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Management of acute musculoskeletal pain (excluding low back pain): a protocol for a systematic review and network meta-analysis of randomised trials

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Abstract

Introduction: Acute, non-low back related musculoskeletal pain is common and associated with significant socioeconomic costs. No review has evaluated all interventional studies for acute musculoskeletal pain, which limits attempts to make inferences regarding the relative effectiveness of treatments.

Methods and analysis: We will conduct a systematic review of all randomised controlled trials evaluating therapies for acute musculoskeletal pain (excluding low back pain). We will identify eligible, English-language, trials by a systematic search of CINAHL, EMBASE, MEDLINE, PEDro and the Cochrane Central Registry of Controlled Trials. Eligible trials will: (1) enrol patients presenting with acute, non-low back related musculoskeletal pain, and (2) randomise patients to alternative interventions or an intervention and a placebo/sham arm. Fractures will be considered ineligible, unless they are non-surgical and therapy is directed at pain relief. Pairs of reviewers will, independently and in duplicate, screen titles and abstracts of identified citations, review the full texts of potentially eligible trials and extract information from eligible trials. We will use a modified Cochrane instrument to evaluate risk of bias.

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to evaluate the quality of evidence supporting treatment effects. When possible, we will conduct: (1) in direct comparisons, a random-effects meta-analysis to establish the effectiveness of therapeutic interventions on patient-important outcomes; and (2) multiple treatment comparison meta-analysis within a frequentist framework to assess the relative effects of treatments. We will use a priori hypotheses to explain heterogeneity between studies and conduct meta-regression and subgroup analyses consistent with current best practices. We will interpret subgroup results according to published credibility criteria.

Ethics and dissemination: No research ethics approval is required for this systematic review. The results of this systematic review will be disseminated through publication in a peer-reviewed journal, conference presentations, and will inform a clinical practice guideline.

Key Words: acute pain; musculoskeletal; intervention; systematic review; network metanalysis

PROSPERO registration number: CRD42018094412

Article Summary

Strengths and limitations

- Our broad study eligibility criteria will increase generalizability of our results.
- We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate our confidence in treatment effects.
- We will optimize interpretability by presenting risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.
- Findings from our review will inform a clinical practice guideline and identify key areas for future research.
- Our results will be limited by possible shortcomings of the primary studies.

Introduction

Acute non-low back related musculoskeletal (MSK) pain, which include strains and sprains, dislocations, and whiplash present for less than 1 month, are associated with considerable morbidity in North America. The Burden of Musculoskeletal Diseases in the United States, 3rd edition, found that sprains and strains are the most frequent injury type for which medical care is sought and the majority of MSK injuries occur among working-age adults.[1] In 2013 there were 2,807,880 emergency department (ED) visits for sports-related injuries in the US,[2] and over 70% of visits to the ED are because of pain-related complaints.[3] Management often yields suboptimal outcomes: a survey of 842 acute pain patients at 20 US and Canadian hospitals found 40% reported their pain did not change or increased after visiting the ED, and 74% of patients were discharged in moderate to severe pain.[4]

Despite the prevalence of acute MSK complaints in primary care, a number of studies have highlighted inadequate pain education of among physicians.[5-7] The availability of numerous pharmacologic and non-pharmacologic therapies complicates the management decisions. A recently published series of 24 systematic reviews of treatment for common acute MSK injuries,[8] suffers from many important limitations, including: (1) selection bias due, in part, to exclusion of studies deemed to be at high risk of bias without empirically exploring if effect estimates differed from studies assigned low risk of bias, (2) interpreting results from individual studies as effective if the mean difference in a given outcome met the minimally important difference (MID) and ineffective if not - an interpretation relies on the unlikely assumption that all patients will experience the same degree of improvement, and fails to consider the distribution around the mean and the proportion of patients that achieve the MID, (3) no appraisal of the overall quality (confidence, certainty) of the evidence, and (4) no

statistical pooling of treatment effects. We propose to conduct a systematic review of randomized trials to assess the comparative effectiveness of available treatments for acute MSK pain (excluding low back pain) and assess quality of evidence using GRADE methodology.

Methods

Protocol registration

The protocol for this systematic review is registered with PROSPERO (CRD42018094412). This review was commissioned by the American Academy of Family Physicians and American College of Physicians and sponsored by the National Safety Council.

Standardized Reporting

We used the PRISMA-P checklist when writing our report.[9]

Information sources

We will identify eligible, English language, RCTs through a systematic search of MEDLINE, EMBASE, CINAHL, PEDro and CENTRAL, from inception of each database through February 2018. Our search has been refined for individual databases by an experienced medical librarian (Appendix). We will scan reference lists of relevant systematic reviews for additional articles.

Eligibility criteria and study selection

We will include therapeutic randomized trials that: 1) enroll adult patients (≥ 18 years) presenting with acute, non-low back related musculoskeletal (MSK) pain (pain with duration less than 4 weeks or defined by authors as "acute") in an outpatient setting, and 2) randomise them to currently available alternative interventions directed at pain relief (pharmacological or non-pharmacological) or a currently available intervention directed at pain relief and a placebo/sham arm. Eligible MSK conditions include sprains and strains. Surgical fractures, non-surgical fractures unless therapy is directed at pain relief, low back pain, neuropathic pain, acute cancer

pain, acute postoperative pain, acute dental pain, pain associated with labour and delivery, visceral pain, pain due to infection, and headaches will be excluded. We have excluded acute low back pain on request by the study funder, as they have previously commissioned evidence syntheses on this topic.[10 11]

Trained reviewers will work independently in pairs to screen titles and abstracts of identified citations, using standardized, pilot-tested forms in DistillerSR, an online systematic review software (Evidence Partners, Ottawa, Canada; http://systematic-review.net/). Teams of reviewers will screen full texts of any articles judged as potentially eligible. Reviewers will discuss disagreements to come to consensus, referring to an adjudicator if necessary. We will measure agreement between reviewers to assess the reliability of full-text review; specifically, we will calculate kappa (κ) values, and interpret them using the following thresholds: <0.20 as slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement and >0.80 as almost perfect agreement.[12]

Data abstraction

We designed standardized data abstraction forms and a detailed instruction video (accessible at: https://www.youtube.com/watch?v=1nwFJ61K3sQ). We will conduct calibration exercises prior to beginning data abstraction to ensure consistency and accuracy of extractions. Teams of reviewers will extract data independently and in duplicate. We will extract the following data from eligible trials into a standardized spreadsheet: study characteristics (e.g. the first author, publication year, country of origin, and funding source), participant and trial characteristics (e.g. sample size, mean age of participants, clinical condition, type and severity of injury, proportion with known chronic pain/condition prior to acute injury, and the proportion receiving opioids at

the time of enrollment), characteristics of interventions and comparators, patient-important outcomes (pain, function, health-related quality of life, patient satisfaction, return to work, proportion of patients with relief, re-injury and all reported adverse events). We used the longest follow-up reported.[13]

Risk of bias assessment

Among eligible studies, we will independently assess the following risk of bias issues: (1) random sequence generation, (2) allocation concealment, (3) blinding of study participants, personnel, and outcome assessors, and (4) incomplete outcome data (≥20% missing data will be considered at high risk of bias).[14] To assess the risk of bias we will use a modified version of the Cochrane risk of bias instrument.[15] Our instrument will use the following responses: 'definitely yes' or 'probably yes' (considered as low risk of bias), or 'definitely no' or 'probably no' (considered as high risk of bias). These response options have published evidence of validity for assessing blinding.[15] Any discrepancy in assessment of risk of bias will be resolved by discussion, or third party adjudication if needed. We will contact authors for missing information regarding risk of bias issues and unpublished data (e.g. effect estimates without accompanying estimates of precision).

Data synthesis

For the purposes of statistical pooling, we will explore treatment effects of interventions across all MSK complaints eligible for this review. However, we will also explore if treatment effects differ by clinical condition or injury severity (see Subgroup analyses, meta-regression and sensitivity analysis, below). Clustering strategies for clinical condition and injury severity will be

informed by the trials eligible for our review, which will be reviewed by our technical expert panel (see Acknowledgement section), blinded to study results.

Methods for direct comparisons

We will pool dichotomous outcomes that are reported by >1 RCT and calculate the relative risk and risk difference (RD), using baseline risk estimates from the placebo arm of eligible studies, and the associated 95% confidence intervals (CIs). We will pool all continuous outcomes that are reported by >1 study and calculate the weighted mean differences (WMDs) and associated 95% CIs. We will employ methods described in Cochrane Handbook to estimate the mean and standard deviation (SD) when median, range, and sample size are reported, and to impute the SD if the standard error or SD for the differences are not reported.[16] For continuous outcomes, when studies reported effect estimates using different measurement instruments that tap into a common construct (e.g. pain), we will first transform all outcomes to a common instrument on a domain-by-domain basis.[17] We will use change scores from baseline to end of follow-up rather than end-of-study scores, in order to account for inter-patient variability. If authors do not report change scores, we will calculate them using the baseline and end-of-study score and a correlation coefficient derived from the largest trial at lowest risk of bias in the meta-analysis that does report a change score. We will use DerSimonian–Laird random-effects models[18] for all pairwise comparisons.

Interpreting effect estimates for continuous outcomes is challenging,[19] and we will present the minimally important difference (MID) for all pooled effect estimates. The MID is the smallest amount of improvement in a treatment outcome that a patient would recognize as

important.[20] If we find multiple MID estimates are available, we will use the smallest difference that has been validated.

However, simply presenting the MID risks interpreting all mean effects that fall below the MID as unimportant, whereas we have found that, typically, mean differences of 1/2 the MID result in RDs of about 10% - a potential benefit that many patients would likely consider important.[21] Thus, concluding that an effect is unimportant requires confidence that the mean difference is less than 1/2 the MID (and perhaps less). To optimize interpretability, we will calculate the RD of achieving the MID, as well as the associated 95%CIs, for all statistically significant WMDs. Specifically, for each individual study, we will assume that the SDs of outcome measurements are the same in both the treatment and control groups, and that change scores in both groups are normally distributed. We will use the median or mean, and SD of the control group, with the established MID for the outcome in question to estimate the probability of achieving ≥MID in the control group. We will use the pooled mean difference (and 95%CI) to estimate the mean (and 95%CI) in the treatment group and calculate the probability (and 95%CI) of achieving ≥MID in the treatment group. Finally, we will use risks in both groups to acquire the RD for achieving ≥MID.

Methods for network meta-analysis

We will perform network meta-analysis (NMA) to synthesize the available evidence from the entire network of trials by integrating direct and indirect estimates for each comparison into a single summary treatment effect. We will use a frequentist random-effects model using the methodology of multivariable meta-analysis to assess the comparative effectiveness of eligible interventions.[22 23]

Although the assumptions for network meta-analysis are similar to conventional meta-analysis, key extra assumptions are transitivity (there are no effect modifiers influencing the indirect comparisons) and coherence (direct and indirect effect estimates being similar).[24] We will identify issues of incoherence by comparing direct evidence (i.e. estimates from pairwise comparisons) with indirect evidence (i.e. estimates from network meta-analysis) using the node splitting method.[25 26] In this approach, incoherence is assessed locally by evaluating the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop. We will assume a common heterogeneity estimate within each loop. We will also confirm the coherence assumption in the entire network using 'design-by-treatment' model as described by Higgins et al.[27] In case we find significant incoherence in the network (highly significant p value from design-by-treatment model), we will perform network meta-analysis using inconsistency model. If using inconsistency model resulted in non-sensical results, we will explore the network for the source(s) of incoherence and further expand (disintegrating interventions based on differences in population or intervention characteristics) or exclude node(s) introducing incoherence in the network (e.g., excluding node(s) with less than 20 events for binary outcomes or comparisons with only one trial with very few participants for continuous outcomes).

We will report our findings with probability statements of intervention effects. Probability rankings allow us to report a chance percentage of which interventions rank higher;[28] however, simplifying the results of a network down to probabilities can lead to misinterpretations, specifically, when particular comparisons (i.e. nodes) are not well-connected or when the quality of evidence varies between comparisons.[29 30] Following display of the rank probabilities using rankogram, we will use the surface under the cumulative ranking (SUCRA)

line to aid in interpretation of relative effect of the interventions. An intervention with a SUCRA value of 100 is certain to be the most effective, whereas an intervention with 0 is certain to be the least effective.[28] We will use STATA (StataCorp, Release 14.2, College Station, Texas, USA) for all statistical analyses. All comparisons will be 2-tailed using a threshold $p \leq 0.05$.

Subgroup analyses, meta-regression and sensitivity analysis

We will use the Q statistic and I^2 to determine statistical heterogeneity for direct meta-analysis.[25] We have developed five hypotheses to explain heterogeneity between trials: (1) different clinical conditions will show different treatment effects; (2) more severe injuries will show smaller treatment effects then less severe injuries; (3) older patients will show smaller treatment effects than younger patients; (4) longer follow-up will show smaller treatment effects than shorter follow-up; and (5) higher dose/intensity of treatment will show larger treatment effects. We will perform subgroup analyses regardless of heterogeneity estimates. Moreover, we will explore the effect of risk of bias (on a component-by-component basis) and reported vs. converted change scores on treatment effects. We will perform a sensitivity analysis that restricts analyses to the treatments for which there are a combined total of at least 500 patients.

Assessing quality of the evidence

We will use the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach to assess the quality of evidence on an outcome-by-outcome basis. The starting point for quality of evidence for randomized trials is high, but may be rated down based on limitations in risk of bias, imprecision, inconsistency, and indirectness and publication bias.[31]

We will also use the GRADE approach to assess quality of evidence for indirect and network (mixed) effect estimates.[32, 33] Indirect effect estimates are calculated from available 'loops' of evidence, which includes first order loops (based on a single common comparator treatment, the difference between the treatment A and B is based on comparisons of A and C as well as B and C) or higher order loops (more than one intervening treatment connecting the two interventions). We will visually examine the network map and where first order loops are available for indirect comparisons, the quality of evidence will be the lower of the ratings for the two direct estimates contributing to the first order loop. In the absence of a first order loop, a higher order loop will be used to rate the quality of evidence and it will be the lower of the quality ratings for the direct estimates contributing to the loop. Further, we may rate down quality further for intransitivity.[33] The transitivity assumption implies similarity of trials in terms of population, intervention, settings, and trial methodology.[34]

Ethics and Dissemination

No research ethics approval is required for this systematic review, as no confidential patient data will be used. The results of this systematic review will be disseminated through publication in a peer-reviewed journal and through conference presentations. Moreover, findings from our review will inform a clinical practice guideline. All amendments to the protocol will be reported in the PROSPERO trial registry.

Discussion

With the high prevalence of acute non-low back MSK pain, the associated high socioeconomic burden and the paucity of evidence on the comparative effectiveness of treatment options, there is an urgent need for a high-quality systematic review to inform evidence-based management of these complaints.

