patients, including concussions [11]. The presence of these uncomfortable symptoms leads to underemployment and productivity loss for a patient suffering from PCS [11]. Thus, it is important to recognize and manage symptoms in a timely and vigorous manner. In order to understand the current treatment options for PCS, understanding the pathophysiology is crucial.

2. Pathophysiology and symptom presentation

Following the physical injury to the head the brain undergoes vast chemical and biological changes. The most common pathological pathway when a mTBI occurs is through the tearing of neuron axons and small blood vessels. This type of injury is known as diffuse axonal injury (DAI). This leads to ischemia and hypoxia of the brain, along with many different chemical changes that lead to inflammation and edema [9]. The brain experiences a loss of regulation in the ion balance of $Na^+/K^+/Ca^{2+}$. Due to the loss of regulation, membrane depolarization of the neuron causes an efflux of potassium out of the cells that are responsible for the release of glutamate, an excitatory amino acid. Glutamate and other excitatory neurotransmitters activate N-methyl-D-aspartate (NMDA) receptors which consequently causes nonspecific initiation of action potentials. In addition, NMDA activation opens the ion-gated channels to allow a large influx of calcium into the neuron [12]. This influx causes the breakdown of excitatory neurotransmitters, causing the production of ROS [13]. Although ROS are produced by essential biological and metabolic processes of the cell and does not cause injury when levels are controlled, excessive amounts are toxic and can cause cellular damage (Fig. 1). ROS can damage essential proteins such as fragmentation and denaturation of collagen, albumin, and others [14]. ROS overproduction is observed in mTBIs, including concussions. These chemical changes can occur in the acute period following the initial injury and can lead to secondary injury. In addition to ROS, other neurotransmitters and inflammatory mechanisms undergo changes leading to greater cellular damage, tissue damage, and possibly brain cell death [13]. This pathophysiology has led to targeted research in the usage of certain medications and nutraceuticals in the treatment of concussions. However, there is yet to be enough evidence to support the benefit of either classes.

While the aforementioned changes take place in the brain, the patient begins to feel the results of these effects through many different symptoms. The symptoms can have a delayed presentation and may occur days to weeks post initial injury. Each symptom falls under one or more of the four domains including: physical, cognitive, emotional, and sleep. Of these domains, the most commonly experienced symptoms, such as headache and difficulty concentrating, fall under both the physical and cognitive domains. The symptoms within these domains are vastly non-specific ranging from headache, dizziness, and many more.

Among the many symptoms a patient experiences post-concussion, headache is the most common and long-lasting. Over 50 % of patients will continue to experience this symptom even one year after the initial injury. Headaches that worsen within seven days after a concussion are known as posttraumatic headache (PTH) and very closely resembles a migraine. Alongside a concussion, a PTH also does not have distinct clinical features other than the fact that it occurs closely to the time of initial injury. PTH is diagnosed and treated depending on factors such as duration, severity, location of headache, and the patient's medical history [15]. Each patient's symptoms may vary in both severity and duration [4]. Harmon depicted the common post-concussion symptoms and how many of the symptoms overlap with the different clinical profiles, including the management of the symptoms in each profile (Fig. 2). Fig. 2 depicts the correlation of patient reported symptoms to the matching clinical profile, such as cognitive and ocular, and how these symptoms present on a physical exam. As the figure illustrates, many of the common symptoms a patient experiences overlap with each other in both clinical profile and management [16].

In addition to headaches, the effect concussions have on a patient's mood and anxiety level is widely known. Aside from the various physiological symptoms a patient may experience, there is growing research on the development of long-term posttraumatic stress disorder (PTSD) in patients who have had a mTBI. Several case reports have shown the correlation of a mTBI and the presence of PTSD [17]. This becomes relevant when discussing both the pharmaceutical and non-pharmaceutical treatment methods that have been explored for PCS. Despite the type of symptoms a patient experiences, treatment must be actively sought to prevent worsening of severity.

3. Non-pharmaceutical therapy

Many different non-pharmaceutical therapies have been explored to

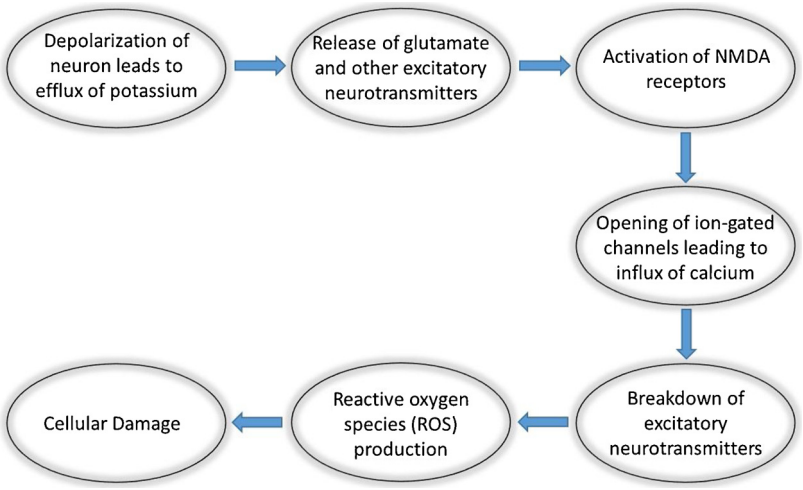

Fig. 1. Biochemical alteration process in the brain following a concussion.

