Therapeutic Class Overview
Scabicides and Pediculicides

Therapeutic Class

- **Overview/Summary:** The agents indicated for the management of scabies and head lice are listed in Table 1. The skin and mucous membrane scabicides and pediculicides are approved to treat pediculosis and scabies.[1-10] Pediculosis is a transmissible infection, which is caused by three different kinds of lice depending on the location: head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*) and pubic region (*Phthirus pubis*). Pediculosis is often asymptomatic; however, itching may occur due to hypersensitivity to lice saliva.[11] Scabies is also a transmissible skin infection caused by the mite *Sarcoptes scabiei.* Mites burrow into the skin and lay eggs, which when hatched, will crawl to the skin's surface and begin to make new burrows. The most common clinical manifestation of scabies is itching, which is due to a hypersensitivity reaction to the mite or mite excrement.[12] When treating scabies and lice, the goal of therapy is to eradicate the parasite. Benzyl alcohol inhibits lice from closing their respiratory spiracles, which causes the lice to asphyxiate.[3] Crotamiton has scabicidal and antipruritic actions; however, the exact mechanism of action is unknown.[4] Lindane is a central nervous system stimulant, which causes convulsions and death of the arthropod.[1,2] Malathion is an organophosphate agent, which inhibits cholinesterase activity.[5] Permethrin disrupts the sodium channel current, which leads to delayed repolarization and paralysis of the arthropod.[1,2] Spinosad causes neuronal excitation, which leads to paralysis and death.[6] The suspension also contains an unspecified amount of benzyl alcohol. Retreatment with benzyl alcohol and permethrin is required after seven to 10 days to eradicate the infestation. The newest agent in the class ivermectin, is pediculicidal but not ovicidal and it is approved as a single application product only.[7] Lindane, malathion, permethrin, spinosad, and piperonyl butoxide and pyrethrins products are available generically, while permethrin, and piperonyl butoxide and pyrethrins products are also available over-the-counter.

Table 1. Current Medications Available in the Therapeutic Class[1-10]

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
Single-Entity Agents			
Benzyl alcohol (Ulesfia®)	Treatment of head lice	Lotion: 5% (227 g/bottle)	-
Crotamiton (Eurax®)	Treatment of scabies	Cream: 10% (2 oz/ tube) Lotion: 10% (2 oz/bottle, 16 oz/bottle)	-
Ivermectin (Sklice®)	Treatment of head lice	Lotion: 0.5% (4 oz/tube)	-
Lindane*	Treatment of head and pubic lice and scabies	Lotion: 1% (2 oz/bottle) Shampoo: 1% (2 oz/bottle)	✔
Malathion (Ovide®*)	Treatment of head lice	Lotion: 0.5% (2 oz/ bottle)	✔
Permethrin*† (Acticin®, Nix Complete Lice System®*†, Nix Crème Rinse®*†)	Treatment of head lice and scabies	Cream: 5% (2 oz/tube) Liquid: 1% (2 oz/bottle)	✔

Generic (Trade Name)	Food and Drug Administration Approved Indications	Dosage Form/Strength	Generic Availability
		Lotion: 1% (2 oz/bottle, 4 oz/bottle)	
Spinosad (Natroba®*)	Treatment of head lice	Topical Suspension: 0.9% (4 oz/bottle)	✔
Combination Products			
Piperonyl butoxide and pyrethrins*† (Licide Complete Lice Treatment Kit®*†, Pronto®*†, RID®*†)	Treatment of head, body and pubic lice	Gel: 4/0.33% (each kit) Shampoo: 4/0.33% (each kit) Solution: 4/0.33% (each kit)	✔

*Generic available in one dosage or strength.
†Over-the-counter product is available in at least one dosage form or strength.

Evidence-based Medicine

- In two, randomized, active-controlled trials in patients with an active head lice infestation, a greater proportion of patients were lice-free 14 days following treatment with spinosad alone compared to patients who received permethrin plus nit combing (P<0.001 for both trials).[13]
- The combined results of two identical, vehicle-controlled trials (N=765) in patients six months and older with head lice showed that significantly more patients treated with ivermectin lotion were lice-free on day two (94.9 vs 31.3%), day eight (85.2 vs 20.8%) and remained lice-free through day 15 (73.8 vs 17.6%; P<0.001 for each day) compared to the vehicle group.[14]
- In two studies comparing benzyl alcohol to its vehicle, the absolute difference in treatment success rate in study one was 71.4% in favor of benzyl alcohol (95% confidence interval [CI], 61.8 to 85.7) and 48.8% (95% CI, 31.1 to 62.0) in study two, again in favor of benzyl alcohol. Benzyl alcohol was associated with a lower risk of treatment failure in both studies (P<0.001 for both).[15]
- For the treatment of lice, permethrin has demonstrated a higher rate of treatment success compared to lindane, following a single application.[16-19] Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective at 14 days following treatment (P>0.01).[20,21] In multiple studies, malathion has been reported to be pediculicidal and ovicidal when compared to permethrin.[22,23]
- In studies comparing various topical agents for the treatment of scabies, a higher cure rate has been demonstrated with permethrin compared to crotamiton and lindane.[24-29] In the largest study completed (N=467), Schultz et al reported that there was a trend towards a higher cure rate with permethrin treatment compared to lindane; however, the difference was not statistically significant.[25]

Key Points within the Medication Class

- According to Current Clinical Guidelines:
  - Head lice treatment can be initiated with permethrin 1% or pyrethrins when resistance to these products is not suspected. These agents are available over-the-counter without a prescription.[29,30]
  - Malathion 0.5% can be used in people who are ≥24 months of age when resistance to permethrin or pyrethrins is documented or when treatment with these products fails despite their correct use. Due to the high alcohol concentration of the product it is highly flammable.[29,30]

  - Permethrin is the most studied pediculicide and is the least toxic to humans. Permethrin is less allergenic than pyrethrins and does not cause allergic reactions in individuals with plant allergies.[30]
  - Lindane has low ovicidal activity (30 to 50% of eggs are not killed), and resistance has been reported worldwide for many years. For these reasons, it should be used cautiously. The Food and Drug Administration (FDA) has warned that incorrect use of lindane can be neurotoxic and its use should be restricted to patients for whom prior treatments have failed or in those patients who cannot tolerate safer medications.[29,30]
  - Lindane should not be used to treat premature infants, persons with the human immunodeficiency virus, seizure disorders, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh <110 pounds.[29,30]
  - Permethrin is the drug of choice for the treatment of scabies. Two (or more) applications may be necessary to eliminate all mites, particularly when treating crusted (Norwegian) scabies.
  - Crotamiton is approved for the treatment of scabies in adults but is frequently associated with treatment failure.[31]
  - Lindane is not recommended as a first-line therapy for the treatment of scabies due to its potential for toxicity with frequent or incorrect use. Lindane should be restricted to patients who have failed recommended therapies or who cannot tolerate recommended treatments.[31]
- Other Key Facts:
  - All recommended first-line therapies are available generically in at least one strength or formulation.[1]
  - According to the manufacturer, spinosad is the first FDA-approved head lice treatment that does not require nit combing following treatment.[33]
  - Ivermectin is approved for use as a single application only and is not indicated for retreatment.[7]
  - Reasons for treatment failure with the topical scabicide and pediculicide products include misdiagnosis, noncompliance, failure to follow instructions correctly, not enough pediculicide applied, reinfestation, and resistance. If resistance is suspected, retreatment should be with a different chemical entity than initially used.[34]

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Therapeutic Class Review
Scabicides and Pediculicides

Overview/Summary

The skin and mucous membrane scabicides and pediculicides are approved to treat pediculosis and scabies.[1-10] Pediculosis is a transmissible infection, which is caused by three different kinds of lice depending on the location: head (*Pediculus humanus capitis*), body (*Pediculus humanus corporis*) and pubic region (*Phthirus pubis*). Pediculosis is often asymptomatic; however, itching may occur due to hypersensitivity to lice saliva.[11] Scabies is also a transmissible skin infection caused by the mite *Sarcoptes scabiei.* Mites burrow into the skin and lay eggs, which when hatched, will crawl to the skin's surface and begin to make new burrows. The most common clinical manifestation of scabies is itching, which is due to a hypersensitivity reaction to the mite or mite excrement.[12]

When treating scabies and lice, the goal of therapy is to eradicate the parasite. Benzyl alcohol inhibits lice from closing their respiratory spiracles, which causes the lice to asphyxiate.[3] Crotamiton has scabicidal and antipruritic actions; however, the exact mechanism of action is unknown.[4] Lindane is a central nervous system stimulant, which causes convulsions and death of the arthropod.[1,2] Malathion is an organophosphate agent, which inhibits cholinesterase activity.[5] Permethrin disrupts the sodium channel current, which leads to delayed repolarization and paralysis of the arthropod.[1,2] Spinosad causes neuronal excitation, which leads to paralysis and death.[6] The suspension also contains an unspecified amount of benzyl alcohol. Retreatment with benzyl alcohol and permethrin is required after seven to 10 days to eradicate the infestation. The newest agent in the class ivermectin, is pediculicidal but not ovicidal and it is approved as a single application product only.[7]

Lindane, malathion, permethrin, spinosad, and piperonyl butoxide and pyrethrins products are available generically, while permethrin, and piperonyl butoxide and pyrethrins products are also available over-the-counter.

