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Approach to investigation and treatment of persistent symptoms following sport-related concussion: a systematic review

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ABSTRACT

Objective To conduct a systematic review of the literature regarding assessment and treatment modalities in patients with persistent symptoms following sport-related concussion (SRC).

Data sources We searched Medline, Embase, SPORTSDiscus, PsycINFO, CINAHL, Cochrane library and ProQuest Dissertation & Theses Global electronic databases.

Study eligibility criteria Studies were included if they were original research, reported on SRC as the primary source of injury, included patients with persistent postconcussive symptoms (>10 days) and investigated the role of assessment or treatment modalities.

Results Of 3225 articles identified in the preliminary search, 25 articles met the inclusion criteria. 11 articles were concerned with assessment and 14 articles with treatment of persistent symptoms following SRC. There were three randomised control trials and one quasi-experimental study. The remainder consisting of cross-sectional studies, historical cohorts and case series.

Summary 'Persistent symptoms' following SRC can be defined as clinical recovery that falls outside expected time frames (ie, >10–14 days in adults and >4 weeks in children). It does not reflect a single pathophysiological entity, but describes a constellation of non-specific post-traumatic symptoms that may be linked to coexisting and/or confounding pathologies. A detailed multimodal clinical assessment is required to identify specific primary and secondary processes, and treatment should target specific pathologies identified. There is preliminary evidence supporting the use of symptom-limited aerobic exercise, targeted physical therapy and a collaborative approach that includes cognitive behavioural therapy. Management of patients with persistent symptoms is challenging and should occur in a multidisciplinary collaborative setting, with healthcare providers with experience in SRC.

postconcussive symptoms. Estimates of the prevalence of prolonged recovery following SRC vary from approximately 10% to 30%, depending on the cohort being investigated and the time frames used to define 'prolonged'.^{4,5}

Persistent symptoms following SRC are a cause of significant morbidity and frustration to the athlete and pose a management challenge to the clinician. While much of the literature to date has focused on acute concussion, high-quality evidence on the assessment and treatment of individuals with persistent symptoms following SRC remains limited.

The primary objective of this paper was to conduct a systematic review of the literature on assessment and treatment modalities in patients with persistent symptoms following SRC. The review also provides guidelines on the key domains that need to be evaluated as part of complete concussion care in the context of prolonged recovery and an outline of the skills and expertise that are appropriate to assess these domains.

METHODS

We addressed the question: *What is the best approach to investigation and treatment of persistent symptoms following SRC?* Specifically, we examined what are the key domains that need to be evaluated as part of complete concussion care in the context of prolonged recovery, and what skills and expertise are appropriate to assess these domains? The review was conducted according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.⁶ Search terms were initially reviewed by the author group to ensure all important concepts were captured. The reviewed search terms and methods were sent to an expert librarian to ensure completeness and accuracy of the search according to the PRESS Guideline Statement and the CADTH Peer Review Checklist.⁷

We searched the following electronic databases: MEDLINE (OVID), EMBASE (OVID), SPORTSDiscus (EBSCOhost), PsycINFO (OVID), CINAHL (EBSCOhost), Cochrane Database of Systematic Reviews (Wiley), Cochrane Central Register of Controlled Trials (Wiley) and ProQuest Dissertation & Theses Database (ProQuest) (for MEDLINE search see online supplementary appendix 1). Appropriate MeSH terms and commands were adapted to each database. The systematic searches were conducted in April 2016 and updated in June 2016.

INTRODUCTION

Historically, patients with sport-related concussion (SRC) have been managed in a uniform fashion consisting mostly of physical and cognitive rest followed by a graded return to routine training and match play, with the expectation that symptoms will spontaneously resolve over time.^{1–4} Although this approach results in successful return to school and sport in most athletes, an important proportion will develop persistent



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We defined 'persistent postconcussive symptoms' as symptoms that persist beyond the expected time frame for clinical recovery (ie, 10 days), consistent with the 4th International Conference on Concussion in Sport.^{4,5}

Articles were included if they met the following criteria:

1. Original research (including randomised control trials (RCTs), quasi-experimental designs, cohort studies, case-control studies or case series)
2. SRC as the primary source of injury
3. Patients with persistent postconcussive symptoms (ie, beyond the acute postinjury period)
4. Reported the outcome of specific assessment or treatment modalities
5. Human studies

Studies were excluded if they were:

1. review articles, case studies, or published only in abstract form;
2. focused on non-sport-related mechanism of injury (eg, falls, assault, motor vehicle accidents and blast injuries);
3. concerned with the assessment or treatment of SRC in the acute postinjury period or cohorts who were asymptomatic at the time of assessment.

There were no limits on language of study.

Study titles and abstracts were assessed against the selection criteria by at least two independent reviewers. The full text of all potentially relevant studies was then independently reviewed by two reviewers to determine final study selection. Discrepancies were resolved by consensus between the two reviewers and/or consultation with a third reviewer.

Selected studies were subgrouped according to assessment (clinical tests, investigations) or treatment (rest, active rehabilitation, targeted therapy, medical intervention) modalities. Data extraction was performed for eligible studies within each subtopic by separate teams consisting of two independent reviewers. Data were extracted using a predetermined standardised form and included information on: study design, participants (sample size, age, sex, sport, duration of symptoms, sampling methods), assessment or treatment modality used, primary outcome measures, key findings and level of evidence (per Oxford Centre of Evidence-Based Medicine).⁸

Teams of two independent reviewers assessed the risk of bias in included studies. Any discrepancies in scoring were resolved by consensus between the two reviewers and/or consultation with a third reviewer. The QUADAS-2 tool was used to assess risk of bias in studies on the assessment of persistent post-concussive symptoms.⁹ The Downs and Black checklist for methodological quality of randomised and non-randomised studies was used to assess the risk of bias in studies on the treatment of persistent postconcussive symptoms.¹⁰ The Downs and Black checklist uses 27 criteria (with a maximum score 33 points) to assess study reporting, external validity, internal validity (eg, bias and confounding) and power. An overall quality score of <14 was considered poor, 15–19 fair, 20–25 good and >26 excellent.

Study homogeneity was assessed visually by examining the data extraction tables. The considerable heterogeneity in subjects recruited, assessments or interventions applied, outcomes measured and timing of assessment reported in the studies that met our inclusion criteria limited meta-analytic possibilities. A narrative synthesis was therefore conducted, with articles grouped according to assessment and treatment modalities.

RESULTS

Overall, 3225 articles were screened for eligibility, with the full text of 133 articles retrieved for detailed evaluation (figure 1). Following full-text review of 30 articles, a further five were excluded, leaving a total of 25 articles that met the inclusion criteria for this review.

