CURRENT APPROACHES TO HEAD LOUSE TREATMENT – A GLOBAL UPDATE

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ABSTRACT
The available treatments for head louse infestation were reviewed in this journal in 2010. Many new options for people treating head louse infestations have been introduced in recent years, but the prevalence of head louse infestation remains stubbornly unchanged. Furthermore, despite the introduction of new treatments, the process of treating infestations appears to be as fraught with problems as ever. It is curious that treatment approaches now differ markedly around the world, with some regions favouring products with a ‘physical action’, while others remain reliant on physiologically active insecticides. This review summarises the differing global approaches and examines the evidence in support of the currently available treatment options for this common problem.

INTRODUCTION
The world of head louse treatments has changed more within the last decade that at any time in history and since writing the last article on head louse treatment for SelfCare there have been numerous changes to the options open to the public. However, despite this it has largely been a matter of plus ça change, plus c’est la même chose in that most new options are either variations upon a theme or else do not address some of the underlying issues that cause problems for care givers and those having head lice.

The other interesting characteristic of the head louse treatment market has been a polarisation of approach by the regulatory authorities in each of the two primary market blocs. Europe and Australia have more or less sidelined or even eliminated conventional neurotoxic insecticides in favour of using some form of ‘physically acting’ treatment, although the interpretation of what constitutes physically acting does stretch the imagination in some cases. In contrast North America,
particularly the USA, has not only remained firmly in the physiologically acting insecticide camp but has to a large degree rejected any acceptance of physically acting preparations. Overall, both approaches have resulted in some paradoxical regulatory decisions.

One interesting aspect of all the changes in product type and choice is that, irrespective of what is being used, and however effective it is either claimed to be or else has been demonstrated to be in clinical studies, the prevalence of infestation does not appear to have been significantly changed. Lice appear to be just as common as before the introduction of new products and care givers appear to have just as much difficulty in treating infestations as ever. Whether this is simply down to human error, as a result of the inherent difficulties involved in accurate and rapid diagnosis, difficulties in applying products adequately and thoroughly, or further selection of louse populations so that the unthinkable possibility, that tolerance of new products may already be upon us, is still not clear. Sufficient to say that many people find their children infested again and again.

I have broken this review down by looking at louse infestation treatment by territory rather than just by product type because this division is more natural and logical under current circumstances.

EUROPE AND AUSTRALIA

When the last review was prepared there were just three preparations based on siloxanes (silicones) of any note in Europe. These were 4% dimeticone lotion (Hedrin 4% lotion, Thornton & Ross Ltd, Huddersfield, UK), 92% dimeticone lotion (Nyda, Pohl-Boscamp GmbH & Co KG, Hohenlockstedt, Germany), and 50:50 isopropyl myristate in cyclomethicone (Full Marks solution, Reckitt Benckiser, Slough, UK). Since then several products have been released based wholly or partially on silicones or other synthetic oils. In addition a number of preparations employing natural oils (fixed vegetable oils or mixtures of essential oils and fixed oils) or naturally or synthetically derived surfactants have also been developed and many of these have been rolled out commercially throughout Europe, parts of the Middle East, and Australasia. Claims for all these products are similar, although most have not released any supporting data from in vitro or clinical studies into the public domain. However, even those with published data sometimes present the reader with variable and confusing outcomes relative to the claims.

Siloxanes and synthetic oils

It was clear from the early reports of trials of silicone products that there were inherent weaknesses in the treatments because they showed a low level of ovicidal activity so, although lice on the hair were killed, a second treatment was required to prevent emerging nymphs from establishing a new infestation\(^2\)\(^-\)\(^6\). These formulations are all essentially similar in that they have a low viscosity of around 15 centistokes (cSt), which makes them runny and difficult to apply consistently, especially to fine hair. The result is that the hair looks saturated long before it is fully soaked by the fluid so some parts can be missed and lice and their eggs incompletely covered. Achieving a thorough coverage is difficult enough for trained and experienced clinical investigators so it must be considerably more difficult for the average care giver with the result that failure to cure could be commonplace.

New products appearing since our last review have mostly aimed to address these problems by
addition of compounds to assist ovicidal effect, and the use of polymers and other thickening agents, together with variations in the dosage form to make application easier. An initial attempt to improve the ovicidal activity of 4% dimeticone lotion by addition of nerolidol, a previously identified ovicidal facilitator⁷, did not improve the activity compared with the original lotion when tested in a naive population in Turkey⁸. However, it was found that shortening the application time for the 4% lotion from 8 hours/overnight to 1 hour increased the efficacy overall [unpublished data], providing evidence that the activity of this type of product could be improved upon.

Subsequent formulation development was designed to improve the manageability during application by increasing the viscosity. Studies using these fluid gel-like preparations have shown a high level of activity when applied for as little as 15 minutes. Two treatments a week apart, using a lower viscosity (circa 65 cSt) gel designed for spraying (Hedrin Once spray gel, Thornton & Ross Ltd), eliminated all lice following the first application⁹, and a comparison between a single application of a slightly more viscous version (around 135 cSt) (Hedrin Once liquid gel) and two applications of 1% permethrin creme rinse (Lyclear creme rinse, Omega Pharma Ltd, London, UK) showed a highly significant (p < 0.001) difference between the treatments in which the 4% dimeticone gel achieved 70% success compared with 15% for permethrin¹⁰.

