

Oral Treatments for Toenail Onychomycosis

A Systematic Review

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Objective: To identify and synthesize the evidence for the efficacy of oral treatments for fungal infections of the toenails.

Design: Systematic review of randomized controlled trials.

Interventions: Oral treatments for dermatophyte infections of the toenails.

Main Outcome Measures: Cure confirmed by microscopy and culture results in patients with clinically diagnosed fungal infections. Data relating to the clinical cure rates were also extracted from the trials.

Results: A pooled analysis of 2 trials comparing mycological cure rates from continuous treatment with terbinafine (250 mg/d for 12 weeks) and continuous treatment with itraconazole (200 mg/d for 12 weeks) found a statistically significant difference in 11- and 12-month

outcomes in favor of terbinafine (risk difference, -0.23 [95% confidence interval, -0.32 to -0.15]; number needed to treat, 5 [95% confidence interval, 4 to 8]). An analysis of clinical cure rates was not possible because of the diversity of definitions used in researching the effectiveness of oral antifungal drugs for onychomycosis. Only 3 trials gave a clear definition of clinical cure and presented data for these outcomes.

Conclusions: There is good evidence that a continuous regimen of terbinafine (250 mg/d) for 3 months is the most effective oral treatment for fungally infected toenails. Consensus among researchers evaluating oral antifungal drugs for onychomycosis is needed to establish meaningful definitions of clinical cure. Most trials were funded by the pharmaceutical industry; we found little independent research, and this may have introduced bias to the review.

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ORAL TREATMENT may be the only effective treatment for infected toenails. A previous systematic review of topical compounds for fungal toenail infections found little evidence of effectiveness for topical therapies.¹

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Griseofulvin, for many years the only oral therapy, is inexpensive but has a protracted administration time. The newer drugs, azoles and allylamines, have improved cure rates of nail infections but are vastly more expensive than griseofulvin, and some general physicians believe that these resources might be more ben-

eficially used to treat potentially life-threatening conditions.²

The ingredient costs of oral antifungal drugs alone accounted for £30 million of the National Health Service (NHS) prescribing budget in 1998 (personal communication, Department of Health, Statistics Division, Branch SD1E, September 1, 1999). Because 5% of UK adults older than 55 years have infected toenails, the prescribing costs—coupled with consultation costs—represent substantial NHS expenditure if all those affected sought treatment.³

Trials of oral antifungal drugs for toenail infections have described a variety of cure rates for the drugs that are prescribed. The present systematic review examines all available data from evaluations of these therapies and includes a statistical summary of their clinical effectiveness.

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METHODS

SEARCH STRATEGY

We searched the following 5 databases up to March 2000: MEDLINE, EMBASE, CINAHL, Bath Information and Data Services (BIDS), and the Cochrane Controlled Trials Register. The MEDLINE search strategy is published elsewhere.⁴ The following 2 economic databases were searched up to January 2000: NHS Economic Evaluation Database (NEED) and ECONLIT. Four other databases were searched up to January 1997: CAB Health Abstracts, HEALTHSTAR, and Database of Abstracts of Reviews of Effectiveness (DARE) but did not identify any additional randomized clinical trials. The following 3 podiatry journals not listed in these databases were searched manually: *The Foot, Journal of British Podiatric Medicine*, and *British Journal of Podiatric Medicine and Surgery*. We obtained the Cochrane Skin Group's partial hand search of the *British Journal of Dermatology*. We searched the bibliographies of all review articles identified and contacted all schools of podiatry in the United Kingdom and pharmaceutical companies to identify unpublished or unlisted trials.

SELECTION CRITERIA

We considered all randomized clinical trials that evaluated oral treatments for dermatophyte infections of the toenails. We included trials that used microscopy and culture to confirm the presence of dermatophytes. We included duplicate trials only once. We excluded trials that also evaluated the treatment of fungal infections of the fingernails in which the foot-specific data were not presented and trials that included patients with yeast and mold infections of the toenails. Four reviewers working in pairs (F.C. and E.B.; R.H. and S.E.M.B.S.) independently applied these criteria to each trial located. There were no European language restrictions.

DATA EXTRACTION AND QUALITY ASSESSMENT

All reviewers independently summarized the included trials and appraised their quality of reporting based on items from published checklists.⁴⁻⁶ The 12-quality criteria included the following: aims clearly defined, prior sample size calculation reported, inclusion and exclusion criteria defined, subjects blinded, method of randomization defined, baseline comparability of groups reported (age, sex, and duration of complaint), interventions defined, outcome assessment blinded, compliance assessed, and trial analyzed by intention to treat.

