Therapeutic Class Overview
Onychomycosis Agents

Therapeutic Class

- **Overview/Summary:** This review will focus on the antifungal agents Food and Drug Administration (FDA)-approved for the treatment of onychomycosis.[1-9] Onychomycosis is a progressive infection of the nail bed which may extend into the matrix or plate, leading to destruction, deformity, thickening and discoloration. Of note, these agents are only indicated when specific types of fungus have caused the infection, and are listed in Table 1. Additionally, ciclopirox is only FDA-approved for mild to moderate onychomycosis without lunula involvement.[1] The mechanisms by which these agents exhibit their antifungal effects are varied. For ciclopirox (Penlac®) the exact mechanism is unknown. It is believed to block fungal transmembrane transport, causing intracellular depletion of essential substrates and/or ions and to interfere with ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).[1] The azole antifungals, efinaconazole (Jublia®) and itraconazole tablets (Onmel®) and capsules (Sporanox®) works via inhibition of fungal lanosterol 14-alpha-demethylase, an enzyme necessary for the biosynthesis of ergosterol. By decreasing ergosterol concentrations, the fungal cell membrane permeability is increased, which results in leakage of cellular contents.[2,5,6] Griseofulvin microsize (Grifulvin V®) and ultramicrosize (GRIS-PEG®) disrupts the mitotic spindle, arresting metaphase of cell division. Griseofulvin may also produce defective DNA that is unable to replicate. The ultramicrosize tablets are absorbed from the gastrointestinal tract at approximately one and one-half times that of microsize griseofulvin, which allows for a lower dose of griseofulvin to be administered.[3,4] Tavaborole (Kerydin®), is an oxaborole antifungal that interferes with protein biosynthesis by inhibiting leucyl-transfer ribonucleic acid (tRNA) synthase (LeuRS), which prevents translation of tRNA by LeuRS.[7] The final agent used for the treatment of onychomycosis, terbinafine hydrochloride (Lamisil®), is an allylamine antifungal. While its mechanism is not known, it is asserted it probably exerts its effect by inhibiting the fungal enzyme squalene monooxygenase, which creates a deficiency in ergosterol, a component of fungal membranes necessary for normal growth.[8]

Table 1. Current Medications Available in the Therapeutic Class[1-8]

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Ciclopirox (Penlac®)	Mild to moderate onychomycosis† of the finger or toenail without lunula involvement	Topical solution: 8%	-
Efinaconazole (Jublia®)	Onychomycosis† of the toenail	Topical solution: 10%	-
Griseofulvin microcrystalline (Grifulvin V®*)	Onychomycosis† of the finger or toenail; tinea corporis, tinea pedis, tinea cruris, tinea barbae, tinea capitis	Oral Suspension: 125 mg/5 mL Tablet: 500 mg	✔
Griseofulvin ultramicrocrystalline (GRIS-PEG®*)	Onychomycosis† of the finger or toenail; tinea corporis, tinea pedis, tinea cruris, tinea barbae, tinea capitis	Tablet: 125 mg 250 mg	✔
Itraconazole (Onmel®, Sporanox®*)	Onychomycosis† of the finger‡ or toenail§, Blastomycosis‡, Histoplasmosis‡, Aspergillosis‡	Capsule: 100 mg Tablet: 200 mg	✔
Tavaborole (Kerydin®)	Onychomycosis† of the toenail	Topical solution: 5%	-
Terbinafine hydrochloride (Lamisil®*)	Onychomycosis† of the finger¶ or toenail¶	Tablet: 250 mg	✔

*Generic available in at least one dosage form or strength
†Caused by Trichophyton rubrum (ciclopirox); caused by trichophyton rubrum and Trichophyton mentagrophytes (efinaconazole, itraconazole [Onmel®], tavaborole); caused by Trichophyton rubrum, Trichophyton tonsurans, Trichophyton mentagrophytes, Trichophyton interdigitalis, Trichophyton verrucosum, Trichophyton megnini, Trichophyton gallinae, Trichophyton crateriform, Trichophyton sulphureum, Trichophyton schoenleinii, Microsporum audouini, Microsporum canis, Microsporum gypseum and Epidermophyton floccosum (griseofulvin); causative pathogens not reported for itraconazole (Sporanox®) or terbinafine
‡Sporanox® tablets only
§Onmel® and Sporanox® tablets only
¶Lamisil® tablets only

Evidence-based Medicine

- Older agents such as itraconazole, griseofulvin and terbinafine HCl have been well studied. In head-to-head studies, terbinafine HCl and itraconazole provided an improved cure rate over griseofulvin microsize and ultramicrosize tablets.[9-13]
- Studies comparing terbinafine HCl to itraconazole have reported inconsistent results with numerous clinical trials reporting improved clinical and/or mycological cure rates with terbinafine HCl while several published studies have shown no difference between the agents.[13-28]
- The safety and efficacy of ciclopirox nail lacquer topical solution has been evaluated in two double-blind placebo-controlled trials which lasted for 48 weeks each. Both studies showed a significant improvement in mycological cure and culture results for ciclopirox compared with placebo (P<0.001 for both outcomes in both studies).[29]
- The safety and efficacy of once daily use of efinaconazole topical solution for the treatment of onychomycosis of the toenail were assessed in two 52-week vehicle-controlled study. The efinaconazole group had complete cure rates of 17.8% and 15.2% of compared to 3.3% and 5.5% in the vehicle group (P<0.001).[30]
- Itraconazole tablets were approved based on one 12 week, randomized, controlled study in patients with onychomycosis. It was compared to itraconazole capsules and placebo. At week-52, 22.3% of patients in the itraconazole tablets group had complete cure compared to 1.0% in the placebo group (P value not reported). The mycological and clinical cure rates were 44% and 6% and 26% and 3% in the itraconazole tablets and placebo groups, respectively (P value not reported). Efficacy results comparing itraconazole to itraconazole capsules were found to be similar (P value not reported).[5,31]
- The safety and efficacy of tavaborole for the treatment of onychomycosis of the toenail was assessed in two 52-week randomized controlled trials compared with vehicle solution. Complete cure rates in the two studies for tavaborole were 6.5% and 9.1% compared with 0.5% and 1.5% for the vehicle group. A greater proportion of patients in the tavaborole-treated groups experienced mycological cure and complete or almost complete cure compared to vehicle-treated groups (P values not reported).[5]

