

# Is This the Right Drug or the Dose for the Management of Onychomycosis?

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## Introduction

Onychomycosis is a fungal infection of the toenails and fingernails that results in thickening, discoloration, splitting as well as lifting of the nails from the nail bed. It affects 14% of the total world population, with more prevalence in elders and diabetics. Both dermatophytes (*Trichophyton rubrum* or *T. mentagrophytes*) and nondermatophytes (*Scopulariopsis brevicaulis*, *Aspergillus spp*, *Fusarium spp*, and sometimes *Candida spp*) have been identified as etiologic agents of onychomycosis. The treatment of onychomycosis is known to be challenging since it is a chronic condition, difficult to eradicate and tends to relapse [1]. The pharmacotherapy of onychomycosis involves prolonged systemic or oral antifungal therapy due to slow overturn rate of nail as well as limited blood circulation into the affected nail bed. However, complete cure that involves a clinical cure (normal nail morphology) and mycological cure (both negative microscopy and dermatophyte culture), is often unattainable. In recent years the development of antifungal drugs of second generation (fluconazole, itraconazole, and terbinafine) has produced notable, long-term cure rates with shorter treatment period and improved safety profiles as compared to the first generation antifungal agents. However, different dosage regimens of various antifungal agents have been used by various researchers in clinical trials in order to ensure the complete eradication of the fungal infection in a shorter period with better efficacy.

## Antimycotics Used to Treat Onychomycosis

The attempts have been made since ages to cure onychomycosis. However, there have been a number of failures in treatment and development programs. The prerequisite of treatment of the disease is the penetration of drug to the infected nail bed; however, low permeation rate of drugs necessitates prolonged treatment times.

### First generation oral antifungals

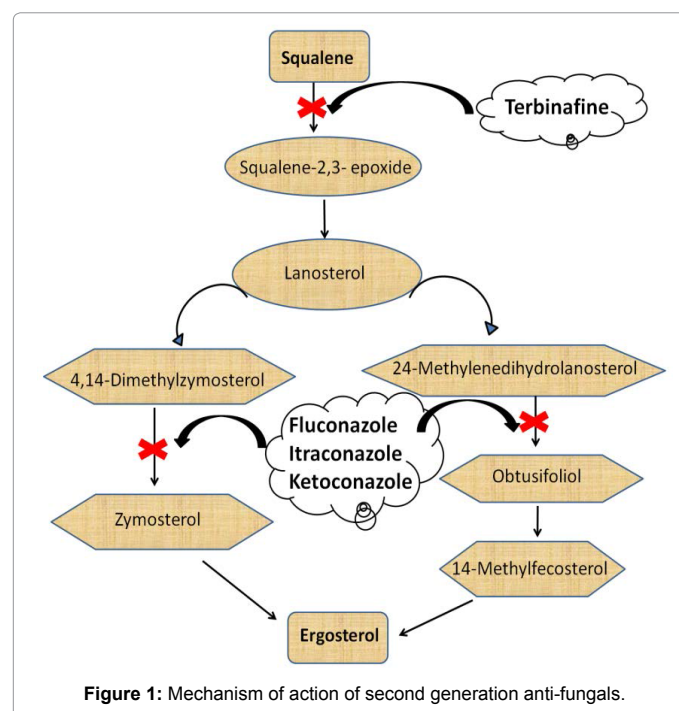
**Griseofulvin:** Griseofulvin has been in the market since last 40 years and represented a promising advancement in antifungal therapy. The drug was found to be active against growing hyphae. In addition, it inhibits nucleic acid synthesis, and arrests fungal cell mitosis in metaphase. However, its effectiveness in onychomycosis is questionable, because of its limited spectrum of activity against dermatophytes only and hence, a longer duration of therapy is required [2]. The fungistatic effect of griseofulvin is believed to be confined in the nail matrix only, hence, only the newly grown nail plate is cleared of the invading fungus. Due to poor retention of the drug in the nail plate after the cessation of oral dosing, a continuous therapy for a prolonged period of time becomes a requisite to maintain the therapeutic level of drug in the nail plate, owing to slow growth of the nail. The prolonged therapy is generally associated with a number of side effects resulting in poor patient compliance, which in turn leads to meager success rate and recurrence of infection [3]. Additionally, the cost of prolonged daily therapy with griseofulvin could be unaffordable.

**Ketoconazole:** Ketoconazole was the first orally active imidazole having a broad spectrum of activity against dermatophytes as well as non-dermatophytes. However, the prolonged oral delivery of ketoconazole is associated with a number of adverse effects including

hypersensitivity reactions, nausea, vomiting, headache, abdominal pain, pruritus, and fever and drug interactions. The major drug interactions of ketoconazole were observed with the drugs metabolized by the cytochrome P-450 system, as well as with certain other drugs (warfarin, rifampin, isoniazid, cyclosporine, terfenadine, cisapride) [4]. Moreover, the prolonged ketoconazole therapy necessitates regular liver function testing that was due to the hepatotoxicity [5]. Hence, the use of ketoconazole for an extended period was restricted prior to the invention of new antifungal agents because of its poor safety and efficacy data.

