Systematic review of clinical efficacy of topical treatments for head lice

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Abstract

Objectives—To collect and evaluate all trials on clinical efficacy of topical treatments for head lice.

Design—Systematic review of randomised trials identified from following data sources: Medline, International Pharmaceutical Abstracts, Science Citation Index, letters to key authors and companies, and hand search of journals.

Setting—Trials in schools or communities.

Subjects—Patients infested with lice.

Main outcome measure—Cure rate (absence of live lice and viable nits) on day 14 after treatment.

Results—Total of 28 trials were identified and evaluated according to eight general and 18 lice specific criteria. Of the 14 trials rated as having low to moderate risk of bias, seven were selected as they used the main outcome measure. These seven trials described 21 evaluations of eight different compounds and placebo (all but two evaluations were of single applications). Only permethrin 1% creme rinse showed efficacy in more than two studies with the lower 95% confidence limit of cure rate above 90%.

Conclusions—Only for permethrin has sufficient evidence been published to show efficacy. Less expensive treatments such as malathion and carbaryl need more evidence of efficacy. Lindane and the natural pyrethrins are not sufficiently effective to justify their use.

Introduction

Head lice are among the most common of human ectoparasites, though they are not vectors of serious diseases and in many cases do not cause symptoms.^{1,3} Treatment with natural pyrethrins has been known for more than 100 years, and lindane has been used since the second world war. The synthetic pyrethrins were marketed in the 1950s, malathion and carbaryl in the '60s, and permethrin in the '80s. Although products abound, the prevalence of head lice remains high and epidemics occur regularly despite all efforts at control.^{3,5} Problems such as fear of insects (entomophobia), fear of stigmatisation, and denial of infection by patients and schools may cause undertreatment, overtreatment, and unnecessary prophylaxis, which can lead to development of resistance and insufficient control of epidemics.⁶ Furthermore, many of the commercially available treatments might be underdosed, incorrectly labelled, or ineffective.

Our aim was to collect and evaluate all trials of clinical efficacy of topical treatments for head lice.^{7,8}

Methods

We searched for trials of topical treatments for people infested with head lice (*Pediculus humanus*

capitis) in which the outcome was measured clinically by inspection of the scalp to determine cure rate (absence of live lice and viable nits).

SEARCH STRATEGY

We searched the medical literature in Medline (1966 to March 1995 using the MESH keywords "Pediculosis," "Lice," "Pediculus"), in International Pharmaceutical Abstracts, and in the Science Citation Index without restriction for language of publication. We scanned the references of all identified clinical trials. We sent letters requesting information about unpublished studies to seven key authors in the subject, to the pharmaceutical companies active in this subject, and to the World Health Organisation centre Vector Biology Control. We hand searched journals in which key references were published for comments, letters, or corrections in the year after publication of the key reference.

REVIEW

We focused on clinical efficacy—the result of pediculidity, ovicidity, and residual activity—and so we chose cure rate as the main outcome measure for clinical evaluation. The cure rate is the percentage of patients cured after application of the treatment (the 95% confidence interval = $p \pm 1.96 \sqrt{p(100-p)/n}$, where p is the sample percentage and n the number of subjects in the study). Determination of the cure rate by experienced evaluators—on the basis of visual inspection for viable nymphs in nits, hatching nymphs, and adult lice (with a $\times 10$ magnifying lens)—has an acceptable specificity and sensitivity.⁹ We considered an interval of 14 days between treatment and evaluation to be optimal as this would allow evaluation of the combined effect of pediculidity (on living lice), ovicidity (on ripening eggs), and residual activity (on hatching nymphs and reinfesting lice).