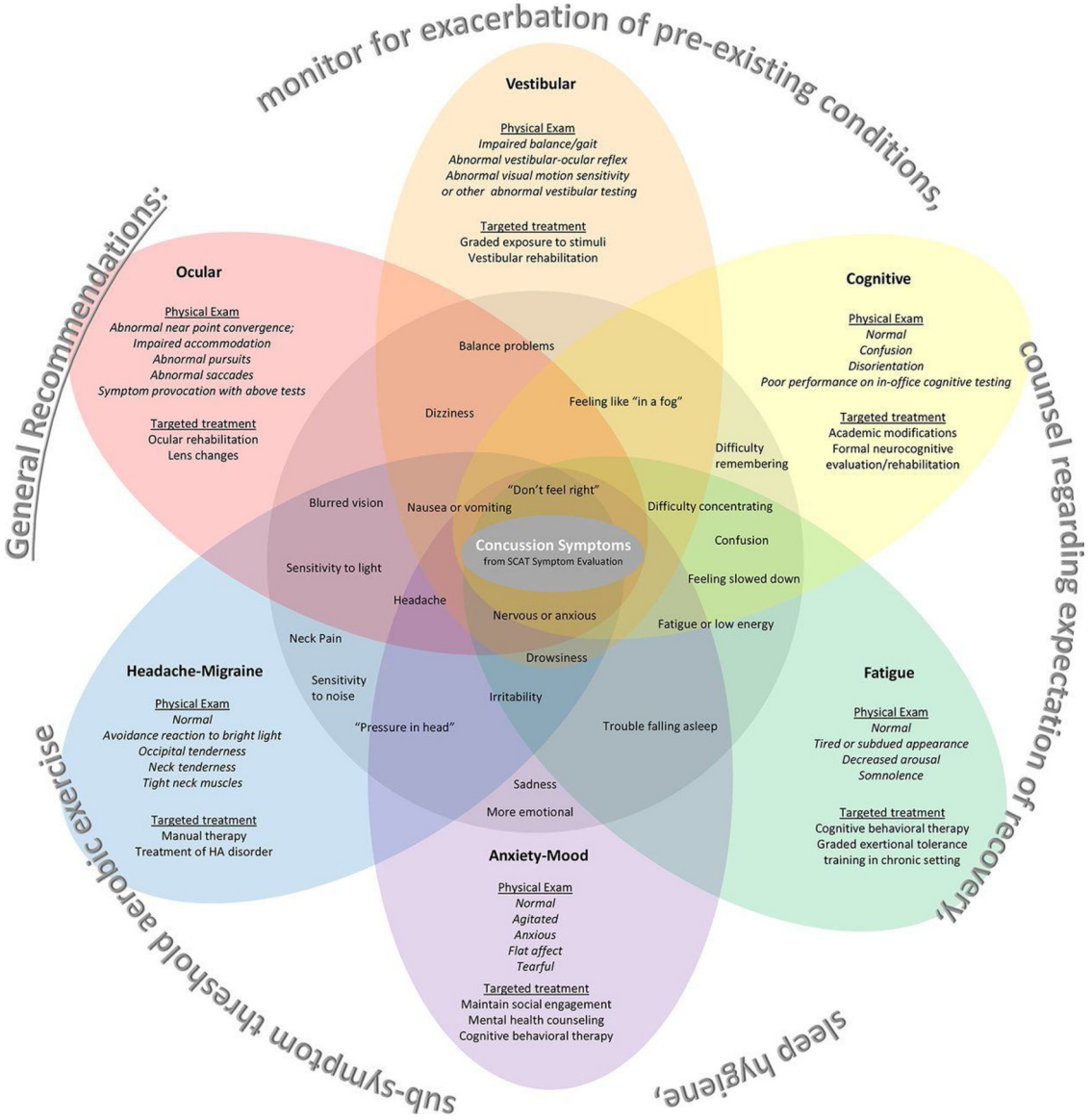

Fig. 2. Common post-concussive symptoms and their correlating treatments. (Harmon et al., 2019).

increase the rate of symptom resolution compared to pharmaceutical options in post-concussion patients.

3.1. Electroencephalogram (EEG) Neurofeedback

The relationship between PTSD and mTBIs have been shown in many studies. Studies have suggested that this relationship is largely dependent on stress reactions that create a stressful environment for the brain. Cortisol is a common biomarker used to measure stress levels and is known to inhibit growth factors for neuroplasticity. Management of cortisol and stress levels in a patient may be beneficial in PCS recovery. Thus, the potential benefits of EEG neurofeedback in mTBI and PCS treatment has been explored. Neurofeedback training works to help change the patient's irregular brain waves in amplitude, frequency, and coherency. This treatment method works as a training procedure to directly alter the biochemical and physiological response a mTBI patient has to a stressful environment. It has been shown that increasing alpha levels increases relaxation levels, thus allowing a decrease in anxiety and a more ideal recovery environment for the brain.

