Interventions for treating scabies (Review)

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[Intervention Review]

Interventions for treating scabies

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ABSTRACT

Background

Scabies is an intensely itchy parasitic infection of the skin caused by the *Sarcoptes scabiei* mite. It is a common public health problem with an estimated global prevalence of 300 million cases. Serious adverse effects have been reported for some drugs used to treat scabies.

Objectives

To evaluate topical and systemic drugs for treating scabies.

Search strategy

In February 2007, we searched the Cochrane Infectious Diseases Group Specialized Register, CENTRAL (*The Cochrane Library* 2006, Issue 1), MEDLINE, EMBASE, LILACS, and INDMED. In March 2007, we also searched the grey literature and sources for registered trials. We also checked the reference lists of retrieved studies.

Selection criteria

Randomized controlled trials of drug treatments for scabies.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. Results were presented as risk ratios with 95% confidence intervals and data combined where appropriate.

Main results

Twenty small trials involving 2392 people were included. One trial was placebo controlled, 16 compared two or more drug treatments, two compared treatment regimens, and one compared different drug vehicles.

Fewer treatment failures occurred by day seven with oral ivermectin in one small trial (55 participants). Topical permethrin appeared more effective than oral ivermectin (85 participants, 1 trial), topical crotamiton (194 participants, 2 trials), and topical lindane (753 participants, 5 trials). Permethrin also appeared more effective in reducing itch persistence than either crotamiton (94 participants, 1 trial) or lindane (490 participants, 2 trials). One small trial did not detect a difference between permethrin (a synthetic pyrethroid) and a natural pyrethrin-based topical treatment (40 participants).

No significant difference was detected in the number of treatment failures between crotamiton and lindane (100 participants, 1 trial), lindane and sulfur (68 participants, 1 trial), benzyl benzoate and sulfur (158 participants, 1 trial), and benzyl benzoate and natural synergized pyrethrins (240 participants, 1 trial); all were topical treatments. No trials of malathion were identified.

No serious adverse events were reported. A number of trials reported skin reactions in participants randomized to topical treatments. There were occasional reports of headache, abdominal pain, diarrhoea, vomiting, and hypotension.

Authors' conclusions

Topical permethrin appears to be the most effective treatment for scabies. Ivermectin appears to be an effective oral treatment. More research is needed on the effectiveness of malathion, particularly when compared to permethrin, and on the management of scabies in an institutional setting and at a community level.

PLAIN LANGUAGE SUMMARY

Interventions for treating scabies

Scabies is a parasitic infection of the skin. It occurs throughout the world, but is particularly problematic in areas of poor sanitation, overcrowding, and social disruption, and is endemic in many resource-poor countries. The global prevalence of scabies is estimated at 300 million cases, but the level of infection varies between countries and communities. The female mite burrows into the skin to lay eggs which then hatch out and multiply. The infection can spread from person to person via direct skin contact, including sexual contact. It causes intense itching with eruptions on the skin. Various drugs have been developed to treat scabies, and herbal and traditional medicines are also used. The review of trials attempted to cover all these. The authors identified 20 small trials involving 2392 people, with 17 of the trials taking place in resource-poor countries. Permethrin appeared to be the most effective topical treatment for scabies, and ivermectin appeared to be an effective oral treatment. However, ivermectin is unlicensed for this indication in many countries. Adverse events such as rash, vomiting, and abdominal pain were reported, but the trials were too small to properly assess serious but rare potential adverse effects. No trials of herbal or traditional medicines were identified for inclusion.

BACKGROUND

What is scabies?

Scabies is an intensely itchy parasitic infection of the skin that is caused by the *Sarcoptes scabiei* mite. It occurs throughout the world, but is particularly problematic in areas of poor sanitation, overcrowding, and social disruption. The global prevalence of scabies is estimated at 300 million cases (Alexander 1984), with large variations between countries. In the UK, no up-to-date robust prevalence data exist, but general practitioners recorded approximately 1200 new cases per year in the 1990s (Downs 1999). In resource-rich communities, scabies tends to occur in cyclical epidemics, particularly within institutional-living situations such as nursing homes (Scheinfeld 2004) or the army (Mimouni 1998; Mimouni 2003). There is some seasonal variation with incidence being greater in the winter than the summer, perhaps related to the tendency for more indoor overcrowding in colder weather (Downs 1999). In resource-poor communities, the occurrence pattern is quite different with the disease being endemic in many areas (Chosidow 2000). For example, the prevalence of scabies among the remote Aboriginal communities of Northern Australia is around 50% in children and 25% in adults (Wong 2002). The prevalence of infection in a community is potentially influenced by changes in social attitudes, population movements, wars, misdiagnosis, inadequate treatment, and changes in the immune status of the population. Scabies infestation represents a considerable burden of ill health in many communities, and although the disease is rarely life threatening, it causes widespread debilitation and misery (Green 1989).

The life cycle of *S. scabiei* begins with the pregnant female laying two to three eggs a day in burrows several millimetres to several centimetres in length in the stratum corneum (outermost layer) of the skin. After about 50 to 72 hours, larvae emerge and make new burrows. They mature, mate, and repeat this 10- to 17-day cycle. Mites usually live for 30 to 60 days (Green 1989).

Humans are the main reservoir for *S. scabiei* var. *hominis* (variety of the mite named to reflect the main host species). Scabies is usually spread person to person via direct skin contact, including sexual contact, though transfer via inanimate objects such as clothing or furnishings is also possible (Hay 2004). The mite can burrow beneath the skin within 2.5 minutes, though around 20 minutes is more usual (Alexander 1984). The level of infectiousness of an individual depends in part on the number of mites harboured, which can vary from just a single mite to millions (Chosidow 2000). Humans can also be transiently infected by the genetically distinct animal varieties of *S. scabiei* (eg var. *canis*), though cross infectivity is low (Fain 1978; Walton 2004).

Clinical infection with the scabies mite causes discomfort and often intense itching of the skin, particularly at night, with irritating papular or vesicular eruptions. While infestation with the scabies mite is not life threatening, the severe, persistent itch debilitates and depresses people (Green 1989). The classical sites of infestation are between the fingers, the wrists, axillary areas, female breasts (particularly the skin of the nipples), peri-umbilical area, penis, scrotum, and buttocks. Infants are usually affected on the face, scalp, palms, and soles. Much of the itching associated with scabies is as a result of the host immune reaction, and symptoms can take several weeks to appear after initial infection in a person exposed to scabies for the first time. Symptoms appear after a much shorter interval (one to two days) after reinfestation (Arlian 1989).

A more severe or 'crusted' presentation of infestation is associated with extreme incapacity and with disorders of the immune system, such as HIV infection. Clinically this atypical form of scabies presents with a hyperkeratotic dermatosis resembling psoriasis. Lymphadenopathy and eosinophilia can be present, but itching may be unexpectedly mild. Patients with crusted scabies may harbour millions of mites and are highly infectious (Meinking 1995a). The dermatological distribution of mites in such patients is often atypical (eg including the head), and treatment in hospital is often advised (Chosidow 2000).

Complications are few although secondary bacterial infection of the skin lesions by group A *Streptococcus pyogenes* or *Staphylococcus aureus*, or both, can occur following repeated scratching, particularly in warmer climates (Meinking 1995a). Secondary infection with group A *Streptococcus* can lead to acute glomerulonephritis, outbreaks of which have been associated with scabies (Green 1989).

Diagnosis, treatment, and prevention

Diagnosis on clinical grounds is usually made on a history of itching (particularly if contacts are also affected) and the finding of lesions in the classical sites. The diagnosis can in most cases be confirmed by microscopically identifying a mite, egg, or mite faeces in a skin scraping, or by extracting a mite from a burrow (Chosidow 2000).

Various treatments are available for scabies. These include sulfur compounds, which have been used for centuries; benzyl benzoate (first used in 1931); crotamiton (used since the late 1970s); hexachlorocyclohexane, which is also known as gamma benzene hexachloride or the commercial purified form lindane ('lindane' is used in this review) (available since 1948); malathion (used since the mid 1970s); permethrin (first licensed in 1985 by the US Food and Drug Administration); and oral ivermectin (first used in humans in the 1980s). A number of herbal remedies have also been proposed (Oladimeji 2000; Alebiosu 2003; Oladimeji 2005).

Serious adverse effects have been associated with the use of some antiscabietic treatments. Convulsions and aplastic anaemia have been reported with the use of lindane (Rauch 1990; Elgart 1996), and an increased risk of death amongst elderly patients has been reported with the use of ivermectin (Barkwell 1997).

Evidence of cure ideally requires follow up for about one month. This allows time for lesions to heal and for any eggs and mites to

reach maturity if treatment fails (ie beyond the longest incubation interval). Patients should be warned that itching may persist for one to two weeks after treatment, even if the mite is successfully eradicated (Buffet 2003). Because of this delay in symptom relief it may sometimes be difficult to distinguish reinfestation from primary treatment failure.

Contacts of cases are usually advised to treat themselves at the same time as the case in order to reduce the risk of reinfestation (Orkin 1976). Prevention is based on principles common to most infectious diseases, that is, limitation of contact with the mite.

Using data from randomized controlled trials, this review examines the existing evidence of effectiveness of treatments for scabies.

OBJECTIVES

To evaluate topical and systemic drugs for treating scabies.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Children or adults with a clinical or parasitological diagnosis of scabies.

Types of interventions

Intervention

- Drug treatment (systemic or local).
- Herbal or traditional medicine treatment.
- Any combination of above.
- Treatment of contacts in addition to cases.

Control

- Placebo or no intervention.
- A different drug intervention, drug intervention vehicle, intervention regimen, or combination of interventions.
- Different or no treatment of contacts.

Types of outcome measures

Primary

- Treatment failure in a clinically diagnosed case.
- Treatment failure in a parasitologically confirmed case.

Treatment failure is defined in both the above cases as the persistence of original lesions, the appearance of new lesions, or confirmation of a live mite.

Secondary

- Persistence of patient-reported itch.

Adverse events

- Serious adverse event that leads to death, is life threatening, results in persistent or significant disability or incapacity, or requires hospitalization.
- Adverse event that requires discontinuation of treatment.
- Other adverse event.

Search methods for identification of studies

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

Databases

We searched the following databases using the search terms and strategy described in Appendix 1: Cochrane Infectious Diseases Group Specialized Register (February 2007); Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2007, Issue 1); MEDLINE (1966 to February 2007); EMBASE (1974 to February 2007); LILACS (1982 to February 2007); and INDMED (February 2007).

