Potential Targets for Conservative Interventions for Acute Concussions

Subjects: Clinical Neurology

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The conservative paradigm is applicable to pain management for sports injuries. While pain is an injury symptom in the acute period, it can become uncoupled in the sub-acute phase from the injury that first caused it, evolving into its own distinct disease state. Classic examples of this in sports are when acute neck or back injuries transition into chronic low back pain (CLBP) or whiplash-associated disorders (WADs).

Keywords: concussion ; mild traumatic brain injury (mTBI) ; central sensitization ; sports-related concussion ; peripheral sensitization ; glymphatic system

1. Introduction

By viewing persistent post-concussion symptoms (PPCS) as a form of nociplastic pain secondary to central sensitization, it reveals a time-dependent process that can potentially be interrupted. Recognizing this temporal dimension is key, as it points to a critical therapeutic window for early intervention. The strategic goal is to prevent the neuroplastic changes that are responsible for pain chronification, in line with the International Olympic Committee consensus statement referred to above [1].

Here, researchers cover five components of the central sensitization process specific to concussions that can be targeted with conservative treatments in the acute period:

- Peripheral sensitization;
- Cerebral metabolic dysfunction;
- Neuroinflammation;
- Glymphatic system dysfunction;
- Pain catastrophizing.

As will become clear, certain interventions can potentially positively affect multiple central sensitization-related targets. This supports a clinical intervention strategy that is multimodal in nature, consistent with conservative management principles. In **Table 1**, selected interventions that address two or more of the five targets described above are presented.

Table 1. Selected interventions that address multiple CS-related targets.

Intervention	Target *	Author, Study Details **	Summary of Findings
Early Exercise	**PS, CN, NI, GO, PC**	**Leddy, et al. (2023) [2]; MA (*n* = 9432)**	**Early physical activity and prescribed exercise improved recovery by a mean of −4.64 days (95% CI −6.69, −2.59).**
		Grool, et al. (2016) [3]; CS (*n* = 2413)	**Early participation (<7 days) in physical activity compared with no physical activity was associated with lower risk of PPCS (413 [24.6%] patients vs. 320 [43.5%] patients; RR, 0.75 [95% CI, 0.70–0.80]).**
Deep Breathing	**CN, NI, GO, PC**	**Cook et al. (2021) [4]; P (*n* = 15)**	**Following deep breathing exercises, participants reported significant reduction in stress (r = 0.57), tension (r = 0.73), fatigue (r = 0.73), and confusion (r = 0.67), with large effect sizes.**

Intervention	Target *	Author, Study Details **	Summary of Findings
Cold Therapy	PS, CN	Al-Husseini, et al. (2022) [5], RCT (*n* = 132)	The proportion of players with prolonged symptoms (>14 days) was 24.7% in the cold therapy intervention group and 43.7% in controls ($p < 0.05$)
Mindfulness	NI, PC	Acabchuk, et al. (2021) [6], MA (*n* = 532)	Meditation, yoga, and mindfulness-based interventions lead to significant improvement of overall symptoms compared to controls (d = 0.41; 95% CI [0.04, 0.77]; τ2 = 0.06).
Melatonin	NI, GO	Barlow, et al. (2019) [7], MA (*n* = 15)	Meta-analysis of pre-clinical data showed a positive effect of melatonin on neurobehavioral outcome (SMD = 1.51 (95% CI: 1.06–1.96)), neurological status (SMD = 1.35 (95% CI: 0.83–1.88)), and cognition (SMD = 1.16 (95% CI: 0.4–1.92)) after TBI.
		Cassimatis, et al. (2022) [8], MA (*n* = 251)	Eight of nine mTBI studies reported positive sleep outcomes after melatonin treatment, with significant improvements in subjective sleep quality, objective sleep efficiency, and total sleep, and reductions in self-reported fatigue, anxiety, and depressive symptoms.
Omega oils	NI, GO	Miller, et al. (2022) [9], RCT (*n* = 40)	In SRCs, the treatment group took 2 g of docosahexaenoic acid (DHA) daily for 12 weeks. The DHA group were symptom-free earlier than the placebo group (11.0 vs. 16.0 days, $p = 0.08$) and had a shorter RTP time (14.0 vs. 19.5 days, $p = 0.12$).
Vitamin D	CN, NI	Sharma, et al. (2020) [10], RCT (*n* = 35)	In moderate to severe TBI, Vitamin D bolus in the acute period showed significant improvements in cognitive and physiological outcomes. Inflammatory markers were also significantly decreased in the treatment group (IL-6 $p = 0.08$, TNF-α $p = 0.02$).

