Systematic Review and Meta-analysis on Synthetic Antifungal versus Keratolytic Agents for Topical Treatment of Pityriasis Versicolor

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ABSTRACT

Background. Pityriasis versicolor is a common fungal infection of the superficial skin layer caused by *Malassezia furfur*, a normal commensal in the skin. Keratolytic agents are popular, cheap, and readily available over-the-counter treatments for pityriasis versicolor. Conventional antifungal agents are more expensive, requiring prescription, and may induce resistant strains. However, evidence of their comparative safety and efficacy is still lacking.

Objectives. To assess the efficacy and safety of synthetic antifungals compared to keratolytic agents in the topical treatment of pityriasis versicolor through a systematic review.

Methods. We searched the following databases: MEDLINE (from 1966) through PubMed, CENTRAL (Issue 9 of 12, September 2021), EMBASE (from 1974), LILACS (from 1987); Herdin (from 1970), www.clinicaltrials.gov, www.isrctn.com, www.trialregister.nl. We contacted researchers in the field, hand searched relevant conference abstracts, and the Journal of the Philippine Dermatological Society 1992-2019. We included all randomized controlled trials involving patients with diagnosed active pityriasis versicolor where topical antifungal was compared with a topical keratolytic for treatment. Two review authors independently applied eligibility criteria, assessed risk of bias using the Cochrane collaboration tool, and extracted data from included studies. We used RevMan 5.3 to pool dichotomous outcomes using risk ratios (RR) and continuous outcomes using the mean difference (MD), using random-effects meta-analysis. We tested for statistical heterogeneity using both the Chi^2 test and the I^2 test. We presented results using forest plots with 95% confidence intervals. We planned to create a funnel plot to determine publication bias but were unable to due to few studies. A Summary of Findings table was created using GRADE profile software for the primary outcomes.

Results. We included 8 RCTs with a total of 617 participants that compared azole preparations (ketoconazole, bifonazole and econazole) versus keratolytic agents (selenium sulfide, adapalene, salicylic-benzoic acid). Pooled data showed that azoles did not significantly differ from keratolytic agents for clinical cure (RR 0.99, 0.88, 1.12; 4 RCTs, N=274, I^2=55%; very low-quality evidence), and adverse events (0.59 [0.17, 2.06]; very low-quality evidence) based on 6 RCTs (N=536). There were two patients given a keratolytic agent (selenium sulfide shampoo) who had acute dermatitis and discontinued treatment.

Conclusion. It is uncertain whether topical azoles are as effective as keratolytic agents in clinical clearance and occurrence of adverse events in patients with pityriasis versicolor. A wider search of grey literature and local studies are warranted. Larger RCTs with low risk of bias are recommended.

Keywords: azole, antifungal, keratolytic, pityriasis versicolor, tinea versicolor

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INTRODUCTION

Pityriasis versicolor, also called tinea versicolor, is a common fungal infection of the superficial skin layer caused by *Malassezia furfur*, a normal commensal in the skin. Typical skin lesions consist of finely scaling macules and patches mostly on the upper trunk and proximal limbs. Discoloration of the skin, either hypo- or hyperpigmented, or occasionally erythematous, is usually the primary reason for consultation. Pityriasis versicolor is most common in children and young adults, especially in tropical countries,[1] with 12% prevalence in patients seen at the OPD, most commonly in young adults.[2] It was the second most common fungal skin infection diagnosed in children seen at a dermatology referral center in Colombia[3] and the third most common in adults seen at a dermatology unit of a medical center in Angola[4]. It is highly recurrent especially in the summer and may be itchy and red in warm weather.

Active pityriasis versicolor is diagnosed clinically by the typical skin lesions and confirmed by the presence of short hyphae and clusters of spores ('spaghetti and meatballs') under light microscopy using a potassium hydroxide smear of the skin scales.[5] A yellowish to greenish fluorescence may also be seen in some strains using the Wood's lamp (ultraviolet A). Fungal culture or skin biopsy are not routinely done.

Although a benign condition, pityriasis versicolor has been shown to have a moderate effect on the quality of life of affected patients (mean dermatology life quality index, DLQI, scores = 7.50, SD 4.45), like scabies (7.14, SD 2.19) and contact dermatitis (7.25, SD 3.78).[6]

Topical treatment is the first line of therapy for pityriasis versicolor.[7] Oral medications are only given if there is failure of topical therapy or recurrent and extensive cases.[8,9] Topical agents range from specific antifungal, either fungicidal or fungistatic, to non-specific keratolytic agents used to increase shedding of the superficial skin cells together with the fungal elements.

Specific antifungals may inhibit enzymes in the fungal cell membrane synthetic pathway, and can be fungicidal, when they inhibit an earlier pathway, or fungistatic, when they inhibit a later pathway.[10] Fungicidal agents include allylamines and benzylamines, which inhibit the squalene epoxidase enzyme, thereby causing accumulation of squalene, which is toxic to the fungal membrane and lethal to fungi. Fungistatic agents such as azoles inhibit the enzymes that prevent formation of ergosterol, thus inhibiting the growth and development of fungi. Other antifungals work by lowering the intracellular pH, subsequent inhibition of glycolysis and growth (benzoic acid);[11] increasing the intracellular levels of copper which damage iron-sulphur clusters of proteins that are essential for fungal metabolism (zinc pyrithione);[12] or chelating metal ions that lead to inhibition of metal-dependent enzymes needed for cellular metabolism (ciclopirox olamine).[13]

Non-specific keratolytic agents used for pityriasis versicolor work by desquamation of the entire superficial skin layer and eliminating the fungi in the process. Examples include beta-hydroxy acids (e.g., salicylic acid) and alpha-hydroxy acids (e.g., glycolic, lactic acid), that dissolves the lipid between cornified cells of the skin; sulfur and its derivatives (selenium sulfide, sodium thiosulfate) that have both irritant effect and antifungal activity.[14] Others indirectly cause skin shedding by their irritant action (e.g., benzoyl peroxide, adapalene, propylene glycol).

A systematic review and meta-analysis of controlled trials in 2020 by Hu et al. could not establish evidence to prove relative efficacy of different treatment regimens or therapeutic agents due to poorly reported, low quality and underpowered clinical trials.[15] The review suggested that longer courses of treatment, higher concentrations of active ingredients in the topical preparations may be more effective. UpToDate recommends the following topical agents as first line therapy: topical azoles, terbinafine, ciclopirox olamine, selenium sulfide and zinc pyrithione.[8] Other recommended topical agents were Whitfield ointment, sulfur-salicylic acid, benzoyl peroxide and propylene glycol.[8] There are also varied formulations (shampoo, gel cream, lotion, soap, and foam), concentrations and dosage regimens. Keratolytic agents may result in peeling skin and other side effects such as mild skin irritation. Sulfur-containing products may smell a bit like rotten eggs, and when in shampoo formulation may also dry out the skin (Informedhealth.org).[16] However, since they are less expensive and more readily available as over-the-counter preparations, they may be the preferred treatment for resource-poor communities.

Evidence for the relative efficacy of the less expensive but potentially more irritating traditional keratolytic agents (sulfur or exfoliant-based) versus the more expensive fungicidal or -static agents which can potentially induce resistance are still lacking.

Thus, there is a need to evaluate the efficacy and safety of synthetic topical antifungals compared to keratolytic agents in the treatment of pityriasis versicolor.

OBJECTIVES

To determine the efficacy and safety of synthetic topical antifungals versus keratolytic agents in the treatment of patients with pityriasis versicolor.

METHODS

The systematic review protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) and is available upon request from the author. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist in the reporting of this review.[17]

Inclusion criteria

Types of studies

We included randomized controlled trials on the treatment of pityriasis versicolor. We excluded trials on prophylaxis.