Grey literature

In March 2007, we searched the following sources for published and unpublished trials using the term 'scabies': British Library Index of Conference Proceedings (catalogue.bl.uk/); British Library for Development Studies (blds.ids.ac.uk/blds/); BRIDGE (www.bridge.ids.ac.uk/index.html); Social Care Online (www.scie-socialcareonline.org.uk/); EconLit; ERIC; Institute for Development Studies (www.ids.ac.uk/ids/particip/information/readrm.html); IIED (www.iied.org/); and GrayLit Network (graylit.osti.gov/).

Registered trials

In March 2007, we searched the following sources for registered trials using the term 'scabies': Current Controlled Trials (www.controlled-trials.com/); Thompson CenterWatch Clinical Trials Listing Service (www.centerwatch.com/); US National Institutes of Health ClinicalTrials.gov (www.clinicaltrials.gov/); TrialsCentral (www.trialscentral.org/); and the UK Department of Health National Research Register (www.nrr.nhs.uk/).

Reference lists

We checked the reference lists of all retrieved trials.

Data collection and analysis

Selection of studies

All identified trials were entered into a trials register. MS and PJ independently applied the inclusion criteria to the potentially relevant trials. If a trial's eligibility was unclear, we attempted to contact the trial authors for further information. MS reassessed all included and excluded trials cited in the previous review version (Walker 2000). Where the review authors disagreed, the Co-ordinating Editor of the Cochrane Infectious Diseases Group was consulted, and a consensus reached among the three parties; this process was also used for assessing the risk of bias in trials, and extracting data. The trial reports were scrutinized to ensure that multiple publications from the same trial were included only once. We listed the reasons for excluding studies in the 'Characteristics of excluded studies'.

Data extraction and management

We independently extracted data from the newly included trials. Where important data were missing, we attempted to contact the trial authors for further information. MS entered the data into Review Manager 4.2. We extracted data to allow an intention-to-treat analysis; where the number or participants randomized were different to the number analysed, we calculated and recorded the percentage lost to follow up. For each dichotomous outcome, we recorded the number of participants experiencing the event in each arm of the trial.

Assessment of risk of bias in included studies

Both authors independently assessed the risk of bias in the newly included trials. We assessed the generation of allocation sequence and allocation concealment as adequate, inadequate, or unclear (Juni 2001). We assessed the inclusion of randomized participants in the analysis to be adequate if greater than 80%. We recorded who was blinded (eg participants or investigators) rather than using potentially ambiguous terms such as double blind or single blind. MS reassessed the included trials from the previous review version (Walker 2000).

Data synthesis

MS analysed the data using Review Manager 4.2. The included trials all reported dichotomous outcomes. We recorded both the number of participants experiencing an event (eg treatment failure) and the number analysed in each treatment group. We undertook an available case analysis, that is, participants were analysed in the group to which they were randomized regardless of treatment received, but only where an outcome was recorded (Higgins 2005). Results were presented as risk ratios (RRs) with 95% confidence intervals (CIs) around these estimates. RRs less than one were taken to demonstrate a favourable outcome of the intervention of interest, and these are presented to the left of the line of no effect. We assessed heterogeneity by visually inspecting forest plots, calculating an I^2 value, and carrying out a chi-squared test for heterogeneity. Significant heterogeneity was assumed to be present if the I^2 value was greater than 50% or if the chi-squared test was significant at the 0.1 level. Where we detected significant heterogeneity and it was appropriate to combine the trials in a meta-analysis, we used a random-effects model; otherwise we used a fixed-effect model. We explored one potential source of heterogeneity by stratifying the analyses into two groups on the basis of the diagnosis: clinical or parasitological. Parasitological confirmation of diagnosis is likely to be more accurate than clinical assessment alone.

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of studies awaiting assessment; Characteristics of ongoing studies.

Trial selection

Of the 70 trials identified and included in our trials register, 50 were excluded (see 'Characteristics of excluded studies') and 20 met the inclusion criteria (see 'Characteristics of included studies'). All trials were identified from published literature. Two studies are awaiting assessment: Gallegos 1996 and Daneshpajooh 2000. Daneshpajooh 2000 is awaiting translation, and Gallegos 1996 has not yet been retrieved despite several attempts. One ongoing study, Naeyaert ongoing, has also been identified.

Trial location

Seventeen of the 20 included studies were conducted in resource-poor countries, although one, Schultz 1990, was a large multicentre trial involving eight centres (four sexually transmitted disease clinics, two dermatology clinics, and two family practice clinics), with one of the family practice centres in Mexico and the others in the USA. Of the other three trials, one was carried out in the USA (Hansen 1986) and two in Italy (Amerio 2003; Biele 2006).

Participants

Three trials included only adults (Chouela 1999; Amerio 2003; Biele 2006), six included only children (Maggi 1986; Schenone 1986; Taplin 1990; Avila-Romay 1991; Brooks 2002; Singalavanija 2003); and the other 11 included both adults and children. The total number of participants randomized in the 20 trials was 2392; all had a clinical diagnosis of scabies, with a subset of 903 identified as having their diagnosis confirmed parasitologically.

Interventions

The effectiveness of the following drugs was tested: topical benzyl benzoate; crotamiton; decamethrin; lindane; permethrin; synergized natural pyrethrins; sulfur; and oral ivermectin. Sixteen trials compared one drug with at least one other drug, one trial compared ivermectin against placebo, two trials compared different drug treatment regimens, and one trial compared two different vehicles for the same drug. No randomized controlled trials investigating malathion were identified.

Clinicians and drug companies recommended treatment of family members and close contacts at the same time as cases, to improve cure rates and reduce reinfection (Taplin 1986). None of the trials tested this hypothesis. Close and family contacts in both intervention and control groups were treated, however, in all but six trials (Hansen 1986; Maggi 1986; Amer 1992; Macotela-Ruiz 1993; Amerio 2003; Biele 2006).

Four trials stipulated that a bath or shower should be taken before treatment (Gulati 1978; Schenone 1986; Taplin 1990; Avila-Romay 1991); and nine trials stipulated that participants should change and wash their linen after treatment (Avila-Romay 1991; Glaziou 1993; Chouela 1999; Usha 2000; Madan 2001; Nnoruka 2001; Brooks 2002; Singalavanija 2003; Zargari 2006).

Dosing and regimen

Benzyl benzoate

The strength of the topical benzyl benzoate solution varied between 10% (Glaziou 1993; Brooks 2002; Biele 2006) and 25% (Gulati 1978; Nnoruka 2001). The treatment regimen was different in each trial: it was applied once and left overnight in Brooks 2002; applied twice, 12 hours apart in Glaziou 1993; applied three times, 12 hours apart in Gulati 1978; applied on five consecutive days in Biele 2006; and a single application was left for 72 hours in Nnoruka 2001.

Crotamiton

A 10% topical preparation was used in two trials (Taplin 1990; Amer 1992). It was applied overnight on two consecutive nights in Amer 1992, and was applied once overnight in Taplin 1990.

Decamethrin

Schenone 1986 compared 0.02% decamethrin lotion applied daily for two days repeated on two more days a week later with 0.02% decamethrin lotion applied daily for four consecutive days.

Lindane

Each lindane trial used a 1% topical preparation, except for Singalavanija 2003, which used a 0.3% preparation. The number of applications ranged from one (Hansen 1986; Maggi 1986; Taplin 1986; Schultz 1990; Chouela 1999) to two (Amer 1992; Zargari 2006) to seven (Singalavanija 2003). Maggi 1986 compared a single application of lindane left on for four days, washed off and then repeated after a week with a single one-hour application of lindane, repeated after a week.

Permethrin

A 5% topical preparation was used in each permethrin trial. The number of applications ranged from one (Schultz 1990; Taplin 1990; Usha 2000) to two (Amer 1992; Zargari 2006) to two consecutive overnight applications repeated after 14 days (Amerio 2003).

Synergized natural pyrethrins

A 0.16% topical preparation of natural pyrethrins synergized with pyperonil butoxide was used in Amerio 2003, applied on two successive nights and repeated 14 days later. In Biele 2006, a 0.165% preparation was applied on three consecutive days.

Sulfur

Two of the three sulfur trials used a 10% topical preparation (Avila-Romay 1991; Singalavanija 2003). In the third trial, Gulati 1978, the strength of the preparation was not stated. Avila-Romay 1991 compared sulfur in cold cream with sulfur in pork fat; both medications were applied nightly for three nights and then once three nights later. Singalavanija 2003 applied the sulfur on seven consecutive nights. Gulati 1978 applied sulfur once in the morning, once in the evening, and once again the next morning; treatment was repeated after 10 days if lesions persisted.

Ivermectin

The oral dose of ivermectin varied from a 100 µg/kg bodyweight (Glaziou 1993) to 200 µg/kg bodyweight (Macotela-Ruiz 1993; Usha 2000; Madan 2001; Nnoruka 2001; Brooks 2002). The Chouela 1999 trial used an ivermectin dose between 150 µg/kg and 200 µg/kg bodyweight. Each trial gave a single dose.

Length of follow up

Follow up ranged from seven days to one month. In 11 trials it was possible to extract outcome data at 28 to 31 days after treatment (Hansen 1986; Taplin 1986; Schultz 1990; Taplin 1990; Amer 1992; Glaziou 1993; Madan 2001; Nnoruka 2001; Amerio 2003; Singalavanija 2003; Biele 2006). Follow up was at 21 days in two trials (Schenone 1986; Brooks 2002); 14 to 15 days in five trials (Gulati 1978; Maggi 1986; Chouela 1999; Usha 2000; Zargari 2006); and seven to 10 days in the remaining two trials (Avila-Romay 1991; Macotela-Ruiz 1993).

Outcome measures

The review's primary outcome measure (treatment failure) was reported in 19 of the 20 trials. Six of these 19 trials reported treatment failure in both clinically diagnosed cases and in microscopically confirmed cases (Schultz 1990; Taplin 1990; Amer 1992; Amerio 2003; Singalavanija 2003; Biele 2006); the other 13 trials reported treatment failure in clinically diagnosed cases who may or may not have been confirmed microscopically. Seven trials reported the secondary outcome measure (itch persistence) in addition to treatment failure (Hansen 1986; Schultz 1990; Taplin 1990; Brooks 2002; Amerio 2003; Singalavanija 2003; Biele 2006). Itch persistence alone was reported by Maggi 1986. Adverse events were reported as an outcome in all trials except Gulati 1978 and Maggi 1986.

The seven trials that reported on itch varied in their methods to assess this outcome:

- Hansen 1986: did not report on the method used.
- Maggi 1986: participants reported on itch using a three-point scale ("absent", "moderate", and "intense") before and after treatment; numbers in each category were reported.