The commercial success of the early siloxane products, as well as the promise of a reasonable level of efficacy in use, has spawned a plethora of newer formulations throughout Europe, Australia, and South America. Most of these products, if they have been tested at all, have only been evaluated in vitro/ex vivo¹¹-¹⁴, with few reaching clinical trial evaluation and even fewer having data released into the public domain. In many cases the synthetic oils have been mixed with essential oils, fixed vegetable oils, various types of polymers, and even surfactants so that in these hybrid formulations it is difficult to determine what the mode of action is and what component of the preparation is delivering the activity.

Some synthetic oil-based products have been subjected to clinical investigation and generally show a similar activity for these variant oil mixtures relative to that of the products already mentioned. These include a spray containing dimethiconol, a hydroxyl version of the linear siloxane dimeticone, in complex with castor oil dissolved in isopropanol (Itax lotion, Pierre Fabre Laboratories, Castres, France). This product has been tested in one observational cohort study performed in Sri Lanka in which 86/108 (79.6%) of those treated were louse free immediately following a second treatment given 7 days after the first application¹⁵. No further follow ups were made so it is possible that this may be a slight overestimate of efficacy as some earlier trials have shown a decrease in the success rate over the week following a second application of treatment¹³-¹⁵. A different aerosol spray product, comprising 20% tocopheryl acetate dissolved in cyclomethicone, was compared with 1% permethrin creme rinse in a trial in the UK and worst case analysis showed that it cured 13/23 (56.5%) versus 5/22 (22.7%) success for permethrin (p = 0.033)¹⁶.

A study was conducted in a school in Rome, Italy, using 4% dimeticone lotion as a potential prophylactic agent in which every child in the selected classrooms was provided with enough lotion to perform two treatments a week apart at home. At the start of the study 23/131 (17.6%)
children were found to have lice by detection combing. The children were then re-examined after 7 days and although only seven of those originally infested still had lice a further seven had acquired them during that week and by the thirtieth day the infestation rate was 26/131 (19.1%)\(^a\). The authors suggested that this approach could be an effective model for prophylaxis of head lice in small communities but their outcome figures indicate otherwise, possibly because only the children in the classroom were treated, ignoring siblings who were not at school and who were likely to re-infest those who had been treated. Given the apparently high reinestation rate, the effectiveness of treatment by the care givers at home was not as high as would be required to adequately reduce infestation in the community, although it was generally in line with what has been found for the 4% dimeticone lotion in other studies\(^{5,17}\).

**Natural oils and surfactants**

This group includes both fixed vegetable oils and essential oils. Generally essential oil-based products using the oils at therapeutic levels are most popular in Australia. Although many products in Europe contain small quantities of essential oils or individual monoterpenes they would probably have little therapeutic activity and are present mostly to provide odour and to satisfy consumers of a wish for some kind of link with natural products.

Eucalyptus and tea tree oils are almost central to Australian society so in the development of non-pesticide based treatments these have become the first choice active substances. A search through the Australian Register of Therapeutic Goods found at least 35 registered or listed products for use against head lice (this list did not include medical devices, e.g. products based on silicones, etc.) of which all but six were based on plant extracts of some form. Both eucalyptus and tee tree oils had been incorporated into a number of products at sub-therapeutic levels for some time past as fragrances and additional components but now they have moved into the main category of active substances. However, the vast majority are currently being sold with no publicly available evidence of whether they work or not.

The previous SelfCare review reported the efficacy of three applications of a lotion containing 11.0% eucalyptus oil and 1.1% lemon tea tree oil (MOOV Head Lice Solution, Ego Pharmaceuticals, Melbourne, Australia) as 33/40 (87.5%) cure\(^{18}\). Perhaps not surprisingly the high level of essential oil in the product resulted in a six-fold higher rate of application site irritation than either of the other products used in the study, although there are no reports of eucalyptus oils being sensitizers. However, since that study there has been one report of a seizure apparently induced by the use of eucalyptus oil for treating head louse infestation\(^{19}\). A similar concentration of essential oils was used in a different product based on 10.0% tea tree (melaleuca) oil together with 1.0% lavender oil (NeutraLice Natural Lotion, Key Pharmaceuticals, Macquarie Park, Australia), which, used in a similar manner to the eucalyptus lotion, found 41/42 (97.6%) of children free from lice one day after the third treatment. The same efficacy was obtained for a benzyl alcohol and mineral oil-based lotion (NeutraLice Advance, Key Pharmaceuticals, Australia) claimed to act by ‘suffocation’ (41/42 = 97.6%) compared with 10/40 (10.0%) success using the synergised pyrethrín mousse\(^{20}\). In this study also, the essential oil product elicited more irritant application site adverse reactions than the other formulations. A third study, in which 92 children were treated using a single application of
lotion after which between 10 and 41 louse eggs were removed from the scalp by cutting individual egg bearing hairs, treated 31 with the 10.0% melaleuca lotion, 30 with the 11.0% eucalyptus lotion, and 31 with the benzyl alcohol lotion. It found that 44.4% of the eggs treated using melaleuca oil failed to hatch whereas all but 3.3% of the eucalyptus oil treated eggs did hatch. However, the benzyl alcohol product proved more ovicidal by inhibiting hatch in 68.3% of eggs.