Medications

Table 1. Medications Included Within Class Review[1,3-10]

Generic Name (Trade name)	Medication Class	Generic Availability
Single-Entity Agents		
Benzyl alcohol (Ulesfia®)	Scabicide and pediculicide	-
Crotamiton (Eurax®)	Scabicide and pediculicide	-
Ivermectin (Sklice®)	Scabicide and pediculicide	-
Lindane	Scabicide and pediculicide	✔
Malathion (Ovide®*)	Scabicide and pediculicide	✔
Permethrin*† (Acticin®, Nix Complete Lice System®*†, Nix Crème Rinse®*†)	Scabicide and pediculicide	✔
Spinosad (Natroba®*)	Scabicide and pediculicide	✔
Combination Products		
Piperonyl butoxide and pyrethrins*† (Licide Complete Lice Treatment Kit®*†, Pronto®*†, RID®*†)	Scabicide and pediculicide	✔

*Generic available in one dosage or strength.
†Over-the-counter product is available in at least one dosage form or strength.

Indications

Table 2. Food and Drug Administration-Approved Indications[1,3-10]

Drug(s)	Scabies	Head Lice	Head and Pubic Lice	Head, Body, and Pubic Lice
Single-Entity Agents				
Benzyl alcohol		✔ *		
Crotamiton	✔			
Ivermectin		✔ *		
Lindane	✔ †		✔ ‡	
Malathion		✔		
Permethrin	✔ §	✔ ‖		
Spinosad		✔ ¶		
Combination Products				
Piperonyl butoxide and pyrethrins				✔

* In patients ≥6 months of age.
† Lindane lotion is reserved for patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of scabies.
‡ Lindane shampoo is reserved for patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of head or public lice.
§ Permethrin cream is indicated for the treatment of scabies.
‖ Permethrin lotion/cream rinse and liquid are indicated for the treatment of head lice.
¶ In patients ≥4 years of age.

In addition to its Food and Drug Administration-approved indication, permethrin may also be used off-label in the treatment of papulopustular rosacea, and crotamiton has been used in the treatment of head lice.[1]

Pharmacokinetics

Table 3. Pharmacokinetics[1,2]

Generic Name	Bioavailability (%)	Absorption (%)	Renal Excretion (%)	Active Metabolites	Serum Half-Life (hours)
Single-Entity Agents					
Benzyl alcohol	Not reported	Not reported	Not reported	Not reported	Not reported
Crotamiton	Not reported	Not reported	Not reported	Not reported	Not reported
Ivermectin	Not reported	Not reported	Not reported	Not reported	Not reported
Lindane	Not reported	10	Not reported	Not reported	18
Malathion	Not reported	8	Not reported	Not reported	1.2 to 7.6
Permethrin	Not reported	≤2	Not reported	Not reported	Not reported
Spinosad*	Not reported	Not reported	Not reported	Not reported	Not reported
Combination Products					
Piperonyl butoxide and pyrethrins	Not reported	Not reported	Not reported	Not reported	Not reported

* In a pharmacokinetic study, the plasma spinosad concentrations in samples obtained from 14 patients with head lice, were below the limit of detection following a single 10 minute topical treatment. In addition, the bioavailability of benzyl alcohol, which is contained in the topical suspension, is unknown as plasma concentrations were not determined in the evaluated subjects.[6]

Clinical Trials

Clinical studies evaluating the safety and efficacy of the topical pediculicide and scabicide products for their respective Food and Drug Administration-approved indications are described in Table 4.[13-39]

Benzyl alcohol has been evaluated in two multicenter, randomized, double-blind, vehicle-controlled studies in patients (six months and older) with an active head lice infestation (N=628). In both studies, two

applications of benzyl alcohol were associated with a significantly greater chance of treatment success (zero live lice 14 days following final treatment), compared to vehicle (P<0.001). The absolute difference in treatment success rates in study one was 71.4% in favor of benzyl alcohol (95% confidence interval [CI], 61.8 to 85.7) and 48.8% (95% CI, 31.1 to 62.0) in study two, again in favor of benzyl alcohol. In both studies, there was a lower incidence of treatment failure associated with benzyl alcohol compared to vehicle (3.3 vs 83.6% and 14.3 vs 60.7% in studies one and two, respectively; P<0.001 for both).[25]

In studies comparing various topical agents for the treatment of scabies, a higher cure rate has been reported with permethrin compared to crotamiton and lindane.[13-18] In the largest study completed (N=467), Schultz et al reported that there was a trend towards a higher cure rate with permethrin compared to lindane, however the difference was not statistically significant.[14] Both lindane and permethrin have also been compared to ivermectin for the treatment of scabies. While a study by Madan et al demonstrated a lower cure rate after four weeks with lindane compared to ivermectin (44.44 vs 82.60%; P value not reported), Chouelea and colleagues reported similar efficacy between the two agents.[19,20] Results from another study found that after a single application, permethrin was associated with a higher cure rate compared to ivermectin (95 vs 70%; P value not reported).[21]

Permethrin has demonstrated a higher rate of treatment success compared to lindane in the treatment of lice, when both were administered as a single application.[27-30] Compared to the combination of pyrethrins and piperonyl butoxide, permethrin was more efficacious several days following treatment; however, one study found the agents to be equally effective after 14 days (P>0.01).[31,32] In multiple studies, malathion has been reported to be pediculicidal and ovicidal when compared to permethrin.[33,36]

The combined results of two identical, vehicle-controlled trials (N=765) in patients six months and older with head lice showed that significantly more patients treated with ivermectin lotion were lice-free on day two (94.9 vs 31.3%), day eight (85.2 vs 20.8%) and remained lice-free through day 15 (73.8 vs 17.6%; P<0.001 for each day) compared to the vehicle group.[26]

Spinosad has been evaluated in two randomized, active-controlled trials (N=1,038) of patients with an active head lice infestation. Patients received spinosad without nit combing or permethrin 1% topical solution with nit combing. Fourteen days following treatment, the spinosad without nit combing treatment arm had a greater proportion of lice-free patients compared to permethrin with nit combing (P<0.001 for both trials). Moreover, the majority of patients treated with spinosad required only one course of treatment, compared to the majority of permethrin-treated patients who required two courses of treatment (P values not reported).[39]

Table 4. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Scabies				
Haustein et al[13] Lindane (1 and 0.3%) vs permethrin (5 and 2.5%) vs benzyl benzoate (20 and 10%)*	AC, OL Adults and children with scabies	N=194 3 weeks	Primary: Efficacy (cure rate) Secondary: Adverse events	Primary: While permethrin and benzyl benzoate were 100% effective, lindane was 92% effective (treatment failures in three adults and two children). Lindane was significantly less effective compared to permethrin and benzyl benzoate (P<0.025). Secondary: Benzyl benzoate had more immediate (22%) and late (42%) adverse events compared to the other treatment arms.
Schultz et al[14] Lindane lotion 1% vs permethrin cream 5%	AC, MC, RCT Patients with scabies who had otherwise normal skin in non-infested areas	N=467 1 month	Primary: Efficacy (cure rate) Secondary: Adverse events	Primary: One hundred and eighty one of 199 (91%) and 177 of 205 (86%) patients treated with permethrin and lindane, respectively had complete resolution after treatment (P=0.18). Secondary: The most frequent adverse events were transient burning or stinging and new or increased pruritus. Events were more frequent following permethrin treatment and appeared to be related to the severity of the infestation.
Zargari et al[15] Lindane cream 1% vs permethrin cream 5%	AC, DB, RCT Patients ≥5 years of age with scabies	N=99 2 weeks	Primary: Efficacy (cure rate) Secondary: Not reported	Primary: After two weeks, permethrin provided an improvement in 84.6% of patients compared to 48.8% of patients receiving lindane (P<0.0001). Secondary: Not reported
Taplin et al[16] Lindane lotion 1%	AC, RCT Patients with microscopically	N=23 1 month	Primary: Efficacy (cure rate)	Primary: Three of 23 (13%) patients who received lindane were free of scabies at study midpoint (two weeks). After one month, 15 of 23 (65%) patients who received lindane were considered cured (P value not

