Pediculicides and Scabicides
Drug Class Review

Benzyl alcohol
Crotamiton
Ivermectin
Lindane
Malathion
Permethrin
Piperonyl butoxide and Pyethrins
Spinosad

Final Report
January 2014

Review prepared by:
Melissa Archer, PharmD, Clinical Pharmacist
Carin Steinvoort, PharmD, Clinical Pharmacist
Bryan Larson, PharmD, BCPS, Clinical Pharmacist
Gary Oderda, PharmD, MPH, Professor

University of Utah College of Pharmacy
Copyright © 2014 by University of Utah College of Pharmacy
Salt Lake City, Utah. All rights reserved.

Table of Contents

Executive Summary 3

Introduction 4

Disease Overview 4

Scabies 4

Lice 5

Table 1. Comparison of the Pediculicides and Scabicides 6

Mechanism of Action 9

Table 2. Pharmacokinetic and pharmacodynamics of the Pediculicides and Scabicides 11

Methods 13

Clinical Efficacy 13

Adverse Drug Reactions 15

Table 3. Adverse Events Reported with the Pediculicide and Scabicide Agents 16

Summary 17

Evidence Table. Clinical Trials Evaluating the Pediculisides and Scabicides 20

References 18

Executive Summary

Introduction: Eight pediculicide and scabicide agents are currently available for use in the United States and are indicated in the treatment of lice and scabies infestations. The topical agents are available as creams, gels, lotions, rinses, solutions and shampoos. One oral agent is available for use: ivermectin. Each of the agents have varying potencies and rates of skin penetration and, subsequently, different administration regimens.

Infestations with ectoparasites, like lice and scabies, are common throughout the world and can have a significant impact on public health. Symptoms associated with an ectoparasite infection include disabling pruritus, secondary infection, and transmission of life-threatening diseases. Worldwide, scabies affects nearly 300 million people. In the US, lice infestations occur in approximately 6-12 million children each year. The pediculicide and scabicide agents work by inducing neurotoxicity in lice and scabies, resulting in paralysis and death. Benzyl alcohol is the only agent that affects the respiratory system of lice and scabies and results in asphyxiation rather than neurotoxicity. In general, the agents are safe and effective but may be associated with ectoparasite resistance or neurotoxicity in humans if used incorrectly.

Clinical Efficacy: One systematic review and twelve randomized controlled trials were included for evaluation of the pediculicide and scabicide agents. Six of the studies evaluated the agents in the treatment of lice and seven of the studies evaluated the agents in the treatment of scabies. The majority of the available clinical evidence evaluating treatments for lice infestation compares topical malathion lotion, topical permethrin cream and topical/oral ivermectin formulations. Overall, the evidence suggests similar rates of cure between the agents. Higher eradication rates were reported with malathion and ivermectin therapy compared to treatment with permethrin. The majority of the available clinical evidence evaluating treatments for scabies infestations compares topical permethrin cream to oral or topical ivermectin therapy. Similar rates of cure were reported between the agents at the end of the treatment periods but the evidence suggests topical permethrin and ivermectin have quicker onsets of action and induction of cure than oral ivermectin. No differences in adverse events were reported between any of the agents in clinical trials.

Adverse Drug Reactions: The most common adverse events reported with the pediculicide and scabicide agents are local reactions (burning, itching, erythema). In general, the topical agents are not systemically absorbed and are not associated with neurotoxic adverse events in humans. No serious adverse events have been reported with permethrin, ivermectin, benzyl alcohol, crotamiton and spinosad. Malathion is contraindicated in neonates and infants and is flammable. Lindane is the only agent with a black box warning for risk of severe neurologic toxicities and is contraindicated in patients with uncontrolled seizure disorders and in premature infants.

Summary: Overall, selection of a pediculicide and scabicide agent and preparation should be based on both patient-related and drug-related factors including age of the patient, location of infestation and the presence or absence of other complicating factors.

Introduction

Pediculicidal and scabicidal agents are indicated in the treatment of lice and scabies infestations. Currently, seven pediculicidal agents (benzyl alcohol, ivermectin, lindane, malathion, permethrin, piperonyl butoxide/pyethrins, spinosad) and three scabicidal agents (crotamiton, lindane, permethrin) are available for use in the United States.[1, 2] See Table 1 for a comparison of all the available agents. The majority of the agents are available in topical formulations. Ivermectin is the only oral treatment available for the treatment of a louse infestation. Oral ivermectin is not currently approved for use in scabies by the United States Food and Drug Administration (FDA) but may be considered an effective treatment option. Many of the pediculicide agents are available over the counter and all of the scabicide agents are only available by prescription.

Disease Overview

Infestations with ectoparasites, like lice and scabies, are common throughout the world and can have a significant impact on public health.[3] Concerning symptoms associated with an ectoparasite infection include disabling pruritus, secondary infection, and transmission of life-threatening diseases. In the United States, more people die each year from ectoparasite stings than from the bites of poisonous snakes. Worldwide, scabies affects nearly 300 million people and, in the US, lice infestations occur in approximately 6-12 million children each year. Ectoparasites infections may occur more frequently in patients who are institutionalized or immunocompromised but people of all ages, genders and races can be affected. Ectoparasites derive nourishment and shelter from the skin or hair of other animals. They may penetrate the skin or attach superficially with their teeth or claws. In either case, ectoparasites prompt a hypersensitivity reaction and severe pruritus in their host.[3]