MYCOLOGICAL AND CLINICAL CURE RATES (OUTCOMES)

Reports were scrutinized for cure rates from mycological investigations (microscopy and culture) and clinical cure rates. The definition(s) of clinical cure was noted, and data that could be used in a reanalysis (absolute numbers or means and a measure of variance) sought.

STATISTICAL ANALYSIS

For each trial we calculated the cure rates at follow-up (3, 6, 9, and 12 months) from the reported mycological results, with "cure" defined as negative results on microscopy and no growth of dermatophyte in culture. We also collected data regarding clinical cure. We estimated the difference in the proportion of patients cured with 95% confidence intervals in the unpaired proportions that constitute the risk difference.⁷ We also calculated the numbers needed to treat for those comparisons that were statistically significantly different. To estimate differences between treatments, we pooled trials that evaluated similar interventions and controls. Because there was clear evidence of heterogeneity between trials ($P < .001$ for the Q-combinability test [part of the DerSimonian-Laird random effects analysis], which is known to have low power) we used a random effects model.⁸ Finally, we combined the evidence of direct "head-to-head" treatment comparisons.

RESULTS

We identified 50 trials evaluating treatment efficacy,⁹⁻⁵⁸ 32 of which we included⁹⁻⁴⁰ (**Tables 1, 2, 3, 4**, and **5**, available at <http://www.archdermatol.com>). Eighteen trials were excluded for the following reasons: duplicate reports,^{42,43,46,48-50,52,53} combined hand and feet data or combined with topical data,^{41,47,51,54,55,57} no mycology assessment,⁵⁶ protocol deviation,⁴⁵ and data not clearly presented.^{44,58}

MYCOLOGICAL CURE RATES AND EFFECTIVENESS

Itraconazole vs Terbinafine: 12-Week Outcomes After 12 Weeks of Treatment

We found 6 placebo-controlled trials of terbinafine and itraconazole that presented outcomes at 12 weeks¹¹⁻¹⁶: 3 trials evaluating itraconazole vs placebo ($N=433$) found that itraconazole had greater effectiveness,¹¹⁻¹³ and 3 trials evaluating terbinafine vs placebo ($N=337$) found that terbinafine was more effective.¹⁴⁻¹⁶ We regarded outcomes at 3 months as clinically irrelevant; a more clinically

meaningful assessment of the treatment were outcomes at 9 months.

Itraconazole vs Terbinafine: 11- and 12-Month Outcomes After 12 Weeks of Treatment

Only 2 trials of direct comparisons between treatment with itraconazole (200 mg/d) and terbinafine (250 mg/d) gave data on outcomes at 11 and 12 months. These were pooled in a meta-analysis using a random effects model, which showed a risk difference in favor of terbinafine (-0.23 [95% CI, -0.15 to -0.32] ($N=501$) (**Figure**).^{30,40} Both trialists found terbinafine to produce clinically significant improvements in the length of the unaffected nail in great toenails.

Dose-Finding Studies of Itraconazole and Terbinafine Treatments

Two studies compared different regimens of itraconazole with terbinafine.^{17,38} Tosti et al³⁸ compared intermittent treatment with itraconazole (400 mg/d) with

intermittent treatment with terbinafine (500 mg/d) and continuous treatment with terbinafine (250 mg/d) (N=60), while Evans and Sigurgeirsson¹⁷ compared 12- and 16-week regimens of continuous terbinafine (250 mg/d) with intermittent itraconazole (400 mg/d) for 12 and 16 weeks (N=421). The resultant data from these 2 trials lie within the confidence intervals for the dose-finding analysis, which suggest no advantage in higher or prolonged dosages.

Only 1 trial investigated the use of terbinafine in a dosing schedule.¹⁸ Alpsoy et al¹⁸ did not detect a difference in cure rates when comparing a continuous regimen of terbinafine (79%) with an intermittent regimen (74%), but the trial population was small (N=47).

