REVIEW ARTICLE

A SYSTEMATIC REVIEW OF TREATMENTS FOR MILD TRAUMATIC BRAIN INJURY IN ADULTS: HEADACHE-MIGRAINE, OCULOMOTOR, AND VESTIBULAR CONCUSSION SUBTYPE OUTCOMES

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KEYWORDS

Traumatic brain injury

TBI

Concussion

Headaches

Migraines

ABSTRACT

Context: Up to 15% of concussed patients experience persistent symptoms and functional impairment following injury. This is often related to headaches, dizziness, imbalance, and visual disturbances.

Objectives: To perform a systematic review of the evidence for interventions used to manage postconcussion symptoms in working-aged adults falling within the headache-migraine, ocular, and vestibular postconcussion symptom cluster subtypes.

Methods: A literature search was performed according to the PRISMA statement. PubMed, OVID, Cochrane Central, PEDro, OSTEMED, and the grey literature checklist were searched from the dates of creation of each database through December 29, 2020. The outcome measures were compared by generating the standardized mean difference (SMD) with 95% confidence intervals. GRADE (Grading of Recommendations, Assessment, Development and Evaluation) was used to rate the overall quality of the evidence.

Results: The literature search identified 496 candidate studies. After removing duplicates, 352 studies remained. The titles and abstracts of the remaining studies were screened for eligibility and 343 studies were excluded. The full text of the remaining nine studies was assessed for eligibility and risk of bias. None of these studies was excluded. This left nine studies for qualitative and quantitative analysis.

Conclusions: Moderate-quality evidence suggests 4 interventions show promise for treating adults with headache-migraine, ocular, and vestibular postconcussion subtype symptoms.

INTRODUCTION

Clinical symptoms of mild traumatic brain injury (mTBI) typically resolve spontaneously, with 80%–90% of concussed older adolescents and adults returning to preinjury levels of clinical function within 2 weeks.[1] However, up to 15% of concussed patients experience persistent symptoms and functional impairment following injury that may have severe personal costs and make it hard to resume their normal jobs and lives. Workers that sustain an mTBI have a higher risk of being out of work five years after the trauma compared to their noninjured peers. Patients in their thirties and with a higher education were found to be at higher risk of experiencing these long-term consequences.[2]

Concussions produce a heterogenous variety of symptoms, presentations, and clinical courses. The most common presenting clusters of symptoms can be used to classify probable and possible mTBI into subtypes, which can be used to develop targeted treatment strategies.[3] Headache is the most common postconcussion symptom reported by adults with a prevalence of 86%–96%.[4] Patients with headache-migraine concussion subtype (HCS) symptoms often complain of associated nausea, vomiting, and sensitivity to light and sound. Premorbid headache conditions place individuals at greater risk of postconcussion headaches.[3]

The oculomotor concussion subtype (OCS) presents with oculomotor and visual dysfunction. These dysfunctions may be detected by assessing saccades, smooth pursuit, convergence, and fixation. Oculomotor dysfunction is often found in association

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with vestibular symptoms. Patients presenting with this subtype report difficulty with visual activities (e.g., eye strain, photophobia, blurred or double vision, frontal headaches, pressure behind the eyes, vision-derived nausea, poor depth perception, difficulty tolerating visually complex environments, worsening of premorbid visual impairment).[3] Convergence insufficiency occurs in up to 65% of patients with concussion, smooth pursuit dysfunction affects approximately 60% of concussed patients, and saccadic dysfunction is present in about 30% of concussed patients.[5]

The vestibular concussion subtype (VCS) presents with at least one of the following symptoms: dizziness, fogginess, lightheadedness, nausea, vertigo, or disequilibrium. These symptoms are provoked by dynamic movement. Dysfunction may affect gait and balance. Patients with this concussion subtype often demonstrate concurrent neurocognitive defects and symptoms related to anxiety.[5] Dizziness affects about 67% of patients with concussion.[5]

There is a tremendous amount of literature reviewing concussion management; however, much of this literature includes studies of children with sports-related concussions. It is often said that children are not small adults. The converse is also true, adults are not large children. The objective of this manuscript is to perform a systematic review of the evidence for interventions used to manage headache-migraine, ocular, and vestibular postconcussion subtype symptoms in working-aged adults.

METHODS

A literature search was performed on December 29, 2020, in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. Clinical trials studying treatment outcomes of patients diagnosed with concussion or mild to moderate traumatic brain injury (TBI) were used to generate this systematic review. There were no outside sources of funding for this research project and institutional review board approval was not required.

Studies were identified by searching PubMed, OVID, Cochrane Central, PEDro, and OSTEMED, and using the Canadian Agency for Drugs and Technologies in Health grey literature checklist. The search was limited to English language publications. The dates of coverage for each database search were from the creation of the database through December 29, 2020. The following search strategy was used to search each database: ((Concussion OR mild traumatic brain injury OR postconcussion syndrome OR postconcussion symptoms) AND (vestibular OR ocular OR cognition OR anxiety OR depression OR headache OR fatigue) AND (management OR treatment)).

Eligibility assessment was performed in an unblinded standardized manner by a single reviewer. To be eligible for this systematic review, the considered study had to be a clinical trial; the subjects had to be human; the population had to be of working age (16−70 years); the study had to be published in English; and the outcomes had to be presented numerically with 95% confidence intervals (CIs), standard deviations, or standard errors.

The outcome measures of the intervention and control groups for each study were compared by calculating standardized mean differences (SMD) with 95% CIs. Grand means would have been calculated if more than one study of the same intervention had assessed the same outcome and had lacked significant heterogeneity.[6] Statistical analysis was performed using Microsoft Excel 360.

GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) was used to rate the overall quality of the evidence for risk of bias, inconsistency, indirectness, imprecision, publication bias, and magnitude of effect. The GRADE ratings of very low, low, moderate, or high-quality evidence reflect the extent to which one can be confident that the effect estimates are correct.[7] A mechanistic approach was used to minimize the risk of the single reviewer introducing bias during this process.