Our proposed review has several strengths in relation to existing reviews. First, we will include all nonpharmacological and pharmacological treatment options for all acute MSK complaints (excluding low back pain). It is plausible that individual acute MSK complaints respond similarly to similar interventions, and thus by pooling across individual injuries, it may be possible to provide a more precise estimate of treatment effect. Second, we will update the search to present date. Third, we will use the GRADE approach to evaluate the quality of evidence supporting treatment effects. Fourth, we will ensure interpretability by presenting RDs and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.

A potential limitation will be the nature of available treatment comparisons to build robust networks for our analyses. The findings of our review will help inform patients with acute non-low back related MSK pain about their therapeutic options, identify key areas for research, and facilitate a clinical practice guideline for the management of acute, non-low back related MSK pain.

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Author Contributions: All authors made substantial contributions to conception and design. JWB and BS drafted the article, and SC, RC, PJH, YO, CM, AL and GHG revised it critically for important intellectual content. All authors provided final approval of the version to be published. JWB is the guarantor of the review protocol.

Data sharing: Statistical code and dataset available from Dr. Sadeghirad (e-mail: b.sadeghirad@gmail.com).

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Competing interests: None declared.

Patient consent: Not required.

Provenance and peer review: This review was commissioned and externally peer reviewed.

References

1. United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS) Rosemont, IL. 2014 [Third Edition [Available from: http://www.boneandjointburden.org accessed March 3rd 2017.

2. Agency for Healthcare Research and Quality (AHRQ), Center for Delivery O, and Markets, Healthcare Cost and Utilization Project (HCUP),. National Inpatient Sample (NIS) and Nationwide Emergency Department Sample (NEDS), 2013.

3. Todd KH, Miner JR. Pain in the emergency room. In: Fishman SM, Ballantyne JC, Rathmell JP, eds. Bonica's Management of Pain. Philadelphia, PA, USA: Lippincott, Williams and Wilkins 2010:1576–87.

4. Todd KH, Ducharme J, Choiniere M, et al. Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. *The journal of pain : official journal of the American Pain Society* 2007;8(6):460-6. doi: 10.1016/j.jpain.2006.12.005 [published Online First: 2007/02/20]

5. Vadivelu N, Mitra S, Hines R, et al. Acute pain in undergraduate medical education: an unfinished chapter! *Pain practice : the official journal of World Institute of Pain* 2012;12(8):663-71. doi: 10.1111/j.1533-2500.2012.00580.x [published Online First: 2012/06/21]

6. Fishman SM, Young HM, Lucas Arwood E, et al. Core competencies for pain management: results of an interprofessional consensus summit. *Pain medicine (Malden, Mass)* 2013;14(7):971-81. doi: 10.1111/pme.12107 [published Online First: 2013/04/13]

7. Watt-Watson J, Murinson BB. Current challenges in pain education. *Pain management* 2013;3(5):351-7. doi: 10.2217/pmt.13.39 [published Online First: 2014/03/25]

8. Côté P, Shearer H, Ameis A, et al. Enabling recovery from common traffic injuries: A focus on the injured person. January 31, 2015; UOIT-CMCC Centre for the Study of Disability Prevention and Rehabilitation.

9. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015;4:1. doi: 10.1186/2046-4053-4-1 [published Online First: 2015/01/03]

10. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):493-505. doi: 10.7326/m16-2459 [published Online First: 2017/02/14]

11. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):480-92. doi: 10.7326/m16-2458 [published Online First: 2017/02/14]

12. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33(1):159-74. [published Online First: 1977/03/01]

13. Tendal B, Nuesch E, Higgins JP, et al. Multiplicity of data in trial reports and the reliability of meta-analyses: empirical study. *Bmj* 2011;343:d4829. doi: 10.1136/bmj.d4829 [published Online First: 2011/09/01]

14. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi: http://dx.doi.org/10.1136/bmj.d5928

15. Akl EA, Sun X, Busse JW, et al. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;65(3):262-67. doi: http://dx.doi.org/10.1016/j.jclinepi.2011.04.015

16. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions, version [5.1.0] (updated March 2011). The Cochrane Collaboration, 2011.

17. Thorlund K, Walter SD, Johnston BC, et al. Pooling health-related quality of life outcomes in meta-analysis-a tutorial and review of methods for enhancing interpretability. *Res Synth Methods* 2011;2(3):188-203. doi: 10.1002/jrsm.46 [published Online First: 2011/09/01]

18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;7(3):177-88.

19. Busse JW, Bartlett SJ, Dougados M, et al. Optimal Strategies for Reporting Pain in Clinical Trials and Systematic Reviews: Recommendations from an OMERACT 12 Workshop. *The Journal of rheumatology* 2015;42(10):1962-70. doi: 10.3899/jrheum.141440 [published Online First: 2015/05/17]

20. Schunemann HJ, Guyatt GH. Commentary--goodbye M(C)ID! Hello MID, where do you come from? *Health services research* 2005;40(2):593-7. doi: 10.1111/j.1475-6773.2005.00374.x [published Online First: 2005/03/15]

21. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *[Submitted]* 2018(Accepted for publication)

22. White IR. Network meta-analysis. *The Stata Journal* 2015;15(4):951–85.

23. White IR, Barrett JK, Jackson D, et al. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;3(2):111-25. doi: 10.1002/jrsm.1045 [published Online First: 2012/06/01]

24. Donegan S, Williamson P, D'Alessandro U, et al. Assessing key assumptions of network meta-analysis: a review of methods. *Res Synth Methods* 2013;4(4):291-323. doi: 10.1002/jrsm.1085

25. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60. doi: http://dx.doi.org/10.1136/bmj.327.7414.557

26. Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *J Am Stat Assoc* 2006;101(474):447-59. doi: 10.1198/016214505000001302

27. Higgins JP, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3(2):98-110. doi: 10.1002/jrsm.1044 [published Online First: 2012/06/01]

28. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64(2):163-71. doi: http://dx.doi.org/10.1016/j.jclinepi.2010.03.016

29. Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Systematic reviews* 2017;6(1):79. doi: 10.1186/s13643-017-0473-z [published Online First: 2017/04/14]

30. Trinquart L, Attiche N, Bafeta A, et al. Uncertainty in Treatment Rankings: Reanalysis of Network Meta-analyses of Randomized Trials. *Ann Intern Med* 2016;164(10):666-73. doi: 10.7326/m15-2521 [published Online First: 2016/04/19]

31. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-26. doi: 10.1136/bmj.39489.470347.AD

32. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:5630. doi: 10.1136/bmj.g5630

33. Brignardello-Petersen R, Bonner A, Alexander PE, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *Journal of clinical epidemiology* 2018;93:36-44. doi: 10.1016/j.jclinepi.2017.10.005 [published Online First: 2017/10/21]

34. Salanti G, Higgins JP, Ades A, et al. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008;17(3):279-301.

Appendix: Literature Search Strategies

Summary of search and strategies ACP Acute MSK Pain

Feb 14, 2018
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
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1 exp arm injuries/ or athletic injuries/ or exp joint dislocations/ or exp fractures, bone/ or fractures, cartilage/ or exp hand injuries/ or exp hip injuries/ or exp leg injuries/ or exp neck injuries/ or occupational injuries/ or exp shoulder injuries/ or exp soft tissue injuries/ or exp "sprains and strains"/ or exp tendon injuries/ or exp Compartment Syndromes/ or exp Bone Malalignment/ (300813)
2 (exp Musculoskeletal system/ or musculoskeletal diseases/ or osteitis/ or exp cartilage diseases/ or exp fasciitis/ or exp bursitis/ or exp metatarsalgia/ or exp synovitis/ or muscle cramp/ or myalgia/ or exp tendinopathy/) and pain*.ti,ab. (87772)
3 Musculoskeletal Pain/ or Neck Pain/ or Acute Pain/ or exp Arthralgia/ (19422)
4 (Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (111653)
5 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)).tw. (14400)
6 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)).tw. (235481)
7 or/1-6 (587971)
8 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (810530)
9 ((treatment or control) adj3 group*).ab. (511607)
10 (allocat* adj5 group*).ab. (20402)
11 ((clinical or control*) adj3 trial).ti,ab,kw. (226548)
12 or/8-11 (1258485)
13 7 and 12 (46565)
14 exp animals/ not humans.sh. (4424690)
15 13 not 14 (42705)
16 adult.mp. or middle aged.sh. or age:.tw. (8090446)
17 15 and 16 (30798)
18 limit 15 to "all adult (19 plus years)" (28434)
19 17 or 18 (31999)
20 treatment outcome/ (824861)
21 Pain Measurement/ (75370)

22 "Recovery of Function"/ (42703)
23 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)).mp. (586581)
24 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (628803)
25 Return to Work/ or Return to Sport/ or ((return or resump*) adj3 (work or sport or play or activit*)).mp. (16520)
26 pain*.jw,ti. (199639)
27 pain*.ab. /freq=2 (243208)
28 or/20-27 (2035376)
29 19 and 28 (20709)
30 exp appendicitis/ or exp Back Pain/ or Labor Pain/ or exp Pain, Postoperative/ or exp Toothache/ or headache/ or exp Headache disorders/ or exp dentistry/ or exp Neoplasms/ (3499077)
31 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*)).mp. (118740)
32 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or metastas*).mp. (463484)
33 or/30-32 (3631063)
34 29 not 33 (13769)
35 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (7012189)
36 34 and 35 (9481)
37 Osteoarthritis/ (33247)
38 exp arthroplasty/ or exp arthroscopy/ or bone transplantation/ (101224)
39 su.fs. (1807708)
40 or/37-39 (1863671)

Feb 14, 2018
Database: Embase <1974 to 2018 February 13>
Search Strategy:
---
1 limb injury/ or exp arm injury/ or exp leg injury/ or exp limb fracture/ or sport injury/ or exp joint injury/ or musculoskeletal injury/ or exp cartilage injury/ or exp "ligament and tendon injury"/ or medial tibial stress syndrome/ or muscle injury/ or overexertion/ or exp sprain/ or fracture/ or avulsion fracture/ or clavicle fracture/ or comminuted fracture/ or fracture dislocation/ or exp fracture healing/ or intraarticular fracture/ or exp joint fracture/ or exp limb fracture/ or exp multiple fracture/ or exp scapula fracture/ or stress fracture/ or neck injury/ or whiplash injury/ or occupational accident/ or soft tissue injury/ or compartment syndrome/ (382802)
Annotation: includes arm injury/ or exp arm fracture/ or elbow dislocation/ or elbow injury/ or exp forearm injury/ or exp hand injury/ or exp shoulder injury/ or exp wrist injury/ or leg injury/ or exp ankle injury/ or exp foot injury/ or exp hip injury/ or exp knee injury/ or exp leg fracture/ or tibia torsion/ or exp ankle injury/ or exp dislocation/ or exp hip injury/ or intraarticular

fracture/ or exp joint fracture/ or exp knee injury/ or posttraumatic arthropathy/ or exp wrist injury/
2 (exp musculoskeletal system/ or exp musculoskeletal disease/) and pain*.ti,ab. (312623)
3 musculoskeletal pain/ or neck pain/ or shoulder pain/ or arthralgia/ (86878)
4 or/1-3 (692780)
Annotation: emtree terms condition MSK pain
5 (Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (147804)
6 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)).tw. (16617)
7 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)).tw. (305948)
8 or/5-7 (444822)
Annotation: free text terms condition MSK pain
9 4 or 8 (897318)
Annotation: MSK pain
10 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (25540585)
11 human/ or normal human/ or human cell/ (19287963)
12 10 and 11 (19240053)
13 10 not 12 (6300532)
14 9 not 13 (837728)
15 random:.tw. or placebo:.mp. or double-blind:.tw. (1509046)
Annotation: HIRU specific RCT filter
16 ((treatment or control) adj3 group*).ab. (723604)
17 (allocat* adj5 group*).ab. (26448)
18 ((clinical or control*) adj3 trial).ti,ab,kw. (327340)
19 or/15-18 (2107446)
Annotation: modified RCT filter
20 14 and 19 (95790)
Annotation: MSK pain with mod RCT filter
21 treatment outcome/ (762155)
22 outcome assessment/ (400641)
23 pain measurement/ (4687)
24 exp pain assessment/ (134012)
25 convalescence/ (42381)
26 return to sport/ or return to work/ (4870)
27 work resumption/ (3467)

28 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)).mp. (790797)
29 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (911685)
30 ((return or resump*) adj3 (work or sport or play or activit*)).mp. (23514)
31 pain*.jw,ti. (269095)
32 pain*.ab. /freq=2 (358966)
33 or/21-32 (2816037)
34 20 and 33 (58373)
Annotation: MSK pain with mod RCT and outcome
35 exp appendicitis/ or exp backache/ or labor pain/ or exp postoperative complication/ or exp tooth disease/ or headache/ or exp dentistry/ or exp malignant neoplasm/ or exp metastasis/ (4067682)
36 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*)).mp. (189693)
37 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or metastas* or appendicitis).mp. (778837)
38 35 or 36 or 37 (4238484)
39 34 not 38 (30664)
Annotation: mod RCT set
40 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (9180696)
Annotation: Gill 2014 primary care plus sport
41 39 and 40 (21784)
42 exp osteoarthritis/ (110006)
43 bone transplantation/ or exp bone graft/ (46349)
44 exp orthopedic surgery/ (406039)
Annotation: includes exp joint surgery/ or exp arthroplasty/
45 su.fs. (1950489)
46 or/42-45 (2224706)

Cochrane Library
Search Name: 2017-08-22 ACP acute msk pain search
Date Run: 14/02/18 20:52:03.682
Description:

ID Search Hits
#1 Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD 13121
#2 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) near/3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)) 2044

#3 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) near/3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)) 38249
#4 #1 or #2 or #3 47667
#5 ((disability or function* or recover* or pain* or analog*) near/3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)) 109526
#6 VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement 139538
#7 ((return or resump*) near/3 (work or sport or play or activit*)) 3128
#8 pain*:so 8908
#9 pain*:ti 34759
#10 #5 or #6 or #7 or #8 or #9 214594
#11 #4 and #10 24648
#12 (pain* near/3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*)) 20816
#13 sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or metastas* 27428
#14 #12 or #13 45616
#15 #11 not #14 18297
#16 clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport* 937038
#17 #15 and #16 in Trials, with Wounds Group, Injuries Group, Pain, Palliative and Supportive Care Group, Musculoskeletal Group, Bone, Joint and Muscle Trauma Group, Back Group or Occupational Safety and Health Group in Review Groups

CINAHL

S73	S66 NOT S72	5,571
S72	S67 OR S68 OR S69 OR S70 OR S71	224,577
S71	(MM "Surgery, Operative+")	211,375
S70	(MH "Arthroscopy")	4,418
S69	(MH "Arthroplasty")	1,646
S68	(MH "Bone Transplantation")	3,342
S67	(MH "Osteoarthritis+")	13,152
S66	S64 AND S65	8,761