Key Points within the Medication Class

- Treatment guidelines for onychomycosis infections have not been updated recently, with the last update being in 2005.[32,33]
- According to Clinical Guidelines:[32,33]
    - Oral therapy is more effective, and should be utilized in more serious cases.
    - Combination therapy with an oral and topical agent may be useful in the more severe cases.
    - Oral terbinafine or itraconazole is recommended over griseofulvin due to a much higher cure rate.
    - Neither guideline mentions newer agents as they were not FDA-approved at the time of publication
- Other Key Facts:[1-8]
    - Treatment with topical therapy is longer than oral therapy. Oral therapy with terbinafine HCl or itraconazole is six to 12 weeks depending on indication compared with upwards of 48 weeks with topical therapies.
    - Limited systemic absorption with the topical agents provides reduced adverse effects, usually limited to local reactions.
    - Oral therapy is associated with more side effects and drug interactions that may limit use.

- In addition to a black-box warning for drug interactions, itraconazole has a black-box warning regarding its use in patients with congestive heart failure, which may have a negative inotropic effect.
- Itraconazole tablets (Onmel®) does not provide any clinical advantage over the generic 100 mg capsules other than reduced pill burden.
- Ciclopirox and griseofulvin are approved in pediatric patients (age ≥12 years and ≥2 years, respectively).
- No dosage adjustment is required for any renal or hepatic impairment for any agent; however, terbinafine HCl is not recommended in patients with creatinine clearance (CrCl) <50 mL/min.
- Terbinafine HCl and ciclopirox are pregnancy category B, while griseofulvin is X. Itraconazole, efinaconazole and tavaborole are listed as pregnancy category C; however, itraconazole tablets and capsules are contraindicated in pregnant patients or to women contemplating pregnancy.
- Other formulations of itraconazole (oral solution, Sporanox®), terbinafine HCl (granules, Lamisil®) and ciclopirox (gel, cream, lotion, suspension and shampoo) do not carry an FDA-approved indication for onychomycosis.
- Only griseofulvin microcrystalline, griseofulvin ultramicrocrystalline and terbinafine HCl are available generically.

References

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Therapeutic Class Review
Onychomycosis Agents

Overview/Summary

This review will focus on the antifungal agents Food and Drug Administration (FDA)-approved for the treatment of onychomycosis.[1-9] Onychomycosis is a progressive infection of the nail bed which may extend into the matrix or plate, leading to destruction, deformity, thickening and discoloration. Of note, these agents are only indicated when specific types of fungus have caused the infection, and are listed in Table 2. Additionally, ciclopirox is only FDA-approved for mild to moderate onychomycosis without lunula involvement.[1] The mechanisms by which these agents exhibit their antifungal effects are varied. For ciclopirox (Penlac®) the exact mechanism is unknown. It is believed to block fungal transmembrane transport, causing intracellular depletion of essential substrates and/or ions and to interfere with ribonucleic acid (RNA) and deoxyribonucleic acid (DNA).[1] The azole antifungals, efinaconazole (Jublia®) and itraconazole tablets (Onmel®) and capsules (Sporanox®) works via inhibition of fungal lanosterol 14-alpha-demethylase, an enzyme necessary for the biosynthesis of ergosterol. By decreasing ergosterol concentrations, the fungal cell membrane permeability is increased, which results in leakage of cellular contents.[2,5,6] Griseofulvin microsize (Grifulvin V®) and ultramicrosize (GRIS-PEG®) disrupts the mitotic spindle, arresting metaphase of cell division. Griseofulvin may also produce defective DNA that is unable to replicate. The ultramicrosize tablets are absorbed from the gastrointestinal tract at approximately one and one-half times that of microsize griseofulvin, which allows for a lower dose of griseofulvin to be administered.[3,4] Tavaborole (Kerydin®), is an oxaborole antifungal that interferes with protein biosynthesis by inhibiting leucyl-transfer ribonucleic acid (tRNA) synthase (LeuRS), which prevents translation of tRNA by LeuRS.[7] The final agent used for the treatment of onychomycosis, terbinafine hydrochloride (Lamisil®), is an allylamine antifungal. While its mechanism is not known, it is asserted it probably exerts its effect by inhibiting the fungal enzyme squalene monooxygenase, which creates a deficiency in ergosterol, a component of fungal membranes necessary for normal growth.[8]

