Reviewer’s report

Title: A highly efficacious pediculicide based on dimeticone: randomized observer blinded comparative trial in patients with severe infestation

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Reviewer: Ian F Burgess

Reviewer’s report:

This is an important article describing a clinical investigation of a novel head louse treatment product. It contains a number of important features in the methodology that can provide lessons for other investigators in this field and also highlights some of the difficulties in conducting studies of this type.

Minor revision points

General:

1. The title of the manuscript refers to "patients with severe infestation". However, nowhere in the text is this qualified by examples or numbers.

2. Throughout the text the authors refer to product brand names, often in place of active substance names. In general it is preferable to refer to active substances, with limited reference to product brands at appropriate points where this actually provides clarification or distinction form other products of a similar type.

3. The second point may be as a result of translational issues but I think it important to make it clear that the dimeticone product should be referred to as a “silicone” product rather than a “silicon” product (see Objective paragraph of the Abstract) as silicon products not only cover a considerably wider range of materials, many of which are inorganic in nature, but also has a different connotation in terms of pest control.

Abstract:

1. There is an extraneous sentence at the end of the Abstract “Text for this section of the abstract.”, which should be deleted.

Methods:

1. Page 7, lines 18-19. The statement, “This is considered the most sensitive method to diagnose active lice infestation [19].” made on these lines is incorrect. In the cited review I believe I made it clear that the opinion that wet combing may be the most sensitive method for detecting lice was that of the authors of the paper being reviewed. If this was not clear I apologise to Prof Heukelbach and his colleagues. Evidence from Mumcuoglu et al. (ref 20) and from Balcioglu et al. (2008) show a greater efficiency of dry combing.

Results:
1. Page 13, lines 18 and 20. I think the term “conjunctivitis” is not strictly applicable to the adverse event as this normally implies a microbial infection. Perhaps “ocular inflammation” would be more appropriate as the rest of the text suggests that this was a transient irritant effect relieved by washing with water.

Discussion:

1. Page 15, lines 1-6. This is an interesting comment and observation about the overall efficacy of permethrin and the apparent lack of resistance to that insecticide in the louse population in Brazil. However, since permethrin is one of the most potent insecticides that ever employed against head lice, but one of the most susceptible to resistance, it is hard to understand how the permethrin product could perform so badly in the absence of resistance. It is possible resistance exists but is not yet confirmed, in much the same way as malathion resistance was not confirmed from the sample examined by Thomas et al. (2006) in Wales, where resistance to malathion treatment products is well known by practitioners in the field. I think a less categorical statement about resistance and the efficacy of the permethrin product from the authors would be appropriate in this respect.

Major/compulsory revision points

Background:

1. Page 4, lines 23-24. The description of the permethrin product “1% permethrin in an aqueous solution (Kwell®),” is not factually correct. I am not sure of the composition of the preparation in Brazil but an aqueous “solution” of permethrin cannot exist as permethrin is water insoluble. Please provide a more accurate description of the product.

Methods:

2. Page 6, lines 2 and 8. The eligibility criteria and location information both describe the requirement for participants to remain available at the resort for 9 days. In view of the authors’ wishes to conform to the suggestions of the Cochrane review protocol for interventions for head louse treatment in other aspects of this study I am surprised that the authors have not adhered to what that review, and the earlier systematic review by Vander Stichele et al.(BMJ, 1995), considered of greater importance that the whole treatment/evaluation period should be at least 14 days or else should have the final assessment 7 days after the last application of treatment. I understand that in the circumstances some of the children involved may not have wishes to be away from home for such a period of time but this could have been addressed at the outset by making it an inclusion criterion and thus filtering out potential problems at enrolment. Some explanation is provided in the Discussion section but this does not make it clear why it was “impossible to extend the holiday camp to 14 days”. The authors should therefore provide a fuller justification of why this cornerstone of the two systematic reviews was not addressed.

3. Page 6, lines 11-12; and 14-15. In the Intervention section, the dimeticone
product is described as “equivalent in composition to NYDA”, and later it is stated “The first product was prepared at the Department of Pharmacy of the Federal University of Ceará by an experienced pharmacist.” This information clearly indicates that the dimeticone product under evaluation was not actually NYDA, as stated throughout the text, but rather it was a parallel formulation. At first sight this may not appear important, provided all the components were identical. However, the product marketed under the name NYDA is produced in an approved pharmaceutical facility under protocols governing Good Manufacturing Practice (GMP) and would have data for stability based on several batches of material manufactured in the same way using the same batch sizes. These stability data would also cover aspects of the product in relation to the container. From my experience relatively small batch samples produced other than in the final production facility do have slightly different characteristics from larger batch samples, especially when using relatively highly volatile silicone compounds such as are present in NYDA. Therefore, it is wrong and misleading for the authors to state that they were testing NYDA even if the materials used were identical chemically and from the same production source as the named product. However, if the materials were from exactly the same source, and were otherwise identical to those used in the branded product, why did the investigators not use the branded product? This section requires some explanation as to:

a. Why the branded product was not used

b. Whether the constituents were identical and from the same source as the components of the branded product

c. Whether the containers were identical to those used for the branded product

d. Whether any stability was conducted on the samples prepared in the University

In addition the authors need to explain why they did not use the branded product for their investigation when they did use a branded product for the comparator. Irrespective of the answers provided for the questions and point above, the authors should not use the name “NYDA” to describe the preparation used, partly as highlighted in the General comment above, but also because the product was not NYDA, and it should be made clear to the reader that the product was a dimeticone based product that in its constituents it was similar to NYDA.

