Review Article

Nail Society of India (NSI) Recommendations for Pharmacologic Therapy of Onychomycosis

Abstract

Onychomycosis (OM) is the commonest cause of dystrophic nails, responsible for upto 50% of cases. Apart from significantly damaging the nails, quality of life, and self-image of the sufferer, it also acts as a reservoir of fungal infections carrying important implications for emerging recalcitrant dermatophytoses. Treatment of OM is based on guidelines released almost a decade back, in addition to published literature and personal preferences. Hence, an expert group of nail society of India (NSI) worked towards drafting these guidelines aimed at compiling recommendations for pharmacologic treatment of OM, based on scientific evidence, along with practical experience. The group did an extensive analysis of available English language literature on OM published during the period 2014–2022. The evidence compiled was graded and discussed to derive consensus recommendations for practice. Special focus was placed on combination therapies and adjunct therapies, including experience of members, to improve treatment outcomes.

Keywords: *Antifungal, grade of recommendation, itraconazole, level of evidence, onychomycosis, terbinafine, tinea unguium*

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Introduction

Onychomycosis (OM) is an intriguing problem for dermatologists around the world. Dermatophytes are the major cause, conventionally accounting for 90% cases, with the most common causative pathogens being *Trichophyton rubrum, T. mentagrophytes,* and *Epidermophyton floccosum*.[1,2] Yeasts and non-dermatophyte molds (NDM) are considered almost equally responsible for other cases. Though OM is a slow infection, it is not expected to clear spontaneously. Complications are known to occur, especially in populations at risk. OM acts as a reservoir of infection for the individual, family, or society at large, assuming significance with emergence of recalcitrant dermatophytoses.[2]

Pharmacologic therapy forms the backbone of OM treatment, with treatment decisions being based on factors like disease severity, etiology, and patient specifics. Mostly, treatment choices are based on expert group recommendations/guidelines; however, such recommendations were last published in 2014.[3] No such recommendations have been available in the Indian scenario, taking into account the etiological agents and patient factors. Hence, Nail Society of India (NSI) expert group compiled these recommendations based on evidence available in the literature.

Materials and Methods

The NSI expert group identified key aspects in pharmacologic management of OM. Based on this, PubMed and Cochrane databases were searched for published literature using the keyword "onychomycosis." Articles published in English language from 2014–2022, including meta-analyses, reviews, clinical studies, reports, and case series, were retrieved, read, and relevant cross-references examined. The relevant data were assigned levels of evidence (LoE) as per the Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence scheme [Table 1].[4] Treatment-related practice recommendations were derived and discussed by the group, to assign grades of recommendation (GOR) [Table 2].[4] The same was recorded in a narrative format.

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Aim of Treatment

A lag period of 12–18 months (toenail) or 4–6 months (fingernail) is expected between completion of pharmacologic therapy and normalised clinical appearance of nail. Upto 10% of a nail may remain abnormal in appearance even after mycologic cure. Thus, to avoid over-treatment, it becomes important to identify treatment endpoints. Table 3 enlists various definitions of treatment endpoints reported in the literature.[5] Although, effective treatment is best defined by nil fungal isolation, limited access to mycology laboratories necessitates the use of clinical indicators. The clinical signs to be assessed for response to treatment include appearance of normal-looking nail, any areas of onycholysis, subungual hyperkeratosis, paronychia, discoloration, or fragility. Endpoints have been defined as *Clinical Cure* (100% clearance of signs) or *Clinical Success* (<10% affected nail as compared to baseline, but with normalized nail growth) [LOE-II].[6] Patient-reported outcomes (PRO) like embarrassment, discomfort, footwear limitation, and pain should also be assessed to determine the patient's quality of life (QOL).[7]

Practice Points: *Endpoint of therapy should be taken as mycological cure for research purposes, and wherever feasible in clinical situations. However, where such facility is not available, one should follow the recommendations regarding duration of therapy with the selected anti-fungal, and encourage and ensure follow-up till clinical cure is achieved (GOR-B).*

Pharmacologic Treatment Options

Pharmacological treatment for OM can be systemic or topical, used singly, or as combination therapy.

Systemic therapy

Oral therapy is the mainstay for achieving mycologic cure in OM. Indications for systemic therapy are enumerated in Table 4.[8] Most of the systemic drugs interfere with ergosterol synthesis, leading to arrested cell growth. This effect may be fungicidal or only fungistatic (for some drugs). Though effective *in vitro*, the *in vivo* efficacy may be poor due to nail architectural alterations secondary to OM, hampering drug diffusion.

The most frequently used systemic drugs, terbinafine and itraconazole, are approved for OM in most countries including India.[9] Fluconazole is used off-label, though it is approved in Europe and China.[10] Table 5 summarizes the basic pharmacology of systemic antifungals used in OM. Ketoconazole and griseofulvin are no longer recommended for OM.

1. Terbinafine

Terbinafine was approved for OM by EU (1991) and USFDA (1996). It is an inhibitor of the fungal enzyme squalene epoxidase, resulting in raised levels of squalene, which prevents development of functional fungal cell membrane (fungicidal *in vitro*), and causes a deficiency of ergosterol (fungistatic action).[11] It is most effective against dermatophytes; but not as effective against *Candida*. Among NDMs, it may be effective against *Aspergillus spp.*[12]

Continuous dosing schedule has high mycological cure rate (MCR) (79% and 70% for fingernails and toenails, respectively) and clinical cure rate (CCR) (59% and

Table 1: Oxford Centre for Evidence-Based Medicine (OCEBM) levels of evidence

Level of Evidence	Type of Study
I	Systematic reviews of RCT or individual RCT
II	Systematic reviews of cohort studies or individual cohort study
III	Systematic reviews of cohort studies, good quality case-control, or case-control study
IV	Case-series, poor-quality cohort, or case-control studies
V	Expert opinion

Table 2: Grades of recommendation

Grade	Level of evidence
A	Consistent level 1 studies
B	Consistent level 2 or 3 studies, or extrapolations from level 1 studies
C	Level 4 studies or extrapolations from level 2 or 3 studies
D	Level 5 evidence or inconsistent studies at any level

Table 3: Definitions of endpoint of treatment for onychomycosis being used in the literature

Endpoint of therapy	Definition
Mycological cure (MC)	Negative microscopy and culture (on 2 consecutive occasions, 4-weeks apart)
Clinical cure (CC)	Complete absence of all lesions on each nail (based on sequential photographs) OR Residual disease, which is <10% of original disease surface
Complete cure	Both mycological and clinical cure
Clinical improvement	Reduction in total affected nail area which is >20% compared to baseline

