TITLE: Lindane and Other Treatments for Lice and Scabies: A Review of Clinical Effectiveness and Safety

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CONTEXT AND POLICY ISSUES:

Head lice infestation (Pediculosis capitis) affects millions of children and adults worldwide each year.[1] Direct head-to-head contact is the most common mode of transmission.[2] The highest prevalence of infestation occurs in school aged children aged three to eleven years, with girls being more commonly affected than boys.[1,2] Although head lice are not generally associated with serious morbidity, they are responsible for significant social embarrassment and lost productivity in schools or offices.[1] Scabies, an infestation of the skin by the mite Sarcoptes scabiei, represents a common public health concern particularly in overcrowded communities with a high prevalence of poverty.[3] Scabies is transmitted by close-person contact and occasionally by clothing or linens.[3] Complications include secondary bacterial infections and post-streptococcal glomerulonephritis.[3]

Topical products available in Canada for the treatment of head lice and scabies are presented in Appendix 1 and Appendix 2. Insecticidal agents such as permethrin and lindane have historically been considered the standard treatments for head lice and scabies.[2,3] Toxicity is low following topical administration of permethrin due to minimal percutaneous absorption.[4] However, several jurisdictions have banned lindane due to concerns of neurotoxicity and bone marrow suppression, as well as potential negative effects on the environment (contamination of waste water).[5] Furthermore, widespread use of permethrin, pyrethrins/piperonyl butoxide, and lindane has led to resistance and higher rates of treatment failure.[6] Resistance patterns and rates to these agents in Canada have not yet been studied.[6]

Due to concerns surrounding resistance and neurotoxicity, patients and caregivers have searched for alternative treatments. Oral ivermectin (Stromectol®), a compound initially used to treat intestinal worms, is available through the Health Canada Special Access Programme for the treatment of lice and scabies.[7] The advantages of ivermectin are oral dosing, increased compliance, and lack of treatment associated dermatitis.[8] However, ivermectin is not recommended in pregnant and lactating women or in children who weigh less than 15 kg due

the risk of systemic adverse effects.[8] Additional products that have been investigated but are not currently available on the Canadian market include malathion (an organophosphate insecticide), and spinosad (a fermentation product of the soil bacterium Saccharopolyspora spinosa) that are both neurotoxic to the head louse.[9] Agents that do not have a neurotoxic mechanism of action have also been investigated due to the low possibility of resistance and neurotoxicity in humans. Health Canada has recently approved the use of isopropyl myristate 50% for the treatment of head lice in children four years of age and older.[6] This agent dissolves the waxy exoskeleton of the louse, leading to dehydration and death.[6] Other products not yet licensed for use in Canada, including benzyl alcohol, coconut and anise, and dimeticone, coat and asphyxiate the louse.[9-11]

An assessment of newer therapies is needed to guide treatment decisions in patients who have failed conventional treatments due to resistance, non-compliance, or adverse effects. This report reviews evidence for the clinical effectiveness and safety of interventions for the management of head lice and scabies.

RESEARCH QUESTIONS:

1. What is the safety of lindane for the treatment of patients with lice and scabies?

2. What is the clinical effectiveness and safety of alternative treatments for eradicating lice and scabies?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, The Cochrane Library (Issue 4, 2010), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI (Health Devices Gold), EuroScan, international health technology agencies, and a focused Internet search. The search was limited to English language articles published between January 1, 2005 and May 10, 2010. Filters were applied to limit the retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, controlled clinical trials and observational studies. This search was supplemented by hand searching the bibliographies of selected papers.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, systematic reviews and meta-analyses are presented first. These are followed by randomized controlled trials (RCTs), controlled clinical trials, and observational studies. RCTs not included in the identified systematic reviews were appraised separately in the report.

SUMMARY OF FINDINGS:

One systematic review[1] and eight RCTs[10-15] assessing the clinical effectiveness and safety of various interventions for the treatment of head lice were identified. No controlled clinical trials assessing interventions for head lice were identified. One systematic review,[16] two RCTs,[17,18] and one controlled clinical trial[19] assessing the clinical effectiveness and safety of various interventions for the treatment of scabies were identified. Two observational studies assessing the safety of interventions for the management of lice[20] and scabies[21] in pregnant women were identified. A United States (US) Food and Drug Administration (FDA) advisory on the safety of

topical lindane products used for the treatment of lice and scabies was also retrieved.[22] No health technology assessments for either indication were identified.

INTERVENTIONS FOR LICE:

Systematic reviews and meta-analyses

A systematic review evaluating different treatments for head lice was published in 2009.[1] A database search was used to identify systematic reviews or RCTs published between 1966 and June 2008. A total of 10 RCTs (1173 participants) and 1 systematic review (7 RCTs; 726 participants) were identified. A GRADE evaluation based on consistency of results across studies and the generalisability of populations or outcomes was performed to evaluate the quality of the evidence for the interventions included in the review. This quality assessment did not consider methodological flaws regarding randomization, allocation concealment, or blinding.

