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REVIEW PAPER

The use of topical metronidazole in the management of seborrheic dermatitis – a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Introduction and aim. Topical metronidazole, with its well-known anti-inflammatory and antibacterial properties, could be beneficial for managing seborrheic dermatitis (SD), but studies report conflicting results. The aim was to evaluate the efficacy and safety of topical metronidazole in the treatment of SD.

Material and methods. A systematic search of Medline, Embase, and CENTRAL was conducted from inception to April 2024. Randomized controlled trials (RCTs) comparing metronidazole to any comparator for SD were included in this study. Data were pooled using random-effects models.

Analysis of the literature. Seven RCTs were included. Overall, topical metronidazole did not significantly reduce SD symptom severity when compared to any comparator/treatment. However, it significantly reduced symptom severity compared to placebo after 4 to 8 weeks (standardized mean difference (SMD) -3.00, 95% CI, -5.21 to -0.78). Specifically for facial SD, metronidazole showed significant symptom reduction (SMD -0.85, 95% CI, -1.41 to -0.29). No significant differences were found in the proportion of patients with clinical improvement or side effect frequency. Most studies had a high risk of bias and lacked information on missing data and assessor masking.

Conclusion. Topical metronidazole demonstrates potential for managing SD, but current trials lack quality. Larger, high-quality trials are needed to confirm its efficacy and compare it with other treatments for SD.

Keywords. dermatitis, meta-analysis, metronidazole, seborrheic

Introduction

Seborrheic dermatitis (SD) is a common chronic inflammatory skin condition characterized by erythema, scaling, and pruritus, mainly affecting areas rich in sebaceous glands such as the scalp, face, and trunk. While the pathogenesis is not fully understood, fungal overgrowth, particularly of *Malassezia* species, and the dysregulation of immune responses play pivotal roles in its

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development.[1] Treatment typically involves topical antifungal and anti-inflammatory agents, and also phototherapy. Thus, corticosteroids and calcineurin inhibitors aim to reduce inflammation, while topical antifungals such as azoles, ciclopirox olamine, and zinc pyrithione attempt to combat *Malassezia* overgrowth. Additionally, keratolytic agents like salicylic acid, tar, selenium sulfide, and zinc pyrithione are used to soften and remove dermal crusts. Many of these treatments appear to have multiple mechanisms of action, with the nature of some mechanisms being quite obscure.[2,3]

Metronidazole, a synthetic nitroimidazole derivative, is primarily known for its antimicrobial activity against anaerobic bacteria but also for its potentially useful anti-inflammatory properties. It has been shown to be effective in treating various dermatological conditions and was the original topical therapy approved exclusively for rosacea, where it still has a central role in management.[4] Although the possible mechanisms of action in the management of SD are not fully understood, its observed anti-inflammatory effects alone make it an intriguing option for therapy. Several randomized controlled trials (RCTs) assessing the effectiveness of topical metronidazole in treating SD have been conducted, but they have yielded conflicting findings. For example, Parsad et al. randomized 44 patients with SD to receive either 1% topical metronidazole gel or a placebo, and subsequently observed a statistically significant reduction in the mean severity score at 8 weeks.[5] Conversely, Koca et al. conducted an RCT comparing 0.75% metronidazole gel to a placebo for 8 weeks (n=84) and found no statistically significant difference in the change in mean severity score between the two groups by the end of the study.[6]

Despite the availability of various treatments for SD, there remains a critical need for effective therapies with minimal side effects. The inconsistent findings from previous randomized controlled trials (RCTs) underscore the necessity for further investigation into the efficacy of topical metronidazole. As such, a comprehensive synthesis of existing data via a systematic review and subsequent meta-analysis is required to provide a clearer understanding of topical metronidazole's potential role in managing SD. To our knowledge, this study represents the first systematic review and meta-analysis on this topic. By consolidating evidence from multiple RCTs, it aims to provide valuable insights that could inform clinical practice and shape the direction of future research on the topic.

Aim

This systematic review and meta-analysis aimed to assess the efficacy and safety of topical metronidazole in the treatment of SD.

