

Title: Treatment and prevention of acute and recurrent ankle sprain injury: an overview of systematic reviews with meta-analysis

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Abstract

Background: Ankle sprains are highly prevalent with a high risk of recurrence.

Consequently, there is a significant amount of research reports examining strategies for treating and preventing acute and recurrent sprains (otherwise known as Chronic Ankle Instability [CAI]), with a coinciding proliferation of review articles summarising these reports.

Objective: To provide a systematic overview of the systematic reviews evaluating treatment strategies for acute ankle sprain and CAI.

Design: Overview of intervention systematic reviews.

Participants: Individuals with acute ankle sprain/CAI.

Main outcome measurements: The primary outcomes were injury/re-injury incidence and function.

Results: Forty-six papers were included in this systematic review. The reviews had a mean score of 6.5/11 on the AMSTAR quality assessment tool. There was strong evidence for bracing and moderate evidence for neuromuscular training in preventing recurrence of an ankle sprain injury. For the combined outcomes of pain, swelling and function after an acute sprain there was strong evidence for non-steroidal anti-inflammatory drugs and early mobilisation, with moderate evidence supporting exercise and manual therapy techniques. There was conflicting evidence regarding the efficacy of surgery and acupuncture for the treatment of acute ankle sprains. There was insufficient evidence to support the use of ultrasound in the treatment of acute ankle sprains.

Conclusions: For the treatment of acute ankle sprain, there is strong evidence for non-steroidal anti-inflammatory drugs and mobilisation, with moderate evidence supporting exercise and manual therapy techniques, for pain, swelling and function. There is strong evidence to support the use of exercise therapy and bracing for preventing CAI.

What is already known

- A large number of systematic reviews detail treatment strategies for ankle sprain.
- This makes appraisal of the literature difficult for clinicians.
- The best treatment strategy for acute ankle sprain remains unclear.
- It is also unclear how best to prevent ankle sprain recurrence.

What are the new findings

- Exercise therapy and taping/bracing are effective in the management of acute/recurrent ankle sprain.
- Ultrasound, acupuncture and manual therapy do not seem to be effective in the treatment of recurrent ankle sprain.
- Surgery for acute/recurrent ankle sprain should only be considered on an individual basis.

INTRODUCTION

The incidence of ankle sprain is high, posing a significant risk for participants of a wide range of activity types and sports [1]. Ankle sprain is associated with significant socioeconomic cost in addition to the acute debilitating symptoms (which include pain, swelling and impaired function); each year, over two million ankle sprains are treated in US and UK emergency departments [2-5]. The long-term prognosis of acute ankle sprain is poor, with a high proportion of patients (up to 70%) reporting persistent residual symptoms and injury recurrence [6 7]. 'Chronic ankle instability' (CAI) is the encompassing term used to describe the chronic symptoms that may develop following an acute ankle sprain, with injury recurrence at the epicentre of the chronic paradigm [8].

There is an abundance of literature evaluating treatment strategies for acute ankle sprains and/or CAI. In accordance with this, a large number of systematic reviews have emerged to combine these studies' findings to synthesise and extract the best evidence for treatment guidelines. However, there are now such a large number of systematic reviews that identification, appraisal and consideration of each individual paper is not feasible for practitioners. This issue is further compounded by the probability that these reviews vary in quality and scope (with several reviews for one prevention/treatment type) and their inclusion of papers with a high degree of overlap in the injury target (acute ankle sprain/CAI). Thus there is a need to collate this evidence in a non-biased, systematic manner to ascertain evidence based recommendations for the treatment of acute ankle sprain and CAI.

The aim of this paper was to provide a systematic overview of the systematic reviews evaluating treatment strategies for acute ankle sprain and CAI. A secondary aim was to identify the current gaps in the literature for researchers, and identify any conflicting evidence between reviews.

METHODOLOGY

Protocol

The study protocol was developed using the framework described by Smith et al [9], which relates to the methodology of conducting a systematic review of systematic reviews of healthcare interventions. The protocol for the review was not pre-registered prior to its completion.

In January 2016, we undertook a computerized literature search of the following databases from inception: Pubmed, PEDro, Scopus, Web of science, EBSCO and the Cochrane library [10]. The database search was further supplemented with a manual search of the reference lists in each review. These processes retrieved a set of systematic reviews closely related to the treatment of ankle sprain injuries and CAI.

The empirical search strategy was developed in accordance with the recommendations outlined by Montori et al, [11]. The search strategy was constructed for medline and completed in a stepwise manner using the Boolean operators (Table 1)

Table 1. Search strategy.

Steps	Text string
(1)	ankle[Text Word]
(2)	sprain OR strain OR rupture OR instability OR unstable OR repeated OR recurrent OR multiple OR functional OR functionally OR chronic OR chronically
(3)	intervent*[Title/Abstract] OR rehab*[Title/Abstract] OR prevent*[Title/Abstract] OR therap*[Title/Abstract]
(4)	(#1 AND #2 AND #3)
(5)	meta-analysis[Publication Type] OR meta-analysis[Title/Abstract] OR meta-analysis[MeSH Terms] OR review[Publication Type] OR search*[Title/Abstract]
(6)	#4 AND #5

The search strategy was adapted for each database on the basis of previously published recommendations [12]. No restrictions (including language) were applied in any of the databases when the search was completed. One investigator reviewed all the titles produced by the database searches, and retrieved suitable abstracts. Implied suitability via abstract review dictated the retrieval of full texts.

Inclusion/exclusion criteria

Our inclusion criteria were as follows: (1) the study must be a systematic review, which was defined as a research study that collects and evaluates multiple studies, and that limits inclusion bias of authors by using a clearly defined search strategy; (2) it must evaluate the efficacy of an intervention for the treatment and/or prevention of acute ankle sprain and/or CAI; (3) the efficacy of the intervention must be measured by means of an experimentally quantifiable outcome (detailed later). CAI patients were defined by having a history of at least one ankle sprain, a history of the previously injured ankle joint 'giving way' and/or recurrent sprain and/or 'feelings of instability' [8]. No restrictions were applied with regards to the intervention type or sample population of the studies included in the review papers.


Data extraction

A data extraction form was devised by all the authors. Data extraction was performed by one author.. A random sample of the studies were selected and doublechecked by a second reviewer, to ensure quality. Data extraction included information related to both the review itself [including study details (author, year of publication and title), the injury type(s), outcome(s), intervention type(s) and main findings], and the individual studies included in the reviews

[including study details (author, year of publication and title), design [randomised controlled trial (RCT)/non-RCT], sample population (% males vs females), experimental group N, control group N, injury type(s), intervention type(s), comparison type (s), protocol, outcome(s), findings (number of injuries in the control/experimental groups), conclusions]. For studies in which an exercise therapy intervention was administered, the total 'dose' of the intervention (in minutes) was calculated and extracted.

Reviews were divided as to whether they concerned the treatment of acute ankle sprain or CAI (injury type). Due to the potential overlap of treatment goals, any review that evaluated the efficacy of a prevention strategy for a new or recurrent ankle sprain with sufficient follow-ups (≥ 12 months) was also grouped into the 'CAI treatment' division, as recurrent ankle sprain injury is considered to be at the centre of the CAI paradigm [13]. No restrictions were placed on the severity or type of ankle sprain sustained (lateral/medial/syndesmotic). Intervention types were divided into surgical and non-surgical. Non-surgical interventions were further sub-classified into physiotherapeutic (including exercise and manual therapies), external support (including taping, bracing and orthotics), electrophysical (including cryotherapy and any type of electrotherapies), pharmacological (including medications) and complementary (acupuncture; aromatherapy; and herbal medicines) agents. These interventions were chosen following a thorough review of the literature and on the basis of the classification system utilised by Bleakley et al, [14].

The outcomes of interest were delineated into primary and secondary types. The primary outcomes were (re-) injury incidence/prevalence and/or self-reported function/disability based on a validated questionnaire for ankle joint function [13]. The secondary outcomes included pain, strength, range of motion (ROM), proprioception and muscle activity in the region of ankle joint, in addition to performance measures (which included biomechanical

analyses of static/dynamic postural control, gait or jumping/landing tasks). A schematic depicting the above mentioned classification system is depicted in Figure 1. 

Risk of bias assessment

The quality of the systematic reviews was independently assessed by two authors (CD and SH) using the AMSTAR tool [15]. Any disagreement between authors was resolved by group consensus. Where reviews provided an overall quality assessment of the included studies (items #7/8 of the AMSTAR tool), those tools were extracted as potentially valuable research resources.

Analysis

To fulfil our primary objective, the main conclusions from each systematic review concerning injury and intervention type were extracted. The reviews were categorised as 'high' or 'low' quality based on an arbitrary score of 7/11 on the AMSTAR quality rating. This 'high' quality threshold was subsequently used in conjunction with the AMSTAR quality scores to conduct a best evidence synthesis of the reviews. The outcomes, intervention type, main results and conclusions relating to our predined primary and secondary outcomes (defined in data extraction) from the high quality reviews (i.e. rating ≥ 7), were compiled in tabular format, and stratified according to intervention type. This best evidence synthesis was conducted in order provide a reference point for the interventions with the strongest evidence supporting or opposing their use.

Additionally, the individual papers included in each review were perused; if they reported on any of the primary or secondary outcomes, they were considered to have likely informed the conclusions of the review for the outcome in question. The reference for each individual paper was extracted in such situations. In situations where there were contradictory

conclusions from reviews the individual quality rating of each review was presented (to contextualise a given conclusion to the overall quality of the review that made it); if the conclusions between different reviews were in agreement, the quality range (lowest and highest) of the reviews in question were presented.

