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Interventions for ulceration and other skin changes caused by nerve damage in leprosy (Review)

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[Intervention Review]

Interventions for ulceration and other skin changes caused by nerve damage in leprosy

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ABSTRACT

Background

At the end of 2016, 145 countries reported to the World Health Organization (WHO) over 173,000 new cases of leprosy worldwide. In the past 20 years, over 16 million people have been treated for leprosy globally. The condition's main complications are injuries and ulceration caused by sensory loss from nerve damage. In this review we explored interventions to prevent or treat secondary damage to the skin in people affected by leprosy (Hansen's disease). This is an update of a Cochrane Review published in 2008.

Objectives

To assess the effects of education, information, self-care programmes, dressings, skin care, footwear and other measures for preventing and healing secondary damage to the skin in persons affected by leprosy.

Search methods

We updated our searches of the following databases up to July 2018: the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, AMED, LILACS, and CINAHL. We also searched five trial registers, three grey literature databases, and the reference lists of included studies for further references to relevant randomised controlled trials (RCTs).

Selection criteria

RCTs or quasi-RCTs or randomised cross-over trials involving anyone with leprosy and potential damage to peripheral nerves who was treated with any intervention designed to prevent damage, heal existing ulcers, and prevent development of new ulcers. Eligible comparisons were usual care, no interventions, or other interventions (e.g. other types of dressings or footwear).

Data collection and analysis

We adhered to standard methodological procedures expected by Cochrane. Primary outcomes were prevention of ulcer(s), healing of existing ulcer(s) and adverse events. We used GRADE to assess the certainty of evidence for each outcome.

Main results

We included 14 trials (854 participants). Eleven studies reported on gender (men: 472, women: 157). Participant age varied from 18 to 74 years. Most participants had a single, mainly non-infected, wound on one foot, which had been there for less than a year. Only seven studies reported whole study duration (there was no follow-up post-treatment), which was on average six months (range: 1 to 12 months). The studies were conducted in Brazil, Ethiopia, Egypt, Indonesia, Mexico, South Korea, and India. Many 'Risk of bias' assessments were rated as unclear risk due to limited information. Six studies had high risk of bias in at least one domain, including selection and attrition bias.

Thirteen studies evaluated different interventions for treating existing ulcers, one of them also evaluated prevention of new ulcers. One study aimed to prevent skin changes, such as cracking and fissures. Investigated interventions included: laser therapy, light-emitting diode (LED), zinc tape, intralesional pentoxifylline, pulsed magnetic fields, wax therapy, ketanserin, human amniotic membrane gel, phenytoin, plaster shoes, and footwear.

We are uncertain about the following key results, as the certainty of evidence is very low. All time points were measured from baseline.

Three studies compared zinc tape versus other interventions and reported results in favour of zinc tape. One study compared zinc tape versus magnesium sulphate: at one month the number of healed ulcers and reduction in mean ulcer area was higher with zinc tape (risk ratio (RR) 2.00, 95% confidence interval (CI) 0.43 to 9.21, and mean difference (MD) -14.30 mm^2, 95% CI -26.51 to -2.09, respectively, 28 participants). Another study compared zinc tape and povidone iodine and found that even though there was a greater reduction in ulcer area after six weeks of treatment with zinc tape, there was no clear difference due to the wide 95% CI (MD 128.00 mm^2, 95% CI -110.01 to 366.01; 38 participants). The third study (90 participants) compared adhesive zinc tape with gauze soaked in Eusol, and found the healing time for deep ulcers was less compared to zinc tape: 17 days (95% CI 12 to 20) versus 30 days (95% CI 21 to 63). Adverse events were only collected in the study comparing zinc tape with gauze soaked in Eusol: there were no signs of skin sensitisation in either group at two months.

Two studies compared topical phenytoin versus saline dressing and reported results in favour of phenytoin. One study reported a greater mean percentage reduction of ulcer area after four weeks with phenytoin 2% (MD 39.30%, 95% CI 25.82 to 52.78; 23 participants), and the other study reported a greater mean percentage reduction of ulcer volume (16.60%) after four weeks with phenytoin (95% CI 8.46 to 24.74; 100 participants). No adverse events were observed with either treatment during the four-month treatment period (2 studies, 123 participants). Prevention of ulcers was not evaluated in these nor the zinc studies, as the interventions were not for preventative use.

Two studies compared protective footwear (with or without self-care) with either 1) polyvinyl chloride (PVC) boots, or 2) pulsed magnetic fields plus self-care and protective footwear. In the study comparing canvas shoes versus PVC boots, none of the 72 participants with scars at the start of the study developed new ulcers over one-year follow-up. Healing of ulcers was assessed in 38 participants from this study, but we are unclear if there is a difference between groups. In the study comparing pulsed magnetic fields (in addition to self-care and protective footwear) to only self-care and footwear in 33 participants, we are uncertain if the mean volume of ulcers at four to five weeks' follow-up was different between groups; this study did not evaluate the prevention of ulcers. Information for adverse events was only reported in the study comparing canvas shoes with PVC boots; the authors stated that the PVC boots could become hot in strong sunlight and possibly burn the feet.

Authors' conclusions

Based on the available evidence, we could not draw firm conclusions about the effects of the included interventions. The main evidence limitations were high or unclear risk of bias, including selection, performance, detection, and attrition bias; imprecision due to few participants in the studies; and indirectness from poor outcome measurement and inapplicable interventions. Future research should clearly report important outcomes, such as adverse events, and assess widely available interventions, which should include treatments aimed at prevention. These trials should ensure allocation concealment, blinding, and an adequate sample size.

PLAIN LANGUAGE SUMMARY

Treatments for ulcers (wounds) and other skin changes in people with leprosy

Review question

We reviewed the evidence about the effects of treatments (e.g. education, self-care, dressings, skin care, or footwear) designed to prevent or treat skin damage in people with leprosy and those with potential damage to peripheral nerves. Treatments could be compared against usual care, no treatment, or another treatment. Evidence is current to July 2018.

Background

Leprosy (Hansen's disease) is a long-lasting, infectious global disease, which may lead to complications like injuries and development of wounds (ulcers), particularly on the feet. Long-term nerve and muscle damage impacts a person's quality of life, leading to mental and financial difficulties. Late diagnosis is the greatest cause of disability, so the key to effective management is early diagnosis and treatment, and early recognition and management of nerve damage, combined with effective health education to prevent limb damage. This review aimed to address uncertainties regarding the best way to prevent and treat skin damage.

Study characteristics

We included 14 trials (854 participants with leprosy). Participants mostly had only one wound on one foot. Wounds were mainly simple (not infected) and varied in size and depth, and were less than one year old; some wounds were more complicated. Participants ranged from 18 to 74 years old. In the 11 studies which reported gender, more men were included. Studies were conducted in Brazil, Ethiopia, Egypt, Indonesia, Mexico, South Korea, and India, in mainly outpatient clinics. Most studies did not report funding sources.

Treatments were mostly compared to dry dressings or dressings soaked in differing solutions. Other comparisons included special plaster, canvas shoes, and foot soak.

Key results

Treatments evaluated included: laser therapy, light-emitting diode (LED), zinc tape or paste, pentoxifylline injections, exposure to pulsed magnetic fields, wax therapy, ketanserin gel, amniotic membrane gel, phenytoin powder, plaster shoes, and footwear. Outcomes were measured from the beginning of treatment. The following key results are based on very low-certainty evidence, so we are not sure of these results.

Three studies compared zinc tape with other interventions: magnesium sulphate glycerin, povidone iodine, or gauze soaked in Eusol. After one month of treatment, the number of healed ulcers was higher and the ulcer area was lower in the zinc tape group compared with magnesium sulphate glycerin. There was no clear difference in the reduction of ulcer area at six weeks when comparing zinc tape to povidone iodine. The healing time for deep ulcers in the zinc tape group was 17 days compared to 30 days with gauze soaked in Eusol. This study also reported no signs of skin sensitisation in either group at two months; the other two studies provided no data on adverse events.

Two studies compared topical phenytoin to salt water dressing. One study showed a greater reduction in ulcer area with phenytoin. The other study found a greater reduction in ulcer volume in favour of phenytoin. Both studies measured this outcome after four weeks of treatment. No adverse events were observed in either study.

The five studies just described did not assess prevention of ulcers, as the therapies were for treatment rather than prevention.

Two studies compared protective footwear (with or without self-care) with either polyvinyl chloride (PVC - a form of plastic) boots, or pulsed magnetic fields plus self-care and protective footwear. In the study comparing canvas shoes versus PVC boots, none of the participants who had scars at the start developed new ulcers over one year. There was no clear difference between the groups in the number of people whose ulcers had healed. In the study assessing pulsed magnetic fields, prevention of new ulcers was not measured; however, there was no clear difference between groups in volume of ulcers four to five weeks after the start of treatment. Only one study reported information about adverse events: the PVC boots could become very hot in strong sunlight, with the possibility of burning.

Certainty of the evidence

We judged the evidence as very low certainty, meaning the results are ambiguous. There were concerns regarding how participants were allocated to treatments, whether participants and study investigators knew which treatment had been received, and the number of participants who dropped out of the studies.

Summary of findings for the main comparison. Zinc tape compared to magnesium sulphate glycerin for ulceration caused by nerve damage in leprosy

Zinc tape compared to magnesium sulphate glycerin for ulceration caused by nerve damage in leprosy

Patient or population: ulceration caused by nerve damage in leprosy
Setting: outpatient clinic, India (Walton 1986)
Intervention: zinc tape
Comparison: magnesium sulphate/glycerin

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with magnesium sulphate/glycerin	Risk with Zinc tape				
Primary outcome: prevention of ulcers	-	-	-	-	-	Not reported
Primary outcome: healing of ulcers (number of ulcers healed after 1 month)	Study population		RR 2.00 (0.43 to 9.21)	28 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
	143 per 1000	286 per 1000 (61 to 1000)				
Primary outcome: healing of ulcers (mean ulcer area (mm^3) Follow-up: mean of one month	The mean ulcer area was 56.7	MD 14.3 lower (26.51 lower to 2.09 lower)	-	28 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Priimary outcome: adverse events	-	-	-	-	-	Not reported
Secondary outcome: quality of life	-	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	-	-	-	-	-	Not reported
Secondary outcome: costs	-	-	-	-	-	Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD**: mean difference; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by four levels to very low-certainty evidence. Two levels due to study limitations (such as 35% lost to follow-up, consecutive cases were randomly allocated, no blinding of outcome assessor, and potential unit of analysis error). Also downgraded two levels for imprecision due to sparse data and wide confidence intervals.

Summary of findings 2. Zinc tape compared to povidone iodine (10%) for ulceration and other skin changes caused by nerve damage in leprosy

Zinc tape compared to povidone iodine (10%) for ulceration and other skin changes caused by nerve damage in leprosy

Patient or population: ulceration and other skin changes caused by nerve damage in leprosy
Setting: outpatient clinic, Indonesia (Overbeek 1991)
Intervention: zinc tape
Comparison: povidone iodine (10%)

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with povidone iodine (10%)	Risk with zinc tape				
Primary outcome: prevention of ulcers	-	-	-	-	-	Not reported
Primary outcome: healing of ulcers (mean reduction of ulcer area at 6 weeks (mm^2))	The mean reduction of ulcer area at six weeks was 260	MD 128 higher (110.01 lower to 366.01 higher)	-	38 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: adverse events	-	-	-	-	-	Not reported
Secondary outcome: quality of life	-	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	-	-	-	-	-	Not reported
Secondary outcome: costs	-	-	-	-	-	Not reported

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD**: mean difference; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by four levels to very low-certainty evidence. Two levels due to study limitations (quasi-randomised trial, high loss to follow-up, and no reporting of blinding of outcome assessor), and two levels due to imprecision (1 study, few participants, wide confidence interval).

Summary of findings 3. Adhesive zinc tape compared to gauze soaked in eusol for ulceration caused by nerve damage in leprosy

Adhesive zinc tape compared to gauze soaked in eusol for ulceration caused by nerve damage in leprosy

Patient or population: ulceration caused by nerve damage in leprosy
Setting: hospital in India (Söderberg 1982)
Intervention: adhesive zinc tape
Comparison: gauze soaked in eusol

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with gauze soaked in eusol	Risk with adhesive zinc tape			
Primary outcome: prevention of ulcers	-	-	-	-	Not reported
Primary outcome: healing of ulcer (days)	Total number of participants was 90 and they had a total of 128 plantar ulcers[b]. The average healing time was shorter for the group treated with zinc tape. The results varied between the two hospitals involved. In one hospital, it took about 20 days (CI 18 to 23) for superficial ulcers to heal in the zinc tape group versus about 30 (CI 27 to 33) in the gauze group. For deep ulcers the average healing time was two weeks more. In the other hospital, the average number of days to heal in the zinc tape group for superficial wounds was about 13 (CI 9 to 15) days and 23 (CI 16 to 28) days in the gauze group. For deep ulcers it took 17 days (CI 12 to 20) in the zinc tape group and 30 (CI 21 to 63) in the gauze group.		-	90 (1 RCT)	⊕⊖⊖⊖ Very low[a]
Primary outcome: adverse events (skin	The study authors reported: "No signs of skin sensitization were observed in either the tape-treated or the gauze-treated wounds".		-	90 (1 RCT)	⊕⊖⊖⊖ Very low[a]

sensitisation at 2 months)					
Secondary outcome: quality of life	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	Not clear how or if this was adequately measured. However, the study authors say: "The zinc tape has the following advantages: 1. shorter healing time, 2. low cost, 3. easy application, 4. more convenient for patients: (a) can be worn under shoes without causing pressure; (b) socially more acceptable, no bandages are needed".		-	90 (1 RCT)	⊕⊖⊖⊖ Very low[a]
Secondary outcome: costs	-	-	-	-	Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by four levels to very low-certainty evidence. Two levels due to study limitations (allocation random alternate basis, no blinding outcome assessor, and inadequate reporting of data), and two levels for imprecision (few participants)).
[b] There was a lack information on how many participants and how many ulcers (deep or superficial ulcers) there were in intervention and control group.

Summary of findings 4. Topical ketanserin (2%) compared to clioquinol cream (3%) or zinc paste for ulceration caused by nerve damage in leprosy

Topical ketanserin (2%) compared to clioquinol cream (3%) or zinc paste for ulceration caused by nerve damage in leprosy

Patient or population: ulceration caused by nerve damage in leprosy
Setting: outpatient clinic, Mexico (Salazar 2001)
Intervention: topical ketanserin (2%)
Comparison: clioquinol cream (3%) or zinc paste

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with clioquinol cream (3%) or zinc paste	Risk with topical ketanserin (2%)				
Primary outcome: prevention of ulcers	-	-	-	-	-	Not reported
Primary outcome: healing of ulcers (healing of ulcer at 3 months)	Study population		RR 6.00 (1.45 to 24.75)	66 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
	61 per 1000	364 per 1000 (88 to 1000)				
Primary outcome: adverse events (assessed at 3 months as minimum, moderate or severe)	Treatment was not suspended in any of the patients because of side effects		-	66 (1 RCT)	⊕⊖⊖⊖ Very low[b]	-
Secondary outcome: quality of life	-	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	-	-	-	-	-	Not reported
Secondary outcome: cost of intervention	-	-	-	-	-	Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by four levels to very low-certainty evidence. Two levels due to study limitations (randomisation procedure not reported, blinding not reported, and unclear if appropriate statistical analysis used) and two levels due to imprecision (1 study, very wide confidence interval).
[b]Downgraded by four levels to very low-certainty evidence. Two levels due to study limitations (randomisation procedure not reported, blinding not reported), one level due to indirectness (not clear how side effects were measured and reported), and one level due to imprecision (1 study).

Summary of findings 5. Topical phenytoin compared to saline dressing for ulceration and other skin changes caused by nerve damage in leprosy

Topical phenytoin compared to saline dressing for ulceration and other skin changes caused by nerve damage in leprosy

Patient or population: ulceration and other skin changes caused by nerve damage in leprosy
Setting: hospital, India
Intervention: topical phenytoin: 2% (Bhatia 2004), unknown (Bansal 1993)
Comparison: saline dressing

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with saline dressing	Risk with topical phenytoin (2%)				
Primary outcome: prevention of ulcers	-	-	-	-	-	Not reported
Primary outcome: healing of ulcers (mean percentage of ulcer volume reduction at 4 weeks (Bansal 1993))	The mean percentage reduction of ulcer volume was 55.5%	MD 16.60% higher (8.46 higher to 24.74 higher)	-	100 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: healing of ulcers (mean percentage reduction of ulcer size area at 4 weeks (Bhatia 2004))	The mean percentage reduction of ulcer size area was 49.1%	MD 39.30% higher (25.82 higher to 52.78 higher)		23 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: adverse events (up to 4 weeks)	No adverse effects were observed in any of the patients treated with phenytoin or normal saline.		-	123 (2 RCTs)	⊕⊖⊖⊖ Very low[b]	-
Secondary outcome: quality of life	-	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	-	-	-	-	-	Not reported
Secondary outcome: cost of intervention	-	-	-	-	-	Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD**: mean difference; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by four levels to very low-certainty evidence. Two levels due to study limitations (non-adequate random sequence generation, unit of analysis error) and two levels due to imprecision (sparse data and consequently wide confidence interval).
[b]Downgraded by four levels to very low-certainty evidence. Two levels due to study limitations (unclear whether allocation was concealed and high risk of attrition bias) and two levels due to imprecision (sparse data).

Summary of findings 6. Footwear - canvas shoes compared to PVC boots for ulceration and other skin changes caused by nerve damage in leprosy

Footwear - canvas shoes compared to PVC boots for ulceration and other skin changes caused by nerve damage in leprosy

Patient or population: ulceration and other skin changes caused by nerve damage in leprosy
Setting: community practice, Ethiopia (Seboka 1998)
Intervention: footwear - canvas shoes
Comparison: footwear - PVC boots

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with PVC boots	Risk with canvas shoes				
Primary outcome: prevention of ulcer (number of persons developing new ulcers at 1 year)	None of the 45 participants with scars developed new ulcers	None of the 27 participants with scars developed new ulcers	-	72 (1 RCT)	⊕⊖⊖⊖ Very low[a]	Seventy-two participants had scars (not ulcers) at the start of the study (27 in canvas group, 45 in PVC group) and none of these developed new ulcers during the year.
Primary outcome: healing of ulcer (number of persons being ulcer-free at 1 year)	Study population		RR 1.16 (0.77 to 1.74)	38 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
	692 per 1000	803 per 1000 (533 to 1000)				
Primary outcome: healing of ulcer (number of persons having ulcers not healed at 1 year)	Study population		RR 0.52 (0.15 to 1.75)	38 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
	308 per 1000	160 per 1000 (46 to 538)				
Primary outcome: adverse events	One adverse comment was that PVC boots could become very hot in strong		-	38 (1 RCT)	⊕⊖⊖⊖ Very low[b]	-

	sunlight, with possibility of burning the feet				
Secondary outcome: quality of life	- -	-	-	-	Not reported
Secondary outcome: acceptability of treatment	The canvas shoes were socially acceptable, but 85% of farmers rated them as good for their work, rather than "excellent" (8%) at first follow-up at three months. More than 80% rated the PVC boots as excellent for social acceptability and work suitability.	-	110[d] (1 RCT)	⊕⊕⊕⊖ Moderate[c]	-
Secondary outcome: costs	See comment	-	110[d] (1 RCT)	-	Costs not reported. Study authors only reported that canvas shoes and PVC boots cost the same. PVC boots are more durable than canvas shoes.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by four levels to very low-certainty evidence. Two levels due to study limitations (unclear randomisation, unclear blinding) and two levels due to imprecision (1 study, small number of participants, wide confidence interval).
[b]Downgraded by four levels to very low-certainty evidence. Two levels due to study limitations (unclear randomisation, unclear blinding), one level due to indirectness (unclear how this outcome was measured), and one level for imprecision.
[c]Downgraded by one level to moderate-certainty evidence. One level due to study limitations (unclear randomisation, unclear blinding).
[d]For these outcomes, the results are reported for all 110 participants in the study (i.e. those with existing ulcers and those with no existing ulcers).

Summary of findings 7. Padded moulded double-rocker plaster shoe compared to padded below-knee plaster for ulceration and other skin changes caused by nerve damage in leprosy

Padded moulded double-rocker plaster shoe compared to padded below-knee plaster for ulceration and other skin changes caused by nerve damage in leprosy

Patient or population: ulceration and other skin changes caused by nerve damage in leprosy
Setting: outpatient clinic, India (Pring 1982)
Intervention: padded moulded double-rocker plaster shoe
Comparison: padded below-knee plaster

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with padded below-knee plaster	Risk with padded moulded double-rocker plaster shoe				
Primary outcome: prevention of ulcer	-	-	-	-	-	Not reported
Primary outcome: healing of ulcer (ulcers fully or nearly healed at 6 weeks)	Study population		RR 0.96 (0.77 to 1.19)	55 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
	875 per 1000	840 per 1000 (674 to 1000)				
Primary outcome: adverse events	-	-	-	-	-	Not reported
Secondary outcome: quality of life	-	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	Study authors stated: "The MD shoe is more acceptable to the patient"		-	55 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Secondary outcome: costs of intervention	Study authors stated: "The MD shoe is .....cheaper to apply and, more important.."		-	55 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD**: moulded double-rocker; **RCT**: randomised controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded by four levels to very low-certainty evidence. Two levels due to study limitations (no information on baseline characteristics; unit of analysis is ulcers, not patients; unclear randomisation procedure; unclear if blinding of outcome assessor), one level due to indirectness (padded moulded double-rocker plaster shoe and padded below-knee plasters might not be acceptable interventions today for people with leprosy), and one level due to imprecision (1 study, small number of participants).