Scabies

Sarcoptes scabiei, or scabies, are named the human itch mite and are the most common cause of itching dermatosis.[3] The itching and rash seen with a scabies infection result from burrowing of the skin by a mite and development of subsequent hypersensitivity reaction. The initial infestation can remain asymptomatic for up to 4-6 weeks while a reinfestation will elicit an immediate sensitization reaction and pruritus. Transmission occurs primarily by intimate interaction (i.e. crowding, multiple sexual partners). Without host contact, the mites die within a day and transmission via contaminated bedding or clothing is rare. Host immunity and scratching at the site of infection serve to limit most infestations (<15 mites/person). Hyperinfestation (1000+ mites/person), also termed crusted scabies or Norwegian scabies, may occur in patients with glucocorticoid use, with immunodeficiency, or with a neurologic illness which limits scratching.[3]

Treatment of a scabies infection may include use of both a scabicidal agent and an antipruritic.[3] Scabicides are applied and massaged onto skin of the entire body from the neck to the toes and are washed off after eight hours with soap and water. Permethrin may be less toxic than lindane and are effective against lindane-resistant infestations. Treatment of crusted scabies

requires use of a keratolytic agent such as 6% salicylic acid and a scabicidal agent. Ivermectin is not currently approved for use in scabies by the U.S. Food and Drug Administration (FDA) but a single oral dose, or two oral doses separated by 1-2 weeks in crusted scabies, may be effective. Successfully treated scabies infections are noninfectious within a day but the itching and rash may persist for weeks to months. Re-treatment with topical agents is often unnecessary and may worsen pruritus and contact dermatitis. Antihistamines, salicylates, and calamine lotion may be used to reduce pruritus. Topical glucocorticoids should only be used after successful treatment of the infection for lingering itching. Bedding and clothing are effectively treated by heating in a clothes dryer at 55°C (131°F) for 30 min or by heat-pressing.[3]

Lice

Louse infestation, or lice, is divided into three types Pediculus humanus capitis (head louse), Pediculus humanus corporis (body louse, clothes louse), or Pthirus pubis ("crab" louse, pubic louse).[3] Transmission of head lice occurs by direct head-to-head contact and infestations are usually asymptomatic but may be associated with itching. All lice attach their eggs to hair or clothing and the nymph hatches approximately ten days later but the empty egg, or nit, may remain attached for months. Without host contact, head lice die in about a day and transmission via contaminated articles is rare. Body lice attach to clothing except when feeding and transmission occurs via direct contact or by sharing of clothing and bedding. If separated from their host, body lice die within about two days. Body lice infestations are found most commonly in disaster victims or indigent people who are in close contact with other infested individuals. Body lice are vectors for transmission of louse-borne typhus, relapsing fever and trench fever. Pruritic lesions from body lice bites are common and chronic infestations may result in a post-inflammatory skin reaction termed vagabonds' disease. Pubic lice is transmitted primarily by sexual contact but may be transmitted by close nonsexual contact. Without a host, pubic lice die within 1-2 days. Intensely pruritic lesions from pubic lice bites are common.[3]

Treatment of a lice infection may include use of a pediculicide agent, an antipruritic, and the mechanical removal of lice and their eggs.[3] In general, treatment of lice is recommended if live lice are discovered; presence of nits alone is only evidence of former infestation. Treatment of an active head or pubic lice infestation requires topical application of a pediculicide agent mechanical removal and, potentially, a second application 7-10 days later. Mechanical removal of lice and eggs by a fine-toothed comb without topical treatment usually fails to eliminate infestations. Resistance to the most commonly used agents (permethrin, lindane) has been reported and newer pediculicides containing benzyl alcohol, dimethicone, or spinosad are available. The American Academy of Pediatrics[4] recommends permethrin 1% or pyrethrins as first line treatment options for head lice when resistance is not suspected. These agents are available over-the-counter and can be initiated without a prescription. Malathion may be used in people who are 24 months of age or older when resistance to permethrin or pyrethrins is documented or when there is a treatment failure. Other treatments can be considered for people who cannot tolerate these agents or who do not prefer to use a pediculicide. Body lice are treated by bathing and changing clothes. Application of topical pediculicides from head to toe may be required for some patients. Bedding and clothing should be washed and/or heat-pressed.[3]

Table 1. Comparison of the Pediculicides and Scabicides[1, 2]

Topical Agent	Dosage Form	Indications	Dosing Recommendations	Generic Availability
Benzyl alcohol (Ulesfia; Zilactin [OTC])	Zilactin [OTC]: Mouth/Throat Gel; 10% [contains propylene glycol, sd alcohol] Ulesfia: Lotion; 5% [contains polysorbate 80, trolamine (triethanolamine)]	Gel: Temporary relief of pain caused by cold sores/fever blisters (FDA approved in ages ≥2 years and adults) Lotion: Treatment of head lice infestation (FDA approved in ages ≥6 months and adults)	Gel: Moisten cotton swab with several drops of liquid; apply to affected area up to 4 times/day; do not use for more than 7 days Lotion: Apply to dry hair, saturate completely, leave on for 10 minutes, rinse thoroughly with water; repeat in 7 days. Hair length 0-2 inches: 4-6 oz Hair length 2-4 inches: 6-8 oz Hair length 4-8 inches: 8-12 oz Hair length 8-16 inches: 12-24 oz Hair length 16-22 inches: 24-32 oz Hair length >22 inches: 32-48 oz	No
Crotamiton (Eurax)	Cream: 10% (60 g) Lotion: 10% (60 g, 454 g)	Treatment of scabies (Sarcoptes scabiei) and symptomatic treatment of pruritus Not approved for use in pediatric patients	Wash thoroughly, towel dry, then apply a thin layer and massage drug onto skin of the entire body from the neck to the toes. Repeat application in 24 hours. Take a cleansing bath 48 hours after the final application. May repeat in 7-10 days if needed	No
Ivermectin (Sklice; Stromectol)	Sklice: Lotion, 0.5% (117 g) Stromectol: Oral Tablet, 3 mg	Lotion: Topical treatment of head lice (Pediculus capitis) infestation Tablet: Treatment of Strongyloidiasis of the intestinal tract due to the nematode parasite Strongyloides stercoralis; Onchocerciasis due to the immature form of the nematode parasite Onchocerca volvulus	Lotion: Apply sufficient amount (up to 1 tube) to completely cover dry scalp and hair; for single-dose use only; Children ≥6 months Tablet: Take as a single dose or repeated dose- depending on infection; Children ≥15 kg	No