S65 TI (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*) OR AB (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or

family or communit* or ambulatory or centre* or center* or office or sport*)
1,131,403

S64 S51 NOT S63 15,217

S63 S60 OR S61 OR S62 359,216

S62 TX sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or metastas* 35,825

S61 TX (pain* N3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*)) 49,583

S60 S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 329,798

S59 (MH "Neoplasms+") 240,613

S58 (MH "Dentistry+") 47,838

S57 (MH "Headache+") 16,196

S56 (MH "Toothache") 327

S55 (MH "Postoperative Pain") 8,206

S54 (MH "Labor Pain") 1,533

S53 (MH "Back Pain+") 18,740

S52 (MH "Appendicitis") 1,293

S51 S17 AND S39 AND S48 20,097

S50 S48 AND S49 20,097

S49 S17 AND S39 33,880

S48 S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 457,089

S47 SO pain* 30,433

S46 TI pain* 68,365

S45 TX ((disability or function* or recover* or pain* or analog*) N3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)). 143,200

S44 TX VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement 174,142

S43 TX ((return or resump*) N3 (work or sport or play or activit*)) 6,311

S42 (MH "Job Re-Entry") OR (MH "Sports Re-Entry") OR (MH "School Re-Entry") 6,819

S41 (MH "Pain Measurement") 27,842

S40 (MH "Treatment Outcomes") 150,811

S39 S37 NOT S38 563,918

S38 (MH "Animals+") 37,258

S37 S24 OR S29 OR S36 568,264

S36 S30 OR S31 OR S32 OR S33 OR S34 OR S35 495,048

S35 (MH "Prospective Studies+") 213,854

S34 (MH "Evaluation Research+") 41,488

S33 (MH "Comparative Studies") 101,882

S32 "latin square" 138

S31 (MH "Study Design") OR (MH "Crossover Design") OR (MH "Experimental Studies+")
207,529

S30 (MH "Random Sample+") 67,305

S29 S25 OR S26 OR S27 OR S28 211,728

S28 "random*" 203,059

S27 "placebo*" 33,694

S26	(MH "Placebos")	8,296
S25	(MH "Placebo Effect")	1,210
S24	S18 OR S19 OR S20 OR S21 OR S22 OR S23	195,829
S23	"triple-blind"	136
S22	"single-blind"	8,460
S21	"double-blind"	29,322
S20	clinical W3 trial	124,429
S19	"randomi?ed controlled trial*"	69,029
S18	(MH "Clinical Trials+")	155,173
S17	S5 OR S10 OR S15	132,229
S16	S11 OR S15	132,229
S15	S12 OR S13 OR S14	98,300
S14	TX ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) N3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*))	78,680
S13	TX ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) N3 (injur* or impair* or imping* or sprain* or strain* or tear or torn))	10,622
S12	TX Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD	20,095
S11	S5 OR S10	91,140
S10	S8 AND S9	Display
S9	TI pain* OR AB pain*	Display
S8	S6 OR S7	Display
S7	(MH "Musculoskeletal Diseases") OR (MH "Cartilage Diseases+") OR (MH "Fasciitis+") OR (MH "Foot Diseases+") OR (MH "Golf Elbow") OR (MH "Heel Pain") OR (MH "Joint Diseases") OR (MH "Muscular Diseases") OR (MH "Arthralgia+") OR (MH "Bursitis+") OR (MH "Contracture+") OR (MH "Metatarsalgia") OR (MH "Shoulder Instability, Anterior") OR (MH "Shoulder Instability, Multidirectional") OR (MH "Shoulder Instability, Posterior") OR (MH "Synovitis")	Display
S6	(MH "Musculoskeletal System") OR (MH "Cartilage+") OR (MH "Fascia+") OR (MH "Ligaments+") OR (MH "Muscles+") OR (MH "Bone and Bones") OR (MH "Arm Bones+") OR (MH "Foot Bones+") OR (MH "Leg Bones+") OR (MH "Pelvic Bones+") OR (MH "Joints+")	Display
S5	S1 OR S2 OR S3 OR S4	Display
S4	(MH "Neck Pain")	Display
S3	(MH "Arthralgia+")	Display
S2	(MH "Compartment Syndromes") OR (MH "Anterior Compartment Syndrome") OR (MH "Ischemic Contracture")	Display

S1 (MH "Arm Injuries+") OR (MH "Athletic Injuries+") OR (MH "Dislocations+") OR (MH "Fractures+") OR (MH "Hand Injuries+") OR (MH "Leg Injuries+") OR (MH "Ligament Injuries+") OR (MH "Neck Injuries+") OR (MH "Occupational-Related Injuries") OR (MH "Soft Tissue Injuries+") OR (MH "Sprains and Strains+") OR (MH "Tendon Injuries+")
Display

PEDro, yields 645

March 13, 2018

Abstract & Title: acute
AND
Problem: pain
AND
Method: Clinical trial

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4 & 8
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	16

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	18
Sponsor	#5b	Provide name for the review funder and / or sponsor	18
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	18
Rationale	#6	Describe the rationale for the review in the context of what is already known	6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8 & 9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	25-32
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9 & 10
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9 & 10

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9 & 10
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10 & 11
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10-14
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14 & 15

BMJ Open

Management of acute musculoskeletal pain (excluding low back pain): a protocol for a systematic review and network meta-analysis of randomised trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024441.R1
Article Type:	Protocol
Date Submitted by the Author:	30-Oct-2018
Complete List of Authors:	Busse, Jason; McMaster University, Anesthesia; McMaster University, Clinical Epidemiology & Biostatistics Craigie, Samantha; McMaster University Sadeghirad, Behnam; McMaster University Couban, Rachel; McMaster University, Michael G. DeGroote Institute for Pain Research and Care Hong, Patrick; University of Ottawa Faculty of Medicine Oparin, Yvgeniy; McMaster University Department of Medicine May, Curtis; University of British Columbia Faculty of Medicine Lok, Annie; McMaster University Department of Anaesthesia Guyatt, Gordon; Mcmaster University, Clinical Epidemiology and Biostatistics
Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Evidence based practice
Keywords:	acute pain, musculoskeletal, intervention, systematic review, network metanalysis

Management of acute musculoskeletal pain (excluding low back pain): a protocol for a systematic review and network meta-analysis of randomised trials

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Abstract

Introduction: Acute, non-low back related musculoskeletal pain is common and associated with significant socioeconomic costs. No review has evaluated all interventional studies for acute musculoskeletal pain, which limits attempts to make inferences regarding the relative effectiveness of treatments.

Methods and analysis: We will conduct a systematic review of all randomised controlled trials evaluating therapies for acute musculoskeletal pain (excluding low back pain). We will identify eligible, English-language, trials by a systematic search of CINAHL, EMBASE, MEDLINE, PEDro and the Cochrane Central Registry of Controlled Trials from inception to February 2018. Eligible trials will: (1) enrol patients presenting with acute, non-low back related musculoskeletal pain (duration of pain ≤ 4 weeks), and (2) randomise patients to alternative interventions or an intervention and a placebo/sham arm. Fractures will be considered ineligible, unless they are non-surgical and therapy is directed at pain relief. Pairs of reviewers will, independently and in duplicate, screen titles and abstracts of identified citations, review the full texts of potentially eligible trials and extract information from eligible trials. We will use a modified Cochrane instrument to evaluate risk of bias. Disagreements will be resolved through discussion to achieve consensus.

We will use the GRADE system to evaluate the quality of evidence supporting treatment effects. When possible, we will conduct: (1) in direct comparisons, a random-effects meta-analysis to establish the effectiveness of therapeutic interventions on patient-important outcomes; and (2) multiple treatment comparison meta-analysis to assess the relative effects of treatments. We will use a priori hypotheses to explain heterogeneity between studies. We will use STATA 14.2 for all analyses.

Ethics and dissemination: No research ethics approval is required for this systematic review. The results of this systematic review will be disseminated through publication in a peer-reviewed journal, conference presentations, and will inform a clinical practice guideline.

Key Words: acute pain; musculoskeletal; intervention; systematic review; network meta-analysis

PROSPERO registration number: CRD42018094412

Article Summary

Strengths and limitations

- Our broad study eligibility criteria will increase generalizability of our results.
- We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate our confidence in treatment effects.
- We will optimize interpretability by presenting risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.
- Findings from our review will inform a clinical practice guideline and identify key areas for future research.
- Our results will be limited by possible shortcomings of the primary studies.

Introduction

Acute non-low back related musculoskeletal (MSK) pain, which include strains and sprains, dislocations, and whiplash present for less than 1 month[1], are associated with considerable morbidity in North America. The Burden of Musculoskeletal Diseases in the United States, 3rd edition, found that sprains and strains are the most frequent injury type for which medical care is sought and the majority of MSK injuries occur among working-age adults.[2] In 2013 there were 2,807,880 emergency department (ED) visits for sports-related injuries in the US,[3] and over 70% of visits to the ED are because of pain-related complaints.[4] Management often yields suboptimal outcomes: a survey of 842 acute pain patients at 20 US and Canadian hospitals found 40% reported their pain did not change or increased after visiting the ED, and 74% of patients were discharged in moderate to severe pain.[5]

Despite the prevalence of acute MSK complaints in primary care, a number of studies have highlighted inadequate pain education of among physicians.[6-8] The availability of numerous pharmacologic and non-pharmacologic therapies further complicates management decisions. Currently available treatments include opioids, nonsteroidal anti-inflammatory drugs, muscle relaxants, acetaminophen, exercise, supervised rehabilitation, joint manipulation and mobilization, massage, acupuncture and acupressure, ultrasound, low-level laser therapy, and transcutaneous electrical nerve stimulation.

A recently published series of 24 systematic reviews of treatment for common acute MSK injuries,[9] suffers from many important limitations, including: (1) selection bias due, in part, to exclusion of studies deemed to be at high risk of bias without empirically exploring if effect estimates differed from studies assigned low risk of bias, (2) interpreting results from individual studies as effective if the mean difference in a given outcome met the minimally

important difference (MID) and ineffective if not - an interpretation that relies on the unlikely assumption that all patients will experience the same degree of improvement, and fails to consider the distribution around the mean and the proportion of patients that achieve the MID, (3) no appraisal of the overall quality (confidence, certainty) of the evidence, and (4) no statistical pooling of treatment effects. We propose to conduct a systematic review of randomized trials to assess the comparative effectiveness of available non-surgical treatments for acute MSK pain (excluding low back pain) and assess quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Methods

Protocol registration

The protocol for this systematic review is registered with PROSPERO (CRD42018094412). This review was commissioned by the American Academy of Family Physicians and American College of Physicians and sponsored by the National Safety Council.

Standardized Reporting

We used the PRISMA-P checklist when writing our report.[10]

Information sources

We will identify eligible, English language, randomized clinical trials (RCTs) through a systematic search of MEDLINE, EMBASE, CINAHL, PEDro and CENTRAL, from inception of each database through February 2018. Our search has been refined for individual databases by an experienced medical librarian (Appendix). We will scan reference lists of included studies and relevant systematic reviews for additional eligible articles.

Eligibility criteria and study selection

We will include therapeutic trials that: 1) enroll adult patients (≥ 18 years) presenting with acute, non-low back related MSK pain (pain with duration < 4 weeks or defined by authors as "acute") in an outpatient setting, and 2) randomise them to currently available, non-surgical, alternative interventions directed at pain relief (pharmacological or non-pharmacological) or a currently available, non-surgical, intervention directed at pain relief and a placebo/sham arm. Eligible MSK conditions include sprains and strains. Surgical fractures, non-surgical fractures unless

therapy is directed at pain relief, low back pain, neuropathic pain, acute cancer pain, acute postoperative pain, acute dental pain, pain associated with labour and delivery, visceral pain, pain due to infection, and headaches will be excluded. We will exclude interventions targeted at treatment of acute low back pain on request by the study funder, as they have previously commissioned evidence syntheses on this topic.[11 12]

Ten teams of trained reviewers will work independently in pairs to screen titles and abstracts of identified citations, using standardized, pilot-tested forms in DistillerSR, an online systematic review software (Evidence Partners, Ottawa, Canada; http://systematic-review.net/). The same teams of reviewers will screen full texts of any articles judged as potentially eligible. Reviewers will discuss disagreements to come to consensus, referring to an adjudicator if necessary. We will measure agreement between reviewers by calculating kappa (κ) values to assess the reliability of full-text review, and interpret them using the following thresholds: <0.20 as slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement and >0.80 as almost perfect agreement.[13]

Data abstraction

We designed standardized data abstraction forms and a detailed instruction video (accessible at: https://www.youtube.com/watch?v=1nwFJ61K3sQ). We will conduct calibration exercises prior to beginning data abstraction to ensure consistency and accuracy of extractions. Seven teams of reviewers will extract data independently and in duplicate. We will extract the following data from eligible trials into a standardized spreadsheet: study characteristics (e.g. the first author, publication year, country of origin, and funding source), participant and trial characteristics (e.g. sample size, mean age of participants, clinical condition, type and severity of injury, proportion

with known chronic pain/condition prior to acute injury, and the proportion receiving opioids at the time of enrollment), characteristics of interventions and comparators, patient-important outcomes (pain, function, health-related quality of life, patient satisfaction, return to work, proportion of patients with relief, re-injury and all reported adverse events). We will extract pain at any time-point, whereas for other outcomes, we will use the longest follow-up reported.[14]

Risk of bias assessment

Among eligible studies, we will independently assess the following risk of bias issues: (1) random sequence generation, (2) allocation concealment, (3) blinding of study participants, personnel, and outcome assessors, (4) incomplete outcome data (≥20% missing data will be considered at high risk of bias), and (5) other sources of bias. [15] To assess the risk of bias we will use a modified version of the Cochrane risk of bias instrument.[16] Our instrument will use the following responses: 'definitely yes' or 'probably yes' (considered as low risk of bias), or 'definitely no' or 'probably no' (considered as high risk of bias). These response options have published evidence of validity for assessing blinding.[16] Any discrepancy in assessment of risk of bias will be resolved by discussion, or third party adjudication if needed. We will contact authors for missing information regarding risk of bias issues and unpublished data (e.g. effect estimates without accompanying estimates of precision).

Data synthesis

MSK complaints are increasingly being considered together as risk factors[17], prognosis[18] and, because treatments are often similar, in guideline recommendations.[19] [20] For the purposes of statistical pooling, we will explore treatment effects of interventions across all MSK complaints

eligible for this review; however, we will also explore if treatment effects differ by clinical condition or injury severity. Clustering strategies for clinical condition and injury severity will be informed by the trials eligible for our review, which will be reviewed by a technical expert panel, blinded to study results. Treatment effects will be pooled using the longest follow-up time reported, except for pain, which will be pooled at the most commonly reported short, medium and long-term follow-up times reported. For our review, these categories will be 30 to 120 minutes post-treatment (short), 1 to 7 days post-treatment (medium), and 3 to 12 weeks post-treatment (long). As such, a single trial could contribute to up to 3 time-points for our pooled results for pain relief. Alternately, trials that reported pain relief at time points outside of these timeframes would not contribute data for our analyses of pain relief.

