ABSTRACT

Seborrheic dermatitis (SD) is a chronic inflammatory disorder that causes erythema and flaking in areas with high concentrations of sebaceous glands. The face and scalp are the most frequently affected areas although the involvement of multiple sites is common. Dandruff is regarded as a mild non-inflammatory form of SD. It is a common scalp disorder causing social embarrassment for those afflicted by it.

The cause of SD/dandruff appears to be related to the composition of the sebaceous gland secretions, the proliferation of Malassezia yeasts, and the host immune response. Treatment options include topical agents containing antifungal agents, keratolytic agents, and anti-inflammatory agents. This article reviews the etiology, clinical presentation, and topical treatment options for dandruff/SD based on published articles.

Keywords: dermatitis, dandruff, topical treatment

INTRODUCTION

Dandruff (also known as pityriasis capitis, p. simplex capillitii, p. simplex capitis, and p. sicca) and seborrheic dermatitis (pityrosporal dermatitis) are chronic, scaling disorders affecting the scalp and skin sites rich with sebaceous glands. They are common disorders causing cosmetic problems, anxiety, and discomfort to as many as 50% of the population between the ages of 15 - 50 years. Dandruff is considered by many authors as a less severe form of seborrheic dermatitis. It is characterized by the appearance of loosely adherent white or gray flakes, localized diffusely or in patches in the scalp, accompanied by itching and dry feeling of the scalp with no apparent inflammation. Flakes of dandruff may be observed beyond the scalp region on eyelashes, eyebrows, eye and nose corners, and regions in the ears. Seborrheic dermatitis (SD), as compared to dandruff, appears as margined lesions or patches covered with frequent flakes that have progressed to being yellow, with moist, greasy skin texture accompanied by visible redness (surface erythema) as definite signs of inflammation. Unlike dandruff, SD can appear beyond the scalp, particularly the face (forehead, eyebrows, eyelashes, beard, mustache, anterior hairline, nasolabial folds), the external auditory canals and behind ears, back of the neck, the axilla, groin, and anterior chest.

Dandruff and SD can result from interconnected exogenous as well as endogenous factors. The main etiologies include: fungal (Malassezia spp.) and bacterial infections, sebaceous gland secretions, and individual sensitivity. They can occur in any ethnicity and gender; they are more prevalent in males than females as male hormones are likely to play a role in their formation. The incidence is more in adolescents and young adults and increases again in those above the age of 50 years. They are aggravated by seasonal
changes as humidity, heat and sun exposure, or by trauma, emotional stress, with higher prevalence in those with altered immunity such as HIV/AIDS, Parkinson's disease, multiple sclerosis, depression, and alcoholism. Genetic bases, host immune response, oxidative stress, nutritional, neurogenic and emotional factors have all been shown to play a role for the etiopathogenesis of dandruff/SD.

Topical pharmacological therapy of dandruff/seborrhic dermatitis

The goal of treatment of dandruff/SD is to achieve symptomatic improvement by controlling itching and normalizing skin function through controlling scalp flaking rather than curing the condition. Safety, efficacy, ease of use, age of the patient, and cost of treatment are important factors that must be considered during the selection of optimal treatment to provide the best clinical outcome. Patients should be educated about special attention to hygiene, and at least three times a week of hair washing to remove excessive fat. They should also be encouraged to sunlight exposure, provided that protection is taken against sun damage. Agents that irritate active lesions, such as keratolytic preparations or mechanical removal of scales should be avoided. The use of hair oils must be avoided but the use of emollients is beneficial.

A variety of topical therapeutic agents have been tried clinically for the treatment of dandruff/SD. Such agents can be divided according to their mechanisms of action into categories including antifungal, anti-inflammatory and keratolytic agents. However, many of the current treatments have multiple effects, thereby combatting skin changes on multiple levels. Such agents are available in the market as various topical formulations (shampoos, creams, lotions, emulsions, hair oils, etc.); and are discussed in the following sections.