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs permethrin cream 5%	confirmed scabies		Secondary: Not reported	reported). At study midpoint (two weeks) 11 of 23 patients who received permethrin were considered cured (48%). After one month, two patients who received permethrin had scabies resulting in a cure rate of 91% (P<0.025). Secondary: Not reported
Taplin et al[17] Permethrin cream 5% vs crotamiton cream 10%	AC, DB, RCT Treatment of scabies in children 2 months to 5 years of age	N=47 1 month	Primary: Efficacy (cure rate) Secondary: Not reported	Primary: Fourteen of 47 (30%) children were considered cured two weeks after permethrin treatment compared to only 6 of 47 (13%) subjects treated with crotamiton (P<0.0001). Four weeks following treatment, a higher percentage of patients treated with permethrin were considered cured compared to patients who received crotamiton (89 vs 60%; P=0.002). Secondary: Not reported
Amer et al[18] Lindane 1% vs permethrin 5% vs crotamiton 10%	AC, RCT Patients microscopically diagnosed with scabies	N=150 1 month	Primary: Efficacy (cure rate) Secondary: Adverse events	Primary: After four weeks of treatment, the cure rates were 84, 98 and 88% for patients receiving lindane, permethrin and crotamiton treatment, respectively (P values not reported). Secondary: No adverse events were reported.
Chouela et al[19] Lindane solution 1%	AC, DB, DD, PG, PRO, RCT Patients	N=53 1 month	Primary: Clinical healing Secondary:	Primary: At day 15 following treatment, 14 patients (74%) in the ivermectin group showed healing of their scabies compared to 13 patients (54%) in the lindane group (P=0.22).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs ivermectin in a single oral dose of 150 to 200 µg/kg of body weight	diagnosed with scabies		Adverse events	There was no difference in efficacy between lindane and ivermectin treatments after 29 days (95 vs 96%; P>0.99). Secondary: Adverse events from the treatments were few, mild and transient.
Madan et al[20] Lindane lotion 1% vs ivermectin in a single oral dose of 200 µg/kg body weight	AC, RCT Patients with scabies	N=200 1 month	Primary: Efficacy (cure rate) Secondary: Adverse events	Primary: In the ivermectin group, 82.60% of the patients showed marked improvement after four weeks compared to 44.44% of patients in the lindane group (P<0.0001). Secondary: One severe headache was reported in the ivermectin treatment group.
Usha et al[21] Permethrin cream 5% vs ivermectin in a single oral dose of 200 µg/kg body weight	AC, RCT Patients ≥5 years of age with microscopically diagnosed scabies and family contacts	N=85 2 months	Primary: Efficacy (cure rate) Secondary: Not reported	Primary: A cure rate of 70% was reported after a single dose of ivermectin, and increased to 95% following two doses at a two-week interval. Two weeks following a single application, permethrin was associated with a significantly higher rate of symptomatic improvement compared to oral ivermectin (97.8 vs 75.0%; P<0.001). All patients were considered to have been cured within two months following treatment. Secondary: Not reported
Goldust et al[22] Permethrin cream 5% vs ivermectin in a single oral dose of 200 µg/kg body weight	AC, RCT Patients aged 2 to 84 years of age with a diagnosis of scabies and family contacts	N=242 4 weeks	Primary: Efficacy (cure rate) Secondary: Not reported	Primary: Two weeks following treatment, a similar proportion of patients treated with permethrin cream or oral ivermectin experienced a cure (92.5 vs 85.9%; P=0.42). Twenty six patients who had not improved were crossed over to the other treatment group. When crossed over, seven patients in the permethrin 5% group who experienced treatment failure continued to have severe itching when treated with ivermectin. In contrast, all 17

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				patients not responding to ivermectin who were then treated with permethrin showed improvement in itching and skin lesions. Secondary: Not reported
Chhaiya et al[23] Permethrin cream 5% vs ivermectin in a single oral dose of 200 µg/kg body weight vs ivermectin lotion 1%	AC, OL, PG, RCT Patients five to 80 years of age with clinically-diagnosed scabies and presence of typical scabei lesions like papules, nodules, or vesicles at classical sites	N=315 4 weeks	Primary: Efficacy (cure rate) Secondary: Complete relief of pruritus	Primary: Significantly fewer patients treated with oral ivermectin compared to ivermectin lotion or permethrin cream were cured at one week (30 vs 69.3 and 74.8%, respectively; P<0.05) and two weeks (63 vs 100 and 99%, respectively; P<0.05). There was no statistically significant difference in cure rates between the three treatments by three or four weeks following treatment (P>0.05 for both). Secondary: Patients treated with ivermectin lotion and permethrin cream experienced significantly higher pruritus cure rates compared to oral ivermectin at two (P<0.05) and three weeks (P<0.05). By week four, 95, 99 and 98% of patients treated with oral ivermectin, ivermectin lotion and permethrin cream, respectively, were cured of pruritus (P>0.05).
Head, Body, or Pubic Lice				
Barker et al[24] Benzyl alcohol lotion 5% applied three times, at weekly intervals, (on day 0, day 7 and day 14) vs pyrethrins and piperonyl butoxide aerosol mousse applied twice (on day 0 and day 7)	RCT, SB Primary school-aged children four to 12 years of age and their siblings with live head lice in their hair or on their scalp	N=132 8 or 15 days (one day after the last treatment)	Primary: Louse free rate assessed one day after the last treatment Secondary: Louse free rate on day one (one day after the first application)	Primary: In the ITT population, 97.6% of patients receiving tea tree oil and lavender oil solution and 97.6% of patients receiving benzyl alcohol were louse-free one day after the last treatment compared to 25.0% of patients receiving pyrethrins and piperonyl butoxide (both, P<0.0001). In the per protocol population, 97.6% of patients receiving tea tree oil and lavender oil solution and 100% of patients receiving benzyl alcohol were louse-free one day after the last treatment compared to 33.3% of patients receiving pyrethrins and piperonyl butoxide (both, P<0.0001). Secondary: In the ITT population, 90.3% of patients receiving tea tree oil and lavender oil solution and 69.4% of patients receiving benzyl alcohol

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs tea tree oil and lavender oil solution applied three times, at weekly intervals, (on day 0, day 7 and day 14) Nit combining was not allowed.				were louse-free on day one compared to 43.3% of patients receiving pyrethrins and piperonyl butoxide (P=0.001 and P=0.0329, respectively). The difference in the louse-free rates for tea tree oil and lavender oil solution and benzyl alcohol was not significant (P=0.1009). In the per protocol population, 90.0% of patients receiving tea tree oil and lavender oil solution and 72.4% of patients receiving benzyl alcohol were louse-free on day one compared to 57.1% of patients receiving pyrethrins and piperonyl butoxide (P=0.0196 and P=0.2986, respectively). The most commonly reported adverse events with tea tree oil and lavender oil solution were stinging, flaky scalp/dry scalp and erythema. The most common adverse event with benzyl alcohol was flaky scalp/dry scalp. In the pyrethrins/piperonyl butoxide group, flaky scalp/dry scalp and erythema were reported.
Meinking et al[25] Phase II Trials Benzyl alcohol 2.5 to 10% lotion applied on day 0 and day 7 (BAL) vs placebo or active control (RID®) Phase III Trials Benzyl alcohol 5% lotion applied on day 0 and day 7 (BAL) vs	AC, PC, RCT, SB (3 Phase II trials) and DB, PC, RCT (2 Phase III trials) and ES, OL (1 trial) Phase II Trials Patients two to 70 years of age with head lice Phase III Trials and ES, OL Trial Children six months of age and older with head lice	N=459 (6 trials) Up to 21 days	Phase II Trials Primary: Treatment success seven days after final treatment Secondary: Not reported Phase III Trials Primary: Treatment success 14 days after final treatment Secondary: Treatment failure	Phase II Trials Primary: In the Phase IIa study, the BAL 5%, BAL 10% and RID® treatment groups had fewer live lice in comparison with the placebo group (P=0.004). The kill rate (ratio of total lice minus live lice/total lice) was >80% in the patients who received any of the active treatments and <20% in patients who received placebo (P<0.001). No significant differences were observed among the groups at day 15; however, the placebo group was treated with the active treatment at the day eight visit. The efficacy outcome one week later showed 70% overall success with BAL 5%, BAL 10%, and RID®, while the vehicle group demonstrated 53% success after one week treatment. In the Phase IIb study, all patients treated achieved 100% treatment success one week after treatment regardless of treatment duration. In the Phase IIc study, BAL 5% was more effective than BAL 2.5%, although not statistically significant, with treatment success rates of

