CADTH

CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

Exercise for the Treatment of Ankle Sprain: A Review of Clinical Effectiveness and Guidelines

Service Line:	Rapid Response Service
Version:	1.0
Publication Date:	April 3, 2020
Report Length:	26 Pages

CADTH

Authors: Khai Tran, Suzanne McCormack

Cite As: Exercise for the Treatment of Ankle Sprain: A Review of Clinical effectiveness and Guidelines. Ottawa: CADTH; 2020 Apr. (CADTH rapid response report: summary with critical appraisal)

ISSN: 1922-8147 (online)

Disclaimer: The information in this document is intended to help Canadian health care decision-makers, health care professionals, health systems leaders, and policy-makers make well-informed decisions and thereby improve the quality of health care services. While patients and others may access this document, the document is made available for informational purposes only and no representations or warranties are made with respect to its fitness for any particular purpose. The information in this document should not be used as a substitute for professional medical advice or as a substitute for the application of clinical judgment in respect of the care of a particular patient or other professional judgment in any decision-making process. The Canadian Agency for Drugs and Technologies in Health (CADTH) does not endorse any information, drugs, therapies, treatments, products, processes, or services.

While care has been taken to ensure that the information prepared by CADTH in this document is accurate, complete, and up-to-date as at the applicable date the material was first published by CADTH, CADTH does not make any guarantees to that effect. CADTH does not guarantee and is not responsible for the quality, currency, propriety, accuracy, or reasonableness of any statements, information, or conclusions contained in any third-party materials used in preparing this document. The views and opinions of third parties published in this document do not necessarily state or reflect those of CADTH.

CADTH is not responsible for any errors, omissions, injury, loss, or damage arising from or relating to the use (or misuse) of any information, statements, or conclusions contained in or implied by the contents of this document or any of the source materials.

This document may contain links to third-party websites. CADTH does not have control over the content of such sites. Use of third-party sites is governed by the third-party website owners' own terms and conditions set out for such sites. CADTH does not make any guarantee with respect to any information contained on such third-party sites and CADTH is not responsible for any injury, loss, or damage suffered as a result of using such third-party sites. CADTH has no responsibility for the collection, use, and disclosure of personal information by third-party sites.

Subject to the aforementioned limitations, the views expressed herein are those of CADTH and do not necessarily represent the views of Canada's federal, provincial, or territorial governments or any third party supplier of information.

This document is prepared and intended for use in the context of the Canadian health care system. The use of this document outside of Canada is done so at the user's own risk.

This disclaimer and any questions or matters of any nature arising from or relating to the content or use (or misuse) of this document will be governed by and interpreted in accordance with the laws of the Province of Ontario and the laws of Canada applicable therein, and all proceedings shall be subject to the exclusive jurisdiction of the courts of the Province of Ontario, Canada.

The copyright and other intellectual property rights in this document are owned by CADTH and its licensors. These rights are protected by the Canadian *Copyright Act* and other national and international laws and agreements. Users are permitted to make copies of this document for non-commercial purposes only, provided it is not modified when reproduced and appropriate credit is given to CADTH and its licensors.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **Requests@CADTH.ca**

Abbreviations

AGREE	Appraisal of Guidelines, Research and Evaluation
AMSTAR	Assessing the Methodological Quality of Systematic Reviews
NSAIDS	Non-steroidal anti-inflammatory drugs
PRICE	Protection, rest, ice, compression, and elevation
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized controlled trial
RICE	Rest, ice, compression, and elevation
SR	Systematic review
VAS	Visual analog scale

Context and Policy Issues

In Canada, 35% of injuries are related to sport or exercise.[1] Ankle injuries (sprain or strain) are among the most common types of injury (51%) presenting to the primary care offices and emergency departments.[1] There are three types of ankle sprain, the location of which is determined by the mechanism of injury: lateral ankle sprain (most common), medial ankle sprain, and syndesmotic sprain (high ankle sprain).[2] Ankle sprain is classified based on clinical signs and functional loss, as follows: grade 1 (mild stretching of a ligament), grade 2 (more severe injury involving incomplete tear of a ligament), and grade 3 (complete tear of a ligament).[2]

The immediate goal for treatment of ankle sprain is to reduce pain and swelling. The RICE (rest, ice, compression, elevation) approach has been commonly used in the first two to three days following injury, although evidence on the effectiveness of RICE alone is still lacking.[2] Non-steroidal anti-inflammatory drugs (NSAIDs) can be used to reduce pain. However, the use of NSAIDs may delay the natural healing process due to their inflammatory suppressed mechanism.[3] Other modes of non-pharmacological treatment of ankle sprain, depending on the severity of the injury, include exercise, immobilization, manual mobilization and rehabilitation.[2] Early mobilization through exercise right after lateral ankle sprain is often the integral component of the treatment.[2] However, this is in direct contrast to the RICE method, and the clinical effectiveness of exercise remains controversial, despite the existence of multiple exercise-based physiotherapy programs with different content and parameters for treatment of ankle sprain.[4-6]

The aim of this report is to review the evidence regarding the clinical effectiveness of exercise for the treatment of individuals with ankle sprain. This report also aims to review the evidence-based guidelines regarding the use of non-pharmacological interventions for the treatment of individuals with ankle sprain.

Research Questions

1. What is the clinical effectiveness of exercise for the treatment of individuals with ankle sprain?
2. What are the evidence-based guidelines regarding the use of non-pharmacological interventions for the treatment of individuals with ankle sprain?

Key Findings

This review included two systematic reviews and two randomized controlled trials regarding the clinical effectiveness of exercise for the treatment of individuals with ankle sprain, and one guideline regarding the use of non-pharmacological interventions in this population.

Based on the findings of the systematic reviews that compared structured exercise-based rehabilitation plus usual care versus usual care alone, or supervised rehabilitation versus home exercise, there were no significant differences between treatment groups in terms of foot and ankle function, pain, subjective ankle instability, or subjective recovery. The results for ankle sprain recurrence were mixed. Specifically, one systematic review showed significant reduction in ankle sprain recurrence in those who received exercise-based rehabilitation plus usual care compared with usual care alone at 7 to 12 months, but not at 3 to 6 months of follow-up. In the other systematic review, one study showed that there was a significantly lower proportion of patients with recurrent ankle sprain in the supervised rehabilitation versus home exercise group, while the other study found no significant difference between groups.

One randomized controlled trial found that compared with the traditional PRICE (protection, rest, ice, compression, and elevation) treatment, early mobilization using a stretch band ankle traction technique resulted in no significant differences in ankle strength, ankle function, pain and number of days to returning to sport in children and adolescents.

Another randomized controlled trial compared Wii Fit™ exercise therapy with conventional physical therapy and with no therapy, and found no significant differences between treatment groups for ankle function, pain, time to returning to sport, and self-reported satisfaction and effectiveness.