The characteristics of the included articles are summarised in table 1A and B. The 25 articles included 1035 concussed athletes with persistent symptoms (579 (56%) males, 456 (44%) females) from different sports, mainly at the high school and collegiate levels. Some articles also included patients with non-SRC mechanism of injury (n=11). Most articles recruited patients from university-based or paediatric hospital-based sports medicine or concussion clinics. In total, 15/25 (60%) of articles targeted children and adolescents and 10 included adult cohorts.

There was marked heterogeneity in the definition of 'persistent symptoms' used. One article used >10 days,¹¹ which is consistent with the definition from the 4th International Conference on Concussion in Sport.^{4,5} Ten articles used either >21 days or >28 days/month to define persistent symptoms.^{12–21} Four articles used >6 weeks or >2 months.^{22–25} The remaining 10 articles did not provide a specific definition for 'persistent symptoms' but included patients with a broad range of symptom duration (ie, 9 days to >9 months).^{26–35} Symptom reports were heterogeneous and commonly included headache, poor concentration, memory problems, fatigue, sleep difficulties, dizziness, irritability and feeling 'more emotional', nervous or anxious.

Assessment of persistent postconcussion symptoms

The findings of 11 articles on the assessment of persistent symptoms following SRC are summarised in table 2A. The overall quality of the studies was low (level IV), and there was a moderate risk of bias (QUADAS-2 results are summarised in table 3). All the studies were cross-sectional or case series in design and thus have limited ability to infer a causal association, which may be threatened by selection bias and recall bias and have limited generalisability.

Graded aerobic exercise test

Studies using a graded aerobic exercise test identified significant physiological differences in patients with persistent symptoms compared with matched controls (eg, shorter exercise duration, lower heart rate at test cessation and higher rating of perceived exertion).^{22,26}

Other clinical tests

Using simple clinical tests (eg, evaluation of gross extraocular movements and smooth pursuits, near-point convergence, and horizontal and vertical saccades and modified head-shake test), deficits were observed to be common in a cohort of adolescent patients with SRC.²⁷ Moreover, the prevalence of dysfunction was reported to be higher in patients with persistent symptoms.²⁷

Advanced investigation techniques

Five small cross-sectional studies and one case series on advanced investigation techniques for the assessment of persistent symptoms following SRC were included. Differences between cohorts of patients with persistent symptoms and controls were reported on electroencephalography (EEG) (eg, smaller event-related potential amplitudes on a working memory (WM) task),²⁸ functional magnetic resonance imaging (fMRI) (eg, reduced activation patterns, particularly in the dorsolateral prefrontal cortex on a WM task)^{14,29–31} and advanced MRI techniques (eg, altered

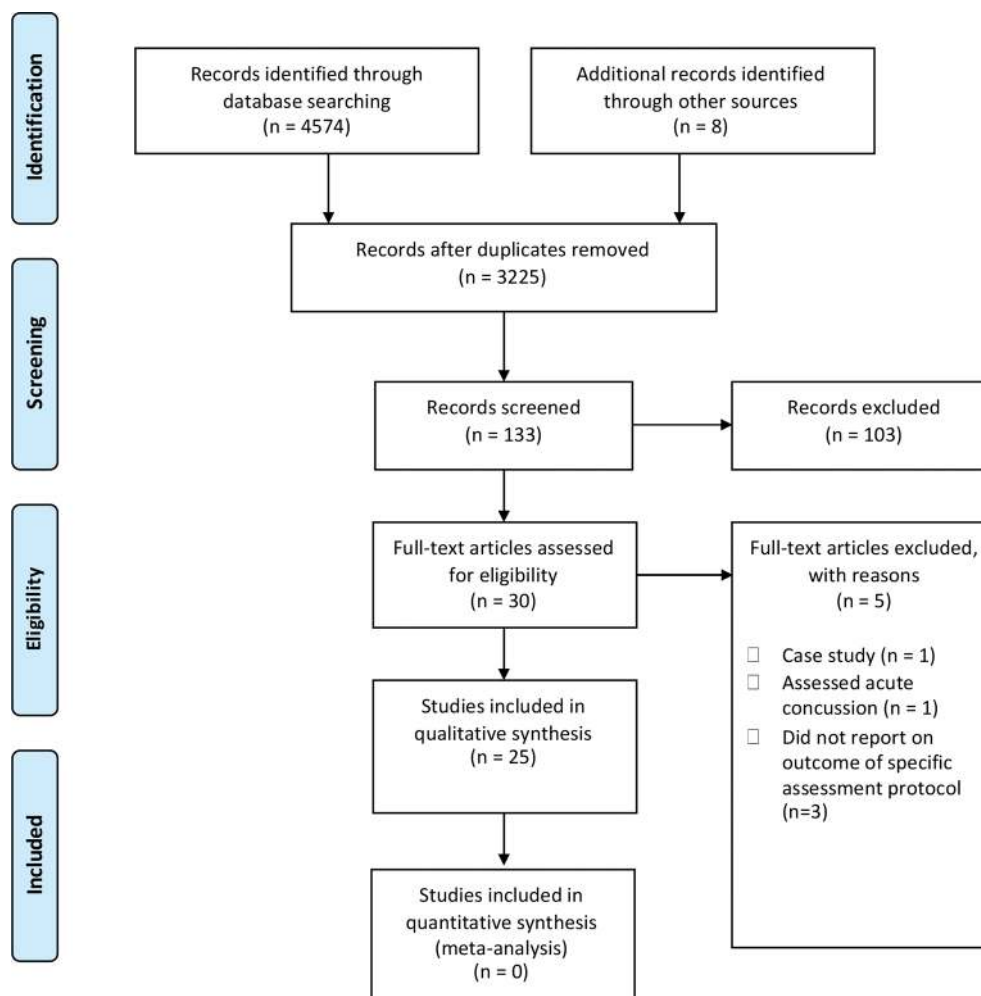


Figure 1 Study identification and PRISMA (2009) flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

patterns of brain activation on magnetic resonance spectroscopy and white matter changes on diffusion tensor imaging).³²

Treatment of persistent postconcussion symptoms

The results of 14 articles on the treatment of persistent symptoms following SRC are summarised in [table 2B](#). There were three small RCTs, one small quasi-experimental study, one historical cohort studies and nine caseseries. On Downs and Black assessment, only the RCTs were rated as good (score=23). All other studies were rated as poor (score <15). The main limitations were selection bias and failure to include control participants for comparison.