There has also been a trial of an essential oil-based shampoo containing an unspecified concentration of eucalyptus together with powerful surfactants including sodium lauroyl sarcosinate and cocamide diethanolamine in comparison with a 1.0% malathion shampoo, using three applications of each a week apart. These shampoos were actually used as ‘foaming lotions’ because they were applied to dry hair, left for 15 minutes for eucalyptus or 5 minutes for malathion, and then rinsed out, which would have increased the concentration of the active substances on the lice compared with the dosing provided using conventional shampoo methods of applying to wet hair. The result at day 21 was a success rate for the eucalyptus shampoo of 66/106 (62.3%) versus 42/104 (40.4%) for malathion.

Since the year 2000 over 40 papers have reported the activity of plant derived extracts against head lice or their eggs. The majority of these studies were based in Asia and investigated plant extracts from widely used food additive or traditional medicine origins. However, none of these materials have been formulated as products and, even where some are used locally by herbal and traditional medicine practitioners; none have been subjected to any form of clinical study. Of the few reports of clinical investigations, most have been conducted in small villages in developing countries, which does nothing to provide evidence of likely effectiveness of those formulations were they to be used in Western Europe or North America where lice have been subjected to multiple exposures to a wide range of chemical entities and pharmaceutical excipients found in commonly used toiletry products. For example, a study performed in a rural village in Egypt looked at the activity of a neem-based shampoo on the lice in vivo and the picked out eggs in vitro. A single 10 minute treatment was claimed effective to immobilise all lice and prevent all louse eggs from hatching by asphyxiation, a postulation that was claimed to be supported by further observations of shampoo flowing into the tracheae. Clearly the authors did not understand the physics of water based fluids applied to lipid coated surfaces and the fact that a water based shampoo would have a surface tension too great to enter even quite a wide capillary tube let alone the narrow and complex structure of the louse spiracle that is structured to keep watery fluids out.

A study performed in France investigated the activity of an oily product containing andiroba, coconut, and rapeseed oils together with quassia vinegar resulted in 27/30 (90.0%) cure after three applications over 14 days. However, the participants also used a willow bark extract shampoo, which the same manufacturer also happens to claim as a treatment product, in place of their regular shampoo twice each week plus, for those with long hair, use of the manufacturer’s detangling spray. So which of those products, or the combination of the products, achieved the therapeutic outcome is impossible to determine.

A trial of a shampoo that was believed to contain soya oil as its occlusive component showed a better activity using two double 30 minute applications 9 days apart in comparison with 0.5%
alcoholic permethrin lotion, with 28/45 (62.2%) success using the shampoo and 16/46 (34.8%) successes using the lotion\textsuperscript{27}. Approximately a quarter of the participants in both groups experienced application site adverse reactions of irritation due to either the high concentration of surfactant in the shampoo or the alcohol in the lotion. Subsequently, however, when a copy of a formulation document came to light it transpired that the investigators had been misled into believing the shampoo contained soya oil and it was concluded that the activity of the shampoo was entirely due to the high level of surfactants\textsuperscript{28}.

A straightforward evaluation of a surfactant looked at the activity of cocamide diethanolamine (cocamide DEA), at one time a commonly used component of many shampoos, particularly those used to remove traces of conditioner and other hair treatments. This study conducted in the late 1990s, when non-insecticide products were not available, was made based on reports originating from the same institute that had developed the ‘soya’ shampoo described above. The 10.0% cocamide aqueous lotion was effective in only 60 minutes against lice and their eggs \textit{in vitro} but when used clinically in comparison with 1% permethrin both products performed badly with only 3/23 (13.0%) successes in the cocamide DEA group and 5/21 (23.8%) success with permethrin\textsuperscript{29}. A follow up trial using the same mixture but applied either for 2 hours on two occasions a week apart or a single overnight application, in both cases concentrating the lotion on the hair by evaporating water off using a hair dryer, resulted in only 10/56 (17.9%) cure using two treatments and 19/56 (33.9%) cure using a single overnight treatment\textsuperscript{29}. Although many lice were reported dead by parents seeing them on the children’s pillows or in the bath, enough insects or their eggs survived to render treatment ineffective. This study showed that just because a surfactant has a powerful emulsifying action it does not necessarily remove the waterproofing lipids from the louse cuticle and it is possible that those that survived treatment did so because they had become tolerant through previous exposure to toiletry shampoos.