The included guideline recommends the use exercise therapy in combination with functional support (i.e., ankle brace) or manual mobilization in the treatment of acute lateral ankle sprain (level 2 evidence). The guideline does not recommend the use of RICE (rest, ice, compression, and elevation) alone (level 2 evidence), or other therapies such as acupuncture, vibration therapy, laser therapy, ultrasound, electrotherapy, short wave therapy and Bioptron light therapy (level 3 evidence) in the treatment of acute lateral ankle sprain. The strength of the recommendation statements were not indicated.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were ankle sprains and exercise or other non-pharmacologic therapies. Search filters were applied to limit retrieval to guidelines for question two only. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2015 and March 5, 2020.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients (of any age) with ankle sprain of any grade
Intervention	Q1: Exercise interventions (e.g., mobilization, balance exercises, strength training, range of motion exercises, exercise guided by a physiotherapist) Q2: Non-pharmacological interventions (e.g., exercise, external supports, RICE method, immobilization)
Comparator	Q1: Pharmacotherapy (e.g., ibuprofen, acetaminophen, opioids); non-pharmacological treatments (e.g., external supports, immobilization, RICE method, alternative exercises); surgery; no treatment (i.e., no exercise); any combination of the listed comparators (e.g., pharmacotherapy and exercise) Q2: No comparator
Outcomes	Q1: Clinical effectiveness (e.g., ankle function [e.g., Karlsson ankle function scale score], pain, quality of life, time to return to activities, risk for re-injuries) Q2: Recommendations regarding best practices (e.g., treatment protocols, appropriate patient populations)
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, and evidence-based guidelines

RICE = rest, ice, compression, and elevation.

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria in Table 1 or if they were published prior to 2015. The identified primary studies that were captured in the included systematic reviews (SR) were excluded. A SR that had relevant included studies fully captured in a more recent included SR was also excluded.

Critical Appraisal of Individual Studies

The included SRs were critically appraised by one reviewer using the Assessing the Methodological Quality of Systematic Reviews version 2 (AMSTAR 2) checklist.[7] The critical appraisal checklist of the Joanna Briggs Institute was used to assess the quality of the included randomized controlled trials (RCTs).[8] The quality of the included evidence-based guideline was assessed using the Appraisal of Guidelines for Research and Development (AGREE) II instrument.[9] Summary scores were not calculated for the included studies; rather, the strengths and limitations were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 520 citations were identified in the literature search. Following screening of titles and abstracts, 492 citations were excluded and 28 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of the 28 potentially relevant articles, 23 publications were excluded for various reasons, while five publications met the inclusion criteria and were included in this report. These comprised two SRs, two primary studies

(both RCTs), and one guideline. Appendix 1 presents the PRISMA flowchart[10] of the study selection.

Summary of Study Characteristics

The detailed characteristics of the included SRs,[11,12] (Table 2) primary studies[13,14] (Table 3) and one guideline[15] (Table 4) are presented in Appendix 2.

Study Design

Both included SRs[11,12] selected only RCTs, which were identified from searches of multiple databases from database inception to January 2017 and to September 2014, respectively. The PEDro scale (a 10-point scale) was used to assess the methodological quality of RCTs in both SRs. One RCT[5] was included in both SRs. This RCT was included in the meta-analysis of one SR,[11] and narratively synthesized in the other SR.[12] The findings of that RCT were therefore excluded from the summary of findings of the latter SR (in order to avoid double-counting those results).

Both included primary studies[13,14] were single (assessor) blinded, parallel RCTs. The required sample size was calculated a priori in one RCT,[13] but not in the other.[14] Data were analyzed using the intention-to-treat approach in both RCTs.

The included guideline[15] was developed by a multidisciplinary guideline committee in the Netherlands. The committee included healthcare professionals who were directly or indirectly involved in the care of patients with lateral ankle sprain. The guideline used systematic methods to search for, select, and synthesize evidence. The recommendations were evidence-based and consensus based. The quality of the included studies was assessed and classified from level A1 (SR) to level D (expert opinion). Each statement of the recommendations was not rated, but only presented with the associated level of evidence (level 1 = Research of level A1 [SR] or at least two examinations of level A2 [RCTs], to level 4 = opinion of experts). The guideline was peer-reviewed and published in 2018.

Country of Origin

The included SRs were conducted by authors from Ireland[11] and USA.[12] The included RCTs were conducted by authors from USA[13] and Switzerland.[14] The included guideline was conducted by authors from the Netherlands.[15]

Patient Population

Both SRs[11,12] included adult patients with acute ankle sprain recruited from emergency departments, physician offices or physical therapy clinics. The mean age of patients was from 25 to 36 years in one SR[11] and from 34 to 39 years in the other.[12]

One RCT[13] included children and adolescents with acute lateral ankle sprain (mostly grade 2; 71%) recruited from Nationwide Children's Hospital sports medicine or physical therapy clinics, with mean age of 14.5 years. The other RCT[14] included adult patients with grade 1 (61%) and grade 2 (39%) lateral ankle sprain, and with mean age of 34 years.

The target population for the included guideline[15] was patients with acute lateral ankle sprain. The intended users of the guideline were healthcare professionals.

Interventions and Comparators

One SR[11] included seven RCTs (n = 1,417; ranging from 48 to 522 participants) that compared structured exercise-based rehabilitation plus usual care with usual care alone. The training volume of the exercise-based rehabilitation programs in the cited RCTs consisted of 10 to 60 minutes per session, five to 84 total number of exercises, and 3.5 to 21 hours of total rehabilitation time (median 12 hours). Exercise content varied between programs, although most placed emphasis on postural balance. Usual care in the cited RCTs consisted of various components of PRICE (protection, rest, ice, compression and elevation), with or without advice on early weight-bearing and basic ankle mobilization.

The other SR[12] included four RCTs (n = 322; ranging from 47 to 102 participants) that compared supervised rehabilitation exercise with unsupervised home exercise. Two cited RCTs compared nine 30-minute treatment sessions (that included balance, walking, running and jump exercise) with advice for early mobilization/weight bearing and home exercises with written instructions. One cited RCT used a three-phase intervention protocol based on severity and progress of recovery (acute, mobilization and strengthening). The components included active range of motion, stretching, strengthening, taping/strapping, balance training and dynamic and functional training. Patients in the comparator group received instruction booklet, tubular bandage, resistance bands, and wobble boards to do the exercises at home. The last relevant RCT provided group physical therapy for the intervention group that involved early ankle mobilization, strength, mobility, and balance. The comparator group received similar information, but did the exercises at home.

One included RCT[13] compared early elastic band mobilization provided by therapists with PRICE instructed by physicians. The elastic band mobilization involved three directions of pulling: horizontal elastic band traction, vertical elastic band traction, and horizontal elastic band traction with overpressure setup. Both groups received standard physical therapy care, and patients had to complete all three phases of the standard therapy before being discharged.

The other included RCT[14] had three treatment groups that compared Wii Fit™ exercise therapy, conventional physical therapy, and no exercise therapy (control). In the Wii Fit™ exercise group, patients were provided with Wii balance board, Wii Fit™ software, and detailed instructions to perform exercise at home. Patients practiced with physical therapist on four preselected balance games: ski slalom, penguin slide, table tilt and balance bubble. Patients independently carried out their rehabilitation program for 6 weeks, with a minimum 2 times per week, and 30 min per session. In the conventional physical therapy group, patients received education on joint mobilization, muscle strengthening, and proprioceptive exercises, and practiced at home in nine 30-minute sessions over 6 weeks. In the control group, patients did not receive any exercise therapy or any further advice or instructions during follow-up periods, but they received standard instructions at the emergency department.

The interventions and practices considered in the included guideline[15] were diagnosis, treatment and prevention for ankle sprain. Treatment interventions covered in the guideline included RICE, NSAIDs, immobilization, functional treatment (i.e., functional support, exercise, manual mobilization) and other therapies (e.g., acupuncture, vibration therapy, laser therapy, ultrasound, electro therapy, short wave therapy and Bioptron light therapy).