Material and methods

The protocol for this study was registered with Open Science Framework (https://doi.org/10.17605/OSF.IO/9X48M). This review employed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline.[7]

We identified relevant studies through a systematic search of Medline, Embase and the Cochrane CENTRAL Register of Controlled Trials from inception to April 13, 2024. We also manually checked the reference lists of included studies to further identify any relevant studies. There were no language restrictions. The search strategy is provided in Appendix S1. Two reviewers (E.L. and S.S.) independently performed screening of titles and abstracts for relevance and selected studies after examining the full text of potentially eligible articles. Any discrepancies were resolved through discussion with the third reviewer (S.V.).

Studies included were the RCTs identified as above, and which also met the following criteria: a) participants were adults or adolescents diagnosed by a healthcare practitioner (explicitly stated or implied within context), with SD of the scalp, face or both, based on clinical case definition, with or without laboratory confirmation and b) studies comparing metronidazole at any strength and dose, and any topical formulations, to placebo, no treatment, or any active interventions (e.g., topical antifungal drugs). Primary outcomes were, a) symptom severity scores for erythema, pruritus and scaling, etc., measured using any type of systematic symptom severity assessment-and, b) the proportion of individuals who experienced clinical resolution and/or global improvement of symptoms (defined as ≥50% symptom improvement) based on physician assessment. A very important secondary outcome in this study was the frequency of side-effects.

Data extraction

Requisite data were extracted independently and in duplicate by two reviewers (E.L. and S.K.) and entered into a custom-designed data extraction form. For all outcomes, we used the initial number of participants randomized to each trial arm and performed the analyses irrespective of how the authors of the original trials had analyzed the data (intention-to-treat principle).[8] Two reviewers (E.L. and S.S) independently assessed the risk of bias within each study by using the Cochrane Risk of Bias (ROB 2.0) tool.[9] Each domain was assessed and categorized into low risk, high risk, or unclear risk of bias. Discrepancies were resolved by consensus.

Statistical analysis

Data were pooled using the DerSimonian and Laird random-effects model.[10] For continuous outcomes such as improvement in symptom severity, we used

the standardized mean difference (SMD) with its 95% confidence interval (Cl) in summarizing results. For dichotomous outcomes such as the proportion of persons who had clinical resolution/global improvement of symptoms, we expressed the estimate of effect size as a risk ratio (RR) with 95% CI. Thus, RR >1 reveals a beneficial effect of the treatment. Adverse events data were also summarized with RRs. In each meta-analysis, we evaluated heterogeneity by using the I^2 statistic.[11] We assessed publication bias using funnel plot asymmetry and small-study effects using Egger's regression test.[12] A p-value of less than 0.10 was taken as statistical evidence of the presence of small-study significant effects. We performed subgroup analyses based on the comparison group as available. Statistical analyses were conducted using STATA version 16.0 (StataCorp, College Station, TX, USA).

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach was used to rate the quality of evidence (high, moderate, low, and very low) of estimates derived from meta-analyses using the GRADEpro program version 3.6.1 (McMaster University, 2014).[13]

Analysis of the literature

The database search yielded 2480 records. The removal of 736 duplicates, left 1744 titles and abstracts, which were screened according to the predetermined eligibility criteria. A total of 271 studies were retrieved for further screening, of which 263 were excluded as they were not investigating topical metronidazole in the treatment of SD. Overall, 7 studies were included in this systematic review (Fig. 1).