Rest

Clinical improvement was reported in children and adolescents with persistent postconcussion symptoms following a period (≥ 1 week) of cognitive and physical rest, in two small retrospective studies.^{33 36}

Targeted therapy

Based on the findings of one RCT and one small retrospective case series, a physical therapy programme was beneficial (eg, improved symptom scores, resolution of deficits on clinical examination and greater likelihood of return to sport) for the treatment of patients with persistent postconcussive symptoms.^{11 34} In a single RCT, a ‘collaborative care’ approach,

which included cognitive behavioural therapy (CBT) (as well as psychopharmacology in severe or recalcitrant cases), resulted in clinically and statistically significant improvements in post-concussive symptoms at 6 months when compared with ‘usual care’ (ie, review by sports medicine physician, MRI, formal neuropsychological testing, hypnotic medication and/or a subsymptom threshold exercise programme where relevant).²⁰ Targeted cognitive therapy, in patients with persistent postconcussive symptoms referred to a speech-language pathology clinic, reported ‘good’ outcomes using an individualised approach to treatment.²⁵

Active rehabilitation

One RCT,²¹ one quasi-experimental study,²⁴ and three small case series^{16 17 23} demonstrated a reduction in symptoms, improvement in exercise tolerance and return to normal lifestyle and sport participation in patients treated with an individualised subsymptom threshold aerobic exercise programme.

Medical intervention

The use of amantadine in a small cohort of adolescents with persistent symptoms resulted in greater improvements in symptoms and cognitive performance when compared with historical controls.¹⁸ In a retrospective review of medical records of adolescent patients treated at a regional concussion clinic, 17% of patients (68/400) were treated with amitriptyline for post-traumatic headache. Of these, 82% of patients reported a benefit

Table 1 Characteristics of studies meeting inclusion criteria:**(A) Assessment of persistent symptoms following SRC.**

Study	Study design	Method of assessment	Setting (country)	Participants				Controls or comparison group (n)	Duration of symptoms
				n	sex	Age (mean (SD) years)	Sport		
Kozlowski <i>et al</i> (2013) ²⁶	Cross-sectional	Graded exercise test	University-based sports medicine clinic (USA)	34	17M:17F	25.9 (10.9)	Mixed (SRC and non-SRC), no details on sport	22	Average time from injury=226 days
Leddy <i>et al</i> (2015) ¹²	Case series	Graded exercise test	University-based concussion clinic (USA)	128	69M:59F	Physiological group: 28.0 (13.9); CV group: 26.4 (13.0)	Mixed (SRC and non-SRC), no details on sport	Nil	>21 days
Clausen <i>et al</i> (2016) ²²	Cross-sectional	Graded exercise test	University-based concussion clinic (USA)	9	All female	Mean 23.0 (6.0)	Soccer, basketball, volleyball	13	>6 weeks (and <12 weeks)
Ellis <i>et al</i> (2015) ²⁷	Cross-sectional	Vestibulo-ocular testing	Concussion clinic (Canada)	24	9M:15F	16.0 (1.6)	Baseball, basketball, skating, football, hockey, skiing, snowboarding, soccer, volleyball, other	77 with acute SRC	Median time from injury=69.5 days
Heyer <i>et al</i> (2016) ¹³	Case series	Tilt table	Hospital-based paediatric headache clinic (USA)	34	8M:26F	Range: 13–18	Mixed (SRC and non-SRC), no details on sport	Nil	>21 days
Gosselin <i>et al</i> (2012) ²⁸	Cross-sectional	EEG	University health centre (Canada)	44	21M:23F	30.3 (11)	Mixed (SRC and non-SRC), no details on sport	40	Average time from injury=7.6 months (SD 8.4)
Chen <i>et al</i> (2007) ¹⁴	Cross-sectional	fMRI	University-based sports medicine clinic (Canada)	18	All male	Low PCS group: 26.9 (5.6); high PCS group: 30.8 (5.8)	No details on sport	10	>1 month
Chen <i>et al</i> (2008) ²⁹	Cross-sectional	fMRI	University-based sports medicine clinic (Canada)	40	All male	No depression group: 26.0 (5.6); mild depression group: 29.0 (6.7); moderate depression group: 30.0 (3.4)	No details on sport	16	Average time from injury=4.9 (SD 4.7) –7.3 (SD 9.6) months
Chen <i>et al</i> (2008) ³⁰	Case series	fMRI	University-based sports medicine clinic (Canada)	9	All male	Improved group: 33.8 (5.6); not-improved group: 29.6 (5.1)	No details on sport	6	Assessed 1–9 month/s postinjury
Keightley <i>et al</i> (2014) ³¹	Cross-sectional	fMRI	Children's hospital (Canada)	15	7M:8F	14.5 (2.3)	Soccer, football, swimming, other	15	Assessed 9–90 days postinjury
Bartnik-Olson <i>et al</i> (2014) ³²	Cross-sectional	MRI/MRS	University-based medical centre (USA)	15	12M:3F	14.8 (2.8)	Football, soccer, softball	15	Average time from injury=5.8 (SD 4.8) months

CV, cervicogenic/vestibular; EEG, electroencephalogram; F, female; fMRI, functional MRI; M, male; MRS, magnetic resonance spectroscopy; n, number; PTM, post-traumatic migraine; SRC, sports-related concussion.

CBT, cognitive behavioural therapy; F, female; n, number; M, male; RCT, randomised controlled trial; SRC, sport-related concussion.

(B) Treatment of persistent symptoms following SRC.

Study	Study design	Treatment modality	Setting (country)	Participants				Controls or comparison group (n)	Duration of symptoms
				n	Sex	Age (mean(SD) years)	Sport		
Moser <i>et al</i> (2012) ²⁶	Case series	Rest	Sports concussion clinic (USA)	13	6M:7F	15.8 (2.7)	Ice hockey, lacrosse, soccer, basketball, football	Nil	>31 days
Moser <i>et al</i> (2015) ³³	Case series	Rest	Sports concussion centre (USA)	13	7M:6F	15.1 (1.5)	Basketball, football, ice hockey, lacrosse, soccer, snowboarding	Nil	Information not supplied
Gagnon <i>et al</i> (2009) ¹⁶	Case series	Subsymptom threshold activity	Paediatric hospital based concussion clinic (Canada)	16	11M:5F	14.3 (2.3)	Rugby, football, soccer, hockey, other (also includes two non-SRC)	Nil	>4 weeks
Gagnon <i>et al</i> (2016) ¹⁷	Case series	Subsymptom threshold activity	Paediatric hospital based concussion clinic (Canada)	10	7M:3F	16.3 (1.3)	Football, soccer, basketball, hockey, snowboarding	Nil	>3 weeks
Leddy <i>et al</i> (2010) ²³	Case series	Subsymptom threshold activity	University-based concussion clinic (USA)	12	7M:5F	27.9 (14.3)	Mixed (SRC and non-SRC), no details on sport	Nil	>6 weeks (and <52 weeks)
Leddy <i>et al</i> (2013) ²⁴	Quasi experimental	Subsymptom threshold activity	University-based concussion clinic (USA)	8	4M:4F	Exercise group: 25.8 (6.1); stretching group: 23.2 (6.2)	Mixed (SRC and non-SRC), no details on sport	4	>6 weeks (and <52 weeks)
Kurowski <i>et al</i> (2016) ²¹	RCT	Subsymptom threshold activity	Community-based head injury clinics and emergency departments (USA)	30	13M:17F	Exercise group 15.2 (1.4); stretching group 15.5 (1.8)	Mixed (SRC and non-SRC), no details on sport	15	>4 weeks
Hugentobler <i>et al</i> (2015) ³⁴	Case series	Physical therapy Paediatric hospitalbased	physical therapy clinic (USA)	6	4M:2F	17.0 (1.7)	Ice hockey, lacrosse, soccer, swimming, dance	Nil	19–192 days

Continued

Table 1 Continued

(B) Treatment of persistent symptoms following SRC.