To ascertain the quality of eligible randomized controlled trials, the author used the National Institute for Health and Care Excellence (NICE) methodology checklist for reviewing randomized controlled trials (RCTs). The NICE methodology checklist is a tool used to qualitatively assess RCTs for risk of four types of bias: selection bias, performance bias, attrition bias, and detection bias.8 As there was only one reviewer, a quantifiable measure for determining risk of bias was incorporated into the NICE checklist. Each category of bias was initially assigned the value of one. One point was added for each "No" or "Unclear" answer. The remaining value was the quality measure for the given type of potential bias (4 = high risk, 3 = moderate-high risk, 2 = low-moderate risk, 1 = low risk). The quality measures were summed and then divided by four to generate the average risk of bias for each included RCT.

Joanna Briggs Institute (JBI) critical appraisal checklist for case series was used to assess the methodological quality of any case series meeting eligibility criteria.[9] The JBI critical appraisal tool for case series studies includes ten questions addressing the internal validity and risk of bias of case series designs, particularly confounding, selection, and information bias, in addition to the importance of clear reporting. Once again, as there was only one reviewer, a quantifiable measure for determining risk of bias was incorporated into the JBI checklist. Each case series began with an assigned value of one and a point was added for each negative response on the questionnaire. The final value was the quality measure for overall risk of potential bias (4 = high risk, 3 = moderate-high risk, 2 = low-moderate risk, 1 = low risk).

For both checklists, if the average risk of bias was between 1.0 and 2.0, the risk of within-study bias was deemed to be low. If the average risk of bias was between 2.01 and 3.0, the risk of within-study bias was considered serious. If the average risk of bias was between 3.01 and 4.0, the risk of within-study bias was determined to be very serious.

Inconsistency was considered when more than one study compared the same intervention and control using a similar outcome measure. Inconsistency was investigated using forest plots. To be consistent, each point estimate must rest within the 95% CIs of the comparable studies. If any point estimates fell outside the CIs, serious inconsistency was deemed to exist

among the considered studies. Very serious inconsistency was determined to exist when any of the CIs failed to overlap each of the other included CIs.

Indirectness exists when the study population differs from the population of interest; when the study intervention differs from the intervention of interest; when the study outcome differs from the outcome of interest; or when the interventions of interest are not tested head to head. If any one of these conditions were met, serious indirectness was noted. If two or more of these conditions were met, very serious indirectness was deemed to be present.

Serious imprecision was determined to be present when the 95% CI for the point estimate of effect of a study or group of studies crossed the null effect line. Serious imprecision was also considered to be present if a study's authors noted that the study was underpowered. Very serious imprecision existed when the CI crossed the null effect line and the contralateral clinically meaningful effect line.

Publication bias usually exists when a literature search fails to identify studies with negative outcomes. Publication bias was considered when more than one study compared the same intervention and control using a similar outcome measure and the included studies failed to present any negative findings. A funnel plot was chosen as the means of presenting this assessment.

Results of the analyses were used to generate an evidence profile table and summary of findings tables with forest plots.

RESULTS

The literature search identified 496 candidate studies. After removing duplicates, 352 studies remained. The titles and abstracts of the remaining studies were screened for eligibility and 343 studies were excluded. The full text of the remaining nine studies was assessed for eligibility and risk of bias. None of these studies was excluded. This left nine studies for qualitative and quantitative analysis (Figure 1). A summary of the interventions and controls from each of the studies is presented in Table 1 (see online version).

One study was found to be at high risk for selection bias. Two studies were at high risk for performance bias. The average risk of bias was determined to be severe for three of the studies. None of the studies was determined to have a very serious average risk of bias (Table 2) (see online version).

Studies examining headache-migraine symptom cluster subtype included four discrete interventions, four controls, and four intervention and control pairs, resulting in six measured outcomes. For oculomotor subtype outcomes, there were two unrelated interventions, two controls, two intervention and control pairs, and 11 outcomes. Under the vestibular subtype, there were two interventions, one control, and two intervention and control pairs, producing four measured outcomes. Table 2 is an evidence profile table that presents the bias assessment, quality assessment, and SMD results for each of the studies' outcome measures. No grand means were generated due to heterogeneity of injury to group allocation time, treatments, outcome measures, and timing of outcome measurement.

Synthesis of results

HEADACHE-MIGRAINE POSTCONCUSSION SYMPTOM CLUSTER SUBTYPE (FIGURE 2)

Frequency

Very low-quality evidence showed group cognitive behavioral therapy (CBT) designed to manage postconcussion headaches did not decrease the frequency of postconcussion headaches when compared to being on a waitlist [n = 71; SMD (95% CI) = 0.15 (-0.31–0.62)].[10]

Intensity (corresponding SCAT-5 symptoms: headache and "pressure in head")

Moderate-quality evidence disclosed group CBT increased outcome measures of headache intensity [n = 71; SMD (95% CI) = 0.62 (0.14−1.09)].10 Moderate-quality evidence suggested erenumab, a calcitonin gene-related peptide inhibitor, improved measures of headache intensity when measured at 12 weeks' post treatment initiation [n = 100; SMD (95% CI) = -0.67 (-0.95 to -0.38)].11 Low- and very-low–quality evidence determined hyperbaric oxygen therapy (HBOT) did not reduce measures of headache intensity at 2-year [n = 40; SMD (95% CI) = 0.49 (-0.15–1.12)] and 3-year [n = 14; SMD (95% CI) = 0.19 (-0.92–1.29)] follow-up evaluations relative to sham treatment.12 Moderate-quality evidence showed 22 weeks of multidisciplinary care (MDC) that included psychological interventions reduced measures of postconcussion headache intensity relative to usual care [n = 89; SMD (95% CI) = -0.58 (-1.01 to -0.16)].[13]

OCULAR POSTCONCUSSION SYMPTOM CLUSTER SUBTYPE (FIGURE 2)

Photosensitivity (corresponding SCAT-5 symptom: sensitivity to light)

Moderate-quality evidence suggested use of nonliquid crystal display (non-LCD) screens produced fewer photosensitivity symptoms [n = 58; SMD (95% CI) = -3.75 (-4.61 to -2.90)] and lower symptom severity [n = 58; SMD (95% CI) = -4.61 (-5.59 to -3.62)] than use of liquid crystal display (LCD) screens after a 30-minute reading task was performed by postconcussion subjects.[14]

