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ORIGINAL ARTICLE

Comparative efficacy and safety of oral ivermectin, topical permethrin, and its combination in the treatment of scabies: a systematic literature review

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ABSTRACT

INTRODUCTION Oral ivermectin is an approved first-line option to topical permethrin in Europe and Japan for the treatment of classic scabies, while combination oral ivermectin and topical permethrin is used in clinical practice for extensive or recurrent cases. There is unclear evidence on comparative efficacy and safety.

OBJECTIVES To review the evidence on efficacy and safety of oral ivermectin versus topical permethrin or its combination in the treatment of classic scabies.

METHODS We searched PubMed from January 1, 2016 up to August 7, 2021 for systematic reviews that included RCTs comparing oral ivermectin versus topical permethrin or its combination in the clinical treatment of scabies. We described the characteristics of included studies, assessed reporting quality, and summarized results and conclusion.

RESULTS We included five systematic reviews. Permethrin did not differ from oral ivermectin in cure rate at the 3 to 6-week time point but had an earlier cure at 1-2 weeks. Adverse effects did not significantly differ and were few, mild, and transient with both treatments. The evidence ranged widely from low to high certainty and mainly came from three moderate-to-high quality systematic reviews. Combination oral ivermectin and topical permethrin was ranked higher in efficacy but lower in safety compared to either drug alone in one moderate validity network meta-analysis.

CONCLUSION There is varying certainty of evidence suggesting comparable efficacy and safety of oral ivermectin versus topical permethrin. Limited evidence suggest higher efficacy and lower safety of combination oral ivermectin and topical permethrin compared to either drug alone. An updated systematic review and network meta-analysis is warranted.

KEYWORDS scabies, ivermectin, permethrin, effectiveness, efficacy, safety

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INTRODUCTION

Scabies is a highly prevalent and neglected tropical skin disease (skin NTD by World Health Organization),[1–3] ranging from 0.2% to 71.4%[4] in prevalence especially among young children (below 6 years)[5] and the elderly (> 70 years).[6] In the Philippines, limited community surveys showed scabies to be among the top three most common skin diseases: ranging from 2.01% (N = 5121, six leprosy-endemic areas nationwide, 1999-2000)[7] to 24.6% (two urban poor communities in Manila).[8] Scabies ranked 4th among new cases (4%), and new and existing cases (4.25%) for all outpatient dermatology consults from selected institutions from 2011–2019 (Philippine Dermatological Society-Health Information System).

The typical skin lesions of scabies are linear burrows under the skin and itchy excoriated papules and can be confirmed by direct identification of mites, eggs, or fecal material, either through light microscopic examination of skin scrapings, or using a high-powered imaging device or dermoscopy.[9–11] A hypersensitivity reaction to the mite and its fecal material is responsible for the severe itch. The number of mites in classic or ordinary scabies in healthy individuals is usually five or fewer, but may number in the millions in crusted scabies in patients who are immunocompromised (taking steroids or other immunosuppressants), transplant patients, with cancer or diabetes or human immunodeficiency virus (HIV), on dialysis, and the elderly.

There was a 45% chance of misdiagnosing scabies with other skin conditions (atopic dermatitis, dyshidrotic eczema, pyoderma, contact dermatitis or insect bite reaction) prior to the current consult.[10]

There is also a delay in the symptoms of skin inflammation and itching until 2–6 weeks after the onset of infestation. The mean duration between the onset of symptoms and the first consultation of patients with scabies with a derma-

tologist was 77.1 days (SD 63.7) (range, 4 to 720 days) in a survey in two hospital clinics in Cameroon (N=255). At the first consultation with a dermatologist, 74.9% had already tried previous treatment, such as antibiotics, antifungals, antihistamines or plant-based medicines.[11] Common complications of scabies due to scratching include impetigo, which may lead to septicemia and post-streptococcal immune sequelae such as rheumatic heart disease and glomerulonephritis.[12–14] Infected skin lesions should be treated with an appropriate prescription antibiotic (CDC 2020).[15]

Scabies is curable using either topical medications, oral medications, or a combination of both. The first line of treatment often consists of topical neurotoxic insecticidal agents (permethrin, ivermectin, malathion, spinosad, lindane, and benzyl benzoate), leading to paralysis and death of the mites. An alternative for pregnant women and small infants is sulfur, a topical non-specific irritant agent that eliminates mites through peeling of the skin. The most commonly recommended first-line treatment for classic scabies in most clinical practice guidelines and currently used in local practice is topical permethrin (Table 1). It works by blocking sodium channels leading to delayed depolarization, paralysis, and death of mites and eggs. However, topical treatment is challenging since it requires whole body application; thus, expensive and inconvenient, leading to poor compliance and treatment failure from inadequate application.[16] In addition, the presence of impetiginized or eczematous lesions may preclude its use as topical permethrin may cause skin irritation. Resistance to permethrin has also been reported in Paris[17] and Austria.[18]

Ivermectin, an old broad-spectrum antiparasitic drug, is the only oral scabicide used in mass drug administration in endemic communities[19] and FDA-approved for scabies in some European countries, Japan, and Australia is ivermectin, an old broad-spectrum antiparasitic drug (Table 1). Combination oral and topical treatment has also been used not only in crusted scabies, but in recurrent, extensive, or recalcitrant classic scabies in vulnerable populations such as those with diabetes mellitus[20] and residents in elderly homes.[21] Combination oral ivermectin and topical permethrin has been used in a few randomized controlled trials (RCTs) and showed greater efficacy although adverse events were also higher than either drug alone.[22,23]