Study	Study design	Treatment modality	Setting (country)	Participants				Controls or comparison group (n)	Duration of symptoms
				n	Sex	Age (mean(SD) years)	Sport		
Schneider <i>et al</i> (2014) ¹¹	RCT	Physical therapy	University-based sports medicine centre (Canada)	31	18M:13F	Treatment group (n=15): age range 12–27 years	No details on sport	16	>10 days
McCarty <i>et al</i> (2016) ²⁰	RCT	Collaborative care including CBT	Paediatric hospitalbased concussion clinic	49	17M:32F	Treatment group (n=25): 15.1 (1.6) years	Mixed (SRC and non-SRC), no details on sport	24	>1 month
Sohlberg and Ledbetter (2015) ²⁵	Case series	Speech pathology	University-based speech-language clinic (USA)	24	10M:14F	17.5 (3.2)	Basketball, cheerleading, cycling, dancing, football, long board, pole vaulting, softball, soccer	Nil	>2 months
Reddy <i>et al</i> (2013) ¹⁸	Historical cohort	Amantadine	University-based sports medicine concussion programme (USA)	25	11M:14F	15.7 (1.4)	No details on sport	25	>21 days
Dubrovsky <i>et al</i> (2014) ³⁵	Case series	Nerve blocks for persistent headache	Paediatric hospitalbased concussion clinic (Canada)	28	6M:22F	14.6 (1.7)	Mixed (SRC and non-SRC), no details on sport	Nil	Average time from injury to treatment=70 (±54.2) days
Bramley <i>et al</i> (2015) ¹⁹	Case series	Amitriptyline for persistent headache	University hospitalbased concussion clinic (USA)	400	248M:152F	13–18 years	Mixed (SRC and non-SRC), no details on sport	Nil	>1 month

with amitriptyline.³⁵ In a similar cohort, there was ‘good’ therapeutic effect of local anaesthetic nerve blocks of the scalp in those with acute and persistent headaches after mild TBI.³⁵

SUMMARY AND RECOMMENDATIONS

The assessment and treatment of persistent symptoms following SRC has advanced significantly in recent years. This systematic review identified 25 articles that met the inclusion criteria, with 11 articles focused primarily on assessment and 14 articles on treatment of persistent symptoms following SRC. With the exception of three recent RCTs on treatment modalities,^{11 20 21} the overall quality of the included articles was low, with a moderate to high risk of bias.

Definition

There was marked heterogeneity in the definition of ‘persistent’ postconcussive symptoms, with definitions ranging from >10 days¹¹ to >2 months.^{22–25} Prospective cohort studies in a range of sports have consistently demonstrated that the majority of cases of SRC in adult populations resolve clinically within 10–14 days of injury,^{37–40} although the timeframe for recovery may be greater in children and adolescent athletes.^{41 42}

Recommendations

- ▶ A standard definition for persistent postconcussive symptoms is needed to ensure consistency in clinical management and research outcomes.
- ▶ Use of the term ‘persistent symptoms’ following SRC should reflect clinical recovery that falls outside expected time frames. Persistent postconcussive symptoms can be defined as >10–14 days in adults and >4 weeks in children.
- ▶ Given the heterogeneity in clinical presentation, it may be beneficial to classify different phenotypic clusters based on the domains affected (eg, headache syndrome, vestibular, psychological, physiological and neurocognitive) because

a definition based on time frames alone is unlikely to improve understanding of persistent symptoms or treatment paradigms.

Assessment

Multiple aetiological factors may contribute to the persistence of symptoms following SRC, and these aetiological factors may coexist. Prolonged symptoms may reflect a *primary* persistent change in brain function or a manifestation of co-existing or confounding processes, such as depression, headache syndromes, vestibular or oculomotor dysfunction and so on.^{12 27 43} Key objectives of the clinical assessment should therefore be to identify specific pathologies that may be contributing to the persistence of symptoms. To achieve this objective, a detailed multi-modal assessment is required.

Symptoms

Common persistent symptoms following SRC (eg, headache, poor concentration, memory problems, fatigue, sleep difficulties, dizziness, irritability, feeling ‘more emotional’, nervous or anxious) are non-specific and are commonly reported with orthopaedic injuries, psychological problems (eg, anxiety or depression), chronic pain syndromes and even in healthy controls.^{44–48} Comorbidities in the presence of SRC (eg, injury to the cervical spine) can also result in similar clinical presentations.⁴⁹ Psychiatric comorbidity is high in individuals with persistent postconcussive symptoms and may increase symptom reporting.^{50 51}

Assessment of symptoms should extend beyond the standard postconcussion-graded symptom checklist. For example, obtaining a detailed headache profile (eg, type, location, pattern, past or family history of migraine) may assist in identifying an underlying headache disorder such as migraine, tension headache, occipital neuralgia or cervicogenic headache.^{52 53} Clinical information about sleep disturbance and drug or alcohol use may

Table 2 Summary of results of studies meeting inclusion criteria**(A) Assessment of persistent symptoms following SRC**