1. Antifungals

Antifungal medications have been used as a potential first-line treatment for dandruff/SD. They are used topically in an attempt to inhibit the growth and reduce the colonization of Malassezia yeast, the main causative agent of dandruff/SD. Antifungal agents which have been clinically evaluated for the treatment of dandruff/SD are discussed below.

a. Azoles

Azoles represent the largest class of antifungals. Topical azoles that have been studied in the treatment of dandruff/SD in different topical preparations include clotrimazole, fluconazole bifonazole, miconazole, ketoconazole, climbazole sertaconazole, and flutrimazole.

Azoles inhibit fungal cytochrome P450 (CYP) enzyme lanosterol 14α-demethylase, thereby inhibit the biosynthesis of ergosterol, the main sterol in the fungal cell membrane. Some azoles such as ketoconazole, bifonazole, and sertaconazole have additional anti-inflammatory activity as they inhibit 5-lipoxygenase production which then blocks leukotriene B4 synthesis in the skin. Such an effect provides an additional advantage to these drugs making them beneficial in alleviating symptoms of SD since the conditions are mostly accompanied by inflammatory reactions.

Ketoconazole, the most commonly prescribed azole antifungal, is available as 1% and 2% shampoo, a 2% cream, a 2% oil-in-water emulsion, and a 2% foaming gel. All of these preparations are effective in the treatment of dandruff/SD.
Bifonazole 1% cream, applied once daily for 4 weeks, is usually effective in the treatment of face and scalp SD, and bifonazole 1% gel is effective for the treatment of body SD with similar effectiveness as other antifungal preparations\textsuperscript{14,15}.

Climbazole 1% shampoo was effective in treating scalp SD upon once-daily application, but 1% ketoconazole shampoo showed superior efficacy\textsuperscript{16}.

Fluconazole 2% shampoo and gel were also found to be effective in the treatment of scalp and facial SD\textsuperscript{17,18}. Miconazole 2% rinse and shampoo have been effective in the treatment of scalp SD with miconazole shampoo being as effective as 2% ketoconazole shampoo\textsuperscript{19}.

Both clotrimazole 1% cream and sertaconazole 2% cream was found to be efficient in the treatment of facial SD. However, sertaconazole had higher efficacy than clotrimazole 1% cream and a comparable therapeutic effect to ketoconazole 2% cream\textsuperscript{20} and sertaconazole 2% gel applied once a day every 3 days for 4 weeks was clinically superior to ketoconazole 2% gel for scalp SD\textsuperscript{21}. The anti-\textit{Malassezia furfur} activity of flutrimazole 1% gel was similar to ketoconazole 2% gel when used in patients with dandruff/SD at a dose of three applications per week for 28 days\textsuperscript{22}.

b. Hydroxypyridones

Hydroxypyridones are another class of antifungals, the main members of which are ciclopirox and its salt ciclopirox olamine (ciclopiroxolamine), in addition to piroctoneolamine. These agents are active against a broad spectrum of fungi including \textit{Malassezia} spp., and also exhibit activity against several gram-positive and gram-negative bacteria. They act by inhibiting cellular uptake of essential compounds via the cell membrane and in higher concentrations, disturb the cellular permeability and inhibit ATP-synthesis of the fungal cell. They are also involved in the chelation of polyvalent cations such as Fe\textsuperscript{3+} and Al\textsuperscript{3+}, thereby creating a larger, combined polyvalent cation, which has an inhibitory effect on enzymes that are involved in the cellular processes of fungi. Ciclopiroxolamine and ciclopirox acid have also displayed mild anti-inflammatory effects\textsuperscript{23,24}.

Application of ciclopirox 1% shampoo twice a week or application of 0.77% gel twice a day for 4 weeks has demonstrated efficacy in for scalp SD\textsuperscript{25,26}.

Ciclopiroxolamine, the salt form of ciclopirox, is slightly more soluble and has the same pharmacological properties as ciclopirox. A study reported that 1.5% ciclopiroxolamine shampoo was at least as effective as 2 % ketoconazole shampoo in the treatment of scalp SD\textsuperscript{27}, and 1% ciclopiroxolamine cream used twice daily for 4 weeks was as effective as ketoconazole 2% foaming gel in mild-to-moderate facial SD\textsuperscript{28}.