Generally speaking, systemic therapy with terbinafine hydrochloride (HCl) or itraconazole has been shown to be more effective in treating onychomycosis of the toe or fingernail compared to the griseofulvin products.[9-13] When comparing terbinafine HCl to itraconazole, numerous studies suggest terbinafine HCl is more effective; however, there are several studies that found itraconazole to be just as effective as terbinafine HCl.[13-28] The remaining topical agents, ciclopirox, efinaconazole, and tavaborole, have limited head-to-head data, but all provide a statistically significant improvement in cure rates compared with placebo.[5,29-30] A study published evaluating the efficacy of itraconazole tablets asserted that when compared to itraconazole capsules, cure rates were similar; however, no rates or statistical analysis was provided.[31] Treatment guidelines for onychomycosis infections have not been updated recently, with the last update being in 2005. Both guidelines state that oral therapy is more effective, and should be utilized in more serious cases. Additionally, combination therapy with an oral and topical agent may be useful in the more severe cases. Both guidelines recommend oral terbinafine or itraconazole over griseofulvin due to a much higher cure rate. Neither guideline mentions newer agents as they were not FDA-approved at the time of publication.[32,33]

Oral therapy with terbinafine HCl or itraconazole is significantly shorter duration than local therapy or treatment with oral griseofulvin. Oral therapy with terbinafine HCl or itraconazole is six to 12 weeks depending on indication compared with upwards of 48 weeks with topical therapies. However, oral therapies are associated with significantly more drug interactions. Itraconazole, for example, has a black box warning that notes it is contraindicated when certain other agents are prescribed. The black box warning for itraconazole also lists congestive heart failure as a contraindication due to its negative inotropic effects. Ciclopirox and griseofulvin are approved in pediatric patients (age ≥12 years and ≥2 years, respectively). No dosage adjustment is required for any renal or hepatic impairment for any agent; however, terbinafine HCl is not recommended in patients with creatinine clearance (CrCl) <50 mL/min. Terbinafine HCl and ciclopirox are pregnancy category B, while griseofulvin is X. Itraconazole, efinaconazole and tavaborole are listed as pregnancy category C; however, itraconazole tablets and

capsules are contraindicated in pregnant patients or to women contemplating pregnancy. Other formulations of itraconazole (oral solution, Sporanox®), terbinafine HCl (granules, Lamisil®) and ciclopirox (gel, cream, lotion, suspension and shampoo) do not carry an FDA-approved indication for onychomycosis and will not be covered in this review. Only griseofulvin microcrystalline, griseofulvin ultramicrocrystalline and terbinafine HCl are available generically.

Medications

Table 1. Medications Included Within Class Review[1-8]

Generic Name (Trade name)	Medication Class	Generic Availability
Ciclopirox (Penlac®)	Antifungal	-
Efinaconazole (Jublia®)	Antifungal (azole)	-
Griseofulvin microcrystalline (Grifulvin V®*)	Antifungal	✔
Griseofulvin ultramicrocrystalline (GRIS-PEG®*)	Antifungal	✔
Itraconazole (Onmel®, Sporanox®*)	Antifungal (azole)	✔
Tavaborole (Kerydin®)	Antifungal (oxaborole)	-
Terbinafine hydrochloride (Lamisil®*)	Antifungal (allylamine)	✔

*Generic available in at least one dosage form or strength

Indications

Table 2. Food and Drug Administration Approved Indications[1-8]

Generic Name	Onychomycosis†		Other Indication(s)
	Fingernail	Toenail	
Ciclopirox	✔ *	✔ *	
Efinaconazole		✔	
Griseofulvin	✔	✔	Tinea corporis (body/skin), pedis (athlete's foot), cruris (groin and thigh), barbae (barber's itch), capitis (scalp)
Itraconazole	✔ ‡	✔ §	Blastomycosis‡, Histoplasmosis‡, Aspergillosis‡
Tavaborole		✔	
Terbinafine HCl	✔ ¶	✔ ¶	

HCl=hydrochloride
*Mild to moderate onychomycosis without lunula involvement
†Caused by Trichophyton rubrum (ciclopirox); caused by trichophyton rubrum and Trichophyton mentagrophytes (efinaconazole, itraconazole [Onmel®], tavaborole); caused by Trichophyton rubrum, Trichophyton tonsurans, Trichophyton mentagrophytes, Trichophyton interdigitalis, Trichophyton verrucosum, Trichophyton megnini, Trichophyton gallinae, Trichophyton crateriform, Trichophyton sulphureum, Trichophyton schoenleinii, Microsporum audouini, Microsporum canis, Microsporum gypseum and Epidermophyton floccosum (griseofulvin); causative pathogens not reported for itraconazole (Sporanox®) or terbinafine
‡ Sporanox® tablets only
§ Onmel® and Sporanox® tablets only
‖ Sporanox® oral solution only
¶ Lamisil® tablets only

Pharmacokinetics

Pharmacokinetic studies for the onychomycosis antifungals are limited. Standard pharmacokinetic parameters such as absorption, bioavailability, renal excretion, half-life, are not routinely reported in the FDA-approved labels of these agents. Variance in kinetic parameters such as absorption and half-life is observed for many of the topical agents. Differences in kinetics can be attributed to dose and length of therapy. Overall, pharmacokinetic parameters for these agents are insignificant when comparing one another.[1-8,34-36]

Clinical Trials

The safety and efficacy of the agents used to treat onychomycosis are summarized in Table 3.[5,9-31] The methodologies used for these studies differ greatly from one to another, with an important difference being how the researchers defined the term cure in each study.