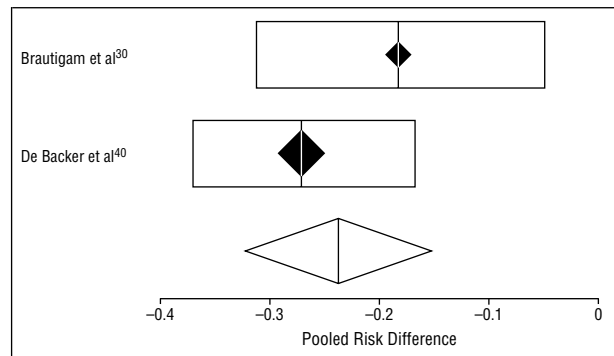
Three trials evaluated the value of continuous and intermittent dosage schedules of itraconazole. Havu et al²¹ found that the cure rate was not significantly different between 3 months of continuous treatment with itraconazole (200 mg/d) and an intermittent (1 week of treatment in every 4 [1:4]) regimen of 400 mg/d (N=121). De Doncker et al²⁰ evaluated 2 different intermittent schedules of itraconazole of 3 and 4 months (400 mg/d; 1:4 weeks) and found that the cure rates at 24 weeks were 64% for patients who received the shorter treatment and 72% for those who received 4 months of treatment.²⁰ The trial had a small number of patients (N=50), and no significant difference was detected between the treatments. Shemer et al¹⁰ also did not find that a higher long-term cure rate was associated with a 200-mg/d continuous regimen of itraconazole compared with either of the 2 intermittent regimens (1:4 weeks) for 12 or 16 weeks (N=64).¹⁰

Griseofulvin vs Itraconazole

Three studies comparing the effectiveness of itraconazole and griseofulvin produced poor cure rates.^{28,29,36} Two studies with small numbers of patients (N = 80) did not detect a difference in patient outcomes with griseofulvin (500 mg/d) and itraconazole (100 mg/d) taken for 24 to 36 weeks: Walsoe et al²⁹ found that none of their 19 patients were cured with either drug while the 61 patients in the trial by Piepponen et al²⁸ had cure rates of 30% in the griseofulvin arm and 36% in the itraconazole arm. Korting et al³⁶ compared 2 different dosages of griseofulvin (660 mg/d and 990 mg/d) with 100-mg/d dosage of itraconazole taken for 18 months but detected no difference in the cure rates (N=108). The cure rates were 6% in both griseofulvin arms and 8% in the itraconazole arm.

Griseofulvin vs Terbinafine

Two studies compared terbinafine (250 mg/d) and griseofulvin (1000 mg/d) for 6 to 12 months of treatment and concluded that the 250-mg/d dosage of terbinafine is the superior treatment at 12- and 18-month outcomes.^{32,34} Faergenann et al³³ reported that 500 mg of griseofulvin taken daily for 1 year had a significantly poorer cure rate than 250 mg of terbinafine taken daily for 3 months.³³ The cure rates were 84% in the terbinafine arm compared with 45% in the griseofulvin arm.



Risk difference plots (random effects). Pooled risk difference, -0.23 (95% confidence interval, -0.15 to -0.32).

Griseofulvin vs Ketoconazole

Poor cure rates also occurred after 6 to 11 months of treatment with ketoconazole (200 mg/d) and treatments with griseofulvin (1000 mg/d and 500 mg/d).^{26,27} These small trials did not detect differences between the cure rates of the 3 different treatments.

Dose-Finding Studies for Fluconazole

We included 2 dose-finding studies evaluating fluconazole. Ling et al²⁴ compared treatment with fluconazole (450 mg/wk) for 4, 6, and 9 months vs placebo. Cure rates were 61% for 9 months of treatment, with significantly lower rates for shorter treatment times (4 months, 34%). Scher et al²⁵ detected improved cure rates associated with higher dosages of 150 mg, 300 mg, and 450 mg of fluconazole (once weekly) were compared with placebo, and the 450-mg/wk dosage produced the highest cure rate (62%) after a maximum of 12 months.

CLINICAL CURE RATES

A great deal of variation in the definition of clinical cure was found between the included trial reports. **Table 6** gives the various definitions stated in the methods sections of each of the included trials. Table 6 also specifies whether the clinical cure data presented in the reports are complete or incomplete.

The reviewers found deviations from the stated methods in most trial reports for clinical cure data. Sometimes deviations occurred when undefined clinical cure data were presented.^{13,31,37,39} In most reports the reverse was true: authors stated their intention to evaluate the effect of the drug of interest on certain clinical signs and symptoms but failed to present separate data for them. Instead, an estimate of "clinical success" was made without explicit reference to any individual clinical feature.* Some authors simply failed to present data for all intended outcomes.^{15,36,38} The use of line graphs, means without measures of variance, and *P* values to present clinical cure data hampered the production of a coherent data summary of clinical cure rates.^{13,16,18,19,28,34,40}

*References 9, 12, 20-23, 25, 26, 29, 30, 32.