Overall, the largest body of evidence was for the clinical effectiveness of permethrin compared with lindane. The evidence for the majority of treatment comparisons was ranked as either low or very low because of the limited number of studies. The authors noted that there were no standard criteria for judging treatment success or what constituted infestation.

Key findings are summarized below:

- Malathion lotion may be more effective for lice eradication than phenothrin or permethrin.
- Results from RCTs comparing malathion or permethrin to wet combing were conflicting. This may have been the result of varying resistance patterns based on geographic location.
- Permethrin was more effective for eradicating lice than lindane. Although lindane has been associated with central nervous system toxicity, there were no reports of serious adverse effects in the identified trials.
- Adding trimethoprim-sulfamethoxazole (TMP-SMX) to topical permethrin may be more effective for the eradication of lice than permethrin alone. However, several cases of severe itchiness were reported with the use of TMP-SMX.
- Dimeticone may be more effective for eradicating lice than malathion.
- Dimeticone and phenothrin appeared to be equally effective for the eradication of lice. Significantly fewer irritant scalp reactions were noted with dimeticone compared with phenothrin.
- Most interventions, with the exception of TMP-SMX, were generally well tolerated with no reports of serious adverse effects.
- There was insufficient evidence to judge whether combinations of insecticides increased effectiveness when compared with single insecticides or other treatments.

- There was insufficient evidence to assess the effectiveness of herbal oils compared with other treatments for head lice.

Based on these findings, the authors concluded that permethrin, malathion, and dimeticone were likely to be beneficial for the treatment of head lice.[1]

Randomized controlled trials

Details regarding study objectives, methods, outcomes, and the authors' conclusions from eight identified RCTs[10-15] are provided in Table 1.

Results are summarized below:

- A cluster-randomized trial (n=376 households; 812 patients) conducted in seven geographically diverse sites (four in the UK, and one each in Ireland, France and Israel) showed that for treatment-resistant head lice, oral ivermectin was statistically significantly superior to malathion lotion for eliminating lice.[12] There were no significant differences in adverse effects between the two treatment groups and younger children (age 2 to 5 years) in general had fewer adverse effects than older children (6 to 14 years). One serious adverse effect was observed in each treatment group. Trial limitations included unclear allocation concealment and a non-diverse study population.

- One RCT (n=100) conducted in the UK showed that a coconut and anise spray was statistically significantly more effective than permethrin lotion for the treatment of head lice.[10] Stinging or burning sensations on the scalp or neck were the most frequently reported adverse effects in both groups. No serious adverse effects were reported. Results may have been biased in favor of coconut and anise spray due to the lower dose of permethrin used (0.43% lotion versus the conventional 1% lotion). Other limitations included small sample size and caregivers that were not blinded to the intervention used. Randomization by patient rather than household cluster could have increased the risk of re-infestation by household members receiving the less effective treatment.

- Two cluster randomized trials (n=250 patients) conducted in ten geographically diverse sites in the US showed that benzyl alcohol 5% lotion is statistically significantly more effective than placebo for the management of head lice.[13] Application site irritation and numbness were the most frequently reported adverse effects in the benzyl alcohol group. Children as young as six months did not appear to have a higher risk of experiencing adverse effects than older children. There were no serious adverse effects reported in either group. Based on these findings, the FDA approved benzyl alcohol lotion in 2009 for use in patients six months of age or older. Trial limitations included small sample size and a lack of details regarding baseline clinical and demographic characteristics and methods for randomization. Allocation concealment or blinding were not reported.

- Two cluster randomized trials (n=347 households; 916 patients) conducted in 12 geographically diverse sites in the US indicated that spinosad was statistically significantly more effective than permethrin with nit-combing for the treatment of head

lice.[14] Most spinosad-treated participants were cured after one application, while most permethrin-treated patients required two applications. There were no severe adverse effects reported and overall, participants using spinosad had fewer adverse events than those using permethrin. Application-site swelling occurred statistically significantly more frequently in the permethrin group than in the spinosad group. Trial limitations included caregivers not being blinded to the intervention and unclear allocation concealment.

- Results from an RCT (n=145) conducted in Brazil suggested that dimeticone was statistically significantly more effective than permethrin for the eradication of head lice.[11] However, a reduction in the percentage of participants who were lice free from day 2 (the day after the first application) to day 7 (the day before the second application) suggests the possibility that dimeticone may not cure patients of head lice infestation after one application. Patients were only followed for a total of nine days (one day after the second treatment). Testing for head lice infestation on day 14 or later would be necessary to establish superiority of dimeticone over permethrin. Two cases of mild eye irritation occurred in the dimeticone group but no serious averse effects were reported. Trial limitations include a non-diverse study population, short follow-up, small sample size, caregivers not blinded to intervention, and unclear allocation concealment. Enrolled children were placed in a holiday resort for the duration of the study and allowed to play with each other regardless of the treatment received. This may have caused an underestimation of effectiveness due to re-infestation.

