Oral treatments for toenail onychomycosis: a systematic review

Authors' objectives
To determine the efficacy of oral treatments for fungal infections of the toenails.

Searching
MEDLINE, CINAHL, EMBASE, databases on BIDS, and the Cochrane Controlled Trials Register were searched up to March 2000. The search strategy for MEDLINE was stated as being published elsewhere. NHS EED and EconLit (both to January 2000) and CAB Health, HealthSTAR and DARE were also searched. Three podiatry journals not listed in the databases mentioned were searched manually: The Foot, the Journal of British Podiatric Medicine and the British Journal of Podiatric Medicine and Surgery. The Cochrane Skin Group's partial manual search of the British Journal of Dermatology was obtained. In addition, the bibliographies of all reviews were examined and all schools of podiatry in the UK and pharmaceutical companies were contacted for additional and unpublished trials. Studies that were published in any European language were included.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) were included in the review.

Specific interventions included in the review
Studies of oral treatments for dermatophyte infections of the toenails were eligible for inclusion. The included studies compared the following agents with each other and/or placebo: itraconazole (100 to 400 mg/day), terbinafine (250 to 500 mg/day), griseofulvin (500 to 1,000 mg/day), ketoconazole (200 mg/day) and fluconazole (150 to 450 mg/day). The studies used intermittent or continuous regimens of itraconazole. The duration of treatment ranged from 12 weeks to 18 months.

Participants included in the review
Studies of patients with dermatophyte infections of the toenails were eligible if the diagnosis was confirmed by microscopy and culture. Studies of patients with dermatophyte infection of the fingernails were excluded unless they presented separate data for the toenails. Studies of patients with yeast and mould infections of the toenails were excluded. The most commonly identified organism was Trichophyton rubrum (68 to 100% of identified fungi).

Outcomes assessed in the review
The primary outcome in the review was the mycological cure rate. Cure was defined as negative microscopy and no growth of dermatophyte in culture. Other outcomes were clinical cure rates and adverse events. The definitions of clinical cure varied widely in the included studies, and some studies did not define this outcome.

How were decisions on the relevance of primary studies made?
Four reviewers working in pairs independently selected the studies for inclusion.

Assessment of study quality
Study quality was assessed using the following criteria: definition of aims, prior sample size calculation, inclusion and exclusion criteria defined, patients blinded, method of randomisation described, baseline comparability of the treatment groups (age, gender, duration of condition), interventions defined, outcome assessment blinded, compliance assessed, and intention-to-treat analysis. All of the reviewers (number not stated, but there were seven authors) independently assessed validity.

Data extraction
All of the reviewers (number not stated, but there were seven authors) independently extracted the data. The data extracted included cure results, definition of clinical cure, and the absolute numbers or mean values and a measure of variance. For each study, the mycological cure rates at 3, 6, 9 and 12 months were calculated.

**Methods of synthesis**

**How were the studies combined?**
Studies reporting mycological cure rates were grouped by the interventions compared and a narrative synthesis was undertaken. The pooled risk difference (RD) and 95% confidence interval (CI) for the mycological cure rate of itraconazole, compared with terbinafine, at 11 to 12 months were calculated using a random-effects model. The number-needed-to-treat (NNT) and 95% CI were also calculated for this comparison.

**How were differences between studies investigated?**
Statistical heterogeneity was tested using the Q statistic for the one reported meta-analysis.

**Results of the review**

Thirty-two RCTs were included; the total number of patients was not reported in the text.

**Study quality.**

The average quality score was 6.7 out of 12 points. There were several methodological problems: blinded outcome assessment, the method used to conceal randomisation, and the baseline comparability of the treatment groups was not always reported; the inclusion and exclusion criteria were unclear; the reported data were incomplete; the outcome 'clinical success' was not always defined; and the presentation of the results was poor, with no measures of variance or P-values. Most of the trials were funded by pharmaceutical companies.

**Mycological cure rates.**

The 3 RCTs (433 patients) of itraconazole versus placebo found that itraconazole increased the cure rates at 12 weeks. The 3 RCTs (337 patients) of terbinafine versus placebo found that terbinafine increased the cure rates at 12 weeks. The 2 RCTs (501 patients) of itraconazole versus terbinafine found that terbinafine significantly increased the mycological cure rate at 11 and 12 months' follow-up after 3 months of treatment. The RD was -0.23 (95% CI: -0.15, -0.32) and the NNT was 5 (95% CI: 4, 8).