Types of participants

We included studies with participants clinically diagnosed with pityriasis versicolor by either a physician, nurse, or a trained health worker, through visual examination with laboratory mycologic confirmation. Tinea versicolor was defined as presence of finely scaling macules or patches, confirmed with presence of short hyphae and clustered spores using a potassium hydroxide smear.

Types of interventions

We included studies of synthetic topical antifungal agents, such as azoles and allylamines, that inhibit fungal enzymes, either in pure form or as the main ingredient of a combination product. Azoles consist of clotrimazole, econazole, efinaconazole, ketoconazole, luliconazole, miconazole, oxiconazole, sertaconazole, and sulconazole. Allylamines consist of terbinafine, butenafine, and naftifine.

We also included other antifungal agents that did not work through inhibition of fungal enzymes, such as zinc pyrithione, benzoic acid, and ciclopiroxol amine. We excluded (post hoc) natural products such as herbal preparations that were not recommended in any practice guidelines. We excluded studies wherein the antifungal intervention also contained a keratolytic agent.

Types of comparator

We included as comparator keratolytic agents such as adapalene, benzoyl peroxide, glycolic acid, lactic acid, propylene glycol, salicylic acid, and sulfur-based products such as selenium sulfide and sodium thiosulfate.

We included keratolytic comparator agents that also contained an antifungal. We excluded studies when the comparator was a placebo or vehicle, or another antifungal, or the same antifungal but with different concentration or formulation.

We included studies with any topical formulation (shampoo, lotion, mousse, foam, creme rinse, spray, ointment, or oil) or concentration of the antifungal or keratolytic. We included studies with any number of applications, any interval between applications, and any method or duration of application. We included studies whether the interventions were self-administered or administered by parent, caregiver, or any trained personnel (e.g., physician, nurse, health worker).

Types of outcome measures

Primary outcomes

1. Clinical cure rate 14 days after end of treatment defined by proportion of participants with no visible scaling as assessed by the investigator.
2. Treatment-related adverse events (minor and serious), such as stinging, itching, burning, redness, swelling, which were observed or gathered by investigators through interview, or self-reported by participants, anytime during the study, after the first treatment is given.

Minor adverse events may be mild (no limitation of normal activities, e.g., tolerable adverse event which disappears with washing off the product) or moderate (some limitation of normal activities, e.g., tolerable adverse event which continues for hours after washing off the product).

Serious adverse events were defined as any severe adverse event with inability to carry out usual activities or which required discontinuation of treatment, e.g., intolerable adverse event that required washing off the product before the application time is completed.

Secondary outcomes

3. Mycologic cure rate 14 days after end of treatment defined as absence of hyphae in a potassium hydroxide smear using light microscope as assessed by the investigator.
4. Clinical severity score of zero at final assessment, defined as absence of clinical signs and symptoms such as pruritus, scaling, or redness.
5. Patient satisfaction such as cosmetic acceptability, ease of use, pleasant feel on hair or scalp, willingness to use product again if needed, by participant/caregiver/investigator, at final assessment.
6. Quality of life score, using a validated QOL scale, either by participant or proxy.
7. Complete cure (post-hoc) defined as clinical and mycologic cure.

Exclusion criteria

If a study did not report any outcome which can be converted into the above outcomes, it was excluded.

Search methods for identification of studies

We searched for all potentially relevant studies regardless of language or publication status (published, unpublished, in press, and ongoing).

Electronic searches

We searched the following databases up to September 2021: MEDLINE (from 1966) through PubMed, CENTRAL (Issue 9 of 12, September 2021), EMBASE (from 1974), LILACS (from 1987) through the VHL portal; using the search strategies (Appendix A). We searched the local database, Herdin (from 1970) using the search words "tinea versicolor," and "pityriasis versicolor."

Trial registers

We searched for study protocols and reports up to September 2021 using the search words: "tinea versicolor," and "pityriasis versicolor" in the following trial registries:

Clinicaltrials.gov, The Meta Register of Controlled Trials (www.controlled-trials.com), and Philippine Health Research Registry (www.registry.healthresearch.ph).

Searching other resources

We searched the reference lists of all trials retrieved by the search, as well as review articles cited as references. We searched for but did not find any unpublished or ongoing trials by contacting researchers or organizations in the field (Philippine Dermatological Society, Philippine Pediatric Society). We hand searched relevant journals (Journal of the Philippine Dermatological Society 1992-2019, Journal of the Philippine Pediatric Infectious Diseases Society, 1996-2019).

Data collection and analysis

Selection of studies

Titles and abstracts from the search were independently prescreened by two authors based on eligibility criteria for potentially relevant studies. These two authors were not blinded as to the names of the authors, institutions, journal of publication and results when they applied the eligibility criteria.

Full texts of all potentially relevant studies were assessed for eligibility. Disagreements between the two authors was resolved through discussion or a third author. When studies were excluded, an explanation was stated in the results.

Data extraction and management

Two authors independently extracted data from the included studies using a pretested data extraction form. Any disagreement was resolved by discussion or the third author.

Original authors of study reports were contacted to ask details of missing data or items needing clarification.

Data items extracted

Methods – study design, duration, and inclusive dates

Participants – number, type, mean age (SD) or age range, setting, country, diagnostic criteria and method, inclusion/exclusion criteria

Interventions – description of antifungal and the comparator keratolytic agent, dosage and method of application, co-intervention, integrity of intervention

Outcome measures – outcome measures collected and reported

Assessment of risk of bias in included studies

Two authors independently assessed the risk of bias in included studies in seven domains, namely sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and 'other issues.' Risk of bias was assessed as "low risk", "high risk", or "unclear", and was recorded for each study in the "risk of bias" tables in RevMan 5.4, and summarized in tables and graphs. Any disagreement was resolved through discussion or a third author.

Data synthesis

We pooled all studies that compared an antifungal vs a keratolytic regardless of specific drug, preparation, dose, and dosing frequency. If there were enough studies, we would have done subgroup analyses to determine impact of these intervention characteristics. Otherwise, we just discussed it in study limitations and implications for research.

Measures of treatment effect

For dichotomous outcomes, risk ratio and 95% confidence intervals were used, while for continuous outcomes, mean difference and SD were used.

Unit of analysis issues

The unit of analysis was the participant. In trials with more than one treatment arm, we planned to combine interventions with the same mode of action as one group, and intervention arms which were not relevant to the review question were excluded.

In trials wherein cluster randomized design is used, we planned to compute for effective sample size using the formula: effective sample size = sample size / design effect, with design effect = 1 + (M-1)(ICC), M is average cluster size, ICC is intracluster coefficient.

Dealing with missing data

We planned to do intent-to-treat analysis by analyzing non-compliant participants or protocol violators in the group they were randomized to, regardless of how the original authors analyzed them. One author (Shi 2012) excluded the actual outcome value of 10 participants (6 for ketoconazole group vs 4 for adapalene group) who either discontinued therapy or used other antifungal drugs; however, author did not reply to email inquiry. Another author (Katsambas 1996) excluded two participants in selenium group who discontinued therapy due to adverse events from clinical cur outcome; however, author did not have any email address and was not contacted. If there were missing data (e.g., participants lost to follow-up who did not have any outcome assessments at relevant timepoints), we excluded them from the main analysis (=Available case analysis) (Chu 1984, 1/20 bifonazole group; Katsambas, 11/76 for econazole and 7/74 for selenium). We conducted sensitivity analysis to determine the impact of worst case and best-case scenario analysis on the robustness of the main analysis.

Assessment of heterogeneity

We assessed heterogeneity using visual inspection of the forest plots to check for overlapping confidence intervals. We also computed for chi-squared test for heterogeneity at 10% level of significance, and I^2 statistic. If I^2 value is >50%, heterogeneity was assessed to be significant, and if >75%,

it was assessed to be substantial. If significant heterogeneity exists, random effects model was used, otherwise, fixed effects model was used.