* PS = peripheral sensitization, CN = cerebral neurometabolism, NI = neuroinflammation, GO = glymphatic optimization, PC = pain catastrophizing. ** CS = cohort study, MA = meta-analysis, RCT = randomized clinical trial, P = pilot study.

2. Reducing Peripheral Sensitization

Sustained peripheral pain signaling and peripheral sensitization are the initiating mechanisms of the central sensitization process. Animal models of central sensitization highlight the need for ongoing nociceptive input to drive this phenomenon, suggesting a therapeutic benefit in aggressively reducing such input in the acute period. This approach, particularly in perioperative medicine, has shown promise in mitigating central sensitization-related chronic pain [11].

Since the peripheral source of pain in concussion occurs primarily through the ophthalmic branches of the trigeminal nerve (V1) that innervate the meninges and cranial periosteum [12] and secondarily through CGRP-mediated activation of the trigeminal ganglion and trigeminocervical nucleus, the treatment of peripheral trigeminal hypersensitivity may help abort the development of PPCS [13][14][15].

2.1. Exercise

Clinical data on early exercise in the past decade have revolutionized the treatment of concussion injuries, with high quality evidence supporting this intervention [2][16]. For most studies, early exercise describes the initiation of physical activity in the first 48–72 h after injury. One of the many benefits of exercise is that it reduces peripheral sensitization through mechanisms such as endorphin release and changes in pain modulation systems [17]. Importantly, symptom-limited exercise should be prescribed, as overexertion may lead to symptom exacerbation and the worsening of peripheral sensitization [18].

2.2. Analgesics

Analgesic therapy can be effective at decreasing peripheral sensitization. Non-steroidal anti-inflammatory drugs (NSAIDs) normalize the heightened pain threshold linked to inflammation by inhibiting prostaglandin formation at peripheral and central sites [19]. Acetaminophen achieves peripheral prostaglandin inhibition and can positively affect several central anti-nociception processes [20]. The perioperative use of preventative analgesia with these and other drugs successfully reduces central sensitization-related chronic pain after surgery [21][22].

In the concussion literature, a randomized clinical trial found that a combination of NSAIDs and acetaminophen showed the most promising results in terms of reducing the number of headache days and return to school time [23]. On the other hand, the 5P cohort study (referenced above) showed that emergency room administration of the OTC oral analgesics

had no impact on the presence of headaches at the 7-day follow up. There was no mention of whether it was a one-time dose or if treatment was continued at home [24].

2.3. Cold Therapy

Cold therapy to the head and neck may potentially reduce peripheral sensitization. Cold compresses alleviate pain by slowing pain signal transmission to the central nervous system and cell metabolism. Additionally, cold reduces inflammation, constricts vessels, and decreases the release of chemical pain mediators, leading to an increased pain threshold and reduced pain [25].

In concussions, branches of the trigeminal nerve that innervate the cranial periosteum show an acute inflammatory response after closed head trauma [13], suggesting that topical cooling may mediate acute trigeminal hypersensitivity in the cutaneous nerves of the scalp and neck. In the clinical literature, one study found that concussed subjects self-reported temporary relief from physical symptoms after head cooling [26]. In another group of studies, players receiving head–neck cooling have shorter return-to-play times than controls in several studies [5][27].

2.4. Physical Therapy

Physical therapy can help reduce hypersensitivity of the balance system. Vestibular therapy has shown promising results when instituted early in cases where there are balance issues. In vertiginous states, there is hypersensitivity in the balance organs, just as there is with other sensory inputs. Just like with exercise, the goal of vestibular therapy is to engage in symptom-limited movements to challenge and reset hypersensitivity in the balance system. Cervical therapy has also been shown to be beneficial in select cases when started early. Importantly, the neck has cross-signaling from trigeminal inputs in the cervicotrigeminal nucleus.