Table 6. Definitions of Clinical Cure in Onychomycosis Trials

Study, y	Definition of Clinical Cure	Presented Data*
Elewski et al, ¹³ 1997	A global evaluation of cleared or markedly improved	Incomplete
Jones and Zaias, ¹² 1996	100% Healthy nail growth, percentage of the nail involved, and length of involved nail	Incomplete
Goodfield et al, ¹⁴ 1992	Not defined	NR
Watson et al, ¹⁵ 1995	Unaffected nail length (millimeters); onycholysis, hyperkeratosis, paronychia inflammation, and brittleness graded 0 to 3.	Incomplete
Svejgaard et al, ¹⁶ 1997	Unaffected nail length (percentages) and subungual keratosis	Incomplete
Evans and Sigurgeirsson, ¹⁷ 1999	100% Clear toenail, global assessments by physicians and patients, and at least 5-mm unaffected nail growth	Complete
Alpsy et al, ¹⁸ 1996	3-Point scale to measure onycholysis, hyperkeratosis, paronychia inflammation, and puritis	Incomplete
Tausch et al, ¹⁹ 1997	Infected nail length (percentages) onycholysis, hyperkeratosis, brittleness, and paronychia inflammation.	Incomplete
De Donker et al, ²⁰ 1996	Infected nail length (percentages), onycholysis, and subungual hyperkeratosis	Incomplete
Havu et al, ²¹ 1997	Percentage area, onycholysis, hyperkeratosis, discoloration	Incomplete
Drake et al, ²² 1997	Unaffected nail length (millimeters and percentages), patients' assessment	Incomplete
Van der Shroeff et al, ²³ 1992	Onycholysis, hyperkeratosis, and paronychia inflammation	Incomplete
Ling et al, ²⁴ 1998	Clinically normal nail with complete regrowth of healthy tissue	Complete
Scher et al, ²⁵ 1998	Length of affected nail (percentage scales: 0, 0%; 1, 1%-24%; 2, 25%-49%; 3, 50%-74%; 4, 75%-99%; and 5, 100%), length of onychomycosis, hyperkeratosis, and discoloration	Incomplete
Svejgaard, ²⁶ 1985	Decrease in the area of involved nail, brittleness, subungual hyperkeratosis, and onycholysis	Incomplete
Cullen et al, ²⁷ 1987	Not clear	NR
Piepponen et al, ²⁸ 1992	Area of unaffected nail on 5-point scale, nail color, thickness, and brittleness	Incomplete
Walsoe et al, ²⁹ 1990	Area of affected nail (percentages)	Incomplete
Brautigam et al, ³⁰ 1995	Unaffected nail plate (percentages) on a 3-point scale (0%-30%, 30%-60%, and >60%); onycholysis, hyperkeratosis, brittleness, and paronychia inflammation measured on a 4-point scale	Incomplete
Honeyman et al, ⁹ 1997	Onycholysis, hyperkeratosis, paronychia inflammation, and length of unaffected nail	Incomplete
Arenas et al, ³¹ 1995	Patients' evaluation (very good, good, not very good), nail changes, and nail growth	Incomplete
De Backer et al, ⁴⁰ 1996	Area of affected nail (millimeters), hyperkeratosis, onycholysis, paronychia inflammation	Incomplete
Baran et al, ³² 1997	Not clear	NR
Faergenann et al, ³³ 1995	Not stated	NR
Hofman et al, ³⁴ 1995	Area of unaffected nail (millimeters)	Incomplete
Kavli et al, ³⁵ 1984	Not clear	NR
Korting et al, ³⁶ 1993	Area of nail involvement, dyschromasia, subungual keratosis, nail dystrophy, and paronychia	Incomplete
Haneke et al, ³⁷ 1998	Cured or markedly improved, with or without residual nail malformation	Incomplete
Billstein et al, ³⁹ 1999	Not stated	NR
Gupta et al, ¹¹ 2000	Clear of all signs with or without residual malformation or markedly improved	Complete
Shemer et al, ¹⁰ 1999	Onycholysis, hyperkeratosis, discoloration, length of unaffected nail (ratio)	Incomplete
Tosti et al, ³⁸ 1996	4-Point scale based on the presence of onycholysis, subungual hyperkeratosis, and nail discoloration; residual malformation	Incomplete

*Complete indicates that data were presented as absolute numbers or as percentages for the stated defined outcome; incomplete, that all the a priori stated data were either not presented for the stated outcomes or were presented as a line graph or a mean without a variance; and NR, not reported.

