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Abbreviated Update
Drugs for Lice and Scabies

Month/Year of Review: May 2012
Current PDL Class: Topical Antiparasitics
New drugs: spinosad 0.9% topical suspension (Natroba™) — **Manufacturer:** ParaPRO LLC
ivermectin 0.5% topical lotion (Sklice™) — DPT Laboratories LTD
New indication: ivermectin 3mg & 6mg oral tablets (Stomectol™) — Merck & Co., Inc.

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
- 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, SPINOSAD 0.9 % SUSPENSION (pending review), IVERMECTIN 0.5% LOTION (pending review).

Previous HRC Conclusions (April 2010):

- No evidence was found to support a difference in efficacy/effectiveness between members of this class.
- No evidence was found to support a difference in harms between members of this class other than lindane (CNS toxicity, rare/severe pediatric seizures, low ovicidal activity, resistance).
- Recommend inclusion of permethrin to assure adequate coverage for scabies, and consider including OTC and prescription medications.
- Consider excluding lindane.

Reason for Review:

In April 2010, the Oregon Health Resources Commission (HRC) evaluated the comparative effectiveness evidence of the topical antiparasitics. A December 2009 Provider Synergies Review[1] was used as the evidence source. Since this review, two new drugs have been approved by the FDA for the treatment of peduculosis capitis (spinosad 0.9% topical suspension[2] and ivermectin 0.5% lotion[3]). In addition, oral ivermectin[4] has been studied for treatment of peduculosis capitis off-label. Clinical Evidence[5] (June 2010) and The Canadian Agency for Drugs and Technologies in

Health[6] (May 2010) published comparative reviews. Additionally, the American Academy of Pediatrics[7] published updated treatment guidelines in August 2010.

Research Questions:

- Are the new agents more effective for treating peduculosis capitis than currently available agents?
- Are the new agents safer than currently available agents?
- Are there unique patients or situations where the new agents may be more effective or safer than currently available agents?

Conclusions:

- 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 studied is not available in the same vehicle in the United States.

Recommendations:

- Make both spinosad 0.9% topical suspension or ivermectin 0.5% lotion due to insuffient evidence of effectiveness or safety relative to permethrin.
- No action recommended for oral ivermectin. It is currently available without restriction.

Background:

There are three varieties of parasitic lice affecting humans: Pediculus humanus capitis (head lice), Pediculus humanus humanus (body lice) and Phthirus pubis (pubic lice or "crabs").[8] The new drugs are indicated only for head lice so it will be the focus of this update and background. Head lice are found worldwide, among all socioeconomic backgrounds, affecting children and females predominantly.[8] Black children are less commonly affected, possibly due to hair type.[8] Disease is spread through direct contact via playmates, clothing, combs, headphones, towels and beds.[8] The life span of a female louse is about one month and she is expected to lay about 7-10 eggs (aka nits) daily.[8] The nits are cemented to the base of host hair and hatch in eight days releasing nymphs that mature in another eight days.[8] Both adult sexes feed on the scalp and adjacent face and neck.[8] Most patients are asymptomatic and prognosis is almost harmless.[5] Itching and erythema may be due to an allergic reaction to the lice saliva.[8] Secondary streptococcal and staphylococcal pyoderma may occur.[5] Resistance to topical insecticides is a growing concern and varies geographically. [8]

Methods:

A Medline literature search ending March Week 1 2012 for new systematic reviews and randomized controlled trials (RCT's) comparing medications head-to-head in the treatment of peduculosis was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane

Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines. After review of the citations from Medline, 2 new relevant head-to-head trials[9 10] and 2 new systematic reviews[5 6] were evaluated.

Systematic Reviews:

CADTH[6] published a review June 11, 2010 that focused on both head lice and scabies. Search dates for the head lice portion ran from January 1, 2005 to May 10, 2010. The largest body of evidence was for the comparison of permethrin to lindane. The evidence for the majority of comparisons was ranked as low or very low due to the limited number of studies. The authors noted there was no standard criteria for judging success of treatment. Relevant key findings were:

- Permethrin was more effective for eradicating lice than lindane. Although lindane has been associated with central nervous system toxicity, there were no reports of serious adverse effects in the identified trials.
- Malathion lotion may be more effective for lice eradication than phenothrin or permethrin.
- Results from RCTs comparing malathion or permethrin to wet combing were conflicting. This may have been the result of varying resistance patterns based on geographic location.
- There was insufficient evidence to judge whether combinations of insecticides increased effectiveness when compared with single insecticides or other treatments.

