ClinicalEvidence

Scabies

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ABSTRACT

INTRODUCTION: Scabies is a common public health problem. In many resource-poor settings, scabies is an endemic problem; whereas in industrialised countries, it is most common in institutionalised communities. METHODS AND OUTCOMES: We conducted a systematic review and aimed to answer the following clinical questions: What are the effects of topical treatments for scabies? What are the effects of systemic treatments for scabies? We searched: Medline, Embase, The Cochrane Library, and other important databases up to July 2013 (Clinical Evidence reviews are updated periodically; please check our website for the most up-to-date version of this review). We included harms alerts from relevant organisations such as the US Food and Drug Administration (FDA) and the UK Medicines and Healthcare products Regulatory Agency (MHRA). RESULTS: We found five studies that met our inclusion criteria. We performed a GRADE evaluation of the quality of evidence for interventions. CONCLUSIONS: In this systematic review, we present information relating to the effectiveness and safety of the following interventions: benzyl benzoate (topical), crotamiton (topical), ivermectin (oral), malathion (topical), permethrin (topical), and sulfur compounds (topical).

QUESTIONS

INTERVENTIONS

Key points

- Scabies is an infestation of the skin by the mite *Sarcoptes scabiei*. In adults, the most common sites of infestation are the fingers and the wrists, although infection may manifest in older people as a diffuse truncal eruption.

  It is a very common public health problem. In many resource-poor settings, scabies is an endemic problem; whereas in industrialised countries, it is most common in institutionalised communities.

- Topical permethrin seems highly effective at increasing clinical cure of scabies within 28 days.

  Topical permethrin use has been associated with isolated reports of serious adverse effects, including death.

- Topical crotamiton seems effective at increasing clinical cure of scabies at 28 days, although it is less effective than topical permethrin.

- We found insufficient evidence to judge the effectiveness of topical benzyl benzoate, topical malathion, or topical sulfur compounds for treating scabies.

- Oral ivermectin seems more effective at increasing clinical cure of scabies compared with placebo. It may be more effective at increasing clinical cure compared with topical benzyl benzoate. However, it may be less effective than topical permethrin in the short-term.

  There have been isolated reports of severe adverse effects with oral ivermectin, including death and convulsion, but these are rare.

  Observational data suggest that oral ivermectin may be effective in certain circumstances, such as when included in the treatment of hyperkeratotic crusted scabies, in people with concomitant HIV, and in treating outbreaks in residential facilities.

  Although tested in RCTs, oral ivermectin is not presently licensed for the treatment of scabies in most countries. It is only available on a named patient basis in the UK.

- Topical lindane use has either been restricted or is not available in many parts of the world owing to the mounting evidence for serious adverse effects. We have not included it in this review. However, it may be the most effective treatment that is locally available in some countries. Harms must be carefully weighed against benefits before it is used.

Clinical context

DEFINITION

Scabies is an infestation of the skin by the mite *Sarcoptes scabiei*. [1] Typical sites of infestation are skin folds and flexor surfaces. In adults, the most common sites are between the fingers and on the wrists, although infection may manifest in older people as a diffuse truncal eruption. In infants and children, the face, scalp, palms, and soles are also often affected. Infection with the scabies mite causes discomfort and intense itching, particularly at night, with irritating papular or vesicular eruptions. The discomfort and itching can be especially debilitating in immunocompromised people, such as those with HIV/AIDS.

INCIDENCE/ PREVALENCE

Scabies is a common public health problem. In many resource-poor settings, scabies is an endemic problem; whereas in industrialised countries, it is most common in institutionalised communities. Case studies suggest that epidemic cycles occur every 7 to 15 years, and that these partly reflect the population's immune status.

AETIOLOGY/ RISK FACTORS

Scabies is particularly common where there is social disruption, overcrowding with close body contact, and limited access to water. [2] Young children, immobilised older people, people with HIV/AIDS, and other medically and immunologically compromised people are predisposed to infestation and have particularly high mite counts. [3] Although not based on RCT evidence, treating family members and other close contacts at the same time as treating the index case is advisable to minimise reinfection and further spread. Clothing and bed linen belonging to the index case should also be washed. [4]

PROGNOSIS

Scabies is not life-threatening but the severe, persistent itch and secondary infections may be debilitating. Occasionally, crusted scabies develops. This form of the disease is resistant to routine treatment and can be a source of continued reinfestation and of spread to others.

