

Efficacy and safety of topical antifungals in the treatment of dermatomycosis: a systematic review

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Summary

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The analysis of comparative efficacy and safety of topical antifungals in the literature is restricted to the treatment of tinea pedis and onychomycosis. Therefore our objective was to evaluate and compare the efficacy and safety of topical antifungals used in the treatment of dermatomycosis, we performed a comprehensive search for randomized controlled trials (RCTs) in the following databases: Medline, Cochrane Central Register of Controlled Trials, EMBASE, Lilacs and International Pharmaceutical Abstracts, we identified studies that compared the use of topical antifungals with other antifungals or with placebo published up to July 2010 in English, Spanish or Portuguese. The quality of reporting was assessed according to the Jadad scale; only studies with a score of 3 or more were included. The outcomes evaluated were mycological cure at the end of treatment, sustained cure, occurrence of adverse events and tolerability, including withdrawals due to adverse events. A total of 104 RCTs satisfied the inclusion criteria, containing a total of 135 comparisons, with 55 out of 120 possible comparisons among the 16 drugs evaluated. Pooled data on efficacy showed that all the antifungals were better than placebo. There were no significant differences among antifungal classes. No differences were found in safety or tolerability in any direct comparison. Sensitivity analysis indicated the robustness of the findings. Our results indicate the clear superiority of topical antifungals over placebo but that there is no consistent difference among classes. Mixed treatment comparisons are necessary to rank antifungals, as direct comparisons among many of them are lacking.

Dermatomycosis are fungal infections that are widespread throughout the world, and they are an important cause of morbidity.^{1–3} Dermatophytosis, caused by different species of dermatophytes, is one of the more common infections. However, commensal yeasts such as *Malassezia furfur* and *Candida* spp., are also important causative agents of dermatomycosis.⁴

Diagnosis depends on a combination of clinical and laboratory data, including physical examination of the lesions and microscopic visualization of microorganisms in potassium hydroxide and their growth in culture. Treatment consists of the use of topical or oral antifungals or a combination of these, depending on the site, extent of infection and the causative organism.^{5–7}

In most episodes of infection, management with topical antifungals is effective; these are available over the counter in most places and are divided in two main classes: azoles and allylamines. These are cheaper than oral formulations and cause minimal adverse effects.^{8,9}

Only two quantitative systematic reviews relating to the treatment of dermatomycosis with topical antifungals have been published to date, both limited to the management of tinea pedis.^{8,10} For this reason, we performed a comprehensive systematic review and meta-analysis to determine the efficacy and safety of topical antifungals in the treatment of any dermatomycosis.

Methods

Search strategy and selection criteria

A systematic review was conducted according to the Cochrane Collaboration guidelines.¹¹ We performed a comprehensive search for randomized controlled trials (RCTs) using as descriptors the names of the antifungals of interest (amorolfine, bifonazole, butenafine, ciclopiroxolamine, clotrimazole, econazole, fenticonazole, flutrimazole, isoconazole, ketoconazole, miconazole, naftifine, oxiconazole, sertaconazole, terbina-

fine and tioconazole) combined with the terms 'random', 'controlled trial' and 'controlled clinical trial'. The terms 'vaginal', 'vulvovaginal' and 'oropharyngeal' were included in the search preceded by the Boolean operator 'NOT', so as to include only studies assessing the topical use of interventions. The search strategies used for each database are described in Appendix S1 (see Supporting information).

The following databases were included in the search: Medline, Cochrane Central Register of Controlled Trials, EMBASE, Lilacs and the International Pharmaceutical Abstracts. Studies published up to July 2010 in English, Spanish or Portuguese, that compared the use of topical antifungals in the treatment of dermatomycosis with the use of other antifungals or with placebo were included.

Two reviewers (I.R. and A.S.) independently selected studies based initially on their title and abstract. Only RCTs that evaluated the treatment of any dermatomycosis, including cutaneous candidiasis and that of tinea pedis, corporis, cruris and versicolor were included. We excluded onychomycosis from the study as its treatment duration is much longer when compared with other dermatomycosis. Tinea capitis was also excluded as it is not treated with topical antifungals.

