

Primary Literature

- i. Suschka S et al. Clinical comparison of the efficacy and tolerability of once daily Canesten with twice daily Nizoral (clotrimazole 1% cream vs. ketoconazole 2% cream) during a 28-day topical treatment of interdigital tinea pedis. *Mycoses*. 2002; 45: 91 – 96.

Study Objective

The author's main objective was to determine the efficacy and tolerability of 1% clotrimazole cream, applied once a day, compared to 2% ketoconazole cream, applied twice a day, for patients with interdigital tinea pedis.

Methods

Design: Randomized comparison trial.

Allocation: Patients were recruited and randomized evenly into the two treatment arms.

Blinding: Double-blinded

Follow-up period: The rating of signs and symptoms, the microscopy, the fungal cultures and the recording of adverse events were performed after 14, 28 and 56 days. The duration of treatment with either of the creams was for 28 days.

Setting: Not defined

Participants: A total of 108 patients were enrolled, when the clinical signs and symptoms of tinea pedis were confirmed by a KOH-microscopy. The two groups were similar in patient characteristics (age, weight, gender, height). Main exclusion criteria were if the tinea pedis was the 'moccasin' or plantar type, if the tinea pedis was with concomitant onychomycosis or if any concomitant therapy with local systemic corticosteroids or antibiotics had been started.

Intervention: Clotrimazole 1% topical cream applied once daily compared to ketoconazole 2% cream applied twice daily. To maintain double-blinded principle, a placebo cream was given to the clotrimazole group for their second application.

Outcomes: The primary outcomes in this trial were the efficacy (cure or improvement) and the tolerability of the creams after 28 days of therapy.

Patient follow-up: 108 patients were enrolled; however, only 100 patients' data were included in the efficacy evaluation and 106 patients' data were included in the tolerability evaluation. Patient exclusion was due to either non-appearance or missing data after 28 days.

Main Results

After 28 days of therapy, the number of patients with a cure or improvement in symptoms was 62.0% for clotrimazole and 64% for ketoconazole. The results at 56 days were 66% and 60% for clotrimazole and ketoconazole, respectively. Mycological response revealed a negative culture and microscopy in 53.1% vs. 52.1% of the patients after 14 days for clotrimazole and ketoconazole, respectively. After 28 days, the culture was negative in 76.0% vs. 79.2% for clotrimazole and ketoconazole, respectively. Finally, after 56 days, clotrimazole had a negative culture in 83.7% of patients, compared to 76.9% for ketoconazole, indicating that clotrimazole may have a better long-term efficacy. The percentage of patients who had been cured with clotrimazole after 28 days and had not experienced another infection was 38%, compared with 30% of those who had been treated with ketoconazole. The remission and improvement rates of the overall signs and symptoms saw a benefit for clotrimazole; during observation, after 14 days, the two agents were similar with 94.0% improvement. After 28 days, the improvement was 98.0% vs. 94.0% and it was 96.0% vs. 82.0% after 56 days, in favour of clotrimazole.

With regard to safety, the incidence of adverse events was low and comparable between the two treatments. However, concerning the remission and improvement rates of signs and symptoms, a superiority of clotrimazole could be made for pruritus (97.8% vs. 89.6%), burning/stinging (97.5% vs. 89.4%) and vesiculation (95.8% vs. 88.0%) after 28 days.

Conclusions

Clotrimazole and ketoconazole were shown to be equally effective, safe and well-tolerated for the treatment of interdigital tinea pedis, with some advantage in relapse rates with clotrimazole. There was also a clear advantage for patients treated with clotrimazole; it was a once daily application and compliance to the regimen is important. To cure all signs and symptoms, a 4-week treatment period is recommended to prevent against relapse.

Comments

In this study, clotrimazole was shown to be as effective and as safe as ketoconazole, but because its regimen was once a day as compared to twice a day, it will be an easier treatment to adhere to for patients.

Definite strengths to this article were that it was double-blinded, the patients were randomized and the randomization was concealed until the end of the study. Although ketoconazole was a twice a day application, the clotrimazole group had a twice a day regimen as well, with a placebo cream as their 'evening' dose. In addition to this, the cream preparations were identical in terms of consistency, smell, colour and shape. Patient characteristics were almost identical in both groups: same numbers of males and females, similar ages and similar weight and height. All patients had a clinical diagnosis of a fungal infection (through KOH microscopy and culture) and signs and symptoms of a fungal infection of the foot.