We evaluated all identified clinical trials with regard to eight general criteria of quality in clinical trials (adapted from Chalmers *et al*¹⁰) and 18 criteria specific for head lice treatment (see table I). We developed these specific criteria after studying the literature to systematically screen the trials for flaws in design, execution, or reporting. Firstly, we made a structured abstract of each clinical trial according to recommended guidelines.¹¹ Each of us then independently assessed the trials. Trials were rejected if four or more flaws in general criteria or 12 or more flaws in treatment specific criteria were found. The remaining trials were rated as having a low risk of bias if less than eight specific criteria were flagged, or a moderate risk of bias if otherwise. Again, we set these cut off points for rating of quality after studying the literature. The structured abstracts, assessment scores, and overall ratings were submitted to an advisory panel (four physicians and a community pharmacist) and discussed until consensus was reached. Of the trials of

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TABLE I—Criteria of quality in evaluation of design, execution, and reporting of trials on clinical efficacy of topical treatment for head lice

Item No	Criterion
<i>General</i>	
1	Randomisation procedure
2	Concealment of allocation to patients
3	Concealment of allocation to investigators
4	Precision of definition of exclusion criteria
5	Handling and reporting of drop outs
6	Ethical procedures*
7	Statistical procedures
8	Appropriateness of conclusions
<i>Treatment specific</i>	
1	Documentation of prior exposure of screened population to pesticides (therapeutic or agricultural)
2	Documentation of history of previous lice treatment and comorbidity of index patients
3	Quality of informed consent procedure (involvement of parents)
4	Inclusion criteria (definition of "current" head lice infection)
5	Specification of the formulation of active ingredients
6	Storage and manipulation of pharmaceutical compound
7	Time and season of study
8	Prevalence of lice in study area
9	Standardisation of cotreatment and swimming
10	Identity of applicants and evaluators
11	Application procedure
12	Intensity of tracing contacts
13	Use of nit combs
14	Documentation of pediculicidity
15	Documentation of ovidicity
16	Documentation of residual activity
17	Documentation of cure rate
18	Adverse events reported

*More relevant to good clinical practice than evaluation of bias.

acceptable methodological quality, we selected those in which the main outcome measure was the cure rate at 14 days after treatment.

Results

SELECTION OF TRIALS

We identified 28 trials of clinical efficacy, 27 from the computer databases¹²⁻³⁸ and one supplied by an author in reply to our request.³⁹ We also identified an internal document of the Wellcome company describing a series of 11 small ($11 < n < 74$) unpublished comparative trials of permethrin and malathion performed between 1983 and 1986 and apparently yielding high cure rates for permethrin and malathion.⁴⁰

As we decided not to accept the company's demands for confidentiality, the full texts of these studies were not made available to us and these trials were not included in the analysis. Hand searching did not reveal additional relevant reports of trials. The search in the Science Citation Index showed only limited citing activity in this field. An official of WHO confirmed that the debate on the choice of head lice treatment for the list of essential drugs had been based on expert opinion without a formal literature review. Narrative reports of studies and older reports of treatment campaigns⁴¹⁻⁴⁵ were not included in the analysis.

Four studies were not controlled,^{12 18 26 39} three studies (two of malathion and one of permethrin) were placebo controlled,^{15 21 23} and the remaining 21 studies were comparisons between two or more active substances. We rated the quality of the identified trials according to the criteria in table I and rejected 14 of the trials because of an excess of general or treatment specific flaws (table II). Seven trials were excluded from the analysis, although their methodological quality was acceptable, because the cure rate was not determined on day 14 after treatment (three measured cure rate on day 7,^{15 21 38} and four measured it on day 21 or later^{16 29 30 32}). The characteristics of the excluded trials are listed in table III.

The remaining seven trials were of acceptable methodological quality and had the cure rate on day 14 as main outcome measure.^{14 22-24 27 28 36} Five of the trials had an overall quality rating of low risk of bias, while two had a moderate risk of bias (table II). Three trials were conducted in an area with high background prevalence of head lice ($> 50\%$ of screened population).^{14 23 24}

RESULTS OF SELECTED TRIALS

In the seven selected trials 21 individual evaluations of topical treatments were performed, comparing placebo and eight compounds (lindane, bioresmethrin, chlorphenamide, δ -phenothrin, pyrethrin, malathion, carbaryl, and permethrin), and all but two evaluations^{27 36} were of single applications (table IV). We juxtapositioned the results obtained in different trials