Only trials that evaluated mycological cure based on microscopy and/or culture to establish the presence of fungal species were included. The intervention consisted of any topical antifungal regardless of pharmaceutical dosage form, concentration, drug regimen, duration of therapy or pharmacological class. We excluded studies that used a crossover methodology.

Data extraction and assessment of trial quality

Data extraction was performed by two reviewers (I.R. and A.S.) independently and included study design, baseline characteristics, health intervention, drug regimen, efficacy, safety and tolerability. Any discrepancies in data collection were resolved through consensus and a third reviewer (C.J.C.) was consulted when necessary.

The efficacy outcomes evaluated were mycological cure at the end of treatment, defined as cure obtained until 7 days following the end of treatment, and sustained cure, defined as cure maintained for at least 14 days after the conclusion of treatment. When more than one sustained cure result was described, we prioritized those for which the time interval of monitoring was greater. For both outcomes, the cure had to be confirmed by culture and/or microscopy. The clinical cure rate was not evaluated as this is a subjective outcome. Trials that only showed this rate were excluded.

The safety outcomes evaluated were the occurrence of adverse events and tolerability, including withdrawals due to adverse events.

The methodological quality of each RCT included was evaluated using a method assessment tool published by Jadad *et al.*,¹² described in Appendix S2 (see Supporting information). Only studies with a score of 3 or more were included. To assess the risk of bias in the included studies, we used the Cochrane Collaboration tool, an evaluation in which critical

assessments are separated into different domains in order to consider the following types of bias: selection, performance, detection, attrition, reporting and other biases.¹¹

Statistical analysis

For the efficacy outcome, we used the random-effects model and inverse variance method to pool the odds ratios (ORs) from individual studies. For the safety and tolerability outcomes, we employed the statistical method of Peto, which is appropriate when the number of observed events is small and similar in both experimental and control groups,¹¹ as expected when evaluating adverse events associated with topical therapy with antifungal agents. The OR and the corresponding 95% confidence interval (CI) were calculated and pooled using a fixed-effects model.

The heterogeneity of treatment effects was evaluated by the inconsistency index (I^2). Values of I^2 lower than 25% were considered to show low heterogeneity, whereas values between 25 and 50% were considered moderate to high. In meta-analyses with $I^2 > 50%$ (high heterogeneity), sensitivity analyses were performed to determine whether the study characteristics and statistical methods could have influenced the results. A sensitivity analysis was conducted by the hypothetical removal of each study from the meta-analysis and evaluation of its impact on the overall result. Moreover, the studies were pooled into subgroups based on the dermatomycosis evaluated. All analyses were carried out using Review Manager v. 5.1 statistical software (<http://ims.cochrane.org/revman/download>).

Results

Systematic review of the literature

Of the 4443 articles initially identified, 4183 were excluded after title/abstract review and another 59 after full-text analysis because they did not meet the inclusion criteria. In addition, 97 articles were excluded for being duplicates. Thus, 104 RCTs satisfied the inclusion criteria and were included in the meta-analysis. As some articles reported more than one study, we included a total of 135 studies. Of these, 73 compared antifungals with placebo and 62 compared antifungals with each other (Fig. 3). The studies included 15 795 participants, of which 66% were men, and the weighted mean age was 38.4 years. We found 55 of the 120 possible comparisons among the 16 drugs evaluated (Fig. 2). For details about the characteristics of the studies, see Appendix S3 (see Supporting information).