Lindane	Lotion: 1% (60 mL) Shampoo: 1% (60 mL)	Lotion: Treatment of Sarcoptes scabiei (scabies) Shampoo: Treatment of Pediculus capitis (head lice) and Phthirus pubis (crab lice)	Scabies: Apply thin layer from neck to toes; after 8-12 hours, bathe and remove the drug. Do not retreat. Do not leave on for more than 12 hours. Head lice, crab lice: Apply to dry hair for 4 minutes; add small quantities of water to hair until lather forms, then rinse hair thoroughly and comb with a fine tooth comb to remove nits. Do not retreat. *Contraindicated in premature infants **Use with caution in infants, small children, the elderly, and patients weighing <50 kg	Yes
Malathion (Ovide)	Lotion: 0.5% (59 mL) [contains isopropyl alcohol]	Topical treatment of Pediculus capitis (head lice and their ova) in Adults and Children ≥6 years	Apply sufficient amount to cover and thoroughly moisten dry hair and scalp; shampoo after 8-12 hours. If required, repeat with second application in 7-9 days. *Use is contraindicated in neonates and infants.	Yes
Permethrin (Acticin; Elimite)	Cream: 5% (60 g) [may contain formaldehyde solution] Lotion: 1% (59 mL)	Single-application treatment of infestation with Pediculus humanus capitis (head louse) and its nits or Sarcoptes scabiei (scabies); indicated for prophylactic use during epidemics of lice	Head lice: Wash hair with shampoo, towel dry, apply cream rinse to saturate hair, scalp, behind ears and at base of neck; leave on hair for 10 minutes; remove nits. May repeat in 1 week. In resistance, apply to clean, dry hair and leave on overnight (8-14 hours) under a shower cap. Scabies: Apply cream from head to toe; leave on for 8-14 hours before washing off with water; may reapply in 1 week FDA-approved for use in children ≥2 months of age.	Yes
Piperonyl butoxide and Pyethrins [OTC] (Pronto, RID, others)	Shampoo A-200 Lice Treatment Kit: Pyrethrins/piperonyl butoxide and Permethrin spray 0.5% Licide Pronto Complete Lice Removal System: Pyrethrins/piperonyl butoxide and Benzalkonium chloride	Treatment of Pediculus humanus infestations (head lice, body lice, pubic lice, and their eggs)	Apply to completely wet infested area, soak for 10 minutes, wash and rinse with large amounts of warm water, use fine-toothed comb to remove lice and eggs from hair. Treatment may be repeated if necessary once in a 24-hour period and in 7-10 days to kill newly hatched lice. FDA-approved for use in children ≥4 years of age.	No

	[antiseptic] Pronto Plus Lice Killing Mousse Shampoo Plus Natural Extracts and Oils Pronto® Plus Lice Killing Mousse Shampoo Plus Vitamin E RID® Maximum Strength Oil Pronto Plus Warm Oil Treatment and Conditioner			
Spinosad (Natroba)	External Suspension: 0.9% (120 mL) [contains benzyl alcohol, cetearyl alcohol, fd&c yellow #6 (sunset yellow), isopropyl alcohol, propylene glycol]	Topical treatment of head lice (Pediculosis capitis) infestation in adults and children ≥4 years of age Unlabeled Use: Topical treatment of head lice (Pediculosis capitis) infestation in children ≥6 months and <4 years of age	Apply to cover dry scalp and hair; repeat with second application in 7 days if needed	Yes

Mechanism of Action

The pediculicide and scabicide agents are neurotoxic in lice and scabies, resulting in paralysis and death.[1-3] Benzyl alcohol is the only agent that affects the respiratory system of lice and scabies and results in asphyxiation rather than neurotoxicity. The neurotoxic agents require an intact nervous system to be effective. A second application is often required as newborn larvae do not have an intact nervous system for several days after hatching. Benzyl alcohol is not ovicidal and may also require a repeat treatment. Lindane is not ovicidal but is neurotoxic in humans and a second treatment is generally not recommended. Malathion is both pediculicidal and ovicidal but must be remain on the hair and skin for up to 12 hours and is highly flammable. Spinosad is not ovicidal but is not metabolized and is still effective days later when the nervous system of newborn larvae develops.[1-3] See Table 2 for a summary of the pharmacologic features of the pediculicide and scabicide agents.

Permethrin interferes with the sodium channels of insects, resulting in neurotoxicity and paralysis.[1, 2] Mutations in the sodium transport proteins have been associated with resistance. Permethrin is similar to the natural insecticide found within the flower species *Chrysanthemum cinerariifolium*. Many over-the-counter (OTC) topical permethrin formulations are currently available for the treatment of lice and a prescription-strength 5% cream formulation is available for the treatment of scabies. Permethrin may be used in children aged 2 months and up.

Pyrethrins + piperonyl butoxide has a similar mechanism of action as permethrin with the additional action of piperonyl butoxide as a synergist and is available in many over-the-counter topical formulations; including lotions, gels, shampoos, and mousses.[1, 2]

Lindane is an organic chloride compound which over stimulates the nervous system and leads to insect paralysis.[1, 2] Lindane has been used as a commercial insecticide and several cases of neurotoxicity in humans have been reported. Lindane is recommended as second-line treatment and should be limited to a single application.