Introducing a ‘novel’ surfactant that may have a different emulsifying activity is one option for an alternative treatment that may avoid issues with ‘tolerance’ and also address some of the skin irritancy issues raised by conventional detergents. Once such surfactant is 1,2-octanediol that has been used as an emollient, humectant, and antimicrobial preservative in cosmetics and toiletries. Raising the concentration of this diol to 5.0% was found to be highly effective in either an alcoholic or aqueous vehicle\textsuperscript{30}. Not surprisingly clinical studies showed that, although the alcoholic solution was more effective using a short application time, it was significantly (p < 0.045) more irritant whereas the aqueous preparation was better tolerated and nearly as effective if applied overnight with 31/40 (77.5%) cure compared with 24/40 (60%) using the alcoholic version for 2 hours\textsuperscript{30}. This was comparable with the result from an earlier three centre study in which the alcohol product applied for 2 hours achieved 70.9% (124/175) cure but 87.9% (153/174) cure if applied for 8 hours. Both alcohol-based treatment groups were significantly (p < 0.0005) more effective that 0.5% malathion liquid, which cured 81/171 (47.4%) participants\textsuperscript{30}. Interestingly, the same active substance has also been shown to be capable of helping prevent an infestation from establishing using a 1.0% mixture, formulated as a detangling conditioner spray, that was combed through the hair at least twice each week after hair washing. In a double-blind cross-over trial of 63 children
aged 4-16 years who were the youngest members of their families attending school, and were deemed at high risk of infestation, the 1.0% octanediol formulation was found to be significantly (p = 0.0129) advantageous for preventing an infestation establishing compared with a placebo spray over a 12 week long study31.

This result is in contrast with an investigation of a repellent formulation conducted in the mid-1990s. During a laboratory investigation of the activity of piperonal against lice for pediculicidal activity, as noted briefly in the SelfCare previous review, it was found that lice coming into contact with treated surfaces were repelled32. The compound was subsequently formulated as a 5.0% spray for routine (daily) use and was marketed for several years in Britain and France. A field study comparing the product with a placebo spray and a control group in a double-blind trial over a period of 22 weeks, involving 166 children from a close religious community in North London with a high risk of louse transmission, found that although fewer of the 41 infestations detected were in the piperonal group there was no significant difference (p = 0.4386) between the groups33. It was concluded that a more efficient, and cost effective, method of avoiding infestation would be regular detection combing to check for lice rather than using repellents33.

In view of the above, it is curious to note that one company in Australia has recently started selling a 5.0% piperonal spray repellent. However, interest in repellents is strong in Australia as shown by a report of an in vitro study in which four products were compared for repellent effects on laboratory reared body lice with observations made at 2, 4, and 8 hours34. Such a long exposure is not realistic given that events likely to lead to transmission of head lice probably last no longer than a few minutes at most, and in many cases may last just a few seconds35. On that basis the earliest reported observation of repellent effect was probably the most useful and showed that two products based entirely on plant extracts were ineffective, probably because the volatile components of essential oil, which are possibly those most likely to be effective, had evaporated by the time of the observation. However, another study has questioned the activity of essential oils in favour of the effects of oily materials leaving hair unattractive to lice36. Two other products, one containing an emulsifier and dimeticone and the other based on diisopropyl adipate, trimethylpentanediol/adipic acid/glycerine crosspolymer, and tocopherol exhibited 52.5% and 92.3% repellence respectively. The authors recognised that the combination of lipid-like compounds in the more successful products leaves a residue on the test substrate that probably discouraged lice from crawling on it34.

THE AMERICAS

Although herbal extract and physically acting products have made some inroads into the markets of South America, particularly Argentina, they are not available in most countries and not recognised by the Food and Drug Administration in the USA who steadfastly ignore the fact that most of the competent authorities in the rest of the world consider them safe enough to be sold as medical devices. Consequently, the majority of people attempting to control head louse infestation in the Americas are still using a limited range of insecticide-based treatments, nearly all of which utilise permethrin, natural pyrethrum, or some other pyrethroid as the active substance, all of which are susceptible to resistance. In fact this region has been more closely investigated for the presence
and extent of distribution of the point recessive mutations within the \( \alpha \)-subunit gene of the voltage-sensitive sodium channels that go to make up knockdown resistance (\( kdr \)). This mutation conveys resistance to DDT and the pyrethroids by inhibiting the agonistic neuroexcitatory effect of these insecticides that results in nerve depolarisation and hyperexcitation\(^{37}\). This form of resistance was first identified in head lice in the USA, in Massachusetts and Florida\(^{38}\), and has since been demonstrated widely throughout North America\(^{39,40}\) and also in Argentina\(^{41}\).

**Alternative treatments**

Argentina has stood out in this area of development because there is an active research group operating there that can test materials and provide data on new developments to local manufacturers. As a result there has been quite extensive investigation of the activity of essential oils from local plants against insecticide resistant head lice, some of which has resulted in modifications to commercial products to improve the activity of the insecticides or else to bypass the issue by using physical modes of action\(^{42-49}\). Other investigations have involved some patent mining to revisit compounds rejected in the early 1980s such as aliphatic lactones, which were found to have limited ability to kill lice but did show repellence equivalent to piperonal\(^{50}\). Also medium chain aliphatic alcohols, the longer chain versions of which, such as cetyl alcohol, are used in conditioning rinses, have been shown to enhance the activity of insecticides and other formulations, with some gradation of activity, the best of which proved to be 1-dodecanol\(^{51}\). However, this research group has not undertaken any clinical studies so the only available data regarding efficacy of the products are what have been observed *in vitro*.