### Second generation oral antifungals

The second generation of antifungals includes azoles and allylamine (terbinafine). The azoles and allylamines block the pathway of ergosterol synthesis at different points, which results in difference of implications for efficacy and side effects these drugs Figure 1 and Table 1 summarizes



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Variable	Griseofulvin	Ketoconazole	Fluconazole	Itraconazole	Terbinafine
Route of administration	Oral	Oral / Topical	Oral or intravenous	Oral	Oral / Topical
Associated Problems	Tolerance, longer treatment length	Toxicity, Interactions	Interactions, Microbe resistance	Interactions	Adverse Effects
Affinity for keratin	Low	High	High	High	High
Indicated for skin infection	+	+	+	+	+
Indicated for nail infection	-	-	+	+	+
Commercial Dosage Forms Available	Suspension (125 mg / 5ml); Tablet (125 mg, 250 mg, 500 mg)	Cream (2%), Gel (2%), Shampoo (2%), Tablet (250mg)	Suspension (50 mg/5ml, 200 mg/5ml), Injectable (200 mg/100ml, 400 mg/200ml), Tablet (50 mg, 100 mg, 150 mg, 200 mg)	Capsules (100 mg), Tablet (200 mg), Solution (10 mg/ml)	Tablet (250 mg), Gel (1%), Cream (1%), Solution (1%), Spray (1%)

Table 1: Key characteristics of oral antifungal agents.

Nature of study	No. of subjects	Stage of Onychomycosis	Dosage Regimen	Follow up period	Observation	Remarks	Ref.
*	20	Severe	150 mg once a week for 9.3 months	6 months	92% of toenails were clinically and mycologically free.	Effective in the long-term therapy of onychomycosis.	[10]
Open-labelled, non-comparative study	16	Finger and toenail	150 mg daily for 6 months	*	No adverse effect was observed.	Safe and efficacious, however, further studies are needed to determine a cost-effective dosing regimen.	[11]
Pilot study	11	Toenail of fingernail	Group I: Eight patients received 300 mg once weekly Group II: one patient received 200 mg once weekly Group III: two patients received 100 or 200 mg of fluconazole every other day.	*	6 patients with toenails involved were clinically cured after a mean treatment duration of 6 months, and all five patients with fingernails involved were cured after 3.7 months.	Intermittent fluconazole, taken once weekly or on alternate days, is a well-tolerated and efficacious method to treat onychomycosis.	[12]
An open-label, noncomparative, multicenter study	114	Toenail	150-mg fluconazole once per week	1, 3 and 6 months	After 6 months Clinical cure: 54% Mycological cure: 76%.	Well tolerated with adverse events of mild-to-moderate severity.	[13]
A placebo-controlled, randomized, double-blind trial	362	Finger or toenail	150, 300, and 450 mg once weekly for 6 months	*	Clinical cure amongst all the doses was between 80 and 90% Mycological cure was 53, 59, and 61% for 150, 300 and 450 mg dose, respectively.	All the regimens were Well tolerated and incidence and severity of adverse events were similar for fluconazole- and placebo-treated patients.	[14]
*	50	Finger and toenail	400 mg once weekly for 12 months	*	21.2% patients achieved mycological eradication, yet no clinical cure was obtained, while, 12.1% patients showed mycological and clinical failure.	High efficacy, good tolerance and low therapy costs.	[15]

\* Not mentioned

Table 2: Clinical studies of fluconazole carried out by various researchers.

the comparison of some key characteristics of the first generation (griseofulvin and ketoconazole) and second generation (itraconazole, fluconazole, terbinafine) antifungal drugs [6].

**Fluconazole:** Fluconazole, a water soluble bis-triazole drug, is available commercially in oral and intravenous dosage forms. The drug has high bioavailability (>90%) which is due to the physiochemical properties of the drug like low molecular weight and high water solubility. The drug is shown to have high affinity towards keratin which was evidenced by its detection in skin within 3 h of initial therapy. In case of nails, an investigation found the concentration of fluconazole to be 1.3 and 1.8 µg/g on 1st and 14th day of treatment (50 mg per day), respectively in healthy male volunteers [7]. In a long term study (6 months) on healthy and diseased nails, the drug was found to retain in the nail plate (2 µg/g) for around 5 months after discontinuation of therapy [8].

Gupta et al. (2013) compared databases of different researchers to study the relationships between fluconazole doses, cure rates and duration of therapy. The findings of the analysis concluded that longer

treatments, but not higher weekly fluconazole doses, results in better cure rates for toenail, and possibly fingernail, onychomycosis. The lowest dose of 150 mg weekly for more than 6 months was recommended for onychomycosis [9]. Table 2 summarizes clinical studies carried out by various researchers in order to optimize the dosage regimen of fluconazole.

**Itraconazole:** Itraconazole, a triazole derivative was approved by FDA in 1995 for the management of onychomycosis and is available as capsule and oral solution. The broad spectrum activity, high affinity for keratin and pharmacokinetic profile of itraconazole is accountable for its high efficacy as compared to other antifungals. Although, initially the drug was indicated for the treatment of onychomycosis due to dermatophytes, it has also found to be effective against non-dermatophytes. It is rapidly absorbed, attains the peak level within 4h and undergoes extensive metabolism by the liver. The observed absolute oral bioavailability of itraconazole is about 56% [7]. The drug reaches the nail plate within 24 h of administration and can be observed in the distal part of the nail plate even after one month of initiation of therapy

