FOCUSED CLINICAL QUESTION

In a 30yo active military male suffering from post-traumatic headaches (PTH) during physical exertion, is a progressive aerobic exercise program effective for decreasing headache pain with physical activity?

AUTHOR

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CLINICAL SCENARIO

The patient is a 30-year-old active military male approximately 3 months after suffering a concussion in the line of active duty. He has been treated with rest and medication for continuing headache pain that severely limits the physical activity he must perform in order to return to full duty. After a month of progressive aerobic exercise rehabilitation, he is able to walk on a treadmill for 7 minutes with no incline, reaching only 45-50% of his age-predicted maximum heart rate before being limited by significantly increased headache pain.

I worked with many patients of this description throughout my clinical at Fort Bragg. While several individuals, such as this patient, showed only small improvements with exercise training, the large majority who followed a progressive exercise program based on maximum heart rate reached during the Buffalo Concussion Treadmill Test were able to return to full duty and exercise without significant headache limitations.

Concussion and mild-traumatic brain injury (mTBI) are relatively common in active military members[1], and I am not aware of a well-known consensus on the effectiveness of this type of exercise treatment for chronic exertional headache symptoms. As chronic post-concussion symptoms, such as headache pain, often limit return to job and physical activity requirements for these service-members[1], investigating this topic could help me more effectively treat patients with this chronic, debilitating problem in future practice.

SUMMARY OF SEARCH
[Best evidence appraised and key findings]

- Currently, there is no evidence investigating specifically post-traumatic headache pain with physical exertion in any population. However, initial stages of lower-level research have been performed investigating effects of progressive aerobic exercise on post-concussion syndrome (PCS) symptoms, including headache, and return to activity. Ten studies were identified that met inclusion/exclusion criteria, and three of the most relevant were chosen for review and discussion.
- Only initial stages of research have been completed to address exercise treatment for chronic post-traumatic concussion symptoms. Thus, the existing evidence is of relatively low quality, lacking randomization, large sample sizes, and specific comparison to other forms of treatment. However, available research consistently suggests that controlled progressive aerobic exercise training at a sub-symptom level based on heart rate reached during treadmill testing may be both safe and effective in decreasing chronic PCS symptom severity and decreasing activity limitations due to symptom exacerbation with exertion.
- Further higher level research with larger sample sizes, randomization, and samples specific to the military population should be completed in the future. Comparison of different types of progressive aerobic exercise (stationary bike, treadmill, elliptical, etc.), comparison to the more traditional prescription of rest, and standardization of most effective exercise protocol may all be important points of focus in future research.

CLINICAL BOTTOM LINE

The evidence suggests that progressive sub-symptom aerobic exercise training may be safe and likely to decrease headaches with activity in a patient with exertional post-traumatic headache. Generally, it is accepted that the beneficial clinical effects in athletic populations may be generalized to military patients due to similarly vigorous activity requirements. However, due to the small quantity of relevant research, best clinical judgement and patient preferences should also be taken into account to make the most informed treatment decisions.

This critically appraised topic has been individually prepared as part of a course requirement and has been peer-reviewed by one other independent course instructor

SEARCH STRATEGY

Terms used to guide the search strategy			
Patient/Client Group	**I**ntervention (or Assessment)	**C**omparison	**O**utcome(s)
military army male* man men soldier* young adult* post-traumatic post traumatic concussion* post-concussion syndrome postconcussion syndrome traumatic brain injur* exertion* headache*	aerobic exercise rehab* progress*	N/A	headache* exertional headache* posttraumatic headache* post-traumatic headache* headache symptom* activity exertion* pain

Final search strategy:

1. exercise
2. (headache* OR exertional headache* OR posttraumatic headache* OR post-traumatic headache*)
3. (concussion* OR brain concussion* OR post-concussion syndrome OR postconcussion syndrome OR traumatic brain injur*)
4. (military OR army OR soldier*)
5. #1 AND #2 AND #3 AND #4
6. #1 AND #2 AND #3

Databases and Sites Searched	**Number of results**	**Limits applied, revised number of results (if applicable)**
PubMed	32	
SPORTDiscus	18	
CINAHL	16	

INCLUSION and EXCLUSION CRITERIA

Inclusion Criteria
• RCTs, controlled trials, uncontrolled trials, case series, systematic reviews, meta-analyses • Published up to September 2015 • Protocol that included aerobic exercise intervention • Population with average age between 25 and 40 years old • Included headache symptoms as an outcome measure • Published in English
Exclusion Criteria
• Studies involving participants suffering primarily from non post-traumatic headache types (ie cervicogenic, migraine, etc.) • Studies evaluating intervention for headache during acute concussion treatment • Single case studies • Abstracts, conference proceedings, letters to the editor, dissertations, narrative review articles