AIMS OF INTERVENTION

To eliminate the scabies mites and ova from the skin; to cure pruritus (itching); to prevent reinfestation; to prevent spread to other people; with minimal adverse effects.

OUTCOMES

Treatment failure new lesions (i.e., visible burrows and papular/vesicular eruptions) and/or recovery of live mites at 7 or more days after treatment, which is the time it takes for lesions to heal and for eggs and mites to reach maturity if treatment fails; **serious adverse effects** (e.g., adverse effects requiring hospitalisation).

METHODS

Clinical Evidence search and appraisal July 2013. The following databases were used to identify studies for this systematic review: Medline 1966 to July 2013, Embase 1980 to July 2013, and The Cochrane Database of Systematic Reviews 2013, issue 2 (1966 to date of issue). Additional searches were carried out in the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment (HTA) database. We also searched for retractions of studies included in the review. An information specialist identified the titles and abstracts in an initial search, which an evidence scanner then assessed against predefined criteria. An evidence analyst then assessed full texts for potentially relevant studies against predefined criteria. An expert contributor was consulted on studies selected for inclusion. An evidence analyst then extracted all data relevant to the review. Study design criteria for inclusion in this review were: published RCTs and systematic reviews of RCTs in the English language, at least single-blinded, and containing more than 20 individuals, of whom more than 80% were followed up. There was no minimum length of follow-up. We excluded all studies described as 'open', 'open label', or not blinded unless blinding was impossible. We included RCTs and systematic reviews of RCTs where harms of an included intervention were assessed, applying the same study design criteria for inclusion as we did for benefits. In addition, we use a regular surveillance protocol to capture harms alerts from organisations such as the FDA and the MHRA, which are added to the reviews as required. To aid readability of the numerical data in our reviews, we round many percentages to the nearest whole number. Readers should be aware of this when relating percentages to summary statistics such as relative risks (RRs) and odds ratios (ORs). We have performed a GRADE evaluation of the quality of evidence for interventions included in this review (see table, p 12). The categorisation of the quality of the evidence (high, moderate, low, or very low) reflects the quality of evidence available for our chosen outcomes in our defined populations of interest. These categorisations are not necessarily a reflection of the overall methodological quality of any individual study, because the Clinical Evidence population and outcome of choice may represent only a small subset of the total outcomes reported, and population included, in any individual trial. For further details of how we perform the GRADE evaluation and the scoring system we use, please see our website (www.clinicalevidence.com).

QUESTION What are the effects of topical treatments for scabies?

OPTION PERMETHRIN (TOPICAL)

- For GRADE evaluation of interventions for Scabies, see table, p 12 .
- Topical permethrin seems highly effective at increasing clinical cure of scabies within 28 days.
- Topical permethrin use has been associated with isolated reports of serious adverse effects, including death.

Benefits and harms

Topical permethrin versus placebo:

We found no systematic review or RCTs. For further information on the safety of topical permethrin, see the Comment section.

Topical permethrin versus topical crotamiton:

We found one systematic review (search date 2010), [5] which identified two RCTs.

Treatment failure

Topical permethrin compared with topical crotamiton Topical permethrin seems more effective than topical crotamiton at reducing the proportion of people with failed clinical cure at 28 days (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Failed clinical cure					
[5] Systematic review	194 adults and children with clinically and microscopically diagnosed scabies 2 RCTs in this analysis	**Proportion of people with failed clinical cure , 28 days** 6/97 (6%) with topical permethrin 25/97 (26%) with topical crotamiton As scabies was clinically diagnosed and parasitologically confirmed in all cases, the comparative treatment failure rates described for clinically diagnosed cases apply equally to parasitologically diagnosed cases in these RCTs Medications were applied for either 8 to 10 hours or overnight for 2 consecutive nights	RR 0.24 95% CI 0.10 to 0.55 P = 0.0007	●●○	permethrin