Oral ivermectin was first introduced in the 1980s for onchocerciasis, filariasis, and malaria control programs[24] and recently has been approved for use in ectoparasitic infections (scabies and pediculosis) by WHO.[25,26] Oral ivermectin is recommended as one of the first-line treatments for both classic and crusted scabies in only three clinical practice guidelines (CPGs) in the US (2021 CDC STI),[27] Europe (2017),[28] and Japan (2017).[29] Oral ivermectin is approved for scabies in France (2001), and other European countries followed suit, but not in the USA, UK or the Philippines[30,31] where it is only approved as an anti-nematodal agent.

Oral ivermectin blocks a class of ligand-gated chloride ion channels in the scabies mite, leading to persistently open channels. Excessive release of the neurotransmitter gamma-aminobutyric acid (GABA) in the nervous system of the mite leads to its death. Due to variable expression of the ligand-gated channels depending on the life cycle of the mite, ivermectin is active only against mobile stages (larva, nymphs and adults) and not the neurologically immature eggs.[32] Therefore, it requires a second dose two weeks after the first dose, or once the eggs have developed into adults. In crusted scabies, oral ivermectin is given more than two doses and is combined with topical scabicides and keratolytic creams. Resistance to ivermectin was reported in Australia in two patients with crusted scabies who received multiple doses.[33]

Adverse events reported in people receiving oral ivermectin in RCTs for classical or uncomplicated scabies included aggravation of symptoms (including pruritus), irritation, headache, nausea, pustular rash, cellulitis, abdominal pain and mild diarrhea.[34] Rare cases of suspected neurological serious adverse drug reactions (sADRs) were reported in 18 patients with scabies or acarodermatitis after intake of ivermectin.[35,36] The mechanism responsible for the encephalopathy was believed to be a passage of ivermectin through the blood-brain barrier due to overdose or mutation of transporters/metabolism factors (e.g., polymorphism of MDR1 gene; deficiency in P-glycoproteins). The safety of oral ivermectin in pregnant/breastfeeding women[37] and children below 15 kg body weight[38] is not yet established and thus, oral ivermectin has limited use for scabies in these special populations.

After the treatment that has effectively killed all mites and eggs, pruritus and skin lesions may persist within six weeks due to hypersensitivity reaction to the mites and its feces.[39] Treatment failure should not be diagnosed before six weeks have elapsed. If itching is still present more than two to four weeks after treatment or if new burrows or pimple-like rash lesions continue to appear, retreatment may be necessary.

To date, there is no local CPG on scabies management although permethrin 5% cream or lotion, or sulfur 5-10% ointment are commonly used and listed in the Philippine National Formulary (PNF) (2019) and price index (2021).[40–43] Oral ivermectin has only been recently added in the PNF 2021[42] due to its purported role in coronavirus disease 2019 (COVID-19) treatment.[44] It was approved for compassionate use in COVID-19 for certain hospitals, which required a signed written informed consent for off-label use of medication/s and/or use of investigational drug/s for COVID-19.[45]

There is unclear evidence on the comparative effectiveness of oral ivermectin versus topical permethrin or its combination as well as the optimal dosing regimen in the treatment of scabies to guide its off-label use in local clinical practice. Thus, this review aims to summarize the current evidence on the efficacy

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Table 1. Pharmacodynamic and pharmacokinetic information for oral ivermectin and topical permethrin in treatment of scabies

Scabicide (Drug Class)	Year Developed or Introduced	Mode of Action	Pharmacokinetic Data	Recommended Dosage Regimen for Classic Scabies	Special Precautions	Common Adverse effects
ORAL IVERMECTIN (Avermectin)	1988 (for onchocerciasis), 2001 (1st approved in France for scabies)	Neurotoxic/Adulticidal Binds to glutamate-gated chloride ion channels in nerve and muscle cells leading to increased permeability to chloride ions, and neuromuscular paralysis[30]	**Absorption** May be increased with a high-fat meal[46] **Distribution** Vd: 3.1 to 3.5 L/kg in healthy volunteers; mean 9.9 L/kg (range: 6.9 to 15.3 L/kg) in patients with onchocerciasis; high concentration in the liver and adipose tissue; does not readily cross the blood-brain barrier[47,48] **Protein binding** ~93% primarily to albumin[47] **Metabolism** Hepatic via CYP3A4 (major), CYP2D6 (minor), and CYP2E1 (minor) **Half-life elimination** 18 hours **Time to peak, serum** ~4 hours **Excretion** Feces; urine (<1%)[49]	Single oral dose of 200 µg/kg body weight in tablet form May be repeated once after 1–2 weeks.	Do not use in children weighing less than 15 kg or in pregnant women. Pregnancy (category C). Caution with breastfeeding. Caution with severe hepatic impairment	**Dermatologic** Pruritus, rash **Systemic** Fever, myalgia, headache[47]
TOPICAL PERMETHRIN (Synthetic pyrethroid)	1986	Neurotoxic/Both ovicidal and adulticidal Disrupts sodium ion influx through the nerve cell membrane channels, delaying repolarization	**Absorption** Negligible systemic absorption **Excretion** 0.5% in urinary excretion 168 hrs. post-dose[50]	Permethrin 5% cream applied to all areas of the body from the neck down and washed off after 8–14 hrs. May be repeated once after 1 week	Pregnancy (Category B) and lactation Do not use for infants <2 months old	**Dermatologic** Burning, numbness, stinging, tingling, rash, erythema, pruritus, eczema, localized oedema. **Systemic (Accidental toxic ingestion)** Epidermal lesions, sore throat, nausea, vomiting, abdominal pain, gastrointestinal mucosal irritation, salivation, respiratory distress and headaches in humans[51]