TABLE II—Assessment of 28 trials according to eight general and 18 treatment specific criteria of quality

Study	General item No*									Treatment specific item No*																		Total	Risk of bias
	1	2	3	4	5	6	7	8	Total	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18		
Trials of acceptable quality with cure rate at day 14																													
Maunder ¹⁴	F		F	F					3	F	F	f		F	F				F		F			f	f		9	Moderate	
Brandenburg <i>et al</i> ²²		F		F	F				3	F				F	F	F							f		f		5	Low	
Taplin <i>et al</i> ²³				F					1												f		f		f		3	Low	
Bowerman <i>et al</i> ²⁴		F			F				2	F	f			F	F								f	f	f		7	Low	
Carson <i>et al</i> ²⁷		F		F					2				f	F		f	f						f	f	f		7	Low	
DiNapoli <i>et al</i> ²⁸		F		F	F				3					F		f	f		F				f	f	f		7	Low	
Clore <i>et al</i> ²⁴			F	F					2		F		f	F	F		f				f		f	f	f		9	Moderate	
Trials of acceptable quality without cure rate at day 14																													
Taplin <i>et al</i> ²³	F								1	F	F		F	F	f									f	f		7	Low	
Mathias <i>et al</i> ²⁶				F	F	F			3					F	F	F		F		f			f		f	f	8	Moderate	
Urcuyo <i>et al</i> ²¹			F	F					2		F			F	F	F					f					f	8	Moderate	
Miller <i>et al</i> ²⁹				F					1	F	F			F	F	f	F			f	F			f	f		10	Moderate	
Kyle ³⁰				F	F				2	f	f			F	F	f				f	F		f	f	f		10	Moderate	
Sexton <i>et al</i> ²²				F	F				2	f	f			F	F	F		f		f	F		f	f	f		11	Moderate	
Chosidow <i>et al</i> ²⁸		F					F		2	f	F			F									f	f	F	f	7	Low	
Trials of unacceptable quality																													
Blommers <i>et al</i> ²²	F			F	F	F			4	F	F	F		F		F	F	F	F	F	F		f	F	F	F	14	High	
Preston <i>et al</i> ²³				F	F	F		F	4	F	F	f		F	F	f			f	f	F		F	F	f		12	High	
De Boer ¹⁷		F	F	F	F	F			5	F	f	F		F	F	F			f	f			f	f	f		13	High	
De Boer <i>et al</i> ²⁸	F		F	F	F	F			5	F	F	f		F	F	f	f		f	F		f	f	f			12	High	
Mazas <i>et al</i> ²⁹	F		F		F	F			4	f	F	F		F	F	F	f	F		f				f	f	F	13	High	
Donaldson <i>et al</i> ²⁰				F	F				2	F	f			F		f	F		f	f	F		f	f	f	f	13	High	
Armoni <i>et al</i> ²⁵	F			F	F		F		4	F	F	f		F	F	F	f		f	f					f		10	High	
Mazas <i>et al</i> ²⁶	F			F	F	F			4	F	F	F	f	F	F	f	F		f	F					f	f	13	High	
Rousset <i>et al</i> ²⁹	F		F	F	F	F			5	F	F	F	f	F	F	F	F			F			f			f	11	High	
Mathias <i>et al</i> ²¹		F		F		F		F	4	F	F	f		F	f						f						8	High	
Doss <i>et al</i> ²³				F	F				2	f	f			F	F	F		F		f	F		f	f	f		12	High	
Jolley <i>et al</i> ²⁴				F					1	f	f			F	F		f		F		f	F		f	f	f	12	High	
Fan <i>et al</i> ²⁵	F			F	F	F			4	F	F	F		F				F	F	f		F		f	f		12	High	
Burgess <i>et al</i> ²⁷	F	F		F		F		F	5	F	F		f				F				F		f	F	F		8	High	

*See table 1 for details of items.
F=major flaw; f=minor flaw.

