Identifying potential moderators of first-line treatment effect in patients with musculoskeletal shoulder pain: a systematic review

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ABSTRACT

Background: Commonly used conservative shoulder pain treatments include: advice/analgesia, exercise/manual therapy and, corticosteroid injection. Moderators, patient/clinical attributes influencing treatment effect, facilitate clinical decision-making by identifying which patients might respond best to specific treatments. This review summarises results of studies aiming to identify/test treatment effect moderators.**Methods:** Randomised controlled trials (RCTs) containing some form of, or suggested moderation/subgroup analysis (sample size >20, and >10 subjects in smallest subgroup), comparing above treatments against physical/functional/pain outcomes, in adults with shoulder pain were searched for in Medline, Embase, PsychInfo, CINAHL, AMED, Pedro, Cochrane Database. Cochrane Risk of Bias tool and Pincus criteria for moderation analysis were applied.**Results:** Six RCTs aiming to identify/test moderators and 16 suggesting potential moderators were included and data narratively synthesised. One trial offered confirmatory level moderation (Pincus criteria). Graded exercise had smaller effect in those with painful arc at baseline, compared against without, although lacked statistical significance (mean difference −14.0 shoulder disability (0–100 scale), 95% CI's [−28.1, 0.1], $p = 0.05$). Twenty other factors with insufficient level moderation evidence were identified.**Discussion:** Review highlights lack of high-quality evidence for moderators of treatment effect of shoulder pain treatments. Future research should address proposed candidate moderators, using robust moderation methodologies to inform clinical decision-making.

Keywords: Shoulder ; physiotherapy ; primary care ; systematic review ; clinical reasoning ; evidence based physiotherapy/medicine; EBM ; methodology

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Introduction

Primary care is commonly the first point of access for individuals with shoulder pain. Although half of those with shoulder pain consult their GP only once [1,2], apart from back and knee pain, primary care consultation rates for shoulder disorders are disproportionately higher than other MSK conditions [3,4]. Shoulder pain has a poor pattern of recovery (prognosis); >70% have pain for more than 6 weeks [5] and only 50% of new episodes demonstrate complete recovery within six months [6–8], rising to only 60% after 12 months [7]. Effective first-line treatment of shoulder pain, therefore, remains a significant clinical challenge.

In spite of numerous randomised controlled trials (RCTs) in shoulder pain that demonstrate short-term intervention effectiveness, including for exercise and corticosteroid injection [9–14], evidence is lacking for interventions with long-term effectiveness or that achieve clinically meaningful treatment effects. Variable prognosis of patients with shoulder pain [6,8,15], coupled with acknowledged diagnostic challenges [16], have prompted the exploration of prognosis-based first-line treatment strategies.

Recent shoulder studies and reviews have identified predictors of outcome regardless of treatment (prognostic factors), or investigated predictors of outcome in a cohort of patients all receiving similar treatments (e.g. physiotherapy-led intervention) [17–20]. However, predictors of outcome in such clinical cohorts do not aid understanding of how patient outcomes may vary in response to different treatments, or to treatment versus no treatment. Moderators of treatment effect are patient/clinical attributes that influence the effect of treatment [21], facilitating clinical decision-making by identifying the likely responders (and non-responders) to specific treatments [22]. Currently, the key moderators for commonly used first-line interventions for shoulder pain are unknown.

Aims of the review

We, therefore, undertook a systematic review to inform the first-line treatment decision-making by summarising the available evidence of potential moderators for three commonly used shoulder pain interventions: advice and analgesia, exercise and/or manual therapy and corticosteroid joint injection. To achieve this aim, we sought to identify studies that make a differential treatment recommendation. These studies were divided into two categories: (i) studies that aimed to identify or test treatment moderators and conducted a form of moderation analysis and (ii) studies that suggested, without data analysis, a potential moderator.

Methods

A systematic review was undertaken that

1. Searched for randomised controlled trials in shoulder pain that aimed to analyse moderation or included suggestions of potential moderators for the following commonly used first-line treatments: (a) education, advice, analgesia; (b) exercise and/or strengthening exercise; and (c) corticosteroid injection
2. Identified and appraised the methods used to identify moderators
3. Identified potential moderators for (a) advice and analgesia, (b) exercise and/or strengthening exercise and (c) corticosteroid injections in patients with musculoskeletal shoulder pain, to inform the first-line treatment decision making.

Types of studies

Included studies were randomised controlled trials (gold standard for revealing moderators of treatment effect [23,24]); that aimed to identify or test treatment moderators and/or conducted moderation analyses or any form of subgroup analysis where patients were grouped on the basis of pre-determined prognostic factors and the treatment effect was compared across subgroups. Included studies had a minimum number of 10 participants in the smallest subgroup [25] to have sufficient sample size in which to determine meaningful subgroup effects [26].

Types of participants

Studies included adults (aged 18 years or older) with non-traumatic, unilateral musculoskeletal shoulder pain. Non-traumatic musculoskeletal shoulder pain was defined as soft tissue strains/sprains, tendonitis, bursitis, capsulitis within or local to the glenohumeral joint. Studies including patients with traumatic, inflammatory, rheumatological, degenerative conditions, or osteoarthritis were excluded from this review.

Types of interventions

Included studies involved one or more of the following most commonly used first-line interventions:

1. Education, advice and/or pain relief delivered by a healthcare practitioner.
2. Mobilising or strengthening exercise or manual therapy treatment to joints and/or soft tissue delivered by a physiotherapist or physical therapist (USA definition).
3. Corticosteroid injection delivered by a primary care doctor (GP), rheumatologist, orthopaedic surgeon, physiotherapist or physical therapist.

Outcomes of interest

Studies were included if they had at least one functional (including joint assessment, disability, or work) or pain-related outcome.

Search methods for identifying studies

Database (Medline, Embase, PsycINFO, CINAHL, AMED, Pedro, and Cochrane) searches began at the earliest offered date. Searches were conducted up to January 2019. Search terms (Table 1) for shoulder conditions and relevant interventions were identified from Cochrane reviews [27,28] and supplemented with key words from previous reviews and relevant research studies. A methods filter was used to identify RCTs [29]. Inclusion of additional publications was identified through supplemental searching of included article reference lists and liaison with clinical and academic experts in the field of shoulder pain.

