

Some conservative strategies are effective when added to controlled mobilisation with external support after acute ankle sprain: a systematic review

Chris M Bleakley, Suzanne M McDonough and Domhnall C MacAuley

University of Ulster
N Ireland

Questions: Which intervention(s) best augment early mobilisation and external support after an acute ankle sprain? What is the most appropriate method of preventing re-injury? **Design:** A systematic review of randomised controlled trials published from 1993 to April 2005. **Participants:** People with an acute ankle sprain. **Intervention:** Any pharmacological, physiotherapeutic, complementary or electrotherapeutic intervention added to controlled mobilisation with external support. Immobilisation, surgical intervention, and use of external ankle supports in isolation were excluded. **Outcomes:** Pain, function, swelling, re-injury, and global improvement; assessed at short, intermediate, and long-term follow-up. **Results:** 23 trials were included with a mean PEDro score of 6/10. There was strong evidence that non-steroidal anti-inflammatory drugs can reduce pain and improve short-term ankle function. There was moderate evidence that neuromuscular training decreases functional instability and minimises re-injury; and that comfrey root ointment decreases pain and improves function. There was also moderate evidence that manual therapy techniques improve ankle dorsiflexion. There was no evidence to support the use of electrophysical agents or hyperbaric oxygen therapy. Very few long-term follow-ups were undertaken, and few studies focused on preventing long-term morbidity. **Conclusions:** Non-steroidal anti-inflammatory drugs, comfrey root ointment, and manual therapy can significantly improve short-term symptoms after ankle sprain, and neuromuscular training may prevent re-injury. More high quality studies are needed to develop evidence-based guidelines on ankle rehabilitation beyond the acute phases of injury management. [Bleakley CM, McDonough SM, MacAuley DC (2008) Some conservative strategies are effective when added to controlled mobilisation with external support after acute ankle sprain: a systematic review. *Australian Journal of Physiotherapy* 54: 7–20]

Key words: Systematic Review, Ankle Sprain, Management

Introduction

Ankle sprains, particularly those of the lateral ligament complex, are among the most common injuries to the musculoskeletal system (van Dijk 2002). Recurrence rates are high (Yeung et al 1994) and many patients experience long term residual symptoms that limit lifestyle (Braun 1999) and affect athletic performance (Anandacoomarasamy and Barnsley 2006, Yeung et al 1994).

The three main interventions commonly described after ankle sprain are: surgery, immobilisation, or functional treatment (Kerkhoffs et al 2002a). Functional treatment has been defined as an early mobilisation program, used in association with an external ankle support (Kerkhoffs et al 2002a). There is evidence that early mobilisation with an external support is more effective than both surgery and cast immobilisation after an ankle sprain (Kerkhoffs et al 2002a, Kerkhoffs et al 2002b, Kerkhoffs et al 2002c, Pijnenburg et al 1999, Shrier, 1995). Although surveys of physiotherapy practice (Larmour et al 2002, Roebroek et al 1998) have shown that early controlled mobilisation with external support is the most common intervention after ankle sprain, it is often combined with a range of other interventions including; electrophysical agents, narcotics, neuromuscular training, strengthening exercises, manual therapy, and compression.

A number of systematic reviews have investigated

the effectiveness of such additional interventions. A comprehensive review (Ogilvie-Harris and Gilbert 1995) of 32 025 patients from a total of 84 studies (published from 1966 to 1993), only found strong evidence to support the use of non-steroidal anti-inflammatory drugs after ankle sprains. More recent reviews (Zoch et al 2003, van der Wees et al 2006) found moderate evidence that exercise and manual therapy may also be beneficial in rehabilitation after ankle injury; however, these reviews focused primarily on healthy people and/or people with chronic ankle instability. In general, there is little high-quality evidence available to suggest which interventions are most effective in the management of acute ankle sprains, and it is not yet clear which combination of interventions best augment early mobilisation with an external support. Moreover, the most effective method of preventing long-term problems such as chronic ankle instability and recurrent sprains is unknown. Therefore the research questions were:

1. Which intervention(s) best augment early mobilisation and external support after an acute ankle sprain?
2. What is the most appropriate method of preventing re-injury?

The study aimed to build on previously published reviews, and to update the clinical evidence base for the management of acute ankle sprains.

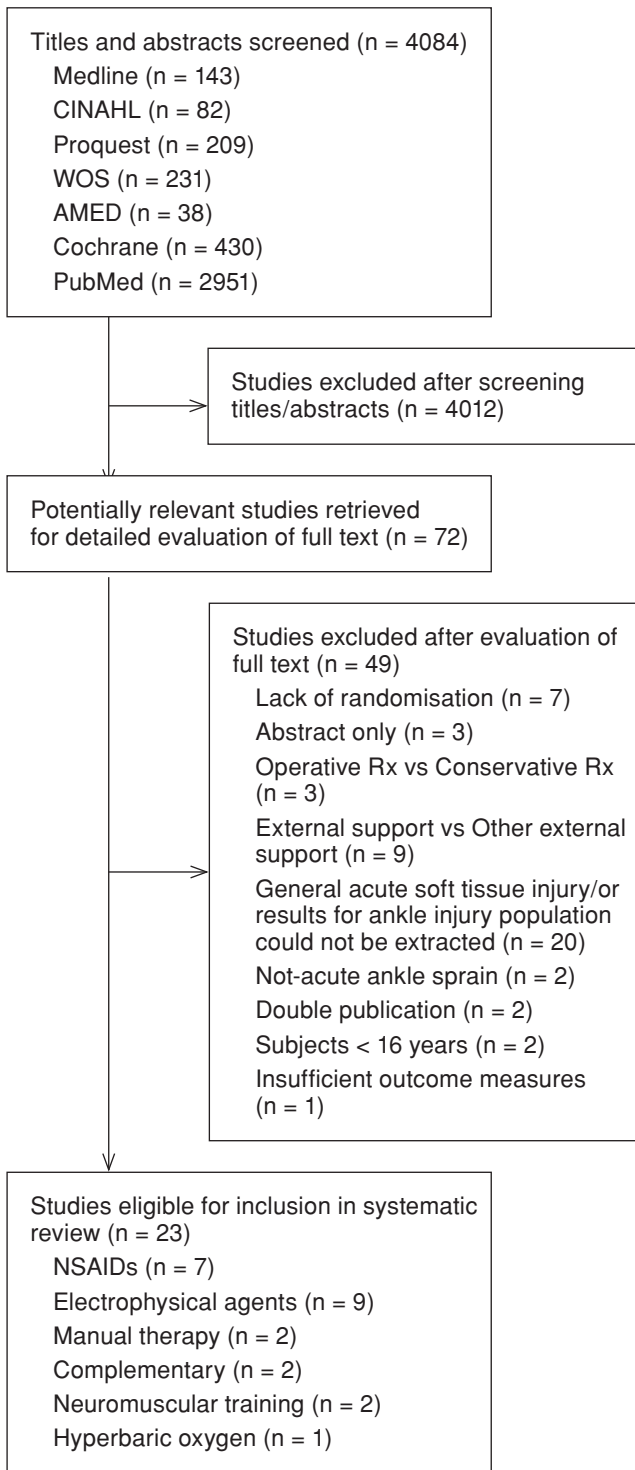


Figure 1. Identification and selection of randomised controlled trials.

Method

Identification and selection of studies

To be included in the review, studies had to: be a randomised controlled trial, be published in English as a full paper, and participants should be adults with acute ankle sprain. There should be physiotherapeutic (including exercise therapy /neuromuscular training), electrotherapeutic, complementary, or pharmacological intervention (used either in isolation or in combination with placebo or other therapies). Comparisons should have been made to no

intervention, placebo, or to a different physiotherapeutic, electrotherapeutic, complementary or pharmacological intervention. Trials of surgery and ankle immobilisation were excluded, as were trials investigating external ankle supports in isolation. These interventions have been assessed stringently in Cochrane reviews (Kerkoffs et al 2002a, 2002b, 2002c). Data were sought for the following outcomes: pain, swelling, function, re-injury, and overall (global) improvement.

Relevant studies were identified using a computer-based literature search of nine databases (1993 to April 2005), hand searching of key journals (n = 10) and a 'related article search' (n = 12). As Ogilvie-Harris and Gilbert (1995) had comprehensively reviewed the evidence base up to 1993, searches were not performed prior to this date. One reviewer (CB) conducted all the searches, and assessed studies for eligibility making the final inclusion/exclusion decisions. There was no blinding to author, place of publication, or results.