TABLE III—Overview of clinical trials excluded from analysis

Study	Treatment (single application unless stated otherwise)	No of index patients	Cure rate (%)	Percentage difference in cure rate from highest outcome (95% confidence interval)
<i>Trials of acceptable quality without cure rate at day 14</i>				
Taplin <i>et al</i> (cure rate at day 7) ¹⁵	Malathion 0.5% lotion	65	95	
	Control vehicle	47	45	50 (35 to 65)*
Matthias <i>et al</i> (cure rate at day 28-40) ¹⁶	Malathion 0.5% lotion	29	76	
	Lindane 1% shampoo	33	78	2 (0 to 23)
Urcuyo <i>et al</i> (cure rate at day 7) ²¹	Malathion 0.5% lotion	61	85	
	Control vehicle	58	7	78 (67 to 89)*
Miller <i>et al</i> (cure rate at day 21) ²⁸	δ -Phenothrin 0.2% lotion	32	100	
	δ -Phenothrin 0.2% lotion	24	100	0
Kyle (cure rate at day 21) ³⁰	δ -Phenothrin 0.2% shampoo	39	87	
	Malathion 0.5% lotion	38	82	5 (0 to 21)
Sexton <i>et al</i> (cure rate at day 21-28) ³²	δ -Phenothrin 0.2% shampoo	27	96	
	Carbaryl 0.5% lotion	23	87	9 (0 to 25)
Chosidow <i>et al</i> (cure rate at day 7) ³⁸	Malathion 0.5% lotion	94	95	
	δ -Phenothrin lotion	95	39	56 (45 to 67)*
<i>Trials of unacceptable quality</i>				
Blommers <i>et al</i> ²	Lindane 1% lotion†	110		
	Uncontrolled			
Preston <i>et al</i> ³	Carbaryl 0.5% lotion	5		
	Carbaryl 1% gel shampoo	26		
De Boer ¹⁷	Malathion 0.5% lotion	51		
	Bioallethrin 1.8%+butoxide	76		
De Boer <i>et al</i> ⁸	Malathion 0.5% lotion	51		
	Uncontrolled			
Mazas <i>et al</i> ⁹	Permethrin 1% lotion	10		
	Permethrin 1% lotion	10		
Donaldson <i>et al</i> ²⁰	δ -Phenothrin 0.2% shampoo	42		
	Carbaryl 1.5% gel shampoo	34		
Armoni <i>et al</i> ²⁵	Pyrethrin 0.3%+butoxide shampoo	50		
	Pyrethroid 0.66%+butoxide spray	50		
	Malathion 0.4% lotion	50		
	Carbaryl 0.6% shampoo	50		
	Carbaryl 0.5% lotion	50		
Mazas <i>et al</i> ²⁶	Malathion 0.5% lotion	37		
	Uncontrolled			
Rousset <i>et al</i> ⁹	Bioallethrin 0.66%+butoxide spray	100		
	Uncontrolled			
Mathias <i>et al</i> ³¹	Lindane 1%	25		
	Pyrethrin 0.3%+butoxide	28		
Doss <i>et al</i> ³³	δ -Phenothrin 0.2% lotion	50		
	Malathion 0.5% lotion	23		
	Carbaryl 0.5% lotion	28		
Jolley <i>et al</i> ³⁴	δ -Phenothrin 0.2% shampoo	25		
	Carbaryl 0.5% shampoo	25		
Fan <i>et al</i> ³⁵	Permethrin 1% creme rinse	529		
	Bioallethrin 0.66% spray	314		
	Malathion 1% lotion	519		
	Lindane 1% powder	249		
Burgess <i>et al</i> ³⁷	Synergised pyrethrin mousse	42		
	Permethrin 1% creme rinse	10		

*Significant difference (zero not included in 95% confidence interval of difference).

