

Relationship of Treatment-Resistant Head Lice to the Safety and Efficacy of Pediculicides

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Head lice infestation is a common and growing problem that primarily affects school-aged children. Most cases of head lice are diagnosed and treated by nonphysicians. Misdiagnosis may lead to treatment when no lice are present. Treatment failure may lead to repeated use of and improperly applied pediculicides, potentially resulting in overexposure to pesticides. These treatment failures are primarily due to the emergence of treatment-resistant lice. In regions where resistant lice are common, patients may self-treat numerous times with over-the-counter pediculicides before seeking treatment from a physician. Resistance has decreased the efficacy of lindane, a prescription pediculicide that has been used for decades. In addition, the Food and Drug Administration recently warned of potentially serious adverse effects associated with lin-

dane and recommended strict controls for its use. Malathion, recently reintroduced in the United States as a prescription pediculicide, has not been associated with treatment resistance or notable adverse effects, although it is flammable due to its alcohol base. Because of concerns about decreasing efficacy due to resistance and safety concerns about over-the-counter products and some prescription pediculicides, a reassessment of pediculicide safety is warranted. The safety and efficacy of commonly used over-the-counter and prescription pediculicide products are discussed, along with the safety and efficacy of other treatments, such as ivermectin, that are not indicated for the treatment of head lice but are being used increasingly.

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Head lice infestation is an annoying and common problem, particularly among children. Estimates of the incidence of head lice range from 6 million to 12 million infestations annually in the United States alone.¹ Head lice generally infest children aged 3 to 12 years and members of their families. Most research supports the view that the number of infestations is increasing, primarily because of emerging treatment resistance.^{2,3}

Historically, diagnoses of head lice infestations by nonphysicians and the easy availability of safe and effective over-the-counter pediculicides for self-treatment have essentially removed the physician from the treatment process. However, the potential for misdiagnosis by nonphysicians and the resulting improper use of pediculicides raise concerns about unsafe use of these products, specifically, when no lice are present or when products are used excessively.³ Treatment guidelines still recommend use of over-the-counter pediculicides in most cases, but generally at a

maximum of only 2 applications.^{1,4} Physician involvement usually is recommended if lice are not eradicated after the first 2 attempts. However, evidence from a recent efficacy study suggests that patients may treat themselves numerous times before seeking medical help.³ This raises the issue of whether overtreatment results in increased exposure to pediculicidal ingredients that may produce adverse effects. A related issue is the growing problem of resistance, which has been attributed to several causes, including pediculicide residue on the hair, exposure of lice to sublethal doses, and inadequate concentration levels within products.³

Prescription pediculicide safety also should be reevaluated. Recent labeling changes made to lindane substantially restrict its use, although it is possible that many physicians are unaware of these changes. In light of the warnings about this product, the place of lindane in the treatment algorithm seems uncertain. Also, treatment resistance to lindane has substantially reduced its efficacy.³ The other prescription choice is 0.5% malathion, which has been reintroduced but perhaps has not been fully appreciated by the medical profession, judging by lindane sales.

Considering the lack of physician oversight in the diagnosis and treatment of head lice, the potential misuse and overuse of over-the-counter products, and the recent safety concerns about lindane, a review of the safety of both over-the-counter and prescription pediculicides is warranted. This article discusses the safety of available over-the-counter pyrethroid products, of the 2 approved prescription pediculicides lindane and malathion, and of

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products being used that are not indicated for the treatment of head lice.

OVER-THE-COUNTER PYRETHROIDS

Pyrethrin

Topical pyrethroids, including pyrethrin and permethrin, are derived from the extract of a chrysanthemum species related to ragweed, *Chrysanthemum cinerariaefolium*.^{2,5,6} Pyrethrin is used in several over-the-counter products in synergized formulations of 0.33% pyrethrin in 4% piperonyl butoxide. The pediculicidal effects of pyrethrin products are due to their ability to disrupt neuronal sodium channels, which paralyzes and kills the lice.^{6,7} The addition of piperonyl butoxide is believed to increase pediculicidal effects by inhibiting drug metabolism via the cytochrome P-450 enzymatic system, causing insecticide to accumulate to more potent levels within the louse.²