RESULTS OF SEARCH

Summary of articles retrieved that met inclusion and exclusion criteria

Author (Year)	Study quality score	Level of Evidence	Study design
1. Weightman MM, Bolgla R, McCulloch KL, Peterson MD. (2010)	AMSTAR 4/11	3-a	Systematic Review
2. Schneider KJ, Iverson GL, Emery CA, et al. (2013)	AMSTAR 8/11	3-a	Systematic Review
3. Leddy JJ, Willer B. (2013)	AMSTAR 4/11	3-a	Systematic Review
4. Baker JG, Freitas MS, Leddy JJ, et al. (2012)	Downs & Black 24/29	3-b	Retrospective case control
5. Leddy JJ, Koslowski K, Donnelly JP, et al. (2010)	Downs & Black 25/29	4	Prospective case series
6. Ellis MJ, Leddy JJ, Willer B. (2014)	AMSTAR 4/11	3-a	Systematic Review
7. Leddy JJ, Cox JL, Baker JG, et al. (2013)	Downs & Black 25/29	4	Prospective case series
8. Silverberg et al. (2013)	AMSTAR 3/11	3-a	Systematic Review
9. Leddy JJ, Cox JL, Baker JG, et al. (2013)	Downs & Black 24/29	4	Prospective case series
10. Makdissi M, Cantu RC, Johnston KM, et al (2013)	AMSTAR 8/11	3-a	Systematic Review

BEST EVIDENCE

The following 3 studies were identified as the 'best' evidence and selected for critical appraisal. Reasons for selecting these studies were:

- **Schneider et al. (2013):** This review is at the highest level of evidence available on the topic and also has the highest AMSTAR score for methodological quality available at this level. While it is not specific to the military population, it focuses on effectiveness of exercise or rest for decreasing symptoms of PCS, including headaches. It also recognizes the limitations of the current evidence.
- **Leddy et al. (2010):** This study is a lower level of evidence but investigates the exact outcome and intervention targeted by the clinical question. It also provides specific statistics to strengthen the more qualitative analysis in the available systematic reviews. It is not specific to the military population but includes the targeted age range and includes athletes who tend to have physical demands similar to the vigorous requirements of the military.
- **Leddy & Willer (2013):** This review is also at the highest level of evidence available. While it has a lower AMSTAR quality score than some other systematic reviews, it is more directly related to the effect of graded aerobic exercise treatment on post-concussion headache symptoms. It also provides good backing for its conclusions based on higher level physiologic evidence of autoregulatory dysfunction following concussion and the links this has to both headaches and exercise.

SUMMARY OF BEST EVIDENCE

(1) Description and appraisal of *The effects of rest and treatment following sport-related concussion: a systematic review of the literature* by Schneider et al. (2013).

Aim/Objective of the Study/Systematic Review:
The objective of the study was to assess the current evidence for utilization of rest and various rehabilitation strategies in management of sport related concussion symptoms.

Study Design

[e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant]

Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.

- Systematic review of literature
- Methods: Two searches were performed including these databases: PubMed, CINAHL, PsychInfo, Cochrane Controlled Trials Registers, Health STAR, Sport Discus, EMBASE, Web of Science, and ProQuest. The first search focused on the use of rest in management of sport-related concussion. The second search focused on benefit of treatment/rehab strategies in management of sport-related concussion. The Oxford Centre for Evidence Based Medicine was used to determine level of evidence for each study. Quality of evidence for each study was evaluated using Downs and Black criteria.
- Search strategy:
  - Rest: Various combinations of the following keywords were used to search databases: Brain Concussion, Post-Concussion Syndrome, Sport-related concussion, mild traumatic brain injury, Rest, treatment outcome, Cognitive rest, Physical exertion, Therapy, Rehabilitation, Treatment, Sport.
  - Treatment: Various combinations of the following keywords were used in the search: Brain Concussion, Post-Concussion Syndrome, Sport-related concussion, mild traumatic brain injury, Therapy, Treatment Outcome, Rehabilitation, treatment, Exercise therapy, Exercise, Brain training, Cervical spine, Neck, Vertigo, Dizziness, Headache, Postural Balance, Cognitive therapy, pharmacotherapy.
- A-priori selection criteria
  - Randomised controlled trials, cohort studies, quasi-experimental designs, case series, case crossover studies, case studies, peer-reviewed published articles, abstracts
  - Participants with symptoms caused by sport-related concussion
  - Assessment of effects of rest period or treatment/rehab for management of sport-related concussion
- Data Extraction included study design, participant information (sample size, age, gender), treatment information (type, intensity, duration), results, effect size, means with 95% CIs (if possible, 95% CIs calculated if not in original study), conclusions and author comments.

Setting

[e.g., locations such as hospital, community; rural; metropolitan; country]

- Outpatient settings including medical and physical therapy clinics, outpatient hospital programs, high school and college level medical clinics
- Some interventions were performed partially as home-based programs
- The country where each included study took place was not specified

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

- Rest: 3 retrospective case series with a total of 328 participants post-concussion, including male and female high school and college aged athletes.
- Treatment: 11 studies with a total of 129 male and female participants post-concussion. Study types included 4 case studies, 3 case series, 2 case cross-overs, 1 retrospective quasi-experimental, and 1 randomized controlled trial. Ages included high school, college, and adult aged athletes. Participant characteristics varied too much for meta-analysis to be performed. All studies related to medication use included only one participant except for the study regarding amantadine.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control

Rest: Individuals who continued with cognitive and physical activity after concussion. Specific criteria for levels of activity were not provided.