†Two applications.

for the same compounds, and the figure shows the cure rates for each compound. The cure rate with placebo was 6%,²³ showing the lack of placebo effect and spontaneous remission with this condition. We found six evaluations of lindane; in none of them did the lower confidence limit of the cure rate exceed 90%, and in two trials even the upper confidence limit was below 90%. For the natural pyrethrines (pyrethrin, bioresmethrin, chlorphenamide, and δ -phenothrin), all the evaluations resulted in cure rates with lower confidence limits below 90%. Only one evaluation was available for carbaryl 0.5% lotion and malathion 0.5% lotion, both giving cure rates with lower confidence limits above 90%. We found five evaluations of permethrin 1% creme rinse (in a single application of 10 minutes) with cure rates of nearly 100% and lower 95% confidence limits above 90%. Two of these studies were high quality studies in populations with a high background prevalence of head lice (> 50% of screened population infested).^{23 24}

We also made an intrastudy comparison of the two largest trials.^{22 24} Both trials were of high quality and compared single applications of permethrin 1% creme rinse with lindane 1% shampoo. The odds ratio of treatment failure for lindane versus permethrin was 15.11 (95% confidence interval 4.60 to 49.62) in one study²² and was 15.28 (5.13 to 45.52) in the second study.²⁴ After performing a Breslow-Day test for homogeneity of odds ratios ($P=0.99$), we obtained the Mantel-Haenszel summary odds ratio of 15.18 (7.99 to

28.84). Hence, the risk of treatment failure was likely to be at least eight times higher with lindane than with permethrin.

Discussion

Our aim was to collect details of all trials on the clinical efficacy of treatment for head lice and to describe the results of the trials that were not invalidated by too many flaws. To our surprise, we found only 28 published studies.

METHODS OF REVIEW

We cannot exclude the possibility that important research findings were missed by our method of retrieval. We did not engage in a hand search of core journals, as recommended for structured reviews,⁴⁶ because there did not seem to be a core group of journals, where research publications are concentrated,⁴⁷ for this subject. Our failure to obtain the full text of unpublished trials comparing permethrin with malathion excluded evidence for the efficacy of malathion.

In this first systematic approach to the treatment of head lice it was not possible to determine the acceptance criteria a priori. The rating system was instead developed after study of the identified trials. We chose cure rate at 14 days as the main outcome measure since it was the most commonly used criterion for efficacy and is, in our opinion, the most appropriate outcome

TABLE IV—Overview of included trials

Study	Treatment (single applications unless stated otherwise)	No of index patients	Cure rate (%)		Percentage difference in cure rate at day 14 from highest outcome (95% confidence interval)
			Day 7	Day 14	
Maunder ¹⁴	Carbaryl 0.5% lotion	81		100	
	Carbaryl 0.5% shampoo	64		97	3 (0 to 7)
	Bioresmethrin 0.2% lotion	49		92	8 (0 to 7)
	Chlorphenamide 0.2% lotion	93		86	14 (7 to 21)*
	Lindane 0.5% lotion	97		91	9 (3 to 15)*
	Lindane 1% shampoo	57		86	14 (5 to 23)*
Brandenburg <i>et al</i> ²²	Malathion 0.5% lotion	108		98	2 (0 to 5)
	Permethrin 1% creme rinse	257	99	99	
	Lindane 1% shampoo	251	92	85	14 (9 to 19)*
Taplin <i>et al</i> ²³	Permethrin 1% creme rinse	29	100	97	
	Control vehicle	34	9	6	91 (81 to 100)*
Bowerman <i>et al</i> ²⁴	Lindane 1% (non-random)	30	67	43	
	Permethrin 1% creme rinse	195	99	98	
Carson <i>et al</i> ²⁷	Lindane 1% shampoo	99	90	76	22 (13 to 31)*
	Permethrin 1% creme rinse	27	96	100	
Di Napoli <i>et al</i> ²⁸	Pyrethrin 0.3% lotion†	31	45	94	6 (0 to 14)
	Permethrin 1% creme rinse	107	98	96	
Clore <i>et al</i> ²⁶	Permethrin 0.3% lotion	106	85	62	34 (24 to 44)*
	Lindane 1% shampoo†	30	80	93	
	Permethrin 1% creme rinse	32	91	87	6 (0 to 21)
	Pyrethrin 0.3% five brands	31	79	86	7 (0 to 18)

*Significant difference (zero not included in 95% confidence interval of difference).