Clinical Evidence[5] posted a review of the literature through June 2010. Relevant key findings were:

Likely to be beneficial

- Malathion lotion may increase lice eradication compared with placebo, phenothrin, or permethrin. Current best practice is to treat with two applications 7 days apart, and to check for cure at 14 days.
- Permethrin may be more effective at eradicating lice compared with placebo or lindane. CAUTION: Lindane has been associated with central nervous system toxicity.
- Spinosad may be more effective at eliminating lice than permethrin.

Trade off between benefits and harms

- Oral ivermectin may be more effective at eradicating head lice than malathion in people with previous failed treatment with insecticides.

Unknown effectiveness

- We don't know whether pyrethrum is beneficial compared with other insecticides.
- Benzyl alcohol may be more effective at eradicating lice than placebo. However, we don't know whether benzyl alcohol is more effective than insecticides or other treatments used in routine clinical practice.
- Studies comparing malathion or permethrin with wet combing have given conflicting results, possibly because of varying insecticide resistance.

- We don't know whether combinations of insecticides are beneficial compared with single agents or other treatments.

New Guidelines:

The American Academy of Pediatrics[7] recommendations regarding drug selection are:

- Unless resistance has been proven in the community, 1% permethrin or pyrethrins can be used for treatment of active infestations.
- Instructions on the proper use of products should be carefully communicated. Because current products are not completely ovicidal, applying the product at least twice, at proper intervals, is recommended if permethrin or pyrethrin products are used or if live lice are seen after malathion therapy.
- If resistance to available OTC products has been proven in the community, if the patient is too young, or if parents do not wish to use a pediculicide, consider recommending "wet-combing" or an occlusive method (such as petroleum jelly or Cetaphil), with emphasis on careful technique, and repeating for at least 2 weekly cycles,
- Benzyl alcohol 5% can be used for children older than 6 months, or malathion 0.5% can be used for children 2 years old or older, in areas where resistance to permethrin or pyrethrins has been demonstrated or for a patient with a documented infestation that has failed to respond to appropriately administered therapy with permethrin or pyrethrins.
- New products should be evaluated for safety and effectiveness.

Randomized Controlled Trials (RCTs):

No head to head studies comparing ivermectin 0.5% lotion to currently available therapies were identified. It was approved based upon two phase III placebo controlled trials.

Stough et al[10] is an investigator blinded, RCT including two identical phase III studies comparing spinosad 0.9% topical suspension without nit-combing to permethrin 1% with nit-combing. A third arm with spinosad 0.9% topical suspension with nit-combing was performed but results were only reported in combination with the first spinosad arm for adverse events. There were 87.4% of the spinosad patients lice free at 14 days compared to 48.3% of permethrin treated patients (RR 1.93 95% CI: 1.73 – 2.16). However, this study was rated poor because it was not blinded to patient or care-giver and it was unclear if the evaluators were blinded. The allocation concealment method was not reported. Thus the results need to be interpreted with some suspicion. Withdrawals were not reported and reported adverse events (limited to dermatologic) were not appreciably different.

Chosidow et al[9] is a good quality, double-blind RCT that compares oral ivermectin 400 mcg/kg to a single application of malathion 0.5% lotion. The exact malathion preparation is not available in the United States, though it is available in the same strength as a topical lotion. This study admitted only patients that had previously failed either permethrin or malathion within the 2-6 weeks prior. It was pre-established as a non-inferiority study at ARR 5% for the primary outcome of proportion of patients lice free at Day 15. It met non-inferiority but did not establish superiority (ARR 10.2% 95% CI: 4.6–15.7, NNT 10). There was a response of 378 (95.2%) in the ivermectin group compared to 352 (85.0%) in the malathion group (RR: 1.12 95% CI: 1.07 -1.17). Withdrawals due to adverse events were not appreciably different.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Lice free at 14 days
2) Withdrawals due to adverse effects