- Results from a RCT (n=60) conducted at one US center showed that isopropyl myristate was statistically significantly more effective than pyrethrins/piperonyl butoxide for the eradication of head lice.[15] However, 43.3% of participants in the isopropyl myristate required three applications. There were no significant differences between the two treatment groups in the frequency of adverse effects. Mild redness, rash, burning, stinging, and dry scalp were the most frequently reported adverse effects in both groups. No serious adverse effects were reported. Limitations included small sample size, caregivers that were not blinded to the intervention used, unclear allocation concealment, and a lack of reporting of baseline characteristics or methods for randomization. Randomization by patient rather than household cluster may have increased the risk of re-infestation by household members receiving the less effective treatment.

Table 1: Summary of results from RCTs evaluating interventions for lice

Objectives	Methods	Outcomes	Authors' Conclusions
Chosidow, 2010[12]			
To assess the efficacy and safety of oral ivermectin compared with malathion lotion for patients with difficult-to-treat head lice.	**Design** Multi-center, cluster-randomized, double-blind, double-dummy. (n=376 households; 812 patients). **Inclusion criteria** All household members (at least 2 years of age weighing at least 15 kg) with live lice not eradicated by a	**Lice-free on day 15** *ITT Population* Ivermectin 95.2% Malathion 85.0% Absolute difference 10.2% (95% CI 4.6 to 15.7; p<0.001)	For difficult-to-treat head lice infestation, oral ivermectin given twice a day at a 7-day interval has superior clinical effectiveness

Objectives	Methods	Outcomes	Authors' Conclusions
	pyrethroid-based or malathion insecticide 2 to 6 weeks before enrollment. **Population** 86.9% female Median age 10 years (interquartile range 7 to 14) Mean weight 40 ± 22 kg **Interventions** Ivermectin 400 μg/kg orally (n=398 patients) versus Malathion 0.5% lotion (n=414 patients) Each given as two applications at a 7-day interval. No other pediculicidal treatments (including nit combing) were permitted throughout the study. **Primary end point** The absence of head lice on day 15.	**Adverse effects** There were no significant differences between the two treatment groups in frequency of adverse effects. Abdominal pain and headache were the most frequently reported adverse effects in both groups. Younger children (age 2 to 5 years) had fewer adverse effects than older children (6 to 14 years). One serious adverse effect was reported in each group (convulsions in a 7-year old girl treated with ivermectin and severe headache in an 11-year old girl treated with malathion; both cases resolved).	when compared to topical 0.5% malathion lotion.
Burgess, 2010[10]			
To compare the efficacy of a coconut and anise spray with permethrin lotion for the management of head lice.	**Design** Single-center, assessor-blinded (single-blinded) (n=100) **Inclusion criteria** All family members at least 2 years of age with lice. **Population** 80.0% female Median age 10 years (range 2 to 49) **Interventions** Coconut and anise spray (n=50) versus Permethrin 0.43% lotion (n=50) Each given as two applications at a 9-day interval. Family members who were ineligible to participate were offered treatment with 4%	**Lice-free on day 14** *ITT Population* Coconut and anise 82.0% Permethrin 42.0% Absolute difference 40.0% (95% CI 22.5 to 57.5; p<0.0001) **Adverse effects** There were no significant differences in the frequency of adverse effects between the two treatment groups. Stinging or burning sensations on the scalp or neck were the most frequently reported adverse effects in both groups.	Coconut and anise spray can be a significantly more effective alternative treatment to permethrin for the treatment of head lice.

Objectives	Methods	Outcomes	Authors' Conclusions
	dimeticone lotion. **Primary end point** Elimination of infestation on day 14.	There were no reports of serious adverse effects.	
Meinking, 2010[13]			
To compare the clinical effectiveness and safety of benzyl alcohol with placebo for the management of head lice.	**Design** Two multi-center, cluster-randomized, double-blind, RCTs. (n=125 patients in each trial) **Inclusion criteria** Household members 6 months or older with live lice. The youngest household member was used for the primary efficacy endpoint. **Interventions** Benzyl alcohol 5% lotion (RCT1 n=63; RCT2 n=64) versus Placebo (RCT1 n=62; RCT2 n=61) Each given as two applications at a 7-day interval. **Primary end point** The absence of live lice 14 days after final treatment.	**Lice-free on day 14** *ITT Population RCT1* Benzyl alcohol 76.2% Placebo 4.8% Absolute difference 71.4% (95% CI 61.8 to 85.7; p<0.001) *ITT Population RCT2* Benzyl alcohol 75.0% Placebo 26.2% Absolute difference 48.8% (95% CI 31.1 to 62.0; p<0.001) **Adverse effects** There were no serious adverse effects reported in either group. Application site irritation and numbness were the most frequently reported adverse effect in the benzyl alcohol group. Children as young as 6 months did not appear to be at greater risk for adverse effects.	Benzyl alcohol lotion 5% should be a preferred alternative to currently approved pesticide products.
Stough, 2009[14]			
To compare the clinical effectiveness and safety of spinosad with permethrin for the management of head lice.	**Design** Two multi-center, cluster-randomized, assessor-blinded (single-blinded) RCTs. RCT1 (n=180 households; 499 patients), RCT2 (n=167 households; 417 patients) **Inclusion criteria** Household members 6 months or older with three or more live lice. The youngest household member	**Lice-free on day 14** *ITT Population RCT1* Spinosad 84.6% Permethrin 44.9% Absolute difference 39.7% (p<0.001) *ITT Population RCT2* Spinosad 86.7% Permethrin 42.9%	Spinosad is a more convenient and effective treatment than permethrin for the treatment of head lice.