Older agents such as itraconazole, griseofulvin and terbinafine HCl have been well studied. In head-to-head studies, terbinafine HCl and itraconazole provided an improved cure rate over griseofulvin microsize and ultramicrosize tablets.[9-13] Studies comparing terbinafine HCl to itraconazole have reported inconsistent results with numerous clinical trials reporting improved clinical and/or mycological cure rates with terbinafine HCl while several published studies have shown no difference between the agents..[13-28]

The safety and efficacy of ciclopirox nail lacquer topical solution has been evaluated in two double-blind placebo-controlled trials which lasted for 48 weeks each. These trials included patients with at least one great toenail which was infected and there was no lunula involvement. In addition to daily application of ciclopirox, monthly removal of the unattached, infected toenail by the investigator was done. At baseline, patients had 20 to 65% involvement of the target great toenail plate. Both studies showed a significant improvement in mycological cure and culture results for ciclopirox compared with placebo (P<0.001 for both outcomes in both studies). There was also a statically significant difference in terms of treatment success in favor of ciclopirox (study A, 6.5% vs 0.9%, P=0.031; study B, 12% vs 0.9%, P=0.001). However, only one study showed a statistical difference between ciclopirox and placebo in terms of treatment cure. Study A showed a cure rate of 5.5% for ciclopirox and 0.9% for placebo (P=0.059) whereas study B showed a cure rate of 8.5% for ciclopirox and 0% for placebo (P=0.001).[29]

The safety and efficacy of once daily use of efinaconazole topical solution for the treatment of onychomycosis of the toenail were assessed in two 52-week multi-center, randomized, double-blind, vehicle-controlled, parallel-group clinical trials in patients 18 to 70 years of age with 20 to 50% clinical involvement of the target toenail. The complete cure rate was assessed four weeks after completion of therapy at week 52. In terms of efficacy results, 17.8 and 15.2% of the efinaconazole group had complete cure compared to 3.3% and 5.5% in the vehicle group. Efinaconazole was superior to vehicle in all prospectively defined primary and secondary endpoints, which included mycologic cure, complete or almost complete cure, treatment success, and unaffected new toenail growth (P<0.001 for all).[30]

Itraconazole tablets were approved based on one 12 week, randomized, multi-center, placebo-controlled study in patients with onychomycosis. It was compared to itraconazole capsules and placebo. The primary endpoint of the study was the proportion of patients with a complete cure at 52 weeks. At week-52, 22.3% of patients in the itraconazole tablets group had complete cure compared to 1.0% in the placebo group (P value not reported). The mycological and clinical cure rates were 44% and 6% and 26% and 3% in the itraconazole tablets and placebo groups, respectively (P value not reported). Efficacy results comparing itraconazole to itraconazole capsules were found to be similar (P value not reported).[5,31]

The safety and efficacy of tavaborole for the treatment of onychomycosis of the toenail was assessed in two 52-week multi-center, randomized, double-blind, vehicle-controlled clinical trials in patients 18 to 88 years of age with 20 to 60% clinical involvement of the target toenail. The trials compared 48-weeks of once daily treatment with tavaborole to the vehicle solution. The complete cure rate was assessed four weeks after completion of therapy at week 52. The primary endpoint of complete cure was defined as 0% involvement of the target toenail in addition to mycologic cure. In terms of efficacy results, 6.5% and 9.1% of the tavaborole group had complete cure compared to 0.5% and 1.5% in the vehicle group. A greater proportion of patients in the tavaborole-treated groups experienced mycological cure and complete or almost complete cure compared to vehicle-treated groups (P values not reported).[5]

Table 3. Clinical Trials

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Data on file[5] (NCT01302119 and NCT01270971) tavaborole QD vs vehicle QD	DB, MC, PC, RCT Patients from 18 to 88 years of age with toenail distal lateral subungual onychomycosis without dermatophytomas or matrix involvement affecting ≥1 great toenail	Study 1: N=593 Study 2: N=601 48 weeks of double-blind treatment Four week post-treatment follow-up	Primary: Complete cure Secondary: Mycologic cure, complete or almost complete cure	Primary: The trials demonstrated complete cure at four weeks post-treatment in more tavaborole-treated patients compared to vehicle-treated patients (study 1: 6.5% versus 0.5%; P value not reported, study 2: 9.1% versus 1.5%; P value not reported). Secondary: A greater proportion of tavaborole-treated patients also experienced mycological cure and complete cure or almost complete cure compared to vehicle-treated patients (study 1: 31.1% versus 7.2%, and 15.3% versus 1.5%; P value not reported for both endpoints, study 2: 35.9% versus 12.2% and 17.9% versus 3.9%; P value not reported for both endpoints).
Korting et al[9] Griseofulvin ultramicrosize 660 mg daily for up to 18 months vs griseofulvin ultramicrosize 990 mg daily for up to 18 months vs itraconazole 100 mg daily for up to 18 months	OL, RCT Patients with clinically confirmed tinea unguium of the toenails, fingernails, or both	N=109 18 months	Primary: Clinical response, compliance, adverse effects Secondary: Not reported	Primary: There was no significant difference in the cure or partial cure rates between the griseofulvin ultramicrosize 660 mg, griseofulvin ultramicrosize 990 mg, and itraconazole groups (six, 14, and 19%, respectively; P=0.2097). There was no significant difference in the rates of marked improvement between the griseofulvin ultramicrosize 660 mg, griseofulvin ultramicrosize 990 mg, and itraconazole groups (36, 44, and 39%, respectively; P value not reported). No significant difference in compliance was observed between groups (P value not reported). Itraconazole was significantly better tolerated compared to both griseofulvin ultramicrosize groups (P≤0.0322). Secondary: Not reported
Hoffman et al[10]	DB, RCT	N=195	Primary:	Primary:

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Griseofulvin micronized 1,000 mg daily for 48 weeks vs terbinafine 250 mg daily for 24 weeks followed by 24 weeks of placebo	Patients 21 to 93 years of age with clinically confirmed distal subungual onychomycosis of the toenails	72 weeks	Mycological cure, clinical response, time to mycological cure Secondary: Not reported	Mycological cure increased during active therapy in both groups, and slightly decreased in the terbinafine group while sharply decreasing in the griseofulvin group during the follow-up period. At week 48, 88% of terbinafine patients and 82% of griseofulvin patients had negative cultures, while these numbers decreased to 81 and 62% respectively at the end of the study (P=0.02). The time to negative culture was 130 days in the terbinafine group and 172 days in the griseofulvin group (P=0.036). The mean global score in the terbinafine group decreased from 6.3 to 1.4 at week 48 and 0.8 at the end of the study, compared to 7.0 in the griseofulvin group decreasing to 1.7 at week 48 and 1.8 at the end of the study (P=0.010). Secondary: Not reported
Haneke et al[11] Terbinafine 250 mg daily for 12 weeks vs griseofulvin microsize 500 mg daily for 12 weeks After 12 weeks of treatment, all patients received an additional 12 weeks of placebo followed by 6 months follow-up.	DB, MC, RCT Patients 18 years of age and older with clinically confirmed distal subungual onychomycosis of the fingernails	N=180 1 year	Primary: Clinical response, mean global score, mycological cure, mean time to negative culture Secondary: Not reported	Primary: Mycological cure rates increased in both groups during active treatment and continued in the terbinafine group during follow-up while remaining steady in the griseofulvin group (P values not reported). At week 24, 90% of patients in the terbinafine group and 64% of patients in the griseofulvin group were mycologically cured (P value not reported). At the end of the study, 92% of patients in the terbinafine group and 63% of patients in the griseofulvin group were mycologically cured (P≤0.001). Mean time to negative culture was 73 days in the terbinafine group and 93 days in the griseofulvin group (P value not reported). The length of unaffected nail increased in the terbinafine group from 3.2 to 11.4 mm (week 24) and 12.4 mm (end of study). In the griseofulvin group, it increased from 2.6 to 9.5 mm (week 24) and decreased to 8.7 mm at the end of the study (P=0.006 between groups at the end of the study).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				The mean global scores decreased in the terbinafine group from 5.8 to 0.9 (week 24) and 0.4 (end of study). In the griseofulvin group, the scores decreased from 5.7 to 1.8 (week 24) and increased to 2.2 at the end of the study (P=0.028 at week 24, P≤0.001 at end of study). Secondary: Not reported
Faergemann et al[12] Terbinafine 250 mg daily for 16 weeks vs griseofulvin 500 mg daily for 52 weeks Patients in either group who did not respond after 16 weeks were switched to OL terbinafine treatment for 16 weeks and 20 weeks of follow-up.	DB, PG, RCT Adult patients with culture-proven tinea of the toenails	N=89 52 weeks	Primary: Complete cure, mycological cure Secondary: Not reported	Primary: Significantly more patients in the terbinafine group were completely cured (42%) compared to patients in the griseofulvin group (2%) at the end of the study (P≤0.0005). Significantly more patients in the terbinafine group experienced mycological cure (84%) compared to patients in the griseofulvin group (45%) at the end of the study (P≤0.0005). Of the patients who switched to OL treatment with terbinafine, 44% were cured at the end of the study (week 52 or 20 weeks after cessation of OL terbinafine) compared to 18% in the griseofulvin group (P value not reported). Secondary: Not reported
Haugh et al[13] Terbinafine 250 mg daily for 3 or 6 months vs griseofulvin 500 or	MA Patients diagnosed with onychomycosis	N=2,063 3 to 11 months	Primary: Mycological cure at the end of the studies, negative microscopy or culture at specified time	Primary: *Terbinafine vs placebo (three trials)* After 12 weeks, a significant advantage in mycological cure rates was seen in favor of the terbinafine group compared to the placebo group (P value not reported). *Terbinafine vs itraconazole (four trials)* At the end of the study periods, a statistically significant advantage in achieving negative culture and microscopy was seen in favor of terbinafine compared to