When significant heterogeneity exists, we planned subgroup analysis to determine the possible cause of heterogeneity.

Assessment of reporting biases

We searched for unpublished trials and ongoing trials using trial registers and contacting authors and organizations to avoid publication bias. We planned to construct a funnel plot to determine publication bias but were unable to due to few studies.

Data synthesis

For dichotomous outcomes we reported risk ratios with 95% confidence intervals. For continuous outcomes, we used mean differences and standard deviation or standardized mean differences, if they used different scales. Data was pooled for studies which were clinically homogenous.

Subgroup analysis and investigation of heterogeneity

We were only able to do one prespecified subgroup analysis based on climate (tropical vs non-tropical). The rest of prespecified possible effect modifiers (immune status and extent of disease) could not be investigated due to few studies and lack of reporting by studies. Subgroup analyses for immune status could not be done since studies either excluded immunocompromised or did not report; extent of disease not possible due to only two studies that reported extent (Bakr, Shi) – with <25% surface area involved. We could not subgroup post hoc according to specific type of drug since each study compared a different antifungal vs keratolytic.

Sensitivity analysis

We planned to test the robustness of our results by performing the following sensitivity analyses:

1. Excluding trials with high risk or unclear risk of bias.
2. For missing data, we compared worst- and best-case scenario analysis for dichotomous outcomes - imputing the worst outcome for the intervention and the best outcome for the control (worst case scenario analysis); imputing the best outcome for the intervention and the worst outcome for the control (best case scenario analysis);
3. Excluding outlier studies
4. Excluding pharmaceutical industry-sponsored studies, defined as those initiated by the pharmaceutical industry or where investigators received honoraria from the companies. Studies where the pharmaceutical companies provided only the medications will not be excluded.

Summary of findings table

We used GRADEPro software (V. 2021) to create the Summary of findings table for the primary outcomes. Using the GRADE approach, we assessed the certainty of the body of evidence, taking into consideration risk of bias, inconsistency, imprecision, indirectness, and publication bias.

RESULTS

We identified 797 records from the databases and 2 from secondary sources (Aggarwal 2003; Shi 2012). Out of 799 records, we removed 122 duplicate records, and screened 677 titles and abstracts. We retrieved 17 full text articles or abstracts, of which 5 were excluded, one was an ongoing trial, and 3 were awaiting classification) (Appendix B). Eight RCTs were included in the qualitative review, of which all studies were included in the meta-analysis (Figure 1).

Description of included studies

The eight RCTs in this review included data from 617 patients.[18–25] Sample sizes ranged from 38 (Chu 1984) to 200 (Ansarin 2005). All were two-arm studies except Bakr 2019, which had three arms, although we did not analyze the 3rd arm, which gave both ketoconazole and adapalene as a combination regimen, since it was not relevant to this review. Participants were mostly adults 18 to 40 years of age. Seven studies included participants who were diagnosed with pityriasis versicolor based on direct microscopy of skin

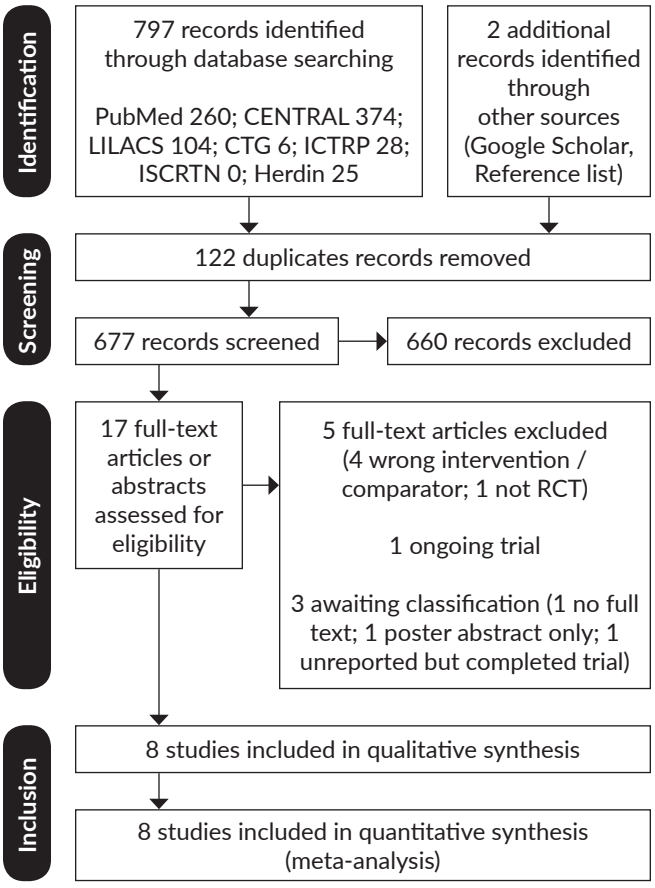

Figure 1. PRISMA study flow diagram.

scrapings, whereas the diagnosis in one study was based on clinical findings alone (Bakr 2019).

Three RCTs were conducted in Asia (1 each in China, Egypt, India, and Iran) while 4 were from Europe (2 London 1 UK, 1 Greece). All eight RCTs were published sparsely between 1973 to 2019 (2 in 1970s; 1 each in 1980s and 1990s; 2 in 2000s, and 2 in 2010s). Three studies received study medications from the manufacturer of the azole drug (Ansarin 2005; Clayton 1973; Clayton 1977) while one study author (Chu 1984) was a research fellow of the manufacturer of the azole drug.

Azole interventions used were ketoconazole (4 studies),[18,19,20,26] clotrimazole (2 studies),[24,25] bifonazole[21] and econazole,[22] while keratolytic agent comparators included selenium sulfide (4 studies)[18,19,21,22] 3% salicylic acid and 6% benzoic acid in an emulsifying base (Whitfield's ointment), (2 studies)[24,25] and adapalene (2 studies).[20,26] Azoles were in shampoo preparation (4 studies), cream (3 studies), and solution (1 study), while the keratolytic was mostly in shampoo formulation (4 studies), ointment (2 studies) and gel (2 studies). Four studies compared various azole preparations to selenium sulfide 2.5% shampoo. Application of azole preparations varied from once a day of econazole shampoo for 6 days to daily bedtime application of bifonazole solution for 2 weeks, to twice daily application of clotrimazole cream for 4 weeks. Ketoconazole shampoo was used once to thrice a week for 3 weeks. Selenium sulfide shampoo usage in the different studies varied at once a day for 3 days, once a day for 6 days, once a week for 3 weeks and thrice a week for 3 weeks. Whitfield's ointment was given twice daily for four weeks. Clinical cure and mycologic cure was measured separately in five studies, complete cure in two studies. Adverse events were reported in all studies.

The characteristics of the eight included studies are in Appendix C.

Risk of bias in included studies

There was high risk of performance bias in 7 0% of studies and detection bias in 6 0% (Figure 2). All included studies had high (5 studies) or unclear overall risk of bias (3 studies). High risk of bias in at least one domain was present in 5 of the 8 studies, due to lack of blinding of participants, personnel, and/or outcome assessors, and attrition bias (Figure 3).

Effects of interventions

There is little or no difference between azoles and keratolytic agents in terms of clinical cure (RR 1.01 [0.91, 1.12]; 5 RCTs, N=305) (Figure 4). There was no significant heterogeneity (I^2=39%) despite four different azoles (ketoconazole in three studies, bifonazole, clotrimazole, econazole) and keratolytic agents (selenium sulfide shampoo in three studies, adapalene, salicylic acid-benzoic acid [Whitfield's ointment], as well as different formulations for the azoles (shampoo, cream, and solution) and keratolytic agent (shampoo, ointment, gel). In addition, two keratolytic agents contained antifungal ingredients (benzoic acid in Whitfield's ointment) or has antifungal action as well (selenium sulfide shampoo). This could not be explored in a formal subgroup analysis due to lack of studies. However, we noted that the sole study (Shi 2012) that used a purely keratolytic agent (adapalene) (versus four other studies that used selenium sulfide or salicylic acid-benzoic acid, with both keratolytic and antifungal action), did not differ from the main analysis (RR 0.99, 0.83, 1.18).