2.5. Sensory Protection

Photophobia is common in the acute period after concussion [28], reflecting underlying trigeminal sensory nerve hypersensitivity. Because intrinsically photosensitive retinal ganglion cells (ipRGCs) are sensitive to 480 nm light, FL-41 glasses and other tinted lenses are applied in cases of post-concussive photophobia [29][30]. The use of ear plugs in phonophobia may be helpful in the short term, but there are no data to support this. For sensory hypersensitivity, treatment involves gradual and systematic sound desensitization rather than total deprivation [31].

3. Addressing Cerebral Metabolic Dysfunction

The neurometabolic consequences of concussion drive central sensitization-related changes by amplifying peripheral sensitization and secondary injury in the brain. Numerous ionic, metabolic, and physiological changes occur acutely after concussions, which contribute to migraine-phenotype symptoms [32]. Cortical spreading depolarization, like those seen in migraines, may represent the initiating event in this cascading metabolic dysfunction [33]. Depolarization results in excess glutamate, which in turn triggers an ionic imbalance that leads to the overactivity of sodium–potassium pumps, causing an increase in energy demand in the form of adenosine triphosphate (ATP). This intensifies the need for glucose metabolism and oxygen at a time when cerebral blood flow (CBF) is impaired [34]. These changes overload mitochondria, altering their membrane permeability and triggering oxidative stress through the production of reactive oxygen species (ROS) [32][35]. This neurometabolic cascade coincides with the first week after injury, the window of time when clinical symptoms are the most severe after concussions and when central sensitization-related changes begin to occur.

3.1. Mitochondrial Support

Interventions for acute mitochondrial dysfunction in concussions are a promising and exciting area of study. Because early mitochondrial dysfunction is seen in acute mTBI [36], addressing mitochondrial impairment may enhance mTBI outcomes [37].

Creatine supplementation may help with the metabolic crisis after concussions, with preclinical evidence supporting both preventative effects of symptoms when taken before injury and recovery effects when taken after injury [38]. In addition to its role in sustaining ATP concentrations and cellular bioenergetics [39], creatine is believed to contribute to preserving mitochondrial membrane potential and reducing intramitochondrial reactive oxygen species and calcium [40]. There are only limited human trial data on creatine in TBI patients, but the results were uniformly positive [41][42]. The prevalence of creatine supplementation in athletes is unknown. It is not a banned supplement, but high-school athletic professionals are prohibited from recommending it in certain states. As more data on the benefits of creatine supplementation for concussion treatment (both before and after injury) become clear, this prohibition may be revised.

Ketogenic diets are also being explored for their ability to mitigate mTBI-related glucose hypometabolism [43], with pilot clinical trials in PPCS patients showing promising results [43][44]. Like creatine, ketone bodies serve as an energy substrate, bypassing glycolysis to undergo direct metabolism via the tricarboxylic acid cycle. This process enhances oxygen metabolism, supports mitochondrial function, and reduces oxidative stress and glutamate-induced injury [45].

Another compound of interest is ubiquinol (coenzyme Q-10), which has been shown to preserve mitochondria and reduce oxidative stress in animal TBI models [46].

Vitamin D is now known to be a critical mitochondrial transcription factor, and, in preclinical models of neurodegenerative disease, it rescues mitochondria from oxidative stress [47][48].

3.2. Exercise

Exercise is a powerful intervention for the post-concussion metabolic crisis because it increases CBF, which in turn increases oxygen and glucose delivery [49]. Multiple studies have documented that CBF is decreased in the acute and subacute periods after SRCs [50]. While not quantified in any studies, the beneficial effects seen with early post-concussion exercise may be related to its ability to increase CBF.

3.3. Deep Breathing

Clinical evidence shows that regular deep breathing exercises significantly increase blood oxygen levels [51]. Furthermore, breathing exercises have been shown to decrease mitochondrial-related biomarkers of oxidative stress in a variety of clinical contexts [52].

3.4. Cold Therapy

Vigorous exercise may lead to hyperthermia, which can exacerbate concussion-related glucose hypometabolism. Therefore, cooling after exercise may improve outcomes in this regard by reducing hyperthermia-related neurometabolic burden [53].