Table 1. Systematic review search terms (Medline).

1	Shoulder Pain/
2	Shoulder Impingement Syndrome/
3	Rotator Cuff/
4	((shoulder* or rotator cuff) adj5 (bursitis or frozen or impinge* or tendinitis or tendonitis or pain*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
5	rotator cuff.mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
6	adhesive capsulitis.mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
7	capsular syndrome.mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
8	exp Bursitis/
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	exp Rehabilitation/
11	exp Physical Therapy Modalities/
12	exp Musculoskeletal Manipulations/
13	exp Exercise Movement Techniques/
14	(rehabilitat* or physiotherap* or physica therap* or manual therap* or exercise* or mobilis*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
15	10 or 11 or 12 or 13 or 14
16	exp Injections/
17	((steroid* or corticosteroid* or subacromial or sub-acromial) adj5 inject*).mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
18	Injections, Intra-Articular/

19	"joint inject*".mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
20	((corticosteroid or triamcinolone or lederspan or hydrocortisone or methylprednisolone or depo medro* or anti inflammat*) adj inject*).ab,ti.
21	16 or 17 or 18 or 19 or 20
22	clinical trial.pt.
23	random*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
24	((single or double) adj (blind* or mask*)).mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
25	placebo*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
26	22 or 23 or 24 or 25
27	9 and 15 and 21 and 26

Study selection

Studies were selected based on the criteria in Table 2. One reviewer applied the selection criteria to retrieve publication titles. Two reviewers independently screened each abstract and 10 abstracts were triple screened for eligibility. Full texts were subjected to data extraction, risk of bias assessment and methodological appraisal by two reviewers. Reviewers did not assess studies where they declared conflict of interest by authorship/collaboration.

Table 2. Selection criteria for studies to be included in the review.

Inclusion criteria	Exclusion criteria
RCT design	Non-RCT design
Adult human participants	Non-human or child participants
Musculoskeletal shoulder pains: Dysfunction, pain or symptoms in the glenohumeral region ± surrounding soft tissue including but not limited to: soft tissue strains/sprains, tendonitis, bursitis, capsulitis	Traumatic shoulder pains e.g. fracture or dislocation
Comparison of one or more of the below against each other or any other intervention:(i) Advice, education and pain relief (delivered by a primary care health professional(ii) Manual therapy and/or strengthening and/or mobilising exercises delivered by a Physiotherapist or Physical Therapist(iii) Corticosteroid injection (± analgesia)	Comparison of any of the below exclusively against a control: (i) Advice, education and pain relief (delivered by a primary care health professional(ii) Manual and/or strengthening and/or mobilising exercises delivered by a Physiotherapist or Physical Therapist (iii) Corticosteroid injectionNon-steroid and/or analgesic injections e.g. hyaluronic acid
Any attempt at subgroup analysis	Failure to conduct any form of subgroup analysis
Outcome measured using multiple measures: physical, functional or pain	Solely occupational/work function or absenteeism/presenteeism outcome measures
More than 20 participants in trial (minimum 10 per arm)	Less than 20 participants in trial (under 10 per arm)

Data extraction

Data extraction and appraisal forms were piloted using a published secondary data analysis of a large RCT in back pain [30] and iteratively amended. For secondary analysis studies, full trials were used to judge methodological quality and bias.

Assessment of bias

The Cochrane Risk of Bias (ROB) tool [29] was applied in each included study to estimate likelihood that the reported intervention effect is true, i.e. the extent to which results of a study are valid.

Assessment of methodological quality of moderation analysis

The quality of moderation analyses in included studies was assessed using criteria defined by [24]: a priori and evidence-based hypotheses, measurement of moderators prior to randomisation, reliability and valid outcome and process factors and an explicit test of interaction between outcome and moderator. Formal and valid moderation analysis in a randomised controlled trial consists of stratified or subgroup analysis (of both intervention and comparator group), defined *a priori* in the trial protocol, powered to detect significant differences, with presentation of treatment effects for categories of the potential moderator [31,32]. Subgroup significance testing is generally conducted in regression analysis by adding a 'moderator * treatment' interaction term to the model, which also includes treatment and predictor variables [32]. Each study was classified according to these criteria as having confirmation, exploratory or insufficient levels of evidence of moderation.

Evidence synthesis

A meta-analysis or meta-regression was not possible because of the heterogeneity in patient population, settings, interventions, and outcomes used. Studies included in this review were divided into (i) studies aiming to identify or test treatment moderation and/or some form of moderation or subgroup analysis, and (ii) studies that suggested potential moderators of treatment effect without formal analyses.

Assessment of risk of bias and quality appraisal was only conducted on studies with moderation analysis (group i above). A narrative synthesis describing identified subgroup analyses, taking account of risk of bias and listing candidate moderators in trials without formal moderation analysis was conducted.

Results

A PRISMA flow diagram [33] is presented in Figure 1. Electronic database searches identified 1869 citations. After removing duplicates, titles of 1275 citations were screened and 890 studies were removed. With consensus from two reviewers, a further 293 studies were removed. Ninety-two full texts were read, and 21 articles were deemed relevant. Reference list screening identified seven further articles, one of which was included in the review. In total, 22 studies were included in this review, six of which attempted moderation analysis or included a formal moderation analysis (Table 3). Data on inclusion and exclusion criteria, primary outcome, follow-up, interventions studies and treatment duration are presented. Table 4 details the moderation analysis design of each study listed in Table 3.

Figure 1. PRISMA systematic review flow chart.