Study Endpoints:

1) Lice free at 14 or 15 days
2) Withdrawals due to adverse effects

Reference / Study Design[a]	Patient Population Demographics/ Inclusion/ Exclusion	Intervention Description / Length of Tx	n= ITT / m-ITT / safety analysis /Attrition (rate)	Results[2]: Primary Endpoint / Relevant Secondary Endpoint (s)	ARR / NNT[b]	Safety: Withdrawals d/t ADE / ADEs	ARI / NNH[b]	Quality Rating / Interval Validity Risks of Bias / External Validity Concerns
Stough 2009[10] 2-identical phase III, MC, RCT, PG, SB (investigator),	12 US research centers Sep 2007 – Apr 2008 Mean age (14-19 yrs) Age Range (0.5–84 yrs) Female % (76.2-86.4) **Includes:** ≥ 6 months old with active head lice as diagnosed by "trained evaluator" or house-hold member **Excludes:** - Hx of sensitivity to pediculicides or hair care products, - a skin condition that could interfere with the scalp evaluation - previous tx with a pediculicide within 48 hrs, - household with >6 members with head lice or where 1 infected member would not enroll in the study or use the rescue lice treatment - use of an excluded medication or systemic antibiotic - pregnant or breastfeeding - drug abuse within 12 months - Participation in a clinical trial within 30 days	4:4:1 ratio to 1 of 3 treatment groups: **S** -Spinosad 0.9% no nit-combing x7 days; if live lice present x additional 7 days. **PC** – Permethrin 1% with nit combing x7 days; if live lice present x additional 7 days. **SC** – Spinosad 0.9% with nit combing x7 days; if live lice present x additional 7 days. All individuals in a single household were treated with a single agent. **Txs not allowed:** -topical salicylic acid, -topical corticosteroids, -anthralin, -vitamin D analogs, -retinoids, -immunosuppressants -topical hair growth formulations, -topical dandruff treatments	**ITT:** *Individual (household)* 1038 (391) **S:** 446 (174) **PC:** 470 (173) **SC:** 122 (44) **Safety (≥ 1 treatment):** **S+SC:** 552 **PC:** 457 **Attrition: n (%)** S: 32 (7.2%) PC: 47 (10.0%) SC: 10 (8.2%)	**Primary:** proportion of participants lice free @ 14 days **S:** 376 (87.4%) **PC:** 205(48.3%) **SC:** NR (NR %) **RR:** 1.93 **95% CI:** 1.73 – 2.16 **P** <0.001 **Secondary:** proportion of patients lice free @ 7 days **S:** 309 (73.4%) **PC:** 115(24.8%) **SC:** NR (NR %) **RR:** 2.83 **95% CI:** (2.39 -3.37)	**ARR:** 40% **NNT:** 2 **ARR:** 44.8% **NNT:** 2	**Withdrawals d/t ADE**: NR **Ocular hyperemia:** **S+SC:** 12 (2.2%) **PC:** 15 (3.3%) **RR:** 0.66 **95% CI:** 0.31 – 1.40 **P**= 0.329 **Application site erythema:** **S+SC:** 17 (3.1%) **PC:** 31 (6.8%) **RR:** 0.45 **95% CI:** 0.25 – 0.81 **P**= 0.007 **Application site irritation:** **S+SC:** 5 (0.9%) **PC:** 7 (1.5%) **RR:** 0.59 **95% CI:** 0.19 – 1.85 P=0.395	**ARI: -**1.1% **NNT:** NS **ARI:** -3.7% **NNH:** 27 **ARI:** -0.6% **NNT:** NS	**Quality Rating: POOR** **Internal Validity RoB:** Selection- Centralized randomization but unclear allocation concealment Performance-no blinding of patients or care-givers Detection-unclear blinding of evaluators Attrition-low attrition; data provided for ITT calculation **External Validity:** Recruitment-Not reported Patient characteristics-older than likely to use. Setting-Not reported Outcomes – - Efficacy: Evaluator training and criteria not well described but outcome itself is clinically relevant. - Safety: FDA agreed to reduced safety evaluations based upon Phase II trial results. First 25 qualifying pediatric participants in each study had clinical laboratory assessments on days 0 (screening) and 14 only. Results not reported; authors state in text there were no serious ADEs in spinosad group and 3 serious ADEs in permethrin group.