Objectives	Methods	Outcomes	Authors' Conclusions
	was used for the primary efficacy endpoint. **Population** 81.8% to 86.4% female Mean age 15 to 17 years (range 0.5 to 84) **Interventions** Spinosad 0.9% creme rinse without nit-combing (RCT1 n=243; RCT2 n=203) versus Permethrin 1% creme rinse with nit-combing (RCT1 n=256; RCT2 n=214) Each given at a 7-day interval if live lice were present. No other pediculicidal treatments were permitted throughout the study. Family members not enrolled in the study were given pyrethrin 0.33% /piperonyl butoxide 4%. **Primary end point** The absence of live lice 14 days after last treatment.	Absolute difference 43.8% (p<0.001) **Patients cured after one application** Spinosad 63.8% to 86.2% Permethrin 39.7% to 35.5% (p value not reported) **Adverse effects** No serious adverse events were reported. The most frequently observed adverse effects in both groups were eye or scalp irritation. A significantly higher number of patients experienced application-site swelling in the permethrin group (31 versus 17 for spinosad; p=0.007).	
Heukelbach, 2008[11]			
To assess the efficacy and safety of dimeticone when compared to permethrin for the management of head lice.	**Design** Single-center, assessor-blinded (single-blinded). (n=145) **Inclusion criteria** Children aged between 5 and 15 years with one or more active head lice found by visual inspection. **Population** 24.8% female Median age 10 years (interquartile range 7 to 12) **Interventions** Dimeticone 92% (topical compounded product) (n=73) versus Permethrin 1% lotion (n=72)	**Lice-free on day 2** *ITT Population* Dimeticone 94.5% Permethrin 66.7% Absolute difference 27.8% (p<0.0001) **Lice-free on day 7** *ITT Population* Dimeticone 64.4% Permethrin 59.7% Absolute difference 4.7% (p=0.5) **Lice-free on day 9** *PP Population* Dimeticone 97.2% Permethrin 67.6%	Dimeticone is a safe and highly efficacious pediculicide.

Objectives	Methods	Outcomes	Authors' Conclusions
	Each given as two applications at a 7-day interval. Nit combing was not permitted after treatment. **Primary end point** The proportion of participants cured of head lice infestation 1 and 6 days after the first treatment and 1 day after the second treatment.	Absolute difference 29.6% (p<0.0001) **Adverse effects** No serious adverse events were reported. Two cases of mild eye irritation occurred in the dimeticone group.	
Kaul, 2007[15]			
To determine the safety and efficacy of isopropyl myristate 50% as a pediculicide rinse.	**Design** Single-center, assessor-blinded (single-blinded). (n=60) **Inclusion criteria** Presence of at least 3 live head lice at baseline evaluation. **Population (those that completed study)** 98.0% female Age range 4 to 56 years **Interventions** Isopropyl myristate 50% rinse (n=30) one to three applications given at a 7-day interval versus Pyrethrin 0.33%, piperonyl butoxide 4% (n=30) one to two applications given at a 7-day interval. One infested household member was treated with isopropyl myristate and the remainder in the household with the standard course of pyrethrin/piperonyl butoxide. **Primary end point** Absence of live lice on day 21.	**Lice-free on day 21** *PP Population* Isopropyl myristate 56.6% Pyrethrin/piperonyl butoxide 20% Absolute difference 36.6% (p<0.05) **Number of applications** 13 (43.3%) patients in isopropyl myristate group received three applications. 28 (93.3%) patients in pyrethrin/piperonyl butoxide group required two applications. **Adverse effects** There were no significant differences between the two treatment groups in the frequency of adverse effects. Mild redness, rash, burning, stinging, and dry scalp were the most frequently reported adverse effects in both groups. No serious adverse effects were reported.	Isopropyl myristate is a safe and effective therapy for the treatment of head lice in children and adults.