Argentina is not quite alone in investigating the activity of new and existing products. A similar *in vitro* study conducted in the USA looked at the effect of eucalyptus oil and clove oil, singly or in combination, on two isolates of lice, one resistant to permethrin and the other susceptible to insecticides, that were reared on an artificial feeder in the laboratory. Eucalyptus oil was more active than clove oil, both singly and in three ratios of mixture, but was less effective than the two pyrethroid insecticides, phenothrin and pyrethrum, tested in parallel. However, there was no difference in toxicity in a direct comparison using the oil against the two isolates of head lice, indicating that resistance to pyrethroids did not affect eucalyptus in those tests. The investigators concluded that essential oils of this type could be effective provided safety and formulation issues could be addressed\(^{52}\). Other studies in the Americas included a questionnaire study in Cuba that identified more than 40 methods for treating lice, the most frequently used of which were alcohol and the insecticides lindane and DDT\(^{53}\). Several of the other things that people had tried were potentially highly toxic including some veterinary and agricultural insecticides as well as petroleum, kerosene, and vehicle brake fluid. In rural areas a variety of herbal materials had also been tried including tobacco, neem, and añil, the latter derived from *Indigofera tinctoria* (true indigo)\(^{53}\) or *I. suffructicosa* (Guatemalan indigo)\(^{54}\), both of which contain a number of rotenoids, including the recognised insecticide rotenone.

Extracts of the native plant pawpaw, *Asimina triloba*, (not to be confused with papaya) of southeastern United States containing annonaceous acetinogens, a group of polyketide compounds claimed to have insecticidal activity were incorporated into shampoo along with thymol and tea
tree oil. Various combinations and concentrations were tested both in vitro and in uncontrolled applications to human volunteers. Three applications over three weeks, along with combing, were claimed to eliminate all signs of lice in the hair\textsuperscript{55}. However, since all the eggs and nits were removed by combing it is quite possible the lice were eliminated by the same means. The shampoo (PawPaw Lice Remover Shampoo, Nature’s Sunshine Products Inc., Provo, Utah) was sold for a while in Utah, USA, but has now been withdrawn for reasons unexplained.

A laboratory study conducted in Brazil compared the effectiveness of various commercial products containing insecticide, commercial herbal products, and home remedies, using lice collected from the locality. It found that two permethrin products (Kwell\textsuperscript{®}, GlaxoSmithKline, Rio de Janeiro, Brazil; and Clean Hair\textsuperscript{®}, Neo Química, Anápolis, Brazil) were able to kill more than 90% of the lice whereas other permethrin and deltamethrin products killed fewer than 60% while the two commercially available herbal treatments, one including 10\% *Simarouba amara* (Marupa) (Piolho e Lêndeaa\textsuperscript{®}, Belém Jardim, Belo Horizonte, Brazil), which contains various quassinoid triterpenes and the other 10\% *Pilocarpus pennatifolius* (Jaborandi) (Pilogeni\textsuperscript{®}, Laboratório Simões, Rio de Janeiro, Brazil), which contains pilocarpine and other alkaloids, did not kill the insects. Of the home remedies pure coconut oil was most successful, eliminating 80\% of the lice in this study\textsuperscript{56}.

A somewhat bizarre consequence of the FDA’s failure to recognise physically acting products as medical devices has resulted in manufacturers resorting to other pathways in order to sell their products. One route is to sell the product with a comb included in the pack and call it a ‘combing aid’. This approach has been taken by a number of ‘white label’ producers who sell product into the louse treatment salons where in addition to nit combing the operators often use the combing aid-type products to kill lice while they are combing, thus facilitating the effectiveness of their services. Many of these preparations are following developments in Europe and Australia and basing the formulations on dimeticone or other siloxane and oil mixtures.

To date only one North American-based study has investigated dimeticone for its activity against lice. This open label investigation of 100\% 350 cSt dimeticone product (LiceMD\textsuperscript{®} Pesticide Free, Reckitt Benckiser, Parsippany-Troy Hills, New Jersey) engaged parents to apply the product to their children’s dry hair and 10 minutes later comb through to remove the lice and eggs. Up to two more applications could be given if the school nurses found either lice or louse eggs/nits following treatment. Of the 97 enrolled children 39 were excluded from analysis for a variety of reasons, including a misdiagnosis of active infestation in eight\textsuperscript{57}. After the first application of treatment 57/58 (98.3\%) of the analysed participants were free of lice, although only 32 were free of louse eggs/nits. By day 14, after up to three applications of product 55/57 (96.5\%) were free of lice and 46/57 (80.7\%) free of eggshells\textsuperscript{57}. Most participants required only one treatment but 10 needed two applications and five received three treatments. The large number of participants with louse eggshells remaining after treatment is indicative of a comb that does not work – the comb included in the pack is a plastic comb with relatively widely spaced teeth – and it is surprising that even after three applications of a viscous silicone that is difficult to wash from the hair anyone was still found with lice, unless the treatments were incompletely applied.

The other side of the ‘grey market’ of unlicensed products is a group of preparations that are
identified by the FDA as ‘unlisted homeopathic products’. This category is a real hotchpotch of formulations that manage to escape further scrutiny by claiming the active substance is *natrum muriaticum* (sodium chloride) given as various homeopathic potencies according to the product in question. Several of these products are sold as medical devices in Europe or Australia or even Listed products in Australia with other named ingredients in those territories such as essential oils and physically occlusive materials like isopropyl myristate. Many products in the grey market make obscure claims that have not yet been challenged in any way and mostly they are only sold as ‘combing aids’ along with a comb, irrespective of their pedigree elsewhere. However, there are some that do make claims and can even back up those with evidence.