Accommodation (corresponding SCAT-5 symptom: blurred vision)

Moderate-quality evidence showed oculomotor rehabilitation improved measures of postconcussion amplitude of accommodation [n = 24; SMD (95% CI) = 0.99 (0.14−1.84)] and accommodative facility [n = 24; SMD (95% CI) = 0.98 (0.13−1.83)] relative to sham rehabilitation.[15]

Convergence (corresponding SCAT-5 symptom: blurred vision)

Moderate-quality evidence also showed oculomotor rehabilitation improved postconcussion convergence insufficiency symptom score [n = 24; SMD (95% CI) = -2.55 (-3.62 to -1.47)], near point convergence break [n = 24; SMD (95% CI) = -1.04 (-1.89 to -0.19)], and near point convergence recovery [n = 24; SMD (95% CI) = -0.87 (-1.71 to -0.03)] relative to sham rehabilitation.[16] However, moderate-quality evidence determined

oculomotor rehabilitation did not improve postconcussion stereoacuity [n = 24; SMD (95% CI) = -0.717 (-1.54−0.11)].[16]

Oculomotor reading behaviors

Low-quality evidence revealed oculomotor rehabilitation did not improve measures of reading rate [n = 24; SMD (95% CI) = 0.59 (-0.23−1.40)], reading comprehension [n = 24; SMD (95% CI) = 0.23 (-0.57−1.03)], or grade level efficiency [n = 24; SMD (95% CI) = 0.46 (-0.35−1.27)] in postconcussion subjects.[17]

VESTIBULAR POSTCONCUSSION SYMPTOM CLUSTER SUBTYPE (FIGURE 2)

Balance (corresponding SCAT-5 symptom: poor balance/ coordination)

Low-quality evidence determined 22 weeks of MDC did not improve self-reported measures of balance in postconcussion subjects relative to usual care [n = 89; SMD (95% CI) = -0.40 (-0.82 to 0.02)].[13] Moderate-quality evidence determined 8 weeks of vestibular rehabilitation did not improve measures of postconcussion balance compared to usual care that included Epley and BBQ roll maneuvers for subjects with a positive Dix-Hallpike maneuver [n = 57; SMD (95% CI) = -0.39 (-0.92−0.13)].[18]

Vestibular symptoms (corresponding SCAT-5 symptom: dizziness)

Moderate-quality evidence suggested 22 weeks of MDC with a robust psychological component did improve measures of postconcussion vestibular symptoms compared to usual care [n = 89; SMD (95% CI) = -0.44 (-0.86 to -0.02)].13 Low-quality evidence disclosed vestibular rehabilitation did not improve measures of postconcussion vestibular symptoms relative to usual care that included Epley and BBQ roll maneuvers for subjects with a positive Dix-Hallpike maneuver [n = 63; SMD (95% CI) = -0.27 (-0.77−0.23)].[18]

FIGURE 1:

Literature search flow diagram.

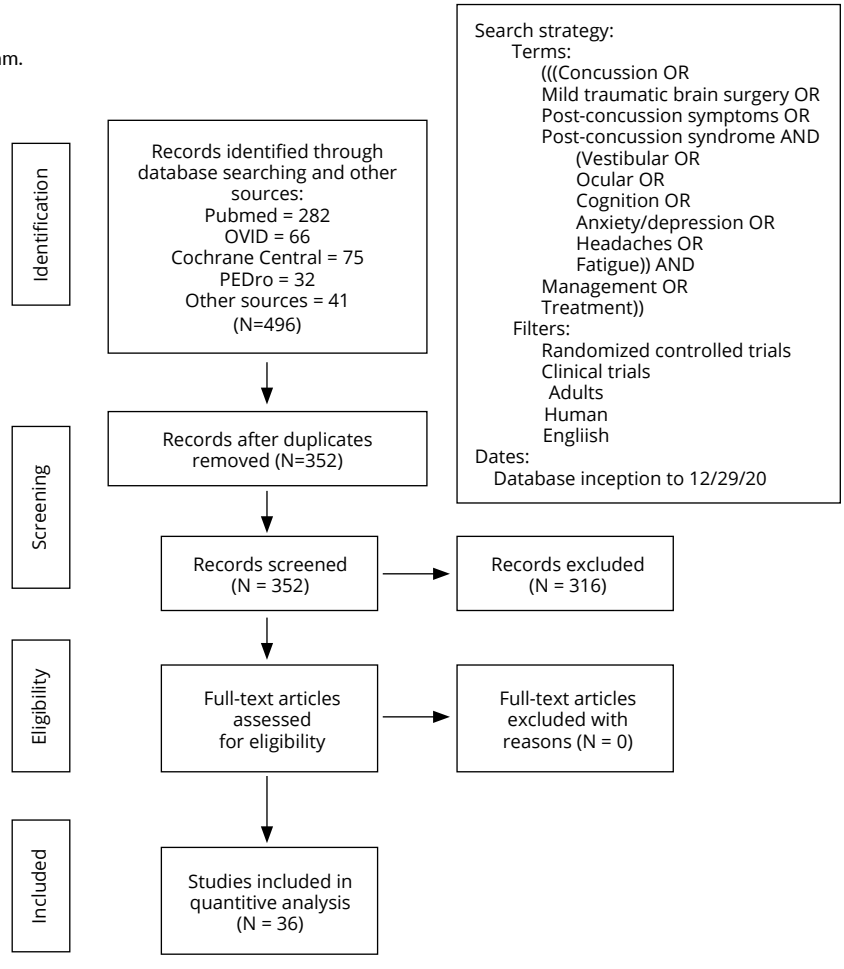

TABLE 1:
Summary of the studies meeting inclusion criteria.