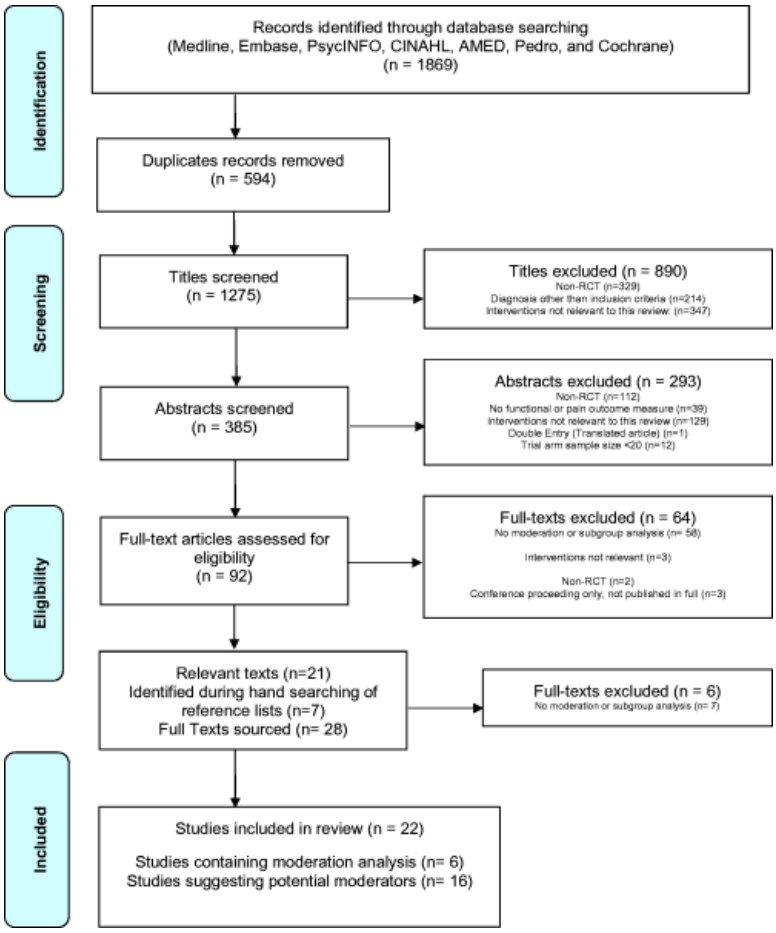


Table 3. Description of Studies attempting moderation analysis.

Reference, setting, country	Inclusion criteria	Primary outcomes	Follow-up	Interventions studied
Gammaitoni et al. [34], Medical Centre, USA	>18 years, unilateral shoulder pain, >2/52 duration	Patient Global Assessment of Satisfaction (PGAS). Patient Global Impression of Change (PGIC). Shoulder range of motion. Pain intensity and pain interference scores.	2/524/526/52	One 10 mg/mL triamcinolone acetonide injectionHeated lidocaine/tetracaine (HLT) patch applied twice daily for 14 days
Geraets et al. [35], Primary Care, Netherlands	Chronic shoulder complaints > 3/12 duration, living in Limburg, the Netherlands	Main Complaints Instrument, Shoulder Disability Questionnaire (SDQ), Perceived recovery (yes/no)	12/52	Up to 18 × 60 min of graded exercise therapy sessions over 12 weeksUsual care as per the Dutch College of General Practitioners

Reference, setting, country	Inclusion criteria	Primary outcomes	Follow-up	Interventions studied
Thomas et al. [36], Primary Care, UK	Patients consulting with an episode of unilateral shoulder pain	Shoulder Disability Questionnaire (SDQ)	6/52, 6/12	Up to 8 × 20 min of physiotherapy sessions (exercise, manual therapy) over 6/52One local corticosteroid injection
van der Windt et al. [37], Primary Care, The Netherlands (Secondary Analysis of van der Windt, 1998)	Patients who consulted their general practitioner (GP) for a painful stiff shoulder were considered for participation	General improvement, Main complain severity, Pain, Functional disability	3/52, 7/52 post treatment, 3/12, 6/12, 12/12 post randomisation	Up to 3 intra-articular 40mg triamcinolone acetonide injections over 6 weeks6-week physiotherapy programme (joint mobilisation, exercise)
Zheng et al. [38], Primary Care, The Netherlands (Secondary Analysis of van der Windt, 1998)	Painful restriction of glenohumeral mobility, aged >18 years	General improvement according to the patient, severity of main complaint, pain, and functional disability	3/52, 7/52 post treatment, 3/12, 6/12, 12/12 post randomisation	Up to 3 × 40mg triamcinolone acetonide intra-articular injections over 6 weeksPhysiotherapy (6 weeks) (joint mobilisation, exercise)
Yang et al. [39], Secondary Care, Taiwan	Shoulder complaints > 3 months & > 50% loss of passive range in 2 or more of: forward flexion, abduction, or external rotation in neutral); and >3 months complaint duration	Shoulder ROM, disability assessment (FLEX-SF), Shoulder complex kinematics (FASTRAK motion analysis system)	4/52, 8/52	Control and criteria-control groups: passive mobilisation & stretching techniques, electrotherapy modalities, and active exercises, twice weekly, 3/12. End-range mobilisation/scapular mobilisation treatment approach (EMSMTA): control treatment PLUS mobilisation and scapular mobilisation, twice weekly, 3/12.

×/52 denotes × weeks. ×/12 denotes × months.

PGAS: Patient Global Assessment of Satisfaction; PGIC: Patient Global Impression of Change; SDQ: Shoulder Disability Questionnaire; FLEX-SF: Flexi-Level Scale of Shoulder Function; Mg/mL: milligrams per millilitre.

Table 4. Methods and results of statistical analysis of moderation.