Exploratory meta-analyses of the individual studies were performed for the primary outcome of (re-) injury incidence where possible. Only RCTs were included in pooling. Data [experimental group N and injuries after follow-up, control group N and injuries after follow-up; total dose of exercise (where appropriate)] were entered into the Cochrane Collaboration Review Manager (4.2) software program. Study effect estimates were calculated using odds ratios (OR) with 95% confidence intervals (95% CI). Studies were weighted by sample size. Data were assessed for heterogeneity based on the Q test in conjunction with the I² statistic. The significance for Chi² was set at P < 0.1. I² values greater than 50% were considered to represent substantial heterogeneity [16]. In cases where substantial heterogeneity was present a random effects model was used. Accordingly, OR values were used to enable several Forest plots.

RESULTS

Search results

The initial search strategy produced 2,506 articles. A PRISMA diagram of the search strategy is available in Figure 1. A total of 46 systematic reviews met the inclusion criteria [14 17-61].


The quality of the included reviews is displayed in Table 2.

Forty of the reviews performed some kind of quality assessment of their included studies (Supplemental Table 2).

Table 2. Quality of the included reviews as rated on the AMSTAR scale.

Author	Year	AMSTAR criteria										Total	
		1	2	3	4	5	6	7	8	9	10		11
Baltaci	2003	0	0	0	1	0	1	0	0	0	0	0	2
Bleakley	2004	1	0	1	0	0	1	1	1	1	0	0	6
Bleakley	2008	1	0	1	0	0	1	1	1	0	0	0	5
Brantingham	2009	1	1	1	1	1	1	1	1	0	1	1	10
De Vries	2006	1	1	1	0	1	1	1	1	1	1	1	10
Dizon and Reyes	2010	1	1	1	1	0	1	1	1	1	0	1	9
Evans	2012	1	0	1	1	0	1	0	0	0	0	0	4
Feger	2015	0	0	1	0	1	1	1	1	1	0	0	6
Handoll	2001	1	0	1	1	1	1	1	1	1	1	1	10
Jones	2007	0	0	1	1	0	1	0	0	0	0	0	3
Kemler	2011	0	0	1	0	1	1	1	1	1	0	1	7
Kerkhoffs	2001	1	1	1	1	1	1	1	1	1	0	1	10
Kerkhoffs	2003	1	1	1	1	0	1	1	0	1	0	1	8
Kerkhoffs	2007	1	1	1	0	1	1	1	1	1	0	1	9
Kim	2014	1	1	1	1	1	1	1	1	1	0	1	10
Lihua	2012	1	1	0	0	0	1	1	0	0	1	0	5
Loudon	2014	1	0	1	0	0	1	1	1	0	1	0	6
Loudon	2008	1	0	0	0	0	1	1	1	0	1	0	5
McGuine	2003	1	0	1	0	0	1	0	0	0	0	0	3
Mckee	2008	1	0	1	0	0	1	1	1	0	0	0	5
O'Driscoll	2011	1	0	1	0	0	1	1	1	1	0	1	7
Park	2013	1	1	1	1	0	1	1	1	1	0	1	9
Parlamas	2013	1	1	1	0	0	1	1	0	0	0	0	5
Petersen	2013	1	0	1	0	0	1	1	1	0	1	0	6
Pijnenburg	2000	1	0	1	0	1	1	1	1	1	0	0	7
Postle	2012	1	1	1	1	1	1	1	0	1	0	0	8
Refshauge	2003	1	0	0	0	0	0	0	0	0	0	0	1
Schifftan	2015	1	1	1	0	0	1	1	1	1	0	1	8
Seah	2011	0	0	0	0	0	1	1	1	0	0	0	3
Terada	2013	1	0	1	1	0	1	1	1	0	0	0	6
Thacker	1999	1	0	1	1	0	0	1	1	1	0	0	6
Thacker	2003	1	0	1	1	0	0	1	1	0	0	0	5
van den Bekerom	2012	1	1	1	1	1	1	1	1	1	1	1	11
van den Bekerom	2011	1	0	1	0	0	1	1	1	1	0	0	6
van der Wees	2006	1	1	1	1	1	1	1	1	1	1	0	10
van Ochten	2014	1	0	1	0	0	1	1	1	1	0	0	6
van Os	2005	1	1	1	0	0	1	1	0	1	0	0	6
van Rijn	2010	1	0	1	0	0	1	1	1	1	0	1	7
Verhagen	2000	1	0	1	0	0	1	1	0	0	0	0	4
Verhagen	2010	1	0	1	0	0	1	1	1	0	0	0	5
Webster	2010	1	0	1	0	0	1	1	1	0	0	0	5
Wikstrom	2009	1	0	1	0	1	0	1	1	1	1	1	8
Woitzik	2015	1	0	1	0	0	1	1	1	1	0	1	7
Wortmann	2013	1	0	0	0	0	1	0	0	0	0	0	2
Zech	2009	1	1	1	0	1	1	1	1	1	0	1	9
Zoch	2003	0	0	1	0	1	1	1	1	0	0	0	5

Items legend: 1. Was an “a priori” design provided? 2. Was there duplicate study selection and data extraction? 3. Was a comprehensive literature search performed? 4. Was the status of publication (i.e., grey literature) used as an inclusion criterion? 5. Was a list of studies (included and excluded) provided? 6. Were the characteristics of the included studies provided? 7. Was the scientific quality of the included studies assessed and documented? 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? 9. Were the methods used to combine the findings of studies appropriate? 10. Was the likelihood of publication bias assessed? 11. Were potential conflicts of interest included?

Following the removal of duplicated papers, these reviews collectively included 309 individual reports. Additional information extracted from these studies segregated by injury and intervention is available in the supplementary information for this article; due to the large volume of extracted information, only information relating to the primary outcomes (injury [re-]incidence/function) has been presented in the main text; all information related to the individual studies included in the reviews/the secondary outcomes is available in the supplemental documents¹. Please refer to supplemental Table 1 for the results of the individual studies with respect to the primary and secondary outcomes. 

There was a significant amount of overlap between the reviews regarding the injury type of interest, with 15 reviews being classified as investigating treatment strategies for both acute ankle sprain and CAI [14 17 19 24 28 32 34 37 41 43 45 50 52 53 60]. Twenty reviews investigated treatment strategies for acute ankle sprain specifically [18 21-23 26 27 29-31 39 40 44 46-49 54 55 58 61]. Nine reviews investigated treatment strategies for CAI specifically [20 33 35 36 42 51 56 57 59]. Two reviews investigated treatment strategies for syndesmotic ankle sprain, however these only included case-studies and did not report on either of our primary or secondary outcomes [25 38]. Eight of the reviews evaluated surgical interventions for the treatment of acute ankle sprain [20 25 29 31 38-40 51] with forty-five evaluating some kind of non-surgical intervention [14 17-61]. The results and conclusions from the reviews ranking as 'high' quality have been synthesised in a best evidence synthesis table (Table 3), stratified by the intervention type.

Table 3. Results of the best evidence synthesis from the reviews deemed as 'high' (≥ 7 on the AMSTAR tool) quality. Reviews have been stratified by intervention type.

Study	AMSTAR	Outcome (s)	Intervention	Results	Review Conclusion	Summary
Exercise therapy						
De Vries 2006	10	Functional outcome, Subjective stability, Recurrent injury, Pain, Swelling	Any type of treatment for chronic lateral ankle instability was considered	10 included studies; Data from 3 out of 4 studies showed a better outcome for neuromuscular training compared with no training There is limited to moderate evidence to support improvements in dynamic postural stability, and patient perceived functional stability through neuromuscular training in subjects with CAI. There is limited evidence of effectiveness for neuromuscular training for improving static postural stability, active and passive joint position sense, isometric strength, and a reduction in injury recurrence rates.	Neuromuscular training alone appears effective in the short term. There is insufficient evidence to support any one surgical intervention over another surgical intervention for CAI but it is likely that there are limitations to the use of dynamic tenodesis. Strong evidence of effectiveness was lacking for all outcome measures. All but one of the studies included in the review were deemed to have a high risk of bias, and most studies were lacking sufficient power. Therefore, in future we recommend conducting higher quality RCTs using appropriate outcomes to assess for the effectiveness of neuromuscular training in overcoming sensorimotor deficits in subjects with CAI.	+
O'Driscoll 2011	7	Re-injury, Postural stability, strength, self-reported function	Exercise therapy (neuromuscular)	The results indicated that there is no statistically significant difference in recurrent injury between the addition of proprioceptive exercises during the rehabilitation of patients following ankle ligament injury ($p < 0.68$). The addition of proprioceptive training demonstrated a significant reduction in subjective instability and functional outcomes ($p < 0.05$)	Further study is warranted to develop the rigour of the evidence-base and to determine the optimal proprioceptive training programme following ankle ligament injury with different populations.	?
Postle 2012	8	Re-injury, self reported function	Exercise therapy (proprioceptive exercise)	Results of the meta-analysis combining all participants, irrespective of ankle injury history status, revealed a significant reduction of ankle sprain incidence when proprioceptive training was performed compared to a range of control interventions (relative risk = 0.65, 95% CI 0.55–0.77). Exercise therapy was effective in reducing the risk of recurrent sprains after acute ankle sprain: RR 0.37 (95% CI 0.18 to 0.74). No effects of exercise therapy were found on postural sway in patients with functional instability: SMD: 0.38 (95% CI -0.15 to 0.91). Four studies demonstrated an initial positive effect of different modes of manual mobilisation on dorsiflexion range of motion.	Proprioceptive training programmes are effective at reducing the rate of ankle sprains in sporting participants, particularly those with a history of ankle sprain. Current evidence remains inconclusive on the benefits for primary prevention of ankle sprains. It is likely that exercise therapy, including the use of a wobble board, is effective in the prevention of recurrent ankle sprains. Manual mobilisation has an (initial) effect on dorsiflexion range of motion, but the clinical relevance of these findings for physiotherapy practice may be limited.	+
Schifftan 2015	8	Re-injury	Exercise therapy (proprioceptive training)	There was limited to moderate evidence to suggest that the addition of supervised exercises to conventional treatment leads to faster and better recovery and a faster return to sport at short-term follow-up than conventional treatment alone.	Additional supervised exercises compared with conventional treatment alone have some benefit for recovery and return to sport in patients with ankle sprain, though the evidence is limited or moderate and many studies are subject to bias.	+
van der Wees 2006	10	Re-injury, postural stability, range of motion	Exercise therapy and manual mobilisation	Balance training improves postural control (ES = - 0.857, $P < 0.0001$).	Balance training improves postural control scores after both acute and lateral ankle trauma. However, further research should	+
van Rijn 2010	7	Pain, instability, re-injury	Exercise (additional supervised exercises compared with conventional treatment alone)			+
Wikstrom 2009	8	Postural Control	Exercise (balance training)			+