AUTHOR (YEAR)	AGE	INJURY TO ALLOCATION TIME	INTERVENTION	CONTROL	COMMENTS
Ashina (2020)[11]	18 to 65 years	Mean of 59 months ± 54 months	Erenumab: 100 subjects received at least 1 dose of erenumab	Observational	Industry sponsored. Outcomes were measured at 12 weeks. 78 subjects reported at least 1 adverse event, the most common being constipation. 2 subjects experienced dizziness and worsening headache
Hart (2019)[12]	> 18 years	Not specified	HBOT: 40 chamber sessions at 1.5 atmospheres pressure with 100% oxygen over a 12-week period	Sham: 40 sessions consisting of room air at 1.2 atmospheres of pressure	This study is set apart by a 24-month and 36-month measurement of outcomes. Selection bias may have influenced the extended follow-up results, with the 24- and 36-month follow-up rates falling well below the 80% follow-up threshold that is proposed to be a threat to validity
Kjeldgaard (2014)[10]	18 to 65 years	Mean of 27 months	CBT (group): used a structured protocol for each weekly session. Week 1: introduction to the group and the diagnosis. Week 2: introduction to the cognitive model and the stress-pain connection, identification of stressors, and setting goals. Week 3: discussed memory problems and the connection to headaches. A breathing exercise was introduced as a relaxation technique. Week 4: reviewed memory and reading strategies, and management of energy. Progressive muscle relaxation was also taught. Week 5: introduction to the pain model and discussion of acceptance and behavior toward headache. A breathing exercise with body scan was presented. Week 6: reviewed acceptance of the present headache state and management of energy. Visualization of a pleasant place was taught as method of relaxation. Week 7: discussion of defining and identifying negative automatic thoughts (NAT). Week 8: introduced how to examine NAT and develop alternative more adaptive thoughts. Visualization problem solving also introduced. Week 9: discussion of integration and maintenance of new techniques and concepts		

TABLE 1 CONT.:
Summary of the studies meeting inclusion criteria.

AUTHOR (YEAR)	AGE	INJURY TO ALLOCATION TIME	INTERVENTION	CONTROL	COMMENTS
Kleffelgaard (2019)[18]	16 to 65 years	Mean of 3.5 months ± 2.1 months	Vestibular rehabilitation (group): twice weekly for 8 weeks. The intervention consisted of guidance, individually tailored exercises, a home exercise program, and an exercise diary. Exercises were Brandt-Daroff exercises for benign paroxysmal positional vertigo, habituation exercises for motion sensitivity and central posttraumatic vertigo, gaze-stabilization exercises for symptoms exhibited during eye-head coordination and reduced vestibulo-ocular reflex, and exercises for reduced balance, focusing on improving sensory integration. The home exercise program included 2 to 5 individually modified exercises and general physical activity	Usual care: did not receive any rehabilitation intervention in place of the group-based vestibular rehabilitation intervention. However, not to treat posttraumatic benign paroxysmal positional vertigo was deemed a conflict of research ethics, because of the strong existing evidence on the effect of canalith repositioning procedure. Therefore, patients with a positive Dix-Hallpike or roll test were treated with Epley and BBQ roll maneuvers	Outcomes were measured at 8 weeks. No adverse events of the intervention were registered
Mansur (2018)[14]	16 to 67 years	Not specified	Non-LCD screen	LCD screen	Randomized crossover design with outcomes measured before and after a 30-minute reading task on 2 consecutive days
Rytter (2019)[13]	18 to 65 years	> 6 months	Multidisciplinary care: psychoeducation, group therapy, psychological counselling, exercise training, and physiotherapeutic coaching. Length of the program was 22 weeks divided into 2 modules	Usual care: ranged from no treatment at all to referral to individual discipline-specific therapies	Usual care had a great degree of variability as to what treatments were offered, how much treatment was provided and at what intensity treatments were delivered. Given the complexity of the intervention, the study does not allow for one to determine whether the treatment effect is due to program intensity, interdisciplinary approach, accommodation of individual needs, or a combination of these factors. Nor does it allow one to ascertain the relative contributions of the individual treatment components

TABLE 1 CONT.:
Summary of the studies meeting inclusion criteria.

AUTHOR (YEAR)	AGE	INJURY TO ALLOCATION TIME	INTERVENTION	CONTROL	COMMENTS
Thiagarajan (2013)[16]	23 to 33 years	1 to 10 years	Oculomotor rehabilitation: twice per week, for a total of 6 weeks. At a session, each oculomotor component (version, vergence, and accommodation) was trained for 15 minutes, with 5-minute rest periods between each component. For this study only vergence training and related outcomes were presented	Sham training	Crossover, interventional, experimental design with subject blinded. Assessed convergence. Seriously underpowered
Thiagarajan (2014)[15]	23 to 33 years	1 to 10 years	Oculomotor rehabilitation: as described in Thiagarajan (2013). For this study, only the accommodative responsivity and related results were presented	Sham training	This is the second paper using data obtained from Thiagarajan (2013). Assessed accommodation. Crossover, interventional, experimental design with subject blinded. Seriously underpowered
Thiagarajan (2014)[17]	23 to 33 years	1 to 10 years	Oculomotor rehabilitation: as described in Thiagarajan (2013). For this study, only the reading-related oculomotor behavior and related results were presented	Sham training	This is the third paper using data obtained from Thiagarajan (2013). Assessed reading rate. Crossover, interventional, experimental design with subject blinded. Seriously underpowered

DISCUSSION

There is no high-quality evidence for treatment in postconcussion patients that meets inclusion criteria for this review. However, moderate-quality evidence from this systematic review has found two interventions that have shown promise for treating HCS symptoms and two interventions that show promise for treating OCS symptoms. No intervention was superior to Epley and BBQ roll maneuvers for VCS symptoms.