EEG neurofeedback could potentially expedite the initiation of the relaxation state in patients who have PCS. A study evaluated 4 groups of subjects experiencing TBI: 1) neurofeedback receiving group within the spontaneous recovery period, 2) neurofeedback receiving group post-spontaneous recovery period, 3) treatment as usual group within the spontaneous recovery period, and 4) treatment as usual group post-spontaneous recovery period. Both groups that received neurofeedback treatment (NFT), either in the spontaneous recovery period or post-spontaneous period, were all grouped as NFT. The remaining groups that received standard treatment were grouped into as the "treatment as usual group" (TAU). TAU consisted of routine treatment by the neurosurgical team, ranging from various surgical procedures and drugs to reduce edema of the brain. Post-assessment of patients' conditions was conducted via the Perceived Stress Scale (PSS) and Visual Analogue Scale (VAS) to rate the severity and presence of symptoms. In addition to the two self-reported scales, serum analysis of cortisol using ELISA was collected at 45–60 days post preassessment. The variables observed included: 1) severity, 2) nausea, 3) seizures, 4) use of anti-epileptic drugs, 5) ENT (ear, nose, and throat) bleeds, 6) loss of consciousness, 7) amnesia, and 8) surgical intervention. The results showed the NFT group had significantly more severe symptoms and more perceived stress on the VAS and PSS scale. In addition, no significant differences at baseline were found for biochemical variables, including

cortisol levels. These results suggest that neurofeedback may not be an effective treatment to reduce stress for injured patients. Although the mechanism and benefits of neurofeedback sounds promising, there is still a lack of favorable research to apply this treatment method to every mTBI patient and may not be as effective or timely favorable compared to other methods [18].

In addition, studies have been conducted to evaluate the efficacy of neurofeedback treatment in patients with mTBIs and moderate closed head injuries (CHI). In one particular study, twenty-one patients who had experienced moderate CHIs with various injury-to-test intervals were assigned to either receive NFT or participate in computer-based attention training. Abnormalities in a PCS patient's EEG included diffuse slowing with an enhancement of slow theta (4 − 7 Hz) activity and suppression of fast beta (13 − 20 Hz) activity. These changes in the EEG represent axonal injuries due to the mTBI. The participants were screened with computerized tomography (CT) scans to show any lesions of the brain. Some of the patients in the sample showed the following lesions: bilateral haematoma, frontoparietal haematoma, temporal lobe contusions, frontotemporal contusions, and bilateral contusions. Although there were differences in the presence of lesions in the sample, the patients' level of brain damage was similar in severity. The baseline-EEG pre-therapy and EEG post-therapy for the twelve CHI patients receiving NFT were recorded. The main aim of NFT was to increase the suppressed mean amplitude of 13 − 20 Hz EEG activity through beta training. Patients either received ten NFT sessions, each lasting thirty minutes, over the course of two weeks or ten computer-based attention trainings, also lasting thirty minutes for two weeks.

Eight of the twelve NFT receiving patients that started with low beta amplitudes had a statistically significant increase of 1 μV in the beta activity post-treatment. In addition, these patients were able to maintain a statistically significant ($p = 0.012$) increase in beta activity for a longer duration. The computer-based attention training group also showed improvements in beta activity acutely. However, their overall beta amplitudes did not change over the entire course of treatment. In addition, four of the twelve patients receiving NFT demonstrated a decrease, rather than an increase, in beta activity following treatment. The small sample size of the study and the difference in the overall beta activity of the NFT receiving group prevent this study's findings to be conclusive for all PCS and mTBI patients. [19]

3.2. Prescribed rest

The most common recommendation following a concussion is prescribed rest. This rest consists of symptom-limited cognitive and physical rest for no less than 24 − 72 h post-injury. After this acute rest period, moderate activity, both cognitive and physical, is recommended to eventually reach pre-injury activity levels [16]. Rest is recommended due to the sensitive condition of the brain following a concussion. Due to the disturbance of the brain's chemical homeostasis, especially in glutamate and calcium levels, a concussed brain is more vulnerable to additional injuries. This puts the brain at an increased risk to more severe injuries if it were to encounter further trauma or stressful conditions [20]. A study evaluated the difference in the level of brain in male athletes who had a mTBI within 1–14 months prior to the study and had persisting PCS. The athlete group was compared to a control group consisting of subjects without a concussion history. Both the athlete group and control group were matched in age and gender. Through various verbal and visual working memory tasks, the level of the subjects' brain activation was assessed with functional magnetic resonance imaging (fMRI). The results demonstrated that PCS patients had an activation level that was significantly higher compared to those without PCS. The excessive activation is one of the brain's compensatory methods to make up for the loss of function post-concussion [21]. This excess activation leads to further production of ROS, potentially leading to more cellular distress. This suggests that rest is necessary to control the brain's excessively activated cognitive activity.