[10-16]. The diffusion of the drug into the distal part of the nail occurs via nail bed that is further confirmed due to the presence of two fold-higher drug concentration in subungual nail material than in distal nail clippings of a patient treated for one month. Itraconazole is found to be present in the nail for longer period of time than fluconazole or terbinafine and could be detected even after 9 months of termination of therapy [6]. The oral therapies have usually been recommended as a continuous-dosing regimen for the treatment of onychomycosis. For example, primarily the suggested dose of itraconazole for the management of onychomycosis was 200 mg per day for 3 months. Pharmacokinetic data of itraconazole in the nail bed observed from this study was further utilized to develop an alternative optimal dosage regimen for the treatment of onychomycosis. The treatment course with itraconazole was suggested to be curtailed to only one week interval owing to its rapid penetration and protracted persistence in the nail even after the discontinuation of drug. Moreover, the shorter dosing regimens have merits in terms of being cost effective and higher patient compliance as compared with longer regimens. Therefore, itraconazole has been assessed in intermittent dosing or “pulse therapy” regimens. Pulse therapy with itraconazole embodies dosing for 1 week (pulse) per month for a set number of months [17]. The instances of regimens that have been investigated for safety and efficacy in randomized trials included a three and a four pulse regimen with doses of 200 mg of itraconazole twice daily [18,19] and a two pulse regimen with 200 mg of itraconazole twice daily [17,20-22]. Data from clinical practice and clinical trials indicate that the 1-week pulse regimen of itraconazole is well tolerated and associated with a favorable safety profile [23]. This might lead to the conclusion of using 200 mg one week pulse regimen as efficacious and safer dosage regimen. Table 3 summarizes the various clinical studies involving different regimens of itraconazole and the cure rate obtained.

**Terbinafine:** Terbinafine is an allylamine derivative reported to have a broad spectrum activity against dermatophytes, certain dimorphic fungi, yeasts and moulds, but has less activity against *C. albicans* infections. Being lipophilic in nature it gets distributed in tissues like skin, fat, and nails. The drug showed high cure rates (80%)

with 20% relapse rate and minimal side effects when administered in dermatophytic infections of the toenails for 12 months. In subsequent trials, concise treatment times were evaluated as the mycologic cure was observed early in these studies. In an investigation, 250 mg per day of terbinafine or placebo was given to 85 patients with mycologically proven dermatophyte onychomycosis of the toenails (75 patients) or fingernails (10 patients) for the period of 12 weeks, with long term follow up till 36 weeks. The observations revealed the mycological cure rate of 82% and 12% at follow up among terbinafine treated and placebo treated patients, respectively. The clinical cure rates of fingernail infections were observed to be 71% in terbinafine treated patients at follow up. The findings demonstrated the statistically significant advantage of terbinafine over placebo [24,25].

Subsequently, various studies are summarized in Table 4 that were conducted varying the dosage regimens and treatment periods in order to obtain higher clinical and mycological cure rate. From the above studies [26-30], it could be inferred that pulse therapy was equally efficacious as that of the continuous therapy and in certain cases it was even better. Thus, the former regimen can be preferred owing to the cost effectiveness of the treatment.

Some investigations were carried out in order to compare different available antifungals so as to determine the most reliable and efficacious antifungal agent. Table 5 enlists the comparison of clinical studies of antifungal agents [31-35]. From these findings, terbinafine was found to be more efficacious than other antifungals for the management of onychomycosis.

### Topical therapy

The cure of onychomycosis is known to be strenuous since it is chronic, difficult to obliterate and tends to relapse [36-39]. The pharmacotherapy for onychomycosis widely involves the oral antifungals because their systemic or circulatory distribution allows them to penetrate the nail apparatus and the nail plate. Unfortunately, oral therapy is generally coupled with serious side effects, drug interactions, and high recurrence rates. Therefore, topical therapy is an attractive option due to its non-

Nature of study	No. of subjects	Site or Stage of Onychomycosis	Dosage Regimen	Follow up period	Observation	Remarks	Ref.
Multicenter, randomized, double blind, placebo controlled	73	Fingernail	200 mg twice daily, or placebo for the first week of each month for 2 consecutive months	19 weeks	Clinical success: 77% in drug treated vs 0% in placebo treated patients. Mycological cure: 73% in drug treated vs 13% in placebo treated patients.	Short term pulse therapy is effective and well tolerated.	[17]
*	50	Toenail	400 mg per day d given for 1 week each month for 3 to 4 months	Upto 1 year	Clinical Cure was 76 to 84%. Mycological Cure was 72 - 80 %.	Pulse therapy with itraconazole is an effective and safe treatment option for onychomycosis as the drug persist in nail for a prolonged time even after the discontinuation of therapy.	[18]
Multicentre, Double blind, Parallel group study	129	Distal subungual onychomycosis of toenail	Group I: 200 mg daily for 3 months (continuous therapy); Group II: 400 mg daily 1 week per month for 3 months (pulse therapy)	9 months	Clinical success: 69%, in Group I and 81% in Group II. Mycological cure: 66 and 69% in Group I and II, respectively.	Both regimens are effective, safe and well tolerated.	[19]
Multicenter, randomized, double blind, placebo controlled	214	Toenail	200 mg capsules once daily for 12 weeks	9 months	Clinical success: 65% in itraconazole treated patients versus 3% of placebo treated patients Mycological cure: 54% in itraconazole treated patients and 6% of placebo treated patients.	Continuous therapy of itraconazole is highly effective, well-tolerated therapy for the management of toenail onychomycosis.	[24]