Woitzik 2015	7	Self reported recovery, pain, instability	Exercise	The evidence suggests that for recent lateral ankle sprain: Rehabilitation exercises initiated immediately post-injury are as effective as a similar program initiated one week post-injury; supervised exercise provides no additional benefit when added to education and advice (including home exercises) compared to education and advice (including home exercises) alone.	determine the optimal dosage, intensity, type of training, and a risk reduction/preventative effect associated with balance training after both acute and chronic ankle trauma. For recent lateral ankle sprains, similar outcomes are offered between an accelerated exercise program and exercises given one week post-injury.	+
Zech 2009	9	Recurrent sprains and giving way episodes/postural control/proprioception/Muscle reaction time to sudden perturbation/Ankle joint functionality scores/Muscle strength/EMG/Edema	Exercise (proprioceptive/neuromuscular)	Proprioceptive/neuromuscular exercise was effective at increasing functionality as well as at decreasing the incidence of recurrent injuries and "giving way" episodes after ankle sprains	It can be concluded that proprioceptive and neuromuscular interventions after ankle injuries can be effective for the prevention of recurrent injuries	+
Conclusions:	There is strong evidence for the use of exercise therapy for preventing ankle re-injury incidence and improving self reported function. One high quality review found no evidence for the addition of supervised exercises to unsupervised home based exercise. There is limited - moderate evidence supporting the use of exercise therapy for improving postural stability (2 reviews supporting and one finding no effect).					
Manual therapy						
Brantingham 2009	10	Self-reported function, ROM, pain, swelling, proprioception, stabilometry	Manual Therapy	There is a level of B or fair evidence for manipulative therapy of the ankle and/ or foot combined with multimodal or exercise therapy for ankle inversion sprain	Larger, methodologically improved, and well-funded randomized controlled and clinical trials, as well as observational, clinical, and basic science research, case series, and studies, are both needed and merited.	+
van der Wees 2006	10	Re-injury, postural stability, range of motion	Exercise therapy and manual mobilisation	Exercise therapy was effective in reducing the risk of recurrent sprains after acute ankle sprain: RR 0.37 (95% CI 0.18 to 0.74). No effects of exercise therapy were found on postural sway in patients with functional instability: SMD: 0.38 (95% CI -0.15 to 0.91). Four studies demonstrated an initial positive effect of different modes of manual mobilisation on dorsiflexion range of motion.	It is likely that exercise therapy, including the use of a wobble board, is effective in the prevention of recurrent ankle sprains. Manual mobilisation has an (initial) effect on dorsiflexion range of motion, but the clinical relevance of these findings for physiotherapy practice may be limited.	?
Conclusions	There is limited evidence supporting the use of manual therapy for treatment of acute ankle sprain injury. At present, there does not appear to be any negative effects of adding manual therapy to an exercise therapy programme. Further research is warranted to determine whether manual therapy results in any long term benefits in either acute ankle sprains or CAI.					
Surgery						
De Vries 2006	10	Primary outcomes: Functional outcome, Subjective stability Secondary outcomes: Recurrent injury, Pain, Swelling	Any type of treatment for chronic lateral ankle instability was considered	10 included studies; Data from 3 out of 4 studies showed a better outcome for neuromuscular training compared with no training	Neuromuscular training alone appears effective in the short term. There is insufficient evidence to support any one surgical intervention over another surgical intervention for CAI but it is likely that there are limitations to the use of	?

Kerkhoffs 2007	9	re-injury; persistent pain; subjective instability.	Surgical compared with conservative interventions.	<p>There is insufficient evidence available from randomised controlled trials to determine the relative effectiveness of surgical and conservative treatment for acute injuries of the lateral ligament complex of the ankle in adults.</p> <p>With respect to giving-way, a significant difference was noted between operative treatment and functional treatment (relative risk, 0.23; 95 percent confidence interval, 0.17 to 0.31) in favour of operative treatment and a significant difference was also noted between functional treatment and treatment with a cast for six weeks (relative risk, 0.69; 95 percent confidence interval, 0.50 to 0.94) in favour of functional treatment. With respect to residual pain, no significant difference was found between operative and functional treatment and a significant difference was found between functional treatment and treatment with a cast for six weeks (relative risk, 0.67; 95 % confidence interval, 0.50 to 0.90).</p>	<p>dynamic tenodesis.</p> <p>Given the risk of operative complications and the higher costs (including those of hospital admission) associated with surgery, the best available option for most patients would be conservative treatment for acute injuries and close follow up to identify patients who may remain symptomatic. High quality randomised controlled trials of primary surgical repair versus the best available conservative treatment for well-defined injuries are required.</p> <p>We concluded that a no-treatment strategy for ruptures of the lateral ankle ligaments leads to more residual symptoms. Operative treatment leads to better results than functional treatment, and functional treatment leads to better results than cast immobilization for six weeks.</p>	?
Pijnenburg 2000	7	Pain & self reported function (giving way)	Any			+
Conclusions	There is limited evidence supporting surgery for the treatment of lateral ankle ruptures compared to no treatment for self reported function. However, there are higher risks of complications with surgical interventions.					
External support						
Dizon & Reyes 2010	9	Re-injury	External ankle supports	<p>The main finding was the reduction of ankle sprain by 69% (OR 0.31, 95% CI 0.18–0.51) with the use of ankle brace and reduction of ankle sprain by 71% (OR 0.29, 95% CI 0.14–0.57) with the use of ankle tape among previously injured athletes.</p> <p>The main finding was a significant reduction in the number of ankle sprains in people allocated external ankle support (RR 0.53, 95% CI 0.40 to 0.69). This reduction was greater for those with a previous history of ankle sprain, but still possible for those without prior sprain. There was limited evidence for reduction in ankle sprain for those with previous ankle sprains who did ankle disk training exercises</p>	<p>No type of ankle support was found to be superior than the other.</p>	+
Handoll 2001	10	Ankle re-injury, instability	External ankle support; ankle disk training; stretching; health education programme and controlled rehabilitation.	<p>Best evidence syntheses only demonstrated a better treatment result in terms of functional outcome for bracing in comparison to other forms of external support. There were no differences for any other outcomes (e.g. re-injuries, residual complaints)</p> <p>Persistent swelling at short-term follow-up was less with lace-up ankle support than with semi-rigid ankle support (RR 4.2 95% CI 1.3–14), an elastic bandage (RR 5.5; 95% CI 1.7–18) and tape (RR 4.1; 95% CI 1.2–14). One trial reported better results for subjective instability using the</p>	<p>Participants with a history of previous sprain can be advised that wearing such supports may reduce the risk of incurring a future sprain.</p>	+
Kemler 2011	7	Re-injuries, pain, swelling, instability, and functional outcomes	External support (comparison of different types)		<p>Further research should focus on economic evaluation and on different types of ankle brace, to examine the strengths and weaknesses of ankle braces for the treatment of acute ankle sprains.</p>	+
Kerkhoffs 2003	8	Swelling, instability	External Support (comparison of different types)		<p>We conclude that an elastic bandage is a less effective treatment. Lace-up supports seem better, but the data are insufficient as a basis for definite conclusions.</p>	+

				semi-rigid ankle support than the elastic bandage (RR 8.0; 95% CI 1.0–62).	
Conclusions	There is strong evidence supporting the use of external support (in the form of taping or bracing) for reducing re-injury incidence and improving self reported function. There is moderate evidence suggesting bracing may be superior for self reported function in comparison to taping.				

Complementary (acupuncture)

Kim 2014	10	Self reported function, re-injury	Acupuncture	<p>The currently available evidence from a very heterogeneous group of randomised and quasi-randomised controlled trials evaluating the effects of acupuncture for the treatment of acute ankle sprains does not provide reliable support for either the effectiveness or safety of acupuncture treatments, alone or in combination with other non-surgical interventions; or in comparison with other non-surgical intervention</p> <p>Acupuncture was more effective than various controls in relieving pain, facilitating return to normal activity, and promoting quality of life, but these analyses were based on only a small number of studies. Acupuncture did not appear to be associated with adverse events.</p>	<p>Future rigorous randomised clinical trials with larger sample sizes will be necessary to establish robust clinical evidence concerning the effectiveness and safety of acupuncture treatment for acute ankle sprains</p> <p>Given methodological shortcomings and the small number of high-quality primary studies, the available evidence is insufficient to recommend acupuncture as an evidence-based treatment option. This calls for further rigorous investigations.</p>	?
Park 2013	9	Pain	Acupuncture			+
Conclusions	There is limited evidence based primarily on low quality studies supporting the use of acupuncture for pain relief in ankle sprain injury. There is limited evidence demonstrating no effect of acupuncture on self reported function and re-injury incidence.					