In addition, another study was conducted to evaluate the relationship between prescribed rest and the time to PCS symptom resolution. The post-concussion symptom scale (PCSS), balance error scores, and cognitive activity scale were used to evaluate the symptom recovery duration in patients who had sustained a mTBI within three weeks of the study. The PCSS scale rates the severity of the symptoms commonly experienced by the patient, including headache, sensitivity to external stimuli, and mood alterations. In addition to the PCSS, the cognitive activity scale assigns a patient in categories zero to four, with zero being complete cognitive rest and four being full cognitive activity. It was demonstrated that patients with the highest level of cognitive activity experienced longer times to symptom resolution, than those who had controlled cognitive activity [22]. Similar results were found by Majerske and coworkers when evaluating neurocognitive performance in relation to activity intensity post-concussion. Athletes who were prescribed rest and restricted cognitive activity performed the best on neurocognitive tests and reported the lowest PCS symptom scores [23]. Prescribed rest has been the most popular and adapted protocol of concussions for decades. However, other studies have shown that there may be no benefit of cognitive activity restriction in PCS symptom resolution. Gibson et al. found no statistically significant relationship between cognitive rest and the duration of PCS symptoms in athletes post-concussion [24].

Furthermore, it has recently been reported that restricted activity actually results in delayed recovery and more symptoms [16]. A study evaluating children and adolescents post-concussion and the effects of strict rest illustrated that these participants reported more post-concussive symptoms overall. In addition, symptom resolution of the strict rest group took several days longer compared to the participants who had a higher activity level. Prolonged strict physical inactivity can lead to further development of secondary symptoms, such as depression, anxiety, and fatigue [6]. In a different study, patients who were prescribed strict rest reported more symptoms 10 days after initial injury than those who were not restricted from moderate cognitive and physical activity [25]. Early introduction of moderate exercise appeared to improve symptomatic outcomes rather than delayed exercise in participants [26]. Prescribed rest has been the primary treatment choice for concussions, but like the other treatment options, the results and benefits may be questionable.

Nevertheless, rest in the acute injury phase has its place in therapy, as the brain is in a more vulnerable state and needs time to stabilize. Certain studies have shown that in experimental animal data, there is a lower concentration of ATP, as well as structural alterations of the mitochondria in the brain. Lack of rest in the acute period may lead to an increased metabolic demand of the brain before it has had a chance to recover. Although post-concussion treatment is largely based on specific patient characteristics, a period of prescribed rest may benefit all post-concussion patients in the acute phase [27].

3.3. Osteopathic medicine and physical therapy

As the initial injury is caused by a biomechanical force, physical rehabilitation has been utilized and researched for the therapeutic benefits in PTH. Improvement has been shown with patients receiving physical therapy (PT) when compared to those who have not. However, these studies only evaluate PT as an adjunct to other medications and treatments rather than monotherapy [28]. Osteopathic cranial manipulative medicine (OCMM) is a non-pharmacologic method that has recently been evaluated as a potential alternative treatment. OCMM is based off of the idea that the anatomy of the cranium reflects the human body as a whole. OCMM utilizes the primary respiratory mechanism as its main treatment component, which consists of the mobility of the cranial bones, sacrum, dural membranes, central nervous system, and cerebrospinal fluid [29]. This treatment aims to alleviate cranial bony and myofascial dysfunctions that have resulted from various physical injuries [30]. A previous study showed that 95 % of

patients who have had a TBI showed at least one pattern of cranial strain and 87 % had at least one or more bony motion restrictions [31]. As PCS is a result of a mTBI, it is hypothesized that OCMM may benefit these patients. Approximately 71 % of the participants who completed the two treatment sessions of OCMM showed improvements in their post-concussive symptoms with no adverse effects (worsened headaches, dizziness, and increased pain). However, the remaining portion of the participants showed a significant worsening of PCS. The positive findings in this study may be reflective of the natural recovery of the patient, rather than the direct effects of OCMM treatment. OCMM may have use as a potential adjunctive therapy, rather than a monotherapy option, in PCS. However, with the small sample size of only nine-participants in this study, more research is necessary to conclude any therapeutic benefits [30].

Similar to OCMM, various PT treatments involving vestibular/oculomotor and cervical rehabilitation have been evaluated for efficacy as PCS treatment. Although many of them are not aware, many PCS patients have concurrent injuries to the spine and other areas of the body caused by the initial physical force. Potentially due to this reason, in addition to other medical conditions the patient may have, very few patients spontaneously recover from a concussion. In a recent retrospective cohort study, researchers have evaluated the efficacy of PT as a treatment for PCS [6]. According to the type of symptoms, various forms of PT including cardiovascular, vestibular/oculomotor, cervicothoracic, and other areas of exercise were prescribed to patients. Following an initial physical evaluation, a PCS phenotype was assigned and the aligning treatment plan was designed. For example, if the patient's primary symptoms included sensitivity to light, difficulty concentrating, and visual problems, the patient's PCS phenotype correlated to vestibular and oculomotor injury. Following this general assessment, patients received a series of specific screening tests to evaluate the need for PT prescribed by the sports physical therapist. The PT therapies ranged from jogging, stationary cycling, repositioning procedures, and joint and soft-tissue mobilization. After 4 PT visits over the course of the 3 months, patients' recovery of symptoms were assessed with the PCSS [6]. An average improvement of 9 points on the PCSS, correlating to a higher symptom recovery level than the minimum clinically important difference of 6.8 points was reported. Despite the promising results, this approach may not be applicable to the general PCS patient population. Over 75 % of this study's cohort only experienced either peripheral vestibular disorder or cervicothoracic dysfunction. As peripheral vestibular disorder and cervicothoracic dysfunction only represent two of the PCS phenotypes, this study's findings can only be applied to those particular patients. These results may also be influenced by the natural recovery over time and not the direct effect of PT treatment. Additionally, the small sample size of this study is another limitation in stating PT as a treatment for the entire PCS patient population [6].

