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Pharmacotherapy of Ectoparasitic Infections

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Abstract

Epizoonoses such as scabies, lice and cimicosis are common, vexing disorders that occur worldwide. Historically, many treatment modalities have been employed in the management of these disorders, and most of the drugs described in this review are of historical interest and no longer recommended or in widespread use because of their wide spectrum of adverse effects. More recently, reports documenting resistance against various antiectoparasite drugs, complicated and

severe courses of the diseases, and adverse effects of drug therapy have prompted the development of new treatment strategies and drugs for optimal disease management.

Because the strategies currently recommended for the treatment of ectoparasites differ worldwide, this review proposes a rational approach to selecting the best therapeutic agent by comparing the pharmacokinetics, pharmacodynamics, drug efficacy and adverse effects. A literature search of the currently Internet accessible libraries PubMed, Medline and Ideal library, of citations of articles found there, and from communications with the Federal Institute for Drugs and Medical Devices, Germany, was conducted based on this approach.

One major observation of this literature search is that permethrin is the treatment of choice for lice and scabies in the US and in Great Britain, whereas lindane is still recommended for scabies in most other European countries because of its longer-standing record of effectiveness. Although permethrin has not yet been proven to be more effective than lindane in treating infections with these ectoparasites, it currently appears to have the best efficacy versus safety profile of topical treatments for scabies and lice.

Ivermectin is a newer oral drug for the treatment of ectoparasites, which has been used with great success in the treatment of onchocercosis and other endoparasites. Although ivermectin appears to be a promising drug, its role in the treatment of ectoparasitic infections will be clarified as more study data become available.

Finally, it is important to emphasise the clinical aspects of ectoparasite therapy and that providing the patient with optimal instructions on the use of topical therapeutics is of great importance in avoiding adverse effects and assuring complete removal of the ectoparasite, thereby avoiding the development of drug-resistance.

Scabies (*Sarcoptes scabiei*), pediculosis (lice, including *Pediculus capitis*, *Pediculus humanus* and *Phthirius pubis*), pulicosis (*Pulex irritans*) and cimicosis (*Cimex lectularius*) are common skin infections with an increasing incidence. Although it was thought that insufficient hygiene and inferior socioeconomic conditions were prominent risk factors, it is now clear that these disorders are occurring with increasing incidence in developing countries as well. Pulicosis and cimicosis are treated symptomatically and by eradication of the source of infestation. Scabies and pediculosis can be treated with a variety of specific drugs, which are described and discussed in this review with special regard to therapeutic spectrum, pharmacological characteristics and clinical features.

1. Clinical Manifestations

1.1 Scabies

Scabies is usually found on the wrists, penis, scrotum, arch of the foot, axillae, umbilicus, inframammary areas, anogenital area and in the interdigital spaces. Only in babies, small children and in patients with crusted (Norwegian) scabies, is the head affected. The predominant symptom is intense pruritus, which is aggravated by the warmth of the bed. Visible tracts may develop in the stratum corneum of infected skin, with the mite seen at the end as a small black spot. However, in endemic regions in tropical countries, tracts are uncommon. The diagnosis is confirmed by micro-

scopic visualisation of the mite from a mineral oil scalpel scraping of a suspected lesion.

In Norwegian scabies, all skin manifestations are more severe and the entire integument including the scalp can be affected by such crusted lesions. This form of scabies is usually observed in immunocompromised patients, such as those with AIDS, or elderly people.

Bacterial superinfection (pyoderma) of the affected areas may complicate scabies. Scabies should be considered in the differential diagnosis in all patients with unexplained pruritus, especially severe pruritus.

Scabies mites are transmitted by close contact, e.g. sexually (infection of the anogenital areas), or by simple contact between family members, nurses and patients in nursing homes, kindergarten teacher and children, or in other housings where people share a small living space. Therefore, all close contacts of a patient should also be treated to remove such potential sources of reinfection.

Other mite infections include trombidosis (harvest mites, chiggers, *Trombicula autumnalis*), acrodermatitis urticaroides (*Pediculoides ventricosus*), gamadiosis (*Dermanyssinus avium*) and cheyletielosis (*Cheyletiella* species). In contrast to scabies, these infestations are treated only symptomatically.

1.2 Pediculosis

Lice are wingless, blood-sucking ectoparasites with a high host specificity. They can transmit a variety of infections, such as the Mediterranean spotted fever (*Rickettsia cornoii*), epidemic typhus (*Rickettsia prowazecki*) or endemic typhus (*Rickettsia mooseri*). In pediculosis capitis (*P. capitis* or head lice), lice almost always affect the scalp and the female leaves its eggs (nits) close to the scalp, where they adhere very tightly to the hair. In pediculosis corporis (*P. humanus*, or body louse), the eggs are deposited in the clothes of infested individuals. The entire body may be affected by excoriations and secondary eczematisation and bacterial infection. Pediculosis pubis (*P. pubis*, or crab louse), is a sexually transmitted form of pediculosis characterised by excoriations in the groin with secondary local infestations with typical blue-grey macules (maculae caeruleae) on the lower trunk and the inner thighs. The diagnosis can be made by microscopic visualisation in a mineral oil preparation of a scalpel scraping or by dermatoscopy.

1.3 Cimicosis

Bites of *C. lectularius* (bedbugs), a 0.5cm flat oval-shaped parasite, are usually painless and appear in a linear pattern on exposed skin. They usually form extremely pruritic, haemorrhagic, indurated and chronic plaques. Parasitic faeces may mark the path of the parasite between the host and the bedding. Treatment of cimicosis consists of the elimination of the source of the bedbugs and symptomatic antipruritic therapy.

1.4 Pulicosis

The human flea (*P. irritans*) is 1 to 3mm in size and is the most common cause of pulicosis in addition to the dog flea (*Ctenocephalides canis*), the cat flea (*Ctenocephalides felis*), the rat flea (*Xenopsylla cheopsis*) and the chicken flea (*Ceratophyllus gallinae*). The infestation is usually obtained in public places (e.g. shopping areas, cinemas) and in pet-owning homes. Painful pruritic urticarial papules with central haemorrhage are found. Pulicosis is treated symptomatically in addition to the elimination of the source by treatment of the infected animal and its surroundings.