Methods for direct comparisons

We will pool dichotomous outcomes that are reported by >1 RCT and calculate the relative risk and risk difference (RD), using baseline risk estimates from the placebo arm of eligible studies, and the associated 95% confidence intervals (CIs). We will pool all continuous outcomes that are reported by >1 study and calculate the weighted mean differences (WMDs) and associated 95% CIs. We will employ methods described in Cochrane Handbook to estimate the mean and standard deviation (SD) when median, range, and sample size are reported, and to impute the SD if the standard error or SD for the differences are not reported.[21] For continuous outcomes, when studies report effect estimates using different measurement instruments that tap into a common construct (e.g. pain), we will first transform all outcomes to a common instrument on a domain-by-domain basis.[22] We will use change scores from baseline to end of follow-up rather than end-of-study scores, in order to account for inter-patient variability. If authors do not report change scores, we

will calculate them using the baseline and end-of-study score and a correlation coefficient derived from the largest trial at lowest risk of bias in the meta-analysis that does report a change score. We will use DerSimonian–Laird random-effects models[23] for all pairwise comparisons.

Interpreting effect estimates for continuous outcomes is challenging,[24] and we will present the minimally important difference (MID) for all pooled effect estimates. The MID is the smallest amount of improvement in a treatment outcome that a patient would recognize as important.[25] If we find multiple MID estimates are available, we will use the smallest difference that has been validated.

However, simply presenting the MID risks interpreting all mean effects that fall below the MID as unimportant, whereas we have found that, typically, mean differences of 1/2 the MID result in RDs of about 10% - a potential benefit that many patients may consider important.[26] Thus, concluding that an effect is unimportant requires confidence that the mean difference is less than 1/2 the MID (and perhaps less). To optimize interpretability, we will calculate the RD of achieving the MID, as well as the associated 95% CIs, for all statistically significant WMDs. Specifically, for each individual study, we will assume that the SDs of outcome measurements are the same in both the treatment and control groups, and that change scores in both groups are normally distributed. We will use the median or mean, and SD of the control group, with the established MID for the outcome in question to estimate the probability of achieving ≥ MID in the control group. We will use the pooled mean difference (and 95% CI) to estimate the mean (and 95% CI) in the treatment group and calculate the probability (and 95% CI) of achieving ≥ MID in the treatment group. Finally, we will use risks in both groups to acquire the RD for achieving ≥ MID.

Methods for network meta-analysis

We will perform network meta-analysis to synthesize the available evidence from the entire network of trials by integrating direct and indirect estimates for each comparison into a single summary treatment effect. We will use a frequentist random-effects model using the methodology of multivariable meta-analysis to assess the comparative effectiveness of eligible interventions.[27 28]

Although the assumptions for network meta-analysis are similar to conventional meta-analysis, key extra assumptions are transitivity (there are no effect modifiers influencing the indirect comparisons) and coherence (direct and indirect effect estimates being similar).[29] We will identify issues of incoherence by comparing direct evidence (i.e. estimates from pairwise comparisons) with indirect evidence (i.e. estimates from network meta-analysis) using the node splitting method.[30 31] In this approach, incoherence is assessed locally by evaluating the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop. We will assume a common heterogeneity estimate within each loop. We will also confirm the coherence assumption in the entire network using a 'design-by-treatment' model.[32] In case we find significant incoherence in the network (highly significant p value from design-by-treatment model), we will perform network meta-analysis using an inconsistency model. If using an inconsistency model results in non-sensical results, we will explore the network for the source(s) of incoherence and further expand (disintegrating interventions based on differences in population or intervention characteristics) or exclude the node(s) introducing incoherence into the network (e.g., excluding node(s) with less than 20 events for binary outcomes or comparisons with only one trial with very few participants for continuous outcomes).

We will report our findings with probability statements of intervention effects. Probability rankings allow us to report a chance percentage of which interventions rank higher;[33] however, simplifying the results of a network down to probabilities can lead to misinterpretations, specifically, when particular comparisons (i.e. nodes) are not well-connected or when the quality of evidence varies between comparisons.[34 35] Following display of the rank probabilities using rankogram, we will use the surface under the cumulative ranking (SUCRA) line to aid in interpretation of relative effect of the interventions. An intervention with a SUCRA value of 100 is certain to be the most effective, whereas an intervention with 0 is certain to be the least effective.[33] We will use STATA (StataCorp, Release 14.2, College Station, Texas, USA) for all statistical analyses. All comparisons will be 2-tailed using a threshold $p \leq 0.05$.

Subgroup analyses, meta-regression and sensitivity analysis

We will use Cochran's Q statistic and I^2 to determine statistical heterogeneity for direct meta-analysis.[30] We have developed five hypotheses to explain heterogeneity between trials: (1) different clinical conditions will show different treatment effects; (2) more severe injuries will show smaller treatment effects than less severe injuries (e.g. higher grades of strains and sprains vs. lower grades); (3) older patients will show smaller treatment effects than younger patients; (4) longer follow-up will show smaller treatment effects than shorter follow-up; and (5) higher dose/intensity of treatment will show larger treatment effects. We will perform subgroup analyses regardless of heterogeneity estimates. Moreover, we will explore the effect of risk of bias (on a component-by-component basis) and reported vs. converted change scores on treatment effects.

Assessing quality of the evidence

We will use the GRADE approach to assess the quality of evidence on an outcome-by-outcome basis. The starting point for quality of evidence for RCTs is high, but may be rated down based on limitations in risk of bias, imprecision, inconsistency, and indirectness and publication bias.[36] When there are at least 10 studies for meta-analysis[37 38], we will assess publication bias by visual assessment of asymmetry of the funnel plot and calculated Begg's test.

We will also use the GRADE approach to assess quality of evidence for indirect and network (mixed) effect estimates.[39 40] Indirect effect estimates are calculated from available 'loops' of evidence, which includes first order loops (based on a single common comparator treatment, the difference between the treatment A and B is based on comparisons of A and C as well as B and C) or higher order loops (more than one intervening treatment connecting the two interventions). We will visually examine the network map and where first order loops are available for indirect comparisons, the quality of evidence will be the lower of the ratings for the two direct estimates contributing to the first order loop. In the absence of a first order loop, a higher order loop will be used to rate the quality of evidence. We may rate down quality of evidence further for intransitivity.[40] The transitivity assumption implies similarity of trials in terms of population, intervention, settings, and trial methodology.[41]

It is very rare for a network meta-analysis to establish a single treatment option as clearly superior to all others. We will categorize interventions according to three categories: (1) those that are clearly superior, (2) those with intermediate effectiveness, and (3) those that are inferior. Treatments no better than placebo will be in the lowest tier, those better than placebo in tier 1 (likely intermediate); those superior to at least 1 tier 1 treatment will be judged superior. Treatments will be further categorized according to quality of evidence supporting those estimates (high and moderate vs. low or very low). Interventions with moderate or high quality

evidence will be ranked as either 'among the most effective', 'inferior to the most effective / superior to the least effective', or 'among the least effective'. Interventions supported by low or very low quality evidence will be ranked into the same 3 categories but prefaced with 'may be' to acknowledge the reduced confidence in supporting evidence (e.g. 'may be among the most effective') and will be presented separately from those supported by moderate or high quality evidence.

Ethics and Dissemination

No research ethics approval is required for this systematic review, as no confidential patient data will be used. The results of this systematic review will be disseminated through publication in a peer-reviewed journal and through conference presentations. Moreover, findings from our review will inform a clinical practice guideline. All amendments to the protocol will be reported in the PROSPERO trial registry.

Patient and Public Involvement

No patients were involved in setting the research question, in developing plans for design, interpretation, reporting or implementation of the study. We plan to disseminate the results of this study to organisations supporting patients with acute MSK pain.

Discussion

With the high prevalence of acute non-low back MSK pain, the associated socioeconomic burden and the paucity of evidence on the comparative effectiveness of treatment options, there is an urgent need for a high-quality systematic review to inform evidence-based management of these complaints.

Our proposed review has several strengths in relation to existing reviews. First, we will explore all currently available non-pharmacological and pharmacological treatment options for all acute MSK complaints (excluding low back pain) reported among eligible trials. It is plausible that individual acute MSK complaints respond similarly to similar interventions, and thus by pooling across individual injuries, it may be possible to provide a more precise estimate of treatment effect. Second, we will update the search to present date. Third, we will use the GRADE approach to evaluate the quality of evidence supporting treatment effects. Fourth, we will ensure interpretability by presenting RDs and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.

A potential limitation will be the nature of available treatment comparisons to build robust networks for our analyses. The findings of our review will help inform patients with acute non-low back related MSK pain about their therapeutic options, identify key areas for research, and facilitate a clinical practice guideline for the management of acute, non-low back related MSK pain.

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Author Contributions: All authors made substantial contributions to conception and design. JWB and BS drafted the article, and SC, RC, PJH, YO, CM, AL and GHG revised it critically for important intellectual content. All authors provided final approval of the version to be published. JWB is the guarantor of the review protocol.

Data sharing: Statistical code and dataset available from Dr. Sadeghirad (e-mail: b.sadeghirad@gmail.com).

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Competing interests: None declared.

Patient consent: Not required.

Provenance and peer review: This review was commissioned and externally peer reviewed.

References

1. Olsen MF, Bjerre E, Hansen MD, et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC medicine* 2017;15(1):35. doi: 10.1186/s12916-016-0775-3 [published Online First: 2017/02/22]

2. United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS) Rosemont, IL. 2014 [Third Edition [Available from: http://www.boneandjointburden.org accessed March 3rd 2017.

3. Agency for Healthcare Research and Quality (AHRQ), Center for Delivery Organization and Markets Healthcare Cost and Utilization Project (HCUP). National Inpatient Sample (NIS) and Nationwide Emergency Department Sample (NEDS), 2013.

4. Todd KH, Miner JR. Pain in the emergency room. In: Fishman SM, Ballantyne JC, Rathmell JP, eds. Bonica's Management of Pain. Philadelphia, PA, USA: Lippincott, Williams and Wilkins 2010:1576–87.

5. Todd KH, Ducharme J, Choiniere M, et al. Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. *The journal of pain : official journal of the American Pain Society* 2007;8(6):460-6. doi: 10.1016/j.jpain.2006.12.005 [published Online First: 2007/02/20]

6. Vadivelu N, Mitra S, Hines R, et al. Acute pain in undergraduate medical education: an unfinished chapter! *Pain practice : the official journal of World Institute of Pain* 2012;12(8):663-71. doi: 10.1111/j.1533-2500.2012.00580.x [published Online First: 2012/06/21]

7. Fishman SM, Young HM, Lucas Arwood E, et al. Core competencies for pain management: results of an interprofessional consensus summit. *Pain medicine (Malden, Mass)* 2013;14(7):971-81. doi: 10.1111/pme.12107 [published Online First: 2013/04/13]

8. Watt-Watson J, Murinson BB. Current challenges in pain education. *Pain management* 2013;3(5):351-7. doi: 10.2217/pmt.13.39 [published Online First: 2014/03/25]

9. Côté P, Shearer H, Ameis A, et al. Enabling recovery from common traffic injuries: A focus on the injured person. January 31, 2015; UOIT-CMCC Centre for the Study of Disability Prevention and Rehabilitation.

10. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015;4:1. doi: 10.1186/2046-4053-4-1 [published Online First: 2015/01/03]

11. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):493-505. doi: 10.7326/m16-2459 [published Online First: 2017/02/14]

12. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):480-92. doi: 10.7326/m16-2458 [published Online First: 2017/02/14]

13. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33(1):159-74. [published Online First: 1977/03/01]

14. Tendal B, Nuesch E, Higgins JP, et al. Multiplicity of data in trial reports and the reliability of meta-analyses: empirical study. *Bmj* 2011;343:d4829. doi: 10.1136/bmj.d4829 [published Online First: 2011/09/01]

15. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi: http://dx.doi.org/10.1136/bmj.d5928

16. Akl EA, Sun X, Busse JW, et al. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;65(3):262-67. doi: http://dx.doi.org/10.1016/j.jclinepi.2011.04.015

17. Taanila H, Suni JH, Kannus P, et al. Risk factors of acute and overuse musculoskeletal injuries among young conscripts: a population-based cohort study. *BMC musculoskeletal disorders* 2015;16:104. doi: 10.1186/s12891-015-0557-7 [published Online First: 2015/05/01]

18. de Vos Andersen NB, Kent P, Hjort J, et al. Clinical course and prognosis of musculoskeletal pain in patients referred for physiotherapy: does pain site matter? *BMC musculoskeletal disorders* 2017;18(1):130. doi: 10.1186/s12891-017-1487-3 [published Online First: 2017/03/31]

19. Australian Acute Musculoskeletal Pain Guidelines Group. Evidence-based management of acute musculoskeletal pain. *ISBN 1 875378 49 9* 2003

20. Babatunde OO, Jordan JL, Van der Windt DA, et al. Effective treatment options for musculoskeletal pain in primary care: A systematic overview of current evidence. *PLoS One* 2017;12(6):e0178621. doi: 10.1371/journal.pone.0178621 [published Online First: 2017/06/24]

21. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions, version [5.1.0] (updated March 2011). The Cochrane Collaboration, 2011.

22. Thorlund K, Walter SD, Johnston BC, et al. Pooling health-related quality of life outcomes in meta-analysis-a tutorial and review of methods for enhancing interpretability. *Res Synth Methods* 2011;2(3):188-203. doi: 10.1002/jrsm.46 [published Online First: 2011/09/01]

23. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;7(3):177-88.