3.4. Hyperbaric oxygen therapy

By understanding the mechanism of DAIs in the brain, hyperbaric oxygen therapy (HBOT) has been researched as a treatment method. HBOT involves a chamber that is slowly pressurized to 1.5–3 times higher than normal air pressure with pure oxygen. This method ideally supplements the hypoxic brain with oxygen [34]. The proposed mechanism of action is through the promotion of angiogenesis. Angiogenesis stimulated with hyperbaric oxygen can potentially increase brain perfusion with better cerebral blood flow (CBF) and cerebral blood volume (CBV). More introduction of blood to the areas of the brain that have become ischemic or hypoxic from the tearing of blood vessels could potentially expedite the recovery process. A study that evaluated the neurotherapeutic effect of HBOT using brain perfusion imaging and clinical cognitive functions demonstrated positive results [9]. HBOT significantly improved cognitive functions, such as information processing, speed, and visual spatial processing. In addition, CBF and CBV increased in regions of the brain that were responsible for visual, sensory-motor, memory, and attention functions. However, despite the promising results, there are limitations to this treatment option. In addition to the small study group, this treatment required numerous hyperbaric oxygen sessions over the week. HBOT requires a high level of compliancy and a substantial amount of time investment as each session consists of 60 min. This treatment option is also not easily accessible to the general mTBI patient population [9].

4. Pharmaceutical therapy

Several pharmacological and supplemental therapies for the treatment of PCS have been explored. Currently, there are no established guidelines for pharmaceutical therapy in the treatment of PCS and mTBI symptoms. However, based on the symptom presentation, pharmaceutical therapy, ranging from over-the-counter analgesics to prescription antidepressants have been explored for potential benefits.

4.1. Anti-inflammatory and analgesic

Acute treatment for concussions is given early and is mostly symptomatic treatment consisting of anti-inflammatory and analgesic medications, including aspirin, ibuprofen, and acetaminophen. Although acute aggressive therapy is needed, large amounts of medication consumption puts patients at a risk of developing medication-overuse headache (MOH) [4]. To prevent the overuse and the development of MOH, a preventative medication may be given if acute treatment is needed for more than three days a week and/or if the patient is at risk for delayed recovery. Similarly to acute treatment selections, preventative treatments are also chosen based on symptom presentation and the patient's additional comorbidities. Some MOH preventative agents include nutraceuticals, such as magnesium, riboflavin, and coenzyme Q10, as well as a range of prescription medications including antidepressants, beta-blockers, anticonvulsants, and neuropathic pain medications [4]. However, when the length of treatment and side effects of these preventative treatments are taken into account for, the level of prevention and protection these supplements provides is questionable.

4.2. Antidepressants

Antidepressants are the most commonly prescribed medications for PCS. Although they are not FDA approved for this use, some selective serotonin reuptake inhibitors (SSRI) have an off-label use to address PCS symptoms [35]. Patients with depression have a deficiency in brain monoaminergic transmitters, including norepinephrine (NE), serotonin (5-HT), and/or dopamine (DA) [10]. The balance and levels of these neurotransmitters play a crucial role in many behavioral symptoms, such as mood, fatigue, and psychomotor agitation [10]. Similarly, the etiology of the comorbidity of depression in mTBI patients seems to relate to the chemical imbalance of neurotransmitters in the brain post-concussion. Studies have evaluated the therapeutic use of SSRI's, specifically sertraline, in the treatment of depression in mTBI patients. A particular study evaluated 15 ambulatory care patients that met the two main inclusion criteria: 1) having sustained a TBI within the past 3–24 months and 2) suffering from MDD based on the Hamilton Depression Rating Scale (HAM-D) and Diagnostic Interview Schedule (DIS) [36]. Patients received 8 weeks of sertraline, starting at a dose of 25 mg that was titrated up to 200 mg a day, based on clinical response and tolerability. Results demonstrated a statistically significant improvement in neuropsychological function and in depression scores on both the HAM-D and DIS scale. In addition, ten participants had a complete remission of depression. With these results, sertraline seems to be a viable treatment option for PCS related symptoms. However, these results were based off of a small subject size with several patients having normal neuropsychological scores at the initial assessment, potentially demonstrating a ceiling effect in the results. Due to these limitations and

lack of further studies, sertraline should not be concluded as a treatment option to the general PCS patient population [36].