Starting with 108 patients, with 54 patients randomized to each arm, follow up for efficacy included 100 patients and for safety, 106 patients. There was a drop-out rate of 7% in

the efficacy results and a 2% drop out rate for safety, which are low rates. For the patients who were not included in the final analysis, their data went missing after 28 days or the patient failed to return for follow up. Follow up was done at the mid-point of the study, day 14, at end of the treatment duration, at day 28, and at day 56. The trial was not stopped early and the patients were evaluated in the groups they were randomized in.

The study size was fairly small, but the determination of efficacy was precise; the authors were diligent in obtaining a negative culture and microscopy analysis before concluding that a cure had occurred. Both clotrimazole and ketoconazole had similar cure rates after 28 days, with clotrimazole having slightly higher remission rates at 56 days. However, this study was not placebo controlled, and therefore the efficacy of the two active ingredients could not truly be reported.

- ii. Ongley R. Efficacy of topical miconazole in the treatment of tinea pedis. *CMAJ*. 1978; 119: 353 – 354.

Study Objective

The author's main objective was to determine the efficacy of 2% miconazole cream in the treatment of bilateral tinea pedis, as compared to 1% tolnaftate cream and placebo.

Methods

Design: Placebo-controlled, double-blind comparison trial

Allocation: The preparations were assigned numerically in coded tubes, and patients were randomized equally to each of the tubes (each foot was treated differently; 20 feet per tube)

Blinding: Double-blind

Follow-up period: Clinical assessment was recorded on days 14 and 28 during therapy, and at 6 weeks after therapy. Mycologic examination was performed at the completion of therapy and at the follow-up visit

Setting: An extended care hospital

Participants: 30 males who were patients at the hospital were enrolled in this study; these patients had bilateral, chronic, non-blistering tinea pedis, proven by examination of scales in KOH and by culture. None had received therapy for tinea pedis in the preceding 6 months.

Intervention: 2% Miconazole cream compared to 1% tolnaftate cream and placebo, each applied twice daily for 28 days.

Outcomes: The primary outcomes in this trial were the efficacy (clinical and mycologic improvement) of the creams after 28 days of therapy

Patient follow-up: All 30 patients were followed up at 6 weeks after the start of therapy

Main Results

At day 14 of therapy, treatment with tolnaftate had the highest clinical improvement numbers, 20 out of 20 treated feet, compared to 8 in the placebo group and 19 in the miconazole arm. When therapy was completed, clinical and mycological examination showed that 19 out of 20 feet in the miconazole arm were cured, as compared to 10 in the placebo group and 15 in the tolnaftate group.

At the six week follow up, all of the patients who had a cure at the 4 week mark with miconazole had remained free of infection, whereas only 2 in the placebo group and 13 in the tolnaftate group remained free of infection.

Conclusions

Miconazole proves to be a useful agent in the treatment of tinea pedis, as it has an exceptional cure rate and a low relapse rate.

Comments

The authors in this study wanted to compare the efficacy of miconazole to tolnaftate and then, compare both agents to placebo. This study concluded that miconazole has an exceptional cure rate and a lower relapse rate as compared to tolnaftate and placebo, making the azole anti-fungal a superior option for the athlete's foot.

Strengths that this study had were the fact that it was double-blinded and that patients were randomized to receive treatment. The patient population, however, was rather small; all participants were males, between the ages of 42 – 93, and aside from the fact that all had bilateral tinea pedis, no other patient demographic information was given. Since both feet were infected, the authors could use each foot as a treatment site, making the sample size doubled. The creams were supplied in identical tubes, with numbers printed as the label; no information was given pertaining to the appearance of the creams.

Follow up occurred on day 14 and day 28 of therapy and then, at 6 weeks after initiating treatment. No patients dropped out in this study and mycological examination was performed to assess cure and remission. The trial was not stopped early. Although only 30 males were included, using each foot as a treatment site allowed the treatment effect to be on a larger scale. For the patients who got two active creams for their feet, the effects of inter-patient variability were non-existent for the anti-fungals and it gave a clearer comparison. Each foot was analyzed with respect to all the feet in the same treatment arm. The presence of cure in the placebo arm was most likely due to the fact that the placebo cream contained ethylene glycol, which has some antimicrobial properties.

The sample size was small and the paper is dated, however, the study occurred in a hospital with qualified personnel administering the creams and results clearly showed favour for miconazole. It was the treatment that maintained its cure rate in the feet it had been used in. This paper also gives evidence for the placement of these two agents in the treatment hierarchy for athlete's foot; if tolnaftate does not work, miconazole would be an option. Alternatively, miconazole could be used as the first-line agent.