2. Treatment of Ectoparasitic Infections

2.1 History

Numerous drugs have proved useful in the topical therapy of scabies and pediculosis. For scabies, lindane and permethrin are the most frequently employed drugs worldwide.[1,2] However, as resistance to these ectoparasites, for example, lindane, permethrin and crotamiton, has increased so has the interest in developing new ectoparasitic drugs.[3-10] In the US and other countries resistance to lindane [γ-hexachlorcyclohexane (γ-HCH)] has been reported in both *S. scabei* and *P. capitis*, *P.*

humanus and *P. pubis*.[1] However, no resistance has been reported so far when lindane is used in combination with benzyl benzoate for both scabies or lice.

Permethrin appears to be the most effective drug in both scabies and pediculosis, with evidence of rare microbial resistance[2] and sufficient (no cross-resistance reported so far) efficacy in lindane-resistant infestations.[6,7,9,11] Most recently, ivermectin, an antiparasitic drug of proven reliability in veterinary medicine and in treating human onchocerciasis, has been shown to be effective in treating scabies and pediculosis.[12,13] All the other agents reviewed in the following sections, such as crotamiton, sulfur, benzyl benzoate, balsam of Peru, organophosphates and organochlorides, and others, appear to be inferior to permethrin, lindane and ivermectin, and are therefore of more historical interest.

In the following sections, each of the anti-ectoparasite agents are discussed, with special regard to dermatopharmacological and dermatotoxicological characteristics, clinical use, adverse effects and other special qualities.

2.2 Topical Therapeutics

2.2.1 Lindane

Lindane is a colourless, crystalline substance and is the only isomer of HCH with insecticidal properties.[14-18] It is named after its discoverer, the chemist van der Linden, who isolated 3 isomers (α, β and γ) of HCH in 1912. In 1935, an HCH isomer mixture was initially patented as an insecticide. Following reports of toxic effects,[17] the use of HCH mixtures (consisting mostly of α- and β-HCH) was prohibited in most parts of the world in the 1970s. Lindane is also forbidden for veterinary use since this compound reaches the ground and water of the surrounding ecosystem. However, in most countries, lindane is still approved for the therapy of ectoparasitic infestations in humans.

A 1% lindane cream was first used for scabies and pediculosis in 1948 by Woolridge,[19] and, for pediculosis, in 1954 by Spühler.[20] Since then, the benefit of this therapy in the treatment of ectoparasitic infections of humans and domestic animals has been confirmed in a large number of publications.[21,22] The broad therapeutic spectrum and the reported clinical efficacy have made lindane a first-line medication. However, the possibility of the development of resistance to this drug has to be kept in mind. One approach to avoid lindane-resistance is to use a formulation containing both lindane and benzyl benzoate, since no reports of resistance to this combination have yet emerged in the literature.

Pharmacokinetics

Lindane is rapidly absorbed from all portals of entry, including the intestine, lung mucosa and other mucous membranes. Transdermal penetration depends on the solvents used and varies from 10% in hydrophilic bases to as much as 90% in lipophilic carriers.[15-17,23-28] After percutaneous absorption, lindane is distributed to all body compartments with highest concentrations occurring in lipid-rich tissue and the skin.[19,26,29,30] It is highly soluble in water and rapidly excreted, with a half-life of 21 to 26 hours.[23,31,32] Compared with other halogenated hydrocarbons, it is much less toxic.[14,26,33]

Xenobiotic metabolising liver enzymes [e.g. cytochrome P450 (CYP) 1A1, CYP2B2, CYP1A2, epoxide hydrolases, glutathion-S-transferases and uracil diphosphate (UDP)-glucuronosyl-transferases] are induced by lindane after topical treatment in rats.[16,34] Induction of liver enzymes in humans following lindane treatment has been reported.[35] The metabolism and secretion of lindane is enhanced by substrates inducing phase I reactions (hydroxylation, dehydrogenation, oxidation) and also phase II reactions (conjugation).[21] In rats and mice, lindane is converted to chlorobenzols and chlorophenols. In humans, mono-, di- and tetrachlorophenols and, to a larger extent, 2,4,6-, 2,3,5- and 2,4,5-trichlorophenols have been identified.[21] No spontaneous or physiological isomerisation between lindane (γ-HCH) and its α- and β-isomers has been documented. This is of great clinical importance since α- and β-HCH are more toxic than lindane, and the elimination half-life of β-HCH is much longer. Metabolites of lindane, such as

glucuronidated and sulfated chlorophenols and other metabolites, are excreted in urine and faeces.

The elimination half-life from rat fat tissues is 7 days for α-HCH, 14 to 28 days for β-HCH and 1 to 2 days for lindane.[36] The elimination half-life for lindane in humans is about 21 to 26 hours.[23,32] β-HCH has the highest bioaccumulation rate and slowest elimination half-life.[37]

Toxicity

The toxic effects of lindane in mammals (mice, rats and humans) resemble those of other pesticides of this group [e.g. dichloro-diphenyl-trichloroethane (DDT)] in causing mainly neurotoxic symptoms.[14,16,20,27] Acute toxicity evaluations found the following lethal dose (LD_{50}) values (mg/kg bodyweight): mouse, 56 to 480; rat, 88 to 300; guinea-pig, 100 to 127; and rabbit, 40 to 200.[14,38-41] Here, oily solvents and concentrated emulsions were much more toxic than dispersions in water.[20] The acute lethal dose LD_{50} of oil-based lindane is 40 to 50 mg/kg bodyweight in dogs.[20] Potentially fatal doses of lindane for humans range from 10 to 20 mg/kg bodyweight. However, much higher amounts have been reported to be tolerated after suicidal oral ingestion (up to 30 mg/kg bodyweight). Although children are generally much more susceptible to toxic substances than adults, some children have survived the ingestion of high amounts of lindane (up to 100 to 300 mg/kg).[23,36,42] Acute LD_{50} are estimated to be 150 to 430 mg/kg bodyweight, equal to about 10 to 30g per person.[39,43]

Toxic symptoms in animals include excitation, hypersalivation, vertigo, muscle spasms, tonic-clonic cramps and unconsciousness.[14,22,38,39,44] Acute lindane intoxication in humans results in central nervous system (CNS) symptoms, such as numbness, motor restlessness, anxiety, tremor, cramps and unconsciousness which can evolve to coma and death by respiratory paralysis and/or circulatory collapse within the first 24 hours after oral ingestion.[21,45-48] Reports concerning the acute toxicity of lindane have been mostly derived from observations made after inadequate use of lindane-containing generics.[49-52] In this situation, it has been emphasised that neurotoxic effects do not occur when the drug is used appropriately.[48,50,52]