Methodological quality

Only studies of medium or high quality according to the Jadad scale¹² were included in the meta-analysis, with an average score of 3.6. Of the 59 trials excluded after full review, 35 did not meet the quality criteria proposed by Jadad *et al.*¹² Relevant information such as sequence generation and allocation

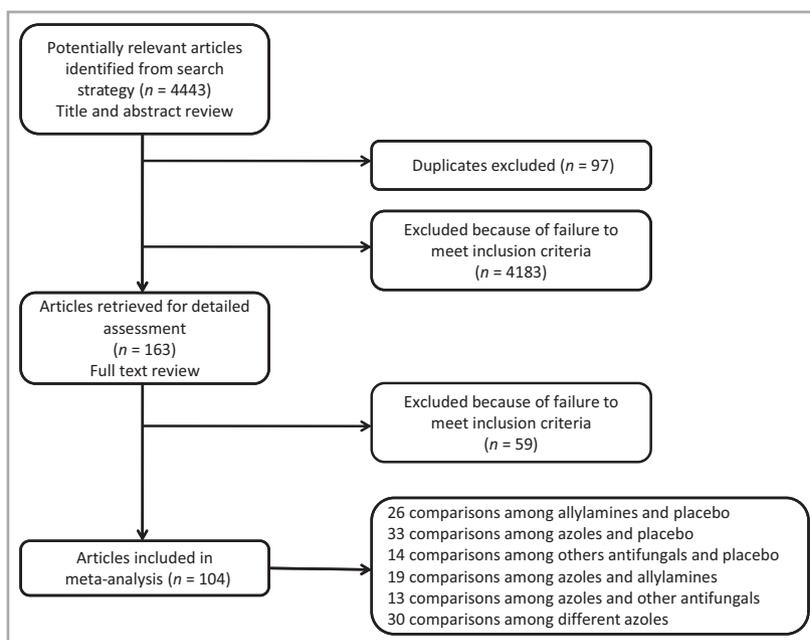


Fig 1. Flowchart of the selection of randomized controlled trials included in the systematic review.

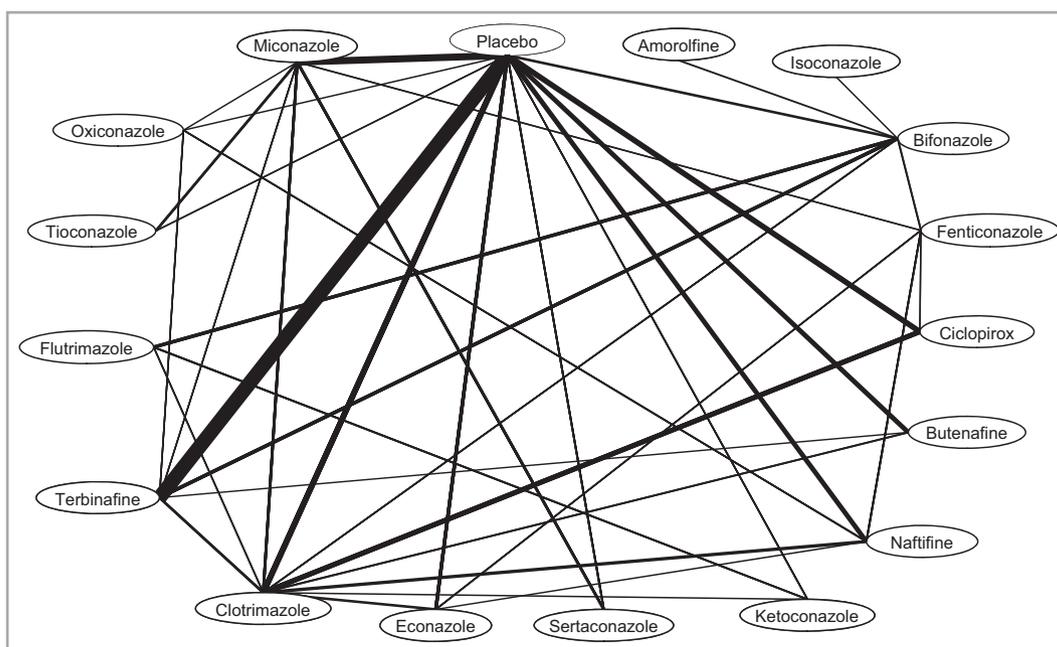


Fig 2. Network of eligible comparisons between topical antifungals and placebo and among them for the treatment of dermatomycosis. This network represents all relationships for both efficacy outcomes evaluated. The width of the line connecting two elements is proportional to the number of comparisons between them. Through the network, it is clear that there is an absence of several head to head comparisons, with only 55 found among the 120 possible comparisons.