24. Busse JW, Bartlett SJ, Dougados M, et al. Optimal Strategies for Reporting Pain in Clinical Trials and Systematic Reviews: Recommendations from an OMERACT 12 Workshop. *The Journal of rheumatology* 2015;42(10):1962-70. doi: 10.3899/jrheum.141440 [published Online First: 2015/05/17]

25. Schunemann HJ, Guyatt GH. Commentary--goodbye M(C)ID! Hello MID, where do you come from? *Health services research* 2005;40(2):593-7. doi: 10.1111/j.1475-6773.2005.00374.x [published Online First: 2005/03/15]

26. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. *[Submitted]* 2018(Accepted for publication)

27. White IR. Network meta-analysis. *The Stata Journal* 2015;15(4):951–85.

28. White IR, Barrett JK, Jackson D, et al. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;3(2):111-25. doi: 10.1002/jrsm.1045 [published Online First: 2012/06/01]

29. Donegan S, Williamson P, D'Alessandro U, et al. Assessing key assumptions of network meta-analysis: a review of methods. *Res Synth Methods* 2013;4(4):291-323. doi: 10.1002/jrsm.1085

30. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60. doi: http://dx.doi.org/10.1136/bmj.327.7414.557

31. Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *J Am Stat Assoc* 2006;101(474):447-59. doi: 10.1198/016214505000001302

32. Higgins JP, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3(2):98-110. doi: 10.1002/jrsm.1044 [published Online First: 2012/06/01]

33. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64(2):163-71. doi: http://dx.doi.org/10.1016/j.jclinepi.2010.03.016

34. Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Systematic reviews* 2017;6(1):79. doi: 10.1186/s13643-017-0473-z [published Online First: 2017/04/14]

35. Trinquart L, Attiche N, Bafeta A, et al. Uncertainty in Treatment Rankings: Reanalysis of Network Meta-analyses of Randomized Trials. *Ann Intern Med* 2016;164(10):666-73. doi: 10.7326/m15-2521 [published Online First: 2016/04/19]

36. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-26. doi: 10.1136/bmj.39489.470347.AD

37. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011; Available from http://handbook-5-1.cochrane.org/ (Accessed October 25, 2018)

38. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(4):1088-101. [published Online First: 1994/12/01]

39. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:5630. doi: 10.1136/bmj.g5630

40. Brignardello-Petersen R, Bonner A, Alexander PE, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *Journal of clinical epidemiology* 2018;93:36-44. doi: 10.1016/j.jclinepi.2017.10.005 [published Online First: 2017/10/21]

41. Salanti G, Higgins JP, Ades A, et al. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008;17(3):279-301.

Appendix: Literature Search Strategies

Summary of search and strategies ACP Acute MSK Pain

Feb 14, 2018
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
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1 exp arm injuries/ or athletic injuries/ or exp joint dislocations/ or exp fractures, bone/ or fractures, cartilage/ or exp hand injuries/ or exp hip injuries/ or exp leg injuries/ or exp neck injuries/ or occupational injuries/ or exp shoulder injuries/ or exp soft tissue injuries/ or exp "sprains and strains"/ or exp tendon injuries/ or exp Compartment Syndromes/ or exp Bone Malalignment/ (300813)
2 (exp Musculoskeletal system/ or musculoskeletal diseases/ or osteitis/ or exp cartilage diseases/ or exp fasciitis/ or exp bursitis/ or exp metatarsalgia/ or exp synovitis/ or muscle cramp/ or myalgia/ or exp tendinopathy/) and pain*.ti,ab. (87772)
3 Musculoskeletal Pain/ or Neck Pain/ or Acute Pain/ or exp Arthralgia/ (19422)
4 (Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (111653)
5 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)).tw. (14400)
6 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)).tw. (235481)
7 or/1-6 (587971)
8 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (810530)
9 ((treatment or control) adj3 group*).ab. (511607)
10 (allocat* adj5 group*).ab. (20402)
11 ((clinical or control*) adj3 trial).ti,ab,kw. (226548)
12 or/8-11 (1258485)
13 7 and 12 (46565)
14 exp animals/ not humans.sh. (4424690)
15 13 not 14 (42705)
16 adult.mp. or middle aged.sh. or age:.tw. (8090446)
17 15 and 16 (30798)
18 limit 15 to "all adult (19 plus years)" (28434)
19 17 or 18 (31999)
20 treatment outcome/ (824861)
21 Pain Measurement/ (75370)

22 "Recovery of Function"/ (42703)
23 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)).mp. (586581)
24 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (628803)
25 Return to Work/ or Return to Sport/ or ((return or resump*) adj3 (work or sport or play or activit*)).mp. (16520)
26 pain*.jw,ti. (199639)
27 pain*.ab. /freq=2 (243208)
28 or/20-27 (2035376)
29 19 and 28 (20709)
30 exp appendicitis/ or exp Back Pain/ or Labor Pain/ or exp Pain, Postoperative/ or exp Toothache/ or headache/ or exp Headache disorders/ or exp dentistry/ or exp Neoplasms/ (3499077)
31 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*)).mp. (118740)
32 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or metastas*).mp. (463484)
33 or/30-32 (3631063)
34 29 not 33 (13769)
35 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (7012189)
36 34 and 35 (9481)
37 Osteoarthritis/ (33247)
38 exp arthroplasty/ or exp arthroscopy/ or bone transplantation/ (101224)
39 su.fs. (1807708)
40 or/37-39 (1863671)

Feb 14, 2018
Database: Embase <1974 to 2018 February 13>
Search Strategy:
---
1 limb injury/ or exp arm injury/ or exp leg injury/ or exp limb fracture/ or sport injury/ or exp joint injury/ or musculoskeletal injury/ or exp cartilage injury/ or exp "ligament and tendon injury"/ or medial tibial stress syndrome/ or muscle injury/ or overexertion/ or exp sprain/ or fracture/ or avulsion fracture/ or clavicle fracture/ or comminuted fracture/ or fracture dislocation/ or exp fracture healing/ or intraarticular fracture/ or exp joint fracture/ or exp limb fracture/ or exp multiple fracture/ or exp scapula fracture/ or stress fracture/ or neck injury/ or whiplash injury/ or occupational accident/ or soft tissue injury/ or compartment syndrome/ (382802)
Annotation: includes arm injury/ or exp arm fracture/ or elbow dislocation/ or elbow injury/ or exp forearm injury/ or exp hand injury/ or exp shoulder injury/ or exp wrist injury/ or leg injury/ or exp ankle injury/ or exp foot injury/ or exp hip injury/ or exp knee injury/ or exp leg fracture/ or tibia torsion/ or exp ankle injury/ or exp dislocation/ or exp hip injury/ or intraarticular

fracture/ or exp joint fracture/ or exp knee injury/ or posttraumatic arthropathy/ or exp wrist injury/
2 (exp musculoskeletal system/ or exp musculoskeletal disease/) and pain*.ti,ab. (312623)
3 musculoskeletal pain/ or neck pain/ or shoulder pain/ or arthralgia/ (86878)
4 or/1-3 (692780)
Annotation: emtree terms condition MSK pain
5 (Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (147804)
6 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)).tw. (16617)
7 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)).tw. (305948)
8 or/5-7 (444822)
Annotation: free text terms condition MSK pain
9 4 or 8 (897318)
Annotation: MSK pain
10 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (25540585)
11 human/ or normal human/ or human cell/ (19287963)
12 10 and 11 (19240053)
13 10 not 12 (6300532)
14 9 not 13 (837728)
15 random:.tw. or placebo:.mp. or double-blind:.tw. (1509046)
Annotation: HIRU specific RCT filter
16 ((treatment or control) adj3 group*).ab. (723604)
17 (allocat* adj5 group*).ab. (26448)
18 ((clinical or control*) adj3 trial).ti,ab,kw. (327340)
19 or/15-18 (2107446)
Annotation: modified RCT filter
20 14 and 19 (95790)
Annotation: MSK pain with mod RCT filter
21 treatment outcome/ (762155)
22 outcome assessment/ (400641)
23 pain measurement/ (4687)
24 exp pain assessment/ (134012)
25 convalescence/ (42381)
26 return to sport/ or return to work/ (4870)
27 work resumption/ (3467)

28 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)).mp. (790797)
29 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (911685)
30 ((return or resump*) adj3 (work or sport or play or activit*)).mp. (23514)
31 pain*.jw,ti. (269095)
32 pain*.ab. /freq=2 (358966)
33 or/21-32 (2816037)
34 20 and 33 (58373)
Annotation: MSK pain with mod RCT and outcome
35 exp appendicitis/ or exp backache/ or labor pain/ or exp postoperative complication/ or exp tooth disease/ or headache/ or exp dentistry/ or exp malignant neoplasm/ or exp metastasis/ (4067682)
36 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*)).mp. (189693)
37 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or metastas* or appendicitis).mp. (778837)
38 35 or 36 or 37 (4238484)
39 34 not 38 (30664)
Annotation: mod RCT set
40 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (9180696)
Annotation: Gill 2014 primary care plus sport
41 39 and 40 (21784)
42 exp osteoarthritis/ (110006)
43 bone transplantation/ or exp bone graft/ (46349)
44 exp orthopedic surgery/ (406039)
Annotation: includes exp joint surgery/ or exp arthroplasty/
45 su.fs. (1950489)
46 or/42-45 (2224706)

Cochrane Library
Search Name: 2017-08-22 ACP acute msk pain search
Date Run: 14/02/18 20:52:03.682
Description:

ID Search Hits
#1 Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD 13121
#2 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) near/3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)) 2044

#3 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) near/3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)) 38249
#4 #1 or #2 or #3 47667
#5 ((disability or function* or recover* or pain* or analog*) near/3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)) 109526
#6 VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement 139538
#7 ((return or resump*) near/3 (work or sport or play or activit*)) 3128
#8 pain*:so 8908
#9 pain*:ti 34759
#10 #5 or #6 or #7 or #8 or #9 214594
#11 #4 and #10 24648
#12 (pain* near/3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*)) 20816
#13 sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or metastas* 27428
#14 #12 or #13 45616
#15 #11 not #14 18297
#16 clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport* 937038
#17 #15 and #16 in Trials, with Wounds Group, Injuries Group, Pain, Palliative and Supportive Care Group, Musculoskeletal Group, Bone, Joint and Muscle Trauma Group, Back Group or Occupational Safety and Health Group in Review Groups

CINAHL

S73	S66 NOT S72	5,571
S72	S67 OR S68 OR S69 OR S70 OR S71	224,577
S71	(MM "Surgery, Operative+")	211,375
S70	(MH "Arthroscopy")	4,418
S69	(MH "Arthroplasty")	1,646
S68	(MH "Bone Transplantation")	3,342
S67	(MH "Osteoarthritis+")	13,152
S66	S64 AND S65	8,761

S65 TI (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*) OR AB (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or

	family or communit* or ambulatory or centre* or center* or office or sport*)	1,131,403
S64	S51 NOT S63	15,217
S63	S60 OR S61 OR S62	359,216
S62	TX sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or metastas*	35,825
S61	TX (pain* N3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*))	49,583
S60	S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59	329,798
S59	(MH "Neoplasms+")	240,613
S58	(MH "Dentistry+")	47,838
S57	(MH "Headache+")	16,196
S56	(MH "Toothache")	327
S55	(MH "Postoperative Pain")	8,206
S54	(MH "Labor Pain")	1,533
S53	(MH "Back Pain+")	18,740
S52	(MH "Appendicitis")	1,293
S51	S17 AND S39 AND S48	20,097
S50	S48 AND S49	20,097
S49	S17 AND S39	33,880
S48	S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47	457,089
S47	SO pain*	30,433
S46	TI pain*	68,365
S45	TX ((disability or function* or recover* or pain* or analog*) N3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)).	143,200
S44	TX VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement	174,142
S43	TX ((return or resump*) N3 (work or sport or play or activit*))	6,311
S42	(MH "Job Re-Entry") OR (MH "Sports Re-Entry") OR (MH "School Re-Entry")	6,819
S41	(MH "Pain Measurement")	27,842
S40	(MH "Treatment Outcomes")	150,811
S39	S37 NOT S38	563,918
S38	(MH "Animals+")	37,258
S37	S24 OR S29 OR S36	568,264
S36	S30 OR S31 OR S32 OR S33 OR S34 OR S35	495,048
S35	(MH "Prospective Studies+")	213,854
S34	(MH "Evaluation Research+")	41,488
S33	(MH "Comparative Studies")	101,882
S32	"latin square"	138
S31	(MH "Study Design") OR (MH "Crossover Design") OR (MH "Experimental Studies+")	207,529
S30	(MH "Random Sample+")	67,305
S29	S25 OR S26 OR S27 OR S28	211,728
S28	"random*"	203,059
S27	"placebo*"	33,694

S26	(MH "Placebos")	8,296
S25	(MH "Placebo Effect")	1,210
S24	S18 OR S19 OR S20 OR S21 OR S22 OR S23	195,829
S23	"triple-blind"	136
S22	"single-blind"	8,460
S21	"double-blind"	29,322
S20	clinical W3 trial	124,429
S19	"randomi?ed controlled trial*"	69,029
S18	(MH "Clinical Trials+")	155,173
S17	S5 OR S10 OR S15	132,229
S16	S11 OR S15	132,229
S15	S12 OR S13 OR S14	98,300
S14	TX ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) N3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*))	78,680
S13	TX ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) N3 (injur* or impair* or imping* or sprain* or strain* or tear or torn))	10,622
S12	TX Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD	20,095
S11	S5 OR S10	91,140
S10	S8 AND S9	Display
S9	TI pain* OR AB pain*	Display
S8	S6 OR S7	Display
S7	(MH "Musculoskeletal Diseases") OR (MH "Cartilage Diseases+") OR (MH "Fasciitis+") OR (MH "Foot Diseases+") OR (MH "Golf Elbow") OR (MH "Heel Pain") OR (MH "Joint Diseases") OR (MH "Muscular Diseases") OR (MH "Arthralgia+") OR (MH "Bursitis+") OR (MH "Contracture+") OR (MH "Metatarsalgia") OR (MH "Shoulder Instability, Anterior") OR (MH "Shoulder Instability, Multidirectional") OR (MH "Shoulder Instability, Posterior") OR (MH "Synovitis")	Display
S6	(MH "Musculoskeletal System") OR (MH "Cartilage+") OR (MH "Fascia+") OR (MH "Ligaments+") OR (MH "Muscles+") OR (MH "Bone and Bones") OR (MH "Arm Bones+") OR (MH "Foot Bones+") OR (MH "Leg Bones+") OR (MH "Pelvic Bones+") OR (MH "Joints+")	Display
S5	S1 OR S2 OR S3 OR S4	Display
S4	(MH "Neck Pain")	Display
S3	(MH "Arthralgia+")	Display
S2	(MH "Compartment Syndromes") OR (MH "Anterior Compartment Syndrome") OR (MH "Ischemic Contracture")	Display

S1 (MH "Arm Injuries+") OR (MH "Athletic Injuries+") OR (MH "Dislocations+") OR (MH "Fractures+") OR (MH "Hand Injuries+") OR (MH "Leg Injuries+") OR (MH "Ligament Injuries+") OR (MH "Neck Injuries+") OR (MH "Occupational-Related Injuries") OR (MH "Soft Tissue Injuries+") OR (MH "Sprains and Strains+") OR (MH "Tendon Injuries+")
Display

PEDro, yields 645

March 13, 2018

Abstract & Title: acute
AND
Problem: pain
AND
Method: Clinical trial

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4 & 8
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	16

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	18
Sponsor	#5b	Provide name for the review funder and / or sponsor	18
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	18
Rationale	#6	Describe the rationale for the review in the context of what is already known	6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8 & 9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	25-32
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9 & 10
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9 & 10

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9 & 10
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10 & 11
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10-14
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14 & 15

BMJ Open

Management of acute musculoskeletal pain (excluding low back pain): a protocol for a systematic review and network meta-analysis of randomised trials

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2018-024441.R2
Article Type:	Protocol
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Evidence based practice
Keywords:	acute pain, musculoskeletal, intervention, systematic review, network metanalysis

Management of acute musculoskeletal pain (excluding low back pain): a protocol for a systematic review and network meta-analysis of randomised trials

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Abstract

Introduction: Acute, non-low back related musculoskeletal pain is common and associated with significant socioeconomic costs. No review has evaluated all interventional studies for acute musculoskeletal pain, which limits attempts to make inferences regarding the relative effectiveness of treatments.