Complete cure (post hoc outcome), defined as clinical and mycologic clearance, was reported in two studies but could not be pooled due to substantial heterogeneity (I^2=97%)

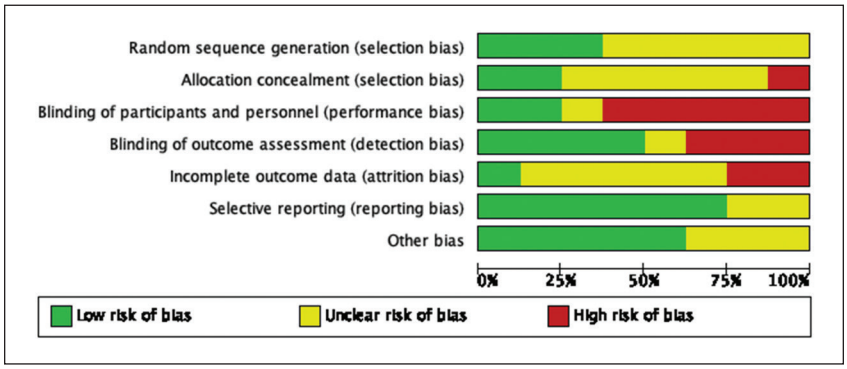

Figure 2. Risk of bias graph.

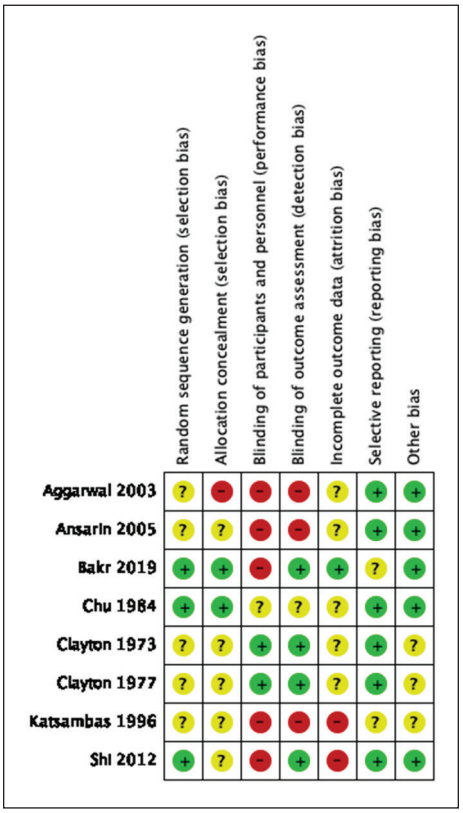

Figure 3. Risk of bias summary.

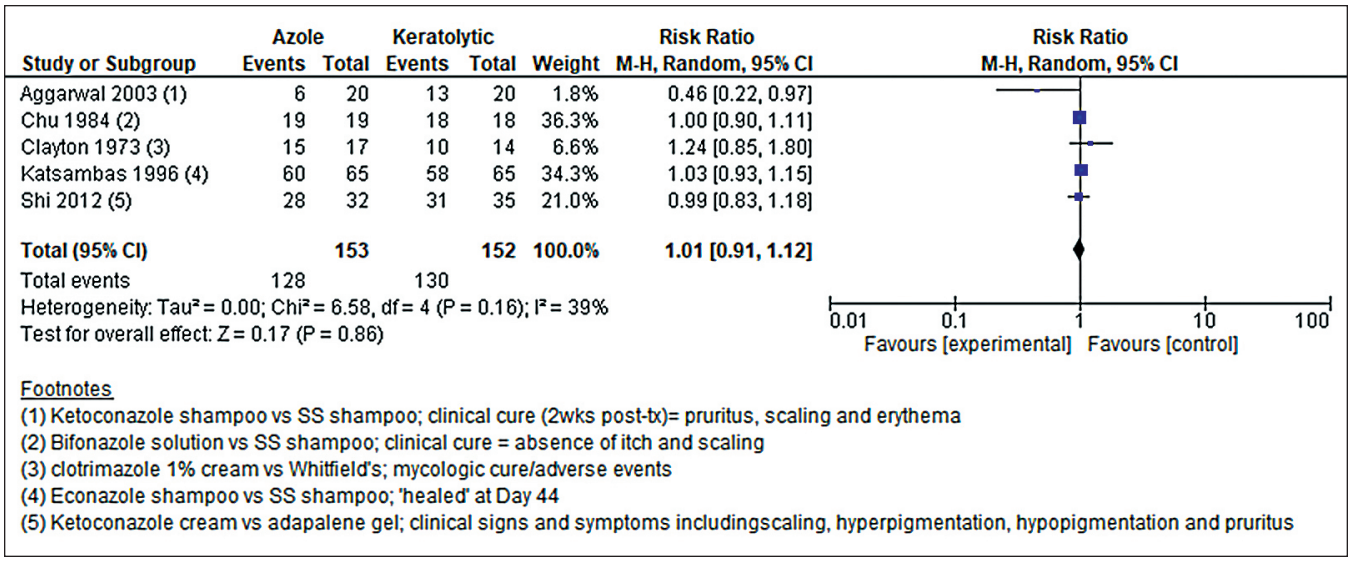

Figure 4. Forest plot of clinical cure for azole vs keratolytic agent comparison.

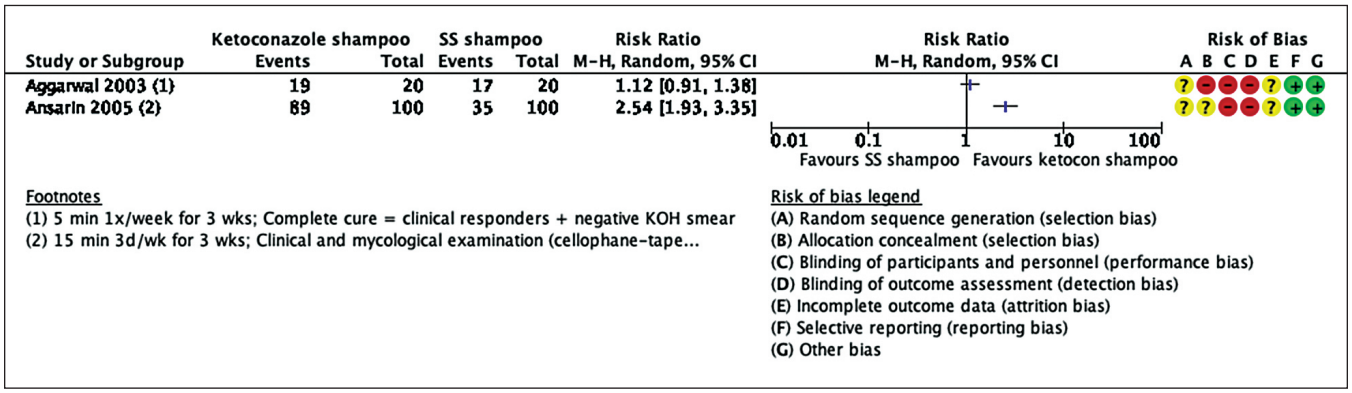

Figure 5. Forest plot of complete cure for ketoconazole shampoo vs keratolytic (selenium sulfide shampoo).