References	Prognostic factors explored or tested as potential moderators	Statistical analysis suggestive of moderation of treatment effect	Moderation findings reported	Appraisal of moderation analysis methodology	Level of moderation evidence (from Table 5)
Gammaitoni et al. [34]	Pain Quality AssessmentScale (PQAS) pain types	Pearson's correlations between candidate predictors (baseline pain quality measures) with outcome, followed by linear regression: step 1 baseline pain quality measures only; step 2: treatment variable added; step 3: interactions between pain quality measures and treatment are added	Hot pain quality: Greater improvement with injection compared to heated lidocaine/tetracaine patch in those with less hot pain versus those with higher scores for hot pain. Treatment*moderator (hot pain score) interaction is statistically significant (beta −.56, $p < 0.05$) sign	Analysis focussed on design of a prediction model. Large number of statistical tests in post hoc and exploratory analyses. No adjustment of alpha level. Very small sample size, limited power to investigate moderation	Insufficient
Geraets et al. [35]	Passive range of external rotation, active range of abduction/elevation, and presence of painful arc, anxiety, depression, somatisation, distress, treatment preference	Multiple linear regression with stepwise forward procedure ($p < 0.10$) to identify prognostic factors and moderators. The final model includes: treatment variable (graded exercise or not), change in pain intensity (prognostic factor), painful arc (potential moderator, and treatment × painful arc interaction	Painful arc: Less improvement in the shoulder disability questionnaire scores with graded exercise therapy compared to usual care in patients with a painful arc at baseline versus those without painful arc. Interaction term between graded exercise therapy and painful arc is reported as significant (*Beta* = −14.0, 95% CI's [−28.1, 0.1], $p = 0.05$)	Interaction test reported as $p = 0.05$, however, CI's cross zero, therefore, judged as not statistically significant. *p*-value either an error in reporting or result of rounding	Confirmatory
Thomas et al. [36]	Treatment preference	The relationship of pre-randomisation treatment preference (candidate predictor) and functional outcome was examined within three groups: those with no treatment preference, those who did receive their preferred treatment, and those who did not receive their preferred treatment	Treatment preference: treatment effect was not moderated by having preference or whether preference was met. Similar difference in outcome were reported regardless of treatment preference (good outcome in those receiving preferred treatment = 55% injection versus 58% physiotherapy; not receiving preferred treatment = 71% injection versus 68% physiotherapy)	Lack of statistical testing of treatment preference as a moderator (treatment × preference interaction was not tested)	Insufficient

References	Prognostic factors explored or tested as potential moderators	Statistical analysis suggestive of moderation of treatment effect	Moderation findings reported	Appraisal of moderation analysis methodology	Level of moderation evidence (from Table 5)
van der Windt et al. [37]	Treatment preference	Exploratory, descriptive subgroup analyses compared treatment success rates across treatment preference subgroups (potential moderator): those without a preference; those allocated to preferred intervention; those not allocated to preferred intervention	Treatment preference: Allocation of preferred treatment appears to have a positive, potentially moderating treatment effect for injections compared with physiotherapy. Complete recovery or considerable improvement was 85% for patients who preferred and received injection versus 43% for those who preferred and received physiotherapy (difference 42%); and 64% (injection) versus 50% (physiotherapy) in those not allocated to their preferred intervention (difference 21%)	Lack of statistical testing of treatment preference as a moderator (treatment x preference interaction was not tested).	Insufficient
Zheng et al. [38]	Age, gender, pain duration of current episode, previous trauma, previous episode of shoulder pain, overuse of shoulder due to usual or unusual activities preceding shoulder pain	Patients were first classified into persistent-recurrent and recovery groups using principal components analysis (PCA) and cluster analysis. Next, regression models were used to explore baseline characteristics associated with shoulder pain recovery profiles, including age, sex, pain duration, previous trauma, previous shoulder pain episodes, and overuse as possible cause of shoulder pain. Treatment was added to the model as a covariate	Age, gender: In the injection group (mostly younger than 60 years old and male), pain severity reduced faster than in those treated with physiotherapy. The authors conclude that: “patients who were treated with corticosteroid injections would get faster recovery from shoulder pain with the treatment effect modified by age and gender	Complex longitudinal analysis models. Treatment × moderator (age and gender) interactions were not tested	Insufficient

References	Prognostic factors explored or tested as potential moderators	Statistical analysis suggestive of moderation of treatment effect	Moderation findings reported	Appraisal of moderation analysis methodology	Level of moderation evidence (from Table 5)
Yang et al. [39]	Scapular orientation relative to thorax: rotation about protraction/retraction (Z°s), rotation about downward/upward rotation (Y°s), rotation about posterior/anterior tipping (X °s)	Controlling for baseline differences between groups, 2-factor ANCOVA mixed models were used to estimate the effect of treatment on all outcomes. Baseline level of the outcome variable was included as a covariate, and treatment and time were included as factors in the model	Patients who met kinematic criteria (having 8°scapular posterior tipping, 97° humeral elevation, and 39° humeral external rotation during arm elevation) had better outcomes from physiotherapy plus mobilisations (EMSMTA). Subjects in the EMSMTA group experienced greater improvement in outcomes compared with the criteria-control group at 4 weeks (21% of hand behind back, 95% CI [0.04, 0.37], $p = 0.005$).) and at 8 weeks, the humeral external rotation and the hand-behind-back reach improved in the manual therapy group as compared with the criteria-control group (23.4 degrees, 95% CI [8.2, 37.3] and 33%, 95% CI [0.17, 0.44], $p = 0.002$ and $p < 0.0005$. At 8 weeks, the Flexi-Level Scale of Shoulder Function (FLEX-SF) disability score improved in the manual therapy as compared with the criteria-control group (7.4 scores, 95% CI [2.6, 12.5], $p = 0.005$)	Study dedicated to evaluating the effect of treatment in patients meeting three specific shoulder kinematic measurements. As the treatment effects are only compared in those meeting the shoulder kinematics criteria (those who did not meet the criteria all received the control treatment), interaction could not be tested	Insufficient

