

# BMJ Open Effectiveness of non-pharmacological treatments for vestibular and oculomotor dysfunction in patients with persistent post-concussive symptoms: protocol for a systematic review and meta-analysis

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## ABSTRACT

**Introduction** Concussion is a form of mild traumatic brain injury that disrupts brain function. Although symptoms are mostly transient, recovery can be delayed and result in persistent postconcussive symptoms (PPCS). Vestibular and oculomotor dysfunction are among the most debilitating impairments associated with PPCS. However, pharmacological interventions for these impairments are associated with deleterious side effects. Accordingly, increasing research has examined the utility of non-pharmacological interventions for PPCS. The aim of this review is to synthesise and evaluate the effectiveness of non-pharmacological interventions for the treatment of vestibular and oculomotor dysfunction for patients with PPCS.

**Methods and analysis** Systematic searches of MEDLINE, PubMed, Web of Science and Scopus will identify randomised controlled trials employing non-pharmacological treatments for vestibular and/or oculomotor dysfunction for PPCS. Such interventions may include, but are not limited to, vestibular rehabilitation, optokinetic stimulation and vestibulo-ocular reflex exercises. Assessments of oculomotor function will include versional eye movements, vergence eye movements, visual-fixation movements and accommodation response. Assessments of vestibular function will include the Fukuda Step test, functional balance tests, force displacement tests, and subjective reports of balance disruption or vertigo. Where appropriate, meta-analyses of standardised mean differences will be conducted using a random effects model for continuous outcomes. For dichotomous outcomes (improved vs not improved following treatment), effects will be expressed as relative risk. The impact of heterogeneity will be calculated using the  $I^2$  statistic. The Physiotherapy Evidence Database scale will be used to determine the methodological quality of individual studies and Grading of Recommendations, Assessment, Development and Evaluations used to assess the certainty and quality of evidence for each outcome.

**Ethics and dissemination** Ethical approval is not required for this review. Findings will be disseminated through peer-reviewed publications and conference presentations.

**PROSPERO registration number** CRD42021254720.

## STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ This systematic review addresses a gap in the current evidence-base by evaluating the effectiveness of non-pharmacological treatments for vestibular and oculomotor dysfunction in patients with persistent postconcussive symptoms.
- ⇒ This review will be conducted using rigorous methodology in accordance with the Cochrane handbook and the results will be reported as stated by Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols statement.
- ⇒ The Grading of Recommendations, Assessment, Development and Evaluations system will be used to ascertain the strength of the evidence base for each outcome.
- ⇒ This review is limited to evidence from randomised control trials.
- ⇒ Non-English electronic databases will not be searched, which may introduce language bias during analyses.

## BACKGROUND

A concussion, or mild traumatic brain injury (mTBI), is the most common form of traumatic brain injury.<sup>1 2</sup> These injuries are induced by impulsive forces to the head, face or neck, resulting in the disruption of brain function.<sup>3</sup> Common symptoms associated with a concussion include headaches, dizziness, mood changes, light sensitivity, fatigue and impaired concentration.<sup>4-7</sup> While these acute symptoms resolve within days for most people, a subset of individuals do not recover fully and experience symptoms that persist beyond 3 months.<sup>7-10</sup> These individuals are categorised as having ‘persistent postconcussive symptoms’ (PPCS).<sup>7 9 11</sup> It is estimated that 5%–43% of individuals with concussion experience postconcussive symptoms, with 22% presenting with three or more persistent symptoms.<sup>12 13</sup> Given that there are currently

no universal guidelines for diagnosing PPCS, prevalence rates vary significantly across studies.

Vestibular and oculomotor dysfunction are well-documented in patients with PPCS.<sup>14–18</sup> The vestibulo-ocular reflex (VOR) is a complex reflex that serves to maintain balance and spatial orientation by stabilising the gaze during head movement.<sup>19</sup> Case studies have shown VOR disruption in those with PPCS.<sup>20–21</sup> Common complaints of vestibular dysfunction include dizziness, vertigo, nausea, fogginess, unsteady gait and postural instability.<sup>15–22</sup> The most common oculomotor disorders following a concussion are convergence insufficiency (affecting the ability of eyes to work together to clearly see nearby objects) and accommodative insufficiency (difficulty when focussing on a nearby object).<sup>23</sup> Symptoms associated with oculomotor dysfunction include difficulty tracking objects, motion sensitivity, eye strain or eye fatigue for near vision, and headache.<sup>15–22</sup> Importantly, evidence has shown that these symptoms of vestibular and oculomotor dysfunction are strong predictors of delayed recovery for patients with PPCS.<sup>14–15–18</sup>