(Figure 5). A probable reason could be the greater dosing frequency in the Ansarin 2005 study that gave it for 15 min 3 days a week for 3 weeks, compared to the Aggarwal 2003 study, which only gave the shampoos for only 5 min once a week for 3 weeks.

There was no significant difference in mycologic cure (RR 1.09 [0.98, 1.20]; 5 RCTs, N=266; I^2=0%; Figure 6) between azoles (85%) and keratolytic agents (78%), with a trend favoring topical azoles. There was no heterogeneity despite the different azole and keratolytic agent types, formulations, and dosage regimens.

Adverse events did not significantly differ (RR 0.61 [0.24, 1.53]: 7 RCTs, N=567; I^2=44%; Figure 7) between azoles and keratolytic agents. There were less adverse events in the azole group (15/280, 4.5%) compared to the keratolytic agent group (31/287, 9.3%) and were mostly mild and consisted of irritation, dryness, and erythema. There was no serious adverse event but there were adverse events in one study (Katsambas 1996) (acute dermatitis) that required discontinuation of intervention in two patients in the keratolytic agent group (SS shampoo). The SS shampoo was given once every evening on days 1–3, then placebo shampoo on days 4–6, then selenium sulfide 2.5% shampoo again on the evening of days 30 and 60.

Patient satisfaction was significantly greater in the azole group than the keratolytic group (RR 1.16, 95% CI 1.06, 1.28; 2 RCTs, N=169; I^2=0%) (Figure 8).

Three studies (N=195) (Aggarwal 2003; Chu 1984; Katsambas 1996) reported few relapses, with no significant difference between azole shampoo and SS shampoo (RR 0.80, 95% CI 0.28, 2.29; I^2=0%) (Figure 9). However, the longest duration study was only 3 months (Aggarwal 2003).

Subgroup analyses

Planned subgroup analyses could only be performed for climate, resulting in no subgroup difference (I^2=0%) between tropical (0.71 [0.28, 1.83]) and non-tropical (RR 1.02 [0.95, 1.10]).

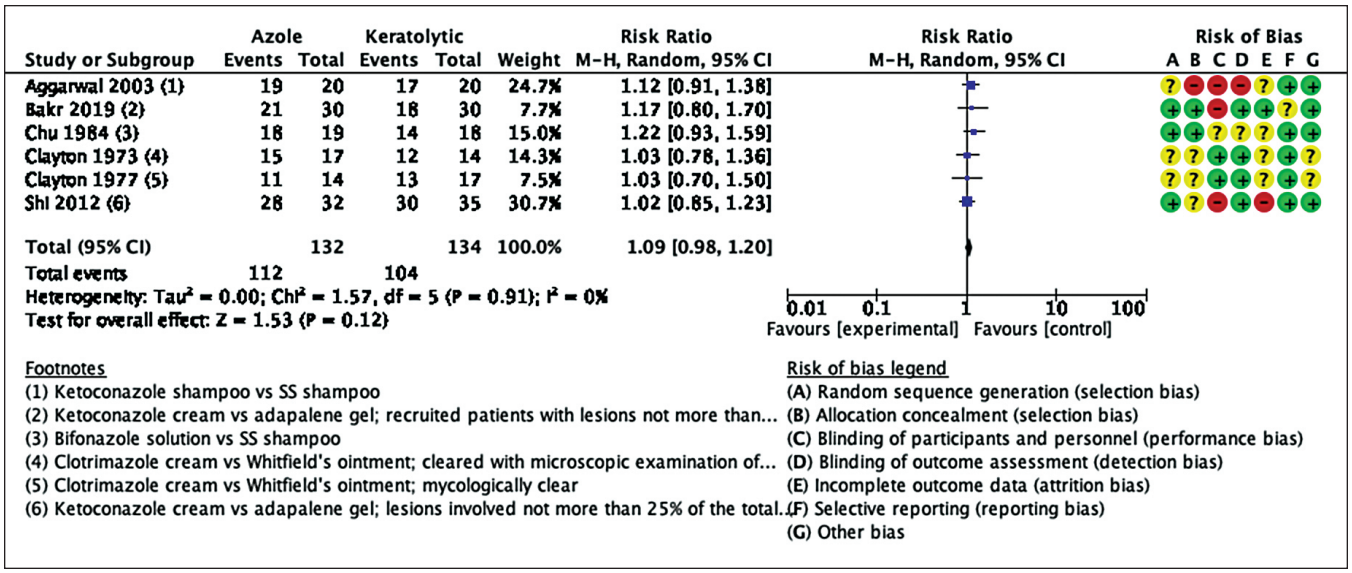

Figure 6. Forest plot for mycologic cure for azole vs keratolytic agent comparison.

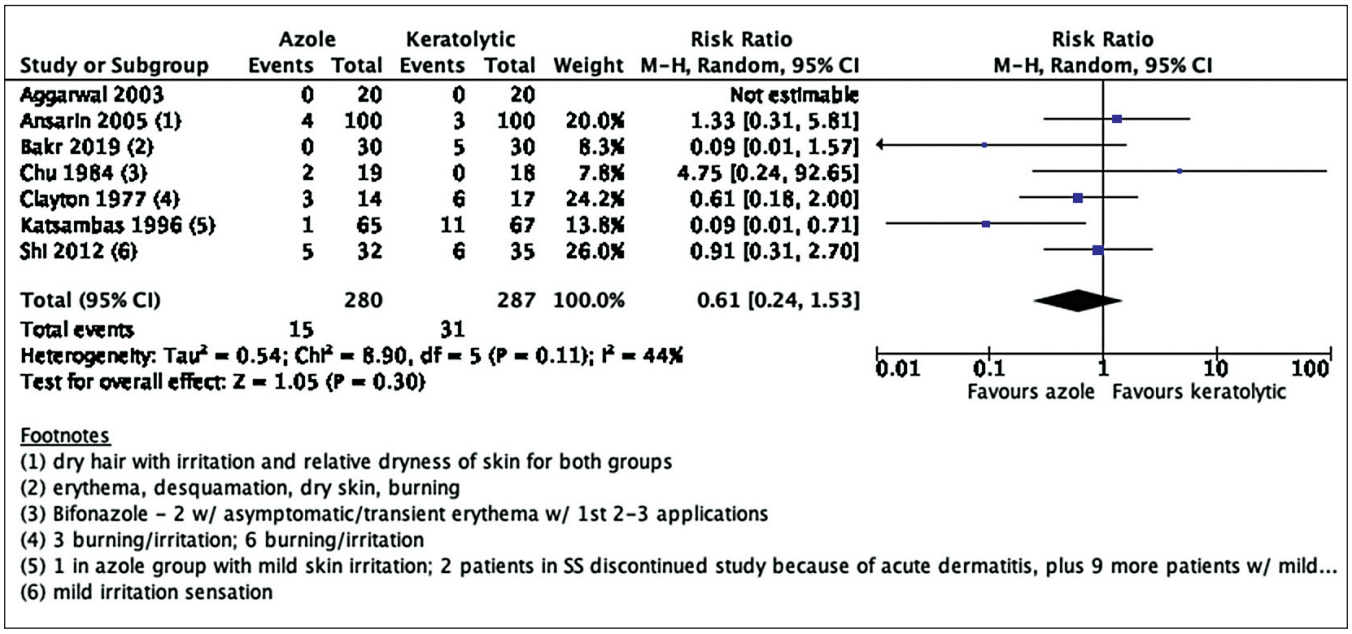

Figure 7. Forest plot for adverse events for azole vs keratolytic agent comparison.

Sensitivity analyses

Sensitivity analysis excluding high risk of bias studies (Aggarwal 2003; Katsambas 1996; Shi 2012), a study with less frequent dosing regimen (once weekly for 3 weeks) and lower cure rate (30%) for ketoconazole shampoo group (Aggarwal 2003), and industry-sponsored studies (Ansarin 2005; Chu 1984; Clayton 1973; Clayton 1977) did not change conclusions for clinical cure, mycologic cure and adverse events (Appendix D).

