REVIEW ARTICLE

Systematic Review of Oral Treatments for Seborrheic Dermatitis

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Abstract

Seborrheic dermatitis (SD) is normally treated with topical corticosteroids and antifungals. Oral therapies can be prescribed in severe or unresponsive cases. This review aims to assess the quantity and quality of published reports on oral therapies for SD. MEDLINE and Embase databases and the reference listings of publications were searched for any publication using oral treatment for SD. The quality of the included publications was assessed using a modified 27 item checklist by Downs and Black. Twenty-one publications (randomized controlled trials, open trials and case reports) covering eight oral therapies (itraconazole, terbinafine, fluconazole, ketoconazole, pramiconazole, prednisone, isotretinoin and homeopathic mineral therapy) were identified. Most of the publications investigated oral antifungals and the quality of the evidence was generally low. The clinical efficacy outcome reported varied considerably between the studies, preventing statistical analysis and direct comparison between treatments. However, ketoconazole therapy was associated with more relapses compared with other treatments. Itraconazole dosing regimen for SD was generally 200 mg/day for the first week of the month followed by 200 mg/day for the first 2 days for 2–11 months. Terbinafine was prescribed at 250 mg/day either as a continuous (4–6 weeks) or as an intermittent regimen (12 days per month) for 3 months. Fluconazole has administered daily (50 mg/day for 2 weeks) or weekly (200–300 mg) for 2–4 weeks. Ketoconazole dosing regimen was 200 mg daily for 4 weeks. Finally, a single 200 mg dose of pramiconazole was administered to patients. This review also highlights key areas for consideration when designing future studies.

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Introduction

Seborrheic dermatitis (SD) is normally a mild but chronic skin disorder that typically affects humans at two time points during their lifespan: infancy and adulthood[1]. Clinically, SD is characterized by scaly and erythematous regions observed at anatomic sites that have a high concentration of sebaceous glands (scalp, face, upper trunk and flexures).[2] The prevalence of SD in the general population has been reported between 2.35% and 11.3% depending on the country studied.[3] A greater occurrence can be observed in the immunocompromised population and individuals with neurological conditions such as Parkinson's disease.[1]

The exact aetiology and pathophysiology of SD are not yet clear.[2,4–6] Hormone levels, sebum production, lipid composition on the skin surface, *Malassezia* species and patient predisposition to immune or inflammatory reactions have been suggested as important factors in the development of SD.[4,6] *Malassezia* spp., formerly known as *Pityrosporum ovale*, is a commensal species on the human skin flora, but is hypothesized to become pathogenic.[7,8] It has been shown that there is a decrease in *Malassezia* spp. population with antifungal treatment in parallel with improvement in SD clinical signs.[2]

The first line treatment for SD is topical treatment with antifungals and corticosteroids.[9,10] Topical corticosteroids are often prescribed to reduce inflammation, however, adverse side-effects are noted with long-term use.[11] Furthermore, they are often associated with poor patient compliance.[12] Oral therapies may be beneficial when multiple anatomic sites are involved,[11] for patients who are unresponsive to traditional topical therapies[13] and/or for those with severe SD.[11]

We conducted a systematic review to assess the quantity and quality of the reported use of oral treatment for SD. An overview

of available oral therapies, their dosing regimens, and their efficacies will also be provided.

Methods

Search strategy

MEDLINE and Embase were searched on September 6, 2012. There were no date restrictions or language restrictions on the initial search in MEDLINE, which included the MeSH terms, 'Dermatitis, Seborrheic' and 'Administration, Oral' with all of their entry terms. Drug names including: terbinafine, fluconazole, ketoconazole, itraconazole and pramiconazole were also used to provide a more inclusive search. The search in Embase followed the same structure, but was restricted to human trials and English language. Bibliographies of relevant studies were also reviewed.

Search criteria

To provide a comprehensive collection of all relevant studies where oral agents have been used to treat SD, we did not restrict our inclusion criteria to only randomized controlled trials (RCTs). After an initial screening based on title and abstract, the publications were included if they were original reports of clinical and/or mycological efficacy outcomes. Studies were excluded if they did not report data separately for SD or if they were not available in English.