CI=confidence interval; ITT=intent-to-treat; PP=per-protocol

Observational studies

Kennedy et al. examined the safety of permethrin exposure during pregnancy in a prospective cohort study.[20] Women (n=113) who had called the Motherisk Program in Australia and MotherSafe Program in Canada to inquire about the safety of exposure to permethrin for the treatment of head lice were followed to determine the pregnancy outcome. These women were compared with a group (n=113) that had not been exposed to any known teratogenic drugs. The two groups were matched for age, smoking status, alcohol use, time of call, and trimester of exposure. The majority of women were followed-up for 6 to 12 months following delivery of their babies. Results showed no statistically significant differences between groups in any of the pregnancy outcomes (number of live births, spontaneous abortions, therapeutic abortions, major malformations, birth weight, or gestational age). Based on these finings, the authors concluded that the use of permethrin products during pregnancy appears to be relatively safe. However, the study may have been underpowered to detect a statistically significant difference in rare adverse effects due to the small sample size. Another major limitation was that only 31 (27.4%) women were exposed to permethrin during the first trimester.

INTERVENTIONS FOR SCABIES:

Systematic reviews and meta-analyses

Strong et al. published a Cochrane systematic review and meta-analysis in 2007.[16] A literature search was used to identify RCTs published up to March 2007 that compared therapies in children or adults with scabies. The primary outcome was treatment failure (defined as the persistence of original lesions, appearance of new lesions, or confirmation of a live mite). A total of 20 RCTs (2392 participants) with follow-up ranging from one week to one month were identified. Six RCTs described an adequate method of generating the random allocation sequence, six reported adequate allocation concealment, and two described both adequate random sequence generation and adequate allocation concealment. The degree of blinding was unclear in eight RCTs and losses to follow-up were greater than 20% of the enrolled participants in three RCTs. Seventeen of the 20 included studies were conducted in poorer countries with a high prevalence of scabies. Close and family contacts were treated in 14 of the 20 included RCTs. When pooling studies, the random effects model was used if significant heterogeneity was detected; otherwise a fixed effect model was used. A summary of results presented as relative risks (RR) of treatment failure is provided in Table 2.

Key findings are summarized below:

- Permethrin resulted in significantly fewer treatment failures when compared with lindane crotamiton, or ivermectin.
- Ivermectin resulted in significantly fewer treatment failures when compared with lindane or placebo.
- The examined trials failed to detect statistically significant differences in the percentage of treatment failures between ivermectin and benzyl benzoate, permethrin and natural synergized pyrethrins, crotamiton and lindane, lindane and sulfur, benzyl benzoate and sulfur, and benzyl benzoate and natural synergized pyrethrins.

- No serious adverse events were reported in any trial. However, some trials reported skin reactions to topical treatments as well as occasional incidences of headache, abdominal pain, diarrhea, vomiting, and hypotension.

- There was no evidence to judge the clinical effectiveness of malathion or herbal remedies for treating scabies.

Based on these findings, the authors concluded that in patients with scabies, topical permethrin was the most effective treatment. Ivermectin, although less effective than permethrin, was deemed an effective alternative. Limitations of the systematic review included significant heterogeneity in the geographic location, disease prevalence, drug regimens, and the duration of follow-up among trials that compared permethrin with lindane, or ivermectin with benzyl benzoate. This resulted in some uncertainty about the relative effectiveness of these agents. In particular, there was the possibility that in areas of high prevalence, cases of re-infection were more common and may be have been indistinguishable from primary treatment failures. The wide confidence interval around the treatment effect estimate for permethrin versus ivermectin showed uncertainty in the findings from the one small RCT available. Although no serious adverse effects were reported, the trials were not large enough to detect rare adverse effects.

Table 2: Summary of results from systematic review of interventions for scabies[16]

Comparison	Number of RCTs (number of participants)	RR* (95% CI) for Treatment Failure
Ivermectin versus placebo	1 (55)	0.24 (0.12 to 0.51)
Ivermectin versus permethrin	1 (85)	13.50 (1.84 to 99.26)
Ivermectin versus lindane	2 (193)	0.36 (0.23 to 0.58)
Ivermectin versus benzyl benzoate	3 (182)	0.50 (0.20 to 1.25)
Permethrin versus crotamiton	2 (194)	0.24 (0.10 to 0.55)
Permethrin versus lindane	5 (753)	0.32 (0.13 to 0.75)
Permethrin versus synergized natural pyrethrins	1 (40)	9.00 (0.52 to 156.91)
Crotamiton versus lindane	1 (100)	0.46 (0.19 to 1.12)
Lindane versus sulfur	1 (68)	1.13 (0.24 to 5.18)
Benzyl benzoate versus sulfur	1 (158)	3.10 (0.68 to 14.14)
Benzyl benzoate versus synergized natural pyrethrins	1 (240)	1.83 (0.70 to 4.80)

CI=confidence interval; RCT=randomized controlled trial; RR=relative risk
* A RR less than one favored the intervention of interest.

Randomized controlled trials

Details regarding study objectives, methods, outcomes, and the authors' conclusions from two identified RCTs[17,18] are summarized in Table 3.