Outcomes

The outcomes considered in both SRs[11,12] were patient-reported outcomes and recurrence of ankle sprain. Patient-reported outcomes in one SR[11] were Karlsson scores (100-point scale) to evaluate ankle function, Foot and Ankle Outcome score (5 subscales: pain, symptoms, activities of daily living, sport/recreation, and quality of life; maximum score of 100), perceived ankle instability, pain, and adherence to treatment. In the other SR,[12] pain, subjective ankle instability, and subjective recovery were considered as patient-reported outcomes.

One included RCT[13] assessed ankle strength using figure eight tape measurement, and patient-reported outcomes including Foot and Ankle Disability Index (26-item questionnaire with 5-point scale), Foot and Ankle Disability Index sport (additional 8 items), pain using numeric pain rating scale from 0 (no pain) to 10 (worst imaginable pain), and time to return to sport. The outcomes in the other included RCT[14] were patient-reported outcomes including Foot and Ankle Ability Measure (using both activities of daily living subscale and sport subscale), pain at rest and during walking (measured by visual analog scale [VAS], a 10-point scale with 0 for “no pain” and 10 for “severe pain”), and self-reported satisfaction and effectiveness.

The included guideline[15] had recommendations regarding diagnosis, treatment and prevention of ankle sprain. Potential harms of interventions, patients’ perspectives, costs, and organizational aspects were also considered in the development of the recommendations.

Summary of Critical Appraisal

The detailed quality assessments of the included SRs,[11,12] (Table 5) RCTs,[13,14] (Table 6) and guideline[15] (Table 7) are presented in Appendix 3.

The authors of both SRs[11,12] provided appropriate research questions, explanations for selection of the study designs for inclusion in the review, and used comprehensive literature search strategies. The authors performed study selection and data extraction in duplicate, and described the included studies in adequate detail. The authors of both SRs used the PEDro scale (a 10-point scale) to assess the quality of the included RCTs. The authors performed meta-analysis using appropriate methods for statistical combination of the results. The risk of bias in individual studies was accounted for when interpreting and discussing the results. The authors provided satisfactory explanations for any heterogeneity observed in the results. Conflicts of interest and financial disclosure were declared in the reviews.

In terms of limitations, the authors of both SRs[11,12] did not provide explicit statements that protocols had been established prior to the conduct of the reviews. The authors did not provide lists of excluded studies or the sources of funding for the included studies.

In both included RCTs,[13,14] there were some concerns regarding performance bias arising from open-label design, in which participants were aware of their assigned intervention during the trials, and physicians and care givers who delivered the interventions were also aware of participants’ assigned interventions. However, detection bias would probably be minimized due to blinding of outcome assessors in both RCTs. Allocation concealment (i.e., during randomization) was reported in one RCT[14] and not in the other.[13] Treatment groups in both RCTs had numerically similar baseline characteristics (not compared statistically), and were treated identically other than the intervention of interest. In both

RCTs, analyses were conducted based on the intention-to-treat population, and outcomes were measured in a reliable way and appropriate statistical analysis was used. The trial design (i.e., parallel RCT) was appropriate. Average dropout rates in both RCTs were high (21%[14] and 24%[13]), mainly due to loss to follow-up. In one RCT,[13] dropout rate was higher in elastic band traction compared to PRICE (31.8% versus 15.8%). In the other RCT,[14] the dropout rates were 20%, 13% and 30% for Wii Fit™ exercise therapy, conventional physical therapy, and no exercise therapy, respectively.

The included guideline[15] was explicit in terms of scope and purpose (i.e., objectives, health questions and populations), and had clear presentation (i.e., specific and unambiguous recommendations, different options for management of the condition or health issue, and easy to find key recommendations). In terms of stakeholder involvement, the guidelines clearly defined target users and the development groups included individuals from all relevant professional groups, and sought the views and preferences of the target populations. For rigour of development, the guidelines explicitly reported details of systematic searches for evidence, criteria for selecting evidence, strengths and limitations of the body of evidence, methods of formulating the recommendations, health benefits, side effects, and risks in formulating the recommendations, and were peer-reviewed prior to publication. The guideline provided a procedure for updating. For applicability, the guideline was explicit in terms of facilitators and barriers to application, advice and/or tools on how the recommendations can be put into practice, resource (cost) implications, and monitoring and or auditing criteria. For editorial independence, the guideline declared that the funding body had no influence on the content of the guidelines. The competing interests of guideline development group members were reported. Overall, the included guideline had high methodological quality.

Summary of Findings

The main findings and authors' conclusions of the SRs,[11,12] (Table 8), RCTs,[13,14] (Table 9), and guideline[15] (Table 10) are presented in Appendix 4.

Clinical Effectiveness of Exercise

Foot and Ankle function

- Structured exercise-based rehabilitation plus usual care versus usual care alone: One RCT cited in the SR[11] found no significant difference in foot and ankle function (as measured by the Karlsson score) between treatment groups at 4 months of follow-up. Two RCTs cited in the SR[11] also found no significant difference in Foot and Ankle Outcome score between treatment groups at 3 and 6 months of follow-up.
- Early elastic band mobilization versus PRICE: One included RCT[13] showed that, although both groups showed significant improvements at discharge compared to baseline ($P < 0.01$), there were no significant difference between treatment groups for ankle strength and ankle function (Foot and Ankle disability index).
- Wii Fit™ exercise therapy versus conventional physical therapy versus no therapy: One included RCT[14] showed that, although all groups showed significant improvements in foot and ankle ability compared to baseline ($P \leq 0.01$), there was no significant difference between groups.

Pain

- Structured exercise-based rehabilitation plus usual care versus usual care alone: One RCT cited in the SR[11] found no significant difference in pain at 3 months of follow-up.
- Supervised rehabilitation versus home exercise: Two RCTs cited in the SR[12] found no significant difference between groups for pain at 8 weeks and 12 months of follow-up.
- Early elastic band mobilization versus PRICE: One included RCT[13] showed that, although both groups showed significant improvements at discharge compared to baseline ($P < 0.01$), there was no significant difference between treatment groups for pain.[13]
- Wii Fit™ exercise therapy versus conventional physical therapy versus no therapy: One included RCT[14] showed that, although all groups showed significant improvements in pain during walking compared to baseline ($P \leq 0.018$), there was no significant difference between groups.[14]

Subjective ankle instability

- Structured exercise-based rehabilitation plus usual care versus usual care alone: Three RCTs cited in the SR[11] reported this outcome and found no significant difference between treatment groups for subjective ankle instability at 3 and 12 months of follow-up.
- Supervised rehabilitation versus home exercise: Two RCTs cited in the SR[12] reporting this outcome found no significant difference between groups for subjective ankle instability at 8 weeks, 3 months and 12 months of follow-up.

Time to return to sport

- Early elastic band mobilization versus PRICE: One included RCT[13] found that there was no significant difference between treatment groups for number of days for returning to sport.[13]
- Wii Fit™ exercise therapy versus conventional physical therapy versus no therapy: One included RCT[14] found that there was no significant difference between treatment groups in mean delay for returning to sport.[14]

Ankle sprain recurrence

- Structured exercise-based rehabilitation plus usual care versus usual care alone: Pooled results from meta-analysis in the SR[11] showed that structured exercise-based rehabilitation plus usual care significantly reduced recurrence of ankle injury at 7 to 12 months of follow-up ($P = 0.0002$), but not at 3 to 6 months of follow-up.
- Supervised rehabilitation versus home exercise: Two RCTs cited in the SR[12] reported mixed findings. One RCT found that supervised rehabilitation significantly prevented recurrent ankle sprain compared to home exercise at 12 months after initial injury. Other RCT found no significant difference between treatment groups.