4. Decreasing Neuroinflammation

Neuroinflammation is a pivotal component in the initiation of nociplastic pain after concussions because inflammatory mediators and cytokines drive the sensitization of neurons within the CNS [54]. In traumatic brain injuries, CGRP is an integral player in this process by amplifying the microglial response and priming neurons for neuroplastic changes in the trigeminal system [55]. CGRP levels increase after concussions due to an increased expression in trigeminal nociceptors and in response to post-injury cortical spreading depolarization [56]. In animal models, CGRP inhibitors prevent the development of PPCS-like hypersensitivity when delivered in the first two weeks after injury, but not after this period [57]. Clinically, there is evidence that CGRP polymorphism can partially explain clinical outcomes after concussions [58]. Another study found that an intravenous infusion of CGRP triggers migraine-like headaches in people with PPCS, highlighting the significant role of CGRP in the genesis of post-traumatic headaches [59]. These connections suggest that targeting neuroinflammation early after concussion injuries may disrupt the cascade of events, potentially preventing PPCS development [60].

4.1. Nutraceuticals

Several nutraceuticals may be beneficial for reducing concussion-induced neuroinflammation. For instance, Vitamin D may reduce neuroinflammatory and secondary injury effects after concussions [61]. Preclinical studies demonstrate that Vitamin D improves post-mTBI neuroinflammation and oxidative stress [62][63]. Vitamin D has also been shown to decrease CGRP levels in migraineurs [64]. Importantly, TBI patients' low Vitamin D levels are noted to have significantly worse cognitive impairment and poor functional outcomes [10][65], whereas early vitamin D supplementation in deficient patients leads to significant improvement in clinical outcomes [66]. Ubiquinol (coenzyme Q-10) has been shown to decrease oxidative stress and neurodegeneration in TBI animal models [67]. It also has been shown to decrease CGRP and neuroinflammatory markers in migraineurs [68][69]. Other nutraceuticals that have been shown to significantly decrease CGRP in human trials for migraines include melatonin [70] and curcumin (turmeric) [71]. Preclinical data show that omega oils prevent the neuroinflammatory changes in microglia to a pro-inflammatory phenotype, activate neuroprotective cytokines, and mitigate TBI-related blood–brain barrier disruption [72][73].

4.2. Dietary Changes

There is an increasing interest in the impact of diet on concussion outcomes [44][74][75]. Diets rich in red meat, saturated and trans fats, refined sugars, and carbohydrates are associated with neuroinflammation, while neuroprotective and anti-inflammatory effects are linked to diets high in unsaturated, polyunsaturated, and monounsaturated fats, as well as ketogenic and Mediterranean diets, and intermittent fasting [76]. The effects on anti-neuroinflammatory (ANI) diets on TBI outcomes are being worked out in both preclinical [77] and clinical studies [44][78]. Specific supplements have been extensive studied, most notably the use of omega oils [79][80][81]. There is also interest in the impact of TBI on the gut microbiome [82]. Other recommendations include a low glutamate, low tyramine, and low histamine diet combined with the elimination of caffeine from the diet.

4.3. Exercise

Regular moderate-intensity exercise is associated with anti-inflammatory effects [83]. Animal models of TBI support that early exercise reduces markers of neuroinflammation and nociceptive sensitization [84][85]. Further research is being proposed on the role of exercise immunology in TBI outcomes [86].

4.4. Stress Reduction

There is a direct association between psychological stress and neuroinflammation [87]. Stress-reducing interventions like deep breathing and mindfulness-based stress reduction (MBSR) have been shown to decrease biomarkers of neuroinflammation in clinical trials of central sensitization-related symptoms [88]. Multiple clinical trials suggest that mindfulness-based interventions are supportive of mTBI recovery [89].

5. Optimizing Glymphatic System Functioning

The prolonged presence of neuroinflammation in concussions may be associated with dysfunction in the glymphatic system during the acute phase following the injury [90]. The glymphatic system, a waste clearance pathway in the central nervous system, plays a crucial role in removing metabolic byproducts and cellular debris after concussion [91]. Damage-associated molecular patterns (DAMPs) are due to normally intracellular proteins that, when released into the extracellular space after trauma, elicit an immune response. The release of DAMPs is linked to adverse post-TBI outcomes, including diminished memory, altered motor coordination, and cognitive impairments [35]. This debris is normally cleared by the glymphatic system, but, in the aftermath of a concussion, the glymphatic system functioning is decreased by up to 60% [92]. This compromised waste removal process contributes to the sustained inflammatory response to neurotoxic proteins (like tau), which, in turn, is permissive of central sensitization-related neuroplasticity [93]. This is concerning, as cumulative tau deposition around intracerebral vessels is the histological definition of chronic traumatic encephalopathy (CTE) [94]. Therefore, optimizing glymphatic function in the acute period after concussions is an important therapeutic goal [95].