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
placebo OL ES Trial Benzyl alcohol 5% lotion applied on day 0 and day 7 (BAL)			assessed one day after the second treatment ES OL Trial Primary: Treatment success 14 days after final treatment Secondary: Treatment failure assessed one day after the second treatment	90.5% and 81%, respectively (P=0.663). Secondary: Not reported Phase III Trials Primary: BAL 5% demonstrated greater treatment success 14 days after treatment in all subgroups compared to placebo (P<0.001). Secondary: In study 1, 3.3% of the BAL 5% ITT group were treatment failures, compared to 83.6% in the placebo group (P<0.001). In study 2, 14.3% of BAL 5% ITT patients were treatment failures, compared to 60.7% of patients treated with vehicle alone (P<0.001). ES OL Trial Primary: An overall 75.0% treatment success was demonstrated with BAL at the end of study (14 days after the second treatment). Secondary: Treatment success measured one day after the second treatment (day eight) showed 92.2% success.
Pariser et al[26] Ivermectin lotion 0.5% vs vehicle	2 DB, MC, PC, RCT Patients ≥6 months of age with head lice who agreed not to use any other louse treatment, comb out nits, or cut or chemically	N=765 15 days	Primary: Number of index patients who were louse-free by day two and remained louse-free through days eight and 15 (ITT population)	Primary: Significantly more patients treated with ivermectin were free of live lice at the first post-application observation on day two and at the subsequent observations through day 15 (P<0.001 for all). The combined ITT analysis showed that significantly more patients in the ivermectin group were lice-free on day two (94.9 vs 31.3%), day eight (85.2 vs 20.8%) and day 15 (73.8 vs 17.6%) compared to the vehicle group (P<0.001 for each day). Secondary: Results were consistent when cure rates in the extended ITT

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	treat hair		Secondary: Number of index patients plus all enrolled household members who were louse-free by day two and remained louse-free through days eight and 15 (extended ITT population) and safety	populations were analyzed (95.5 vs 35.3% at day two, 88.6 vs 26.2% at day eight and 78.7 vs 22.2% at day 15; P<0.001 for all comparisons). Pruritus, excoriation and erythema were the most common adverse events, occurring in >1% in the vehicle group and <1% in the ivermectin group. There was one severe adverse event (pain in an extremity with vehicle) and no serious adverse events. All other adverse events were mild to moderate. The frequency and severity of adverse events were similar in the two study groups and across age groups. Ocular irritation was noted in seven patients in the ivermectin group and five in the vehicle-control group on day two.
Brandenberg et al[27] Lindane shampoo 1% vs permethrin cream rinse 1%	MC, RCT, SB Patients with head lice	N=573 (559 assessable for tolerance; 508 assessable for efficacy) 2 weeks	Primary: Efficacy (cure rate) Secondary: Tolerance	Primary: At 14 days following treatment, 99% of patients who received permethrin were lice-free compared to 85% of patients treated with lindane (P<0.001). Secondary: Adverse events reported with both treatments, were infrequent, mild, and usually difficult to distinguish from the symptoms of head lice infestation.
Taplin et al[28] Permethrin crème rinse 1% vs lindane shampoo 1% vs placebo	DB, PC, RCT Patients with head lice	N=93 2 weeks	Primary: Efficacy (cure rate) Secondary: Safety	Primary: Ninety seven percent of patients treated with permethrin were lice-free after 14 days compared to 6% of placebo-treated patients (P<0.001) and 43% of the lindane-treated patients. Permethrin was 70% ovicidal compared to 45 and 14% for lindane and placebo, respectively (P<0.001). Secondary: No adverse events were reported during this study.

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Bowerman et al[29] Lindane shampoo 1% vs permethrin crème rinse 1%	RCT Patients with head lice in the Nezahualcoyotl community of Mexico city (296 family groups)	N=1,040 2 weeks	Primary: Efficacy (cure rate) Secondary: Adverse events	Primary: A greater proportion of patients who received permethrin were lice-free two weeks following treatment with permethrin compared to lindane (98 vs 76%; P<0.001). Secondary: Mild dermal reactions, such as pruritus or erythema occurred in 1.2% of permethrin-treated patients and 2.6% of lindane-treated patients.
Kalter et al[30] Lindane shampoo 1% vs permethrin crème rinse 1%	RCT Men with the diagnosis of pediculosis pubis	N=53 10 days	Primary: Efficacy (cure rate) Secondary: Tolerability	Primary: There was no difference in the percentage of patients treated with lindane or permethrin who were cured at the final assessment (60 vs 57%; P>0.05). Secondary: Only one mild adverse reaction was reported in each group.
Carson et al[31] Permethrin crème rinse 1% vs pyrethrins and piperonyl butoxide liquid	RCT Patients ≥4 years of age head lice	N=58 2 weeks	Primary: Efficacy (cure rate) Secondary: Tolerability	Primary: Permethrin was significantly more effective than the combination of pyrethrins and piperonyl butoxide at seven days following treatment with regard to cure rate (96.3 vs 45.2%; P<0.005). There was no statistically significant difference between the treatment groups in subjects who were lice-free at day 14 (100 vs 93.5% in the permethrin and pyrethrins and piperonyl butoxide-treated subjects, respectively; P>0.01). Secondary: No adverse events were reported
DiNapoli et al[32] Permethrin crème rinse 1% vs pyrethrins combined with	MC, R, SB Patients with pediculosis capitis (head lice infestation)	N=435 2 weeks	Primary: Efficacy (cure rate) Secondary: Adverse events	Primary: A total of 98% of the permethrin-treated patients and 85% of the pyrethrins and piperonyl butoxide-treated patients were free of lice at seven days. Prior to nit removal at 14 days, 96% of the permethrin-treated and 62% of the pyrethrins and piperonyl butoxide-treated patients remained lice-free. Secondary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
piperonyl butoxide				Seventeen (7%) permethrin-treated and 32 (16%) pyrethrins and piperonyl butoxide-treated patients reported adverse events.
Roberts et al[33] Malathion lotion 0.5% vs wet combing with a fine-toothed comb	RCT Schoolchildren (aged three to 14 years) in Wales and the United Kingdom	N=81 2 weeks	Primary: Efficacy (cure rate) Secondary: Not reported	Primary: The cure rate was higher for patients treated with malathion compared to wet combing alone (78 vs 38%; P value not reported). Children assigned wet combing were 2.8 times more likely to have lice present at the end of treatment compared to the malathion group (95% CI, 1.5 to 5.2; P=0.0006). Secondary: Not reported
Chosidow et al[34] Malathion lotion 0.5% vs oral ivermectin in a single oral dose of 400 µg/kg	CR, CT, DB, DD, MC Patients ≥2 years of age with confirmed infestation and previously failed treatment with a pyrethroid-based or malathion insecticide two to six weeks before the first visit	N=812 15 days	Primary: Absence of head lice on day 15 Secondary: Absence of live head lice on days two and eight, as well as on days 22 and 29 for patients who entered the extension stage	Primary: On day 15, 95.2% of patients in the ivermectin ITT population were free of head lice compared to 85.0% of patients in the malathion group (difference, 10.2%; 95% CI, 4.6 to 15.7; P<0.001). On day 15, 97.1% of patients in the ivermectin per-protocol population were free of head lice compared to 89.8% of patients in the malathion group (difference, 7.3%; 95% CI, 2.8 to 11.8; P=0.002). Secondary: A higher cure rate (absence of head lice) was achieved by day two in the ivermectin group compared to patients receiving malathion (92.4 vs 82.4%; P<0.001) and day eight (83.6 vs 53.9%; P<0.001). On day 15, eight patients in the ivermectin group and 31 in the malathion group had persistent infestation and entered the extension phase by switching to the other treatment. At day 29, all eight patients (100%) switched from ivermectin to malathion and 30 of the 31 patients (96.8%) switched from malathion to ivermectin lice-free (P values not reported).
Nofal et al[35] Malathion lotion 0.5%	AC, RCT Children with head lice who	N=80 29 days	Primary: Presence of live lice and any side effects at day	Primary: At day eight (after a single dose) there was a trend towards a higher cure rate in the malathion group compared to the ivermectin group, however, the difference was not statistically significant (87.5 vs 77.5%;