Table 4: Indications of systemic therapy in OM

S. No	Clinical characteristics
1	Proximal subungual onychomycosis
2	DLSO affecting >50% of nail plate, nail plate thickness >2 mm, or matrix involvement
3	Involvement of 3 or more nails
4	No or poor response to >6 months of topical monotherapy
5	Dermatophytoma

DLSO=Distal lateral subungual onychomycosis

Table 5: Systemic antifungals for onychomycosis

	Terbinafine	Itraconazole	Fluconazole
Class of drug	Allylamine	Triazole	Triazole
Mechanism of action	Squalene epoxidase inhibitor	Lanosterol 14α demethylase inhibitor	Lanosterol 14α demethylase inhibitor
Pharmacokinetics	Half-life (t1/2) is 36 hrs Oral bioavailability 40% Metabolized by liver 50% reduced clearance in patients with liver cirrhosis and renal insufficiency	Half-life (t1/2) is 21 hrs Oral bioavailability 55% Bioavailability increased with meal/ cola beverage Metabolized by liver 40% renal excretion	Half-life (t1/2) is 30 hrs Oral bioavailability>99% Absorption not much affected by food Limited first pass hepatic metabolism Most of the drug is excreted unchanged
Pharmacokinetics in nail	Detected in distal nail within 1 week Diffuses via both nail bed and nail matrix Achieves almost 10–100 times the MIC for dermatophytes in nail clippings	Detected in distal nail within 1 week Diffuses via both nail bed and nail matrix.	Detected in distal nail within 1 day
Duration of persistence of drug in nails post-treatment	After completion of 6 and 12 weeks of therapy, detected in the nail for 30 and 36 weeks, respectively	Fingernail (2 pulses)- 9 months toenail (3 pulses)-11 months	Persists for 6 months after 1 year of 150 mg/ week
Spectrum of activity	Dermatophytes (FDA approved) Non-dermatophyte molds and *Candida* (off-label use)	Dermatophytes (FDA approved) Non-dermatophyte molds and *Candida* (off-label use)	Off-label use
Recommended Doses (adults)	Continuous therapy: 250 mg daily for 6 weeks for fingernail and 12 weeks for toenail Pulse therapy (off-label): 500 mg daily* for 1 week, followed by 3 weeks of no drug 2/3 pulses-fingernail 3/4 pulses-toenail	Continuous therapy: 200 mg daily for 6 weeks for fingernails and 12 weeks for toenails Pulse therapy: 400 mg daily** for 1 week, followed by 3 weeks of no drug 2/3 pulses-fingernail 3/4 pulses-toenail	Weekly therapy: 150–300 mg weekly for 3-6 months for fingernails and 9-12 months for toenails. To be continued till abnormal appearing nail has grown out
Recommended does (children)	>40 kg-250 mg 20-40 kg-125 mg, <20 kg-62.5 mg Fingernails: 6 weeks Toenails: 12 weeks	Pulse dose-5 mg/kg/day for 1 week Fingernails: 2 pulses Toenails: 3 pulses	3–6 mg/kg once weekly Fingernails: 12 weeks Toenails: 18–26 weeks
Adverse effects	Mild and transient side effects Most common: Taste disturbances, headache, gastrointestinal side effects (diarrhea, dyspepsia, pain, nausea), skin rashes Others: elevation of liver enzymes, visual disturbances Rare: Erythema multiform, Stevens Johnsons syndrome, idiosyncratic hepatobiliary dysfunction	Most common: Headache, gastrointestinal disturbance, drug rash, Rare: hepatic dysfunction	Relatively uncommon: Drug rash, hepatic dysfunction
Contraindications	Allergic reaction to terbinafine	Ventricular dysfunction History of congestive heart failure Co-administration with drugs prolonging QT interval (anti-arrhythmic, cardiac drugs)	Co-administration with drugs known to prolong QT interval

Contd...

Table 5: Contd...

	Terbinafine	Itraconazole	Fluconazole
Drug Interactions	Cytochrome P2D6 substrates including tricyclic anti-depressants, SSRI'S and beta-blockers	Potent CYP3A4 inhibitor; higher potential for drug interactions. Need to monitor renal function with cyclosporine and blood glucose with oral hypoglycemic agents	Oral hypoglycemic agents and warfarin.
FDA Pregnancy Category	Category B	Category C 2 months contraception recommended after treatment	Category C
Lactation	Excreted in breast milk	Excreted in breast milk	Excreted in breast milk

*Terbinafine 500 mg is taken as 250 mg twice a day rather than 500 mg once a day. **Itraconazole 400 mg is taken as 100 mg caps (2 x 2 times) as 200 mg cap twice a day is not FDA approved

38%) (LOE-I).[13-15] Pulse dosing was introduced to improve cost-effectiveness and compliance, while reducing adverse effects and resistance; however, it is not USFDA approved, but used off-label (LOE-IV). Various pulse dosing regimens have been studied in the literature [Table 6].[16-19] However, a meta-analysis of continuous versus intermittent terbinafine dosing concluded that pulse regimens had 13% lower efficacy in achieving mycologic cure; though equal chances of achieving clinical cure (LOE-II).[20] Pulse regimen administering 250 mg daily for 4 weeks with 4 weeks off (2 such pulses) showed best efficacy, with MCR and CCR being comparable with continuous regimen. (LOEII).

Though terbinafine can cause elevations of liver enzymes, only 3.3% of reported events had elevation >2 times the upper limit.[21] Reports of serious hepatic toxicity are distinctly uncommon, that too seen only in patients who have had pre-existing liver disease.[22,23] Terbinafine-associated liver injury is usually reported in 4–6 weeks of treatment and is symptomatic. Hence, baseline and periodic liver function tests may not be needed for every patient on terbinafine.[24] Liver function should be evaluated and drug discontinued if there are any symptoms suggestive of liver dysfunction including nausea, abdominal pain, vomiting, or jaundice.