Natural pyrethrin is affected by heat and light, resulting in instability and lack of residual effect. As a result, pyrethrin has minimal ovicidal effect and generally requires 2 applications approximately 1 week apart to control an infestation effectively.⁵ Although pyrethrins were extremely effective when introduced in the mid-1980s, recent studies indicate that efficacy has decreased substantially because of resistance.^{8,9} One such study designed to assess the lethality of over-the-counter pyrethrin and permethrin products found only 28% insecticidal activity.⁸ Another comparison of efficacy results for commonly used pediculicides in 1984 and 2000 showed a sharp decline in efficacy of pyrethrin products. In 1984, the average killing time of synergized pyrethrin products ranged from 10 to 23 minutes; in the 2000 evaluation, 47% of lice survived after 3 hours of exposure to a pyrethrin product. Also of note was the "resurrection effect" among lice: 75% of lice exposed to a pyrethrin product appeared to be dead 30 minutes after exposure, declining to 53% actually dead at 3 hours.⁹ This phenomenon, in which head lice can revive even after being drenched in insecticide or other agents, is an important factor in the accurate evaluation of pediculicidal activity.

Lice can live for prolonged periods without oxygen, exhibiting no respiratory or muscle movements and appearing to be dead. This explains the belief held by many laypersons that petroleum jelly, mayonnaise, hair pomades, vinegar, olive oil, and tree resin applied to the hair will "smother" lice to death.^{2,10} In fact, these substances merely slow the movement of lice. An adult louse placed in petroleum jelly for 1 hour and then rinsed will regain full motor function within minutes.¹⁰ Head lice inundated with pyrethroid shampoo for an hour and then rinsed with water also have been shown to survive.⁶ Once exposed to pyrethroids, lice develop pyrethroid resistance, making these agents

virtually useless in some parts of the world, such as the United Kingdom.¹¹

Pyrethrin has a favorable safety profile. Although the rigorous testing currently required by the Food and Drug Administration (FDA) was not performed for pyrethrin products when they were first marketed, systematic review of the efficacy and safety results of several studies reveals only minor adverse events.^{5,12} Percutaneous absorption of pyrethrin is minimal; thus, mammalian toxicity is extremely low. Rarely, adverse effects may occur, including skin irritation, rash, redness, and swelling. Patients who are allergic to ragweed may experience wheezing and dyspnea,² and those who are allergic to chrysanthemums should not use pyrethrin-based products.¹ Pyrethrin has not been evaluated for safety in pregnant women and currently carries no pregnancy category rating in its labeling.⁵ As with all pediculicides, safety profiles are based on proper use according to package instructions. Ingestion of any pediculicide can result in systemic toxicity.¹³

Permethrin

Permethrin is a form of pyrethrin that has been altered chemically to provide better stability with exposure to heat and light. Currently, 1% permethrin is considered by many to be the preferred first-line treatment for head lice infestations.^{1,2,5} Permethrin works by paralyzing and killing lice in the same manner as pyrethrin.^{6,7} Unlike natural pyrethrin, permethrin, when first marketed in 1986, was shown to have substantial residual effects, which made 1% permethrin extremely effective in killing both lice and eggs. However, initial studies were conducted on hair that was shampooed with a product designed to strip off residue to ensure bonding of the pediculicide to the hair shaft.³ Conditioners and silicone-based additives in shampoos have impaired the ability of permethrin to adhere to the hair shaft and have reduced its residual effect.^{2,3}

As with pyrethrin, the efficacy of permethrin has decreased over time. In 1999, a study compared the efficacy of permethrin in killing head lice from 2 populations. Lice were removed from children in the United States who had undergone prior treatment and from children in Borneo who were treatment naive. Most of the head lice collected in the United States were not killed by permethrin, and the dose-response curve was not significantly different from zero ($P=.66$). In contrast, the lice collected in Borneo from children who were treatment naive were killed quickly by permethrin, with mortality rates closely correlated with the concentration of permethrin ($P=.008$). These results support the documented claim of permethrin treatment resistance, presumably from repeated product exposure.¹⁴

Another study evaluated the effects of dilution from applying permethrin to towel-dried, shampooed hair. Re-

searchers concluded that varying amounts of water left in wet hair exposed lice to diluted concentrations of permethrin, which may have added to the development of permethrin resistance.^{2,3,5} Although the insecticidal activity of pyrethroids was 100% in the mid-1980s, by 2000 it had decreased to only 28%.⁸ The decreasing efficacy of pyrethroid products in the United States and other regions raises the issue of whether these products are appropriate first-line treatment for head lice in areas where resistance has been documented.