Data extraction and quality assessment

Data extraction forms were used to gather information on clinical trial design (blinding, randomization, and control group), study population (number of participants, gender, mean age, and severity of the disease), treatment schedule (dosing regimen and compliance), and outcomes (time of assessment, assessment criteria, type of analysis, adverse events (AEs), and clinical and mycological outcomes). The quality of the studies was assessed by two independent raters using a modified 27 item checklist by Downs and Black.[14,15] A mean quality score (MQS) and a standard deviation were calculated for each publication. The interrater reliability was assessed using the κ statistic in IBM SPSS Statistics 20 software (Armonk, NY, USA). Case studies were not assessed for quality.

Results

The literature search generated 627 records from MEDLINE and Embase and 154 from other sources for a total of 781 records (Fig. 1). After an initial screen of titles and abstracts and duplicates removal, 235 articles remained. Our search criteria and language restrictions omitted an additional 214 records, resulting in 21 publications included in the analysis.

Of the 21 publications identified, nine were for itraconazole,[12,16–23] three for terbinafine,[24–26] three for fluconazole,[27–29] two for ketoconazole,[30,31] and one for each of pramiconazole,[32] predinisone,[33] isotretinoin[34] and homeopathic mineral therapy.[35] Case reports and studies without the full text availability[27,29] were not evaluated for quality. A κ statistic of 0.551, indicating moderate agreement between raters, was found for the 13 studies evaluated. Five studies[25,26,28,31,35] were RCTs with a MQS varying between 13.5 and 22.0 on a possible 28 point scale. Ten were open studies[12,16–19,23,24,27,29,32] with a MQS varying between 8.5 and 13.5 and six were case reports.[20–22,30,33,34]

Oral antifungal therapies

Itraconazole Six open non-comparative trials[12,16–19,23] and three case studies[20–22] were identified for itraconazole (Table 1). The MQS for the open non-comparative studies ranged from 10.5 to 13.5 on a possible 28 point scale. Sample sizes ranged from 30 to 160 patients with mean ages at 26–33 years and there was a greater percentage of males in each trial. Most of the patients had moderate to severe SD and/or were unresponsive to conventional therapy.

The dosing regimens for all itraconazole studies, except for two case reports, were an initial 200 mg/day for 7 days typically followed by varying lengths of pulse therapy for 2–11 months (Table 1). No obvious patterns could be elucidated between total drug or length of treatment and clinical improvement. Compliance was reported as good or excellent and there were no treatment-related AEs reported.

Erythema and scaling were evaluated in all studies, while additional evaluation criteria differed between studies and included papules, itching, burning and seborrhea (Table 1). The definition for clinical improvement varied between studies, but in general included several levels of improvement. The clinical improvement rate and mycological cure rate varied from 58.6% to 93.0% and 40.0% to 86% respectively. A complete cure rate of 68% was reported by one small study using itraconazole for 12 months. All case studies reported clinical and mycological cure. The optimal clinical response for itraconazole was generally reached within the first month of therapy and was maintained for as long as 3,[17] 6[23] or 14 months.[12]

Terbinafine Two RCTs[25,26] and one open non-comparative trial[24] were found for terbinafine (Table 2). The MQS were 19.2–22.0 for the RCTs and 8.5 for the open study on a possible 28 point scale. The sample sizes were 60,[25] 174[26] and 661[24] with a mean age of 35–39 years and there was a greater percentage of males in each trial. The patients had moderate to severe SD and/or were unresponsive to conventional therapy.

Both RCTs used a continuous dosing regimen of 250 mg/day for 4 or 6 weeks, while the open study used a pulse regimen of 250 mg/day for 12 days each month for 3 months (Table 2). Patient compliance was cited as satisfactory in Vena *et al.*,[26] and not reported in the other studies. No serious AEs were reported in the two RCTs. The open study had the treatment discontinued in 1% of patients due to gastrointestinal complaints, while 5% of patients experienced mild and transient AEs.