Practice Points: *Oral terbinafine should be the first line therapy in dermatophytic OM, administered at a dose of 250 mg once a day. This should be done for 6 weeks for fingernails and 12 weeks for toenails (LOE-I, GOR-A). Continuous regimen should be preferred over pulse or intermittent regimen (LOE-II, GOR-C). Liver function tests at baseline should be done only for patients in whom liver dysfunction is suspected or expected. They should be repeated if any symptoms or signs of liver involvement are noted on follow-up. The drug should be withdrawn if liver enzymes rise 3 times above the reference range (LOE-III, GOR-B).*

2. Itraconazole

Itraconazole continuous therapy for OM was approved by EU (1989) and USFDA (1995). Pulse therapy for fingernail OM was USFDA approved in 1997. Itraconazole exerts a fungistatic action by inhibiting lanosterol 14α demethlyase.[25] Though, FDA approved for dermatophyte OM, itraconazole has been found more effective compared to terbinafine, against *Candida* and NDMs like *Aspergillus*.[26] However, it is ineffective against *Scytalidium spp*. and *Onychocola canadensis* (LOE-III).[27] MCR of 60% and 63% (continuous and pulse therapy, respectively) and CCR of 70% for both have been reported.[28] Intermittent dosing of itraconazole is considered as efficacious as daily dosing as the drug is rapidly detected in the nail plate, achieves good concentration, and persists for a longer period. The drug has been detectable till 9 months in fingernails (after 2 pulses) and 11 months in toe nails (after 3 pulses).[29] USFDA recommends a continuous dosing regimen for dermatophyte toenail OM (even with fingernail involvement); while pulse dosing can be used when only fingernails are involved. However, in many countries, pulse itraconazole (3–4 pulses) is approved for toenail onychomycosis (LOE-IV).[30] Pulse therapy has shown a better adverse effect profile than continuous therapy (LOE-IV).[31]

Poor bioavailability of itraconazole, especially dependence on food and gastric pH, has prompted development of newer formulations. A phase 3, randomized, placebo-controlled, non-inferiority trial, evaluating 200 mg formulation of itraconazole using Meltrex® technology delivery system showed it to be non-inferior and well-tolerated as compared to two 100-mg capsules administered daily for 12 weeks. Cure rates and clinical improvement achieved were comparable. Once daily dosing improved treatment compliance (LOE-I).[32] Super bioavailability itraconazole (SUBA-itraconazole) is based on dispersion of itraconazole drug within a pH-dependent polymer matrix. This has been shown to enhance dissolution and absorption of itraconazole, which is proposed to significantly increase its bioavailability (by 173%). It also reduces variability between patients and minimizes the effect of food or acids (LOE-I).[33] However, comparative trials are awaited.

Abnormality of liver functions is seen more commonly with continuous itraconazole than pulse administration. Serious adverse liver events have been reported in 3.2/100,000

Table 6: Pulse dosing regimens evaluated for terbinafine in the treatment of onychomycosis

Author/Journal published	Recommendations	Outcomes	Conclusions
Gupta *et al*.[16] JEADV 2009	3 Groups: Toenail OM Group I (TOT): Terbinafine 250 mg/d for 4 weeks, followed by 4 weeks off, followed by additional 4 weeks Group II (CTERB): Terbinafine 250 mg/d for 12 weeks Group III: Itraconazole pulse of 200 mg/d twice daily for 7 days on and 21 days off. Three such pulses given	TOT, CTERB, and III groups: Mycological cure rate: 83.7%, 78.1%, 56.7% (P=0.01 for Group I vs. III) Effective cure rates: 79.1%, 65.6%, 36.7% (P <0.001 for Group I vs. III)	Intermittent terbinafine regimen provided similar efficacy and safety to the gold standard continuous terbinafine regimen and better effective cure rates than pulse itraconazole therapy.
Alpsoy *et al*. J dermatol 1996	Group 1: 250 mg/d of terbinafine for 3 months Group 2: 500 mg/d of terbinafine for 7 days for the first week of each month for 3 months	Cure rate 79.2% in Group 1 and 73.9% in Group 2; (P: 0.79).	Continuous and intermittent terbinafine therapy found equally effective for dermatophyte toenail onychomycosis
Warshaw *et al*. Arch Dermatol 2001	3 Groups (4 months each) Standard continuous terbinafine (250 mg/d) Weekly intermittent terbinafine (500 mg/d for 1 week/month) Single dose terbinafine (1000 mg/month)	Complete cure rates: 20%, 40% and 0% in respective groups Mycological cure rates: 40%, 60% and 0% in respective groups	Efficacy of continuous and weekly dosing was comparable. However, monthly doses were not effective
Yadav P *et al*. IJDVL 2015	Two groups Continuous terbinafine 250 mg daily for 12 weeks 3 pulses of terbinafine (each of 500 mg daily for a week) repeated every 4 weeks.	Clinical effectivity: 86.8% vs. 71.1% (P=0.280) Mycological cure rates: 28.9% vs. 18.4% (P=0.280)	Terbinafine pulse dosing as efficacious as continuous dosing

prescriptions.[10,34] Thus, baseline evaluation of liver function is advised in all patients. It should be repeated in patients with any symptoms or signs of liver dysfunction.

Practice points: *Itraconazole pulse therapy is recommended as first line therapy in NDM OM, while for dermatophyte OM it is second line therapy (GOR-B). 2/3 pulses are recommended for fingernails and 3/4 pulses for toenails. It can also be used where the causative agent has not been confirmed, but clinical setting suggests so. A baseline liver function test should be done for all patients. Periodic monitoring is needed only in patients with pre-existing liver disease (GOR-B). Improved formulations could be used in patients with gastrointestinal adverse effects or poor tolerance; however, efficacy needs to be proven in comparative trials (GOR-B).*

Terbinafine vs. Itraconazole

Cochrane review suggests that there is a moderate-quality evidence showing terbinafine to be more effective in achieving mycologic cure (15 studies) and clinical cure (17 studies) as compared to azoles.[35] Not much difference exists with respect to the risk of adverse events (moderate-quality evidence). There is no difference in the recurrence rates seen with these two drugs (low-quality evidence).

Practice Points: *Terbinafine is recommended as first line treatment for onychomycosis (most commonly caused by dermatophytes) with itraconazole being the alternative drug (GOR-B). Where as Itraconazole is the first line drug in Non dermatophytic OM.*

3. Fluconazole

Fluconazole is a triazole drug. Its mechanism of action is similar to itraconazole. It is detectable in the nail plate even 6 months after completing 12 months of weekly therapy, ensuring potential for further improvement even after discontinuation. An MCR of 89–100% and CCR of 76–90% has been reported for fingernail OM.[36] For toenail OM, CCR at 12 months was reported to be 37%, 46%, and 48%, with doses of 150, 300, or 450 mg once weekly, respectively. Additionally, a low recurrence rate of 4% at 6 months after treatment has been reported.[37] Fluconazole has a good safety profile, superior efficacy to topical therapy, but is not superior to terbinafine or itraconazole.[35] (LOE-I).