Summary of findings 8. Exposure to pulsed magnetic fields (in addition to self-care and protective footwear) compared to self-care and footwear for ulceration and other skin changes caused by nerve damage in leprosy

Exposure to pulsed magnetic fields (in addition to self-care and protective footwear) compared to self-care and footwear for ulceration and other skin changes caused by nerve damage in leprosy

Patient or population: ulceration and other skin changes caused by nerve damage in leprosy
Setting: outpatient clinic, India (Sarma 1997)
Intervention: exposure to pulsed magnetic fields (in addition to self-care and protective footwear)
Comparison: self-care and footwear

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with self-care and footwear	Risk with exposure to pulsed magnetic fields (in addition to self-care and protective footwear)			
Primary outcome: prevention of ulcer	-	-	-	-	Not reported
Primary outcome: healing of ulcer (at 4 to 5 weeks)	In the control group, the geometric mean volumes of the ulcers were 2843 cu mm and 1478 cu mm on the day of admission and at the end of treatment (P = 0.03); the corresponding values in the PMF group were 2428 cu mm and 337 cu mm, respectively (P < 0.001). A decrease in the volume of 40% or more was observed in 53% of control patients and 89% of PMF participants (P = 0.02): a decrease of 80% or more was observed in none of the controls and in 33% of PMF participants.		-	33 (1 RCT)	⊕⊖⊖⊖ Very low[a]
Primary outcome 2 (healing of ulcer): Mean volume of ulcers at four to five weeks	The mean volume (cm^2) after four to five weeks was 1.48	MD was 1.14 lower (5.37 lower to 3.09 higher)	-	33 (1 RCT)	⊕⊖⊖⊖ Very low[a]

Primary outcome 3 (adverse events)	-	-	-	-	Not reported
Secondary outcome 1 (quality of life)	-	-	-	-	Not reported
Secondary outcome 2 (acceptability of treatment)	-	-	-	-	Not reported
Secondary outcome 3 (cost of intervention)	The authors state: "The cost of construction of an enclosure is around Rs. 5000/- (about 150 USD) and the function generator together with the centre-zero milliammeter costs another Rs. 6000/- (about 180 USD). Where uninterrupted power supply is a problem, an inverter and a 12-volt battery together costing about RS. 5000/- (about 150 USD) would be required."	-	33 (1 RCT)	⊕⊖⊖⊖ Very low[a]

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD**: mean difference; **PMF**: pulsed magnetic field; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded by three levels. One level due to study limitations (unclear randomisation procedure, 7 of 20 patients lost to follow-up) and two levels due to imprecision (1 study with few participants).

Summary of findings 9. Low-level laser therapy compared to simple dressing for ulceration and other skin changes caused by nerve damage in leprosy

Low-level laser therapy compared to simple dressing for ulceration and other skin changes caused by nerve damage in leprosy

Patient or population: ulceration and other skin changes caused by nerve damage in leprosy
Setting: outpatient clinic in Brasil (Barreto 2010)
Intervention: low-level laser therapy
Comparison: simple dressing

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments

	Risk with simple dressing	Risk with low-level laser therapy				
Primary outcome: prevention of ulcer	-	-	-	-	-	Not reported
Primary outcome: healing of ulcer (size of ulcer (area) at 12 weeks (cm^2))	The mean size of ulcer (area) after 12 weeks was 4.4	MD 0.60 lower (6.47 lower to 5.27 higher)	-	23 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: healing of ulcer (size of ulcer (depth) at 12 weeks (mm))	The mean size of ulcer (depth) after 12 weeks was 5.4	MD 1.30 mm lower (5.26 lower to 2.66 higher)	-	23 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: adverse effects	-	-	-	-	-	Not reported
Secondary outcome: quality of life	-	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	-	-	-	-	-	Not reported
Secondary outcome: costs	Costs not analysed between groups, but trial authors state: "Patients have an average of 3.4 simple dressings per week at the dressing service of UREMC, resulting in an estimated expenditure of USD 100,000 per year on disposable dressing material alone."		-	23 (1 RCT)	⊕⊖⊖⊖ Very low[b]	-

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD**: mean difference; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by four levels. One level due to study limitations (unclear allocation concealment, no blinding of outcome assessor), one level due to indirectness (we are unsure if the intervention - laser therapy - is available to people with ulcers caused by nerve damage in leprosy) and two levels due to imprecision (1 study, small sample size, wide confidence interval).

[b]Downgraded by four levels. One level due to study limitations (unclear allocation concealment, no blinding of outcome assessor), one level due to indirectness (we are unsure if the intervention - laser therapy - is available to people with ulcers caused by nerve damage in leprosy) and two levels due to imprecision (1 study, small sample size).

Summary of findings 10. Intralesional pentoxifylline compared to daily simple dressing for ulceration and other skin changes caused by nerve damage in leprosy

Intralesional pentoxifylline compared to daily simple dressing for ulceration and other skin changes caused by nerve damage in leprosy

Patient or population: ulceration and other skin changes caused by nerve damage in leprosy
Setting: outpatient clinic, Egypt (Mikhael 2015)
Intervention: intralesional pentoxifylline
Comparison: daily simple dressing

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with daily simple dressing	Risk with intralesional pentoxifylline				
Primary outcome: prevention of ulcer	-	-	-	-	-	Not reported
Primary outcome: healing of ulcer (complete healing of ulcer at 4 weeks)	Study population		OR 9.00 (1.64 to 49.45)	40 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
	100 per 1000	500 per 1000 (154 to 846)				
Primary outcome: healing of ulcer (ulcer depth (cm) at 4 weeks)	The mean ulcer depth was 0.45	MD 0.22 cm lower (0.40 lower to 0.04 lower)	-	40 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: adverse events (at 4 weeks)	The patients were asked about any possible side effects such as pain, skin rash, discolouration, or discomfort. There were no side effects, except tolerable pain during the injection in intervention group.		-	40 (1 RCT)	⊕⊖⊖ Very low[b]	-
Secondary outcome: quality of life	-	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	-	-	-	-	-	Not reported
Secondary outcome: cost of intervention	-	-	-	-	-	Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD**: mean difference; **OR**: odds ratio; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by three levels to very low-certainty evidence. One level due to study limitations (unclear allocation concealment and unclear if there was blinding of outcome assessor) and two levels due to imprecision (1 small study, very wide confidence intervals).
[b]Downgraded by three levels to very low-certainty evidence. One level due to study limitations (unclear allocation concealment and unclear if there was blinding of outcome assessor), one level due to imprecision (1 small study) and one level due to indirectness (unclear how information of side effects were documented and if both intervention and control group were asked).

Summary of findings 11. Light-emitting diode (LED) irradiation compared to conventional dressing therapy for ulceration and other skin changes caused by nerve damage in leprosy

Light-emitting diode (LED) irradiation compared to conventional dressing therapy for ulceration and other skin changes caused by nerve damage in leprosy

Patient or population: ulceration and other skin changes caused by nerve damage in leprosy
Setting: hospital/outpatient clinic, Korea (Lee 2012)
Intervention: light-emitting diode (LED) irradiation
Comparison: conventional dressing therapy

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with conventional dressing therapy	Risk with LED irradiation				
Primary outcome: prevention of ulcer	-	-	-	-	-	Not reported
Primary outcome: healing of ulcer (mean change of wound size (mm^3) after 8 months treatment)	The mean change of wound size was 26.55	MD 311.47 higher (106.47 higher to 516.47 higher)	-	60 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: adverse events	-	-	-	-	-	Not reported

Secondary outcome: quality of life	-	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	-	-	-	-	-	Not reported
Secondary outcome: cost of intervention	-	-	-	-	-	Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD**: mean difference; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by three levels to very low-certainty evidence. One level due to study limitations (concealment or sequence generation not reported, no blinding) and two levels due to imprecision (only 1 study, few participants, wide confidence interval).

Summary of findings 12. Wax therapy compared to foot soaks for skin changes caused by nerve damage in leprosy

Wax therapy compared to foot soaks for skin changes caused by nerve damage in leprosy

Patient or population: skin changes caused by nerve damage in leprosy
Setting: hospital, India (Sharma 2005)
Intervention: wax therapy
Comparison: foot soaks

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with foot soaks	Risk with wax therapy				
Primary outcome: healing of ulcer	-	-	-	-	-	Not applicable
Tertiary outcome: prevention and treatment of other skin changes (number of feet being fissure- and callous-free at 6 weeks)	Study population		RR 2.22 (1.07 to 4.60)	44 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
	300 per 1000	666 per 1000				

		(321 to 1000)				
Primary outcome: prevention of ulcer	-	-	-	-	-	Not reported
Primary outcome: adverse effects	-		-	-	-	Not reported
Secondary outcome: quality of life	-		-	-	-	Not reported
Secondary outcome: acceptability of treatment (at 6 weeks)	"Patients given wax therapy felt subjectively much better than those who had foot soaks"		-	44 (1 RCT)	⊕⊖⊖⊖ Very low[b]	-
Secondary outome: cost of intervention	-	-	-	-	-	Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RCT**: randomised controlled trial; **RR**: risk ratio.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by four levels to very low-certainty evidence. One level due to study limitations (unclear allocation concealment, unclear if outcome assessor was blinded, and study authors are not clear in numbers of persons or feet reported), two levels due to imprecision (1 study with 44 participants, wide confidence interval) and one level due to indirectness (wax therapy probably not available to most people with leprosy; treatment is given in hospital).
[b]Downgraded by four levels to very low-certainty evidence. One level due to study limitations (unclear allocation concealment, unclear if outcome assessor was blinded, and study authors are not clear in numbers of persons or feet reported), two levels due to imprecision (1 study with 44 participants) and one level due to indirectness (wax therapy probably not available to most people with leprosy; treament is given in hospital).

Summary of findings 13. hAMMSC-CM + vitamin C compared to hAMMSC-CM for ulceration caused by nerve damage in leprosy

hAMMSC-CM + vitamin C compared to hAMMSC-CM for ulceration caused by nerve damage in leprosy

Patient or population: ulceration caused by nerve damage in leprosy
Setting: outpatient clinic in Indonesia (Prakoeswa 2018)
Intervention: hAMMSC-CM + vitamin C
Comparison: hAMMSC-CM

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with hAMMSC-CM	Risk with hAMMSC-CM + vitamin C				
Primary outcome: prevention of ulcer	-	-	-	-	-	Not applicable
Primary outcome: healing of ulcer (size, cm^2, at 8 weeks)	The mean reduction was 1.70	MD 0.31 cm^2 higher (0.35 lower to 0.97 higher)		44 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: healing of ulcer (depth, cm^2, at 8 weeks)	The mean reduction was 0.35	MD 0.10 cm^2 lower (0.17 lower to 0.03 lower)		44 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: adverse events	"No adverse events were encountered in any group"			44 (1 RCT)	⊕⊖⊖⊖ Very low[b]	-
Secondary outcome: quality of life	-		-	-	-	Not reported
Secondary outcome: acceptability of treatment	-	-	-	-	-	Not reported
Secondary outome: cost of intervention	-	-	-	-	-	Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

__CI:__ confidence interval; __MD__: mean difference; __RCT__: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by three levels to very low-certainty evidence. One level due to study limitations (unclear allocation concealment, unclear if outcome assessor was blinded), two levels due to imprecision (1 study with a total of 66 patients with three arms).
[b]Downgraded by three levels to very low-certainty evidence. One level due to study limitations (unclear allocation concealment, unclear if outcome assessor was blinded, one level due to sparce data (1 study with a total of 66 patients with three arms) and one level due to other considerations (unclear how adverse events were measured).

Summary of findings 14. hAMMSC-CM + vitamin E compared to hAMMSC-CM for ulceration caused by nerve damage in leprosy

hAMMSC-CM + vitamin E compared to hAMMSC-CM for ulceration caused by nerve damage in leprosy

Patient or population: ulceration caused by nerve damage in leprosy
Setting: outpatient clinic in Indonesia (Prakoeswa 2018)
Intervention: hAMMSC-CM + vitamin E
Comparison: hAMMSC-CM

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with hAMMSC-CM	Risk with hAMMSC-CM + vitamin E				
Primary outcome: prevention of ulcer	-	-	-	-	-	Not applicable
Primary outcome: healing of ulcer (size, cm^2 at 8 weeks)	The mean reduction was 1.70	MD 1.14 cm^2 higher (0.35 higher to 0.97 higher)	-	44 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: healing of ulcer (depth, cm^2 at 8 weeks)	The mean reduction was 0.35	MD 0.08 cm^2 lower (0.17 lower to 0.01 higher)	-	44 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: adverse events	Study authors reported: "No adverse events were encountered in any group"			44 (1 RCT)	⊕⊖⊖⊖ Very low[b]	-
Secondary outcome: quality of life	-	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	-	-	-	-	-	Not reported
Secondary outome: cost of intervention	-	-	-	-	-	Not reported

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **MD**: mean difference; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by three levels to very low-certainty evidence. One level due to study limitations (unclear allocation concealment, unclear if outcome assessor was blinded), two levels due to imprecision (1 study with a total of 66 patients with 3 arms).
[b]Downgraded by three levels to very low-certainty evidence. One level due to study limitations (unclear allocation concealment, unclear if outcome assessor was blinded), one level due to sparce data (1 study with a total of 66 patients with 3 arms) and one level due to other considerations (unclear how adverse events were measured).

Summary of findings 15. hAMMSC-CM + vitamin E compared to hAMMSC-CM + vitamin C for ulceration caused by nerve damage in leprosy

hAMMSC- CM +vitamin E compared to hAMMSC-CM + vitamin C for ulceration caused by nerve damage in leprosy

Patient or population: ulceration caused by nerve damage in leprosy
Setting: outpatient clinic in Indonesia (Prakoeswa 2018)
Intervention: hAMMSC-CM + vitamin E
Comparison: hAMMSC-CM + vitamin C

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with hAMMSC-CM + vitamin C	Risk with hAMMSC-CM + vitamin E				
Primary outcome: prevention of ulcer	-	-	-	-	-	Not applicable
Primary outcome: healing of ulcer (size, cm^2, at 8 weeks)	The mean reduction was 2.01	MD 0.83 cm^2 higher (0.03 lower to 1.69 higher)	-	44 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-

Primary outcome: healing of ulcer (depth, cm^2, at 8 weeks)	The mean reduction was 0.25	MD 0.02 cm^2 higher (0.06 lower to 0.10 higher)	-	44 (1 RCT)	⊕⊖⊖⊖ Very low[a]	-
Primary outcome: adverse events	Study authors reported: "No adverse events were encountered in any group"			44 (1 RCT)	⊕⊖⊖⊖ Very low[b]	-
Secondary outcome: quality of life	-	-	-	-	-	Not reported
Secondary outcome: acceptability of treatment	-	-	-	-	-	Not reported
Secondary outome: cost of intervention	-	-	-	-	-	Not reported

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **MD**: mean difference; **RCT**: randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded by three levels to very low-certainty evidence. One level due to study limitations (unclear allocation concealment, unclear if outcome assessor was blinded), two levels due to imprecision (1 study with a total of 66 patients with three arms).
[b]Downgraded by three levels to very low-certainty evidence. One level due to study limitations (unclear allocation concealment, unclear if outcome assessor was blinded, one level due to sparce data (1 study with a total of 66 patients with 3 arms) and one level due to other considerations (unclear how adverse events were measured).

BACKGROUND

We have included a glossary with an explanation of some of the terms used, see Table 1.

Description of the condition

Leprosy (Hansen's disease) is a chronic infectious disease caused by the bacterium *Mycobacterium leprae (M leprae)* (Lockwood 2002a). Official figures show that just over 173,000 people were detected with leprosy in 2016, mainly in Asia, the Americas and Africa. The World Health Organization (WHO) stated that less than 14 countries reported more than 1000 new cases in 2015, suggesting that leprosy is gradually becoming limited to a small number of countries (WHO 2016). The WHO fact sheet on leprosy states that 216,108 people from 145 countries were taking medication for leprosy at the end of 2016 (WHO 2017).

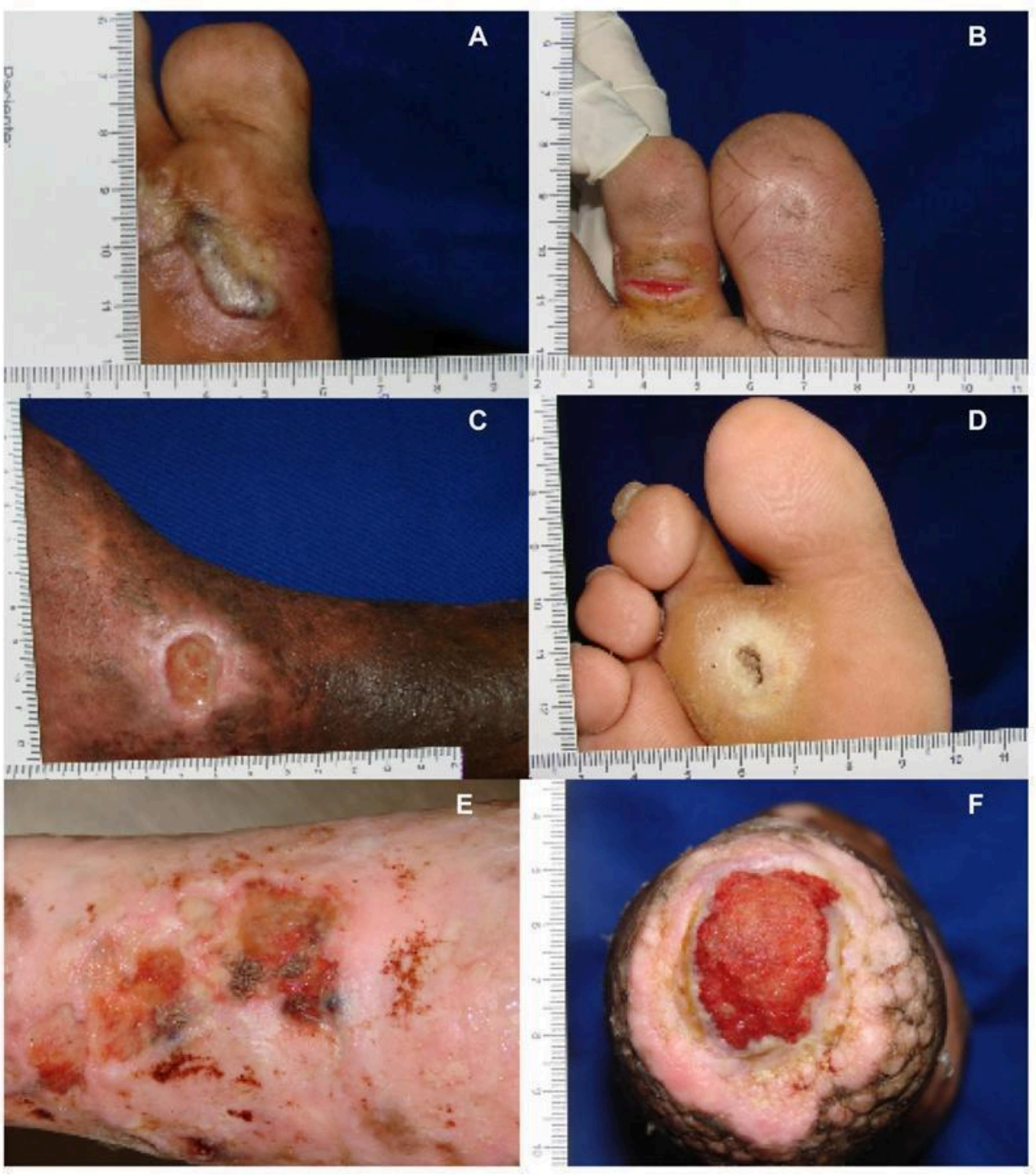
Although the detection rate is declining slowly worldwide, it is rising in a few places (Mandavilli 2019). The proportion of children under 15 years of age among new cases of leprosy ranges widely between countries: from 0.8% to 38.1% in 2015 (mean 8.9%) (WHO 2016). The significant number of childhood cases shows that person-to-person transmission continues to be a problem and many people suffer from the consequences of leprosy (McDougall 2002). Numbers are based on the number of persons with visible impairments of the eyes, hands, and/or feet at the time of diagnosis (WHO disability grade 2). Over 14,000 new cases of leprosy in 2015 were diagnosed with grade 2 disability, which is 2.1 per million population (WHO 2016). In this report, the proportion of new cases with grade 2 disabilities ranged from 4.4% to 25.4%. The numbers of new leprosy cases with disability grade 2 increased from 12,392 in 2006 to 14,059 in 2015 (WHO 2016). The variation can be explained by the methods of detection and reporting in those countries. The low levels of grade 2 disabilities indicates improved disease awareness and early disease detection in communities and health systems. A total of 3039 relapses were reported from 103 countries in 2015 (WHO 2016).

South-East Asia has the highest prevalence of leprosy (persons on leprosy treatment), followed by the Americas, Africa, the Western Pacific, Eastern Mediterranean and Europe. Of all those identified as having the disease, 60% live in India, 13% live in Brazil, and 8% live in Indonesia (WHO 2016).

Leprosy is treated with a combination of immunosuppressive and antibiotic drugs (multidrug therapy) Lockwood 2002a). The drugs are rifampicin, dapsone, and clofazimine, which are effective in killing the bacilli, but do not prevent or treat the nerve inflammation and damage. The inflammation and damage is caused by the immune system responses, requiring other interventions, such as corticosteroids, surgery, or both (Lockwood 2002a). The effectiveness of corticosteroids has been evaluated in a systematic review (Van Veen 2007), whilst surgery for treating nerve damage in leprosy was reviewed in another systematic review (Van Veen 2012). Virtually all people detected with leprosy should be registered with their local health services and treated with multidrug therapy (WHO 2013). People affected by leprosy who are or have been treated with multidrug therapy are not infectious (WHO 2010).

See Figure 1 for pictures of ulcers.

Figure 1. Examples of ulcers in patients with leprosy: (A) Blister formed after walking long distances that later became an ulcer. (B) Fissure on the base of the second toe of the right foot. (C) Right medial malleolus ulcer from a patient with leprosy and HBP. (D) Plantar ulcer on the region of second metatarsal head. (E) Myiasis in a chronic leg ulcer. (F) Chronic ulcer on a lower limb stump. Pictures first appeared in Barreto 2010, with kind permission from Josafá Gonçalves Barreto.



Clinical manifestations and complications

Generally, leprosy starts with a patch or lesion on the skin and enlargement of nerves which may also damage peripheral nerves (Bell 1995; Lockwood 2002a). Often the first signs are a lighter colour patch of skin with loss of hair, sweating and a loss of sensation to temperature and touch and enlarged peripheral nerves when palpated. The principal manifestations are skin patches or lesions with loss of sensation (flat or raised red patches on the skin) and specific enlarged peripheral nerves. The number of lesions may range from one to many depending on a person's immunity. In those with a large number of bacteria, the skin may become diffusely thickened and dry and peripheral nerves enlarged. Inflammation of peripheral nerves can damage nerve function (autonomic, sensory, and motor) and may cause later complications (Bell 1995; Lockwood 2002a). Most complications are the result of nerve damage through direct invasion by the *M leprae* bacteria or inflammation caused by reactions of the person's immune system. If treated early, much of the nerve damage leading to problems in the face, hands, and feet can be prevented (Van Veen 2009).