The underlying cause of the CNS symptoms is a lindane–induced inhibition of the γ-aminobutyric acid (GABA)–regulated resorption of chloride ions in inhibitory synapses[53-55] by induction of a spontaneous release of acetylcholine and an inhibition of Na^+, K^+, Ca^{2+} and Mg^{2+} adenosine triphosphate (ATP)ases[56-60] and a disturbed monoaminooxidase system in the CNS.[61]

Only 2 studies have evaluated subchronic toxicity according to actual toxicological standards. In the first, a dose of lindane 4 mg/kg of food ingested was tolerated over a 3-month period without any signs of toxicity.[62] In the other study, a dose of 25 mg/kg was equally well tolerated.[63] Pigs have been reported to tolerate up to 80mg of lindane per kg of bodyweight for at least 9 months.[64]

Information regarding the chronic toxicity of lindane has been derived mostly from reports of occupational exposures.[21,42,53,65,66] Lindane toxicity from percutaneous exposure was first reported in 1953.[48,65] Available animal studies of toxicity are of limited value since they were conducted before the adoption of current criteria for toxicity studies.[26]

Although even prolonged exposure to lindane has not been shown to be teratogenic, lindane has been found to be toxic to the mother and fetus in various animal models.[26,49,67-76] Standardised *in vitro* mutagenicity tests of lindane have demonstrated neither mutagenic nor clastogenic effects.[35,77,78] Although comet-assay (single cell microgel electrophoresis) revealed an accumulation of DNA strand breaks indicative of some genotoxic effect, this result may not apply *in vivo*.[79] The carcinogenic potential of lindane was first investigated in the 1950s.[80] Since then, numerous studies have documented the generation of neoplastic foci in the rat liver and an overall increased incidence of hepatic tumours in mice.[39,46,81-89] Not all studies have confirmed this tumourgenicity and genotoxicity, with, for instance, DNA damage being observed in nasal but not gastric mucosal cells.[90] Furthermore, in cul-

tured bovine ovarian tubal and uterine cells exposed to lindance, only a weak inhibition of DNA synthesis was found to occur.[91] Studies with rat and human hepatocytes suggest that α-HCH, rather than lindane, exhibits a significant genotoxic potential.[87,92-96]

Lindane may not affect tumour initiation but may accelerate tumour promotion after systemic administration.[79] This may result from lindane–induced oxidative stress, which has been shown to occur both *in vivo*[97-100] and *in vitro*[97] and manifests in the generation of reactive oxygen species.[26] The α- and β- isomers of HCH appear to be strongly carcinogenic,[26,96] but the International Agency for Research Cancer has classified lindane as merely 'possibly carcinogenic'.[93] Industrial grade HCH, which is 65 to 70% β-HCH, is relatively toxic as β-HCH achieves high concentrations in lipid-rich tissues. The lindane used in medical applications is usually more than 99% pure and contains only trace levels of β-HCH.[26,37]

No symptoms of lindane toxicity have been found in workers in factories producing lindane.[29,30,101] Although 64 workers were found to experience neurological symptoms, these workers were also exposed to benzol, which produces symptoms indistinguishable from those associated with lindane.[102] The World Health Organization (WHO) examined 54 insecticide factory workers and found significantly elevated serum lindane concentrations, cholesterol and phospholipid levels, and a shortened amitriptyline elimination half-life.[26] Other studies of groups with occupational exposure to lindane have produced similar findings.[103,104]

There is some evidence that lindane may affect the course of haematological abnormalities, such as aplastic anaemia, thrombocytopenia and pancytopenia,[105-108] but not all studies have been confirmatory.[40,86,109-111] Specifically, Wang and Grufferman[112] found that workers in an environment polluted with HCH have no increased risk for aplastic anaemia. When anaemia has been linked to lindane exposure, it has usually been reported as occurring via inhalation. Notably, in the US, lindane has historically been used widely in household products for eradicating mosquitoes, and inhalation may also have occurred through this route. The US Department of Agriculture and Environmental Protection Agency has banned home use of lindane-containing products, but this ban is not observed in all states. Morgan et al.,[113] in a review of 46 published cases of lindane-associated anaemias, concluded that 11 cases were linked to lindane evaporation, 18 to HCH sprays, 2 to dog shampoos, 7 to contaminated dust and 1 to contaminated ground, with the aetiology of 7 cases entirely unexplained.

The concentration above which poisoning is considered to have occured, that is, the actual limiting concentrations of α- and β-HCH and lindane in serum, blood and lipid-rich tissue are listed in table I.[23,114,115] The values listed for lipid-rich tissue concentrations are not limits but rather mean values derived from tissue obtained from a sample of 20- to 30-year-old pregnant German women. In embryos and deceased fetuses, HCH concentrations of approximately 0.14 mg/kg of lipid-rich tissue have been found. Mean serum lindane concentrations have been reported to be between 0.5 and 1 μg/L in average populations.[37] In certain populations with significant environmental exposures, serum lindane concentrations of up to 3 μg/L blood have been reported.[37] According to the WHO, the acceptable daily intake for lindane is 0.01 mg/kg/day.[26] This guideline serves as a benchmark for nutrition and food regulation laws.

Efficacy and Tolerability

For ectoparasitic therapy, lindane is well tolerated[145,147,48,116] and available as a 0.3% monopreparation in both gel and shampoo formulations or

Table I. Limiting values of hexachlorcyclohexane (HCH)-isomers in human body compartments/tissues (i.e. concentrations above which poisoning is considered to have occurred)

	Serum (μg/L)	Whole blood (μg/L)	Fatty tissue (μg/L)
α-HCH	0.01		4
β-HCH	0.3		140
Lindane (γ-HCH)	0.1	20	22

in combination with other drugs (emulsion: 10g = 9.9ml, containing 30mg lindane, 2.5g benzyl benzoate, 0.3g methyl-4-hydroxybenzoate, sodium salt).[117] Recommended uses include application for 3 consecutive days for scabies and application of the 1% treatment regimen for pediculosis (personal communication, Federal Institute for Drugs and Medical Products, Germany).[26,35,116] To achieve a 96% clinical cure rate, each lindane application should be followed by a 6-hour incubation period.[4,5,118]

In 1980, reports of toxicities ranging from mild neurological symptoms to death resulted in the creation of criteria to evaluate presumed lindane toxicity.[119,120] Surber and Rufli[48] have concluded that lindane can be used safely as long as treatment instructions are followed strictly by patients and their relatives.