Characteristics of studies formally evaluating moderation

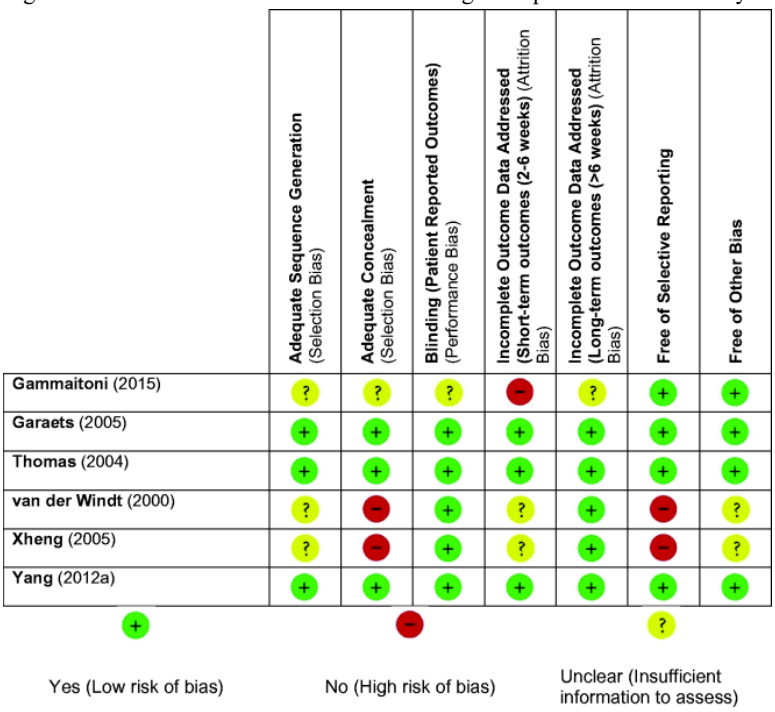
Of the 22 included studies, six studies formally evaluated moderation (Table 1). Study setting varied between primary care and secondary care, as well as country (Netherlands, UK, USA, and Taiwan). Diagnoses of participants varied between chronic shoulder pain, unilateral shoulder pain, shoulder pain, and painful, stiff shoulder. Five studies examined a form of physiotherapy or exercises (mobilising, stretching or strengthening exercises, joint mobilisations or soft tissue massage), four studies trialled corticosteroid injection and one study examined electrotherapy (pulsed ultrasound, short wave diathermy, laser and radial extracorporeal shockwave treatment). All six studies used outcomes for either function, disability, and/or work whilst three used visual analogue scales (VAS) for pain.

Risk of bias

Risk of bias was assessed for the six moderation studies (Figure 2). Two trials had minimum risk of bias [35,39], and four demonstrated some potential for bias. Van der Windt et al. (1998) and Zheng et al. [38] (separate analysis of the same trial) demonstrated potential for selection bias and attrition bias as attrition rate and sequence generation methods were not reported. Only one subgroup analysis was reported and long-term data was not presented by van der Windt et al. [37] or Zheng et al. [38], raising potential for reporting bias. Gammaitoni et al. [34] demonstrated

high risk of detection bias due to open label trial design, whilst insufficient information was presented to judge risks of selection, performance or attrition biases.

Figure 2. Risk of bias item for studies containing attempted moderation analysis.



Quality appraisal of statistical methods for moderation

Conventionally, treatment moderators are identified through testing the interaction between a prognostic factor and a treatment variable [40,41], and/or through *a priori* defined subgroup analyses. Table 4 outlines the approaches taken to identify potential moderators of treatment effect in studies included in this review. Table 5 shows how each of the studies performed against the Pincus criteria [24] for the identification of moderators. Only one study [35] provided a methodologically valid analysis of moderator of treatment effect: presence of painful arc led to a smaller effect on shoulder disability (0–100) of graded exercise therapy compared with usual care only (adjusted mean difference −0.2 for those with painful arc, and 7.3 for those without painful arc at baseline). The interaction test was not statistically significant (regression coefficient −14.0, 95% confidence interval: 028.1–0.1, $p = 0.05$). Seven other potential moderators of outcome were identified that were supported by exploratory level evidence: hot pain quality [34]; treatment preference [36,37]; age [38]; gender [38]; and three specific degrees of scapular and humeral joint positions [39]. Only studies by Geraets et al. [35] and Gammaitoni et al. [34] explicitly tested the interaction between each candidate moderator and specific treatments. Although most studies had evidence-based hypotheses for moderation studies, Gammaitoni et al. [34] and van der Windt et al. [37] did not. It should also be noted that subgroup sizes for all analyses were small and, therefore, offered insufficient statistical power to test moderation.

Table 5. Methodological assessment of attempted moderation analysis (per [24]).

Study	*A priori* hypothesis	Theory and/or evidence driven hypothesis	Moderators measured prior to randomisation	Valid and reliable baseline and process factors	Explicit test of interaction	Total Score	Level of moderation evidence
Gammaitoni et al. [34]	No	Yes	Yes	No	Yes	3	Insufficient

Study	*A priori* hypothesis	Theory and/or evidence driven hypothesis	Moderators measured prior to randomisation	Valid and reliable baseline and process factors	Explicit test of interaction	Total Score	Level of moderation evidence
Geraets et al. [35]	Yes	Yes	Yes	Yes	Yes	5	Confirmatory
Thomas et al. [36]	Yes	Yes	Yes	Yes	No	4	Insufficient
van der Windt et al. [37]	No	No	Yes	Yes	No	2	Insufficient
XZheng (2005) [AQ3]	Yes	Yes	Yes	Yes	Unclear	4	Insufficient
Yang et al. [39]	Yes	Yes	Yes	Yes	No	4	Insufficient

Levels of moderation evidence: Confirmatory Evidence: All 5 items met; Exploratory Evidence: Final 3 items met; Insufficient Evidence: Failure to meet final 3 items.

Discussion

This review aimed to identify moderators or potential moderators of the effects of three commonly used first-line treatments: advice and pain relief, strengthening and/or mobilising exercise delivered by a physiotherapist, and corticosteroid injection in patients with musculoskeletal shoulder pains. Six relevant trials studied potential treatment moderators, and 16 trials included suggestions regarding potential moderators (Figure 3). Only one study conducted a robust moderation analysis: presence of painful arc (versus no painful arc) led to a smaller effect on shoulder disability of graded exercise therapy compared with usual care only, although the test for interaction was not (or perhaps borderline) statistically significant ($p = 0.05$) with the confidence interval including a null result (−28.1 to 0.1). Nine other potential moderators of outcome were identified, however, these were supported by insufficient level evidence (Figure 3), and these do not constitute high quality evidence of moderation of treatment effect.

Figure 3. Summary of review findings.

