

# The Effectiveness of Non-pharmacological Treatments for Vestibular and Oculomotor Deficits in Post-concussive Syndrome: a Protocol for a Systematic Review and Meta-analysis

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## Protocol

**Keywords:** Concussion, mild traumatic brain injury, post-concussive syndrome, vestibulo-ocular reflex, non-pharmacological treatment, vestibular deficits, oculomotor

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# Abstract

**Background:** Concussion is a form of mild traumatic brain injury (mTBI) that disrupts brain function. Although symptoms are mostly transient, recovery can be delayed and result in post-concussive syndrome (PCS). Vestibular and oculomotor deficits are among the most debilitating impairments associated with PCS. Non-pharmacological interventions provide treatment with limited side effects in comparison to pharmacological interventions. The aim of this review is to synthesise and evaluate the effectiveness of non-pharmacological interventions that have been used to target vestibular and oculomotor deficits in PCS.

**Methods:** Advanced searches will be conducted in electronic databases to identify articles eligible for inclusion. Studies employing non-pharmacological treatments for vestibular and/or oculomotor dysfunction in PCS will be included if they meet the eligibility criteria. Outcomes will be those pertaining to measures of oculomotor and vestibular function, in addition to adverse events. Meta-analysis will be undertaken using a random effects model followed by an assessment of clinical significance for each outcome as published in literature.

**Discussion:** While non-pharmacological interventions are used commonly to treat vestibular and oculomotor deficits in PCS, the effectiveness of these treatments is yet to be completely elucidated. The present review will explore the effectiveness of non-pharmacological treatments for vestibular and oculomotor deficits in PCS to inform practice and future research.

**Systematic review registration:** PROSPERO CRD42021254720

## Background

Traumatic brain injuries (TBIs) occur in approximately 69 million individuals each year (1). These injuries are induced by impulsive forces to the head, face, or neck, resulting in the disruption of brain function (2). According to a recent study, the most common causes of TBI were falls (47.2%), road accidents (13.7%), and blunt head trauma (15.4%) (3). However, there is a clear trend of under-reporting these types of injuries (4–8).

Approximately 70–90% of TBI cases are classified as mild traumatic brain injuries (mTBIs), or concussions (1, 4). Common symptoms associated with mTBI/concussion include headaches, dizziness, mood changes, disrupted sleep, light sensitivity, fatigue, and impaired concentration (9–12). While these acute symptoms resolve within days for most people, a subset of individuals do not recover fully and experience symptoms that persist beyond three months (12–15). These individuals are categorised as having 'post-concussive syndrome' (PCS) (12, 14, 16). It is estimated that 5–43% of individuals with mTBI/concussion experience post-concussive symptoms, with 22% diagnosed with PCS (17, 18). Given that there are currently no universal guidelines for diagnosing PCS, prevalence rates vary significantly across studies.

Vestibular and oculomotor deficits are well-documented in PCS (19–23). The vestibulo-ocular reflex (VOR) is a complex reflex that involves the vestibular and visual systems which functions to maintain balance and spatial orientation by stabilizing gaze during head movement (24). Case studies have shown VOR disruption in those with PCS (25, 26). Common complaints of vestibular dysfunction include dizziness, vertigo, nausea, fogginess, unsteady gait, and postural instability (20, 27). Symptoms associated with oculomotor dysfunction include double vision, difficulty tracking objects or focussing, motion sensitivity, photophobia, eye strain, and headache (20, 27). Importantly, evidence has shown that these symptoms of vestibulo-ocular dysfunction are strong predictors of delayed recovery in PCS (19, 20, 23).

Given the impacts of vestibular and oculomotor deficits in PCS, there is a need for effective treatment strategies. Both pharmacological and non-pharmacological interventions are available to treat VOR deficits. However, such pharmacological treatments are commonly associated with side effects, including sedation, drowsiness and dizziness (28). Further, while pharmacological treatments may alleviate concussive symptoms, research suggests such interventions may mask underlying neural dysfunction (20), delay central compensatory mechanisms and contribute to prolonged recovery (15). Others find inconclusive support of pharmacology in PCA (29). Non-pharmacological interventions are therefore recommended commonly. Here, we present a protocol for a systematic review and meta-analysis that aims to synthesis and evaluate the effectiveness of non-pharmacological interventions used to target vestibular and oculomotor functional deficits in PCS.