Immobilisation

Pijnenburg 2000	7	Any	Pain & self reported function (giving way)	<p>With respect to giving-way, a significant difference was noted between operative treatment and functional treatment (relative risk, 0.23; 95 percent confidence interval, 0.17 to 0.31) in favour of operative treatment and a significant difference was also noted between functional treatment and treatment with a cast for six weeks (relative risk, 0.69; 95 percent confidence interval, 0.50 to 0.94) in favour of functional treatment. With respect to residual pain, no significant difference was found between operative and functional treatment and a significant difference was found between functional treatment and treatment with a cast for six weeks (relative risk, 0.67; 95 % confidence interval, 0.50 to 0.90).</p>	<p>We concluded that a no-treatment strategy for ruptures of the lateral ankle ligaments leads to more residual symptoms. Operative treatment leads to better results than functional treatment, and functional treatment leads to better results than cast immobilization for six weeks.</p>	-
Kerkhoffs 2001	10	Pain, swelling, subjective and objective instability, recurrent injury	Immobilisation	<p>There is significant evidence to support functional treatment over immobilisation for multiple outcomes. None of the other results were significantly in favour of immobilisation.</p>	<p>Based on our results, functional treatment currently seems a more appropriate treatment and should be encouraged. Concerning effectiveness, immobilisation, if necessary, should be restricted to certain patients and for short time periods.</p>	-
Conclusions	There is moderate evidence (2 high quality reviews) opposing the use of immobilization in the treatment of ankle sprain injury, in comparison to functional treatment. There is limited to moderate evidence opposing immobilization in comparison to surgical intervention.					

Conventional treatment (RICE)

van den Bekerom 2012	11	Pain, swelling, ankle mobility or range of motion	Rest, ice compression, and elevation (RICE) therapy	Insufficient evidence is available from randomized controlled trials to determine the relative effectiveness of RICE therapy for acute ankle sprains in adults.	Treatment decisions must be made on an individual basis, based on expert opinion and national guidelines	?
Conclusions	There is not sufficient evidence to draw any conclusions regarding the effectiveness of RICE for the treatment of acute ankle sprains. High quality RCTs are required before recommendations can be made.					

+: evidence supporting intervention

-: evidence opposing intervention

?: inconclusive evidence

Acute ankle sprain

Surgical interventions

Six reviews ([20 29 31 39 40 51]; quality range = 5-10) compared surgical to non-surgical interventions for the treatment of acute ankle sprain injury. These reviews contained 82 individual (non-duplicate) papers. Of these eighty-two, thirty-three (32 RCTs, 1 non-RCTs; N = 4080; 65% male, 35% female) evaluated a surgical intervention specifically [62-94].

None of the reviews reported on the primary outcome of recurrence. Function was determined by the time taken to return to activity/work [20 29 31 39 40 51]. Of the six reviews, one (quality = 6/11) advocated conservative management (including physiotherapeutic and external support interventions) over surgery [39], and two (quality = 7/11 [40]; quality = 5/11 [31]) identified that surgery had better outcomes when compared with conservative management in the treatment of acute ankle sprain injury [31 40]. One review (quality = 9) found that there was insufficient evidence to determine the relative effectiveness of either surgical and conservative management in the treatment of an acute AS[29].

Despite its projected benefits, several of the reviews identified the propensity for a surgical intervention to have a higher risk of complication (which included issues such as wound-healing, infection, dystrophy, iatrogenic nerve damage leading to sensory deficit and paresthesia) compared with a conservative intervention [20 29 31 39 40]. A surgical intervention was also associated with greater financial cost [29 40].

Non-surgical interventions

Physiotherapeutic

Eighteen systematic reviews evaluated a physiotherapeutic intervention for the treatment of acute ankle sprain ([14 17 19 23 29 31 32 39 41 44 45 50 52 53 58 60 61 95]; quality range =

Commented [CD1]: Surgical interventions
Of the forty-one studies on which the conclusions of the reviews were likely based, twenty-six evaluated a surgical intervention for management of acute ankle sprain relative to immobilisation, and eight evaluated the efficacy of different surgical interventions relative to one-another. Therefore, only seven studies (all RCTs, N = 483) made the specific comparison of a surgical intervention to a non-surgical control group that completed some kind of active, conventional treatment (such as a physiotherapeutic intervention that involved exercise therapy) (Freeman 1965, Kaikkonen, Kannus et al. 1996, Povacz, Unger et al. 1998, Knop, Thermann et al. 1999, Pihlajamäki, Hietaniemi et al. 2010, Yasui, Takao et al. 2011, Takao, Miyamoto et al. 2012). One of these studies focused on surgical treatment for chronic recurrent ankle sprain (Knop, Thermann et al. 1999). Of the remaining six, three reported that conservative treatment with exercise therapy was superior to surgery (Freeman 1965, Kaikkonen, Kannus et al. 1996, Povacz, Unger et al. 1998), and three reported that surgery was superior to conservative treatment with exercise therapy (Pihlajamäki, Hietaniemi et al. 2010, Yasui, Takao et al. 2011, Takao, Miyamoto et al. 2012) for the primary outcomes of injury recurrence and/or self-reported function.

2-10), which themselves included 213 papers. Of these 213, 118 individual reports were included on removal of papers duplicated between each review. The two main kinds of physiotherapeutic intervention evaluated were exercise therapy and manual therapy

Exercise therapy

Of the eighteen separate systematic reviews, fifteen ([14 17 23 29 31 39 41 44 45 50 52 53 58 60 61]; quality range = 2-10) evaluated the effectiveness of exercise therapy for the treatment of acute ankle sprain. Included in these reviews were forty-one individual papers (33 RCTs, 8 non-RCTs; N = 4680; 68% male, 32% female) wherein exercise therapy was the primary intervention for the treatment of acute ankle sprain [82 96-135].

The reviews were unanimous in their consensus that exercise therapy improves self-reported function following acute ankle sprain [14 17 23 41 44 52 53 60 61]^b. Three of the reviews reported on the primary outcome of recurrence in a sample of individuals with acute ankle sprain [14 39 60]. All three confirmed the effectiveness of exercise therapy for the prevention of recurrence following an acute ankle sprain injury [14 39 60]^d.

Manual therapy

Of the eighteen separate systematic reviews that evaluated a physiotherapeutic intervention, five ([14 19 32 45 50]; quality range 5-10) evaluated the effectiveness of manual therapy for the treatment of acute ankle sprain. Included in these reviews were twelve [136-147] individual papers (all RCTs, N = 687) in which some form of manual therapy technique was utilised in the treatment of acute ankle sprain⁵.

It is unclear whether manual therapy was beneficial for the primary outcomes of self-reported function or injury recurrence [14 19 32 45 50]^{6,7}.

Commented [CD2]: ³*Exercise therapy*

Eleven of the individual papers included in these reviews (all RCTs, N = 536) evaluated the efficacy of an exercise therapy intervention for the primary outcome of self-reported function (Oostendorp 1987, Wester, Jespersen et al. 1996, Hoiness, Engebretsen et al. 2003, Clark and Burden 2005, Bassett and Prapavessis 2007, Bleakley, O'Connor et al. 2007, Hale, Hertel et al. 2007, van Rijn, van Os et al. 2007, van Rijn, van Heest et al. 2009, Hultman, Faltström et al. 2010). Eight of these eleven studies reported a positive outcome for self-reported function following an exercise therapy intervention (Oostendorp 1987, Wester, Jespersen et al. 1996, Clark and Burden 2005, Bleakley, O'Connor et al. 2007, Hale, Hertel et al. 2007, van Rijn, van Heest et al. 2009, Hultman, Faltström et al. 2010), with three reporting no effect (Hoiness, Engebretsen et al. 2003, Bassett and Prapavessis 2007, van Rijn, van Os et al. 2007). The length of follow-up varied considerably in these reports, ranging from between 2-weeks (Bassett and Prapavessis 2007) and 8-months (Wester, Jespersen et al. 1996).

Commented [CD3]: ⁴These conclusions were likely based on six individual cohort analyses (Wester, Jespersen et al. 1996, Holme, Magnusson et al. 1999, Verhagen, van der Beek et al. 2004, McGuine and Keene 2006, Hupperets, Verhagen et al. 2009, van Rijn, van Heest et al. 2009) (all RCTs, N = 1962) wherein the follow-up period was a minimum of 8 months (Wester, Jespersen et al. 1996) and typically one athletic season or year (de Bie, de Vet et al. 1998, Holme, Magnusson et al. 1999, Verhagen, van der Beek et al. 2004, McGuine and Keene 2006, Hupperets, Verhagen et al. 2009, van Rijn, van Heest et al. 2009). Collectively, each of these papers reported a positive effect of exercise therapy for preventing recurrence following an acute ankle sprain injury (Wester, Jespersen et al. 1996, de Bie, de Vet et al. 1998, Holme, Magnusson et al. 1999, Verhagen, van der Beek et al. 2004, McGuine and Keene 2006, Hupperets, Verhagen et al. 2009, van Rijn, van Heest et al. 2009).

Commented [CD4]: ⁵Five of the reviews made specific conclusions regarding the secondary outcomes of proprioception (Baltaci and Kohl 2003, Zoch, Fialka-Moser et al. 2003, Zech, Hubscher et al. 2009, Postle, Pak et al. 2012), strength (Zoch, Fialka-Moser et al. 2003, Zech, Hubscher et al. 2009, Feger, Herb et al. 2015), muscle activity (Zech, Hubscher et al. 2009) and performance (static/dynamic postural control)(Zech, Hubscher et al. 2009, Postle, Pak et al. 2012). Their conclusions were discrepant however in that some reported that the exercise therapy intervention coincided with improvements in these secondary outcomes (quality = 2/11 (Baltaci and Kohl 2003); 6/11 (Feger, Herb et al. 2015); 5/11 (Zoch, Fialka-Moser et al. 2003)) while others concluded that no change had occurred (quality = 8 (Postle, Pak et al. 2012); 9/11 (Zech, Hubscher et al. 2009)). Of the forty-one individual reports which assessed the efficacy of an exercise therapy intervention for ankle sprain, twenty (14 RCTs, 6 non-RCTs; N = 710) evaluated at least one of the secondary outcomes of proprioception, strength, muscle activity and/or static/dynamic postural control (Freeman 1965, Tropp, Ekstrand et al. 1984, Forkin, Koczur et al. 1996, Bernier and Perrin 1998, Holme, Magnusson et al. 1999, Uh, Beynon et al. 2000, Eij...