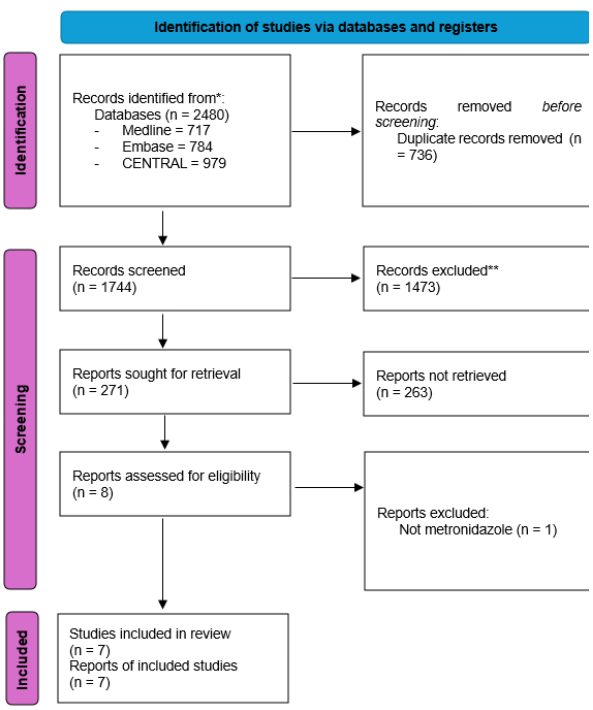

Fig. 1. PRISMA flow diagram

The characteristics of the 7 included studies are summarized in Table 1.[5,6,14–18] The studies were published from 2001 to 2013. Two different strengths of topical metronidazole (0.75% or 1%) had been examined against control or a comparator (topical antifungal or calcineurin inhibitor).

Figures 2 and 3 depicts the risk of bias assessment for each included study. The majority of the studies were rated at overall high risk of bias; most of these studies did not provide sufficient information on missing outcome data and whether outcome assessors were masked.

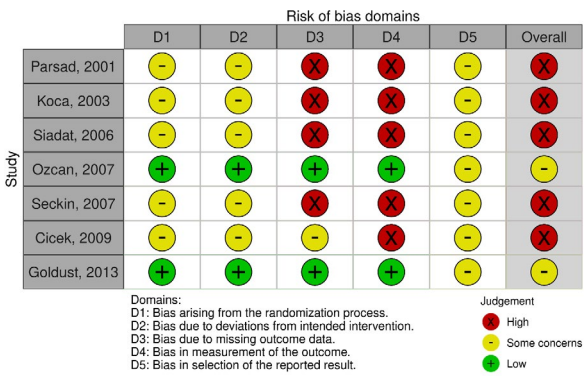

Fig. 2. Risk of bias assessment for each included study

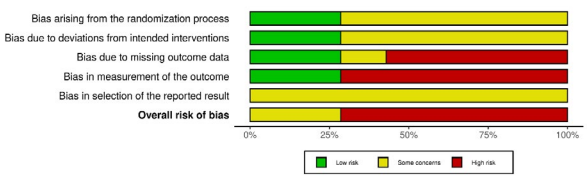

Fig. 3. Summary of the risk of bias assessment for included studies

Overall, there was no statistically significant difference in reduction of SD symptom severity observed between topical metronidazole and any comparator (including control, ketoconazole and pimecrolimus) (Fig. 4). In comparison to a placebo only, the use of topical metronidazole for 4 to 8 weeks shows statistically significant effectiveness in reducing symptom severity (standardized mean difference (SMD), -3.00, 95% confidence interval (CI), -5.21 to -0.78, three RCTs). However, there is a high level of heterogeneity (I^2=96.7%), because the studies differed in the site of the SD (overall or face only), as well as the potency of metronidazole used, and the duration of follow-up. The funnel plot did not reveal a strong indication of publication bias (Fig. 5), and Egger's regression test did not indicate presence of small study effects (p=0.167). In a subgroup analysis that included only studies assessing facial SD, topical metronidazole showed a statistically significant reduction in symptom severity compared to control, with a moderate level of heterogeneity (SMD, -0.85, 95% CI, -1.41 to -0.29, two RCTs, I^2=59.4%) (Fig. 6).