- Schultz 1990: participants reported the presence or absence of itch before and after treatment; numbers in each category were reported.
- Taplin 1990: participants were reported as either having presence or absence of itch; no further details of assessment were given.
- Brooks 2002: participants described itch severity on a visual analogue scale before and after treatment; mean scores were reported along with the number of participants with absence of night-time itch.
- Amerio 2003 and Biele 2006: participants reported on itch using a five-point scale (from 0 = "no itch" to 4 = "severe itch") before and after treatment; mean scores were reported along with the number of participants with complete relief from itching.
- Singalavanija 2003: participants were divided into those who reported a decrease or absence of itch, and those who reported no improvement.

Sources of support

Seven trials stated that funding or support had been provided by drug companies (Taplin 1986; Schultz 1990; Taplin 1990; Glaziou 1993; Usha 2000; Amerio 2003; Zargari 2006).

Background prevalence

Fifteen trial reports did not state the background prevalence of scabies. In the four trials where prevalence was stated, it ranged from 9% in India (Gulati 1978) to 14% among children in a boarding school in Chile (Schenone 1986) to 36% in French Polynesia (Glaziou 1993) to 67% in Panama (Taplin 1990).

Risk of bias in included studies

See Table 1 for a summary assessment and the 'Characteristics of included studies' for details.

Table 1. Risk of bias assessment

Trial	Allocation sequence generation	Allocation concealment	Blinding	Inclusion[a]
Amer 1992	Unclear	Unclear	Unclear	Adequate
Amerio 2003	Adequate	Adequate	Investigators	Adequate
Avila-Romay 1991	Unclear	Unclear	Unclear	Adequate
Brooks 2002	Adequate	Unclear	Investigators	Inadequate

Table 1. Risk of bias assessment (*Continued*)

Biele 2006	Adequate	Unclear	Investigators	Adequate
Chouela 1999	Unclear	Unclear	Described as "double blind"; participants blinded	Adequate
Glaziou 1993	Unclear	Unclear	Outcomes assessor	Adequate
Gulati 1978	Unclear	Unclear	Unclear	Adequate
Hansen 1986	Unclear	Unclear	"Single blind", unclear who was blinded	Adequate
Macotela-Ruiz 1993	Unclear	Unclear	Participant and outcomes assessor	Adequate
Madan 2001	Unclear	Unclear	Outcomes assessor	Inadequate
Maggi 1986	Unclear	Unclear	Unclear	Adequate
Nnoruka 2001	Adequate	Unclear	Unclear	Adequate
Schenone 1986	Unclear	Unclear	Unclear	Adequate
Schultz 1990	Unclear	Adequate	Outcomes assessor	Adequate
Singalavanija 2003	Adequate	Unclear	Unclear	Inadequate
Taplin 1986	Unclear	Adequate	Investigators	Adequate
Taplin 1990	Unclear	Adequate	Investigators	Adequate
Usha 2000	Adequate	Adequate	None	Adequate
Zargari 2006	Unclear	Adequate	Investigators and participants	Adequate

[a] Inclusion of randomized participants in analysis.

Generation of allocation sequence

Six trials described an adequate method of generating a random allocation sequence: by computer in Usha 2000, Brooks 2002, Amerio 2003, and Biele 2006; and by random-number table in Nnoruka 2001 and Singalavanija 2003. The method was unclear in the other trials.

Allocation concealment

Six trials reported adequate allocation concealment: by phone call to third party-based procedure in Amerio 2003; by use of identical coded medication containers in Taplin 1986, Schultz 1990, Taplin 1990, and Zargari 2006; and the author of Usha 2000 confirmed that the allocation was by a third party, not the investigator. The remaining trials had methods of concealment that were either unclear or not reported.

Blinding

Twelve trials reported blinding. In two of these trials both the inves-

tigators or outcome assessors and the participants were described as blinded (Macotela-Ruiz 1993; Zargari 2006), and in eight trials the investigators or outcome assessors alone were described as blinded (Taplin 1986; Schultz 1990; Taplin 1990; Glaziou 1993; Madan 2001; Brooks 2002; Amerio 2003; Biele 2006). Chouela 1999 described the participants as blinded but also reported the trial as "double blind". Hansen 1986 described the trial as "single blind", but it is unclear who was blinded.

Inclusion of randomized participants in the analysis

Ten trials included all randomized participants in the analysis with no mention of losses to follow up. The completeness of follow up was greater than 80% (ie adequate) in seven trials (Hansen 1986; Taplin 1986; Schultz 1990; Taplin 1990; Macotela-Ruiz 1993; Chouela 1999; Zargari 2006). The remaining three trials reported completeness of follow up less than 80% (Brooks 2002 − 27% lost to follow up, Madan 2001 − 25% lost to follow up, Singalavanija 2003 − 32% lost to follow up).

Effects of interventions

1. Ivermectin

Only one trial assessed the effectiveness against placebo, while six trials compared it with another drug.

1.1. Versus placebo (55 participants, 1 trial)

Macotela-Ruiz 1993 compared 200 µg/kg bodyweight oral ivermectin with placebo.

Treatment failure in clinically diagnosed cases

Macotela-Ruiz 1993 reported fewer treatment failures in the ivermectin group at seven days (RR 0.24, 95% CI 0.12 to 0.51; 55 participants, Analysis 1.1).

Adverse events.

None were reported.

1.2. Versus permethrin (88 participants, 1 trial)

Usha 2000 compared 200 µg/kg bodyweight oral ivermectin with 5% topical permethrin cream.

Treatment failure in clinically diagnosed cases

Usha 2000 reported more treatment failures in the ivermectin group at two weeks (RR 13.50, 95% CI 1.84 to 99.26; 85 participants, Analysis 2.1).

Adverse events

Three of 43 participants in the ivermectin group reported aggravation of symptoms (see Table 2).

Table 2. Adverse events

Comparison	Trial	Intervention	Adverse event	n/N[a]
Ivermectin vs placebo	Macotela-Ruiz 1993	Ivermectin	None recorded	-
		Placebo	None recorded	-
Ivermectin vs permethrin	Usha 2000	Ivermectin	Aggravation of symptoms	3/43
		Permethrin	None recorded	-
Ivermectin vs lindane	Chouela 1999	Lindane	Headache	6/27
		Ivermectin	Headache	1/26
			Hypotension	1/26
			Abdominal pain	1/26

Table 2. Adverse events (*Continued*)

			Vomiting	1/26
	Madan 2001	Ivermectin	Severe headache	1/100
		Lindane	None recorded	-
Ivermectin vs benzyl benzoate	Glaziou 1993	Benzyl benzoate	Mild increase in pruritus	5/21
		Ivermectin	None recorded	-
	Nnoruka 2001	Ivermectin	None recorded	-
		Benzyl benzoate	Pruritus and irritation	7/29
	Brooks 2002	Ivermectin	Pustular rash	3/43
			Cellulitis	1/43
		Benzyl benzoate	Burning or stinging	6/37
			Dermatitis	6/37
Permethrin vs crotamiton	Taplin 1990	Permethrin	None recorded	-
		Crotamiton	Worsening of symptoms	10/47
	Amer 1992	Permethrin	None recorded	-
		Crotamiton	None recorded	-
Permethrin vs lindane	Hansen 1986	Permethrin	Mild burning, stinging, or itching	5/49
		Lindane	Mild burning, stinging, or itching	5/50
	Taplin 1986	Permethrin	None recorded	-
		Lindane	None recorded	-
	Schultz 1990	Permethrin	Burning/stinging	23/234
			Pruritus	15/234

Table 2. Adverse events (*Continued*)

			Erythema	5/234
			Tingling	4/234
			Rash	2/234
			Diarrhoea	1/234
			Persistent excoriation	1/234
		Lindane	Burning/stinging	12/233
			Pruritus	17/233
			Tingling	5/233
			Erythema	3/233
			Rash	2/233
			Diarrhoea	1/233
			Contact dermatitis	1/233
			Phemphigus	1/233
			Papular rash	1/233
	Amer 1992	Permethrin	None recorded	-
		Lindane	None recorded	-
	Zargari 2006	Permethrin	Skin irritation	2/59
		Lindane	Skin irritation	1/58
Permethrin vs synergized natural pyrethrins	Amerio 2003	Permethrin	Secondary skin infection	10/20
		Synergized pyrethrins	Secondary skin infection	2/20
Crotamiton vs lindane	Amer 1992	Lindane	None recorded	-
		Crotamiton	None recorded	-

Table 2. Adverse events (*Continued*)

Lindane vs sulfur	Singalavanija 2003	Sulfur	Foul odour	10/50
			Burning	2/50
			Erythema	2/50
		Lindane	Foul odour	3/50
			Burning	6/50
			Erythema	5/50
Benzyl benzoate vs sulfur	Gulati 1978	Benzyl benzoate	None recorded	-
		Sulfur	None recorded	-
Benzyl benzoate vs synergized natural pyrethrins	Biele 2006	Benzyl benzoate	Skin irritation and burning sensations	22/120
		Synergized pyrethrins	Skin irritation and burning sensations	3/120
Lindane: short vs long application	Maggi 1986	Lindane (short course)	None recorded	-
		Lindane (long course)	None recorded	-
Decamethrin: 2-day + 2-day vs 4-day application	Schenone 1986	Decamethrin (both regimens)	Moderate skin hotness	15/127
Sulfur: pork fat vehicle vs cold cream vehicle	Avila-Romay 1991	Sulfur/salicylic acid in pork fat	Pruritus	32/53
			Xerosis	18/53
			Burning sensations	9/53
			Keratosis pilaris	8/53
			Erythema	1/53
		Sulfur in cold cream	Pruritus	18/58
			Xerosis	14/58

Table 2. Adverse events (*Continued*)

			Burning sensations	6/58
			Erythema	6/58
			Keratosis follicularis	1/58

[a] No. participants reporting event/total no. participants.

1.3. Versus lindane (253 participants, 2 trials)

Chouela 1999 compared 150 µg/kg bodyweight oral ivermectin with 1% topical lindane, while Madan 2001 compared 200 µg/kg ivermectin with 1% lindane.

Treatment failure in clinically diagnosed cases

Chouela 1999 found no significant difference between the groups at 15 days (43 participants), while Madan 2001 found that treatment failures were reduced in the ivermectin group at four weeks (RR 0.31, 95% CI 0.18 to 0.54; 150 participants, Analysis 3.1). The trials' combined estimate showed a benefit of ivermectin over lindane (RR 0.36, 95% CI 0.23 to 0.58; 193 participants, Analysis 3.1).

Adverse events

See Table 2. Chouela 1999 reported adverse events in 4/26 participants in the ivermectin group (headache, hypotension, abdominal pain, and vomiting) and in 6/37 participants in the lindane group (headache). Madan 2001 reported an adverse event in 1/100 participants in the ivermectin group (severe headache); there were none in the lindane group.