Treatment: Pharmacologic controls received non-specified standard therapy with no additional medication. Several studies were case studies or series with no control group for comparison. One study utilized graded exertion protocol only as a control in comparison to graded exertion in combination with other therapies. One case crossover study used a 2-3 week baseline period of no added exertional activity as a control comparison.

Experimental

Rest: Interventions in the three studies consisted of some form of cognitive rest or a combination of cognitive and physical rest following concussion. One study prescribed a 1 week duration of rest. Specifics about duration were not provided for the other two studies.

Treatment: Four exercise-based interventions included graded submaximal exercise programs either on a treadmill or stationary bike at 50-80% maximum heart rate for 4-6 weeks 5-6 times per week. Two interventions included a combination of progressive aerobic exercise training, vestibular rehabilitation and manual therapy with one treating patients once a week for 8 weeks. Five studies investigated pharmacologic treatment of post-concussion symptoms with Sumatriptan, intranasal diamin-8-D-arginine vasopressine, and amantadine. One intervention utilized hyperbaric oxygen therapy for five 1-hour sessions.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

Rest: Duration of symptoms including headache pain, ImPACT score, and the Post-Concussion Symptom Scale were utilized as outcome measures. ImPACT is a computerized test that measures symptoms (including headache), verbal/visual memory, reaction time, and processing speed. The Post-Concussion Symptom Scale is a self-report measure of intensity of 22 symptoms with a scale ranging from 0-No symptoms to 6-Severe for each symptom.

Treatment: A numeric pain rating scale for headache ranging from 0-no pain to 10-severe pain was utilized in several studies. The Post-Concussion Symptoms Scale-Revised, ability to return to prior level of physical activity, duration reached on the incremental treadmill exercise test, ImPACT score, graded symptom checklist (26 symptoms rated 0 severity to highest severity at 6), and medical clearance to return to sport given by a blinded sport medicine physician were all used as outcome measures related to concussion symptoms and post-traumatic headache.

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

Data from all included studies was not combined for statistical analysis due to heterogeneity of treatment types and of the samples.

Rest: Duration of symptoms, including headache pain, was significantly less for those not prescribed cognitive rest (29 days) than those prescribed cognitive rest (57 days) at p=.002 in one study. However, another study found that after taking one week cognitive and physical rest, performance on ImPACT was significantly higher with less symptoms (F=10.6, p=.001).

Treatment: Headache pain decreased more with amantadine use than in controls, though both groups improved and no statistical data was provided. Submaximal aerobic training combined with other treatments resulted in ability for participants to return to prior level of physical activity after an average of 4.4 weeks (95% CI 3.1, 5.7) in one study. Mean post-concussion symptoms scale-revised score also decreased from 30 (95% CI 19.8, 40.19) to 6.7 (95% CI 3.91, 8.13).

Graded symptom checklist scores for athletes decreased from 8.57 (95% CI 3.6,13.54) to 5.42 (95% CI 2.85, 7.99) after an average of 25 days (95% CI 18.03,31.97) of submaximal aerobic treadmill training. A paired t-test showed decreased symptom severity after treatment with p=.002 and effect size .72. Participants were also able to exercise for a longer duration without symptoms or headache, improving from 9.75 min (95% CI 5.95, 13.19) to 18.67min (17.23, 20.11) with an effect size of 1.40.

Individuals in a progressive exercise program as well as other therapies were more likely to be medically cleared to return to sport after 8 weeks (Fisher's exact test p<.001).

Original Authors' Conclusions

[Paraphrase as required. If providing a direct quote, add page number]

Very few published studies exist currently to examine the effectiveness of exercise and various other treatment methods for post-concussive symptoms, including headache with exertion. What studies do exist generally lack randomisation, large enough sample sizes, control groups, and prospective designs. Further research is needed to determine most effective rehabilitation protocols for post-concussion symptom treatment.

At this point, the optimal time period for rest and specific type of rest after concussion injury is unknown, and research results are somewhat conflicting and lack long-term follow-up. Due to lack of evidence and safety reasons, it is recommended that individuals return gradually to both physical and cognitive activities after concussion, avoiding symptom aggravation. There is also a lack of research on pharmacologic treatment of headaches after concussion. There is some weak evidence that amantadine may improve post-traumatic

headache pain. There is some evidence for progressive exercise improving headache and other symptoms as well as functional capabilities in those who are slow to recover from concussion. A combined treatment program including both vestibular therapy and progressive exercise may be beneficial in reducing post-concussion symptoms. Cervicogenic headaches after concussion may be improved with cervical manual therapy and neuromotor control exercises.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment on anything you believe was missing in the paper.]