Results are summarized below:

- An open-label RCT (n=103) conducted in India found benzyl benzoate, permethrin, and ivermectin to be equally effective for curing scabies two weeks after the first treatment.[17] No adverse effects were reported. These results were limited by the small sample size which may not have been powered to detect a statistically significant difference among the three treatments. Furthermore, the study had a high dropout rate, especially in the benzyl benzoate group (28.6%), compared with the permethrin (17.6%) and ivermectin (20.6%) groups. The study also lacked details on the baseline clinical characteristics and allocation concealment, and was not blinded.

- Ly et al. conducted an open-label RCT (n=181) in Senegal to compare the safety and efficacy of ivermectin with benzyl benzoate administered once or twice for scabies.[18] To reproduce real world conditions, drug administration was not supervised and compliance was assessed retrospectively by questioning the patients. Patients in the ivermectin group were statistically significantly more compliant than those randomized to either benzyl benzoate arm. The trial was stopped early following an intermediate analysis that showed that benzyl benzoate was statistically significantly more effective than ivermectin for curing scabies. Ivermectin also showed a statistically significantly higher rate of bacterial superinfection than the benzyl benzoate group. Statistically significantly more adverse effects occurred in participants randomized to benzyl benzoate than ivermectin. There were no reports of serious adverse effects. Allocation concealment was not reported and the trial was not blinded.

Table 3: Summary of results from RCTs evaluating interventions for scabies

Objectives	Methods	Outcomes	Authors' Conclusions
Bachewar, 2009[17]			
To compare the safety and efficacy of benzyl benzoate, permethrin, and ivermectin in patients with scabies.	**Design** Single-center, open-label (n=103) **Inclusion criteria** Patients with newly diagnosed scabies who were over the age of 12 years. **Population** 38.8% female Majority (84%) participants aged 12 to 41 years.	**Cure on day 7** Ivermectin 55.6% Permethrin 82.1% Benzyl benzoate 76.0% (p<0.05 for permethrin compared with ivermectin; p=NS for other comparisons) **Cure on day 14** Ivermectin 100% Permethrin 96.4% Benzyl benzoate 92.0% (p value not reported)	Benzyl benzoate should be used first-line for patients with scabies. Ivermectin may be used in non-responders. Benzyl benzoate and ivermectin were the two most cost-effective options.

Objectives	Methods	Outcomes	Authors' Conclusions
	Interventions Ivermectin 200 μg/kg orally (n=34) Permethrin 5% cream (n=34) Benzyl benzoate 25% lotion (n=35) Each given as two applications at a 7-day interval if there were no signs of improvement. All family members and close contacts were treated with benzyl benzoate 25% lotion. **Primary end point** Cure rate (defined as the absence of new lesions) on day 14.	**Adverse effects** No adverse effects were reported.	
Ly, 2009[18]			
To compare the effectiveness of oral ivermectin with benzyl benzoate applied once or twice for scabies.	Single center, open-label (n=181) **Inclusion criteria** Patients with scabies aged 5 to 65 years, weighing more than 15 kg. **Population** 35.9% female Mean age 16.6 years (range 5 to 63 years). **Interventions** Ivermectin 150-200 μg/kg orally given as a single dose (n=65) versus Benzyl benzoate 12.5% lotion given as a single application (BB1;n=68) or as two applications separated by 24 hours (BB2;n=48) Each treatment was repeated on day 7 and day 14 day if there were no signs of improvement. Family members included in the trial were	**Cure on day 14** *ITT Population* Ivermectin 24.6% BB1 54.4% BB2 68.8% (p <0.0001 for both BB groups combined versus ivermectin) **Cure on day 28** *ITT Population* Ivermectin 43.1% BB1 76.5% BB2 95.8% (p <0.0001 for both BB groups combined versus ivermectin) **Number of patients with poor compliance** Ivermectin 3 BB1 12 BB2 17 (p=0.002 ivermectin versus benzyl benzoate groups)	Topical benzyl benzoate, irrespective of the number of applications, is more effective than oral ivermectin for treating scabies in a Senegalese community.

Objectives	Methods	Outcomes	Authors' Conclusions
	treated with the same treatment as the index case. Family members not included in the trial were given one application of benzyl benzoate. **Primary end point** Cure (defined as the disappearance of skin lesions and itching) at day 14.	**Bacterial Superinfection** Ivermectin group 27.6% BB (combined) 7.8% (p=0.006) **Adverse effects** Irritant dermatitis occurred in 12 patients in the BB1 groups and 18 patients in the BB2 group. Gastrointestinal side effects occurred in 7 patients in the ivermectin group. There was a statistically significant difference in the frequency of adverse effects (p=0.02). There were no serious adverse effects reported.	

