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Oral antifungal medication for toenail onychomycosis (Review) Copyright © 2017 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.



## [Intervention Review]

# Oral antifungal medication for toenail onychomycosis

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# ABSTRACT

#### Background

Fungal infection of the toenails, also called onychomycosis, is a common problem that causes damage to the nail's structure and physical appearance. For those severely affected, it can interfere with normal daily activities. Treatment is taken orally or applied topically; however, traditionally topical treatments have low success rates due to the nail's physical properties. Oral treatments also appear to have shorter treatment times and better cure rates. Our review will assist those needing to make an evidence-based choice for treatment.

#### Objectives

To assess the effects of oral antifungal treatments for toenail onychomycosis.

#### Search methods

We searched the following databases up to October 2016: the Cochrane Skin Group Specialised Register, CENTRAL, MEDLINE, Embase, and LILACS. We also searched five trials registers and checked the reference lists of included and excluded studies for further references to relevant randomised controlled trials (RCTs). We sought to identify unpublished and ongoing trials by correspondence with authors and by contacting relevant pharmaceutical companies.

#### **Selection criteria**

RCTs comparing oral antifungal treatment to placebo or another oral antifungal treatment in participants with toenail onychomycosis, confirmed by one or more positive cultures, direct microscopy of fungal elements, or histological examination of the nail.

## Data collection and analysis

We used standard methodological procedures expected by Cochrane.

#### **Main results**

We included 48 studies involving 10,200 participants. Half the studies took place in more than one centre and were conducted in outpatient dermatology settings. The participants mainly had subungual fungal infection of the toenails. Study duration ranged from 4 months to 2 years.

We assessed one study as being at low risk of bias in all domains and 18 studies as being at high risk of bias in at least one domain. The most common high-risk domain was 'blinding of personnel and participants'.

We found high-quality evidence that terbinafine is more effective than placebo for achieving clinical cure (risk ratio (RR) 6.00, 95% confidence interval (CI) 3.96 to 9.08, 8 studies, 1006 participants) and mycological cure (RR 4.53, 95% CI 2.47 to 8.33, 8 studies, 1006 participants). Adverse events amongst terbinafine-treated participants included gastrointestinal symptoms, infections, and headache, but there was probably no significant difference in their risk between the groups (RR 1.13, 95% CI 0.87 to 1.47, 4 studies, 399 participants, moderate-quality evidence).

There was high-quality evidence that azoles were more effective than placebo for achieving clinical cure (RR 22.18, 95% CI 12.63 to 38.95, 9 studies, 3440 participants) and mycological cure (RR 5.86, 95% CI 3.23 to 10.62, 9 studies, 3440 participants). There were slightly more adverse events in the azole group (the most common being headache, flu-like symptoms, and nausea), but the difference was probably not significant (RR 1.04, 95% CI 0.97 to 1.12; 9 studies, 3441 participants, moderate-quality evidence).

Terbinafine and azoles may lower the recurrence rate when compared, individually, to placebo (RR 0.05, 95% CI 0.01 to 0.38, 1 study, 35 participants; RR 0.55, 95% CI 0.29 to 1.07, 1 study, 26 participants, respectively; both low-quality evidence).

There is moderate-quality evidence that terbinafine was probably more effective than azoles for achieving clinical cure (RR 0.82, 95% CI 0.72 to 0.95, 15 studies, 2168 participants) and mycological cure (RR 0.77, 95% CI 0.68 to 0.88, 17 studies, 2544 participants). There was probably no difference in the risk of adverse events (RR 1.00, 95% CI 0.86 to 1.17; 9 studies, 1762 participants, moderate-quality evidence) between the two groups, and there may be no difference in recurrence rate (RR 1.11, 95% CI 0.68 to 1.79, 5 studies, 282 participants, low-quality evidence). Common adverse events in both groups included headache, viral infection, and nausea.

Moderate-quality evidence shows that azoles and griseofulvin probably had similar efficacy for achieving clinical cure (RR 0.94, 95% CI 0.45 to 1.96, 5 studies, 222 participants) and mycological cure (RR 0.87, 95% CI 0.50 to 1.51, 5 studies, 222 participants). However, the risk of adverse events was probably higher in the griseofulvin group (RR 2.41, 95% CI 1.56 to 3.73, 2 studies, 143 participants, moderate-quality evidence), with the most common being gastrointestinal disturbance and allergic reaction (in griseofulvin-treated participants) along with nausea and vomiting (in azole-treated participants). Very low-quality evidence means we are uncertain about this comparison's impact on recurrence rate (RR 4.00, 0.26 to 61.76, 1 study, 7 participants).

There is low-quality evidence that terbinafine may be more effective than griseofulvin in terms of clinical cure (RR 0.32, 95% CI 0.14 to 0.72, 4 studies, 270 participants) and mycological cure (RR 0.64, 95% CI 0.46 to 0.90, 5 studies, 465 participants), and griseofulvin was associated with a higher risk of adverse events, although this was based on low-quality evidence (RR 2.09, 95% CI 1.15 to 3.82, 2 studies, 100 participants). Common adverse events included headache and stomach problems (in griseofulvin-treated participants) as well as taste loss and nausea (in terbinafine-treated participants). No studies addressed recurrence rate for this comparison.