This systematic review scored a 9/11 on the AMSTAR and is at the level of 3a evidence according to the Oxford Centre for Evidence-based Medicine. Search strategy and inclusion/exclusion criteria were determined a-priori, and multiple authors analysed studies and reviewed each other's work to decrease risk of bias. The literature search was comprehensive, and although meta-analysis could not be completed, authors noted that this was due to heterogeneity of treatment types in the available literature. Quality of the included studies was assessed using a validated tool, and a clear supplementary table of study characteristics was provided. The authors accurately describe how the lack of current high quality evidence may affect generalizability and strength of recommendations made based on the included research studies. While authors noted reasoning for excluding some studies, a list of excluded studies was not provided. A table including all author disclosures and affiliations did not reveal any obvious risks for publication bias, but no funnel plot or statistical tests were performed specifically to assess publication bias.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

Results of this systematic review are generally in favour of progressive submaximal aerobic exercise training for decreasing symptoms of post-concussion syndrome and returning athletes to activity without aggravation of symptoms. This recommendation is based on low quality evidence, but improvements were found to be significant in each study with p values $< .05$, indicating a very low probability that favourable results were due to chance. Effect size for submaximal exercise treatment was found to be moderate in one study, indicating increased chance of clinical meaningfulness of results. Also, 95% CIs for symptom severity and tolerance for duration of activity without symptom aggravation indicate that the favourable changes in these variable and the effect size are clinically meaningful. Results of the study comparing only progressive exercise to a combination of progressive exercise with other therapies also found that a combined therapy regimen may be more beneficial for return to sport with little chance of results being due to chance ($p<.001$).

Regarding rest after concussion, results are somewhat mixed. Duration of symptoms was found to be increased with cognitive rest following injury with low probability of results being due to chance ($p=.002$). However, symptoms in another study decreased with one week of rest and low probability of changes being due to chance ($p=.001$). Thus, it is difficult to make a strong recommendation for duration or timing of cognitive or physical rest based on this review.

The review notes that amantadine was found to improve symptoms, verbal memory and reaction time significantly more than no medication, but specific interpretation of results cannot be performed due to lack of other information given about the statistical results of the study. Thus, it is difficult to draw clinically meaningful conclusions about the use of amantadine as a treatment for post-concussion symptoms based on this review.

(2) Description and appraisal of *A preliminary study of subsymptom threshold exercise training for refractory post-concussion syndrome* by Leddy et al. (2010).

Aim/Objective of the Study/Systematic Review:

The purpose of this study was to evaluate the safety and effectiveness of progressive, sub-symptom threshold exercise training (SSTET) to improve symptoms of post-concussion syndrome (PCS).

Study Design

[e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant]

identify data collection/analysis methods.

- Prospective case series without randomization or blinding
- Outcome measures associated with treadmill testing were performed at baseline and every three weeks following until patient was able to exercise to voluntary exhaustion without exacerbation of PCS symptoms. Outcome measures regarding symptom severity and adverse effects were assessed daily. Phone call follow up regarding return to sport/work occurred 3 months after completing treatment.
- Compliance was confirmed by the individual supervising each exercise session.

Setting

[e.g., locations such as hospital, community; rural; metropolitan; country]

- University of Buffalo Sports Medicine Concussion Clinic in Buffalo, NY, USA
- Patients also performed much of the exercise program as an HEP within close vicinity to the concussion clinic

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on key demographic variables; number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

- Eligibility Criteria:
  - Diagnosis of PCS: Fulfill the World Health Organization's criteria for symptoms at rest for at least 6 weeks but less than 52 weeks; Experience symptom aggravation during graded treadmill exercise test
  - Classified as low cardiac risk by the American College of Sports Medicine
- Exclusion criteria: PCS for less than 6 weeks or greater than 52 weeks, focal neurologic deficit, orthopaedic injury, increased cardiac risk, cervical disc herniation, inability to understand English, major depressive disorder, antidepressant/beta-blocker/anti-convulsant use, post-traumatic stress disorder, litigation.
- Convenience sample chosen from patients being treated for PCS at the University of Buffalo Concussion Clinic. A total of 40 patients were considered for inclusion, with 27 being ineligible because they either lived too far from clinic, did not show up for evaluation, had a psychiatric diagnosis, of could not exercise for health reasons. One additional patient chose to drop out because she did not like to exercise.
- The 12 final subjects included 7 males and 5 females with an average age of 27.9 and were an average of 19 weeks post-concussion. 6 were athletes and 6 non-athletes.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control

- Each participant acted as their own control during an initial 2-3 week baseline period during which they did not change their normal daily activity.

Experimental

- After the baseline period, patients performed their second treadmill test at the concussion clinic and performed aerobic exercise at home or at their local sports facility at 80% of their maximum heart rate reached during the test.
- Patients exercised on a treadmill for the same duration as they reached on the treadmill test or until exacerbation of PCS symptoms, whichever occurred first. Exercise was performed once per day 5-6 days per week with supervision of at least one other person.
- Duration and target heart rate were adjusted after each re-evaluation of the treadmill test every 3 weeks. Treatment continued until the patient was able to exercise to voluntary exhaustion on the treadmill test.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

- Treadmill Test following Balke protocol
  - The article authors administered the test at the University of Buffalo Sports Medicine Concussion Clinic.
  - Patient's baseline PCS symptom severity, heart rate and blood pressure were measured.
  - Patients then exercised on a treadmill beginning at 0% incline and 3.3mph. After 1min, incline increased to 2.0%. The incline increased by 1.0% each minute after that with the same speed. This continued until patients experienced exacerbation of symptoms.