Given the impacts of vestibular and oculomotor dysfunction in patients with PPCS, there is a need for effective treatment strategies. Both pharmacological and non-pharmacological interventions are available to treat VOR dysfunction. However, pharmacological treatments have been associated with side effects in up to 16.9% of participants, including sedation, drowsiness and dizziness.<sup>24–28</sup> Further, while pharmacological treatments may alleviate concussive symptoms, research suggests such interventions may mask underlying neural dysfunction,<sup>15</sup> delay central compensatory mechanisms and contribute to delayed recovery.<sup>10</sup> Non-pharmacological interventions are therefore recommended commonly.<sup>10</sup>

Non-pharmacological treatments based on individual disciplines (eg, oculomotor vision treatment or vestibular rehabilitation) have shown mild to moderate effectiveness in treating specific symptoms in patients with PPCS.<sup>29</sup> Other studies have supported interdisciplinary collaboration for patients in this population, such as combining non-invasive brain stimulation with vestibular rehabilitation.<sup>30–31</sup> A previous review by Rytter *et al.*<sup>29</sup> on non-pharmacological treatments for patients with PPCS synthesised the effectiveness of interdisciplinary rehabilitation. While the researchers found studies with positive results, the review excluded younger populations.<sup>29</sup> Given that younger age groups are prone to develop PPCS,<sup>32–33</sup> informative studies in this population may have been overlooked. Further, the previous review was conducted on generalised symptoms of PPCS rather than focussing on treatments for specific symptoms. These exclusions may have limited the results of the search strategy and subsequent analysis of their findings. Further investigations of non-pharmacological treatments targeting symptoms such as vestibular and oculomotor dysfunction in the PPCS population is warranted. Novel therapies such as non-invasive brain stimulation have yet to be synthesised in this field. This study presents a protocol for a

systematic review and meta-analysis that aims to synthesise and evaluate the effectiveness of non-pharmacological interventions for the treatment of vestibular and oculomotor dysfunction in patients presenting with PPCS.

## METHODS

### Protocol development and registration

This protocol was prepared in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols.<sup>34</sup> The protocol has been registered with the International Prospective Register of Systematic Reviews. The Cochrane Handbook of Systematic Reviews will also be used to guide the completion of this review.<sup>35</sup>

### Review question

What is the effectiveness of non-pharmacological interventions for the treatment of symptoms associated with vestibular and oculomotor dysfunction in patients with postconcussive symptoms compared with sham treatment or control?

### Information sources and search strategy

Searches will be conducted in MEDLINE, PubMed, Web of Science and Scopus from database inception. No limits will be placed on language or location of publication. Keywords and Medical Subject Headings related to PPCS treatments for vestibular and oculomotor dysfunction will be used where possible. The core search strategy, which will be modified as needed for each database, is presented in [box 1](#). This core strategy was developed for PubMed and approved by a librarian, experienced in reviews of biomedical literature.

### Other resources

The clinical trials registries of the WHO ([who.int/ictrp/en](http://who.int/ictrp/en)), USA (ClinicalTrials.gov), UK ([ukctg.nihr.ac.uk](http://ukctg.nihr.ac.uk)) and Australia/New Zealand ([anzctr.org.au](http://anzctr.org.au)) will be searched. Google Scholar will also be searched using derivations of “vestibular”, “oculomotor” and “post-concussion” for additional studies. Due to the large number of papers retrieved through Google Scholar searches, only the first

#### Box 1 Advanced search strategy

((Concuss\* OR “PCS” OR “PPCS” OR post-concuss\* OR “mild traumatic brain injury” OR mTBI OR coup-counter coup OR “head injury” OR “head trauma”) AND (exercise OR repositioning OR “physical therapy” OR habituation OR “brain stimulation” OR “magnetic stimulation” OR “transcranial” OR “theta burst” OR “tDCS” OR “tACS” OR “TBS” OR “rTMS” OR “NIBS” OR videonystagmography OR “VNG” OR stimulation OR cortical) AND (“Vestibular ocular reflex” OR “VOR” OR vestibular OR oculomotor OR “VRT” OR gaze OR stabilis\* OR stabiliz\* OR balance OR postur\* OR vergence OR pursuit OR vertigo OR saccades OR accommodation OR optokinetic OR Fukuda OR fixation) AND (“vision therapy” OR “orthoptic” OR “visual training” OR “oculomotor training” OR “oculomotor rehabilitation”))