Self-reported satisfaction and effectiveness

- Supervised rehabilitation versus home exercise: Three RCTs cited in the SR[12] found no significant difference between treatment groups in subjective recovery.
- Wii Fit™ exercise therapy versus conventional physical therapy versus no therapy: One included RCT[14] found that there was no significant difference between treatment groups in satisfaction and effectiveness.[14]

Adherence

- Structured exercise-based rehabilitation plus usual care versus usual care alone: Two RCTs included in the SR[11] found adherence was low in the exercise-based rehabilitation group. Specifically, one RCT reported that 23% of participants were fully compliant across all 8 weeks of rehabilitation, 29% were partially compliant, and 35% were noncompliant (definitions of "compliant", "partially compliant" and "noncompliant" were not provided). Another included RCT found that 27% of participants attended less than 20% of the scheduled appointments for rehabilitation exercises supervised by physical therapist. Adherence was not reported in the usual care groups.

Guidelines Regarding Non-Pharmacological Interventions for Ankle Sprain

The guideline[15] does not recommend the use of RICE (rest, ice, compression, elevation) alone in the treatment of acute lateral ankle sprain, as there was no evidence that RICE alone could have a positive effect on pain, swelling or function (*Level of evidence: 2*). The guideline recommends that the combination of functional support (i.e., ankle brace) and exercise therapy for treatment of acute lateral ankle sprain is preferred over immobilization with plaster cast or rigid support. The guideline noted that there was still contradicting evidence regarding supervised and non-supervised exercise. In cases where immobilization is needed to reduce pain and edema, the guideline does not recommend its use for more than 10 days, and after immobilization starting functional treatment is recommended (*Level of evidence: 2*). The guideline recommends a combination of manual mobilization and exercise therapy to enhance joint mobilization in acute lateral ankle sprain (*Level of evidence: 3*). The guideline does not recommend the use of other therapies such as acupuncture, vibration therapy, laser therapy, ultrasound, electrotherapy, short wave therapy and Bioptron light therapy in the treatment of acute lateral ankle sprain (*Level of evidence: 2*).

Limitations

There were limited numbers of studies included in the SRs regarding rehabilitation exercises. The heterogeneity of the exercise training programs among studies made it difficult to ascertain the effectiveness of exercise therapy. The subjective and objective outcome measures and follow-up periods among studies were not consistent. One SR[11] included patients with ankle sprain of grade 1, 2 and 3, while the other SR[12] did not report the diagnostic grading of ankle injury. The heterogeneity of the populations in terms of degree of injury could be important for interpreting the findings. It remains unclear whether the findings in the SRs are generalizable to the general population setting or to competitive sport medicine settings, as the populations in the included studies were not clearly defined.

This review identified only one RCT that compared the effect of early mobilization using a stretch band ankle traction technique with PRICE in children and adolescents. This review

also identified only one RCT that compared Wii Fit™ exercise therapy with conventional physical therapy and with no therapy. Participants in one included RCT[13] were mostly of grade 2 (71%), while in the other included RCT,[16] most patients were of grade 1 (61%). It was unclear if the findings of these included RCTs could be generalizable to populations other than those under investigation. Both studies did not measure compliance as an outcome.

There was no evidence on the effectiveness of exercise interventions compared to pharmacotherapy, surgery, or exercise in combination with pharmacotherapy or surgery, for the treatment of ankle sprain.

The included guideline did not grade its recommendations (e.g., as “strong” or “weak” recommendations), which were supported by levels of evidence only.

Conclusions and Implications for Decision or Policy Making

This review included two SRs[11,12] and two RCTs,[13,14] regarding the clinical effectiveness of exercise for the treatment of individuals with ankle sprain and one guideline[15] regarding the use of non-pharmacological interventions in this population.

Based on findings of one SR,[11] compared to usual care alone, structured exercise-based rehabilitation plus usual care resulted in no significant differences in terms of foot and ankle function, pain, and subjective ankle instability. There were mixed results for ankle sprain recurrence, such that there was significant reduction in favor of exercise-based rehabilitation plus usual care for ankle reinjury compared with usual care alone at 7 to 12 months, but not at 3 to 6 months of follow-up.

Based on the findings of another SR,[12] supervised rehabilitation compared to home exercise resulted in no significant differences in terms of pain, subjective ankle instability, and subjective recovery. There were also mixed results for ankle sprain recurrence; one study showed that there was a significantly lower proportion of patients with recurrent ankle sprain in the supervised rehabilitation versus home exercise group, while the other included study found no significant difference between groups.

One RCT[13] found that there were no significant differences between early mobilization using a stretch band ankle traction technique and PRICE treatment in outcomes such as ankle strength, ankle function, pain and number of days to returning to sport in children and adolescents.

One RCT that compared Wii Fit™ exercise therapy with conventional physical therapy and with no therapy found no significant differences between treatment groups for ankle function, pain, time to returning to sport, and self-reporting satisfaction and effectiveness.

The included guideline recommends the use exercise therapy in combination with functional support (i.e., ankle brace) or manual mobilization in the treatment of acute lateral ankle sprain. The guideline does not recommend the use of RICE alone in the treatment of acute lateral ankle sprain. The guideline also does not recommend the use of other therapies such as acupuncture, vibration therapy, laser therapy, ultrasound, electrotherapy, short wave therapy and Bioptron light therapy in the treatment of acute lateral ankle sprain.

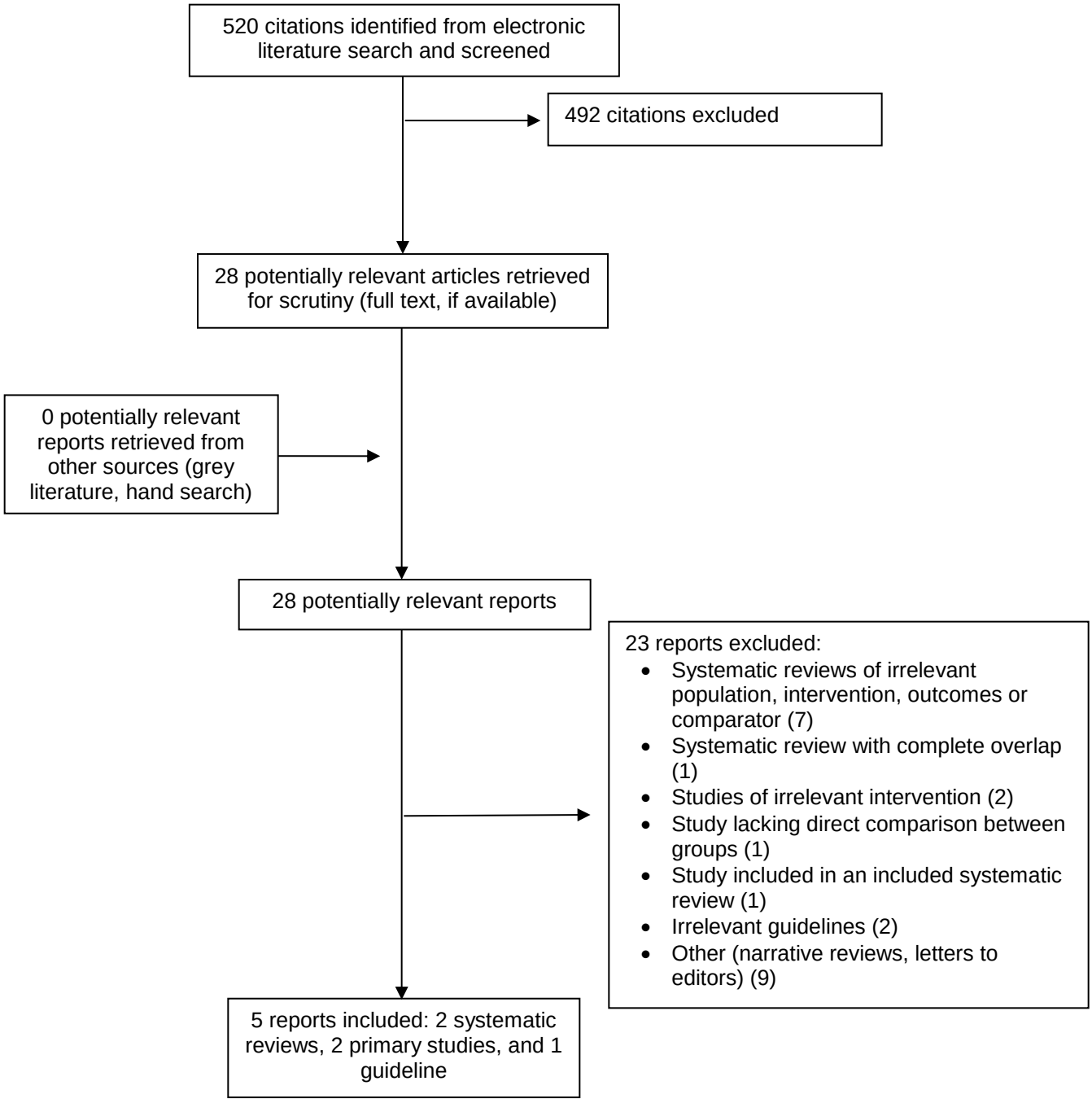
Taken together, evidence in this review showed that overall there were no significant differences in the effectiveness across different exercise interventions compared with indicated comparators for the treatment of ankle sprain. Future well-controlled studies are