\*Not Mentioned

**Table 3:** Clinical studies involving different regimens of itraconazole

Nature of study	No. of subjects	Site or Stage of Onychomycosis	Dosage Regimen	Follow up period	Observation	Remarks	Ref.
Randomized	120	Toenail	250 mg per day for 24 weeks	Upto 48 weeks	Cure rates of 40%, 71% and 79% were observed after 6, 12 and 24 weeks, respectively.	A treatment period of 12 weeks is sufficient.	[26]
*	65	Distal subungual onychomycosis of the fingernails or toenails,	250 mg daily for 48 weeks	6 months	Mycological and clinical cure rates were 70% and 54% for <i>C. albicans</i> , and 85% and 63% for <i>C. parapsilosis</i> , respectively.	In addition to dermatophytes, terbinafine is also effective against non-dermatophytes.	[27]
Multicentre, randomized, double-blind,	118	Toenail	250 mg per day or placebo for 12 weeks	48 weeks	Mycological cure: 94%.	Terbinafine is effective against non-dermatophytes.	[28]
Double blind	148	Finger and toenail	Group I: 250 mg per day for 6 weeks, Group II: 250 mg per day for 12 weeks.	36 weeks	Clinical cure: 45.9% Mycological cure: 58.9%.	In toenail mycoses without visible matrix involvement, 6 weeks treatment of terbinafine is generally not sufficient, whereas, fingernail infections respond well to this short therapy.	[29]
Multicentre, randomized, double blind	618	Distal subungual	Group I: 250 mg daily for 3 months (continuous) Group II: 500 mg daily for 1 week per month for 3 months (pulse)	18 months	Clinical cure: 44.6% and 29.3% in Group I and II, respectively. Mycologic cure: 70.9% and 58.7% in Group I and II, respectively.	Continuous therapy is superior as compared to pulse-dose.	[30]
Open label, randomized	504	Toenail	250 mg per day for 12 weeks with or without aggressive toenail debridement (at baseline and weeks 6, 12, and 24)	48 weeks	Clinical cure: 41.3% Mycological cure: 64.0%.	Debridement showed no effect on mycologic outcomes or clinical effectiveness.	[31]
*	55	Finger and toe nail	500 mg per day for 1 week, followed by a 3-week interval + Topical 1% terbinafine cream was applied daily	1 year	Complete cure: 74.5%.	Safe and cost effective regimen.	[32]
Randomized	76	Toenail	Group I: 250 mg daily for 12 weeks Group II: 3 pulses of terbinafine (each of 500 mg daily for a week) repeated every 4 weeks	24 weeks	Clinical success: 86.8% in group I and 71.1% in Group II. Mycological cure: ~ 75%.	A pulse dosing schedule was as efficacious as in a continuous daily schedule.	[33]

\* Not mentioned

**Table 4:** various studies conducted varying the dosage regimens of Terbinafine.

invasiveness, localized effects and obliteration of systemic adverse events and drug interactions [40]. The primary drawback associated with the existing topical antifungal agent is their inability to penetrate into the nail plate resulting in poor mycological and complete cure rates. Hence, the ideal scenario would be to develop the topical agents that have an escalated nail plate penetration as compared to the existing drugs, as well as obviate the systemic uptake [41].

The conventional topical formulations such as creams or ointments are not suitable vehicles for transungual delivery because of the dissimilarity of nail keratin structure with that of the epidermis. Therefore, products specifically suggested for effective transungual therapy are nail lacquers. The primary drugs used as nail lacquers include ciclopirox (8%) and amorolfine (5%). After solvent evaporation, the concentration of the drug in lacquer increases and the film on the nail plate surface enables prolonged contact of the drug which enhances both nail hydration and drug diffusion through the affected surface.

Until 2013, only three topical nail lacquers i.e. Penlac® (ciclopirox), Ciclopoli® (ciclopirox) and Loceryl® (amorolfine) were approved for the management of onychomycosis in few countries. In 2014, two new topical formulations Kerydin™ (tavaborole) and Jublia® (efinaconazole) which are alcohol based solutions were approved by the USFDA.

**Ciclopirox:** Ciclopirox, a hydroxy-pyridone derivative exhibits a broad spectrum antifungal activity. The drug has been under investigation since 1973, however, it is being used in the lacquer form since 1990s. In nail lacquer formulation, the drug is present as a free acid, while, in other formulations (cream, suspension, shampoo, gel, solution, powder, globules) it is present as ethanalamine salt and the former is known to be a more active form [42,43]. The 8% concentration of drug in nail lacquer increases to about 35% after its application, that is significantly higher than the minimal inhibitory concentration (MIC) for *T. rubrum*, *T. mentagrophytes* and *Candida albicans* [44]. The drug is thought to act by chelating trivalent cations (Fe<sup>3+</sup> and Al<sup>3+</sup>) which results in the inhibition of metal-dependent enzymes (cytochromes, catalases, peroxidases), that in turn reduced the transport of ions through pathogen cytoplasmic membranes as well as reduce nutrient intake. The clinical studies revealing the efficacy of 8% ciclopirox are enlisted in Table 6.

**Amorolfine:** Amorolfine is a morpholine derivative, reported to exhibit a broad spectrum fungicidal and fungistatic activity [45-49]. It acts by inhibiting ergosterol synthesis at two steps i.e by inhibiting delta-14 reductase and delta 7, 8-isomerase. The depletion of ergosterol affects the membrane synthesis of pathogen and causes