**Table 1** Oculomotor assessment outcomes

| Oculomotor assessments                                                | Description of assessment                                                                                                                                                      | Unit of measure                                                                                                                                                                                                                                         |
|-----------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Versional (pursuit, saccades)                                         |                                                                                                                                                                                |                                                                                                                                                                                                                                                         |
| Smooth pursuit                                                        | Measures smooth eye movement where eyes maintain fixation on a moving target                                                                                                   | Speed of eye movement tracking (metres/second or degrees/second), pursuit gain (ratio of eye velocity to target velocity)                                                                                                                               |
| Saccades (horizontal/vertical)                                        | Measures rapid eye movements that shifts the centre of gaze from one part of the visual field to another, primarily toward stationary targets                                  | Latency between target movement and eye movement (milliseconds), velocity of eye movement (metres/second or degrees/second), distance between target and performed movement (millimetres), accuracy of eye movement distance relative to the target (%) |
| King-Devick                                                           | Measures the speed of rapid number naming (reading aloud single-digit numbers from three test cards)—a measurement of saccadic movements                                       | Speed of rapid number naming (score 1–15)                                                                                                                                                                                                               |
| Vergence (convergence, divergence)                                    |                                                                                                                                                                                |                                                                                                                                                                                                                                                         |
| Convergence (near point)                                              | The simultaneous inward movement of both eyes toward each other when viewing an object moving towards the viewer                                                               | Distance at which both eyes can focus on the target object without double vision (centimetres) or loss of focus                                                                                                                                         |
| Divergence                                                            | The simultaneous outward movement of both eyes away from each other when viewing an object moving away from the viewer                                                         | Distance at which both eyes can focus on the target object without double vision (centimetres) or loss of focus                                                                                                                                         |
| SCAT5                                                                 | A concussion assessment tool that encompasses a range of measures including symptom evaluation, cognitive and neurological screening                                           | Outcomes on the presence or absence of blurred vision during eye movement side-to-side and up-and-down (found in the neurological screening section) will be extracted                                                                                  |
| Visual-fixation movements                                             |                                                                                                                                                                                |                                                                                                                                                                                                                                                         |
| Optokinetic nystagmus                                                 | The involuntary, side-to-side eye movements that allow the eyes to maintain fixation on a visual target as it moves past an observer (eg, viewing trees while in a moving car) | Velocity of nystagmus (metres/second or degrees/second), OKN performance gain (ratio of eye tracking velocity to target velocity)                                                                                                                       |
| Accommodation response                                                |                                                                                                                                                                                |                                                                                                                                                                                                                                                         |
| Accommodation                                                         | The process that allows, and maintains, precise focus of an object of interest                                                                                                 | The distance at which an eye can focus on an object (centimetres)                                                                                                                                                                                       |
| OKN, optokinetic nystagmus; SCAT5, Sports Concussion Assessment Tool. |                                                                                                                                                                                |                                                                                                                                                                                                                                                         |

100 articles for each search will be screened for relevance. The reference lists of all full-text articles included in the review will be analysed to identify additional trials. Only peer-reviewed studies from these sources satisfying the eligibility criteria will be included in the systematic review. Where data cannot be extracted from the studies themselves, attempts to contact study authors for primary data will be made. Authors will be contacted two times, 1 week apart. If no response is received in this timeframe, the data will be considered irretrievable.

### Eligibility criteria

Only peer-reviewed randomised controlled trials (RCTs) (available as full-text) employing non-pharmacological interventions for the treatment of vestibular and/or oculomotor dysfunction for patients with PPCS will be included. Concussion is

defined as temporary unconsciousness or confusion caused when a forceful impact on the head, face or neck alters brain function.<sup>36</sup> For this review, PPCS is defined as the persistence of postconcussive symptoms for greater than 3 months after a concussion.<sup>79 11</sup> No restrictions will be placed on participant age or gender. Only RCTs will be included in this review.