We also investigated the effects of high dropout rates in two studies, the Katsambas 1996 study with 20/100 dropouts (20%) (11 for the econazole shampoo group and 9 for the SS shampoo group; 2 of the 9 discontinued due to adverse events) and the Shi 2012 study with13/80 (16.3%) (8 for ketoconazole cream group and 5 for adapalene gel group). Sensitivity analyses for worst-case and best-case scenario sensitivity analyses did not change the conclusions for all three outcomes (clinical cure, mycologic cure, adverse events). However, one study with 31% dropout rate (14/45) (Clayton 1977) did not specify as to which arms the dropouts belonged and its impact could not be investigated (Appendix D).

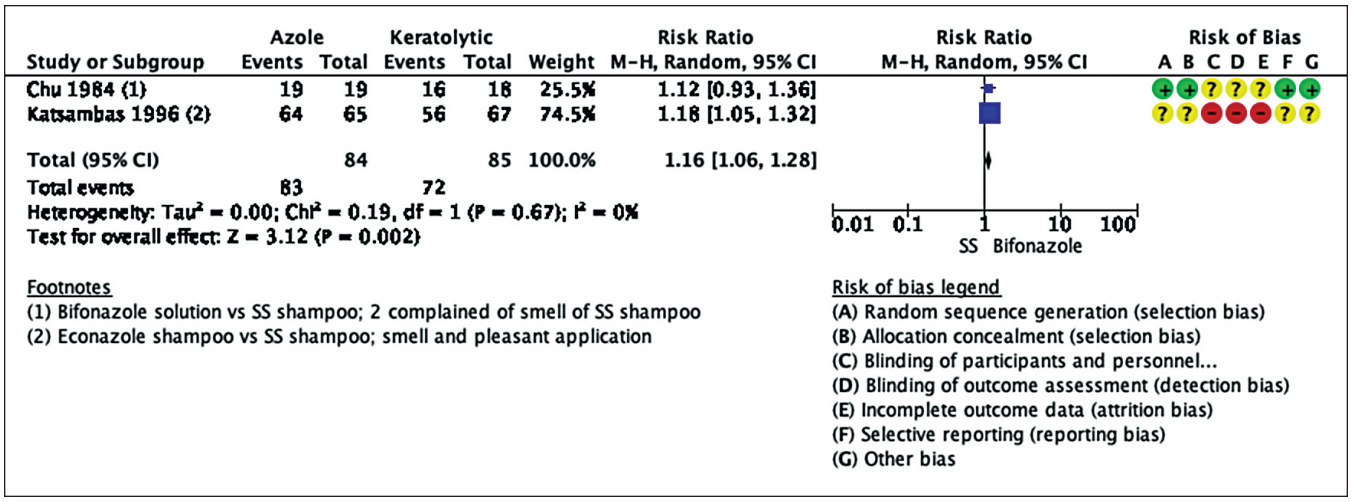

Figure 8. Forest plot for patient satisfaction for azole vs keratolytic agent comparison.

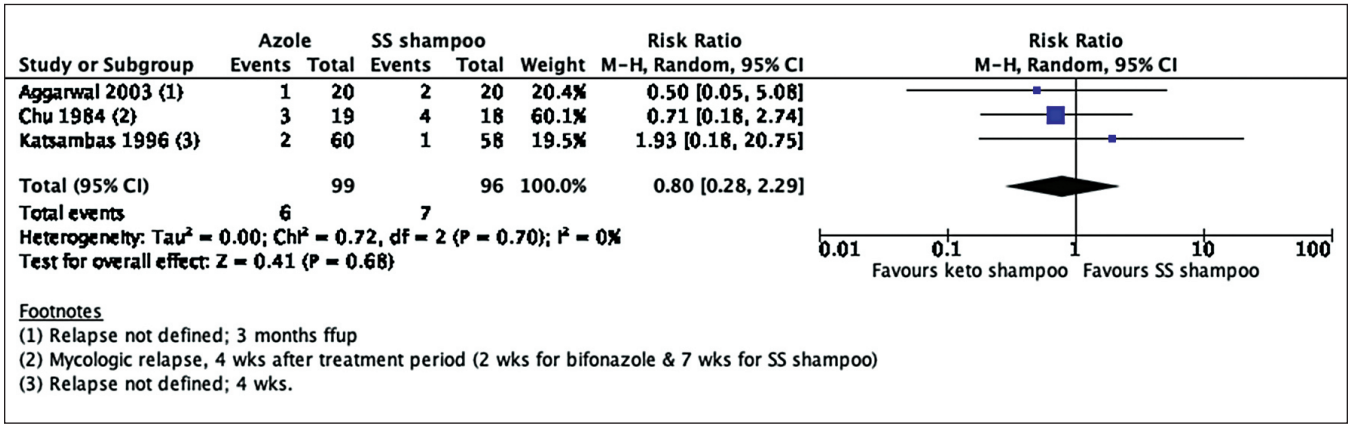

Figure 9. . Forest plot for relapse for azole vs keratolytic agent comparison.

DISCUSSION

Summary of main results

We identified eight RCTs with 617 participants. We pooled together all types of azoles and keratolytic agents, regardless of types of formulations (cream, lotion, shampoo, gel) and dosing regimens (daily to weekly doses followed by weekly or monthly doses). Overall, based on very low quality evidence, it is unclear whether topical azoles and keratolytic agents were equally efficacious for the treatment of tinea versicolor (clinical or mycologic) (Appendix E). We downgraded the evidence for clinical cure due to very serious risk of bias (2 levels) and publication bias (1 level). Adverse events were less common in the azole group but the difference was not significant. They were few, mostly mild in severity, and temporary. These included transient increase in erythema for bifonazole solution, irritation for both azoles (econazole and clotrimazole) and keratolytic agents (selenium sulfide shampoo, adapalene gel). There were two cases of acute dermatitis from selenium sulfide shampoo that required withdrawal from the study. Based on very low quality evidence, we are uncertain on whether azoles differ from keratolytic agents for the occurrence of adverse events (Appendix E). Aside from very serious risk of bias and publication bias, we also downgraded for imprecision. There were few relapses mostly based on short-term timepoints, with uncertain effect estimate between azoles and keratolytic agents. Patient satisfaction was significantly higher with azoles than keratolytic agents.

Overall completeness and applicability of evidence

We only included six studies, conducted over four decades, with the most recent one in 2019. We may have been unable to do an exhaustive search of the grey literature, which is why downgraded by one level for publication bias. We suspect that there may be more unpublished and unregistered studies especially in the early decades prior to required trial registration by journal editors. This may be due to the possible increasing preference for use of azoles as the standard of care, rather than keratolytic agents, as

recommended in recent 2015 Danish practice guidelines.[27] In the early 2000s, there were no evidence-based data, although based on recommendations at the time, pityriasis versicolor should be treated with antimycotics.[28]

The included participants, aged 18 to 40 y/o, did not include children. However, although the evidence may be only based on the adult population, we do not see any reason for the treatment effects to be different for children. The azoles varied in the specific type, formulation, and dosing regimen; but due to few studies, subgroup analysis to determine the most effective preparation could not be done. The topical antifungal preparations found in this review were only limited to azoles (bifonazole, clotrimazole, econazole, and ketoconazole), and did not include other topical antifungals such as allylamines or zinc pyrithione, and other keratolytics, such as benzoyl peroxide, propylene glycol and sulfur-salicylic preparations. Since they have different modes of action, the evidence from this review may not apply to these other antifungals. Some studies only reported mycologic cure (Bakr 2019), when most clinicians, especially in resource-poor or remote communities, often use only clinical resolution to gauge effectiveness of treatment. For those who reported clinical cure, some did not define this outcome, while one study defined it as clinical response, which consisted of healed as well as mild residual disease. (Aggarwal 2003). Adverse events were poorly monitored and reported, and since there were only a few events, the evidence is uncertain. Relapses were few and only reported at a maximum of 3 months post-treatment in three studies (Aggarwal 2003; Chu 1984; Katsambas), while only two studies reported a patient-centered outcome i.e. patient satisfaction (Chu 1994; Katsambas 1996). Sustained cure in a trial of longer duration and quality of life are outcomes that are important in the choice of treatment by patients and clinicians.