Malathion is an organic phosphate compound which binds to acetylcholinesterase and results in paralysis and death.[1, 2] Malathion is metabolized rapidly by human plasma carboxylesterases resulting in selective toxicity in arthropods and a low potential for toxicity in man. However, it is only available in a lotion containing alcohol and is flammable. Malathion is indicated in the treatment of lice in children aged 6 years and older.

Benzyl alcohol inhibits the closing of respiratory spiracles in insects which causes obstruction of the spiracles and subsequent asphyxiation.[1, 2] The unique mechanism of action is less likely to be associated with resistance.

Ivermectin is the only oral medication used in the treatment of scabies and lice.[1, 2] Ivermectin binds to chloride channels in invertebrate nerve cells resulting in hyperpolarization and

death. Ivermectin is indicated in the treatment of onchocerciasis and strongyloidiasis but is used off-label in the treatment of scabies.

Spinosad has a novel mechanism of action compared to come of the other neurotoxic agents in this class. Spinosad targets nicotinic acetylcholine receptors in the nervous system leading to disruption of acetylcholine neurotransmission, hyperexcitation and death. Spinosad has secondary effects as a ɣ-amino-butyric acid (GABA) neurotransmitter agonist. Resistance has not yet been reported with spinosad use.

Crotamiton is a scabicidal agent with a mechanism of action which is not fully known.[1, 2] Crotamiton is recommended for use in patients with contraindications for lindane or permethrin.

Table 2. Pharmacokinetic and pharmacodynamics of the Pediculicides and Scabicides[1, 2]

Agents	Mechanism	Route	Systemic Absorption	Other Notes
Benzyl alcohol	Inhibits closing of respiratory spiracles and causes obstruction of the spiracles and asphyxiation.	Topical	Following prolonged application (30 mins), serum concentrations were detectable (≤3 mcg/mL) at 30 and 60 mins post exposure in patients 6 months to 11 years of age.	Unique mechanism of action; less likely to be associated with resistance
Crotamiton	Unknown	Topical	After topical application, crotamiton is absorbed systemically; 30 minutes after topical application of 500 mg, plasma concentrations exceeded 10 ng/ml and remained between 10 and 20 ng/ml for the following 24 h. The drug rapidly penetrates intact human skin and remains there for at least 24 hours.	Elimination half-life: 30.9 hours Excreted in urine: 4.8-8.8%
Ivermectin	An anthelminthic agent; binds selectively and with strong affinity to glutamate-gated chloride ion channels in invertebrate nerve and muscle cells resulting in increased permeability of cell membranes, hyperpolarization of the nerve or muscle cell, and death.	Oral; Topical	Oral: Bioavailability- Increased with high-fat meal.	Distribution: Vd: 3-3.5 L/kg; does not cross blood-brain barrier Protein binding: ~93% Metabolism: Hepatic via CYP3A4 (major), CYP2D6 (minor), CYP2E1 (minor) Half-life elimination: ~18 hours Time to peak, serum: ~4 hours Excretion: Feces; urine (<1%)
Lindane	Causes hyperstimulation of nervous system resulting in seizures and death of parasitic arthropods.	Topical	Absorption: ~10% systemically	Metabolism: Hepatic Half-life elimination: Children: ~18 hours Time to peak, serum: Children: 6 hours
Malathion	An organic compound that binds to acetylcholinesterase and results in paralysis and death of the insect.	Topical	Percutaneous absorption is very limited; ~4%	Excreted in urine: 1.8-3.3%.

Permethrin	An organic compound that inhibits sodium influx in nerve cell membrane channels in parasites resulting in delayed repolarization, paralysis and death.	Topical	Absorption: <2%	Metabolism: Hepatic via ester hydrolysis to inactive metabolites Excretion: Urine
Piperonyl butoxide and Pyethrins	Inhibits nerve cell membrane function resulting in paralysis and death. Piperonyl butoxide is usually added to decrease the metabolism of pyrethrins in arthropods.	Topical	Absorption: Minimal	Onset of action: ~30 minutes Metabolism: Via ester hydrolysis and hydroxylation
Spinosad	Causes central nervous system excitation and involuntary muscle contractions and death.	Topical	Absorption: Not absorbed topically	Spinosad is thought to be both pediculicidal and ovicidal. Spinosad is the only agent which does not require mechanic lice removal with a comb.

Methods

A literature search was conducted to identify articles addressing clinical safety or efficacy of the pediculicide and scabicide agents within the preceding 20 years, searching the MEDLINE database (1993 – 2013), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE prior to 12/2013, evaluating efficacy of the agents are included. Trials evaluating the pediculicide and scabicide agents prior to 1993 were excluded due to changes in resistance patterns. Trials of monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded.[5-12]

Clinical Efficacy

One systematic review and twelve randomized controlled trials were included for evaluation of the pediculicide and scabicide agents.[13-25] Six of the studies evaluated the agents in the treatment of lice and seven of the studies evaluated the agents in the treatment of scabies.

Treatment of Lice

Six randomized controlled trials published within the preceding 20 years were identified for evaluation of the pediculicide agents.[17, 19, 20, 22, 24, 26] The majority of the available clinical evidence available evaluates topical malathion lotion, topical permethrin cream and topical/oral ivermectin in the treatment of lice. Malathion lotion was compared to permethrin cream in two small comparative clinical trials. Meinking et al (2004)[19] evaluated 66 patients in South Florida with presence of live lice. Patients were randomized to receive malathion 0.5% lotion applied for 20 minutes or permethrin 1% cream applied for 10 minutes with reapplication on day 8, if needed. Malathion had a significantly higher cure rate (98%) compared to permethrin (55%) at the end of the study period ($p < 0.0001$). No differences in adverse events were reported between treatment groups. Meinking et al (2007)[20] conducted a second trial comparing malathion 0.5% gel, malathion 0.5% lotion, and permethrin 1% cream in 174 patients with a diagnosis of lice. Again, topical malathion therapy (both gel and lotion) was superior to topical permethrin therapy in the treatment of lice infestation. Nineteen averse events were reported in the malathion gel treatment group compared to five reported adverse events in the malathion lotion treatment group and one reported adverse event in the permethrin cream treatment group (p = not significant).