RCT - Randomized Controlled Trial; CCT - Clinically Controlled Trial; OECD - Organisation for Economic Co-operation and Development; ITS - Internal transcribed spacer sequence analysis.

and safety of oral ivermectin versus topical permethrin or its combination in the treatment of classic scabies.

METHODS

We searched MEDLINE (PubMed) from August, 2016 to August 7, 2021 using the following search strategy: (("scabi*"[All Fields] OR "scabies"[MeSH Terms] OR "sarcoptes scabiei"[MeSH Terms] OR "antiscab*"[All Fields]) AND "therapy"[MeSH Subheading]) AND ((y_5[Filter]) AND (meta-analysis[Filter] OR review[Filter] OR systematicreview[Filter]) AND (humans[Filter])). We also looked at reference lists and relevant similar articles and citing articles.

We screened the full reports of relevant records based on the following eligibility criteria:

We extracted and summarized the characteristics (patients, intervention, comparator, outcomes, study design). We critically appraised the validity of included systematic reviews using four criteria (appropriateness of criteria for inclusion of studies, thoroughness of search for eligible studies, validity as-

sessment of included studies, and reproducibility of assessments of the studies) from Dans et al. (2017).[52] Systematic reviews were assessed as high validity (4/4 criteria), moderate (3/4), low (2/4), and critically low (1/4). We also assessed the quality of reporting of the review using the 16-item Assessment of Multiple Systematic Reviews 2 (AMSTAR 2) checklist, rating confidence in the results based on the number of critical flaws/weaknesses as: high, moderate, low and critically low.[53] We collected the data for efficacy and safety from the included systematic reviews. We identified limitations and research gaps from the current evidence.

RESULTS

SEARCH FOR STUDIES

We screened the titles and abstracts of 72 records from the PubMed search and one from a reference list and included five systematic reviews on the efficacy and safety of oral ivermectin versus topical permethrin in the treatment of individuals with scabies (Figure 1). Upon reading full texts, we merged one abridged summary (Rosumeck 2019)[54] of an included systematic review (Rosumeck 2018), and excluded two more systematic reviews: one that did not include scabies in its included studies[55] and another that did not have a comparator group.[38]

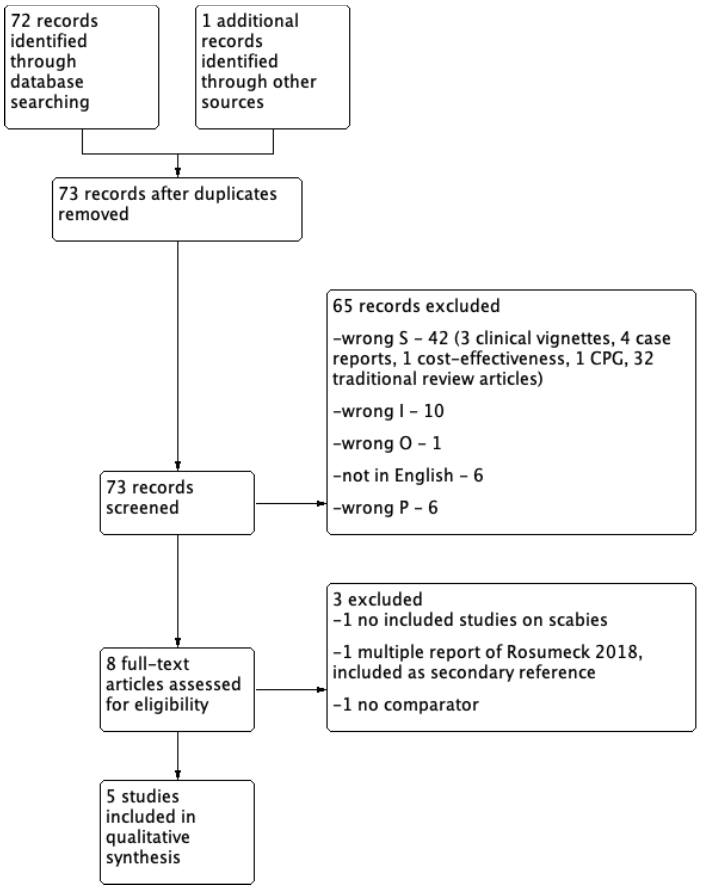

Figure 1. PRISMA flow diagram
P – individual patients with classic scabies; I – oral ivermectin, any dose, any regimen; C – topical permethrin or combination oral ivermectin/topical permethrin, any dose/concentration, any regimen; O – cure, itch relief, recurrence, adverse events, quality of life, other patient-reported outcomes; S – systematic reviews, with or without meta-analysis.