†Two applications.

measure. We preferred not to consider the cure rate at seven days, as hatching of nymphs can take longer than this⁴⁸ and as a week is too short to evaluate the effect of residual activity on reinfestation (which is important in stopping transmission during epidemics).⁴⁹ We have, however, presented cure rates at day 7 and beyond day 14 (tables III and IV), but these results do not challenge the overall conclusions of our review.

DATA EXTRACTION

We presented the efficacy data of each active ingredient by juxtaposition of treatment groups from the seven selected trials. This procedure is methodologically weak but has the advantage of extracting at least some of the limited knowledge from the clinical studies. The representation of the confidence intervals in the figure should be interpreted with caution, as

many of the results fall in the extreme end of the range of cure rates, where confidence intervals based on the sample percentage tend to shrink to zero.

Within the seven selected trials it was difficult to make sensible intrastudy comparisons. The sample size of two of the trials^{27,36} was insufficient for testing relevant differences. Two trials were selected despite flaws in randomisation, one because of the comparison with placebo²³ and one because of the range of products tested.¹⁴ The relevance of testing a product against itself in an underdosed formulation in one study²⁸ can be questioned. Hence, we limited ourselves to the comparison of the two bigger high quality trials, which compared permethrin with lindane.^{22,24}

OTHER ASPECTS OF EVALUATING TREATMENT

We made no attempt to formally weigh criteria such as side effects, toxicity, and cost. In the course of reviewing the literature, we found only one large scale postmarketing surveillance of safety, which provided evidence for the safety of permethrin.⁵⁰

Theoretically, products with residual activity might facilitate selection of resistant strains of head lice, and proposals have been made for a rotational or mosaic treatment strategy.^{49,51} There is no convincing evidence for a need for such a strategy, but development of resistance should be monitored if the therapeutic arsenal diminishes to a few products of proved efficacy.

RECOMMENDATIONS FOR FUTURE TRIALS

The number of well conducted trials of clinical efficacy in this subject of medical and economic importance is limited, and recommendations for treatment published in the medical literature are not sufficiently sustained by the results of research. Our list of treatment specific criteria could be a starting point for evaluation of new trials in the subject. Moreover, inspection of the figure leads us to recommend that only products with an expected cure rate of over 90% should be tested and that this should be done in trials with sufficient power to establish cure rates with a lower confidence limit above 90%. We propose the use of equivalence testing (testing for non-null hypothesis) and of the odds ratio of treatment failure with its 95% confidence interval, as the χ^2 test might not be valid for testing differences in cure rates near 100%. Future research on head lice treatments should preferably test single applications of compounds, as was the case in almost all the acceptable clinical trials in this study. Any treatment for lice might be effective if it is applied repeatedly over a short interval.⁵² We found many examples of instructions on labels

* Double application

Cure rates (95% confidence intervals) at day 14 after treatment for head lice. (Filled rectangles indicate high background prevalence (>50% of screened population infested). Products were applied once unless indicated otherwise)

Key messages

- Although treatments abound, the prevalence of head lice remains high and epidemics occur regularly despite all efforts at control
- In this systematic review we found only 28 randomised trials on clinical efficacy of topical treatments for head lice
- Of these trials, only seven were of acceptable methodological quality and measured outcome at 14 days after treatment (the optimum time to assess clinical efficacy)
- Of the eight different compounds evaluated, only permethrin 1% creme rinse showed efficacy in more than two studies with a lower 95% confidence limit of cure rate above 90%
- Only for permethrin has sufficient evidence been published to show efficacy: less expensive treatments such as malathion and carbaryl need more evidence of efficacy, while lindane and the natural pyrethrins are not sufficiently effective to justify their use

encouraging multiple application, especially with products that lacked well documented efficacy. In some cases these instructions clearly played on people's entomophobia to stimulate consumption, as has been stated by others.⁶

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