Quality of evidence for primary outcomes in included studies

Majority (75%) of studies had high risk of bias for the primary outcomes, mainly due to performance and detection bias. Although some comparisons used both shampoo formulations, the smell of sulfur-containing shampoos can be easily detected by participants. Both the pooled clinical cure and adverse event outcomes had very low quality evidence, due to serious risk of bias, publication bias, and/or imprecision.

Potential biases in the review process

We only included eight studies, all of which were published. No unpublished studies were obtained from search of trial registers and no local studies despite contacting local authors and organizations. We had one study whose full reports was unavailable: Ramali 2002 poster abstract (ketoconazole shampoo vs sodium thiosulfate solution; N=71), and a completed study without published results, NCT04007237 (ketoconazole shampoo vs selenium sulfide shampoo; N=100). Since the two studies with known sample sizes comprise 28% (171/617) of the total number of included participants in our review, they may contribute additional data that can change the evidence. We also had keratolytic agents that had combination of ingredients, some with antifungal activity (salicylic-benzoic acid or Whitfield's ointment), or a single compound that had both keratolytic and antifungal activity (selenium sulfide). Since it was not possible to isolate the various ingredients in these proprietary formulations, we could not determine how much of the effect is contributed by the keratolytic component. In addition, this review was limited to topical synthetic antifungals and did not include plant-based antifungal topical treatments versus topical keratolytics. The addition of plant-based antifungals may change the findings of this systematic review.

Agreements and disagreements with other studies and reviews

The previous systematic review by Hu et al. in 2010 included 93 randomized and non-randomized clinical trials (N=8327) on prophylaxis and treatment of pityriasis versicolor that compared oral or systemic agents with placebo/vehicle, different oral or topical agents, same drug but different dosage or formulation, and oral vs systemic agents.[15] We had two studies in common (Chu 1984; Katsambas 1996) but the Hu review was also not able to pool these studies. A Cochrane review protocol on interventions for pityriasis versicolor was published by Bamford et al. in 2014 but was withdrawn due to lack of progress.[29]

CONCLUSION

It is uncertain whether synthetic topical antifungals are as effective as topical keratolytic agents in achieving clinical cure among patients with pityriasis versicolor when used for either a few days or up to 4 weeks or more. It is also unclear on whether t he incidence of adverse effects differs between the two interventions. Adverse effects were mostly minor and included transient erythema and irritation.

Implications for practice

Based on UpToDate, the currently recommended topical drugs for tinea versicolor include various antifungals (azoles, allylamines, zinc pyrithione) but only one keratolytic agent (selenium sulfide) (Goldstein 2020). The evidence suggests that topical keratolytic agents with antifungal activity (such as selenium sulfide or Whitfield's ointment) or without antifungal activity (adapalene) may be as effective and safe as the synthetic topical antifungals, but this needs to be confirmed. The latter are more expensive, prescription-based, and may not be widely available especially in remote areas. In the Philippines, other keratolytic agents that are cheap and widely used include sulfur-salicylic acid soaps and sodium thiosulfate solution which we did not find evidence for.

Implications for research

A more comprehensive search, especially of grey literature, can be done to augment the number of studies to reduce publication bias. Conference proceedings, technical reports from government agencies and research groups, doctoral or masteral dissertations, can be searched for additional evidence. If enough studies are found, a network meta-analysis may be conducted to simultaneously compare the different azoles and keratolytic agents. Larger RCTs with good methodologic quality especially in blinding of patients, personnel and outcome assessors must be conducted. Patient-reported outcomes such as quality of life or treatment adherence and acceptability are also essential in the formulation of recommendations for clinical practice guidelines. Determining which drug leads to less recurrence may be crucial to lessen the impact of this superficial but cosmetically disfiguring skin infection. Plant-based topical antifungal preparations can also be included in future systematic reviews because these are also used in resource-poor settings.

Statement of Authorship

RNFG contributed in the conceptualization, writing of protocol, acquisition and analysis of data, and writing of manuscript. BLD contributed in the conceptualization, protocol draft, analysis, revision of manuscript, and final approval of the version to be published. MCFRB contributed in the analysis of data, drafting, and final approval of the version to be published. MBTGP contributed in the acquisition and analysis of data. AAA contributed in the acquisition and analysis of data, revising, and final approval of the version to be published.

Author Disclosure

All authors declare that there is no conflict of interest.

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APPENDICES

Appendix A. Search Strategies

Table A1. MEDLINE search strategy (24 Sep 2021)

10	#8 and #9	260
9	(((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (clinical trials as topic[mesh:noexp]) OR (randomly[tiab]) OR (trial[ti])) NOT (animals[mh] NOT humans[mh]))	1,329,485
8	#1 or #2 or #3 or #4 or #5 or #6 or #7	3,839
7	malassezia	2,743
6	malassezia[MeSH Major Topic]	1,484
5	pityrosporum	2,867
4	pityriasis versicolor	1,512
3	tinea flava	1,229
2	tinea versicolor	1,227
1	tinea versicolor[MeSH Major Topic]	731

Table A2. CENTRAL search strategy (24 Sep 2021)

#1	tinea versicolor	193
#2	pityriasis versicolor	139
#3	tinea flava	1
#4	MeSH descriptor: [Tinea Versicolor] explode all trees	93
#5	pityrosporum	52
#6	malassezia	167
#7	#1 or #2 or #3 or #4 or #5 or #6 with Cochrane Library publication date Between Jan 1000 and Sep 2020, in Trials	374
#8	#1 or #2 or #3 or #4 or #5 or #6 with Cochrane Library publication date Between Jan 1000 and Sep 2021, in Trials	373

LILACS search strategy (Sept 24, 2021)

tw:((tw:(tinea versicolor)) OR (tw:(pityriasis versicolor)) OR (tw:(tinea flava))) AND (db:("LILACS") AND type_of_study:("clinical_trials"))

Appendix B. List of Excluded, Ongoing, Awaiting Classification Studies

Study ID	Category	Reason for exclusion
Balachandran 1987[30]	Excluded	Wrong study design (Not an RCT)
Del Palacio 1987[32]	Excluded	Wrong intervention (oral azole)
Di Fonzo 2008[33]	Excluded	Wrong comparator (both azole)
Hull 2004[34]	Excluded	Wrong intervention (both keratolytic)
Shi 2015[23]	Excluded	Wrong comparator (combination of an azole and a keratolytic)
NCT04007237	Studies Awaiting Classification	Completed but no study report
Ramali 2002	Studies Awaiting Classification	Conference poster abstract only
Comaish 1974[31]	Studies Awaiting Classification	No full text
RBR-3jtxjs	Ongoing	Not completed