## Methods/design

This protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (30). The protocol has been registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42021254720).

## Review question

What is the effectiveness of non-pharmacological treatments for vestibular and oculomotor deficits in post-concussive syndrome?

## Search strategy

Searches will be conducted in MEDLINE, PubMed, Web of Science and Scopus. The clinical trials registries of the World Health Organisation ([who.int/ictrp/en](http://who.int/ictrp/en)), US ([ClinicalTrials.gov](http://ClinicalTrials.gov)), UK ([ukctg.nihr.ac.uk](http://ukctg.nihr.ac.uk)) and Australia/New Zealand ([anzctr.org.au](http://anzctr.org.au)) will also be searched. No limits will be placed upon language or location of publication. Keywords and medical subject headings (MeSH) related to PCS treatments for vestibular and oculomotor deficits will be used. The core search strategy, which will be modified depending upon the requirements of each database, is presented in Table 1.

**Table 1.** Advanced search strategy

(Concuss\* OR PCS OR post-concuss\* OR "mild traumatic brain injury" OR mTBI OR coup-countercoup OR "head injury" OR "head trauma" OR "second impact syndrome") AND (Vestibular ocular reflex OR vestibular OR VRT OR gaze OR stabilisation OR exercise OR repositioning OR oculomotor OR Physical Therapy OR habituation OR postural OR balance OR stimulation OR TMS OR rTMS OR tACS OR tDCS OR ECS OR TBS).

## Other resources

Google Scholar will be searched using derivations of "vestibular", "oculomotor", and "post-concussion" for additional studies. Due to the large quantity of paper retrieved through Google Scholar searches, only the first 100 articles for each search will be screened for relevance. The reference lists of all relevant articles will be analysed to identify additional trials. Studies from these sources satisfying the eligibility criteria will be included in the systematic review.

## Eligibility criteria

### Types of participants

No restrictions will be placed upon participant age or gender. Only populations with post-concussion syndrome (PCS) will be eligible for inclusion. For this review, PCS defined as any number of post-concussive symptoms persisting for greater than 3 months after a mTBI/concussion (12, 14, 16).

## Inclusion criteria

1. Full-text articles
2. Randomised and non-randomised controlled trials, and crossover study designs
3. Only studies employing non-pharmacological treatments for vestibular and/or oculomotor dysfunction in PCS will be included

## Exclusion criteria

1. Grey literature (e.g., government reports, conference abstracts)
2. Studies investigating treatment of PCS for symptoms not associated with vestibular and/or oculomotor dysfunction
3. Studies investigating pharmacological interventions for PCS symptoms associated with vestibular and/or oculomotor dysfunction

# Interventions

Studies of non-pharmacological treatment for vestibular and oculomotor functional outcomes will be included. Such interventions may include, but are not limited to, vestibular rehabilitation, optokinetic stimulation and VOR exercises. These interventions will be compared to control group comparisons that may be either no treatment or under sham conditions.

## Outcomes

Primary outcomes will include measures of oculomotor and vestibular function. Assessments of oculomotor function will include versional eye movements (pursuit, saccades), vergence eye movements (convergence and divergence), and visual-fixation movements (gaze holding, optokinetic responses, VOR). Assessments of vestibular function and balance will include the Fukuda Step test, functional balance tests, force displacement tests with eyes open and/or closed, as well as subjective reports of balance disruption and vertigo. A secondary outcome will include any information provided on adverse events associated with the non-pharmacological interventions for PCS.