No study addressed quality of life.

## **Authors' conclusions**

We found high-quality evidence that compared to placebo, terbinafine and azoles are effective treatments for the mycological and clinical cure of onychomycosis, with moderate-quality evidence of excess harm. However, terbinafine probably leads to better cure rates than azoles with the same risk of adverse events (moderate-quality evidence).

Azole and griseofulvin were shown to probably have a similar effect on cure, but more adverse events appeared to occur with the latter (moderate-quality evidence). Terbinafine may improve cure and be associated with fewer adverse effects when compared to griseofulvin (low-quality evidence).

Only four comparisons assessed recurrence rate: low-quality evidence found that terbinafine or azoles may lower the recurrence rate when compared to placebo, but there may be no difference between them.

Only a limited number of studies reported adverse events, and the severity of the events was not taken into account.

Overall, the quality of the evidence varied widely from high to very low depending on the outcome and comparison. The main reasons to downgrade evidence were limitations in study design, such as unclear allocation concealment and randomisation as well as lack of blinding.

# PLAIN LANGUAGE SUMMARY

## What is the best medication for a fungal infection of the toenail?

## **Review question**



Trusted evidence. Informed decisions. Better health.

We aimed to find out which medications, taken by mouth for at least six weeks, are the most effective at curing fungal infection of the toenail, a condition that is known as onychomycosis, in people of any age. We compared these medications to each other or placebo (an inactive drug or treatment).

## Background

Fungal infection of the toenails is a common condition, which has a low risk of complications and associated health risks. However, for those severely affected, it might affect normal daily activities.

Medication taken by mouth appears to cure the condition more quickly and effectively than topical treatment. There are three main antifungal medications: griseofulvin, different medications in the azole group (itraconazole, fluconazole, albaconazole, posaconazole, ravuconazole), and terbinafine.

We wanted to assess the following two main outcomes.

- 1. Does the nail look normal after treatment (clinical cure)?
- 2. Is the nail free from fungus at a microscopic level (mycological cure)?

#### **Study characteristics**

We identified 48 studies with 10,200 participants of both sexes. The average age of the participants across studies ranged from 36 to 68; most studies included participants aged 18 and over. Our included studies compared the three main groups of medication against each other or to placebo. Most studies took place in outpatient dermatology settings in the USA and Europe. The participants mainly had fungal infection under the toenails. A small number of studies included a specific group of participants, such as those with diabetes. All but one study looked at fungal infections caused by dermatophyte, which are fungi that digest keratin. Study duration ranged from 4 months to 2 years, with most lasting 12 to 15 months.

#### **Key results**

The evidence is current to October 2016.

We found high-quality evidence that compared with placebo, both terbinafine and azoles are more effective for achieving a normal-looking nail and curing the toenail infection (i.e. looking at the microscopic level to see if the fungus is gone). Terbinafine or azoles may also prevent the infection reoccurring more than placebo (low-quality evidence). There was probably no significant difference in the risk of adverse events reported when comparing either azoles or terbinafine with placebo (moderate-quality evidence). The most common adverse events amongst terbinafine-treated and azole-treated participants included stomach problems and headache.

We found that compared to azoles, terbinafine was probably more effective in curing the nails in terms of appearance and infection (moderate-quality evidence). The risk of side effects was probably the same for both treatments (moderate-quality evidence), and the most common adverse events in both groups were headache, viral infection, and rash. There may be no difference in recurrence rate (low-quality evidence).

A third type of treatment, griseofulvin, was probably as effective as the azole medications in curing the nails in terms of appearance and infection (moderate-quality evidence), but it may be less effective than terbinafine when assessing the same outcomes (low-quality evidence). Griseofulvin caused more side effects than the other two treatments, although the quality of the evidence was moderate (compared to azole) to low (compared to terbinafine). The most common adverse events in both groups included stomach problems and feeling sick. We are uncertain about the effect of griseofulvin compared to azoles on the rate of recurrence, and studies comparing terbinafine and griseofulvin did not assess this outcome.

## **Quality of the evidence**

The evidence for the primary outcomes of cure (in terms of appearance and infection) was high to moderate quality except for the comparisons of griseofulvin versus terbinafine (low quality) and combination terbinafine plus azole versus terbinafine alone (very low quality). The evidence quality for side effects was mainly moderate, but two comparisons had low evidence for this outcome. Not all comparisons measured recurrence rate, and the available evidence was based on low- to very low-quality evidence. No studies reported on participants' quality of life. Many studies had problems in the study design: it was often unclear how they decided which participants would receive which treatment or ensured that participants weren't aware of the treatment allocation. Many studies also did not use a placebo.