Study	Method of assessment	Key outcome measures	Key results	Level of evidence
Kozlowski <i>et al</i> (2013) ²⁶	Graded exercise test (Balke protocol)	Graded symptom checklist, physiological measures (HR, BP, RPE), test duration	Persistent symptoms group had lower exercise test duration (8.5±4.4 min vs 17.9±3.6 min; $p<0.001$), HR (142.8±24.1 vs 175.2±17.4; $p<0.001$) and systolic BP (142.1±18.3 mm Hg vs 155.5±24.5 mm Hg; $p=0.02$), and higher diastolic BP (78.4±10.2 mm Hg vs 73.5±11.7 mm Hg; $p=0.03$) compared with controls	4
Leddy <i>et al</i> (2015) ¹²	Graded exercise test (Balke protocol)	Graded symptom checklist	Graded exercise test and clinical examination were used to divide subjects with PCS into 'physiological PCS' (abnormal treadmill performance and a normal cervical/vestibular physical examination) or 'cervicogenic/vestibular PCS' (normal treadmill performance and an abnormal cervical/vestibular physical examination). No differences were demonstrated between the groups on symptoms alone	4
Clausen <i>et al</i> (2016) ²²	Graded exercise test and measures of cerebral blood flow velocity (CBFV) using transcranial doppler	Physiological measures during exercise treadmill test (including BP and minute ventilation (VE)), end-tidal CO ₂ (PETCO ₂) and CBFV	At baseline, participants with PCS had significantly lower VE (18%) and greater PETCO ₂ (5%) and CBFV (14%) versus controls at similar workloads in association with appearance of symptoms and premature exercise cessation. Following a 12-week subsymptom threshold aerobic exercise programme VE, PETCO ₂ , CBFV and exercise tolerance normalised	4
Ellis <i>et al</i> (2015) ²⁷	Vestibular-ocular clinical examination (including evaluation of gross extraocular movements and smooth pursuits, near-point convergence, and horizontal and vertical saccades and modified head-shake test)	Graded symptom checklist, presence of VOD	22 of the 77 patients (28.6%) with acute SRC and 15 of the 24 (62.5%) with PCS met the clinical criteria for VOD. There was a significant increase in the adjusted odds of developing PCS among patients with acute SRC who had VOD compared with those without VOD (adjusted OR 4.10; 95% CI 1.04 to 16.16)	4
Heyer <i>et al</i> (2016) ¹³	Head upright tilt table (HUT) testing - used to divide the groups into 'normal', 'syncope' and 'postural tachycardic syndrome (POTS)' groups	Graded symptom checklist; self-reported levels of light-headedness (over preceding 7 days), frequency of symptoms	Patients with POTS had higher symptom scores than normal patients ($p<0.001$) and higher ratings of light-headedness than both normal patients ($p=0.015$) and patients with syncope ($p=0.04$). 12 patients with POTS underwent repeat tilt table testing within 3–6 months. 9 of 12 (75%) no longer met POTS diagnostic criteria. All patients with resolution of POTS had corresponding improvements in symptoms, including light-headedness and vertigo.	4
Gosselin <i>et al</i> (2012) ²⁸	EEG evaluating ERP during a WM task	Amplitude and latency of frontal (N200 and N350) and parietal (P200 and P300) ERP waves	Mild TBI group had a lower percentage of correct answers on behavioural performance on the WM task ($p<0.05$) and smaller amplitudes of both frontal N350 and parietal P300 ERP components when compared with controls ($p<0.05$). Smaller ERP amplitudes were associated with slower reaction times and worse accuracy on the WM task among patients with MTBI ($p<0.05$)	4
Chen <i>et al</i> (2007) ¹⁴	fMRI—using a verbal and non-verbal WM task	fMRI, computerised cognitive test battery (CogState Sport)	Accuracy and speed on the cognitive test battery were comparable for the control and low PCS group. The moderate PCS group showed significantly slower response times than the control group on the matching ($p<0.05$) and one-back tasks ($p<0.05$). fMRI showed reduced task-related activation patterns in the DLPC for both low and moderate PCS groups. Severity of PCS predicted fMRI blood oxygen level-dependent signal changes in cerebral prefrontal regions.	4
Chen <i>et al</i> (2008) ²⁹	Beck depression inventory II used to stratify subjects into no (score 0–9), mild (10–19) or moderate (20–29) depression. Structural MRI (including T1, T2 and fluid-attenuated inversion recovery sequences), fMRI using a WM task.	fMRI, response speed and accuracy on the WM task and voxel-based morphometry examining grey matter concentration on structural imaging	There was no performance difference between the groups. Athletes with concussion with depression symptoms showed reduced activation in the DLPC and striatum and attenuated deactivation in medial frontal and temporal regions. The severity of symptoms of depression correlated with neural responses in brain areas that are implicated in major depression.	4
Chen <i>et al</i> (2008) ³⁰	fMRI—using a verbal and non-verbal WM task.	fMRI, response speed and accuracy on the WM task and voxel-based morphometry examining grey matter concentration on structural imaging	There was no performance difference between the groups. Despite normal structural MRI findings, all symptomatic concussed athletes initially showed atypical brain activation patterns in the DLPC. Compared with the initial postinjury evaluation, those athletes at follow-up with PCS resolved showed significant increases in activation in the left DLPC. Concussed athletes whose PCS status remained unchanged at follow-up continued to show atypical activation in DLPC.	4

Continued

Table 2 Continued

(A) Assessment of persistent symptoms following SRC

Study	Method of assessment	Key outcome measures	Key results	Level of evidence
Keightley <i>et al</i> (2014) ³¹	fMRI—using a verbal and non-verbal WM task.	fMRI, neuropsychological testing	Concussed group had (1) significantly worse performances on the WM tasks, Rey figure delayed recall and verbal fluency; (2) significantly reduced task-related activity in bilateral DLPC, left premotor cortex, supplementary motor area and left superior parietal lobule during performance of verbal and non-verbal WM tasks and (3) less activation in the dorsal anterior cingulate cortex, left thalamus and left caudate nucleus during the non-verbal task.	4
Bartnik-Olson <i>et al</i> (2014) ³²	MRI and MRS	PWI, three-dimensional (3D) magnetic resonance spectroscopic imaging and DTI	In the bilateral thalami, patients with SRC showed reduced CBF ($p=0.02$, $p=0.02$) and relative cerebral blood volume (CBV; $p=0.05$ and $p=0.03$), compared with controls. NAA/creatinine (Cr) and NAA/choline (Cho) ratios were reduced in the corpus callosum ($p=0.003$; $p=0.05$) and parietal white matter ($p<0.001$; $p=0.006$) of subjects with SRC, compared with controls. DTI revealed decreased fractional anisotropy and increased radial diffusivity in patients with persistent symptoms following SRC compared with controls.	4

BP, blood pressure; CBF, cerebral blood flow; DLPC, the dorsolateral prefrontal cortex; DTI, diffusion tensor imaging; EEG, electroencephalogram, ERP, event-related potential; fMRI, functional MRI; HR, heart rate; MRS, magnetic resonance spectroscopy; MTBI, mild TBI; NAA, N-acetylaspartate; PCS, post-concussion syndrome; PWI, perfusion-weighted imaging; RPE, rating of perceived exertion; SRC, sport-related concussion; TBI, traumatic brain injury; VOD, vestibulo-ocular dysfunction; WM, working memory.