concealment were insufficient in the majority of the studies included. However, the baseline characteristics of patients included in each group were homogeneous, indicating that the absence of information about the allocation should not have affected the confidence of the results obtained. Blinding was reported as satisfactory in almost 53% of the studies included, although we believe that the mycological cure outcome was not likely to be influenced by lack of blinding.

Efficacy

Azoles vs. placebo

Twenty-eight studies, comprising a total of 3044 patients, compared the azoles bifonazole, clotrimazole, econazole, ketoconazole, miconazole, oxiconazole, sertaconazole and tioconazole with placebo. The concentration of these drugs was

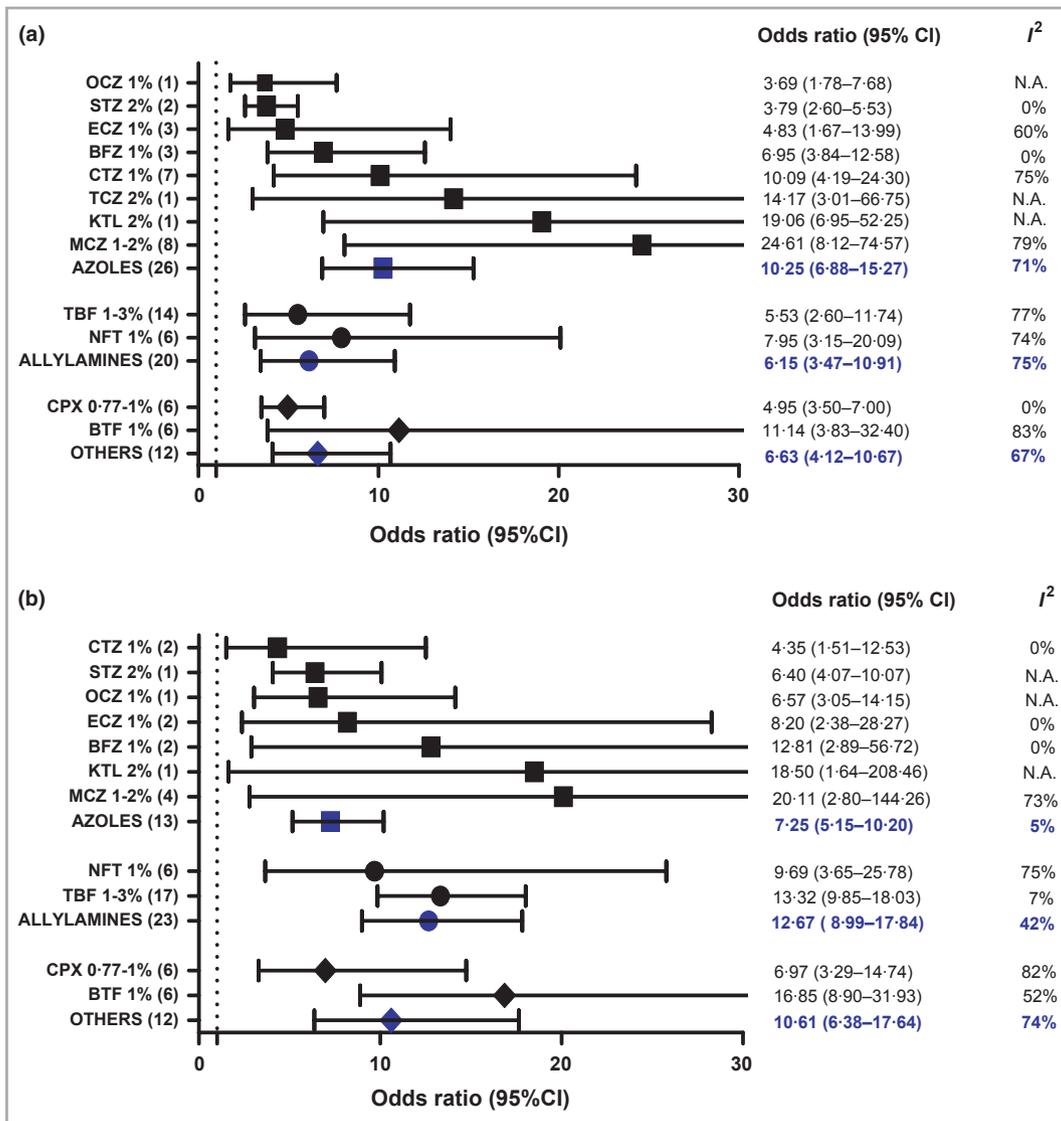


Fig 3. Forest plots comparing the efficacy of antifungals vs. placebo for mycological cure at the end of treatment (a) and sustained cure (b) outcomes. The symbols represent the measure of effect (odds ratio) obtained with each drug, the horizontal line indicating the 95% confidence interval (CI) found. The concentrations of drugs reported in the randomized controlled trials are described. The number of studies found for each drug is indicated in parentheses. I², inconsistency index, representing the degree of heterogeneity among the studies included in the meta-analysis; N.A., I² is not applicable, as only one study for the drug in question was found; BFZ, bifonazole; BTF, butenafine; CPX, ciclopiroxolamine; CTZ, clotrimazole; ECZ, econazole; KTL, ketoconazole; MCZ, miconazole; NFT, naftifine; OCZ, oxiconazole; STZ, sertaconazole; TBF, terbinafine; TCZ, tioconazole.

1% or 2% and they were used for 2–6 weeks. In terms of mycological cure at the end of treatment, meta-analysis of data from 26 RCTs estimated the pooled OR as 10.25 (95% CI 6.88–15.27), favouring azoles. There was a high degree of heterogeneity (I² = 71%) among the studies selected for the meta-analysis. Sensitivity