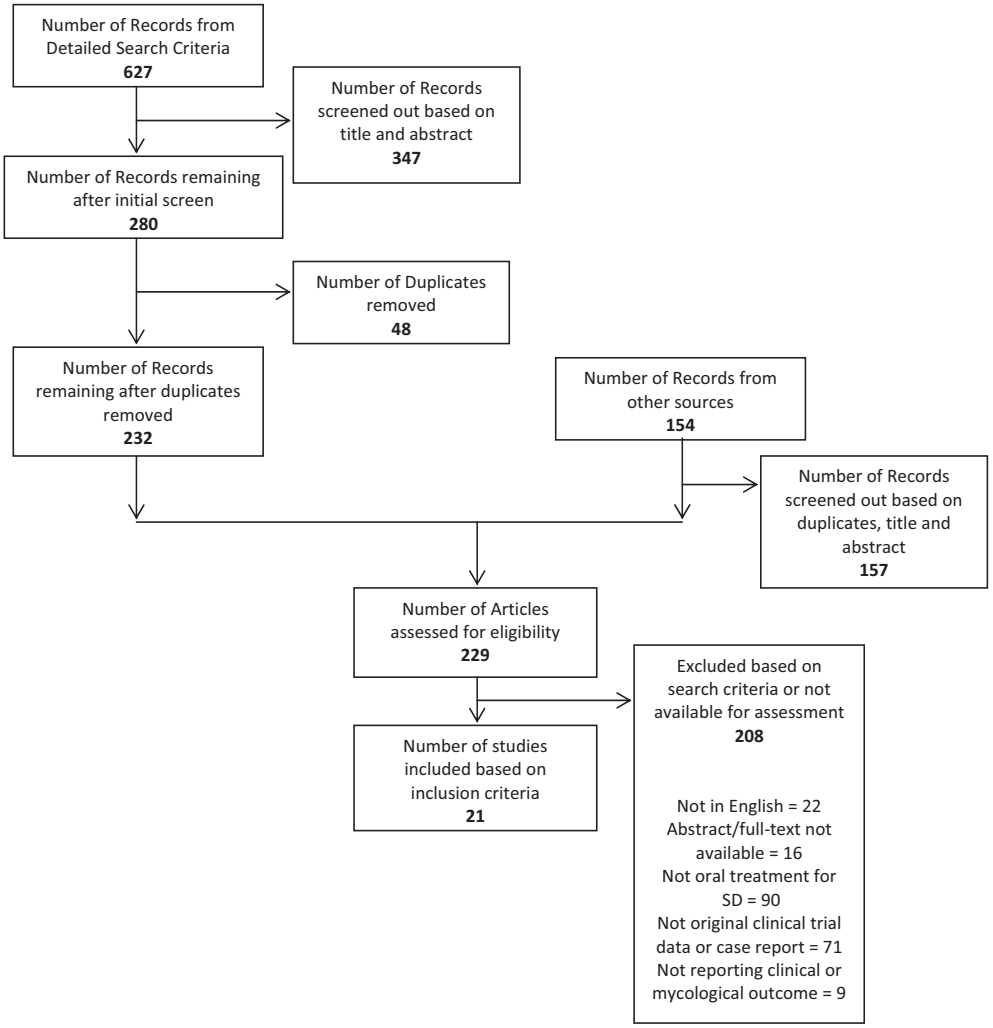

Figure 1 Literature search for reports on oral treatments for seborrheic dermatitis.

Erythema and scaling were evaluated in all studies, while additional evaluation criteria differed between studies and included papules, itching and seborrhea (Table 2). In one RCT, terbinafine induced significant changes in global clinical score compared with baseline and placebo treatment at the end of treatment (Table 2) and after 8 weeks of follow-up.[25] In the open study, clinical improvement in 82.8% of patients and complete cure in 22% were observed.[24] Interestingly, Vena *et al.* found statistically significant difference in the rate of patients clinically improved between the terbinafine and placebo groups for SD in non-exposed skin regions, but not for SD in exposed skin regions (Table 2).[26] With daily terbinafine, the clinical response obtained at 1 month of therapy was maintained until the end of study, that is, 3 months,[25] whereas the clinical response with pulse terbinafine continued to improve at every month of the 4-month study.[24]