needed to determine the effectiveness of different types of exercise programs with specific content and volume that is optimally suited for the general population, competitive sport medicine settings, or populations of different grades of ankle injury.

References

1. Billette J-M, Janz T. Injuries in Canada: Insights from the Canadian Community Health Survey. Ottawa (ON): Statistics Canada; 2011: https://www150.statcan.gc.ca/n1/pub/82-624-x/2011001/article/11506-eng.htm. Accessed 2020 Mar 20.
2. Maughan KL. Ankle sprain. In: Post TW, ed. *UpToDate*. Waltham (MA): UpToDate; 2020: www.uptodate.com. Accessed 2020 Mar 20.
3. Stovitz SD, Johnson RJ. NSAIDs and musculoskeletal treatment: what is the clinical evidence? *Phys Sportsmed.* 2003;31(1):35-52.
4. van der Wees PJ, Lenssen AF, Hendriks EJ, Stomp DJ, Dekker J, de Bie RA. Effectiveness of exercise therapy and manual mobilisation in ankle sprain and functional instability: a systematic review. *Aust J Physiother.* 2006;52(1):27-37.
5. van Rijn RM, van Os AG, Kleinrensink GJ, et al. Supervised exercises for adults with acute lateral ankle sprain: a randomised controlled trial. *Br J Gen Pract.* 2007;57(543):793-800.
6. Brison RJ, Day AG, Pelland L, et al. Effect of early supervised physiotherapy on recovery from acute ankle sprain: randomised controlled trial. *BMJ.* 2016;355:i5650.
7. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ.* 2017;358:j4008. http://www.bmj.com/content/bmj/358/bmj.j4008.full.pdf. Accessed 2020 Mar 20.
8. Checklist for Randomized Controlled Trials. Adelaide (AU): Joanna Briggs Institute; 2017: https://joannabriggs.org/sites/default/files/2019-05/JBI_RCTs_Appraisal_tool2017_0.pdf. Accessed 2020 Mar 20.
9. Agree Next Steps Consortium. The AGREE II Instrument. [Hamilton, ON]: AGREE Enterprise; 2017: https://www.agreetrust.org/wp-content/uploads/2017/12/AGREE-II-Users-Manual-and-23-item-Instrument-2009-Update-2017.pdf. Accessed 2020 Mar 20.
10. 10. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol.* 2009;62(10):e1-e34.
11. 11. Bleakley CM, Taylor JB, Dischiavi SL, Doherty C, Delahunt E. Rehabilitation Exercises Reduce Reinjury Post Ankle Sprain, But the Content and Parameters of an Optimal Exercise Program Have Yet to Be Established: A Systematic Review and Meta-analysis. *Arch Phys Med Rehabil.* 2019;100(7):1367-1375.
12. 12. Feger MA, Herb CC, Fraser JJ, Glaviano N, Hertel J. Supervised rehabilitation versus home exercise in the treatment of acute ankle sprains: a systematic review. *Clin Sports Med.* 2015;34(2):329-346.
13. 13. Iammarino K, Marrie J, Selhorst M, Lowes LP. Efficacy of the Stretch Band Ankle Traction Technique in the Treatment of Pediatric Patients with Acute Ankle Sprains: A Randomized Control Trial. *Int J Sports Phys Ther.* 2018;13(1):1-11.
14. 14. Punt IM, Ziltener JL, Monnin D, Allet L. Wii Fit TM exercise therapy for the rehabilitation of ankle sprains: Its effect compared with physical therapy or no functional exercises at all. *Scand J Med Sci Sports.* 2016;26(7):816-823.
15. 15. Vuurberg G, Hoorntje A, Wink LM, et al. Diagnosis, treatment and prevention of ankle sprains: update of an evidence-based clinical guideline. *Br J Sports Med.* 2018;52(15):956.
16. 16. Punt IM, Armand S, Ziltener JL, Allet L. Effect of Wii Fit TM exercise therapy on gait parameters in ankle sprain patients: A randomized controlled trial. *Gait Posture.* 2017;58:52-58.

Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes
Bleakley et al., 2019[11] Ireland Funding: Not reported	Objective: To determine if exercise-based rehabilitation reduces reinjury following acute ankle sprain. Total 7 RCTs (n = 1,417; ranging from 48 to 522) Quality assessment tool: PEDro scale (a 10-point scale) Databases (search date): Cochrane Central Register of Controlled Trials (1991 to January 2017), EMBASE (1974 to January 2017), and MEDLINE (1946 to January 2017) Data analysis: Meta-analysis; subgroup analysis based on training volume and exercise content; sensitivity analysis based on study quality.	Patients with ankle sprain recruited from emergency department and/or primary care facilities Mean age: Range from 25 to 36 years % Female: Range from 32 to 56 Time since injury at recruitment: From acute period to less than 2 months Diagnosis: Ankle sprain of grade 1, 2 or 3 Previous injury to ankle: 3 studies not stated; 4 studies with mixed population (first time injury and reinjury) Follow-up: range from 3 months to 12 months	Intervention: Structured exercise-based rehabilitation plus usual care Training volume: – Minutes per rehabilitation session: 10 to 60 – Total number of exercises: 5 to 84 – Total rehabilitation time: 3.5 to 21 hours (median 12 hours) Exercise content: Varied between programs. Most programs placed emphasis on postural balance. Comparator: Usual care (various components of PRICE [protection, rest, ice, compression, and elevation]) either with or without advice on early weight-bearing and basic ankle mobilization. Follow-up: range from 3 months to 12 months	– Reinjury – Patient-reported outcomes (Karlsson scores [100-point scale] for ankle function; Foot and Ankle Outcome score [5 subscales: pain, symptoms, activities of daily living, sport/recreation, and quality of life; max score of 100]; perceived ankle instability; and pain) – Adherence
Feger et al., 2015[12] USA Funding: Not reported	Objective: To compare the efficacy of supervised rehabilitation versus home exercise in treatment of acute ankle sprain. Total 4 RCTs (n = 322) Quality assessment tool: PEDro scale Databases: Pubmed, Web of Science, CINAHL, and Medline Search date: Database inception to September 2014	Patients with acute lateral ankle sprain recruited from physician offices, emergency departments, or physical therapy clinics. Mean age: Range from 34 to 39 years Diagnosis: Grade not specified Time since injury at recruitment: two studies included patients who were treated within one	Intervention: Supervised rehabilitation – Two studies had nine 30-minute treatment sessions that included balance, walking, running and jump exercises – One study used a three-phase intervention protocol based on severity and progress of recovery (acute, mobilization and strengthening). The components included active range of motion, stretching, strengthening,	– Patient self-reported outcomes (pain, subjective ankle instability, subjective recovery; expressed as Cohen's *d* effect sizes) – Ankle sprain recurrence