Methods and analysis: We will conduct a systematic review of all randomised controlled trials evaluating therapies for acute musculoskeletal pain (excluding low back pain). We will identify eligible, English-language, trials by a systematic search of CINAHL, EMBASE, MEDLINE, PEDro and the Cochrane Central Registry of Controlled Trials from inception to February 2018. Eligible trials will: (1) enrol patients presenting with acute, non-low back related musculoskeletal pain (duration of pain ≤ 4 weeks), and (2) randomise patients to alternative interventions or an intervention and a placebo/sham arm. Fractures will be considered ineligible, unless they are non-surgical and therapy is directed at pain relief. Pairs of reviewers will, independently and in duplicate, screen titles and abstracts of identified citations, review the full texts of potentially eligible trials and extract information from eligible trials. We will use a modified Cochrane instrument to evaluate risk of bias. Disagreements will be resolved through discussion to achieve consensus.

We will use the GRADE system to evaluate the quality of evidence supporting treatment effects. When possible, we will conduct: (1) in direct comparisons, a random-effects meta-analysis to establish the effectiveness of therapeutic interventions on patient-important outcomes; and (2) multiple treatment comparison meta-analysis to assess the relative effects of treatments. We will use a priori hypotheses to explain heterogeneity between studies. We will use STATA 14.2 for all analyses.

Ethics and dissemination: No research ethics approval is required for this systematic review. The results of this systematic review will be disseminated through publication in a peer-reviewed journal, conference presentations, and will inform a clinical practice guideline.

Key Words: acute pain; musculoskeletal; intervention; systematic review; network meta-analysis

PROSPERO registration number: CRD42018094412

Article Summary

Strengths and limitations

- Our broad study eligibility criteria will increase generalizability of our results.
- We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to evaluate our confidence in treatment effects.
- We will optimize interpretability by presenting risk differences and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.
- Findings from our review will inform a clinical practice guideline and identify key areas for future research.
- Our results will be limited by possible shortcomings of the primary studies.

Introduction

Acute non-low back related musculoskeletal (MSK) pain, which include strains and sprains, dislocations, and whiplash present for less than 1 month[1], are associated with considerable morbidity in North America. The Burden of Musculoskeletal Diseases in the United States, 3rd edition, found that sprains and strains are the most frequent injury type for which medical care is sought and the majority of MSK injuries occur among working-age adults.[2] In 2013 there were 2,807,880 emergency department visits for sports-related injuries in the US,[3] and over 70% of visits to the emergency department are because of pain-related complaints.[4] Management often yields suboptimal outcomes: a survey of 842 acute pain patients at 20 US and Canadian hospitals found 40% reported their pain did not change or increased after visiting the emergency department, and 74% of patients were discharged in moderate to severe pain.[5]

Despite the prevalence of acute MSK complaints in primary care, a number of studies have highlighted inadequate pain education of among physicians.[6-8] The availability of numerous pharmacologic and non-pharmacologic therapies further complicates management decisions. Currently available treatments include opioids, nonsteroidal anti-inflammatory drugs, muscle relaxants, acetaminophen, exercise, supervised rehabilitation, joint manipulation and mobilization, massage, acupuncture and acupressure, ultrasound, low-level laser therapy, and transcutaneous electrical nerve stimulation.[9-12]

A recently published series of 24 systematic reviews of treatment for common acute MSK injuries,[13] suffers from many important limitations, including: (1) selection bias due, in part, to exclusion of studies deemed to be at high risk of bias without empirically exploring if effect estimates differed from studies assigned low risk of bias, (2) interpreting results from individual studies as effective if the mean difference in a given outcome met the minimally

important difference (MID) and ineffective if not - an interpretation that relies on the unlikely assumption that all patients will experience the same degree of improvement, and fails to consider the distribution around the mean and the proportion of patients that achieve the MID, (3) no appraisal of the overall quality (confidence, certainty) of the evidence, and (4) no statistical pooling of treatment effects. We propose to conduct a systematic review of randomized trials to assess the comparative effectiveness of available non-surgical treatments for acute MSK pain (excluding low back pain) and assess quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Methods

Protocol registration

The protocol for this systematic review is registered with PROSPERO (CRD42018094412). This review was commissioned by the American Academy of Family Physicians and American College of Physicians and sponsored by the National Safety Council.

Standardized Reporting

We used the PRISMA-P checklist when writing our report.[14]

Information sources

We will identify eligible, English language, randomized clinical trials (RCTs) through a systematic search of MEDLINE, EMBASE, CINAHL, PEDro and CENTRAL, from inception of each database through February 2018. Our search has been refined for individual databases by an experienced medical librarian (Appendix). We will scan reference lists of included studies and relevant systematic reviews for additional eligible articles.

Eligibility criteria and study selection

We will include therapeutic trials that: 1) enroll adult patients (≥ 18 years) presenting with acute, non-low back related MSK pain (pain with duration < 4 weeks or defined by authors as "acute") in an outpatient setting, and 2) randomise them to currently available, non-surgical, alternative interventions directed at pain relief (pharmacological or non-pharmacological) or a currently available, non-surgical, intervention directed at pain relief and a placebo/sham arm. Eligible MSK conditions include sprains and strains. Surgical fractures, non-surgical fractures unless

therapy is directed at pain relief, low back pain, neuropathic pain, acute cancer pain, acute postoperative pain, acute dental pain, pain associated with labour and delivery, visceral pain, pain due to infection, and headaches will be excluded. We will exclude interventions targeted at treatment of acute low back pain on request by the study funder, as they have previously commissioned evidence syntheses on this topic.[9,10]

Ten teams of trained reviewers will work independently in pairs to screen titles and abstracts of identified citations, using standardized, pilot-tested forms in DistillerSR, an online systematic review software (Evidence Partners, Ottawa, Canada; http://systematic-review.net/). The same teams of reviewers will screen full texts of any articles judged as potentially eligible. Reviewers will discuss disagreements to come to consensus, referring to an adjudicator if necessary. We will measure agreement between reviewers by calculating kappa (κ) values to assess the reliability of full-text review, and interpret them using the following thresholds: <0.20 as slight agreement, 0.21–0.40 as fair agreement, 0.41–0.60 as moderate agreement, 0.61–0.80 as substantial agreement and >0.80 as almost perfect agreement.[15]

Data abstraction

We designed standardized data abstraction forms and a detailed instruction video (accessible at: https://www.youtube.com/watch?v=1nwFJ61K3sQ). We will conduct calibration exercises prior to beginning data abstraction to ensure consistency and accuracy of extractions. Seven teams of reviewers will extract data independently and in duplicate. We will extract the following data from eligible trials into a standardized spreadsheet: study characteristics (e.g. the first author, publication year, country of origin, and funding source), participant and trial characteristics (e.g. sample size, mean age of participants, clinical condition, type and severity of injury, proportion

with known chronic pain/condition prior to acute injury, and the proportion receiving opioids at the time of enrollment), characteristics of interventions and comparators, patient-important outcomes (pain, function, health-related quality of life, patient satisfaction, return to work, proportion of patients with relief, re-injury and all reported adverse events). We will extract pain at any time-point, whereas for other outcomes, we will use the longest follow-up reported.[16]

Risk of bias assessment

Among eligible studies, we will independently assess the following risk of bias issues: (1) random sequence generation, (2) allocation concealment, (3) blinding of study participants, personnel, and outcome assessors, (4) incomplete outcome data (≥20% missing data will be considered at high risk of bias), and (5) other sources of bias. [17] To assess the risk of bias we will use a modified version of the Cochrane risk of bias instrument.[18] Our instrument will use the following responses: 'definitely yes' or 'probably yes' (considered as low risk of bias), or 'definitely no' or 'probably no' (considered as high risk of bias). These response options have published evidence of validity for assessing blinding.[18] Any discrepancy in assessment of risk of bias will be resolved by discussion, or third party adjudication if needed. We will contact authors for missing information regarding risk of bias issues and unpublished data (e.g. effect estimates without accompanying estimates of precision).

Data synthesis

MSK complaints are increasingly being considered together as risk factors,[19] prognosis, [20] and treatments are often similar in guideline recommendations.[21,22] For the purposes of statistical pooling, we will explore treatment effects of interventions across all MSK complaints eligible for

this review; however, we will also explore if treatment effects differ by clinical condition or injury severity. Clustering strategies for clinical condition and injury severity will be informed by the trials eligible for our review, which will be reviewed by a technical expert panel, blinded to study results. Treatment effects will be pooled using the longest follow-up time reported, except for pain, which will be pooled at the most commonly reported short, medium and long-term follow-up times reported by trials eligible for our review. For our review, these categories will be 30 to 120 minutes post-treatment (short), 1 to 7 days post-treatment (medium), and 3 to 12 weeks post-treatment (long). As such, a single trial could contribute to up to 3 time-points for our pooled results for pain relief. Alternately, trials that reported pain relief at time points outside of these timeframes would not contribute data for our analyses of pain relief.

Methods for direct comparisons

We will pool dichotomous outcomes that are reported by >1 RCT and calculate the relative risk and risk difference (RD), using baseline risk estimates from the placebo arm of eligible studies, and the associated 95% confidence intervals (CIs). We will pool all continuous outcomes that are reported by >1 study and calculate the weighted mean differences (WMDs) and associated 95% CIs. We will employ methods described in Cochrane Handbook to estimate the mean and standard deviation (SD) when median, range, and sample size are reported, and to impute the SD if the standard error or SD for the differences are not reported.[23] For continuous outcomes, when studies report effect estimates using different measurement instruments that tap into a common construct (e.g. pain), we will first transform all outcomes to a common instrument on a domain-by-domain basis.[24] We will use change scores from baseline to end of follow-up rather than end-of-study scores, in order to account for inter-patient variability. If authors do not report change scores, we

will calculate them using the baseline and end-of-study score and a correlation coefficient derived from the largest trial at lowest risk of bias in the meta-analysis that does report a change score. We will use DerSimonian–Laird random-effects models [25] for all pairwise comparisons.

Interpreting effect estimates for continuous outcomes is challenging,[26] and we will present the minimally important difference (MID) for all pooled effect estimates. The MID is the smallest amount of improvement in a treatment outcome that a patient would recognize as important.[27] If we find multiple MID estimates are available, we will use the smallest difference that has been validated.

However, simply presenting the MID risks interpreting all mean effects that fall below the MID as unimportant, whereas we have found that, typically, mean differences of 1/2 the MID result in RDs of about 10% - a potential benefit that many patients may consider important.[28] Thus, concluding that an effect is unimportant requires confidence that the mean difference is less than 1/2 the MID (and perhaps less). To optimize interpretability, we will calculate the RD of achieving the MID for all statistically significant WMDs. Specifically, for each individual study, we will assume that the SDs of outcome measurements are the same in both the treatment and control groups, and that change scores in both groups are normally distributed. We will use the median or mean, and SD of the control group, with the established MID for the outcome in question to estimate the probability of achieving ≥ MID in the control group. We will use the pooled mean difference to estimate the mean in the treatment group and calculate the probability of achieving ≥ MID in the treatment group. Finally, we will use risks in both groups to acquire the RD for achieving ≥ MID.

Methods for network meta-analysis

We will perform network meta-analysis to synthesize the available evidence from the entire network of trials by integrating direct and indirect estimates for each comparison into a single summary treatment effect. We will use a frequentist random-effects model using the methodology of multivariable meta-analysis to assess the comparative effectiveness of eligible interventions.[29,30]

Although the assumptions for network meta-analysis are similar to conventional meta-analysis, key extra assumptions are transitivity (there are no effect modifiers influencing the indirect comparisons) and coherence (direct and indirect effect estimates being similar).[31] We will identify issues of incoherence by comparing direct evidence (i.e. estimates from pairwise comparisons) with indirect evidence (i.e. estimates from network meta-analysis) using the node splitting method.[32,33] In this approach, incoherence is assessed locally by evaluating the consistency assumption in each closed loop of the network separately as the difference between direct and indirect estimates for a specific comparison in the loop. We will assume a common heterogeneity estimate within each loop. We will also confirm the coherence assumption in the entire network using a 'design-by-treatment' model.[34] In case we find significant incoherence in the network (highly significant p value from design-by-treatment model), we will perform network meta-analysis using an inconsistency model. If using an inconsistency model results in non-sensical results, we will explore the network for the source(s) of incoherence and further expand (disintegrating interventions based on differences in population or intervention characteristics) or exclude the node(s) introducing incoherence into the network (e.g., excluding node(s) with less than 20 events for binary outcomes or comparisons with only one trial with very few participants for continuous outcomes).

We will report our findings with probability statements of intervention effects. Probability rankings allow us to report a chance percentage of which interventions rank higher;[35] however,

simplifying the results of a network down to probabilities can lead to misinterpretations, specifically, when particular comparisons (i.e. nodes) are not well-connected or when the quality of evidence varies between comparisons.[36,37] Following display of the rank probabilities using rankogram, we will use the surface under the cumulative ranking (SUCRA) line to aid in interpretation of relative effect of the interventions. An intervention with a SUCRA value of 100 is certain to be the most effective, whereas an intervention with 0 is certain to be the least effective.[35] We will use STATA (StataCorp, Release 14.2, College Station, Texas, USA) for all statistical analyses. All comparisons will be 2-tailed using a threshold $p \leq 0.05$.

Subgroup analyses, meta-regression and sensitivity analysis

We will use Cochran's Q statistic and I^2 to determine statistical heterogeneity for direct meta-analysis.[32] We have developed five hypotheses to explain heterogeneity between trials: (1) different clinical conditions will show different treatment effects; (2) more severe injuries will show smaller treatment effects than less severe injuries (e.g. higher grades of strains and sprains vs. lower grades); (3) older patients will show smaller treatment effects than younger patients; (4) longer follow-up will show smaller treatment effects than shorter follow-up; and (5) higher dose/intensity of treatment will show larger treatment effects. We will perform subgroup analyses regardless of heterogeneity estimates, if there are at least 2 trials in each subgroup. Moreover, we will explore the effect of risk of bias (on a component-by-component basis) and reported vs. converted change scores on treatment effects.

Assessing quality of the evidence

We will use the GRADE approach to assess the quality of evidence on an outcome-by-outcome basis. The starting point for quality of evidence for RCTs is high, but may be rated down based on limitations in risk of bias, imprecision, inconsistency, and indirectness and publication bias.[38] When there are at least 10 studies for meta-analysis,[39,40] we will assess publication bias by visual assessment of asymmetry of the funnel plot and calculated Begg's test.