Furthermore, a different study evaluated the use of sertraline in post-TBI patients and its effectiveness in reducing symptoms, including post-TBI depression. The inclusion criteria included: eighteen years or older, have a history of TBI with a documented loss of consciousness or other evidence of a TBI, and be at least 6 months postinjury. In this ten-week double-blinded randomized controlled study, patients received either sertraline or a placebo. Patients' level of depression and anxiety symptoms were assessed with the HAM-D scale at the beginning of the trial, every two weeks throughout the treatment, and immediately at the conclusion of the ten-week treatment. The sertraline-treated group received a range of 25 − 100 mg daily. The results indicate that of the forty-one patients that completed the trial for the entire ten weeks, 59 % of the sertraline-treated group and 32 % of the placebo-treated group had a 50 % decrease in depression from baseline. Although there was a decrease in severity of post-TBI depression and anxiety, the p-value of 0.15 demonstrates that the data was not statistically significant [37].

Additionally, amitriptyline, a tricyclic antidepressant, has been explored as a potential antidepressant that can be utilized for PCS and post-TBI depression. In an open trial, twenty-two patients were administered 200 − 300 mg of amitriptyline daily for a total of four weeks. The control group of non-TBI patients with depression were compared to mTBI patients with a high level of depression at baseline, based on the HAM-D scale. The patients that did not respond to amitriptyline were given a three to seven day treatment-free period, then switched to phenelzine 60–65 mg/daily. As a monoamine oxidase inhibitor, phenelzine increases levels of serotonin and dopamine within the brain. No significant improvement was shown for both amitriptyline and phenelzine treated post-TBI patients. The study's small sample size and inconclusive data makes it difficult to conclude the level of efficacy of both amitriptyline and phenelzine for the treatment of PCS [38].

Another widely used SSRI in the treatment of depression and symptom relief in PCS is fluoxetine. In an open-label pilot study, five patients who have experienced mild to severe TBI were given fluoxetine hydrochloride 20 − 60 mg/day. These patients had either no or moderate depression and had no history of previous antidepressant use. The participants were assessed for cognitive and memory function based on the HAM-D scale at baseline and after eight months of fluoxetine treatment. Although only a small size, there was a statistically significant improvement in the severity of symptoms including mood and memory with a p-value < 0.05. Improvements were also seen attentional-motor speed tasks and a letter-number sequencing subtest, reflecting the level of a "working memory" of the patients. However, the small sample size of five patients makes the application of these findings difficult to be applied to all PCS patients [39].

4.3. Amantadine

Amantadine is a medication that has been researched specifically for headaches in PCS. As a NMDA receptor antagonist, amantadine has previously been studied for its use in other TBI symptoms, such as impulsive behavior and disinhibition caused by frontal lobe disorders. NMDA receptor activation following a concussion leads to non-specific neuron activation leading to the production of ROS. By using NMDA receptor antagonists, the firing of non-specific action potentials can be stopped to prevent further cellular injury. In addition, NMDA receptor antagonists are also used for its anesthetic and analgesic effects by blocking the transfer of electric signals between neurons in the brain and spinal column [40]. When studied for its analgesic effects in PTH, the treatment course required an intake of 100 mg twice per day for 2 months. Although eighty-percent of patients showed improvement in headache severity, one-third of the participants discontinued the course due to side effects, including worsened headaches. Furthermore, amantadine treatment did not show any improved response in the other common symptoms of PCS, such as inattention and dizziness. While amantadine seems to be a potential treatment, more studies are necessary to properly evaluate its benefits and risks in this patient population [41].

4.4. OnabotulinumtoxinA (BOTOX®)

Regardless of the PTH phenotype, early and aggressive therapy is important to prevent further worsening of the headache. Typically, if the initial trauma does not result in a loss of consciousness or vomiting, neuroimaging is not necessary. Due to the resemblance of PTH to migraines and the lack of evidence-based PTH treatment options, patients are often prescribed migraine treatments, such as triptans [4]. More invasive procedures, such as *BOTOX®* and facet blocks, have gained popularity. *BOTOX®* seems to be an ideal treatment as it is the only FDA approved treatment for chronic migraines. As a neuromuscular blocker, *BOTOX®* is thought to inhibit the peripheral signaling process to the central nervous system, preventing central sensitization and therefore decreasing the sensation of pain in both migraines and PTH [42]. Central sensitization is a protective mechanism that involves the enhancement in the function of neurons in nociceptive pathways. This results in the perception of pain even in the absence of a noxious stimuli and ultimately leads to pain hypersensitivity. Central sensitization can be caused by continuous stimuli or by an intense noxious stimuli, including the biomechanical force that causes a concussion [43]. When the mechanism of action of *BOTOX®* and the resemblance of PTH to migraines is taken into account, *BOTOX®* may be a reasonable treatment method. A case study evaluated the effects of *BOTOX®* in a female patient who had PTH for 5 years. The patient was given local *BOTOX®* injections of 22 IU in the muscles of the facial area, including the frontalis and corrugator supercilii muscles. The patient reported a decrease in pain on the pain scale after 5 days of the initial injection and was completely symptom free after 10 days [44]. The results seem promising, however, as this was only a single case study, *BOTOX®* cannot be concluded as a single treatment option for PTH [44].