Practice Points: *Fluconazole is recommended as second line therapy in individuals requiring systemic therapy, where terbinafine or itraconazole cannot be used. Weekly 150 mg for 6 months (fingernails) or 12 months (toenails), or longer may be used (LOE-I, GOR-B).*[37]

Topical therapy

Topical therapy offers the advantages of lesser adverse effects, no drug interactions or need for laboratory monitoring. However, effectiveness is less due to

inadequate penetration (increased nail thickness and subungual hyperkeratosis),[38] immune privilege, and poor compliance with prolonged duration. Higher cost of therapy, especially of newer agents, is also a deterrent. Early initiation of topical therapy and concomitant tinea pedis management improves treatment outcomes.[39] Table 7 summarizes indications for using topical monotherapy.[40]

Approved topical antifungals for nail include ciclopirox, amorolfine, efinaconazole, and tavaborole. Ciclopirox (1999), efinaconazole (2014), and tavaborole (2014) are USFDA approved agents while amorolfine is approved in Europe and Australia. Topical therapy relies heavily on special formulations to ensure penetration [Table 8].[41-43] Among these are lacquers designed as transungual drug delivery systems. They act by producing a water-insoluble film on the nail plate, which contains the drug. This ensures a prolonged contact and better absorption of the active drug within the nail.

Table 7: Indications for topical monotherapy in patients with onychomycosis

S. No.	Clinical characteristics
1	DLSO affecting <50% of the nail plate without matrix involvement yellow streaks along lateral margin of nail yellow onycholytic areas in central nail (dermatophytoma)
2	"Classical" white superficial onychomycosis (WSO)
3	Onychomycosis due to molds (poor response to systemic antifungals) except *Aspergillus spp*.
4	Patients unwilling or unable to tolerate oral therapy
5	Patients with contraindications for oral therapy
6	Patients who require maintenance therapy after oral therapy

Table 8: Methods to improve penetration of topical antifungal therapy in onychomycosis

Penetration enhancement method	Examples
Transungual drug delivery systems (TUDDS)	Water-insoluble polymers, which create a film on the nail surface. They need daily or weekly application and removal with organic solvents or nail filing
	Water-soluble solutions like hydroalcoholic solutions of hydroxypropyl chitosan. Their invisible non-irritating film can also be easily removed.
Chemical penetration enhancers[43]	Dimethyl sulfoxide
	Urea
	Bioadhesive polymers like Carbopol 971P, Klucel MF
	Surface modifiers like tartaric acid and phosphoric acid gel
Physical methods	Ultrasound-mediated drug delivery system
	Lasers
	Photo-dynamic therapy (PDT)
	Iontophoresis
Mechanical methods	Nail avulsion
	Nail abrasion
Novel drug delivery systems[44]	Nanoparticles
	Liposomes
	Microemulsions
	Hydrogels and *in situ* gels.

1. Ciclopirox Olamine

Ciclopirox is a hydroxypyridone antifungal which acts at the cell membrane, disrupting its integrity and affecting active membrane transport. It also inhibits essential respiratory enzymes.[44] Ciclopirox is effective against dermatophytes, *Candida*, and some NDM species.[45]

Ciclopirox is used as 8% nail lacquer, applied daily on the nail plate and hyponychium with 5 mm of surrounding skin, with a brush applicator. It is removed weekly with alcohol, followed by trimming and filing of nail. Monthly, debridement by treating physician is recommended (LOE-IV).[8] Treatment is recommended for 24 weeks (fingernails) and 48 weeks (toenails). MCR for toenails range from 29% to 36%, whereas CCR ranges from 5.5% to 8.5%.[46]

Adverse effects are limited to a mild burning sensation or pruritus. It is a pregnancy category B drug; however, excretion in breast milk is still not known. Hence, treatment should be deferred in pregnant and lactating women (LOE-V).[46]

Practice Points: *Ciclopirox olamine 8% nail lacquer monotherapy is of limited efficacy with low compliance rates; however, it could be considered with proper methodology, for patients in whom topical therapy is indicated, or systemic therapy is contraindicated (LOE-III, GOR-C).*

2. Amorolfine

It is a morpholine antifungal that interferes with fungal sterol synthesis. It is a broad-spectrum fungistatic and fungicidal drug, which is active against all three categories of fungi causing OM.[47] It is available as 5% nail lacquer. Weekly or twice weekly application is recommended on the nail plate after gentle filing. The recommended duration of therapy is 6–12 months. Amorolfine persistence in the nail plate is considered significantly longer than ciclopirox, even 14 days after last application. Thus, it provides a durable "reservoir effect,"[3] making weekly application feasible (LOE-I).[48] Amorolfine is effective for post-treatment prophylaxis to prevent recurrence (LOE-III).[49]

Regarding its efficacy, an open-label, randomized study conducted on 456 patients reported CCR of 54.2% and 46.0% with twice or once weekly application, respectively, for 6 months. MCR was 76.1% for twice and 70.6% with once weekly application.[50] Though, twice-weekly application showed better results, data were insufficient

to establish its superiority (LOE-IV). Adverse effects are limited, with only mild burning sensation or pruritus being reported. The drug is preferably avoided during pregnancy, and lactation as sufficient data regarding safety is not available (LOE-V).

Practice Points: *Amorolfine lacquer, once-weekly application can be used as monotherapy whenever topical therapy is indicated. The drug is not yet approved by USFDA, though approved in Europe and Australia. It offers the advantage of better compliance, and can also be used to prevent recurrences (LOE-III, GOR-C).*

Amorolfine vs. ciclopirox

Comparative studies between the two agents are limited. Monti *et al*. compared fingernail penetration of hydrosoluble nail lacquer containing 8% ciclopirox with water-insoluble 5% amorolfine lacquer applied twice a week. In this *in vivo* study, ciclopirox exhibited better nail penetration and higher predicted efficacy as compared to amorolfine.[51] A recent study by Pinto *et al*. used matrix assisted laser desorption ionization mass spectrometry imaging (MALDI-MSI) to visualize the drug penetration through nail plate. It showed a deeper penetration through nail plate by amorolfine as compared to ciclopirox.[52]

Practice Points: *Due to lack of sufficient literature, it is recommended that the choice between ciclopirox and amorolfine may be made based on local availability, and ease of application for the patient, so as to maximize compliance and better treatment outcomes (GOR-D). Cost advantage with either agent may be minor, considering varying frequency of application (GOR-D).*

3. Luliconazole 5% nail solution

Luliconazole is an inhibitor of sterol 14α-demethylase, with a broad-spectrum activity, and a low affinity for keratin. This allows a rapid release of the drug from the nail plate to the nail bed. Thus, as compared to other azoles, its potency is unaffected by keratin.[52] However, there is very limited literature regarding its efficacy, and there are no comparative data. A multicenter, double-blind, randomized phase III study comparing luliconazole 5% nail solution for 48 weeks with vehicle alone, in patients with DLSO showed statistically significant improvement in CCR (14.9% vs. 5.1%) and negative direct microscopy rate (45.4% vs. 31.2%). No serious adverse events were reported.[53]

Practice Points: *Currently, there is low level evidence to recommend or refute luliconazole therapy in OM (LOE-III). Future controlled studies can help assess its efficacy (GOR-D).*

4. Efinaconazole

Efinaconazole is a triazole antifungal with both *in vitro* and *in vivo* activity against dermatophytes, NDMs, and *Candida spp*. It was approved by the USFDA (2014) for toenail OM caused by *T. rubrum* and *T. mentagrophytes,* as a 10% once daily solution.[8] It is available in a few countries, but currently not in India.