After skin application, a water-resistant depot form of lindane develops on the stratum corneum. 90% of this is absorbed into the skin within 18 hours.[20,121,122] In general, lindane should be applied only on dry skin as taking a bath or shower before use can significantly increase the percutaneous absorption.[123] Lindane does not typically induce irritation. The WHO has noted that allergic reactions manifesting as dermatitis, rhinitis or conjunctivitis can occur.[35] In contrast, a multicentre study did not observe any allergic or irritant reactions.[124,125] The only well described local adverse effect is the 'postscabies dermatitis' induced usually by an inappropriate use of various topical cosmetics after termination of lindane therapy.[126]

The percutaneous absorption of lindane[24,28,49,121,122,127-134] and relative risks of common scabicidic drugs have been extensively investigated.[1,2,22,44,123,135,136] Serum lindane concentrations of individuals not directly exposed to lindane have been found to be as high as 3 ng/L. Lange et al.[129] have made the following observations regarding the percutaneous absorption of lindane after topical application on the entire body of a 0.3% emulsion:[24,129,132-134] in the healthy, untreated population of a German city, mean serum lindane concentration approximated 3 μg/L. Within 3 to 5 hours after topical whole body application with a 0.3% lindane emulsion, the serum lindane concentrations in treated patients increased to approximately 10 ng/L. The rate of absorption of drug could be decreased by showering with soap and water 8 to 12 hours after topical treatment. Washing or bathing too soon led to a sharp reduction in absorption and concomitant reduction in therapeutic effect. After 3 days of therapy over excoriated skin, male patients developed maximum serum lindane concentrations of 425 μg/L, whereas the maximum concentration in healthy volunteers was 9.5 μg/L.

After a single topical application of lindane (1% lindane, 330 to 660 mg/dose), Hosler et al.[137] found healthy adults developed no adverse effects and had maximal plasma lindane concentrations of 4 to 24 μg/L. Remarkably, the modest levels of absorption of lindane recorded in this study were sufficient to induce hepatic enzymes, and hence the metabolism of simultaneously applied antipyrines. These findings have been confirmed by further investigations that revealed a similarly elevated plasma clearance of antipyrines.[2]

After a single topical application of 50g of a 0.3% lindane emulsion, the serum lindane concentrations in adult patients with scabies were 200 ng/L.[24] Four to 8 hours after a single topical application of 1% lindane emulsion, maximum serum concentrations of 7 to 64 μg/L and a serum elimination half-life of 17.9 to 21.4 hours were seen in healthy children.[127,128] The quantity of lindane absorbed was inversely proportional to body surface area and weight, but independent of the applied dose. In further evaluations in children, maximum serum concentrations 2 hours after use of a 1% lindane shampoo were 0.3 to 2.5 μg/L. Four patients were retreated after 5 days, and during this second treatment cycle average lindane concentrations approximated 0.3 μg/L. Peak lindane concentrations 2 to 6 hours after retreatment ranged from 1.7 to 6.1 μg/L.[127,128] Since babies and small children have a relatively high ratio of body surface area to total bodyweight, children may develop a

post-treatment systemic concentration of lindane which is over twice as high as that seen in adults.[48]

When skin is infected or damaged, as in psoriasis, atopic dermatitis or various ichthyoses, the percutaneous absorption of lipophilic substances such as lindane is increased.[2,138] 15 minutes after application of lindane, a 3-year-old child with bullous ichthyosiform erythroderma experienced nausea and vomiting, followed by CNS symptoms 2 hours later.[139] Similar reports led to the Canadian recommendation to avoid the use of lindane on babies and small children.[139]

After topical application of lindane, breastfeeding mothers have developed milk lindane concentrations of 60 times those in untreated women. The low amounts of lindane found in untreated populations apparently derive from exposure to pesticides.[140] However, in contrast with some other antiparasitic drugs, lindane has been associated with minimal maternal and fetal risk when used in pregnancy.[50,52]

Although lindane can accumulate in body tissues during therapy, its rapid elimination following discontinuation of treatment ensures that no significant long term accumulation occurs.[141] No increase in excretion of lindane has been observed in patients on low calorie diets that require endogenous mobilisation of lipid-rich tissues.[142]

In summary, lindane is administered differently in the treatment of scabies and pediculosis.[48] Furthermore, babies and children under 10 years of age being treated for scabies require tailored treatment regimens, and in some countries, such as the US, lindane is generally not used to treat young children. Comparative studies have revealed that lindane may be slightly less effective than permethrin for the treatment of scabies and pediculosis (tables II and III). However, its combination with benzyl benzoate make it a reliable treatment option which can be relatively safely applied. In addition, a recently published study showed that permethrin was not more effective than lindane.[158]

2.2.2 Permethrin

Permethrin, is a synthetic pyrethoid and potent insecticide.[28] Permethrin is soluble in 95% ethanol, ether, acetone, petroleum distillate, other hydrocarbons and most organic solvents; it is weakly soluble in propylene glycol and insoluble in water.[159] Industrial grade permethrin is comprised of equal proportions of the cis and trans isomers.[159] Since the cis isomer is relatively more toxic and slowly secreted, permethrin used in medical applications consists predominantly of the trans isomer. Pyrethrum, the source drug for permethrin, consists of 6 active pyrethins, which are extracted from chrysanthemums and cause neurological paralysis in insects. Permethrin is the only photostable and relatively nontoxic member of this group.[11,118,145,146] From 1979 to 1984, more than 4000 tons of permethrin, mostly for agricultural use, were produced worldwide.[159]

Permethrin is the most expensive topical antiparasitic currently available in the US for the treatment of scabies and lice.[28,160] In Germany, commercially available pyrethrum-containing preparations include solutions of varying concentrations (50ml containing 0.22g permethrin, 100g solution containing 0.3g pyrethrum extract, 50ml solution containing 0.22g permethrin) and a shampoo (100g solution containing 0.3g pyrethrum extract).[117] In the US, permethrin has been available for more than 15 years as a 1% solution for treatment of lice, and for 11 years as a 5% cream for scabies.[2,161]