First Author, Publication Year, Country, Funding	Objectives, Types and Numbers of Primary Studies Included, Quality Assessment Tool, Databases and Search Date	Patient Characteristics	Interventions and comparators	Outcomes
	Data analysis: Meta-analysis	week of injury; two studies did not report time since injury.	taping/strapping, balance training and dynamic and functional training. – One study had education on early ankle mobilization, strength, mobility, and balance, and group physical therapy 2 hours per week. Comparator: Unsupervised home exercise – Two studies advised for early mobilization/weight bearing and home exercises with written instructions – One study provided an instruction booklet, Tubigrip, Thera-band resistance bands, and wobble boards. – One study gave education on early ankle mobilization, strength, mobility and balance with a balance board. Follow-up: 6 weeks to 1 year	

PRICE = protection, rest, ice, compression, and elevation; RCTs = randomized controlled trials.

Table 3: Characteristics of Included Primary Studies

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
Iammarino et al., 2018[13] USA Funding: Not reported	Single blinded, parallel, 1:1 ratio RCT Sample size calculation: Yes ITT: Yes	Children and adolescents with acute lateral ankle sprain recruited from Nationwide Children's Hospital sports medicine or physical therapy clinics	Early elastic band mobilization (n = 22) provided by therapists. Three directions of pulling with elastic band are horizontal elastic band traction, vertical elastic band traction, and	PRICE (n = 19) instructed by physicians Plus standard treatment program involving three phases of physical therapy, from ankle mobilization to	– Pain (NPRS) – Ankle range of motion – Ankle muscle strength – Self-reported outcome measures (FADI [26-item

First Author, Publication Year, Country, Funding	Study Design and Analysis	Patient Characteristics	Interventions	Comparators	Outcomes
	Statistical analysis: Appropriate	Mean age: 14.5 years (range 10 to 17 years) % Female: 46 Diagnosis: Grade 1 (24%), grade 2 (71%), grade 3 (5%) Average days since injury: 4.7 Pain (NPRS): 4.9	horizontal elastic band traction with overpressure setup. Plus standard treatment program involving three phases of physical therapy, from ankle mobilization to treadmill walk to treadmill running	treadmill walk to treadmill running	questionnaire] and FADI sport module [additional 8 items]) for foot and ankle disability – Time to return to sport
Punt et al. 2016[14] Switzerland Funding: Office Fédéral du Sport grant	Single blinded, parallel, 1:1:1 ratio RCT Sample size calculation: Not reported ITT: Yes Statistical analysis: Appropriate	Adult patients with mild (grade 1) or moderate (grade 2) lateral ankle sprain Mean age: 34 years % Female: 43 Diagnosis: Grade 1 (61%) and 2 (39%) No previous ankle sprain: 60%	Wii Fit™ exercise therapy: Patients were provided with Wii balance board, Wii Fit™ software, and detailed instructions to perform exercise at home. Patients practiced with physical therapists on 4 preselected balance games: ski slalom, penguin slide, table tilt and balance bubble). Patients independently carried out their rehabilitation program for 6 weeks, minimum 2 times per week, 30 min per session.	Conventional physical therapy: Provided by physical therapist on joint mobilization, muscle strengthening, and proprioceptive exercises. Patients practiced at home in nine 30-minute sessions over 6 weeks. Control: No exercise therapy. Patients received standard instructions at the emergency department.	– Self-reported physical function (FAAM) – Pain (VAS) at rest and while walking – Delay to return to sport – Patient satisfaction with treatment – Subjective perception of the effectiveness of the allocated treatment

FAAM = Foot and Ankle Ability Measure (21-item activities of daily living subscale and an 8-item sports-related subscale, in which each item is scored from 4 “no difficulty” to 0 “unable to do the activity”; FADI = Foot and Ankle Disability Index (26-item questionnaire that uses a 5-point scale [“unable to do” through “no difficulties at all”]); ITT = intention-to-treat; NPRS = numeric pain rating scale from 0 (no pain) to 10 (worst imaginable pain); PRICE = protection, rest, ice, compression, and elevation; RCT = randomized controlled trial; VAS = visual analog scale (10-point scale with 0 for “no pain” and 10 for “severe pain”).

Table 4: Characteristics of Included Guidelines

First Author, Society/Group Name, Publication Year, Country, Funding	Intended Users and Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection and Synthesis	Recommendations Development and Evaluation	Guideline Validation
Vuurberg et al., 2018[15] The Netherlands Funding: The Netherlands organization for health research and development (ZonMw)	Intended users: All healthcare professionals, in both primary care and secondary care settings, involved in the care of patients who have sustained an acute lateral ankle strain. Target population: Patients with acute lateral ankle strain.	Diagnosis, treatment and prevention for lateral ankle sprain	All outcomes related to diagnosis, treatment and prevention for lateral ankle sprain. Potential harm of interventions, patients' perspectives, costs and logistics were also considered.	Systematic methods used to search for evidence, selection and synthesis. This is an update to a previous version of the guideline.	The guideline was developed by a committee including health professionals who were directly involved in the care of patients with lateral ankle sprain in clinical practice or research environments and included general practitioners, emergency physicians, musculoskeletal radiologists, occupational physicians, physical therapists, athletic trainers, sport massage therapists, sport physicians and trauma surgeons. The evidence level[a] was graded based on the methodological quality of the individual studies.[a]	The guideline was peer-reviewed

[a] Level of evidence of conclusions:

Level 1: Research of level A1 (systematic review of at least two independently conducted studies of A2 level) or at least two examinations of level A2 (randomized double-blind comparative clinical research of good quality and sufficient sample size) performed independently of each other with consistent results

Level 2: One examination of level A2 (randomized double-blind comparative clinical research of good quality and sufficient sample size) or at least two examinations of level B (comparative research but not with all the features as mentioned under A2 [this includes patient control research, cohort study]), performed independently of each other

Level 3: One examination of level B (comparative research but not with all the features as mentioned under A2 [this includes patient control research, cohort study]) or C (not comparative research)

Level 4: Opinion of experts

Appendix 3: Critical Appraisal of Included Publications

Table 5: Quality Assessment of Systematic Reviews

AMSTAR 2 Checklist[7]	Bleakley et al., 2019[11]	Feger et al., 2015[12]
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Yes	Yes
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No	No
3. Did the review authors explain their selection of the study designs for inclusion in the review?	Yes	Yes
4. Did the review authors use a comprehensive literature search strategy?	Yes	Yes
5. Did the review authors perform study selection in duplicate?	Yes	Yes
6. Did the review authors perform data extraction in duplicate?	Yes	Yes
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No	No
8. Did the review authors describe the included studies in adequate detail?	Yes	Yes
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	Yes	Yes
10. Did the review authors report on the sources of funding for the studies included in the review?	No	No
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?	Yes	NA
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Yes	No
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?	Yes	No
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Yes	Yes
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	NA	NA
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Yes	Yes

AMSTAR = Assessing the Methodological Quality of Systematic Reviews; NA = not applicable; PICO = Population, Intervention, Comparator, and Outcome; RoB = risk of bias.