Efinaconazole has low keratin affinity like luliconazole, thus ensuring higher availability of free drug.[54] Phase 3 trials involving patients with 20–50% clinical involvement have shown promising results with 48-week treatment, evaluated at 52 weeks. MCR and CCR were better than vehicle (55.3% and 53.4% vs. 18.8% and 15.2%, respectively) (LOE-I).[55] Prolonged use (18-24 months) has shown better efficacy than 12 months of usage.[56]

Efinaconazole is a pregnancy category-C drug (to be avoided in pregnancy), also avoided in breastfeeding women, as human safety data are lacking (LOE-V). Adverse effects include minimal reactions at application site and ingrown toenail.[55]

5. Tavaborole

Tavaborole is also not available in India. It is a benzoxaborole derivative, which acts on aminoacyl-tRNA synthetase.[57] Its broad-spectrum activity is a major advantage, targeting dermatophytes, NDMs, and yeasts as well. Tavaborole 5% solution was approved by USFDA in 2014 for use in toenail onychomycosis caused by *T. rubrum* and *T. mentagrophytes*.[8] MCR were 31.1% and 35.9% and CCR were 6.5% and 9.1%, respectively.[58] It is a pregnancy category-C drug.

Practice Points: *Both Efinaconazole and Tavaborole are currently unavailable in India; however, as per available literature, they hold a promising future, especially in patients where systemic therapy is contraindicated and in pediatric population (GOR-B).*

Other topical agents which have been tried, but with poor quality evidence, include imidazoles (ketoconazole, oxiconazole, tioconazole, bifonazole), allylamines (butenafine, naftifine), and tolnaftate. Vitamin E and oil of bitter orange have also been anecdotally reported.

A Cochrane database systematic review assessing CCR for topical therapies found evidence of high-quality for efinaconazole; moderate-quality for ciclopirox hydro lacquer and tavaborole; low-quality for ciclopirox lacquer; and very low-quality for luliconazole solution.[59] A higher rate of adverse event was found with efinaconazole and tavaborole (high to moderate-quality evidence). The review concluded that CCR with topical treatments are relatively low.[59]

Topical terbinafine 10% has been used as lotion and lacquer in two separate studies, and lacquer was found to be effective for mild-to-moderate onychomycosis improving both clinical and mycological criteria and more beneficial than amorolfine 5%.[60,61]

A network meta-analysis of 19 trials found *Terbinafine* (250 mg daily orally) to be significantly superior

to other drugs, except itraconazole in pulse dosage.[62] It also found fluconazole 150-450 mg, efinaconazole, tavaborole, ciclopirox, terbinafine nail solution, and amorolfine to be significantly superior to placebo.

Practice points: *Systemic treatment is superior to topical therapy, hence should be started wherever possible. Terbinafine (250 mg once a day) or itraconazole (400 mg pulse) are systemic agents of choice (GOR-A, LOE-I). Newly developed topicals may have better MCR as compared to pre-existing topical treatments; however, this difference may not be statistically significant. Their cost and availability also needs to be kept in mind (GOR-D).*

Modified Regimens

Failure of monotherapy is known in OM. Plausible causes include anti-fungal resistance, inability to achieve biologically effective drug concentration, pre-existing nail dystrophy, or slow rate of nail growth making them predisposed to reinfection.[63] Modifications listed below can help reduce the chances of failure.

Combination therapy

Failure of response to monotherapy within 6 months is an indication to consider combination approach (LOE-IV). A combination of two antifungals with different mechanisms of action and/or mode of delivery should be preferred. Studies have shown amorolfine combination works better than monotherapy (LOE-I).[64] It has been shown to improve fungistatic activity, cost-effectiveness, and treatment efficacy. A multi-center randomized study combining weekly amorolfine 5% lacquer (12 months) with terbinafine 250 mg daily (3 months) was shown to have better efficacy than terbinafine alone (59.2% vs. 45.0%).[64] Ciclopirox nail lacquer combination as compared to oral terbinafine alone showed higher MCR (88.2% vs. 64.7%) (LOE-III).[65]

Practice Points: *Scientific evidence supporting the use of combination therapy with different classes of drugs has shown to improve treatment outcomes. Thus, it is recommended in patients with indications for systemic therapy (GOR-A). Both ciclopirox (GOR-C) and amorolfine (GOR-B) may be used for combination therapies; however, amorolfine has better evidence base and convenient dosing schedule.*

Sequential therapy

Sequential therapy involves the use of two systemic drugs with different mechanisms, to reduce cumulative dose and duration of treatment. A randomized multicenter study evaluating the efficacy of 2 pulses of itraconazole followed by 1-2 pulses of terbinafine versus 3-4 pulses of terbinafine alone showed better response with sequential therapy both in MCR (72% vs. 48.9%) and CCR (52% vs. 32%) (LOE-I).[66]

Practice Points: *Currently, there is low level evidence to recommend or refute sequential therapy in OM (LOE-III). Future controlled studies can help assess its efficacy (GOR-D).*

Supplemental/Booster therapy

Supplemental/booster therapy involves additional drug dosing, over and above the recommended course to "boost" anti-fungal action. This may be an additional 4 weeks of terbinafine or itraconazole administered 6 to 9 months after the initiation of antifungal therapy.[67] This is considered an ideal "window of opportunity" based on pharmacokinetic data.[68] It helps improve cure rates in patients with slow growth of nails, plate thickness >2 mm, involvement of lateral edge or >75% plate, matrix involvement, or immunosuppression.

Practice Points: *It is recommended to use booster therapy for the above stated indications, keeping the safety profile and drug interactions in mind (LOE-IV, GOR-D).*

Adjuvant Measures

Various modalities which can add on to the efficacy of drugs administered are summarized in Table 9. These are mostly physical methods which may or may not be applicable in all cases uniformly.[69,70]

Practice Points: *Physical modalities can be recommended as adjunctive treatment in cases with deformed or thick*

Table 9: Adjuvant measures for the treatment of onychomycosis

Adjuvant measure	Description
Mechanical removal/ reduction of infected nail plate using a nail clipper	Removal of plate as far down as possible under the onycholysis.
	Sanding or cutting of nail plate that is adherent, with the help of clippers.
Surgical removal	This is for painful or extremely infected nails or for severely dystrophic nails.
	However, not very encouraging results.
Nonsurgical avulsion of dystrophic nail	Hypertrophic mycotic nail may be occluded with 40% urea cream under tape, in addition to oral therapy.
	The procedure also facilitates subsequent treatment with topical antifungal agents.
	Adjunctive therapy with urea has shown statistically significant improvement in few studies with tolerable side effects like periungual maceration and redness.[71]
Iontophoresis	Low-level electrical current helps increase drug transport across nail plate (semipermeable barrier).
	Combining this technique with terbinafine therapy may optimize terbinafine's penetration of the nail bed and matrix, leading to higher cure rates.

nails. These enhance the penetration of antifungal agents; but cannot be stand-alone therapy (GOR-C).