Adverse effects

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Serious adverse effects					
[5] Systematic review	96 children (aged 2 months–5 years) with clinically and microscopically diagnosed scabies Data from 1 RCT	**Adverse effects/worsening of symptoms , 28 days** 0/48 (0%) with topical permethrin 10/48 (21%) with topical crotamiton It was not clear whether worsening of symptoms was an adverse effect of the intervention or was related to the underlying disease process	Significance not reported		

Topical permethrin versus oral ivermectin:

We found one systematic review (search date 2010), [5] which identified two RCTs. We did not report one of the RCTs, as it had greater than 20% attrition. We found two subsequent RCTs comparing topical permethrin with oral ivermectin. [6] [7]

Treatment failure

Topical permethrin compared with oral ivermectin Topical permethrin may be more effective than oral ivermectin at reducing the proportion of people with treatment failure at up to 2 weeks, but we don't know how they compare in the longer term (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment failure					
[5] Systematic review	95 people Data from 1 RCT	**Treatment failure , 2 weeks** 1/45 (2%) with topical permethrin 12/40 (30%) with oral ivermectin	RR 13.50 95% CI 1.84 to 99.26	●●●	permethrin
[7] RCT	242 adults and children (aged 2–84 years) with clinically and microscopically diagnosed scabies	**Clinical cure rate (absence of new lesions and all old lesions healed) , 2 weeks** 112/121 (93%) with topical permethrin 104/121 (86%) with oral ivermectin	P = 0.42	⟷	Not significant
[6] RCT **3-armed trial**	120 adults and children (aged >5 years and/or >15 kg) with clinically and microscopically diagnosed scabies	**Clinical cure (reduction in number of lesions and grade of pruritus by 50% or more) , 2 weeks** 33/38 (87%) with topical permethrin 31/40 (78%) with oral ivermectin (single dose) 26/39 (67%) with oral ivermectin (2 doses, 2 weeks apart)	P values not reported No significant differences observed between topical permethrin and oral ivermectin (1 and 2 doses)		
[6] RCT **3-armed trial**	120 adults and children (aged >5 years and/or >15 kg) with clinically and microscopically diagnosed scabies	**Treatment failure (no improvement in pruritus or skin lesions, appearance of new lesions or persistence of mites and their products on microscopy) , 4 weeks** 2/38 (5%) with topical permethrin 4/40 (10%) with oral ivermectin (single dose) 4/39 (10%) with oral ivermectin (2 doses, 2 weeks apart)	P = 0.769	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [5] [6] [7]

Comment: Dermatological adverse effects have been documented with all topical treatments for scabies.

From 1990 to 1995, six adverse events were reported per 100,000 units of topical permethrin distributed in the US (one central nervous system adverse effect reported per 500,000 units of permethrin distributed). [8] Resistance to permethrin seems rare. [8]

Comparative adverse effects of treatments for scabies:
It is difficult to draw firm conclusions on the relative occurrence of severe adverse effects of different preparations of topical permethrin because of incomplete information on incidence in relation to its use. However, there have been isolated reports of severe adverse effects with permethrin, including death, [5] dystonia (after labelled use), [9] and congenital leukaemia (after misuse of permethrin in a pregnant woman). [10]

Although not included in this review, topical lindane is a long-standing scabicide that has now been restricted or made unavailable in many parts of the world owing to mounting evidence for serious adverse effects, including seizure and death. [11] [12] However, topical lindane may be the most effective treatment that is locally available in some countries. Harms must be carefully weighed against benefits before it is used.

Safety results from trials and observational studies need to be summarised, particularly regarding additional risks in infants and pregnant women.

OPTION CROTAMITON (TOPICAL)

- For GRADE evaluation of interventions for Scabies, see table, p 12 .
- Topical crotamiton seems to be effective at increasing clinical cure at 28 days, although it is less effective than topical permethrin.

Benefits and harms

Topical crotamiton versus placebo:
We found no systematic review or RCTs.