Topical malathion was compared to oral ivermectin in two comparative clinical trials. Choisdow et al[23] conducted a large study of 812 patients aged >2 years old with presence of live lice not eradicated with topical treatment received within the preceding 2-6 weeks. Ivermectin was given in a dose of 400 mcg/kg and malathion 0.5% lotion was applied for 10-12 hours and each treatment was repeated on day 8. On day 15, oral ivermectin produced a higher cure rate (95.2%) compared to topical permethrin (85%, $p < 0.0001$). Serious adverse events were reported in one patients taking ivermectin and two patients receiving malathion. Nofal et al[24] evaluated 80 children with head lice randomized to receive oral ivermectin at a dose of

200mcg/kg or malathion 5% lotion applied for 8-12 hours with repeat administration on day 8. No differences in safety or efficacy were reported between the treatment groups in these school-aged students. Overall, cure rate was ~92-95% on day 15 for all children.

One trial evaluating three different topical strengths (0.15%, 0.25%, 0.5%) of ivermectin lotion is available. A total of 78 patients aged 6 months or older with presence of live lice were included in the evaluation. According to the trial conducted by Meinking et al (2013)[20], all three formulations are more effective than placebo with ivermectin 0.5% lotion producing the highest eradication rate (73.7% compared to 50-55% for the lower potencies and 8.7% for placebo). No differences in adverse events were reported between treatment groups. One trial of spinosad is available for evaluation. Stough et al[22] conducted a large trial of 1038 patients aged 6 months or older with lice. Patient were randomized to receive permethrin 1% cream in combination with nit combing or spinosad 0.9% cream without nit combing. At the end of the study period (14-21 days) more patients receiving spinosad were lice-free (84-86%) compared to the patients receiving permethrin (42-44%, $p < 0.001$). Erythema was reported numerically more in the permethrin treatment group (n=31) compared to the spinosad treatment group (n=17; p = NS), although the results were not statistically significant. No differences in application-site irritation were reported between treatment groups (n= 7 and 5, respectively; p = NS). No comparative clinical trials evaluating benzoyl alcohol or piperonyl butoxide/pyethrins in the treatment of lice infestations are available for evaluation.

Treatment of Scabies

One systematic review and six randomized controlled trials published within the preceding 20 years were identified for evaluation of the scabicide agents.[13-16, 18, 21, 25] The systematic review was published in 2007 and included 22 clinical trials of over 2600 patients.[18] Treatment interventions included: benzyl benzoate, crotamiton, lindane, permethrin, pyrethrins, sulfur, and ivermectin. According to the review, treatment with topical permethrin is the most effective option for the treatment of scabies. Ivermectin may be considered an effective alternative oral treatment option. More research is needed to determine the efficacy and place in therapy for the other agents. No differences in adverse events were reported between treatment groups.

The majority of the remaining clinical evidence included in this review evaluates topical permethrin cream compared to oral or topical ivermectin in the treatment of scabies. Sharma et al[25] evaluated 120 patients at least 5 years old or greater than 15kg with a clinical diagnosis of scabies. Patients were randomized to receive ivermectin 200mcg/kg in a single or double dose regimen or permethrin 5% cream single application. At the end of week one, permethrin was associated with reduced lesion count and pruritus compared to oral ivermectin. By week 4, no differences in symptoms or cure rates were reported between treatment groups. Goldust et al (2012)[14] evaluated 242 patients aged 2-84 years with a diagnosis of scabies. Patients were randomized to one single 200mcg/kg ivermectin dose or a two-application permethrin 5% cream regimen. At the end of the study period, no differences in safety or efficacy were reported between treatment groups. Goldust et al (2013)[15] conducted a second trial, this time comparing topical ivermectin to topical permethrin. A total of 380 patients were randomized to receive topical ivermectin or permethrin applied from head to two for 1-2 doses separated by 7 days. Overall, no differences in efficacy were reported between treatment groups. Chhaiya et al[13]

evaluated 315 patients aged 5-80 years with clinically diagnosed scabies. Patients were randomized to receive ivermectin topical lotion, ivermectin oral tablets, or permethrin topical cream. At weeks one and two, both topical permethrin and topical ivermectin produced higher cure rates compared to oral ivermectin ($p < 0.05$). By week four, no differences in cure rates were reported between treatment groups. This suggests topical permethrin and ivermectin have faster onsets of action than oral ivermectin.

Lindane was evaluated in two trials in the treatment of scabies infestation. Zargari et al[21] evaluated 99 patients aged over 5 years with a scabies infection. Patients were randomized to receive lindane or permethrin cream applied from head to toe for 12 hours. Eradication rates were significantly higher in the permethrin treatment group (84.6%) compared to the lindane treatment group (48.9%, $p<0.05$). No differences in adverse events were reported between treatment groups. Goldust et al (2013)[16] evaluated 440 patients with scabies randomized to receive topical lindane 1% lotion applied twice in a 7 day period or oral ivermectin for one 200mcg/kg dose. At the end of the study period (4 weeks) oral ivermectin had a significantly higher cure rate (81.8%) compared to topical lindane (63.6%, $p<0.05$). This data suggest lindane may not be as effective as permethrin or ivermectin in the treatment of scabies.