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
vs oral ivermectin in a single oral dose of 200 µg/kg	were attending an outpatient clinic.		eight, 15 and 29 Secondary: Not reported	P>0.05). The cure rate increased in both treatment groups after nonresponders were given a second dose (day 15), but the difference remained nonsignificant (95.0 vs 92.5% for malathion and ivermectin, respectively; P>0.05). By day 29, cure rates remained similar between the malathion and ivermectin treatment groups (80 vs 75%, respectively; P>0.05). Secondary: Not reported
Meinking et al[36] Malathion lotion 0.5% vs permethrin crème rinse 1%	Observer-blinded Patients with head lice	N=66 15 days	Primary: Efficacy (cure rate) Secondary: Not reported	Primary: At day 15, malathion was significantly more pediculicidal and ovicidal compared to permethrin (P<0.0001). Secondary: Not reported
Hipolito et al[37] Permethrin crème rinse 1% vs trimethoprim and sulfamethoxazole oral suspension 10 mg/kg/day vs permethrin crème rinse 1% plus trimethoprim and sulfamethoxazole oral	MC, RCT Children aged two to 13 years	N=115 1 month	Primary: Efficacy (cure rate) Secondary: Adverse events	Primary: At the two-week follow-up, treatment success was reported in 79.5, 83.0 and 95.0% of patients who received permethrin, trimethoprim and sulfamethoxazole, and permethrin plus trimethoprim and sulfamethoxazole, respectively (P values not reported). At the four-week follow-up, successful treatment was reported for 72.0, 78.0 and 92.5% of those receiving permethrin, trimethoprim and sulfamethoxazole, and permethrin with trimethoprim and sulfamethoxazole groups, respectively (P values not reported). The absolute risk reduction for recurrence comparing permethrin to trimethoprim and sulfamethoxazole was 6%, trimethoprim and sulfamethoxazole to permethrin combined with trimethoprim and sulfamethoxazole was 14%, and permethrin vs permethrin combined with trimethoprim and sulfamethoxazole was 20% (P=0.03).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
suspension 10 mg/kg/day				Secondary: There were three trimethoprim and sulfamethoxazole-related rashes. Of the 115 participants, eight had minor adverse reactions to the treatment.
Meinking et al[38] Malathion 0.5% gel administered for 30, 60 or 90 minutes or malathion lotion 0.5% vs permethrin crème rinse 1%	AC, PG, RCT, investigator-blinded Patients with ≥3 live lice and 10 viable eggs	N=174 15 days	Primary: Efficacy (cure rate) Secondary: Safety results	Primary: At the end of the treatment period, malathion gel had a cure rate of 98, 93 and 86% when administered for 30, 60 or 90 minutes, respectively (P<0.05 for all time periods). Malathion lotion had a cure rate of 97% (P=0.0006). All groups were compared to permethrin which had a cure rate of 45%. Secondary: Adverse events were mild to moderate with erythema, headaches and nausea being the most common across all treatment groups.
Stough et al[39] Spinosad 0.9% topical suspension without nit combing vs permethrin 1% topical solution with nit combing vs spinosad 0.9% topical suspension with nit combing	2 AC, MC, PG, RCT, SB Healthy patients ≥6 months of age with head lice	N=1,038 14 days (up to 21 days for patients who received a second course of treatment)	Primary: Efficacy (cure rate) Secondary: Proportion of patients requiring one or two treatments	Primary: Treatment with spinosad without nit combing resulted in a significantly greater proportion of lice-free patients 14 days after treatment compared to permethrin with nit combining (P<0.001 for both trials). Results were similar when data from all of the patients (primary and nonprimary) were analyzed regardless of how many treatments were received. Both treatments were well tolerated, and no severe adverse events were reported. The most common adverse events were eye and scalp irritation. Overall, spinosad-treated patients had fewer adverse events; however, only application site erythema was significantly more frequent with permethrin-treated patients (P=0.007). Secondary: Overall, the majority of spinosad-treated patients (with or without nit combining) required only one treatment application for complete

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				eradication of lice, whereas the majority of permethrin-treated patients required two treatments. In trial one, 94.2 and 68.1% of spinosad without nit combining- and permethrin with nit combing-treated patients required only one treatment (P value not reported). The corresponding numbers in trial two were 93.1 and 62.4%, respectively (P value not reported). After two treatments, 55.7 and 64.3% of spinosad without nit combing-treated patients were lice-free in both trials, compared to 33.3 and 27.1% of permethrin with nit combing-treated patients (P values not reported).

*Not available in the United States.
Study abbreviations: AC=active control, CI=confidence interval, CR=cluster randomized, CT=controlled trial, DB=double-blind, DD=double-dummy, ES=extension study, ITT=intent-to-treat, MC=multicenter, OL= open-label, PC=placebo controlled, PG=parallel-group, PRO=prospective, R=randomized, RCT=randomized controlled trial, SB=single-blind.

Special Populations

Table 5. Special Populations[1,3-10]

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Single-Entity Agents					
Benzyl alcohol	Safety and efficacy in elderly patients have not been established. FDA-approved for use in children ≥6 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown; caution is advised.
Crotamiton	Safety and efficacy in elderly patients have not been established. Not approved for use in pediatric populations.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Unknown: caution is advised.
Ivermectin	Safety and efficacy in elderly patients have not been established. FDA-approved for use in children ≥6 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Yes*
Lindane	Safety and efficacy in elderly patients have not been established. Should not be used in very young children or premature infants due to risk of seizures and death.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	C	Enters breast milk; use is contra-indicated.
Malathion	Safety and efficacy in elderly patients	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown: risk cannot be ruled out;

Generic Name	Population and Precaution				
	Elderly/ Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	have not been established. FDA-approved for use in children ≥6 years of age.				caution is advised.
Permethrin	Safety and efficacy in elderly patients have not been established. FDA-approved for use in children ≥2 months of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	Unknown: risk cannot be ruled out; caution is advised.
Spinosad	Safety and efficacy in elderly patients have not been established. FDA-approved for use in children ≥4 years of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	B	No
Combination Products					
Piperonyl butoxide and pyrethrins	Safety and efficacy in elderly patients have not been established. FDA-approved for use in children ≥2 years of age.	Not studied in renal dysfunction.	Not studied in hepatic dysfunction.	Piperonyl butoxide- Unknown Pyrethrins- C	Unknown: risk cannot be ruled out; caution is advised.

FDA=Food and Drug Administration.
* Following oral administration, ivermectin is excreted in human milk in low concentrations; this has not been evaluated following topical administration.