The safety profile of permethrin is favorable, with low risk for mammalian toxicity. Unlike pyrethrin, permethrin does not cause allergic reactions in people with plant allergies.¹ Adverse effects of permethrin include edema, erythema, hypoesthesia, and pruritus. A postmarketing surveillance study designed to assess the safety of 1% permethrin creme rinse evaluated 18,950 patients. Adverse events occurred at a rate of 2.2 per 1000 treatments with permethrin. No serious adverse events were reported.¹⁵ Permethrin is classified and labeled as a pregnancy category B drug, meaning that fetal risk has not been studied in a population of pregnant women and that animal reproduction studies have shown no fetal risk or that adverse events in animal studies have not been confirmed in human studies.¹⁶

PRESCRIPTION PEDICULICIDES

Lindane

Lindane is an organochloride marketed in a 1% concentration shampoo. This agent has been used to treat head lice for more than 50 years but recently came under increased scrutiny because of its toxic adverse effects. Lindane has neurotoxic properties similar to those of DDT, killing lice by overstimulation of the parasite's central nervous system.⁵ Although lindane was once considered a primary treatment of head lice, poor efficacy and serious adverse events have resulted in use restrictions. Resistance to lindane is widespread and has resulted in decreased efficacy in the United States. In a recent comparison of lindane, malathion, pyrethrin, and permethrin used to treat both treatment-sensitive and treatment-resistant lice collected from a patient population in Florida, 1% lindane was the slowest and least effective product, apparently killing no lice after 10 minutes, the recommended application time for lindane shampoo. After 3 hours of exposure, only 17% of lice were dead.³

Lindane can be absorbed into adipose and neural tissue in humans and has been associated with serious adverse events. The FDA evaluated reports of adverse events and determined that most occurred in patients who used lindane in excessive amounts or misused the product. However, serious adverse events also occurred among 20% of patients who used the product according to label directions.

The most common reason for misuse of lindane was reapplication after initial treatment failure.¹⁷

Adverse events associated with lindane include neurotoxicity and, in rare cases, death. Neurologic effects include dizziness, seizures, headache, and paresthesia. These symptoms have been shown to occur in patients who used the product properly as well as in those who misused it. Lindane use has been associated with 3 confirmed deaths and 14 unconfirmed deaths. The 3 confirmed deaths were attributed to misuse of the product, including multiple topical applications and, in one case, ingestion by an adult. Among the 14 unconfirmed deaths, 4 occurred in children, 9 in adults, and 1 in a patient whose age was unknown. All deaths but 1 were associated with topical use.¹⁷

In response to these reports, the FDA issued a public health advisory emphasizing the following points about lindane use for the treatment of scabies and lice.¹⁷

- Lindane is a second-line treatment that should be used only in patients who cannot tolerate first-line treatment or in whom first-line treatment with safer products has failed.
- Lindane should not be reapplied if initial treatment fails.
- Certain patients are at increased risk for adverse events, including infants, children, elderly persons, persons with skin conditions that might increase systemic absorption, and those who weigh less than 49.5 kg.
- Lindane is contraindicated for patients with uncontrolled seizure disorders and for those with known sensitivity to lindane or its components.

Patients at increased risk for seizure include those with human immunodeficiency virus infection, history of head trauma or prior seizure, tumor of the central nervous system, or severe hepatic cirrhosis. People who use alcohol excessively, who have abruptly stopped using alcohol or sedatives, or who use medications known to lower seizure threshold are also at increased risk for neurologic adverse events.¹⁷

The adverse effects associated with lindane are serious enough that recommendations range from using it with caution¹ to withdrawing it from the market entirely.³ The sale of any product containing lindane for the treatment of lice or scabies in humans has been banned by the state of California because of concerns about neurotoxicity and negative effects on the environment.¹⁸ Recommendations for the withdrawal of lindane products are based on concerns that its poor efficacy will result in reapplication and overuse, which increase the risk of adverse events.³

Malathion

Malathion is an organophosphate that kills lice by inhibiting cholinesterase. Currently marketed in a 0.5% concentration, malathion is the fastest and most effective pediculi-

cide available, killing 88% of lice in 10 minutes and 100% in 20 minutes.³ Malathion also binds to sulfur atoms in the hair shaft, which provides residual ovicidal effects.⁵

