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Month/Year of Review: September 2013 **Date of Last Review:** May 2012
PDL Classes: Topical Antiparasitics **Source Document:** OSU College of Pharmacy

Current Status of PDL Class:

- Preferred Agents: PERMETHRIN CREAM, PERMETHRIN LIQUID, PIP BUTOX/PYRETHRINS/PERMETH KIT, PIPERONYL BUTOXIDE/PYRETHRINS GEL, PIPERONYL BUTOXIDE/PYRETHRINS KIT, PIPERONYL BUTOXIDE/PYRETHRINS LIQUID, PIPERONYL BUTOXIDE/PYRETHRINS SHAMPOO , SPINOSAD 0.9% (NATROBA®) SUSPENSION
- Non Preferred: BENZYL ALCOHOL 5 % LOTION, CROTAMITON 10 % CREAM, CROTAMITON 10 % LOTION, LINDANE 1 % LOTION, LINDANE 1 % SHAMPOO, MALATHION 0.5 % LOTION, POTASS HYD/GLYCO/PQ10/HE-CELL GEL, IVERMECTIN 0.5% LOTION (SKLICE®)

Previous Conclusions and Recommendation:

- There is insufficient evidence of superiority of either spinosad 0.9% topical suspension or ivermectin 0.5% lotion over permethrin.
- There is insufficient evidence that either spinosad 0.9% topical suspension or ivermectin 0.5% lotion are safer than permethrin.
- No unique patient groups or situations were identified where either spinosad 0.9% topical suspension or ivermectin 0.5% lotion are safer or more effective than permethrin.
- For patients that have failed permethrin or malathion, there is moderate evidence from one good quality RCT that oral ivermectin is more effective than malathion 0.5% lotion. However, oral ivermectin is not FDA approved for this indication and the malathion lotion studies is not available in the same vehicle in the US.
- Continue to include permethrin as preferred to assure adequate coverage for scabies.

Conclusions and Recommendations:

- There is no new clinical evidence for efficacy or safety that disputes permethrin as first-line therapy for the treatment of lice.
- No further review or research needed at this time
- Evaluate comparative costs in executive session; Make spinosad 0.9% (Natroba®) non-preferred.

Methods:

A Medline OVID search was conducted with the following search terms: permethrin, piperonyl butoxide, pyrethrins, spinosad, lindane, crotamiton, malathion, benzoyl alcohol, ivermectin, topical antiparasitic, lice, scabies, pediculosis capitis, pediculocide and scabicide. The search was limited to English language articles of controlled trials conducted on humans published from March 2012 to July week three 2013. The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Systematic Reviews:

None

Guidelines:

The International Journal of STD and AIDs published the 2010 European guidelines for treatment of scabies.[1] Levels of evidence were assessed based on their level of scientific evidence and guideline recommendations were graded in accordance with the Oxford Centre for Evidence-Based Medicine levels of evidence. A Grade A recommendation is one based on clinical studies of good quality and consistency addressing the specific recommendations and including at least one randomized trial, a Grade B study is based on well-conducted clinical studies, but without randomized clinical trials, and a Grade C recommendations is made despite the absence of directly applicable clinical studies of good quality.

The recommendations for the treatment of scabies:

- Permethrin cream 5% is considered effective and well-tolerated (level of evidence Ib; grade A recommendation)
- Benzyl benzoate lotion (10 to 25%) is also effective but requires application on more than one day (level of evidence III; grade B recommendation)
- Ivermectin can be given orally as a repeated dose (200 mg/kg) two weeks apart. Comparisons with lindane and benzyl benzoate show conflicting results with regard to efficacy (level of evidence Ib; grade A recommendation)
- A foam-based preparation of synergized pyrethrins is available in some countries and may be as effective as permethrin (level of evidence II; grade B recommendation)

The 2010 updated recommendations from the Center of Disease Control (CDC) for the treatment of scabies were reviewed. [2] The CDC guidelines are developed by the CDC staff, and public and private sector experts on sexually transmitted diseases (STD). These individuals reviewed literature for inclusion in the guideline based on four questions: 1) treatment of infection based on microbiologic eradication, 2) alleviation of signs and symptoms, 3) prevention of sequelae, and 4) prevention of transmission. Evidence quality was not analyzed.