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
1,000 mg daily for 3 or 11 months vs itraconazole 200 mg daily or 400 mg intermittently (for 1 of every 4 weeks) for 3 or 4 months vs placebo			points Secondary: Not reported	itraconazole (P value not reported). No significant differences in the occurrence of adverse events were reported. *Terbinafine vs griseofulvin (two trials)* Significantly higher rates of negative microscopy and culture were observed in the terbinafine groups at week 24 compared to the griseofulvin groups (P values not reported). Secondary: Not reported
Brautigam[14] Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg daily for 12 weeks	DB, MC, PG, RCT Patients 18 years of age and older with a clinical diagnosis of distal subungual or proximal onychomycosis of the toenails	N=195 52 weeks	Primary: Mycologic cure, clinical efficacy Secondary: Not reported	Primary: Significantly more patients in the terbinafine group had experienced mycological cure (81.4%) compared to patients in the itraconazole group (63.1%; P<0.01) at week 52. At week 52, 91.9% of cultures were negative for dermatophytes in the terbinafine group compared to 66.6% in the itraconazole group (P<0.0001). The mean time to the first negative culture was significantly shorter in the terbinafine group (8.52 weeks) compared to the itraconazole group (11.64 weeks; P<0.05). Terbinafine was significantly more effective in increasing the length of unaffected nail compared to itraconazole (P value not reported). At week 52, a significantly lower number of patients in the terbinafine group had >60% of the nail plate affected (3.5% of patients) compared to the number of patients in the itraconazole group (15.5% of patients; P<0.05). Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Evans et al[15] Terbinafine 250 mg daily for 12 or 16 weeks vs itraconazole 200 mg daily for 1 of every 4 weeks for 12 (3 cycle) or 16 weeks (4 cycle)	DB, DD, MC, PG, RCT Patients 18 to 75 years of age with a clinical diagnosis of onychomycosis of the toenail confirmed by positive results on mycological cure and microscopy	N=496 72 weeks	Primary: Mycologic cure Secondary: Clinical cure, complete cure, clinical effectiveness, global assessments by physician and patient	Primary: Mycologic cure rates were significantly higher in both terbinafine groups (81 and 80% respectively) compared to the itraconazole groups (41 and 53% for the three-cycle and four-cycle itraconazole groups respectively; P<0.0001). Secondary: Clinical cure rates were significantly higher in the terbinafine groups compared to the itraconazole groups (P≤0.0022). Complete cure rates were significantly higher in the continuous terbinafine group compared to both itraconazole groups (P≤0.0044). Clinical effectiveness and global assessments were significantly higher for the continuous terbinafine groups compared to the itraconazole groups (P<0.0001).
Sigurgeirsson et al[16] Terbinafine 250 mg daily for 12 or 16 weeks vs itraconazole 400 mg daily for 1 of every 4 weeks for 12 (3 cycles) or 16 (4 cycles) weeks	DB, DD, PRO, RCT Patients 18 to 75 years of age with onychomycosis of the toenail confirmed by culture finding infection with a dermatophyte	N=158 72 weeks	Primary: Proportion of patients who remained mycologically cured at the end of follow-up without requiring continued treatment with terbinafine Secondary: Clinical cure, complete cure, clinical and mycological relapse over time,	Primary: Significantly more patients originally treated with terbinafine were mycologically cured at the end of the study compared to patients originally treated with itraconazole (46% compared to 13%; P<0.001). Secondary: Significantly more patients originally treated with terbinafine were clinically cured at the end of the study compared to patients originally treated with itraconazole (42% compared to 18%; P<0.002). Significantly more patients in the terbinafine group maintained complete cure at the end of the study compared to patients in the itraconazole group (P<0.005). At the end of the study, significantly fewer terbinafine patients had mycologically relapsed compared to itraconazole patients (23% compared to 53%; P<0.01). At the end of the study, significantly fewer terbinafine patients had clinically relapsed compared to itraconazole patients (21% compared to 48%; P<0.05). Ninety-two percent of patients who originally received terbinafine and