Only Ling et al,²⁴ Evans and Sigurgeirsson,¹⁷ and Gupta et al¹¹ presented data in absolute numbers for clinical cures they defined a priori. These authors evaluated different drugs. Ling et al²⁴ found that people who took fluconazole, 450 mg once weekly for 9 months, had the highest percentage of clinically normal nail with complete regrowth of healthy tissue at 6-month follow-up (37%). Evans and Sigurgeirsson¹⁷ found that a higher proportion of people who took terbinafine, 250 mg/d for 16 weeks, had 100% clear toenail and at least 5 mm of unaffected nail growth compared with people randomized to either 250 mg/d of terbinafine for 12 weeks or a 1 week in 3- or 4-intermittent cycle of itraconazole (400 mg/d). In both these trials the clinical cure rates were consistent with the mycological cure rates. Gupta et al¹¹ compared intermittent itraconazole treatment (400 mg/d) with placebo and found that the proportion of patients who were clear of all signs of infection or markedly improved reflected the rates determined by mycological investigation. However, the proportion deemed clinically cured in the placebo arm was much lower than the proportion found to be cured using the mycological outcome criteria (1% and 28%, respectively).

MICROORGANISMS

Trichophyton rubrum was the most commonly identified infecting organism in all the included studies, with proportions reported to be from 68% to 100% of the identified fungi. Other species included *Trichophyton mentagrophytes*, *Trichophyton tonsurans*, *Trichophyton interdigital*, *Trichophyton soudanense*, and *Epidermophyton floccosum*. The review included trials with patients who had dermatophyte infection only; therefore, we cannot make conclusions about the efficacy of oral antifungals in the treatment of nondermatophyte onychomycosis.

QUALITY SCORES

The average score for all trials included in the review was 6.7 of 12.0. Blinded outcome assessment was only reported in 1 study,³⁴ and the method used to conceal the random allocation from the researchers was reported in 4.^{17-19,32} In 2 trials the inclusion/exclusion criteria were unclear,^{19,34} but all of the included trials reported clear aims. Only half of the included trials reported compa-

nable populations of patients at baseline for the duration of infection.*

ADVERSE EVENTS

With the exception of 1 trial,⁹ all reported adverse events. The frequency of adverse events was not significantly different between treatment and placebo arms for terbinafine, itraconazole, and fluconazole.^{12-15,22-26} The data from dose-finding studies do not suggest that shorter treatment times (including intermittent regimens) result in fewer reported adverse events. No trials with placebo controls were identified for evaluations of griseofulvin and ketoconazole.

COMMENT

We found 32 randomized evaluations of terbinafine, itraconazole, griseofulvin, fluconazole, and ketoconazole that met our inclusion criteria. No difference in outcomes was detected between terbinafine (250 mg/d) and itraconazole (400 mg/d) at 3 months. However, a pooled analysis of mycological cure rates taken at 11 and 12 months (Figure) showed that terbinafine (250 mg/d) was more effective than itraconazole (400 mg/d) in the treatment of fungally infected toenails in the longer term.

The 1999 trial by Evans and Sigurgeirsson¹⁷ was not included in the meta-analysis because it compared continuous dosages of terbinafine (250 mg/d) with intermittent regimens of itraconazole (400 mg/d). The cure rates achieved in the terbinafine arms of the trial, relative to the itraconazole arms, are consistent with the meta-analysis in the Figure and provide evidence that continuous treatment with terbinafine (250 mg/d) is significantly more effective than an intermittent regimen of itraconazole (400 mg/d). The small trial by Alpsy et al¹⁸ and data from the arm of the trial evaluating intermittent and continuous dosages of terbinafine in the study by Tosti et al³⁸ both suggest that high levels of effectiveness can be achieved using an intermittent regimen of terbinafine, but this needs to be evaluated in a large randomized controlled trial.

There is no evidence that intermittent regimens of itraconazole produce statistically different cure rates from continuous schedules. Nor is there evidence that intermittent regimens or shorter treatment times result in fewer reported adverse events.