Initially, the small sensory and autonomic nerve fibres in the skin are damaged, causing local loss of hair, inability to sweat and difficulty detecting temperature and touch sensations. Damage to peripheral nerves can lead to more widespread skin dryness, loss of sensation, and weakness or paralysis of muscles in areas of the body supplied by the affected nerve. The eyes, hands, and feet, with loss of sensation, paralysis and dryness, are at a higher risk of injury and require daily self-care. The dry skin can lead to cracks. If cracks, injuries, and ulcerations are not cared for and rested, they can become infected and lead to further injury and destruction, resulting in visible damage and destruction of the eyes, hands, and feet. These are easily seen impairments; this destruction and paralysis are visible and commonly known as grade 2 disability in leprosy (Lockwood 2002a). If a new leprosy case is seen with a visible grade 2 disability (WHO 2013), then the diagnosis has been late. Community health education programmes, health systems, or both, need to explore strategies to improve early disease detection as well as early detection of nerve function loss and treatment.

The peripheral nerves may be enlarged and/or painful with or without loss of function (sensory loss or muscle weakness). Common enlarged nerves are the auricular nerve, facial nerve, radial cutaneous and ulnar cutaneous and ulnar nerve at the elbow, peroneal nerve, posterior tibial and sural nerves. Nerve palpation for enlargement and pain plus testing for sensory loss and muscle weakness are important parts of the routine clinical exam.

Peripheral nerve function is tested in the face by checking corneal sensation (trigeminal nerve) and eye closure weakness (facial nerve). Peripheral nerve function in the upper extremities evaluates sensory areas and muscle strength of areas innervated by the ulnar and median nerves. Peripheral nerve function in the lower limb evaluates sole sensory loss (posterior tibial nerve) and strength in raising the foot upwards towards the shin or dorsiflexion (peroneal nerve).

Major areas affected by nerve damage in leprosy are the hands (especially the palms), feet (especially the soles), and eyes (Lockwood 2002a). The main complication of sensory nerve damage and the loss of intrinsic muscle function is ulceration, particularly of the feet (de Win 2002; Lockwood 2002a). The multidrug therapy offered to people infected with *M leprae* is efficacious in killing the bacilli if given for a sufficient length of time of six to 12 months (WHO 2006). Even with treatment, some people with leprosy can have immune reactions during and after treatment that require immediate action to reduce the inflammation to prevent or minimise permanent secondary damage to skin and peripheral nerves. If the reaction is not identified and treated adequately, damage cannot be reversed (Lockwood 2002a; Van Veen 2009).

Late diagnosis is the greatest cause of disability, followed by reactions that happen before, during, and after treatment. Frequently, they are either not identified, not treated adequately, or both. It is assumed that for those with permanent nerve damage, further damage and complications may be reduced by good self-care practices, the use of protective footwear, surgery, etc (Lockwood 2002a). Existing WHO 2011 guidelines emphasise the importance of preventing disabilities and mention "identify", "train", "support" and "integrate" as being important principles. Some strategies are suggested as follows (WHO 2011, page 11).

- "Involve persons affected by leprosy to encourage individuals to go for early evaluation."
- "Formally engage persons affected by leprosy in the promotion of self-care and the identification of people in need of practising self-care."
- "Involve persons affected by leprosy in identifying individuals in need of aids and appliances such as protective footwear."

Successful rehabilitation is an important issue that can be achieved through a combination of efforts made by the community and the individuals with their families (WHO 2011). In September 2018, India's Supreme Court ruled that "the government must end discriminatory laws, conduct regular surveillance to detect new cases, provide treatment to everyone who needs it, and promote awareness of leprosy as a curable disease" (Mandavilli 2019).

Diagnosis

Leprosy is diagnosed clinically by the following principal signs (Lockwood 2002a):

- skin lesions with a decrease in sensation, i.e. parts of the skin may feel numb and not able to detect temperature, touch, or painful stimuli such as a pin prick;
- thickened (enlarged) peripheral nerves that can easily be felt through the skin; and/or
- positive smear, i.e. evidence of the causative bacterium, *M leprae*, using microscopic examination of a sample of tissue (skin smear).

Skin biopsy is also used for the diagnosis (Singh 2011).

Classification

There are two main forms of classification (Lockwood 2002b): 1) the Ridley-Jopling scheme; and 2) the WHO operational classification of paucibacillary/multibacillary classification.

Ridley-Jopling scheme

This scheme classifies leprosy on a scale from 'tuberculoid' to 'lepromatous', based on the clinical appearance and bacterial index of lesions (Lockwood 2002b). 'Tuberculoid' indicates that the body's immunity is good and there are few skin lesions. 'Lepromatous' means that the body has a poor immune response to the mycobac-

teria, and there is uncontrolled bacterial multiplication, many skin lesions, and also lesions in the mucosa of the nose and mouth. Peripheral nerve damage can occur at any point on the scale. Between the extremes of 'tuberculoid' and 'lepromatous' are the 'unstable borderline tuberculoid' and 'borderline lepromatous' forms (Lockwood 2002b).

WHO operational classification

This classification is based on the number of skin lesions (Britton 2004):

- paucibacillary - up to five lesions
- multibacillary - more than five lesions (or a positive smear at any site).

This is a simple classification scheme that makes treatment simpler for field workers, but it is less specific than the Ridley-Jopling scheme. The WHO operational classification system is the most widely used.

Impact

Nerve damage can happen before, during, and after chemotherapy treatment. It affects approximately 30% of people diagnosed with leprosy (2.6% with paucibacillary, 37% with multibacillary, 2 years after diagnosis and multidrug therapy treatment; Lockwood 2001). Data from 2002 showed that approximately 6% to 9% of people with newly-diagnosed leprosy presented with grade 2 disabilities (visible deformity or damage present), and as many as 20% to 56% of people have established nerve damage at diagnosis (Lockwood 2002c). These figures vary from country to country and between disease types. Penna 2017 demonstrated the progression of impairments/disability in around 30% of participants after multidrug therapy completion.

Description of the intervention

Leprosy is treated with multidrug therapy. Other interventions, which we will not cover in this review, are aimed at treating immune reactions with corticosteroids, surgery, or both (Lockwood 2002a).

The interventions of relevance to this review are those used in leprosy care which are aimed at the prevention and/or treatment of secondary damage to skin, nerves, and limbs. Preventive interventions include information, education, footwear and self-care. Foot soaks, Vaseline and wax therapy are also meant to prevent ulcers and skin changes. Interventions aimed at treating ulcers include footwear, dressings (i.e. zinc tape, saline, iodine, gauze soaked in different ointments, dry dressings), self-care, information and education (Lockwood 2002a). Therapies like different ointments and gels for topical use; other dressings; and laser, light-emitting diode (LED), or pulsed magnetic fields have been used in trials to aid healing of existing ulcers.

Usual care that aims to prevent ulcers might be information, education, footwear and self-care. Usual care for people that have developed ulcer(s) could also be footwear, self-care, dry dressings, or dressings with saline. Surgical interventions are not covered in our review.

How the intervention might work

The rationale behind the use of, for example, appropriate footwear is to protect feet from secondary damage that can lead to superficial sores on the soles of the feet, and later ulcers and secondary infections (McDougall 2002). Many other interventions have been tried in healing such ulcers (Srinivasan 1989).

Self-care includes daily management to reduce the effects of nerve function impairment (Lockwood 2002a). Education, information, and empowerment of those affected by leprosy (and their carers) is part of some leprosy programmes (Cross 2005a; Cross 2005b; McDougall 2002).

As for dressings, phenytoin is a topical dressing thought to enhance cutaneous healing (Hokkam 2011). Zinc tape is also thought to enhance healing, as zinc might play a part in the healing of wounds. Over many years ordinary adhesive zinc tape has been used (Kumar 1986). Dry dressings and saline dressings are used to protect ulcers from contamination and thus enhance healing.

Adverse reactions to any dressings could be allergic or local irritation or pain associated with application or injection. Other adverse effects might be disadvantages related to time and resources for the person involved (hospitalisation, frequent visits to outpatient clinics, etc.).

Why it is important to do this review

The key to effective management of leprosy is early diagnosis and treatment, and early recognition and management of nerve damage, combined with effective health education to prevent limb damage (Lockwood 2002a; Lockwood 2002b). Successful treatment of nerve damage itself can be effective for preventing ulcer development. Corticosteroids have been used for this purpose (Lockwood 2002a). However, a systematic review of three RCTs comparing prednisolone with placebo or comparing different doses of corticosteroids did not show a statistically significant long-term effect (Van Veen 2007). Also, corticosteroids are not well tolerated by everyone and may cause harmful effects (Lockwood 2002a). It is therefore still of importance to find the best way to prevent or treat skin damage.

People with leprosy are, after a few days on chemotherapy, no longer infectious and can lead a normal social life. This has contributed to the management of leprosy programmes worldwide moving away from clinics dedicated to the treatment of leprosy, to primary healthcare services in general (Lockwood 2002a; WHO 2010). Despite the opportunity to live a normal social life, long-term nerve and muscle damage can lead to great psychosocial and financial difficulties, social stigmatisation, and decreased quality of life for people with leprosy. Care and awareness of limb use will in all circumstances be necessary, and education of those with leprosy is considered a central element to achieve a satisfactory level of self-care (Lockwood 2002a).

Why we presented a new protocol

When we made the decision to update our review from 2008 (Reinar 2008), we wanted to do this by way of a new protocol. In the new protocol the numbers of prespecified outcomes were reduced to those that are most clinically relevant, and it includes both RCTs and quasi-RCTs.

We included RCTs and quasi-RCTs where the method of allocation was such as alternation, date of birth, or case record number (Higgins 2011*).* This deviates from the previous protocol (Reinar 2003). In our published review (Reinar 2008), we identified and included

three studies with an alternating allocation procedure, four studies reported as RCTs, and one study for which we could not determine whether the allocation procedure had been random or quasi-random.

The reason for including quasi-randomised trials was that the risk of bias is not necessarily very different. According to Altman and Bland, quasi-random methods are "in principle unbiased - being unrelated to patients' characteristics - problems arise from the openness of the allocation system" (Altman 1999). This point was elaborated in Chalmers 1999. As for RCTs, the results from a study by Pildal 2005, revealed that of 96 studies not reporting on the concealment of the allocation procedure, only 15 (16%) actually had reported in the respective study protocols that concealment would be done. In the randomised studies that we included, none reported on concealment. On this basis, we assumed that most likely the randomised studies had not concealed allocation and so did not deviate from quasi-randomised trials in that respect. Consequently, they would all be prone to selection bias. Therefore, we chose to display the whole of the evidence base that had used these two designs, a decision we affirmed in the protocol.

OBJECTIVES

To assess the effects of education, information, self-care programmes, dressings, skin care, footwear and other measures for preventing and healing secondary damage to the skin in persons affected by leprosy.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomised controlled trials (RCTs), quasi-RCTs, and randomised cross-over trials. We did not include observational studies. Quasi-RCTs were defined as trials with an allocation procedure such as alternation, date of birth or case record number.

Types of participants

People with leprosy and potential damage to peripheral nerves who were on multidrug treatment or were post-treatment. We considered studies that included participants living in the community or those that were hospitalised. Case definitions were typically based on the Ridley-Jopling scheme or the World Health Organization (WHO) operational classification of paucibacillary/multibacillary classification. However, we also included studies that did not specify the diagnostic criteria. We included studies with participants of all ages, genders, all countries, and all kinds of ulcers caused by leprosy. Studies with a subset of leprosy participants would have been included if they constituted more than 90%.

Types of interventions

Education, information, self-care programmes, dressings (i.e. zinc tape, saline, iodine, gauze soaked in different ointments, dry dressings), skin care, footwear, or other measures designed to prevent or treat damage.

Comparisons might be usual care, no interventions, or other interventions (for example, other types of dressings, other types of footwear, other measures designed to prevent or treat damage). Interventions could be given in primary care, outpatient units, or in hospitals.

Types of outcome measures

Primary outcomes

- Prevention of ulcer(s), as measured in the studies at typically six weeks or less, up to three months, six months, or one year or more.
- Healing of existing ulcer(s), as measured in the studies at six weeks or less, up to three months, six months, or one year or more (e.g. number of ulcers healed, size of ulcers, number of new ulcers).
- Adverse events, either those sufficiently serious to stop the intervention, or minor ones reported by participants.

Secondary outcomes

- Quality of life measures or other psychological or functional measures.
- Acceptability of treatment by person affected by leprosy, as measured in the studies.
- Cost of intervention, as direct costs, if reported by study authors.

Tertiary outcome

- Prevention or treatment of other skin changes, such as cracking, thickening or pigmentary changes.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press, or in progress).

Electronic searches

For this update, we revised all our search strategies in line with current Cochrane Skin practices. Details of the previous search strategies are available in Reinar 2008.

The Cochrane Skin Information Specialist searched the following databases up to 25 July 2018.

- Cochrane Skin Group Specialised Register using the search strategy in Appendix 1.
- Cochrane Central Register of Controlled Trials (CENTRAL; 2018, Issue 6), in the Cochrane Library using the strategy in Appendix 2.
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 3.
- Embase via Ovid (from 1974) using the strategy in Appendix 4.
- CINAHL (Cumulative Index to Nursing and Allied Health Literature) (EBSCO) using the strategy in Appendix 5.
- AMED (Allied and Complementary Medicine Database) using the strategy in Appendix 6.
- LILACS (Latin American and Caribbean Health Science Information Database) using the strategy in Appendix 7.

Trial registers

We (LF, LMR) searched the following trial registers for ongoing trials using the term 'lepro*' up to 24 February 2019.

- ISRCTN registry (www.controlled-trials.com).

- ClinicalTrials.gov (www.clinicaltrials.gov).
- Australian New Zealand Clinical Trials Registry (www.anzctr.org.au).
- World Health Organization International Clinical Trials Registry Platform (ICTRP) (apps.who.int/trialsearch/).
- EU Clinical Trials Register (www.clinicaltrialsregister.eu/).

Searching other resources

Grey literature

We (LF, LMR) searched for grey literature to identify studies not indexed in the databases listed above, using the following databases up to 24 February 2019.

- OpenSIGLE (www.opengrey.eu) (search phrase: leprosy and ulcer*).
- OAIster (www.oclc.org/oaister) (search phrase: kw:leprosy ti:leprosy ulcer*).
- Grey Literature Report (www.greylit.org) (search phrase: leprosy).

References from published papers

We checked the bibliographies of included studies and identified reviews for further references to relevant trials.

We did not search for unpublished and ongoing trials by corresponding with authors, field experts, or experts on tropical medicine or leprosy or both (deviation from protocol).

Adverse effects

We did not perform a separate search for adverse effects of the target interventions. We considered adverse effects described in the trials we read in full text only. We considered all adverse effects reported in the included trials.

Data collection and analysis

Some parts of the methods section of this review use text that was originally published in other Cochrane Reviews co-authored by KGB (predominantly Larun 2015).

Selection of studies

Two review authors (LMR, LF) independently screened all titles and abstracts identified in the literature searches for RCTs and quasi-RCTs. We excluded studies that clearly did not have a trial design with random or quasi-random allocation of participants. Before inclusion or exclusion, the same two review authors independently read the full text of studies that we assessed as eligible. At this point, we discussed any disagreement with a third review author (KGB), and decisions were made by consensus. We made judgements based on the inclusion criteria stated above (Criteria for considering studies for this review).

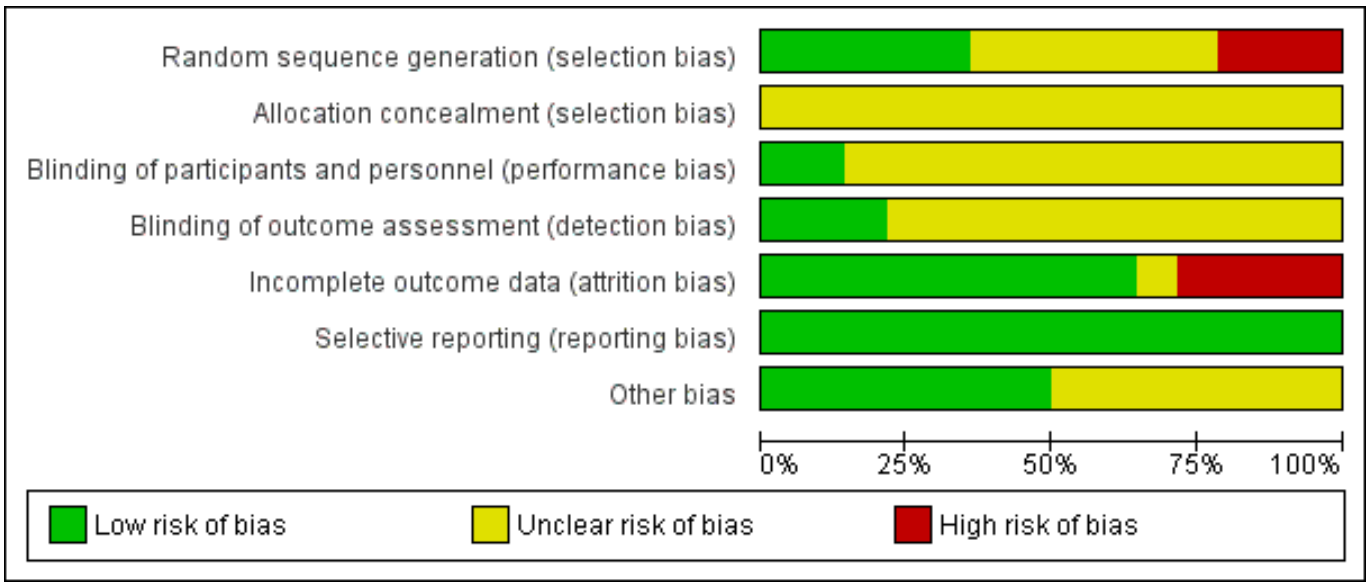
Data extraction and management

Two review authors (LMR, LF) independently performed the data extraction and entered data onto a data extraction form. One author (LMR) entered data into Review Manager (Review Manager 2014), and one review author (LF) checked the Review Manager file. We were not blinded to the names of trial authors or journals. We used the same piloted data extraction form that we used for our previous review (Reinar 2008). The data items we extracted were title, country where study took place, type of study, type of participants, type of interventions, control group interventions, setting, number of eligible participants, number entered into each study group, demographical data of participants, primary and secondary outcomes, results, unit of allocation, unit of analysis and length of follow-up.

Assessment of risk of bias in included studies

We (LMR, LF) used Cochrane's 'Risk of bias' tool to make judgements of low, high, and unclear risk of bias for all included studies for all outcomes (Higgins 2011). We discussed any disagreement with a third review author (KGB), and decisions were made by consensus. We also presented the review authors' judgement about each 'Risk of bias' item presented as a percentage across all included studies as a 'Risk of bias' graph (Figure 2).

Figure 2. 'Risk of bias' graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



We assessed selection bias by judging and reporting methods used for sequence generation and allocation concealment. Quasi-randomised trials were judged as 'high risk of bias' regarding sequence generation and unclear for concealment of allocation. Randomised trials not reporting on allocation concealment were judged as 'unclear'. We assessed performance bias by judging and reporting any blinding of participants, personnel, and outcome assessors. We also looked for and reported any other threats to validity concerning systematic differences between groups in the care provided. We assessed detection bias by judging and reporting any blinding of participants, personnel, and outcome assessors. We assessed attrition bias by looking for systematic differences in loss to follow-up between groups. We also looked for and reported other potential threats to validity concerning systematic differences between groups in how outcomes were determined. We assessed reporting bias (selective outcome reporting) by examining the protocol or methods section of the included study for mention of outcomes that were not reported later in the study or for outcomes that would have been expected to have been measured. If our search had identified study protocols we would have used these in the assessment of potential publication bias. We assessed other risks of bias by judging and reporting, for example, avoidance of cointerventions, differences in baseline characteristics, recruiting bias, or inappropriate influence of funder. We did not exclude studies at high risk of bias.

We summarised 'Risk of bias' assessments for each key outcome for each study in a 'Risk of bias' summary table (Figure 3).

Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.