Adverse Drug Reactions

In general, the pediculicide and scabicide agents are well tolerated. The most common adverse events reported with the agents are dermatologic in nature, including burning, itching, and erythema.[1, 2] The agents are neurotoxic in lice and scabies but usually do not produce neurotoxicity in humans. Lindane is the only agent with a black box warning for risk of severe neurologic toxicities, including seizures and death. Lindane is contraindicated in patients with uncontrolled seizure disorders and in premature infants. Lindane should only be used as a second-line treatment option in patients who are not able to tolerate or have failed other treatments. Malathion is contraindicated in neonates and infants because their scalps may be more permeable to absorption of the topical drug. The malathion formulation currently available for use in US contains alcohol, is flammable and must remain on the skin for 8-12 hours, which may put the individual at increased risk for adverse events. Permethrin has the most clinical safety and efficacy evidence available for its use in the treatment of lice and scabies and appears to be the safest treatment option. However, resistance to permethrin has been reported and this may limit its use. No serious adverse events have been reported with ivermectin use in the treatment of lice or scabies. Limited safety evidence is available for benzyl alcohol, crotamiton and spinosad. In clinical studies, no differences in safety were reported between any of the pediculicide and scabicide agents.[1, 2] See table 3 for a summary of the adverse event data available in package inserts for the pediculicide and scabicide agents.

Table 3. Adverse Events Reported with the Pediculicide and Scabicide Agents[1, 2]

Adverse Event	Benzyl alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Piperonyl butoxide/Pyethrins	Spinosad
Central Nervous System Effects	NR	NR	NR	Reported	NR	Reported	NR	NR
Dermatological Effects								
Alopecia	NR	NR	NR	Reported	NR	NR	NR	0.1-1%
Burning	NR	NR	<1%	Reported	NR	1-10%	Reported	NR
Dermatitis	NR	Reported	<1%	Reported	NR	NR	NR	0.1-1%
Dryness	NR	NR	<1%	NR	NR	NR	NR	0.1-1%
Erythema	10%	NR	NR	NR	NR	1-10%	NR	3%
Irritation	NR	Reported	NR	NR	Reported	NR	Reported	1%
Numbness	NR	NR	NR	NR	NR	1-10%	NR	NR
Pruritus	12%	Reported	NR	Reported	NR	1-10%	Reported	NR
Rash	NR	Reported	NR	NR	NR	1-10%	NR	NR
Gastrointestinal Effects	NR	NR	NR	Reported	NR	Reported	NR	NR
Other								
Conjunctivitis	NR	NR	<1%	NR	Reported	NR	NR	NR
Edema	NR	NR	NR	NR	NR	1-10%	NR	NR
Cardiac events	NR	NR	NR	Reported	NR	NR	NR	NR
Ocular irritation	6%	NR	<1%	NR	NR	NR	NR	2%
Paresthesia	NR	NR	NR	Reported	NR	NR	NR	NR

Summary

Eight pediculicide and scabicide agents are currently available for use in the United States and are indicated in the treatment of lice and scabies infestations. The topical agents are available as creams, gels, lotions, rinses, solutions and shampoos. One oral agent is available for use: ivermectin. Each of the agents have varying potencies and rates of skin penetration and, subsequently, different administration regimens. In general, choice of pediculicide or scabicide agent is determined by clinical judgment based upon location of infestation, prior treatment, and complicating conditions (infection, age of patient, resistance).

One systematic review and twelve randomized controlled trials were included for evaluation of the pediculicide and scabicide agents. Six of the studies evaluated the agents in the treatment of lice and seven of the studies evaluated the agents in the treatment of scabies. The majority of the available clinical evidence evaluating treatments for lice infestation compare topical malathion lotion, topical permethrin cream and topical/oral ivermectin formulations. Overall, the evidence suggests similar rates of cure between the agents. Higher eradication rates were reported with malathion and ivermectin therapy compared to treatment with permethrin. The majority of the available clinical evidence evaluating treatments for scabies infestations compares topical permethrin cream to oral or topical ivermectin therapy. Similar rates of cure were reported between the agents at the end of the treatment periods but the evidence suggests topical permethrin and ivermectin have quicker onsets of action and induction of cure than oral ivermectin. No differences in adverse events were reported between any of the agents in clinical trials.

The most common adverse events reported with the pediculicide and scabicide agents are local reactions (burning, itching, erythema). In general, the topical agents are not systemically absorbed and are not associated with neurotoxic adverse events in humans. No serious adverse events have been reported with permethrin, ivermectin, benzyl alcohol, crotamiton and spinosad. Malathion is contraindicated in neonates and infants and is flammable. Lindane is the only agent with a black box warning for risk of severe neurologic toxicities and is contraindicated in patients with uncontrolled seizure disorders and in premature infants. Overall, selection of a pediculicide and scabicide agent and preparation should be based on both patient-related and drug-related factors including age of the patient, location of infestation and the presence or absence of other complicating factors.