Commented [CD5]:

⁶ However, all five reviews concluded that manual ankle joint mobilisation has short-term benefits for the secondary outcome of pain (van der Wees, Lenssen et al. 2006, Bleakley, McDonough et al. 2008, Brantingham, Globe et al. 2009, Terada, Pietrosimone et al. 2013, Loudon, Reiman et al. 2014). Furthermore with regards to ROM, manual joint mobilisation was considered to acutely increase ankle joint dorsiflexion ROM (van der Wees, Lenssen et al. 2006, Terada, Pietrosimone et al. 2013, Loudon, Reiman et al. 2014). Importantly, it remains unclear whether these findings translate to long-term benefits for the primary outcomes of recurrence and self-reported function (van der Wees, Lenssen et al. 2006, Bleakley, McDonough et al. 2008, Terada, Pietrosimone et al. 2013, Loudon, Reiman et al. 2014).

⁷Of the individual papers included in these reviews most had a follow-up period of less than 48 hours (Green, Refshauge et al. 2001, Collins, Teys et al. 2004, Vicenzino, Branjerdporn et al. 2006, Lopez-Rodriguez, de-las-Penas et al. 2007, Reid, Birmingham et al. 2007 (...)

Electrophysical agents

Seven systematic reviews evaluated an electrophysical intervention of some kind for the treatment of acute ankle sprain ([14 18 45 49 52 53 95]; quality = 6.7[2]). Fifty papers (on removal of duplicates) were included in these reviews. Of these fifty papers, twenty-one (all RCTs, N = 1459; 59% male, 41% female) evaluated the effectiveness of an electro-physical agent in the treatment of acute ankle sprain injury [120 124 148-166]⁸.

Applications of ice and compression or the use of elevation do not seem to be effective for improving the primary outcomes of self-reported function or recurrence following acute ankle joint sprain compared with no treatment [18 95]. Three reviews concluded that treatment success was achieved on the basis of an exercise therapy intervention that was often combined with a rest/ice/compression/elevation (RICE) protocol [52 53 95].

None of the reviews determined any beneficial effect of ultrasound in the treatment of acute ankle sprain injury [14 49]. However, there are very few trials evaluating the effectiveness of ultrasound therapy for acute ankle sprains [49], and fewer still have considered the range of intervention parameters available [14 49]. Similarly, the evidence for the efficacy of laser, electrical stimulation and hyperbaric oxygen therapies is limited due to a lack of related research [14 45].

External support

Six systematic reviews evaluated an external support of some kind for the treatment of acute ankle sprain ([26 28 39 44 53 61]; quality range 3-10). These reviews included 46 individual papers. Twenty-four of these (23 RCTs, 1 non-RCT; N = 2141, 66% male, 34% female) evaluated some kind of external support (which included taping, bracing, and orthoses⁹) in the treatment of acute ankle sprain injury [103 105 116 126 135 167-185].

Commented [CD6]: ⁸*Electrophysical agents*

Only two of the individual studies evaluated laser therapy (de Bie, de Vet et al. 1998, Stergioulas 2004) and electrical stimulation (Peer, Barkley et al. 2009, Sandoval, Ramirez et al. 2010), and only one study evaluated the effectiveness of hyperbaric oxygen (Borromeo, Ryan et al. 1997), thus limiting the conclusions that could be made about these types of electrophysical agents.

Of the individual reports, only one had a follow-up period >6-months (de Bie, de Vet et al. 1998); the majority of the studies had a follow-up of less than 1-week (Cote, Prentice et al. 1988, Michlovitz, Smith et al. 1988, Laha 1989, Sloan, Hain et al. 1989, Oakland and Rapier 1993, Stergioulas 2004, Peer, Barkley et al. 2009, Sandoval, Ramirez et al. 2010). The most frequently reported outcomes were those in relation to acute symptoms of the ankle joint sprain (pain, swelling, ROM, weight-bearing ability, return to work). Only 3 studies reported on the primary outcomes of recurrence or self-reported function (Michlovitz, Smith et al. 1988, Wilkerson and Horn-Kingery 1993, de Bie, de Vet et al. 1998). Michlovitz et al (Michlovitz, Smith et al. 1988) evaluated the efficacy of electrical stimulation combined with a cryotherapeutic intervention for the treatment of acute ankle sprain and found no differences between the treatment and control groups for the outcome of recurrence. The follow-up period in this study was <1 week (Michlovitz, Smith et al. 1988), which further limits the conclusions that can be made. Wilkerson et al (Wilkerson and Horn-Kingery 1993) evaluated the efficacy of combined cryotherapy and compression in the treatment of acute ankle sprain, finding that the treatment groups (who received focal compression) achieved a better result for the primary outcome of self-reported function. Finally, de Bie et al (de Bie, de Vet et al. 1998) in a study with a 12-month follow-up period found no differences between laser therapy and a control group for either self-reported function or recurrence. The only secondary outcome reported on in the individual studies was postural stability (Zammit and Herrington 2005) and ROM (van Lelieveld 1979, Michlovitz, Smith et al. 1988, Airaksinen, Kolari et al. 1990, Borromeo, Ryan et al. 1997, Nyanzi, Langridge et al. 1999, Zammit and Herrington 2005, Peer, Barkley et al. 2009, Sandoval, Ramirez et al. 2010) with only two of these studies

Commented [CD7]: ⁹*External support*

⁹Of the twenty-four individual reports, only two (which were in separate reviews) evaluated orthoses in the treatment of acute ankle sprain injury (Neumann, Wittkamper et al. 1994, Ashton-Miller, Ottaviani et al. 1996). The remaining papers all evaluated some kind of taping and/or bracing intervention for the treatment of acute ankle sprain (Pasila, Visuri et al. 1975, Allen and McShane 1985, Jongen, Pot et al. 1992, Sommer and Schreiber 1993, Twellaar, Veldhuizen et al. 1993, Dettori, Pearson et al. 1994, Leanderson and Wredmark 1995, Zeegers 1995, Karlsson, Eriksson et al. 1996, Reinhardt and Tiedemann 1999, Matsusaka, Yokoyama et al. 2001, Boyce, Quigley et al. 2005, Beynnon, Renstrom et al. 2006, Mickel, Bottoni et al. 2006, Bassett and Prapavessis 2007, van Rijn, van Os et al. 2007, Cooke, Marsh et al. 2009, Lamb, Marsh et al. 2009, McGuine, Brooks et al. 2011, Babins 2012, Lardenoye, Theunissen et al. 2012, McGuine, Hetzel et al. 2012). Five of these studies reported on the primary outcome of recurrence, with all documenting a positive effect of the taping/bracing intervention (Sommer and Schreiber 1993, Mickel, Bottoni et al. 2006, McGuine, Brooks et al. 2011, Babins 2012, McGuine, Hetzel et al. 2012). Nine studies reported on the primary outcome of self-reported function (Sommer and Schreiber 1993, Twellaar, Veldhuizen et al. 1993, Leanderson and Wredmark 1995, Zeegers 1995, Boyce, Quigley et al. 2005, Bassett and Prapavessis 2007, Cooke, Marsh et al. 2009, Lamb, Marsh et al. 2009, Lardenoye, Theunissen et al. 2012). With the exclusion of two papers, one with unclear findings (Twellaar, Veldhuizen et al. 1993) and another reporting no advantage (Zeegers 1995), these studies advocated a positive effect of taping/bracing in the treatment of acute ankle sprain. The follow-up period in these studies ranged from ≥1 year (Twellaar, Veldhuizen et al. 1993, Neumann, Wittkamper et al. 1994, Karlsson, Eriksson et al. 1996, Mickel, Bottoni et al. 2006, McGuine, Brooks et al. 2011, Babins 2012, McGuine, Hetzel et al. 2012), ≤1 year (Beynnon, Renstrom et al. 2006, Cooke, Marsh et al. 2009, Lamb, Marsh et al. 2009) and ≤6-months (Dettori, Pearson et al. 1994, Leanderson and Wredmark 1995, Reinhardt and Tiedemann 1999, Matsusaka, Yokoyama et al. 2001, Boyce, Quigley et al. 2005, van Rijn, van Os et al. 2007, Lardenoye, Theunissen et al. 2012).

The reviews were unanimous in their consensus that braces and taping are effective in the treatment of acute ankle sprains for the primary outcomes of self-reported function and recurrence [26 28 39 44 53 61]^[10,11].

Complementary

Three systematic reviews evaluated some kind of complementary medicine for the treatment of acute ankle sprain ([14 30 37]; quality range 5-10). These three reviews included sixty individual papers. There were two papers duplicated between these reviews, leaving fifty-eight individual reports. Of these fifty-eight, thirty-five (all RCTs; N = 2358, 67% male, 33% female) evaluated some kind of complementary medicine in the treatment of acute ankle sprain injury [186-220]. Acupuncture was the primary focus of the reviews however [14 30 37].

Two of the reviews (quality = 5/11[14] ; 10/11[30]) reported that there were insufficient data to determine the relative effectiveness of complementary medicine in the treatment of acute ankle sprain for self-reported function or injury recurrence^[2].

The final review (quality = 9/11) concluded that acupuncture was likely to have a therapeutic effect in improving acute symptoms, but acknowledged that the results were likely to be overestimated due to the low quality of the included studies [37].

On this basis, the evidence for the efficacy of complementary therapies in the treatment of acute ankle sprain for the primary outcomes of injury recurrence/self-reported function is inconclusive.

Pharmacological

Three systematic reviews evaluated some kind of pharmacological intervention for the treatment of acute ankle sprain ([14 30 44]; quality range 3-10). These reviews included 47

Commented [CD8]: ¹⁰Despite the agreement between the reviews, a number acknowledged that there were still too few studies in this area, that the available studies were at a high risk of bias, lacked power and that the cost-effectiveness of this intervention still needs to be clarified (van Rijn, van Ochten et al. 2010, Kemler, van de Port et al. 2011).

¹¹While none of the reviews made conclusions regarding any of the secondary outcomes, one of the individual studies reported on the secondary outcome of static postural control (Matsusaka, Yokoyama et al. 2001) and reported that taping improved postural sway.