	Potential Moderator			Moderator Suggested		
Patient Factor	Confirmatory Evidence	Exploratory Evidence	Insufficient Evidence	Exploratory subgroup analysis	Potential confounding effect	Without statistical analyses
Painful arc	✓					
Hot pain quality			✓			
Gender			✓	✓	✓	
< 8° of scapular posterior tipping			✓			
< 97° of humeral elevation			✓			
< 39° of humeral external rotation during arm elevation			✓			
Symptom Duration			✓	✓		
Functional Limitation			✓			
Muscle Tightness				✓		
Treatment Preference			✓			✓
Age			✓	✓		
Shoulder restriction				✓		
Shoulder Complaint				✓		
Hand Complaint				✓		
Neck restriction				✓		
Baseline symptom duration				✓	✓	✓
Diagnosis of rheumatoid arthritis					✓	
Diagnosis of frozen shoulder					✓	
Number of muscles with active trigger points					✓	
Baseline disability					✓	✓
Baseline pain					✓	
Presence of pain, dysfunction or both pain and dysfunction						✓
Pain at rest						✓
Pain frequency						✓
Pain on movement						✓
Night pain						✓
Joint end feel						✓
Stage of frozen shoulder						✓
Failure of conservative treatments						✓
Pre-treatment clinical index						✓

Methodological issues identified

Methodological pitfalls in identifying treatment effect moderators are highlighted in this review, including importance of *a priori*, evidence-based hypotheses, adequate statistical power, and interaction testing between potential moderators and treatments. This review found more exploratory subgroup analyses than pre-planned moderation analyses, with only one trial having conducted moderation analysis in a robust manner according to published quality criteria [35]. Post-hoc moderation or sub group analyses are especially prone to error due to testing several hypotheses (multiplicity) and having insufficient sample sizes to test these hypotheses robustly [42]. Since moderation analy-

sis requires at least four times the sample size of a routine RCT to test the interaction between prognostic factor and treatment [43], interactions between potential moderators and outcome in trials without a priori hypotheses of moderation and sufficiently large sample size are likely to be statistically insignificant due to original trials being underpowered to detect clinically important moderators of treatment effect [25,44]. Therefore, and also to avoid spurious findings (type 1 error) and the associated risks of testing every possible hypothesis, Pincus et al. [24] recommend less than 5 *a priori,* evidence/theory-based subgroup hypotheses.

Turner et al. [45] recommend adjustment of p values to a more conservative $p < 0.01$ when testing more than three hypotheses. All studies identified by this review failed to conduct this adjustment, increasing risk of type 1 error. Whilst adjustment of p values should indeed be considered in future moderation analyses, this field would benefit more from the conduct of large, sufficiently powered trials. Such trials could compare commonly used interventions for shoulder pain and investigate a limited number of plausible patient or shoulder pain characteristics as potential moderators of effect. As the PROGnosis RESearch Strategy (PROGRESS) Partnership [46] highlight, robust statistical methodology has the potential to offer clinically informative moderation and sub-group analysis that would help build understanding of which patients might benefit most from these specific treatments.

Comparison with other reviews and studies

Previous reviews have not investigated moderators of treatment effect in shoulder pain. Chester et al. [17] identified predictors of response to physiotherapy treatment in patients with shoulder pain, however, prediction of outcome of physiotherapy is not simply equivalent to the identification of moderators for physiotherapy treatment outcome. In spite of this, some findings were similar to this review: increased baseline disability and longer symptom duration were predictors of negative outcome of physiotherapy treatment, with inconsistent findings for age and baseline range of movement. This review's finding that gender is a potential treatment effect moderator in patients with shoulder disorders is also in line with Blangsted et al. [47] who demonstrated an interaction between gender and treatment in a subgroup analysis.

Authors examining other musculoskeletal pain sites have sought to identify moderators of the effect of specific interventions. In the field of back pain, Underwood et al. [30] identified that treatment preference moderated response to treatment. In contrast, our review found insufficient evidence to determine whether treatment preference is a potential moderator for patients with shoulder pain. Gurung et al. [48] reviewed moderators for low back pain treatments and identified a moderate level of evidence for age, employment status, narcotic medication use, treatment expectation and education as treatment moderators. In contrast, we did not find any confirmatory evidence for age or treatment expectation as treatment moderators for patients with shoulder pain. Gurung et al. also identified a weaker level of evidence for gender, psychological distress, pain/disability and quality of life as treatment moderators for low back pain. Our review concurs, as we found some exploratory level evidence for age, pain/disability and quality of life as treatment moderators for patients with shoulder pain.

Chester et al. [49] demonstrated in a single-treatment cohort study that psychological factors were consistently associated with patient-rated outcome. However, as previously stated, prediction of outcome of a single treatment does not equate to evidence of treatment effect modification. Similarly, Coronado et al. [50] highlight that optimism decreases the negative relationship between pain catastrophising and function in patients receiving either exercise-based treatment or manual therapy. This suggests that there may be scope in future to explore further the relevance of psychologically informed physiotherapy in patients with shoulder pain. However, this analysis consisted of pooling of data from two separate arms in their RCT (exercises versus manual therapy). Although Coronado et al. [50] refer to optimism as a moderator of the relationship between catastrophising and function, due to having pooled both treatment groups into one group, it was not possible to test an interaction between treatment and optimism. Therefore, this does not represent a moderation of treatment effect, in the manner that this review concerns.

In people with musculoskeletal pain more broadly, Turner et al. [45] failed to demonstrate that greater baseline somatisation, greater depressive symptoms, higher number of pain sites, more rumination, catastrophising, and higher perceived stress moderated effect of cognitive behavioural therapy. The study by Turner et al. highlights the challenges in demonstrating moderation of treatment effect, even with good methods and sound hypotheses. Therefore, it is not currently known whether other psychological factors (anxiety, depression, psychosocial determinants of health and well-being including work-load and sport participation, chronic widespread pain, multi-site pain, employment status, analgesic medication and education) that have been identified as predictors of outcome in shoulder pain

[20,51,52] also moderate treatment effect of the three commonly used shoulder pain interventions explored in this review.