CHARACTERISTICS OF INCLUDED SYSTEMATIC REVIEWS

We summarized the characteristics of five included systematic reviews (SR) (Table 2). The primary authors of two SRs were from Germany, and there was one primary author each from Australia, South Africa, and Thailand. One SR was a Cochrane systematic review (Rosumeck 2018).[56] The lowest number of included studies was 15 in two reviews (Dhana 2018; Rosumeck 2018), which only compared oral ivermectin and topical permethrin, while the highest number was 52 (Thadanipon 2019),[57] which compared nine scabicides and placebo/no treatment. There was an overlap of 30 included studies between two or more reviews, and a total of 50 unique studies. For data synthesis, three SRs did pairwise meta-analysis while only one SR used network meta-analysis (NMA) (Thadanipon 2019); one SR only did qualitative synthesis and did not do meta-analysis due to clinical heterogeneity (May 2019).[58]

All SRs included patients with scabies; May et al. (2019) also included patients with impetigo and fungal skin infections; May et al. (2019) and Dressler et al. (2016) included studies on both treatment of individual patients and mass drug administration in endemic settings. One SR compared five topical (benzyl benzoate, crotamiton, ivermectin, permethrin, and sulfur) and one oral scabicide (oral ivermectin) (Dressler 2016).[59] The largest SR with network meta-analysis (NMA) by Thadanipon et al. (2019) compared oral ivermectin, eight other topical scabicides (benzyl benzoate, crotamiton, herbal medicine, ivermectin, lindane, malathion, permethrin, and sulfur), placebo/no treatment, and combination oral ivermectin and topical permethrin.[57]

QUALITY OF INCLUDED SYSTEMATIC REVIEWS

Confidence in the results of the five systematic reviews based on the AMSTAR 2 tool rating ranged from high (Rosumeck 2018) to moderate (May 2019) to critically low (Dressler 2016; Dhana 2018; Thadanipon 2019) (Table 3). The number of critical flaws for the latter three reviews were mostly due to items 2 (adequacy of the literature search) and 15 (assessment of presence and likely impact of publication bias), while non-critical weaknesses were due to items 3 (explanation of study design of included studies), 10 (sources of funding of included studies), 12 (potential impact of risk of bias on evidence synthesis), and 13 (consideration of risk of bias in interpretation and discussion of review results) (Appendix 1).

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Table 2. Summary of characteristics (participants, interventions comparators, outcomes, study design) of included systematic reviews

Characteristic	Thadanipon 2019	May 2019[65] (Australia)	Rosumeck 2018[63] (Germany) (Cochrane SR)	Dhana 2018[67] (South Africa)	Dressler 2016[66] (Germany)
Participants	Individual patients with scabies	Indigenous peoples and populations in resource-limited settings (low, low-middle, middle-income countries) and resource-limited populations in OECD countries with diagnosis of impetigo, scabies, crusted scabies, tinea capitis, tinea corporis or tinea ungiuum; Any age or sex	Children or adults of both sexes with a diagnosis of classical scabies, as defined by the study authors	Patients with scabies	Patients with scabies, and whole populations with high prevalence of scabies who received therapeutic and/or preventive treatment
Interventions	9 scabicides (benzyl benzoate, crotamiton, herbal medicine, topical/oral ivermectin, lindane, malathion, permethrin, sulfur, synergized pyrethrins) or placebo/no treatment	Any clinical or public health interventions to reduce skin infections	Topical or systemic ivermectin, topical permethrin	Topical or oral ivermectin	Topical benzyl benzoate, crotamiton, ivermectin, permethrin, and sulfur; Systemic ivermectin
Comparators	Any of above interventions *Excluded: Studies that compared a single drug in different dosages or formulations*	Any comparator (including oral and topical ivermectin, permethrin, crotamiton, lindane, benzyl benzoate + disulfiram)	Any of above interventions	Permethrin	Any of above interventions *Exclusion: Placebo-controlled trials and trials comparing different dosage forms*
Outcomes	**Primary** Clinical cure or microscopic/ parasitic cure **Secondary** Persistent itching, Reinfestation, adverse events	Not stated	**Primary** Complete clearance (outcome assessment at 7, 14, and 30 days' post-initiation of treatment) **Secondary** Number of people retreated Number of people with at least one adverse event Number of people withdrawn from study due to adverse event	**Primary** Treatment failure (as defined in individual studies, although required that the definition include persistent lesions, new lesions, or confirmation of a live mite) **Secondary** Persistence of itch Adverse effects	Efficacy and safety
Study Design	RCTs	Experimental (RCTs, CCTs, before-and-after studies, ITS analyses) or observational study (cohort and ecological studies)	RCTs	Peer-reviewed RCTs	RCTs Excluded: case report, letter, historical article
Filters	Humans *Exclusion:* *Study which does not provide sufficient data for pooling after 3 attempts of contacting the author every 2 weeks* *Study published in languages which reviewers later cannot translate*	English language	None as to language or publication status	None stated	None stated

Using the critical appraisal criteria from Dans et al. (2017), the criteria that were most commonly not fulfilled were: thoroughness of search and assessment of validity of included studies, which were only both addressed in Rosumeck 2018 SR. Four SRs were rated to have low to moderate validity while only one had a high validity rating (Rosumeck 2018) (Table 3).