- Heart rate and Borg scale rating of perceived exertion (RPE) were measured every minute. Blood pressure was measured every 2 minutes. Participants were monitored for any adverse effects for an hour following termination of the test. VO_2 was estimated based on treadmill speed and incline reached.
  - Reaching voluntary exhaustion at or near age-predicted maximum heart rate without symptom exacerbation was considered successful completion of the test.
- Adverse reactions to exercise
- Graded symptom checklist (GSC) for severity of PCS symptoms over the prior 24 hours: Patients rated themselves on 26 symptoms from 0 severity to highest severity at 6.
- Return to work/sport

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

- No adverse reactions were reported. One participant did report slightly increased symptoms during the first week of treatment but these were not directly related to exercise and did not qualify as adverse events.
- GSC: Total mean baseline symptom score was 9.67. Specifically for athletes, the baseline mean was 8.57 and for non-athletes 10.99. The mean score for the entire treatment period was 5.42, significantly reduced from baseline according to a paired t-test (p=.002). All participants reported more decreased symptom level during the treatment period than during the baseline control period.
  - Simulation Modeling Analysis: 8 of 11 subjects (1 of the 12 was excluded from SMA analysis because he did not provide enough symptom information) reported decreased symptom level at the p<.02 level of significance. All patients demonstrated a pattern of decreasing symptom level as the treatment period went on with at least a significance level of p<.02.
  - Cohen's d: 2.50
- Average symptom exacerbation occurred at a heart rate of 147 +/- 27bmp at baseline. After completion of treatment, average maximum heart rate reached during exercise increased to 179 +/- 17bpm with no symptom aggravation and p<.001. Exercise time without symptom exacerbation increased from 9.75 +/- 6.38 min to 18.67 +/- 2.53 min after treatment with p=.001. The correlation coefficient was r=-.55 with p=.04 for the relationship between exercise capacity (maximum heart rate reached during exercise) and symptom level. Treatment period necessary to reach voluntary exhaustion with symptom exacerbation ranged from 11 to 112 days.
- At follow-up, 10 of 12 participants were still symptom-free at rest. One had migraine headaches, which were experienced prior to concussion as well. One had cognitive and visual symptoms. 100% of subjects had returned to full work, school, and athletic activities.

Original Authors' Conclusions

[Paraphrase as required. If providing a direct quote, add page number]

- PCS may be safely treated using an individualized and progressive sub-symptom aerobic exercise rehabilitation program. Patients significantly improved symptom levels, exercise capacity without symptom aggravation, and sport/work/school tolerance after completion of this type of treatment. The rate of symptom improvement was directly related to exercise intensity achieved without symptom exacerbation during treatment. Most commonly reported symptoms limiting exercise initially were headache, head pressure, and dizziness. Researchers postulated that these symptoms may be related to deficits in cerebral autoregulation caused by concussion, and that progressive exercise re-trained the brain to regulate cerebral blood flow when blood pressure rose during exercise, thus decreasing headache/pressure and dizziness symptoms. Essentially, progressive aerobic exercise may help to re-establish physiologic homeostasis after injury
- Further randomized controlled studies are necessary to support this case series and investigate the slight possibility that PCS symptoms could have resolved spontaneously without intervention. The likelihood of spontaneous resolution in this study is highly unlikely since subjects had been symptomatic for months prior to the study and did not improve during the 2-3 week control period. Further research may also address the role of physiologic assessment in diagnosis of PCS and determining when patients may safely return to full activity.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment on anything you believe was missing in the paper.]

This study scored a 25/29 on the Downs & Black Checklist for study quality and is at the 4 level of evidence according to the Oxford Centre for Evidence-based Medicine. While this study is of a lower evidence level, researchers report specific statistics and probability values relevant to main outcomes. Authors provide adequate details in all paper sections for study replication and interpretation of results. While the population

affected by PCS, which increases the study's external validity. Because neither participants nor those measuring outcomes were blinded, consequent bias could decrease the study's internal validity. The lack of randomization could further decrease internal validity by introducing selection bias to the study. No a-priori power analysis was completed, but effect size and statistical significance were both reported for main outcomes. However, researchers do recognize these limitations in the paper and call for further higher level research to provide more powerful, generalizable and valid results.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

Results of this study suggest that a controlled progressive aerobic exercise rehabilitation program may reduce symptom level and activity limitations due to exacerbation of symptoms with exertion in those with chronic PCS symptoms, including headache. Generalizability of these findings to larger populations with PCS is limited by the small sample size, and lack of randomization limits the confidence with which one can say that results were definitely not biased or due to confounding variables. However, the large value for Cohen's d indicates a large standardized effect size, which increases the likelihood that the study results demonstrate clinically meaningful change, especially since the results showing improvement with treatment were statistically significant ($p<.05$). This means that the probability of the differences in symptom level and exercise capacity after treatment being due to chance is small and that these differences were of great enough magnitude to be important clinically. While an a-priori power analysis was not completed, the combination of statistical significance and a large effect size indicate that the study was sufficiently powered to find a clinically meaningful effect. Thus, this study provides clinically meaningful data that this type of exercise program may be utilized safely and effectively to decrease PCS symptoms, including headache, but support of other existing studies and future larger randomized trials may help strengthen these conclusions.