For the treatment of scabies, the CDC recommends:

- Permethrin cream 5% applied to all areas of the body from the neck down and washed off after 8 to 14 hours

Or

- Ivermectin 200 µg/kg taken orally, repeat in two weeks

Alternative

- Lindane 1% one ounce of lotion (or 30 g of cream) applied in a thin layer to all areas of the body from the neck down and thoroughly washed off after 8 hours

New Trials (Appendix 1):

A total of 19 citations resulted from the initial Medline search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, 4 relevant clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Burgess et al compared topical dimeticone gel with permethrin cream rinse for the eradication of head lice.[3] Subjects (n = 90) were randomized to one application of dimeticone or two applications of permethrin in this open label controlled trial. The endpoint was measured after two weeks. Dimeticone treated subjects were significantly more likely to be lice-free than the permethrin subjects (69.8% vs. 14.9%; 95% CI 4.69 to 37.07). This was a fair quality trial with detailed explanations of study procedures.

Three recent trials compared ivermectin and permethrin for the treatment of scabies. Goldust et al conducted a trial to examine the efficacy of treating scabies with permethrin versus ivermectin.[4] Subjects (n= 242) with a scabies infection and their households (aged three to 78 years old) were randomized to either a single dose of oral ivermectin or two applications of topical permethrin. The primary outcome was eradication of scabies after two weeks defined as the absence of new lesions and all old lesions healed. At week two the difference between the two treatments was nonsignificant: 92.5% of permethrin and 85.9% of ivermectin subjects were scabies-free (p = 0.42). This was a poor quality trial. Because of the differences in administration and lack of double dummy, the impartiality of the investigators seems questionable. Randomization and allocation concealment were not described and the results were not analyzed

as intention-to-treat.

Chhaiya et al also examined the comparative efficacy of ivermectin and permethrin for treatment of scabies infections in an open label controlled trial.[5] Patients (n = 315) were randomized to a single application of one of three treatments: oral ivermectin, topical permethrin or topical ivermectin. Subjects were followed for four weeks, if no evidence of a cure was seen at week one, two or three an additional or application was given. Patients in the oral ivermectin group had a significantly lower cure rate than either topical preparation at week one: 74.8% in permethrin group, 30% in oral ivermectin group, and 69.3% in topical ivermectin group ($P < 0.05$). The same trend continued at the end of second week: 99% in permethrin group, 63% in oral ivermectin group, and 100% in topical ivermectin group ($P < 0.05$). There was no statistical difference between topical ivermectin and permethrin. At the end of the third week there was no statistical difference between the three groups and a 100% cure rate was observed in both the permethrin and topical ivermectin group while 99% in the oral ivermectin group ($P = 0.367$). This was a poor quality study with little information provided concerning randomization and allocation concealment. Study treatment regimens did not follow standard clinical practice for either medication.

Two multisite, randomized, double-blind studies (n=289) compared a single application of 0.5% ivermectin lotion with a vehicle control for the eliminations of infestations in patients 6 months of age or older.[6] The final visit was on day 15 and if any live lice were present at this visit, the study treatment was considered to have failed. The primary efficacy end point was the number of index patients who were louse-free by day 2 and remained louse-free through days 8 and 15. Significantly more patients in the ivermectin group than in the vehicle-control group were free of live lice on day 2 (94.9% vs. 31.3%; $p<0.001$, NNT 2) and at subsequent observations through day 15 (73.8% vs. 17.6%; $p<0.001$, NNT 2). Pruritus, excoriation, and erythema were the most common adverse events (1% in vehicle-control group and less than 1% in the ivermectin group). In this population, the use of an active comparator group would have been more relevant. In addition, trials that use single-dose treatment may not fully evaluate the true effectiveness of lice treatments since repeat treatment is typically required.[7]

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
None

References:

1. Scott GR, Chosidow O. European guideline for the management of scabies, 2010. *International Journal of STD & AIDS*. 2011;22(6):301–303. doi:10.1258/ijsa.2011.011112.