Of all these fringe preparations only one has been subjected to a clinical study, a 1.0% sodium chloride spray (LiceFreee Spray®, Tec Laboratories Inc., Albany, Oregon) in comparison with 1.0% permethrin creme rinse. In this single-blind randomised trial the spray was applied to dry hair and left for 1 hour to dry after which the hair was combed to look for live lice. The spray was then not washed out for 24 hours. The permethrin rinse was applied to washed and towel dried hair and left for 10 minutes, as per instructions. A second application of either treatment could be applied after 8 days if lice were seen. It appears there was one drop out in each group so the final intention to treat outcome was 17/21 (80.9%) success for the salt spray and 9/21 (42.9%) for permethrin after 14 days. So, how could a simple salt solution eliminate head louse infestation? If that were true any child spending much time in the sea should be louse free, but of course that is not the case.

What the report fails to state is that the saline spray product is preserved with benzyl alcohol, a material that has otherwise been approved by the FDA as a pediculicide in its own right. While it is true that the benzyl alcohol licensed product contains 5.0% benzyl alcohol the preservative level is unlikely to exceed 0.5%, a level that is also found in the MOOV eucalyptus and NeutraLice tea tree products described above. The 5.0% benzyl alcohol lotion (Ulesfia® Lotion, Zylera Pharmaceuticals, Research Triangle Park, North Carolina) in an emulsion base with added mineral oil has been shown to have a high level of efficacy when applied in sufficient quantity. The report described several Phase II and Phase III clinical investigations but did not make it clear exactly how many participants were enrolled overall and the trials employed different dosing methods, and concentrations of active in the early stages. Efficacy overall in the Phase III studies averaged 75.4%.

It was claimed that the mode of action is that the benzyl alcohol ‘stuns’ the muscles controlling the necks of the tracheae so that they remain open, allowing the mineral oil to block the system resulting in suffocation. However, the quantity of mineral oil in the emulsion, although not specified in the ingredient list, is low so it could not separate out from the emulsion to occlude the tracheae. Furthermore there is considerable misunderstanding of how louse spiracles work. The muscle, which has long been misnamed as the ‘occlusor muscle’, is supposedly ‘stunned’ by the treatment and could not function to actively close the opening as its positioning in relation to the external cuticle where it is anchored, and the insertion of the other end onto the chitinous rod that is fixed onto the trachea, is such that if the muscle relaxed, as would happen if ‘stunned’, the trachea would be closed. The tracheae can only be opened if the muscle contracts, which is unlikely to be the case if ‘stunned’. More likely, the mode of action is a direct effect of the benzyl
alcohol on the lice, for example it has been identified as a membrane ‘fluidiser’ and exhibits various other activities at the cellular level, which leads to a question of the role of benzyl alcohol in the products where it is used as a preservative. Since the essential oil products are only applied for 10 minutes the low concentration of benzyl alcohol would have little effect but leaving the salt spray lotion to dry and then wash off the next day could in theory increase the dose that lice are exposed to by a factor between 2 and 10 depending upon how much benzyl alcohol is in the spray and deliver a greater exposure to the chemical than the 5% benzyl alcohol lotion (See Box 1 for how this is estimated).

Box 1: The effect of formulation on efficacy

Just as with most medications measuring the dose of a pediculicide is essentially a relationship between concentration and time. Of course, in this case we are not measuring the dose to the human so the actual quantity of study medication applied is not important, especially because that would vary so much according to the length and thickness of the hair on the head. So, dose is measured at the surface of the louse as a function of the base level of the active substance (not making allowance for the concentration effects due to evaporation of solvents) in relation to how long the product is applied to the head.

For the comparison between the effects of, for example, the 5% benzyl alcohol lotion applied for 10 minutes and another product, containing 0.1% benzyl alcohol as a preservative applied until the next day, the outcome effects could be surprising. In this example the estimated effect achievable by the 10 minutes application using 5% benzyl alcohol in dose/exposure terms, e.g. 5% x 10 minutes = 50 dose units. However, if the other product contained 0.1% benzyl alcohol (a commonly used level for preservative) after 60 minutes the lice would have been exposed to 0.1 x 60 = 6 dose units but after 24 hours without washing the exposure would be 0.1 x 60 x 24 = 144 dose units, considerably more than the dosing given by the 5% lotion.

In general the possible effects of preservatives and other excipients are not considered by regulators when examining marketing applications for products like pediculicides. However, in the examples given where benzyl alcohol is used as a preservative it does raise the question as to just what might be an active substance and what an excipient?

Neurotoxic compounds

Most developments for treatment of head louse infestation in North America since the last SelfCare review have been applications of conventional neuroactive insecticide compounds to topical dosage forms. These products are all currently prescription only, which limits their use because many prescribers still rely on lindane and malathion preparations.