Commented [CD9]:

¹²*Complementary*
All three reviews raised concerns over the quality of the included studies (Bleakley, McDonough et al. 2008, Park, Hahn et al. 2013, Kim, Lee et al. 2014), leading to reservations about the conclusions that could be made. Pooled analyses were either not completed (Bleakley, McDonough et al. 2008) or were limited by the substantial heterogeneity of the included studies (Kim, Lee et al. 2014). The studies included were generally considered to be small (Egger, Juni et al. 2003), of poor quality (Kim, Lee et al. 2014), were contradictory in their findings (Kim, Lee et al. 2014), and were often of Chinese origin (Park, Hahn et al. 2013); Chinese studies were considered to be more likely to publish positive outcomes (Vickers, Goyal et al. 1998, Park, Hahn et al. 2013), thus the effect size the studies included in these reviews may have been inflated because of poor methodological design and conduct (Egger, Juni et al. 2003). Of the thirty-five individual reports, two studies (Koll, Buhr et al. 2004, Kucera, Barna et al. 2004) (both RCTs, N = 346) evaluated the efficacy of comfrey root ointment compared to a placebo treatment for the outcomes of pain and swelling over a short-term follow-up period (≤ 2 weeks). Both studies supported a beneficial effect for this topically applied cream for these outcomes (Koll, Buhr et al. 2004, Kucera, Barna et al. 2004). The remaining thirty-three (Cho 1977, Paris, Baynes et al. 1983, Ruan 1995, Ruan and J 1995, Yu and Yuan 1995, Yu and Shuo 1996, Yu 1999, Ge and Ma 2000, Ge and Ma 2000, Li 2002, Jian and Wang 2004, Wei, Jin et al. 2004, Wang 2005, Zhao and Shanghai 2005, Hao and Wang 2006, He and Xu 2006, Wu 2006, Wu 2007, Zhou 2008, Luo, He et al. 2009, Wang and Sun 2009, He, Diao et al. 2010, Ni and Li 2010, Tang, Jiang et al. 2010, Wei and Zhejiang 2010, Zheng and Wang 2010, Jiang and Wang 2011, Sun, Chao et al. 2011, Sun and Ju 2011, Zhang and Zhang 2011, Chen, Wang et al. 2012, Zhang 2012, Shi 2013) studies all investigated some kind of acupuncture intervention for the treatment of acute ankle joint sprain, and likely informed the conclusions made by each of the systematic reviews. Only two of these thirty-three had a follow-up period longer than 1-month (He, Diao et al. 2010, Tang, Jiang et al. 2010), and only one study reported on the primary outcome of self-reported function (He, Diao et al. 2010). No studies evaluated the effect of acupuncture on injury recurrence and none provided any analysis of the secondary outcomes of strength, proprioception, static/dynamic postural control or muscle activity (Cho 1977, Paris, Baynes et al. 1983, Ruan 1995, Ruan and J 1995, Yu and Yuan 1995, Yu and Shuo 1996, Yu 1999, Ge and Ma 2000, Ge and Ma 2000, Li 2002, Jian and Wang 2004, Wei, Jin et al. 2004, Wang 2005, Zhao and Shanghai 2005, Hao and Wang 2006, He and Xu 2006, Wu 2006, Wu 2007, Zhou 2008, Luo, He et al. 2009, Wang and Sun 2009, He, Diao et al. 2010, Ni and Li 2010, Tang, Jiang et al. 2010, Wei and Zhejiang 2010, Zheng and Wang 2010, Jiang and Wang 2011, Sun, Chao et al. 2011, Sun and Ju 2011, Zhang and Zhang 2011, Chen, Wang et al. 2012, Zhang 2012, Shi 2013). The majority of the studies compared acupuncture to some type of Chinese medicine (such as a Chinese skin patch or herbal medication) (Ruan 1995, Yu and Shuo 1996, Ge and Ma 2000, Li 2002, Wei, Jin et al. 2004, Hao and Wang 2006, Wu 2006, Wang and Sun 2009, Jiang and Wang 2011, Zhang and Zhang 2011) or electrophysical agent (Cho 1977, Paris, Baynes et al. 1983, Yu and Shuo 1996, Jian and Wang 2004, Wang 2005, Zhao and Shanghai 2005, He and Xu 2006, Zhou 2008, Ni and Li 2010, Tang, Jiang et al. 2010, Wei and Zhejiang 2010, Zheng and Wang 2010, Zhang 2012). Only one study compared combined acupuncture and exercise to an exercise ...

papers (all RCTs; N = 6395, 62% male, 38% female). There were no papers duplicated between these reviews. Thirteen papers (N = 2423, 47% male, 53% female) evaluated any pharmacological agent [which typically included non-steroidal anti-inflammatory drugs (NSAIDs)] in the treatment of acute ankle sprain as the primary intervention [136 186 187 196 199 220-227]^[13].

Due to the short follow-up periods in the individual studies, no conclusions could be made for the primary outcomes of self-reported function or injury recurrence.

Chronic ankle instability

None of the included reviews evaluated the efficacy of electrophysical agents, pharmacological interventions or complementary medicine for the treatment of CAI or recurrent ankle sprains.

Surgical interventions: chronic ankle instability

Two reviews ([20 51]; quality range 6-10) evaluated the efficacy of surgery for the specified treatment of CAI or recurrent ankle sprains^[14]. Included in these reviews were twenty-four individual papers, 8 of which evaluated a surgical intervention for the treatment of CAI or chronic recurrent ankle sprain (all RCTs; N = 533; 64% male, 36% female)[62-64 71 72 94 228 229].

None of the reviews specifically investigated whether a surgical intervention was superior to conservative management for CAI. In the majority of the individual studies, a surgical intervention was often only implemented provided conservative management had failed [62-64 94 228 229]. Furthermore, none of the individual reports had a non-surgical control group [51], and none of the studies reported on the primary outcome of re-injury incidence [62-64 71 72 94 228 229]^[15].

Commented [CD10]: ¹³Pharmacological

Only one of the eleven papers that evaluated a NSAIDs in the treatment of acute ankle sprain had a follow-up period longer than 1-month (Slatyer, Hensley et al. 1997), and none of the studies reported on the primary outcome of self-reported function. Only one study reported on the primary outcome of injury recurrence, however, the follow-up period in this study was eight days only (Dreiser and Riebenfeld 1993). None of the studies reported on the secondary outcomes of strength, proprioception, static/dynamic postural control, ankle joint ROM or muscle activity. Thus the clinical relevance of the short-term symptomatic relief gained by using NSAIDs remains unclear.

With regards to the secondary outcome of pain, Bleakley et al. concluded that there was "strong evidence to support the use of non-steroidal anti-inflammatory drugs for short-term symptomatic relief immediately after ankle sprain." Only one study in the review by Kim et al (Kim, Lee et al. 2014), used NSAIDs and the results in that study were not stated (Wei, Jin et al. 2004). Similarly, one study in the review by Seah et al. (Seah and Mani-Babu 2011), evaluated hyaluronic acid injections for the treatment of acute ankle sprain and concluded that this treatment is relatively novel but may have a role in expediting return to sport (Petrella, Petrella et al. 2007).

Commented [CD11]: Surgical interventions

¹⁴A frequent inclusion criterion of these studies was mechanical laxity at the ankle joint (Larsen 1990, Hennrikus, Mapes et al. 1996, Karlsson, Eriksson et al. 1997, Karlsson, Lundin et al. 1999, Rosenbaum, Engelhardt et al. 1999, Hoiness, Engebretsen et al. 2003).

Commented [CD12]: ¹⁵A number of conclusions were made in

each of the reviews (de Vries, Krips et al. 2006, van Ochten, van Middelkoop et al. 2014). First, there was no significant difference for the primary outcome of self-reported function between anatomic and non-anatomic surgical reconstruction techniques (de Vries, Krips et al. 2006). However non-anatomic reconstruction techniques were considered to pose a greater risk for nerve injury (Hennrikus, Mapes et al. 1996) and not as effective for the correction of excessive talar tilt (Rosenbaum, Engelhardt et al. 1999). One study (Karlsson, Eriksson et al. 1997) comparing two anatomic reconstruction techniques found no difference in any of their clinical outcomes but operation time was significantly shorter in the reinsertion group (de Vries, Krips et al. 2006).

Non-surgical interventions: chronic ankle instability

Twenty three reviews evaluated the efficacy of a physiotherapeutic intervention (which included exercise and manual therapies) in the treatment of CAI or recurrent ankle sprain injury ([17 19 20 23 32-36 41-43 45 46 50 51 54-57 59-61]; quality range 1-10). Following removal of duplicates, these reviews included 122 individual papers (83 RCTs, 39 non RCTs; N = 26349, 82% male, 18% female).

Exercise therapy

Twenty two of the included reviews evaluated exercise therapy for treating CAI or recurrent ankle sprain ([17 19 20 23 33-36 41-43 45 46 50 51 54-57 59-61]; quality range 1-10).

Included in these reviews were 114 individual reports, with sixty-one of these papers evaluated the efficacy of exercise therapy for the treatment of CAI or recurrent ankle sprain specifically (42 RCTs 19 non-RCTs; N = 13963; 70% male, 30% female) [65 96-99 101-104 106 107 110-113 118 119 121-123 128-135 230-262].

Exercise therapy is generally considered effective in the treatment of CAI for the outcomes of self-reported function [20 23 41 45 51 57 60] and ankle sprain re-injury incidence [33-36 42 43 46 50 51 54 55 60]^[16,17,18,19,20].

Manual therapy

Five reviews ([19 32 45 50 51]; quality range 6-10) evaluated the effect of ankle joint mobilisation in CAI populations. Of the 122 individual papers included in these reviews, twelve (all RCTs, N = 340; insufficient data to calculate male:female ratio) evaluated some kind of manual therapy in the treatment of ankle sprain [137-147 263].