(3) Description and appraisal of *Use of graded exercise testing in concussion and return-to-activity management* by Leddy & Willer (2013).

Aim/Objective of the Study/Systematic Review:

The purpose of this study was three-fold

- Define the pathophysiology of concussion and post-concussion syndrome (PCS).
- Review the effectiveness of exercise testing in assessing physiologic recovery from acute effects of concussion.
- Review evidence for utilizing an aerobic exercise program to help individuals with concussion or PCS return to activity.

Study Design

[e.g., systematic review, cohort, randomised controlled trial, qualitative study, grounded theory. Includes information about study characteristics such as blinding and allocation concealment. When were outcomes measured, if relevant]

Note: For systematic review, use headings 'search strategy', 'selection criteria', 'methods' etc. For qualitative studies, identify data collection/analyses methods.

- Literature Review
- Search Strategy: No strategy identified.
- Selection Criteria: No selection criteria identified beyond evidence generally referencing concussion or post-concussion syndrome.
- Methods: The two authors reviewed available evidence qualitatively to form conclusions regarding the review objectives. No statistical analyses or meta-analysis were performed.

Setting

[e.g., locations such as hospital, community; rural; metropolitan; country]

- The majority of study locations were not specified. The evidence regarding Buffalo Concussion Treadmill Testing (BCTT) was performed in a laboratory environment with a home exercise component.

Participants

[N, diagnosis, eligibility criteria, how recruited, type of sample (e.g., purposive, random), key demographics such as mean age, gender, duration of illness/disease, and if groups in an RCT were comparable at baseline on

key demographic variables, number of dropouts if relevant, number available for follow-up]

Note: This is not a list of the inclusion and exclusion criteria. This is a description of the actual sample that participated in the study. You can find this descriptive information in the text and tables in the article.

- Few details about designs of the included studies were provided.
- Participants of studies included athletes, military, and non-athletes. General ages included high school, college, and adult.
- Studies with participants in acute and chronic stages of concussion/TBI were included in the review.
- At least two small, non-randomized controlled studies of adults with PCS symptoms were included. One also separated participants into groups with either physiologic, cervicogenic or vestibular origins of their PCS symptoms.

Intervention Investigated

[Provide details of methods, who provided treatment, when and where, how many hours of treatment provided]

Control

- One study utilized a control group that performed no intervention
- One study utilized a placebo stretching intervention
- One referenced study specified complete rest as the control intervention

Experimental

- Graded aerobic exercise interventions were the focus of experimental groups
  - One study described using gradual physical conditioning, general coordination exercise, visualization, education, and motivational methods
  - The Zurich Consensus Statement recommends that patients begin a progression from light activity to sport/work specific activity once they are symptom-free at rest. Recurrence of symptoms, such as headache, indicates the need to return to the prior level of activity for extended time. Specifics of the protocol were not provided.
  - Several of the included studies utilized progressive aerobic activity based on gradually increasing percentages of the threshold heart rate measured during the initial BCTT. The patient began exercising for 20 minutes per day, 5-6 days per week at 80% of his/her BCTT threshold heart rate for 2 weeks. Exercise was performed supervised on a stationary bike, treadmill or elliptical. If the patient could complete 20 minutes of exercise at this level at the end of 2 weeks without PCS symptoms aggravation, including headache pain, he/she increased exercise heart rate by 5bpm for non-athletes or 10bpm for athletes. If they could not complete 20 minutes without significant symptom aggravation, they remained at that exercise level. This re-evaluation was repeated every 2 weeks until the patient reached 85-90% of their age-predicted maximum heart rate. At this point, graduated sport or work specific protocol based on the Zurich guidelines began. If PCS symptoms returned, the BCTT was repeated, and the patient's exercise was returned to less intensive levels as necessary to avoid excessive symptom exacerbation. This intervention took place in a lab or clinic with PT supervision.
  - One study used the BCTT protocol above for those with physiologic PCS symptoms and combined the protocol with specific treatment for non-physiologic symptoms due to cervicogenic or vestibular post-concussion symptoms.
  - One study used the BCTT protocol, but patients performed the exercise program as an HEP and were contacted via phone or email to increase exercise target heart rate every 2 weeks as long as they were responding well to the program. Patients were required to have supervision and wear a heart rate monitor during exercise.