Malathion was first approved for treatment of head lice 2 decades ago but was withdrawn from the US market by the manufacturer because of the better convenience and cosmetic appeal of over-the-counter products; however, it remained on the European market. Recently in the United States, 0.5% malathion was reintroduced. In a comparison study of commonly used pediculicides, malathion was extremely effective in quickly killing both treatment-sensitive and treatment-resistant head lice in a population of patients who had self-treated repeatedly with over-the-counter products.³ Malathion resistance has been reported in Europe; the lack of effect may be related to its continuous use during the past 20 years, variations in formulations marketed in Europe and the United States, and potential misuse.³ Comparison of malathion efficacy in lice from a patient population in Panama in 1984 and treatment-sensitive and treatment-resistant lice from a population in Florida in 2000 showed no decrease in efficacy over time.^{3,9}

Another recent study comparing 0.5% malathion to permethrin evaluated effects in lice from Ecuador and from 3 geographical regions in the United States.¹⁹ DNA sequencing was used to determine the presence of resistance mutations in lice. Lice with confirmed mutations showed varying degrees of permethrin resistance; however, no malathion resistance was detected. Malathion killed permethrin-resistant lice approximately 10 times faster than permethrin. Investigators remarked that kill times observed in their study, compared with other efficacy studies, were longer for both malathion and permethrin because of differences in the *in vitro* bioassay techniques used. Standardizing the way in which pediculicidal activity is measured to facilitate comparisons between studies is recommended.¹⁹

The safety profile of malathion is favorable; only minor adverse events have been reported, including scalp irritation and conjunctivitis.^{5,12} 0.5% Malathion lotion has a pregnancy category B designation and has not been tested in patients younger than 2 years. Two safety issues related to malathion continue to concern both consumers and health care professionals: (1) 0.5% Malathion lotion has a high alcohol content (78%), which makes it potentially flammable. The product label advises patients to avoid lighted cigarettes, open flames, and electric heat sources. (2) Confusion exists about the difference between agricultural and pharmaceutical grades of malathion. Laypersons and health care providers are generally aware that malathion is a widely used agricultural pesticide. Malathion products not intended for human use may contain impurities, whereas pharmaceutical-grade malathion has a high level of purity.³ Toxicity associated with malathion has

been attributed to metabolites of agricultural-grade malathion or, possibly, to the impurities contained in agricultural products.²⁰ No similar toxic effects have been reported in association with purer pharmaceutical-grade malathion in pediculicides.⁵ An absorption study of malathion applied to the scalps of healthy volunteers found no effect on plasma or erythrocyte cholinesterase levels, which have been used to measure toxicity effects after exposure to organophosphates. No evidence of adverse effects of malathion were seen on either intact or damaged skin.²¹

OTHER TREATMENT CONSIDERATIONS

Other products used as pediculicides include prescription products that are not indicated for the treatment of head lice, as well as herbal remedies. Ivermectin, an anthelmintic agent, is used orally for treatment of intestinal parasites and onchocerciasis.^{1,22} Both oral and topical formulations have been effective in killing head lice.^{1,2,21,22} Ivermectin exerts its antiparasitic effects by causing permeability in nerve and muscle cells, thereby increasing exposure to chloride ions, which results in paralysis and death. Oral ivermectin was tested in a dose of 200 µg/kg. After 14 days, 77% of patients responded to treatment, but most of them needed a second dose.²³ Because the plasma half-life of oral ivermectin is 16 hours, a second dose on day 8 is recommended to kill lice that hatch after the initial dose has worn off. Oral ivermectin exerts its insecticidal effects only on lice that feed from their hosts. Also, topical ivermectin in a 1% concentration applied for 10 minutes has shown promising results that warrant additional testing.^{2,22} No studies have been conducted to compare the efficacy of ivermectin with currently accepted pediculicides, and the FDA has not approved the drug for this use. Oral ivermectin should be administered with caution to children who weigh less than 15 kg because of potential adverse effects on neurotransmission.^{1,2} Although the Mazzotti reaction, an allergic and inflammatory response, occurs occasionally because of the deaths of many parasites in onchocerciasis and other filarial diseases, this reaction does not occur with the treatment of head lice infestations.²⁴ Of note, this reaction may include pruritus, fever, headache, edema, lymphadenopathy, myalgia, and generalized body aches.