Few studies have been conducted to evaluate the efficacy of piroctone olamine shampoo in dandruff/SD. One study reported that 1% piroctone olamine shampoo treatment with an extended 5-minute residence time benefited more than 1% ketoconazole shampoo treatment\textsuperscript{29}. Another study compared shampoo containing climbazole or piroctoneolamine beside herbal extracts and found that both are effective in the reduction of dandruff /SD symptoms but climbazole seems to be more effective than piroctoneolamine\textsuperscript{30}.

c. Allylamines and Benzylamines

Allylamines (terbinafine, naftifine) and benzylamines (butenafine) exhibit their antifungal action by inhibiting squalene epoxidase, resulting in accumulation of squalene and deficiency of ergosterol, an
essential component of the fungal cell membrane. Such actions lead to inhibition of ergosterol biosynthesis and are the reason for antifungal effects. They have also been associated with anti-inflammatory activity, an effect which could have additional benefit during treatment of skin conditions associated with inflammation.31, 32

Terbinafine 1% cream applied twice daily is safe and effective as ketoconazole 2% cream for facial SD after 4 weeks of treatment.33 A 1% solution, used once a day for 4 weeks, improved the lesions of scalp SD and reduced the number of Malassezia organisms colonizing the treated areas.34 Naftifine hydrochloride 1% gel applied twice daily for 4 weeks, is a safe and effective topical treatment for moderate scalp SD, and butenafine hydrochloride 1% cream applied twice daily for 3 weeks is safe and effective for managing facial SD.35

2. Anti-inflammatory agents

a. Corticosteroids

Topical corticosteroids of varying potencies have traditionally been used as first or second-line agents in the treatment of SD. They reduce inflammation and relieve erythema and itching. Their use should be reserved to control acute flares and applied to limited body area, for a short period (1-4 weeks depending upon the severity of disease) since response to them is usually rapid, and there have been cases of skin atrophy, telangiectasias, folliculitis, and hypertrichosis associated with prolonged use.37 Hydrocortisone (1% liniment and solution, 0.1% lotion) applied once daily for up to 4 weeks is effective for hairy areas and scalp SD, while hydrocortisone (1% cream, ointment) applied twice daily for 4 weeks is effective for non-scalp SD.38

Other low potency topical corticosteroids effective for the treatment of SD include desonide (0.05% lotion, gel, cream),39, 40 and alclometasone dipropionate (0.05% cream, ointment).41

Medium to high potency topical steroids used in the treatment of SD include betamethasone valerate (0.05% or 0.1% lotion, 0.1% solution, cream, foam),42, fluocinoloneacetonide (0.01% solution, shampoo) 44, clobetasol propionate (0.05% shampoo),45, clobetasole 17-butyrate (0.1% cream) 47 and mometasonefuroate (0.1% solution, cream).48

High potency corticosteroids may be used only for a short duration (2 weeks) in the treatment of acute phase SD because of the adverse reaction profile, and the potential of rebound dermatitis which may occur in patients attempting to stop topical steroid therapy after long-term continued use.49

b. Calcineurin inhibitors

Calcineurin inhibitors (pimecrolimus and tacrolimus) have been used for the treatment of SD due to their anti-inflammatory effects, and are not associated with the side effect profile of corticosteroids. They act by inhibiting calcineurin, a calcium-dependent phosphatase enzyme necessary for T-lymphocytes and mast cell activation. Such an inhibition prevents the release of pro-inflammatory cytokines and consequently will produce an anti-inflammatory effect.50 Pimecrolimus and tacrolimus have also been found to have antifungal effects on M. furfur and other Malassezia strains.51 Tacrolimus (0.03% or 0.1% ointment) applied twice daily is effective in short term management of SD exacerbations on the face, scalp, and chest.52 Pimecrolimus is reported to be more lipophilic than tacrolimus; thus, it has a higher affinity to skin, with 9-10 times slower permeation than tacrolimus and 70-110 times slower permeation than corticosteroids. Topical
pimecrolimus is associated with a lower risk of systemic exposure and subsequent systemic side effects\(^{53}\). Such properties give pimecrolimus 1% cream greater cosmetic acceptability and therapeutic potential in treating steroid-resistant SD and in the relapsing or resistant trunk and facial SD\(^{54,55}\).