References

1. AHFS Drug Information, ed *AHFS 2013 Drug Information*. Bethesda, MD: American Society of Health-System Pharmacists; 2013.
2. Lexi-Comp I, ed *Drug Information Handbook.* 21st ed. Hudson, OH: Lexi-Comp; 2013.
3. Pollack RJ. Ectoparasite Infestations and Arthropod Bites and Stings. . In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principles of Internal Medicine*. 18th ed. New York: McGraw-Hill; 2012.
4. Frankowski BL, Bocchini JA, Jr. Head lice. *Pediatrics.* Aug;126(2):392-403.
5. Barnett E, Palma KG, Clayton B, Ballard T. Effectiveness of isopropyl myristate/cyclomethicone D5 solution of removing cuticular hydrocarbons from human head lice (Pediculus humanus capitis). *BMC Dermatol.*12:15.
6. Cole SW, Lundquist LM. Spinosad for treatment of head lice infestation. *Ann Pharmacother.* Jul;45(7-8):954-959.
7. Dawes M, Hicks NR, Fleminger M, Goldman D, Hamling J, Hicks LJ. Evidence based case report: treatment for head lice. *BMJ.* Feb 6 1999;318(7180):385-386.
8. Dodd CS. WITHDRAWN: Interventions for treating headlice. *Cochrane Database Syst Rev.* 2006(4):CD001165.
9. Goldust M, Rezaee E, Raghifar R, Naghavi-Behzad M. Comparison of permethrin 2.5 % cream vs. Tenutex emulsion for the treatment of scabies. *Ann Parasitol.*59(1):31-35.
10. Greive KA, Lui AH, Barnes TM, Oppenheim VM. A randomized, assessor-blind, parallel-group, multicentre, phase IV comparative trial of a suffocant compared with malathion in the treatment of head lice in children. *Australas J Dermatol.* Aug;51(3):175-182.
11. Koch T, Brown M, Selim P, Isam C. Towards the eradication of head lice: literature review and research agenda. *J Clin Nurs.* May 2001;10(3):364-371.
12. Vander Stichele RH, Dezeure EM, Bogaert MG. Systematic review of clinical efficacy of topical treatments for head lice. *BMJ.* Sep 2 1995;311(7005):604-608.
13. Chhaiya SB, Patel VJ, Dave JN, Mehta DS, Shah HA. Comparative efficacy and safety of topical permethrin, topical ivermectin, and oral ivermectin in patients of uncomplicated scabies. *Indian J Dermatol Venereol Leprol.* Sep-Oct;78(5):605-610.
14. Goldust M, Rezaee E, Hemayat S. Treatment of scabies: Comparison of permethrin 5% versus ivermectin. *J Dermatol.* Jun;39(6):545-547.
15. Goldust M, Rezaee E, Raghifar R, Hemayat S. Treatment of scabies: the topical ivermectin vs. permethrin 2.5% cream. *Ann Parasitol.*59(2):79-84.
16. Goldust M, Rezaee E, Raghifar R, Naghavi-Behzad M. Ivermectin vs. lindane in the treatment of scabies. *Ann Parasitol.*59(1):37-41.
17. Meinking TL, Mertz-Rivera K, Villar ME, Bell M. Assessment of the safety and efficacy of three concentrations of topical ivermectin lotion as a treatment for head lice infestation. *Int J Dermatol.* Jan;52(1):106-112.
18. Strong M, Johnstone P. Interventions for treating scabies. *Cochrane Database Syst Rev.* 2007(3):CD000320.
19. Meinking TL, Vicaria M, Eyerdam DH, Villar ME, Reyna S, Suarez G. Efficacy of a reduced application time of Ovide lotion (0.5% malathion) compared to Nix creme rinse (1% permethrin) for the treatment of head lice. *Pediatr Dermatol.* Nov-Dec 2004;21(6):670-674.
20. Meinking TL, Vicaria M, Eyerdam DH, Villar ME, Reyna S, Suarez G. A randomized, investigator-blinded, time-ranging study of the comparative efficacy of 0.5% malathion gel versus Ovide

Lotion (0.5% malathion) or Nix Creme Rinse (1% permethrin) used as labeled, for the treatment of head lice. *Pediatr Dermatol.* Jul-Aug 2007;24(4):405-411.

21. Zargari O, Golchai J, Sobhani A, et al. Comparison of the efficacy of topical 1% lindane vs 5% permethrin in scabies: a randomized, double-blind study. *Indian J Dermatol Venereol Leprol.* Jan-Feb 2006;72(1):33-36.

22. Stough D, Shellabarger S, Quiring J, Gabrielsen AA, Jr. Efficacy and safety of spinosad and permethrin creme rinses for pediculosis capitis (head lice). *Pediatrics.* Sep 2009;124(3):e389-395.

23. Chosidow O, Giraudeau B, Cottrell J, et al. Oral ivermectin versus malathion lotion for difficult-to-treat head lice. *N Engl J Med.* Mar 11;362(10):896-905.

24. Nofal A. Oral ivermectin for head lice: a comparison with 0.5 % topical malathion lotion. *J Dtsch Dermatol Ges.* Dec;8(12):985-988.

25. Sharma R, Singal A. Topical permethrin and oral ivermectin in the management of scabies: a prospective, randomized, double blind, controlled study. *Indian J Dermatol Venereol Leprol.* Sep-Oct;77(5):581-586.

26. Chosidow O, Chastang C, Brue C, et al. Controlled study of malathion and d-phenothrin lotions for Pediculus humanus var capitis-infested schoolchildren. *Lancet.* Dec 24-31 1994;344(8939-8940):1724-1727.

Evidence Table. Clinical Trials Evaluating the Pediculisides and Scabicides

Reference/Study Design	N	Patient Selection	Treatment Interventions	Significant Outcomes	Adverse Effects
Systematic Reviews					
Strong et al, 2007[18] Systematic Review of 20 clinical trials	2392	Children or adults with a clinical or parasitological diagnosis of **scabies**	Benzyl Benzoate Crotamiton Decamethrin Lindane Permethrin Pyrethrins Sulfur Ivermectin	Permethrin > Ivermectin ≥ Benzyl Benzoate = Crotamiton = Decamethrin = Lindane = Pyrethrins = Sulfur	No significant differences between agents. Adverse events reported in studies: -Treatment failure -Itching persistence -Skin reactions -Gastrointestinal irritation -Headache
Randomized Controlled Trials					
Meinking et al, 2004[19] Randomized controlled trial; single-blind	66	Patients in South Florida aged 6–70 with at least 3 live **lice** and 10 viable eggs upon initial visual examination	Malathion 0.5% Lotion applied for 20- minutes Permethrin 1% Crème Rinse applied for 10-minutes May receive re-treatment with same agent on day 8	Malathion > Permethrin ($p < 0.0001$)	Scalp burning Malathion: 1 Permethrin: 0
Zargari et al, 2006[21] Randomized controlled trial; double-blind	99	Patients aged 5+ with **scabies**	Lindane 1 % cream (n = 47) Permethrin 5% cream (n = 52) Applied from head to toe and rinsed off 12 hours	Permethrin > Lindane ($p < 0.05$)	Irritation Lindane: 1 Permethrin: 2