Nature of study	No. of subjects	Site or Stage of Onychomycosis	Dosage Regimen	Follow up period	Observation	Remarks	Ref.
Double blind, randomized, comparative	372	Toenail	Group I: Terbinafine; 250 mg/day (Continuous) Group II: Itraconazole; 200 mg/day for 12 weeks	*	Clinical cure: 76.2% in Group I and 58.1% in Group II. Mycological Cure: 73% in Group I and 45.8% in group II.	Terbinafine is more efficacious as compared to itraconazole.	[34]
Double blind, randomized, multicenter, comparative	137	*	Group I: Terbinafine (250 mg daily for 12 weeks) Group II: Fluconazole (150 mg once weekly for 12 weeks) Group III: Fluconazole (once weekly for 24 weeks)	*	Clinical cure: 67%, 21% and 32% in Group I, II and III, respectively. Mycological cure: 89%, 51% and 49%, in Group I, II and III, respectively.	Terbinafine is more effective than fluconazole.	[35]
Single blind, randomized, multicentre, comparative	190	Toenail	Group I: Itraconazole pulse (200 mg twice daily for 1 week) followed by terbinafine pulse (250 mg twice daily for 1 week) Group II: 3 or 4 pulses of terbinafine	72 weeks	Clinical cure: 56.0% and 38.9% in Group I and II, respectively. Mycological cure: 72.0% in Group I versus 48.9% in Group II.	Sequential pulse therapy with itraconazole and terbinafine more is effective and safe.	[36]
Double-blind, double-dummy study	151	Toenail	Group I: Terbinafine 250 mg/day for 12 or 16 weeks (continuous) Group II: Itraconazole 400 mg/day for 1 week in every 4 weeks for 12 or 16 weeks (intermittent)	54 months	Mycologic cure: 46% in Group I and 13% group II. Mycological Relapse rate: 23% and 53% in Group I and II, respectively. Clinical relapse rate: 21% and 48% in Group I and II, respectively.	Continuous terbinafine provided superior efficacy and lower rates of relapse as compared to intermittent itraconazole.	[37]
Open labeled, randomized, comparative	50	Distal subungual toenail onychomycosis	Group I: 150 mg fluconazole once weekly for 3 months Group II: 200 mg itraconazole twice daily during the first week of each month of 3 month of treatment period Group III: 250 mg per day terbinafine for 3 months	6 months	Clinical cure rates: 81.3%, 77.8% and 37.5% in Group I, II and III, respectively. Mycological cure: 75%, 61.1% and 31.2% in Group I, II and III, respectively.	Fluconazole was least effective. With regard to cost-effectiveness, side effects and the cure rates, terbinafine could be the drug of choice in the short-term treatment of toenail onychomycosis.	[38]
Long term Prospective	73	Toenail	Group I: Terbinafine 250 mg/day (continuous) Group II: Itraconazole 400 mg/day for 1 week per month	36 months	Relapse Rate: 11.9% in Group I and 35.7% in Group II.	Terbinafine provide better long-term success than itraconazole.	[39]

\* Not mentioned

**Table 5:** Comparison of clinical studies of different antifungal agents.

No. of subjects	Site or Stage of Onychomycosis	Dosage Regimen	Follow up period	Observation	Remarks	Ref.
460	Mild to moderate toe onychomycosis	Group I: Ciclopirox once daily for 48 weeks Group II: Vehicle treated in US and other countries	*	Mycological cure: ~ 32% in Group I and ~ 10% in Group II in US. In the non-US studies, the mycologic cure rates ranged from 46.7% to 85.7%.	Excellent safety profile; a treatment choice with a favorable benefit-to-risk ratio.	[45]
460	Affected nail area between 20% and 65%	Group I: Ciclopirox once daily for 48 weeks Group II: Vehicle	3 months	Mycologic cure: 34% in Group I and 10% in Group II. Clinical cure: 8% in Group I and 1% in Group II.	Safe and effective.	[46]
215	Finger and toenail onychomycosis with diabetes	Once daily for 6 months	*	Ciclopirox nail lacquer reduced the mean affected nail area from 64.3% at baseline to 41.2% at 3 months and 25.7% at 6 months.	Safe and effective for the topical treatment of onychomycosis in patients with diabetes.	[47]
49	Distal subungual onychomycosis with diabetes	Once daily for 48 weeks	*	Clinical cure: 63.4% Mycological cure: 54.3	Safe and effective treatment for distal subungual onychomycosis in patients with diabetes mellitus.	[48]
40	Distal and lateral subungual and lateral subungual toenail onychomycosis	Once daily for 9 months	*	22% of the patients had complete cure.	Low cure rate, can be used in patients who would not or cannot tolerate oral therapy.	[49]

\* Not mentioned

**Table 6:** Clinical studies investigation efficacy of ciclopirox.

non-typical spherical sterols to accumulate in the fungal cytoplasmic membranes [50] which will in-turn affect the synthesis of membrane. The pharmacokinetic properties of the drug results in high penetration through the nail plate with minimal systemic absorption. Because of the solvent evaporation, the concentration of amorolfine increases from 5% to 27% [51]. Because of the pharmacokinetic profile of amorolfine, the drug has good penetration through the nail to the nail bed with minimal systemic absorption. Table 7 summarizes the clinical trials investigating the safety and efficacy of amorolfine in case of onychomycosis.

The findings obtained by different researchers revealed that no significant difference was obtained in cure rates with the application of once weekly or twice weekly of the nail lacquer. Therefore, once weekly use of nail lacquer containing 5% amorolfine can be preferred owing to patient compliance as well as cost effectiveness.

### Combination therapy

The monotherapy is undoubtedly efficacious in short term; however, a complete and long lasting cure is often unattainable. In those cases, combination therapy has been found to be promising in ameliorating the overall cure rate of onychomycosis [52-55]. The use of combination approach and the application of antifungal drug synergy is a well-known concept in mycology. The combination of two or more drugs can result in augmented efficacy, rapidity of effects, a broader spectrum of activity and improved patient tolerability [55-59]. The benefits of combination therapy were first shown with griseofulvin as the standard therapy for the treatment of onychomycosis (due to dermatophytes) for the last 30 years. More recently, combinations of newer generation of drugs have been shown to have greater efficacy than griseofulvin (Table 8).