Secondary Literature

- i. Hart R et al. Systematic review of topical treatments for fungal infections of the skin and nails of the feet. *BMJ* 1999; 319: 79 – 82.

Study objectives

The authors' objectives in this systematic review were to determine the evidence for the efficacy and cost effectiveness of the current topical treatments for superficial fungal infections of the feet (tinea pedis).

Scope

72 randomized control trials were included in this review, 70 for skin infections and 2 for nail infections. For skin infections, 31 trials compared a single active treatment with placebo where 27 trials compared two active treatments. Twelve trials compared more than two treatments within the same trial.

In the skin infection trials, azoles (bifonazole, clotrimazole, and miconazole) were assessed in 46 trials, allylamines (naftifine and terbinafine) in 27, tolnaftate in five, and undecenoic acid in four. Patients were followed for 12 weeks for cure of infection in all but one trial. For the two nail infections, amorolfine 5% nail lacquer was assessed for 6 weeks and clotrimazole solution and tea tree oil were assessed for 6 months.

The mean number of quality criteria met by the 72 included trials (two for nail infections) was 6.3 out of 12. Only 19 trials reported the method of randomization and blinded outcome assessment was reported in only 10 trials.

Methods

How studies were identified: Authors searched Medline, Embase, CINAHL, BIDS, the Cochrane Controlled Trials Register, CAB-Health, Healthstar, DARE, the NHS Economic Evaluation Database, and Econlit up to December 1997. By hand, they consulted *Foot*, the *Journal of British Podiatric Medicine*, and the *British Journal of Podiatric Medicine and Surgery*. In addition to this, they searched the bibliographies of their review papers, the details of the Cochrane Skin Group's recent search of the *British Journal of Dermatology*, and they contacted international pharmaceutical companies and all schools of podiatry in the United Kingdom.

Number and type of trials included: All randomized control trials were considered for this review. Studies focusing on skin infections had to have used microscopy and culture to determine the presence of dermatophytes. For nail infections, the determination of dermatophytes had to be done by culture in order to be included.

Although no language restrictions were applied, trials that were excluded were those covering sites other than the foot (including trials that looked at both hand and foot) and

where data related specifically to the foot could not be extracted.

Other relevant information: Both reviewers independently summarised the trials included, and they appraised their quality of reporting using a structured data extraction tool of 12 quality criteria.

Main results

For azoles versus placebo, the pooled relative risk of failure to cure superficial foot infections was 0.54. Alkylamines did better against placebo with a relative risk of failure to cure of 0.30. Compared against one another, azoles and alkylamines, efficacy was slightly higher in the alkylamines. Other topical anti-fungals for skin infections included undecenoic acid and tolnaftate, which had pooled relative risk of failure to cure of 0.28 and 0.46, respectively. In nail infections, amorolfine had a cure rate of approximately 90% after 6 weeks, where clotrimazole and teat tree oil had cure rates of only 10% after 6 months. Unfortunately, there was little evidence to assess tolnaftate against placebo or to compare azoles, undecenoic acid, and tolnaftate with each other.

For cost effectiveness, undecenoic acid had the cheaper average cost per cure compared to the azoles when purchased over the counter. On the other hand, alkylamines cost approximately 2.5 times more than azoles, and the difference in cure rate between these two classes is small. Therefore, the most cost effective strategy is to treat first with an azole or undecenoic acid and to reserve alkylamines for treatment failures. For nail infections, little can be concluded about the role of the over-the-counter agents in curing infected toenails

Conclusions

Allylamines, azoles, and undecenoic acid were efficacious in placebo controlled trials. There are sufficient comparative trials to judge relative efficacy only between allylamines and azoles. Allylamines cure slightly more infections than azoles but are much more expensive. The most cost effective strategy is first to treat with azoles or undecenoic acid and to use allylamines only if that fails.

Comments

The objective of this systematic review was clearly stated at the beginning: the authors were looking for the rate of cure that was confirmed by microscopy and culture for patients with clinically diagnosed fungal infections of the skin and nails. They also looked at the cost-effectiveness of these anti-fungals by looking through an extensive collection of trials.