The toxicity of permethrin has been found to be very low. The Committee on Toxicology of the US National Research Council declared in 1994 that 'although permethrin is highly toxic for insects and other arthropods, it is one of the less toxic insecticides for humans'.[162] In 1990, the WHO noted that while 'no undesired adverse effects could be observed during the use of permethrin in humans over many years, . . . investigations concerning the exposure of humans to this drug should be continued'.[163] Unfortunately, this study evaluated only occupationally exposed individuals and not patients treated with permethrin for scabies or lice. Whereas permethrin is believed to be much less toxic than lindane, no toxicity studies directly comparing the 2 drugs have yet been performed.[135,164]

Table II. Clinical studies of the effectiveness of products to treat scabies

Reference	Treatment	Study design	Time to cure	Comparative effectiveness (cure rate)	Significance	Adverse effects
Haustein & Hlawa[143] (1989)	Lindane *vs* permethrin *vs* benzyl benzoate	Nonblind	3 weeks	Lindane 92%, permethrin 100%, benzyl benzoate 100%	Lindane less effective ($p < 0.025$)	Benzyl benzoate had more immediate (22%) and late (42%) adverse effects
Schulz et al.[144] (1990)	Lindane *vs* permethrin	Multicentre, randomised	1 month	Lindane 86%, permethrin 91%	Equally effective significance not reported	No significant differences in adverse effects
Taplin et al.[145] (1986)	Lindane *vs* permethrin	Randomised	1 month	Lindane 65%, permethrin 91%	Lindane less effective ($p < 0.025$)	None
Taplin et al.[146] (1990)	Permethrin *vs* crotamiton	Randomised	1 month	Permethrin 89%, crotamiton 60%	Crotamiton less effective ($p < 0.025$)	None
Amer & el Gharib[147] (1992)	Lindane *vs* permethrin *vs* crotamiton	Randomised	1 month	Lindane 84%, permethrin 98%, crotamiton 88%	Lindane and crotamiton less effective ($p < 0.025$)	No significant differences in adverse effects
Glaziou et al.[148] (1993)	Ivermectin *vs* benzyl benzoate	Randomised	1 month	Lindane 70%, benzyl benzoate 48%	Significance not reported	Ivermectin dose too low
Alberici et al.[149] (2000)	Ivermectin in otherwise healthy patients *vs* ivermectin in patients with HIV	Nonblind	1 month	Ivermectin in healthy patients 100%, patients with HIV 91%	Significance not reported	No adverse effects
Wolff & Kock[12] (1998)	Ivermectin	Nonblind	1 month	Invermectin 100%	3 patients required a second dose of ivermectin	Increase of liver enzymes in 1 patient
Tausch[150] (1999)	Crotamiton	Multicentre, randomised	1 month	Crotamiton 100%	$p \leq 0.001$	No adverse effects
Chouela et al.[151] (1999)	Ivermectine *vs* lindane	Randomised, prospective, controlled, double-blind	1 month	Ivermectin 96%, lindane 96%	Similar effects of both drugs ($p < 0.02$) equally effective	No significant adverse effects

The risk of experiencing toxic symptoms from an overdose of topical permethrin (5% cream) may be 40 to 400 times lower than the same risk after use of excessive quantities of topical lindane (1% lotion).[28] The toxic effects of permethrin have been reviewed by the Department of Pesticide Regulation of the California Environmental Protection Agency.[165]

Table III
Landscape

Pharmacokinetics

The long term effects of permethrin on humans, unlike those of lindane, have not yet been studied in depth.[1,2,4,145,146,11,118,135,166,167] It has been shown that permethrin and lindane are equally well absorbed across guinea-pig skin. In contrast, lindane absorption on human skin has been found to be 20-fold greater than that of permethrin.[28] After it is percutaneously absorbed, permethrin is rapidly cleaved to inactive metabolites by skin esterases. The metabolites are then promptly excreted in the urine.[28,168-172] After topical application of permethrin, the ratio of cis to trans isomers of permethrin in the skin has been observed to equilibrate to about 2.8. In plasma and brain, this ratio varies from 0.7 to 1.3.[28,173] Some investigators have found post-treatment plasma permethrin concentrations to be undetectable (Estes and Estes,[160] Meinking,[159] Taplin et al.[146]).

Toxicity

The LD_{50} in the rat is 3000 mg/kg,[146,169] while that in humans has been estimated to be 1 to 2 g/kg bodyweight.[2] Only 1 death due to the oral intake of permethrin has been described in the literature.[32]

Therapy

Permethrin should be washed off 8 to 14 hours after topical application to minimise the risk of allergic contact dermatitis. This is particularly important when using formulations containing formaldehyde.[159] Studies comparing topical application of 5% permethrin and 1% lindane have found the former to be a more effective scabicide (91 *vs* 65% healing) [table II].[145] In addition, permethrin has been shown to be more effective than crotamiton (90 *vs* 60%) in treating children (ages 2 months to

Table III. Clinical studies of the effectiveness of products to treat pediculosis

Reference	Treatment	Study design	Time to cure	Comparative effectiveness (cure rate)	Significance	Adverse effects
Brandenburg et al.[152] (1986)	Lindane *vs* permethrin	Randomised	1 week	Lindane 92%, permethrin 99%	Lindane less effective ($p < 0.001$)	Similar mild adverse effects
Taplin et al.[145] (1986)	Permethrin *vs* placebo and lindane comparison group	Randomised, lindane comparison group	1 week	Lindane 67%, permethrin 100%, placebo 9%	Permethrin more effective than placebo ($p < 0.001$)	Similar mild adverse effects
Bowerman et al.[153] (1987)	Lindane *vs* permethrin	Randomised	1 week	Lindane 90%, permethrin 99%	Permethrin more effective ($p < 0.001$)	Similar mild adverse effects
Kalter et al.[154] (1987)	Lindane *vs* permethrin (pediculosis pubis)	Randomised	1 week	Lindane 60%, permethrin 57%	No significant differences	Similar adverse effects
Fusia et al.[155] (1987)	Lindane *vs* pyrethrins	Alternating treatment trial	1 week	Lindane 88%, pyrethrins 95%	No significant differences	None
Carson et al.[156] (1988)	Permethrin *vs* pyrethrins	Randomised	1 week	Permethrin 96%, pyrethrins 45%	No significant differences	None
Di Napoli et al.[157] (1988)	Permethrin *vs* pyrethrins	Randomised	1 week	Permethrin 98%, pyrethrins 85%	No significant differences	More skin problems after treatment failure with permethrin