Fluconazole From three publications using oral fluconazole for SD treatment (Table 3), the full manuscript was available only for one RCT.[28] This study had a MQS of 17.5 of 28. The sample size was 63 with a mean age of 30 years and a greater percentage of males. The patients had mild to moderate SD. Very little information on the participants was given in the abstracts of the other two studies. The participants had stage I to III SD in one open comparative study[27] and *Malassezia* spp. positive SD in the other open non-comparative study.[29]

The dosing regimen used varied between studies (Table 3). Two studies used a pulse regimen of 300 mg once per week for 2 weeks[28] or 200 mg once per week for 4 weeks.[29] The other study used a continuous regimen of 50 mg daily for 2 weeks with or without topical treatment with clobetasol propionate 0.05% ointment.[27] Participant compliance was not reported. In the placebo-controlled trial, two patients treated with fluconaz-

Table 1 Itraconazole

Regimen		Length of treatment	Total drug (g)	Study	SD	Clinical evaluation	Clinical improvement	Clinical cure	Mycological cure	MQS ± SD (Max 28)
Part I	**Part II**									
Open non-comparative studies										
200 mg/day for 7 days	NA	1 week	1.4	Caputo[18]	NA	Itching, burning, erythema, scaling/desquamation, seborrhea	149/160 = 93.0%* ITT analysis at 1 month	NA	74/110 = 67% at 1 month	12.0 ± 1.4
200 mg/day for 7 days (first week of the first month)	200 mg once every 2 weeks for 18 weeks	6 months	3.2	Shemer[23]	Moderate to severe	Itching, burning, erythema, scaling	Significant improvement in mean scores of erythema, scaling, and itching at 24 weeks (n = 55 or 60)	NA	~40% (n = 55 or 60) at 24 weeks	10.5 ± 2.1
200 mg/day for 7 days (first week of the first month)	200 mg/day for the first 2 days of every month	3 months	2.2	Das[19]	Severe, unresponsive to conventional therapy	Itching, burning, erythema, scaling/desquamation, seborrhea	25/30 = 83.3%† ITT analysis at 3 months	NA	Results not reported	10.5 ± 0.7
				Kose[17]			17/29 = 58.6%‡ ITT analysis at 3 months	14/29 = 48.3% ITT analysis at 3 months	25/29 = 86% ITT analysis at 3 months	12.0 ± 0.0
		12 months	5.8	Baysal[12],§	Not responding to corticosteroids	Erythema, papules, scaling/squamation	25/28 = 89.3%¶ PP analysis at 12 months	19/28 = 67.8% PP analysis at 12 months	NA	13.5 ± 0.7
				Khondker[16]	NA		26/37 = 70.3%** ITT analysis at 12 months	NA	NA	10.5 ± 4.9
Case reports										
400 mg/day for 8 days + topical therapy	200 mg/day for 13 days + topical therapy	3 weeks	5.8	Ran[22]	Severe	NA	NA	Clinical cure	Mycological cure	NA
100 mg/day for 4 weeks††	100 mg twice a week for 4 weeks‡‡	2 months	3.8	Ninomiya[20]	Seborrheic Blepharitis‡‡ Unresponsive to corticosteroid	NA	NA	Clinical cure	Mycological cure	NA

Table 1 *Continued*

Regimen		Length of treatment	Total drug (g)	Study	SD	Clinical evaluation	Clinical improvement	Clinical cure	Mycological cure	MQS ± SD (Max 28)
Part I	**Part II**									
200 mg/day for 7 days/month	NA	5 months	7.0	Ninomiya[21]	Seborrheic Blepharitis‡‡ Concomitant onycho-mycosis	NA	NA	Clinical cure	Mycological cure	NA

*Clinical improvement = excellent, good or moderate improvement.
†Clinical improvement = markedly effective or moderate effective.
‡Clinical improvement = markedly effective or effective response.
§Additional 1% hydrocorticone cream twice daily during the first month.
¶Clinical improvement = complete, marked or moderate improvement.
**Clinical improvement = at least 25% clearing.
††Based on information reported in the discussion of Nimomiya 2002.
‡‡Seborrheic Blepharitis in these two conditions was not comparable to typical seborrheic dermatitis of the eyelid.
ITT, Intention To Treat; MQS, mean quality score, NA, not available or not applicable; PP, Per Protocol; SD, standard deviation.