Adverse Drug Events

Table 6. Adverse Drug Events (%)[1,3-10]

Adverse Event(s)	Single-Entity Agents							Combination Products
	Benzyl alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad	Piperonyl Butoxide and Pyrethrins
Central Nervous System								
Ataxia	-	-	-	✔	-	-	-	-
Dizziness	-	-	-	✔	-	-	-	-
Fever	-	-	-	-	-	✔	-	-
Headache	-	-	-	✔	-	✔	-	-
Pain	-	-	-	✔	-	-	-	-
Seizures	-	-	-	✔	-	✔	-	-
Dermatological								
Alopecia	-	-	-	✔	-	-	0.1 to 1	-
Application site dryness/exfoliation	-	-	-	-	-	-	0.1 to 1	-
Dermatitis	-	✔	<1	✔	-	-	-	-
Dry skin	-	-	<1	-	-	-	0.1 to 1	-
Erythema	10	-	-	-	-	1 to 10	3	-
Itching	-	-	-	-	-	✔	-	-
Irritation of skin and scalp	-	✔	-	-	✔	-	1	✔
Mild transient burning/stinging	-	-	<1	✔	-	1 to 10	-	✔
Numbness	-	-	-	-	-	1 to 10	-	-
Pruritus	12	✔	-	✔	-	1 to 10	-	✔
Pyoderma	7	-	-	-	-	-	-	-
Rash	-	✔	-	-	-	1 to 10	-	-
Urticaria	-	-	-	✔	-	-	-	-
Gastrointestinal								
Abdominal pain	-	-	-	-	-	✔	-	-
Diarrhea	-	-	-	-	-	✔	-	-
Nausea	-	-	-	✔	-	✔	-	-

Adverse Event(s)	Single-Entity Agents							Combination Products
	Benzyl alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad	Piperonyl Butoxide and Pyrethrins
Vomiting	-	-	-	✔	-	✔	-	-
Other								
Aplastic anemia	-	-	-	✔	-	-	-	-
Cardiac arrhythmia	-	-	-	✔	-	-	-	-
Conjunctivitis (if eye contact)	-	-	<1	-	✔	-	-	-
Edema	-	-	-	-	-	1 to 10	-	-
Hematuria	-	-	-	✔	-	-	-	-
Hepatitis	-	-	-	✔	-	-	-	-
Ocular edema	-	-	-	-	-	-	2	-
Ocular irritation/hyperemia	6	-	<1	-	-	-	2	-
Paresthesia	-	-	-	✔	-	-	-	-
Pulmonary edema	-	-	-	✔	-	-	-	-

* Malathion is an insecticide/pesticide. Inadvertent transmucosal will manifest as excessive cholinergic activity (e.g., increased sweating, salivary and gastric secretion, gastric and uterine motility, and bradycardia). Additionally, malathion contains flammable alcohol and should not be exposed to an open flame or electric heat, including hair dryers and electric curlers.

✔ Frequency not specified (includes post marketing and case reports).

- Event not reported.

Contraindications

Table 7. Contraindications[3-10]

Contraindication(s)	Single-Entity Agents							Combination Products
	Benzyl alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad	Piperonyl Butoxide and Pyrethrins
Sensitivity or allergy to any active or inactive ingredient in the product	-	✔	-	✔	✔	✔	-	✔

Contraindication(s)	Single-Entity Agents							Combination Products
	Benzyl alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad	Piperonyl Butoxide and Pyrethrins
Use in infants <2 months of age	-	-	-	-	-	✔*	-	-
Use in neonates and infants; scalps are more permeable and may have increased absorption	-	-	-	-	✔	-	-	-
Use in patients with crusted (Norwegian) scabies and other skin conditions (e.g., atopic dermatitis, psoriasis) that may increase systemic absorption of the drug	-	-	-	✔	-	-	-	-
Use in patients with known uncontrolled seizure disorders	-	-	-	✔	-	-	-	-
Use in premature infants	-	-	-	✔	-	-	-	-

*Lotion formulation.

Warnings/Precautions

Table 8. Warnings and Precautions[3-10]

Warning(s)/ Precaution(s)	Single-Entity Agents							Combination Products
	Benzyl alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad	Piperonyl Butoxide and Pyrethrins
Accidental ingestion in pediatric patients may occur; administer only under direct adult supervision	-	-	✔	-	-	-	-	-

Warning(s)/ Precaution(s)	Single-Entity Agents							Combination Products
	Benzyl alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad	Piperonyl Butoxide and Pyrethrins
Acutely inflamed skin or raw or weeping surface; product should not be applied until the acute inflammation has subsided	-	✔	-	-	-	-	-	-
Benzyl alcohol toxicity; not recommended in infants <6 months old; potential for increased systemic absorption	-	-	-	-	-	-	✔	-
Chemical burns including second-degree burns and stinging sensation	-	-	-	-	✔	-	-	-
Contact dermatitis	✔	-	-	-	-	-	-	-
Eye irritation; avoid eye exposure and flush immediately with water if comes into contact with eyes	✔	✔	-	✔	✔	-	-	-
Flammable; wet hair and lotion should not be exposed to open flames or electric heat sources, smoking should be avoided when applying product or while hair is wet, and hair should be allowed to dry naturally and remain uncovered after application	-	-	-	-	✔	-	-	-
Neonatal toxicity; risk of gasping syndrome if used in neonates	✔	-	-	-	-	-	-	-

Warning(s)/ Precaution(s)	Single-Entity Agents							Combination Products
	Benzyl alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad	Piperonyl Butoxide and Pyrethrins
Pregnancy; if the person applying could be pregnant, contact should be avoided, other treatments may be preferable in pregnant patients	-	-	-	✔	-	-	-	-
Seizures and deaths have been reported following use with repeat or prolonged application, but also in rare cases following a single application used according to directions	-	-	-	✔	-	-	-	-
Severe irritation or sensitization; treatment should be discontinued and appropriate therapy should be instituted	-	✔	-	-	-	-	-	-
Skin irritation; discontinue product until resolves and reapply, if irritation occurs then physician should be consulted	-	-	-	-	✔	-	-	-
Skin irritation; treatment may exacerbate symptoms of itching, redness, and swelling	-	-	-	-	-	✔	-	-
Use in children; product should only be used on children under the direct supervision of an adult, keep out of reach of	✔	-	-	-	✔	-	-	-

Warning(s)/ Precaution(s)	Single-Entity Agents							Combination Products
	Benzyl alcohol	Crotamiton	Ivermectin	Lindane	Malathion	Permethrin	Spinosad	Piperonyl Butoxide and Pyrethrins
children								
Use in infants, children, the elderly, and individuals with other skin conditions (e.g., atopic dermatitis, psoriasis) and in those who weigh less than 50 kilograms; caution recommended as they may be at risk of serious neurotoxicity	-	-	-	✔	-	-	-	-

Black Box Warning for Lindane[8]

WARNING
Only use lindane in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of scabies. Neurologic toxicity: Seizures and deaths have been reported following lindane use with repeat or prolonged application, but also in rare cases following a single application used according to directions. Exercise caution when using lindane in infants, children, the elderly and individuals with other skin conditions (e.g., atopic dermatitis, psoriasis) and in those who weigh less than 110 lbs (50 kg) as they may be at risk of serious neurotoxicity. Contraindications: Lindane is contraindicated in premature infants and individuals with known uncontrolled seizure disorders. Proper use: Instruct patients on the proper use of lindane, the amount to apply, how long to leave it on, and avoiding retreatment. Inform patients that itching occurs after the successful killing of scabies and is not necessarily an indication for retreatment with lindane.

Drug Interactions

There are no significant drug interactions with the scabicides and pediculicides.[3-10] Lindane should be used with caution with any drug that is known to lower the seizure threshold. These include antipsychotics, antidepressants, theophylline, cyclosporine, mycophenolate, tacrolimus, penicillins, imipenem, fluoroquinolones, chloroquine, isoniazid, meperidine, radiographic contrast media, centrally active anticholinesterases, and methocarbamol.[8]

Dosage and Administration

Table 9. Dosing and Administration[3-10]

Generic Name	Adult Dose	Pediatric Dose	Availability
Single-Entity Agents			
Benzyl alcohol	Head lice: Lotion: apply sufficient lotion to dry hair to completely saturate the scalp; leave for 10 minutes, then rinse off with water; repeat treatment after seven days	Head lice: Lotion: apply sufficient lotion to dry hair to completely saturate the scalp; leave for 10 minutes, then rinse off with water; repeat treatment after seven days	Lotion: 5% (227 g/bottle)
Crotamiton	Scabies: Cream, lotion: prior to application, patients should bathe or shower. A thin layer of cream or lotion should be thoroughly massaged into all skin surfaces from the chin down to the toes including all skin folds and creases. Crotamiton is left on the skin and a second application is advisable 24 hours later. The patient should take a	Scabies: Cream, lotion: prior to application, patients should bathe or shower. A thin layer of the cream or lotion should be thoroughly massaged into all skin surfaces from the chin down to the toes including all skin folds and creases. Crotamiton is left on the skin and a second application is advisable 24 hours later. The patient should take a	Cream: 10% (2 oz/ tube) Lotion: 10% (2 oz/bottle, 16 oz/bottle)