Assessment of methodological quality of studies

Two reviewers (CB, SMcD) assessed the quality of eligible studies using the Physiotherapy Evidence Database (PEDro) scale (<http://www.pedro.fhs.usyd.edu.au/>). Disagreement or ambiguous issues were resolved by consensus discussion or consultation with a physiotherapy evidence database project officer. PEDro uses 11 criteria, and reviewed studies were awarded one point for each criterion that was clearly satisfied. Criterion 1 is a measure of the external validity, and is not included in the final PEDro score (range 0–10). Studies scoring > 6/10 were considered high quality (Table 1).

Data analysis

One reviewer (CB) extracted data using a standardised extraction form. Interventions were broadly categorised as electrophysical, non-steroidal anti-inflammatory drugs, neuromuscular, manual, complementary and alternative medicine, and other interventions. When data were available from published reports, the primary researcher (CB) extracted raw data from key outcome measures. This was entered into the Cochrane Collaboration Review Manager (4.2) software program. Standardised mean differences (95% CI) (Herbert 2000a) were calculated for continuous data or risk ratios (95% CI) for dichotomous data (Herbert 2000b). Trials in each category were assessed for clinical heterogeneity with respect to their inclusion and exclusion criteria (eg, age, injury severity, intervention parameters). For the purposes of interpretation of results, the following levels of evidence were used (van Tulder et al 2003): *Strong evidence* – consistent findings among multiple higher quality randomised controlled trials; *Moderate evidence* – consistent findings among multiple lower quality randomised controlled trials and/or one higher quality randomised controlled trial; *Limited evidence* – one lower quality randomised controlled trial; *Conflicting evidence* – inconsistent findings among multiple randomised controlled trials; *No evidence* – no randomised controlled trials.

Results

Identification and selection of studies

Seventy-two studies were identified from the initial search. After review of the complete texts, 49 studies were excluded leaving 23 eligible randomised controlled trials. Figure 1 shows the process of study selection and the number of studies excluded at each stage, with reasons for exclusion.

Table 1. PEDro scores for included studies (n = 23).

Study	Random allocation	Concealed allocation	Groups similar at baseline	Participant blinding	Therapist blinding	Assessor blinding	< 15% dropouts	Intention-to-treat analysis	Between-group difference reported	Point estimate and variability reported	Total (0 to 10)
Borromeo et al (1997)	Y	N	Y	Y	N	Y	Y	Y	Y	Y	8
Campbell & Dunn (1994)	Y	Y	Y	Y	Y	Y	N	Y	Y	N	8
Cote et al (1988)	Y	N	Y	N	N	N	Y	N	Y	Y	5
De Bie et al (1988)	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	9
Dreiser et al (1993a)	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Dreiser et al (1993b)	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Eisenhar et al (2003)	Y	N	N	N	N	N	N	Y	Y	Y	4
Ekman et al (2002)	Y	N	Y	N	N	N	Y	Y	Y	Y	6
Green et al (2001)	Y	Y	N	N	N	Y	Y	Y	Y	Y	7
Holme et al (1999)	Y	N	N	N	N	N	N	N	Y	Y	3
Koll et al (2004)	Y	N	N	N	N	N	Y	Y	Y	Y	5
Kucera et al (2004)	Y	N	N	Y	Y	N	Y	Y	Y	Y	7
Laba (1989)	Y	N	Y	N	N	N	Y	N	N	N	3
Mazieres et al (2005)	Y	N	Y	Y	Y	N	N	Y	Y	Y	7
Michlovitz et al (1988)	Y	N	N	N	N	N	Y	N	Y	Y	4
Nyanzi et al (1999)	Y	N	Y	Y	Y	Y	Y	N	Y	Y	8
Petrella et al (2004)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Slatyer et al (1997)	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	10
Sloan et al (1989)	Y	N	N	N	N	Y	N	N	Y	N	3
Stergioulas (2004)	Y	N	N	Y	Y	Y	Y	N	Y	Y	7
Watts & Armstrong (2001)	Y	Y	N	N	N	N	Y	Y	Y	Y	6
Wester et al (1996)	Y	N	N	N	N	N	N	N	Y	Y	3
Wilkerson & Horn Kingery (1993)	N	N	N	N	N	N	Y	N	Y	Y	3

Quality of studies

Nine studies (Cote et al 1988, Eisenhart et al 2003, Holme et al 1999, Koll et al 2004, Laba 1989, Michlovitz 1988, Sloan et al 1989, Wester et al 1996, Wilkerson and Horn-Kingery 1993) scored less than 6/10, and overall there was a mean PEDro score of 6/10. The scores on each of the 10 criteria and total scores for each study are presented in Table 1. In general, blinded application of intervention was rare, and only five trials (Campbell and Dunn 1994, Green et al 2001, Petrella et al 2004, Slatyer et al 1997, Watts and Armstrong 2001) used allocation concealment during recruitment of participants.

Although a number of studies carried out similar comparisons, the effect sizes from individual trials could not be pooled for statistical analysis. This was due largely to heterogeneity of the type of intervention, the dosage of intervention, the timing and type of outcome measures, or insufficient reporting of data. Key study characteristics and outcomes are summarised in Table 2.

Effect of intervention

Effect sizes for key outcomes (ankle pain/ankle function) are summarised in Table 3 and 4.

Traditional non-steroidal anti-inflammatory drugs vs placebo (n = 4): Four high quality studies (Campbell and Dunn 1994, Dreiser et al 1993a, Mazieres et al 2005, Slatyer et al 1997) compared the effects of traditional non-steroidal anti-inflammatory drugs to placebo. The majority of outcomes were recorded in the short term, and only one study (Slatyer et al 1997) collected data for longer than two weeks post injury. Slatyer et al (1997) found that piroxicam (40 mg/day for the first two days post injury and 20 mg/day for the next five) significantly improved function at day 14, 1 month, 3 months, and 6 months after injury using a sample of army recruits. It must be noted however that Slatyer et al (1997) also reported a significantly higher incidence of mechanical instability at days 3, 7, and 14, and restrictions in short term ankle range of movement in the intervention group.

Campbell and Dunn (1994) compared the effectiveness of active topical ibuprofen gel, to placebo gel. The active gel (5% ibuprofen) significantly decreased subjective pain scores, at days 2 and 3 post sprain, compared to the placebo gel. Dreiser et al (1994) found that Fluriprofen patches (40 mg) had no significant effect at day 3 post injury, but made significant improvements in both pain and swelling by day 7, compared to placebo patches. Similarly, Mazieres et al (2005) found that a 7 day course with a ketoprofen (100 mg) patch, significantly reduced pain and disability on activity at days 3, 7 and 14 post injury.

Selective vs traditional non-steroidal anti-inflammatory drugs/placebo (n = 3): A large study by Ekman et al (2002) found that Celecoxib (400 mg/day) was significantly better than placebo at reducing pain and improving function on days 4 and 8 post injury, however there were no differences at day 11. Similarly, Dreiser and Reibenfeld (1993) found that Nemisulide (200 mg/day) significantly improved pain and function at day 4 (as measured by the global assessment of efficacy and safety).

Two large studies by Ekman et al (2002) (n = 443) and Petrella et al (2004) (n = 397) compared Celecoxib (400 mg/day) to ibuprofen (2400 mg/day) and Naproxen (1000

mg/day) respectively. Both studies found no significant differences in pain or global function at days 4, 8 and 11. In one study (Petrella et al 2004), Celecoxib was associated with significantly less dyspepsia than Naproxen (RR 0.25, 95% CI 0.07 to 0.87 and NNT 22, 95% CI 8 to 36).

Electrophysical agents (n = 9): Three studies (de Bie et al 1998, Nyanzi et al 1999, Stergioulas 2004) compared the effects of electrotherapy modalities to placebo, and de Bie et al (1998) also compared the effects of different electrotherapy dosages. Although all three studies scored greater than 7/10 on the quality rating, effect sizes were small, and few significant differences were reported. Nyanzi et al (1999) found no difference between ultrasound and placebo ultrasound in terms of short term pain, swelling, and function. de Bie et al (1998) found that participants receiving placebo laser had significantly better function at days 10 and 14 when compared to both low level laser therapy and high level laser therapy. Although high level laser therapy significantly reduced the rate of re injury compared to low level laser therapy, at 12 months post injury there were no other significant differences reported between groups. In contrast, Stergioulas (2004) found that participants treated with low level laser therapy (initiated within 8 hours post injury) had significant reductions in swelling at 24 hours, 48 hours, and 72 hours post injury in comparison those treated with rest, ice, compression, and elevation alone, and rest, ice, compression, and elevation plus placebo laser.

