Clinical Criteria for Determining Optimal Head Lice Treatment

Brought to you by Cipher Pharmaceuticals with contributions from Dr. Christopher Belcher, MD, FAAP

Dated Clinical Evidence Requires Us To Rethink Head Lice Treatment

A quick review of the references we use for our clinical evidence regarding head lice treatment reveals that much of the evidence has become dated and doesn't reflect today's real-word situations. A shining example of this fact is the statistic that head lice affects approximately 6 to 12 million people a year in the United States.[1] The statistic was first cited in literature in 1986.[2] The US population at the time was 240.1 million according to US Census data.[3] In 2017, US Census data cite the US population at 325.7 million. The lack of clarity around such evidential facts begs the question, "Are we underestimating the condition, and is there other established clinical evidence that we need to re-evaluate?" From wide-spread lice resistance making an entire class of agents ineffective, to a far greater understanding of safety concerns about drugs approved decades ago, we now have a pressing need to rethink our approach to head lice treatments.[4]

Currently, there are no clinical practice guidelines (CPGs) for the treatment of head lice, which incorporates an extensive review of clinical literature and grades the reliability and predictability of the clinical evidence. CPGs have become an essential, useful, and integral part of the practice of medicine. The reasons why CPGs have proven

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to be so useful is related to the needs they address from the perspective of physicians and patients. Physician needs stem from the overwhelming amount of new information generated that requires systematic analysis, synthesis, and translation into specific clinically applicable recommendations. Patient needs arise from the desire of an increasingly well-informed public, seeking evidence-based information in making joint decisions with their physicians. It is in the patient-physician clinical encounter setting that guidelines are likely at their best in helping make appropriate decisions in each specific situation.[16]

In lieu of any defined CPGs for the treatment of head lice, it is incumbent upon practitioners to not only do their own systematic analyses, synthesis, and translation into a specific clinical approach from available clinical trial data, but, they must also remain current with subsequent literature that has evolved post approval by the FDA. This data for many of the drugs we utilize for head lice infestations are often found to be invaluable as they provide a body of evidence regarding a drug's continued safety and efficacy within a broader patient population over an extended period. Even in the face of ever-growing lines in practice waiting rooms, physicians and healthcare practitioners must do a better job of staying current with the most recent available data if we are to expect an improvement in our clinical outcomes.

Re-evaluate And Critique the Clinical Evidence

Many medical associations and societies have adopted protocols and methodologies for evaluating clinical evidence. They not only outline specific criteria for evaluating evidence but also identify methodologies for adoption and adaptation for local use.[11]

As part of a re-evaluation of the clinical evidence for pharmacodynamic agents used for head lice infestations, an example of a proven approach for analyzing evidence can be found within that of the Infectious Disease Society of America's GRADE Strength of Recommendations and Quality of the Evidence system.[5] The IDSA began to deploy the use of the GRADE system with new guidelines and guideline updates beginning in the Fall of 2008. GRADE recommendations range from strong, high-quality evidence to weak, very low-quality evidence. The scheme classifies recommendations according to the balance between benefits, risks, burden, and cost—and the degree of confidence in estimates of benefits,

risks, and burden. The system classifies the quality of evidence according to factors that include the risk of bias, the precision of estimates, the consistency of the results, and the directness of the evidence.

When reviewing the literature for head lice drugs, a proposed methodology to enact would have us all critiquing the evidence by the following factors:

> **"The clinical trials for many drugs still utilized today for head lice treatment were conducted decades ago.[6]"**

1. Risk of Bias (Potential Limitations of Study Design and Execution)

When was the clinical trial conducted for FDA review and approval?

- The clinical trials for many drugs still utilized today for head lice treatment were conducted decades ago.[6] Study designs including methods to perform randomization; diversity; controls—the convening of data and safety monitoring committees; and analyses have all been updated and changed in recent years to generate more reliable and predictable outcomes.[7,8] Recent clinical trial evidence provides practitioners far greater insight into the safety profiles of the drugs we utilize, and reflect current market and environmental impacts. A deeper investigation of the clinical evidence of head lice treatments can reveal if the clinical trial analyzed the safety profile of the drug for systemic absorption, toxicities, lab abnormalities, and environmental (resistance) effects. It could also provide us with a strong body of evidence of the drug's activity as an ovicidal and pediculicidal agent.

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What type of clinical trial does the evidence come from?

- Preclinical study evidence provides detailed information on dosing, toxicity levels, safety, and potential efficacy—helping us understand any potential lab abnormalities.[9]
- Phase I clinical trial evidence, typically derived from a small set of healthy subjects—20 to 80—provides evidence on how a drug interacts with the human body in healthy subjects, and determines safety in humans, an appropriate dosage, and possible adverse events.[9] Relating to head lice treatments, this phase defines our understanding and evidence of systemic absorption and toxicities for a particular drug.[10]

> **"...our evidence for evaluation should come from clinical trials that are multicenter, double-blinded trials involving a large number of subjects who have been randomized to receive the drug being tested, or a currently approved drug for the treatment of head lice in a head-to-head fashion and under real-world conditions."**

- Phase 2 clinical trial evidence is derived from subjects with head lice infestations and involves up to a few hundred subjects.[9] It is designed to provide additional evidence about the safety of the drug and establish proof of the drug's mechanism of action on the condition of head lice.[10]
- Phase 3 clinical trial evidence, derived from a hundred to a few thousand subjects with head lice, determines whether or not a drug offers a treatment benefit to the specific population of subjects with head lice vs. the risk.[9] It also confirms the levels of adverse events, and with head-to-head trials, compares the drug to other currently approved drugs.[7,10]

How was the clinical trial conducted?

- To limit bias on outcomes, ideally, our evidence for evaluation should come from clinical trials that are multicenter, double-blinded trials involving a large number of subjects who have been randomized to receive the drug being tested, or a currently approved drug for the treatment of head lice in a head-to-head fashion and under real-world conditions.
- Many products that are used for head lice have clinical evidence generated from open-label or single-center trials that are observational as well as with non-FDA validated endpoints, and due to the nature of these trial types, are unable to remove biases that can be inherent in the outcomes derived from the clinical trial.[6]

2. Body of Evidence (Factors That Are Both Human and Environmental)

What impact, if any, will natural evolution have on clinical outcomes?

- As we are trying to eradicate a parasite, the natural evolution of the parasite does play a significant role in our evaluation of clinical evidence. Since the late 1990's through 2014, several clinical trials have demonstrated a loss of effectiveness with several drugs often used to treat head lice.[6,12-14] More recent clinical evidence has provided us definitive evidence for the loss of effectiveness, which is due to resistance, specifically from gene mutations within lice.[4]

What clinical evidence updates have been provided from the FDA Postmarketing Surveillance Programs?

- FDA maintains a system of postmarketing surveillance and risk assessment programs to identify adverse events that did not appear during the drug approval process.[15] FDA monitors adverse events such as adverse reactions and side effects. The Agency uses this information to update drug labeling, and, on rare occasions, to re-evaluate the approval or marketing decision. The FDA has posted findings, precautions, and warnings from their surveillance and risk assessment programs regarding several head lice medications that are often used.

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Strong Analyses and Critique Should Provide Better Outcomes

A willingness to take the time to evaluate the body of evidence available to us today regarding the effectiveness and safety of head lice medications can significantly impact patient outcomes. Deepening our implicit knowledge regarding the benefits and risks of each available head lice treatment as outlined in the clinical trial literature, will evolve our ability to be an authoritative arbiter of the appropriate medical intervention.

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