ole were found to have abnormalities in liver function tests and one of them discontinued therapy.[28]

In the RCT, erythema and scaling were evaluated at nine different anatomic sites based on a Seborrheic Dermatitis Area Severity Index (SDASI) with a maximum value of 12.6, which was not previously validated.[28] As shown in Table 3, the mean decrease in SDASI score at week 6 was similar in the fluconazole and placebo groups. In the open non-comparative study,[29] all four participants showed clinical improvement and mycological cure. Finally, in the open study comparing continuous fluconazole monotherapy with combined therapy with topical ointment,[27] all participants showed clinical improvement but clinical and mycological cure rates were higher in the combined therapy group (Table 3). No information on the time course of response to fluconazole was reported.

Ketoconazole One cross-over RCT[31] has been conducted for ketoconazole and six cases were reported in a case series[30] (Table 4). The MQS was 17.5 of 28 for the trial. Its sample size was 19 with an age range of 18–60 years and there was a greater percentage of males. The severity of SD was not reported but the trial was performed during the winter months, a time when SD is usually exacerbated. All six reported cases had abundant *Malassezia ovalis* cells on direct examination.

The dosing regimen consisted of 200 mg/day for 4 weeks or an unspecified duration (Table 4). Patient compliance was not reported, and two of 19 patients were withdrawn from the trial, one of which developed a diffuse rash.

In the trial, significant improvement compared to placebo was seen in scalp scaling, scalp erythema and SD scores at other sites (Table 4). The six patients in the case series who were treated with ketoconazole were classified as clinically cured.[30] Based on the data presented graphically in the cross-over study, the clinical improvement achieved with ketoconazole after the first 4 weeks of therapy was not maintained in the second 4 weeks of placebo.[31]

Pramiconazole A pilot study investigated the use of pramiconazole to treat SD.[32] This publication combined two studies: an observational study as control group and an open non-comparative trial. The MQS was 12 ± 2.8 of 28. Seventeen participants (11 men and 6 women) with a mean age of 41.5 were untreated, while ten (5 men and 5 women) with a mean age of 44.4 years were treated with pramiconazole. Participants with SD involving the scalp and face were included in both studies, but it was specified that the participants in the observational study experienced recurrent episodes for at least 3 years.

The dosing regimen was a single 200 mg dose of pramiconazole. The dose was administered by the investigator so patient compliance was not a concern. The AEs reported were not related to the trial medication.

In the control group, there was no significant change in the median scores for global clinical assessment, scaliness and pruri-

Table 2 Terbinafine

Regimen		Length of treatment	Total drug (g)	Study	SD	Clinical evaluation	Clinical improvement		Clinical cure	Mycological cure	MQS ± SD (Max 28)
Part I	Part II						Terbinafine	Control			
Randomized controlled trials											
250 mg/day	NA	4 weeks (+8 weeks of follow-up)	7.0	Scaparro[25]	Moderate to severe	Itching, erythema, scaling	Decrease in Mean Global Score* of 6.7 ± 0.3 (n = 30) ITT analysis at 4 weeks **P < 0.0001**†	Decrease in Mean Global Score* of 1.5 ± 0.4 (n = 30) ITT analysis at 4 weeks	NA	NA	19.2 ± 2.1
		6 weeks (+4 weeks of follow-up)	10.5	Vena[26]	Moderate to severe, Located on non-exposed skin regions	Erythema, papules, scaling/ squamation, pruritus, seborrhea	28/40 = 70.0%‡ PP analysis at 6 weeks **P = 0.03**	15/33 = 45.4%‡ PP analysis at 6 weeks	NA	NA	22.0 ± 1.4
					Moderate to severe, Located on exposed skin regions		19/35 = 54.3%‡ PP analysis at 6 weeks **P = 0.55**	25/41 = 61.0%‡ PP analysis at 6 weeks	NA	NA	
Open non-comparative studies											
250 mg/day for 12 days/ month	NA	3 months (+1 month follow-up)	9.0	Cassano[24]	Moderate to severe, unresponsive to conventional therapy	Erythema, scaling, seborrhea, itching	454/548 = 82.8%§ PP analysis at 3 months	NA	120/548 = 22% PP analysis at 3 months	NA	8.5 ± 0.7

*Global clinical score based on the patients most severe body region at baseline.