5.1. Circadian Therapy

The glymphatic system is linked to sleep and the circadian system, with over 80% of glymphatic system clearance occurring during deep sleep [96][97][98]. Because sleep is also pathologically disturbed after concussion injuries [99][100], circadian therapy interventions are important early interventions. Melatonin has been extensively studied as an adjuvant therapy for concussions, with a meta-analysis showing positive sleep-related outcomes in 8 of 9 studies [8]. Limiting blue light via screen-time restriction positively impacts concussion recovery time [101]. Morning blue light therapy is associated with improvement in multiple concussion outcomes in patients with established PPCS [102]. Finally, because sleep apnea significantly disrupts glymphatic function [103] and is associated with poor outcomes in concussion [104], screening for and treatment of sleep apnea is recommended in concussion injuries. Other interventions along these lines include sleep hygiene, cognitive behavioral therapy (CBT), and prescribed exercise [95].

5.2. Omega Oils

Numerous studies demonstrate the positive impact of omega oils on sleep quality and their influence on circadian variations in blood pressure, potentially through direct effects on melatonin release and norepinephrine regulation [105][106]. Additionally, in a TBI animal model, omega oils were found to enhance glymphatic drainage, reducing neurological impairment after simulated injury; this effect was directly related to improved glymphatic clearance [73].

5.3. Exercise and Deep Breathing

Because exercise increases blood pressure and CSF flow, it has a positive effect on glymphatic functioning [107][108]. Similarly, deep breathing influences glymphatic clearance by increasing the flow magnitude of CSF [109].

6. Pain Catastrophizing

Another possible target to prevent the central sensitization process after concussion is pain catastrophizing in the acute period [110]. Pain catastrophizing is the putative link between trait anxiety and post-concussion symptoms [111]. Pain catastrophizing involves an exaggerated negative mental outlook toward pain, magnifying its threat, fostering feelings of helplessness, and contributing to increased distress and disability. Several orthopedic studies have linked pain catastrophizing with the development of nociplastic pain and central sensitization [112][113][114].

In concussion research, pain catastrophizing subscales (rumination, magnification, and helplessness) show significant correlations with pain severity, the number of reported post-concussion symptoms, psychological distress, and functional levels [115]. These findings are related to studies on the relationship between trait resilience (arguably the opposite of pain catastrophizing) and concussion outcomes. Reduced resilience is linked to increased symptoms and a prolonged recovery from SRCs, whereas high resilience shows the opposite [116][117].

6.1. Mindfulness, Meditation, and Deep Breathing

There is significant clinical evidence that trait mindfulness is negatively associated with pain catastrophizing [118][119] and that mindfulness exercises may help abort pain catastrophizing [88][120][121]. A recent meta-analysis examining the impact of post-mTBI interventions like mindfulness, meditation, and yoga revealed substantial improvement in overall symptoms when compared to control groups, including improvements in mental health, physical well-being, cognitive performance, and overall quality of life [6]. In a pilot study, deep breathing exercises in concussion patients was associated with decreased stress and tension [4].

6.2. Coaching

The use of coaching in pain management is gaining interest. Clinical trials of health coaching to aid with stress management and goal-setting in chronic pain patients show reduced psychological stress and improved resilience [122]. In the concussion literature, web-based resources combined with weekly coaching sessions produced improved outcomes and high patient satisfaction rates [123]. In a randomized trial, collaborative care, where coping skills, relaxation strategies, sleep hygiene, and positive thinking techniques were coached, showed significantly improved results in PPCS patients [124]. In another randomized trial, the addition of weekly motivational interviewing and CBT significantly improved multiple mTBI outcome measures [125]. Another randomized trial showed that regular telephonic follow-up using motivational and behavioral activation approaches resulted in significantly lower depression scores, including in those with preexisting depression [126].

6.3. Exercise

There is evidence that exercise can improve pain catastrophizing by influencing the fear center of the brain. Voluntary exercise stimulates neurons in the mesolimbic system, including in the amygdala. This has been suggested as the mechanism by which exercise aids in overcoming fear-avoidance behaviors associated with chronic pain conditions [127].

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