4. Page 7, lines 19-20 and Page 8, lines 5-7. The authors state that “Diagnostic wet combing was performed after the application of a commercially available conditioner” on days 2, 7 and 9 and that “It was assumed that the therapeutic effect of wet combing in participants still having viable head lice on their scalp after the first treatment would be similar in both treatment groups.” Firstly, wet combing is regarded by many as an intervention in its own right, thus it is possible that some of the outcome measures were confounded by this additional intervention, not specifically in the removal of lice, but because the conditioning agents employed in the wet combing have activity against lice (McMullen [Eames] 2004; Pearlman 2004). The assumption that the effect may be equal in both groups may be reasonable but cannot be confirmed and any differences
may have gone undetected, especially since the second wet combing was conducted just 24 hours prior to the second application of product. If the permethrin preparation was based on a conditioner-like formulation, as many such products are, lice exposed to this product would likely already have been selected for any tolerance of the conditioner components whereas those treated using dimeticone may have shown a difference of susceptibility. As the activity of conditioner components to kill or immobilise lice is relatively slow, as suggested by McMullen and Pearlman, any toxic effects may not have been identified by the investigators when they examined the lice removed during combing. Therefore the authors need to address this possibility in their evaluation and part of the explanation will relate to the formulation used for the permethrin requested above.

5. Page 8, line 18. Why was the assessment of cosmetic acceptability made only 6 hours after application of the products when the dimeticone product was still in the hair? Alternatively, if the assessment was made 6 hours after the product was washed out this should be clarified.

Discussion:

2. Page 14, line 3. I think the statement “It reduced the degree of itching impressively” is misleading as the information in the Results section suggests the reduction of itching was similar in the two treatment groups. A more conservative statement re itching would be more appropriate.

3. Page 14, paragraph 2. This paragraph contains some statements that may be contentious or inaccurate. The authors say the study was “designed in a way to avoid an artificial increase of efficacy” but it is difficult to justify this statement based on the examples they give.

a. Recruiting participants from a population with a high prevalence of infestation is of no influence if those participants are then quarantined in a holiday camp. They have no more risk of reinfection than in any other setting and, in fact, this action is more likely to reduce the risk of reinfection, which could actually have the opposite effect and artificially increase the efficacy of treatment.

b. It is hard to see how not using a detection comb for detection of infestation at the outset could act to prevent an artificial increase of efficacy unless the person had only one louse and that insect was removed at enrolment. However, if the combing is performed without removing lice from the head there should be no impact on outcome.

c. It is possible that visual inspection could result in more people with a greater intensity of infestation being enrolled, but neither the authors of this paper, nor those of other studies, have produced clear evidence that intensity of infestation makes successful treatment more difficult, although there is some observational evidence that this may be the case.

This paragraph should either be completely revised or else deleted.

4. Page 15, lines 9-11. In this section the authors say “...we have shown that the vast majority of those study participants that were cured on day 2, but infested
day 7, had vital adult lice detected on this day.” However, I am not clear as to whether this means that only adult lice were found. On Page 12, lines 9-13 it is simply stated that the children “had adult head lice”. Does this mean they had only adult head lice or did some of them have a mixture of stages? This should be made clear as in some cases there could have been reinfestation on top of, for example, nymphs that emerged from eggs that were not killed by the initial treatment. Additional information is therefore required.

5. Page 15, lines 24-25. In commenting on other studies using dimeticone the authors have made the statement “It can be assumed that the number of head lice per capita was moderate or low in these studies, as compared to our study population.” I think this should be qualified because in the text of one of the publications (reference 17) it states “Twenty eight participants had more than 20 lice on either day 2 or day 6. Five of these had more than 20 lice removed on both days, with more newly hatched nymphs found on day 6 (mean 250 insects; range 81-823 insects) than on day 2 (74; 24-151).” The authors should give additional information on the levels of infestation they discovered in order to justify such a statement, as suggested in my General minor point 1.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I am a consultant to various companies involved in the development of treatments in this category and have received reimbursements and/or fees for specified contractual work from different organizations and companies that would both gain and lose by the publication of this paper. I have no personal competing financial interests nor any personal competing non-financial interests.