We will also use the GRADE approach to assess quality of evidence for indirect and network (mixed) effect estimates.[41,42] Indirect effect estimates are calculated from available 'loops' of evidence, which includes first order loops (based on a single common comparator treatment, the difference between the treatment A and B is based on comparisons of A and C as well as B and C) or higher order loops (more than one intervening treatment connecting the two interventions). We will visually examine the network map and where first order loops are available for indirect comparisons, the quality of evidence will be the lower of the ratings for the two direct estimates contributing to the first order loop. In the absence of a first order loop, a higher order loop will be used to rate the quality of evidence. We may rate down quality of evidence further for intransitivity.[42] The transitivity assumption implies similarity of trials in terms of population, intervention, settings, and trial methodology.[43]

It is very rare for a network meta-analysis to establish a single treatment option as clearly superior to all others. We will categorize interventions according to three categories: (1) those that are clearly superior, (2) those with intermediate effectiveness, and (3) those that are inferior. Treatments no better than placebo will be in the lowest tier, those better than placebo in tier 1 (likely intermediate); those superior to at least 1 tier 1 treatment will be judged superior. Treatments will be further categorized according to quality of evidence supporting those estimates (high and moderate vs. low or very low). Interventions with moderate or high quality

evidence will be ranked as either ‘among the most effective’, ‘inferior to the most effective / superior to the least effective’, or ‘among the least effective’. Interventions supported by low or very low quality evidence will be ranked into the same 3 categories but prefaced with ‘may be’ to acknowledge the reduced confidence in supporting evidence (e.g. ‘may be among the most effective’) and will be presented separately from those supported by moderate or high quality evidence.

Ethics and Dissemination

No research ethics approval is required for this systematic review, as no confidential patient data will be used. The results of this systematic review will be disseminated through publication in a peer-reviewed journal and through conference presentations. Findings from our review will inform a clinical practice guideline. All amendments to the protocol will be reported in the PROSPERO trial registry.

Patient and Public Involvement

No patients were involved in setting the research question, in developing plans for design, interpretation, reporting or implementation of the study. We plan to disseminate the results of this study to organisations supporting patients with acute MSK pain.

Discussion

With the high prevalence of acute non-low back MSK pain, the associated socioeconomic burden and the paucity of evidence on the comparative effectiveness of treatment options, there is an urgent need for a high-quality systematic review to inform evidence-based management of these complaints.

Our proposed review has several strengths in relation to existing reviews. First, we will explore all currently available non-pharmacological and pharmacological treatment options for all acute MSK complaints (excluding low back pain) reported among eligible trials. It is plausible that individual acute MSK complaints respond similarly to similar interventions, and thus by pooling across individual injuries, it may be possible to provide a more precise estimate of treatment effect. Second, we will update the search to present date. Third, we will use the GRADE approach to evaluate the quality of evidence supporting treatment effects. Fourth, we will ensure interpretability by presenting RDs and measures of relative effect for all outcomes reported, and by presenting our findings with GRADE evidence profiles.

A potential limitation will be the nature of available treatment comparisons to build robust networks for our analyses. The findings of our review will help inform patients with acute non-low back related MSK pain about their therapeutic options, identify key areas for research, and facilitate a clinical practice guideline for the management of acute, non-low back related MSK pain.

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Author Contributions: All authors made substantial contributions to conception and design. JWB and BS drafted the article, and SC, RC, PJH, YO, CM, AL and GHG revised it critically for important intellectual content. All authors provided final approval of the version to be published. JWB is the guarantor of the review protocol.

Data sharing: Statistical code and dataset available from Dr. Sadeghirad (e-mail: b.sadeghirad@gmail.com).

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Competing interests: None declared.

Patient consent: Not required.

Provenance and peer review: This review was commissioned and externally peer reviewed.

References

1. Olsen MF, Bjerre E, Hansen MD, et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. *BMC medicine* 2017;15(1):35. doi: 10.1186/s12916-016-0775-3 [published Online First: 2017/02/22]

2. United States Bone and Joint Initiative: The Burden of Musculoskeletal Diseases in the United States (BMUS) Rosemont, IL. 2014. Third Edition [Available from: http://www.boneandjointburden.org accessed March 3rd 2017.

3. Agency for Healthcare Research and Quality (AHRQ), Center for Delivery Organization and Markets Healthcare Cost and Utilization Project (HCUP). National Inpatient Sample (NIS) and Nationwide Emergency Department Sample (NEDS), 2013.

4. Todd KH, Miner JR. Pain in the emergency room. In: Fishman SM, Ballantyne JC, Rathmell JP, eds. Bonica's Management of Pain. Philadelphia, PA, USA: Lippincott, Williams and Wilkins 2010:1576–87.

5. Todd KH, Ducharme J, Choiniere M, et al. Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. *The journal of pain : official journal of the American Pain Society* 2007;8(6):460-6. doi: 10.1016/j.jpain.2006.12.005 [published Online First: 2007/02/20]

6. Vadivelu N, Mitra S, Hines R, et al. Acute pain in undergraduate medical education: an unfinished chapter! *Pain practice : the official journal of World Institute of Pain* 2012;12(8):663-71. doi: 10.1111/j.1533-2500.2012.00580.x [published Online First: 2012/06/21]

7. Fishman SM, Young HM, Lucas Arwood E, et al. Core competencies for pain management: results of an interprofessional consensus summit. *Pain medicine (Malden, Mass)* 2013;14(7):971-81. doi: 10.1111/pme.12107 [published Online First: 2013/04/13]

8. Watt-Watson J, Murinson BB. Current challenges in pain education. *Pain management* 2013;3(5):351-7. doi: 10.2217/pmt.13.39 [published Online First: 2014/03/25]

9. Chou R, Deyo R, Friedly J, et al. Nonpharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):493-505. doi: 10.7326/m16-2459 [published Online First: 2017/02/14]

10. Chou R, Deyo R, Friedly J, et al. Systemic Pharmacologic Therapies for Low Back Pain: A Systematic Review for an American College of Physicians Clinical Practice Guideline. *Ann Intern Med* 2017;166(7):480-92. doi: 10.7326/m16-2458 [published Online First: 2017/02/14]

11. Qaseem A, Wilt TJ, McLean RM, Forciea MA; Clinical Guidelines Committee of the American College of Physicians. Noninvasive Treatments for Acute, Subacute, and Chronic Low Back Pain: A Clinical Practice Guideline from the American College of Physicians. Ann Intern Med. 2017; 166(7): 514-530.

12. Motov S, Strayer R, Hayes BD, Reiter M, Rosenbaum S, Richman M, Repanshek Z, Taylor S, Friedman B, Vilke G, Lasoff D. The Treatment of Acute Pain in the Emergency Department: A White Paper Position Statement Prepared for the American Academy of Emergency Medicine. J Emerg Med. 2018; 54(5): 731-736.

13. Côté P, Shearer H, Ameis A, et al. Enabling recovery from common traffic injuries: A focus on the injured person. January 31, 2015; UOIT-CMCC Centre for the Study of Disability Prevention and Rehabilitation.

14. Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic reviews* 2015;4:1. doi: 10.1186/2046-4053-4-1 [published Online First: 2015/01/03]

15. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics* 1977;33(1):159-74. [published Online First: 1977/03/01]

16. Tendal B, Nuesch E, Higgins JP, et al. Multiplicity of data in trial reports and the reliability of meta-analyses: empirical study. *Bmj* 2011;343:d4829. doi: 10.1136/bmj.d4829 [published Online First: 2011/09/01]

17. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928. doi: http://dx.doi.org/10.1136/bmj.d5928

18. Akl EA, Sun X, Busse JW, et al. Specific instructions for estimating unclearly reported blinding status in randomized trials were reliable and valid. *J Clin Epidemiol* 2012;65(3):262-67. doi: http://dx.doi.org/10.1016/j.jclinepi.2011.04.015

19. Taanila H, Suni JH, Kannus P, et al. Risk factors of acute and overuse musculoskeletal injuries among young conscripts: a population-based cohort study. *BMC musculoskeletal disorders* 2015;16:104. doi: 10.1186/s12891-015-0557-7 [published Online First: 2015/05/01]

20. de Vos Andersen NB, Kent P, Hjort J, et al. Clinical course and prognosis of musculoskeletal pain in patients referred for physiotherapy: does pain site matter? *BMC musculoskeletal*

disorders 2017;18(1):130. doi: 10.1186/s12891-017-1487-3 [published Online First: 2017/03/31]

21. Australian Acute Musculoskeletal Pain Guidelines Group. Evidence-based management of acute musculoskeletal pain. *ISBN 1 875378 49 9* 2003
22. Babatunde OO, Jordan JL, Van der Windt DA, et al. Effective treatment options for musculoskeletal pain in primary care: A systematic overview of current evidence. *PLoS One* 2017;12(6):e0178621. doi: 10.1371/journal.pone.0178621 [published Online First: 2017/06/24]
23. Higgins JP, Green S. Cochrane Handbook for Systematic Reviews of Interventions, version [5.1.0] (updated March 2011). The Cochrane Collaboration, 2011.
24. Thorlund K, Walter SD, Johnston BC, et al. Pooling health-related quality of life outcomes in meta-analysis-a tutorial and review of methods for enhancing interpretability. *Res Synth Methods* 2011;2(3):188-203. doi: 10.1002/jrsm.46 [published Online First: 2011/09/01]
25. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controlled clinical trials* 1986;7(3):177-88.
26. Busse JW, Bartlett SJ, Dougados M, et al. Optimal Strategies for Reporting Pain in Clinical Trials and Systematic Reviews: Recommendations from an OMERACT 12 Workshop. *The Journal of rheumatology* 2015;42(10):1962-70. doi: 10.3899/jrheum.141440 [published Online First: 2015/05/17]
27. Schunemann HJ, Guyatt GH. Commentary--goodbye M(C)ID! Hello MID, where do you come from? *Health services research* 2005;40(2):593-7. doi: 10.1111/j.1475-6773.2005.00374.x [published Online First: 2005/03/15]

28. Busse JW, Wang L, Kamaleldin M, et al. Opioids for Chronic Noncancer Pain: A Systematic Review and Meta-analysis. JAMA. 2018; 320(23): 2448-2460.

29. White IR. Network meta-analysis. *The Stata Journal* 2015;15(4):951–85.

30. White IR, Barrett JK, Jackson D, et al. Consistency and inconsistency in network meta-analysis: model estimation using multivariate meta-regression. *Res Synth Methods* 2012;3(2):111-25. doi: 10.1002/jrsm.1045 [published Online First: 2012/06/01]

31. Donegan S, Williamson P, D'Alessandro U, et al. Assessing key assumptions of network meta-analysis: a review of methods. *Res Synth Methods* 2013;4(4):291-323. doi: 10.1002/jrsm.1085

32. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ* 2003;327(7414):557-60. doi: http://dx.doi.org/10.1136/bmj.327.7414.557

33. Lu G, Ades AE. Assessing evidence inconsistency in mixed treatment comparisons. *J Am Stat Assoc* 2006;101(474):447-59. doi: 10.1198/016214505000001302

34. Higgins JP, Jackson D, Barrett JK, et al. Consistency and inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Synth Methods* 2012;3(2):98-110. doi: 10.1002/jrsm.1044 [published Online First: 2012/06/01]

35. Salanti G, Ades AE, Ioannidis JPA. Graphical methods and numerical summaries for presenting results from multiple-treatment meta-analysis: an overview and tutorial. *J Clin Epidemiol* 2011;64(2):163-71. doi: http://dx.doi.org/10.1016/j.jclinepi.2010.03.016

36. Mbuagbaw L, Rochwerg B, Jaeschke R, et al. Approaches to interpreting and choosing the best treatments in network meta-analyses. *Systematic reviews* 2017;6(1):79. doi: 10.1186/s13643-017-0473-z [published Online First: 2017/04/14]

37. Trinquart L, Attiche N, Bafeta A, et al. Uncertainty in Treatment Rankings: Reanalysis of Network Meta-analyses of Randomized Trials. *Ann Intern Med* 2016;164(10):666-73. doi: 10.7326/m15-2521 [published Online First: 2016/04/19]

38. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336(7650):924-26. doi: 10.1136/bmj.39489.470347.AD

39. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. 2011; Available from http://handbook-5-1.cochrane.org/ (Accessed October 25, 2018)

40. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics* 1994;50(4):1088-101. [published Online First: 1994/12/01]

41. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014;349:5630. doi: 10.1136/bmj.g5630

42. Brignardello-Petersen R, Bonner A, Alexander PE, et al. Advances in the GRADE approach to rate the certainty in estimates from a network meta-analysis. *Journal of clinical epidemiology* 2018;93:36-44. doi: 10.1016/j.jclinepi.2017.10.005 [published Online First: 2017/10/21]

43. Salanti G, Higgins JP, Ades A, et al. Evaluation of networks of randomized trials. *Stat Methods Med Res* 2008;17(3):279-301.