There was no evidence of significantly different rates of effectiveness in direct comparisons between itraconazole and griseofulvin or between itraconazole and ketoconazole, but the sample sizes in these trials were small. Fluconazole also produced only modest cure rates after particularly prolonged treatment times.

A large variety of signs and symptoms are used in dermatology research to establish the clinical cure rates of drugs used in the management of toenail onychomycosis. The lack of standardization of definitions for clinical cure, together with fairly arbitrary methods of data collection and presentation, render these outcomes meaningless in a systematic review of the literature. Future researchers of effective oral treatments for onychomycosis should clearly define the out-

comes of interest, specify the mode of measurement, and ensure a clear presentation of the data. Consensus among the dermatology community about the most important signs and symptoms of clinical cure and methods of measurement for onychomycosis would be particularly helpful.

Twenty-two trials included in this systematic review were supported by pharmaceutical companies. All produced data to endorse the use of the sponsor's product, and it is possible that the conclusions of the present systematic review are compromised by a publication bias. The small number of trials in the meta-analysis for 11- and 12-month outcomes (Figure) make it difficult to use a funnel plot, but commercial influence and small sample sizes are 2 features frequently associated with such bias. This only serves to reinforce the need for a trial amnesty in which unpublished data are made available, otherwise independently funded research may be the only route to unbiased estimates of the effects of oral antifungal drugs.

CONCLUSIONS

Based on the mycological cure rates in our systematic review, it appears that a continuous regimen of terbinafine (250 mg/d) is the most effective oral therapy for the long-term management of fungally infected toenails. A standardization of methods regarding the collection and presentation of data regarding complete clinical cure is required to allow future researchers to compare the effect of oral antifungal agents on clinical outcomes in the treatment of onychomycosis. A consensus between clinicians and researchers regarding the best way to collect and present those secondary outcomes is needed.

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Table 1. Oral Antimycotic Treatments vs Placebo

Study, y	Treatment (Dose, mg/d)	Sample Size, No.	Length of Treatment, wk	Length of Follow-up, wk	Cure Rate, No. (%)	Risk Difference (95% CI)/NNT (95% CI)*
Elewski et al, ¹³ 1997	Itraconazole (200)	110	12	12	69 (54)	0.6 (0.4 to 0.7)/2 (2 to 3)
	Placebo	104	12	12	6 (6)	
Jones and Zaias, ¹² 1996	Itraconazole (200)	36	12	12	24 (69)	0.6 (0.4 to 0.8)/2 (2 to 3)
	Placebo	37	12	12	2 (6)	
Gupta et al, ¹¹ 2000	Intermittent itraconazole (400)	78	12 (1:4)†	48	51 (65)	0.6 (0.5 to 0.7)/2 (2 to 3)
	Placebo	74	12 (1:4)†	48	1 (1)	
Goodfield et al, ¹⁴ 1992	Terbinafine (250)	70	12	48	38 (73)	0.5 (0.4 to 0.6)/2 (2 to 3)
	Placebo	29	12	48	1 (6)	
Watson et al, ¹⁵ 1995	Terbinafine (250)	56	12	24	33 (59)	0.5 (0.3 to 0.6)/2 (2 to 3)
	Placebo	55	12	24	5 (9)	
Svejgaard et al, ¹⁶ 1997	Terbinafine (250)	63	12	12	49 (66)	0.4 (0.2 to 0.5)/3 (2 to 3)
	Placebo	64	12	12	24 (33)	

*CI indicates confidence interval; NNT, number needed to treat.

†For the intermittent schedule, 1:4 indicates 1 week of treatment in every 4 weeks.

Table 2. Oral Antimycotic 4-Arm Trials

Study, y	Treatment (Dose, mg/d)	Sample Size, No.	Length of Treatment, wk	Length of Follow-up, wk	Cure Rate, No. (%)	Risk Difference (95% CI)/NNT (95% CI)*
Evans and Sigurgeirsson, ¹⁷ 1999	Terbinafine (250)	124	12	72	81 (76)	-0.6 (-0.4 to -0.8)/4 (3 to 5)
	Intermittent itraconazole (400)	126	12 (1:4)†	72	41 (38)	
	Terbinafine (250)	120	16	72	80 (81)	
Shemer et al, ¹⁰ 1999	Intermittent itraconazole (400)	126	16 (1:4)†	72	53 (49)	0.2 (0.2 to 0.4)/5 (3 to 9)
	Itraconazole (200)	16	12	48	11 (68)	
	Intermittent itraconazole (200)	16	12 (1:4)†	48	8 (50)	
	Itraconazole (200)	16	16	48	10 (64)	
Billstein et al, ³⁹ 1999	Intermittent itraconazole (200)	16	16 (1:4)†	48	10 (64)	0.8 (0.5 to 1.33)/NR
	Terbinafine (250)	29	12	72	11 (37)	
	Terbinafine (250)	27	16	72	10 (71)	
	Terbinafine (250)	26	24	72	17 (94)	
	Placebo	27	24	72	0	Reference