Studies of non-pharmacological treatment for vestibular and oculomotor outcomes will be included. A non-pharmacological treatment refers to an intervention where pharmaceutical medications are not considered part of the treatment.<sup>37</sup> Such interventions may include, but are not limited to, vestibular rehabilitation, optokinetic stimulation and VOR exercises. These interventions will be compared with control groups that may be either no treatment or sham conditions. Interventions that have

**Table 2** Vestibular assessment outcomes

| Assessment                                | Description of assessment                                                                                                                                          | Unit of measure                                                                                                                                                                       |
|-------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Posturography                             | Measures upright posture, balance and sense of equilibrium by standing on a force platform                                                                         | Shift in centre of pressure will be used to calculate distance (millimetres), sway (millimetres/second), velocity (millimetres/second) in anterior-posterior/medial-lateral direction |
| Fukuda step test                          | Used to determine if there is unilateral vestibular weakness: subject with eyes closed and arms stretched out, stepping in place                                   | Degree of rotation (from baseline or zero degrees)                                                                                                                                    |
| SCAT5                                     | A concussion assessment tool that encompasses a wide range of measures including symptom evaluation, cognitive screening, neurological screening and memory recall | Outcomes on the balance examination as 'number of errors' (found in the neurological screening section) will be extracted                                                             |
| SCAT5, Sports Concussion Assessment Tool. |                                                                                                                                                                    |                                                                                                                                                                                       |

been delivered standalone or in combination with other interventions will also be included. Studies that include participants taking pharmacological treatments that may influence vestibular or oculomotor outcomes, such as gabapentin or memantine (treatments for abnormal eye movements)<sup>38</sup> or vestibular suppressants (such as clonazepam and other benzodiazepines),<sup>39</sup> will be excluded from this review.

Primary outcomes will include measures of oculomotor and vestibular function. Outcomes that assess both constructs concurrently will also be analysed. Assessments of oculomotor function will include analyses of (i) versional eye movements (pursuit, saccades), (ii) vergence eye movements (convergence and divergence), (iii) visual-fixation movements (gaze holding, optokinetic responses, VORs) and (iv) accommodative response. Measurement outcomes of oculomotor function are listed in [table 1](#). Studies presenting continuous data (amplitude, duration, peak velocity and accuracy of eye movements) and

dichotomous data ('improved' or 'not improved' following treatment) will be included.

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. Measurement outcomes of vestibular function are listed in [table 2](#). Studies presenting continuous data (amplitude, duration, error count) and dichotomous data ('improved' or 'not improved' following treatment) will be included.

Assessments of combined vestibulo-oculomotor function will include VORs and vestibular/ocular-motor screening with inclusion of continuous (velocity, accuracy) and dichotomous ('improved' or 'not improved') data. Measurement outcomes of vestibulo-oculomotor function are listed in [table 3](#). A secondary outcome will include any information provided on adverse events associated with the non-pharmacological interventions for PPCS.

**Table 3** Combined vestibulo-oculomotor assessment outcomes

| Assessment                                                             | Description of assessment                                                                                                                                       | Unit of measure                                                                                                                                                                                                                    |
|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gaze stability                                                         | Ability to maintain a steady gaze on an object while the head is moving                                                                                         | Most rapid head movement velocity where visual acuity is maintained (degrees/second)                                                                                                                                               |
| VOMS                                                                   | Subjective measures comparing symptoms at baseline to symptoms after testing smooth pursuits, saccades, convergence, VOR and visual motion sensitivity          | Self-reported measures: headache, dizziness, nausea, brain fog                                                                                                                                                                     |
| Head impulse testing                                                   | Assesses VOR function with eyes fixed on a target while examiner rotates the head                                                                               | Presence/absence of compensatory saccade back to target after head rotation, or video capture (degrees/second)                                                                                                                     |
| Rotational chair test                                                  | Eye movements are monitored during a series of tests using videonystagmography goggles while a person is situated in a computerised chair that changes position | Eye movements in response to various head angular accelerations during rotational chair test (degrees/second), nystagmus measured as slow-phase velocity (degrees/second), VOR suppression (% of gain reduction or degrees/second) |
| VOMS, vestibular/ocular-motor screening; VOR, vestibulo-ocular reflex. |                                                                                                                                                                 |                                                                                                                                                                                                                                    |

## Data management and extraction

The Cochrane Data Collection Form for Intervention Reviews<sup>40</sup> will be used to extract study characteristics and outcome data. This will include extraction of the following data: study details (author, year, sample size, study design, date of publication, country of publication), participant characteristics (sample size, diagnosis/symptoms, age, sex), treatment characteristics (modality, duration, number of sessions), outcome measures, treatment effects (mean and SD). Two review authors will pilot the form on a randomly selected subset of 10% of included studies.<sup>35</sup> Pilot testing of the forms will include a computation of the reviewers' reliability. Reviewers will extract data independently and in duplicate from each eligible study.