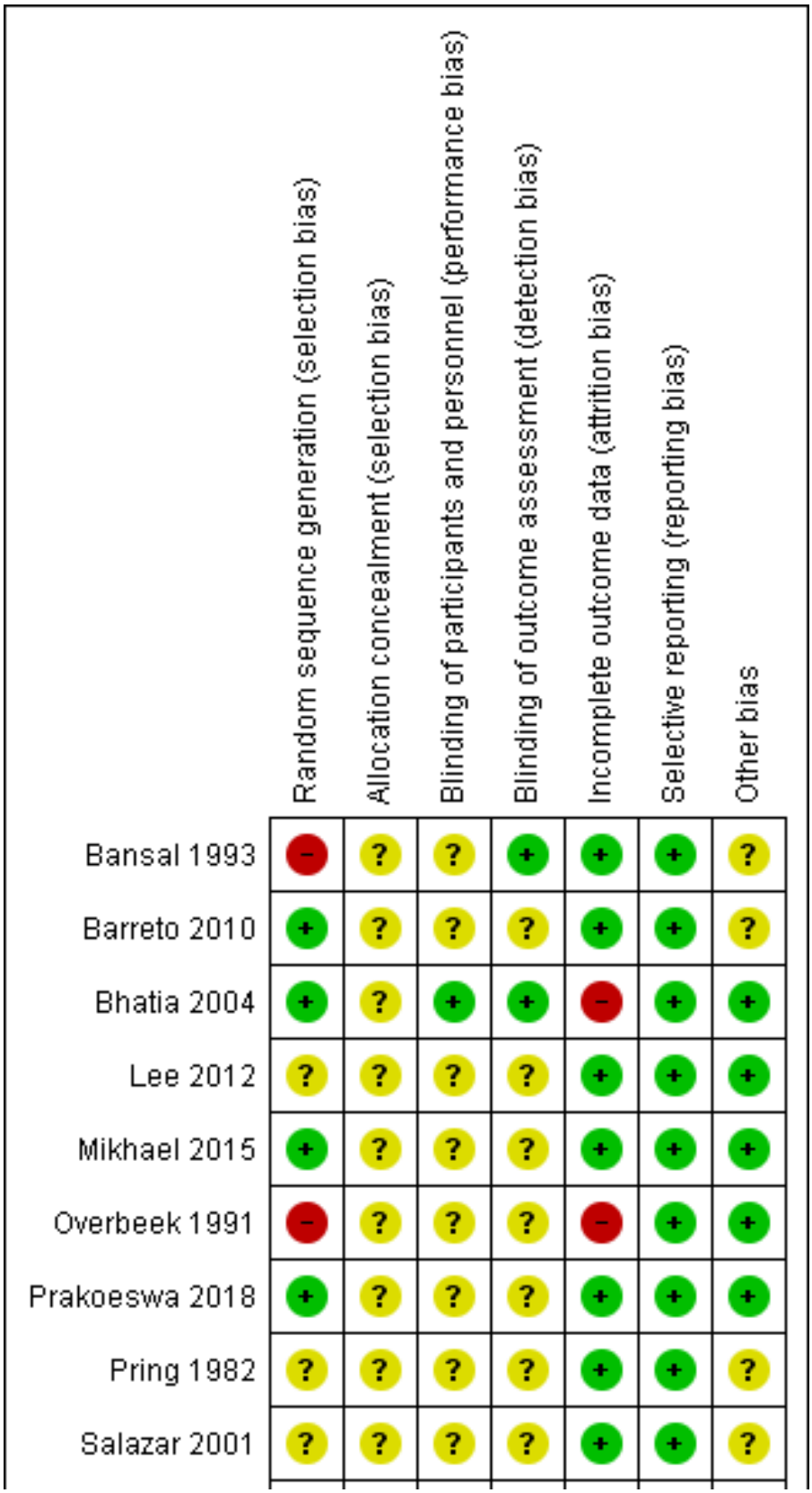
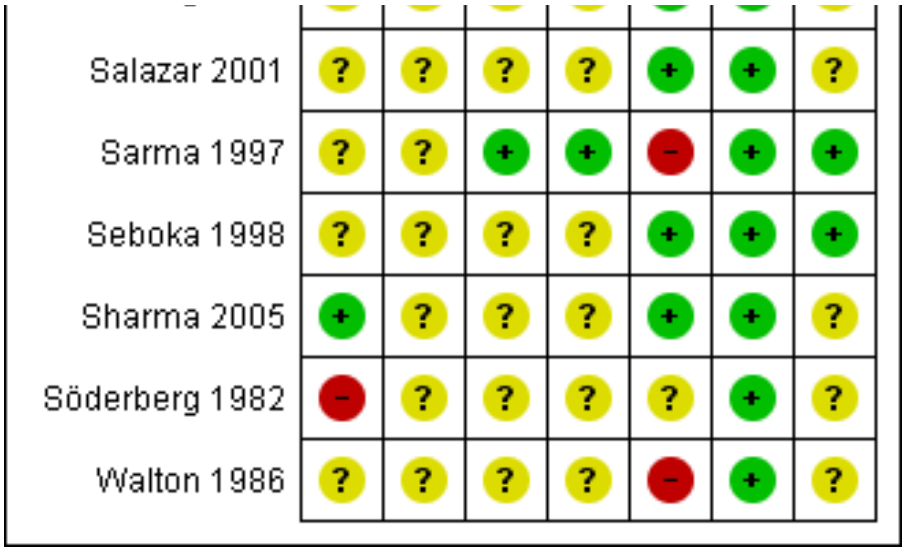


Figure 3. (Continued)



Measures of treatment effect

Dichotomous data

Effect estimates based on dichotomous data were reported as risk ratios (RRs) with 95% confidence intervals (CIs).

Continuous data

We calculated continuous outcomes as mean differences (MD) with 95% CIs.

If different scales had been used for the same outcome, we would have calculated standardised mean differences (SMDs) to allow pooling. Studies which reported change data would have been pooled with studies using post-test data in the same meta-analysis, with change data and endpoint data as subgroups.

Unit of analysis issues

Cluster-randomised trials

Unit of analysis errors may occur if analyses are conducted on a different level to the allocation. Authors of cluster-randomised trials may fail to account for the intraclass correlation coefficient (ICC), leading to a 'unit of analysis' error; whereby CIs are unduly narrow and statistical significance overestimated (Divine 1992). If we had included a cluster-randomised trial and clustering had not been accounted for in primary studies, we would have contacted the corresponding author to obtain the ICC, if we thought it would make a difference to the results. In that case, we could have adjusted for this by using methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) (chapter 16.3). If cluster studies are appropriately analysed taking into account the ICC, and relevant data are reported, synthesis with other studies will be possible using the generic inverse variance technique. In that case, we would have presented data adjusted for the clustering effect as if from a parallel-group randomised study, but we would have performed sensitivity analysis in which such studies would have been excluded.

For this update, we did not identify any cluster-randomised trials. However, since some trials randomised participants of which some had several ulcers, there is for these studies, an element of clustering. In principle, this should have been accounted for in the analysis. In the studies that explicitly included people with several ulcers without reporting how this was handled in the analysis, we made a note of this in the Characteristics of included studies table. However, we judged that the clustering was not comprehensive enough to make any difference to the reported results.

Multiple levels of intensity

One study may address the effects of the same intervention with multiple levels of intensity (e.g. frequency of follow-up). In that case, for dichotomous outcomes we would have summed up the sample sizes and the number of people with events across all relevant intervention groups. For continuous outcomes, we would have combined means and standard deviations using methods described in chapter 7 (section 7.7.3.8) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Multiple interventions

Studies may also combine several interventions with one comparison group. We did not identify any studies with multiple interventions. In that case, we would have analysed the effects of each intervention group versus the comparison separately, but divided the total number of participants in the comparison group. In the case of continuous outcomes the total number of participants in the comparison group would also have been divided, but the means and standard deviations would have been left unchanged (see chapter 16, section 16.5.4 in Higgins 2011).

Randomised cross-over trials

If we had found and included randomised cross-over trials we would have analysed data from the first period only.

Dealing with missing data

We planned to carry out analyses of all outcomes of interest according to the participants' allocated treatment, irrespective of whether they received that treatment or not. However, some studies had loss to follow-up of participants. In these cases, we did not attempt to impute missing data.

For studies published in the previous 10 years, we contacted two trial authors to ask for data and more information, but neither of them responded.

Assessment of heterogeneity

When we judged that the included trials were too clinically heterogeneous to warrant a formal meta-analysis, we did not perform a meta-analysis, but presented the results of the included trials in a narrative format.

In the case of a meta-analysis, we would have assessed statistical heterogeneity on the basis of the *Cochrane Handbook for Systematic Reviews of Interventions* recommendations: I^2 values of 0% to 40% might not be important; 30% to 60% may represent moderate heterogeneity; 50% to 90% may represent substantial heterogeneity; 75% to 100% may represent considerable heterogeneity (Higgins 2011).

In addition to the I^2 value (Higgins 2011), we would have presented the Chi^2 statistic and its P value and considered the direction and magnitude of the treatment effects. The Chi^2 test is underpowered to detect heterogeneity in meta-analyses with few studies (Higgins 2011), and hence a P value of 0.10 would have been used as a threshold of statistical significance.

Assessment of reporting biases

We attempted to obtain unpublished results to minimise the risk of reporting bias. There were too few studies in each comparison to perform funnel plots to identify publication bias.

Data synthesis

We presented the results of trials we assessed to be too heterogeneous to combine in a narrative format. The results of single studies are illustrated in forest plots for visualisation. In a meta-analysis we would have estimated the effect across studies by using a random-effects model because we would have expected some clinical heterogeneity (slightly different interventions, populations and comparators) among studies. Where results are estimated for individual studies with low numbers of outcomes (< 10 in total) or where the total sample size is less than 30 participants and a risk ratio is used, we also reported the proportion of outcomes in each treatment group together with a P value from a Fisher's exact test

(Higgins 2011). We created the forest plots using Review Manager 5 (Review Manager 2014).

Subgroup analysis and investigation of heterogeneity

We did not have sufficient data to undertake subgroup analyses according to the study's classification of disease severity.

Sensitivity analysis

No study results were pooled in this review. Accordingly, we could not perform sensitivity analysis for pooled results separately by addressing the effects on the results of excluding:

- studies assessed as being at high risk of bias;
- quasi-randomised trials; and
- cluster-randomised trials.

'Summary of findings' table

We (LMR, LF) used the GRADE approach to assess the certainty of the body of evidence (GRADE Handbook 2013). We produced 'Summary of findings' tables presenting the overall certainty of evidence for primary and secondary outcomes for each comparison. The outcomes reported in our 'Summary of findings' tables are as follows.

- Prevention of ulcers
- Healing of ulcers
- Adverse events
- Quality of life
- Acceptability of treatment
- Costs

We used GRADEpro to prepare the 'Summary of findings' tables (GRADEpro GDT 2018). We judged the following domains in all included studies: study design, risk of bias, inconsistency, indirectness, imprecision and other considerations. We made an overall assessment of the certainty of the evidence as high, moderate, low, and very low (Higgins 2011, chapter 11). Any disagreements were discussed with a third review author (KGB) and were resolved by reaching consensus.

RESULTS

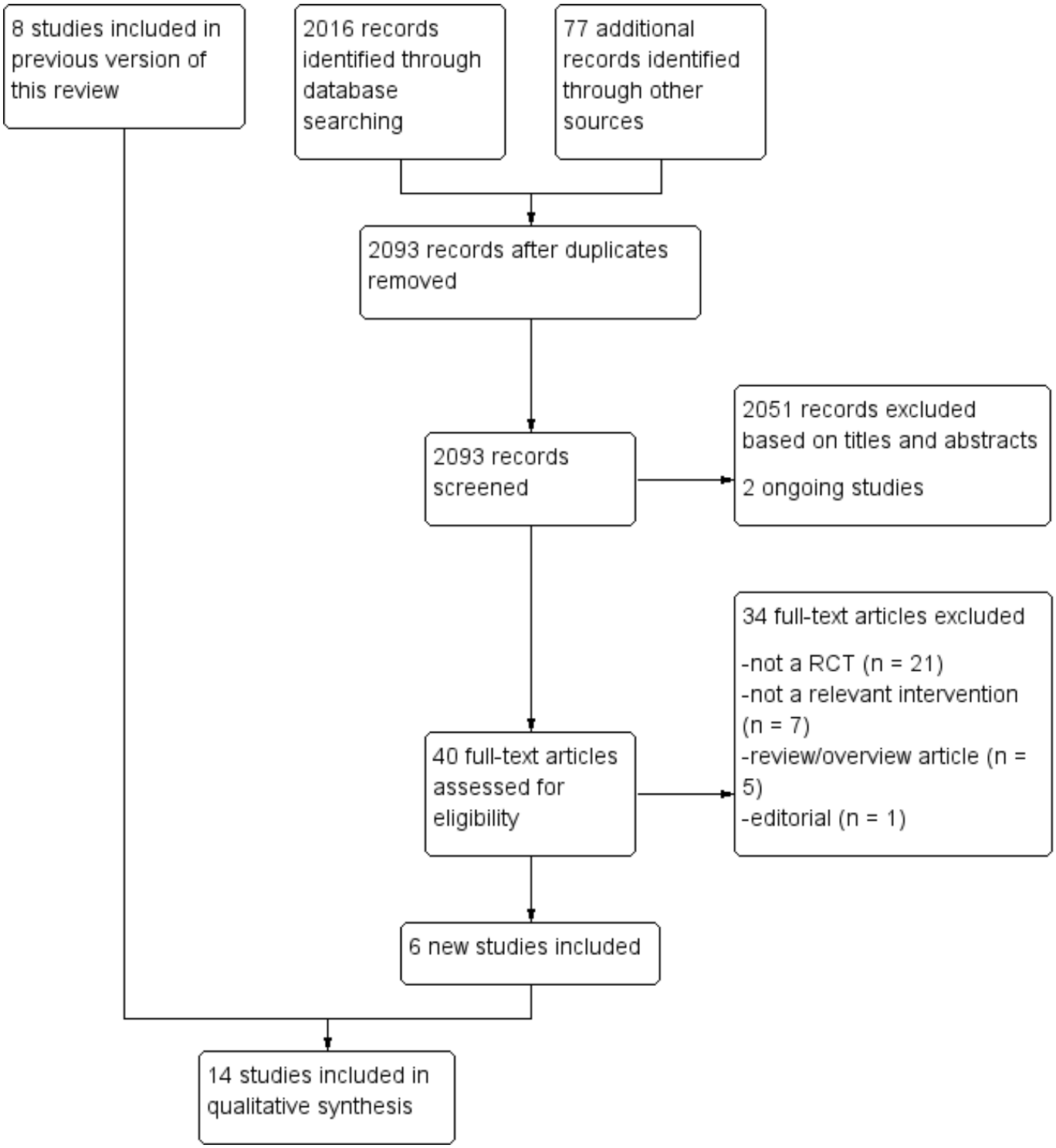
Description of studies

See Characteristics of included studies.

Results of the search

The searches for this update identified 2093 citations to potentially relevant new trials. We excluded 2051 references based on titles and abstracts. We identified two relevant ongoing studies (CTRI/2012/12/003178; NCT03072004; see Characteristics of ongoing studies). We assessed the remaining 40 records in full text, and excluded 34 (Characteristics of excluded studies). We included six new studies, along with eight studies from the previous review, which brought the total number of included studies to 14 (Characteristics of included studies). See the study flow diagram for a summary of the screening process (Figure 4).

Figure 4. Study flow diagram.



Included studies

Design

We included 14 trials (randomised and quasi-randomised) with a total of 854 participants. The studies were published between 1982 and 2018. Two studies had three arms, and one study reported on two separately conducted trials (multicentre study). The initial assessment and baseline reporting of leprosy and damage to peripheral nerves was recorded in varying details, as was the reporting of outcome measurements and results.

Sample sizes

All included trials were small, with between 25 and 110 adult participants affected by leprosy.

Participants

In 12 of the studies, all participants had ulcers at trial entry. In one study (Seboka 1998), some of the participants had scars, not ulcers. One study only included participants with anaesthetic feet with fissures or callosities, or both (Sharma 2005). The participants were aged between 18 and 74 years, but age was not reported in four studies (Pring 1982; Sharma 2005; Söderberg 1982; Walton 1986). Gender was not reported in three studies (Pring 1982; Sharma 2005; Walton 1986), but information from the remaining studies suggests there were more men amongst the participants (472 men and 157 women).

All studies except Sharma 2005 included participants affected by leprosy with plantar ulcers, and three studies also included participants with ulcers elsewhere, mostly the hands (Bansal 1993; Lee 2012; Salazar 2001). The majority of participants had only one wound (ulcer) on one foot. The wounds were mainly simple (not infected) and they varied in size and depth; some wounds were more complicated. The majority of participants had their wounds for less than a year.

Setting

The trials took place in Brazil, Ethiopia, Egypt, Indonesia, Mexico, South Korea, and most in India. Four studies were hospital based (Bansal 1993; Bhatia 2004; Sharma 2005; Söderberg 1982), while nine were based at outpatient clinics (Barreto 2010; Overbeek 1991; Prakoeswa 2018; Pring 1982; Salazar 2001; Seboka 1998; Sarma 1997; Mikhael 2015; Walton 1986). One study included both in- and outpatients (Lee 2012).

Interventions

The studies evaluated various treatment interventions: low laser therapy (3 times per week) (Barreto 2010), light-emitting diode (LED; 20 minutes) (Lee 2012), weekly injected intralesional pentoxifylline (Mikhael 2015), daily to weekly zinc tape (Overbeek 1991; Söderberg 1982), zinc tape in addition to self-care and sandals (Walton 1986), padded moulded double-rocker plaster shoe (in addition to education) (Pring 1982), topical ketanserin (every 12 hours) (Salazar 2001), topical human amniotic membrane-mesenchymal stem cell-conditioned medium (every 3 days) (Prakoeswa 2018), daily pulsed magnetic fields (in addition to self-care and protective footwear) (Sarma 1997), PVC boots (daily) (Seboka 1998), daily wax therapy (Sharma 2005), and daily topical phenytoin dressings (Bansal 1993; Bhatia 2004).

Comparisons

Nine of the interventions were compared to dry dressings or dressings soaked in differing solutions. Padded, moulded double-rocker plaster shoes were compared to padded below-knee plasters, which were the traditional method; PVC boots were compared to canvas shoes; and hot wax therapy was compared to 20 minutes foot soak in water plus Vaseline.

Duration

Four interventions were given for four weeks (Bansal 1993; Bhatia 2004; Sarma 1997; Walton 1986), three were given for six weeks (Pring 1982; Overbeek 1991; Sharma 2005), three were given for eight weeks (Mikhael 2015; Prakoeswa 2018; Söderberg 1982), two were given for 12 weeks (Barreto 2010; Salazar 2001), and one intervention was given for 12 months (Seboka 1998). Lee 2012 did not report duration of treatment period, but the whole study lasted eight months.

Outcomes

All trials but one reported as the primary outcome 'Healing of existing ulcers', measured either as proportion healed or number of ulcers healed. Adverse events were covered in a few trials, but there was limited information on how this outcome was measured. Costs were not systematically assessed, and neither were acceptability of treatment nor any quality of life measures. The follow-up period from baseline varied from one month to one year. The follow-up period did not, in any trials, go beyond the study duration, and outcomes were measured either during the trials or at the end of study duration, or both.

Typical outcome measures were number of ulcers healed, size of ulcers or reduction of ulcer size, number of new ulcers, ulcer-free at one year, ulcers not healed, ulcers fully healed, and use of adapted footwear.

None of the 14 included studies measured quality of life. Prevention of ulcers was only reported in Seboka 1998. Only one study measured our tertiary outcome: prevention or treatment of other skin changes, such as cracking, thickening or pigmentary changes (Sharma 2005).

Funding sources

The included studies were funded by trusts, universities, research councils, leprosy trusts, and government grants. However, the majority of studies did not report funding source (Characteristics of included studies).

Excluded studies

We excluded 34 of the studies we read in full text (Characteristics of excluded studies). The main reason for exclusion was that they were not randomised trials (21 studies), they did not have a relevant intervention (7 studies), or publication type (being reviews or an editorial; 6 studies). One controlled trial evaluated wax therapy for dry feet (Mahajan 1995), but was not included because the allocation procedure seemed to be neither random nor quasi-random.

Risk of bias in included studies

We assessed all studies for risk of bias (Characteristics of included studies). Due to generally poor reporting it was often difficult to make the assessments; hence, we rated many assessments at unclear risk of bias. We rated seven studies at high risk of bias in at least one domain including selection bias (random sequence generation) (Bansal 1993; Overbeek 1991; Söderberg 1982), attrition bias (Bhatia 2004; Overbeek 1991; Sarma 1997; Walton 1986). We did not consider any studies to be at low risk of bias for all domains. Please see Figure 2 for the 'Risk of bias' summary: review authors' judgements about each domain for each included study, and see Figure 3 for the 'Risk of bias' graph: review authors' judgements about each domain presented as percentages across all included studies.

Allocation

We judged three trials to be clearly quasi-randomised and we rated these at high risk of selection bias from random sequence generation (Bansal 1993; Overbeek 1991; Söderberg 1982). Two trials were

potentially quasi-randomised (Salazar 2001; Walton 1986), but as we were not sure, we assessed them as having unclear randomisation procedures along with four other studies (Lee 2012; Pring 1982; Sarma 1997; Seboka 1998). We assessed five studies as having adequate randomisation sequence generation (Barreto 2010; Bhatia 2004; Mikhael 2015; Prakoeswa 2018; Sharma 2005). We considered all studies at unclear risk of selection bias regarding allocation concealment due to limited information reported in the publications.

Blinding

Although participants in many cases could have been blinded to their intervention, this was usually not described or reported in the included trials. Two studies reported that the patient and health care providers as well as the outcome assessor were blinded and we accordingly considered these as having low risk of performance and detection bias (Bhatia 2004; Sarma 1997), while Bansal 1993 reported only blinding of outcome assessor (low risk of detection bias). We considered the remaining studies as having unclear risk of performance and detection bias.

Incomplete outcome data

We had some concerns about attrition bias in four studies mainly due to loss of follow-up (Bhatia 2004; Overbeek 1991; Sarma 1997; Walton 1986); therefore, we considered these studies at high risk of attrition bias. We rated one study as unclear on attrition bias (Söderberg 1982) and we considered the remaining studies at low risk of attrition bias.

Selective reporting

We have no reason to suspect any selective reporting in the studies. However, for all but one study we did not have access to the study protocols (Barreto 2010), but we did inspect the methods section in each study. We assessed all studies as having low risk of selective reporting.

Other potential sources of bias

We considered seven studies to be at unclear risk of other biases. Five studies randomised some participants with more than two ulcers (Bansal 1993; Barreto 2010; Pring 1982; Salazar 2001; Walton 1986), but the average cluster size was so small (less than 1.5) that the potential impact of a unit of analysis error was negligible. Hence, we considered these at unclear risk of other biases. Another study did not report clearly the number of feet included in the analyses, so we also considered this study at unclear risk of other biases (Sharma 2005). There was a unit of analysis error (90 participants with 128 ulcers) in Söderberg 1982. There was also a difference between hospitals in the proportion of participants who wore shoes in this study which might influence the results.

We considered the remaining seven studies to be at low risk of other biases.

Effects of interventions

See: **Summary of findings for the main comparison** Zinc tape compared to magnesium sulphate glycerin for ulceration caused by nerve damage in leprosy; **Summary of findings 2** Zinc tape compared to povidone iodine (10%) for ulceration and other skin changes caused by nerve damage in leprosy; **Summary of findings 3** Adhesive zinc tape compared to gauze soaked in eusol for ulceration caused by nerve damage in leprosy; **Summary of findings 4** Topical ketanserin (2%) compared to clioquinol cream (3%) or zinc paste for ulceration caused by nerve damage in leprosy; **Summary of findings 5** Topical phenytoin compared to saline dressing for ulceration and other skin changes caused by nerve damage in leprosy; **Summary of findings 6** Footwear - canvas shoes compared to PVC boots for ulceration and other skin changes caused by nerve damage in leprosy; **Summary of findings 7** Padded moulded double-rocker plaster shoe compared to padded below-knee plaster for ulceration and other skin changes caused by nerve damage in leprosy; **Summary of findings 8** Exposure to pulsed magnetic fields (in addition to self-care and protective footwear) compared to self-care and footwear for ulceration and other skin changes caused by nerve damage in leprosy; **Summary of findings 9** Low-level laser therapy compared to simple dressing for ulceration and other skin changes caused by nerve damage in leprosy; **Summary of findings 10** Intralesional pentoxifylline compared to daily simple dressing for ulceration and other skin changes caused by nerve damage in leprosy; **Summary of findings 11** Light-emitting diode (LED) irradiation compared to conventional dressing therapy for ulceration and other skin changes caused by nerve damage in leprosy; **Summary of findings 12** Wax therapy compared to foot soaks for skin changes caused by nerve damage in leprosy; **Summary of findings 13** hAMMSC-CM + vitamin C compared to hAMMSC-CM for ulceration caused by nerve damage in leprosy; **Summary of findings 14** hAMMSC-CM + vitamin E compared to hAMMSC-CM for ulceration caused by nerve damage in leprosy; **Summary of findings 15** hAMMSC-CM + vitamin E compared to hAMMSC-CM + vitamin C for ulceration caused by nerve damage in leprosy

None of the 14 included studies measured quality of life (secondary outcome). Prevention of ulcers (primary outcome) was only reported in Seboka 1998. Only one study measured our tertiary outcome (prevention or treatment of other skin changes such as cracking, thickening or pigmentary changes) (Sharma 2005).