Recurrence/Relapse

OM is most likely to recur within the first two years of successful therapy in 20–25% cases (overall recurrence rates being 10-53%).[71] It could be a relapse or reinfection. Recurrences show a genetic predisposition and are more common in susceptible population. Biofilm formation could be a major cause as it increases resistance to treatment due to the extra-cellular matrix (ECM) formed by fungi, which shields them further, forming a reservoir of infection.[72] Measures to help prevent recurrence are summarized in Table 10.[69]

Practice points: *Preventing recurrence of OM should be a primary aim of treatment of OM. Thus, measures to prevent recurrence should be considered and implemented right from the beginning (LOE-V, GOR-D).*

Conclusions

Onychomycosis is an age-old as well as an emerging nail disorder, commonly encountered by dermatologists. Poor cure rates and high recurrence rates make the treatment challenging. These Indian recommendations summarize the evidence available regarding pharmacologic management of onychomycosis, offering practical measures based on associated best level of evidence and grades of recommendation. The aim is to aid practicing clinicians in choosing an appropriate approach suited to the clinical setting, based on scientific evidence. The recommendations also highlight areas of uncertainty as well as directions for future research.

Author contributions

KM and CG have equally contributed to the design and writing of the manuscript and are accountable for all aspects of the work. All other authors offered critical comments and helped edit the draft. All authors are responsible for ensuring accuracy and integrity of the manuscript.

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Conflicts of interest

There are no conflicts of interest.

Table 10: Measures to prevent recurrence of onychomycosis

Category	Focus area	Specific measures
Patient-oriented measures	Footwear as fomites	Fomites play an important role in re-infection and recurrence of onychomycosis-footwear is of paramount importance
		Discard old footwear (ideal, but may not be practical)
		Naphthalene mothballs can be put in shoes, enclosed tightly in a plastic bag for 3 days. This is followed by airing (to remove the naphthalene odor).
		Continuous application of antifungal powders in the shoes
		For socks, hot cycle wash (60°C for 45 min) is recommended to eradicate dermatophytic elements
		Copper oxide impregnated socks[73]
	Care of feet	Regular foot hygiene
		Avoid walking barefoot or sharing slippers in public changing rooms or swimming pools-use flip-flops instead
	Nail trimming	Regular trimming of nails
		Avoid sharing of nail clippers
	Family as a source of infection	Assessment and treatment of other family members with dermatophyte infection
	Cosmetic/parlor procedures	To take due precautions while undergoing any manicures and pedicures
		Use of sterile instruments
		Avoiding cuticle damage
Physician- oriented measures	Accurate Diagnosis	Determining the exact etiological agent (Dermatophyte vs. NDM vs. *Candida*) helps in choosing most appropriate treatment
	Drug-related advise	To emphasize about long-term compliance in first visit
		Appropriate drug-related advice like taking itraconazole with food and right method of application of topical agents
	Combination therapy	Consider combination therapy, extended therapy or sequential therapy according to patient profile and response achieved
	Post-treatment advice	Twice-weekly topical antifungal solution for prophylaxis.
		Prophylactic treatment with amorolfine lacquer (once every 2 weeks for 3 years) reduces recurrence.[74]