EFFICACY AND SAFETY

Data on efficacy and safety are summarized in Table 4. For the three systematic reviews that had pooled analyses, there were

similar results showing no significant difference in oral ivermectin versus topical permethrin with RRs for cure rate hovering around the line of no difference (RR=1.0) especially for the later time point of measurement (3–6 weeks after treatment). For the Thadanipon 2019 review, permethrin had a higher cure rate at 1–2 weeks based on the network effect (RR 1.16, 1.05, 1.27) but no significant difference in persistent itching (0.76, 0.49, 1.17) compared to oral ivermectin.[57] At 3–6 weeks, there was no significant difference between permethrin and oral ivermectin for cure (RR 1.03, 0.96, 1.11) and composite adverse events (RR 1.10, 0.83, 1.48). Based on direct comparisons alone (10 RCTs), adverse events were lower from oral ivermectin (60/642, 9.3%) than topical permethrin (76/607, 12.5%) but this was inconclusive due to a wide confidence interval (RR 0.84, 95% CI 0.61, 1.17), while cure rate was slightly lower for oral ivermectin (525/641, 81.9%) compared to permethrin (523/606, 86%). Ranking the interventions using the surface under the cumulative ranking curve (SUCRA), combination permethrin plus oral ivermectin had the strongest evidence for highest cure at 1-2 weeks (SUCRA: 93.4) and 3-6 weeks (SUCRA: 93.1). There was no significant difference in persistent itching between permethrin and oral ivermectin (network RR 0.76, 95% CI 0.49, 1.17). Overall ranking showed that topical ivermectin had the lowest chance of persistent itching (SUCRA: 98.4), and synergized pyrethrins had the lowest adverse reactions (SUCRA: 98.0). There was no single treatment that ranked highest in all outcomes.

The Cochrane systematic review by Rosumeck et al. (2018) compared oral or topical ivermectin to topical permethrin in 13 RCTs (N=1456). They concluded that oral ivermectin may be less effective than topical permethrin for complete clearance after one week (ivermectin 43% vs permethrin 65%; RR 0.65, 0.54, 0.78; 6 studies, N=613; low certainty evidence) but did not differ from topical permethrin for cure at three weeks (ivermectin 68% vs permethrin 74%; RR 0.91, 0.76, 1.08; 5 studies, N = 459; low certainty evidence). Oral ivermectin may not differ from topical permethrin in number of participants with at least one adverse event (ivermectin 5% vs permethrin 4%; RR 1.30 (0.35, 4.83); 4 studies, N = 502; low certainty evidence). Adverse events were few, mild, and did not require withdrawal of drug: severe itching, secondary bacterial infections, headache and nausea for oral ivermectin, and erythema, burning and pruritus with topical permethrin.

Two other non-Cochrane reviews by Dressler et al. (2016) (6 RCTs) and Dhana et al. (2018) (15 RCTs, N=2172) compared oral ivermectin and topical permethrin for treatment of scabies.[59,60] Dressler et al. (2016) only did one meta-analysis for reduction in lesion count showing no significant difference between permethrin and oral ivermectin (RR 1.07, 95% CI 1.00, 1.15; 2 RCTs, N = 83; I^2 = 0%), and just did a narrative synthesis and stated the range of treatment effects (RRs) for the rest of the comparisons. Dhana et al. did one meta-analysis using treatment failure (time points not specified) and showed that oral ivermectin was significantly less effective than topical permethrin (RR 1.33, 95% CI 1.04, 1.72; 14 RCTs, N = 1792; I^2 = 0%). However, no time points were specified, which means that the effect estimate may have been pooled from studies that measured the outcome at varying time points. No adverse event outcomes were reported in both systematic reviews.

A systematic review by May et al. (2019) on treatment, prevention and public health control of four common skin infections (scabies, crusted scabies, impetigo and fungal skin infections) in resource-poor communities (search date not stated) included both RCTs and observational studies.[58] Based on individual RCTs, lesion count and pruritus were significantly lower for permethrin at one week while clinical cure at four weeks was the same as oral ivermectin (2 RCTs, moderate to high quality evidence). There was superior symptom relief with permethrin at two weeks, while clinical cure was the same as oral ivermectin (1 RCT; low quality evidence). However, there was no effect estimates (e.g., relative risk or mean scores) given to support the results. The review authors concluded that there was moderate to high-quality evidence that strongly recommends the use of either oral ivermectin or topical permethrin for the treatment of scabies.[61–64] Adverse events were not reported, although this outcome was specified in the Methods section of the systematic review.

DISCUSSION

SUMMARY OF MAIN FINDINGS

Overall, the included systematic reviews were consistent in showing comparable efficacy and safety between oral ivermectin and topical permethrin at around the 3 to 6-week time point, although an earlier cure was seen with permethrin at the 1 or 2-week time point. Adverse events were few, mild, and transient; severe itching, secondary bacterial infections, headache and nausea for oral ivermectin, and erythema, burning and pruritus with topical permethrin. However, the certainty of evidence was ascertained in only three SRs, and had varying levels. In two SRs with meta-analyses, the evidence was rated as low to moderate certainty, mainly due to serious risk of bias, heterogeneity in study characteristics especially variability in dosing regimens, and poor reporting. In a third SR without meta-analysis that included only low-income settings, evidence from individual RCTs was rated as moderate to high.

