

# An Overview of Medicated Shampoos Used in Dandruff Treatment

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## ABSTRACT

Dandruff is often seen in the primary care setting as well as in the dermatology field. In this article, we review the most commonly prescribed topical shampoos for treating dandruff and compare their efficacy in eradicating the symptoms of dryness and flaking of the scalp, along with providing relief of associated pruritus. Examples of such agents include keratolytics, regulators of keratinization, antimicrobials, and naturopathic therapies. We examine their mechanisms of action and their efficacy in treating dandruff.

## INTRODUCTION

Also known as *pityriasis simplex capillitii*, *p. simplex capitis*, and *p. sicca*, dandruff is defined as a diffuse, slight-to-moderate scaling of the scalp with varying degrees of irritation or erythema. It is often associated with sensations of intermittent pruritus and dryness. The characteristic flaking and scaling of the scalp suggest impairment in the desquamation process.

Generally, dandruff is thought to represent the mildest form of seborrheic dermatitis of the scalp. Its pathogenesis remains to be completely elucidated, although the yeast organism *Malassezia* has been proposed as an etiological factor.<sup>1</sup>

More than seven species of *Malassezia* (i.e., *M. globosa*, *M. restricta*, *M. obtusa*, *M. slooffiae*, *M. sympodialis*, *M. furfur*, and *M. pachydermatis*) exist, and their growth may be exacerbated by the hypersecretion of sebum and hyperproliferation of the stratum corneum (the protective barrier layer of the skin). To date, the species *M. globosa* and *M. restricta* have been most closely associated with dandruff in humans.<sup>2</sup> *Malassezia* may stimulate cytokine production by keratinocytes (epidermal cells that synthesize keratin), further contributing to the inflammatory component of seborrheic dermatitis and dandruff.<sup>3</sup>

Light and electron microscopy have demonstrated the presence of *Malassezia* in the setting of hyperproliferation, parakeratotic nuclei, increased lipid droplets within corneocytes (keratinocyte remnants), decreased desmosomes, and frequent separation between corneocytes, causing clumping of groups of these cells. The use of ketoconazole, zinc pyrithione, and selenium sulfide typically results in improvement, thereby supporting the role of *Malassezia* in the pathogenesis of dandruff.<sup>4</sup>

Therapeutic shampoos offer a convenient option for treating scaling and pruritus of the scalp. These products have the advantage of being more cosmetically elegant than other topi-

cal formulations, such as solutions, ointments, and foams. The shampoos simultaneously clean the hair and scalp by emulsifying oily secretions while treating the underlying disease. It is recommended that patients apply and lather the shampoo, leave it on the scalp for five to 10 minutes, and then rinse.

The shampoo is typically applied once a day for two weeks, then one to two times a week thereafter for maintenance. Although many dermatological conditions can affect the scalp, this article focuses on dandruff and the available treatment options.

## KERATOLYTIC SHAMPOOS

The pathogenesis of dandruff involves hyperproliferation, resulting in deregulation of keratinization. The corneocytes clump together, manifesting as large flakes of skin. Essentially, keratolytic agents, such as salicylic acid and sulfur, loosen the attachments between the corneocytes and allow them to be washed away with shampooing.<sup>5</sup> Keratolytics soften, dissolve, and release the adherent scale seen in dandruff, although the mechanism is not fully understood.

### Salicylic Acid

Salicylic acid is a beta-hydroxy acid keratolytic agent that is useful in removing scaly, hyperkeratotic skin; it decreases cell-to-cell adhesion between corneocytes. Although the mechanism of action of organic acids is unclear, it may involve the release of desmogleins and the disintegration of desmosomes. Activation of an endogenous pathway, responsible for normal cell separation, may also be involved, but this hypothesis has not been confirmed.<sup>6</sup>

### Sulfur

Sulfur is a yellow, nonmetallic element with both keratolytic and antimicrobial properties. The keratolytic effect is thought to be mediated by the reaction between the sulfur and the cysteine in keratinocytes, whereas the antimicrobial effect may depend on the conversion of sulfur to pentathionic acid by normal skin flora or keratinocytes.<sup>7,8</sup> The keratolytic properties may promote fungal shedding from the stratum corneum.<sup>9</sup> The precise mechanism of action is still unknown.<sup>10</sup>

Leyden et al. studied the combination of 2% sulfur and 2% salicylic acid in a shampoo base (e.g., Sebulex, Westwood Squibb) in a double-blind, controlled trial using both clinical assessment of scaling and corneocyte counts.<sup>11</sup> They observed significantly greater and earlier reductions in both the degree of scaling and in corneocyte counts in subjects using the 2% sulfur/2% salicylic acid combination than in those using either the active ingredient alone or the shampoo vehicle.