*CI indicates confidence interval; NNT, number needed to treat; and NR, not reported.

†For the intermittent schedule, 1:4 indicates 1 week of treatment in every 4 weeks.

Table 3. Dose-Finding Studies

Study, y	Treatment (Dosage)	Sample Size, No.	Length of Treatment, wk	Length of Follow-up, wk	Cure Rate, No. (%)	Risk Difference (95% CI)/ NNT (95% CI)*
Alpsoy et al, ¹⁸ 1996	Terbinafine (250 mg/d)	24	12	48	19 (79)	0.5 (-0.2 to 0.2)/NR
	Intermittent terbinafine (250 mg/d)	23	12 (1:3)†	48	17 (74)	
Tausch et al, ¹⁹ 1997	Terbinafine (250 mg/d)	72	6	48	43 (59)	0.1 (-0.02 to 0.2)/NR
	Terbinafine (250 mg/d)	76	12	48	55 (72)	
De Doncker et al, ²⁰ 1996	Intermittent itraconazole (200 mg/d)	25	12 (1:4)†	24	16 (64)	0.08 (-0.2 to 0.3)/NR
	Intermittent itraconazole (200 mg/d)	25	16 (1:4)†	24	18 (72)	
Havu et al, ²¹ 1997	Itraconazole (200 mg/d)	62	12	52	41 (66)	0.03 (-0.13 to 0.2)/NR
	Intermittent itraconazole (200 mg/d)	59	12 (1:4)†	52	41 (69)	
Drake et al, ²² 1997	Terbinafine (250 mg/d)	140	12	48	98 (70)	0.2 (0.1 to 0.3)/NR
	Terbinafine (250 mg/d)	142	24	48	124 (87)	0.6 (0.5 to 0.7)/NR
	Placebo	71	24	48	6 (9)	Reference
Van der Schroeff et al, ²³ 1992	Terbinafine (250 mg/d)	30	6	48	12 (41)	0.1 (-0.1 to 0.3)/NR
	Terbinafine (250 mg/d)	34	12	48	24 (71)	0.4 (0.2 to 0.6)/NR
	Terbinafine (250 mg/d)	34	24	48	28 (82)	Reference
Ling et al, ²⁴ 1998	Fluconazole (150 mg/wk)	78	16	15	24 (34)	0.2 (0.1 to 0.4)/4 (3 to 7)
	Fluconazole (150 mg/wk)	84	26	15	40 (49)	0.3 (0.1 to 0.4)/4 (3 to 6)
	Fluconazole (150 mg/wk)	86	39	15	46 (61)	0.5 (0.3 to 0.6)/2 (2 to 3)
	Placebo	83	39	15	6 (8)	Reference
Scher et al, ²⁵ 1998	Fluconazole (150 mg/wk)	89	12 (Maximum)	18	38 (53)	0.2 (0.1 to 0.4)/3 (2 to 5)
	Fluconazole (300 mg/wk)	88	12 (Maximum)	18	42 (59)	0.3 (0.2 to 0.5)/3 (3 to 5)
	Fluconazole (450 mg/wk)	92	12 (Maximum)	18	47 (61)	0.3 (0.2 to 0.5)/3 (3 to 4)
	Placebo	92	12 (Maximum)	18	12 (16)	Reference

*CI indicates confidence interval; NNT, number needed to treat; and NR, not reported.

†For the intermittent schedule, 1:3 and 1:4 indicate 1 week of treatment in every 3 and 4 weeks, respectively.