1.4. Versus benzyl benzoate (212 participants, 3 trials)

Brooks 2002 compared 200 µg/kg bodyweight oral ivermectin with 10% topical benzyl benzoate. Glaziou 1993 compared 100 µg/kg bodyweight ivermectin with 10% benzyl benzoate. Nnoruka 2001 compared 200 µg/kg bodyweight ivermectin with 25% benzyl benzoate.

Treatment failure in clinically diagnosed cases

See Analysis 4.1. No significant difference between the two groups was found in Brooks 2002 (at 3 weeks, 80 participants) or Glaziou 1993 (at 30 days, 44 participants). Nnoruka 2001 found a significant difference in favour of ivermectin at 30 days (RR 0.13, 95% CI 0.03 to 0.53; 58 participants, Analysis 4.1.1). The trials' combined estimate showed no significant difference for treatment failure (RR 0.50, 95% CI 0.20 to 1.25, random-effects model; 182 participants, Analysis 4.1.1); statistical heterogeneity was detected between the trials (chi-squared test 7.94, df 2, P = 0.02; I^2 74.8%).

Itch persistence

See Analysis 4.1.2. Brooks 2002 found no significant difference in the number of participants who reported night-time itch at three weeks (58 participants).

Adverse events

All three trials reported adverse events (see Table 2). Brooks 2002 reported adverse events in 4/43 participants in the ivermectin group (pustular rash, cellulitis) and in 12/37 participants in the benzyl benzoate group (burning or stinging, dermatitis). Glaziou 1993 and Nnoruka 2001 reported adverse events only in the benzyl benzoate group: 5/21 participants (mild increase in pruritus) in Glaziou 1993; and 7/29 participants (pruritus and irritation) in Nnoruka 2001.

2. Permethrin

2.1. Versus crotamiton (196 participants, 2 trials)

Two trials compared 5% permethrin with 10% crotamiton (Taplin 1990; Amer 1992).

Treatment failure

See Analysis 5.1. Participants in both trials had their scabies clinically diagnosed and microscopically confirmed. The comparative treatment failure rates described for clinically diagnosed cases therefore apply equally to microscopically diagnosed cases in these trials. Taplin 1990 found that treatment failure was reduced in the permethrin group after 28 days (RR 0.26, 95% CI 0.11 to 0.65; 94 participants, Analysis 5.1.3). Amer 1992 found no significant difference in outcome between the groups after 28 days (100 participants). A combined estimate showed a benefit of permethrin over crotamiton (RR 0.24, 95% CI 0.10 to 0.55; 194 participants, Analysis 5.1.1).

Itch persistence

See Analysis 5.1. Permethrin reduced the number of participants with itch persistence in Taplin 1990 (RR 0.26, 95% CI 0.11 to 0.65; 94 participants, Analysis 5.1.3)).

Adverse events

See Table 2. Taplin 1990 reported no adverse events in the permethrin group, but did report adverse events in 10/47 participants in the crotamiton group (worsening of symptoms). Amer 1992 reported no adverse events.

2.2. Versus lindane (835 participants, 5 trials)

Five trials compared 5% topical permethrin with 1% topical lindane (Hansen 1986; Taplin 1986; Schultz 1990; Amer 1992; Zargari 2006).

Treatment failure in clinically diagnosed cases

See Analysis 6.1. Two trials found permethrin to be superior – after four weeks in Amer 1992 (RR 0.08, 95% CI 0.01 to 0.57; 100 participants, Analysis 6.1.1) and after one month in Taplin 1986 (RR 0.22, 95% CI 0.05 to 0.95; 51 participants, Analysis 6.1.1). Zargari 2006 reported fewer treatment failures in the permethrin group after 14 days (RR 0.15, 95% CI 0.06 to 0.40; 99 participants, Analysis 6.1.1), while no benefit was found for either treatment by Hansen 1986 (28 days, 99 participants) or Schultz 1990 (28 +/- 7 days, 404 participants). The trials' combined estimate showed permethrin to be superior to lindane (RR 0.32, 95% CI 0.13 to 0.75, random-effects model; 753 participants, Analysis 6.1.1); statistical heterogeneity was detected (chi-squared test 11.83, df 4, P = 0.02; I^2 66.2%).

Treatment failure in microscopically confirmed cases

See Analysis 6.1. Permethrin was superior in Amer 1992 after four weeks (RR 0.08, 95% CI 0.01 to 0.57; 100 participants, Analysis 6.1.2) and in Taplin 1986 after one month (RR 0.25, 95% CI 0.06 to 1.05; 46 participants, Analysis 6.1.2), while Schultz 1990 found no significant difference between the groups (338 participants). The trials' combined estimate showed no significant difference between permethrin and lindane (RR 0.31, 95% CI 0.09 to 1.09, random-effects model; 484 participants, Analysis 6.1.2), but statistical heterogeneity was detected between the trials (chi-squared test 5.72, df 2, P = 0.06; I^2 65.1%).

Itch persistence

See Analysis 6.1. The two trials that reported on itch persistence found different effects: Hansen 1986 found no significant difference between the two interventions after 28 days (99 participants), whereas Schultz 1990 found permethrin to be superior after 28 +/- 7 days (RR 0.56, 95% CI 0.37 to 0.86; 391 participants, Analysis 6.1.3). A combined estimate showed permethrin to be superior (RR 0.62, 95% CI 0.44 to 0.87; 490 participants, Analysis 6.1.3).

Adverse events

See Table 2. Hansen 1986 recorded mild burning, stinging, or itching in both groups (5/49 participants in the permethrin group, 5/50 participants in the lindane group). Schultz 1990 reported adverse events in 51/234 participants in the permethrin group (burning/stinging, pruritus, erythema, tingling, rash, diarrhoea, persistent excoriation) and in 43/233 participants in the lindane group (burning/stinging, pruritus, tingling, erythema, rash, papular rash, diarrhoea, contact dermatitis, phemphigus). Zargari 2006 reported skin irritation in both groups (2/59 participants in the permethrin group, 1/58 participant in the lindane group). Amer 1992 and Taplin 1986 both reported no adverse events.

2.3. Versus synergized natural pyrethrins (40 participants, 1 trial)

Amerio 2003 compared 5% topical permethrin with topical 0.16% natural pyrethrins synergized with 1.65% pyperonil butoxide.

Treatment failure

All participants had their scabies both clinically diagnosed and microscopically confirmed. There were no treatment failures in either group after 28 days (40 participants).

Itch persistence

See Analysis 7.1.There was no significant difference in itch persistence between the two groups after 28 days (40 participants).

Adverse events

See Table 2. Ten of the 20 participants in the permethrin group and two of the 20 participants in the synergized pyrethrin group were reported as having secondary skin infections requiring antibiotic treatment. It was not clear from the trial report whether this was considered an adverse event or rather a baseline characteristic.

3. Other drug comparisons

3.1. Crotamiton versus lindane (100 participants, 1 trial)

Amer 1992 compared 10% topical crotamiton with 1% topical lindane.

Treatment failure

See Analysis 8.1. All participants in Amer 1992 had their scabies both clinically diagnosed and microscopically confirmed. There was no significant difference in treatment failure between the two groups after 28 days (100 participants).

Adverse events

None were reported.

3.2. Lindane versus sulfur (100 participants, 1 trial)

Singalavanija 2003 compared 0.3% topical lindane with 10% topical sulfur.

Treatment failure in clinically diagnosed cases

See Analysis 9.1. There was no significant difference between the two groups after 28 days in Singalavanija 2003 (68 participants).

Itch persistence

See Analysis 9.1. There was no significant difference between the groups in the number of participants in whom itch persisted at 28 days (68 participants).

Adverse events

See Table 2. The reported adverse events (foul odour, burning, erythema) occurred in the sulfur group (14/50 participants) and the lindane group (14/50 participants).

3.3. Benzyl benzoate versus sulfur (158 participants, 1 trial)

Gulati 1978 compared 25% topical benzyl benzoate with topical sulfur ointment.

Treatment failure in clinically diagnosed cases

See Analysis 10.1. There was no significant difference between the two groups after 15 days in Gulati 1978 (158 participants).

Adverse events

None were reported.

3.4. Benzyl benzoate versus synergized natural pyrethrins (240 participants, 1 trial)

Biele 2006 compared 10% topical benzyl benzoate with topical 0.165% natural pyrethrins synergized with 1.65% pyperonil butoxide.

Treatment failure

See Analysis 11.1. All participants had their scabies both clinically diagnosed and microscopically confirmed. There was no significant difference in treatment failure between the two groups after four weeks in Biele 2006 (240 participants).

Itch persistence

See Analysis 11.1. There was no significant difference in itch persistence between the two groups after four weeks (240 participants).

Adverse events

Twenty-two of the 120 participants in the benzyl benzoate group and three of the 120 participants in the synergized natural pyrethrins group experienced skin irritation and burning sensations after drug application (see Table 2).

4. Length of treatment comparisons

4.1. Lindane: short application versus long application (87 participants, 1 trial)

Treatment failure

Maggi 1986 did not assess this outcome measure.

Itch persistence

A short application of lindane reduced itch persistence at 14 days (RR 0.34, 95% CI 0.12 to 0.98; 87 participants, Analysis 12.1). However, the trial authors did suggest that the pruritus experienced by the participants could have been due to a lindane-associated contact dermatitis.

Adverse events

None other than pruritus (see above) were reported.

4.2. Decamethrin: two-day plus two-day application versus four-day application (127 participants, 1 trial)

Treatment failure in clinically diagnosed cases.

There were no treatment failures in either group in Schenone 1986 after 21 days: 0/53 treatment failures in the two-plus-two-day group; and 0/74 treatment failures in the four-day group. Five participants in each group received a second treatment at seven days due to the presence of active lesions. This second treatment consisted of two applications of 0.02% decamethrin on consecutive days.

Adverse events

Fifteen of 127 participants experienced "moderate skin hotness" after application of decamethrin (see Table 2).

5. Drug vehicle comparisons

5.1. Sulfur: pork fat vehicle versus cold cream vehicle (51 participants, 1 trial)

Treatment failure in clinically diagnosed cases

See Analysis 13.1. There was no significant difference in the number of treatment failures between the two groups after 10 days in Avila-Romay 1991 (51 participants).

Adverse events

See Table 2. Pruritus, xerosis, burning sensation, and erythema were reported for cases and contacts in both groups. There were

adverse events in 68/53 participants in the pork fat vehicle group, including keratosis pilaris. There were adverse events in 45/58 participants in the cold cream vehicle group, including keratosis follicularis.