Topical crotamiton versus topical permethrin:
See option on Topical permethrin, p 3 .

Comment: Dermatological adverse effects have been documented with all topical treatments for scabies.

The contributors would like to stress that, based on the current evidence, topical permethrin is more effective than topical crotamiton (see option on Topical permethrin, p 3).

Comparative adverse effects of treatments for scabies:
See comment on Topical permethrin, p 3 .

OPTION BENZYL BENZOATE (TOPICAL)

- For GRADE evaluation of interventions for Scabies, see table, p 12 .
- We found insufficient evidence to judge the effectiveness of topical benzyl benzoate compared with placebo or other topical treatments for scabies.
- Topical benzyl benzoate may be less effective than oral ivermectin at increasing clinical cure of scabies.

Benefits and harms

Topical benzyl benzoate versus placebo:

We found no systematic review or RCTs.

Topical benzyl benzoate versus topical sulfur ointment:

We found one systematic review (search date 2010), [5] which identified one RCT (158 adults and children) comparing topical benzyl benzoate with topical sulfur ointment.

Treatment failure

Topical benzyl benzoate compared with topical sulfur ointment We don't know how topical benzyl benzoate and topical sulfur ointment compare at reducing the proportion of people with treatment failure at 15 days (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment failure					
[5] Systematic review	158 adults and children with clinically diagnosed scabies Data from 1 RCT	**Treatment failure , 15 days** 8/89 (9%) with topical benzyl benzoate 2/69 (3%) with topical sulfur ointment	RR 3.10 95% CI 0.68 to 14.14	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [5]

Topical benzyl benzoate versus oral ivermectin:

See option on Oral ivermectin, p 7 .

Comment:

Dermatological adverse effects have been documented with all topical treatments for scabies.

Non-randomised trials suggest that benzyl benzoate has variable effectiveness (as low as 50%). [13] [14] The low cure rate may be related to the concentration of the preparation.

A study carried out in Nigeria (58 people), which compared topical benzyl benzoate with oral ivermectin, found that topical benzyl benzoate was associated with skin irritation and itching in about 25% of cases. Adverse events were not reported for oral ivermectin. [5] [15]

OPTION MALATHION (TOPICAL)

- For GRADE evaluation of interventions for Scabies, see table, p 12 .
- We found no RCT evidence assessing the effectiveness of topical malathion for treating scabies.

Benefits and harms

Topical malathion:

We found one systematic review on treatments for scabies (search date 2010), [5] which identified no RCTs on the effects of topical malathion.

Comment: Dermatological adverse effects have been documented with all topical treatments for scabies.

Case series suggest that topical malathion is effective in curing infestation with scabies, with a cure rate of over 80% of people at 4 weeks. [16] [17] [18] The safety results from trials and observational studies need to be systematically reviewed, particularly with regard to additional risks in infants and pregnant women.

OPTION SULFUR COMPOUNDS (TOPICAL)

- For GRADE evaluation of interventions for Scabies, see table, p 12 .
- We found insufficient evidence to judge the effectiveness of topical sulfur compounds for treating scabies.

Benefits and harms

Topical sulfur compounds versus placebo:

We found one systematic review on treatments for scabies (search date 2010), [5] which identified no RCTs on the effects of topical sulfur compounds compared with placebo.

Topical sulfur compounds versus topical benzyl benzoate:

See option on Topical benzyl benzoate, p 5 .

Comment: Dermatological adverse effects have been documented with all topical treatments for scabies.

QUESTION What are the effects of systemic treatments for scabies?

OPTION IVERMECTIN (ORAL)

- For GRADE evaluation of interventions for Scabies, see table, p 12 .
- Oral ivermectin seems more effective at increasing clinical cure of scabies compared with placebo. It may be more effective at increasing clinical cure compared with topical benzyl benzoate. However, it may be less effective than topical permethrin in the short-term.
- There have been isolated reports of severe adverse effects with oral ivermectin, including death and convulsion, but these are rare.
- Observational data suggest that oral ivermectin may be effective in some circumstances, such as when included in the treatment of hyperkeratotic crusted scabies, in people with concomitant HIV, and in treating outbreaks in residential facilities.
- Although tested in RCTs, oral ivermectin is not presently licensed for the treatment of scabies in most countries.
- Oral ivermectin is only available on a named patient basis in the UK.