Rytter and colleagues compared MDC to usual treatment.[13] The injury to group allocation time for this trial was greater than 6 months. The intervention included psychoeducation, group therapy, psychological counselling, exercise training, and physiotherapeutic coaching for each subject. Usual-care treatment ranged from no treatment at all to referral to individual discipline-specific therapies.[13] Their results showed an improvement of HCS and VCS outcomes measures. The intervention in this trial was very structured, with each subject receiving each of the available interventions rather than receiving care as needed. The subjects in this trial were at least 6 months beyond their sustained head injury. This may have weeded out individuals who had spontaneous resolution of their symptoms. This suggests that early care provides little if any benefit for most patients who have sustained a concussion. This is interesting considering there is evidence suggesting psychological distress is common in the initial days following concussion. The degree of psychological distress correlates well with postconcussion syndrome symptom severity independent of injury severity and preexisting psychiatric disorders.[19]

Hyperbaric oxygen therapy (HBOT) is thought to treat TBI through generation of oxygen radicals, which facilitate production of neurotrophic growth factors and vascular endothelial growth factor, neural stem cell proliferation and mobilization, and modification of gene expression.[20] However, the findings of this review did not suggest a benefit for treating posttraumatic headache. The average risk of bias was found to be low for the included trial.

The intervention consisted of 40 chamber sessions at 1.5 atmospheres with 100% oxygen over a 12-week period. The intervention was compared to sham therapy involving 40 chamber sessions consisting of room air at 1.2 atmospheres. This result is disappointing; however, there is a great deal of debate regarding use of a sham control in HBOT research. The minimal elevated pressure a patient can sense is about 1.2 atmospheres, depending on the rate of change. This pressure can induce an elevation in tissue oxygenation of approximately 50% when the patient is breathing room air.[20] This is important to recognize because "sham" treatment under such conditions has been used as a "placebo" in experimental trials, when it may be a low-dose treatment. The results should not be generalized since the study recruited current or former military personnel who sustained head injuries in the line of duty. A larger proportion of these subjects may have experienced blast injuries, multiple TBIs, and posttraumatic stress disorder (PTSD) while also being skewed toward being younger and male without chronic medical conditions such as chronic obstructive pulmonary disease (COPD), diabetes, or coronary artery disease.

FIGURE 2:

Summary of findings for the headache-migraine postconcussion symptom cluster subtype, the oculomotor postconcussion symptom cluster subtype, and the vestibular postconcussion symptom cluster subtype. The solid vertical line is the null effect line. The dashed vertical lines are the minimal clinical effect lines. The side of the null effect line, indicative of a positive or negative effect, is dependent on the outcome measure. atm., atmospheres; SMD, standardized mean difference; CBT, cognitive behavioral therapy.

	Author (year)	Quality	Sample Size	SMD	Lower CI	Upper CI
Headache-Migraine						
CBT (group) vs Wait-list						
Headache frequency (26 weeks)	Kjeldgaard (2014)	Very Low	71	0.1528	-0.3135	0.6191
Headache intensity (26 weeks)	Kjeldgaard (2014)	Moderate	71	0.6158	0.1393	1.0923
Erenumab vs Baseline						
Headache intensity (12 weeks)	Ashina (2020)	Moderate	100	-0.6700	-0.9548	-0.3851
Hyperbaric Oxygen (1.5 atm) vs Sham						
Headache intensity (2 years)	Hart (2019)	Low	40	0.4890	-0.1470	1.1249
Headache intensity (3 years)	Hart (2019)	Very Low	14	0.1938	-0.9018	1.2893
Multidiciplinary Care vs Usual care						
Headache intensity (22 weeks)	Rytter (2019)	Moderate	89	-0.5810	-1.0052	-0.1568
Ocular	**Author (year)**	**Quality**	**Sample Size**	**SMD**	**Lower CI**	**Upper CI**
Non-LCD Screen vs LCD Screen						
Photosensitivity (Immediate)/SCAT-3 symptom severity	Mansur (2018)	Moderate	58	-4.6082	-5.5921	-3.6242
Photosensitivity (Immediate)/SCAT-3 No. of symptoms	Mansur (2018)	Moderate	58	-3.7547	-4.6101	-2.8992
Oculomotor Rehabilitation vs Sham						
Accommodation (15 weeks)/Amplitude of accommodation OU	Thiagarajan (2014)	Moderate	24	0.9932	0.1451	1.8412
Accommodation (15 weeks)/Accommodative facility OU	Thiagarajan (2014)	Moderate	24	0.9794	0.1326	1.8261
Convergence (15 weeks)/Convergence insufficiency symptom score	Thiagarajan (2014)	Moderate	24	-2.5456	-3.6221	-1.4691
Convergence (15 weeks)/Near point convergence break (cm)	Thiagarajan (2014)	Moderate	24	-1.0417	-1.8944	-0.189
Convergence (15 weeks)/Near point convergence Recovery (cm)	Thiagarajan (2014)	Moderate	24	-0.8694	-1.7066	-0.032
Convergence (15 weeks)/Stereoacuity (arc sec)	Thiagarajan (2014)	Moderate	24	-0.7173	-1.5428	0.1082
Reading (15 weeks)/Visagraph reading rate (wpm)	Thiagarajan (2014b)	Low	24	0.5872	-0.23	1.4045
Reading (15 weeks)/Visagraph comprehension (%)	Thiagarajan (2014b)	Low	24	0.2309	-0.5719	1.0337
Reading (15 weeks)/Visagraph comprehension (%)	Thiagarajan (2014b)	Low	24	0.457	-0.3535	1.2676
Vestibular	**Author (year)**	**Quality**	**Sample Size**	**SMD**	**Lower CI**	**Upper CI**
Multidisciplinary Care vs Usual Care						
Balance (22 weeks)	Rytter (2019)	Low	89	-0.396	-0.8156	0.0236
Vestibular symptoms (22weeks)	Rytter (2019)	Moderate	89	-0.4406	-0.8612	-0.0201
Vestibular Rehabilitation vs Usual Care						
Balance (8 weeks)	Kleffelgaard (2019)	Moderate	57	-0.3921	-0.9183	0.1341
Vestibular symptoms (8 weeks)	Kleffelgaard (2019)	Low	63	-0.2697	-0.7659	0.2264

TABLE 2:

GRADE evidence profile table of measured outcomes in the context of the postconcussion symptom cluster subtypes.