Five low quality studies (Cote et al 1988, Laba 1989, Michlovitz et al 1988, Sloan et al 1989, Wilkerson and Horn-Kingery 1993) and one high quality study (Watts and Armstrong 2001) assessed the effectiveness of various components and combinations of using rest, ice compression and elevation but few significant differences were reported. Cote et al (1988) found ice submersion (with simultaneous exercises) to be significantly more effective than heat and contrast therapy at reducing swelling between 3 and 5 days post ankle sprain, no long-term follow-up was undertaken. Michlovitz et al (1988) found the addition of either low- (28 pulses per second) or high-frequency electrical stimulation (80 pulses per second) to ice intervention had no significant effect on short term swelling, pain, or range of movement, and single applications of ice and compression were no more effective than compression alone (Wilkerson and Horn-Kingery 1993) or standard intervention (Laba 1989, Sloan et al 1989). Watts and Armstrong (2001) focused primarily on the compressive component of the rest, ice, compression, and elevation regime, but found no significant differences in participants using double tubigrip bandaging and a group receiving standard advice.

Manual therapy (n = 2): In a high quality study, Green et al (2001) assessed the effect of adding six sessions of ankle mobilisations, to a standard regime. Results showed that significantly more participants in the mobilisation group had full range of movement into ankle dorsiflexion, by day 8–10 post injury, compared to those receiving standard intervention. Similarly, a lower quality study by Eisenhart et al (2003) found that the addition of a single manipulation (plus soft tissue techniques), to standard rest, ice, compression, and elevation, resulted in significantly greater range of movement, in comparison to rest, ice, compression, and elevation alone at week 1.

Table 2. Summary of included randomised controlled trials.

Study	Participants	Intervention	Outcome measures
NSAIDs			
Campbell & Dunn (1994)	Incl = Ankle sprain with no instability, < 24 hr n = 100 (51) Age = Gp A 29.4 yr (SE 1.7); Gp B 29.3 (SE 2)	A = Ibuprofen, n = 51 (26), topical cream, 5% Ibuprofen, 4 inches of cream x 4/day B = Placebo, n = 49 (25), identical cream base no Ibuprofen, 4 inches of cream x 4/day All groups = Written advice on rest, ice, walking, and exercise	Pain = 10 cm VAS Function = Walking ability on 4 point scale Follow-up = Day 1-7
Dreiser et al (1993a)	Incl = Ankle sprain > 5 on VAS, < 48 hours n = 130 Age = 18-70 yr	A = Flurbiprofen, n = 65, 40 mg patch B = Placebo, n = 66, identical but non medicated patch All groups = 12 hrs/day for 7 days	Pain = VAS Swelling = Ankle circumference (tape measure) Function/global improvement = functional incapacity on 4 point scale; overall efficacy 4 point scale Follow-up = Day 3, 7
Mazieres et al (2005)	Incl = Acute ankle sprain G1/2, > 5/10 on pain scale, < 48 hrs n = 163 Age = Gp A 38.9 yr (SD 14); Gp B 34.4 yr (SD 14)	A = Ketoprofen patch, n = 81, 1x 100 mg patch/day for 2 wks B = Placebo patch, n = 82, identical patch with no active ingredient/day for 2 wks All groups = Rescue medication	Pain = VAS Swelling = Ankle circumference (tape measure) Function = 4 point scale Follow-up = Day 3,7,14
Slatyer et al (1997)	Incl = Ankle sprain G1/2/3, < 24 hours n = 364 Age = 18-30 yr	A = Piroxicam, n = 184, 40 mg for 2 days, 20 mg for 5 days B = Placebo, n = 180) 40 mg for 2 days, 20 mg for 5 days All groups = cryotherapy, elevation, analgesia, ultrasound, proprioceptive/strength exs, passive mobs, focal compression, graded exs	Pain = VAS Swelling = Volumetric/clinical assessment Function = Time to return to training Follow-up = Day 3, 7, 14; Month 1, 3, 6
Dreiser et al (1993b)	Incl = Ankle sprain < 5/10 on VAS n = 60 Age = Gp A 34.9 yr (SD 3.8), Gp B 39.6 yr (SD 4.8)	A = Nemisulide, n = 30, 100 mg x 2/day for 8 days B = Placebo, n = 30, 100 mg x 2/day for 8 days All groups = Paracetamol if required	Pain = VAS Swelling = Volumetry Function = Overall efficacy and safety on verbal rating scale/functional impairment Re-injury Follow-up = Day 4, 8
Ekman et al (2002)	Incl = Ankle sprain G1/2, < 48 hours n = 443 Age = Gp A 31.3 yr (SD 12.1), Gp B 30.4 yr (SD 10.5), Gp C 29.8 yr (11.9)	A = Celecoxib, n = 147, 200 mg x 2/ day for 10 days B = Ibuprofen, n = 155, 800 mg x 3 / day for 10 days C = Placebo, n = 141, 10 days All groups = RICE, other standard therapeutic modalities	Pain = VAS Global improvement/function = 5 point scale Follow-up = Day 4, 8, 11
Petrella et al (2004)	Incl = Acute first or second degree ankle sprain, < 48 hrs n = 397 Age = Gp A 29.5 yr (SE 0.78), Gp B 30.6 yr (SE 0.9)	A = Celecoxib, n = 198 B = Naproxen, n = 198 All groups = RICE, crutches, ankle band/taping, strengthening, air cast	Pain = VAS Global improvement/function = 5 point scale Follow-up = Day 4, 8

Table 2. Summary of included randomised controlled trials (*continued*).

Study	Participants	Intervention	Outcome measures
Electrophysical agents			
Cote et al (1988)	Incl = Ankle sprain, acute G 1 or 2 ankle injuries n = 30 Age = 18–22 yr	A = Cold submersion, n = 10, water bath at 50–60° F B = Hot submersion, n = 10, water at 102–106° F C = Contrast therapy water at 102–106° F (3 min)/50–60° F (1 min) All groups = A single 20-minute intervention on day 3, 4 and 5 post injury. Ankle exercises were carried out during immersion	Swelling = Volumetry Follow-up = Day 3–5
de Bie et al (1998)	Incl = Ankle sprain mild–severe, < 24hrs n = 217 Age = Gp A 33.2 yr (SD 10.4), Gp B 30.2 yr (SD 9.6), Gp C 30.9 yr (SD 10.3)	A = HLLT, n = 72, 5 J/cm ² , 5000 Hz B = LLLT, n = 74, 0.5 J/cm ² , 500 Hz Both A and B: 904 nm Ga As, peak power 25 W, pulse duration 200 nsec, 200 sec per point C = Placebo, n = 71, 0 J/cm ² All groups = Standard Rx: paracetamol, ankle brace, advice on balance, WB and mobility exs	Pain = VAS Swelling = Volumetry Function = 100 point scale/subjective recovery (10 point scale) Re-injury Follow-up = Day: 5, 10, 14, 28; Month: 3, 6, 9, 12
Laba (1989)	Incl = Ankle sprain, acute < 48 hours, grade 3/4 ankle n = 30 Age = 13–56 yr	A = Ice, n = 14, 2 litres of crushed ice, through a single layer of damp towelling, secured with an elastic crepe bandage, with elevation. A single 20 minute intervention on day 1 post injury B = No ice, n = 16, 60% of the 'no ice' group applied ice as a self-treatment prior to entry into the study. All groups = A standardised set of exercises and ultrasound	Pain = 5 point descriptive scale Swelling = Volumetry Follow-up = Day 1
Nyanzi et al (1999)	Incl = Ankle sprain with no bony injury, < 100 hrs n = 58 Age = 50 yr (range 14–65)	A = Ultrasound, n = 29, 3 MHz, 0.25 W/cm ² , space ratio 1:4, 10 min; 1 Rx/day for 3 days B = Placebo, n = 29, Electronically disable treatment head All groups = paracetamol, tubigrip, advice on elevation, WB	Pain = VAS Swelling = Ankle circumference (tape measure) Function = Weight bearing (scales) Follow-up = Day 1–3, 14
Michlovitz et al (1988)	Incl = Ankle sprains, acute < 28 hours, grade 1 or 2 n = 30 Age = 18–38 yr	A = Ice pack, n = 10 B = Ice plus High Voltage Pulsed Stimulation (HVPS), n = 10, frequency of 28 pps C = Ice plus HVPS, n = 10, frequency of 80 pps All groups = A single 30-minute intervention on day 1, 2 and 3 post injury. Affected lower extremity elevated to 45 degrees during intervention, ice pack held in place with elastic wrap	Pain = VAS Swelling = Volumetry Function = Active dorsiflexion ROM Re-injury Follow-up = Day 1 and 3
Sloan et al (1989)	Incl = Ankle sprain, acute < 24 hrs n = 143 Age = 24 yr (range 16–50)	A = Ice/compression and elevation, n = ?, cooling ankle: single 30 min intervention within 24 hrs of injury B = Dummy ice/compression, no elevation, n = ? All groups = Advice on compression and elevation, an elastic support, paracetamol and ibuprofen	Pain = Daily diary (VAS?) Swelling = Soft tissue swelling index on X-ray Function = Weight-bearing (linear grading scale) Follow-up = Day 7
Stergioulas (2004)	Incl = Ankle sprain, < 8hrs n = 47 Age = 18–26 yr	A = RICE, n = 16 B = RICE plus placebo LLLT, n = 16 C = RICE plus LLLT, n = 16, 820nm GaAlAs, power output, 40mW, freq 16Hz, 1.2 Joules/point. 10 joints Rxed in total All groups = NWB, 20 minutes ice x 3/day with elevation, elastic wrap during day	Swelling = Volumetry Follow-up = Day 1, 2 and 3
Watts & Armstrong (2001)	Incl = Acute ankle sprains, G1/2 n = 197 Age = Gp A 32.7 yr (SD 11.2), Gp B 32.8 yr (SD 11.6)	A = Double Tubigrip, n = 105 B = No Double Tubigrip, n = 92 All groups = Advice on exs, analgesia	Pain = Sleep disturbance, pain killers (yes/no) Function = Mobility (days to walking unaided); number of days off work Follow-up = Week 1