There is limited evidence for efficacy and safety of combination oral ivermectin and topical permethrin. In one SR and network meta-analysis, the combination regimen was ranked as having superior efficacy but with higher rate of adverse effects over oral ivermectin or topical permethrin alone. However, the SR was appraised to be of low-to-moderate validity with a critically low rating in confidence in its results. The evidence for the combination treatment arm was based on a single 3-arm RCT and there was no grading of certainty of evidence.

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Table 3. Summary of AMSTAR-2 rating and critical appraisal of included systematic reviews

	Thadanipon 2019 (Thailand)	May 2019 (Australia)	Rosumeck 2018 (Germany)	Dhana 2018 (South Africa)	Dressler 2016 (Germany)
AMSTAR-2 Confidence Rating in Results (Appendix 1)	Critically low Number of critical flaws: 2 Number on non-critical weaknesses: 4	Moderate Number of critical flaws: 0 Number on non-critical weaknesses: 3	High Number of critical flaws: 0 Number on non-critical weaknesses: 2	Critically low Number of critical flaws: 5 Number on non-critical weaknesses: 4	Critically low Number of critical flaws: 2 Number on non-critical weaknesses: 3
Critical Appraisal for Validity (Painless EBM criteria) (Appendix 2)	Moderate 2.5/4	Moderate 2.5/4	High 4/4	Moderate 2.5/4	Low 2.0/4

AMSTAR - A MeaSurement Tool to Assess systematic Reviews; EBM - Evidence-Based Medicine

QUALITY OF SYSTEMATIC REVIEWS

Varying thoroughness of methodological reporting and validity resulted in different ratings for confidence in the results from the five systematic reviews, thereby weakening the collective strength of the evidence. If we were to base our evidence from the highest rated Cochrane systematic review by Rosumeck et al. (2018), the best available evidence would point to comparable efficacy and safety between oral ivermectin and topical permethrin, with an earlier cure with permethrin at 1–2 week time point. However, comparative efficacy and safety between combination oral ivermectin and topical permethrin versus each drug alone is limited since the only systematic review that provided evidence was of moderate validity and with critically low confidence in its results. This evidence needs to be confirmed by including more RCTs and conducting an appropriate meta-analysis with grading of certainty of evidence.

COMPARISON WITH PREVIOUS LITERATURE REVIEWS

Our literature review had three systematic reviews[56,57,60] in common with a 2019 effectiveness review by the Canadian Agency for Drugs and Technologies in Health (CADTH) that searched between January 1, 2014 to April 17, 2019.[65] Aside from the three SRs, the CADTH effectiveness review also included one recent RCT and three CPGs (2 European[28,66] and 1 Japanese[29]).[65] Overall, they noted that the trend in efficacy and safety was consistent among the studies. They concluded that oral ivermectin may be less clinically effective than topical permethrin in the first 1–2 weeks following treatment but there was no difference at later time points (4 weeks onwards). They also stated that there was no difference in adverse events between the two interventions. However, they noted that most of the RCTs in the systematic reviews and evidence base were of limited quality, small sample sizes, with deficiencies in adverse event reporting and considerable uncertainty regarding effectiveness results. They concluded that there was lack of applicability in the Canadian treatment setting since most of the studies in the three previous SRs as well as the RCT were conducted in Asia, while the CPGs were European, German, and Japanese. Oral ivermectin also did not have an approved indication for scabies since it is only approved by Health Canada for treating strongyloidiasis and onchocerciasis. The Canadian Pediatric Society Position Statement 2015[67] has recommended topical permethrin as the first line treatment to the patients with scabies and their close contacts. In contrast, since the Philippine setting is more similar to the Asian studies included in the reviews, the applicability of the results may be greater in our setting.

Our literature review included two additional SRs not found in the Canadian health technology review: by May et al. (2019), which was specifically on resource-limited settings, and Dressler et al. (2016). May et al. (2019) strongly recommended either oral ivermectin or topical permethrin for scabies treatment based on moderate to high quality evidence (Grade IA). Similarly, the second systematic review by Dressler et al. (2016) concluded similar efficacy between oral ivermectin or topical permethrin.

STRENGTHS AND LIMITATIONS OF INCLUDED SYSTEMATIC REVIEWS

We summarized strengths and limitations of included systematic reviews in Table 5. In the Thadanipon 2019 et al. (2019) SR/NMA, it was not explicitly stated how many and which studies out of 52 total RCTs contributed indirect evidence to each network effect.[57] It was also noted that they included 13/52 studies (published 2012 to 2014) comparing various scabicides that were authored or co-authored by Dr. Goldust from the Department of Dermatology, Tabriz University of Medical Sciences, Tabriz, Iran. This author published eight studies [63,64,68–71] that were separately analyzed and labelled as trials of limited plausibility by the systematic review by Dressler et al. in 2016.[59] In a published letter of concern to the editor of Annals of Parasitology, the following issues were raised by Dressler et al. citing five published studies of Dr. Goldust: 1) reported numbers of patients are often multiples of ten (whether number eligible/enrolled/lost to follow up/cured), 2) inconsistencies within each publication.[72] Dr. Goldust published an erratum in the same year stating that

Table 4. Summary of results on efficacy and safety of scabies interventions based on included systematic reviews