Outcome Measures (Primary and Secondary)

[Give details of each measure, maximum possible score and range for each measure, administered by whom, where]

- Primary: Buffalo Concussion Treadmill Test (BCTT)
  - First, baseline heart rate, blood pressure, and symptom severity (0-10 on visual analog scale) are measured. The individual begins walking on a treadmill at 3.6mph with 0% incline. At one-minute intervals, the incline is increased by 1% while maintaining the same speed. Rating of perceived exertion (RPE, Borg scale) and symptom severity are evaluated each minute. Heart rate and blood pressure are measured every 2 minutes. The test is stopped either at 20 minutes or if symptoms increase by 3 or more points from baseline on the VAS or RPE reaches at least 19. If the patient reaches the maximum incline, speed is then increased by .4mph each minute until criteria for ceasing the test are reached.
- Secondary:
  - Computerized Neuropsychological (cNP) tests, including ANAM and ImPACT
    - Automated Neuropsychological Assessment Metrics (ANAM): Assessment developed by the U.S. Department of Defense to assess attention, concentration, reaction time, memory, processing speed, decision-making, and executive function. Often used to evaluate cognitive changes overtime for

ImPACT: Measures symptoms (including headache), verbal/visual memory, reaction time, and processing speed.
    - Brain functioning indicators: fMRI cortical connectivity and activation, amounts of brain-derived neurotrophic factor (BDNF), autonomic regulation during exercise, including heart rate and blood pressure.

Main Findings

[Provide summary of mean scores/mean differences/treatment effect, 95% confidence intervals and p-values etc., where provided; you may calculate your own values if necessary/applicable]

- Few statistics or specific numerical results were provided for the included studies. No adverse effects were reported for any graded exercise program.
- 100% of high school students post-TBI returned to sport without recurrent PCS symptoms after the BCTT protocol followed by the Zurich Guidelines for graduated return to play in one study. 48% of these athletes scored below average on cNP testing on the same day they completed the BCTT with no symptom exacerbation.
- BCTT gradual exercise progression protocol resulted in significantly improved heart rate and blood pressure regulation, as well as increased rate of recovery and restored sport/work functioning significantly more than no intervention in individuals with physiologic TBI symptoms lasting longer than 3 weeks. Those with cervicogenic, vestibular or a combination of disorders had similar results when BCTT protocol was combined with treatment specific to the non-physiologic disorder.
- Gradual reintegration of cognitive and physical activity after the initial 3 days post-injury in adults is more effective in improving post-concussion symptoms than continued total rest in the acute period. Continued rest is associated with physical deconditioning and secondary symptoms, including fatigue and depression, especially in athletes or very active individuals.
- The BCTT accurately differentiated between individuals with physiologic, cervicogenic, vestibular, affective, and migraine origins of symptoms, including headache.
    - Physiologic: Distinct sub-maximal threshold limited by sudden increase in symptoms, including headache.
    - Cervicogenic: No distinct submaximal threshold and able to exercise to exhaustion near maximum heart rate. Initial posterior headache improved early in exercise but usually returned near maximal heart rate and exhaustion.
    - Migraine: BCTT not performed if migraine present. If able to test, no distinct submaximal threshold and able to exercise to near maximum heart rate and exhaustion without symptoms.
    - Affective: No distinct submaximal threshold and able to exercise to exhaustion. Initially flat/depressed mood usually improved with exercise.
    - Vestibular: No distinct submaximal threshold. Able to exercise to exhaustion near maximum heart rate. Vertigo was not usually experienced during the test, but symptoms of mild blurred vision, trouble focusing, or lightheadedness often occurred.
- fMRI cortical connectivity and activation, levels of BDNF, and cerebral blood flow regulation were significantly improved with aerobic exercise

Original Authors' Conclusions

[Paraphrase as required. If providing a direct quote, add page number]

- Rest beyond 3 weeks after TBI seems detrimental to recovery both cognitively and physically. Regular aerobic exercise seems to be safe and beneficial for improving brain and physical functioning, as well as decreasing post-concussive symptoms.
- The BCTT is an accurate, safe and functionally relevant measure of physiologic recovery and indicator of readiness to return to regular activity (sport or work) for individuals with post-concussion symptoms, including headache, more than 3 weeks post-injury. The BCTT may be a more accurate indicator of readiness to return to play/work than computerized cognitive tests in these chronic stages of concussion/mTBI.
- The BCTT can guide an individualized subthreshold graded aerobic exercise program that can safely and effectively improve symptoms, including headache, brought on by exertional activity, as well as speed up return to activity and prior functioning better than no intervention or continued rest beyond 3 weeks post-injury. This intervention may be effective for individuals with not only physiologic origins of post-concussion symptoms, but also other origins of symptoms.
- Further research, including higher level randomized controlled trials, regarding exercise testing and treatment for those with chronic concussion symptoms is necessary to specify the mechanisms by which exercise benefits these individuals.

Critical Appraisal

Validity

[Identify the strengths and limitations of the study, including potential sources of bias. Comment on the overall methodological quality (including the score) as you determined from your assessment of the article. Comment

on anything you believe was missing in the paper.]