DISCUSSION

The review's objective was to evaluate the effectiveness of current treatments for scabies in order to inform practice and guide future research. The previous version of this review noted that clinicians faced considerable uncertainty when choosing the best treatment for scabies (Walker 2000). Six years later the picture is a little clearer, but there are still considerable gaps in our knowledge.

Trial quality

All 20 included trials were designed to test the effectiveness of one or more treatments for scabies. Methodological quality varied between trials. Only two trials described both adequate randomization sequence generation and adequate allocation concealment, and the majority of the reports described neither adequately. The degree of blinding was unclear in eight of the 20 identified trials, and losses to follow up were greater than 20% of the enrolled participants in three of the trials.

Effectiveness

The results of this review suggest that topical permethrin is emerging as the treatment of choice. Permethrin has been tested against topical crotamiton, topical lindane, and oral ivermectin in randomized controlled trials, and it appears to be superior to all three in terms of minimizing treatment failure in participants with a clinical diagnosis of scabies. There was significant statistical heterogeneity in the results of the five trials that compared permethrin with lindane, and the combined estimate of treatment effect should therefore be viewed with some caution. This heterogeneity may be explained in part by the trials' clinical and methodological diversity: they were different in terms of geographical location, disease prevalence, methodological factors (randomization, blinding, losses to follow up), treatment regimen, and length of follow up. In particular, it may be expected that in areas of high prevalence cases of reinfection are more common, and these may be indistinguishable from primary treatment failures.

In the subgroup of participants with microscopically confirmed scabies, permethrin was again superior to crotamiton, but no difference was seen when permethrin was compared with lindane. Permethrin also appears to be better at relieving itch than either crotamiton or lindane (itch was not reported as a separate outcome in the ivermectin versus permethrin trial). Unfortunately no trials comparing permethrin with either topical sulfur or topical benzyl benzoate were identified; permethrin's relative effectiveness against these treatments therefore remains unknown.

In some countries natural pyrethrin-based topical treatments are available as an alternative to permethrin cream (Biele 2006). Pyrethrins are naturally occurring insecticidal compounds found in the *Compositae* family of plants (Wagner 2000), whereas permethrin is a synthetic pyrethroid analogue. Results from the two Italian trials included in this review suggest that pyrethrin is equivalent in effectiveness to both permethrin and benzyl benzoate.

Trials comparing crotamiton with lindane, lindane with sulfur, and sulfur with benzyl benzoate have all produced equivocal results, suggesting that there is no single most effective treatment out of these four topical options. In most countries the choice is in any case restricted, either due to lack of availability, or the lack of a licence for scabies.

Ivermectin is currently the only oral treatment for scabies that is in routine use. It appears to be as effective as topical benzyl benzoate, and better than topical lindane or oral placebo. Again, there was significant statistical heterogeneity in the results of the three trials that compared ivermectin and benzyl benzoate, which may be explained by differences in drug regimen and length of follow up between the trials. The length of follow up in the ivermectin versus placebo trial was very short (seven days). Ideally follow up should be at around one month since itching can persist for several weeks after treatment, even in the absence of active infestation. It is possible then that some participants in this trial were incorrectly classified as treatment failures, and the results should therefore be viewed with some caution.

An advantage of an oral antiscabietic treatment over a topical one is ease of use, particularly in hot humid climates, when engaging in mass treatment, or when treating children. However, 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.

Topical ivermectin has also been suggested to be effective after success in uncontrolled studies (Yeruham 1998; Victoria 2001). At present there is no commercially available topical ivermectin preparation available for the treatment of scabies, and randomized controlled trials are needed to evaluate this potential new treatment option.

There are still no published reports of randomized controlled trials that test the effectiveness of malathion against either placebo or another drug, despite almost 30 years passing by since a non-controlled study first suggested that the drug was effective (Hanna 1978). The 2006 British National Formulary recommends malathion as a treatment of choice along with permethrin (BNF 2006), despite the lack of evidence from randomized controlled trials. Such a trial comparing malathion with permethrin is needed to test their relative effectiveness.

We found trials of the herbal remedies toto soap (Alebiosu 2003) and lippia oil (Oladimeji 2000; Oladimeji 2005), but these trials did not meet the review's inclusion criteria. Both treatments look

promising, but randomized controlled trials making direct comparisons with the existing best treatments are needed to assess their true relative effectiveness.

Treatment regimen was assessed in two trials. Maggi 1986 found that a one-hour application of lindane reduced itch compared with a much longer four-day application; the authors suggested that the itch may, at least in part, have been due to a dermatitis caused by the lindane treatment itself. Schenone 1986 compared two different regimens using decamethrin, a pyrethroid insecticide in the same class as permethrin. All participants were cured in both groups. Decamethrin is not commercially available for the treatment of scabies and we found no trials that tested its effectiveness against other treatments. Decamethrin (as deltamethrin) is usually used as an agricultural insecticide and its safety as an antiscabietic medication has not been established (WHO 1990).

The formulation of a topically applied product may influence its efficacy. For example, a 1% permethrin formulation marketed for the treatment of head lice appears to be less effective than the conventional antiscabietic 5% preparation, according to case reports (Cox 2000). None of the trials included in this review directly compared different strength formulations of the same treatment. One trial compared different vehicles for the same drug (Avila-Romay 1991). Cold cream as a treatment vehicle for sulfur may be more effective than pork fat, with fewer adverse events. For resource-poor countries this could be a cheap and safe option, which in some circumstances might also be more culturally acceptable.

This review did not seek to assess the relative cost effectiveness of the various treatments for scabies; however, large cost differences are apparent. In the UK, permethrin is at least 10 times more expensive per treatment (£5.52 per 30 g of cream) than benzyl benzoate (£0.62 per 100 mL) and about twice as expensive as crotamiton (£2.99 per 100 mL) and malathion (£2.35 per 100 mL) (BNF 2006). When lindane was marketed in the UK it was a fifth the cost of permethrin per treatment (BNF 1997).

We did not specifically attempt to assess the effectiveness of treatments for crusted scabies, and none of the included trials selected participants with this diagnosis. Caution should therefore be exercised in generalizing the results of this review to the treatment of patients with atypical severe scabies infection. This is an important area where more research is needed.

Caution should also be exercised in generalizing these results, which were obtained from trials that recruited individual participants (mostly in the outpatient setting), to the management of outbreaks in institutions. Given the burden of disease caused by scabies within institutions, such as long-term healthcare facilities, the inclusion of such patients in randomized controlled trials of effectiveness would be beneficial.

Mass treatment of a community in order to eradicate scabies has been tested in two studies (Dunne 1991; Bockarie 2000), both of which used oral ivermectin. Unfortunately neither of these studies met the review's inclusion criteria (Bockarie 2000 was an uncontrolled trial, and Dunne 1991 recruited participants on the basis of a diagnosis of onchocerciasis). Further research is needed to test the effectiveness, safety, and practicality of this approach to the management of scabies, particularly in areas of high prevalence.

Safety

Serious adverse events leading to death or permanent disability were not reported in any of the included or excluded trials. This review did not seek to systematically review the literature on the safety of antiscabietic treatments, but a number of notable reports of serious adverse events that have been published elsewhere are discussed below.

Convulsions and aplastic anaemia have both been reported with the use of lindane (Rauch 1990; Elgart 1996); in some cases this being thought to be due to the application of the drug to non-intact skin. Lindane was withdrawn by the manufacturer from the UK market in 1996, but this was for commercial and not toxicological reasons. In 1995, the US Food and Drug Administration designated lindane as a second-line treatment due to its potential toxicity; only to be used in those who have failed to respond to, or who are intolerant of, other antiscabietic treatments (WHO 2003).

Ivermectin has been very widely used in the treatment of onchocerciasis (predominantly in adults) and even with repeated doses serious adverse effects have been rare (DeSole 1989; Pacque 1990). However, an increased risk of death among a group of elderly patients with scabies in a long-term care facility has been reported (Barkwell 1997). Whether this was due to ivermectin or to interactions with other scabicides, including lindane and permethrin, or other treatments such as psychoactive drugs was not clear and there was considerable discussion of the validity of this report (Bredal 1997; Coyne 1997; Diazgranados 1997; Reintjes 1997).

Rare adverse reactions have been reported with the use of both permethrin (dystonia, Coleman 2005) and natural pyrethrin (fatal asthma, Wagner 2000).

The relative purity of the active ingredients of certain topical treatments and their isomeric ratios may also affect drug toxicity. In particular, very little is known about the effects of exposure to different isomeric grades of permethrin. Clinical grade material is 25:75 cis isomer:trans isomer and agricultural grade is 40:60. The cis isomer has 10 times the acute toxicity and there could be dangers in people in resource-poor countries using agricultural-grade permethrin for treating human infestations (personal communication from Ian Burgess, Medical Entomology Centre, Cambridge). Similar problems have been reported with the inappropriate use of agricultural grade malathion for treating human infestations (Petros 1990).

A search of the WHO Adverse Drug Reaction Database in 1998 for a previous version of this review found reports of serious adverse drug reactions for convulsions (benzyl benzoate 4, crotamiton 1, lindane 38, malathion 2, permethrin 6) and death (benzyl benzoate 0, crotamiton 1, lindane 1, malathion 0, permethrin 5) (Walker 2000). A search for this update of the review of the UK

Medicines and Healthcare Products Regulatory Agency database of suspected drug reactions found reports for convulsions (benzyl benzoate 1, crotamiton 0, lindane 3, malathion 0, permethrin 0, sulfur 0, ivermectin 1) and death (benzyl benzoate 0, crotamiton 0, lindane 1, malathion 0, permethrin 1 (intra uterine death), sulfur 0, ivermectin 3) (MHRA 2006). 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.

AUTHORS' CONCLUSIONS

Implications for practice

On the basis of the available evidence from randomized controlled trials, topical permethrin appears to be the most effective treatment for scabies. Ivermectin appears to be an effective oral treatment, but in many countries it is not licensed for this indication.

Implications for research

Trials are needed to evaluate the relative effectiveness of malathion against permethrin, and the relative effectiveness of herbal treatments against existing treatments. The effectiveness of topical ivermectin also needs to be explored. The most appropriate treatment for the severe crusted form of scabies has not yet been established in randomized controlled trials.

Researchers should ensure that toxicity and safety outcomes are systematically collected in future trials as well as being notified through routine monitoring of adverse events in clinical practice.