The search that the authors used was comprehensive; multiple search engines were utilized. In addition to this, they also search the bibliographies of the papers they found and also searched for unpublished and unlisted trials. While the inclusion and exclusion criteria were clearly stated, the MESH terms were not included in this paper. This review is also slightly out-dated, with information up to December 1997 and is also solely based in the United Kingdom. The authors who reviewed the information did so independently and they applied a structured

data extraction tool of 12 quality criteria. These criteria were: aims clearly defined, prior sample size calculation reported, inclusion and exclusion criteria defined, subjects blinded, method of randomisation defined, baseline comparability of groups reported (age, sex, and duration of complaint), interventions defined, outcome assessment blinded, compliance assessed, and trial analysed by intention to treat. However, the mean number of quality criteria met by the 72 included trials was 6.3 out of 12; this means that not all of the trials reviewed had reported their blinding or their method of randomization.

For the calculation of the rates of cure for the different anti-fungals, the authors used the data from the follow-up portions of the studies, with 95% confidence intervals. They also calculated the relative risk of failure for each of the agents with 95% confidence intervals. The economic analysis of the agents was also extensively done by the authors. Again, it was based on United Kingdom prices in the late nineties.

This review focused only randomized controlled trials that reported efficacy and on cost-effectiveness, not tolerability or relapse rates. While safety data was lacking in this review, the authors were able to find head-to-head studies between the azoles and allylamines. The length of the trials reviewed was adequate; 12 weeks was the duration for all trials except one, which had a 24-week duration.

Despite some flaws, the evidence was favourable for allylamines, azoles and undecenoic acid. Even though the allylamines had the best cure in the shortest amount of time, they were only slightly better than the cheaper azoles. This led the authors to conclude that the cheaper, over-the-counter azoles (and also undecenoic acid) should be used as first line and the allylamines for treatment failures.

- ii. Crawford F et al. Athlete's Foot and Fungally Infected Toenails. *BMJ*. 2001; 322: 288 – 289

Study objectives

To determine the effectiveness and safety concerns of different topical treatments for athlete's foot and fungally infected toenails.

Scope

The main outcomes for the studies that were reviewed were the rates of fungal eradication and the clinical improvement of symptoms.

For allylamines, the authors looked at a systemic review dealing with 12 randomized controlled trials for agents like terbinafine against placebo for 4 weeks. 1433 patients with athlete's foot were included in this trial and follow-up was 6 – 8 weeks. A smaller randomized control trial compared allylamines to one another for treatment efficacy in 60 patients.

For azoles, 17 randomized controlled trials containing 1259 patients with athlete's foot were looked at. The duration of treatment was for 4 weeks and all were against placebo. Follow up was 6 – 10 weeks. Another 12 randomized controlled trials compared the azoles to each other; 584 patients were treated for 3 – 4 weeks and follow up was from 3 – 10 weeks. Finally, azoles were also compared against the allylamines; 12 randomized controlled trials were found. 1487 patients with athlete's foot either had 4 weeks of azole therapy or 1 – 6 weeks of allylamine therapy.

Other topical anti-fungal medications, like undecenoic acid and tolnaftate, were also addressed in one systemic review. One randomized controlled trial compared ciclopiroxolamine to placebo in 144 patients with a fungal foot infection for 4 weeks, with a follow up in 6 weeks. Another randomized controlled trial looked at topical griseofulvin against placebo in 94 patients. Undecenoic acid against placebo was found in 4 randomized controlled trials; 223 patients were treated. Lastly, a four week therapy of tolnaftate versus placebo was in 3 randomized controlled trials that included 148 people and a follow up of 5 – 8 weeks.

In nail infections, only one systematic review was found, containing two randomized controlled trials with a total patient population of 153 people. These studies unfortunately did not report the blinding or the method of randomization.

Methods

How studies were identified: The authors searched Medline, Embase and the Cochrane Controlled Trials Register for systematic reviews and randomized control trials

Number and type of trials included: Systematic reviews, containing randomized controlled trials, and other randomized controlled trials were included. Papers that did not

use microscopy and culture for diagnosis or as an outcome measure were excluded, as were any studies that did not contain information pertaining to the feet.

Other relevant information: As noted by the authors, some of the trials looked at did not report patient demographic information or the method of randomization.

Main results

For allylamines, the larger systematic review found that they reduced the risk of treatment failure; the absolute risk reduction was 54% and the relative risk reduction was 67%. The number needed to treat was 2 after six weeks. The authors found that for comparing one allylamine to the other, there was no significant difference between naftifine and terbinafine (absolute risk of treatment failure was 75% and 81% respectively). Although this review did not report the frequency of side effects, the authors found that topical allylamines had few reports of severe local irritation.