Appendix C. Characteristics of included studies

Author (Year Published)	Methods	Participants	Intervention	Comparator	Outcomes
Aggarwal (2003)[18]	RCT India Single center N = 40 Duration: 3 mos.	Patients with tinea versicolor Average age: 22.9 and 21.2 years Exclusion - Systemic or topical antimycotic therapy within a month of the start of the study - Associated dermatophyte infections - Any serious concomitant illness	Ketoconazole 2% shampoo (n=20) applied for five minutes OW for three weeks	Selenium sulfide 2.5% shampoo (n=20) applied for five minutes OW for three weeks	1. Clinical assessment (pruritus, scaling and erythema) (scale of 0-3) 2. Global assessment: healed, mild residual disease, considerable residual disease, unchanged or deteriorated 3. Responders = healed + mild residual disease 4. Mycologic cure = negative KOH smear 5. Complete Cure = clinical responders + mycologic cure 6. Relapse
Ansarin (2005)[19] *Arabic language* *Pharma-provided study medication*	RCT Iran (two hospitals) N=200 Duration: 4 wks. (=1 wk post-treatment)	Patients >12 y/o with tinea versicolor Sex: Mostly F (54 v 58%) Age: mostly 20-40 years old Exclusion - Pregnant and lactating women - Other skin conditions who were likely to be irritated by shampooing - Systemic antifungal medications in the past month or selenium sulfide, ketoconazole or zinc pyrithion shampoos in the last 2 weeks	Ketoconazole 2% shampoo applied for 15 minutes three days a week for three consecutive weeks	Selenium sulfide 2.5% shampoo applied for 15 minutes three days a week for three consecutive weeks	1. Complete cure (Clinical and mycological cure) (cellophane tape test and Wood's lamp) 2. Adverse events
Bakr (2019)[20]	RCT Egypt N=90 Duration: 4 wks.	Patients with hyperpigmented or hypopigmented PV Age: 18 years old and above 67M / 23F Exclusion - Pregnant and nursing women - Facial lesions or lesions more than 25% of the total trunk area - Systemic or topical antimycotic agents at least 1 month before the study - Allergy to ketoconazole or adapalene	Ketoconazole 2% cream (n=30) BID x 4 wks	Adapalene 0.1% gel (n=30) BID x 4 wks. *3rd arm: Combination ketoconazole-adapalene (not included in analysis)	1. Mycologic cure 2. Adverse events 3. Patient satisfaction

Appendix C. Characteristics of included studies *(continued)*

Author (Year Published)	Methods	Participants	Intervention	Comparator	Outcomes
Chu (1984)[21] *Dr. Chu is a senior fellow of Wellcome, manufacturer of Mycospor (bifonazole)*	RCT UK N=38 Duration: 4 wks. post-treatment 1 with missing data for bifonazole	Patients over 18 years of age with a clinical diagnosis of pityriasis versicolor, confirmed by direct microscopic examination of skin scrapings using the Parker Quink/KOH method Mean age 31 (SD 11) years; mostly male Exclusion -Cconcomitant or mixed infection requiring additional antibiotic therapy -Topical or systemic antifungal agents within the previous 4 weeks -Suspected of having a hypersensitivity to any of the imidazole group of drugs	Bifonazole 1% solution applied OD at bedtime for two weeks	Selenium sulphide 2.5% shampoo applied for 5 minutes before rinsing OD for 6 days, then OW for 6 weeks	1. Clinical cure 2. Mycologic cure 3. Mycological relapse
Clayton (1973)[38] *Study medication provided by Bayer*	RCT N=35 Author is from London, UK	Patients with tinea versicolor confirmed by microscopy aged 20-30 years old	Clotrimazole 1% cream, apply twice daily to the affected areas for 4 weeks	Salicylic acid 3% plus benzoic acid 6% in an emulsifying base (Whitfield's ointment), apply twice daily to the affected areas for 4 weeks	Clinical cure (2, 4 and 8 weeks after initiation of treatment)
Clayton (1977)[25] *Letter to editor* *Study medication provided by Bayer*	RCT N=45 Author is from London, UK	All patients seen at the skin department who were positive for *M. furfur* on skin scrapings were included in the study More than 75% were 20–28 years old	Clotrimazole 1% cream, apply twice daily to the affected areas for 4 weeks	Salicylic acid 3% plus 6% benzoic acid 6% in an emulsifying base (Whitfield ointment), Apply twice daily to the affected areas for 4 weeks	1. Mycological cure 2. Adverse events
Katsambas (1996)[22]	RCT Greece N=150 Duration of study: 74 days 18 w/ missing data (11 for econazole; 7 for selenium; additional 2 who discontinued treatment due to acute dermatitis for selenium group)	Positive Wood's light examination, positive KOH preparation for the responsible pathogen Exclusion - pregnant women and breast-feeding mothers - known allergy to one of the components of the tested preparations, - topical or systemic therapy with otherantimycotics, antimicrobials, antipruritics, and corticosteroids, either within 2 weeks prior to the study or during the study - diabetes mellitus and malignant tumors	Econazole 1% shampoo, once every evening on days 1–6, 30 and 60	Selenium Sulfide 2.5% shampoo, once every evening on days 1–3, then placebo shampoo on days 4–6, then selenium sulfide 2.5% shampoo again on the evening of days 30 and 60	1. Clinical cure 2. Adverse events 3. Patient satisfaction 4. Relapse
Shi (2012)[26]	RCT China N=67 Duration: 4 wks. 13 with missing data (8 for ketoconazole and 5 for adapalene)	Han people with mostly truncal lesions Mean age: 27.2 (8.2) – 30.6 (7.6) years 43M / 37F Positive KOH examination (=spaghetti and meatballs) Exclusion - Pregnant women or nursing mothers - Allergy to ketoconazole or adapalene - Systemic or topical antimycotic agents at least 1 month prior to the study - Serious concurrent diseases or other fungal infections	Ketoconazole 2% cream - BID x 2 wks	Adapalene gel - BID x 2 wks	1. Mycologic cure 2. Clinical cure 3. Adverse events

OW, once weekly; OD, once daily; BID, twice daily

Appendix D. Sensitivity Analyses

Type of Analysis	Clinical Cure RR [95% CI]	Mycologic Cure RR [95% CI]	Adverse Events RR [95% CI]
Main analysis	1.01 [0.91, 1.12]	1.09 [0.98, 1.20]	0.61 [0.24, 1.53]
Worst-case scenario sensitivity analysis	0.98 [0.83, 1.15]	1.03 [0.90, 1.16]	1.16 [0.60, 2.21]
Best-case scenario sensitivity analysis	0.98 [0.81, 1.19]	1.14 [1.02, 1.27]	0.46 [0.17, 1.26]
Sensitivity analysis excluding outlier (inferior dosing regimen, Aggarwal 2003)	1.02 [0.95, 1.09]	1.07 [0.95, 1.21]	0.61 [0.24, 1.53]
Sensitivity analysis excluding industry sponsored (Ansarin 2005; Clayton 1973; Clayton 1977; Chu 1984)	0.95 [0.76, 1.19]	1.08 [0.94, 1.23]	0.25 [0.04, 1.67]

Appendix E. Summary of Findings Table (Primary Outcomes): Azoles vs Keratolytic Agents

Outcome No. of participants (studies)	Relative effect [95% CI]	Anticipated absolute effects (95% CI)			Certainty
				Difference	
Clinical Cure No. of participants: 274 (4 RCT)	RR 0.99 [0.88, 1.12]	87.0%	86.1% (76.5 to 97.4)	0.9% fewer (10.4 fewer to 10.4 more)	⨁◯◯◯ VERY LOW [a,b]
Adverse Events No. of participants: 536 (6 RCT)	RR 0.59 [0.17 to 2.06]	9.3%	5.5% (1.6 to 19.1)	3.8% fewer (7.7 fewer to 9.8 more)	⨁◯◯◯ VERY LOW [a,b,c]

** The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).*

CI: confidence interval; RR: risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

Explanations
[a] Large majority of studies (>75%) with high risk of bias due to unblinded outcome assessors, participants, and personnel (downgraded by 2 levels)
[b] Publication bias is suspected due to few studies over 4 decades (downgraded by 1 level)
[c] Wide confidence interval crossed significant benefit and harm (downgraded by 2 levels)