Interventions for people with leprosy and existing ulcer(s)

Zinc tape compared to magnesium sulphate/glycerin

One study with 28 participants evaluated the effect of zinc tape versus sulphate/glycerin (Walton 1986), but the number of healed ulcers (primary outcome) was higher with zinc tape after one month; however, the 95% confidence interval (CI) included 1, showing some uncertainty (risk ratio (RR) 2.00, 95% CI 0.43 to 9.21; Analysis 1.1; Fisher's exact test P = 0.65; 4/14 versus 2/14 participants). In addition, the mean ulcer area was smaller in the zinc tape group (mean difference (MD) -14.30 mm^2, 95% CI -26.51 to -2.09; Analysis 1.2). We judged the evidence to be of very low certainty and accordingly have very little confidence in the effect estimate. We downgraded due to study limitations (such as 35% loss to follow-up, consecutive cases were randomly allocated, no blinding of outcome assessor, and potential unit of analysis error. We also downgraded for imprecision due to sparse data and wide CIs. The study authors did not report adverse events, acceptability of treatment or costs. See Summary of findings for the main comparison.

Zinc tape compared to povidone iodine

One study (Overbeek 1991), with 38 participants evaluated the effect of zinc tape versus povidone iodine (10%) on healing of ulcers (primary outcome). The authors did not detect a clear difference in the mean reduction of ulcer area at six weeks between the two groups because the result was highly imprecise (MD 128.00 mm^2, 95% CI -110.01 to 366.01; Analysis 2.1). We judged the evidence to

be of very low certainty, and consequently we have very little confidence in the effect estimate. We also downgraded due to study limitations (quasi-randomised trial, high loss to follow-up, and no reporting of blinding of outcome assessor), and due to imprecision (1 study, few participants, wide CI). The study authors did not report prevention of ulcers, adverse events, acceptability of treatment or costs. See Summary of findings 2.

Zinc tape compared to gauze soaked in Eusol

One study with 90 participants evaluated the effect of applications of zinc or gauze soaked in Eusol on healing of ulcer(s) (primary outcome) after one month (Söderberg 1982); the results were extracted from a figure in the publication. The participants had a total of 128 plantar ulcers. The average healing time was shorter for the group treated with zinc tape. The results varied between the two hospitals involved. In one hospital it took about 20 days (95% CI 18 to 23) for superficial ulcers to heal in the zinc tape group versus about 30 (95% CI 27 to 33) in the gauze group. For deep ulcers the average healing time was two weeks more. In the other hospital the average number of days to heal in the zinc tape group for superficial wounds were about 13 (95% CI 9 to 15) days and 23 (95% CI 16 to 28) days in the gauze group. For deep ulcers it took 17 days (95% CI 12 to 20) in the zinc tape group and 30 (95% CI 21 to 63) in the gauze group. There was a lack of information on how many participants and how many ulcers (deep or superficial ulcers) there were in the intervention and control group. We judged the evidence to be of very low certainty and have very little confidence in the reported results. For adverse events, the study authors reported that there were no signs of skin sensitisation in either group. We downgraded due to study limitations (allocation random alternate basis, no blinding of outcome assessor, and inadequate reporting of data), and due to imprecision (few participants). No signs of adverse events (skin sensitisation - primary outcome) were observed. In terms of acceptability of treatment and costs, the authors reported that the zinc tape had a shorter healing time, lower cost, easier application and was more convenient for participants, and that it could be worn under shoes without causing pressure and was socially more acceptable with no bandages needed. However, it was not clear how the study measured these findings and no further data were reported. See Summary of findings 3.

Topical ketanserin (2%) compared to clioquinol cream (3%) or zinc oxide paste

One study with 66 participants evaluated the effect of topical ketanserin (2%) versus clioquinol cream (3%) or zinc oxide paste (Salazar 2001), and showed a benefit of topical ketanserin on the 'risk' of ulcer healing (primary outcome) (RR 6.00, 95% CI 1.45 to 24.75; Analysis 3.1) after three months. We judged the evidence to be of very low certainty and have very little confidence in the effect estimate. We downgraded due to study limitations (randomisation procedure not reported, blinding not reported, and unclear if appropriate statistical analysis used) and due to imprecision (1 study, very wide CI). The authors reported that treatment was not suspended in any of the participants due to adverse events (primary outcome) (very low-certainty evidence), study limitations (randomisation procedure not reported, blinding not reported), indirectness (not clear how side effects were measured and reported), or due to imprecision (1 study). The study authors did not report acceptability of treatment or costs. See Summary of findings 4.

Topical phenytoin (2% or 4%) compared to saline dressing, and topical 4% phenytoin versus 2% phenytoin

Two studies with a total of 123 participants at inclusion evaluated the effect of topical phenytoin versus saline dressing on healing of ulcer(s) (primary outcome) at four weeks (Bansal 1993; Bhatia 2004). Bansal 1993 alternately assigned 50 participants to a phenytoin group and 50 to a saline group. The dose of phenytoin was not reported. Ten participants had two ulcers each and for these, one ulcer was treated with phenytoin and one with saline. The authors reported that MD in percentage ulcer volume reduction at four weeks were 16.60% (95% CI 8.46 to 24.74) (Analysis 4.1). The other study made three comparisons: both 2% and 4% phenytoin were compared to saline dressings and 4% phenytoin was compared to 2% phenytoin (Bhatia 2004). The outcome was mean percentage reduction of ulcer size area. In the comparison of 2% phenytoin with saline dressings, the ulcers of 23 participants out of the 30 included, were measured. MD in percentage reduction at four weeks was 39.30% (95% CI 25.82 to 52.78) in favour of the 2% phenytoin group (Analysis 5.1). Bhatia 2004 also compared 4% phenytoin to saline dressings. The intervention group had 15 participants included and of these the ulcers of five participants were measured (Bhatia 2004). MD in percentage reduction of ulcer size area between groups was 40.90 (95% CI 27.69 to 54.11) (Analysis 6.1). However, the number of participants in the table are not consistent with those given in the text. In the text it stated that the ulcers of 11 participants in both phenytoin groups, i.e. 2% and 4%, had healed, which means that the ulcers of 11 participants must have been measured. Regarding the third comparison in Bhatia 2004, 4% compared to 2% phenytoin, the MD between groups in percentage reduction of ulcer size area was 1.60% (95% CI -12.05 to 15.25) (Analysis 7.1). No adverse effects (primary outcome) were observed in any of the participants treated with phenytoin or normal saline.

As we do not know which solution of phenytoin Bansal 1993 used we could not pool the results. We judged the evidence for the results of these comparisons to be of very low certainty and consequently, we have very little confidence in the effect estimates. We downgraded due to study limitations (1 study was not adequately randomised and potentially had unit of analysis error (Bansal 1993), attrition bias (Bhatia 2004), and no information on allocation concealment) and imprecision (wide CIs (both studies)). The study authors did not report acceptability of treatment or costs. See Summary of findings 5.

Footwear - canvas shoes compared to PVC boots

One study, with a total of 110 participants (farmers in Ethiopia), evaluated the effect of canvas shoes versus PVC boots on number of persons being ulcer-free at one year (Seboka 1998). Of the 110 participants, 38 had ulcers at baseline, thus the study evaluated both prevention of ulcers (primary outcome) and healing of ulcers (primary outcome). Seventy-two participants had scars (not ulcers) at the start of the study (27 in the canvas group, 45 in the PVC group) and none of these developed new ulcers during the year. In the 38 participants who had ulcers at baseline, there was little or no difference between groups in the number of people with healed ulcers at one year (RR 1.16, 95% CI 0.77 to 1.74; Analysis 8.1). They also reported the number of persons having ulcers not healed after one year (RR 0.52, 95% CI 0.15 to 1.75; Analysis 8.2; Fisher's exact test P = 0.41; 4/25 versus 4/13 participants). The width of the CIs around the effect estimates for both outcomes makes the results inconclusive. Amongst the 110 participants, none developed new

ulcers (only one was lost to follow-up). They also reported on adverse events that PVC boots could become very hot in strong sunlight, with the possibility of burning feet. We judged the evidence to be of very low certainty and have very little confidence in the result. We downgraded due to study limitations (unclear randomisation, unclear blinding) and due to imprecision (1 study, wide CI).

On acceptability of treatment (secondary outcome) the study authors reported that the canvas shoes were socially acceptable, but 85% of the farmers rated them as good for their work, rather than "excellent" (8%) at first follow-up at three months. The study authors reported that PVC boots were well liked and not stigmatising. We are moderately confident in this result, and have downgraded due to imprecision (1 study). Costs were not reported, but the study authors state that canvas shoes and PVC boots cost the same and that PVC boots are more durable than canvas shoes. See Summary of findings 6.

Padded moulded double-rocker plaster shoe compared to padded below-knee plaster

One study with a total of 47 participants, with a total of 55 ulcers, evaluated the effect of padded moulded double-rocker plaster shoe versus padded below-knee plaster on ulcers healed (primary outcome) or nearly healed after six weeks (Pring 1982). The authors reported an effect size of RR 0.96 (95% CI 0.77 to 1.19; Analysis 9.1). We judged the evidence to be of very low certainty and have very little confidence in the effect estimate. We downgraded due to study limitations (no information on baseline characteristics; unit of analysis is ulcers, not participants; unclear randomisation procedure; unclear if blinding of outcome assessor), and due to indirectness (padded moulded double-rocker plaster shoe and padded below-knee plasters might not be acceptable interventions today for people with leprosy), and due to imprecision (1 study, small number of participants). The authors reported acceptability and cost (secondary outcomes), but gave no information on how they were measured. They stated that the plaster shoes were more acceptable to persons with leprosy, and that the below-knee plaster immobilises the foot more. The moulded double-rocker plaster shoe is also cheaper. Adverse events were not reported. See Summary of findings 7.

Pulsed magnetic fields (in addition to self-care and protective footwear) compared to self-care and footwear

One study with a total of 40 (7 excluded during study) participants evaluated the effect of pulsed magnetic fields (in addition to self-care and protective footwear) compared to self-care and footwear on healing of ulcers (primary outcome) at four to five weeks (Sarma 1997). 'Pulsed magnetic fields' are low-frequency, low-intensity pulsed magnetic fields inducing no significant heating of the tissue. The authors reported in the control group that the geometric mean volumes of the ulcers were 2843 cu mm^3 and 1478 cu mm^3 on the day of admission and at the end of treatment (P = 0.03); the corresponding values in the pulsed magnetic field group were 2428 cu mm^3 and 337 cu mm^3, respectively (P < 0.001). A decrease in the volume of 40% or more was observed in 53% of control participants and 89% of pulsed magnetic field participants (P = 0.02): a decrease of 80% or more was observed in none of the controls and in 33% of pulsed magnetic field participants. The difference in ulcer volumes between the two treatment strategies did not reach statistical significance (MD -1.14 cm^3, 95% CI -5.37 to 3.09; Analysis 10.1). We judged the evidence to be of very low certainty, and have very little confidence in the effect estimate. We downgraded due to study limitations (unclear randomisation procedure, 7 of 20 participants excluded) and due to imprecision (1 study with few participants). The authors reported the costs (secondary outcome) of the equipment used: "The cost of construction of an enclosure is around Rs. 5000/- (about 150 USD) and the function generator together with the centre-zero milliammeter costs another Rs. 6000/- (about 180 USD). Where uninterrupted power supply is a problem, an inverter and a 12-volt battery together costing about RS. 5000/- (about 150 USD) would be required". The study authors did not report adverse events, or acceptability of treatment. See Summary of findings 8.

Low-level laser therapy compared to simple dressing

One study with 25 participants (Barreto 2010), evaluated the effect of low-level laser therapy compared to simple dressing on ulcer size after 12 weeks (primary outcome - healing of ulcer). As with regards to the ulcer size, the results were inconclusive (MD -0.60 cm^2, 95% CI -6.47 to 5.27; Analysis 11.1). The study also reports the differences in ulcer depth (MD -1.30 mm, 95% CI -5.26 to 2.66; Analysis 11.2).

We judged the evidence to be of very low certainty and have very little confidence in the effect estimates. We downgraded due to study limitations (unclear allocation concealment, no blinding of outcome assessor), and due to indirectness (we are unsure if the intervention - laser therapy - is available to people with ulcers caused by nerve damage in leprosy) and due to imprecision (1 study, small sample size, wide CI). The study authors reported costs (secondary outcome). Costs were not analysed between groups, but the trial authors state: "Patients have an average of 3.4 simple dressings per week at the dressing service of UREMC, resulting in an estimated expenditure of USD 100,000 per year on disposable dressing material alone." The study authors did not report adverse events or acceptability of treatment. See Summary of findings 9.

Intralesional pentoxifylline compared to daily simple dressing

One study with 40 participants evaluated the effect of intralesional pentoxifylline (injection) compared to daily simple dressing on healing of ulcer(s) (primary outcome) (Mikhael 2015). The authors found a risk ratio (RR) of 5.00 (95% CI 1.25 to 19.99) for healing of ulcers at eight weeks (Analysis 12.1). They also found a MD in ulcer depth of -0.22 cm (95% CI -0.40 to -0.04, Analysis 12.2). We judged the evidence to be of very low certainty and have very little confidence in the effect estimates presented. We downgraded due to study limitations (unclear allocation concealment and unclear if there was blinding of outcome assessor) and due to imprecision (1 small study, very wide CIs). The participants were asked about possible side effects. The only adverse events (secondary outcome) reported was tolerable pain during the injection (very low-certainty evidence). We downgraded due to study limitations mentioned and in addition it was unclear how information of side effects was documented and if both intervention and control group were asked. The study authors did not report acceptability of treatment or costs. See Summary of findings 10.

Light-emitting diode (LED) compared to conventional dressing therapy

One study with 60 participants evaluated the effect of light-emitting diode (LED, infrared or long visible wavelength light) compared to conventional dressing therapy on mean change of wound size (primary outcome - healing of ulcer) (Lee 2012). The study authors reported that the average reduction in wound size was 26.55 mm3/

day in the control group and 338.02 mm3/day in the LED group (MD 311.47, 95% CI 106.47 to 516.47; Analysis 13.1). The research period was eight months, but the exact length of follow-up was not reported. We judged the evidence to be of very low certainty and have very little confidence in the effect estimates. We downgraded due to study limitations (concealment or sequence generation not reported, no blinding) and due to imprecision (only 1 study, few participants, wide CI). The study authors did not report on adverse events, or on acceptability of treatment or costs. See Summary of findings 11.

Topical human amniotic membrane-mesenchymal stem cell-conditioned medium gel alone, with vitamin C or with vitamin E

One study with 66 participants and three arms evaluated the effect of topical human amniotic membrane-mesenchymal stem cell-conditioned medium (hAMMSC-CM) and a mixture of topical hAMMSC-CM + vitamin C and hAMMSC-CM + vitamin E on healing of ulcer (primary outcome) (Prakoeswa 2018). The three arms, with 22 participants each, evaluated hAMMSC-CM + vitamin C versus hAMMSC-CM , hAMMSC-CM + vitamin E versus hAMMSC-CM and hAMMSC-CM + vitamin C versus a mixture of topical hAMMSC-CM + vitamin E. When comparing hAMMSC-CM + vitamin C versus hAMMSC-CM the authors found a mean difference (MD) at eight weeks follow-up in ulcer size of 0.31 cm^2 (95% CI -0.35 to 0.97, Analysis 14.1) and ulcer depth of -0.10 cm^2 (95% CI -0.17 to -0.03, Analysis 14.2). For hAMMSC-CM + vitamin E versus hAMMSC-CM the MD in ulcer size was 1.14 cm^2 (95% CI 0.32 to 1.96, Analysis 15.1) and ulcer depth was -0.08 cm^2 (95% CI -0.17 to 0.01, Analysis 15.2). Finally, when comparing hAMMSC-CM + vitamin C versus a mixture of topical hAMMSC-CM + vitamin E, the MD in ulcer size was 0.83 cm^2 (95% CI -0.03 to 1.69, Analysis 16.1) and ulcer depth was 0.02 cm^2 (95% CI -0.06 to 0.10, Analysis 16.2). Overall there was little or no difference between the treatment groups.

We judged the evidence to be of very low certainty and have very little confidence in the effect estimates presented. We downgraded due to study limitations (unclear concealment of allocation, unclear if there was blinding of outcome assessor, clinician or patient) sparse data and imprecision (only 1 study, few participants). The study authors reported that no adverse events (such as allergy or infection) were encountered in any group. The study authors did not report acceptability of treatment or costs. See Summary of findings 13; Summary of findings 14; Summary of findings 15.

Interventions for people with leprosy and no existing ulcer(s)

Wax therapy compared to foot soaks

One study, with a total of 44 participants, evaluated the effect of wax therapy compared to foot soaks, and the authors reported that the participants who were in the group that were given wax therapy felt subjectively much better than those who had foot soaks (acceptability of treatment - secondary outcome) (Sharma 2005). The study also measured the skin being fissure and callous-free (tertiary outcome) and results were in favour of wax therapy at six weeks (RR 2.22, 95% CI 1.07 to 4.60; Analysis 17.1). However, we judged this evidence to be of very low certainty and have very little confidence in this evidence. We downgraded the evidence for the results of these two outcomes due to study limitations (unclear allocation concealment, unclear if outcome assessor was blinded, and study authors are not clear in numbers of persons or feet reported), and due to imprecision (1 study with 44 participants, wide CI) and due to indirectness (wax therapy probably not available to most people with leprosy as treatment is given in hospital). Adverse events and cost of intervention were not reported. See Summary of findings 12.

DISCUSSION

Summary of main results

It is not possible to draw any firm conclusions based on the available evidence, which was of very low certainty.

We have presented results for our primary outcomes, measured by the following key comparisons.

- Zinc tape compared to magnesium sulphate glycerine (Summary of findings for the main comparison).
- Zinc tape compared to povidone iodine (10%) (Summary of findings 2).
- Adhesive zinc tape compared to gauze soaked in Eusol (Summary of findings 3).
- Topical phenytoin compared to saline dressing (Summary of findings 5).
- Footwear - canvas shoes compared to PVC boots (Summary of findings 6).
- Exposure to pulsed magnetic fields (plus self-care and protective footwear) compared to self-care and footwear (Summary of findings 8).

Only one of the trials measured our primary outcome 'prevention of ulcers(s)': the study compared canvas shoes with PVC boots, and none of the participants developed new ulcers during the duration of the trial (1 year). Seventy-two participants had scars (not ulcers) at the start of the study (27 in the canvas group and 45 in the PVC group). Although, it is worth noting that some treatments are not intended to prevent ulcers.

Healing of existing ulcers was measured by all of the key comparisons, as follows.

- There were more healed ulcers and a greater reduction in mean ulcer area in the zinc tape group compared to the magnesium sulphate glycerine group.
- Although there was a bigger reduction in mean ulcer area with zinc tape, there was no clear difference between zinc tape and povidone iodine.
- The healing time for deep ulcers in the zinc tape group was 17 days compared to 30 days in a group whose ulcers were treated with gauze soaked in Eusol.
- Two studies suggested that topical phenytoin had a better effect on healing of ulcers compared to saline dressing: a greater mean percentage reduction of ulcer area/volume with phenytoin.
- There was no clear difference in achieving healed ulcers or becoming ulcer-free in those wearing canvas shoes compared to PVC boots.
- There was no clear difference in volume of ulcers between people exposed to pulsed magnetic fields (plus self-care and protective footwear) versus those who practiced self-care and wore protective footwear.

Half of the key comparisons measured and reported adverse events, either those sufficiently serious to stop the intervention, or minor ones reported by participants.

- There were no signs of skin sensitisation in either of the following groups: zinc tape or gauze soaked in Eusol.
- No adverse effects were observed in those treated with phenytoin or normal saline.
- Comparing canvas shoes with PVC boots, the only issue reported was that the PVC boots could become very hot in strong sunlight, leading to the possibility of burnt feet.

Some key treatment categories, such as self-care programmes, education, information, dry dressings, or skin care were not assessed by any included study, but in some studies, they may have been added to the intervention or used in the control groups. None of the 14 included studies measured quality of life. Only one study measured our tertiary outcome, 'prevention or treatment of other skin changes, such as cracking, thickening or pigmentary changes'.

Overall completeness and applicability of evidence

The findings of this review did not allow us to fully address our objectives; we are restrained by the limited types of interventions assessed, the included studies not reporting our outcomes of interest (apart from healing of ulcers), and the general low certainty of the evidence we could include.

Many of the included studies assessed novel interventions in single small trials, which were not sufficiently powered to provide meaningful, reliable results. However, the studies were based in the Americas, Africa, and Asia, and thus involved the community of people affected by leprosy. In general, the follow-up time for the outcome, 'healing of existing ulcers' was adequate.

A number of important interventions were not assessed by the included studies. These included self-care programmes, education, information, dry dressings, or skin care; however, in some studies, they may have been added to the intervention or used in the control groups.

Only one study measured prevention of ulcer(s) and prevention or treatment of other skin changes; however, healing of existing ulcer(s) was very well measured. Adverse events were mentioned in some studies, but it was often unclear how this outcome was measured. None of the studies reported any quality of life measures. The acceptability of treatment was reported in a few studies, but we generally lack information on how this outcome was measured. A few studies reported the direct cost involved.