Table 1. Characteristics of included studies*

Author, year	Country	Participants	Participants age Mean±SD (years)	Sample size	Intervention (I)	Control/ comparator (C)	Duration of treatment
Parsad, 2001[5]	NR	SD, diagnosed according to clinical criteria	I: 23.8 C: 24.2	Metronidazole (n=22), vehicle (n=22)	Metronidazole 1% gel twice daily	Vehicle gel twice daily	8 weeks
Koca, 2003[6]	Turkey	Mild to moderate SD of the face, diagnosed according to clinical criteria	I: 35.9±5.87 C: 32±6.47	Metronidazole (n=50), vehicle (n=34)	Metronidazole 0.75% gel twice daily	Vehicle gel twice daily	8 weeks
Cicek, 2009[14]	Turkey	Face SD, diagnosed clinically	I: 30.7±7.35 C: 31.6±8.27	Metronidazole (n=21), pimecrolimus (n=21)	Metronidazole 0.75% gel twice daily	Pimecrolimus 1% cream twice daily	8 weeks
Siadat, 2006[15]	Iran	Face SD, confirmed by a dermatologist	I: 27.4 C: 25.5	Metronidazole (n=28), vehicle (n=28)	Metronidazole 1% gel	Vehicle gel	8 weeks
Ozcan, 2007[16]	Turkey	SD, diagnosed according to clinical criteria	I: 26±11.5 C: 26±8.7	Metronidazole (n=33), vehicle (n=34)	Metronidazole 0.75% gel twice daily	Vehicle gel twice daily	4 weeks
Seckin, 2007[17]	Turkey	Face SD	I: 42.1 C: 34.7	Metronidazole (n=30), vehicle (n=30)	Metronidazole 0.75% gel once in the morning + ketoconazole cream as vehicle once in the evening	Ketoconazole 2% cream once in the evening + metronidazole gel as vehicle once in the morning	4 weeks
Goldust, 2013[18]	Iran	SD	I: 30.18 ±12.64 C: 34.14 ±10.68	Metronidazole (n=78), sertaconazole (n=78)	Metronidazole 1% gel twice daily	Sertaconazole 2% cream twice daily	4 weeks

* NR – not reported

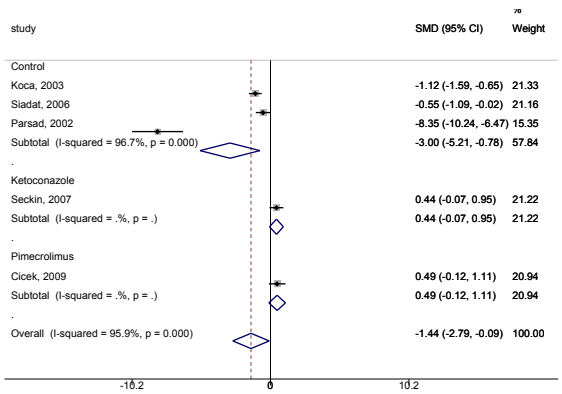

Fig. 4. Forest plot showing meta-analysis of comparison: Metronidazole vs any comparator, outcome: mean reduction in severity of symptoms

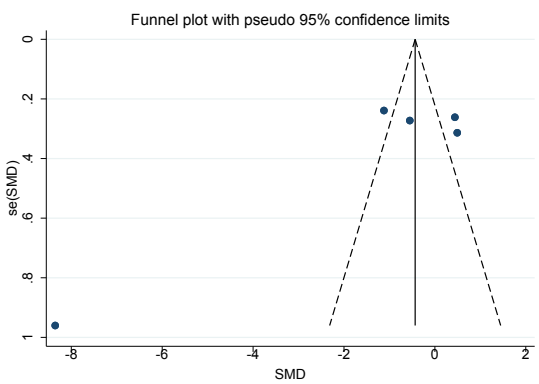

Fig. 5. Funnel plot of comparison: Metronidazole vs any comparator, outcome: mean reduction in severity of symptoms

In a meta-analysis of data from four RCTs, no statistically significant difference was observed for the proportion of patients who had clinical resolution and/or global improvement of symptoms (risk ratio (RR), 2.06, 95% CI, 0.97 to 4.37, I^2=68%) (Fig. 7). Conversely, in a subgroup analysis that included only studies assessing overall SD, use of topical metronidazole showed a statistically significant improvement (RR, 3.86, 95% CI, 1.65 to 9.07, two RCTs, I^2 = 0%) (Fig. 7).