†For comparisons of individual and global scores with baseline values and between terbinafine and placebo groups.

‡Clinical improvement = greater than or equal to 50% improvement in baseline clinical score without intake of rescue medication.

§Clinical improvement = greater than or equal to 50% improvement in baseline clinical score.

ITT, Intention To Treat; MQS, mean quality score; n, number of patients; NA, not available or not applicable; PP, Per Protocol; SD, standard deviation.

P-values of treatment are indicated in bold.

Table 3 Fluconazole

Regimen		Length of treatment	Total drug (g)	Study	SD	Clinical evaluation	Clinical improvement		Clinical cure	Mycological cure	MQS ± SD (Max 28)
Part I	Part II						Fluconazole	Control			
Randomized controlled trial											
300 mg once per week	NA	2 weeks (+4 weeks of follow-up)	0.6	Cömert[28]	Mild to moderate	Erythema, scaling/ desquamation based on a SDASI*	Decrease in SDASI score of 0.24 ± 0.15 (n = 27) PP analysis at 6 weeks ***P* > 0.05**	Decrease in SDASI score of 0.30 ± 0.19 (n = 23) PP analysis at 6 weeks	NA	NA	17.5 ± 3.5
Open comparative study											
50 mg/day	NA	2 weeks	0.7	Zisova[27]	Stage I, II and II	NA	11/11 = 100%†	NA	3/11 = 31.5%	8/11 = 74%‡	NA§
50 mg/day + topical therapy							27/27 = 100%†		23/27 = 85%	25/27 = 93%‡	
Open non-comparative study											
200 mg once per week	NA	4 weeks	0.8	Zisova[29]	NA¶	NA	4/4 = 100%**	NA	NA	4/4 = 100%	NA§

*SDASI = not validated Seborrheic Dermatitis Area Severity Index evaluating nine weighted anatomic sites.

†Clinical improvement = clinical improvement and clinical cure.

‡Fungal testing negative for *Malassezia* spp.

§Data from abstract only and full text was not available for quality assessment.

¶Seborrheic Blepharitis.

**Clinical symptoms 'withdrew' in all patients.

ITT, Intention To Treat; n, number of patients; MQS, mean quality score; NA, not available or not applicable; PP, Per Protocol; SD, standard deviation.

P-values of treatment are indicated in bold.

Table 4 Ketoconazole

Regimen		Length of treatment	Total drug (g)	Study	SD	Clinical evaluation	Clinical improvement		Clinical cure	Mycological cure	MQS ± SD (Max 28)
Part I	Part II						Ketoconazole	Control			
Randomized controlled trial											
200 mg/day of ketoconazole or placebo for 4 weeks (cross-over)	200 mg/day of placebo or ketoconazole for 4 weeks	8 weeks	5.6	Ford[31]	NA	Erythema, scaling/desquamation. itching, SD in general	Part I & II: Scalp: Scaling only: 12/17 = 70.6% ***P* < 0.01** Erythema only: 7/10 = 70% ***P* < 0.05** Other sites: All signs: 11/15 = 73.3% ***P* < 0.01**	Part I: Scalp: Scaling only: 0/7 = 0% Erythema only: 1/4 = 25% Other sites: All signs: 0/6 = 0%	Part I & II: Other sites: All signs: 10/15 = 66.7%	NA	13.5 ± 3.5
Case report series											
200 mg/day for an unspecified duration	NA	NA	NA	Conti-Diaz[30]	Abundant *M. ovalis* cells	NA	NA	NA	The number of patients from a total of 6 was not specified.	NA	NA

MQS, mean quality score; NA, not available or not applicable; SD, standard deviation.

P-values of treatment are indicated in bold.

tus during the 14 days of observation, and only 12% (2/17) of the participants showed a spontaneous clinical improvement. In contrast, the treated group had a significant improvement ($P < 0.05$) in median scores global clinical assessment, scaliness and pruritis at day 7 and day 28 compared with baseline.[32] A significant reduction in living yeast was noticed only in the treated group. No clinical assessment was performed after day 28.