Table 6: Quality Assessment of Randomized Controlled Trials

JBI Critical Appraisal Checklist for RCT	Iammarino et al., 2018[13]	Punt et al., 2016[14]
1. Was true randomization used for assignment of participants to treatment groups?	Yes	Yes
2. Was allocation to treatment groups concealed?	NR	Yes
3. Were treatment groups similar at the baseline?	Yes	Yes
4. Were participants blind to treatment assignment?	No	No
5. Were those delivering treatment blind to treatment assignment?	No	No
6. Were outcomes assessors blind to treatment assignment?	Yes	Yes
7. Were treatment groups treated identically other than the intervention of interest?	Yes	Yes
8. Was follow up complete and if not, were differences between groups in terms of their follow up adequately described and analyzed?	Yes (ITT)	Yes (ITT)
9. Were participants analyzed in the groups to which they were randomized?	Yes	Yes
10. Were outcomes measured in the same way for treatment groups?	Yes	Yes
11. Were outcomes measured in a reliable way?	Yes	Yes
12. Was appropriate statistical analysis used?	Yes	Yes
13. Was the trial design appropriate, and any deviations from the standard RCT design (individual randomization, parallel groups) accounted for in the conduct and analysis of the trial?	Yes	Yes

ITT = intention-to-treat; JBI = Joanna Briggs Institute; NR = not reported; RCT = randomized controlled trial.

Table 7: Quality Assessment of Guidelines

AGREE II checklist[9]	Vuurberg et al., 2018[15]
Scope and purpose	--
1. Objectives and target patient population were explicit	Yes
2. The health question covered by the guidelines is specifically described	Yes
3. The population to whom the guideline is meant to apply is specifically described	Yes
Stakeholder involvement	--
4. The guideline development group includes individuals from all relevant professional groups	Yes
5. The views and preferences of the target population have been sought	Yes
6. The target users of the guideline are clearly defined	Yes
Rigour of development	--
7. Systematic methods were used to search for evidence	Yes
8. The criteria for selecting the evidence are clearly described	Yes
9. The strengths and limitations of the body of evidence are clearly described	Yes

AGREE II checklist[9]	Vuurberg et al., 2018[15]
10. The methods of formulating the recommendations are clearly described	Yes
11. The health benefits, side effects, and risks have been considered in formulating the recommendations	Yes
12. There is an explicit link between the recommendations and the supporting evidence	Yes
13. The guideline has been externally reviewed by experts prior to its publication	Yes
14. A procedure for updating the guideline is provided	Yes
Clarity of presentation	--
15. The recommendations are specific and unambiguous	Yes
16. The different options for management of the condition or health issue are clearly presented	Yes
17. Key recommendations are easily identified	Yes
Applicability	--
18. The guideline describes facilitators and barriers to its application	Yes
19. The guidelines provides advice and/or tools on how the recommendations can be put into practice	Yes
20. The potential resource (cost) implications of applying the recommendations have been considered	Yes
21. The guideline presents monitoring and/or auditing criteria	Yes
Editorial independence	--
22. The views of the funding body have not influenced the content of the guideline	Yes
23. Competing interests of guideline development group members have been recorded and addressed	Yes

AGREE = Appraisal of Guidelines, Research and Evaluation.

Appendix 4: Main Study Findings and Authors' Conclusions

Table 8: Summary of Findings of Systematic Reviews

Main Study Findings	Author's Conclusions
Bleakley et al., 2019[11]	
Structure exercise-based rehabilitation plus usual care versus usual care alone[a] Reinjury – At 3 to 6 months (3 RCTs): OR (95% CI) = 0.87 (0.48 to 1.58); I^2 = 0%; P = 0.65 – At 7 to 12 months (4 RCTs): OR (95% CI) = 0.53 (0.38 to 0.73); I^2 = 22%; P = 0.0002 – Sensitivity analysis: At 7 to 12 months (2 high-quality RCTs): OR (95% CI) = 0.60 (0.49 to 0.89) Incidence rate of injury (self-reported) after adjusting for age, type of sport, and level of sports participation – At 12 months (1 RCT): RR (95% CI) = 0.63 (0.45 to 0.88) Patient-reported outcomes – Karlsson score (100-point scale) (to assess ankle function) At 4 months (1 RCT): MD (95% CI) = 1.1 (-0.46 to 2.66) – Overall Foot and Ankle Outcome score (5 subscales: pain, symptoms, activities of daily living, sport/recreation, and quality of life, with a maximum score of 100) At 3 months (1 RCT): MD (95% CI) = 7.7 (-6.8 to 22.3) At 6 months (1 RCT): MD (95% CI) = 8.5 (-6.6 to 23.5) – Subjective ankle instability At 3 months (1 RCT): OR (95% CI) = 1.05 (0.47 to 2.37) At 3 months (1 RCT): OR (95% CI) = 17.2 (0.9 to 325.4) At 12 months (1 RCT): OR (95% CI) = 0.87 (0.4 to 1.89) – Pain At 3 months (1 RCT): OR (95% CI) = 1.00 (0.06 to 16.97) Adherence – 1 RCT: 23% of participants were fully compliant across all 8 weeks of rehabilitation, 29% were partially compliant, and 35% were noncompliant. – 1 RCT: 27% of participants in the supervised rehabilitation exercise group attended less than 20% of the schedule appointments for rehabilitation exercises supervised by physical therapist.	*"Exercise-based rehabilitation reduces the risk of reinjury following acute ankle sprain when compared with usual care alone. Future research must explicitly report all details od administered exercise-based rehabilitation programs."*[11] (p. 1367)
Feger et al., 2015[12]	
Supervised rehabilitation versus home exercise Patient self-reported outcomes at 8 weeks and 12 months (results were reported graphically) – Pain (2 RCTs): No significant difference between groups – Subjective ankle instability (2 RCTs): No significant difference between groups – Subjective recovery (2 RCTs): No significant difference between groups Ankle sprain recurrence (data not shown)	*"Compared with unsupervised home exercise programs resulted in (1) less pain and subjective instability at intermediate follow-up (8 weeks after injury), but no differences in self-reported outcomes at longer follow-up periods (3 and 12 months after injury), (2) greater pain and strength and joint position sense, but worse postural control, at the 4-month follow-up, and (3) inconclusive results regarding*

Main Study Findings	Author's Conclusions
– 1 RCT: There was a significantly lower in the proportion of patients with recurrent ankle sprain in the supervised rehabilitation versus home exercise group at 12 months after initial injury. – 1 RCT: No significant difference between group.	*prevention of recurrent ankle sprain in the 12 months after injury."*[12] (p. 333)

CI = confidence interval; MD = mean difference; OR = odds ratio; PRICE = protection, rest, ice, compression, and elevation; RCTs = randomized controlled trials; RR = relative risk.