Table 2. Summary of included randomised controlled trials (*continued*).

Study	Participants	Intervention	Outcome measures
Wilkinson & Horn Kingery (1993)	Incl = Acute ankle sprains G2. n = 34 Age = 20.9 (SD 1.1) 18–28 yr	A = Uniform compression, n = 12 B = Continuous focal compression, n = 12 Both groups A and B = Ice pack directly to the skin for 20–30 minutes each day, during the acute phase of injury C = Focal compression with simultaneous cryotherapy (applied over a cotton sock). Changed every 4 hrs, n = 10 All groups = Airstirrup brace Duration of compressive intervention not specified	Function = 100 point subjective scale Follow-up = Function recorded each day post injury until participants achieved a functional score of 90/100
Manual therapy, neuromuscular training, complementary/alternative medicine			
Borromeo et al (1997)	Incl = Ankle sprains G1/2/3, < 72 hrs n = 32 Age = 24.2 yr (range 15–55)	A = Hyperbaric oxygen, n = 18, 100% oxygen/2 atmospheres (210 minutes of Rx over 1 week) B = Placebo, n = 18, air, 1.1 atmospheres absolute pressure All groups = NSAID, strapping, standard Rx	Pain = VAS Swelling = Volumeter Function = 7 point scale/time to full recovery Follow-up = 3 weeks
Eisenhart et al (2003)	Incl = Acute ankle sprains G1/2, < 24 hrs n = 55 Age = 31 yr	A = A single osteopathic manipulation, n = 28, plus RICE and analgesics B = Advice on RICE/analgesics, n = 27	Pain Swelling Follow-up = Day 5/7
Green et al (2001)	Incl = Ankle sprain, < 72 hours, severe enough to require assisted ambulation n = 41 (38) Age = Gp A 26.1 yr (SD 2.0), Gp B 24.9 yr (SD 1.6)	A = Physiological mobilisation plus RICE, n = 22 (19) every other weekday for 2 weeks post injury (maximum of 6 sessions) B = RICE, n = 19 All groups = RICE elastic bandage, elevation, taping	Function = range of movement/return to normal activity/walking/sports (days) Follow-up = Before and after each session and one day after discharge from the trial
Holme et al (1999)	Incl = Ankle sprain G1/2/3, < 24 hrs n = 92 (71) Age = Gp A. 27.4 yr (SD 4.6), Gp B 25.5 yr (SD 3.8)	A = Supervised N/M exs, n = 46 (29). Rehabilitation program (ankle mobilisation, strength, mobility and balance exercises) for 1 hour, twice weekly. B = Advice on N/M exs, n = 46 (42) (ankle mobilisation, strength, mobility and balance exercises)	Function = strength (isokinetic dynamometer)/postural sway (force plate center of pressure) Re-injury Follow-up = 12 months
Koll et al (2004)	Incl = Acute ankle distortion < 6hrs n = 143 Age = 18–60 yr	A = Comfrey ointment (Symphytum Officinale L.), n = 80, applied 4 times/day for 8 days B = Placebo ointment, n = 63, applied 4 times/day for 8 days All groups = 2g of cream, 4 applications/day for 8 days	Pain = VAS Swelling = Ankle girth (figure of 8) Global improvement = 4 point scale Follow-up = Day 0, 4, 7
Kucera et al (2004)	Incl = Acute ankle sprain, < 24hrs n = 203 Age = 31.8 yr (range 18–50)	A = Comfrey ointment (10% Symphytum herb), n = 104 B = comfrey ointment (1% Symphytum herb), n = 99 All groups = 2–3 g of cream, 3 applications/day	Pain = VAS Swelling = Ankle girth (figure of 8) Function = Functional impairment on 10 point scale Global improvement = Physician-rated using five point scale Follow-up = Day 3/4, 7, 14
Wester et al (1996)	Incl = Acute ankle sprain G2, negative anterior drawer or talar tilt n = 61 (48) Age = 25 yr (SD 7.2)	A = Wobble board, n = 24, 15 min/day for 12 weeks B = Standard Rx, n = 24 All groups = Advice on immobilisation, elevation 2 days, compression bandage for 1 week	Pain = Yes/no Swelling = Volumeter Function = Pain free return to sport (yes/no) Re-injury Follow-up = Week 1, 6, 12; Month 7–8
Incl = inclusion criteria, VAS = visual analogue scale, n = number of participants randomised (number of participants completing the study), Gp = group, RICE = rest, ice, compression, elevation, Rx = prescription, Volumetry = water displacement			

Table 3. SMD (95% CI) or RR (95% CI) for reduction in ankle pain at short-term (0–1 week), intermediate-term (1–12 weeks), and long-term (> 12 weeks) follow-up.

Intervention	Short-term follow-up	Intermediate-term follow-up	Long-term follow-up
Traditional NSAIDs			
Piroxicam vs placebo (Slatyer et al 1997)	Inadequate reporting of outcome	—	—
Ibuprofen gel vs placebo (Campbell & Dunn 1994)	SMD 1.12 (0.51 to 1.69)	—	—
Flurbiprofen vs placebo (Dreiser et al 1993a)	SMD 0.2 (0.14 to 0.55)	—	—
Ketoprofen vs placebo (Mazieres et al 2005)	SMD 0.4 (0.09 to 0.7)	SMD 0.6 (0.27 to 0.9)	—
Selective NSAIDs			
Nemisulide vs placebo (Dreiser et al 1993b)	SMD 1.24 (0.68 to 1.79)	—	—
Celecoxib vs placebo (Ekman et al 2002)	SMD 0.37 (0.14 to 0.6)	SMD 0.2 (-0.03 to 0.4)	—
Celecoxib vs ibuprofen (Ekman et al 2002)	SMD 0.1 (-0.13 to 0.33)	SMD 0.03 (-0.2 to 0.25)	—
Celecoxib vs naproxen (Petrella et al 2004)	SMD 0.18 (-0.02 to 0.38)	—	—
Electrophysical agents			
LLLT vs placebo (de Bie et al 1988)	SMD 0.18 (-0.15 to 0.6)	SMD 0.18 (-0.15 to 0.5)	—
Ultrasound vs placebo (Nyanzi et al 1999)	SMD 0.13 (-0.39 to 0.64)	SMD 0.14 (-0.37 to 0.66)	—
Ice/compression vs no intervention (Laba 1989)	RR 0.88 (0.62 to 1.14)	—	—
Ice/compression vs dummy ice/compression (Sloan et al 1989)	Inadequate reporting of outcome	—	—
Ice and exercise vs heat (Cote et al 1988)	—	—	—
Ice vs Ice and electrical stimulation (Michlovitz et al 1988)	SMD -0.6 (-1.5 to 0.3)	—	—
Manual therapy			
Accessory mobilisation/RICE vs RICE alone (Eisenhar et al 2003)	—	—	—
Accessory mobilisation vs RICE (Green et al 2001)	—	—	—
Complementary/alternative medicine			
Comfrey root vs placebo (Koll et al 2004)	Inadequate reporting of outcome	—	—
Comfrey root vs placebo (Kucera et al 2004)	SMD 0.57 (0.29 to 0.85)	SMD 0.31 (0.03 to 0.59)	—
Hyperbaric oxygen vs placebo (Borromeo et al 1997)	—	—	—
Neuromuscular training			
Wobble board vs standard intervention (Wester et al 1996)	RR 1.0 (0.89 to 1.13)	RR 0.57 (0.19 to 1.7)	—
Supervised rehab vs advice (Holme et al 1999)	—	—	—

Dash (—) = pain not assessed at this time point, RICE = rest, ice, compression, and elevation.