BB=benzyl benzoate; CI=confidence interval; ITT=intent-to-treat; NS=non-significant

Controlled clinical trials

Khan et al. compared the clinical efficacy and safety of oral ivermectin (n=15) with topical permethrin (n=15) for the treatment of scabies in a non-randomized open-label comparative study.[19] Patients 12 years of age or older either received two oral doses of 200 μg/kg ivermectin or permethrin 5% lotion at a seven-day interval. Efficacy was evaluated as cure (defined as the relief of symptoms and disappearance of all lesions) two weeks after treatment. Mean age was 35.93 ± 25.53 years in the ivermectin group and 37.80 ± 22.79 years in the permethrin group. Eleven (36.7%) patients were female. All patients completed therapy and the cure rate was 100% in both groups. No serious adverse effects were observed in either group. In the permethrin group, 86% of patients complained of local irritation. The authors concluded that ivermectin is a safe and effective alternative to permethrin for the treatment of scabies. Limitations of this study included a lack of randomization and blinding. Furthermore, this study was underpowered to detect a statistically significant difference between the two treatments.

Observational studies

Mytton et al. assessed the safety of benzyl benzoate or permethrin during pregnancy for the treatment of scabies in a retrospective cohort study.[21] Women in Thailand treated with either benzyl benzoate 25% lotion (n=444) or permethrin 4% lotion (n=196) were identified from a manual search of antenatal records. Each case of scabies was paired with four scabies-free controls matched for gravidity, age, smoking status, period of treatment, and gestational age at

treatment (n=1,1776 for benzyl benzoate; n=784 for permethrin). Results showed that there were no statistically significant differences for outcomes of pregnancy (proportion of abortions, congenital abnormalities, neonatal deaths, stillbirths, premature babies, mean birth weight, and gestational age). Women were statistically significantly more likely to receive a second treatment for scabies if the first treatment was benzyl benzoate (16.4% versus 9.7% with permethrin; p=0.038). Overall, only 66 (10.9%) of treatments occurred during the first trimester. The authors concluded that benzyl benzoate and permethrin are safe in the second and third trimesters of pregnancy. Study limitations included the low number of first trimester exposures, limited power to detect a statistically significant difference in pregnancy outcome, and a lower dose of permethrin used (4% lotion versus the conventional 5% lotion).

FDA Public Health Advisory

The FDA has issued an advisory concerning the use of lindane-containing products for the treatment of lice and scabies.[22] Post-marketing surveillance data presented in the report indicate that neurologic toxicity resulting in seizures and death has been reported following topical lindane therapy. However, most of these reports occurred in patients with contraindications to lindane and after prolonged or repeated application of lindane. Cases following a single application of lindane were uncommon. Twenty percent of patients with serious outcomes, including disability and hospitalizations, used lindane according to the directions on the label. All deaths occurred as a result of not using lindane in accordance with the label, including using multiple applications or oral ingestion. A safe interval for the reapplication of lindane has not been established. Based on these findings, the FDA stated that the benefits of lindane outweighs the risks when it is used as directed.

Limitations

- Systematic reviews of interventions for the management of lice or scabies identified limited numbers of comparative RCTs that were heterogeneous in terms of definitions for treatment outcomes, disease prevalence, drug regimens, and duration of follow-up.
- Majority of the studies were underpowered to detect infrequent potentially serious adverse events.
- Randomizing individuals rather than households (cluster randomization) may have affected the estimation of efficacy by increasing the potential for re-infestation from treatment failures within the household.
- Majority of the available studies in scabies were conducted in third world countries and were generally of poor quality (small sample size, unblinded).
- The small sample size and non-diverse study populations in many of the identified studies limited the generalizability of findings to other patient populations such as neonates, patients with significant comorbidities, pregnant or breastfeeding women, and the elderly.
- Two observational studies that assessed the safety of interventions for head lice or scabies in pregnant women were limited by the low number of women exposed to treatments in the first trimester. Furthermore, although the exposed and control groups in both studies were matched for various characteristics, observational studies have a higher potential for selection bias than RCTs.

CONCLUSIONS AND IMPLICATIONS FOR DECISION OR POLICY MAKING:

In summary, there are several promising new treatments for the management of head lice including ivermectin, malathion, benzyl alcohol, spinosad, isopropyl myristate, and dimeticone. However, benzyl alcohol has only been shown to be clinically effective compared to placebo. Further RCTs are needed to establish the clinical effectiveness of benzyl alcohol relative to other treatments for head lice. The available evidence suggests that permethrin and ivermectin may be the most clinically effective therapies for scabies. Due to limitations noted in the identified studies, further research is required to establish the clinical effectiveness of emerging therapies for lice and scabies.

Most interventions appeared to be well tolerated. One RCT reported seizures in one patient treated with ivermectin for head lice. The majority of the included studies were not powered to detect rare adverse effects. Larger studies and post-marketing surveillance is required to confirm the safety of newer interventions, particularly when used in neonates, the elderly, patients with significant comorbidities, and pregnant or lactating women. There have been reports of neurotoxicity and death with the use of lindane. However, most of these reports occurred following misuse of the product. There was no evidence of serious adverse effects associated with the use of lindane for lice or scabies in the identified systematic reviews.