The first of the new neurotoxic agents was spinosad, a derivative from Saccharopolyspora spinosa, an aerobic, mycelium forming, actinomycete isolated from a defunct sugar cane processing plant. The active components Spinosyn A and Spinosyn D exhibit a hitherto unique mode of action on insect nicotinic acetylcholine receptors. This material is available as a 0.9% creme rinse (Natroba™, ParaPRO LLC, Carmel, Indiana) and was compared with 1.0% permethrin creme rinse, both applied for 10 minutes, in two multi-centre, evaluator blinded, clinical studies that treated whole families with the same product but only evaluated the youngest in the household for analytical purposes. Some participants received a single application of product while others, who still had lice after 7 days, were treated a second time. The numbers and disposition of participants is not clear from...
the report but it appears that a total of 446 individuals from 174 households were treated with spinosad creme rinse while 470 from 173 households were treated using permethrin. The actual number of successful treatments overall is also not clear, being given only as 84.6% and 86.7% for spinosad over the two studies compared with 44.9% and 42.9% respectively for permethrin, without explaining whether those figures were for the intention to treat group or the per-protocol group. This spinosad product is somewhat curious in that it also contains 10.0% benzyl alcohol – twice the level of the registered benzyl alcohol treatment product. So what component delivers the louse killing effect – spinosad or benzyl alcohol?

Ivermectin was reported highly effective in the previous SelfCare review from a large study using oral ivermectin in comparison with malathion lotion, with a success rate of 97.1%. However, both regulators and practitioners showed hesitancy about using this medication orally, with the result that only a few treatments of difficult cases have been given on a named-patient basis. Much more acceptable would be a topical application product so a dose ranging study compared three concentrations of ivermectin, 0.15%, 0.25%, 0.5%, in a lotion formulation applied for 10 minutes. As with so many publications describing North American clinical studies of head louse treatments, the true outcomes were not clear, being given as percentage success and p values at different time points after treatment but without making it clear whether these were intention to treat or per-protocol results, because the actual data were not provided. Of the three concentrations compared with placebo divided between 78 participants, the 0.5% lotion was most effective with 73.7% of participants louse free on day 15 after treatment. A clearer guide to the efficacy of this product (Sklice, Arbor Pharmaceuticals LLC, Atlanta, Georgia) was given by two further studies in which 780 people were evaluated for safety but 249 children, the youngest participant in the household taken as the index case, were analysed in the intention to treat population divided between a single 10 minute application of 0.5% ivermectin lotion and the vehicle placebo. The overall outcome assessment at day 15 found 104/141 (73.8%) of those on ivermectin to be louse free compared with 26/148 (17.6%) on placebo.

This product is intended as a single dose product based on the indication that the ivermectin may prevent some louse eggs from hatching but if any nymphs emerge they have been shown to take reduced blood meals, if they feed at all, and none of those in the experimental system developed beyond the second nymphal stage. Consequently, exposure to the low doses of ivermectin left on the eggshells after treatment and possibly on the hair on which they were laid provided sufficient exposure to have an effect to inhibit the feeding process. However, such exposures must have a warning attached. The first study of 1.0% permethrin creme rinse conducted in Panama showed that about one third of louse eggs hatched after treatment but the nymphs were intoxicated by residual insecticide from the surrounding hair. Such residues were considered a benefit during marketing of the product but, over several hair washes with modern toiletry shampoo and conditioners, the deposit of insecticide leaches away so that ultimately it results in levels too low to have any physiological effect. Just such diluted residues of permethrin are believed to have been important contributors to the selection of the resistance that now blights use of pyrethroid insecticides for louse control.
OTHER METHODS OF TREATMENT

In all territories combs of various types have always been sold. Of course, combs have been used for centuries for removing lice and sometimes are good enough to remove louse eggs. Few of the modern ones are as simple and straightforward as the Sacker comb produced in the 1930s, although many combs currently available are neither convenient to use nor are they efficacious at removing either lice or their eggs because the teeth are either too far apart or not set into the comb base consistently. Some long toothed combs make strong claims for their efficacy but few have actually been subjected to investigation. One study compared two widely used plastic combs and two metal pin combs and showed that an ABS comb with close spaced teeth (PDC comb, KSL Consulting, Helsingø, Denmark) was only significantly (p = 0.007) more effective than a ‘dust’-type comb (Nopucid®, ELEA SA, Buenos Aires, Argentina) at removing third stage nymphs and no different for removing other life stages. Of the metal pin combs, one with smooth pins (KSL Consulting) was found to be less effective overall than one with grooved teeth (Assy®, Buenos Aires, Argentina), being most significantly different when it came to removing eggs and nits (p = 0.001). Curiously, however, in a comparison between the PDC comb and the Assy, the latter only performed significantly better at removing eggs (p = 0.0001) and first stage nymphs (p = 0.03), with no difference for identification of other life stages.

There are numerous versions of combs that are electrically powered. Most of these claim to kill lice by electrocution; by charging alternate teeth so that when lice come into contact a current passes from the charged tooth, through the louse, and into the next tooth with the result that the insect sustains a burn on its cuticle that results in leakage of fluid; if it had not already been pulled from the hair by the combing process. However, most of these combs have teeth too far apart to remove the youngest louse nymphs and none have any effect on louse eggs. None of these combs has any clinical evidence to support the claims. Other combs include lights that claim to make lice and louse eggs more visible by shining a near ultraviolet beam onto the hair in front of the comb’s teeth (Nitview® Ledcomb, Laboratorios Rovi Farmaceuticos, Madrid, Spain) with the claim that the LED light makes them glow, supported by ‘fake’ images on some of the advertising online. This is entirely misleading because only nits (hatched eggshells) and dandruff reflect near UV to appear to ‘glow’, lice and unhatched eggs do not reflect UV, so anyone using such a comb could be misled into thinking they had treated successfully if they no longer saw bright objects. More likely to be an effective diagnostic and treatment product is a new comb that uses a more or less conventional tooth unit mounted into an electrically powered suction device (LiceTec V-Comb, ToLife Technologies, Pty Ltd, Welshpool, WA, Australia) so that lice and their eggs can be removed and trapped in disposable mesh capsules fitted into the body of the machine. So far this comb has not been subjected to a clinical investigation.