(B) Treatment of persistent symptoms following SRC

Study	Treatment modality	Key outcome measures	Key results	Level of evidence	Downs and Black score
Moser <i>et al</i> (2012) ³⁶	Rest	Graded symptom checklist, computerised cognitive test battery (ImPACT)	Performance on ImPACT pretest and posttest demonstrated improved cognitive function (verbal memory, visual memory, processing speed) $p=0.001$ and total symptoms $p=0.001$.	4	11
Moser <i>et al</i> (2015) ³³	Rest	Graded symptom checklist, computerised cognitive test battery (ImPACT).	Significant difference between pretest and posttest scores in all four IMPACT composite scores (verbal memory $p=0.004$. Visual memory $p=0.002$. Reaction time $p=0.006$. Motor speed $p=0.017$ and in the total symptoms score ($p=0.02$).	4	11
Gagnon <i>et al</i> (2009) ¹⁶	Subsymptom threshold activity	Graded symptom checklist, time to return to normal physical activity	All subjects were reported to recover (ie, return to normal lifestyle and sport participation). Mean duration of intervention=4.4 weeks (SD 2.6).	4	5
Gagnon <i>et al</i> (2016) ¹⁷	Subsymptom threshold activity	Graded symptom checklist, Beck Depression Inventory, Paediatric Quality of Life Multidimensional Fatigue Scale, balance and coordination, computerised cognitive test battery (ImPACT).	Symptoms decreased between start of intervention and the 6-week follow-up assessment ($p=0.004$). Subjects recovered in a mean of 6.8 weeks (range of 2–15 weeks).	4	9
Leddy <i>et al</i> (2010) ²³	Subsymptom threshold activity	Graded symptom checklist, exercise duration, time to return to work/sport	Overall symptom reduction from baseline to post-treatment ($p=0.002$); all individuals were reported to have recovered at 1.6–16 weeks. Exercise time improved significantly from a baseline mean of 9.75 (6.38) min to 18.67 (2.53) min at treatment termination ($p=0.001$)	4	10
Leddy <i>et al</i> (2013) ²⁴	Subsymptom threshold activity	fMRI using a math task from the Automated Neuropsychological Assessment Metrics (ANAM), performance on ANAM, HR on treadmill test, number of symptoms on post-concussion symptom scale.	After treatment, the exercise group did not differ from healthy controls, but the stretching group had less activity in the cerebellum ($p<0.05$), the anterior cingulate gyrus and thalamus ($p<0.001$) than healthy controls. Following treatment, the exercise group had greater exercise HR ($p<0.001$) and less symptoms ($p<0.0004$) compared with stretching group. Cognitive performance did not differ by group or time.	3	11
Kurowski <i>et al</i> (2016) ²¹	Subsymptom threshold activity	Graded symptom checklist	Patients in the active treatment group demonstrated a greater rate of symptom improvement than the stretching group ($p=0.044$). The effect size for the difference between the groups was moderate to large (Cohens d 0.81 across time points and 0.51 at week 7).	2	23

Continued

Table 2 Continued

(B) Treatment of persistent symptoms following SRC

Study	Treatment modality	Key outcome measures	Key results	Level of evidence	Downs and Black score
Hugentobler <i>et al</i> (2015) ³⁴	Physical therapy	Graded symptom checklist, clinical evaluation of the cervical spine, oculomotor screen and postural control assessment (BESS)	All patients had lower resting symptom severity at the final session. 4/6 patients made fewer errors on the BESS. Improvements were also observed in symptom scores, gaze stability, balance and postural control measures and patient self-management of symptoms. One patient had returned to full preinjury activity levels at the time of their final assessment. 4/6 had returned to preinjury levels within 3–6 months of discharge from physical therapy.	4	4
Schneider <i>et al</i> (2014) ¹¹	Physical therapy	Primary outcome = time to medical clearance to return to sport (as determined by blinded study sport medicine physician according to best practice guidelines). Secondary outcome measures=11 point Numeric Pain Rating Scale score, Activities-specific Balance Confidence Scale, Dizziness Handicap Index, SCAT2, Dynamic Visual Acuity, Head Thrust Test, modified Motion Sensitivity Test, Functional Gait Assessment, Cervical Flexor Endurance and Joint Position Error test.	73% (11/15) in intervention group were medically cleared compared with 7% (1/14) of the control group. Individuals in the treatment group were 3.91 (95% CI 1.34 to 11.34) times more likely to be medically cleared to return to sport by 8 weeks when compared with the control group	2	23
McCarty <i>et al</i> (2016) ²⁰	Collaborative care including CBT	Primary outcome measures: graded symptom checklist, PHQ-9 to assess depressive symptoms, PROMIS-PA8 (version a) to assess anxiety symptoms, Paediatric Quality of Life Inventory (PedsQL), self-reported satisfaction with care	'Collaborative care' group experienced clinically and statistically significant improvements in postconcussive symptoms in addition to functional gains at 6 months compared with 'Usual care'. Six months after the baseline assessment, 13.0% of intervention patients and 41.7% of control patients reported high levels of postconcussive symptoms ($p=0.03$), and 78% of intervention patients and 45.8% of control patients reported $\geq 50\%$ reduction in depression symptoms (relative risk 1.71, 95% CI 1.05 to 2.79, $p=0.02$). No changes between groups were demonstrated in anxiety symptoms. Median number of CBT sessions=8 (range 0–12). 1/3 of patients received subsequent medications.	2	23
Sohlberg and Ledbetter (2015) ²⁵	Cognitive rehabilitation	Client selected functional goal	83% of clients achieved self-selected functional goals	4	3
Reddy <i>et al</i> (2013) ¹⁸	Amantadine	Graded symptom checklist, computerised cognitive test battery (ImPACT) performed at the time of initial assessment and 40–50 days postinjury	At the pretest the amantadine treated group were significantly lower than controls on verbal memory ($p=0.007$) and visual memory ($p=0.04$), and higher on total symptoms ($p=0.01$). Participants in both groups reported a decrease in symptoms and demonstrated improvement in verbal and visual memory, visual processing speed and reaction time scores from pre to post-test. Improvements were larger in the amantadine treatment group on verbal memory ($p=0.07$), visual memory ($p=0.04$) and total symptoms ($p=0.01$)	4	12
Dubrovsky <i>et al</i> (2014) ³⁵	Nerve blocks for persistent headache	Review of clinical history and patient satisfaction survey to assess response to injection; 'good' therapeutic effect defined as benefit sustained >24 hours and/or requested repeat injection, partial therapeutic benefit defined as benefit <24 hours.	Patients received 1–6 injections (mean 2.1), all patients reported reduction in headache intensity. Mean (SD) preinjection and postinjection headache scores were 5.6 (1.6) and 0.4 (0.9); 93% good therapeutic effect, 7% partial effect. 23/28 responded to the survey (82%), 83% recalled immediate relief of headaches, 61% indicated improved or resolved headaches in days to weeks following injection	4	5

Continued

Table 2 Continued

(B) Treatment of persistent symptoms following SRC

Study	Treatment modality	Key outcome measures	Key results	Level of evidence	Downs and Black score
Bramley <i>et al</i> (2015) ¹⁹	Amitriptyline for persistent headache	Review of clinical history to assess response to medication	Median time to recovery=80 days for females versus 34 days for males, n=68 (17%) were prescribed amitriptyline— 82% (95% CI 70% to 91%) reported improvement in their symptoms, 23% (95% CI 12% to 38%) reported side effects.	4	6

BESS, balance error scoring system; CBT, cognitive behavioural therapy; PHQ-9, patient health questionnaire 9; PROMIS, patient reported outcome measurement information system; RCT, randomised controlled trial; SCAT, sport concussion assessment tool; SRC, sport-related concussion.

also be beneficial in identifying secondary causes of persistent symptoms.