Oral administration of the antibiotic cotrimoxazole may be an effective treatment of head lice infestation. The rationale is that, because lice depend on their symbiotic bacteria for survival, a blood meal containing antibiotics might kill the symbiotes, which have been identified by 16S recombinant DNA genetic sequencing to belong to a distinct lineage in the γ subdivision of the proteobacteria.²⁵ These bacterial symbiotes have been sequestered within the louse for centuries, mutating to a genetic sequencing considerably different from the bacteria living free within our envi-

ronment. Many of the characteristics of these primary symbiotes reflect evolution toward a close partnership with their host.²⁵ Entomological studies have shown that certain antibiotics can slow egg maturation and egg production of lice and extend duration of all instar stages. Nevertheless, no antibiotics given to the host to date have proved to be therapeutically curative.²⁵ Recent clinical studies support the fact that using cotrimoxazole for head lice improves efficacy only slightly and that combining insecticides with this antibiotic provides no statistically significant synergistic effects.^{5,26-28}

Anise oil, an herbal product, has recently garnered attention for producing pediculicidal effects. A combination of anise, ylang-ylang, and coconut oils was shown in a small study (N=119) to produce fairly high efficacy rates.²⁹ The anise oil combination produced no serious adverse effects in this study; however, anise possesses neurotropic substances that have been shown to cause convulsions and lethal toxicity in mice.³⁰ Consumption of anise by humans can produce movement abnormalities, vomiting, and nystagmus, according to an epidemiological review of pediatric emergency department visits.³¹ Considering the potential for anise to block γ -aminobutyric acid neurotransmitter substances,³² this herb may produce toxic effects that currently are not appreciated. Although many plants naturally produce insecticides for their own protection that may be synthesized for use by humans, such as pyrethroids, some of these insecticidal chemicals produce toxic effects as well. The safety and efficacy of herbal products are currently not regulated by the US FDA.

Manual nit removal is mentioned often in the lay press as an effective means of controlling head lice infestation. Many nit combs and removal kits are advertised for head lice control. However, manual removal is not as effective as pediculicides and does not improve results, even when used as an adjunct to pediculicide treatment.³³ The amount of time required by parents and children at one sitting can be extensive, depending on the length of the child's hair, and this process must be repeated for several days.

CONCLUSIONS

Several current treatment guidelines for head lice recommend use of permethrin as first-line therapy with repeated application if necessary.^{1,4} Permethrin products have extremely favorable side-effect profiles and are safe when used according to instructions. Unfortunately, overuse and misuse of permethrin have produced treatment-resistant lice. Parents who become frustrated by the continued presence of lice after treatment may further contribute to resistance by repeatedly applying over-the-counter treatments, using excess product, or applying product for longer peri-

ods than recommended. In a recent study, investigators evaluating the efficacy of pediculicides remarked that the patients from whom they collected lice had treated themselves an average of 5 times before seeking medical assistance to eradicate head lice.³ Although over-the-counter products are extremely safe, this level of repeated use is inadvisable, if only because it contributes to resistance and ultimately does not eradicate the infestation.

The poor efficacy and potentially serious adverse effects associated with lindane have made it a treatment to be used only if no other therapy is effective or appropriate.⁴ Malathion appears to provide superior efficacy and safety and is preferred among prescription treatments. For patients who have readily available access to a physician, especially in regions where pyrethroid resistance has been observed, malathion is the preferred first-line treatment.²

Despite the best efforts of school nurses and laypersons, who frequently make decisions about treatment of lice infestations in schools, the current approach to treating head lice is misdirected because infestations continue to spread and respond less to treatment. Head lice infestations do not pose serious health hazards, but they cause substantial frustration, lost time from school and work, and financial consequences for repeated treatments. Except for lindane, currently available pediculicides are generally safe when used according to directions. As such, it is tempting for physicians to dismiss the seriousness of head lice infestations; however, to do so ignores larger issues associated with increasing treatment resistance and further loss of efficacy. Physicians must work to reestablish their role in treating head lice infestations with the intention of introducing safer, more effective management of pediculicides. Patients who have access to health care coverage should be encouraged to visit a physician to ensure proper diagnosis and quick and complete eradication of head lice. Physicians are best qualified to determine treatment plans and should supervise head lice eradication, even when over-the-counter products are used. Currently, malathion is the only pediculicide with no documented resistance in the United States, but the potential exists for developing resistant lice if this product is overused or misused in the same way as pyrethroids and lindane. Physician guidance is essential in promoting its proper use.

Primary care physicians and pediatricians should inform parents that head lice infestation is a condition that should be diagnosed and treated under the supervision of a physician. For communities in which parents and children do not make regular visits to physicians for financial or cultural reasons, school nurses should be encouraged to work with physicians or public health personnel to ensure that pediculicides are used safely and in ways designed to slow the development of treatment-resistant lice.

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