Table 4. Oral Antimycotic 2-Arm Trials

Study, y	Treatment (Dose, mg/d)	Sample Size, No.	Length of Treatment, wk	Length of Follow-up, wk	Cure Rate, No. (%)	Risk Difference (95% CI)/ NNT (95% CI)*
Svejgaard, ²⁶ 1985	Ketoconazole (200)	9	45.9 (Average)	Not clear	1 (11)	0.1 (0.09 to 0.3)/9 (3 to ∞)†
	Griseofulvin (500)	7	38.1 (Average)	Not clear	0	
Cullen and Cullen, ²⁷ 1987	Ketoconazole (200)	14	24	24	5 (35)	-0.05 (-0.4 to 0.3)/NR
	Griseofulvin (1000)	12	24	24	5 (42)	
Piepponen et al, ²⁸ 1992	Itraconazole (100)	31	24-36	40	10 (37)	0.08 (-0.13 to 0.31)/NR
	Griseofulvin (500)	30	24-36	40	7 (30)	
Walsole et al, ²⁹ 1990	Itraconazole (100)	9	24	24	0	-0.004 (-0.17 to 0.18)/NR
	Griseofulvin (500)	10	24	24	0	
Brautigam et al, ³⁰ 1995	Terbinafine (250)	86	12	52	70 (81)	0.18 (0.05 to 0.31)/6 (4 to 21)
	Itraconazole (200)	84	12	52	53 (63)	
Arenas et al, ³¹ 1995	Terbinafine (250)	27	12	36	23 (100)	0.19 (-0.02 to 0.4)/NR
	Itraconazole (200)	26	12	36	17 (100)	
De Backer et al, ⁴⁰ 1996	Terbinafine (250)	186	12	48	119 (73)	0.2 (0.1 to 0.3)/5 (4 to 8)
	Itraconazole (200)	186	12	48	77 (46)	
Baran et al, ³² 1997	Terbinafine (250)	62	52	52	47 (90)	-0.1 (-0.2 to 0.04)/5 (2 to 4)
	Griseofulvin (1000)	58	52	52	37 (69)	
Faergenann et al, ³³ 1995	Terbinafine (250)	43	16	52	36 (84)	0.3 (0.1 to 0.5)/3 (2 to 6)
	Griseofulvin (500)	41	52	52	19 (45)	
Hofmann et al, ³⁴ 1995	Terbinafine (250)	83	24	72	52 (81)	0.1 (0.001 to 0.2)/NR
	Griseofulvin (1000)	88	24	72	42 (62)	
Honeyman et al, ⁹ 1997	Terbinafine (250)	64	16	52	61 (95)	0.1 (0.01 to 0.2)/10 (5 to 143)
	Itraconazole (200)	70	16	52	59 (83)	
Kavli et al, ³⁵ 1984	Ketoconazole (200)	14	16	24	4 (28)	0.2 (-0.09 to 0.5)/NR
	Ketoconazole (200) + urea cream	15	16	24	8 (53)	

*CI indicates confidence interval; NNT, number needed to treat; and NR, not reported.

†NNT with an infinite CI is a point estimate; it includes the possibility of no benefit or harm.

Table 5. Oral Antimycotic 3-Arm Trials

Study, y	Treatment (Dose, mg/d)	Sample Size, No.	Length of Treatment, wk	Length of Follow-up, wk	Cure Rate, No. (%)	Risk Difference (95% CI)/NNT (95% CI)*
Korting et al, ³⁶ 1993	Griseofulvin (660)	36	78	77	2 (6)	0.02 (-0.08 to 0.1)/NR
	Griseofulvin (990)	36	78	77	2 (6)	0.02 (0.8 to 0.1)/NR
	Itraconazole (100)	36	78	77	3 (8)	Reference
Haneke et al, ³⁷ 1998	Itraconazole (200)	538	26	26	238 (76)	-0.17 (-0.1 to 0.2)/6 (5 to 9)
	Itraconazole (200)	450	12	12	222 (74)	-0.2 (-0.1 to 0.2)/5 (4 to 7)
	1% Miconazole cream	363	26	26	97 (60)	Reference
Tosti et al, ³⁸ 1996	Intermittent terbinafine (500)	21	16 (1:4)†	43	16 (80)	-0.09 (-0.3 to 0.15)/NR
	Intermittent itraconazole (400)	20	16 (1:4)†	43	15 (75)	-0.01 (-0.27 to 0.25)/NR
	Terbinafine (250)	19	16	43	16 (94)	Reference

*CI indicates confidence interval; NNT, number needed to treat; and NR, not reported.

†For the intermittent schedule, 1:4 indicates 1 week of treatment in every 4 weeks.