Approaches to the control of outbreaks in institutions and public health programmes to control scabies in populations with high prevalence require evaluation.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Amer 1992

Methods	Design: randomized controlled trial Generation of allocation sequence: "according to code" Allocation concealment: unclear Blinding: unclear Inclusion of randomized participants in the analysis: 100%
Participants	Number: 150 enrolled (all ages; sex not stated) Inclusion criteria: clinically diagnosed and microbiologically confirmed scabies Exclusion criteria: significant impetiginization
Interventions	1. 5% permethrin (50 participants) 2. 10% crotamiton (50 participants) 3. 1% lindane (50 participants) Each medication applied "neck to toe" on 2 successive nights
Outcomes	1. Number of participants clinically cured (no new lesions and all original lesions healed) at 28 days

Amer 1992 (*Continued*)

Notes	Location: Egypt Date: not stated Colour photographs used for comparison before and after treatment

Amerio 2003

Methods	Design: randomized controlled trial Generation of allocation sequence: computer generated Allocation concealment: phone call-based procedure Blinding: investigators only Inclusion of randomized participants in the analysis: 100%
Participants	Number: 40 enrolled (mean age 44, standard deviation 17; 19 males, 21 females) Inclusion criteria: immunocompetent; aged 18 to 75; microscopically confirmed uncomplicated scabies Exclusion criteria: HIV positive; severe renal failure; liver insufficiency; acute or chronic leukaemia; lymphoma; use of antiscabietic preparations in previous 30 days; pregnancy; breastfeeding
Interventions	1. 5% permethrin cream (20 participants) 2. 0.16% natural pyrethrins synergized with pyperonil butoxide (1.65%) in thermolabile foam ("Milice", Mipharm, Italy) (20 participants) Both medications applied to entire body surface except head for 8 h overnight on 2 consecutive days, and then same treatment repeated after 14 days
Outcomes	1. Number of participants with clearance of lesions at 4 weeks 2. Number of participants with complete relief of itching at 4 weeks Not included in this review: 3. Number of participants with clearance of lesions at 2 weeks 4. Number of participants with complete relief of itching at 2 weeks 5. Clinical grading score (semi-quantitative measure of numbers of lesions) at 2 and 4 weeks 6. Itching score at 2 and 4 weeks 7. Numbers of days taking antihistamine drugs 8. Numbers of participants with secondary skin infection
Notes	Location: Italy Date: March 2001 to October 2001 Trial supported by unrestricted grant from Mipharm SpA

Avila-Romay 1991

Methods	Design: randomized controlled trial Generation of allocation sequence: "randomly assigned" Allocation concealment: unclear Blinding: unclear Inclusion of randomized participants in the analysis: 100%
Participants	Number: 51 cases and 60 contacts enrolled (children 6 to 17 years old; sex not stated) Inclusion criteria: clinically compatible lesions associated with itching Exclusion criteria: secondary infection
Interventions	1. 10% sulfur in pork fat with 1% salicylic acid as preservative (25 cases and 28 contacts) 2. 10% sulfur in cold cream (26 cases and 32 contacts) Both medications applied nightly for 3 nights then once 3 nights later, average dose 7 g Both medications applied by the patients from shoulders to feet for about 5 minutes, under supervision of a physician
Outcomes	1. Number of cases clinically cured (absence of cutaneous lesions and itching) at 10 days 2. Secondary cutaneous reactions in cases and contacts Not included in this review: 3. Patient preference (not further defined)
Notes	Location: Mexico; participants from a house for orphan children Date: not stated 60 contacts also randomly assigned to treatment with sulfur in either pork fat or cold cream

Biele 2006

Methods	Design: randomized controlled trial Generation of allocation sequence: computer generated Allocation concealment: unclear Blinding: investigators Inclusion of randomized participants in the analysis: 100%
Participants	Number: 240 enrolled (aged 18 to 75 years, mean age 31 years (pyrethrin group) and 30 years (benzyl benzoate); males only) Inclusion criteria: clinically diagnosed and microscopically confirmed scabies Exclusion criteria: treatment for scabies within previous 15 days; renal failure (plasma creatinine > 2.5 mg/dL); liver insufficiency (alanine aminotransferase or aspartate aminotransferase > 3 upper normal limit); acute or chronic leukaemia or lymphoma
Interventions	1. 10% benzyl benzoate lotion ("SCAB", PentaMedical, Milan, Italy), topical application on 5 consecutive days (120 participants) 2. 0.165% natural pyrethrins synergized with pyperonil butoxide (1.65%) in thermolabile foam ("Milice", Mipharm, Italy), topical application on 3 consecutive days (120 participants) Both treatments were applied to all skin surfaces from scalp to soles of feet Treatment was repeated after 2 weeks if participant was not considered clinically cured

Biele 2006 (*Continued*)

Outcomes	1. Number of participants clinically cured at 4 weeks 2. Number of participants with relief of itching at 4 weeks 3. Adverse events Not included in this review: 4. Number of participants with clearance of lesions at 2 weeks 5. Clinical grading score (semi-quantitative measure of numbers of lesions) at 4 weeks 6. Itching score at 4 weeks
Notes	Location: Italy Date: October 2003 to July 2004

Brooks 2002

Methods	Design: randomized controlled trial Generation of allocation sequence: computer generated Allocation concealment: unclear Blinding: investigators Inclusion of randomized participants in the analysis: 73% (30/110 lost to follow up)
Participants	Number: 110 enrolled (children 6 months to 14 years old; sex not stated) Inclusion criteria: clinically diagnosed scabies Exclusion criteria: treatment for scabies within previous 2 months; major intercurrent illness; history of meningitis or neurological illness
Interventions	1. Oral ivermectin 200 μg/kg bodyweight single dose (55 participants) 2. 10% benzyl benzoate applied neck to toe overnight (55 participants)
Outcomes	1. Number of participants clinically cured (defined as absence of skin lesions) at 3 weeks 2. Number of participants with persistence of night-time itch at 3 weeks 3. Adverse events Not included in this review 4. Itch severity 5. Numbers of lesions
Notes	Location: Vanuatu Date: January to April 2001 Family contacts treated with same drug as the participant Author confirmed equal numbers of participants randomized to each intervention

Chouela 1999

Methods	Design: randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: participants (study described as double blind) Inclusion of randomized participants in the analysis: 81% (10/53 participants lost to follow up or withdrew)
Participants	Number: 53 enrolled (aged over 18 years with a mean age of 40.8 years; 19 males, 34 females) Inclusion criteria: clinical or parasitological signs compatible with scabies Exclusion criteria: pregnancy; breastfeeding; treatment for scabies within previous 4 weeks; renal dysfunction; hepatic dysfunction; concomitant antidepressant; anxiolytic or antipruritic drug use; severe immunodeficiency; HIV infection; clinically high risk for HIV; neoplasia affecting immunity; immunosuppressive treatment; gastrointestinal dysfunction; history of convulsions
Interventions	1. Single dose of oral ivermectin, 150 to 200 μg/kg in 6 mg tablets plus single topical application of 60 mL placebo solution (26 participants) 2. Single topical application of 60 mL 1% lindane topical solution plus placebo tablets (27 participants) Both placebo and 1% lindane solutions applied neck to toe and kept on for 8 h Not included in this review: 3. Second dose of oral ivermectin, 150 to 200 μg/kg in 6 mg tablets plus single topical application of 60 mL placebo solution at 15 days for treatment failures in intervention group 1 (ivermectin) 4. Second topical application of 60 mL 1% lindane topical solution plus placebo tablets at 15 days for treatment failures in intervention group 2 (lindane)
Outcomes	1. Number of participants cured at 15 days (defined as absence of pruritus and clinical lesions or a reduction of signs and symptoms to a score of 1 (mild pruritus and mild lesions)) 2. Adverse events Not included in this review 3. Number of participants receiving second dose at 15 days who were cured at 29 days
Notes	Location: Argentina Date: April 1996 to February 1997 Members of the same household who were infested but could not be included in the study treated with 1% lindane (adults) or 6% sulfur cream (infants)

Glaziou 1993

Methods	Design: randomized controlled trial Generation of allocation sequence: "randomly allocated" Allocation concealment: unclear Blinding: outcomes assessor Inclusion of randomized participants in the analysis: 100%

Glaziou 1993 (*Continued*)

Participants	Number: 44 enrolled (aged 5 to 56 years, mean 17.5 years; 23 males, 21 females) Inclusion criteria: clinically diagnosed scabies defined as the association of pruritus with at least 1 classical burrow Exclusion criteria: other disease; pregnancy; abnormal physical examination (except for cutaneous lesions); abnormal laboratory screen; refused consent
Interventions	1. Oral ivermectin 100 µg/kg bodyweight single dose (23 participants) 2. 10% benzyl benzoate applied to entire body except head on 3 occasions 12 h apart (21 participants)
Outcomes	1. Number of participants clinically cured at 30 days (defined as complete disappearance of initial lesions and pruritus) 2. Adverse events Not included in this review: 3. Number of participants clinically cured at 7 days 4. Number of participants clinically cured at 14 days 5. Mean clinical score (based on number and activity of lesions)
Notes	Location: French Polynesia Date: 1992 All household contacts treated at same time as the participant with 10% benzyl benzoate Merck Sharp and Dohme supplied the ivermectin tablets at no cost

Gulati 1978

Methods	Design: randomized controlled trial Generation of allocation sequence: "cases ... divided at random" Allocation concealment: unclear Blinding: unclear Inclusion of randomized participants in the analysis: 100%
Participants	Number: 158 enrolled (mean age 16.6 years; 75 males, 83 females) Inclusion criteria: clinical diagnosis of scabies Exclusion criteria: none stated
Interventions	1. 25% benzyl benzoate emulsion (89 participants) 2. Sulfur ointment (69 participants) Both medications "applied all over the body after a thorough scrub bath with soap and water once in the morning, then again at night and again the next morning" Treatments were repeated in those whose lesions persisted after the 10th day
Outcomes	1. Number of participants with clinically assessed "clearance of lesions" at 15 days Not included in this review: 2. Numbers of participants with clearance of lesions at 3 to 5, 6 to 8, 9 to 11, and 12 to 14 days 3. Number of days until clearance of lesions

Gulati 1978 (*Continued*)

Notes	Location: India Date: not stated Family contacts treated concurrently with same drug as the participant 33% of participants had secondarily infected lesions Prevalence of scabies in this study was 158/1727 (9.1%)

Hansen 1986

Methods	Design: randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear, "single blind" Inclusion of randomized participants in the analysis: 95% (5/104 lost to follow up)
Participants	Number: 104 enrolled (aged 2 to 71 years) Inclusion criteria: clinical and/or microscopic diagnosis of scabies Exclusion criteria: none stated
Interventions	1. 1% lindane lotion (50 participants) 2. 5% permethrin lotion (49 participants) Both medications applied as a single application
Outcomes	1. Number of participants with absence of lesions at 28 days 2. Number of participants with persistence of pruritus at 28 days 3. Adverse events Not included in this review: 4. Number of participants with absence of lesions at 14 days
Notes	Location: not stated Date: not stated Data taken from a conference abstract