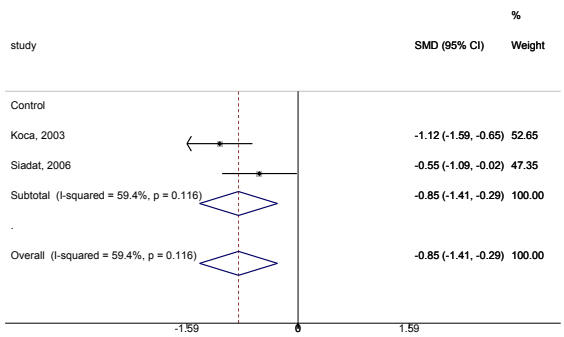

Fig. 6. Forest plot showing meta-analysis of comparison: Metronidazole vs control, outcome: mean reduction in severity of symptoms (facial SD only)

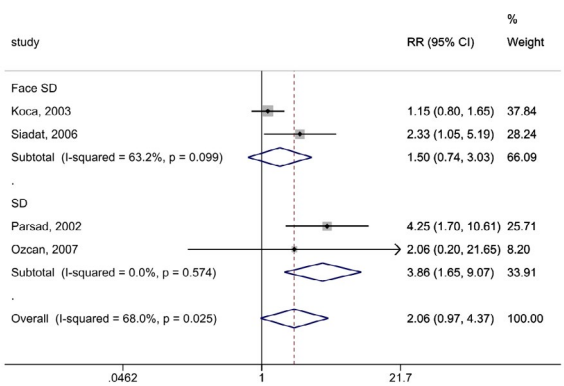

Fig. 7. Forest plot showing meta-analysis of comparison: Metronidazole vs control, outcome: proportion of persons who had clinical resolution/global improvement of symptoms based on physician assessment

There was no statistically significant difference detected in the occurrence of side effects between topical metronidazole and control (SMD, 2.07, 95% CI, 0.66 to 6.47, three RCTs, I^2=20.2%) (Fig. 8).

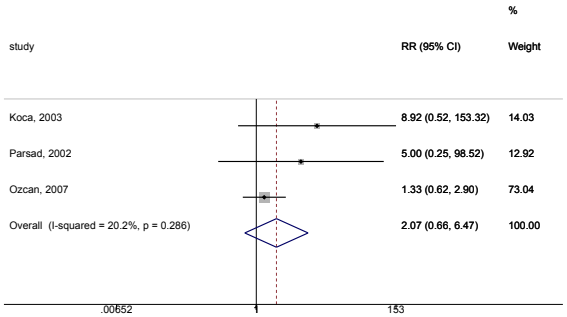

Fig. 8. Forest plot showing meta-analysis of comparison: Metronidazole vs control, outcome: side effects

Overall, the quality of evidence based on applying GRADE criteria to findings from the meta-analysis was generally rated as very low to low (Fig. 9).

Discussion

SD is a common chronic dermatological disorder that affects persons of all ages. There is no definitive treatment for SD, but topical steroids and antifungal agents are commonly used to control the condition. It is suggested that topical metronidazole could be useful in treating SD because of its anti-inflammatory effects. However, the efficacy of metronidazole for that purpose remains controversial. Several small-sized RCTs have been conducted to assess the efficacy of metronidazole in treating SD but the findings were inconsistent. Because studies with small sample sizes are typically associated with inflated effects, we performed a meta-analysis of these trials to provide a more precise quantitative summary of efficacy. This systematic review and meta-analysis represents the first comprehensive evaluation of topical metronidazole for the treatment of SD.

Our findings suggest that topical metronidazole may be effective for the treatment of SD compared to no treatment; however, the quality of the trials included in our review was generally poor. To establish a more robust understanding of its efficacy, there is a clear need for higher quality trials with larger sample sizes. Furthermore, none of the trials included in our analysis provided solid evidence regarding the comparative effectiveness of topical metronidazole against other treatment modalities for SD. Therefore, further research is warranted to clarify the comparative efficacy and safety profile of topical metronidazole in the management of SD.

The clinical effectiveness of topical antifungals and anti-inflammatories is well-established in treating SD but their prolonged usage may be associated with local adverse effects, such as antifungal-related contact dermatitis.[19] Although the frequency cannot be reliably estimated, post-marketing surveillance of ketoconazole shampoo has reported incidents of hair discoloration, abnormal hair texture, itching, skin burning sensation, contact dermatitis, hypersensitivity reactions including angioedema, alopecia, rash, urticaria, skin irritation, dry skin, and application site reactions.[20] The prolonged use of another approach to treatment, the use of topical corticosteroids, is contra-indicated due to the potential risks of skin atrophy, striae, telangiectasias, hypopigmentation, and tachyphylaxis.[21] Another concern is corticosteroid withdrawal can occur upon cessation after prolonged use.[22] Because SD is a chronic condition, ongoing maintenance therapy is often necessary, necessitating prolonged use over several weeks to months of treatment.[23] In view of the above information, it can be seen that, a variety of other treatment options are needed to effectively manage SD.