Of course, details about the life cycle of lice are critical for adequate therapy whatever method is used. It has always been thought that louse eggs take around 7 days to hatch, which is why it is recommended that many products be applied for a second time after one week. Other considerations were that a few eggs might hatch up to 3 days later, which is why German products are reapplied on days 8 or 9 and why American products are reapplied 7-10 days after the first.
None of these are wholly satisfactory because there is an element of uncertainty about just when to reapply. Unfortunately, a recent analysis of lice collected post-treatment during a series of 20 clinical studies showed that, in the 23/1895 cases where only newly hatched nymphs were collected from study participants following treatment, it appeared that louse eggs could hatch up to 13 days after laying\textsuperscript{73}. This means that perhaps a more reliable regimen of treatment could include three treatments a week apart instead of just two, a process that could prevent new infestations arising from emerging nymphs, which have previously been thought to be due to reinfection from untreated contacts.

Finding a treatment that eliminates louse eggs would avoid this problem arising and two treatments aim to achieve that. The first is a mechanical treatment employing warm, dry air delivered through a novel rubber comb-like device. This product AirAllé (Larada Sciences, Salt Lake City, Utah, USA) has been shown in comparison with other warm air delivery systems to eliminate louse eggs most efficiently with up to 99.2\% efficiency\textsuperscript{74,75}. This treatment product is currently only available through professional louse treatment salons due to its size and cost. However, it is believed that a hand-held consumer version may be developed. Nevertheless, a product like this does require some considerable input in time, requiring at least 30 minutes to cover the whole scalp so consumers may find it less attractive. An alternative that is in process of licensing in the USA is a product containing abamectin, specifically developed to kill louse eggs by targeting the metalloprotease enzymes that allow lice and other insects to break through the tough chorionic membrane that surrounds and protects the developing embryo\textsuperscript{76}. In, as yet unpublished, phase III clinical trials this product is reported in press releases to have shown 81.5\% success after 14 days, using a single 10 minute application of the lotion, in double blind studies involving 704 participants. Whether this is going to provide the answer to dealing with the head louse problem, or just another quite effective product that does not do as well in the hands of consumers as when used by professional investigators, remains to be seen. In any case, the development process has taken around 10 years so far and it may be some time yet before it reaches the market.

Of course, if all else fails one approach to treatment is to comb everything out. The limitations of combs have already been referred to above but these are not the only impediments to removing all louse eggs and nits. For most observers only the hatched eggshells (nits) are visible because they reflect incident light. Eggshells containing an embryo often blend in with the hair on which they are laid, especially those that are newly laid close to the scalp. Consequently, finding them in order to remove them is often a near impossible task so products have been developed to make them stand out by staining them a contrasting colour. The first of these, an aerosol based on a PVP/VA copolymer a plasticiser and a pink dye (Neon Nits®, Neon Nits LLC, Dayton, Tennessee, USA) was relatively sticky, messy, and required brushing from the hair. It has now been replaced by a white version because many people found the pink stained hair, scalp, and the hands of care givers. A more recent product (Apaisyl Détect Lentes, Merck Médication Familiale, Dijon, France) is applied as a water based gel and rinsed out within 2 minutes leaving louse eggs and nits stained blue. This also needs some care in application but washes off hair and skin relatively easily. Irrespective of whether you can find them, hitherto no product has been successful for facilitating louse egg
removal, despite numerous claims of effectiveness by various manufacturers\textsuperscript{77,78}, because the glue-like substance holding them onto the hairs grips so tightly and cannot be dissolved chemically without damaging hair. However, a new product launched in June 2016 has been demonstrated \textit{in vitro} to significantly reduce the forces required to release and slide eggs and nits along the hairs [unpublished data], which should make the task of nit removal less onerous, especially where ‘no nit policies’ still operate.

CONCLUSION

The treatment of head louse infestation continues to evolve but remains focused on two main approaches: ‘physically acting’ treatments based largely on natural substances, synthetic oils or surfactants and ‘physiologically active’ insecticides, both sometimes used with physical removal techniques. The adoption of these tactics differs markedly between global markets, in part reflecting prevailing regulatory attitudes.

Establishing efficacy for head louse treatments is challenging and studies must take account of: the lifecycle of the louse, the transmission of infestation in social groupings, and the difficulties inherent in treating the hair of young children. Failure to address some or all of these factors, sometimes compounded by failure to control for the presence of active excipients, means that much of the evidence on head lice treatments is difficult to interpret.

Head lice infestation remains an intractable problem, which has spawned a plethora of products claiming to provide a solution. Making sense of the options available requires rigorous clinical research that takes account of the practical challenges inherent in treating young children, so that results can be applied successfully in the real world.

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