Macotela-Ruiz 1993

Methods	Design: randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: participants and outcomes assessor Inclusion of randomized participants in the analysis: 100%
Participants	Number: 55 enrolled (aged over 5 years;18 males mean age 25 +/- 4 years, 37 females mean age 24 +/- 16 years) Inclusion criteria: clinical diagnosis of scabies Exclusion criteria: pregnancy; breastfeeding; impaired renal function; impaired liver function; treatment for scabies within previous 3 weeks

Macotela-Ruiz 1993 (*Continued*)

Interventions	1. Oral ivermectin 200 µg/kg bodyweight single dose (29 participants) 2. Placebo (26 participants)
Outcomes	1. Number of participants clinically cured at 7 days (as defined as absence of itching and no dermatologically active lesions) 2. Adverse events
Notes	Location: Mexico Date: not stated Trial stopped at 7 days as ivermectin group significantly clinically better

Madan 2001

Methods	Design: randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: outcomes assessor Inclusion of randomized participants in the analysis: 75% (50/200 lost to follow up)
Participants	Number: 200 enrolled (aged over 5 years; 132 males, 68 females) Inclusion criteria: clinical diagnosis of scabies (defined as nocturnal itching and/or family contact with similar complaint and/or typical lesions) Exclusion criteria: pregnancy; breastfeeding; severe cardiovascular, respiratory, or central nervous system disorders
Interventions	1. Oral ivermectin 200 µg/kg bodyweight single dose (100 participants) 2. 1% lindane lotion applied neck to toe and left on overnight (100 participants)
Outcomes	1. Number of participants clinically cured at 4 weeks (defined as no signs or symptoms of scabies) 2. Adverse events Not included in this review: 3. Number of participants clinically cured at 2 weeks 4. Number of patients with good improvement at 4 weeks
Notes	Location: India Date: not stated Microscopic confirmation of diagnosis in 170/200 (85%) of participants Family contacts treated with 25% benzyl benzoate lotion for 3 days

Maggi 1986

Methods	Design: randomized controlled trial Generation of allocation sequence: "randomly selected" Allocation concealment: unclear Blinding: unclear Inclusion of randomized participants in the analysis: 100%
Participants	Number: 87 enrolled (children, age range not stated) Inclusion criteria: scabies, not further explained Exclusion criteria: pyodermatitis
Interventions	1. 1% lindane suspension applied topically from chin to feet; 2 x 1-h applications 7 days apart (45 participants) 2. 1% lindane suspension applied topically from chin to feet; 2 series of 4 daily applications, 7 days apart (42 participants)
Outcomes	1. Number of participants with absence of pruritus at 14 days Not included in this review: 2. Number of participants with absence of pruritus at 7 days 3. Numbers of participants with excoriations or burrows at days 7 and 14
Notes	Location: Chile Date: March to November 1985

Nnoruka 2001

Methods	Design: randomized controlled trial Generation of allocation sequence: random-number table Allocation concealment: unclear Blinding: unclear Inclusion of randomized participants in the analysis: 100%
Participants	Number: 58 enrolled (aged 5 to 63 years, mean 27.9 years; 35 males, 33 females) Inclusion criteria: clinically diagnosed scabies (microbiologically confirmed in 43/58) Exclusion criteria: aged < 5 years
Interventions	1. Oral ivermectin 200 µg/kg bodyweight single dose (29 participants) 2. 25% benzyl benzoate emulsion applied neck to toe and left for 72 h (29 participants)
Outcomes	1. Number of participants clinically cured at 30 days (defined as complete disappearance of initial lesions and pruritus) 2. Adverse events Not included in this review: 3. Number of participants clinically cured at 7 days 4. Number of participants clinically cured at 14 days 5. Response of pruritus (graded on subjective scale) at 7, 14, and 30 days 6. Mean clinical score (based on number and activity of lesions)

Nnoruka 2001 (*Continued*)

Notes	Location: Nigeria Date: June 1998 All household contacts treated at same time as the participant (treatment not stated)

Schenone 1986

Methods	Design: randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: unclear Blinding: unclear Inclusion of randomized participants in the analysis: 100%
Participants	Number: 127 enrolled (aged 4 to 19 years; 53 males, 74 females) Inclusion criteria: clinical diagnosis of scabies Exclusion criteria: none stated
Interventions	1. 40 mL of 0.02% decamethrin lotion, applied everywhere except skull and face, daily for 2 days, and repeated on 2 more days 1 week later (53 participants) 2. 40 mL of 0.02% decamethrin lotion, applied everywhere except skull and face, daily for 4 days (74 participants)
Outcomes	1. Number of participants clinically cured at 21 days (defined as no active lesions)
Notes	Location: Chile (18 boarding schools in Santiago) Date: 1985 Prevalence amongst boarding school children (aged 4 to 19): 127/868 (14.6%) Contacts treated with single dose of 0.02% decamethrin

Schultz 1990

Methods	Design: randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: medication supplied to each trial centre in identical coded boxes Blinding: outcomes assessor Inclusion of randomized participants in the analysis: 87% (63/467 participants not analysed (for primary outcome))
Participants	Number: 467 enrolled (aged 2 months to 75 years, mean age 22.1 years; 297 males, 170 females) Inclusion criteria: clinical diagnosis of scabies Exclusion criteria: pregnancy; breastfeeding; treatment with ectoparasiticide within previous 3 weeks; renal impairment; hepatic impairment; known allergy to permethrin or lindane
Interventions	1. 5% permethrin cream applied to entire body below ears, single application (234 participants) 2. 1% lindane lotion applied from neck down, single application (233 participants)

Schultz 1990 (*Continued*)

Outcomes	1. Number of participants clinically cured at 28 +/- 7 days (defined as all original lesions healed and no new lesions) 2. Number of participants with persistence of itch 3. Adverse events Not included in this review: 4. Number of participants clinically cured at 14 +/- 3 days 5. Number of microbiologically confirmed cases clinically cured
Notes	Location: USA and Mexico (4 sexually transmitted diseases clinics, 2 dermatology clinics, and 2 family practice clinics, 1 of which was in Mexico and all others in USA) Date: not stated Personal contacts of 85% of participants provided with 1% lindane for their use Study supported in part by a grant from Burroughs Wellcome (manufacturers of permethrin) who also provided statistical assistance

Singalavanija 2003

Methods	Design: randomized controlled trial Generation of allocation sequence: random-number table Allocation concealment: unclear Blinding: unclear Inclusion of randomized participants in the analysis: 68% (32/100 participants lost to follow up)
Participants	Number: 100 enrolled (aged 6 months to 13 years; 60 males, 40 females) Inclusion criteria: clinically diagnosed and microbiologically confirmed scabies Exclusion criteria: resident in an orphanage; serious central nervous system illness; malnutrition; immunodeficiency
Interventions	1. 10% sulfur ointment (50 participants) 2. 0.3% lindane gel (50 participants) Both medications applied neck to toe by parents for 7 consecutive nights
Outcomes	1. Number of participants clinically cured (no new lesions and healing of all old lesions) at 4 weeks 2. Number of participants with decrease or absence of itching at 4 weeks 3. Adverse events Not included in this review: 4. Number of participants clinically cured (no new lesions and healing of all old lesions) at 2 weeks 5. Number of participants with decrease or absence of itching at 2 weeks 6. Number of participants with absence of parasites on skin scraping at 2 and 4 weeks
Notes	Location: Thailand Date: December 1999 to May 2000 Contacts treated with either 25% benzyl benzoate (adults) or 10% sulfur (children)

Taplin 1986

Methods	Design: randomized controlled trial Generation of allocation sequence: "randomized code" Allocation concealment: identical coded medication tubes; codes held by sponsor Blinding: investigators Inclusion of randomized participants in the analysis: 98% (1/52 participant lost to follow up)
Participants	Number: 52 enrolled (aged 2 to 40 years, mean age 9 years; 22 males, 29 females, 1 gender not stated) Inclusion criteria: clinically diagnosed scabies (confirmed microscopically in 46/52 cases) Exclusion criteria: unwell; febrile; taking any medication; treatment with pediculicides, scabicides, or other topical agent in previous 3 months
Interventions	1. 5% permethrin cream (27 participants) 2. 1% lindane lotion (25 participants) Both medications applied as a single application head to toe
Outcomes	1. Number of participants with no new lesions and healing of all original lesions at 1 month 2. Adverse events Not included in this review: 3. Number of participants with no new lesions and healing of all original lesions at 2 weeks
Notes	Location: Panama Date: not stated All family contacts treated with 1% lindane lotion Photographs taken before and after treatment and distribution of any lesions noted on diagrams Study supported in part by a grant from Burroughs Wellcome (manufacturers of permethrin)

Taplin 1990

Methods	Design: randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: "medications supplied in identical ... tubes that were coded and randomized" Blinding: investigators Inclusion of randomized participants in the analysis: 98% (2/96 participants lost to follow up)
Participants	Number: 96 enrolled (aged 2 months to 5 years; 42 males, 54 females) Inclusion criteria: clinical diagnosis and the recovery of at least 1 live mite Exclusion criteria: none stated
Interventions	1. 10% crotamiton cream (48 participants) 2. 5% permethrin cream (48 participants) Both medications applied as single application from head to toe and left for 8 to 10 h

Taplin 1990 (*Continued*)

Outcomes	1. Number of participants with no new lesions and all original active lesions healed at 28 days 2. Number of participants with persistence of pruritus at 28 days 3. Adverse events Not included in this review: 4. Number of participants with no new lesions and all original active lesions healed at 14 days 5. Number of participants with persistence of pruritus at 14 days
Notes	Location: Panama Date: 1985 Household contacts were treated with 5% permethrin cream 65/96 (68%) participants had secondary cutaneous infection Study supported in part by a grant from Burroughs Wellcome (manufacturers of permethrin)

