

# Safe and Effective Treatment of Seborrheic Dermatitis

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*Seborrheic dermatitis is a common chronic inflammatory skin disorder that can vary in presentation from mild dandruff to dense, diffuse, adherent scale. The disorder occurs throughout the world without racial or geographic predominance; it is more common in males than females. Its precise etiology remains unknown, but the condition is strongly associated with lipophilic Malassezia yeasts found among the normal skin flora and represents a cofactor linked to several risk factors, including T-cell depression, increased sebum levels, and activation of the alternative complement pathway. The goal of treatment is symptom control, with an emphasis on the importance of maintaining patient adherence to therapy to achieve low rates of recurrence. Available therapies include corticosteroids, antifungal agents, immunomodulators, and medicated keratolytic shampoos. Although corticosteroids are associated with recurrence, they sometimes may be recommended in combination with antifungal agents. Antifungal therapy is considered primary, but some agents are more effective than others because of their favorable pharmacokinetic profiles, high rates of absorption, anti-inflammatory and antipruritic properties, and vehicle.*

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Seborrheic dermatitis, a common skin disorder that typically presents as erythematous plaques or patches, can vary from mild dandruff to dense, diffuse, adherent scale affecting areas of the head and trunk where sebaceous glands are prominent, including the scalp, nasolabial folds, chest, eyebrows, and ears. A chronic inflammatory disorder, its precise etiology remains unknown, though it is associated with genetic, environmental, and general health factors, as well as lipophilic *Malassezia* yeasts.<sup>1,2</sup>

In seborrheic dermatitis, plaques typically appear as red, flaky, greasy-looking patches of skin; the amount of flaking and erythema varies from patient to patient. Seborrheic dermatitis typically presents as a condition of the scalp, which is a unique environment in humans—warm and dark, and particularly hospitable to infections and infestations introduced by fingers, hats, combs, or styling implements.<sup>3</sup> Distribution is symmetric, commonly presenting in hairy areas of the head (ie, scalp, scalp margin, eyebrows, eyelashes, beard, mustache) but also on the forehead and in external ear canals; nasolabial folds; and body folds, including the axillae, navel, groin, and inframammary and anogenital areas.<sup>2</sup> Lesions typically worsen during the winter, while sun exposure during the warmer months appears to improve the clinical appearance of the disease.<sup>4</sup> Scratching and emotional stress tend to aggravate the condition.<sup>5,6</sup>

## EPIDEMIOLOGY OF SEBORRHEIC DERMATITIS

To emphasize the widespread prevalence of seborrheic dermatitis, some authors have noted that dandruff, the mildest form of seborrheic dermatitis,<sup>7</sup> occurs in 15% to 20% of the population, though it is important to differentiate between seborrheic dermatitis of the scalp and any scalp flaking, regardless of etiology.<sup>1</sup> In general, the prevalence of seborrheic dermatitis ranges from 1% to 3% in the immunocompetent population<sup>7</sup>

and greatly increases in the immunocompromised population, particularly patients with AIDS.<sup>6</sup>

Seborrheic dermatitis is more common in males than females, probably because androgens stimulate sebum production. In general, the condition initially appears during the teenaged years or 20s, with a waxing and waning course throughout adulthood.<sup>2</sup> Adolescents, young adults, and adults older than 50 years are most commonly affected; however, an Australian survey of 1116 children aged 11 days to 5 years 11 months found the overall prevalence of seborrheic dermatitis to be 10.0% in boys and 9.5% in girls, suggesting that the condition also is common in early childhood.<sup>8</sup>

Seborrheic dermatitis occurs throughout the world in patients of various ethnicities and races.

The epidemiology of dermatologic disease rarely has been studied in populations with skin of color, though the report of one US survey comparing the most commonly treated dermatologic conditions in black and white patients found seborrheic dermatitis to be among the top 5 diagnoses in black patients but not white patients.<sup>9</sup>

### ETIOLOGY OF SEBORRHEIC DERMATITIS

Dawson<sup>10</sup> emphasized that seborrheic dermatitis must be viewed as more than a superficial disorder of the stratum corneum. It is a condition in which the epidermis is substantially altered by hyperproliferation, excess intercellular and intracellular lipids, interdigitation of the corneal envelope, and parakeratosis. The etiology of seborrheic dermatitis appears to depend

Table 1.