This study scored a 4/11 on the AMSTAR and is at the level of 3a evidence according to the Oxford Centre for Evidence-based Medicine. Search strategy, inclusion/exclusion criteria, and databases searched were not described. Two researchers wrote the review, but whether they both reviewed all relevant articles and how consensus was reached was not described, which could indicate higher risk of bias. A list of included and excluded studies and specific characteristics of every study were not clearly provided. Authors did not formally assess publication bias but stated that no conflict of interest existed and provided a list of affiliations and organizations providing financial support. Authors noted that available research on the topic is limited and includes mainly low levels of evidence, which may affect generalizability and strength of conclusions. The authors included some indirectly related higher level studies regarding exercise effects on brain functioning, providing additional scientific support for validity of their findings.

Interpretation of Results

[This is YOUR interpretation of the results taking into consideration the strengths and limitations as you discussed above. Please comment on clinical significance of effect size / study findings. Describe in your own words what the results mean.]

Results of this review are in favour of progressive submaximal aerobic exercise training and testing using the BCTT for decreasing symptoms of post-concussion syndrome and returning athletes to activity more quickly and without exacerbation of symptoms. This conclusion is based on low quality evidence but in these early stages of research, no higher quality studies are available, and the authors provide reasonable scientific backing to bolster the strength of their recommendations. However, the review is mainly qualitative and no combined statistical analyses were performed, so the significance of all results, effect sizes and confidence intervals cannot be utilized for interpretation of clinical significance or likelihood of overall results being due to chance.

EVIDENCE SYNTHESIS AND IMPLICATIONS

Clinical Implications

Based on the compilation of this best evidence, it seems that a progressive submaximal aerobic exercise program may be beneficial in decreasing symptoms of post-concussion syndrome, including post-traumatic headache pain with exertion. This type of rehab may also help patients return to full activity without being limited by headache symptom aggravation. A strong recommendation for progressive exercise training cannot be made at this point due to the low quality of evidence currently available and small samples of various studies, as well as heterogeneity of treatments and samples between studies. Few studies directly compare this type of treatment to other options, such as medication, rest or other types of exercise training. No studies explicitly investigated effects on headache pain with exertion, but included this in evaluation of post-concussion symptoms in general. Thus, a strong recommendation cannot be made for progressive aerobic exercise relative to other treatment options or specifically for directly decreasing headache pain with exertion in patients post-concussion.

However, results from all available research consistently found beneficial effects of a controlled progressive aerobic exercise program in individuals with chronic post-concussion symptoms, such as headache. Additionally, physiologic studies of brain function have shown many beneficial effects of aerobic exercise on cerebral blood flow and related autonomic regulation[11,12]. Current evidence consistently indicates that these autoregulatory factors are inhibited both acutely and chronically after brain injury[13]. These deficits may be a major cause of increased headache with exertion because intracranial pressure cannot be maintained with the changes in mean arterial pressure resulting from exercise[13]. Consequently, it seems realistic based on physiologic research that an aerobic exercise program should improve post-traumatic headache pain caused by activity after concussion by affecting the mechanisms that cause these deficits.

Thus, it may be reasonable to say that based on what evidence is currently available, use of progressive aerobic exercise training at a submaximal level may be beneficial for decreasing headache pain with physical activity in a patient post-concussion. However, clinicians should use this information along with their best clinical judgment and patient preferences to make the most informed clinical treatment decisions.

Research Implications

There is an overall lack of studies investigating the effect of a progressive aerobic exercise program specifically on post-traumatic headache pain. However, several studies address the reduction of post-concussion syndrome (PCS) symptoms, including headache, following such a program. These investigations are significantly limited in power and generalizability due to very small sample sizes, and may be at increased risk of bias due to lack of blinding and randomization. All evidence is Level 3 or 4 on the Oxford Centre for Evidence-Based Medicine scoring system, and no randomized controlled trials have been published meeting the criteria at this time. Systematic reviews addressing the topic generally lack evaluation of publication bias and may not all include adequate detail about studies included/excluded from the literature review. Studies specifically of military

personnel are lacking, so conclusions from studies in the general population and athletes are generalized to the military population. While athletes and military share many similar physical demands, this generalization may indicate some further reservations with interpreting findings for the population noted in the clinical question.

Implications for further study of this subject include need for higher level research with randomization and larger sample sizes to evaluate the clinical effectiveness of submaximal progressive aerobic training compared to controls, as well as compared to other available treatments for post-traumatic headache. More long-term follow up is also necessary to evaluate whether improvements made after treatment are sustained. Research regarding the most effective timing post-injury, intensity, duration, and frequency of exercise sessions is also lacking at this time and somewhat varied across studies included in this review, indicating need for further research on the specifics of this treatment in order to optimize effectiveness.

It seems that research on the subject of aerobic exercise as a treatment for post-traumatic headaches as a symptom of PCS is just in the beginning stages and as such includes mainly lower levels of evidence. However, findings from this limited evidence are consistent as to the effectiveness of a graduated exercise program for improving PCS symptoms, including headache pain.

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