The authors found that azoles also reduced the risk of treatment failure; the absolute risk reduction was 42% and the relative risk reduction was around 69%. The number needed to treat was 2. There were no significant differences between the azoles and as compared to the allylamines, azoles had similar efficacy. It was noted, however, that allylamines could be applied for a shorter duration (1 week) to get the same results as a 4 week azole treatment. Again, this review did not specify adverse effects, but the authors found reports of local irritation.

For the other topical agents, ciclopiroxolamine also reduced the risk of treatment failure; its absolute risk reduction was 48%, with a relative risk reduction of 52%. Griseofulvin had similar results with an absolute risk reduction of 47% and a relative risk reduction of 71%. Undecenoic acid also had similar numbers with an absolute risk reduction of 46% and a relative risk reduction of 59%. Finally, tolnaftate had an absolute risk reduction of 44% and a relative risk reduction of 63%. All of these agents had a number needed to treat of 2. These studies also did not report adverse events.

In nail infections, the systematic review had insufficient evidence to draw conclusions.

Conclusions

In short, the authors categorized the different topical agents in terms of their effectiveness. Those that entered the “Beneficial” category included the allylamines, the azoles, undecenoic acid and tolnaftate. Those that were placed in the “Likely to be Beneficial” category were topical ciclopiroxolamine and topical griseofulvin. Finally, for fungal nail infections, the topical treatments looked at were placed in the “Unknown Effectiveness” category, due to the authors’ inability to draw conclusions on the insufficient evidence presented.

Comments

Another systematic review based in the United Kingdom, the authors’ looked at the clinical cure rates and the resolution of symptoms at follow up for different anti-fungals.

Although a smaller scope of databases was searched, the trials were up to May 2000, making it more current. There was no mention of MESH terms or patient demographics. A similar quality review was done on the studies in this review and, like the previous systematic review, a 6.3 out of 12 was calculated. However, in this review, the criteria of that quality assessment were not included. In addition to this, tolerability was not included in this review, but the authors did mention that from a few trials, only mild, local irritation was reported with the topical products. This review did not give many details in terms of its methods and this is a huge drawback. However, the sample size from all the trials looked at was relatively large for most of the agents. In addition to this, the only included trial types were randomized controlled trials and systematic reviews, which are very reputable sources.

There were multiple trials that were assessed: most versus placebo, but the allylamines and azoles did have head-to-head studies. Numbers needed to treat were included in this study along with absolute risk reduction and 95% confidence intervals. In this review, there was more evidence for tolnaftate and its effectiveness for treating athlete's foot. Although allylamines had faster cure rates than azoles, there was a discrepancy in whether or not allylamines have a significant improvement in the rate of cure.

- iii. Crawford F and Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database of Systematic Reviews*. 2007; 3: 1 – 155.

Study objectives

The authors in this review aimed to determine and evaluate the literature for the effectiveness of topical treatments for fungal infections of the feet and nails.

Scope

All randomized controlled trials were included in this review. In terms of patient demographics, all men and women of any age were included in this study as long as they had a fungal infection of the feet or nails that was confirmed with microscopy and culture. In addition to this, only topical treatments were included, either compared to placebo, other treatments or no treatments. Primary outcomes that the authors looked for were the rate of treatment failure at follow up and the quality of life as measured by the cosmetic acceptability of the treatment product and the resolution of symptoms. Secondary outcomes were the measurement of recurrence and side effects.

67 trials relating to topical treatments of foot infections were included; 29 of those compared an active ingredient to placebo, 25 of those compared two active ingredients to one another and 13 of those compared more than two treatment regimens within the same study. While 11 studies were identified, only 6 studies relating to treating nail infections were reviewed; the main exclusion criteria for nail infection treatment were if the study included both nail and feet treatment.

With allylamines for foot infections, both naftifine and terbinafine were examined at multiple durations of therapy (1 – 6 weeks) against placebo, against an alternate dosing regimen of the same drug or against each other. Azoles were also examined against placebo, against an alternate dosing regimen and against others in the same class, but they were also compared to allylamines as well. Other topical anti-fungals included butenafine, ciclopiroxolamine, undecenoic acid, tea tree oil, tolciolate and tolnaftate.