Reference / Study Design[a]	Patient Population Demographics/ Inclusion/ Exclusion	Intervention Description / Length of Tx	n= ITT / m-ITT / safety analysis / Attrition (rate)	Results[2]: Primary Endpoint / Relevant Secondary Endpoint (s)	ARR / NNT[b]	Safety: Withdrawals d/t ADE / ADEs	ARI / NNH[b]	Quality Rating / Interval Validity Risks of Bias / External Validity Concerns
Chosidow[9] 2010 MC, cluster-randomized, DB, DD, XO	7 centers (4 in UK, 1 in Ireland, 1 France, 1 Israel) Mar 9 – Sep 14, 2004. Median Age: 10 Female 87% **Inclusion criteria:** - ≥2 years, ≥15 kg, - head-lice infestation (defined as the presence of live lice) confirmed by study staff by combing the dry hair with a dedicated fine-toothed comb,24 Live lice seen during this examination were counted, to provide baseline data. - previously failed a pyrethroid-based or malathion insecticide **Exclusion criteria:** -PG/breastfeeding -active scalp disease -use of pediculicidal treatment within 2 weeks prior. -hair style precluding comb use, dyes, bleach, perm or hair relaxing in previous 2 weeks -prior residence of Africa known to be endemic for oncocerciasis, lymphatic flariasis, loa loa -known or suspected intestinal helminth infection -known hypersensitivity to either study drug.	2 stage; 1-first 15 days 2-those not lice free XO **I:** Ivermectin 3 mg tablets (400mcg/kg) + placebo 100% isopopanol lotion. **M:** placebo tablets + 0.5% malathion lotion.	Clusters = Households **ITT (LOCF):** Indivs (households) **I:** 397 (184) **M:** 414 (191) **PP:** Indivs (households) **I:** 349 (166) **M:** 364 (171) **Attrition:** **I:** 12.3% **M**: 12.1%	**Primary:** Lice free on Day 15 **I:** 378 (95.2%) **M** 352 (85.0%) **RR:** 1.12 **95% CI:** 1.07 -1.17 P <0.001 **Secondary**: Lice free on Day 29 **I:** 382 (96.2%) **M** 362 (87.4%) **RR:** 1.10 **95% CI:** 1.06 -1.15 P <0.001	**ARR:** 10.2% **NNT:** 10 **ARR:** 8.8% **NNT:** 11	**Withdrawal d/t ADE:** **I:** 7 (1.76%) **M:** 5 (1.21%) **RR:** 1.46 **95% CI:** 0.47 – 4.56 The following specific adverse events led to discontinuation: in the ivermectin group, impetigo (in two patients), nausea or vomiting (in one), gastroenteritis (in three), and convulsions (in one), and in the malathion group, rash or urticaria (in three patients) and gastroenteritis (in two).	**ARR:** 0.06% **NNT:** NS	**Quality Rating: Good** **Internal Validity RoB:** Selection- Centralized randomization/Allocation concealment not reported Performance-low risk; good blinding Detection- low risk; good blinding Attrition- Low risk due to low attrition and even distribution between groups. ITT analysis used with LOCF which biases towards the null. **External Validity:** Recruitment- Patients were recruited from the community by advertising or nurse outreach. Patient characteristics- similar to patients likely to use. Setting- Patients were recruited from the community by advertising or nurse outreach. Outcomes- Appropriate and relevant. **Analysis:** -99% power for noninferiority (noninferiority margin 5%) - >96% power for the superiority step.

[a]Study Design: RCT= randomized trial, MC= Multicenter, PC=placebo-controlled, DB= double blind, PG=Parallel Group, XO=cross-over

[b]Results abbreviations: RR = Risk Ratio, ARR = absolute risk reduction, ARI = absolute risk increase, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis, LOCF = last observation carried forward

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