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### REGULATORS OF KERATINIZATION

#### Zinc

It is thought that zinc pyrithione (ZPT) heals the scalp by normalizing epithelial keratinization, sebum production, or both. Some studies have also shown a significant reduction in the numbers of yeast organisms after the application of zinc pyrithione.<sup>12,13</sup>

A study by Warner et al. demonstrated a dramatic reduction of the structural abnormalities found in dandruff with the use of zinc pyrithione shampoo:<sup>14</sup> the number of *Malassezia* organisms decreased, parakeratosis was eliminated, and corneocyte lipid inclusions were diminished. Therefore, normalization of the stratum corneum ultrastructure by zinc pyrithione is thought to be secondary to the correction of the pathology in the living epidermal layers.

#### Tar

Although tars have been classically used to treat psoriasis, they offer an effective therapy option in treating dandruff as well. Problems with staining, odor, and messiness in its application make tar a second-line therapy for most patients.

*Tar gels* contain coal tar extract, and they are generally less messy and smelly than tar itself. *Tar shampoos* work through antiproliferative and cytostatic effects, although definitive analyses are difficult because of the large number of biologically active components in coal tar products. Tar products disperse scales, which may reduce *Malassezia* colonization.<sup>15</sup> In the mouse model, topical application of tar suppresses epidermal DNA synthesis.<sup>16</sup>

Pierard-Franchimont et al. conducted a randomized, double-blind study to compare two groups of 30 volunteers with moderate-to-marked dandruff using either a non-tar shampoo (2% salicylic acid, 0.75% piroctone olamine, and 0.5% elubiol) or 0.5% coal tar shampoo.<sup>17</sup> They observed a significantly greater reduction of *Malassezia* species counts in the non-tar group; however, subjects in both groups experienced clinical improvement.

#### Steroids

The pharmacokinetic properties of topical corticosteroids depend on the structure of the agent, the vehicle, and the skin onto which it is applied. Topical corticosteroids work via their anti-inflammatory and antiproliferative effects. On the scalp, lotions or solutions having moderate-to-high potency are typically used.

Clobetasol propionate 0.05% (Clobex, GlaxoSmithKline) is available in a shampoo form. Although no studies currently exist regarding the efficacy of steroid shampoos in managing dandruff, the efficacy of topical steroid applications has long proved effective in treating the condition.<sup>18</sup> Topical steroids are often used in combination with other dandruff treatments such as antifungal agents.

### ANTIMICROBIAL AGENTS

#### Selenium Sulfide

It is thought that selenium sulfide controls dandruff via its anti-*Pityrosporum* effect rather than by its antiproliferative effect;<sup>19</sup> however, it also significantly reduces the rate of cell turnover. It has anti-seborrheic properties and appears to produce a

cytostatic effect on cells of the epidermis and follicular epithelium. Selenium sulfide is available over the counter as a 1% shampoo and by prescription only as 2.25% (Selsab, Doak Dermatologics) and 2.5% shampoos.

A study by Danby et al. compared ketoconazole 2% shampoo (e.g., Nizoral, McNeil Consumer) with selenium sulfide 2.5% shampoo (e.g., Selsun) in 246 patients with moderate-to-severe dandruff in a randomized, double-blind, placebo-controlled trial.<sup>20</sup> Both ketoconazole and selenium sulfide were effective in treating dandruff, but ketoconazole was better tolerated because of its fewer adverse drug effects (ADEs).

Excessive oiliness of the scalp is a significant ADE for many patients who regularly use selenium sulfide to control dandruff. Pierard-Franchimont and Pierard studied the sebum excretion rate in 52 men using anti-dandruff treatments.<sup>21</sup> At the end of the five-week treatment period, the rates of sebum excretion showed an average increase of 58% with the use of selenium sulfide, an increase of 3% with ketoconazole, and an increase of 5% with econazole (e.g., Spectazole, OrthoNeutrogena).

Rapaport compared the anti-dandruff efficacy of four shampoos in 199 patients: selenium sulfide 1% (Selsun Blue, Chattem, Inc.), zinc pyrithione 1% (Head and Shoulders, Procter & Gamble) coal tar extract 5% (Tegrin, GlaxoSmithKline), and a shampoo vehicle (Flex, Revlon).<sup>22</sup> Subjects using Selsun Blue experienced significantly greater improvement of symptoms than did any of the other groups.