Strengths and limitations

The strengths of this review included the use of search strategies from existing relevant systematic reviews [27,28] to ensure our searches were appropriately specified and the risk of missing relevant publications was minimised. Our classification of the results into two levels of evidence: (i) studies aiming to identify or test moderators and (ii) studies suggesting potential moderators, allows for a clearer interpretation of the current evidence in the literature. Methodological appraisal of moderation analyses using a published tool also facilitated a conservative interpretation of the strength of evidence about potential moderators.

A limitation of our review was that it was not possible to perform a meta-analysis due to the heterogeneity of existing studies, but testing of moderators will generally require a meta-analysis of individual patient data from multiple trials, as candidate moderators generally concerns patient-level factors [53]. However, our review was still able to identify some potential moderators and one confirmed moderator of commonly used shoulder pain treatments.

Conclusion

This review has found little evidence for moderators and, based in an assessment using the Pincus criteria, highlighted many methodological issues in the conduct of moderation analysis in trials of primary care interventions for shoulder pain. The CHAMP checklist [54] has recently been introduced and is specifically designed for the critical appraisal of moderation analysis. Future researchers can use this checklist during design, execution and reporting stages of future moderation analyses. At present, the quantity and quality of existing evidence exploring moderators of treatment effect in shoulder pain is insufficient and does not inform clinical decision-making. Aside from the single treatment moderator identified by this review (Table 4), other suggested potential moderators identified (Table 6) are heavily caveated, as they have not yet been statistically tested. Future moderation analysis to explore whether the different factors identified by this review do indeed moderate response to specific treatments would be useful, providing that existing methodological recommendations about how to identify treatment moderators (considered in this review) are followed.

Table 6. Results of studies suggesting potential moderators.

Reference, setting, country	Inclusion criteria	Primary outcomes	Follow-up	Interventions studied	'Potential moderators' suggested
Abdelshafi et al. [55], Rheumatology & Rehabilitation Out-Patient Depts., Egypt	Chronic shoulder pain > 3 months duration, unresponsive to conventional treatment	Active and passive Range of Movement (ROM), Shoulder pain and disability index (SPADI)	1/52, 4/52, 12/52	Rehabilitation programme only (Exercises, Ultrasound, Short Wave), three times weekly, duration unclearContinuous supra-scapular nerve block (SSNB) under ultrasound guidance in addition to rehabilitation programme, three times weekly, duration unclear Intra-articular corticosteroid injection in addition to rehabilitation programme	In those who received SSNB, having a diagnosis of rheumatoid arthritis (B) was associated with improvement in pain (mean ± SD SPADI pain for SSNB: 44±9; injection: 55±8.7; rehabilitation: 62.5±8, $p = 0.018$) and disability (total SPADI for SSNB: 45.8±12; injection: 56.9±13.2; rehabilitation: 60.9 ± 11.2, $p=0.04$) and having frozen shoulder (B) was associated with improvement in disability (total SPADI for SSNB: 66.4±11; injection: 56.4±13.9; rehabilitation: 52.9 ± 10, $p = 0.02$)
Arslan et al. [56], Dept Physical Medicine & Rehabilitation, Turkey	Total range of motion <50%	ROM, Pain Visual Analogue Scale (VAS)	2/52, 12/52	Local corticosteroid injection-Physiotherapy and a non-steroidal anti-inflammatory drug	Analysis stratified by baseline symptom duration (B) but no differences between interventions were found. Data with and without this adjustment not shown
Bennell et al. [57], Primary Care, Australia	Chronic rotator cuff disease	SPADI, Pain VAS, Participants' perceived global rating of change overall	11/52, 22/52	10 active treatments comprised a manual therapy and home exercise programme, 10 weeks10 Placebo treatment comprised inactive ultrasound therapy and application of an inert gel, 10 weeks	Whether pain, dysfunction, or both are the patients' primary problems (C) may help indicate what kind of treatment is appropriate (C)
Bron et al. [58], Primary Care, Netherlands	Unilateral non-traumatic shoulder pain for > 6 months, aged 18 and 65 years	Passive ROM, Number of trigger points, Disabilities of the arm and shoulder (DASH), Quality of life (RAND-36), Beck Depression Infantry (BDI-II)	6/52, 12/52	Intervention Group (Trigger point release, intermittent ice application, stretching exercises), weekly up to 12 weeks Wait-and-See	Number of muscles with active trigger points (B), Passive ROM (B), Baseline Disability (DASH) (B). Multiple linear regression with baseline DASH score as a covariate demonstrated a significantly higher DASH questionnaire score at 12 weeks of 7.447 (95% CI: 2.14, 12.75) in the intervention group compared with the control group. Adjustment for covariates (number of muscles with active trigger points and passive ROM) had no influence on this result. Data not shown