For patients who require frequent use of topical corticosteroids, alternative treatments such as topical

Metronidazole compared to Control for SD

Certainty assessment							Summary of findings				
Participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Control	With Metronidazole		Risk with Control	Risk difference with Metronidazole
Symptom severity score (Metronidazole vs Control)											
(5 RCTs)	very serious	serious	serious	very serious	none	⨁◯◯◯ Very low	NA	NA	-	The mean symptom severity score (Metronidazole vs Control) was **0**	**0** (0 to 0)
Symptom severity score (Metronidazole vs Placebo)											
(3 RCTs)	very serious	not serious	serious	not serious	none	⨁◯◯◯ Very low	NA	NA	not estimable	0 per 1,000	
Symptom improvement (Metronidazole vs Control)											
(4 RCTs)	very serious	serious	serious	serious	none	⨁◯◯◯ Very low	NA	NA	not estimable	0 per 1,000	
Symptom severity score: Face only (Metronidazole vs Placebo)											
(2 RCTs)	serious	serious	not serious	not serious	none	⨁⨁◯◯ Low	NA	NA	not estimable	0 per 1,000	

Fig. 9. Summary of findings

calcineurin inhibitors (tacrolimus 0.1% ointment and pimecrolimus 1% cream), crisaborole 2% cream, or roflumilast 0.3% foam may be considered. These alternatives do not produce the adverse effects associated with topical corticosteroids, such as skin atrophy and telangiectasias.[24] However, topical calcineurin inhibitors received a boxed warning from the U.S. Food and Drug Administration due to concerns about a potential association with lymphoma and skin cancer.[25,26] Consequently, the American Academy of Dermatology advises against continuous long-term use of topical calcineurin inhibitors and recommends limiting their application.[27] Furthermore, the high cost of topical calcineurin inhibitors could limit their general use.[23]

The use of systemic antifungals is hindered by various limitations, including the risk of systemic side effects such as abnormal liver function or gastrointestinal disorders, and potential interactions with other concurrent systemic medications.[28] Another commonly used treatment, zinc pyrithione has recently been classified as carcinogenic, mutagenic or reproductive toxicity in cosmetics by EU commission regulation 2021/1902.[29] Hence, considering these constraints, there is a clear need to explore and consider alternative therapeutic options for the management of SD. The long-term safety record and very low costs of topical metronidazole would merit it being a treatment of choice even if it were only equally effective as existing treatments.

SD often occurs concurrently with rosacea, making it one of the most common skin conditions to coexist with rosacea. Although these two disorders are unrelated, a clinical study revealed that 26% of patients with rosacea also had facial SD, and 28% had SD of the scalp.[30] In cases of coexistent facial SD and rosacea, effectively treating both conditions can be challenging. Prolonged use of even mild topical corticosteroids, prescribed for SD, may worsen rosacea and should ideally be avoided or used sparingly and intermittently. Conversely, topical metronidazole 1% gel or cream, commonly used for rosacea, may also alleviate mild SD.[31]

Given the recurrent nature of SD, periodic treatments are necessary to maintain the disease in remission. While treatment with topical antifungals and anti-inflammatory agents are typically effective, some patients may not respond adequately.[4] Therefore, topical metronidazole potentially provides a viable therapeutic alternative to the reliance on topical steroids in this subset of patients. Additionally, it is important to note that there are only very limited studies comparing the efficacy of metronidazole to other treatments such as topical corticosteroids, antifungals, and calcineurin inhibitors. Further research, particularly high-quality RCTs, is needed to better understand the comparative effectiveness of these treatment options in managing SD.