**Different regimens of itraconazole and terbinafine.**

The results from 2 RCTs (481 patients) suggested that higher and prolonged dosages did not increase the cure rates. One small RCT (47 patients) found no significant difference between continuous and intermittent terbinafine; the cure rates were 79 and 74%, respectively. One RCT (121 patients) found no significant difference between continuous and intermittent itraconazole after 3 months. One small RCT (50 patients) found no significant difference in the cure rates at 24 weeks between intermittent itraconazole for 3 compared with 4 months (64 versus 72%). One small RCT (64 patients) found no significant difference between continuous and intermittent itraconazole.

**Griseofulvin versus itraconazole, terbinafine or ketoconazole.**

Two small RCTs (80 patients) and one larger RCT (108 patients) found no significant difference in the cure rates between griseofulvin (500 mg to 990 mg/day) and itraconazole (100 mg/day). All 3 trials found low cure rates: 0% with griseofulvin and 0% with itraconazole; 30% with griseofulvin and 36% with itraconazole; and 6% with griseofulvin and 8% with itraconazole. Three RCTs found that terbinafine (250 mg/day) increased the mycological cure rates in comparison with griseofulvin (500 to 1,000 mg/day). The cure rates in one RCT were 84% with terbinafine versus 45% with griseofulvin. Two RCTs found no difference between griseofulvin (500 and 1,000 mg) and ketoconazole (200 mg).

**Dose and duration of fluconazole treatment.**
One RCT found that 4 months of treatment significantly reduced the cure rates in comparison with 9 months treatment; the cure rates were 34 and 61%, respectively. One RCT found that 450 mg fluconazole increased the cure rates in comparison with doses of 150 and 300 mg; the cure rate was 62% with 450 mg.

Clinical cure rates (3 RCTs evaluating different drugs).

One RCT found that 450 mg fluconazole taken for 9 months increased the proportion of patients with clinically normal nail and regrowth of healthy tissue at 6 months (37%), compared with fluconazole for 4 or 6 months or placebo. One RCT found that 250 mg terbinafine for 16 weeks increased the proportion of patients with clear toenails and at least 5 mm unaffected growth, compared with 250 mg terbinafine for 12 weeks or intermittent 400 mg itraconazole. One RCT found that itraconazole was more effective than placebo. Two RCTs found consistency between mycological and clinical cure rates, but one RCT found that clinical cure rates (1%) were lower than mycological cure rates (28%) with placebo.

Adverse events (31 RCTs).

Studies found no significant difference in adverse events between active treatment with itraconazole, terbinafine or fluconazole and placebo.

Authors' conclusions
The most effective oral treatment for fungal infection of toenails was terbinafine, 250 mg/day, given continuously for 3 months.

CRD commentary
The review question was clear in terms of the study design, intervention, participants and outcomes. Several relevant sources were searched and attempts were made to locate unpublished studies. The search terms for one database were stated as being available in another report. Two reviewers selected the studies and at least two reviewers assessed validity and extracted the data; this reduced the potential for bias and errors. Validity was assessed using defined criteria. There was limited information on the included studies in the text of the review, although the study details were reported as being available on the Archives of Dermatology website; full access to the contents requires a subscription. The studies were appropriately grouped by outcome and then by the drugs compared. However, the results were not reported consistently in terms of either the actual values or statistical significance, and this hindered interpretation. In addition, the results were not discussed with respect to study validity. One meta-analysis was reported, but it was unclear why some meta-analyses (e.g. of placebo-controlled trials) were not undertaken. It was also unclear in which meta-analysis(es) significant heterogeneity was found. Caution is therefore required when interpreting the results.

Implications of the review for practice and research
Practice: The authors state that terbinafine, 250 mg/day, given continuously for 3 months is the most effective oral treatment for fungal infection of the toenails.

Research: The authors state that a meaningful definition of clinical cure is required, and that the methods used to collect and present data on complete clinical cure require standardisation.

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