Until further information is available, treatment decisions for patients with lice or scabies may be based on knowledge of local resistance patterns and individualized patient tolerability.

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Appendix 1: Products available in Canada for the treatment of head lice [23,24]

DRUG PRODUCTS	ADMINISTRATION	CONTRAINDICATIONS	ADVERSE EFFECTS
Permethrin 1% Kwelleda-P® Creme Rinse Nix® Creme Rinse	Shampoo hair, towel dry. Saturate hair and scalp and leave on for 10 minutes, rinse. Repeat after 7 days if live lice are observed.	Allergy to permethrin, any synthetic pyrethroid or pyrethrins, or to chrysanthemums. Safety and efficacy has not been evaluated in children under the age of 2 years, in pregnant or lactating women.	Itchiness, burning/stinging, tingling, numbness of scalp, redness, swelling; usually mild and transient.
Pyrethrins/piperonyl butoxide R&C® Shampoo/Conditioner Pronto® Lice Killing Shampoo	Saturate dry hair and scalp and leave on for 10 minutes. Apply a little water and work into lather, rinse. Repeat treatment in 7 to 10 days. Do not exceed 2 applications within 24 hours.	Allergy to ragweed, chrysanthemums or other pyrethrin products. Safety and efficacy has not been evaluated in children under the age of 2 years, in pregnant or lactating women.	Few adverse effects although contact dermatitis and eye irritation have been reported.
Isopropyl myristate 50% Resultz™	Apply to dry hair and scalp and leave on for 10 minutes, rinse. Repeat in 7 days	Should not be used in children under the age of 4 years.	May cause local irritation.
Lindane 1% Hexit™ Shampoo PMS-Lindane Shampoo	For head lice, apply shampoo to dry hair or skin. Massage for 4 minutes. Add water a little a time to produce a lather and massage for another 4 minutes, rinse. Do not re-treat with lindane if live lice are observed; consult physician.	Hypersensitivity to lindane, history of seizures, extensive dermatitis (e.g. psoriasis or atopic dermatitis), skin rash, skin abrasion, inflammation, Norwegian (crusted) scabies, premature neonates. Use with caution in children under the age of 6 years, pregnant or nursing women, and in patients weighing less than 50 kg.	Contact dermatitis, eczematous eruptions, itchiness, rash, burning, stinging. Inhalation of lindane vapors may lead to nausea, vomiting, headache, irritation of ears, nose and throat. Neurotoxicity (e.g. dizziness, seizures, death) has been reported after repeated or prolonged application, or in high-risk populations (e.g. young children, elderly, patients with extensive skin disease).

Appendix 2: Products available in Canada for the treatment of scabies [23,24]

DRUG PRODUCTS	ADMINISTRATION	CONTRAINDICATIONS	ADVERSE EFFECTS
Permethrin 5% Kwelleda-P® Lotion Nix® Dermal Cream	Massage into all skin areas from neck to soles of feet. Leave on for 12 to 14 hours then wash off. Repeat after 7 to 10 days if live mites or new lesions appear.	Allergy to permethrin, any synthetic pyrethroid or pyrethrins, or to chrysanthemums. Safety and efficacy has not been evaluated in children under the age of 2 years, or in pregnant or lactating women.	Itchiness, burning/stinging, tingling, redness, numbness, swelling; usually mild and transient.
Crotamiton 10% Eurax® Cream	Apply to cover entire skin surface from neck to toes and repeat in 24 hours; wash off 48 hours after last application. Repeat after 7 to 10 days if live mites still present.	Hypersensitivity to crotamiton. Not recommended for patients with exudative or vesicular dermatitis. Safety and efficacy has not been evaluated in children, or in pregnant or lactating women.	Local irritation, contact dermatitis, itching, rash.
Sulfur 5-10% (ointment extemporaneously compounded)	Apply to all skin areas from neck to soles of feet at bedtime daily for 5 to 7 days	Hypersensitivity to sulfur. Safe for children less than 2 months old and pregnant women.	Local irritation or dermatitis with repeated applications, malodourous.
Lindane 1% Hexit™ Lotion PMS-Lindane Lotion	Massage into all skin areas from neck to soles of feet. Leave on for 8 to 12 hours then wash off. Do not re-treat with lindane if live mites or new lesions appear; consult physician.	Hypersensitivity to lindane, history of seizures, extensive dermatitis (e.g. psoriasis or atopic dermatitis), skin rash, skin abrasion, inflammation, Norwegian (crusted) scabies, premature neonates. Use with caution in children under the age of 6 years, pregnant or nursing women, and in patients weighing less than 50 kg.	Contact dermatitis, eczematous eruptions, itchiness, rash, burning, stinging. Inhalation of lindane vapors may lead to nausea, vomiting, headache, irritation of ears, nose and throat. Neurotoxicity (e.g. dizziness, seizures, death) has been reported after repeated or prolonged application, or in high-risk populations (e.g. young children, elderly, patients with extensive skin disease).