Van Cutsem et al. compared the *in vitro* antifungal activity of ketoconazole 2%, selenium sulfide 2.5%, and zinc pyrithione 1% and 2% against *M. furfur* in guinea pigs.<sup>23</sup> Ketoconazole was found to be the most effective for reducing *M. furfur* counts, but results with selenium sulfide and 1% and 2% zinc pyrithione were comparable. The anti-dandruff effects of ketoconazole were superior to those of selenium sulfide and zinc pyrithione.<sup>23,24</sup> Selsab (Doak) is a prescription-only combination of selenium sulfide 2.25% in a urea vehicle with zinc pyrithione.

#### Imidazole Antifungal Agents

Imidazole topical antifungals such as ketoconazole act by blocking the biosynthesis of ergosterol, the primary sterol derivative of the fungal cell membrane. Changes in membrane permeability caused by ergosterol depletion are incompatible with fungal growth and survival.<sup>25,26</sup>

Ketoconazole is a broad-spectrum antimycotic agent that is active against both *Candida albicans* and *M. furfur*. Of all of the imidazoles currently available, ketoconazole has become a leading contender among treatment options because of its effectiveness in treating seborrheic dermatitis. A ketoconazole 1% shampoo has been approved for over-the-counter use, and a 2% shampoo is available by prescription (Nizoral). Rare ADEs include irritation and stinging.

Ketoconazole 2% shampoo has been studied extensively in more than 2,000 patients with dandruff or seborrheic dermatitis. Compared with placebo, the shampoo has been consistently more effective.<sup>27-29</sup>

In a randomized study comparing the efficacy of a four-week trial of ketoconazole 2% shampoo with zinc pyrithione 1% shampoo, Pierard-Franchimont et al. found ketoconazole to be statistically significantly superior (with subjects showing a 73% improvement) to the other (a 67% improvement).<sup>30</sup>

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In a separate study, Saple and associates examined a combination of ketoconazole 2% shampoo and zinc pyrithione 1% shampoo among 236 patients with dandruff, with good-to-excellent alleviation of erythema and itching and with minimal ADEs.<sup>31</sup>

Van Cutsem et al. also demonstrated that ketoconazole was more effective than zinc pyrithione or selenium sulfide in reducing *Malassezia* counts.<sup>23</sup>

### Hydroxypyridones

In contrast to the imidazole antifungals, the hydroxypyridones do not affect sterol biosynthesis; instead, they interfere with the active transport of essential macromolecule precursors, cell membrane integrity, and cell respiratory processes

of dermatophytes and yeasts.<sup>32</sup>

Ciclopirox 1% (Loprox, Medicis), a member of the hydroxypyridone family, has broad-spectrum action against dermatophytes, yeast, and fungi. Its anti-inflammatory activity has been demonstrated in human polymorphonuclear cells. This agent also inhibits prostaglandin and leukotriene synthesis.<sup>33</sup>

Lee et al. compared the efficacy of ketoconazole 2% shampoo (e.g., Nizoral) with ciclopirox olamine 1.5% shampoo (Stieprox, Stiefel Laboratories, not available in the U.S.) for the treatment of mild-to-moderate dandruff in 57 patients.<sup>34</sup> A progressive decrease in dandruff scores was observed throughout the treatment period of both shampoos. However, the ciclopirox patients experienced a slightly increased incidence of pruritus during the

Table 1 Review of Medicated Shampoos Used in the Treatment of Dandruff

Generic Name	Trade Name	Active Ingredient	
Salicylic acid	T-Sal	Salacid 3%	
	Baker's P&S	Salacid 2%	
	Ionil Plus	Salacid 2%	
Salicylic acid and sulfur	MG 217 Tar-Free Shampoo	Salacid 3%, sulfur 5%	
	Sebulex	Salacid 2%, sulfur 2%	
Zinc pyrithione	Head & Shoulders	Zinc pyrithione 1%	
	Zincon	Zinc pyrithione 1%	
	Dandrex	Zinc prithione 1%	
	Sebulon	Zinc pyrithione 2%	
	DHS Zinc	Zinc pyrithione 2%	
	ZNP Bar	Zinc pyrithione 2%	
	Theraplex Z	Zinc pyrithione 2%	
Tar	Pentrax	Coal tar extract 7%	
	T-Gel XS	Solubilized coal tar extract 4%	
	Doak-Tar	Solubilized coal tar extract 3%	
	T-gel	Solubilized coal tar extract 2%	
	Ionil T	Coal tar solution 1%	
	Zetar	Whole coal tar 1%	
	DHS Tar	Coal tar 0.5%	
	Tegrin	Coal tar solution 7%	
	Polytar	Polytar 4.5%	
	Reme <sup>l</sup> T	Coal tar 5%	
	Selenium sulfide	Selsun Blue	Selenium sulfide 1%
Head & Shoulders Intensive Treatment		Selenium sulfide 1%	
Selenium sulfide 1%		Selenium sulfide 1%	
Selseb		Selenium sulfide 2.25%	
Selsun 2.5%*		Selenium sulfide 2.5%	
Exsel 2.5%*		Selenium sulfide 2.5%	
Selenium sulfide 2.5%*		Selenium sulfide 2.5%	
Ketoconazole	Nizoral	Ketoconazole 1%	
	Nizoral*	Ketoconazole 2%	
Ciclopirox	Loprox*	Ciclopirox	
Clobetasol	Clobex*	Clobetasol 0.05%	
Combinations	Sebutone	0.5% coal tar extract with salicylic acid 2% and sublimed sulfur 2%	
	X-Seb T Plus	Coal tar extract 10% with salicylic acid 3%	
	Tarsum	Coal tar extract 10% with salicylic acid 2%	