References

1. Raghavendra KR, Yadav D, Kumar A, Sharma M, Bhuria J, Chand AE. The non-dermatophyte molds: Emerging as leading cause of onychomycosis in south-east Rajasthan. Indian Dermatol Online J 2015;6:92–7.
2. Rafat Z, Hashemi SJ, Saboor-Yaraghi AA, Pouragha B, Taheriniya A, Moosavi A, *et al*. A systematic review and meta-analysis on the epidemiology, casual agents and demographic characteristics of onychomycosis in Iran. J Mycol Medicale 2019;29:265–72.
3. Ameen M, Lear JT, Madan V, Mohd Mustapa MF, Richardson M. British Association of Dermatologists' guidelines for the management of onychomycosis 2014. Br J Dermatol 2014;171:937-58.
4. OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. Available from http://www.cebm.net/index.aspx?o=5653. [Last accessed on 2022 Jun 08].
5. Scher RK, Tavakkol A, Sigurgeirsson B, Hay RJ, Joseph WS, Tosti A, *et al*. Onychomycosis: Diagnosis and definition of cure. J Am Acad Dermatol 2007;56:939–44.
6. Singal A, Khanna D. Onychomycosis: Diagnosis and management. Indian J Dermatol Venereol Leprol 2011;77:659-72.
7. Wang J, Wiznia LE, Rieder EA. Patient-reported outcomes in onychomycosis: A review of psychometrically evaluated instruments in assessing treatment effectiveness. Skin Appendage Disord 2017;3:144-55.
8. Lipner SR, Scher RK. Onychomycosis: Treatment and prevention of recurrence. J Am Acad Dermatol 2019;80:853-67.
9. Gupta AK, Mays RR, Versteeg SG, Piraccini BM, Takwale A, Shemer A, *et al*. Global perspectives for the management of onychomycosis. Int J Dermatol 2019;58:1118–29.
10. Gupta AK. Systemic Antifungal agents. In: Wolverton SE, Wu JJ, editors. Comprehensive Dermatologic Drug Therapy. 3rd ed. St. Louis, MO: Elsevier Health Sciences; 2019. p. 105.
11. Ryder NS. Terbinafine: Mode of action and properties of the squalene epoxidase inhibition. Br J Dermatol 1992;126:2–7.
12. Gupta AK, Drummond-Main C, Cooper EA, Brintnell W, Piraccini BM, Tosti A. Systematic review of non-dermatophyte mold onychomycosis: Diagnosis, clinical types, epidemiology, and treatment. J Am Acad Dermatol 2012;66:494-502.
13. Tausch I, Bräutigam M, Weidinger G, Jones TC. Evaluation of 6 weeks treatment of terbinafine in tinea unguium in a double-blind trial comparing 6 and 12 weeks therapy. The Lagos V Study Group. Br J Dermatol 1997;136:737-42.
14. Van der Schroeff JG, Cirkel PK, Crijns MB, Van Dijk TJ, Govaert FJ, Groeneweg DA, *et al*. A randomized treatment duration-finding study of terbinafine in onychomycosis. Br J Dermatol 1992;126(Suppl 39):36-9.
15. Consumer information. PrLAMISIL* (terbinafine hydrochloride) 250 mg tablets. Available from: https://www.novartis.ca/sites/www.novartis.ca/files/lamisil_patient_e_1.pdf. [Last accessed on 2022 Dec 27].
16. Gupta AK, Lynch LE, Kogan N, Cooper EA. The use of an intermittent terbinafine regimen for the treatment of dermatophyte toenail onychomycosis. J Eur Acad Dermatol Venereol 2009;23:256–62.
17. Alpsoy E, Yilmaz E, Basaran E. Intermittent therapy with terbinafine for dermatophyte toe-onychomycosis: A new approach. J Dermatol 1996;23:259–62.
18. Warshaw EM, Carver SM, Zielke GR, Ahmed DD. Intermittent terbinafine for toenail onychomycosis: Is it effective? Results of a randomized pilot trial. Arch Dermatol 2001;137:1253.
19. Yadav P, Singal A, Pandhi D, Das S. Comparative efficacy of continuous and pulse dose terbinafine regimes in toenail dermatophytosis: A randomized double-blind trial. Indian J Dermatol Venereol Leprol 2015;81:363-9.
20. Gupta AK, Paquet M, Simpson F, Tavakkol A. Terbinafine in the treatment of dermatophyte toenail onychomycosis: A meta-analysis of efficacy for continuous and intermittent regimens. J Eur Acad Dermatol Venereol 2013;27:267-72.
21. Gupta AK. Systemic Antifungal agents. In: Wolverton SE, Wu JJ. Comprehensive Dermatologic Drug Therapy. 3rd ed. St. Louis, MO: Elsevier Health Sciences; 2019. p. 98-119.
22. Wang Y, Lipner SR. Retrospective analysis of adverse events with systemic onychomycosis medications reported to the United States Food and Drug Administration. J Dermatolog Treat 2021;32:783-7.
23. O'Sullivan DP, Needham CA, Bangs A, atkin K, Kendall FD. Postmarketing surveillance of oral terbinafine in the U.K.: Report of a large cohort study. Br J Clin Pharmacol 1996;42:559–65.
24. Sun CW, Hsu S. Terbinafine: Safety profile and monitoring in treatment of dermatophyte infections. Dermatol Ther 2019;32:e13111.
25. Haria M, Bryson HM, Goa KL. Itraconazole. A reappraisal of its pharmacological properties and therapeutic use in the management of superficial fungal infections. Drugs 1996;51:585–620.
26. Tosti A, Piraccini BM, Lorenzi S, Iorizzo M. Treatment of nondermatophyte mold and Candida onychomycosis. Dermatol Clin 2003;21:491–7.
27. Gupta AK, Kohli Y, Batra R. *In vitro* activities of posaconazole, ravuconazole, terbinafine, itraconazole and fluconazole against dermatophyte, yeast and non-dermatophyte species. Med Mycol 2005;43:179–85.
28. Gupta AK, Ryder JE, Johnson AM. Cumulative meta-analysis of systemic antifungal agents for the treatment of onychomycosis. Br J Dermatol 2004;150:537–44.
29. Willemsen M, De Doncker P, Willems J, Woestenborghs R, Van de Velde V, Heykants J, *et al*. Post-treatment itraconazole levels in the nail. New implications for treatment in onychomycosis. J Am Acad Dermatol 1992;26:731–5.
30. Gupta AK, Ryder JE. The use of oral antifungal agents to treat onychomycosis. Dermatol Clin 2003;21:469–79.
31. Gupta AK, Lambert J, Revuz J, Shear N. Update on the safety of itraconazole pulse therapy in onychomycosis and dermatomycoses. Eur J Dermatol 2001;11:6–10.
32. Maddin S, Quiring J, Bulger L. Randomized, placebo-controlled, phase 3 study of itraconazole for the treatment of onychomycosis. J Drugs Dermatol 2013;12:758–63.
33. Abuhelwa AY, Foster DJ, Mudge S, Hayes D, Upton RN. Population pharmacokinetic modeling of itraconazole and hydroxyitraconazole for oral SUBA-itraconazole and sporanox capsule formulations in healthy subjects in fed and fasted states. Antimicrob Agents Chemother 2015;59:5681-96.
34. Orion E, Matz H, Wolf R. The life-threatening complications of dermatologic therapies. Clin Dermatol 2005;23:182–92.
35. Kreijkamp-Kaspers S, Hawke K, Guo L, Kerin G, Bell-Syer SE, Magin P, *et al*. Oral antifungal medication for toenail onychomycosis. Cochrane Database Syst Rev 2017;7:CD010031.
36. Brown SJ. Efficacy of fluconazole for the treatment of onychomycosis Ann Pharmacother 2009;43:1684–91.
37. Gupta AK, Drummond-Main C, Paquet M. Evidence-based optimal fluconazole dosing regimen for onychomycosis treatment. J Dermatolog Treat 2013;24:75-80.