2. Workowski KA, Berman S, Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep*. 2010;59(RR-12):1–110.

3. Burgess IF, Brunton ER, Burgess NA. Single application of 4% dimeticone liquid gel versus two applications of 1% permethrin creme rinse for treatment of head louse infestation: a randomised controlled trial. *BMC Dermatology*. 2013;13(1):5. doi:10.1186/1471-5945-13-5.

4. Goldust M, Rezaee E, Hemayat S. Treatment of scabies: Comparison of permethrin 5% versus ivermectin. *The Journal of Dermatology*. 2012;39(6):545–547. doi:10.1111/j.1346-8138.2011.01481.x.

5. Chhaiya SB, Patel VJ, Dave JN, Mehta DS, Shah HA. Comparative efficacy and safety of topical permethrin, topical ivermectin, and oral ivermectin in patients of uncomplicated scabies. *Indian J Dermatol Venereol Leprol*. 2012;78(5):605–610.

6. Pariser DM, Meinking TL, Bell M, Ryan WG. Topical 0.5% ivermectin lotion for treatment of head lice. N Engl J Med. 2012 Nov;367(18):1687-93.

7. Gunning K, Pippitt K, Kiraly B, Sayler M. Pediculosis and scabies: treatment update. Am Fam Physician. 2012 Sep 15;86(6):535-41.

Appendix 1: Abstracts of Randomized Control Trials

Goldust M, Rezaee E, Hemayat S. Treatment of scabies: Comparison of permethrin 5% versus ivermectin. *The Journal of Dermatology*. 2012;39(6):545–547. doi:10.1111/j.1346-8138.2011.01481.x.

Scabies is an ectoparasitic, highly contagious skin disease caused by a mite called Sarcoptes scabiei. The insecticides ivermectin and permethrin are commonly used for treatment of scabies. This study aimed at comparing the efficacy of oral ivermectin with topical permethrin in treating scabies. Two hundred and forty-two patients with scabies attending the dermatology outpatient department of Sina Hospital, Tabriz University of Medical Sciences were admitted. Patients were divided into two groups randomly. The first group and their family contacts received 5% permethrin cream and the other received oral ivermectin. Treatment was evaluated at intervals of 2 and 4 weeks. A single dose of ivermectin provided a cure rate of 85.9% at a 2-week interval, which increased to 100% after crossing over to the permethrin group at a 4-week interval. Twice application of permethrin with a 1-week interval was effective in 92.5% of patients, which increased to 94.2% after crossing over to the ivermectin group at a 4-week interval. Permethrin-treated patients recovered earlier. Twice application of permethrin with a 1-week interval is superior to a single dose of ivermectin. The temporal dissociation in clinical response suggests that ivermectin may not be effective against all the stages in the life cycle of the parasite.

Burgess IF, Brunton ER, Burgess NA. Single application of 4% dimeticone liquid gel versus two applications of 1% permethrin creme rinse for treatment of head louse infestation: a randomised controlled trial. *BMC Dermatology*. 2013;13(1):5. doi:10.1186/1471-5945-13-5.

Background: A previous study indicated that a single application of 4% dimeticone liquid gel was effective in treating head louse infestation. This study was designed to confirm this in comparison with two applications of 1% permethrin.

Methods: We have performed a single centre parallel group, randomised, controlled, open label, community based trial, with domiciliary visits, in Cambridgeshire, UK. Treatments were allocated through sealed instructions derived from a computer generated list. We enrolled 90 children and adults with confirmed head louse infestation analysed by intention to treat (80 per-protocol after 4 drop outs and 6 non-compliant). The comparison was between 4% dimeticone liquid gel applied once for 15 minutes and 1% permethrin creme rinse applied for 10 minutes, repeated after 7 days as per manufacturer's directions. Evaluated by elimination of louse infestation after completion of treatment application regimen.