			later with repeat treatment after 1 week		
Meinking et al, 2007[20] Randomized controlled trial; single-blind	174	Patients of all ages with at least 3 live **lice** and 10 viable eggs upon initial visual examination	Malathion 0.5% Gel applied for 30, 60, and 90 minute applications Malathion 0.5% Lotion applied for 20- minutes Permethrin 1% Crème Rinse applied for 10-minutes	Malathion Gel (30 min) > Malathion Lotion > Permethrin	<u>Adverse events</u> Malathion Gel: 19 Malathion Lotion: 5 Permethrin: 1
Stough et al, 2009[22] Randomized controlled trial; single-blind; multi-center	1038	Patients $\geq$6 months with **Lice**	Permethrin 1% with nit combing Spinosad 0.9% without nit-combing Retreatment allowed with same agent if needed	Spinosad > Permethrin ($p < 0.001$)	<u>Ocular hyperemia</u> Permethrin: 15 Spinosad: 12 <u>Application-site erythema</u> Permethrin: 31 Spinosad: 17 <u>Application-site irritation</u> Permethrin: 7 Spinosad: 5
Chosidow et al, 2010[23] Randomized controlled trial; double-blind; multi-center	812	Patients aged $\geq$2 years with live **lice** not eradicated by topical insecticide used 2 to 6 weeks prior to enrollment	Ivermectin at a dose of 400 mcg per kilogram of body weight Malathion 0.5% lotion Each given on days 1 and 8	Ivermectin > Malathion ($p \leq 0.002$)	<u>Serious adverse events</u> Ivermectin: 1 (Seizure) Malathion: 2 (Headache) <u>Treatment-related discontinuation rate</u> Ivermectin: 7

					Malathion: 5 <u>Treatment-related adverse event</u> Ivermectin: 30 Malathion: 45
Nofal et al, 2010[24] Randomized controlled trial	80	Children with head **lice**	Ivermectin 200 mcg per kilogram of body weight Malathion 5% Lotion A second dose was given at day 8	Ivermectin = Malathion	<u>Skin reaction</u> Ivermectin: 2 (itching) Malathion: 3 (burning)
Sharma et al, 2011[25] Randomized controlled trial; double-blind	120	Patients >5 years of age and/or >15 k with a clinical diagnosis of **Scabies**	Ivermectin 200 mcg/kg/dose in a single dose Ivermectin 200 mcg/kg/dose in a double dose regimen repeated at 2 week interval Permethrin 5% cream	Week one: Permethrin <u>></u> Ivermectin (both groups) Week four: Permethrin = Ivermectin (both groups)	<u>Adverse events:</u> Oral ivermectin: 6 (headache, nausea) Topical ivermectin: not reported Permethrin: 5 (burning, itching)
Goldust et al, 2012[14] Randomized controlled trial; double-blind	242	Patients aged 2–84 years with a diagnosis of **scabies**	Ivermectin for one 200 mcg⁄kg dose (n = 121) Permethrin 5% Cream applied twice in a 7-day span for 12 hours (n = 121) *In case of treatment failure, the patient was crossed over to the other	Permethrin = Ivermectin	<u>Irritation after application</u> Ivermectin: 3 Permethrin: 6

			group		
Chhaiya et al, 2012[13] Randomized controlled trial	315	Patients aged 5-80 years with clinically-diagnosed **scabies**	Ivermectin 1% lotion applied once for 8 hours Ivermectin tablet for one 200 mcg⁄kg dose Permethrin 5% Cream applied once for 8 hours	Week one: Permethrin ≥ Topical Ivermectin > Oral Ivermectin ($p < 0.05$) Week two: Permethrin = Topical Ivermectin > Oral Ivermectin ($p < 0.05$) Week three: Permethrin = Topical Ivermectin = Oral Ivermectin	<u>Adverse events</u> Permethrin: 1 (burning) Topical Ivermectin: 0 Oral Ivermectin: 2 (headache, pruritus)
Goldust et al, 2013[16] Randomized controlled trial	440	Patients with **Scabies**	Ivermectin for one 200 mcg⁄kg dose (n = 121) Lindane 1% lotion applied twice in a 7-day span	Week two: Ivermectin ≥ Lindane, p = NS Week four: Ivermectin > Lindane, $p < .05$	Not reported
Goldust et al, 2013[15] Randomized controlled trial	380	Patients with **Scabies**	Ivermectin 1% lotion at a dose of 400 microg/kg, repeated once the following week Permethrin 2.5% cream applied twice at one week intervals *If there was treatment failure at the 2-week follow-up, treatment was	Ivermectin = Permethrin	Not reported

			repeated.		
Meinking et al, 2013[17] Randomized controlled trial; double-blind	78	Patients aged ≥6 months and weighing ≥15 kg with presence of live **Lice**	Topical Ivermectin 0.15% Topical Ivermectin 0.25% Topical Ivermectin 0.5% Vehicle One 10-min application	Topical Ivermectin 0.5% ≥ Topical Ivermectin 0.25% = Topical Ivermectin 0.15% > Vehicle ($p < 0.05$)	Adverse events Ivermectin 0.5%: 6 Ivermectin 0.25%: 3 Ivermectin 0.15%: 7 Vehicle: 6