\* Available only by prescription.

Adapted from Wolverton SE, ed. *Comprehensive Dermatologic Drug Therapy*. Philadelphia, PA: WB Saunders; 2001:647-658. © Elsevier, Inc.<sup>5</sup>

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post-treatment phase. The investigators concluded that ciclopirox olamine was effective and safe for mild-to-moderate dandruff, although ketoconazole was somewhat more effective in treating the pruritus associated with dandruff.

Altmeyer and Hoffman performed a double-blind, vehicle-controlled, randomized study to compare the vehicle with three different concentrations of ciclopirox shampoo: 0.1%, 0.3%, and 1%.<sup>35</sup> A total of 203 patients were enrolled in the study. Although all of the ciclopirox-treated participants tended to show improvement, the most pronounced improvement was noted in the ciclopirox 1% group. All concentrations were found to be safe and well tolerated. Ciclopirox 1% is available as a prescription medication.

Combining ciclopirox olamine 1.5% with salicylic acid 3% allows better access of ciclopirox olamine to the underlying diseased area via the activity of the salicylic acid in decreasing the hyperkeratotic scale.<sup>36</sup> A randomized, single-blind, single-center trial study, sponsored by Stiefel International and conducted by PPD Development, was conducted to compare the efficacy of the combination ciclopirox olamine 1.5% and salicylic acid 3% shampoo with ketoconazole 2% shampoo (Nizoral). Both patient groups showed significant improvement in seborrheic dermatitis and dandruff, but only the ciclopirox/salicylic acid group showed significantly diminished itching. The two shampoos were comparable in their efficacy.<sup>36</sup>

### NATUROPATHIC AND HOMEOPATHIC THERAPIES

#### Tea Tree Oil

Tea tree oil is the essential oil of the leaves of the Australian *Melaleuca alternifolia* tree. Its activity *in vitro* has been demonstrated against numerous dermatophyte species and yeasts. Of these organisms, *M. furfur* appears to be the most susceptible to tea tree oil; the effect of the oil on dandruff is often attributed to its antifungal activity.<sup>37</sup>

Tea tree oil is a mixture of hydrocarbons and terpenes, consisting of almost 100 substances. The antimicrobial property is attributed primarily to the major component, terpinen-4-ol.<sup>38</sup> Tea tree oil represents a sound alternative for patients with dandruff who prefer a natural product and who are willing to shampoo their hair daily.

A study by Satchell et al. consisted of a randomized, single-blind, parallel group study in 126 patients with mild-to-moderate dandruff.<sup>39</sup> The group using 5% tea tree oil showed a 41% improvement, compared with an 11% improvement in those using placebo. The tea tree oil was well tolerated.

#### Other Agents

Alternative agents that have been shown to control the growth of *Malassezia* species include honey and cinnamic acid, however, further studies are needed to determine the efficacy of these treatments.<sup>40,41</sup>

### CONCLUSION

It is our opinion that moderate-to-severe dandruff is most effectively treated with ketoconazole 2% shampoo, sometimes in combination with a high-to-superpotent steroid solution to control inflammation. Ciclopirox shampoo is also highly effective. For mild-to-moderate dandruff, shampoos containing salicylic acid or selenium sulfide often work well and are an affordable and readily available option for patients.

Many therapeutic options for dandruff are available in shampoo vehicles. These formulations offer a safe option for treating this common dermatological condition. The efficacy of various treatments varies among individuals, and combination treatment is often useful in patients who do not respond to a single agent.

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