38. Murdan S. Enhancing the nail permeability of topically applied drugs. Exp Opin Drug Deliv 2008;5:1267-82.
39. Gupta AK, Lynch LE. Onychomycosis: Review of recurrence rates, poor prognostic factors, and strategies to prevent disease recurrence. Cutis 2004;74:10–5.
40. Tabara K, Szewczyk AE, Bienias W, Wojciechowska A, Pastuszka M, Oszukowska M, *et al*. Amorolfine vs. ciclopirox-lacquers for the treatment of onychomycosis. Postepy Dermatol Alergol 2015;32:40-5.
41. Lorizzo M, Piraccini BM, Tosti A. Today's treatment options for onychomycosis. J Dtsch Dermatol Ges 2010;8:875–9.
42. Grover C, Khurana A. An update on treatment of onychomycosis. Mycoses 2012;55:541-51.
43. Dhamoon RK, Popli H, Gupta M. Novel Drug Delivery Strategies for the Treatment of Onychomycosis. Pharm Nanotechnol 2019;7:24-38.
44. Wolverton, Belenky P, Camacho D, Collins JJ. Fungicidal drugs induce a common oxidative-damage cellular death pathway. Cell Rep 2013;3:350-8.
45. Bohn M, Kraemer KT. Dermatopharmacology of ciclopirox nail lacquer topical solution 8% in the treatment of onychomycosis. J Am Acad Dermatol 2000;43:S57-69.
46. Aventis Pharma. Penlac (Ciclopirox Topical Solution, 8% w/w) Nail Lacquer. Available from https://pdf.hres.ca/dpd_pm/00015736.PDF. [Last accessed on 2022 Jun 08].
47. Galderma (U.K) Ltd. Curanail 5% w/v Medicated Nail Lacquer. Available from https://www.medicines.org.uk/emc/prod uct/9436/smpc. [Last accessed on 2022 Jun 08].
48. Sidou F, Soto P. A randomized comparison of nail surface remanence of three nail lacquers, containing amorolfine 5%, ciclopirox 8% or tioconazole 28%, in healthy volunteers. Int J Tissue React 2004;26:17-24.
49. Sigurgeirsson B, Olafsson JH, Steinsson JT, Kerrouche N, Sidou F. Efficacy of amorolfine nail lacquer for the prophylaxis of onychomycosis over 3 years. J Eur Acad Dermatol Venereol 2010;24:910–5.
50. Reinel D. Topical treatment of onychomycosis with amorolfine 5% nail lacquer: Comparative efficacy and tolerability of once and twice weekly use. Dermatology 1992;184:21–4.
51. Monti D, Herranz L, Bo D, Subissi A. Nail penetration and predicted mycological efficacy of an innovative hydrosoluble ciclopirox nail lacquer vs. a standard amorolfine lacquer in healthy subjects. J Eur Acad Dermatol Venereol 2013;27:e153-8.
52. Brown M, Turner R, Nakamura N. Nail permeation and depth profiling of luliconazole, a novel imidazole antifungal agent, for the topical treatment of onychomycosis. Poster presented at the 53rd Inter- science Conference on Antimicrobial Agents and Chemotherapy (ICAAC); September 10–13, Denver, CO, USA, 2013.
53. Watanabe S, Kishida H, Okubo A. Efficacy and safety of luliconazole 5% nail solution for the treatment of onychomycosis: A multicenter, double-blind, randomized phase III study. J Dermatol 2017;44:753-9.
54. Gupta AK, Stec N, Summerbell RC, Shear NH, Piguet V, Tosti A, *et al*. Onychomycosis: A review. J Eur Acad Dermatol Venereol 2020;34:1972-90.
55. Elewski BE, Rich P, Pollak R, Pariser DM, Watanabe S, Senda H, *et al*. Efinaconazole 10% solution in the treatment of toenail onychomycosis: Two phase III multicenter, randomized, double-blind studies. J Am Acad Dermatol 2013;68:600–8.
56. Gupta AK, Cooper EA. Long-term efficacy and safety of once-daily efinaconazole 10% topical solution (Jublia) for dermatophyte toenail onychomycosis: An interim analysis. Skin Therapy Lett 2021;26:5-10.
57. Rock FL, Mao W, Yaremchuk A, Tukalo M, Crépin T, Zhou H, *et al*. An antifungal agent inhibits an aminoacyl-tRNA synthetase by trapping tRNA in the editing site. Science 2007;316:1759-61.
58. Kerydin (tavaborole) topical solution, 5% [package insert]. Melville, NY: Fougera Pharmaceuticals. Available from: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid51ae61072-bca0-43f0-a741-07bda2d50c87. [Last accessed on 2022 Jun 08].
59. Foley K, Gupta AK, Versteeg S, Mays R, Villanueva E, John D. Topical and device-based treatments for fungal infections of the toenails. Cochrane Database Syst Rev 2020;1:CD012093.
60. Blume-Peytavi U, Tosti A, Falqués M, Tamarit ML, Carreño C, Galván J, Tebbs V. A multicentre, randomised, parallel-group, double-blind, vehicle-controlled and open-label, active-controlled study (versus amorolfine 5%), to evaluate the efficacy and safety of terbinafine 10% nail lacquer in the treatment of onychomycosis. Mycoses 2022;65:392-401.
61. Gupta AK, Surprenant MS, Kempers SE, Pariser DM, Rensfeldt K, Tavakkol A. Efficacy and safety of topical terbinafine 10% solution (MOB-015) in the treatment of mild to moderate distal subungual onychomycosis: A randomized, multicenter, double-blind, vehicle-controlled phase 3 study. J Am Acad Dermatol 2021;85:95-104.
62. Gupta AK, Daigle D, Foley KA. Network meta-analysis of onychomycosis treatments. Skin Appendage Disord 2015;1:74-81.
63. Baran R, Kaoukhov A. Topical antifungal drugs for the treatment of onychomycosis: An overview of current strategies for monotherapy and combination therapy. J Eur Acad Dermatol Venereol 2005;19:21-9.
64. Baran R, Sigurgeirsson B, de Berker D, Kaufmann R, Lecha M, Faergemann J, *et al*. A multicentre, randomized, controlled study of the efficacy, safety and cost-effectiveness of a combination therapy with amorolfine nail lacquer and oral terbinafine compared with oral terbinafine alone for the treatment of onychomycosis with matrix involvement. Br J Dermatol 2007;157:149-57.
65. Avner S, Nir N, Henri T. Combination of oral terbinafine and topical ciclopirox compared to oral terbinafine for the treatment of onychomycosis. J Dermatolog Treat 2005;16:327-30.
66. Gupta AK, Lynde CW, Konnikov N. Single-blind, randomized, prospective study of sequential itraconazole and terbinafine pulse compared with terbinafine pulse for the treatment of toenail onychomycosis. J Am Acad Dermatol 2001;44:485-91.
67. Piérard GE, Piérard-Franchimont C, Arrese JE. The boosted oral antifungal treatment for onychomycosis beyond the regular itraconazole pulse-dosing regimen. Dermatology 2000;200:185-7.
68. Pierard GE, Pierard-Franchimont C, Arrese JE. The boosted antifungal topical treatment (BATT) for onychomycosis. Med Mycol 2000;38:391-2.
69. Mahajan K, Sharma S, Sardana K, Gupta A. Superficial fungal infections. In: Sardana K, Mahajan K, Mrig PA, editors. Fungal Infections Diagnosis and Treatment. 1st ed. CBS Publishers; 2017. p. 103-5.
70. Dars S, Banwell HA, Matricciani L. The use of urea for the treatment of onychomycosis: A systematic review. J Foot Ankle Res 2019;12:22.
71. Piraccini BM, Sisti A, Tosti A. Long-term follow-up of toenail onychomycosis caused by dermatophytes after successful treatment with systemic antifungal agents. J Am Acad Dermatol 2010;62:411–4.
72. Gupta AK, Daigle D, Carviel JL. The role of biofilms in

onychomycosis. J Am Acad Dermatol 2016;74:1241–6.
73. Zatcoff RC, Smith MS, Borkow G. Treatment of tinea pedis with socks containing copper-oxide impregnated fibers. Foot (Edinb) 2008;18:136-41.
74. Shemer A, Gupta AK, Kamshov A, Babaev M, Farhi R, Daniel CR 3rd, *et al*. Topical antifungal treatment prevents recurrence of toenail onychomycosis following cure. Dermatol Ther 2017;30. doi: 10.1111/dth.12545.