Reference, setting, country	Inclusion criteria	Primary outcomes	Follow-up	Interventions studied	'Potential moderators' suggested
Carette et al. [59], Outpatient Rheumatology clinics, Canada	Adhesive capsulitis of <1 year's duration	SPADI, quality of life (SF-36), Active and passive ROM	6/52, 3/12, 6/12, 12/12	All patients were taught a simple, 10-minute exercise programme and randomised into 1 of 4 groups:Corticosteroid injection followed by supervised physiotherapy) Corticosteroid injection alone Saline injection followed by supervised physiotherapy Saline injection alone	Pain at rest, pain frequency, pain on movement, night pain and joint end-feel (C) implied as different treatment provided for acute and chronic patients
Crawshaw et al. [60], Primary Care, UK.	Adults >40 years with sub-acromial impingement syndrome, moderate or severe shoulder pain	SPADI	12/52	Injection plus exercise Exercise only, up to 12 weeks	Baseline pain and disability score (B), baseline pain VAS (B) entered as covariates. Data with and without covariates not shown
Dickens et al. [61], Secondary Care, UK.	Subacromial impingement syndrome	Constant Score	6/12	Physiotherapy (individualised treatment), < 6 monthsControl (No treatment)	Younger age (C), higher baseline disability (Constant) score (C)
Diercks et al. [62], Secondary Care, Netherlands	Idiopathic frozen shoulder syndrome	ROM: Forward elevation, lateral elevation, external & internal rotation.	3/12, 6/12, 9/12, 12/12, 15/12, 18/12, 21/12, 24/12	Intensive physical rehabilitation treatment (stretching group), 2 × 45 min. exercise sessions weekly, up to 12 weeksSupportive therapy and exercises within the pain limits (supervised neglect group)	Stage of Frozen Shoulder (C)
Engebretsen et al. [63], Outpatient physical medicine and rehabilitation, Norway	Subacromial shoulder pain lasting at least three months	SPADI	6/52, 12/52, 18/52	Supervised exercise regimen, 2 × 45 min. exercise sessions weekly, up to 12 weeksRadial extracorporeal shockwave treatment (REST), weekly for 4–6 weeks	Gender (adjusted for in regression and analysis stratified for gender) (B). At 18 weeks the treatment effect was −8.4 SPADI points (95% CI: −16.5, −0.6, p = 0.047) in favour of supervised exercise. The treatment effect was consistent when adjusted for sex (p = 0.049)
Gialanella et al. [64], Secondary Care, Italy	Full thickness rotator cuff tears	Constant–Murley scale, Pain VAS	3/12, 6/12	Single intra-articular injection Two injections at 21-day intervalsNo treatment (control group)	Failure of conservative treatments, increasing night pain, acute or inflammatory stages of disease (all C)

Reference, setting, country	Inclusion criteria	Primary outcomes	Follow-up	Interventions studied	'Potential moderators' suggested
Hay et al. [65], Primary Care, UK	Those > 18 years, consulting general practitioner with new episode of unilateral shoulder pain	Shoulder disability questionnaire (SDQ)	6/52, 6/12	Corticosteroid injectionsCommunity based physiotherapy, up to 8 20 min sessions in 6 weeks	Age, sex, symptom duration, shoulder restriction, painful arc of movement, restricted neck movements (all A). Data not shown.
Hsu et al. [66], long-term care home, Canada	Self-reported discomfort in upper limb	The Nursing Home Physical Performance Test (NHPPT), modified Physical Activity Enjoyment Scale (PACES), pain numeric rating scale, AROM shoulder, Global Perceived Rating of Change (GPRC)	4/52	Standard exercise groupStandard exercise plus Wii group	Responders to Wii intervention more likely than non-responders to report having baseline shoulder symptoms (X^2= 6.05; p = 0.014) & hand symptoms (X^2= 6.35; p = 0.012) (both A)
Pajareya et al. [67], Rehabilitation Dept, Thailand.	Shoulder pain, limitation of passive ROM, interference with activities of daily living	SPADI, ROM,	3/52	IbuprofenIbuprofen and physical therapy, 3 times weekly, 3 weeks	Patient treatment preference (C)
Petri et al. [68], Veterans Screening & Rheumatology Clinics, USA	Painful abduction, painful arc, or tenderness over the supraspinatus insertion	Active and passive ROM, presence of painful arc, whether shoulder pain was exacerbated by resisted internal or external rotation pain VAS, limitation of function	2/52, 4/52	Subacromial bursa injection with 4 cc of 1% lidocaine, plus naproxen Subacromial bursa injection with 3 cc of 1%lidocaine and 1cc of 40 mg/ml triamcinolone, plus naproxen Subacromial bursa injection with 3 cc of 1% lidocaine and 1 cc of 40 mg/ml triamcinolone, plus placebo pill Subacromial bursa injection with 4 cc of 1% lidocaine, plus placebo pill	Symptom duration (C), pretreatment clinical index (C)
Ryans et al. [69], Primary Care, UK	Adhesive capsulitis	SF-36, Hospital Anxiety and Depression Scale (HADS), Active and passive ROM, SDQ	6/52, 16/52, 24/52	Intra-articular triamcinolone injectionPhysiotherapy, 8 session, 4 weeksInjection plus physiotherapySaline injection alone	Baseline disability (C)

Reference, setting, country	Inclusion criteria	Primary outcomes	Follow-up	Interventions studied	'Potential moderators' suggested
Yang et al. [70], Hospital, Taiwan	Reduced internal rotation at shoulder	Muscle tightness measured on computerised myotonometer, Flexilevel Scale of Shoulder Function (FLEX-SF)	4/52	Massage on the posterior deltoid, infraspinatus, and teres minor, 18 min, twice weekly for 4 weeksControl Treatment: Light hand touch on the muscles, 10 min, twice weekly for 4 weeks	Less baseline symptom duration, muscle tightness & shoulder function (all B) in responders to massage compared with non-responders, $p < 0.005$). Symptom duration (mean ± SD days) in Responsive (R): 11.7 ± 3.4, Non-Responsive (NR):17.9 ± 4.8). Posterior Glenohumeral Internal Rotation in degrees (°): R: 68.6 ± 12.1, NR: 32.2 ± 10.8. FLEX-SF: R: 43.3 ± 4.8, NR: 38.2 ± 2.8

A: exploratory subgroup analysis; B: prognostic factors or potential confounders but not tested as moderator; C: attributes narratively mentioned or discussed as potential moderators but not tested in any way as a moderator. Statistical data presented where shown in publication by trial authors.

By establishing a list of 30 patient attributes thought to moderate or potentially moderate treatment effect, this review has begun the process of exploring the evidence of moderators of treatment effect and their role in first-line clinical decision-making for shoulder pain. However, due to lack of evidence, many commonly considered patient attributes do not feature in this review, including psychological attributes such as anxiety or depression, other determinants of health and wellbeing including workload and sport participation and chronic widespread pain or multi-site pain. It is not currently known whether they moderate treatment effect of the three commonly used primary care interventions for musculoskeletal shoulder pain and have a role in helping clinicians choose specific treatments for individual patients. Expert clinician consensus has previously been shown to reflect most statistically selected predictors of outcome and also suggests additional predictors not identified by statistical selection [20]. Therefore, future research should seek to identify expert clinician consensus on the likely most appropriate patient attributes to include in an *a priori*, appropriately powered and statistically robust moderation analysis in shoulder pain.

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