### Seborrheic Dermatitis Risk Factors<sup>1,6</sup>

Risk Factor	Description
Lipids and hormones	Distribution of lesions on the body corresponds to the distribution of sebaceous glands, with excess sebum found on the scalp, nasolabial folds, chest, eyebrows, and ears
	Most common in adolescents and young adults (when sebaceous glands are most active) and adults older than 50 years
Comorbid conditions	Parkinson disease
	Cranial nerve palsies
	Truncal paralyzes
	Mood disorders
	HIV/AIDS
	Some cancers
	Alcoholic pancreatitis
Immunologic factors	Down syndrome
	Depressed levels of helper T cells
	Reduced phytohemagglutinin, concanavalin A stimulation
Lifestyle factors	Lower antibody titers
	Poor nutrition
	Inadequate hygiene practices

Abbreviation: HIV, human immunodeficiency virus.

on 3 factors: sebaceous gland secretions, microfloral metabolism, and individual susceptibility.<sup>10</sup> Many factors have been cited as possible contributors to the development of seborrheic dermatitis (Table 1).

### Role of *Malassezia* Species

Yeasts of the genus *Malassezia* (formerly *Pityrosporum*) are a normal part of the skin flora yet are associated with many common dermatologic disorders, including tinea (or pityriasis) versicolor and *Malassezia* folliculitis. Following some debate in the literature evaluating if yeasts are of primary pathogenic significance or a secondary phenomenon, it has become clear that lipid-dependent *Malassezia* yeasts are causal factors in the development of seborrheic dermatitis, most commonly *Malassezia globosa*, with its high lipase activity, and *Malassezia restricta*. These 2 organisms predominate on the scalp of individuals with seborrheic dermatitis or dandruff.<sup>7,10</sup> Because the disease responds to antifungal medications and *Malassezia* counts diminish as the condition improves, it has been strongly suggested that yeasts play a role in the pathogenesis of seborrheic dermatitis. Genetic and environmental factors as well as comorbid conditions may predispose certain populations to the development of seborrheic dermatitis.<sup>2</sup> In general, patients with seborrheic dermatitis are thought to have higher *Malassezia* counts than healthy controls, though some experts dispute this assumption.<sup>1</sup>

### Other Risk Factors

It also has been observed that individuals with central nervous system disorders appear to be prone to developing extensive seborrheic dermatitis that often is refractory to treatment. In these cases, it has been hypothesized that the infection results from excessive pooling of sebum caused by immobility, which permits increased growth of yeasts.<sup>2</sup> Another confounding factor in the development of seborrheic dermatitis is a compromised immune system. Medications that can induce seborrheic dermatitis or cause it to flare include buspirone hydrochloride, chlorpromazine, cimetidine, gold, griseofulvin, haloperidol, interferon alfa, lithium, methyl dopa, psoralen, and thiothixene.<sup>6</sup>

### DIAGNOSIS OF SEBORRHEIC DERMATITIS

Seborrheic dermatitis usually is diagnosed based on a history of waxing and waning severity and the distribution of involvement on examination. A skin biopsy specimen may be needed in patients with exfoliative erythroderma, and fungal culture may be used to rule out tinea capitis.<sup>6</sup> However, the result of a fungal culture is not always useful in the diagnosis of seborrheic dermatitis because the pathogen is part of normal skin flora.

### TREATMENT OF SEBORRHEIC DERMATITIS

Seborrheic dermatitis is a chronic disease and patients should be informed about the risk for relapse, predisposing factors, and the lifetime need for special attention to hygiene. To remove oils and generally improve the skin, patients should be encouraged to cleanse the affected skin often with soap and water. Patients should engage in outdoor recreation, particularly in the summer, with the goal of improving the condition through exposure to sunlight, providing precautions are taken against sun damage.<sup>2</sup>

### PHARMACOLOGIC OPTIONS

The primary goal of therapy for seborrheic dermatitis is symptom control because, at this time, there is no cure for the disease. Various treatments are used for seborrheic dermatitis, including mild corticosteroids, antifungal agents, immunomodulators, and medicated shampoos.<sup>11</sup> Although mild corticosteroids used alone can be effective in managing symptoms, the disease is likely to recur quickly once steroid therapy is stopped. Antifungal agents should therefore be considered primary therapy.<sup>5,12</sup>

Because seborrheic dermatitis is a chronic recurring skin disorder, the goal of treatment is the development of a safe and effective regimen associated with low rates of recurrence.<sup>12</sup> Accordingly, treatment should incorporate an antifungal agent that is effective and tolerable to the patient, both to reduce relapse and to promote patient adherence. An optimal topical agent is one with good penetration that stays on the skin; has anti-inflammatory properties; and is delivered via a vehicle that enhances penetration, provides a healing environment, and sustains

Table 2.