Generic Name	Adult Dose	Pediatric Dose	Availability
	cleansing bath 24 to 48 hours after the last application to remove any remaining drug. Patients can be retreated after seven days if live mites appear or if no clinical improvement is observed	cleansing bath 24 to 48 hours after the last application to remove any remaining drug. Patients can be retreated after seven days if live mites appear or if no clinical improvement is observed Due to potential lindane toxicity, crotamiton is a drug of choice for young children and pregnant or lactating women in the treatment of scabies. However, crotamiton is not approved by the Food and Drug Administration (FDA) for the treatment of scabies in pediatric patients.	
Ivermectin	Head lice: Lotion: apply to dry hair in an amount sufficient (up to one tube) to thoroughly coat the hair and scalp. Leave lotion in place for 10 minutes and then rinse off with water.	Head lice: Lotion: apply to dry hair in an amount sufficient (up to one tube) to thoroughly coat the hair and scalp. Leave lotion in place for 10 minutes and then rinse off with water. This should be used in children six months or older.	Lotion: 0.5% (4 oz/tube)
Lindane	Head and pubic lice: Shampoo: apply a sufficient quantity of shampoo onto clean, dry hair; generally one ounce is sufficient, no more than two ounces should be used. Work the shampoo into hair thoroughly and allow remaining on hair for four minutes. Add small quantities of water and massage until a good lather forms. Rinse thoroughly and towel dry briskly. Nits should be removed using a nit comb or tweezers. Retreatment is not recommended Scabies: Lotion: one ounce of lindane is generally sufficient to treat the average adult. Do not use more than two ounces for larger adults. The lotion	The use of lindane should be avoided in infants and young children due to a higher incidence of adverse reactions in this age group.	Lotion: 1% (2 oz/bottle) Shampoo: 1% (2 oz/bottle)

Generic Name	Adult Dose	Pediatric Dose	Availability
	should be applied thinly and rubbed in thoroughly. Avoid applying lindane to open cuts. The lotion should be left on for 8 to 12 hours and removed by thorough washing. Retreatment is not recommended		
Malathion	Head lice: Lotion: apply to dry hair in an amount sufficient to thoroughly wet the hair and scalp. Allow hair to dry naturally, do not use an electric heat source, and allow hair to remain uncovered. After 8 to 12 hours, the hair should be shampooed. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs. If lice are still present after seven to nine days, repeat with a second application of lotion	Head lice: Lotion: apply to dry hair in an amount sufficient to thoroughly wet the hair and scalp. Allow hair to dry naturally, do not use an electric heat source, and allow hair to remain uncovered. After 8 to 12 hours, the hair should be shampooed. Rinse and use a fine-toothed (nit) comb to remove dead lice and eggs. If lice are still present after seven to nine days, repeat with a second application of lotion This should be used in children six months or older.	Lotion: 0.5% (2 oz/ bottle)
Permethrin	Head lice: Cream, lotion: a sufficient volume (25 to 50 mL) applied to saturate the hair and scalp. A second application may be indicated if live lice are present seven days or more after the initial application Scabies: Cream: 30 g is usually sufficient for an average adult to provide for a single head to toe application. Repeat dose 14 days later if living mites are observed	Head lice: Cream, lotion: a sufficient volume (25 to 50 mL) applied to saturate the hair and scalp. A second application may be indicated if live lice are present seven days or more after the initial application Scabies: Cream: 30 g is usually sufficient for an average adult to provide for a single head to toe application. Repeat dose 14 days later if living mites are observed This should be used in children two months or older.	Cream: 5% (2 oz/tube) Liquid: 1% (2 oz/bottle) Lotion: 1% (2 oz/bottle, 4 oz/bottle)
Spinosad	Head lice: Suspension: apply sufficient amount to cover dry scalp, then apply to dry hair. Depending on hair length,	Head lice: Suspension: apply sufficient amount to cover dry scalp, then apply to dry hair. Depending on hair length,	Topical Suspension: 0.9% (4 oz/bottle)

Generic Name	Adult Dose	Pediatric Dose	Availability
	apply up to 120 mL (one bottle) to adequately cover scalp and hair. Leave on for 10 minutes, and then thoroughly rinse off with warm water. If live lice are seen seven days following the first treatment, a second treatment should be applied	apply up to 120 mL (one bottle) to adequately cover scalp and hair. Leave on for 10 minutes, and then thoroughly rinse off with warm water. If live lice are seen seven days following the first treatment, a second treatment should be applied This should be used in children four years of age or older.	
Combination Products			
Piperonyl butoxide and pyrethrins	Head, body and pubic lice: Solution: the undiluted liquid should be applied to dry hair and scalp or to any infested area until entirely wet. The liquid should not be used on the eyelashes or eyebrows Shampoo: apply to the affected area until all hair is thoroughly wet and allowed to stand for no longer than 10 minutes. Then, the area should be washed with warm water and shampoo or soap. A fine-toothed comb, usually supplied with the product, should be used to remove dead lice and ova. The treatment should be repeated in 7 to 10 days to assure eradication of unhatched nits. Two consecutive applications should not be administered within 24 hours	Head, body and pubic lice: Solution: the undiluted liquid should be applied to dry hair and scalp or to any infested area until entirely wet. The liquid should not be used on the eyelashes or eyebrows Shampoo: apply to the affected area until all hair is thoroughly wet and allowed to stand for no longer than 10 minutes. Then, the area should be washed with warm water and shampoo or soap. A fine-toothed comb, usually supplied with the product, should be used to remove dead lice and ova. The treatment should be repeated in 7 to 10 days to assure eradication of unhatched nits. Two consecutive applications should not be administered within 24 hours This should be used in children two years of age or older.	Gel: 4/0.33% (each kit) Shampoo: 4/0.33% (each kit) Solution: 4/0.33% (each kit)

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
Centers for Disease Control and	• Treatment for head lice is recommended for persons diagnosed with an active infestation. All household members and other close contacts should

Clinical Guideline	Recommendations
Prevention: **Treatment of Head Lice (2010)**[40]	be checked; those persons with evidence of an active infestation should be treated. • Some experts believe prophylactic treatment is prudent for persons who share the same bed with actively-infested individuals. All infested persons (household members and close contacts) and their bedmates should be treated at the same time. • Retreatment of head lice usually is recommended because no approved pediculicide is completely ovicidal. To be most effective, retreatment should occur after all eggs have hatched and before new eggs are produced. The retreatment schedule can vary depending on whether the pediculicide used is ovicidal. • When treating head lice, non-pharmacologic measures can be combined with recommended medicine; however, such measures generally are not required to eliminate a head lice infestation. <u>Over-the-counter medications</u> • Pyrethrin or permethrin-containing products are approved by the Food and Drug Administration (FDA) for the treatment of head lice and are available over-the-counter. • Pyrethrins only kill live lice, not unhatched eggs (nits). A second treatment is recommended on day nine to kill newly hatched lice before they produce new eggs. • Permethrin is a synthetic pyrethroid similar to naturally occurring pyrethrins. Permethrin kills live lice but not unhatched eggs. Permethrin may continue to kill newly hatched lice for several days after treatment. A second treatment often is necessary on day nine to kill newly hatched lice before they produce new eggs. <u>Prescription medications</u> • Malathion is pediculicidal and partially ovicidal. A second treatment is recommended if live lice still are present seven to nine days after treatment. • Benzyl alcohol lotion 5% kills live lice but does not kill unhatched lice eggs. A second treatment is required nine days after the first treatment to kill any newly hatched lice before they can produce new eggs. • Ivermectin is not ovicidal, but appears to prevent nymphs (newly hatched lice) from surviving. It is effective when given as a single application on dry hair without nit combing. Retreatment should not occur before discussions with the health care provider. • Spinosad kills live lice and unhatched eggs and as a result, retreatment is usually not needed and nit combing is not required. Treatment should not be repeated if live (crawling) lice are seen seven days after the first treatment. • For second-line treatment only: Lindane is an organochloride. The American Academy of Pediatrics no longer recommends using this agent for the treatment of lice. Incorrect use of lindane can be neurotoxic; its use should be restricted to patients for whom prior treatments have failed or who cannot tolerate safer medications. Lindane should not be used to treat premature infants, persons with human immunodeficiency virus, a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 lbs. Retreatment with lindane should be avoided.