Results: Intention to treat comparison of a single dimeticone liquid gel treatment with two of permethrin gave success for 30/43 (69.8%) of the dimeticone liquid gel group and 7/47 (14.9%) of the permethrin creme rinse group (OR 13.19, 95% CI 4.69 to 37.07) ($p < 0.001$). Per protocol results were similar with 27/35 (77.1%) success for dimeticone versus 7/45 (15.6%) for permethrin. Analyses by household gave essentially similar outcomes.

Conclusions: The study showed one 15 minute application of 4% dimeticone liquid gel was superior to two applications of 1% permethrin creme rinse ($p < 0.001$). The low efficacy of permethrin suggests it should be withdrawn.

Chhaiya SB, Patel VJ, Dave JN, Mehta DS, Shah HA. Comparative efficacy and safety of topical permethrin, topical ivermectin, and oral ivermectin in patients of uncomplicated scabies. *Indian J Dermatol Venereol Leprol*. 2012;78(5):605–610. doi:10.4103/0378-6323.100571.

Background: Ivermectin has opened a new era in the management of scabies as orally effective drug. However, topical route has been little explored for ivermectin.
Aims: To compare the efficacy and safety of topical permethrin, oral ivermectin, and topical ivermectin in the treatment of uncomplicated scabies.
Methods: This was an open-label, randomized, comparative, parallel clinical trial conducted in 315 patients, randomly allocated to 3 groups. First group received permethrin 5% cream as single application, second group received tablet ivermectin 200 mcg/kg as single dose, and third group received ivermectin 1% lotion as single application. All the patients received anti-histaminic for pruritus. The patients were followed up at intervals of 1, 2, 3, and 4 weeks. If there were no signs of cure, the same intervention was repeated at each follow up. Primary efficacy variable was clinical cure of lesions. Statistical analysis was done by chi square test and one way ANOVA test using SPSS version 12.
Results: At the end of first week, cure rate was 74.8% in permethrin group, 30% in oral ivermectin group, and 69.3% in topical ivermectin group ($P < 0.05$). At the end of second week, cure rate was 99% in permethrin group, 63% in oral ivermectin group, and 100% in topical ivermectin group ($P < 0.05$). At the end of third week, 100% cure rate was observed in permethrin and topical ivermectin group while 99% in oral ivermectin group ($P = 0.367$). No serious adverse events were observed.
Conclusions: Permethrin and topical ivermectin were equally effective against scabies while oral ivermectin was significantly less effective up to 2 weeks. Topical ivermectin can be used as an alternative to permethrin.

Pariser DM, Meinking TL, Bell M, Ryan WG. Topical 0.5% ivermectin lotion for treatment of head lice. N Engl J Med. 2012 Nov;367(18):1687-93.
Background:The emergence of resistance to treatment complicates the public health problem of head-louse infestations and drives the need for continuing development of new treatments. There are limited data on the activity of ivermectin as a topical lousicide.
Methods: In two multisite, randomized, double-blind studies, we compared a single application of 0.5% ivermectin lotion with vehicle control for the elimination of infestations without nit combing in patients 6 months of age or older. A tube of topical ivermectin or vehicle control was dispensed on day 1, to be applied to dry hair, left for 10 minutes, then rinsed with water. The primary end point was the percentage of index patients (youngest household member with ≥3 live lice) in the intention-to-treat population who were louse-free 1 day after treatment (day 2) and remained so through days 8 and 15.
Results:A total of 765 patients completed the studies. In the intention-to-treat population, significantly more patients receiving ivermectin than patients receiving vehicle control were louse-free on day 2 (94.9% vs. 31.3%), day 8 (85.2% vs. 20.8%), and day 15 (73.8% vs. 17.6%) ($P<0.001$ for each comparison). The frequency and severity of adverse events were similar in the two groups.
Conclusions: A single, 10-minute, at-home application of ivermectin was more effective than vehicle control in eliminating head-louse infestations at 1, 7, and 14 days after treatment. (Funded by Topaz Pharmaceuticals [now Sanofi Pasteur]; ClinicalTrials.gov numbers, NCT01066585 and NCT01068158.).