Other oral therapies

Prednisone Mesquita *et al.* reported a case that involved the successful treatment of SD with the systemic corticosteroid prednisone in a 43-year-old man.[33] The patient had severe SD and was unresponsive to topical therapy. Clinical improvement was noted on a regimen of 0.5 mg/kg/day for 15 days, which was gradually tapered and followed by maintenance therapy (topical corticosteroids and antifungals) to prevent relapses. No AEs were reported.

Isotretinoin Abraham *et al.* reported a case that involved the successful treatment of SD with isotretinoin in a 42-year-old man.[34] The patient was previously unresponsive to oral and topical antibiotics/antifungal therapies. Treatment consisted of 20 mg daily of isotretinion and topical ketoconazole for a period of 1 year. No relapse was noted.

Homeopathic mineral therapy One RCT has been conducted with the homeopathic preparation of potassium bromide, sodium bromide, nickel sulfate and sodium chloride.[35] The MQS was 19.0 ± 1.4 of 28. The sample size was 45 patients with a mean age of 53 years and a greater percentage of males. The participants had a minimum of 20% of surface area of scalp and/or face affected.

The dosing regimen was dependent on the patient weight. The study had two parts: a RCT for homeopathic or placebo solution for 10 weeks and an open trial with only the homeopathic solution for an additional 10 weeks. Patient compliance was monitored but not reported. There were no significant differences in AEs between treatment and control groups.

Clinical improvement was evaluated as percent of improvement in Seborrhea Area and Severity Index (SASI) score with a maximum of 48. Erythema and scaling of the face and scalp were rated independently and weighted based on the percentage of surface area involved. A decrease of 38.5 ± 42.1% (SD) in the SASI was observed for the 16 participants in the homeopathic treatment group evaluated at week 10. In contrast, an increase of 10.8 ± 66.2% (SD) was observed in the 13 participants evaluated in the placebo group. This difference was statistically significant ($P = 0.03020$). In participants treated with homeopathic solution in the two parts of the study, a gradual increase in the mean percent change in SASI was observed until week 15, where it reached a maximum value that was maintained at week 20.

Discussion

The results of our systematic review showed that most of the publications on oral therapies for SD involved the use of antifungals. However, about half of these studies did not report the mycological outcome of the oral treatment (Tables 1–4). This is not surprising for terbinafine, which has been shown to have poor antifungal activity against *Malassezia* spp. and is believed to act through other mechanisms in the treatment of SD.[24] Moreover, the definition of 'clinical improvement' outcome varied between studies. Consequently, it is difficult to ascertain the most effective therapy based on their efficacy outcomes. However, itraconazole, terbinafine, isotretinoin combined with topical ketoconazole and homeopathic solution showed superiority to ketoconazole based on their long-term or sustained outcome.

In the included studies, the patient sample was comparable in terms of the prevalence of SD in the general population and the gender differences.[36] Indeed, mean age in the studies was generally found to be in the third and fourth decades of life and there were a greater percentage of males vs. females in most studies. With the exception of the studies on fluconazole therapy, which included patients with mild to moderate SD, the majority of the patients treated with the oral therapies had moderate to severe SD or was unresponsive to conventional treatments. In terms of safety, no studies reported significant AEs associated with any of the treatment options.

The number and type of publications vary between the oral treatments. Itraconazole was the most frequently reported oral treatment for SD. On the other hand, the newer triazole pramiconazole had the lowest number of publications among the antifungals likely because it is still in development. It is important to note, however, that the quality of the evidence for itraconazole was generally inferior to other treatments such as terbinafine. The studies using itraconazole were not blinded and included no control groups; they were at high risk of bias. Without a placebo group, it is difficult to determine if the patients would have just spontaneously improved, as was reported in the observational study conducted by Pierard *et al.*[32] A variety of dosing regimens were used for the antifungals investigated. The most commonly reported dosing regimen for itraconazole was a pulse regimen generally associated with good clinical and mycological responses (Table 1). Both pulse and continuous regimens have been investigated for terbinafine (Table 2). Due to the differences in sample sizes, outcomes reported and study designs, it is difficult to conclude which of the two treatment regimens gives the best results. Fluconazole was administered daily or weekly at different doses, but the total amount of drug given was similar between studies (Table 3). However, the resulting efficacy outcome varied greatly from no difference with placebo therapy to clinical improvement in all patients. Only a continuous regimen of ketoconazole has been reported for SD, which led to a high rate of clinical improvement and/or cure (Table 4). Finally,

pramiconazole was administered only once and resulted in better clinical improvement than no treatment.