5 years) with scabies.[146] In another study, 2 overnight treatments with 10 or 20% benzyl benzoate and 5% permethrin were uniformly 100% successful in clearing scabies, whereas 3 nights of treatment with 1% lindane had a treatment failure rate of 8%.[143] In general, the treatment success rate is 90 to 100% with permethrin, 84 to 92% with lindane, 60 to 88% with crotamiton and 76 to 100% for benzoyl benzoate (table II).[7,145,146,143,174,175] In addition, permethrin has been observed to be slightly more effective than lindane for the treatment of pediculosis pubis (table II). Permethrin has also been reported as effective in the treatment of various mites infestations, including cheyletiella.[22,159] However, some cases of resistance to permethrin have been described.[176-178]

For the treatment of scabies in the elderly and the treatment of crusted (Norwegian) scabies, Orkin and Maibach and others recommend the use of permethrin cream.[1,135,179,180] In children younger than 2 months, and in pregnant and breastfeeding women, permethrin should be avoided because of the lack of safety data.[1,135] However, 1 case has been reported of the successful treatment without adverse effects of a 23-day-old infant.[181] For children older than 2 months, several authors have suggested the appropriateness of permethrin treatment.[123,145,146,164,175,182]

In summary, permethrin is a drug of first choice for treatment of scabies and lice. However, the possibility of resistance to the drug has to be considered and post-treatment follow-up examinations are indispensable for the clinician to confirm complete removal of the ectoparasite.

2.2.3 Crotamiton

Crotamiton containing scabicides have been widely used since 1946, when *in vitro* tests demonstrated its effectiveness as an antiparasitic agent.[183] Marketed as an antipruritic and ectoparasitic therapy, the drug is available in Germany as a 10% cream, a 10% gel and a 5% lotion).

Pharmacokinetics

After a single topical application of crotamiton 500mg, plasma concentrations reach 10 μg/L after 30 minutes and peak at 20 μg/L within 1 day, with reapplication on consecutive days not resulting in further increases in plasma concentration.[184]

Toxicity

Crotamiton has an extremely low toxic potential (LD_{50} of the rat after subcutaneous injection is 1630 mg/kg), and no toxic effects have been recorded following multiple applications to large areas and to excoriated skin. In a controlled trial in 1997, crotamiton was found to be well tolerated even on scarified skin.[185] Its low toxicity has ensured crotamiton a role in the treatment of children.[186-188]

Therapy

Several studies have documented the clinical efficacy of crotamiton.[150] Crotamiton has been frequently and effectively employed in the treatment of pediculosis.[187,189] However, for the treatment of scabies, crotamiton is slightly less effective than lindane and substantially inferior to permethrin.[146,147,159,118,174,190,191] Low therapeutic efficacy in children may derive from an insufficiently brief incubation with the drug.[150] Most recently, crotamiton has been shown to be highly effective when applied as a scabicide for 5 consecutive days after bathing and changing clothes. The antipuritic effect of crotamiton also appears to contribute to patient comfort.[150]

In general, crotamiton appears to be significantly effective in the treatment of scabies, a notable antipruritic function, and few potential adverse effects.[184,150,192] Importantly, some cases of scabies have been reported to be crotamiton-resistant.[8] Therefore, lindane, permethrin or ivermectin should be generally preferred.

2.2.4 Sulphur

Sulphur has been used for centuries for the treatment of ectoparasitic infestations. In many parts of the world, topical sulphur is still used as a 5 to 20% precipitate in petrolatum[2] and may have a therapeutic benefit in over 80% of patients.[174] Sulphur, when applied topically for 3 consecutive nights, is well tolerated, with some local irritation reported in 28% of treated patients.[193-195] The applied dose should be washed off completely 24 hours after

application and before the next dose is applied. No systemic adverse effects have been reported.

Toxicity studies have yet to be performed. In Germany, preliminary investigations led to concerns that have resulted in the denial of approval for the use of sulphur as a scabicide. In addition, claims that sulphur may have an antipruritic effect have not been substantiated. Orkin and Maibach[44] recommends a less concentrated 6% sulphur precipitate in petrolatum for use in children, infants, and pregnant and breastfeeding women.[44,195]

Since lindane, permethrin and also ivermectin appear to be superior to sulphur in the treatment of ectoparasitic infections, the latter should be used only in situations where the patient can not tolerate any of these agents. Another point is that although sulphur may be quite effective, its use is extremely messy and smelly and consequently not well liked by patients.

2.2.5 Benzyl Benzoate

Benzyl benzoate, an ester of benzoic acid and benzyl alcohol, is one of the active ingredients in balsam of Peru.[196] Benzyl benzoate has been used as an insecticide and preservative since the 1940s.[197] As a preservative, it has been included in both perfumes and food.[198,199] In the US, benzyl benzoate has historically been dispensed as a 10 to 25% lotion, which is applied topically for 3 consecutive days. In Germany, currently available preparations are 10 and 25% solutions, as well as a foam (300g foam contains 7.2g benzyl benzoate) and a powder.[8] However, gel and emulsion formulations of benzyl benzoate in combination with lindane are also available in Germany.

When used as a scabicide, the drug is commonly applied topically after bathing for 2 consecutive days. A 5 to 10% solution is recommended for paediatric populations, and a 25% formulation for adults. However, the drug has more recently been largely replaced by permethrin and lindane as a first-line treatment for scabies and pediculosis.[2]

Pharmacokinetics

Benzyl benzoate is minimally absorbed into the skin.[200,201] The drug that is percutaneously absorbed is then hydrolysed to benzoyl alcohol. Benzoyl alcohol is further oxidised to benzoic acid and renally eliminated as hippuric acid after conjugation with glycine.[202,203]

Toxcity

In general, benzyl benzoate is reported to have very low acute toxicity.[197,203] Exceptions are cats, which are extremely sensitive to it presumably due to a species specific metabolic pathway producing toxic metabolites.[204] The relevant differences between human and cat metabolism have not been characterised.[201]

Adverse Effects

In humans, local irritation, the risk of which has been found to be independent of the drug concentration, is the most frequent adverse effect of benzyl benzoate. Irritation is more likely to occur with benzyl benzoate than with permethrin.[143] Allergic contact dermatitis has also been described with benzyl benzoate.[205] Contact with mucous membranes must be strictly avoided.