Study limitations

The current systematic review has several limitations that need to be acknowledged. Firstly, the search strategy was limited to English language publications only, thereby potentially excluding relevant studies published in other languages. Additionally, the findings of this review are based on RCTs with unclear or high risk of bias. Consequently, our results should be interpreted cautiously, and further research is necessary to validate the findings of this review. Sensitivity analysis was not performed based on risk of bias as assessed by the ROB 2.0 tool. This is because the included studies were either of unclear or high risk of bias. Moreover, high heterogeneity was observed among the included studies, which may impact the robustness and generalizability of our findings.

Conclusion

In conclusion, while topical metronidazole shows potential for treating SD, the overall quality of trials reviewed fall short of the level needed to recommend it as a treatment option. Larger, higher-quality trials are needed to fully understand its efficacy. Additionally, further very carefully designed clinical research is required to determine how metronidazole compares to other treatment options for SD. Cost and safety considerations could well tip the balance towards metronidazole even if it was found only to be equally efficacious as existing treatments.

Declarations

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Author contributions

Conceptualization, E.L. and S.V.; Methodology, E.L. and S.V.; Formal Analysis, E.L. and S.V.; Investigation, E.L., S.S., S.K. and S.V.; Resources, E.L.; Data Curation, S.V.; Writing – Original Draft Preparation, E.L., F.S., and S.V.; Writing – Review & Editing, E.L., S.S., S.K., F.S., S.C. and S.V..; Visualization, S.V.; Project Administration, E.L.

Conflicts of interests

The authors have declared no competing interests.

Data availability

All data generated or analyzed during this study are included in this published article.

Ethics approval

Not applicable.

References

1. Dall'Oglio F, Nasca MR, Gerbino C, Micali G. An Overview of the Diagnosis and Management of SD. *Clin Cosmet Investig Dermatol*. 2022;15:1537-1548. doi: 10.2147/CCID.S284671