### Newer topical solutions

There have been a number of unsuccessful development programs over the past decade as researchers endeavored to formulate antifungals that manifested in vitro activity against the common pathogens causing onychomycosis [60-63]. The discovery of new chemical entities exhibiting a broad spectrum of activity against multiple relevant fungal

pathogens has led to progressive development of the dosage form and formulation for the treatment of different fungal diseases including onychomycosis [64,65].

The newer antifungal agents among azoles are efinaconazole, luliconazole, albaconazole, posaconazole and revuconazole, among benzoxaboroles is tevaborole and among allyl amines are NB-002 and NB-00X. Few amongst them are already commercially available, however, few of them are in different clinical phases.

**Efinaconazole:** Efinaconazole (Jublia® and Clenafin®) is an emerging antifungal therapy for the topical treatment of onychomycosis. Efinaconazole is an inhibitor of sterol 14 $\alpha$ -demethylase and possess broad spectrum antifungal activity against dermatophytes, yeasts and non-dermatophyte molds. It is approved for use in Canada and the USA as a 10% topical solution for the treatment of onychomycosis [66,67].

The physicochemical properties and antifungal activity of drug and the nature of the vehicle are believed to contribute in favorable therapeutic outcomes of onychomycosis. Efinaconazole (10%) solution is found to be significantly more active than amorolfine and ciclopirox lacquers against dermatophytes in an in vivo guinea pig model. The keratin-bound efinaconazole was observed to release more rapidly after repeated washings (85.7% bound; 46% released) as compared to amorolfine (98.1% bound, 6.9% released) and ciclopirox (99.3% bound, 2.4% released) due to its lower affinity towards keratin [67]. The commercial formulation of the drug (solution) comprises of alcohol, lipophilic esters, and cyclomethicone. These components help to create a low surface tension which seems to be ideal for application to the surface of dry nail plate [68,69]. Unlike previous lacquer-based treatments, such as ciclopirox (8%), efinaconazole (10%) solution is effective without concomitant nail debridement between the applications. The studies, including investigation of efinaconazole 10% solution are summarized in Table 9.

**Luliconazole:** Luliconazole is a topical imidazole that has been tested in Phase I/II clinical trials. It is approved for the treatment of dermatomycoses in Japan [70]. A new set of clinical trials has been initiated to investigate luliconazole for the treatment of onychomycosis

No. of subjects	Site or Stage of Onychomycosis	Dosage Regimen	Follow up period	Observation	Remarks	Ref.
554	Finger and Toenails	Group I: Twice weekly for 6 months Group II: Once weekly for 6 months	3 months	Clinical cure: 52% and 46.1% in Group I and II, respectively. Mycological cure: 79.2 and 77.2 in Group I and II, respectively.	No statistically significant difference between the two groups.	[52]
157	More than 80% of the surface area of the nail affected	Group I: 2% amorolfine once weekly for 6 months Group II: 5% amorolfine once weekly for 6 months	3 months	% Cure: 12% and 38% in Group I and II, respectively.	5 % nail lacquer is significantly more effective than 2% of nail lacquer.	[53]
727	Finger or toenail	Group I: 2% amorolfine once weekly for 6 months Group II: 2% amorolfine twice weekly for 6 months Group III: 5% amorolfine once weekly for 6 months Group IV: 5% amorolfine twice weekly for 6 months	3 months	% Cure achieved: 16.3%, 35.8%, 45.6% and 51.8% in Group I, II, III and IV, respectively.	Amorolfine in the form of a 5% lacquer administered either once or twice weekly proved more effective.	[54]
456	Finger and toenails	Group I: 5% amorolfine once weekly for 6 months Group I: 5% amorolfine twice weekly for 6 months	3 months	Overall cure rate: 46% and 54.2% in Group I and II, respectively. Mycological cure rate: 70.6 and 76.1% in Group I and II, respectively.	No significant difference in cure rates.	[55]