Table 4. SMD (95% CI) or RR (95% CI) for improvement in ankle function at short-term (0–1 week), intermediate-term (1–12 weeks), and long-term (> 12 weeks) follow-up.

Intervention	Short-term follow-up	Intermediate-term follow-up	Long-term follow-up
Traditional NSAIDs			
Piroxicam vs placebo (Slatyer et al 1997)	—	RR 1.83 (1.5 to 2.24)	RR 1.12 (1.02 to 1.22)
Ibuprofen gel vs placebo (Campbell & Dunn 1994)	Inadequate reporting of outcome	—	—
Flurbiprofen vs placebo (Dreiser et al 1993a)	RR 0.64 (0.22 to 1.87)	—	—
Ketoprofen vs placebo (Mazieres et al 2005)	SMD 0.46 (0.15 to 0.77)	SMD 0.49 (0.18 to 0.8)	—
Selective NSAIDs			
Nemisulide vs placebo (Dreiser et al 1993b)	RR 2.36 (1.45 to 3.86)	—	—
Celecoxib vs placebo (Ekman et al 2002)	RR 1.62 (1.0 to 2.6)	RR 1.21 (0.58 to 2.52)	—
Celecoxib vs ibuprofen (Ekman et al 2002)	RR 0.91 (0.78 to 1.06)	RR 1.01 (0.93 to 1.11)	—
Celecoxib vs naproxen (Petrella et al 2004)	RR 0.98 (0.88 to 1.1)	—	—
Electrophysical agents			
LLLT vs placebo (de Bie et al 1988)	SMD 0.07 (-0.26 to 0.39)	SMD 0.13 (-0.2 to 0.46)	—
Ultrasound vs placebo (Nyanzi et al 1999)	SMD 0.26 (-0.29 to 0.81)	SMD 0.17 (-0.38 to 0.72)	—
Ice/compression vs no intervention (Laba 1989)	Inadequate reporting of outcome	—	—
Ice/compression vs dummy ice/compression (Sloan et al 1989)	—	—	—
Ice and exercise vs heat (Cote et al 1988)	—	—	—
Ice vs Ice and electrical stimulation (Michlovitz et al 1988)	—	—	—
Manual therapy			
Accessory mobilisation/RICE vs RICE alone (Eisenhar et al 2003)	SMD 0.51 (-0.03 to 1.04)	—	—
Accessory mobilisation vs RICE (Green et al 2001)	RR 4.33 (1.47 to 12.79)	—	—
Complementary/alternative medicine			
Comfrey root vs placebo (Koll et al 2004)	—	SMD 0.5 (0.3 to 0.83)	—
Comfrey root vs placebo (Kucera et al 2004)	SMD 0.42 (0.15 to 0.7)	SMD 0.14 (-0.14 to 0.41)	—
Hyperbaric oxygen vs placebo (Borromeo et al 1997)	SMD 0.12 (-0.53 to 0.77)	—	—
Neuromuscular training			
Balance board vs standard intervention (Wester et al 1996)	—	—	RR 0.46 (0.21 to 1.01)
Supervised rehab vs advice (Holme et al 1999)	—	—	RR 0.24 (0.06 to 0.99)

Dash (—) = ankle function not assessed at this time point, RICE = rest, ice, compression, and elevation.

Complementary and other interventions (n = 3): One high quality study (Kucera et al 2004) and one low quality study (Koll et al 2004) found that application of an ointment consisting of extracts from comfrey root (*Symphytum officinale*) was a safe and effective option in the acute phases after ankle sprain. In both studies, the ointment was applied directly on the ankle 3–4 times per day, with both reporting significantly better reductions in pain and function during a two-week follow-up period, in comparison to placebo. Neither study reported any side effects. Borromeo et al (1997) examined the effectiveness of hyperbaric oxygen therapy compared to placebo, using a study with a small sample size, but high internal validity. Results showed that participants receiving three hyperbaric oxygen therapy sessions (totalling 210 minutes) in the first week after injury had similar levels of function (1 week), and time to recovery, as those receiving placebo therapy.

Neuromuscular training (n = 2): Two lower quality studies (Wester et al 1996, Holme et al 1999) examined the effect of adding neuromuscular exercises to standard rehabilitation after ankle sprain. Wester et al (1996) found that participants using 15 minutes of wobble board training per day had significantly less functional instability and were less likely to re-injure during a follow-up period of (average) 230 days. Holme et al (1999) concluded that participants undertaking a supervised rehabilitation program (strength, mobility and balance exercises) for a 1-hour period, twice weekly, were significantly less likely to suffer re injury than participants participating in basic, non supervised rehabilitation, during a longer follow-up period of 12 months.

Discussion

This study aimed to build on previous research, and update the evidence base for the management of ankle sprain. A level of evidence algorithm (van Tulder et al 2003) was employed to facilitate the interpretation of results. Although this approach has been shown to have some limitations (Ferreira et al 2002), it was used primarily to provide a concise summary of the strength of evidence for each intervention.

The majority of included studies focused on interventions traditionally associated with providing short-term symptomatic relief. There is strong evidence to show that non-steroidal anti-inflammatory drugs can decrease pain and swelling in the acute phases of ankle injury. There is also moderate evidence that manual therapy improves range of movement and that comfrey Root ointment decreases pain and improves ankle function. Although there is moderate evidence that neuromuscular training can decrease complaints of functional instability and re-injury for up to a 12 month period, generally few studies have considered the long term morbidity associated with ankle sprain and few have carried out long-term follow-up.

Non-steroidal anti-inflammatory drugs: There is strong evidence that traditional non-steroidal anti-inflammatory drugs (oral and topical) and selective non-steroidal anti-inflammatory drugs are more effective than placebo in the short-term management of ankle sprains. There is also moderate evidence that traditional non-steroidal anti-inflammatory drugs result in significant improvements in function for up to 6 months post injury. There is strong evidence that traditional non-steroidal anti-inflammatory drugs are equally as effective as selective COX 2 inhibitors, and there is moderate evidence that selective COX 2

inhibitors cause less dyspepsia. Generally, few studies have carried out follow-up beyond two weeks post injury, and the long-term risk of traditional and selective non-steroidal anti-inflammatory drugs requires further study.

In a review of the evidence published prior to 1993, Ogilvie-Harris and Gilbert (1995) found significant evidence that non-steroidal anti-inflammatory drugs are of benefit in short term recovery from ankle sprains. Similarly, quantitative reviews have concluded that topical non-steroidal anti-inflammatory drugs can relieve pain in other acute and chronic soft tissue conditions (Moore et al 1998). In conjunction, there is further high quality evidence from this review that both traditional and selective non-steroidal anti-inflammatory drugs, applied either orally or topically, result in short term improvements after ankle sprain. There is also high quality evidence that traditional non-steroidal anti-inflammatory drugs are equally as effective as selective COX 2 inhibitors, but that selective inhibitors may be associated with less GI disturbance (Petrella et al 2004). Other meta-analysis (Kearney et al 2006) has shown that COX 2 inhibitors moderately increase in the risk of more serious vascular events, and similar risks have been highlighted with high dose ibuprofen (800 mg three times daily) and diclofenac (75 mg twice daily). Although no serious side effects were reported in the current review (despite studies applying similar high dosages) only one study continued follow-up for more than 2 weeks after injury (Slatyer et al 1997). Although Slatyer and colleagues (1997) found improved long term function associated with non-steroidal anti-inflammatory drugs over placebo, it must be noted that higher incidences of mechanical instability and restricted range of movement were reported in the intervention group. The increased mechanical instability may relate to previous evidence suggesting that non-steroidal anti-inflammatory drugs can delay the rate of muscle fibre regeneration (Weiler 1992). Others have warned that excessive use of non-steroidal anti-inflammatory drugs can alleviate the 'alarm system of pain' after injury, and subsequently increase the risk of tissue overload or failure (Leadbetter 1995). Further research and clearer recommendations into the safe use of non-steroidal anti-inflammatory drugs may be needed (Lippi et al 2006).