Outcome	Thadanipon 2019 (Thailand)	May 2019 (Australia)	Rosumeck 2018 (Germany)	Dhana 2018 (South Africa)	Dressler 2016 (Germany)
Total No. of studies (N)	52 RCTs (N=9917) - Oral ivermectin vs permethrin (16 RCTs, N=1986)	19 RCTs and non-randomized studies (N not stated) on directed clinical treatment of scabies, out of 81 studies (mixed skin infections) - Oral vs topical (11 RCTs) - Topical vs other topical (7 RCTs)	15 RCTs (N=1896) , analyzed 13 RCTs (N=1456) - Oral ivermectin vs permethrin cream (7 RCTs; N=743) - Oral ivermectin vs permethrin lotion (2 RCTs; N=227) - Oral vs topical ivermectin (2 RCTs; N=272) - Topical ivermectin vs permethrin (1 RCT; N=210) - Diff doses bet oral ivermectin (2 RCTs; N=353)	15 RCTs (N=2172) - Oral IVM vs permethrin (14 RCTs) - Topical ivermectin vs permethrin (1 RCT)	16 RCTs (N=not stated) - Permethrin vs oral ivermectin (6 RCTs)
Cure	Favors permethrin over oral ivermectin (1-2 wks.) Network effect RR 1.16 [95% CI 1.05, 1.27]; P for inconsistency = 0.99 No difference at 3-6 wks. Network RR 1.03 [0.96, 1.11]; P for inconsistency = 0.993 Combination permethrin + oral ivermectin had highest probability of cure at 1-2 weeks (SUCRA: 93.4) over permethrin (81.9) and oral ivermectin (61.3) Similar trend for 3-6 week cure, combination treatment (93.1) over permethrin (80.6) and oral ivermectin (70.2)	*No event rates nor treatment effects provided Lesion count and pruritus were significantly lower for permethrin at 1 week while clinical cure at 4 weeks was the same as oral ivermectin (2 RCTs, moderate to high quality evidence). Superior symptom relief with permethrin at 2 wks., while clinical cure was the same as oral ivermectin (1 RCT; low quality evidence)	*Favors permethrin cream over oral ivermectin* **Week 1** RR: 0.65 (95% CI 0.54-0.78) (6 RCTs, N=613; I2=35% low certainty evidence) **Week 2** RR: 0.91 (95% CI 0.76-1.08) (5 RCTs, N=459; I2=61%; low certainty evidence) **Week 4** (several dose comparisons) a. 1-dose ivermectin vs 1 application permethrin RR 1.00 (95% CI 0.86-1.16) (1 RCT, N=60; high certainty evidence b. 1 to 3 doses ivermectin vs 1 to 3 applications permethrin: RR 0.92 (95% CI 0.82,, 1.03) (5 RCTs, N=581; I2=74%; low certainty evidence) **Variable timing and no. of retreatment for non-responders* c. 2 doses ivermectin vs 1 application permethrin RR 0.97 (95% CI 0.83, 1.14) (1 RCT, N=55; moderate certainty evidence) *1 dose oral ivermectin vs permethrin lotion (x 1 application) (1 RCT; N=120)* **Week 1** RR 0.93 (95% CI 0.74, 1.17) **Week 2** RR 1.00 (95% CI 0.78, 1.29) *1-dose oral ivermectin vs permethrin lotion x 5 consecutive nights (1 RCT, N=107)* **Week 1** RR 0.70 (95% CI 0.47, 1.03) **Week 2** RR 0.97 (95% CI 0.81, 1.17) **No significant difference bet. 1 vs 2 doses of oral ivermectin at week 4** RR 0.97 (95% CI 0.83, 1.14) (1 RCT, N=80)	No data	No significant difference between permethrin and oral ivermectin RR 1.07 (95% CI 1.00, 1.15); (2 RCTs, N=83; I2=0%)

Persistent itch	No significant difference between permethrin and oral ivermectin Network RR 0.76 (95% CI 0.49, 1.17) Lowest probability of persistent itch was with topical ivermectin (SUCRA: 98.4), followed by permethrin (SUCRA: 79.2) and synergized pyrethrins (SUCRA: 73.4)	No data	No data	No data	No data
Recurrence	Re-infestation was not included in meta-analyses because a limited number of studies provided data regarding this outcome.	No data	No data	No data	No data
Adverse events	No difference bet. permethrin vs oral ivermectin (3-6 wks.) Network effect: RR 1.10 [0.83, 1.48] Relative ranking Oral ivermectin had highest safety rank (SUCRA: 63.8), over permethrin (54.5) and combination oral ivermectin and permethrin (28.0)	No data	≥ 1 AE (Week 4) Favors permethrin RR: 1.30 (95% CI 0.35-4.83) (4 RCTs, N=502; low certainty evidence	No data	No data
Other, specify	No data	No data	No data	Treatment failure: Favors permethrin RR: 1.33 (95% CI 1.04-1.72) (14 RCTs; N=1792) (Time point not given)	No data
Conclusion	Permethrin has faster cure than oral ivermectin at 2 wks. No difference bet oral ivermectin and permethrin for cure and AE (3–6 wks.) Combination permethrin plus oral ivermectin, topical ivermectin, and synergized pyrethrins had the strongest evidence for highest cure, lowest chance of persistent itching, and lowest adverse reactions, respectively. There was no 1 treatment that ranked highest in all aspects.	Moderate- to high- quality evidence supports the use of topical permethrin or oral ivermectin for scabies treatment (GRADE 1A – Strong recommendation; high quality of evidence). (No time point given)	For the most part, no difference in efficacy of permethrin compared to systemic ivermectin. Overall, few and mild adverse events. Confidence in effect estimates was mostly low to moderate. Poor reporting is a major limitation.	Oral ivermectin is less effective than topical permethrin (Time point not given). All agents have low treatment failure rates and are well tolerated.	Oral ivermectin and topical permethrin have similar efficacy.