3. Keratolytics

Topical keratolytic agents work by breaking down and loosening kerneocyte bonds, resulting in decreased scaliness and removal of thick crusts to be washed away. They help aid penetration of topical treatments and have been used for the treatment of SD lesions which are covered with thick adherent scales, particularly in the scalp and face\(^{56}\).

Keratolytics are mostly used as shampoos, these should be left on the hair for at least five minutes to ensure that it reaches the scalp. Patients are advised to apply moisturizing conditioners and scalp oils following their application to avoid hair drying effects caused by keratolytic shampoos. Commonly used keratolytics used for dandruff/SD are discussed below.

a. Salicylic acid

Salicylic acid is reported to have bacteriostatic and fungicidal properties; it is mostly used as 3% shampoo and is applied 2-3 times weekly for the treatment of dandruff\(^{57}\).

b. Sulphur

Sulphur has many dermatological indications, including but not limited to acne vulgaris, rosacea, dandruff, and seborrheic dermatitis. It is used mainly due to its antibacterial, antifungal and keratolytic effects. The keratolytic action of sulphur may promote fungal shedding from the stratum corneum, and is due to its ability to form hydrogen sulfide on interaction with keratinocytes; while the antimicrobial activity is due to the conversion of sulfur to pentathionic acid by normal skin flora or keratinocytes\(^{58}\). Certain precautions are required during the use of sulphur in dandruff. Only small amounts of the product should be rubbed very gently into cleaned, affected portions of non-broken skin near the roots of the hair. Prolonged usage should be avoided and the application of the product stopped if excessive dryness or irritation of skin occurs\(^{59}\). Sulphur is no longer used alone in medical treatment; it is used in combination with salicylic acid or sodium sulfacetamide, with demonstrated efficacy for treatment of dandruff/SD. Sodium sulfacetamide is reported to have antibacterial and anti-inflammatory activity. It is used in a concentration of 10% combined with 5% sulphur; it is available as foam or lotion to be applied twice daily to scalp, face or body\(^{60}\).

c. Coal tar

Coal tar (whole coal tar or crude coal tar extract) has been efficacious against SD particularly in chronic cases, due to its antiproliferative and cytostatic effects\(^{61}\). Tar products disperse scales, which may reduce *Malassezia* colonization. Also, antibacterial and antifungal activity have been described. However, coal tar products are photosensitizers and may cause skin sensitization, and in Europe, a ban on coal tar shampoos has been instituted due to safety concerns. Coal tar products also have problems with staining, odor and messiness in its application making them a second-line therapy for most patients as other effective shampoos are readily available\(^{62,63}\).
Comparative studies have been performed to evaluate the efficacy of products containing coal tar alone or with other drugs such as ciclopirox olamine or ketoconazole. The studies concluded that shampoo containing only coal tar appeared less effective than combination products in the treatment of dandruff/SD.

d. Other keratolytics

Topical urea is a known keratolytic; C8-lipohydroxy acid induces exfoliation and stimulation of epidermal renewal; lactic acid has keratolytic and hydrating properties; azelaic acid modifies epidermal keratinization, and propylene glycol used as an excipient and has keratolytic effects. All these agents also inhibit the growth of bacteria and/or fungi. One study supports the efficacy and safety of 15% azelaic acid gel in facial seborrheic dermatitis. Propylene glycol shampoo and solution (15%) are easy to apply, cosmetically attractive options that have been used successfully in the treatment of dandruff/SD. Such an effect may be due to its antimicrobial activity against *Pityrosporum ovale* (the minimum inhibitory concentration is in the range 3–9%) or due to its action as a keratolytic and penetration-enhancing agent. A liniment base containing 30% propylene glycol was reported to be as effective as plain hydrocortisone or a combination of clotrimazole and hydrocortisone for the treatment of active scalp SD.

**CONCLUSION**

Seborrheic dermatitis and dandruff are chronic, relapsing skin disorders usually requiring repetitive treatment courses. A wide range of therapeutic modalities are currently used for treatment and include antifungal agents, anti-inflammatory and keratolytic agents. Topical therapy has proved to be effective in many studies and should be individualized depending on the condition of each patient.

**CONFLICT OF INTEREST**

The authors declare that they have no conflict of interest.

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