analyses were carried out by pooling the studies into subgroups based on the dermatomycosis evaluated. When the heterogeneity remained high, a hypothetical removal of the studies responsible for that heterogeneity was performed. By the sensitivity analyses performed, the I² decreased, becoming low or moderate, and the OR value remained statistically significant, favouring treatment with azoles.

Interpolation of the data from 13 RCTs comparing the sustained cure rate among azoles and placebo gave an OR of 7.25 (95% CI 5.15–10.20). There was a low degree of heterogeneity (I² = 5%) among the studies selected, indicating consistency in the results. The follow-up period lasted from 2 to 6 weeks after the cessation of treatment.

Allylamines vs. placebo

Naftifine and terbinafine were evaluated in 25 placebo-controlled trials, which included 2001 participants. The concentration of these drugs was 1% or 3% and they were used for 1–4 weeks. In terms of mycological cure at the end of

treatment, meta-analysis of data from 20 RCTs estimated the pooled OR as 6.15 (95% CI 3.47–10.91), favouring allylamines. The interpolated results of the individual studies showed considerable variation between studies ($I^2 = 75\%$). Sensitivity analyses were carried out by pooling the studies into subgroups based on the dermatomycosis evaluated. When the heterogeneity remained high, a hypothetical removal of the studies responsible for that heterogeneity was performed. By the sensitivity analyses performed, the I^2 decreased, becoming low or moderate, and the OR value remained statistically significant, favouring the treatment with allylamines.

Of the 25 RCTs found, 23 showed a sustained cure. Combined data from these studies showed a statistically significant difference favouring allylamines (OR 12.67, 95% CI 8.99–17.84). The I^2 value of 42% reflects the moderate heterogeneity between studies. The follow-up period lasted from 2 to 44 weeks after the cessation of treatment.