Electrophysical agents: There is no evidence to support the use of ultrasound and conflicting evidence to support the use of cryotherapy and low-level laser therapy. Few studies have compared the effects of different dosages of electrophysical agents, and there is no evidence of an optimal mode, duration or frequency for applying ice and / or compression.

Ogilvie-Harris and Gilbert's review (1995) found preliminary evidence that cryotherapy and diathermy (diathermy) are of benefit after ankle sprain but no evidence to support the use of ultrasound and laser therapy. In concurrence, other past reviews (Gam et al 1993, van der Heijden et al 1997, Van der Windt et al 2002) could find few significant effects of electrophysical agents beyond placebo, in the management of a wide range of musculoskeletal injuries.

There are numerous parameter combinations available when applying electrophysical agents and the importance of selecting clinically appropriate parameters for therapies such as laser has been previously highlighted (Bjardal et al 2001). Indeed, more recent recommendations by the World Association of Laser Therapy (WALT 2005) stated that an average power output of 10mW and a minimum dosage of 1J

per point (+50%) represent a clinically appropriate threshold value. It is interesting that both de Bie et al (1999) and Stergioulas (2004) conformed to these recommendations; yet only Stergioulas (2004) reported a positive result. Direct comparison across studies may be difficult, however, as the positive effect reported by Stergioulas' (2004) was restricted to a reduction in swelling, an outcome not assessed by de Bie et al (1999). Furthermore, Stergioulas (2004) recruited participants within 8 hours of their injury and intervention was applied twice a day, whereas de Bie et al (1999) used wider inclusion criteria (24 hrs) with intervention applied just once a day. Recent evidence shows that low level laser therapy can reduce inflammation by inhibiting PGE2 concentrations and cyclo-oxygenase 2 in cell cultures (Sakurai et al 2000) and injured humans (Bjordal et al 2006). One might postulate that the Stergioulas (2004) early, intensive intervention protocol may target this mechanism more effectively.

Despite the preliminary evidence reported from Ogilvie-Harris and Gilbert (1995), none of the included studies in the current review employed a diapulse intervention and there was little evidence to support the use of rest, ice, compression, or elevation when applied as isolated components (ie, compression alone) or as intervention combinations such as ice and compression. Recommending rest, ice, compression and elevation after ankle sprain is common clinical practice, but there are many permutations in relation to the dosage. As highlighted in a previous review (Bleakley et al 2004), the lack of effect of icing after ankle sprain may be due to the tendency to apply inadequate or clinically-ineffective parameters. Furthermore, a number of studies (Wilkerson and Horn-Kingery 1993) used a barrier between the ice pack and the injured tissue, which may mitigate the cooling effect further. Lab-based studies (Ebrall et al 1992, Karunakara et al 1999, Knobloch et al 2006) and clinical evidence (Bleakley et al 2006) suggest that shorter intermittent applications can optimally cool injured tissue without risking deleterious side effects; however further research is required to develop an optimal protocol for rest, ice, compression, and elevation.

Manual therapy: There is moderate evidence that manual therapy can increase ankle range of movement at week 1 post injury. Clinical guidelines suggest that normal range of movement should be achieved within two weeks of ankle sprain (van Dijk 1999). Green et al (2001) found that participants using rest, ice, compression, and elevation, in combination with manual therapy were more likely to reach this milestone compared to those receiving rest, ice, compression, and elevation alone. Restrictions in range of movement after ankle injury are common and often long lasting, with restrictions in posterior talar glide observed for up to 6 months (Denegar et al 2002). There is evidence that such persistent restrictions in talar gliding, can predispose to ankle sprain and fracture (Tabrizi et al 2000), and may contribute to long term ankle problems such as chronic ankle instability (Hertel 2002). This review shows moderate evidence that manual techniques, applied in the acute phases of injury are effective at increasing ankle dorsiflexion. Study follow-up was restricted to 2 weeks, however, and it is not clear if these early gains in range of movement are maintained throughout the later stages of rehabilitation. Interestingly, manual therapy (Mulligan's movement with mobilisation) also results in immediate range of movement gains when applied in the sub-acute phases after ankle sprain (Collins et al 2004) and in participants with recurrent

sprains (Vicenzino et al 2006), but again, the permanence of these changes may need further investigation.

Complementary and alternative medicine: There is moderate evidence that comfrey root ointment can provide short-term relief of symptoms after ankle injury, but the use of hyperbaric oxygen therapy requires further investigation. Complementary and alternative medicine is often used as an umbrella term for a wide range of therapeutic and diagnostic applications that often have little in common, including: acupuncture; aromatherapy; and herbal medicines (Ernst 2001). Although complementary and alternative medicine is traditionally associated with Eastern culture, its popularity with patients seems to be increasing in Western countries, particularly for musculoskeletal conditions (Rao et al 2003). The current attitude of primary care practitioners towards complementary and alternative medicine is more diverse however (Cohen et al 2005, Giannelli et al 2007), with a number of general practitioners expressing reservations over its effectiveness (Gianelli et al 2007). It is not clear how often patients request complementary and alternative medicine, such as herbal medicines, after ankle sprain. Several herbal remedies have shown promising results in alleviating musculoskeletal pain (Ersnt and Chrubasik 2000) and, in accordance, we found evidence that a *symphytum* herb extract cream has a positive effect on acute ankle sprains beyond placebo. Furthermore, there is recent evidence that the *symphytum* herb extract is effective in treating other inflammatory musculoskeletal conditions such as osteoarthritis (Grube et al 2006). Despite the positive clinical evidence, the pathophysiological basis of its benefit is not yet clear. The *symphytum* herb contains allantoin, choline, and rosmarinic acid, constituents which may be responsible for its anti-inflammatory effects (Andres et al 1989).

Neuromuscular training: There is moderate evidence that neuromuscular training can prevent complaints of functional instability and re-injury, and the effectiveness may be enhanced with supervised rehabilitation. Neuromuscular training is a popular intervention with physiotherapists, particularly in the sub-acute phases after ankle injury (Larmour et al 2002); however, we found only two low quality studies focusing on this approach. Wester et al (1996) used wobble (balance) board training only, whereas Holme et al (1999) assessed the effectiveness of a more dynamic, supervised, neuromuscular training program. Both strategies were associated with a decreased incidence of re-injury for an average of 230 days (Wester et al 1996) and 12 months (Holme et al 1996) after ankle sprain.

Despite this preliminary evidence, chronic ankle instability remains a common clinical entity after ankle sprains, characterised by giving way, residual symptoms, decreased function, and re-injury. The development of chronic ankle instability may be related to a number of sensorimotor changes post trauma including: impaired proprioception, arthrogenic muscle inhibition, delayed peroneal reaction time, reduced muscle strength, impaired postural control and altered lower limb movement patterns (Hertel 2002). It is not yet clear if balance board training alone can correct all these sensorimotor deficits. It seems that in primary prevention of ankle sprain, balance board training in isolation may help an athlete avoid a non-contact injury, but it may not be as effective in preventing an injury involving contact with another player (Bahr 2007), particularly at higher speeds. More comprehensive training

strategies incorporating sport- or skill-specific exercise and strengthening, in addition to neuromuscular training, have been most successful in primary prevention of lower limb injuries (Hootman 2007). With continued reports of high recurrence rates and long-term residual symptoms after ankle sprain (Anandacoomarasamy and Barnsley 2006), the prevention of re-injury continues to be the physiotherapist's most important long-term goal. It is therefore important that the moderate evidence supporting use of neuromuscular training, highlighted in the current review, is followed up with higher quality studies incorporating more rigorous, long-term follow-ups.

In conclusion, we have found strong evidence to support the use of non-steroidal anti-inflammatory drugs, and moderate evidence for comfrey root ointment and manual therapy in short-term symptomatic relief immediately after ankle sprain. There is conflicting evidence to support the use of electrophysical agents, however few studies have considered the range of intervention parameters available. There is moderate evidence that early neuromuscular training has a positive effect on pain and ankle function, and that supervised neuromuscular training can decrease the incidence of re-injury for up to 12 months. It is not yet clear if the short-term reduction in pain and swelling associated with non-steroidal anti-inflammatory drugs, complementary and alternative medicine, and manual therapy leads to a successful long-term outcome, and there is no evidence to suggest how longer-term deficits such as chronic ankle instability can be best prevented. Future research must continue to develop evidence-based guidelines on a safe, progressive rehabilitation protocol, whilst respecting the time frame associated with ligament healing. It may be of particular importance to focus on rehabilitation beyond the acute phases of ankle sprain, using high quality studies with long term follow-up.