Search results will be exported to EndNote citation software (EndNote X9) for automated removal of duplicates. Duplicates overlooked by the program will be manually removed. After removal of duplicates, two independent reviewers will screen the remaining articles by title and abstract for relevance using Covidence software (<https://www.covidence.org/>) in accordance with the prespecified 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.

## Assessment of methodological and reporting quality

The methodological quality of each RCT will be assessed using the Physiotherapy Evidence Database (PEDro) scale.<sup>41</sup> This tool demonstrates high inter-rater reliability and assesses internal and external validity.<sup>41</sup> Additionally, the PEDro scale has been identified as more relevant than other tools commonly used to appraise rehabilitation-based intervention studies.<sup>42</sup> 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 6 or more will be classified as high quality, studies scoring 4 or 5 will be considered moderate quality and studies scoring less than 3 will be classified as low quality.<sup>41</sup>

The reporting quality of each RCT will be assessed using the Consolidated Standards of Reporting Trials guidelines.<sup>43</sup> These guidelines offer a standard way for authors to prepare reports of trial findings, facilitating their complete and transparent reporting, and aiding their critical appraisal and interpretation.<sup>43</sup>

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<sup>44</sup> in accordance with the guidelines provided in the Cochrane Handbook of Systematic Reviews.<sup>35</sup> The GRADE system uses the following criteria for assigning 'grades' of evidence:

- High: the authors are very confident that the true effect lies close to that of the estimate of the effect.

- Moderate: the authors are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of effect.
- Low: the authors have limited confidence in the effect estimate; the true effect may be substantially different from the estimate of the effect.
- Very low: the authors have little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

To ensure consistency of GRADE judgements the following criteria will be applied to each domain equally for all key comparisons:

- Limitations of studies: downgrade if less than 75% of included studies are at low risk of bias according to the PEDro checklist.
- Inconsistency: downgrade if heterogeneity is significant ( $p < 0.05$ ) and the  $I^2$  value is more than 50%.
- Indirectness: downgrade if any of the participants were outside the target group.
- Imprecision: downgrade if there were fewer than 400 participants for continuous data, fewer than 300 events for dichotomous data<sup>44</sup> or if CIs or SD were not reported across all studies.
- Publication bias: downgrade if there is direct evidence of publication bias.

If insufficient data is available for meta-analysis, the GRADE criteria will be modified for a narrative synthesis in accordance with the guidelines presented by Murad *et al.*<sup>45</sup> The potential influence of publication bias will be evaluated using Begg's funnel plot.<sup>46</sup>

## Data synthesis

For continuous data, standardised mean differences between end-scores will be calculated. If studies report baseline differences between active and control groups, relative changes from baseline will be calculated. If data are available from at least two studies, meta-analyses will be performed using the software provided by the Cochrane Collaboration, Review Manager (RevMan V.5.4.1).<sup>47</sup> A random-effects model will be used as methodological heterogeneity is inevitable in practitioner-administered interventions.<sup>48</sup> For dichotomous data ('improved' or 'not improved' following treatment), effect measures will be expressed as relative risk.<sup>49</sup> A  $p$  value of  $< 0.05$  will be deemed statistically significant.

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.<sup>35</sup> Separate meta-analyses will be performed for each intervention. If insufficient data is available for meta-analysis, data will be synthesised descriptively.

## Patient and public involvement

SSheeba and RC have both worked as on-field health professionals responsible for the assessment and management of sports-related concussions. The initial concept

of this review was inspired by discussions with patients during follow-up assessments in which several indicated a need for additional non-pharmacological management strategies. There has been no further patient or public involvement beyond this early inspiration.

### 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.<sup>50</sup> There is also a possibility of low-level evidence for treatments of vestibular and oculomotor dysfunction in patients with postconcussive symptoms. The methodological appraisals conducted throughout this review will identify if this is the case such that recommendations to strengthen the body of evidence can be made.

### 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 preliminary searches of relevant databases. This review is expected to be completed by March 2023.

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**Contributors** All authors, SSheeba, RC, SSummers and CB, 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 its accuracy and integrity.

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**Competing interests** None declared.

**Patient and public involvement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

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