Commented [CD13]: Exercise therapy

¹⁶One review by Postle et al stated that the efficacy of exercise therapy for the prevention of recurrence was inconclusive (Postle, Pak et al. 2012). The papers included (Wester, Jespersen et al. 1996, Bernier and Perrin 1998, Holme, Magnusson et al. 1999, Eils and Rosenbaum 2001, Hale, Hertel et al. 2007, Ross, Arnold et al. 2007, Han, Ricard et al. 2009, Hupperets, Verhagen et al. 2009) in the paper by Postle et al (Postle, Pak et al. 2012) were not unique to that review in the context of the eighteen remaining systematic reviews. However, only two of the included studies in the paper by Postle et al (2 RCTs, N = 570) (Wester, Jespersen et al. 1996, Hupperets, Verhagen et al. 2009) examined the effect of exercise therapy on the risk of injury recurrence. Individually, both of these papers reported a reduction in the risk of re-injury following an exercise therapy intervention (Wester, Jespersen et al. 1996, Hupperets, Verhagen et al. 2009). However, when subjected to a meta-analysis, the results indicated that, despite the odds of recurrent ankle injury being twice as high in the groups who did not receive the exercise therapy intervention (Postle, Pak et al. 2012), this was not statistically significant (p = 0.63) (Postle, Pak et al. 2012). The authors attributed this to statistical heterogeneity of the included papers (Postle, Pak et al. 2012).

¹⁷Of the 45 RCTs (from all reviews) that evaluated the efficacy of exercise therapy for the treatment of CAI or recurrent ankle sprain, twenty-three reported on the primary outcome of recurrence. Thirteen (Ekstrand and Gillquist 1983, Tropp, Askling et al. 1985, Wester, Jespersen et al. 1996, Holme, Magnusson et al. 1999, Wedderkopp, Kallott et al. 1999, Stasinopoulos 2004, Verhagen, van der Beek et al. 2004, Emery, Cassidy et al. 2005, McGuine and Keene 2006, Mohammadi 2007, Hupperets, Verhagen et al. 2009, van Rijn, van Heest et al. 2009, Eils, Schröter et al. 2010) of these studies reported that exercise therapy was beneficial in preventing recurrence, and ten reported that it had no effect (Nilsson 1983, Van Mechelen, Klobil et al. 1993, Pope, Herbert et al. 1998, Pope, Herbert et al. 2000, Soderman, Werner et al. 2000, Chaiwanichsiri, Lorprayoon et al. 2005, Olsen, Myklebust et al. 2005, Emery, Rose et al. 2007, van Rijn, van Os et al. 2007, Engebreitsen, Myklebust et al. 2008). Ten of the 45 RCTs reported on the primary outcome of self-reported function, with seven reporting a positive effect of an exercise therapy intervention (Wester, Jespersen et al. 1996, Clark and Burden 2005, Hale, Hertel et al. 2007, McKeon, Ingersoll et al. 2008, van Rijn, van Heest et al. 2009, Dinesha and B 2011), and three reporting no effect (Nilsson 1983, Hoiness, Glott et al. 2003, van Rijn, van Os et al. 2007).

¹⁸Improvements in the secondary outcomes of joint position sense (proprioception) (Refshauge 2003, Loudon, Santos et al. 2008, Zech, Hubscher et al. 2009, Feger, Herb et al. 2015), static/dynamic postural control (Loudon, Santos et al. 2008, Wikstrom, Naik et al. 2009, Zech, Hubscher et al. 2009, Webster and Gribble 2010, O'Driscoll and Delahunt 2011, Postle, Pak et al. 2012, Wortmann and Docherty 2013, Feger, Herb et al. 2015), electromyographic outcomes (such as reaction time) (Loudon, Santos et al. 2008, Zech, Hubscher et al. 2009) and strength (Loudon, Santos et al. 2008, Zech, Hubscher et al. 2009, Feger, Herb et al. 2015) were the variables most commonly evaluated in the aim of ascertaining the mechanism by which improvements in the primary outcomes were likely to be achieved. However, the consensus was not unanimous as to whether any of these variables actually contributed to the aforementioned improvements. Specifically, improvements in proprioception were advocated in some reviews (both of quality = 6/11 (Loudon, Santos et al. 2008, Feger, Herb et al. 2015)) whereas others refuted such claims (quality = 1/11 (Refshauge 2003); 9/11 (Zech, Hubscher et al. 2009)). Similarly, performance measures (including static/dynamic postural control) were deemed to have improved following exercise therapy in some reviews (quality = 5/11 (Webster and Gribble 2010); 8/11 (Wikstrom, Naik et al. 2009); 7/11 (O'Driscoll and Delahunt 2011); 4/11 (Wortmann and Docherty 2013); 5/11 (Loudon, Santos et al. 2008)) and not in others (quality = 8/11 (Postle, Pak et al. 2012); 6/11 (Feger, Herb et al. 2015); 9/11 (Zech, Hubscher et al. 2009)). One review reported that improvements in reaction time were observed after exercise therapy (quality = 5/11 (Loudon, Santos et al. 2008)), while two others did not (quality = 9/11 (Zech, Hubscher et al. 2009); 7/11 (O'Driscoll and Delahunt 2011)). Two reviews advocated the use of exercise therapy in improving the strength of the ankle musculature (quality = 5/11 (Loudon, Santos et al. 2008); 6/...

Regarding the primary outcomes of self-reported function or injury recurrence, five of the individual papers included samples with CAI or recurrent ankle sprains [139 142 144 146 263] and one reported on the primary outcome of self-reported function with a follow-up period that was not immediately post-treatment [139]²¹.

All the reviews identified that manual mobilisation is likely to have an (initial) positive effect on ankle dorsiflexion range of motion [19 32 45 50 51].

External support

Nine systematic reviews evaluated the efficacy of an external support intervention for the treatment of CAI ([21 22 24 34 46 47 54 55 61]; quality range 4-10). These reviews included 115 papers. Of these 115, 63 individual reports were included on removal of papers duplicated between each review. Of the 63 individual reports, thirty-nine (15 RCTs, 24 non-RCTs; N = 8734; 90% male, 10% female) evaluated some kind of external support for the treatment of CAI [108,173,248-263]. The primary outcome in all of the reviews was re-injury incidence.

There was unanimous consensus among the reviews that bracing is effective at preventing a recurrence of an ankle sprain injury [21 22 24 34 46 47 54 55 61]²². With regards to taping, two reviews (quality = 5/11[46]; 4/11 [22]) concluded that its efficacy could not be supported (and that bracing was superior) whereas three reviews (quality = 5/11 [55]; 4/11 [54]; 9/11 [21]) advocated its value in the prevention of ankle sprain recurrence. It remains unclear whether bracing or taping are effective interventions for the primary prevention of an ankle sprain injury [21 24 54]

The reviews identified that the evidence for modified footwear was inconclusive in the prevention of ankle sprain or ankle sprain recurrence [46 47 54]²³.

Commented [CD14]: ²¹*Manual therapy*

All four remaining studies reported improvements in the secondary outcome of ROM following treatment (Vicenzino, Branjerdporn et al. 2006, Kohne, Jones et al. 2007, Reid, Birmingham et al. 2007, Hoch and McKeon 2011), with one study each reporting improvements in proprioception (Kohne, Jones et al. 2007) and postural control (Hoch and McKeon 2011).

Commented [CD15]: *External support*

²²Eighteen (7 RCTs, 11, non-RCTs; N = 4324, 82% male, 18% female) of the individual reports evaluated some kind of bracing intervention for the prevention of ankle sprain or treatment of chronic ankle sprain injury (Bensel and Kaplan 1986, Rovere, Clarke et al. 1988, Sitler, Ryan et al. 1994, Surve, Schwellnus et al. 1994, Amoroso, Ryan et al. 1998, Stasinopoulos 2004, Gribble, Radel et al. 2006, Mickel, Bottoni et al. 2006, Mickel, Bottoni et al. 2006, Curtis, Laudner et al. 2008, DiStefano, Padua et al. 2008, Hardy, Huxel et al. 2008, Kernozek, Durall et al. 2008, Pedowitz, Reddy et al. 2008, Shaw, Gribble et al. 2008, Cloak, Galloway et al. 2010, Gribble, Taylor et al. 2010, Tang, Wu et al. 2010). None of these evaluated the primary outcome of self-reported function, however ten reported on the primary outcome of injury incidence (Bensel and Kaplan 1986, Rovere, Clarke et al. 1988, Sitler, Ryan et al. 1994, Surve, Schwellnus et al. 1994, Amoroso, Ryan et al. 1998, Stasinopoulos 2004, Mickel, Bottoni et al. 2006, Mickel, Bottoni et al. 2006, Curtis, Laudner et al. 2008, Pedowitz, Reddy et al. 2008). Only two of these ten reported that bracing was not effective in the prevention of ankle sprain (Bensel and Kaplan 1986, Curtis, Laudner et al. 2008). Regarding the secondary outcomes, two studies reported a positive effect (Shaw, Gribble et al. 2008, Cloak, Galloway et al. 2010) and three studies reported no effect (DiStefano, Padua et al. 2008, Hardy, Huxel et al. 2008, Gribble, Taylor et al. 2010) for static/dynamic postural control, two studies reported no effect for muscle activity (Gribble, Radel et al. 2006, Kernozek, Durall et al. 2008), and one study showed that bracing restricts ROM (Tang, Jiang et al. 2010).

Commented [CD16]: ²³One of the individual studies included in the review by Verhagen et al (Verhagen, van Mechelen et al. 2000),

identified that the newness of the footwear plays a more important role than shoe height in preventing ankle sprains (with newer footwear considered to decrease risk) (Barrett, Tanji et al. 1993). Three of the individual reports (1RCT, 2non-RCTs; N = 756, 89% male, 11% female) evaluated a footwear intervention. Two reported on the primary outcome of recurrence, one concluding that high top shoes were protective against ankle sprain (Moiler, Hall et al. 2006) and one reporting that they had no effect (Barrett, Tanji et al. 1993). Kerr et al., identified that muscle activity was increased while wearing shoes in response to an inversion perturbation (Kerr, Arnold et al. 2009).