## Data management

Search results will be exported to a citation software (EndNote X9) for automated removal of duplicated articles. Duplicates overlooked by the programme will be manually removed. After the removal of duplicates, two independent reviewers will screen remaining articles by title and abstract for relevance using Covidence software (<https://www.covidence.org/>). These reviewers will subsequently retrieve full-text versions of successfully screened articles and assess these according to the eligibility criteria. An additional reviewer will be consulted where any uncertainty or disagreement regarding the eligibility of studies arises. This selection process will be piloted by the two reviewers prior to commencement of the study screening process. Excluded studies and reasons for exclusions will be recorded.

## Data extraction

Two reviewers will independently extract data from the final list of included studies using a standardised data extraction form, after which the data will be entered into an electronic spreadsheet. The following data, where applicable, will be extracted: study details (author, year, sample size, study design, date of publication, country of publication), participant characteristics (sample size, diagnosis/symptoms, age, sex), treatment characteristics, outcome measures, treatment effects (mean and SD).

## Assessment of methodological quality

The methodological quality of each study will be assessed using the Physiotherapy Evidence Database (PEDro) scale (31). This tool demonstrates high inter-rater reliability and assesses the internal and external validity (31). Additionally, the PEDro scale has been identified as more relevant than other tools commonly used to appraise rehabilitation-based intervention studies (32). Items will be scored as either present (1) or absent (0), and a score out of 10 will be achieved via summation. Disagreements will be

resolved by discussion. Studies scoring six or more will be classified as high quality, and studies scoring five or less will be classified as low quality.

If sufficient data are available for meta-analysis, the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) tool will be used to assess the certainty and quality of evidence (33). Outcomes will be downgraded if the included studies have a significant risk of bias, considerable heterogeneity of results, do not meet the PICO criteria, contain a low sample size, or if confidence intervals (CI) cross the minimal clinically important difference (MCID).

## **Strategy for data synthesis**

Standardized mean differences (SMD) between end-scores will be calculated. If studies report baseline differences between active and control groups, relative changes from baseline will be calculated. Meta-analyses will be undertaken using a random effects model if data are available from at least two studies. A p-value of  $< 0.05$  will be deemed statistically significant. Clinical significance will be assessed by comparing the results of the meta-analysis to the minimal clinical important difference (MCID) for each outcome as published in the literature. The impact of heterogeneity will be calculated using the  $I^2$  statistic and interpreted as follows: 0%-40% may be unimportant; 30%-60% may represent moderate heterogeneity; 50%-90% may represent substantial heterogeneity; and 75%-100% represents considerable heterogeneity (34). Separate meta-analyses will be performed for each intervention. If insufficient data is available, data will be synthesized descriptively.

## **Discussion**

To our knowledge, this review will be the first to systematically explore the effectiveness of non-pharmacological treatments for vestibular and oculomotor deficits in PCS. This research may establish support for the discovery and optimization of treatments for targeted use in PCS populations. The review will also facilitate further research opportunities in this area.

## **Limitations**

Limiting data to full-text published articles may introduce bias through exclusion of data in grey literature. Given that studies with desirable or significant results are more likely to be granted publication, a 'publication bias' may increase estimations of reliable estimates (35).

## **Ethics and dissemination**

This review does not require ethical approval. Results of this review will be presented at scientific meetings and published in peer-reviewed journals. All publications and presentations related to the study will be authorised and reviewed by the study investigators.

## **Review status**

The reviewers have commenced searching relevant studies on the electronic databases. This review is expected to be completed by March 2022.

## Abbreviations

mTBI: mild traumatic brain injury

PCS: post-concussive syndrome

VOR: vestibulo-ocular reflex

PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analyses

## Declarations

*Ethics approval and consent to participate*

This review does not require ethical approval.

*Consent for publication*

All authors consent to the publication of this manuscript.

*Availability of data and material*

*Competing interests*

The authors declare that they have no competing interests.

*Funding*

There is no funding to declare.

*Authors' contributions*

SRS is the guarantor of the review protocol and wrote the draft protocol for the systematic review. All authors, SRS, RC, SJS, and CJB, contributed equally to the design, writing, and editing of the study protocol. All authors agree to be accountable for all aspects of the work to ensure the accuracy and integrity of the work are appropriately investigated and resolved.

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