Clinical Guideline	Recommendations
American Academy of Pediatrics: **Clinical Report-Head Lice (2010)**[41]	Treatment • Therapy could be initiated with permethrin 1% or pyrethrins when resistance to these products is not suspected. These agents are available over-the-counter without a prescription. • Malathion 0.5% can be used in people who are ≥24 months of age when resistance to permethrin or pyrethrins is documented or when treatment with these products fails despite their correct use. • Other treatments can be considered for people who cannot afford or who wish to avoid pediculicides. Improper application of the pediculicide should be considered first as a cause of treatment failure. • Permethrin is the most studied pediculicide in the United States (U.S.) and is the least toxic to humans. Permethrin is less allergenic than pyrethrins and does not cause allergic reactions in individuals with plant allergies. Permethrin leaves a residue on the hair that kills nymphs emerging from the 20 to 30% of eggs not killed by the first application. However, conditioners and silicone-based additives present in almost all currently available shampoos impair permethrin adherence to the hair shaft and reduce its residual effect. Application should be repeated in seven to 10 days if live lice are seen. Many experts now recommend routine retreatment, preferably on day nine. An alternate treatment schedule on days zero, seven, and 13 to 15 has been proposed for nonovicidal products. • Resistance to 1% permethrin has been reported, but the prevalence of this resistance is not known. • Pyrethrins are formulated with piperonyl butoxide. Pyrethrins are neurotoxic to lice but have extremely low mammalian toxicity. Pyrethrins are applied to dry hair and left on for 10 minutes before rinsing out. No residual pediculicidal activity remains after rinsing. In addition, none of these natural pyrethrins are totally ovicidal and 20 to 30% of the eggs remain viable after treatment, requiring a second treatment. New evidence based on the life cycle of lice suggests that retreatment at day nine is optimal. An alternate schedule of three treatments with nonovicidal products on days zero, seven, and 13 to 15 has been proposed. • Malathion is a prescription lotion that is applied to dry hair, left to air dry, then washed off after eight to 12 hours. The current U.S formulation of malathion differs from the malathion products available in Europe in that it contains terpineol, dipentene, and pine needle oil, which themselves have pediculicidal properties and may delay development of resistance. Malathion has high ovicidal activity, and a single application is adequate for most patients. The product should be reapplied in seven to nine days if live lice are still seen. Due to the high alcohol concentration of the product it is highly flammable. • Benzyl alcohol 5% is kills head lice by asphyxiation. Benzyl alcohol is available by prescription and is not ovicidal. It should be applied topically for 10 minutes and repeated in seven days, although as with other nonovicidal products, consideration should be given to retreating in nine days or using three treatment cycles. • Lindane is an organochloride that has central nervous system toxicity in humans. It has low ovicidal activity (30 to 50% of eggs are not killed), and resistance has been reported worldwide for many years. For these reasons, it should be used cautiously. The FDA has warned that lindane shampoo should only be used for patients who cannot tolerate or whose infestation has failed to respond to first-line treatment with safer medications for the

Clinical Guideline	Recommendations
	treatment of head lice.
Center for Disease Control and Prevention Morbidity and Mortality Weekly Report: **Sexually Transmitted Diseases Treatment Guidelines (2010)**[42]	Pediculosis pubis (pubic lice infestation) • Recommended regimens include permethrin 1% cream rinse applied to affected areas and washed off after 10 minutes or piperonyl butoxide and pyrethrins applied to the affected area and washed off after 10 minutes. • Alternative regimens include malathion 0.5% lotion applied for eight to 12 hours and washed off or ivermectin 250 µg/kg orally repeated in two weeks. Scabies • Recommended regimens include permethrin 5% cream applied to all areas of the body from the neck down and washed off after eight to 14 hours or ivermectin 200 µg/kg orally, repeated in two weeks. • Alternative regimens include lindane 1% lotion (one ounce) or cream (30 g) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after eight hours.
Centers for Disease Control and Prevention: **Treatment of Scabies (2010)**[43]	Suggested general guidelines • Lotion or cream should be applied to all areas of the body from the neck down to the feet and toes. When treating infants and young children, scabicide lotion or cream also should be applied to their entire head and neck because scabies can affect their face, scalp, and neck, as well as the rest of their body. The lotion or cream should be applied to a clean body and left on for the recommended time before washing it off. Clean clothing should be worn after treatment. Medications • Permethrin is the drug of choice for the treatment of scabies and is approved in persons at least two months of age. Permethrin kills scabies mite and eggs. Two (or more) applications may be necessary to eliminate all mites, particularly when treating crusted (Norwegian) scabies. • Crotamiton is approved for the treatment of scabies in adults. Crotamiton is not approved for use in children. This agent is frequently associated with treatment failure. • Lindane is not recommended as a first-line therapy. Incorrect use of lindane can be toxic to the brain and other parts of the nervous system; its use should be restricted to patients who have failed recommended therapies or who cannot tolerate recommended treatments. Lindane should not be used to treat premature infants, persons with a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 lbs. • Oral ivermectin may be safe and effective for the treatment of scabies; however, ivermectin is not approved for this use. Oral ivermectin has been reported effective in the treatment of crusted scabies; its use should be considered for patients who have failed treatment with or who cannot tolerate topical medications for the treatment of scabies. The dosage of ivermectin is 200 µg/kg orally. Two or more doses at least seven days apart may be necessary to eliminate a scabies infestation. The safety of ivermectin in children weighing less than 15 kg and in pregnant women has not been established.
Centers for Disease Control and Prevention:	Medications • A lice-killing lotion containing 1% permethrin or a mousse containing pyrethrins and piperonyl butoxide can be used to treat pubic lice. These

Clinical Guideline	Recommendations
Treatment of Pubic Lice (2010)[44]	products are available over-the-counter without a prescription and are safe and effective when used according to instructions on the package. • Lindane shampoo is a prescription medication that can kill lice and lice eggs. However, lindane is not recommended as a first-line therapy. Lindane can be toxic to the brain and other parts of the nervous system; its use should be restricted to patients who have failed treatment with recommended therapies. Lindane should not be used to treat premature infants, persons with a seizure disorder, women who are pregnant or breast-feeding, persons who have very irritated skin or sores where the lindane will be applied, infants, children, the elderly, and persons who weigh less than 110 lbs. • Malathion lotion is a prescription medication that can kill lice and some lice eggs but has not been approved by the FDA for this indication. • Oral ivermectin has been used successfully to treat lice; but only has not been approved by FDA for treatment of lice. Of note, in 2012, a topical formulation of ivermectin was approved for the treatment of head lice infestations.

Conclusions

The skin and mucous membrane scabicides and pediculicides are approved to treat pediculosis and scabies.[1-9] All of the products are available in a generic formulation, with the exception of benzyl alcohol, crotamiton and ivermectin.

Permethrin products are recommended as first-line therapy for treatment of scabies and lice, despite increasing resistance in the United States.[40,41,45] The topical insecticides exert their pediculicidal and scabicidal effects through their neurotoxic actions on lice. Benzyl alcohol acts via asphyxiation of the parasite rather than neuro excitation, theoretically lowering the risk of resistance.[3] Ivermectin and spinosad are two newer agents approved for the treatment of head lice.[6,7] Spinosad is not extensively metabolized, and therefore it is still present, and able to exert its effect when the lice eggs hatch and the nervous system develops. This may prevent the need for a second administration if no live lice are observed several days following the initial application.[6] Ivermectin has been approved for one-time use.[7] Lindane is reserved as second-line therapy and carries a Black Box Warning describing risk of neurotoxicity associated with its use. Other available agents offer alternative options should a resistant case occur, or if a patient fails first-line product.[40,45]

Overall, the comparative success rates of topical pediculicides have been shown to be approximately 57 to 99% with permethrin, 45 to 95% with piperonyl butoxide and pyrethrins, 60 to 88% with lindane and 78% with malathion. The newer agents which include benzyl alcohol, ivermectin and spinosad, have shown cure rates of 75%, 71 to 75% and 93 to 94%, respectively, although there is limited published literature confirming these results.[7,39] Permethrin is recommended as first-line therapy and lindane as second-line in the guidelines by the Centers for Disease Control (CDC) and the American Academy of Pediatrics.[40,45] Crotamiton also has a role as an antipruritic for those with scabies.[40] All patients treated for scabies should expect the rash and itching to continue for approximately two weeks after treatment.48 The CDC recommends permethrin for pediculosis pubis.[44]

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