2. Gupta AK, Bluhm R. SD. *J Eur Acad Dermatol Venereol JEADV*. 2004;18(1):13-26; quiz 19-20. doi: 10.1111/j.1468--3083.2004.00693.x
3. Naldi L, Rebora A. Clinical practice. SD. *N Engl J Med*. 2009;360(4):387-396. doi: 10.1056/NEJMcp0806464
4. Zip CM. Innovative use of topical metronidazole. *Dermatol Clin*. 2010;28(3):525-534. doi: 10.1016/j.det.2010.03.015
5. Parsad D, Pandhi R, Negi K, Kumar B. Topical metronidazole in SD-a double-blind study. *Dermatol Basel Switz*. 2001;202(1):35-37. doi: 10.1159/000051582
6. Koca R, Altinyazar H, Eştürk E. Is topical metronidazole effective in SD? A double-blind study. *Int J Dermatol*. 2003;42(8):632-635. doi: 10.1046/j.1365-4362.2003.01981.x
7. Page MJ, Moher D, Bossuyt PM, et al. PRISMA 2020 explanation and elaboration: updated guidance and exemplars for reporting systematic reviews. *BMJ*. 2021;372:n160. doi: 10.1136/bmj.n160
8. Higgins JPT, Thomas J, Chandler J, Li T, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.4 (updated August 2023). Published online 2023. https://training.cochrane.org/handbook. Accessed January 15, 2024.
9. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *Bmj*. 2019;366:l4898. doi: 10.1136/bmj.l4898
10. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188. doi: 10.1016/0197-2456(86)90046-2
11. Higgins JPT. Commentary: Heterogeneity in meta-analysis should be expected and appropriately quantified. *Int J Epidemiol*. 2008;37(5):1158-1160. doi: 10.1093/ije/dyn204
12. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *Bmj*. 1997;315(7109):629-634. doi: 10.1136/bmj.315.7109.629
13. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 2008;336(7650):924-926. doi: 10.1136/bmj.39489.470347.AD
14. Cicek D, Kandi B, Bakar S, Turgut D. Pimecrolimus 1% cream, methylprednisolone aceponate 0.1% cream and metronidazole 0.75% gel in the treatment of seborrhoeic dermatitis: a randomized clinical study. *J Dermatol Treat*. 2009;20(6):344-349. doi: 10.3109/09546630802687349
15. Siadat A, Iraji F, Shahmoradi Z, Enshaieh S, Taheri A. The efficacy of 1% metronidazole gel in facial SD: a double blind study. *Indian J Dermatol Venereol Leprol*. 2006;72(4):266-269. doi: 10.4103/0378-6323.26745
16. Ozcan H, Seyhan M, Yologlu S. Is metronidazole 0.75% gel effective in the treatment of seborrhoeic dermatitis? A double-blind, placebo controlled study. *Eur J Dermatol*. 2007;17(4):313-316. doi: 10.1684/ejd.2007.0206
17. Seckin D, Gurbuz O, Akin O. Metronidazole 0.75% gel vs. ketoconazole 2% cream in the treatment of facial SD: a randomized, double-blind study. *J Eur Acad Dermatol Venereol JEADV*. 2007;21(3):345-350. doi: 10.1111/j.1468--3083.2006.01927.x
18. Goldust M., Rezaee E., Raghifar R. A double blind study of the effectiveness of sertaconazole 2% cream vs. metronidazole 1% gel in the treatment of SD. *Ann Parasitol*. 2013;59(4):173-177.
19. Gomes TF, Calado R, Matos AL, Gonçalo M. Contact allergy to antifungals: Results of a 12-year retrospective study. *Contact Dermatitis*. 2022;86(6):539-543. doi: 10.1111/cod.14076
20. Nizoral Shampoo (Ketoconazole 2%): Side Effects, Uses, Dosage, Interactions, Warnings. RxList. https://www.rxlist.com/nizoral-shampoo-drug.htm. Accessed July 5, 2024.
21. Coondoo A, Phiske M, Verma S, Lahiri K. Side-effects of topical steroids: A long overdue revisit. *Indian Dermatol Online J*. 2014;5(4):416-425. doi: 10.4103/2229-5178.142483
22. Stacey SK, McEleney M. Topical Corticosteroids: Choice and Application. *Am Fam Physician*. 2021;103(6):337-343.
23. Clark GW, Pope SM, Jaboori KA. Diagnosis and Treatment of SD. *Am Fam Physician*. 2015;91(3):185-190.
24. Gupta A.K., Versteeg S.G. Topical Treatment of Facial SD: A Systematic Review. *Am J Clin Dermatol*. 2017;18(2):193-213. doi: 10.1007/s40257-016-0232-2
25. Tennis P, Gelfand JM, Rothman KJ. Evaluation of cancer risk related to atopic dermatitis and use of topical calcineurin inhibitors. *Br J Dermatol*. 2011;165(3):465-473. doi: 10.1111/j.1365-2133.2011.10363.x
26. Thaçi D, Salgo R. Malignancy concerns of topical calcineurin inhibitors for atopic dermatitis: facts and controversies. *Clin Dermatol*. 2010;28(1):52-56. doi: 10.1016/j.clindermatol.2009.04.001
27. Berger TG, Duvic M, Van Voorhees AS, VanBeek MJ, Frieden IJ, American Academy of Dermatology Association Task Force. The use of topical calcineurin inhibitors in dermatology: safety concerns. Report of the American Academy of Dermatology Association Task Force. *J Am Acad Dermatol*. 2006;54(5):818-823. doi: 10.1016/j.jaad.2006.01.054
28. Yang YL, Xiang ZJ, Yang JH, Wang WJ, Xu ZC, Xiang RL. Adverse Effects Associated With Currently Commonly Used Antifungal Agents: A Network Meta-Analysis and Systematic Review. *Front Pharmacol*. 2021;12:697330. doi: 10.3389/fphar.2021.697330
29. Commission Regulation (EU) 2021/1902 of 29 October 2021 Amending Annexes II, III and V to Regulation (EC) No 1223/2009 of the European Parliament and of the Council as Regards the Use in Cosmetic Products of Certain Substances Classified as Carcinogenic, Mutagenic or Toxic for Reproduction (Text with EEA Relevance). 2021;387. http://data.europa.eu/eli/reg/2021/1902/oj/eng. Accessed May 6, 2024.
30. SD and Rosacea | Rosacea.org. https://www.rosacea.org/patients/seborrheic-dermatitis. Accessed May 6, 2024.
31. SD in adolescents and adults - UpToDate. https://www.uptodate.cn/contents/seborrheic-dermatitis-in-adolescents-and-adults. Accessed May 6, 2024.