Certainty of the evidence

There are 15 different comparisons presented in our 'Summary of findings' table, and the body of evidence for each comparison is very limited for each intervention. In our GRADE outcomes, we downgraded each outcome by at least one level for study limitations, mainly in relation to potential selection, detection, performance, or attrition bias. We downgraded all outcomes but one (acceptability of treatment in Summary of findings 6) for imprecision due to single study data with only a small number of participants analysed. This meant that the 95% CIs surrounding any estimated effect sizes were wide, showing great uncertainty with the evidence provided. Indirectness was also a reason for downgrading in six comparisons: topical ketanserin (2%) compared to clioquinol cream (3%) or zinc paste (Summary of findings 4), footwear - canvas shoes compared to PVC boots (Summary of findings 6), padded moulded double-rocker plaster shoe compared to padded below-knee plaster (Summary of findings 7), low-level laser therapy compared to simple dressing (Summary of findings 9), intralesional pentoxifylline compared to daily simple dressing (Summary of findings 10), and wax therapy compared to foot soaks (Summary of findings 12). Hence, we rated all outcomes as very low certainty, except for acceptability of treatment which we rated as moderate in the comparison of footwear - canvas shoes compared to PVC boots for ulceration and other skin changes caused by nerve damage in leprosy (Summary of findings 6).

Potential biases in the review process

The search for literature in the various databases is finite, until our search dates, so newer studies might be missing. We identified two ongoing studies. Two review authors independently selected studies for inclusion, extracted data, and assessed risk of bias with a third review author acting as arbiter in order to minimise the risk of bias in the review process. In addition, we attempted to contact a few study authors for additional information. None of the review authors had a conflict of interest regarding any of the interventions in this review.

A few studies included participants that had several treated ulcers, and thus an element of clustering. This should have been accounted for in the analysis. In the studies that explicitly included people with several ulcers without reporting how this was handled in the analysis, we made a note of this in the Characteristics of included studies tables. However, we judged that the clustering was not comprehensive enough to make any difference to the reported results.

For this version of the review, we did not search for unpublished and ongoing trials by corresponding with authors; field experts; and experts on tropical medicine or leprosy or both. Thus, there might be a risk we may not have included all the evidence available.

We judged that the clinical heterogeneity between trials was so big that we did not pool any results.

Agreements and disagreements with other studies or reviews

The evidence base is very limited for interventions for ulceration and other skin changes caused by nerve damage in leprosy. As stated in a comment in Srinivasan 1989, lots of interventions have been tried for healing such ulcers and he warned against novel "healing agents". Our review identified many interventions that had been tried out in single trials, hardly any replicated by others. We have not identified other reviews that address interventions for prevention or healing of ulcers and other skin changes in leprosy.

AUTHORS' CONCLUSIONS

Implications for practice

This review aimed to assess the effects of education, information, self-care programmes, dressings, skin care, footwear, and other measures for preventing and healing secondary damage to the skin in persons affected by leprosy. Due to the ambiguity of the evidence (all of our key comparisons were based on very low-certainty evidence), it is not possible to draw firm conclusions regarding the effects of each intervention assessed in this review on our prespecified outcomes.

For some commonly recommended interventions (like self-care, education), there is a lack of trials (but lack of evidence does not mean that interventions do not work).

The evidence presented in this review was mainly based on very small studies, which makes it more difficult to provide reliable conclusions, and these studies assessed different interventions/comparisons, meaning there was too much clinical heterogeneity for meaningful meta-analysis.

Implications for research

Further randomised trials are needed, and they should ensure the following.

- Allocation is concealed.
- Participants and outcome assessors are blinded.
- A sample size calculation is conducted to ensure enough participants are included to detect true effects of the intervention.
- Measures are made to ensure participants are followed up until the end of the study to reduce attrition bias.

Future trials should consult the Cochrane Skin Outcomes Set Initiative to check for any core outcome measures (CS-COUSIN).

Self-care and simple dry dressings should be evaluated in new trials. Phenytoin and zinc tape might deserve further investigation (instead of expensive, novel, hospital-based interventions). It would be helpful if some of the interventions that one or two of the trials indicated might be helpful, were tested in other well-conducted trials. Comparisons could be usual care or other interventions (for example, other types of dressings, other types of footwear, other interventions designed to prevent or treat damage). There is a lack of trials evaluating interventions such as footwear and self-care that aim to prevent ulcers and other skin changes; this should be addressed in future research. Wax therapy to prevent ulcers is another intervention that might be evaluated further; however, it is a therapy that so far is used in specialist care only.

Based on what we have summarised, we suggest that future trialists ensure that they clearly report how they measure side effects, that participants are asked about acceptability of treatment, and that evaluated interventions are available in the community (not only hospital based). Outcomes, such as quality of life, acceptability of the intervention, and costs should be investigated more thoroughly in all new trials. Reporting of trials should follow Consort Guidelines (Moher 2001).

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Diana NJ Lockwood contributed to writing the protocol.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bansal 1993

Methods	Quasi-randomised controlled trial (parallel)
Participants	**Inclusion criteria** • People with trophic leprosy ulcers living in India • Inpatients Participants (n = 100) included in study were between 20 and 60 (majority between 31 and 50) years of age, majority of men (86 men, 14 women). The duration of leprosy was between 5 and 20 years. Ulcer duration was less than two months for the majority of participants, with only one participant having an ulcer for more than six months. The ulcers were mainly situated on the soles of the feet and the majority had discharge that was offensive/purulent. 69 ulcers were progressive, 41 were classified as stationary at baseline. The most common form of leprosy was LL (n = 86), 14 participants were classified as BL.
Interventions	**Intervention group** • Dressing with topical phenytoin powder, strict bed rest, uniform diet (n = 50), four weeks **Control group** • Dressing with normal saline, strict bed rest, uniform diet (n = 50), four weeks "All patients continued to receive their anti leprosy treatment and appropriate antibiotics".
Outcomes	Healing of ulcers measured as mean percentage of ulcer volume reduction weekly, up to 4 weeks follow-up. 100 participants were recruited, randomised and analysed.
Notes	10 participants had 2 ulcers, one ulcer was treated with phenytoin and the other with normal saline **Dates study was conducted**: not reported **Funding source**: "Supported in part by the HBS Trust of Jodhpur, Rajasthan, India" **Declarations of interest**: not reported

Bansal 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quotes: “They were assigned alternately”, “The groups were well matched” Comment: quasi-randomised trial, likely to introduce selection bias
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not reported (but participants could be blinded)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quotes: "Clinical assessment…by an independent observer"…"Accuracy of ulcer volume was established by two independent physicians" (water and syringe – objective) Comment: objective outcome measures and independent observer, detection bias not likely
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: the 100 participants were all hospitalised with bed rest - no attrition bias
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect selective reporting of results
Other bias	Unclear risk	Comment: T-test. 50 participants/55 ulcers (unit of analysis) – might influence the confidence interval, unclear how much

Barreto 2010

Methods	Randomised controlled trial (parallel)
Participants	**Inclusion criteria** Participants (n = 25 of 51 eligible) with leprosy sequela living in Brasil. Some participants had more than one ulcer. Two participants left the trial, so 23 were assessed for baseline characteristics. The majority were men (18 men, 5 women), mean age control group 58.5 years and intervention group 53.3 years. Participants in both groups had been diagnosed with leprosy around 38-39 years earlier. Mean ulcer duration in control group was 71.7 months versus 123.3 months in intervention group at baseline. Five of 12 in control group and 4 of 13 in intervention group used adapted footwear at baseline. The most common form of leprosy was LL.
Interventions	**Intervention group** • Low-level laser therapy (n = 13) 3 times per week for 12 weeks. The equipment used was a TWIN LASER semiconductor laser. The laser probe was kept 1 cm away from target tissue and wound edges were treated using a "spot" technique. **Control group** • Routine treatment: daily simple dressings with sterile gauze after wound cleaning 0.9% physiologic solution, 1% hydrophilic silver sulphadiazine cream (n = 12)

Barreto 2010 *(Continued)*

	Both groups received "orientation about the use of adapted footwear, self-care and the prevention of disabilities". "Surgical debridement was done whenever indicated" All participants were evaluated biweekly.
Outcomes	Ulcer area, ulcer depth, pressure ulcer scale (PUSH), use of adapted footwear, ulcer localisation. Length of follow-up was 12 weeks. Total sample size being evaluated was 51 participants: 25 of these were randomised and 23 were analysed
Notes	Table 1 says there was a total of 91 ulcers, but figure 3 states 14 ulcers in control group and 17 in intervention (experimental) group. Text says 97 ulcers in 51 participants (however, 25 participants were randomised) **Dates study was conducted:** January 2007 to January 2008 **Funding source**: "This work was supported by Secretaria de Ciência, Tecnologia e Insumos Estratégicos, Ministério da Saúde do Brasil, by Conselho Nacional de Pesquisa do Brasil (CNPq), by Secretaria de Estado de Saúde Pública do Estado do Pará (SESPA), by Financiadora de Estudos e Projetos do Governo Federal, Ministério da Ciência e Tecnologia (FINEP 1460/03), by Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), by Pró-Reitoria de Pesquisa / Universidade Federal do Pará (PROPESP/UFPA) and by Fundação de Amparo e Desenvolvimento da Pesquisa (FADESP)." **Declarations of interest**: "The authors declare that they have no competing interests" Clinical trial register identifier: NCT00860717

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Subjects were randomly allocated into two groups. They were allocated to the control group or the intervention group according to a sequence generated by the BioEstat 5.0 software" Comment: appropriate sequence generation
Allocation concealment (selection bias)	Unclear risk	Quote: "After all participants were recruited, they were allocated to the control group or the experimental group according to a sequence generated by the BioEstat 5.0 software" "All stages of the randomisation process were performed by the same researcher …" Comment: but no information on whether the allocation was concealed
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "The laser device used in this trial emitted red visible light and thus limited our ability to blind patients …" Comment: not sure if study personnel were also blinded or if blinding of participants was achieved
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "In order to avoid duplicity in treatment technique and assessment interpretation, all low level laser therapy (LLLT) and ulcer evaluation procedures were performed by one researcher." Comment: it seems likely that the researcher who did the outcome measurements was the same as who performed the intervention, and therefore no blinding could have been used. This could be a potential source for risk of detection bias, but we are unsure.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all subjects included in this trial were evaluated biweekly until the end of the 12-week treatment period or until complete cicatrisation of the treated ulcer. 25 of 51 participants were randomised. Two left the study.

Barreto 2010 *(Continued)*

		12 participants – 14 ulcers at pretest; 12 participants - 14 ulcers at post-test 13 participants – 17 ulcers at pretest; 11 participants - 15 ulcers at post-test
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect selective reporting of results
Other bias	Unclear risk	Comment: intracluster correlation not corrected for. Participants were randomised, data analysed at ulcer level

Bhatia 2004

Methods	Randomised controlled trial, parallel design
Participants	**Inclusion criteria** • Participants with leprosy living in India • Participants in trial were all hospitalised • Aged 18 to 60 years • Simple acute leprosy trophic ulcer (< 3 months duration) Forty-five participants were included in the trial and randomised to three groups, 31 men and 14 women. They were aged between 20 and 60 years. The majority (n = 38) were classified as LL, seven had BL. At baseline mean duration of leprosy 3 to 4 years. Mean duration of ulcer 33 to 46 days. The majority of ulcers were on the soles of the feet with fewer on palms and ankles. More than half of ulcers were infectious (n = 24) with a positive bacterial culture.
Interventions	**Intervention 1** • Topical 2% phenytoin - NaCl soaked gauze once daily for 4 weeks (N = 15) **Intervention 2** • Topical 4% phenytoin - NaCl soaked gauze once daily for 4 weeks (N = 15) **Control intervention** • Sterile gauze soaked in normal saline once daily for 4 weeks (N = 15) All participants were given strict bed rest plus uniform dietary regimen
Outcomes	Percentage reduction in surface area of the ulcers, costs, adverse effects, four weeks follow-up. 45 participants were included, 45 were randomised to three groups of 15, 45 were analysed at two weeks, 28 were analysed at four weeks follow-up
Notes	**Dates study was conducted:** August 2002 to May 2003 **Funding source:** not reported **Declarations of interest**: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "..were randomly assigned according to a table of random numbers to the three groups"

Bhatia 2004 *(Continued)*

		Comment: randomisation method was considered adequate
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: “after breaking the code at the end of the study, it was found that each group had 15 patients”. Comment: probably blinding of participants and personnel
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: “Assessment was performed weekly by a blinded investigator” Comment: outcome assessment was done using blinded conditions
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: all 45 participants were accounted for in the study at 2 weeks. However, at 4 weeks follow-up only 8 participants were accounted for in the intervention group with phenytoin 2%. In the 4% group, only 5 participants were accounted for after four weeks. We judged high risk for attrition bias at four weeks follow-up.
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect selective reporting of results
Other bias	Low risk	Comment: none detected

Lee 2012

Methods	Randomised controlled trial (parallel)
Participants	**Incusion criteria** • "Old" participants with leprosy who have ulcer on hand or foot • Recruited from outpatients and inpatients; South Korea 60 participants were recruited, randomised and analysed. The mean age intervention group at baseline was 74 years; control group was 69 years. The intervention group had 15 men and 15 women; 24 men and six women in the control group. They had ulcers on hands or feet. Specific type of leprosy or classification was not reported
Interventions	**Intervention group** • LED (n = 30). LED irradiation was given for 20 minutes before administering dressing **Control group** • Conventional dressing therapy (n = 30)
Outcomes	Healing of wounds (size). The wounds were observed twice a week in both groups. The research period was 8 months, but exact length of follow-up was not reported; all participants did not join the study at the same time
Notes	Published in Korean. Tables in English. Review authors had help with data extraction and judgement of risk of bias from a Korean speaking person (named in acknowledgements of this review) **Dates study was conducted:** February 2012 to September 2012 **Funding source**: not reported

Lee 2012 *(Continued)*

Declarations of interest: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "We divided ulcers patients into case group (conventional dressing therapy + LED therapy) and control group (only conventional dressing therapy) randomly in out patient department and in ward." Comment: risk of bias was done by a Korean speaking person. Randomisation procedure was not reported
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all participants were accounted for in tables
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect
Other bias	Low risk	Comment: none detected

Mikhael 2015

Methods	Randomised controlled trial (parallel)
Participants	**Inclusion criteria** • Participants with neuropathic lepromatous ulcers, outpatient clinic (N = 40) Intervention group: 32-64 years of age, mean 50.65, 60% men Control group: 40-65 years of age, mean 50.85, 55% men All participants had completed specific multidrug therapy and had neuropathic lepromatous ulcers (classification not reported). The ulcers had no clinically detectable infections.
Interventions	**Intervention group** • Pentoxifylline ampoule (15 mL) (300 mg) was injected using a syringe of 100U and isopropyl alcohol was used as a disinfectant to the ulcer and adjacent skin. Weekly (8 sessions) (n = 20) **Control group**: • Daily simple dressing with sterile gauze and topical placebo (creams contained only the aqueous cream base) was performed (n = 20)

Mikhael 2015 *(Continued)*

Outcomes	Healing of ulcers, in terms of complete or incomplete closure. Participants were photographed at each visit and the ulcer depth was estimated. Participants were asked about side effects. Lenght of follow-up was 8 weeks. 40 participants were randomised, 40 participants were followed up/analysed
Notes	9 participants had diabetes mellitus **Dates study was conducted**: March 2013 to September 2013 **Funding source:** not reported **Declarations of interest:** "There are no conflicts of interest"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Patients were... randomised to receive active or placebo treatment according to a computer-generated sequence.." Comment: randomisation method considered adequate
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not possible
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: complete follow-up
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect selective reporting of results
Other bias	Low risk	Comment: none detected

Overbeek 1991

Methods	Quasi-randomised trial, multicentre trial (10 clinics). Parallel study
Participants	**Inclusion criteria** • People with leprosy and simple plantar ulcers attending outpatient clinic in Indonesia Mean age in intervention group was 44 years and 39 years in control group; 32 men and 6 women. Specific type of leprosy or classification was not reported. 56 participants recruited and randomised, but only 38 were accounted for at follow-up
Interventions	**Intervention group** • Adhesive zinc oxide tape plus povidone iodine (10%) (N = 26) (4 times over 6 weeks)

Overbeek 1991 *(Continued)*

	Control group • Povidone iodine (10%) (N = 12) (4 times over 6 weeks)
Outcomes	Healing of ulcer (size) at six weeks. 38 were analysed/followed up
Notes	Unclear when participants dropped out of study, outcomes reported for 38 participants **Dates study was conducted:** October 1988 to January 1989 **Funding source**: de Nederlandse Stichting voor Leprabestrijding (NSL) **Declarations of interest**: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: “alternerend per polikliniek” (alternating per outpatient clinic) Comment: this is a quasi-randomised trial
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: information not given, we think probably no blinding of participants or personnel
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: information not given, probably no blinding of outcome assessor
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: many (18 of 56) were lost to follow-up (32%), reasons given
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect
Other bias	Low risk	Comment: none detected, study authors state that different methodological problems might have influenced the results

Prakoeswa 2018

Methods	Randomised controlled trial (parallel)
Participants	**Incusion criteria:** Participants with leprosy with chronic plantar ulcer of > 6 weeks, an ulcer depth of < 0.5 cm and a maximum injury area of 9 cm^2 **Exclusion criteria:** Participants who had used systemic corticosteroids in the last two weeks, diabetes or blood disorders or hypersensitivity to film dressings or adhesive plasters.

Prakoeswa 2018 *(Continued)*

	66 people were recruited and randomised into the study and all completed the study protocol. Participants in all three groups had a mean age of around 52 years and were divided almost equally between male and female sexes. Occupation that requires long standing/walking was present in about half the participants in all three groups. Duration of ulcer: for the majority of participants in all groups the duration of the ulcers was 1 to 5 years, about one-third of participants had ulcers for < 1 year and only one participant had the ulcer > 5 years. The study took place in an outpatient clinic at a hospital in Indonesia (Dr Soetomo Teaching Hospital Surabaya).
Interventions	**Intervention group 1:** topical gel hAMMSC-CM only (n = 22), every three days up to eight weeks **Intervention group 2:** a mixture of topical gel hAMMSC-CM + vitamin C (n = 22), every three days up to eight weeks **Intervention group 3:** a mixture of topical gel hAMMSC-CM + vitamin E (n = 22), every three days up to eight weeks All participants had surgical debridement before treatment. The gel was applied every three days until the ulcer closed or for a maximum of 8 weeks. Particiapnts were advised to reduce standing and walking activities, but offloading was not performed.
Outcomes	**Primary outcome:** healing of chronic plantar ulcer (by measuring ulcer size) **Secondary outcome**: adverse events (allergy, infection) 66 participants recruited, 66 randomised and 66 analysed
Notes	**Dates when study was conducted:** not reported **Funding source:** "This work was supported by Minister of Education and Technology Research, Indonesia" **Declarations of interest:** "No potential conflict of interest was reported by the authors."

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "…was randomised with computerized and consecutive sampling" Comment: randomisation method considered adequate
Allocation concealment (selection bias)	Unclear risk	Comment: no information available to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "There were no dropouts in the study." Comment: no attrition bias
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect selective reporting

Prakoeswa 2018 *(Continued)*

Other bias	Low risk	Comment: none identified

Pring 1982

Methods	Randomised controlled trial (parallel)
Participants	**Inclusion criteria** • People with leprosy and simple plantar ulcers, outpatient clinic 47 participants with 55 simple plantar ulcers ("on the plantar surface of the anaesthetic foot that did not involve either the underlying bone joint or tendon". No information on gender or age of participants reported. Classification of leprosy not reported
Interventions	**Intervention group** (n = 31 ulcers): • Padded, moulded double-rocker plaster shoe plus health education (N = 31 ulcers) for 6 weeks **Control group** • Padded, below-knee plaster plus magnesium sulphate glycerine and acriflavine dressing plus health education (N = 24 ulcers) for 6 weeks Unclear if magnesium sulphate and acriflavine (cointerventions) were given in both groups. "Both at the time of application and removal of plasters intensive health education was given on foot care. Participants were taught the principles of daily foot inspection, foot soaking and scraping, and the importance of the regular wearing of soft-lined chappals."
Outcomes	**Primary outcome** • Healing of ulcers at 6 weeks: fully healed, nearly healed or not healed **Secondary outcome** • Acceptability and cost mentioned, no information on how it was measured
Notes	Study took place in either India or Nepal (N = 47, 55 ulcers) **Dates study was conducted:** not reported **Funding source**: not reported **Declarations of interest**: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “The patients were randomly divided into two groups” Comment: randomisation procedure not reported
Allocation concealment (selection bias)	Unclear risk	Comment: no information available to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information available to make a judgement

Pring 1982 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: not detected, all 55 wounds seem to be accounted for
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect
Other bias	Unclear risk	Comment: no information on baseline characteristics. Unit of analysis is ulcers, not participants

Salazar 2001

Methods	Randomised controlled trial/prospective, comparative quasi-experimental study (parallel)
Participants	**Inclusion criteria** • People with leprosy and ulcers living in Mexico • Outpatients Total 66 participants, Group A average age 58 (range 42 to 69), group B average age 57 (range 36 to 69). Total of 36 men and 30 women. Mean duration of ulcers were 48.9 months in group A and 47.6 months in group B. The vast majority of participants had nodular lepromatous leprosy, three were classified as having tuberculoid leprosy.
Interventions	**Intervention group** Topically applied 2% ketanserin gel every 12 hours for 3 months (N = 33) **Control group** Clioquinol 3% or zinc oxide paste every 12 hours for 3 months (N = 33)
Outcomes	Healing of ulcers (measures and photos) side effects (as minimum, moderate or severe). 66 participants recruited, 66 randomised and 66 analysed
Notes	**Dates when study was conducted:** not reported **Funding source**: not reported **Declarations of interest**: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quotes: “a prospective, comparative and quasi-experimental study” “randomly allocated” Comment: randomisation procedure not reported
Allocation concealment (selection bias)	Unclear risk	Comment: no information available to make a judgement

Salazar 2001 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Treatment was not suspended in any of the patients because of side effects and all finished the study". Comment: seems likely that all 66 participants are accounted for
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect selective reporting of results
Other bias	Unclear risk	Comment: unclear if appropriate statistical analyses was used to correct for intracluster correlation. One patient had several ulcers