Benefits and harms

Oral ivermectin versus placebo:

We found one systematic review (search date 2010), [5] which identified one RCT comparing oral ivermectin with placebo. For further information on the safety of oral ivermectin in adults, children, and older people, see the Comment section.

Treatment failure

Oral ivermectin compared with placebo Oral ivermectin seems more effective than placebo at reducing the proportion of people with treatment failure at 7 days (moderate-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment failure					
[5] Systematic review	55 adults and children (aged >5 years) with clinically diagnosed scabies Data from 1 RCT	**Treatment failure , 7 days** 6/29 (21%) with oral ivermectin 22/26 (85%) with placebo RCT stopped at 7 days as the oral ivermectin group was significantly clinically better than the placebo group	RR 0.24 95% CI 0.12 to 0.51	●●○	ivermectin

Adverse effects

No data from the following reference on this outcome. [5]

Oral ivermectin versus topical benzyl benzoate:

We found one systematic review (search date 2010), [5] which identified two RCTs. The review did not perform a meta-analysis of the RCTs; therefore, we have reported the results of the RCTs separately.

Treatment failure

Oral ivermectin compared with topical benzyl benzoate Oral ivermectin may be more effective than topical benzyl benzoate at reducing treatment failure at 30 days, but results are inconsistent (low-quality evidence).

Ref (type)	Population	Outcome, Interventions	Results and statistical analysis	Effect size	Favours
Treatment failure					
[5] Systematic review	58 adults and children (aged 5–63 years) with clinically or microscopically diagnosed scabies Data from 1 RCT	**Treatment failure , 30 days** 2/29 (7%) with oral ivermectin 15/29 (52%) with benzyl benzoate	RR 0.13 95% CI 0.03 to 0.53	●●●	ivermectin
[5] Systematic review	44 adults and children (aged 5–56 years) with clinically diagnosed scabies Data from 1 RCT	**Treatment failure , 30 days** 7/23 (30%) with oral ivermectin 11/21 (52%) with benzyl benzoate	RR 0.58 95% CI 0.28 to 1.22	⟷	Not significant

Adverse effects

No data from the following reference on this outcome. [5]

Oral ivermectin versus topical permethrin:
See option on Topical permethrin, p 3 .

Comment: Dermatological adverse effects have been documented with all topical treatments for scabies.

In adults:
Oral ivermectin has been used widely in adults with onchocerciasis, and two large cohort studies found that, even with repeated doses, serious adverse effects have been rare. [19] [20] The Cochrane review noted that review of the UK MHRA database of suspected drug reactions found one report for convulsions and three for death with oral ivermectin. However, the review also stated that "extreme caution must be shown in interpreting these reports, as they are clearly influenced by the extent to which the products are used and by the quality of the reporting. Neither can a causal link be assumed for any of the reported events". [5]

There is evidence showing that oral ivermectin is associated with serious neurological reactions in people who are heavily infected with the microfilariae of *Loa loa*. [21] [22] The risk of neurological reaction appears to be related to microfilarial load.

In children:
We found no good evidence about its safety in children.

In older people:
An increased risk of death has been reported among older people taking oral ivermectin for scabies in a long-term care facility. [23] It is not clear whether this was caused by oral ivermectin, interactions with other scabicides (including lindane and permethrin), or other treatments such as psychoactive drugs. Other studies reported no such complications from its use in older people. [24]

Comparative adverse effects of treatments for scabies:
See option on Topical permethrin, p 3 .