AUTHOR (YEAR)	COMPARISON (FOLLOW-UP)	MEASURE	DESIGN	TOTAL SUBJECTS	SELECTION BIAS	PERFORMANCE BIAS	ATTRITION	DETECTION BIAS
HEADACHE-MIGRAINE								
Headache Frequency								
Kjeldgaard (2014)[10]	CBT (group)vs waitlist (26 weeks)	Days/ 4 weeks	RCT	81	2	4	2	1
Headache Intensity								
Kjeldgaard (2014)[10]	CBT (group)vs waitlist (26 weeks	0-10 scale	RCT	81	2	4	2	1
Ashina (2020)[11]	Erenumab vs baseline (12 weeks)	HIT-6	CS	100				
Hart (2019)[12]	Hyperbaric oxygen vs sham (2 years)	MPQ-SF	RCT	40	2	2	1	1
Hart (2019)[12]	Hyperbaric oxygen vs sham (3 years)	MPQ-SF	RCT	14	2	2	1	1
Rytter (2019)[13]	Multidisciplinary care vs usual care (22 weeks)	HIT-6	RCT	89	2	3	2	2
OCULAR								
Accommodation								
Thiagara jan (2014)[15]	Oculomotor rehabilitation vs sham (15 weeks)	Amplitude	RC	24	1	2	1	3
Thiagara jan (2014)[15]	Oculomotor rehabilitation vs sham (15 weeks)	Facility OU	RC	24	1	2	1	3
Convergence								
Thiagara jan (2013)[16]	Oculomotor rehabilitation vs sham (15 weeks)	CISS	RC	24	1	2	1	3
Thiagara jan (2013)[16]	Oculomotor rehabilitation vs sham (15 weeks)	NPC Break	RC	24	1	2	1	3
Thiagara jan (2013)[16]	Oculomotor rehabilitation vs sham (15 weeks)	NPC Recovery	RC	24	1	2	1	3
Thiagara jan	Oculomotor rehabilitation	Stereo	RC	24	1	2	1	3
Photosensitivity								
Mansur (2018)[14]	Non-LCD screen vs LCD screen (Immediate)	SCAT-3 Symptom severity	RC	58	4	4	1	1
Mansur (2018)[14]	Non-LCD screen vs LCD screen (immediate)	SCAT-3 No. of symptoms	RC	58	4	4	1	1
Reading								
Thiagara jan (2014)[17]	Oculomotor rehabilitation vs sham (15 weeks)	Reading rate	RC	24	1	2	1	3
Thiagara jan (2014)[17]	Oculomotor rehabilitation vs sham (15 weeks)	Comp	RC	24	1	2	1	3
Thiagara jan (2014)[17]	Oculomotor rehabilitation vs sham (15 weeks)	GLE	RC	24	1	2	1	3

AVERAGE RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	INTERVENTION MEAN	INTERVENTION SD	CONTROL MEAN	CONTROL SD	QUALITY (GRADE)
HEADACHE-MIGRAINE									
Headache Frequency									
2.25	NA	None	Very Serious	NA	26.0 0	5.13	25.10	6.51	Very Low
2.25	NA	None	None	NA	6.34	1.69	5.10	2.27	Mod
1	NA	None	None	NA	57.00	8.20	61.60	5.20	Mod[b]
1.5	NA	Serious[a]	Serious	NA	13.2	9.79	8.80	7.78	Low
1.5	NA	Serious[a]	Very Serious	NA	9.00	15.15	6.40	9.01	Very Low
2	NA	None	None	NA	57.1	8.99	61.77	6.89	Mod
OCULAR									
Accommodation									
1.75	NA	None	None	NA	8.80	1.73	6.90	2.08	Mod
1.75	NA	None	None	NA	11.0	6.93	5.00	5.20	Mod
Convergence									
1.75	NA	None	None	NA	28.00	3.00	37.00	4.00	Mod
1.75	NA	None	None	NA	9.20	3.46	15.60	7.97	Mod
1.75	NA	None	None	NA	11.9	4.50	17.9	8.66	Mod
1.75	NA	None	Serious	NA	22.90	3.81	26.20	5.20	Mod
Photosensitivity									
2.5	NA	None	None	NA	3.00	1.50	12.50	2.50	Mod
2.5	NA	None	None	NA	0.30	0.40	2.00	0.50	MOD
Reading									
1.75	NA	None	Very Serious	NA	177.00	68.59	142.00	48.99	Low
1.75	NA	None	Very Serious	NA	85.00	14.70	81.00	19.60	Low
1.75	NA	None	Very Serious	NA	6.30	5.88	4.10	3.43	Low

TABLE 2. CONT'D.

GRADE evidence profile table of measured outcomes in the context of the postconcussion symptom cluster subtypes.

AUTHOR (YEAR)	COMPARISON (FOLLOW-UP)	MEASURE	DESIGN	TOTAL SUBJECTS	SELECTION BIAS	PERFORMANCE BIAS	ATTRITION	DETECTION BIAS
VESTIBULAR								
Balance								
Rytter (2019)[13]	Multidisciplinary care vs usual care (22 weeks)	UQ	RCT	89	2	3	2	2
Kleffelgaard (2019)[18]	Vestibular rehabilitation vs usual care (8 weeks)	BESS	RCT	57	1	3	1	2
Vestibular symptoms								
Rytter (2019)[13]	Multidisciplinary care vs usual care (22 weeks)	UQ	RCT	89	2	3	2	2
Kleffelgaard (2019)[18]	Vestibular rehabilitation vs usual care (8 weeks)	VSS	RCT	63	1	3	1	2

CISS, Convergence Insufficiency Symptom Score; GLE, Grade Level Efficiency; HIT-6, Headache Impact Test-6; MPQ-SF, McGill Pain Questionnaire-Short Form; NPC, Near Point Convergence; SCAT-3, Sport Concussion Assessment Tool-3; UQ, Unvalidated Questionnaire; VSS, Vertigo Symptom Scale.

[a]Graded down for indirectness. Military sample with high incidence of blast injuries and PTSD.

[b]Graded up for large effect.