Other antifungals vs. placebo

Fourteen RCTs compared other antifungals with placebo. The 12 placebo-controlled trials of butenafine and ciclopiroxolamine yielded a pooled OR of 6.63 (95% CI 4.12–10.67) for mycological cure at the end of treatment. The concentration of these drugs was 0.77% or 1% and they were used for 1–4 weeks. There was a high degree of heterogeneity ($I^2 = 67\%$) among the selected studies.

The results of 12 RCTs were interpolated for the sustained cure outcome, giving an OR of 10.61 (95% CI 6.38–17.64), in favour of the other antifungals. Again, there was a high degree of heterogeneity ($I^2 = 74\%$) among the studies. The follow-up period lasted from 2 to 44 weeks after the cessation of treatment. The results of the studies on topical antifungals vs. placebo are presented in Figure 3.

Azoles vs. allylamines

The meta-analysis included 17 RCTs, with 1781 participants, comparing the allylamines, naftifine and terbinafine (1% or 2%), used for 1–6 weeks with the azoles, bifonazole, clotrimazole, econazole, fenticonazole, miconazole and oxiconazole (1% or 2%), used for 2–6 weeks. In terms of mycological cure at the end of treatment, 15 trials showed a small and not statistically significant difference in favour of allylamines (0.78, 95% CI 0.48–1.24). The same efficacy rate (81%) was obtained for both classes. There was moderate heterogeneity in the results of the individual trials ($I^2 = 45\%$), indicating that high-quality evidence was obtained.

Although the meta-analysis of 15 trials comparing the sustained cure obtained following the use of azoles and allylamines showed a significant result in favour of allylamines (0.55, 95% CI 0.33–0.89), there was evidence of inconsistency, due to the high heterogeneity among trials ($I^2 = 60\%$). This inconsistency may be attributed to one study in particular (Ablon *et al.* 1999).¹³ The hypothetical removal of this study decreased the I^2 to 50% and changed the results of the

analysis, such that there was no difference in efficacy among classes.

Azoles vs. other antifungals

We identified 11 studies, containing a total of 952 patients, comparing the azoles, bifonazole, clotrimazole and fenticonazole (1% or 2%), with antifungals other than allylamines, both used for 2–5 weeks. In terms of mycological cure at the end of treatment, 10 RCTs produced a pooled OR of 0.64 (95% CI 0.40–1.01), favouring the other antifungals, although the difference was not significant. There was consistency among the studies selected ($I^2 = 7\%$).

In terms of sustained cure, the combined data from 10 RCTs showed an OR of 0.79 (95% CI 0.50–1.26), again not reaching statistical significance. The I^2 was 0%.

For details about the sensitivity analysis performed for each meta-analysis with an $I^2 > 50\%$, see Appendix S4 (see Supporting information).

Safety and tolerability

No differences were found in safety or tolerability in all direct comparisons made between antifungals and placebo or among antifungals. Table 1 presents the results obtained regarding comparisons among antifungals and placebo for safety outcome.

As expected, few serious adverse events were reported with the use of any topical antifungal. The adverse events most commonly reported by patients were burning, stinging and itching, all confined to the site of application.

Discussion

Our systematic review and meta-analysis indicate that azoles, allylamines and other antifungals, such as butenafine and ciclopiroxolamine, are all efficacious in the management of any dermatomycosis when compared with placebo. The two other published systematic reviews with meta-analysis performed by Hart *et al.* (1999) and Crawford and Hollis (2007) found similar results for the management of tinea pedis.^{8,10}

The duration of treatment with azoles lasted from 2 to 6 weeks and the efficacy of this class seemed to improve over time. Miconazole showed the best success rate for both efficacy outcomes evaluated. Short treatments in the range of 1–2 weeks with naftifine and terbinafine demonstrated the superiority of allylamines in relation to placebo for both outcomes.