Patient compliance may be influenced by the type of regimen used and, in turn, may influence the therapeutic response. Indeed, a study showed better adherence with intermittent regimen (e.g. weekly) compared with continuous regimens (e.g. daily).[37] When reported, compliance was always satisfactory in the studies included in this review. Thus, it is difficult to draw conclusions about the influence of dosing regimen on the clinical success of these antifungals.

As previously mentioned, the lack of consistency between studies on oral treatment for SD prevented direct comparison between the different therapies. There were differences in the clinical assessment of SD severity, in the efficacy outcomes presented, and in their definition.

As described in the text and shown in Tables 1–4, the clinical signs evaluated varied from one study to another. The two most frequently evaluated clinical signs in the included studies were erythema and scaling/desquamation. With the exception of one study,[35] all the studies reporting their investigator-evaluated severity scale rating used a similar 4-point scale (0 = absent, 1 = mild, 2 = moderate, 3 = intense or severe). The anatomical areas evaluated also varied greatly between studies. Two studies assessed only the most severely affected area,[25,32] whereas the other studies assessed multiple areas including the face, scalp, chest and genital areas. Vena *et al.*[26] showed that the areas non-exposed such as the scalp responded better to antifungal therapy than the areas exposed such as the face and the study by Cömert *et al.*[28] gave more weights to the non-exposed anatomical areas in the calculation of their global clinical score. Thus, variation in the anatomical areas evaluated can contribute to the heterogeneity in efficacy between the studies. Only three studies included a correction factor for the percentage of the area affected by seborrhea dermatitis in their calculation of their clinical score.[12,16,35]

Clinical efficacy was reported differently between studies. Only few studies predefined their efficacy criteria and they can be divided into four groups: (i)changes in index score[24,26,28] (e.g. greater or equal to 50% improvement in baseline index score), (ii) final values of the clinical score[17,23] (e.g. complete improvement = 0, good = 1 or 2, moderate = 3 or 4, failure >5), (iii) percentage of clearing[12,16] (e.g. complete clearing >71%, marked improvement 51–71%, moderate improvement (26–50%), slight improvement <25%), and (iv) global clinical evaluation[32] (e.g.: −2 = much worse, −1 = worse, 0 = unchanged, 1 = slight improvement, 2 = moderate, 3 = marked, 4 = almost complete to complete). However, two of these studies did not present their efficacy outcome as predefined in their methods.[23,28] As shown in Tables 1–4, the definition of the outcome 'clinical improvement' varied. Moreover, some were reported as a rate of participants and others as a clinical score. Of the five studies reporting mycological cure rates, only two studies defined this outcome: one as no presence of spores and the other as negative KOH microscopy. In contrast, the same definition of clinical score equals to zero was used by the four studies reporting clinical cure.[12,24,27,31]

Therefore, the following suggestions are proposed to standardize the clinical evaluation of SD and the reporting of efficacy outcomes:

1 Clinical score = [(face erythema severity index + face scaling severity index)(percentage of face area affected)] + [(scalp erythema severity index + scalp scaling severity index) (percentage of scalp area affected)],
2 Reporting of mean changes in total clinical score, as well as clinical and mycological rates
3 Outcome definitions for rates:
   Clinical improvement = at least 50% improvement of the baseline clinical score
   Clinical cure = participants with clinical score = zero
   Mycological cure = microscopy and culture negative

Conclusion

Literature assessing oral treatments for SD is sparse with only 21 published reports covering eight oral treatments. Consistent with the involvement of *Malassezia* spp., most of the treatments were oral antifungal agents. In general, the quality of the evidence was low due to the absence of blinding and control group in these studies. Statistical analysis of the evidence was not possible due to the heterogeneity between studies.

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