Appendix: Literature Search Strategies

Summary of search and strategies ACP Acute MSK Pain

Feb 14, 2018
Database: OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Search Strategy:
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1 exp arm injuries/ or athletic injuries/ or exp joint dislocations/ or exp fractures, bone/ or fractures, cartilage/ or exp hand injuries/ or exp hip injuries/ or exp leg injuries/ or exp neck injuries/ or occupational injuries/ or exp shoulder injuries/ or exp soft tissue injuries/ or exp "sprains and strains"/ or exp tendon injuries/ or exp Compartment Syndromes/ or exp Bone Malalignment/ (300813)
2 (exp Musculoskeletal system/ or musculoskeletal diseases/ or osteitis/ or exp cartilage diseases/ or exp fasciitis/ or exp bursitis/ or exp metatarsalgia/ or exp synovitis/ or muscle cramp/ or myalgia/ or exp tendinopathy/) and pain*.ti,ab. (87772)
3 Musculoskeletal Pain/ or Neck Pain/ or Acute Pain/ or exp Arthralgia/ (19422)
4 (Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (111653)
5 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)).tw. (14400)
6 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)).tw. (235481)
7 or/1-6 (587971)
8 randomized controlled trial.pt. or randomi?ed.mp. or placebo.mp. (810530)
9 ((treatment or control) adj3 group*).ab. (511607)
10 (allocat* adj5 group*).ab. (20402)
11 ((clinical or control*) adj3 trial).ti,ab,kw. (226548)
12 or/8-11 (1258485)
13 7 and 12 (46565)
14 exp animals/ not humans.sh. (4424690)
15 13 not 14 (42705)
16 adult.mp. or middle aged.sh. or age:.tw. (8090446)
17 15 and 16 (30798)
18 limit 15 to "all adult (19 plus years)" (28434)
19 17 or 18 (31999)
20 treatment outcome/ (824861)
21 Pain Measurement/ (75370)

22 "Recovery of Function"/ (42703)
23 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)).mp. (586581)
24 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (628803)
25 Return to Work/ or Return to Sport/ or ((return or resump*) adj3 (work or sport or play or activit*)).mp. (16520)
26 pain*.jw,ti. (199639)
27 pain*.ab. /freq=2 (243208)
28 or/20-27 (2035376)
29 19 and 28 (20709)
30 exp appendicitis/ or exp Back Pain/ or Labor Pain/ or exp Pain, Postoperative/ or exp Toothache/ or headache/ or exp Headache disorders/ or exp dentistry/ or exp Neoplasms/ (3499077)
31 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*)).mp. (118740)
32 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or metastas*).mp. (463484)
33 or/30-32 (3631063)
34 29 not 33 (13769)
35 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (7012189)
36 34 and 35 (9481)
37 Osteoarthritis/ (33247)
38 exp arthroplasty/ or exp arthroscopy/ or bone transplantation/ (101224)
39 su.fs. (1807708)
40 or/37-39 (1863671)

Feb 14, 2018
Database: Embase <1974 to 2018 February 13>
Search Strategy:
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1 limb injury/ or exp arm injury/ or exp leg injury/ or exp limb fracture/ or sport injury/ or exp joint injury/ or musculoskeletal injury/ or exp cartilage injury/ or exp "ligament and tendon injury"/ or medial tibial stress syndrome/ or muscle injury/ or overexertion/ or exp sprain/ or fracture/ or avulsion fracture/ or clavicle fracture/ or comminuted fracture/ or fracture dislocation/ or exp fracture healing/ or intraarticular fracture/ or exp joint fracture/ or exp limb fracture/ or exp multiple fracture/ or exp scapula fracture/ or stress fracture/ or neck injury/ or whiplash injury/ or occupational accident/ or soft tissue injury/ or compartment syndrome/ (382802)
Annotation: includes arm injury/ or exp arm fracture/ or elbow dislocation/ or elbow injury/ or exp forearm injury/ or exp hand injury/ or exp shoulder injury/ or exp wrist injury/ or leg injury/ or exp ankle injury/ or exp foot injury/ or exp hip injury/ or exp knee injury/ or exp leg fracture/ or tibia torsion/ or exp ankle injury/ or exp dislocation/ or exp hip injury/ or intraarticular

fracture/ or exp joint fracture/ or exp knee injury/ or posttraumatic arthropathy/ or exp wrist injury/
2 (exp musculoskeletal system/ or exp musculoskeletal disease/) and pain*.ti,ab. (312623)
3 musculoskeletal pain/ or neck pain/ or shoulder pain/ or arthralgia/ (86878)
4 or/1-3 (692780)
Annotation: emtree terms condition MSK pain
5 (Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD).tw. (147804)
6 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) adj3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)).tw. (16617)
7 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) adj3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)).tw. (305948)
8 or/5-7 (444822)
Annotation: free text terms condition MSK pain
9 4 or 8 (897318)
Annotation: MSK pain
10 exp animals/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/ (25540585)
11 human/ or normal human/ or human cell/ (19287963)
12 10 and 11 (19240053)
13 10 not 12 (6300532)
14 9 not 13 (837728)
15 random:.tw. or placebo:.mp. or double-blind:.tw. (1509046)
Annotation: HIRU specific RCT filter
16 ((treatment or control) adj3 group*).ab. (723604)
17 (allocat* adj5 group*).ab. (26448)
18 ((clinical or control*) adj3 trial).ti,ab,kw. (327340)
19 or/15-18 (2107446)
Annotation: modified RCT filter
20 14 and 19 (95790)
Annotation: MSK pain with mod RCT filter
21 treatment outcome/ (762155)
22 outcome assessment/ (400641)
23 pain measurement/ (4687)
24 exp pain assessment/ (134012)
25 convalescence/ (42381)
26 return to sport/ or return to work/ (4870)
27 work resumption/ (3467)

28 ((disability or function* or recover* or pain* or analog*) adj3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)).mp. (790797)
29 (VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement).mp. (911685)
30 ((return or resump*) adj3 (work or sport or play or activit*)).mp. (23514)
31 pain*.jw,ti. (269095)
32 pain*.ab. /freq=2 (358966)
33 or/21-32 (2816037)
34 20 and 33 (58373)
Annotation: MSK pain with mod RCT and outcome
35 exp appendicitis/ or exp backache/ or labor pain/ or exp postoperative complication/ or exp tooth disease/ or headache/ or exp dentistry/ or exp malignant neoplasm/ or exp metastasis/ (4067682)
36 (pain* adj3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*)).mp. (189693)
37 (sciatica or backache or dorsalgia or lumbago or toothache or migraine or metastas* or appendicitis).mp. (778837)
38 35 or 36 or 37 (4238484)
39 34 not 38 (30664)
Annotation: mod RCT set
40 (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*).ti,ab. (9180696)
Annotation: Gill 2014 primary care plus sport
41 39 and 40 (21784)
42 exp osteoarthritis/ (110006)
43 bone transplantation/ or exp bone graft/ (46349)
44 exp orthopedic surgery/ (406039)
Annotation: includes exp joint surgery/ or exp arthroplasty/
45 su.fs. (1950489)
46 or/42-45 (2224706)

Cochrane Library
Search Name: 2017-08-22 ACP acute msk pain search
Date Run: 14/02/18 20:52:03.682
Description:

ID Search Hits
#1 Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD 13121
#2 ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) near/3 (injur* or impair* or imping* or sprain* or strain* or tear or torn)) 2044

#3 ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) near/3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*)) 38249
#4 #1 or #2 or #3 47667
#5 ((disability or function* or recover* or pain* or analog*) near/3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)) 109526
#6 VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement 139538
#7 ((return or resump*) near/3 (work or sport or play or activit*)) 3128
#8 pain*:so 8908
#9 pain*:ti 34759
#10 #5 or #6 or #7 or #8 or #9 214594
#11 #4 and #10 24648
#12 (pain* near/3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*)) 20816
#13 sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or metastas* 27428
#14 #12 or #13 45616
#15 #11 not #14 18297
#16 clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport* 937038
#17 #15 and #16 in Trials, with Wounds Group, Injuries Group, Pain, Palliative and Supportive Care Group, Musculoskeletal Group, Bone, Joint and Muscle Trauma Group, Back Group or Occupational Safety and Health Group in Review Groups

CINAHL

S73	S66 NOT S72	5,571
S72	S67 OR S68 OR S69 OR S70 OR S71	224,577
S71	(MM "Surgery, Operative+")	211,375
S70	(MH "Arthroscopy")	4,418
S69	(MH "Arthroplasty")	1,646
S68	(MH "Bone Transplantation")	3,342
S67	(MH "Osteoarthritis+")	13,152
S66	S64 AND S65	8,761

S65 TI (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or family or communit* or ambulatory or centre* or center* or office or sport*) OR AB (clinic* or practi* or primary or physician* or refer* or visit* or outpatient* or consult* or

	family or communit* or ambulatory or centre* or center* or office or sport*)	1,131,403
S64	S51 NOT S63	15,217
S63	S60 OR S61 OR S62	359,216
S62	TX sciatica or backache or dorsalgia or lumbago or toothache or migraine or appendicitis or metastas*	35,825
S61	TX (pain* N3 (chronic or dental or labo?r or back or low back or spine or spinal or lumbar or sciatic* or cancer*))	49,583
S60	S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59	329,798
S59	(MH "Neoplasms+")	240,613
S58	(MH "Dentistry+")	47,838
S57	(MH "Headache+")	16,196
S56	(MH "Toothache")	327
S55	(MH "Postoperative Pain")	8,206
S54	(MH "Labor Pain")	1,533
S53	(MH "Back Pain+")	18,740
S52	(MH "Appendicitis")	1,293
S51	S17 AND S39 AND S48	20,097
S50	S48 AND S49	20,097
S49	S17 AND S39	33,880
S48	S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47	457,089
S47	SO pain*	30,433
S46	TI pain*	68,365
S45	TX ((disability or function* or recover* or pain* or analog*) N3 (measur* or evaluat* or scale or status or test* or assess* or rating* or index or questionnaire)).	143,200
S44	TX VAS or "visual analog*" or "numeric* rating scale" or "point scale" or comfort* or "Disabilities of the Arm Shoulder and Hand" or DASH or "Shoulder Pain and Disability Index" or SPDI or "mcgill pain" or BPI or "brief pain" or improvement	174,142
S43	TX ((return or resump*) N3 (work or sport or play or activit*))	6,311
S42	(MH "Job Re-Entry") OR (MH "Sports Re-Entry") OR (MH "School Re-Entry")	6,819
S41	(MH "Pain Measurement")	27,842
S40	(MH "Treatment Outcomes")	150,811
S39	S37 NOT S38	563,918
S38	(MH "Animals+")	37,258
S37	S24 OR S29 OR S36	568,264
S36	S30 OR S31 OR S32 OR S33 OR S34 OR S35	495,048
S35	(MH "Prospective Studies+")	213,854
S34	(MH "Evaluation Research+")	41,488
S33	(MH "Comparative Studies")	101,882
S32	"latin square"	138
S31	(MH "Study Design") OR (MH "Crossover Design") OR (MH "Experimental Studies+")	207,529
S30	(MH "Random Sample+")	67,305
S29	S25 OR S26 OR S27 OR S28	211,728
S28	"random*"	203,059
S27	"placebo*"	33,694

S26	(MH "Placebos")	8,296
S25	(MH "Placebo Effect")	1,210
S24	S18 OR S19 OR S20 OR S21 OR S22 OR S23	195,829
S23	"triple-blind"	136
S22	"single-blind"	8,460
S21	"double-blind"	29,322
S20	clinical W3 trial	124,429
S19	"randomi?ed controlled trial*"	69,029
S18	(MH "Clinical Trials+")	155,173
S17	S5 OR S10 OR S15	132,229
S16	S11 OR S15	132,229
S15	S12 OR S13 OR S14	98,300
S14	TX ((myofascial or neck* or cervical* or musculoskeletal* or MSK or elbow* or arm* or finger* or hand* or wrist* or forearm* or leg or ankle* or knee* or hip* or foot* or toe* or femur* or radius or radii or tibia* or ulna* or humerus or humeri or metatarsal* or metacarpal* or fibula* or patella* or patellofemoral or carpal* or tarsal* or phalange* or clavicle* or scapula* or bone* or joint* or muscle* or shoulder*) N3 (sprain* or strain* or injur* or impair* or fractur* or break* or broken or disorder* or pain*))	78,680
S13	TX ((ligament or tendon or supraspinatus or infraspinatus or subscapularis or teres minor or teres major or trapezius or deltoid or bicep* or bicipital or coracobrachialis or deltoid or fibularis or talofibular or calcaneofibular or calcaneotibial or tibio* or rotator cuff) N3 (injur* or impair* or imping* or sprain* or strain* or tear or torn))	10,622
S12	TX Arthralgi* or bursitis or capsulit* or epicondyalgia* or epicondylit* or fasciopath* or fasciitis or fascitis or metatarsalgi* or myalgi* or myelitis or myopath* or myosit* or osteitis or osteochondritis or osteomyelitis or polymyosit* or radiculopath* or radiculit* or synovit* or tend?nopath* or tendinit* or tenosynovit* or whiplash or WAD	20,095
S11	S5 OR S10	91,140
S10	S8 AND S9	Display
S9	TI pain* OR AB pain*	Display
S8	S6 OR S7	Display
S7	(MH "Musculoskeletal Diseases") OR (MH "Cartilage Diseases+") OR (MH "Fasciitis+") OR (MH "Foot Diseases+") OR (MH "Golf Elbow") OR (MH "Heel Pain") OR (MH "Joint Diseases") OR (MH "Muscular Diseases") OR (MH "Arthralgia+") OR (MH "Bursitis+") OR (MH "Contracture+") OR (MH "Metatarsalgia") OR (MH "Shoulder Instability, Anterior") OR (MH "Shoulder Instability, Multidirectional") OR (MH "Shoulder Instability, Posterior") OR (MH "Synovitis")	Display
S6	(MH "Musculoskeletal System") OR (MH "Cartilage+") OR (MH "Fascia+") OR (MH "Ligaments+") OR (MH "Muscles+") OR (MH "Bone and Bones") OR (MH "Arm Bones+") OR (MH "Foot Bones+") OR (MH "Leg Bones+") OR (MH "Pelvic Bones+") OR (MH "Joints+")	Display
S5	S1 OR S2 OR S3 OR S4	Display
S4	(MH "Neck Pain")	Display
S3	(MH "Arthralgia+")	Display
S2	(MH "Compartment Syndromes") OR (MH "Anterior Compartment Syndrome") OR (MH "Ischemic Contracture")	Display

S1 (MH "Arm Injuries+") OR (MH "Athletic Injuries+") OR (MH "Dislocations+") OR (MH "Fractures+") OR (MH "Hand Injuries+") OR (MH "Leg Injuries+") OR (MH "Ligament Injuries+") OR (MH "Neck Injuries+") OR (MH "Occupational-Related Injuries") OR (MH "Soft Tissue Injuries+") OR (MH "Sprains and Strains+") OR (MH "Tendon Injuries+")
Display

PEDro, yields 645

March 13, 2018

Abstract & Title: acute
AND
Problem: pain
AND
Method: Clinical trial

Reporting checklist for protocol of a systematic review.

Based on the PRISMA-P guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the PRISMA-P reporting guidelines, and cite them as:

Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart LA. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) 2015 statement. Syst Rev. 2015;4(1):1.

		Reporting Item	Page Number
Identification	#1a	Identify the report as a protocol of a systematic review	1
Update	#1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
	#2	If registered, provide the name of the registry (such as PROSPERO) and registration number	4 & 8
Contact	#3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	1
Contribution	#3b	Describe contributions of protocol authors and identify the guarantor of the review	18
	#4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important	16

		protocol amendments	
Sources	#5a	Indicate sources of financial or other support for the review	18
Sponsor	#5b	Provide name for the review funder and / or sponsor	18
Role of sponsor or funder	#5c	Describe roles of funder(s), sponsor(s), and / or institution(s), if any, in developing the protocol	18
Rationale	#6	Describe the rationale for the review in the context of what is already known	6
Objectives	#7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	7
Eligibility criteria	#8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	8 & 9
Information sources	#9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	8
Search strategy	#10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	25-32
Study records - data management	#11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	9
Study records - selection process	#11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	9
Study records - data collection process	#11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	9 & 10
Data items	#12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	9 & 10

Outcomes and prioritization	#13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	9 & 10
Risk of bias in individual studies	#14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	10
Data synthesis	#15a	Describe criteria under which study data will be quantitatively synthesised	10 & 11
	#15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I2, Kendall's τ)	10-14
	#15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	14
	#15d	If quantitative synthesis is not appropriate, describe the type of summary planned	N/A
Meta-bias(es)	#16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	14
Confidence in cumulative evidence	#17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	14 & 15