"during seven years, our research group conducted a big and multicenter study on comparing different medications with different dosage in the treatment of scabies...led to multiple publications in high impact peer reviewed journals."[73] He stated that there were "minor errors in the releasing of study results" and gave corrections in the data for five publications. [63,64,68,69,74] However, the method of splitting the single big multicenter study with various comparisons (oral ivermectin, permethrin 2.5% cream, permethrin 5% cream, permethrin 5% lotion, lindane 1%, sulfur 10% ointment, malathion, crotamiton 10% cream, topical ivermectin, benzyl benzoate 2.5% emulsion) into separate pairwise comparisons in several publications is unclear.[75] In the later systematic review by Rosumeck et al. (2018), three of these studies were excluded for suspicion of flawed data[56] following a unanimous decision at the 2017 annual meeting of the Cochrane Skin Group . A possible option for future systematic reviews is to clarify with the author the original number of participants randomized to different interventions in the big multicenter study or include the potentially flawed studies but with a sensitivity analysis of the effect estimates excluding these studies. There was also no rating of certainty of evidence although risk of bias of individual studies were assessed and summarized

Table 5. Summary of strengths and limitations of included systematic reviews

	Thadanipon 2019[64] (Thailand)	May 2019[65] (Australia)	Rosumeck 2018[57] (Germany)	Dhana 2018[61] (South Africa)	Dressler 2016[60] (Germany)
Strengths	Did network meta-analysis, with separate networks for different time points for cure; Did subgroup analysis for direct paired meta-analyses Included combination oral ivermectin and topical permethrin as one of the interventions	Specific to resource-poor countries, results more applicable to Philippines	Comprehensive search of 7 databases, grey literature, and trial registers Excluded 3 studies due to questionable validity Did separate pairwise meta-analyses for different time points and dosage regimens; subgroup analyses Rated certainty of evidence	Did pairwise meta-analysis for efficacy outcome	Reported 8 studies separately due to 'limited plausibility'
Limitations	Included 9 studies from group of authors of studies with questionable validity excluded by 2 previous systematic reviews Unclear on number of studies that contributed indirect evidence Did not consider contribution of risk of bias of individual studies in certainty of evidence	Only included English language studies No meta-analysis Did not present treatment effects (e.g., RRs) within the narrative synthesis No adverse event outcomes	Did not do network meta-analysis	Letter to editor only Included 3 studies previously excluded or considered questionable by previous systematic reviews No risk of bias assessment Lumped together studies with different time points and used treatment failure outcome, instead of cure No adverse event outcome	Only searched databases Only did 1 pairwise meta-analysis due to high clinical heterogeneity, and did not rate certainty of evidence

in an appendix.

The Rosumeck et al. (2018) SR only did pairwise meta-analysis using direct evidence comparing ivermectin (topical and oral) to permethrin and found low to moderate certainty of evidence supporting a faster cure for permethrin, although oral ivermectin had comparable efficacy and safety at a later time point. Risk of bias assessment was done and was used to rate the certainty of evidence using the GRADE framework.

Dhana et al. (2018) used treatment failure as the primary outcome but did not subgroup according to time points and it is unclear which time points were included in the meta-analysis in studies with varying time points. May et al. (2019) gave recommendations based on evidence rated as low, moderate, and high, but did not report the actual treatment effects (e.g., relative risk, mean difference) for each comparison.

Dressler et al. (2016) did only one pairwise meta-analysis due to clinical heterogeneity and did not rate the certainty of evidence based on risk of bias assessments. Eight studies were labelled as having limited plausibility (by Dr. Goldust and colleagues) and were not included in the analysis.

In summary, although pooled studies from most systematic reviews showed consistent treatment effects for an earlier cure for permethrin at (1-week or 1 to 2-week time points), no significant difference was seen between oral ivermectin and topical permethrin at a later 3–6 week time point after treatment. The optimal dosing regimen (whether 1 or 2 doses of oral ivermectin) is still unclear. In addition, the evidence comes from studies with mostly unclear or high risk of bias, thereby, rated as low to moderate certainty. Furthermore, the impact of inclusion of possibly flawed studies in the Thadanipon et al. NMA and Dhana et al. SR, should be explored in a sensitivity analysis excluding these studies. The publication of new RCTs since their last search dates in 2017 around four years ago,[76–78] including Philippine RCTs in the local HERDIN database and local journals may potentially change the certainty of evidence and treatment effects and increase applicability of results to our setting. In particular, since permethrin lotion, and not permethrin cream, is the preparation that is marketed locally, studies that used the lotion may have varying results.

CONCLUSION

There is varying certainty of evidence suggesting comparable efficacy and safety of oral ivermectin compared to permethrin in the treatment of classic scabies. There is limited evidence to suggest higher efficacy and lower safety of combination oral ivermectin and topical permethrin compared to either drug alone, but of undetermined certainty. Thus there is a need to conduct a systematic review and network meta-analysis to address evidence gaps to guide clinical practice, health policy, and future research.

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