Sarma 1997

Methods	Randomised controlled trial (parallel)
Participants	**Inclusion criteria** • Ambulatory leprosy patients (aged 20 to 65 years with chronic plantar ulcers (> 3 months duration), living in India 10 participants had simple ulcers, 30 participants had complicated ulcers. No participants had active leprosy and were 20 to 65 years of age. In the final analysis there were 18 men and 13 women. The main duration of ulcers were 2.16 years in control group and 2.12 years in intervention group. Eleven were classified LL, 9 BL, 6 BB and 7 BT
Interventions	**Intervention group** • Self-care and footwear (i.e. same treatment as in control group) in addition to exposure to PMF (sinusoidal form 0.95 Hz to 1.05 Hz; amplitude ± 2400 nano Teslas) for 30 minutes every day for 4 weeks. Supine, head to the east, feet in an east-west direction (N = 20) **Control group** • Daily cleaning of the ulcer with soap and water, soaking of feet in saline, trimming of overhanging edges and heavy callus, debridement and application of acriflavine when necessary, bandaging for 4 weeks and use of protective footwear. No antibiotics (N = 20)
Outcomes	Healing of ulcers, measured by volume calculation. Length of follow-up was 4 to 5 weeks. 40 participants were recruited and randomised, 33 were analysed at the end of treatment. In the end, 10 of 15 in control group and 9 of 18 in intervention group were available for follow-up assessments at 45 to 60 days.
Notes	**Dates when study was conducted**: not reported **Funding source**: not reported **Declarations of interest**: not reported
Risk of bias	

Sarma 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Five patients with simple ulcers and 15 with complicated ulcer were allocated at random to receive standard wound care treatment (c-group) and the remaining to receive standard treatment plus exposure to pulsed magnetic fields (PMF) (study group).” Comment: randomisation procedure not reported
Allocation concealment (selection bias)	Unclear risk	Comment: no information available to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Neither the patient nor the assessing physician (or the para-medical staff) was aware of the identity (PMF or no PMF) of the enclosures." Comment: performance bias not likely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Comment: blinding of outcome assessor, see quote above
Incomplete outcome data (attrition bias) All outcomes	High risk	Quote“ ... deletion of four patients due to irregularity in attendance and three others on account of suspected malignancy of the ulcers.” Comment: likely to introduce some attrition bias
Selective reporting (reporting bias)	Low risk	No reason to suspect selective reporting of results
Other bias	Low risk	None detected

Seboka 1998

Methods	Randomised controlled trial, parallel
Participants	**Inclusion criteria** • Male farmers working and living in Ethiopia with one or more plantar ulcers or with a scar of healed ulcer and with loss of sensation Average age was 45/46 years (range 20 to 70). All were male. Many had clawed toes and bone loss. 38 had ulcers at baseline. 72 had scars, but not ulcers, at baseline. All had loss of sensation, as tested by a 10 gram monofilament.
Interventions	**Intervention group** • PVC boots, deep enough to accommodate an insole without any modification (N = 58, of these 13 had ulcers at baseline) **Control group** • Locally made canvas shoe (N = 52, of these 25 had ulcers at baseline)
Outcomes	**Primary outcome** • Healing of ulcers (measured as number of persons being ulcer-free and number of persons having ulcers not healed at one year) • Prevention of ulcers (measured as numbers developing ulcers during the year)

Seboka 1998 *(Continued)*

	Secondary outcomes • Acceptability of footwear • Costs • "Uppers" remaining in good condition 110 men were randomised and all were followed (at 3, 6 and 12 months) for one year (1 in canvas shoe group lost to follow-up)
Notes	**Dates when study was conducted**: June 1996 **Funding source**: "The footwear programme at ALERT is generously supported by ALM and NSL" **Declarations of interest**: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: “Randomly assigned” Comment: randomisation procedure not reported
Allocation concealment (selection bias)	Unclear risk	Comment: no information available to make a judgement
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: possible to blind patient to study’s hypotheses but no information available to make a judgement
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: only one patient lost at follow-up at 12 months and all outcomes reported (Table 1)
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect
Other bias	Low risk	Comment: study reported in a letter format, but no obvious risks for bias detected

Sharma 2005

Methods	Randomised controlled trial (parallel)
Participants	**Inclusion criteria** • Leprosy patients with anaesthetic feet with fissures and/or callosities • Hospitalised in India **Exclusion criteria** • Active plantar ulcers/infected cracks

Sharma 2005 *(Continued)*

	Participants' characteristics not reported
Interventions	**Intervention group** • Hot wax therapy for feet (paraffin wax with thermostatic machine; temperature below 120° F) once daily for 20 minutes, six weeks (N = 24) **Control group** • Foot soaks in plain water 20 minutes followed by Vaseline application, six weeks (N = 20)
Outcomes	**Primary outcomes** • Number of feet with fissures and/or calluses in categories graded from 0 to 4 at 6 weeks **Secondary outcomes** • Patient's satisfaction reported (but not how it was measured) 44 participants recruited, randomised and analysed. "The condition of the feet was clinically evaluated at the beginning of the study and the final assessment was done at the end of six weeks."
Notes	**Dates study was conducted**: not reported **Funding source:** not reported **Declarations of interest**: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "The allocation was performed in random manner with the help of computer generated random numbers." Comment: selection bias not likely
Allocation concealment (selection bias)	Unclear risk	Comment: not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Comment: all persons seem to be accounted for
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect
Other bias	Unclear risk	Comment: study authors are not clear in numbers of feet reported

Söderberg 1982

Methods	Quasi-randomised trial (parallel groups)
Participants	**Inclusion criteria** • People living in India, hospitalised, with non-complicated ulcers on the soles of feet (N = 90) 90 participants with a total of 128 ulcers. They were hospitalised in two different hospitals. 72 men and 18 women. All participants had disability grade of 1 or 2 (WHO classification)
Interventions	**Intervention group** • Non-porous adhesive zinc tape made of a plastic web coated with an adhesive substance composed of gum, resin and zinc oxide (30%), changed daily to start with, less frequently as wound secretion decreased. (N = 48) **Control group** • Ordinary gauze dressing soaked in Eusol, kept in place with a bandage. New dressings were applied as in intervention group. (N = 42) All participants in Mangalore wore shoes. In Polambakkam 18 wore shoes and 12 did not.
Outcomes	Wound healing time in days. Length of follow-up was 2 months. "The ulcer was accounted healed when complete epithelialization had occurred". 90 participants recruited and randomised, probably all were analysed (as they were inpatients)
Notes	Multicenter trial: Mangalore (M) and Polambakkam (P). Inadequate reporting of data **Dates when study was conducted:** not reported **Funding source:** supported by grants from the Swedish Medical Research Council and the Swedish Agency for Research Co-operation with Developing Countries **Declaration of interest**: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quote: "The patients were selected on a random *alternate* basis without taking into consideration either the type or size of the ulcers." Comment: probably not adequate
Allocation concealment (selection bias)	Unclear risk	Comment: information not given on allocation concealment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: no information given, probably no blinding
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information given, probably no blinding
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Comment: attrition not reported, all participants seem to be accounted for

Söderberg 1982 *(Continued)*

Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect
Other bias	Unclear risk	Comment: there was a difference between hospitals in proportion of participants who wore shoes which might influence results. There was also a unit of analysis error (90 participants with 128 ulcers)

Walton 1986

Methods	Randomised controlled trial (parallel)
Participants	**Inclusion criteria** • People with leprosy living in India with simple plantar ulcers Participants selected from rural area, age and gender and other demographic data collected but not reported
Interventions	**Intervention group** • 2 cm wide strips of zinc tape plus sandals and self-care materials (N = 22) **Control group** • Gauze soaked in MGSA-paste of magnesium sulphate glycerin with proflavin and benzalkonium chloride plus sandals and self-care materials. The foot was bandaged with plain linen bandages (N = 21) "All ulcers in the study were cleaned with an antiseptic solution of cetrimide followed by ethanol which ensures thorough drying, necessary for adhesion of the plaster. Routine debridement of the edges was carried out, and the ulcers probed if necessary, to ensure that there were no deep sinuses." Each patient was supplied with materials to change dressings and supplied with sandals and all were given individually tailored support.
Outcomes	Healing of ulcer at one month of treatment (measured as mm^2 change in ulcer area). Of 63 participants with plantar ulcers 43 were recruited to study and were randomised. 28 participants were analysed after one month
Notes	**Dates study was conducted**: not reported **Funding source:** "RT Walton was supported by a grant from the Medical Research Council" **Declaration of interest**: not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "Consecutive cases were randomly allocated to zinc tape or control group" Comment: unclear how consecutive participants were randomised
Allocation concealment (selection bias)	Unclear risk	Comment: no information available to make a judgement

Walton 1986 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Comment: not reported, probably not blinded
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Comment: no information available to make a judgement
Incomplete outcome data (attrition bias) All outcomes	High risk	Comment: 35% lost to follow-up
Selective reporting (reporting bias)	Low risk	Comment: no reason to suspect selective reporting
Other bias	Unclear risk	Comment: unit of analyses error, intracluster correlation probably not corrected for. Participants were allocated, wounds were measured

BB: mid-borderline
BL: borderline lepromatous
BT: borderline tuberculoid
LED: light-emitting diode
LL: lepromatous leprosy
NaCl: sodium chloride
PMF: pulsed magnetic field
PVC: polyvinyl chloride
WHO: World Health Organization

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Ahrens 1973	Not relevant intervention
Anjayani 2014	Not relevant intervention
Arole 2002	Not randomised trial
Bense 2013	Not randomised trial
Bhatia 1999	Not randomised trial
Blanc 1999	Not relevant intervention
Brito 2013	Not randomised trial
Chattopadhyay 1995	Not randomised trial
Croft 2003	Editorial
Gebre-Yesus 2001	Not randomised trial
Goncalves 2000	Not randomised trial

Study	Reason for exclusion
Hans 1978	Not randomised trial
Hirzel 1986	Not randomised trial
Kappagoda 2012	Review article
Kappagoda 2014	Overview article
Luong 1958	Not randomised trial
Mahajan 1995	Not randomised trial
Majumdar 2010	Not randomised trial
Parikh 1970	Not randomised trial
Parikh 1975	Not relevant intervention
Pattyn 1983	Review
Pattyn 1984	Not relevant intervention
Pattyn 1994	Not relevant intervention
Pinheiro 2014	Not randomised trial
Ravi 2004	Not relevant intervention. Condition also not relevant
Rezette 1956	Not randomised trial
Saraf 2000	Not randomised trial
Sivasubramanian 2018	Not RCT, "Randomization was done based on wound size at the time of screening"
Smith 2000	Not randomised trial
Soares 2013	Not randomised trial
Thakkar 2013	Not randomised trial
Vadher 1992	Review article
Wilder-Smith 2008	Review article
Yosipovitch 1971	Not randomised trial

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2012/12/003178

Trial name or title	Efficacy of autologous platelet-rich fibrin (PRF) over moist sterile saline dressing in chronic trophic ulcers in Hansen's disease patients: a Randomised Control Trial

CTRI/2012/12/003178 *(Continued)*

Methods	Randomised controlled trial
Participants	**Inclusion criteria of the trial** • Patients with Hansen's disease who have chronic trophic ulcers of lower extremity of > 6 months duration • Attending the dermatology outpatient department in JIPMER, • Having an ulcer area of 1 cm x 1 cm to 5 cm x 5 cm, and belonging to stage II or stage III of the European Pressure Ulcer Advisory Panel (EPUAP) scheme
Interventions	**Intervention** Fibrin clot will be applied topically over the ulcer surface at a ratio of 1 mL of clot for every 10 mL of ulcer volume. This is followed by application of secondary dressings with cotton pads and application of a plaster of paris slab for offloading the foot. This process is repeated weekly for 4 weeks. If the ulcer heals prior to 4 weeks then the application of the platelet-rich fibrin is stopped. **Control Intervention** Saline dressings: the ulcer will be cleaned with 0.9% sterile saline. Saline soaked gauzes will be used for dressing. Plaster of paris cast will then be applied. A keyhole window is cut over the ulcer and this process is repeated every 2 days for 4 weeks or until the ulcer heals, whichever comes first
Outcomes	**Primary outcome** • Compare the efficacy of autologous PRF with moist saline dressing in participants with chronic trophic ulcers in leprosy • The antibacterial effect of PRF in vitro **Secondary outcome** • To compare the mean reduction in ulcer area and volume at end of 4 weeks • To compare the percentage of participants who achieved complete healing of ulcer • To compare the time required to achieve complete healing • To determine the antibacterial effect of PRF in vitro • To assess the bacterial colonization of wounds after complete 4 weeks of PRF treatment
Starting date	5 November 2012
Contact information	LAXMISHA CHANDRASHEKAR Address: ASSISTANT PROFESSOR, DEPARTMENT OF DERMATOLOGY, JIPMER, PONDICHERRY-605006 605006 Pondicherry, PONDICHERRY India laxmishac@gmail.com
Notes	We wrote to authors, who replied: "We have not yet published this study. We're in the process of preparing the manuscript" 28.08.2018 (Dr Divya Gupta MD)

NCT03072004

Trial name or title	Low level laser therapy effects in peripheral nerves patient with leprosy

NCT03072004 *(Continued)*

Methods	Randomised controlled trial
Participants	Leprosy patients with neuropathies
Interventions	Low-level laser therapy
Outcomes	Change from baseline conduction velocity at 28 days after low-level laser therapy
Starting date	January 2017
Contact information	Contact: Elaine F Sabino (elainefavarosabino@gmail.com), Centro M Bernardes Goulart (im-bg34998172121oulart@gmail.com), Federal University of Uberlandia
Notes	www.clinicaltrials.gov/ct2/show/study/NCT03072004

PRF: platelet-rich fibrin

DATA AND ANALYSES

Comparison 1. Zinc tape versus magnesium sulphate/glycerin

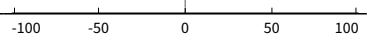
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of ulcers healed after one month	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Mean ulcer area (mm^2) after one month	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Zinc tape versus magnesium sulphate/glycerin, Outcome 1 Number of ulcers healed after one month.

Study or subgroup	Zinc tape n/N	Magnesium sulph/glyc n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Walton 1986	4/14	2/14		2[0.43,9.21]

Analysis 1.2. Comparison 1 Zinc tape versus magnesium sulphate/glycerin, Outcome 2 Mean ulcer area (mm^2) after one month.

Study or subgroup	Zinc tape N	Zinc tape Mean(SD)	Magnesium sulph/glyc N	Magnesium sulph/glyc Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Walton 1986	14	42.4 (15.5)	14	56.7 (17.4)		-14.3[-26.51,-2.09]

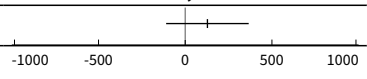


Comparison 2. Zinc tape versus povidone iodine (10%)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction of ulcer area at six weeks (mm^2)	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 2.1. Comparison 2 Zinc tape versus povidone iodine (10%), Outcome 1 Mean reduction of ulcer area at six weeks (mm^2).

Study or subgroup	Zinc tape		Povidone iodine		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Overbeek 1991	26	388 (498)	12	260 (250)		128[-110.01,366.01]

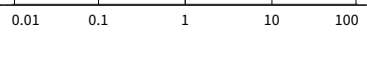


Comparison 3. Topical ketanserin (2%) versus clioquinol cream (3%) or zinc paste

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Healing of ulcer after three months	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 3.1. Comparison 3 Topical ketanserin (2%) versus clioquinol cream (3%) or zinc paste, Outcome 1 Healing of ulcer after three months.

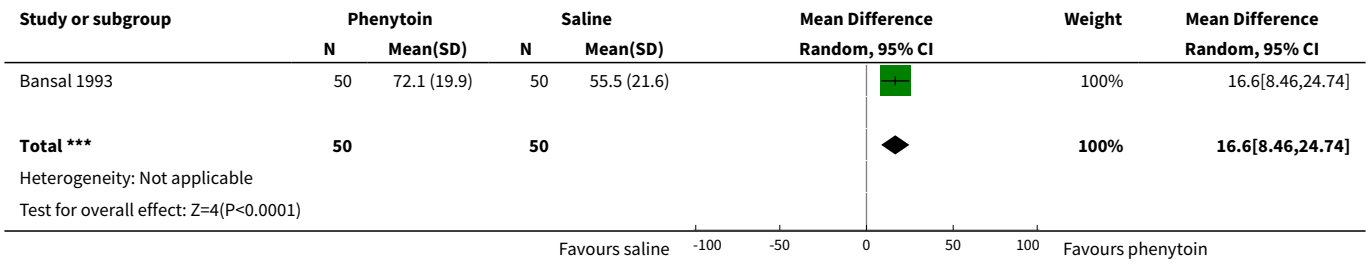
Study or subgroup	Ketanserin (2%)	clioquinol or zinc	Risk Ratio	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI	M-H, Random, 95% CI
Salazar 2001	12/33	2/33		6[1.45,24.75]



Comparison 4. Topical phenytoin (unknown solution) versus saline dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage of ulcer volume reduction at four weeks	1	100	Mean Difference (IV, Random, 95% CI)	16.60 [8.46, 24.74]

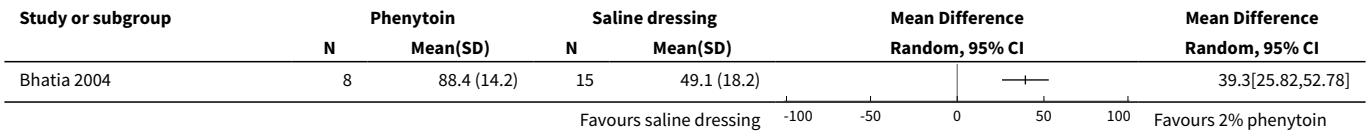
Analysis 4.1. Comparison 4 Topical phenytoin (unknown solution) versus saline dressing, Outcome 1 Mean percentage of ulcer volume reduction at four weeks.



Comparison 5. Topical 2% phenytoin versus saline dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage reduction of ulcer size area at four weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

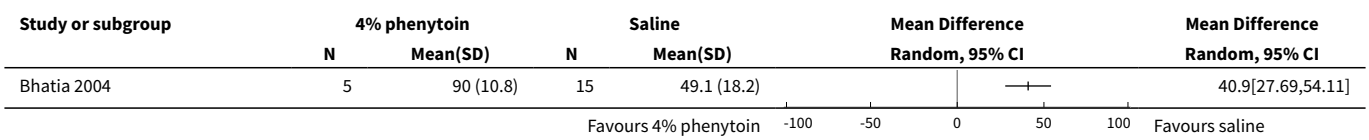
Analysis 5.1. Comparison 5 Topical 2% phenytoin versus saline dressing, Outcome 1 Mean percentage reduction of ulcer size area at four weeks.



Comparison 6. Topical 4% phenytoin versus saline dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage reduction of ulcer area at four weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 6.1. Comparison 6 Topical 4% phenytoin versus saline dressing, Outcome 1 Mean percentage reduction of ulcer area at four weeks.



Comparison 7. Topical 4% phenytoin versus 2% phenytoin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean percentage reduction of ulcer size at four weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 7.1. Comparison 7 Topical 4% phenytoin versus 2% phenytoin, Outcome 1 Mean percentage reduction of ulcer size at four weeks.

Study or subgroup	4% phenytoin N	4% phenytoin Mean(SD)	2% phenytoin N	2% phenytoin Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Bhatia 2004	5	90 (10.8)	8	88.4 (14.2)		1.6[-12.05,15.25]
				Favours 2%	-20 -10 0 10 20	Favours 4% phenytoin

Comparison 8. Footwear - canvas shoes versus PVC boots

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of persons with healed ulcers at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Number of persons having ulcers not healed at one year	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 8.1. Comparison 8 Footwear - canvas shoes versus PVC boots, Outcome 1 Number of persons with healed ulcers at one year.

Study or subgroup	Canvas shoes n/N	PVC boots n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Seboka 1998	20/25	9/13		1.16[0.77,1.74]
		Favours PVC boots	0.5 0.7 1 1.5 2	Favours canvas shoes

Analysis 8.2. Comparison 8 Footwear - canvas shoes versus PVC boots, Outcome 2 Number of persons having ulcers not healed at one year.

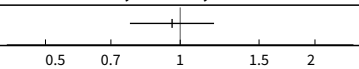
Study or subgroup	Canvas shoes n/N	PVC boots n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Seboka 1998	4/25	4/13		0.52[0.15,1.75]
		Favours canvas shoes	0.01 0.1 1 10 100	Favours PVC boots

Comparison 9. Padded moulded double-rocker plaster shoe versus padded below-knee plaster

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Ulcers fully or nearly healed at six weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 9.1. Comparison 9 Padded moulded double-rocker plaster shoe versus padded below-knee plaster, Outcome 1 Ulcers fully or nearly healed at six weeks.

Study or subgroup	Plaster shoe n/N	Below -knee plaster n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Pring 1982	26/31	21/24		0.96[0.77,1.19]

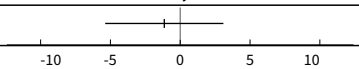


Comparison 10. Exposure to pulsed magnetic fields (in addition to self-care and protective footwear) versus self-care and footwear

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean volume (cm^3) of ulcers at four to five weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 10.1. Comparison 10 Exposure to pulsed magnetic fields (in addition to self-care and protective footwear) versus self-care and footwear, Outcome 1 Mean volume (cm^3) of ulcers at four to five weeks.

Study or subgroup	Magnetic fields N	Magnetic fields Mean(SD)	Self-care N	Self-care Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Sarma 1997	18	0.3 (8.6)	15	1.5 (2.9)		-1.14[-5.37,3.09]



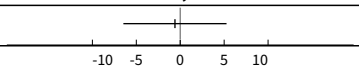
Comparison 11. Low-level laser therapy versus simple dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Size of ulcer (area, cm^2) after 12 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Size of ulcer (depth, mm) after 12 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 11.1. Comparison 11 Low-level laser therapy versus simple dressing, Outcome 1 Size of ulcer (area, cm^2) after 12 weeks.

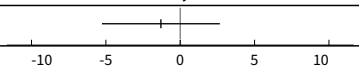
Study or subgroup	Laser therapy N	Laser therapy Mean(SD)	Simple dressing N	Simple dressing Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Barreto 2010	11	3.8 (5.7)	12	4.4 (8.5)		-0.6[-6.47,5.27]



Favours laser therapy — Favours simple dressing

Analysis 11.2. Comparison 11 Low-level laser therapy versus simple dressing, Outcome 2 Size of ulcer (depth, mm) after 12 weeks.

Study or subgroup	Laser therapy N	Laser therapy Mean(SD)	Simple dressing N	Simple dressing Mean(SD)	Mean Difference Random, 95% CI	Mean Difference Random, 95% CI
Barreto 2010	11	4.1 (3.9)	12	5.4 (5.7)		-1.3[-5.26,2.66]



Favours laser therapy — Favours simple dressing

Comparison 12. Intralesional pentoxifylline versus daily simple dressing

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Complete healing of ulcer at 8 weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2 Ulcer depth (cm) at 8 weeks	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

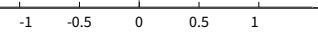
Analysis 12.1. Comparison 12 Intralesional pentoxifylline versus daily simple dressing, Outcome 1 Complete healing of ulcer at 8 weeks.