In a different retrospective consecutive case series, *BOTOX®* was evaluated for its effectiveness in treating headaches in patients with a history of mTBI. The study included 64 male subjects that had varying post-injury times to the first *BOTOX®* injection. The patients were split into different groups based on the type of headache: chronic migraine (CM), cervical dystonia (CD), or mixed syndrome. Regardless of the group patients were place in, all subjects had a diagnosed chronic PTH. Patients in the CM group received 31, 5IU injections in fixed sites (FSFD), while the CD group received injections based on the characteristics of torticollis, a twisted and tilted neck with severe pain. Patients with mixed syndrome received FSFD with either CD or "follow-the-pain" (FTP) treatment where specific areas of discomfort was targeted. The mean number of treatments for each patient ranged from 1 to 19 sessions, with intervals of 40–213 days. Clinical outcomes were measured based on the global evaluation of change (GEC) scale through patient report with options ranging from better, no difference, or worse. Following the study, an improvement in symptoms were only reported by CM patients. In addition, the patients in the study sample were all white males, causing the effects of the agent to be confined to a certain population. The limitations of this study makes it hard for these findings to be applied to all mTBI patients experiencing PTH [45].

Epidural injections have also been explored as a treatment option for patients with potential cervical spine injury due to the initial injury. The ligaments and cervical muscles, among many other structures within the cervical spine, can all be involved in triggering and prolonging PTH. Ultimately, by focusing treatment on the cervical spine, the triggering of PTH could potentially be reduced. Among the interventional treatment options for PTH, peripheral nerve blocks are most commonly used [44]. The theory is based off of the mechanism that by administering anesthetics, such as bupivacaine and lidocaine to the nerve, they can inhibit the feedback process of a headache, thus stopping PTH. Administration of anesthetics at trigger points of the

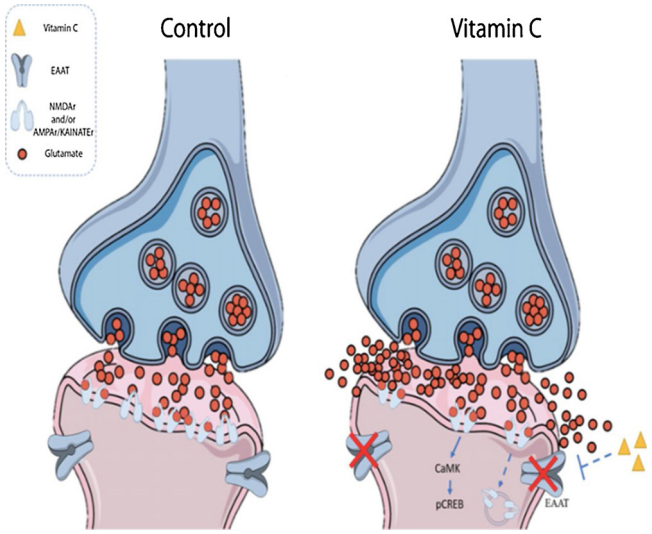

Fig. 3. Model of vitamin C modulation of the glutamatergic system [47].

head and neck have also been used as interventional therapy for PTH [44].

4.5. Nutraceutical supplements

Over the past few years the interest in nutraceutical supplements and their benefits in many disease states have gained immense popularity [16]. Antioxidants, certain B vitamins, omega-3 fatty acids, vitamin D, progesterone, and some others have shown to provide protection and/or accelerate the post-concussion recovery process [16]. By taking the pathophysiology of concussions into account, the effects of antioxidants have been researched to inhibit NADPH oxidase to counteract the secondary ROS production following the injury [46]. Among these numerous antioxidants for the treatment of post-concussive symptoms, melatonin has been a popular choice [46]. As a naturally produced substance in our body, melatonin is well tolerated with few side effects when taken as directed. Melatonin is a potent physiological antioxidant that has neuroprotective, analgesic, and anxiolytic properties that could potentially be favorable to patients who have PCS. As discussed earlier, excessive ROS production is one of the main pathways that cause cellular and tissue damage in PCS. Melatonin could potentially counteract the oxidative stress by acting as an antioxidant. In addition, melatonin's possible activity at the gamma aminobuteric acid (GABA)-ergic system and opiate receptors give its analgesic properties [46]. The analgesia may be beneficial to improve the common symptoms of PCS, such as headaches and pain. In the PLAYGAME pilot trial data from 2013, melatonin showed a significant response compared to other treatments for post-concussive symptoms in children with persistent post-concussion symptoms (PPCS). 83 % of the children who received melatonin showed improvement in PCS symptoms and headaches with a p-value < 0.05. However, with the lack of additional data, further research is needed to conclude melatonin as a PCS treatment option [46].