Given the strength of evidence obtained from the large number of studies ($n = 135$) and participants ($n = 15\,795$), placebo-controlled trials evaluating topical antifungals in the treatment of dermatomycosis can no longer be justified, and only clinical trials comparing two active treatments are recommended. In 2008, Crawford *et al.* published a paper confirming that there is enough evidence to recommend the abandonment of vehicle-controlled trials assessing topical treatments for athlete's foot.¹⁴

Table 1 Antifungals vs. placebo: safety

Antifungal	Number of studies	Number of participants	Adverse events in intervention (%)	Adverse events in control (%)	Odds ratio (95% CI)	P-value	I ² (%)
Bifonazole	3	255	1	2	0.30 (0.03–3.24)	0.32	0
Ketoconazole	2	423	5	3	1.48 (0.51–4.28)	0.47	NE ^a
Clotrimazole	6	1529	3	3	0.91 (0.50–1.67)	0.77	14
Econazole	4	291	3	1	1.51 (0.29–7.98)	0.62	0
Miconazole	7	456	0	0	NE ^b	NE ^b	NE ^a
Oxiconazole	1	266	5	9	0.48 (0.16–1.38)	0.17	NA ^c
Sertaconazole	2	988	8	10	0.78 (0.49–1.23)	0.28	0
Tioconazole	1	58	3	0	4.60 (0.07–284.25)	0.47	NA ^c
Azoles	24	4230	4	4	0.85 (0.62–1.17)	0.31	0
Naftifine	6	526	9	15	0.58 (0.34–1.02)	0.06	0
Terbinafine	15	1204	5	6	0.72 (0.41–1.25)	0.24	0
Allylamines	21	1730	6	9	0.65 (0.44–0.96)	0.03	0
Butenafine	6	882	1	2	0.50 (0.16–1.56)	0.23	29
Ciclopirox	6	799	11	4	0.65 (0.26–1.63)	0.35	0
Others	12	1681	6	3	0.58 (0.28–1.20)	0.14	0

^aNE indicates heterogeneity could not be estimated, as, in most studies included, the number of adverse events found in both treatment and control groups was zero; ^bit was not possible to calculate the odds ratio for miconazole, as the number of adverse events found in both treatment and control groups was zero in all studies included; ^cNA indicates I² is not applicable, because only one study was found for the compared pairs.

Crawford and Hollis reported that direct comparisons of allylamines and azoles showed allylamines to be more efficacious than azoles. This difference among classes was detected in outcomes assessed 6 weeks after treatment began and appeared to remain over longer periods.⁸ A result favouring the use of allylamines was also obtained by Hart *et al.*, although some language bias was detected. Thus eight studies reported in English favoured allylamines, while four foreign language reports showed no difference among azoles and allylamines.¹⁰

Our meta-analysis of RCTs comparing the mycological cure rate obtained with azoles and allylamines show no significant difference among classes, the same efficacy rate (81%) being found for both. For the sustained cure outcome, however, allylamines were found to be superior to azoles, but the result was inconsistent, due to the high degree of heterogeneity (I² = 60%) among the selected studies. Following the sensitivity analysis and hypothetical removal from the meta-analysis of the study by Ablon *et al.*,¹³ the heterogeneity became moderate and the difference among classes became nonsignificant. This study was also excluded from the systematic review conducted by Hart *et al.*,¹⁰ because of an inadequate period of treatment with azoles.

We detected no difference in efficacy among azoles and other antifungals, such as amorolfine, butenafine and ciclopiroxolamine. However, although not significant, the outcome of mycological cure favoured the 'nonallylamine' antifungals. The difference was less obvious when considering sustained cure as the outcome.

No differences were found in the safety or tolerability with any of the antifungal classes. All treatments are generally well tolerated; most of the symptoms reported by patients were mild to moderate and limited to the site of application. It is

important to mention that the number of adverse events mentioned in selected studies may be overestimated or underestimated, as the adverse events associated with the use of topical antifungals are also signs and symptoms of the fungal disease, and it is therefore difficult to determine whether these reactions were due to disease or caused by the drug.