No teratogenic or mutagenic effects have been reported. Studies of the carcinogenic potential of benzyl benzoate have revealed that it may have tumour promoter activity,[205] but no such effects have been reported in humans. Use of benzyl benzoate is forbidden in infants, children, and pregnant and breastfeeding women since paediatric use has been associated with neurological and CNS symptoms.

Therapy

Since only limited pharmacological and toxicological data are available and the drug has significant allergenic potential, benzyl benzoate is not recommendable for routine use as a single ectoparasitic agent. However, when applied in combination with lindane, none of these concerns have so far been confirmed. In addition, no cases of resistance to the benyl benzoate/lindane combination have been reported, suggesting that the combination may be superior to monotherapy with lindane or permethrin.

2.2.6 Balsam of Peru

The active ingredients of this complex mixture are benzyl cinnamon ether and benzyl benzoate.[2]

The use of balsam of Peru for scabies treatment was initially described in France. Treatment entails topical application, which has been known to cause contact dermatitis. Nephrotoxicity can result from the treatment of large areas. Unfortunately, the relationship between dose and toxicity is not well described.[206] Furthermore, studies have not been conducted to compare the relative efficacy of treatment with balsam of Peru and treatment with other anti-scabies drugs. Accordingly, no data concerning resistance to balsam of Peru are known. It may be speculated that resistance profiles are similar to that of benzyl benzoate. Finally, results from studies with lindane, permethrin and ivermectin suggest that balsam of Peru is not required as an anti-ectoparasite therapy.

2.2.7 Organophosphates and Organochlorides

Malathion

Malathion is an organophosphate insecticide of relatively low toxicity which irreversibly blocks the enzyme acetylcholine esterase. Malathion has been used successfully in the treatment of pediculosis capitis.[207] No studies are available regarding its use in scabies. However, because of the potential for severe adverse effects, malathion is not recommended for treatment of human ectoparasite infections.

Dichloro-Diphenyl-Trichloroethane

Dichloro-diphenyl-trichloroethane (DDT), an organochloride insecticide, is quickly absorbed after topical administration in nonpolar solvents. A 6% solution of DDT in alcohol was first used in 1946 for scabies therapy in France.[2] In the US, use has been prohibited since 1972 because of reports of severe toxicities. DDT has been shown to cause dose-dependent haematological, myocardial, renal and CNS adverse effects, which may be life-threatening. Long term use results in tissue accumulation that can culminate in toxic hepatitis. Consequently, DDT is no longer believed to be appropriate for use in humans.

2.2.8 Other Agents

Nitrofurazone

When used as a 0.2% solution for 3 consecutive nights, nitorfuazone has been shown to clear scabies in 70% of patients.[117,174] However, nitrofurazone is not approved for treatment of scabies.

Hexachlorophene

The use of hexachlorophene in scabies has been described but no evidence is available concerning its efficacy. It is not approved for scabies treatment in Germany.[117,208]

Mesulfen

Mesulfen has been tested as a scabicide in Italy,[209] where it was successfully used to treat 10 newborns with scabies. In another study, all patients responded well to a 3- to 9-day regimen employing 50% mesulfen in a spray formulation.[117,210]

Allethrin

No ectoparasitic resistance has yet been described to allethrin. Several formulations are available in Germany.[117]

White Vinegar

White vinegar is a home remedy used to wash off nits in pediculosis capitis.[211]

Formic Acid

An 8% solution of formic acid can be used for the removal of nits but has not been approved for this indication.[212]

2.3 Oral Therapeutics

2.3.1 Ivermectin

The avermectins were discovered at the Kitasato Institute (Tokyo, Japan) and the Merck Institute (Rahway, NJ, USA) during the search for anti-helminthic drugs.[213] Avermectin B1 (abamectin) can be further modified to ivermectin, a substituted avermectin derivative, which is a macrocyclic lactone molecule (22,23-dihidroavermectin) with some similarity to macrolide antibacterials. Ivermectin itself has no antibacterial properties, but does act against various insects, nematodes, filaria and ascarides with animal and

human hosts.[111,213,214] In veterinary medicine, ivermectin is used topically and orally as an antiparasite agent.[12]

Ivermectin has been approved for the treatment of onchocerciasis (*Onchocerca volvulus*) and is believed to act by paralysing the muscles and eyes of the microfilaria.[12,214,215] More than 6 million people in over 30 countries have already been treated with ivermectin for onchocerciasis.[216] Ivermectin has also been found to be effective for the treatment and prophylaxis of infections with *Loa loa* and *Wucheria bancrofti*,[215,217,218] scabies[12,191,148,219-222] and human cutaneous larva migrans ('creeping eruption').[221] In France and the US, ivermectin has been approved since 1997 for the treatment of onchocerciasis and strongyloidiasis, but although the drug is approved for anti-ectoparasitic therapy in veterinary medicine in Germany, it is not yet approved for treatment of scabies in humans.[222]

The use of ivermectin is prohibited in pregnant and breastfeeding women, children younger than 5 years (no data are available for use in children with a bodyweight lower than 15kg), and patients with impairment of the blood-brain barrier.[221,223] Commercially, ivermectin is available as 6mg tablet. Two tablets (0.15 to 0.2 mg/kg bodyweight) are usually taken as a single dose.

Ivermectin acts by blocking the release of GABA from peripheral muscle synapses.[224] Ivermectin may also paralyse muscles by modulating ion pumps (glutamate-dependent chloride ion channels in nerves and muscles of invertebrates).[220] In humans, ivermectin does not cross intact blood-brain barriers.[221,224]

Pharmacokinetics

Ivermectin is rapidly absorbed enterally and reaches maximum therapeutic concentrations within 4 hours of ingestion.[225] Intestinal absorption is improved if ivermectin is taken 2 hours before meals. Peak plasma concentrations are proportional to the dose delivered. Ivermectin and its metabolites are excreted mostly through the faeces, with less than 1% of drug renally eliminated. The plasma half-life is 12 hours for the drug and 3 days for its metabolites.[223]

Toxicity

The toxic effects of ivermectin after a single oral dose for scabies treatment appear to be insignificant.[12] Repeated treatments have also been tolerated without adverse effects.[12,191,220] Prospective studies of toxicities in children younger than 5 years (less than 15kg bodyweight) are planned.[12] One author has claimed a link between ivermectin use and mortality in selected patients.[226] However, since all the reported deaths occurred in elderly and otherwise sick patients as much as 6 months after treatment with ivermectin, the link between drug use and mortality remains speculative. Others have not substantiated this speculation.[227]