There were no articles included in this review that specifically evaluated mood and psychological domains. This is despite these being commonly reported symptoms and targeted areas of treatment following SRC. Nevertheless, tools such the Beck Depression Inventory-II (BDI-II)^{28 29 31 54} or the Patient Health Questionnaire (PHQ-9)⁵⁵ may assist in identifying the presence and severity of an underlying depression. Recent studies also indicate that the Brief Symptom Inventory-18 (BSI-18) may be helpful in identifying the influence of depression, anxiety and somatization, both preinjury and postinjury, in protracted recovery after SRC.⁵⁶

Clinical examination

Components of the clinical examination that may help distinguish between patients with primary or secondary causes of persistent postconcussive symptoms include assessment of vestibular and oculomotor function, the cervical spine and exercise tolerance. For example, specific symptoms (eg, dizziness, headache, neck pain and unsteadiness) and a range of brief clinical tests (including dynamic visual acuity, head thrust test, modified motion sensitivity, functional gait assessment, cervical flexor endurance and joint position error) may help identify vestibular and/or cervical spine deficits in patients with persistent postconcussive symptoms.¹¹

Special tests

The Buffalo concussion treadmill test is a standardised graded aerobic exercise test that is based on the Balke cardiac protocol.^{12 22 26} There is consistent preliminary evidence that the graded

aerobic exercise test is safe, can reliably reveal physiological dysfunction in patients with persistent postconcussive symptoms and can quantify the exercise capacity of these patients to guide treatment.^{22 26 57–59}

Other approaches such as using a tilt table to identify autonomic dysfunction in patients with persistent post-traumatic vertigo and lightheadedness¹³ might be appropriate. However, in the clinical setting, the role for tilt table testing remains unclear and identification of aetiological factors such as autonomic dysfunction may be assessed using simpler measures such as heart-rate variability or orthostatic intolerance, although the evidence for these tests currently remains limited.⁶⁰

Neuropsychological testing

Neuropsychological testing⁶¹ is an important component of the concussion assessment.⁴ While screening computerised neuropsychological test batteries is often used in the acute setting, formal neuropsychological assessment tends to be more commonly used in cases of persistent symptoms. There are limited data, however, on the utility of formal neuropsychological testing in the management of patients with persistent symptoms, and further studies are needed in this domain. In the clinical setting, neuropsychological testing facilitates identification of persistent brain function deficits in patients following SRC. An understanding of these deficits may be useful, for example, in determining cognitive capacity and limitations related to work or school.

Advanced investigation techniques

Standard structural imaging techniques (eg, CT and MRI) have limited value and low yield in patients with persistent

Table 3 Summary of QUADAS2 risk of bias assessment for included studies on assessment of persistent symptoms following SRC.

Study	Risk of bias				Applicability concerns		
	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index	Reference standard
Kozlowski <i>et al</i> (2013) ²⁶	Medium	Medium	Low	Low	Medium	Medium	Medium
Leddy <i>et al</i> (2015) ¹²	Medium	Medium	Low	Low	Medium	Medium	Medium
Clausen <i>et al</i> (2016) ²²	Medium	High	Low	High	Medium	Medium	Medium
Ellis <i>et al</i> (2015) ²⁷	Medium	Medium	Low	Low	Medium	Medium	Medium
Heyer <i>et al</i> (2016) ¹³	High	Medium	Low	Low	Medium	Medium	Medium
Gosselin <i>et al</i> (2012) ²⁸	Medium	Medium	Low	High	High	High	Low
Chen <i>et al</i> (2007) ¹⁴	Medium	Medium	Low	Medium	Medium	Medium	Medium
Chen <i>et al</i> (2008) ²⁹	Medium	Medium	Medium	Low	Medium	Medium	Medium
Chen <i>et al</i> (2008) ³⁰	Medium	Medium	Medium	Medium	Medium	Medium	Medium
Keightley <i>et al</i> (2014) ³¹	Medium	Medium	Low	Low	Low	Low	Low
Bartnik-Olson <i>et al</i> (2014) ³²	Medium	Medium	Low	Medium	Low	Low	Low

SRC, sport-related concussion.

postconcussive symptoms. Advanced investigation techniques (such as fMRI, diffusion tensor imaging, magnetic resonance spectroscopy and quantitative EEG) have demonstrated changes in brain function, brain activation patterns and white matter fibre tracts in cases of concussion with prolonged symptoms. Often, however, these changes exist even when the athlete has recovered clinically and returned to sport. As such, the clinical significance of these changes remains unclear.

Investigations such as EEG and advanced neuroimaging may assist our understanding of the aetiology of persistent symptoms, as outlined in parallel systematic reviews as part of the Consensus Conference.^{62 63} While their role in the clinical setting remains unclear, their use in the research setting should continue to be encouraged.

Overall, the key domains that need to be evaluated as part of complete concussion care in the context of prolonged recovery may include (but are not limited to):

1. Somatic (eg, headache)
2. Cognitive
3. Affective/mental health (depression, anxiety, and so on)
4. Physiological (exercise intolerance)
5. Cervical spine
6. Vestibular
7. Oculomotor
8. Autonomic
9. Sleep
10. Hormonal
11. Loss of cognitive and/or physical stamina

Practitioners who may be a part of the multidisciplinary team to assess or manage these domains may include (but are not limited to): primary care physician, sports physician, physiatrist/rehabilitation physician, physical therapist, certified athletic trainer, exercise physiologist, neurologist, neurosurgeon, neuropsychologist, psychiatrist, psychologist and other specialists (eg, cardiologist, optometrist, ophthalmologist). Ideally, healthcare providers should have specific experience in the management of SRC.