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			mycological and clinical cure over time, effect of subsequent terbinafine treatment on clinical and mycological outcome	subsequently received a second course of treatment with terbinafine after 18 months achieved mycological cure compared to 85% of those originally treated with itraconazole (P value not reported). Similar results were seen with clinical cure rates: it was achieved in 76% of patients originally treated with terbinafine and 77% of patients originally treated with itraconazole (P value not reported).
Sigurgeirsson et al[17] Terbinafine 250 mg daily for 12 weeks (Group T_{12}) or 16 weeks (Group T_{16}) vs itraconazole 400 mg/day for 1 week every 4 weeks for 12 weeks (Group I_3) or 16 weeks (Group I_4)	DB, DD, MC, PG, PRO, RCT Patients 18 to 75 years of age with distal subungual or total dystrophic onychomycosis of the toenails confirmed mycologically	N=507 72 weeks	Primary: Mycological cure Secondary: Clinical cure, complete cure, clinical efficacy, global assessment of efficacy by patient and physician	Primary: Mycological cure rates were 75.7% in the T_{12} group, 80.8% in the T_{16} group, 38.3% in the I_3 group and 49.1% in the I_4 group. Results were statistically significant in favor of the terbinafine regimens (P<0.0001). Secondary: Clinical cure was 53.6, 60.2, 31.8, and 32.1% for the T_{12}, T_{16}, I_3, and I_4 groups respectively, and all were significantly in favor of the terbinafine regimens (P<0.002). Complete cure rates were 45.8, 55.1, 23.4, and 25.9% for the T_{12}, T_{16}, I_3, and I_4 groups respectively, and all were significantly in favor of the terbinafine regimens (P<0.0007). Clinical efficacy rates were significant in favor of the terbinafine regimens (P<0.0001). Global assessment of efficacy by patients was very good or excellent in 78.9, 78.8, 43.9, and 52.3% of patients in the T_{12}, T_{16}, I_3, and I_4 groups, respectively, and were statistically in favor of the terbinafine regimens (P<0.0001). Global assessment of efficacy by physicians was very good or excellent in 78.9, 78.8, 43.9, and 52.3% of patients in the T_{12}, T_{16}, I_3, and I_4 groups, respectively, and these assessments statistically favored the terbinafine regimens (P<0.0001).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Heikkila and Stubb[18] Terbinafine 250 mg daily for 12 or 16 weeks vs itraconazole 400 mg daily for 1 of every 4 weeks for 12 (3 cycles) or 16 (4 cycles) weeks	DB, MC, RCT Finnish participants 18 to 75 years of age with a clinical diagnosis of onychomycosis of the toenail confirmed by culture; this was a 4-year follow-up of Finnish participants in a previous study conducted for 72 weeks	N=76 4 years	Primary: Mycologic cure, clinical cure, complete cure Secondary: Not reported	Primary: At four years, terbinafine was shown to be more effective than itraconazole (P values not reported). At four years, negative microscopy and culture remained unchanged in the terbinafine group treated for 16 weeks, but fell to <50% in all other groups (P values not reported). At four years, clinical and complete cure rates in the terbinafine group treated for 16 weeks was better than the rates seen at 72 weeks (78% compared to 50%), but remained unchanged or worsened in all other groups (P values not reported). Secondary: Not reported
De Backer et al[19] Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg daily for 12 weeks	DB, RCT Patients 18 years of age and older with clinically suspected subungual dermatophyte infections of the toenails confirmed by microscopy and culture	N=372 48 weeks	Primary: Percentage of patients with negative culture at week 48, length of healthy nail, hyperkeratosis, onycholysis, paronychial inflammation, investigator and patient assessment of	Primary: At week 48, significantly more patients in the terbinafine group had negative microscopy results (77.9%) compared to patients in the itraconazole group (55.4%; P<0.0001). At week 48, significantly more patients in the terbinafine group had negative dermatophyte culture results (84%) compared to patients in the itraconazole group (64.3%; P<0.0001). At week 48, significantly more patients in the terbinafine group had negative mycology results (73%) compared to patients in the itraconazole group (45.8%; P<0.0001). At week 48, patients in the terbinafine group had significantly more healthy nail in the big toe compared to patients in the itraconazole group (8.1and 6.4 mm, respectively; P=0.026).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			efficacy of treatment Secondary: Not reported	At week 48, onycholysis score significantly favored terbinafine compared to itraconazole (P=0.001). There was no significant difference in hyperkeratosis scores between groups (P=0.27). Paronychial inflammation was absent in the majority of patients in both groups (P value not reported). The global clinical evaluation of the target nail at week 48 was significantly higher in the terbinafine group (cleared or minimal symptoms) compared to the itraconazole group (76.2 and 58.1%, respectively; P=0.001). Secondary: Not reported
Brautigam et al[20] Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg daily for 12 week	MC, RCT Patients with a clinical diagnosis of distal subungual or proximal onychomycosis and a growth of dermatophytes	N=170 40 week post-treatment follow-up	Primary: Mycological response, area of unaffected nail Secondary: Not reported	Primary: Mycological cure rates were 81% in the terbinafine group and 63% in the itraconazole group (P<0.01). The length of unaffected nail increased to 9.4 mm in the terbinafine group and to 7.9 mm in the itraconazole group (P<0.05). Secondary: Not reported
Tosti et al[21] Terbinafine 250 mg daily (T250) vs terbinafine 500 mg daily for 1 week	OL, RCT Patients with onychomycosis of the toenails or fingernails	N=63 6 month post-treatment follow-up	Primary: Mycological response Secondary: Not reported	Primary: At the end of the follow-up period, 76.5% of patients in the T250 group were cured without residual malformations compared to 50% of patients in the T500 group and 38.1% of patients in the I group (P=0.013 between T250 and I). At the end of the follow-up period, significantly more patients in the I group were considered cured with residual malformations compared to those in the T250 group (P=0.013).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
every month (T500) vs itraconazole 400 mg daily for 1 week every month (I) Treatment was continued for 4 months for toenail infections and for 2 months for fingernail infections.				At the end of the follow-up period, significantly more patients in the I group were considered failures compared to those in the T250 group (P=0.013). Secondary: Not reported
Gupta et al[22] Itraconazole 200 mg/day for weeks 1 to 4 and terbinafine 250 mg/day for weeks 3 to 6 (2-week overlap of itraconazole and terbinafine) (COMBO) vs Continuous terbinafine 250 mg/day for 12 weeks (CTERB) vs	PRO, SB Patients with toenail onychomycosis caused by dermatophytes mycologically cured at 48 weeks after the beginning of therapy based on a last observation carry forward analysis and both clinically and mycologically assessed after week 48	N=106 1.25 to 7 years	Primary: Proportions of participants with mycologic recurrence and recurrence (clinical and/or mycologic) at a post–week 48 visit Secondary: Not reported	Primary: Mycologic recurrence was found to occur in 43% (46 of 106) of all subjects. Mycologic recurrence rates were similar for the CTERB (32%) and TOT (36%) regimens, as well as for the III (59%) and the COMBO (57%) regimens. About half (22 of 43; 51%) of the participants completely cured had recurrence post–week 48. The recurrence rates for complete cure by regimen were similar and ranged from 40 (CTERB) to 67% (COMBO). Similar recurrence rates were generally obtained when participants who received booster therapy were excluded from the analyses. However, the mycologic recurrence rates for CTERB (21%) and III (46%) were lower when the participants requiring booster were excluded. No statistically significant difference was detected between the four treatment groups. Secondary: Not reported