The CBT study that met inclusion criteria for this systematic review was by Kjeldgaard and associates.[10] They compared a group-based CBT intervention to being on a waitlist with the primary outcome of headache. Their trial was the largest with 70 subjects. The mean injury to group allocation time was 27 months. The range was not provided. Their intervention used a structured protocol for nine weekly group-based CBT sessions (Table 1).[10] Their results suggest their program reduced measures of headache intensity. However, there was no improvement in measures of headache frequency, anxiety, depression, or somatization.

There was one randomized, single-blind, sham-controlled crossover trial with 24 subjects that generated three papers comparing oculomotor rehabilitation to sham rehabilitation.[15-17] Injury to allocation time was 1−10 years, and age of subjects was limited to 23−33 years. The outcomes were measured 15 weeks after the start of the trial. Oculomotor rehabilitation was performed twice per week, for a total of 6 weeks. At a session, each oculomotor component (version, vergence, and accommodation) was trained for 15 minutes, with 5-minute rest periods between components.[15-17] Their findings suggested that oculomotor rehabilitation improved measures of amplitude of accommodation and accommodative facility for postconcussion subjects.[15] They also determined that oculomotor rehabilitation improved convergence insufficiency symptom score, near point convergence break, and near point convergence recovery. However, they found no improvement in measures of stereoacuity.[16] The final paper generated from this study examined reading metrics. The study showed that oculomotor rehabilitation did not improve reading rate, reading comprehension, or grade level efficiency.[17] This finding may be related to a cognitive impairment rather than an oculomotor issue.

One study of mTBI patients compared effects of reading from a non-LCD computer screen to reading from and LCD computer screen. The study used a randomized crossover design with outcomes measured before and after a 30-minute reading task on two consecutive days. There were 58 subjects and the injury to group allocation time was not specified.[14] The results showed that the number of postreading symptoms and the severity of symptoms were lower after reading from the non-LCD screen than from the LCD screen. This study can also be interpreted to demonstrate that reading from LCD flat screens appears to worsen postconcussion symptoms. This may be due to postconcussion patients being particularly sensitive to the characteristics of light emitted from LCD screens.

One RCT compared group-based vestibular rehabilitation to usual care.[10] There were 63 subjects in this study, but only 57 completed the balance assessment. The mean time from injury to group allocation was 3.5 months. The intervention group received a group-based vestibular rehabilitation intervention

AVERAGE RISK OF BIAS	INCONSISTENCY	INDIRECTNESS	IMPRECISION	PUBLICATION BIAS	INTERVENTION MEAN	INTERVENTION SD	CONTROL MEAN	CONTROL SD	QUALITY (GRADE)
VESTIBULAR									
Balance									
2.25	NA	None	Serious	NA	3.31	2.64	4.34	25.6	Low
1.75	NA	None	Serious	NA	19.10	10.60	23.0	9.10	Mod
Accommodation									
2.25	NA	None	None	NA	3.51	2.79	4.68	2.51	Mod
1.75	NA	None	Very Serious	NA	6.70	6.00	8.40	6.60	Low

twice weekly for 8 weeks. The intervention consisted of guidance, individually tailored exercises, a home exercise program, and an exercise diary. The exercises were Brandt-Daroff exercises for benign paroxysmal positional vertigo, habituation exercises for motion sensitivity and central posttraumatic vertigo, gaze-stabilization exercises for symptoms exhibited during eye-head coordination and reduced vestibuloocular reflex, and exercises for reduced balance, focusing on improving sensory integration. The home exercise program included two to five individually modified exercises and general physical activity.[10] The control group did not receive any rehabilitation intervention in place of the group-based vestibular rehabilitation intervention. However, not to treat posttraumatic benign paroxysmal positional vertigo was deemed a conflict of research ethics because of the strong existing evidence on the effect of canalith repositioning procedures. Therefore, patients with a positive Dix-Hallpike or roll test were treated with Epley and BBQ roll maneuvers.[10] The results of this study suggested that vestibular rehabilitation did not improve measures of postconcussion anxiety, depression, balance, or vestibular symptoms relative to usual care. However, it is more accurate to state that vestibular rehabilitation provided to all VCS patients is not superior to simply performing canalith repositioning maneuvers for patients presenting with a positive Dix-Hallpike maneuver.

LIMITATIONS

Having a single reviewer and author was the most notable limitation of this systematic review. However, this limitation was mitigated by the author strictly adhering to predefined inclusion criteria and by using algorithmic application of the NICE methodology checklist for RCTs, the JBI critical appraisal checklist for case series, and the GRADE guidelines for rating the quality of evidence for systematic reviews.

Another limitation is the dearth of literature concerning the treatment of adults who sustained concussion unrelated to athletic activities. Generally, the studies meeting inclusion criteria were quite small. This led to relatively wide 95% CIs, which are reflected in the serious and very-serious concerns of imprecision for many of the included studies. An additional limitation lies in the heterogeneity of study designs, injury to group allocation times, outcome measures, and time of outcome measures. Consequently, the author was not able to calculate grand means for any of the studied interventions.

It was also disappointing that no studies examining the effectiveness of manual techniques, including osteopathic cranial manipulative medicine, met inclusion criteria for this review. However, there are case reports that provide anecdotal evidence of a possible therapeutic benefit of receiving osteopathic manipulative treatment, including osteopathic cranial manipulative medicine for adolescents[21,22] and adults[23,24] after sports-related concussions. There was also a retrospective chart review that suggested that osteopathic manipulative treatment was effective for reducing a substantial subset of sports-related postconcussion symptoms for young athletes, including those falling under the HCS, OCS, and VCS.[25]

CONCLUSIONS

To the author's knowledge, this is the most comprehensive review to date that considers the effectiveness of various treatments for HCS, OCS, and VCS symptoms in the working-aged population. Erenumab and psychologically centered MDC improved outcome measures falling under HCS. Oculomotor

rehabilitation and avoiding LCD screens were shown to improve OCS outcome measures. Outcome measures within the realm of VCS demonstrated improvement with psychologically centered MDC, and Epley and BBQ roll maneuvers for positive Dix-Hallpike assessments.

The results of this systematic review should be interpreted cautiously because of small sample sizes, serious risk of bias, imprecision, and indirectness of many of the reviewed studies. In the future, there is a need for high-quality RCTs with larger sample sizes to better demonstrate the effectiveness of the treatments for HCS, OCS, and VCS symptoms.