There was a lack of evidence for the value of orthotics in the treatment of CAI or the prevention of ankle sprain recurrence [22]²⁴.

Commented [CD17]: ²⁴These conclusions were likely based on three of the individual reports (2RCTs, 1non-RCT; N = 545; 99% male, 1% female). Two studies investigated the efficacy of orthotics for preventing ankle sprain recurrence (Tropp, Asklind et al. 1985, Mohammadi 2007) and one for improving dynamic postural stability (Gudibanda and Wang 2005), with no beneficial effects noted.

Meta-analysis

Exercise interventions significantly decreased the risk of sustaining a recurrent ankle sprain (Figure 6; OR=0.59, 95% CI 0.51 to 0.68). An exploratory sensitivity analysis by treatment dose (high dose vs low dose using a median split of 900minutes) was performed. Removal of interventions with a lower dose of total exercise (<900minutes) improved the odds of the exercise intervention for injury risk (Figure 6; OR=0.48, 95% CI 0.37 to 0.63). A summary of the exercise therapy interventions (with overall study quality) presented in the individual papers is presented in supplemental Table 3.

External support interventions were also associated with a significantly decreased risk of sustaining a recurrent ankle sprain (Figure 5; OR=0.38, 95% CI 0.30 to 0.47).

DISCUSSION

This systematic review of systematic reviews of treatment strategies for acute ankle sprain and CAI found 46 reviews which included 309 individual studies. As the conclusions of each review have been presented, the following topics in the treatment of acute ankle sprain/CAI will be clarified and discussed: surgical interventions; conservative interventions; treatment of specific types of ankle sprain injury.

Surgical interventions

Treatment strategies in the current review were divided into surgical and non-surgical types. The surgical literature is sparse however, and never were the long term effects of a surgical intervention on the primary outcome of recurrence investigated. The general consensus of the

reviews that investigated a surgical intervention was that a trial of conservative treatment should always be attempted before surgery is undertaken, that surgery should be considered only in patients with persistent symptoms, and that it should be considered on an individual basis [29 39 40].

Conservative interventions

Meta-analysis

Due to a significant heterogeneity of outcomes, samples, interventions and follow-up periods, meta- analyses were only undertaken to evaluate the effect of exercise and external support interventions on re-injury recurrence in individuals with a history (acute or chronic) of ankle sprain. This analysis elucidated that an exercise intervention can significantly reduce the odds of ankle sprain recurrence, and that this effectiveness is improved if the exercise therapy is given in high (>900 minutes of exercise therapy training) doses. The other meta-analysis conducted as part of this investigation advocated the use of an external support in reducing the odds of ankle sprain recurrence. The review papers equated the efficacy of taping with bracing [54 55] (with a similar re-injury risk reduction of 50% [55], while also reducing the severity of the incurred sprain [54])²⁵.

Exercise therapy

A number of limitations in the available research were acknowledged in the reviews and as such, the findings of the meta-analysis for exercise therapy should be interpreted with caution. Firstly, many of the authors stated that the studies included in their reviews were very heterogeneous [17 20 36 51 60 61]. With regards to the statistical pooling performed as part of the current investigation, reflection of the exercise programs implemented in the individual papers highlights this heterogeneity (Supplementary Table 2). Additionally,

Commented [CD18]: ²⁵Nineteen of the individual reports evaluated some kind of taping intervention for the prevention of ankle sprain recurrence or treatment of CAI (Simon 1969, Garrick and Requa 1973, Ekstrand, Gillquist et al. 1983, Rovere, Clarke et al. 1988, Ashton-Miller, Ottaviani et al. 1996, Matsusaka, Yokoyama et al. 2001, Mickel, Bottoni et al. 2006, Moiler, Hall et al. 2006, Sacco Ide, Takahasi et al. 2006, Sawkins, Refshauge et al. 2007, Spanos, Brunswic et al. 2008, Abian-Vicen, Alegre et al. 2009, Hopper, Samsson et al. 2009, Lohkamp, Craven et al. 2009, Purcell, Schuckman et al. 2009, Refshauge, Raymond et al. 2009, Sanioglua, Ergun et al. 2009, Stoffel, Nicholls et al. 2010). Six studies reported on the primary outcome of injury incidence, four of which reported a positive effect of a taping intervention (Garrick and Requa 1973, Ekstrand, Gillquist et al. 1983, Mickel, Bottoni et al. 2006, Moiler, Hall et al. 2006), with one (Simon 1969) reporting no effect. One study compared bracing against taping for the prevention of ankle sprain, and found bracing to be superior (Rovere, Clarke et al. 1988). No studies evaluated the effect of a taping intervention on the primary outcome of self-reported function. Six studies evaluated the effect of tape on the secondary outcome of static/dynamic postural stability, with one reporting that tape had no effect (Abian-Vicen, Alegre et al. 2009), one reporting a negative effect (Stoffel, Nicholls et al. 2010) and four reporting a positive effect (Matsusaka, Yokoyama et al. 2001, Sawkins, Refshauge et al. 2007, Hopper, Samsson et al. 2009, Purcell, Schuckman et al. 2009) on postural stability outcomes. Two studies determined that taping had no effect on the strength of the ankle musculature (Ashton-Miller, Ottaviani et al. 1996, Spanos, Brunswic et al. 2008), two studies reported that tape created a ROM restriction at the ankle joint (Refshauge, Raymond et al. 2009, Sanioglua, Ergun et al. 2009) while one reported that taping worsened (Sawkins, Refshauge et al. 2007) and another that it improved (Lohkamp, Craven et al. 2009) proprioception.

information regarding the intervention parameters was not adequately described in most studies. Furthermore, several reviews endorsed the completion of additional high quality research to identify the specific parameters (such as the dose, intensity, type) of exercise therapy required to improve long term outcomes [35 41 56 57 60]. It is also currently unknown as to whether exercise therapies reduce the severity an ankle re-injury, or increase the number of exposures before an ankle injury occurs [34]. Finally, there is a lack of evidence which links improvements in the primary outcomes with improvements in secondary outcomes [111] (which could elucidate the mechanistic underpinnings of treatment efficacy).

External supports

Generally, the conclusions of the systematic reviews for an external support that included a taping or bracing intervention identified that their benefit could be enhanced with an appropriately designed exercise therapy program and that the efficacy of these interventions was 'additive' in the secondary prevention of ankle sprains [55]. Braces were recommended for all athletes with a previous history of ankle sprain injury, particularly when engaging in high risk activities such as indoor/court and field sports [22 24]. It was recommended that a brace be worn for a minimum of 6-months after an acute ankle sprain injury to prevent recurrence [46 47], and that the benefit of wearing a brace lasts for up to 1-year following the most recent ankle sprain injury [54]. Next to the recognised preventive effect, the use of external support was considered to result in less severe ankle sprains [54]. With regards to the type of external support recommended, Kerkhoffs et al. and Seah et al both concluded that lace up ankle supports were superior to semi-rigid ankle supports [28 44].

Manual therapy

Studies on the effect of the physiotherapeutic intervention of manual therapy were limited by short follow-up time-frames which impeded extrapolation of the long-term benefits of these techniques for either of the primary outcomes [19 32 45 50 51].

Electrophysical agents

No review investigated the efficacy of electrophysical agents in the treatment of CAI.

Electrophysical agents were not considered effective treatments for acute ankle sprain.

However, the standard practice of applying ice and compression (or the use of elevation) is generally administered concurrently with an exercise therapy intervention [52 53 95]. While it is unknown if a RICE protocol augments the effect of exercise [18], given the strong empirical evidence base and the popularity of cryotherapy treatment (particularly for the secondary outcome of pain), it may be difficult to randomize a subject to a “no ice” group [18]. In conjunction with this point, a number of reviews recognised the paucity of high quality studies evaluating an electrophysical agent in the treatment of acute ankle sprain [14 18 53 95].

Complementary medicine

Similarly, complementary medicine has not been investigated in the treatment of CAI, and is not considered to be effective in the treatment of acute ankle sprain. Both the relevant reviews identified that there seemed to be a short term benefit of complementary medicine for the secondary outcomes of pain and swelling, but cited that it remains unclear as to whether this is clinically meaningful in the long-term for injury recurrence and self-reported function [14 30].

Limitations with this review

This review itself is not without limitations. Firstly, due to the inherent nature of this type of study design, the latest literature is unlikely to be included in even the most recently published systematic reviews and is therefore omitted from this article. Additionally, data extraction was conducted by only one author; while all the authors were involved in devising the data extraction form and two performed the quality review, our protocol could have been improved if two authors had independently extracted the data. A sample of the studies were randomly selected to be double checked by a second reviewer, to ensure quality. However, due to the volume of data and time-intensive nature of this, it was unfeasible for a second reviewer to double extract the data.

Ankle sprain type

Finally, only two of the reviews evaluated treatment strategies in the management of syndesmotic ankle sprain injury; the individual papers included in these reviews were all case studies and as such, no meaningful results could be drawn from them. No reviews were identified which sought to investigate treatment strategies for medial ankle sprain. The remaining reviews either did not present a specific definition of the type of ankle sprain (lateral/medial/syndesmotic), or focused on the most prevalent sub-type of this injury: a lateral ankle sprain [1]. Future research is required to identify the optimal management strategies for medial and syndesmotic ankle sprains.

CONCLUSION

This review summarises the evidence base for a number of interventions designed to treat and prevent acute ankle sprain and CAI. The best evidence synthesis of high quality reviews indicates there is strong evidence for exercise therapy and bracing in preventing recurrence of

an ankle sprain injury. The efficacy of surgery and acupuncture are controversial in the treatment of acute ankle sprains. There is insufficient evidence to support the use of ultrasound in the treatment of acute ankle sprains.

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Conflicts of interest.

The authors' have no conflicts of interest to declare.

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