Study or subgroup	Pentoxifylline n/N	Simple dressing n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Mikhael 2015	10/20	2/20		5[1.25,19.99]

Favours simple dressing — Favours pentoxifylline

Analysis 12.2. Comparison 12 Intralesional pentoxifylline versus daily simple dressing, Outcome 2 Ulcer depth (cm) at 8 weeks.

Study or subgroup	Pentoxifylline		Simple dressing		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Mikhael 2015	20	0.2 (0.2)	20	0.5 (0.4)		-0.22[-0.4,-0.04]



Favours pentoxifylline | Favours simple dressing

Comparison 13. Light-emitting diode (LED) versus conventional dressing

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction in wound size (mm^3) at 8 months	1		Mean Difference (IV, Random, 95% CI)	Totals not selected

Analysis 13.1. Comparison 13 Light-emitting diode (LED) versus conventional dressing, Outcome 1 Mean reduction in wound size (mm^3) at 8 months.

Study or subgroup	LED		Dressing		Mean Difference	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI	Random, 95% CI
Lee 2012	30	338 (410.8)	30	26.6 (399.3)		311.47[106.47,516.47]

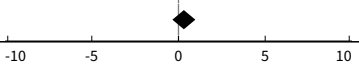
Favours dressing | Favours LED

Comparison 14. hAMMSC-CM + vitamin C versus hAMMSC-CM

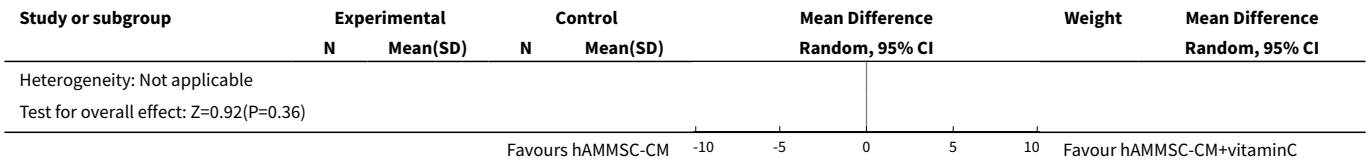
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction (cm^2) in ulcer size at eight weeks	1	44	Mean Difference (IV, Random, 95% CI)	0.31 [-0.35, 0.97]
2 Mean reduction (cm^2) in ulcer depth at eight weeks	1	44	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.17, -0.03]

Analysis 14.1. Comparison 14 hAMMSC-CM + vitamin C versus hAMMSC-CM, Outcome 1 Mean reduction (cm^2) in ulcer size at eight weeks.

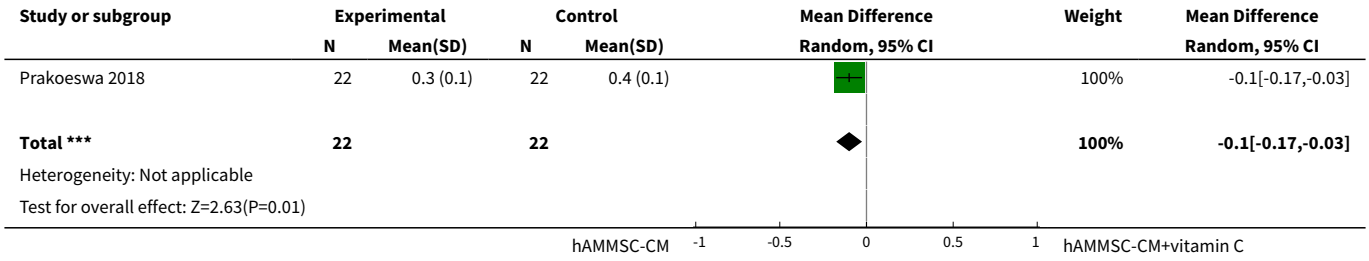
Study or subgroup	Experimental		Control		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Prakoeswa 2018	22	2 (1.2)	22	1.7 (1.1)		100%	0.31[-0.35,0.97]
Total ***	**22**		**22**			**100%**	**0.31[-0.35,0.97]**



Favours hAMMSC-CM | Favour hAMMSC-CM+vitaminC



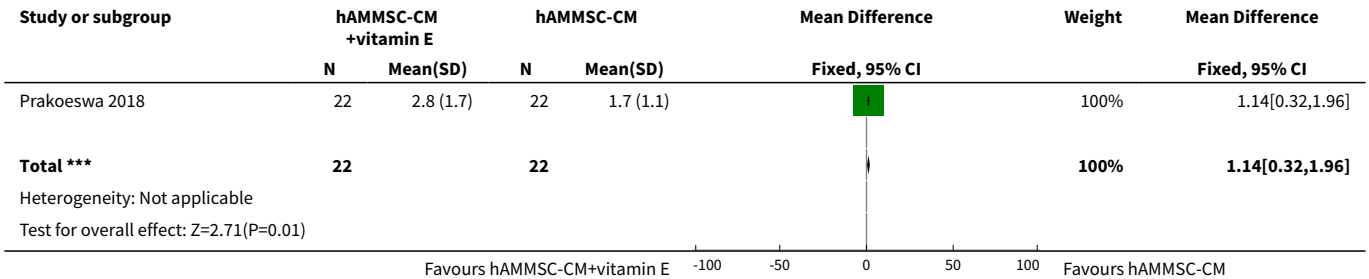
Analysis 14.2. Comparison 14 hAMMSC-CM + vitamin C versus hAMMSC-CM, Outcome 2 Mean reduction (cm^2) in ulcer depth at eight weeks.



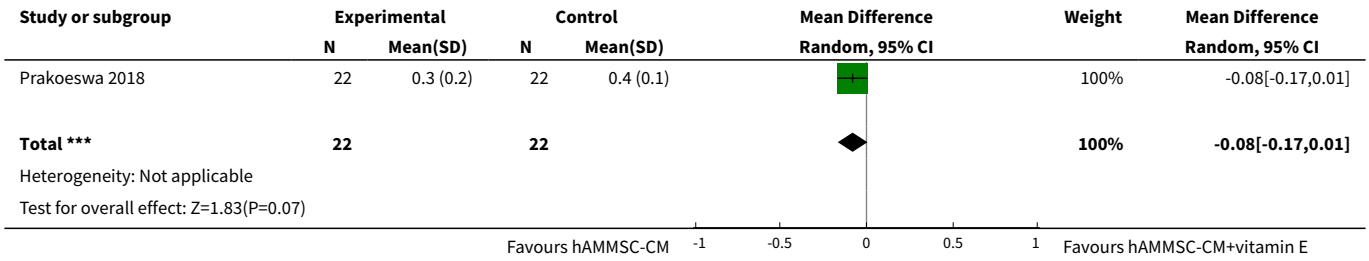
Comparison 15. hAMMSC-CM + vitamin E versus hAMMSC-CM

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Mean reduction (cm^2) in ulcer size at eight weeks	1	44	Mean Difference (IV, Fixed, 95% CI)	1.14 [0.32, 1.96]
2 Mean reduction (cm^2) in ulcer depth at eight weeks	1	44	Mean Difference (IV, Random, 95% CI)	-0.08 [-0.17, 0.01]

Analysis 15.1. Comparison 15 hAMMSC-CM + vitamin E versus hAMMSC-CM, Outcome 1 Mean reduction (cm^2) in ulcer size at eight weeks.



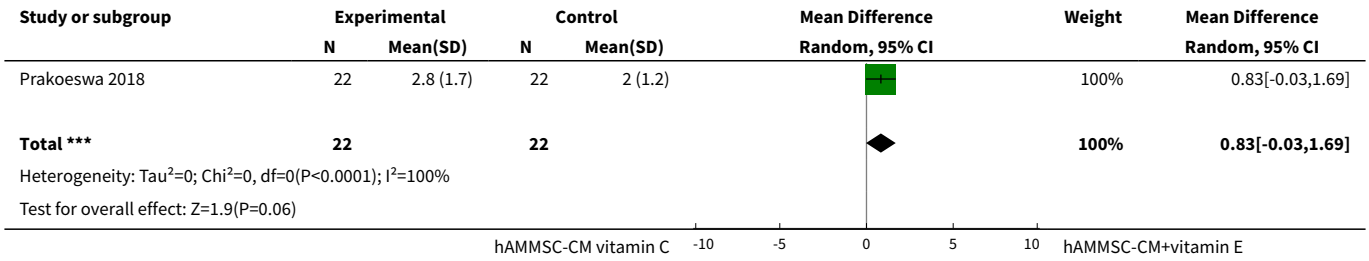
Analysis 15.2. Comparison 15 hAMMSC-CM + vitamin E versus hAMMSC-CM, Outcome 2 Mean reduction (cm^2) in ulcer depth at eight weeks.



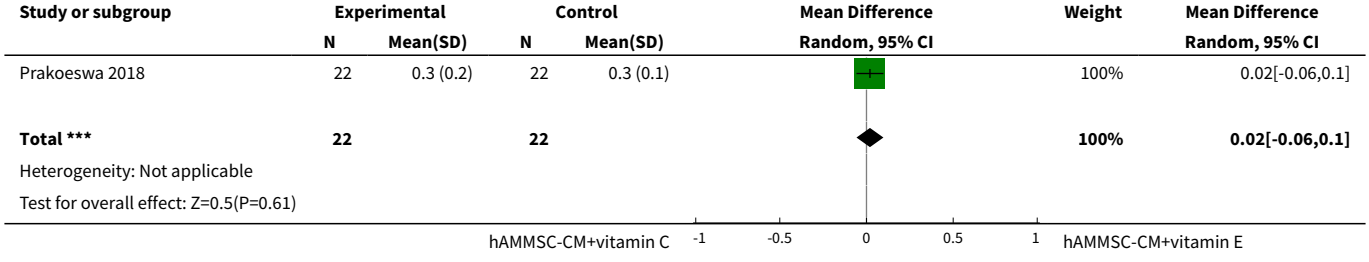
Comparison 16. hAMMSC-CM + vitamin E versus hAMMSC-CM + vitamin C

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean reduction (cm^2) in ulcer size at eight weeks	1	44	Mean Difference (IV, Random, 95% CI)	0.83 [-0.03, 1.69]
2 Mean reduction (cm^2) in ulcer depth at eight weeks	1	44	Mean Difference (IV, Random, 95% CI)	0.02 [-0.06, 0.10]

Analysis 16.1. Comparison 16 hAMMSC-CM + vitamin E versus hAMMSC-CM + vitamin C, Outcome 1 Mean reduction (cm^2) in ulcer size at eight weeks.



Analysis 16.2. Comparison 16 hAMMSC-CM + vitamin E versus hAMMSC-CM + vitamin C, Outcome 2 Mean reduction (cm^2) in ulcer depth at eight weeks.

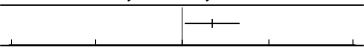


Comparison 17. Wax therapy versus foot soaks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Number of feet being fissure- and callous-free at six weeks	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected

Analysis 17.1. Comparison 17 Wax therapy versus foot soaks, Outcome 1 Number of feet being fissure- and callous-free at six weeks.

Study or subgroup	Wax therapy n/N	Foot soaks n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
Sharma 2005	16/24	6/20		2.22[1.07,4.6]



ADDITIONAL TABLES

Table 1. Glossary of terms

Term	Definition
Afferent nerves	Sensory nerves that carry information from the outside world, such as sensations of heat, cold, and pain, to the brain and spinal cord.
Autonomic fibres	Nerve fibres that collectively make up the sympathetic (involuntary) and parasympathetic ('relaxation response') parts of the autonomic peripheral nervous system. Common symptoms of autonomic nerve damage include an inability to sweat normally and change in vasodilatation.
Bacilli	Plural of bacillus, bacteria.
Capillary haemodynamics	Blood flow in the capillaries, where oxygen transfer occurs in the body.
Efferent nerves	Motor nerves that transmit impulses from the brain and spinal cord to the muscles.
Facial nerve	It is composed of motor, sensory fibres and autonomic fibres. The important motor part innervates the facial muscles responsible for eye closure and mouth and facial movements. In leprosy, the eye is at risk of corneal ulceration for exposure and decreased lachrymal gland function.
Fibroblast	A large flat cell that secretes the proteins that form collagen and elastic fibres and the substance between the cells of connective tissue.
Medial nerve	It is composed of motor, sensory, and autonomic fibres. The autonomic fibres are responsible for sweating and oil gland secretion. Sensation is affected on the lateral side of the forearm and the palmar side of the hand, thumb, index, middle, and half of the ring finger. It innervates the muscles of the hand and in leprosy affects predominately the intrinsic muscles of the thumb, making opposition and prehension difficult. Weakness and paralysis causes the thumb to be flat within the hand.

Table 1. Glossary of terms *(Continued)*

Motor fibres	Motor nerves (or efferent nerves), transmit impulses from the brain and spinal cord to the muscles.
Multibacillary	Having numerous bacilli. "Multibacillary leprosy" classification by World Health Organization for the purpose of treatment is a person with more than five lesions.
Paucibacillary	Having just a few bacilli. "Paucibacillary leprosy" classification by World Health Organization for the purpose of treatment is a person with five or fewer lesions.
Peripheral nerve	A vast transmission network of afferent and efferent nerves from the central nervous system (brain and spinal cord) distally to every other part of the body. The motor, sensory, and autonomic fibres have specific functions within the area innervated by the specific peripheral nerve. Nerves can be composed primarily of motor or sensory fibres or be mixed, having both motor and sensory fibres.
Peroneal nerve	The common peroneal divides into the superficial and deep peroneal branches. The deep branch innervates the muscles of the anterior compartment of the leg (anterior tibial muscle, the long extensor muscle of the big toe and the long extensor muscles of the toes). When weak or paralysed, it makes it difficult to lift the foot and toes as well as evert the foot when walking. In leprosy, it is frequently referred to as "foot drop". Its sensory fibres innervate the lateral dorsal surface of the lower leg and foot. The sensory fibres of the superficial branch provides sensation to the web space of the big toe and the medial surface of the second toe.
Tibial nerve	One of the two major divisions of the sciatic nerve, it courses down the back of the leg to terminate as the medial and lateral plantar nerves in the foot; it supplies the hamstring muscles, the muscles of the back of the lower leg, and the intrinsic muscles of the foot. It causes clawing of the toes if muscles are paralysed. It provides sensation to the back of the leg and sole of the foot. The sensory loss to the sole of the foot puts the foot at high risk for injury and ulceration.
Sensory fibres	Sensory nerves (or afferent nerves), carry information from the outside world, such as sensations of temperature (hot, cold), touch, texture and pain, to the brain and spinal cord. They alert the body to pleasant feelings as well as to danger.
Sural nerve	A sensory nerve in the calf region (sura) of the leg. It is made up of collateral branches of the tibial nerve and common fibular nerve.
Trigeminal nerve	The three-branch trigeminal (fifth cranial) nerve innervating the face, eyes, nose, mouth, and jaws. The corneal sensory loss in leprosy can cause the eye to be at risk for increased dryness and corneal abrasions.
Ulceration	Formation or development of an ulcer. On the skin, it is a loss of epidermis, often part of the dermis and even subcutaneous fat layers of the skin.
Ulnar nerve in the upper extremity	It is composed of motor, sensory, and autonomic fibres. The autonomic fibres are responsible for sweating and oil gland secretion. Sensation is affected on the ulnar (medial) side of the forearm, hand, the palmar side of the 5th and half of the 4th fingers. It innervates the muscles of the hand and in leprosy affects predominately the distal intrinsic muscles used for fine motor tasks. Weakness and paralysis causes finger clawing.
Vasodilation	A widening of the blood vessels caused by a relaxation of the smooth muscle cells in the vessel wall. The sympathetic nervous system has nerves that play an important role in vasodilatation and vasoconstriction.

APPENDICES

Appendix 1. Cochrane Skin Group Specialised Register (CRS-W) search strategy

lepro* or lepra* or hansen*

Appendix 2. CENTRAL (Cochrane Library) search strategy

#1 MeSH descriptor: [Leprosy] explode all trees
#2 hansen*:ti,ab,kw
#3 (lepro* or lepra*):ti,ab,kw
#4 #1 or #2 or #3

Appendix 3. MEDLINE (Ovid) search strategy

1. exp Leprosy/
2. (lepro$ or lepra$).tw.
3. hansen$.tw.
4. Comparative.ti,ab.
5. randomized controlled trial.pt.
6. controlled clinical trial.pt.
7. randomized.ab.
8. placebo.ab.
9. clinical trials as topic.sh.
10. randomly.ab.
11. trial.ti.
12. 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11
13. exp animals/ not humans.sh.
14. 12 not 13
15. 4 or 14
16. 1 or 2 or 3
17. 15 and 16

[Lines 5-14: Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision)]

Appendix 4. Embase (Ovid) search strategy

1. exp leprosy/
2. (lepro$ or lepra$).ti,ab.
3. hansen$.ti,ab.
4. crossover procedure.sh.
5. double-blind procedure.sh.
6. single-blind procedure.sh.
7. (crossover$ or cross over$).tw.
8. placebo$.tw.
9. (doubl$ adj blind$).tw.
10. allocat$.tw.
11. trial.ti.
12. randomized controlled trial.sh.
13. random$.tw.
14. or/4-13
15. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
16. human/ or normal human/
17. 15 and 16
18. 15 not 17
19. 14 not 18
20. comparative.ti,ab.
21. 19 or 20
22. 1 or 2 or 3
23. 21 and 22

Appendix 5. CINAHL (EBSCO) search strategy

S1 TI leprosy OR AB leprosy

S2 TI hansen* OR AB hansen*
S3 (MH "Clinical Trials+")
S4 PT clinical trial
S5 TX (clinic* n1 trial*)
S6 (MH "Random Assignment")
S7 TX random* allocat*
S8 TX placebo*
S9 (MH "Placebos")
S10 (MH "Quantitative Studies")
S11 TX allocat* random*
S12 "randomi#ed control* trial*"
S13 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S14 S3 or S4 or S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 or S13
S15 S1 OR S2
S16 S14 AND S15

Lines S3-S14: SIGN filter for RCTs in CINAHL via EBSCO.

Appendix 6. AMED (Ovid) search strategy

1. exp Leprosy/
2. (lepro$ or lepra$).tw.
3. hansen$.tw.
4. 1 or 2 or 3
5. randomized controlled trial/
6. random allocation/
7. double blind method/
8. single blind method.mp.
9. exp Clinical trials/
10. (clin$ adj25 trial$).mp.
11. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$ or dummy)).mp.
12. (placebo$ or random$).mp.
13. research design/ or clinical trials/ or comparative study/ or double blind method/ or random allocation/
14. prospective studies.mp.
15. cross over studies.mp.
16. Follow up studies/
17. control$.mp.
18. (multicent$ or multi-cent$).mp.
19. ((stud or design$) adj25 (factorial or prospective or intervention or crossover or cross-over or quasi-experiment$)).mp.
20. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. 4 and 20

Appendix 7. LILACS search strategy

lepro$ or lepra$ or hansen$

We searched using the terms above and the Controlled clinical trials topic-specific query filter.

CONTRIBUTIONS OF AUTHORS

LMR was the contact person with the editorial base.
LMR co-ordinated contributions from the co-authors and wrote the final draft of the review.
LF and LMR screened papers against eligibility criteria.
LF obtained data on ongoing and unpublished studies.
LF and LMR appraised the quality of papers.
LF and LMR extracted data for the review and sought additional information about papers.
LMR entered data into RevMan.
KGB, LF and LMR analysed and interpreted data.
KGB, LF and LMR worked on the methods sections.
LF, LL, and LMR drafted the clinical sections of the background and responded to the clinical comments of the referees.
LF, LMR and KGB responded to the methodology and statistics comments of the referees.
LL was the consumer co-author and checked the review for readability and clarity, as well as ensuring outcomes are relevant to consumers.

LMR is the guarantor of the update.

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DECLARATIONS OF INTEREST

Liv Merete Reinar: nothing to declare
Louise Forsetlund: nothing to declare
Linda Faye Lehman: nothing to declare
Kjetil G Brurberg: nothing to declare

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Searches: this is an update (by way of a new protocol) of a review published in 2008 (Reinar 2008). For the previous review, we searched the CD produced of all the papers published in the main leprosy journals back to the 1920s (Leprosy Research Foundation) "Compact disc of leprosy literature, 1913-1991", Loma Linda, California, USA, 1993. We also handsearched the *International Journal of Leprosy* for reports of trials from 1934 to 2005 and checked conference proceedings found in the *International Journal of Leprosy* (1934 to 2005). For this version of the review, we did not search these sources. We did not search for unpublished and ongoing trials by corresponding with authors; field experts; and experts on tropical medicine or leprosy or both.

Objectives: to align with the interventions given in the Methods, we changed the wording of objectives from "To assess the effects of self-care, dressings, and footwear in preventing and healing secondary damage to the skin in persons affected by leprosy" to "To assess the effects of education, information, self-care programmes, dressings, skin care, footwear and other measures for preventing and healing secondary damage to the skin in persons affected by leprosy".

Types of participants: we added further information on diagnosis, setting, age, gender, and subsets of relevant participants: "We considered studies that included participants living in the community or those that were hospitalised. Case definitions were typically based on the Ridley-Jopling scheme or the World Health Organization (WHO) operational classification of paucibacillary/multibacillary classification. However, we also included studies that did not specify the diagnostic criteria. We included studies with participants of all ages, genders, all countries, and all kinds of ulcers caused by leprosy. Studies with a subset of leprosy patients would have been included if they constituted more than 90%."

Types of interventions: we clarified the setting of the interventions: "Interventions could be given in primary care, in outpatient units or in hospitals."

Data extraction and management: we specified that the data extraction form was piloted and which data items were extracted.

Unit of analysis issues: we specified how we handled studies where participants had several treated ulcers, as this kind of study was not anticipated when writing the protocol: "However, since some trials randomised participants of which some had several ulcers, there are for these studies, an element of clustering. In principle, this should have been accounted for in the analysis. In the studies that explicitly included people with several ulcers without reporting how this was handled in the analysis, we made a note of this in the 'Characteristics of included studies' tables. However, we judged that the clustering was not comprehensive enough to make any difference to the reported results."

'Summary of findings' table: we specified that we also included secondary outcomes in the 'Summary of findings' tables.