Correspondence: Chris M Bleakley, Health and Rehabilitation Sciences Research Institute, University of Ulster Jordanstown Campus, Shore Road, Newtownabbey BT37 0QB N Ireland. Email: e10204083@uucde.ulst.ac.uk

References

- Anandacoomarasamy A, Barnsley L (2006) Long term outcomes of ankle inversion injuries. *British Journal of Sports Medicine* 39: 3, e14.
- Andres P, Brenneisen R, Clerc JT (1989) Relating antiphlogistic efficacy of dermatics containing extracts of *Symphytum officinale* to chemical profiles. *Planta Medica* 55: 66–67.
- Bahr R (2007). Can we prevent ankle sprains? In DC MacAuley, TM Best (Eds) *Evidence Based Sports Medicine*. (2nd ed). London: BMJ Books, pp 519–538.
- Bleakley CM, McDonough SM, MacAuley DC, Bjordal JM (2006) Cryotherapy for acute ankle sprains: a randomised controlled study of two different icing protocols. *British Journal of Sports Medicine* 8: 700–705.
- Bleakley C, McDonough SM, MacAuley DC (2004) The use of ice in the treatment of acute soft-tissue injury: a systematic review of randomized controlled trials. *American Journal of Sports Medicine* 32: 251–261.
- Bjordal JM, Lopes-Martins RA, Iversen VV (2006) A randomised, placebo controlled trial of low level laser therapy for activated Achilles tendinitis with microdialysis measurement of peritendinous prostaglandin E2 concentrations. *British Journal of Sports Medicine* 40: 76–80.
- Bjordal JM, Coupe C, Ljunggren AE (2001) Low level laser therapy for tendinopathy. Evidence of a dose response pattern. *Physical Therapy Reviews* 6: 91–99.
- Borromeo CN, Ryan JL, Marchetto PA, Peterson R, Bove AA (1997) Hyperbaric oxygen therapy for acute ankle sprains. *American Journal of Sports Medicine* 25: 619–625.
- Braun BL (1999) Effects of ankle sprain in a general clinic population 6 to 18 months after medical evaluation. *Archives of Family Medicine* 8: 143–148.
- Campbell J, Dunn T (1994) Evaluation of topical ibuprofen cream in the treatment of acute ankle sprains. *Journal of Accident and Emergency Medicine* 11: 178–182.
- Clarke M, Oxman AD (2001) Optimal search strategy for randomised controlled trials. The Cochrane Library, Issue 4. Oxford: Update software.
- Cohen MM, Penman S, Pirota M, Da Costa C (2005) The integration of complementary therapies in Australian general practice: results of a national survey. *Journal of Complementary Medicine* 11: 995–1004.
- Collins N, Teys P, Vicenzino B (2004) The initial effects of a Mulligan's mobilisation with movement technique on dorsiflexion and pain in subacute ankle sprains. *Manual Therapy* 9: 77–82.
- Cote DJ, Prentice WE, Hooker DN, Shields EW (1988) Comparison of three treatment procedures for minimizing ankle sprain swelling. *Physical Therapy* 68: 1072–1076.
- de Bie RA, Henrica CW, de Vet HC, Lenssen TF, Frans AJM, van den Wildenberg FA, Kootstra G, Knipschild PG (1998) Low-level laser therapy in ankle sprains: a randomized clinical trial. *Archives of Physical Medicine and Rehabilitation* 79: 1415–1420.
- Denegar CR, Hertel J, Fonseca J (2002) The effect of lateral ankle sprain on dorsiflexion range of motion, posterior talar glide, and joint laxity. *Journal of Orthopaedic and Sports Physical Therapy* 32: 166–173.
- Dreiser RL, Roche R, De Sahb R, Thomas F, Leutenegger E (1994a) Flurbiprofen local action transcutaneous (LAT): clinical evaluation in the treatment of acute ankle sprains. *European Journal of Rheumatology and Inflammation* 14: 9–13.
- Dreiser RL, Reibenfeld (1993b) A double-blind study of the efficacy of nimesulide in the treatment of ankle sprain in comparison with placebo. *Drugs* 46: 183–186.
- Ebrall PS, Bales GL, Frost BR (1992) An improved clinical protocol for ankle cryotherapy. *Journal of Manual Medicine* 6: 161–165.
- Eisenhart AW, Gaeta TJ, Yens DP (2003) Osteopathic manipulative treatment in the emergency department for patients with acute ankle injuries. *Journal of American Osteopathic Association* 103: 417–421.
- Ekman EF, Fiechtner JJ, Levy S, Fort JG (2002) Efficacy of celecoxib versus ibuprofen in the treatment of acute pain: a multicenter, double-blind, randomized controlled trial in acute ankle sprain. *American Journal of Orthopaedics* 31: 445–451.
- Ersnt E, Chrubasik S. (2000) Phyto-anti-inflammatories: a systematic review of randomized placebo controlled trials. *Rheumatological Disease Clinics of North America* 1: 13–27.
- Ferreira PH, Ferreira ML, Maher C, Refshauge K, Herbert R, Latimer J. (2002) Effect of applying different 'levels of evidence' criteria on conclusions of Cochrane reviews of interventions for low back pain. *Journal of Clinical Epidemiology* 55: 1126–1129
- Gam AN, Giannelli M, Cuttini M, Da Fre M, Buiatti E. (2007) General practitioners' knowledge and practice of complementary/alternative medicine and its relationship with life styles: a population-based survey in Italy. *BMC Family Practice* 8: 30.
- Green S, Buchbinder R, Glazier R (1998) Systematic review of randomized controlled trials of interventions for painful shoulder: selection criteria, outcome assessment, and efficacy. *BMJ* 316: 354–360.