[a] Various components of PRICE (protection, rest, ice, compression, and elevation) either with or without advice on early weight-bearing and basic ankle mobilization.

Table 9: Summary of Findings of Included Primary Studies

Main Study Findings	Author's Conclusions
Iammarino et al., 2018[13]	
Early elastic band mobilization versus PRICE Ankle strength: Both groups showed significant improvements at discharge compared to baseline (P < 0.01). There were no significant differences between treatment groups. Self-reported outcomes: Both groups showed improvements at discharge compared to baseline. There were no significant differences between treatment groups for function and pain. – Foot and Ankle Disability Index (26-item questionnaire with 5-point scale) MD (95% CI) = 3.0 (-5.9 to 12.0); P = 0.49 – Foot and Ankle Disability Index sport (additional 8 items) MD (95% CI) = 3.2 (-0.5 to 7.0); P = 0.09 – Pain (NPRS) MD (95% CI) = -0.01 (-1.0 to 1.0); P = 0.98 Number of days for returning to sport: – Early elastic band mobilization: 26.63 ± 14.82 days – PRICE: 26.33 ± 7.14; P = 0.607 Lost to follow-up: – Early elastic band mobilization: 31.8% – PRICE: 15.8%	*"Early mobilization appears to be safe intervention in pediatric patients with an acute ankle sprain. Early mobilization results in similar outcomes when compared to traditional PRICE treatment. A high drop-out rate in both treatment groups was a limitation of this randomized trial."*[13] (p. 1)
Punt et al., 2016[14]	
Wii Fit™ exercise therapy versus conventional physical therapy versus no therapy Foot and Ankle Ability Measure (ADL subscale) at 6 weeks follow-up – Wii Fit™ - Baseline: 80.2 ± 16.3; 6 weeks: 90.7 ± 13.8; P < 0.001 – Physical therapy - Baseline: 70.8 ± 20.3; 6 weeks: 86.8 ± 15.2; P < 0.001 – No therapy - Baseline: 82.8 ± 13.7; 6 weeks: 88.6 ± 13.3; P = 0.001 Foot and Ankle Ability Measure (sport subscale) at 6 weeks follow-up – Wii Fit™ - Baseline: 49.1 ± 31.9; 6 weeks: 73.7 ± 25.5; P < 0.001 – Physical therapy - Baseline: 31.7 ± 25.8; 6 weeks: 64.0 ± 25.5; P < 0.001 – No therapy - Baseline: 52.6 ± 25.6; 6 weeks: 70.0 ± 26.4; P < 0.001 All groups showed significant improvements in foot and ankle ability compared to baseline (P ≤ 0.01). There was no significant difference between groups (P ≥ 0.344)	*"In conclusion, the Wii Fit™ could be used as an exercise therapy to treatment ankle sprain patients. However, Wii Fit™ was not more effective than only physical therapy, or no exercise therapy. Patients who did not receive treatment showed similar results as people who got any kind of exercise therapy."*[14] (p. 816)

Main Study Findings	Author's Conclusions
Pain (VAS during rest) – Wii Fit™ - Baseline: 1.3 ± 2.2; 6 weeks: 0.6 ± 1.8; P = 0.045 – Physical therapy - Baseline: 1.3 ± 2.1; 6 weeks: 0.9 ± 1.7; P = 0.163 – No therapy - Baseline: 1.1 ± 1.4; 6 weeks: 0.7 ± 1.2; P = 0.091 Pain (VAS during walking) – Wii Fit™ - Baseline: 2.6 ± 2.6; 6 weeks: 0.9 ± 1.9; P < 0.001 – Physical therapy - Baseline: 2.6 ± 2.5; 6 weeks: 1.7 ± 2.5; P = 0.018 – No therapy - Baseline: 2.6 ± 2.1; 6 weeks: 1.7 ± 2.1; P = 0.005 All groups showed significant improvements in pain during walking compared to baseline (P ≤ 0.018). There was no significant difference between groups (P ≥ 0.292). Time to return to sport – Wii Fit™: 27.4 days ± 20.3 – Physical therapy: 39.7 days ± 24.9 – No therapy: 23.0 ± 15.5 No significant difference between groups in mean delay for return to sport (P = 0.065) Self-reported satisfaction and effectiveness – Wii Fit™: 82% – Physical therapy: 88% – No therapy: 56% No significant difference between groups in satisfaction (P = 0.247) and effectiveness (P = 0.326) Lost to follow-up – Wii Fit™: 20% – Physical therapy: 13% – No therapy: 30%	

ADL = activities of daily living; CI = confidence interval; FAAM = Foot and Ankle Ability Measure (21-item activities of daily living subscale and an 8-item sports-related subscale, in which each item is scored from 4 "no difficulty" to 0 "unable to do the activity"; MD = mean difference; NPRS = numeric pain rating scale from 0 (no pain) to 10 (worst imaginable pain); VAS = visual analog scale (10-point scale with 0 for "no pain" and 10 for "severe pain").

Table 10: Summary of Recommendations of Included Guidelines

Recommendations
Vuurberg et al., 2018[15]
Rest Ice Compression Elevation (RICE) *"There is no evidence that RICE alone, or cryotherapy, or compression therapy alone has any positive influence on pain, swelling or patient function. Therefore, there is no role for RICE alone in the treatment of acute LAS (Level 2)[a]."*[15] (p. 6) Immobilization (e.g., lower leg cast) *"Use of functional support and exercise therapy is preferred as it provides better outcomes compared with immobilization. If immobilization is applied to treat pain or edema, it should be for a maximum of 10 days after which functional treatment should be commenced (Level 2)[a]."*[15] (p. 7) Functional treatment in terms of functional support (e.g., ankle brace or tape) *"Use of functional support for 4-6 weeks is preferred over immobilization. The use of an ankle brace shows the greatest effects compared with other types of functional support (Level 2)[a]."*[15] (p. 7)

Recommendations
Functional treatment in terms of exercise *"Exercise therapy should be commenced after LAS to optimize recovery of joint functionality. Whether exercise therapy should be supervised or not remains unclear due to contradictory evidence and requires further research (Level 1)[a]."*[15] (p. 7) Functional treatment in terms of manual joint mobilization *"A combination with other treatment modalities, such as exercise therapy, enhances the efficacy of manual joint mobilization and is therefore advised (Level 3)[a]."*[15] (p. 8) Other treatment modalities *"As no strong evidence exists on the effectiveness of these treatment modalities (acupuncture, vibration therapy, laser therapy, ultrasound, electrotherapy, short wave therapy and Bioptron light therapy), they are not advised in the treatment of acute LAS (Level 2)[a]."*[15] (p. 8)

LAS = lateral ankle sprain; RICE = rest, ice, compression, elevation.

[a] Level of evidence of conclusions:

Level 1: Research of level A1 (systematic review of at least two independently conducted studies of A2 level) or at least two examinations of level A2 (randomized double-blind comparative clinical research of good quality and sufficient sample size) performed independently of each other with consistent results

Level 2: One examination of level A2 (randomized double-blind comparative clinical research of good quality and sufficient sample size) or at least two examinations of level B (comparative research but not with all the features as mentioned under A2 [this includes patient control research, cohort study]), performed independently of each other

Level 3: One examination of level B (comparative research but not with all the features as mentioned under A2 [this includes patient control research, cohort study]) or C (not comparative research)

Level 4: Opinion of experts