REFERENCES

1. McCrea M, Guskiewicz K, Randolph C, et al. Incidence, clinical course, and predictors of prolonged recovery time following sport-related concussion in high school and college athletes. *J Int Neuropsychol Soc*. 2013;19(1):22–33. doi:10.1017/S1355617712000872
2. Graff HJ, Siersma V, Møller A, et al. Labour market attachment after mild traumatic brain injury: nationwide cohort study with 5-year register follow-up in Denmark. *BMJ Open*. 2019;9(4):e026104. doi:10.1136/bmjopen-2018-026104
3. Lumba-Brown A, Teramoto M, Bloom OJ, et al. Concussion guidelines step 2: evidence for subtype classification. *Neurosurgery*. 2020;86(1):2–13. doi:10.1093/neuros/nyz332
4. Scorza KA, Cole W. Current concepts in concussion: initial evaluation and management. *Am Fam Physician*. 2019;99(7):426–434.
5. Zwibel H, Leder A, Yao S, Finn C. Concussion evaluation and management: an osteopathic perspective. *J Am Osteopath Assoc*. 2018;118(10):655–661. doi:10.7556/jaoa.2018.144
6. Thorlund K, Walter SD, Johnston BC, Furukawa TA, Guyatt GH. Pooling health-related quality of life outcomes in meta-analysis—a tutorial and review of methods for enhancing interpretability. *Res Synth Methods*. 2011;2(3):188–203. doi:10.1002/jrsm.46
7. Guyatt G, Oxman AD, Akl EA, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;64(4):383–394. doi:10.1016/j.jclinepi.2010.04.026
8. National Institute for Health and Care Excellence. How we develop NICE guidelines. Accessed January 15, 2021. http://www.nice.org.uk/guidelinesmanual
9. Munn Z, Barker TH, Moola S, et al. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evid Synth*. 2020;18(10):2127–2133. doi:10.11124/JBISRIR-D-19-00099
10. Kjeldgaard D, Forchhammer HB, Teasdale TW, Jensen RH. Cognitive behavioural treatment for the chronic post-traumatic headache patient: a randomized controlled trial. *J Headache Pain*. 2014;15(1):81. doi:10.1186/1129-2377-15-81
11. Ashina H, Iljazi A, Al-Khazali HM, et al. Efficacy, tolerability, and safety of erenumab for the preventive treatment of persistent post-traumatic headache attributed to mild traumatic brain injury: an open-label study. *J Headache Pain*. 2020;21(1):62. doi:10.1186/s10194-020-01136-z
12. Hart BB, Wilson SH, Churchill S, et al. Extended follow-up in a randomized trial of hyperbaric oxygen for persistent post-concussive symptoms. *Undersea Hyperb Med*. 2019;46(3):313–327.
13. Rytter HM, Westenbaek K, Henriksen H, Christiansen P, Humle F. Specialized interdisciplinary rehabilitation reduces persistent post-concussive symptoms: a randomized clinical trial. *Brain Inj*. 2019;33(3):266–281. doi:10.1080/02699052.2018.1552022
14. Mansur A, Hauer TM, Hussain MW, et al. A nonliquid crystal display screen computer for treatment of photosensitivity and computer screen intolerance in post-concussion syndrome. *J Neurotrauma*. 2018;35(16):1886–1894. doi:10.1089/neu.2017.5539
15. Thiagarajan P, Ciuffreda KJ. Effect of oculomotor rehabilitation on vergence responsivity in mild traumatic brain injury. *J Rehabil Res Dev*. 2013;50(9):1223–1240. doi:10.1682/JRRD.2012.12.0235
16. Thiagarajan P, Ciuffreda KJ. Effect of oculomotor rehabilitation on accommodative responsivity in mild traumatic brain injury. *J Rehabil Res Dev*. 2014;51(2):175–192. doi:10.1682/JRRD.2013.01.0027
17. Thiagarajan P, Ciuffreda KJ, Capo-Aponte JE, Ludlam DP, Kapoor N. Oculomotor neurorehabilitation for reading in mild traumatic brain injury (mTBI): an integrative approach. *Neurorehabilitation*, 2014;34(1):129–146. doi:10.3233/NRE-131025
18. Kleffelgaard I, Soberg HL, Tamber AL, et al. The effects of vestibular rehabilitation on dizziness and balance problems in patients after traumatic brain injury: a randomized controlled trial. *Clin Rehabil*. 2019;33(1):74–84. doi:10.1177/0269215518791274.
19. Silverberg ND, Iverson GL. Etiology of the post-concussion syndrome: physiogenesis and psychogenesis revisited. *NeuroRehabilitation*. 2011;29(4):317–329. doi:10.3233/NRE-2011-0708.
20. Marshall T, Henricks C. The next generation in brain recovery and neuroregeneration. *J Am Physicians Surg*. 2017;22(2):44–47.
21. Castillo I, Wolf K, Rakowsky A. Concussions and osteopathic manipulative treatment: an adolescent case presentation. *J Am Osteopath Assoc*. 2016;116(3):178–181. doi:10.7556/jaoa.2016.034
22. Yao SC. Applying osteopathic manipulative treatment to postconcussion syndrome: a case report. *AAO Journal*. 2019;29(4):25–29. doi:10.53702/2375-5717-29.4.25
23. Guernsey DT III, Leder A, Yao S. Resolution of concussion symptoms after osteopathic manipulative treatment: a case report. *J Am Osteopath Assoc*. 2016;116(3):e13–e17. doi:10.7556/jaoa.2016.036
24. Kratz SV. Case report: manual therapies promote resolution of persistent post-concussion symptoms in a 24-year-old athlete. *SAGE Open Medical Case Rep*. 2021;9:2050313X20952224. doi:10.1177/2050313X20952224
25. Chappell C, Dodge E, Dogbey GY. Assessing the immediate effect on osteopathic manipulation on sports related concussion symptoms. *Osteopath Fam Physician*. 2015;7(4):30–35.