### Recommended Treatment Approach

- Start patient on a topical antifungal agent with good minimum inhibitory concentrations against the yeast.
- Additional antifungal assets should include good penetration and absorption, anti-inflammatory properties, and a vehicle that is able to promote efficacy by enhancing penetration.
- If the condition has not resolved or improved, add a topical steroid appropriate for the body area infected.
- Using topical steroids as monotherapy is not recommended because steroids do not kill pathogens, so symptoms will recur when steroids are stopped.

a reservoir of active agent for extended delivery (Table 2).

### Topical Agents

Among the currently available topical azole antifungal agents that have been studied in the treatment of seborrheic dermatitis are clotrimazole, fluconazole, itraconazole, miconazole, ketoconazole, and sertaconazole; of these agents, only ketoconazole, formulated as a cream, gel, and foam, currently is indicated for seborrheic dermatitis. Fluconazole shampoo 2% has been found to be effective in patients with seborrheic dermatitis of the face, though this product currently is not available in the United States<sup>1</sup>; ketoconazole also is formulated as a shampoo but is indicated for tinea versicolor caused by *Malassezia furfur*. Because it can reduce the number of *Malassezia* yeasts on the scalp, miconazole may be effective against seborrheic dermatitis, either as monotherapy or in combination with hydrocortisone.

A number of comparative studies have evaluated the antifungal activity of several azole antifungal agents against *Malassezia* yeasts. In one study, 55 strains of 7 *Malassezia* species were investigated for in vitro susceptibility to ketoconazole, voriconazole, and itraconazole, as well as terbinafine.<sup>13</sup> The study found that all strains of the *Malassezia* species were susceptible to the 3 azoles at low concentrations, though with variations depending on the species involved. Strains of *M furfur* tested with terbinafine ranged from highly susceptible to relatively resistant.<sup>13</sup> Similar results have been reported by researchers who studied 95 *Malassezia* isolates to assess the antifungal activity of ketoconazole, voriconazole, itraconazole, and fluconazole<sup>14</sup> and a group who studied the antifungal activity of ketoconazole, itraconazole, and fluconazole against 28 strains of *M furfur*.<sup>15</sup> Both concluded that all strains of *M furfur* studied were susceptible to all drugs studied, though with some variations.<sup>14,15</sup>

Ciclopirox olamine, which has broad-spectrum antifungal activity as well as an anti-inflammatory effect, has been found to be effective in the treatment of seborrheic dermatitis as a cream with a 1% concentration, gel, and shampoo with a 1% concentration, though only the shampoo is indicated for the treatment of seborrheic dermatitis of the scalp.<sup>1</sup> However, meta-analyses of clinical trials comparing various agents commonly used to treat fungal infections of the foot have shown that ciclopirox is less effective than azoles or allylamines and its cure rates are low.<sup>16</sup>

Another antifungal agent studied for its efficacy in the treatment of seborrheic dermatitis is metronidazole gel, which is indicated for topical treatment of inflammatory lesions of rosacea.<sup>1</sup> The synthetic

allylamine derivatives terbinafine and naftifine, in addition to the benzylamine butenafine, also are available and may be able to reduce the number of *Malassezia* organisms that colonize treated areas, though the minimum inhibitory concentrations (MICs) associated with these drugs are inferior to other agents discussed here. None of these agents currently is indicated for seborrheic dermatitis.<sup>1</sup>

Corticosteroid creams such as desonide, which is formulated as a cream, gel, ointment, lotion, and foam, and hydrocortisone cream, ointment, or lotion are popular therapies for seborrheic dermatitis, sometimes in combination with antibiotics.<sup>1</sup> Steroids, which target inflammation, may be useful ancillary therapies if topical antifungal agents have not eradicated the disease. However, high-potency formulations have been associated with a number of adverse events, including effects on the adrenal cortex as well as the skin, though low-potency topical formulations can provide quick control of flare-ups and relief of pruritus.<sup>11</sup>

Because of their ability to reduce the inflammatory response by inhibiting T lymphocyte activation, immunomodulators have been used to treat seborrheic dermatitis, though they are indicated only for atopic dermatitis. These agents, which are classified as topical calcineurin inhibitors, have been considered safer than corticosteroids for long-term use<sup>6,17</sup>; the US Food and Drug Administration had mandated a black box warning because of safety concerns relative to long-term malignancy risk caused by systemic immunosuppression.<sup>17,18</sup> Examples of topical calcineurin inhibitors include tacrolimus ointments 0.03% and 0.1% and pimecrolimus cream 1%, both indicated as second-line therapy for atopic dermatitis only.<sup>6</sup>

### Other Medications: Shampoos

Seborrheic dermatitis commonly is treated with non-specific agents, some with keratolytic activity. Chiefly formulated as shampoos, keratolytic agents include coal tar and salicylic acid. Neither has antifungal activity; they work by causing cornified epithelium to swell, soften, macerate, and desquamate. Available as over-the-counter products, such as Denorex<sup>®</sup>, Neutrogena T/Gel<sup>®</sup>, and P&S<sup>®</sup> shampoos, these products are widely available and are likely to have been tried by most patients before consulting a dermatologist.