An important feature of cellular injury caused by excessive ROS production is lipid peroxidation. Lipid peroxidation involves the breakdown of the body's structural lipids, including those that make up the cellular membrane and the phospholipid bilayer arrangement. Additionally, lipid peroxidation is a major source of the other by-products that are cytotoxic, including aldehydes that are produced from the breakdown of lipid hydroperoxides [14]. In order to counteract this toxicity, antioxidants can theoretically be beneficial. Two of the most accessible and well-known antioxidants are ascorbic acid (also known as vitamin C) and vitamin E. Besides being an antioxidant itself, vitamin C also transforms vitamin E, a potent lipid peroxidation inhibitor, into its active form. A study conducted in rats showed the co-administration of vitamin C and vitamin E led to a significant decrease in secondary brain injury due to ROS stress compared to either alone [13]. However, at high doses vitamin E can lead to serious side effects, including hemorrhage [13]. Although these findings illustrate that both antioxidants can be utilized as a treatment option for mTBI, this study's results cannot directly be applied to PCS patients, as this is not a human study [13]. In addition, more research has shown that vitamin C actually produces pro-oxidant effects. As indicated earlier, following a concussion there is an excessive release of glutamate in the brain due to the depolarization of neurons, leading to a cascade of reactions that causes further cellular damage and ROS production [47]. A study utilizing lipid peroxidation assays (LPOs) showed that vitamin C significantly increases the oxidant effects of glutamate, leading to further ROS damage [47]. Even without the presence of glutamate, vitamin C alone induces lipid peroxidation in a dose-dependent manner. Statistically significant oxidant effects were shown at all doses tested (from 25 to 200 μM) and when added together with glutamate, produced an additive amount of ROS damage [47].

Excessive amounts of glutamate results in NMDA receptor activation, which ultimately leads to the breakdown of various neurotransmitters that produce ROS. In a particular study, the relationship between vitamin C, including its oxidized form dehydroascorbate (DHA), and NMDA receptor activation was evaluated. NMDA receptor activity can be functionally measured by evaluating [3 H]MK-801 binding. This study showed that both vitamin C and DHA increased [3 H]MK-801 binding, indicating that vitamin C directly correlates with NMDA receptor activity (Fig. 3). Decreased uptake of D-aspartate allows continuous activation of NMDA receptors, thus leading to further ROS production. In addition, neurons treated with ascorbate for 30 min showed decreased membrane surface excitatory amino acid transporters levels. As glutamate is removed from the synaptic cleft via excitatory amino acid transporters (EAAT), the reduction in transporters decreases the uptake of glutamate, causing further accumulation. In addition, increased glutamate levels also led to a profound increase in [3 H]MK-801 binding. These results show that ascorbate inhibits D-aspartate uptake and causes extracellular glutamate accumulation,

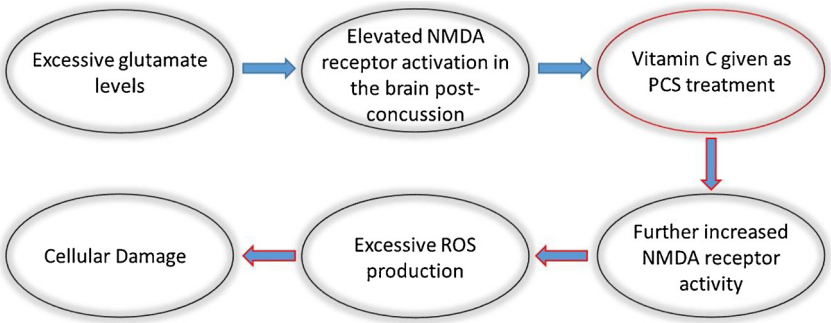

Fig. 4. Potential concerns of Vitamin C produces further cellular injury.

suggesting that vitamin C increases the amount ROS production via multiple mechanisms, leading to cellular injury (Fig. 4) [47].

5. Conclusion

Even with established guidelines by the CDC, the prevalence of mTBIs and the lack of evidence-based treatments is a growing public health concern. The neurochemical disturbances that occur due to this injury lead to many symptoms, including headache and decreased concentration. These symptoms not only decrease the quality of life of the affected individual, but can continue to progress from acute symptoms to chronic medical conditions, including PTH and PTSD. Several different treatment options for these conditions in both the acute and chronic phase have been researched. For non-pharmaceutical options, treatments such as prescribed rest, PT, and EEG neurofeedback have been trialed in patients with non-conclusive efficacy. Pharmaceutical therapies, including antidepressants and analgesics, have also shown little efficacy in mTBI patients. Among the pharmaceutical therapies, nutraceuticals have gained increasing interest for their potential benefits in not just mTBIs, but in other health conditions. Vitamin C has been one of the most widely used nutraceutical in mTBI treatment. As the production of ROS vastly increases following a brain injury, the use of vitamin C, an antioxidant, mechanistically makes sense. However, recent studies suggest vitamin C may actually lead to further cellular injury in the brain. These findings are concerning as the number of mTBI incidences are increasing with very few options for treatment and management of mTBI symptoms. The lack of evaluation on the injury time of the patients and when each treatment was utilized is the main downfall of this area, further requiring more studies.

Declaration of Competing Interest

The authors declare no conflict of interest.

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