Adverse Effects

Adverse effects that have been associated with ivermectin include fever, pruritus, lymph node enlargement and arthralgia. Whether these symptoms are directly related to drug action or secondary to destruction of the filaria remains unclear.[12]

Therapy

In a recent study, 20 patients with scabies were treated with ivermectin 0.2 mg/kg in a single oral dose. 17 were cured (table II),[12] and the remaining 3 experienced recurrence within 4 weeks. Two of the patients lived with large families, the members of which were not treated simultaneously. In the nonresponders (presumably reinfestations), a second administration of ivermectin resulted in clinical cure. No adverse effects of ivermectin use were observed in this study. Another study compared ivermectin (0.1 mg/kg bodyweight) with benzyl benzoate for the treatment of scabies (table II). Treatment was successful in 70% of the patients who received ivermectin and 48% who received benzyl benzoate.[148] Other studies have confirmed the scabicidic efficacy of ivermectin.[219,228,229]

To assess the usefulness of ivermectin in immunocompromised patients, Meinking et al.[191] treated 22 patients with scabies with ivermectin 0.2 mg/kg, of whom 11 were HIV positive (7 with AIDS). All patients, including those with HIV and AIDS, responded well and without adverse effects. Ivermectin has similarly been used successfully for

the treatment of severe, crusted ('Norwegian') scabies.[230] In a recent study, Taplin and Meinking[231] have recommended the combined use of ivermectin and 5% permethrin cream to improve the cure rate in patients with crusted scabies. The optimal dose of ivermectin for any type of scabies appears to be 0.2 mg/kg.[12,191,230] Lawrence et al.[232] and Meinking et al.[191] have strongly encouraged the formal approval of ivermectin for scabies treatment in humans.

2.3.2 Thiabendazole

Thiabendazole is widely used for the treatment of ectoparasitic infestations and endoparasites in South America but rarely in the US.[2] The drug is primarily administered for the treatment of larva migrans (*Ancylostoma brasiliense*) but has also been used successfully for scabies.[3]

Adverse effects include nausea, vomiting, haemolytic anaemia, leucopenia and other haematological problems. Also, occurrence of erythema multiforme and Stevens-Johnson syndrome have been reported.[194]

Thiabendazole, as a 5% cream formulation, can be used for treatment-resistant scabies. A 10% suspension has been shown to achieve an 80% cure rate after a single topical application.[3] Oral administration of 10 to 25 mg/kg for 10 days also has been found to be effective.[233]

2.3.3 Flubendazole

Only 1 study has been conducted to evaluate the usefulness of flubendazole for scabies. The 9 patients involved were treated with an oral dose of 25 mg/kg, and the drug effectively mitigated pruritus without adverse effects. Unfortunately, flubendazole was not successful in clearing the scabies.[233]

3. Conclusions and Future Perspectives

There is an increasing worldwide incidence of ectoparasitic infections such as scabies, pediculosis and pulicosis.[48] In addition, reports on increasing rates of resistance to commonly used scabicidics have become a major issue in the dermatological press. Therefore, this review has aimed to analyse and compare the pharmacological and clinical features of the currently available drugs.

Of the topically applied medications used for scabies, permethrin (5%) and lindane (0.3 or 1%, alone or in combination with benzyl benzoate) have been found to be the most effective agents. Of these, permethrin appears to be the superior agent since resistance to lindane has been reported more frequently than to permethrin. However, a review of the treatment of scabies performed by Walker and Johnstone[158] indicates that the evidence that permethrin is more effective than lindane is inconsistent. Although adverse effects associated with lindane have been frequently mentioned in the literature, in a large trial comparing the use of lindane, permethrin and pyrethroides for the treatment of pediculoses no adverse effects were associated with lindane use.[161]

For the treatment of pediculosis, lindane (1%) and permethrin (1%) are the most effective agents.[234,235] Here, a variety of reports on resistance exist.[176,236-238] It has been suggested that recommendations concerning the drug of choice should depend on the local resistance patterns rather than on other literature remarks.[236] However, the pyrethroid susceptibility (and that for all other drugs) of head lice remains poorly defined in the US as well as in all other countries.[239]

Patients receiving treatment for ectoparasitic infections must be adequately instructed on the use of the medications that are prescribed. Importantly, all family members or other close contacts of a patient should also be examined and treated in the case of suspicious skin manifestations. In patients with excoriated or damaged skin, doses must be adjusted to compensate for increased absorption of topical agents.[238,240] Since scabies mites die within 4 days of being removed from a host, materials that cannot be washed should be stored in a sealed space for 7 days to ensure that all the mites are dead.[205,241] Patients should be informed that post-treatment pruritus can persist for weeks after the eradication of scabies mites.[242] Pruritus can be controlled by the judicious use of oral antihistamines and topical corticosteroids. Two to 4 weeks

after treatment with a scabicide, the skin should be examined to confirm that clinical cure has been achieved.

Pharmacological efficacy and expense must both be considered when selecting an antiparasitic agent. To a considerable extent, the law of the land dictates prescribing patterns. In the US, physicians can choose from among lindane, permethrin and ivermectin; in the UK, permethrin has replaced lindane, which is no longer available; and in Germany, lindane appears to be the drug of choice because of its long-standing record of efficacy and its recommendation by the German pharmaceutical board. A very recent German study recommended the use of permethrin especially in children, pregnant and breast-feeding women with scabies. Ivermectin was recommended only for crusted (Norwegian) scabies.[243] A systematic review of the toxic effects of the topical treatments available for scabies is needed to compare their relative toxicity.[244] Notwithstanding regional and national preferences, permethrin appears to be the most effective and least toxic drug. Except for ivermectin, most of the other drugs in this review are of historical interest and no longer recommended or in widespread use. Ivermectin appears to be a promising drug, and its role in the treatment of ectoparasitic infections will probably be clarified as more study data become available.[151,245]

Finally, it has to be noted that most recent studies revealed evidence that the importance of benzyl benzoate may need be re-evaluated since it has been found to be effective in permethrin-resistant Norwegian scabies,[246] and in combination with ivermectin in patients with relapses after single treatment with ivermectin.[149] Another study demonstrated benzyl benzoate to be as effective as lindane and ivermectin in the treatment of scabies.[247] In conclusion, more research is needed to evaluate the safety and efficacy of scabicidic drugs especially with regard to the rising frequency of resistance.

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