- Green T, Refshauge K, Crosbie J, Adams A (2001) A randomized controlled trial of a passive accessory joint mobilization on acute ankle inversion sprains. *Physical Therapy* 81: 984–994.
- Grube B, Grunwald J, Krug L, Staiger C (2006) Efficacy of a comfrey root (*Symphyti offic. radix*) extract ointment in the treatment of patients with painful osteoarthritis of the knee: results of a double blind, randomized, bicenter, placebo controlled trial. *Phytomedicine* 14: 2–10.
- Hertel J (2002) Functional anatomy, pathomechanics, and pathophysiology of lateral ankle instability. *Journal of Athletic Training* 37: 363–375.
- Herbert RD (2000a) How to estimate effects from reports of clinical trials. I: Continuous outcomes. *Australian Journal of Physiotherapy* 46: 229–235.
- Herbert R.D. (2000b) How to estimate effects from reports of clinical trials. II: Dichotomous outcomes. *Australian Journal of Physiotherapy* 46: 309–313.
- Holme E, Magnusson SP, Becher K, Bieler T, Aagaard P, Kjaer M (1999) The effect of supervised rehabilitation on strength, postural sway, position sense and re-injury risk after acute ankle ligament sprain. *Scandinavian Journal of Medicine and Science in Sports* 9: 104–109.
- Hootman JM (2007) Is it possible to prevent sport and recreational injuries? A systematic review of randomised controlled trials, with recommendations for future work. In DC MacAuley, TM Best (Eds), *Evidence Based Sports Medicine* (2nd ed). London: BMJ Books, pp. 3–18.
- Karunakara RG, Lephart SM, Pinciverio DM (1999) Changes in forearm blood flow during single and intermittent cold application. *Journal of Orthopaedic and Sports Physical Therapy* 29: 177–180.
- Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. (2006) Do selective cyclo-oxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory drugs increase the risk of atherothrombosis? Meta-analysis of randomised controlled trials. *BMJ* 332: 1302–8.
- Kerkhoffs GMMJ, Struijs PAA, Marti RK, Assendelft WJJ, Blankevoort L, Dijk van CN (2002a) Different functional treatment strategies for acute lateral ankle ligament injuries in adults. *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD002938. DOI: 10.1002/14651858.CD002938.
- Kerkhoffs GMMJ, Handoll HHG, de Bie R, Rowe BH, Struijs PAA (2002b) Surgical versus conservative treatment for acute injuries of the lateral ligament complex of the ankle in adults. *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD000380. DOI: 10.1002/14651858.CD000380.pub2.
- Kerkhoffs GMMJ, Rowe BH, Assendelft WJJ, Kelly K, Struijs PAA, van Dijk CN (2002c) Immobilisation and functional treatment for acute lateral ankle ligament injuries in adults. *Cochrane Database of Systematic Reviews*, Issue 3. Art. No.: CD003762. DOI: 10.1002/14651858.CD003762.
- Koll R, Buhr M, Dieter R, Pabst H, Predel HG, Petrowicz O, Gianenetti B, Klingenburg S, Staiger C (2004) Efficacy and tolerance of a comfrey root extract (Extr. Rad. *Symphyti*) in the treatment of ankle distortions: results of a multicenter, randomised, placebo-controlled, double-blind study. *Phytomedicine* 11: 470–477.
- Knobloch K, Grasemann R, Spies M, Vogt PM (2007) Intermittent KoldBlue(R) cryotherapy of 3x10min changes mid-portion Achilles tendon microcirculation. *British Journal of Sports Medicine* 41: e4.
- Kucera M, Barna M, Horacek O, Kovarikova J, Kucera A (2004) Efficacy and safety of topically applied *Symphytum* herb extract cream in the treatment of ankle distortion: Results of a randomised controlled clinical double blind study. *Wien Med Wochenschr* 154: 498–507.
- Laba E (1989) Clinical evaluation of ice therapy for acute ankle sprain injuries. *New Zealand Journal of Physiotherapy* 17: 7–9.
- Larmour P, Robb G, Hing W, Reid D, McNair P (2002) Use of a vignette to investigate the physiotherapy treatment of an acute ankle sprain: Report of a survey of New Zealand physiotherapists. *New Zealand Journal of Physiotherapy* 30: 36–43.
- Leadbetter WB (1995) Anti-inflammatory therapy in sports injury. The role of non-steroidal drugs and corticosteroid injection. *Clinical Journal of Sports Medicine* 14: 353–410.
- Lippi G, Franchini M, Guidi G, Kean WF (2006) Non Steroidal anti-inflammatory drugs in athletes. *British Journal of Sports Medicine* 40: 661–663.
- Mazieres B, Rouanet S, Velicy J, Scarsi C, Reiner V (2005) Topical Ketoprofen Patch (100 mg) for the treatment of ankle sprain. *American Journal of Sports Medicine* 33: 515–523.
- Michlovitz S, Smith W, Watkins M (1988) Ice and high voltage pulsed stimulation in treatment of acute lateral ankle sprains. *Journal of Orthopaedic and Sports Physical Therapy* 9: 301–304.
- Moore RA, Tramer MR, Carroll D, Wiffen PJ, McQuay HJ (1998) Quantitative systematic review of topically applied non-steroidal anti-inflammatory drugs. *BMJ* 316: 333–338.
- Nyanzi CS, Langridge J, Heyworth JR, Mani R (1999) Randomized controlled study of ultrasound therapy in the management of acute lateral ligament sprains of the ankle joint. *Clinical Rehabilitation* 13: 16–22.
- Ogilvie-Harris DJ, Gilbert M (1995) Treatment modalities for soft tissue injuries of the ankle: a critical review. *Clinical Journal of Sports Medicine* 5, 175–186.
- Petrella R, Ekman EF, Schuller R, Fort JG (2004) Efficacy of Celecoxib, a COX-2-Specific Inhibitor, and Naproxen in the management of acute ankle sprain. *Clinical Journal of Sports Medicine* 14: 225–231.
- Pijnenburg AC, Van Dijk CN, Bossuyt PM. (2000) Treatment of ruptures of the lateral ankle ligaments: a meta analysis. *Journal of Bone and Joint Surgery (Am)* 82: 761–773.
- Roebroek ME, Dekker J, Oostendorp RA, Bosveld W (1998) Physiotherapy for patients with lateral ankle sprains. A prospective survey of practice patterns in Dutch primary health care. *Physiotherapy* 84: 421–432.
- Sakurai Y, Yamaguchi M, Abiko Y (2000) Inhibitory effect of low level laser irradiation on LPS-stimulated prostaglandin E2 production and cyclooxygenase-2 in human gingival fibroblasts. *European Journal of Oral Science* 108: 29–34.
- Shrier I (1995) Treatment of lateral collateral ligament sprains of the ankle: a critical appraisal of the literature. *Clinical Journal of Sports Medicine* 5: 187–195.
- Slatyer MA, Hensley MJ, Lopert R (1997) A randomized controlled trial of piroxicam in the management of acute ankle sprain in Australian Regular Army recruits. The Kapooka Ankle Sprain Study. *American Journal of Sports Medicine* 25: 544–553.
- Sloan JP, Hain R, Pownall R. (1989) Clinical benefits of early cold therapy in accident and emergency following ankle sprain. *Archives of Emergency Medicine* 6: 1–6.
- Stergioulas A (2004) Low level laser treatment can reduce edema in second degree ankle sprains. *Journal of Clinical Laser Medicine and Surgery* 22: 125–128.
- Tabrizi P, McIntyre WM, Quesnel MB, Howard AW (2000) Limited dorsiflexion predisposes to injuries of the ankle in children. *The Journal of Bone and Joint Surgery (Br)* 82: 1103–1106.
- Thorsen H, Lonnberg F (1993) The effect of low-level laser therapy on musculoskeletal pain: a meta-analysis. *Pain* 52: 63–66.
- Van der Heijden GJ, van der Windt DA, de Winter AF (1997) Physiotherapy for patients with soft tissue disorders: a systematic review of randomized controlled trials. *BMJ* 315: 25–30.
- Van der Wees PJ, Lenssen AF, Hendriks, EJ, Stomp DJ, Dekker

- J, de Bie RA (2006) Effectiveness of exercise therapy and manual mobilisation in ankle sprain and functional instability: a systematic review. *Australian Journal of Physiotherapy* 52: 27–37.
- Van der Windt DAWM, Van der Heijden GJMG, Van den Berg SGM, Ter Riet G, De Winter AF, Bouter LM (2002) Therapeutic ultrasound for acute ankle sprains. *Cochrane Database of Systematic Reviews*, Issue 1. Art. No.: CD001250. DOI: 10.1002/14651858.CD001250.
- Van Dijk CN (1999) CBO-guideline for diagnosis and treatment of the acute ankle injury. National Organization for Quality Assurance in Hospitals. *Ned Tijdschr Geneesk* 143: 2097–2101.
- Van Dijk CN (2002) Management of the sprained ankle. *British Journal of Sports Medicine* 36: 83–84.
- Van Tulder M, Furlan A, Bombardier C, Bouter L (2003) Updated method guidelines for systematic reviews in the Cochrane Collaboration Back Review Group. *Spine* 28: 1290–1299.
- Vicenzino B, Branjerdporn M, Teys P, Jordan K (2006) Initial changes in posterior talar glide and dorsiflexion of the ankle after mobilization with movement in individuals with recurrent ankle sprain. *Journal of Orthopaedic and Sports Physical Therapy* 36: 464–471.
- Watts BL, Armstrong B (2001) A randomized controlled trial to determine the effectiveness of double Tubigrip in grade 1 and 2 (mild to moderate) ankle sprains. *Emergency Medicine Journal* 18: 46–50.
- Weiler JM (1992) Medical modifiers of sports injury: the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in soft tissue injury. *Clinical Journal of Sports Medicine* 11: 625–644.
- Wester JU, Jespersen SM, Nielsen KD, Neumann L (1996) Wobble board training after partial sprains of the lateral ligaments of the ankle: a prospective randomized study. *Journal of Orthopaedic and Sports Physical Therapy* 23: 332–336.
- Wilkerson GB, Horn-Kingery HM (1993) Treatment of the inversion ankle sprain: Comparison of different modes of compression and cryotherapy. *Journal of Orthopaedic and Sports Physical Therapy* 17: 240–246.
- World Association for Laser Therapy (WALT) (2005) Recommended anti-inflammatory dosage for low level laser therapy. <http://www.walt.nu> [Accessed April 2006]
- Yeung MS, Chan KM, So CH, Yuan WY (1994) An epidemiological survey on ankle sprain. *British Journal of Sports Medicine* 28: 112–116.
- Zoch C, Fialka-Moser V, Quittan M (2003) Rehabilitation of ligamentous ankle injuries: a review of recent studies. *British Journal of Sports Medicine* 37: 291–5.

Statement regarding registration of clinical trials from the Editorial Board of *Australian Journal of Physiotherapy*

This journal now requires registration of clinical trials. All clinical trials submitted to *Australian Journal of Physiotherapy* must have been registered prospectively in a publicly-accessible trials register. We will accept any register that satisfies the International Committee of Medical Journal Editors requirements. Authors must provide the name and address of the register and the trial registration number on submission.