**Table 7:** Clinical trials investigating the safety and efficacy of amorolfine

Combination	No. of subjects	Site or Stage of Onychomycosis	Dosage Regimen	Follow up period	Observation	Remarks	Ref.
Topical tioconazole and oral Griseofulvin	10	Toenail	Group I: 500mg griseofulvin twice daily for one year + Tioconazole (28%) solution to be applied twice daily Group II: 500mg griseofulvin twice daily for one year + Placebo solution to be applied twice daily	*	Complete clinical cure: 69% and 41% in Group I and II, respectively.	Combination therapy produced a more rapid and complete response than when using the oral drug alone.	[56]
Oral Griseofulvin + oral Itraconazole	90	Toenail	Group I: Itraconazole (100mg per day) Group II: Griseofulvin (500 mg daily) Each group was divided into three subgroups that received different topical treatment: antimycotic cream (itraconazole 1%), keratolytic cream (urea 40%), or placebo cream.	*	The itraconazole group showed complete clearance in combination with isoconazole cream in 73.3% patients, in combination with keratolytic cream in 78.5% patients and in combination with placebo cream in 91.6% patients.  The griseofulvin group showed complete clearance in combination with isoconazole cream in 46.1% patients, in combination with keratolytic cream in 42.8% patients, and in combination with placebo cream in 26.6% patients.	The itraconazole group showed better results compared with the griseofulvin group.	[57]
Topical amorolfine and oral terbinafine	147	Toenail onychomycosis with matrix area involvement	Group I: Oral terbinafine 250mg once daily for 6 months + 15 months of once-weekly topical amorolfine lacquer Group II: Oral terbinafine once daily for 12 months + 15 months of once-weekly topical amorolfine lacquer Group III: Terbinafine monotherapy for 12 weeks	18 months	Complete cure rate: 44%, 72.3% and 37.5% in Group I, II and III, respectively.  Mycological cure: 35%, 27.5% and 17.1% in Group I, II and III, respectively.	Combination therapy proved to be effective in severe onychomycosis.	[58]
Topical amorolfine + oral terbinafine	147	Toenail onychomycosis with matrix area involvement	Group I: Oral terbinafine 250mg once daily for 6 months + 15 months of once-weekly topical amorolfine lacquer Group II: Oral terbinafine once daily for 12 months + 15 months of once-weekly topical amorolfine lacquer Group III: Terbinafine monotherapy for 12 weeks	18 months	Mycological cure: 35%, 27.5% and 17.1% in Group I, II and III, respectively.  Overall cure: 44%, 72.3% and 37.5% in Group I, II and III, respectively.	Combination therapy regime with oral and systemic treatment was superior in efficacy as compare to monotherapy.	[59]
Topical amorolfine and oral itraconazole	131	Toenail onychomycosis with matrix area involvement	Group I: Amorolfine 5% nail lacquer once weekly for 24 weeks + 200 mg itraconazole once daily for 6 weeks Group II: amorolfine 5% nail lacquer once weekly for 24 weeks + 200 mg itraconazole once daily for 12 weeks Group III: Itraconazole monotherapy for 12 weeks	24weeks	Mycological cure: 93.3%, 82.9% and 41.17% in Group I, II and III, respectively, in 12 weeks.  Complete cure: 83.7%, 93.9% and 68.8% in Group I, II and III, respectively, in 24 weeks.	Combination therapy proved to be effective in severe onychomycosis.	[60]
Topical amorolfine + oral itraconazole	44 patients per group	Severe toenail onychomycosis	Group I: Amorolfine (5%) nail lacquer once weekly for 24 weeks and + Itraconazole (2 capsules (100mg) once daily for 6 weeks Group II: Amorolfine (5%) nail lacquer once weekly for 24 weeks and + Itraconazole (2 capsules (100mg) once daily for 12 weeks Group III: Monotherapy for Itraconazole for 12 weeks	24 weeks	Mycologic cure: 93%, 83% and 41% in Group I, II and III, respectively at week 12.  Complete cure: 84%, 94% and 69% in Group I, II and III, respectively at week 24.	Combination therapy was clinical effective and cost effective.	[61]
Topical amorolfine and oral Itraconazole and	91	Fingernails	Group I: itraconazole pulse therapy for 2 months and + amorolfine 5% solution nail lacquer for 6 months Group II: Monotherapy with three pulses of itraconazole	3 months	Mycologic cure: 74% and 60% in Group I and II, respectively at 3 months.  Complete cure: 93% and 81% in Group I and II, respectively at 9 months.	Combination therapy was more effective in case of severe onychomycosis than monotherapy.	[62]
Topical ciclopirox + oral terbinafine	73	Moderate to severe	Group I: ciclopirox (8%) once daily for 48 weeks + 4 weeks of terbinafine 250 mg/day, followed by 4 weeks of rest (no terbinafine), then another 4 weeks of terbinafine 250 mg/day Group II: ciclopirox nail lacquer once daily for 48 weeks plus terbinafine 250 mg/day for 12 weeks Group III: terbinafine 250 mg/day for 12 weeks	48 weeks	Mycologic cure: 66.7%, 70.4% and 56% in Group I, II and III, respectively.  Complete cure: 40%, 33.3% and 34.8% in Group I, II and III, respectively.	Combination therapy may be an alternative regimen to continuous terbinafine in the treatment of moderate to severe onychomycosis.	[63]

Oral terbinafine + topical ciclopirox or topical amorolfine	48	Finger and toenail	Group I: Terbinafine 250 mg, one tablet twice daily for seven days every month (pulse therapy) Group II: oral terbinafine pulse therapy + topical ciclopirox olamine 8% to be applied once daily Group III: oral terbinafine pulse therapy plus topical amorolfine hydrochloride 5% to be applied once weekly for 4 months	36 weeks	Clinical cure: 71.73, 82.60 and 73.91% patients in groups I, II and III, respectively. Mycological cure rate: 88.9, 88.9 and 85.7% in groups I, II and III, respectively.	Combination therapy with topical ciclopirox or amorolfine did not show any significant difference in efficacy in comparison to monotherapy with oral terbinafine.	[64]
Topical amorolfine and oral terbinafine	249	Toenail	Group I: amorolfine hydrochloride 5% nail lacquer once weekly for 12 months + Terbinafine 250 mg once daily for 3 months Group II: Terbinafine alone once daily for 3 months	18 months	Complete cure rate: 59.2 and 45% in Group I and II, respectively.	Combination therapy enhanced clinical efficacy and was more cost-effective than terbinafine alone.	[65]