Allylamines are considered safe and tolerable. However, the efficacy results showed no conclusive evidence of their superiority compared with azoles. In addition, allylamine treatment is more expensive. As a cost-effective strategy, azoles are recommended as the first-line therapy, followed by allylamines if these are not effective. However, to confirm this recommendation, pharmacoeconomic studies are required to evaluate the real cost-effectiveness ratio of each therapeutic option.¹⁵

Our study has some limitations. Due to the difficulty of interpolation, the results of the studies were not pooled in the meta-analysis according to the dermatomycosis evaluated. The difficulty of subgroup formation was attributed to the scarcity of studies evaluating the same drug, or antifungals belonging to the same pharmacological class, to treat a specific dermatomycosis. In addition, several studies did not restrict their assessment to a single form of dermatomycosis, as the treatment is similar for all.

Several meta-analysis showed high values of I² (> 50%), indicating inconsistency in the results of the included studies. However, after conducting sensitivity analysis, involving the hypothetical removal of the studies considered responsible for the high heterogeneity reported, and pooling the studies into subgroups based on the dermatomycosis evaluated, the results remained similar to those found prior to performing such analysis, maintaining their statistical significance. This demonstrates that the wide range of effects in the data collected from

many primary studies did not affect the outcomes considered in this study. These findings were similar to those reported in the systematic review conducted by Crawford and Hollis, whose meta-analysis also showed high heterogeneity among the studies selected.⁸

Furthermore, owing to the absence of a sufficient number of good-quality clinical trials that directly compared the antifungal drugs of interest, only 55 comparisons among the 120 possible were found, making the performance of mixed-treatment comparisons necessary in order to establish indirect comparisons among those treatment pairs with common comparators. In the presence of direct and indirect comparisons, these can be interpolated, giving mixed results.^{16,17}

In conclusion, our results showed consistent evidence that all topical antifungals are better than placebo. No consistent differences in efficacy were found among classes. Head-to-head clinical trials comparing azoles with allylamines should be conducted to determine the real difference in efficacy among these classes. No differences were found in safety or tolerability in any direct comparisons, allowing us to conclude that topical therapy with antifungal agents is safe and tolerable.

Due to the absence of a sufficient number of direct comparisons among the antifungals, mixed-treatment comparisons were necessary. Finally, given the difference in cost among the antifungals, pharmacoeconomic analysis is required to determine the most cost-effective therapeutic strategy for each condition.

What's already known about this topic?

- Dermatomycosis are widespread and often the first-line management strategy is the use of topical antifungals.
- Azoles, allylamines, butenafine, ciclopiroxolamine, tolciclate and tolnaftate are all efficacious relative to placebo in the management of tinea pedis.
- Direct comparisons of allylamines vs. azoles in the treatment of tinea pedis show allylamines generally to be more efficacious than azoles.

What does this study add?

- All topical antifungals are better than placebo in the treatment of any dermatomycosis.
- No statistical difference in efficacy was detected among classes (azoles, allylamines and others).
- No differences were found in safety and tolerability in all direct comparisons established between antifungals and placebo and among them.

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Supporting information

Additional supporting information may be found in the online version of this article.

Appendix S1 Search strategies for each electronic database.

Appendix S2 Assessment of methodological quality according to Jadad's criteria.

Appendix S3 Characteristics of randomized controlled trials included in meta-analysis.

Appendix S4 (a) Sensitivity analysis for meta-analysis with $I^2 > 50\%$ comparing azoles or allylamines with placebo for mycological cure at the end of treatment outcome. (b) Sensitivity analysis for meta-analysis with $I^2 > 50\%$ comparing other antifungals with placebo for both efficacy outcomes. (c) Sensitivity analysis for meta-analysis with $I^2 > 50\%$ comparing azoles with allylamines for sustained cure outcome.

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