Other over-the-counter shampoos, including zinc pyrithione and selenium sulfide, do have antifungal activity.<sup>1,6</sup> Many of these products are available over-the-counter, including Head & Shoulders<sup>®</sup> and Denorex (both zinc pyrithione) and Dandrex<sup>®</sup> and Selsun blue<sup>®</sup> (both selenium sulfide), and are likely to have been used by most patients prior to visiting a dermatologist. Other antifungal shampoos include

ciclopirox shampoo 1%, which is indicated for seborrheic dermatitis of the scalp, and ketoconazole shampoo 2%, which is indicated for tinea versicolor.

### **Sertaconazole: Effective Treatment of Seborrheic Dermatitis**

Sertaconazole nitrate cream 2%, indicated for the treatment of tinea pedis in the United States, is an available option for the treatment of seborrheic dermatitis. A broad-spectrum antifungal agent with anti-inflammatory and antipruritic properties, sertaconazole has been shown in controlled studies in Europe to be a safe and effective treatment of seborrheic dermatitis.<sup>19</sup>

*Pharmacokinetics Study*—In a study of the pharmacokinetics and tolerance of sertaconazole after repeated administration, researchers determined that the drug is well-tolerated both locally and systemically.<sup>20</sup> The absorption rate of the drug was both rapid and long lasting, reaching values of 50% between 2 and 4 hours after administration with high absorption (72%) in the stratum corneum 24 hours after administration. Percutaneous absorption following topical administration was low, with no trace of drug detected in blood or urine samples.<sup>20</sup>

*In Vitro Studies*—A comparative study of the antifungal activity of the azoles sertaconazole and bifonazole and the allylamine terbinafine measured MIC values for all 3 agents against a variety of yeasts and dermatophytes. The results demonstrated that sertaconazole was statistically more active than bifonazole and terbinafine against

180 yeast strains, with MIC values that were considerably lower against a variety of *Candida* strains than either comparator agent.<sup>21</sup> Other reports have found the in vitro activity of sertaconazole against many causative organisms associated with fungal infections to be higher than or comparable with other azoles, including ketoconazole, bifonazole, miconazole, econazole, and clotrimazole.<sup>22,23</sup>

*Clinical Studies*—Two European studies evaluated the efficacy and safety of sertaconazole in the treatment of seborrheic dermatitis.<sup>19,24</sup> In a 1994 double-blind randomized trial, sertaconazole gel 2% applied once daily every 3 days for 4 weeks was used to treat seborrheic dermatitis of the scalp in 15 men and women and was compared with placebo.<sup>19</sup> Results showed sertaconazole had a substantial decrease in the severity of the clinical signs of pruritus and desquamation as well as an overall decrease in dermatitis. In addition, of participants with severe disease at baseline, those treated with sertaconazole showed considerable improvement, whereas those treated with placebo showed no clinical improvement.<sup>19</sup>

In a 1997 double-blind, randomized, parallel-group study of sertaconazole gel 2% versus ketoconazole gel 2% used every 3 days for 28 days in 60 males and females with seborrheic dermatitis of the scalp, 28-day therapy with sertaconazole resulted in considerable improvement in the symptoms of desquamation and pruritus and was clinically superior to ketoconazole, an established reference drug. No patients withdrew from the trial because of

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Improvement in symptoms of desquamation and pruritus after treatment with sertaconazole gel 2% or ketoconazole gel 2%. Reprinted with permission from Ferrer Group Research Centre.<sup>25</sup>

adverse events, and the researchers concluded that sertaconazole may be considered an effective treatment of seborrheic dermatitis.<sup>24</sup> The Figure provides a graphic illustration of symptomatic findings.<sup>25</sup>

## CONCLUSION

Seborrheic dermatitis is an extremely common and recurrent dermatitis presenting in individuals of varied ages and ethnicities. Treatment traditionally has involved antifungal agents, alone or in combination with corticosteroids, but there has been a continuing need for additional effective nonsteroidal topical therapies. Because of its demonstrated broad-spectrum antifungal activity against yeasts and dermatophytes, including *Malassezia* species, as well as its anti-inflammatory and antipruritic properties, sertaconazole can be considered a promising nonsteroidal agent for the topical treatment of seborrheic dermatitis.

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