Clinical guide:
Although tested in RCTs, the review noted that "oral ivermectin is not presently licensed for the treatment of scabies in most countries. Ivermectin's effectiveness, cost effectiveness, and safety in mass treatment in areas of high endemicity (preferably as a sustainable public health intervention) need to be further evaluated in larger trials of sufficient power". [5]

Oral ivermectin is only available on a named patient basis in the UK. Due to the apparent lack of ovicidal activity with oral ivermectin, and based on our knowledge of the life-cycle of the scabies mite, it is recommended that a repeat dose of oral ivermectin be given 4 days after the initial dose. [25]

Case series suggest that oral ivermectin may be effective when included in the treatment of hyperkeratotic crusted scabies (also known as Norwegian scabies), [26] [27] [28] [29] in people with concomitant HIV disease [3] and in treating outbreaks in residential facilities. [26] Experience suggests that oral ivermectin is safe in adults and children who are more than 90 cm in height (approximately equivalent to 15 kg in weight) being treated for onchocerciasis. [30] [31] However, no such experience exists for children less than 90 cm in height, and there have been reports of increased risk of death in older people.

GLOSSARY

High-quality evidence Further research is very unlikely to change our confidence in the estimate of effect.

Low-quality evidence Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Moderate-quality evidence Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Onchocerciasis A tropical disease caused by the filarial worm *Onchocerca volvulus*. The disease affects the skin, causing disfiguration and itching, and is a major cause of blindness, particularly in West Africa. The worm is transmitted to humans in its larval stage through the bite of the black fly, genus *Simulium*.

SUBSTANTIVE CHANGES

Benzyl benzoate (topical) One systematic review updated. [5] Categorisation unchanged (unknown effectiveness).

Ivermectin (oral) One systematic review updated. [5] Two RCTs added. [6] [7] Categorisation unchanged (likely to be beneficial).

Malathion (topical) One systematic review updated. [5] Categorisation unchanged (unknown effectiveness).

Permethrin (topical) One systematic review updated. [5] Two RCTs added. [6] [7] Categorisation unchanged (beneficial).

Sulfur compounds (topical) One systematic review updated. [5] Categorisation unchanged (unknown effectiveness).

Crotamiton (topical) One systematic review updated. [5] Categorisation changed from 'beneficial' to 'likely to be beneficial'.

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Competing interests: PJ and MS declare that they have no competing interests.
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Disclaimer

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GRADE **Evaluation of interventions for Scabies.**

Important outcomes			Treatment failure						
Studies (Participants)	Outcome	Comparison	Type of evidence	Quality	Consistency	Directness	Effect size	GRADE	Comment
What are the effects of topical treatments for scabies?									
2 (194) [5]	Treatment failure	Topical permethrin versus topical crotamiton	4	–2	0	0	+1	Moderate	Quality points deducted for sparse data, unclear allocation concealment, and unclear blinding; effect-size point added for RR <0.5
3 (457) [5] [6] [7]	Treatment failure	Topical permethrin versus oral ivermectin	4	–1	–1	0	0	Low	Quality point deducted for incomplete reporting of results; consistency point deducted for inconsistent results among studies (at 2 weeks)
1 (158) [5]	Treatment failure	Topical benzyl benzoate versus topical sulfur ointment	4	–2	0	0	0	Low	Quality points deducted for sparse data and short follow-up
What are the effects of systemic treatments for scabies?									
1 (55) [5]	Treatment failure	Oral ivermectin versus placebo	4	–2	0	0	+1	Moderate	Quality points deducted for sparse data and short follow-up; effect-size point added for RR <0.5
2 (102) [5]	Treatment failure	Oral ivermectin versus topical benzyl benzoate	4	–1	-1	0	0	Low	Quality point deducted for sparse data; consistency point deducted for inconsistent results among studies

We initially allocate 4 points to evidence from RCTs, and 2 points to evidence from observational studies. To attain the final GRADE score for a given comparison, points are deducted or added from this initial score based on preset criteria relating to the categories of quality, directness, consistency, and effect size. Quality: based on issues affecting methodological rigour (e.g., incomplete reporting of results, quasi-randomisation, sparse data [<200 people in the analysis]). Consistency: based on similarity of results across studies. Directness: based on generalisability of population or outcomes. Effect size: based on magnitude of effect as measured by statistics such as relative risk, odds ratio, or hazard ratio.