Methods

How studies were identified: The authors searched the Cochrane Skin Group Specialised Register (using a search strategy mentioned in the appendix), the Cochrane Central Register of Controlled Trials (CENTRAL) (using a search strategy mentioned in the appendix), MEDLINE (OVID) (using a search strategy mentioned in the appendix) and EMBASE using the following keywords: athlete's foot, tinea pedis, topical treatment and onychomycosis.

Other databases that were searched using "athlete's foot" as the search term include Science Citation Index and Social Science Citation Index within BIDS, CAB-Health and Healthstar, the online versions of DARE, NHS Economic Evaluation Database, EconLit

and the Online ARC version of CINAHL. In addition, the bibliographies of the papers found were also searched.

Number and type of trials included: All randomized controlled trials dealing with the use of topical anti-fungal treatments were included in this review, as long as microscopy and culture were used for diagnosis and for treatment evaluation.

Other relevant information: Both reviewers independently summarised the trials included, and they appraised their quality of reporting

Main results

For the placebo-controlled trials, the pooled risk ratios (1 – relative risk reduction) of treatment failure were as followed: the allylamines and butenafine had a risk ratio of 0.33, the azoles and undecanoic acid had a similar risk ratio of 0.30 and 0.29, respectively, ciclopiroxolamine was slightly lower at 0.27 and tolnaftate had the lowest risk ratio of 0.19. In terms of tolnaftate, the authors felt that there simply was not enough data to fully assess this treatment option. When comparing allylamines and azoles to one another, the risk ratio of treatment failure was 0.63 in favour of allylamines.

The authors were diligent in separating the different studies with any of the anti-fungal therapies into treatment outcome categories: short-term outcomes (2 weeks), midterm outcomes (6 weeks) and some treatments even had long-term outcomes (12 weeks). They found that azoles were seen to improve over time; treatment outcomes measured at six weeks showed greater effectiveness than those taken at two weeks. In addition, in comparing allylamines for one week to azoles for four weeks, the allylamines had superior efficacy after six weeks; however, there was insufficient evidence to solidify this conclusion.

For other miscellaneous items, the authors found that using tea tree oil in the treatment of athlete's foot was not supported. Halprogen was more effective than tolnaftate and combinations of salicylic acid and nitrites were more effective than salicylic acid alone.

The evidence of efficacy for topical treatments for infections of the toenails was limited. Ciclopiroxolamine and butenafine had some evidence, even though there were poor cure rates (treatment failure rate of approximately 62% and 20% at 48 weeks, respectively) and therapy must be continued for at least one year. Amorolfine might be a more efficacious option, with a treatment failure rate of 6%, but the authors believe that more research is required in this field in general.

Conclusions

Placebo-controlled trials of allylamines and azoles for athlete's foot consistently produced much higher cure rates than placebo. These two options, along with butenafine, gave the best results. Allylamines cure slightly more infections than azoles, but there is not enough data to fully support this conclusion. Azoles may be more effective at curing athlete's foot than

tolnaftate, but are as effective as undecanoic acid. Further research into the effectiveness of antifungal agents for nail infections is required, as ciclopiroxolamine gave poor cure rates. Amorolfine and butenafine may be superior options.

Comments

The effectiveness and tolerability of topical anti-fungals along with recurrence rates were addressed in this lengthy systematic review for patients with clinically diagnosed fungal infections of the skin and nails. Data was pulled from an array of databases, with studies being included up to 2005. Search terms were included in this review and a fair amount of trials were assessed. Both authors independently summarised the trials and appraised their quality of reporting using a structured data extraction tool. The criteria for this quality assessment were as followed: the method of allocation, the identity of study participants who were blind, the loss to follow-up and exclusions, selective reporting and other forms of bias, such as whether the aims were clearly defined and whether compliance was assessed. Risk ratios were calculated with 95% confidence intervals and because of the heterogeneity between studies, the authors used random-effects models to pool the results.

The durations of the studies looked at were short-term (2 weeks), medium-term (6 weeks) and long term (12 weeks) to reflect clinically important timings. To further solidify their data, the authors also completed a sensitivity analysis to see if the results would change if the poor quality studies had been included. After reviewing the articles, the authors concluded that the randomized control trials were of relatively high quality with good follow-up.

Again, the allylamines were the most effective agent, followed by the azole class. There was not enough evidence to support the use of agents like tolnaftate and butenafine, but there was enough to rule out tea tree oil as a possible alternative agent for fungal infections. The duration of treatment regimens were also compared: different durations for allylamines showed no difference in efficacy, whereas clotrimazole in particular had a higher cure rate at 4 weeks rather than after 1 week.