Usha 2000

Methods	Design: randomized controlled trial Generation of allocation sequence: computer-generated random-number table Allocation concealment: investigators did not take part in allocation Blinding: none Inclusion of randomized participants in the analysis: 100%
Participants	Number: 88 enrolled (aged over 5 years with a mean age of 21.3 years (ivermectin) and 22.4 years (permethrin); 59 males, 26 females) Inclusion criteria: clinical diagnosis (3 out of burrow/lesions in classical sites/nocturnal itch/family history) or microscopic diagnosis Exclusion criteria: pregnancy; breastfeeding; treatment for scabies within previous 1 month; serious central nervous system, hepatic, cardiac, or renal disease
Interventions	1. Oral ivermectin 200 µg/kg bodyweight single dose (43 participants) 2. 5% permethrin cream applied topically overnight (45 participants) Not included in this review 3. Second dose of oral ivermectin, 200 µg/kg for treatment failures in intervention group 1 (12 participants) 4. Second topical application 5% permethrin cream for treatment failures in intervention group 2 (1 participant)
Outcomes	1. Number of participants clinically cured (symptom improvement) at 2 weeks 2. Adverse events Not included is this review: 3. Number of participants clinically cured at 1, 4, and 8 weeks
Notes	Location: India Date: August 1996 to December 1997 Contacts treated with same drug as the index case, except contacts who were children under 5 or pregnant women; these were treated with 12.5% to 25% benzyl benzoate emulsion Author confirmed randomization method and blinding 3 participants in ivermectin group withdrawn due to using additional treatment

Zargari 2006

Methods	Design: randomized controlled trial Generation of allocation sequence: unclear Allocation concealment: "drugs ... packaged in identical appearing tubes and randomized and coded by the manufacturer" Blinding: participants and investigators Inclusion of randomized participants in the analysis: 84.6% (18/117 lost to follow up)
Participants	Number: 117 enrolled (aged 6 to 64 years, mean age 30.2 years +/- 15.3; 55 males and 44 females followed up) Inclusion criteria: clinically diagnosed scabies (defined as burrow or typical lesions at classical sites plus nocturnal pruritus plus similar symptoms in contacts) and/or microscopically diagnosed scabies (demonstration of egg, larvae, mite, or faecal material) Exclusion criteria: < 5 years of age; treatment with antiscabietic medication or topical steroid in previous 4 weeks; pregnancy; breastfeeding; severe central nervous system, hepatic, or renal problems
Interventions	1. 5% permethrin cream (59 participants) 2. 1% lindane cream (58 participants) Both medications applied as a single application head to toe, and repeated 1 week later
Outcomes	1. Number of participants with no new lesions and improvement in itching at 14 days 2. Adverse events
Notes	Location: Iran Date: December 2002 to October 2003 Treatment advised for all family members and close contacts Study supported by Gilaranco Company (manufacturers of permethrin and lindane)

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

Alebiosu 2003	Allocation method inadequate; expressed preference of participants for different interventions taken into account
Amer 1981	Non-randomized study
Bockarie 2000	Non-controlled study
Burgess 1986	Non-randomized study
Cannon 1948	Non-controlled study
Chowdhury 1977	Non-controlled study

(*Continued*)

Cubela 1978	Non-randomized study
Curiati 1984	Non-randomized study
Damodaran 1979	A trial of iron and folic acid supplementation
Dika 2006	Non-controlled study
Dourmishev 1998	Non-controlled study
Dunne 1991	Study participants selected on basis of having onchocerciasis rather than scabies
Gordon 1944	Non-randomized study
Grabner 1970	Non-randomized study
Hamm 2006	Non-controlled study
Hanna 1978	Non-controlled study
Haustein 1989	Non-randomized study
Henderson 1991	Non-randomized study
Henderson 1992	Non-randomized study
Kar 1994	Case study
Kaur 1980	Non-randomized study
Kenawi 1993	Non-randomized study
Konstantinov 1979	Non-randomized study
Landegren 1979	Non-randomized study
López 2003	Non-randomized study
Macotela-Ruiz 1996	Not truly randomized; unbalanced groups
Meinking 1995b	Non-controlled study
Mellanby 1945	Non-randomized study

(*Continued*)

Mozgunov 1978	Non-controlled study
Nag 1995	Non-randomized study
Neto 1984	Non-randomized study
Oladimeji 2000	Participants randomized to 1 of 3 treatments (lippia oil, benzyl benzoate, or liquid paraffin) but no clear randomization within these groups to 36 separate treatment schedule subgroups
Oladimeji 2005	Trial design inadequate with control group consisting of participants excluded from intervention arms
Paasch 2000	Non-randomized study
Paschoal 1985	Not a trial of scabies treatment effectiveness
Pierce 1951	Non-randomized study
Regis 2003	Trial design looks at reinfestation not treatment failure
Reid 1990	Non-controlled study
Sehgal 1972	No assessment of any outcomes were reported
Srinivas 1996	Randomization unclear; comparison of lindane applied by bath, paint brush, and spray
Srivastava 1980	Allocation made on a "random basis and on availability of drugs"
Sule 2007	Non-randomized study
Suvanprakorn 1987	Non-controlled study
Taplin 1983a	Non-randomized study
Taplin 1983b	Non-controlled study
Taplin 1991	Non-controlled study
Tausch 1999	Comparison between 2 different brands of the same drug (10% crotamiton lotion)
Thianprasit 1984	Non-controlled study
Woolridge 1948	Non-controlled study
Yonkonsky 1990	Non-controlled study

Characteristics of studies awaiting assessment *[ordered by study ID]*

Daneshpajooh 2000

Methods	-
Participants	-
Interventions	-
Outcomes	-
Notes	-

Gallegos 1996

Methods	-
Participants	-
Interventions	-
Outcomes	
Notes	-

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

Naeyaert ongoing

Trial name or title	"A randomised, double lind, double dummy study to compare the efficacy and safety of a single administration of ivermectin to a single administration of permethrin for the treatment of scabies"
Methods	-
Participants	Expected enrolment: 160 Minimum age: 5 years Both genders Inclusion criteria: at least 1 of scabies tunnels or positive microscopic examination (acarids, faeces, or ova); at least two of non-specific injuries with a typical distribution pattern, serious itching which increases during the night, or family or contacts with similar complaints Exclusion criteria: treatment for scabies < 4 weeks ago; treatment with corticoids < 1 week ago; pregnancy; breastfeeding; HIV; serious immunodepressive patients; sensitivity or allergy to 1 of the components of the study medication; damage of the central nerve system

Naeyaert ongoing (*Continued*)

Interventions	Administration of ivermectin or permethrin on day 0
Outcomes	Primary: clinical healing of the skin injuries on day 28 Secondary: decrease of itching on day 28; amelioration of the life quality on day 28; number and gravity of adverse events
Starting date	July 2004
Contact information	Jean-Marie Naeyaert, Principal Investigator, University Hospital Ghent, Ghent 9000, Belgium
Notes	ClinicalTrials.gov identifier: NCT00262418

DATA AND ANALYSES

Comparison 1. Ivermectin versus placebo

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure in clinically diagnosed cases	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Ivermectin versus permethrin

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure in clinically diagnosed cases	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Ivermectin versus lindane

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure in clinically diagnosed cases	2	193	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.23, 0.58]

Comparison 4. Ivermectin versus benzyl benzoate

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure and itch persistence	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Treatment failure in clinically diagnosed cases	3	182	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.20, 1.25]
1.2 Itch persistence	1	58	Risk Ratio (M-H, Random, 95% CI)	0.54 [0.29, 1.01]

Comparison 5. Permethrin versus crotamiton

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure and itch persistence	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 Treatment failure in clinically diagnosed cases	2	194	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.10, 0.55]
1.2 Treatment failure in microscopically confirmed cases	2	194	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.10, 0.55]
1.3 Itch persistence	1	94	Risk Ratio (M-H, Fixed, 95% CI)	0.26 [0.11, 0.65]

Comparison 6. Permethrin versus lindane

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure and itch persistence	5		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Treatment failure in clinically diagnosed cases	5	753	Risk Ratio (M-H, Random, 95% CI)	0.32 [0.13, 0.75]
1.2 Treatment failure in microscopically confirmed cases	3	484	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.09, 1.09]
1.3 Itch persistence	2	490	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.87]

Comparison 7. Permethrin versus natural synergized pyrethrins

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure and itch persistence	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Itch persistence	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 8. Crotamiton versus lindane

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Treatment failure in clinically diagnosed cases	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Treatment failure in microscopically confirmed cases	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 9. Lindane versus sulfur

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure and itch persistence	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Treatment failure in clinically diagnosed cases	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Itch persistence	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 10. Benzyl benzoate versus sulfur

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure in clinically diagnosed cases	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 11. Benzyl benzoate versus natural synergized pyrethrins

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure and itch persistence	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.1 Treatment failure in clinically diagnosed cases	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
1.2 Treatment failure in microscopically confirmed cases	1		Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

1.3 Itch persistence	1	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Comparison 12. Lindane: short application versus long application

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Itch persistence	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 13. Sulfur: pork fat vehicle versus cold cream vehicle

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Treatment failure in clinically diagnosed cases	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

WHAT'S NEW

Last assessed as up-to-date: 29 April 2007.

18 August 2008	Amended	Converted to new review format with minor editing.

HISTORY

Protocol first published: Issue 2, 1996

Review first published: Issue 4, 1997

30 April 2007	New citation required and conclusions have changed	2007, Issue 3: A substantive update with new authors. We included nine new trials and excluded two studies (Dunne 1991 and Macotela-Ruiz 1996) included in Walker 2000 after re-evaluation, as noted in the 'Characteristics of excluded studies'. The review has been rewritten and reformatted throughout, and the conclusions of the review have been updated to reflect the new trial evidence. We used more precise definitions in the 'Types of interventions' and separated the 'Types of outcome measures' into primary, secondary, and adverse events. Treatment failure in those clinically diagnosed and treatment failure in those microscopically confirmed are considered as separate outcome measures, while parasitological cure is no longer an outcome measure. We reformatted the search strategy section, but did not attempt to systematically search literature for adverse events. For data analysis, we used relative risks rather than odds ratios, and used a random-effects model for meta-analysis if significant heterogeneity was present. We used available-case analyses rather than intention-to-treat analyses using imputed data.
1 February 2006	New search has been performed	New studies found and included or excluded.
1 January 2000	New search has been performed	2000, Issue 3: Revised, synopsis added, and updated with new studies (Walker 2000).
1 January 1999	New search has been performed	1999, Issue 3: Revised and updated with new studies (Walker 1999b).
1 January 1999	New search has been performed	Revised with new title 'Interventions for treating scabies' (Walker 1999a).

CONTRIBUTIONS OF AUTHORS

Mark Strong and Paul Johnstone jointly authored this review update.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Benzoates [therapeutic use]; Insecticides [therapeutic use]; Ivermectin [therapeutic use]; Lindane [therapeutic use]; Pyrethrins [therapeutic use]; Scabies [drug therapy; *therapy]; Sulfur [therapeutic use]; Toluidines [therapeutic use]

MeSH check words

Adult; Child; Humans