Recommendations

- ▶ Persistence of symptoms following SRC does not reflect a single pathophysiological entity. The term describes a constellation of non-specific symptoms that may be linked to coexisting and/or confounding pathologies that do not necessarily reflect ongoing physiological injury to the brain.
- ▶ A detailed multimodal clinical assessment is needed to identify specific primary and secondary processes that may be contributing to persistence of symptoms following SRC. At a minimum, this requires a comprehensive history and focused physical examination (including assessment of cervical spine, vestibular and oculomotor function, and in individuals with exercise intolerance, a systematic evaluation of exercise tolerance).
- ▶ Currently, the added benefit of investigations such as EEG, advanced neuroimaging techniques, genetic testing and biomarkers remains unclear, but use in the research setting will continue to evolve our understanding of the aetiology of persistent symptoms following SRC.
- ▶ Multiple subsystem involvement may occur in individuals with persisting symptoms following SRC but evidence evaluating the coexistence and interaction between symptoms is limited and requires further evaluation.
- ▶ Ultimately, a detailed multimodal assessment may facilitate classification of phenotypic, structural, proteomic and

genetic signatures of different injury subtypes, which will assist in improved consistency of research/reporting, facilitate understanding of the pathogenesis of injury and allow development of targeted interventions for cases of persistent symptoms following SRC.

Treatment

The approach to patients with persistent symptoms following SRC has traditionally been based largely on an extension of the guidelines for acute injuries (ie, rest until symptoms resolve) or interventions used in other forms of TBI.⁵⁸ Many of these treatments have been used empirically but have limited scientific evidence.

While an initial brief period of physical and cognitive rest (ie, 24–48 hours) may be important in the management of acute concussion, there is limited evidence that further rest is beneficial in cases where symptoms are prolonged. Two articles included in the systematic review suggested a period of rest may improve symptoms and function in cohorts of children and adolescents with persistent postconcussive symptoms.^{33 36} Both articles, however, had significant methodological limitations, were threatened by recall bias and lacked control or comparison groups, making it difficult to determine whether any positive findings can be ascribed specifically to the intervention or simply reflected natural resolution of the symptoms with time. Moreover, compliance was not monitored and the benefits may have been conferred by relative rest rather than complete physical and cognitive rest.

A CBT intervention embedded in a collaborative care treatment model reduced persistent symptoms in a mixed SRC and non-SRC adolescent cohort,²⁰ providing preliminary support for the role of CBT in the management of persistent postconcussive symptoms. Although this also highlights the importance of an integrated model of care (involving primary care, sports medicine, rehabilitation medicine, neurology, neuropsychology, psychiatry) for the management of patients with persistent symptoms following SRC.

Two articles that met the inclusion criteria for this review, including one RCT, demonstrated a benefit of a targeted multifaceted physical therapy programme for the management of patients with persistent postconcussive symptoms, particularly in patients identified with clinical features consistent with a cervical spine and/or vestibular cause of symptoms.^{11 34} A structured exercise programme, involving individualised aerobic activity performed at an intensity that does not exacerbate symptoms, was also safe and may be effective in the treatment of children and adolescents,^{16 17 21} and older cohorts^{23 24} with persistent postconcussive symptoms.

Studies on the pharmacological treatment of persistent symptoms following SRC were

limited, and of low quality. Despite their widespread empiric use, currently, there is no compelling evidence to support the use of pharmacological measures such as peripheral nerve blocks, amitriptyline or amantadine in the treatment of patients with persistent postconcussive symptoms.

Recommendations

- ▶ Treatment for individuals with persistent symptoms following SRC should target specific primary and secondary diagnoses identified on assessment.
- ▶ Individualised symptom-limited aerobic exercise is safe and may be effective in the treatment of patients with 'physiological' persistent postconcussive symptoms.

- ▶ A targeted physical therapy programme may be of benefit particularly if the patients have clinical features consistent with cervical spine and/or vestibular disorders.
- ▶ A collaborative approach including CBT may have additional benefits in the treatment of persistent symptoms following SRC.
- ▶ Currently, there is no compelling evidence to support the use of pharmacotherapy in the management of persistent symptoms following SRC.
- ▶ Evaluation of multifaceted treatments for persistent symptoms following SRC is an area for further evaluation.
- ▶ Further high-quality randomised controlled trials on the effects of treatment for persistent symptoms following SRC are required.
- ▶ Overall, these difficult cases should be managed in a multidisciplinary collaborative setting by healthcare providers with experience in SRC.

Review limitations

The main limitation to our systematic review was the large degree of heterogeneity and low methodological quality of the included studies. In addition, the wide diversity in definitions of 'persistent symptoms', outcome measures used and timing of assessments limited our ability to compare studies and conduct a meta-analysis. Furthermore, we only included studies that evaluated investigation or treatment of SRC. Studies including other causes of mild TBI may provide further evidence for assessment and treatment modalities that may also be useful in the population with SRC. Finally, there was an inherent limitation related to publication bias. The small number of included articles and their heterogeneity, however, limited our ability to evaluate the extent of publication bias.

CONCLUSIONS

'Persistent symptoms' following SRC can be defined as clinical recovery that falls outside expected time frames (ie, >10–14 days in adults and >4 weeks in children). It does not reflect a single pathophysiological entity, but describes a constellation of non-specific post-traumatic symptoms that may be linked to coexisting and/or confounding pathologies. A detailed multimodal clinical assessment is required to identify specific aetiologies that may be contributing to persistence of post-traumatic symptoms. At a minimum, the assessment should include a comprehensive history, focused physical examination and special tests where indicated (eg, graded aerobic exercise test). Treatment should target specific pathologies identified. There is preliminary evidence supporting the use of symptom-limited aerobic exercise, targeted physical therapy and a collaborative approach that includes CBT. Currently, there is no compelling evidence to support the use of pharmacotherapy. Overall, these are difficult cases that should be managed in a multidisciplinary collaborative setting, with healthcare providers with experience in SRC.

What is already known?

- ▶ Most patients with sport-related concussion (SRC) recover progressively and uneventfully when managed with a brief period of rest and graded return to play. Some patients, however, have persistent symptoms following SRC.
- ▶ Currently, there is limited evidence to help guide clinical assessment and treatment of persistent symptoms following SRC.

What are the new findings?

- ▶ A detailed, multimodal clinical assessment is required to identify specific aetiologies that may be contributing to persistence of post-traumatic symptoms. At a minimum, the assessment should include a comprehensive history, focused physical examination and special tests where indicated (eg, graded aerobic exercise test).
- ▶ Treatment should target specific pathologies identified on assessment. Overall, there is preliminary evidence supporting the use of symptom-limited aerobic exercise, targeted physical therapy and a collaborative approach that includes cognitive-behavioural therapy. Currently, there is no compelling evidence to support the use of pharmacotherapy.
- ▶ Persistent symptoms following SRC reflect difficult cases that should be managed in a multidisciplinary collaborative setting, with healthcare providers with experience in SRC.

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