\*Not mentioned

**Table 8:** Clinical trials investigating efficacy of different combination of antifungal agents.

No. of subjects	Site or Stage of Onychomycosis	Dosage Regimen	Follow up period	Observation	Remarks	Ref.
Study 1: N = 870; Study 2: N <sub>2</sub> = 785	Distal lateral subungual onychomycosis	Group I: Efinaconazole 10% solution once daily for 48 weeks Group II: Vehicle treated	4 weeks	Mycologic cure: significantly greater (~ 53%) in Group I than Group II. Complete cure: ~16% in Group I and ~ 4% in Group II.	A viable alternative to oral treatment options.	[66]
135	Distal lateral subungual onychomycosis	Group I: Efinaconazole 10% solution (with semioclusion), Group II: Efinaconazole 10% solution (without semioclusion), Group III: efinaconazole 5% solution, Group IV: vehicle (once daily for 36 weeks)	4 weeks	Mycologic cure: 83%, 87%, and 87% in Group I, II and III, respectively. Complete cure: was numerically higher in all active groups (16%-26%) compared with vehicle (9%).	Efinaconazole 10% solution (with or without semioclusion) was more effective than vehicle.	[68]
1,655	Mild to moderate	Group I: Efinaconazole 10% solution once daily for 48 weeks Group II: Vehicle treated	*	Mycologic cure: 58.2% and 55.5% in mild and moderate onychomycosis, respectively, in Group I and 25.0% and 14.1%, respectively, in Group II.	A useful topical option in the treatment of mild-to-moderate onychomycosis.	[69]

\* Not mentioned

**Table 9:** Clinical studies including investigation of efinaconazole 10% solution.

in other markets also like USA. A pharmacokinetic study of luliconazole, in 24 participants with moderate-to-severe DLSO of both great toenails has recently been completed. The participants applied 20 mg/mL luliconazole, which is twice the recommended daily dose, for 29 days with a seven day follow-up. The pharmacokinetic assessment revealed that the systemic distribution of the drug was low (0.083-0.100 ng/ml) with the drug steady state achieved at eighth day. The drug was detected in the systemic circulation of several patients during the seven day follow-up period. The median concentration of luliconazole in the nail at this time point was 34.65 mg/g [71].

**Tevaborole:** Tevaborole, an oxaborole antifungal agent, is merchandised by Anacor Pharmaceuticals, CA, USA under the trade name “Kerydin”. The drug got its FDA approval in 2014 for the treatment of fungal infection of the nail plate as well as of the nail bed. It acts by impeding protein synthesis of the pathogen by inhibiting the enzyme cytosolic leucyl-transfer RNA synthetase (LeuRS). The latter plays a significant role in protein synthesis pathway in the fungus. The inhibition of protein synthesis results in inhibition of cell growth and ultimately leads to eradication of fungus [72].

The topical use of tevaborole is preferred over the oral therapy so as to reduce the incidence of systemic side effects. The drug obliterates the use of debridement of the affected nail, which is often invasive and painful. The drug- drug interactions are to lesser extent in case of

tevaborole as it has shown negligible inhibition of cytochrome P450 enzyme. Moreover, the safety and efficacy of the drug is found to be analogous to other available topical antifungal agents [73].

After obtaining the reasonable results from two clinical trials carried out by Ancor Pharmaceuticals, CA, USA; the findings from other multicentric analogous trials are also keenly anticipated to be successful. These clinical trials have imparted the advantage of assessment of systemic doses along with the different dosage forms apart from topical application. Some of them have accomplished clinical phases I and II [74]. The strong antifungal action of this drug is due to the presence of a very small element of boron in its structure. The drug possesses high patient compliance because of its topical application with negligible side effects. An extensive research is still required to ascertain the efficacy of this drug in comparison to other topical agents available.

### Other investigational drugs for onychomycosis

The management of onychomycosis is a known to be a challenging endeavor owing to low cure rates and recurrence [75-80]. Due to this new molecules are gaining attraction of the researchers and subsequent clinical trials of these molecules indicate an equal investment for pharmaceutical companies. These drugs are under investigation for the treatment of onychomycosis, which vary widely from initial in vitro studies to gold-standard Phase III studies [81-84]. Table 10 enlists



Drug	Route of administration	Clinical Phase	Recommended Regimen	Ref.
Albaconazole	Oral	Phase II	Four 100 mg capsules daily for 36 weeks	[75,76]
Posaconazole	Oral	Phase III	200 mg per day	[77,78]
Ravuconazole	Oral	Phase III	200 mg per day for 12 weeks	[79,80]
NB-002 and NB-00X	Topical	Phase II	0.5% once daily for mild DLSO, 0.5% twice daily for moderate DLSO and 0.25% twice daily for severe DLSO for 42 weeks	[81]
TDT-067: Terbinafine in Transfersome	Topical	Phase II	1.5% TDT-067 for 12 weeks	[82,83]
Terbinafine nail solution	Topical	Phase III	10% solution for 12 weeks	[84,85]

**Table 10:** List of newer antifungal agents.

some these drugs which are being watch over by the clinicians for their efficacy and safety profile.

## Conclusion

The stress has been laid upon by regulatory agencies on the importance of assessing the drug- dose response relationship and if possible, exposure-response relationship for the safety and effectiveness during drug development under clinical trials or even during post market surveillance/launch. The information collected from various clinical trials are defined and elaborated in the interest of patients. FDA and other regulatory agencies play a major role in clinical trial design and analysis. Various consonances are developed and set to encourage sharing of data in order to use correct drug and dose for the patients.

In case of onychomycosis, the major barriers affecting drug development for onychomycosis are the formidable barrier properties of the nail plate and an incomplete understanding of virulence factors of dermatophilic fungi, which impedes our understanding of novel drug targets. In order to achieve the complete cure and to shorten the treatment period so as to enhance the patient's compliance, extensive research is going on and still requires more efforts in order to develop new drugs and to specify their dosage regimen.

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