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
Intermittent terbinafine (250 mg/day for 4 weeks on, 4 weeks off, 4 weeks on) (TOT) vs Pulsed itraconazole (one pulse = 200 mg twice daily for 7 days on, 21 days off) for three pulses (III)				
Chang et al[23] Terbinafine, itraconazole, fluconazole (with or without topical agents)	MA Patients aged ≥18 years with superficial dermatophytosis (tinea pedis, tinea manus, tinea corpora, and tinea cruris) or onychomycosis who were receiving oral antifungal therapy for 2 or more weeks	N=19,298 (122 trials) Variable duration	Primary: Cumulative incidence of patients who withdrew from the study because of adverse reactions Secondary: Cumulative incidence of patients stopping treatment because of elevation of serum	Primary: For continuous oral antifungal therapy, the pooled risks of treatment discontinuation because of adverse reactions were 3.44% (95% CI, 2.28 to 4.61%) for terbinafine 250 mg/day; 1.96% (95% CI, 0.35 to 3.57%) for itraconazole 100 mg/day; 4.21% (95% CI, 2.33 to 6.09%) for itraconazole 200 mg/day; and 1.51% (95% CI, 0 to 4.01%) for fluconazole 50 mg/day. For intermittent or pulse therapy, the pooled risks of treatment discontinuation because of adverse reactions were 2.09% (95% CI, 0 to 4.42%) for terbinafine; 2.58% (95% CI, 1.15 to 4.01%) for itraconazole; 1.98% (95% CI, 0.05 to 3.92%) for fluconazole 150 mg/week and 5.76% (95% CI, 2.42 to 9.10%) for fluconazole 300 to 450 mg/week. Secondary: The incidence of liver injury associated with oral antifungal therapy was less than 2% in general. For the risks of having elevated serum transaminase levels that required treatment termination, the pooled risk estimates for continuous therapy ranged

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
			transaminase levels and cumulative incidence of patients developing elevation of serum transaminase levels during treatment but not requiring discontinuation	from 0.11% (itraconazole 100 mg/day) to 1.22% (fluconazole 50 mg/day). The pooled risk estimates for pulse therapy ranged from 0.39% (fluconazole 150 mg/week and itraconazole 400 mg/day) to 0.85% (fluconazole 300 to 450 mg/week). The pooled risks of developing elevated serum transaminase levels not requiring treatment discontinuation was on the order of 1.5% for continuous regimens and 1% for intermittent regimens evaluated.
Gupta et al[24] Terbinafine 250 mg daily for 12 weeks vs itraconazole 200 mg BID for 1 week given as 3 pulses	PRO, RCT Patients 60 years of age and older with dermatophyte onychomycosis of at least 1 great toe	N=101 18 months	Primary: Mycologic cure, clinical efficacy Secondary: Not reported	Primary: At month 18, the mycological cure rate in the terbinafine group was 64 vs 62.7% in the itraconazole group (P value not reported). No significant difference was found between groups. At month 18, clinical efficacy was 62.0% in the terbinafine group and 60.8% in the itraconazole group (P value not reported). No significant difference was found between groups. Secondary: Not reported
Degreef et al[25] Itraconazole 200 mg daily for 12 weeks vs terbinafine 250 mg daily for 12 weeks	DB, MC, PG, RCT Patients 18 to 65 years of age with clinically suspected and microscopically and culturally proven	N=297 36 weeks	Primary: Mycologic cure Secondary: Investigator's global clinical evaluation of response to	Primary: A similar number of patients were mycologically cured (79 in the terbinafine group and 78 in the itraconazole group; P value not reported). Secondary: Clinical response rates were similar between the groups (P<0.1). Complete clinical cure rates were similar between the groups (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
	onychomycosis of the toenail		treatment defined as clinical response, percentage of total affected nail area, total number of infected nails, signs and symptoms of onycholysis, hyperkeratosis, paronychial inflammation and discoloration	The mean percentage of affected nail area and the mean number of nails infected decreased similarly in the two groups (P values not reported). Signs and symptoms of infections improved comparably in the two groups (P value not reported).
Bahadir et al[26] Itraconazole 100 mg BID for the first week of 3 consecutive months vs terbinafine 250 mg daily for 3 months	RCT Patients with clinically and mycologically confirmed onychomycosis	N=60 24 week post-treatment follow-up	Primary: Therapeutic response Secondary: Not reported	Primary: Healing was achieved in 60.0% of itraconazole patients and 68.5% of terbinafine patients, remission was achieved in 28.0% of itraconazole patients and 25.7% of terbinafine patients, and failure was reported in 4.00% of itraconazole patients and 2.85% of terbinafine patients (P=0.50) Secondary: Not reported
Arenas et al[27] Terbinafine 250 mg daily for 3 months vs	CS, OL, PRO Patients 18 years of age and older with onychomycosis	N=53 9 months	Primary: Culture and potassium hydroxide smear results, affected nail area, medical	Primary: At the end of treatment, rates of positive potassium hydroxide smears were similar between groups (21.7% for itraconazole and 23.5% for terbinafine; P value not reported). At the end of treatment, there was one positive culture in the terbinafine group and at the end of follow-up, there was one positive culture in the itraconazole

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
itraconazole 200 mg daily for 3 months			evaluation of treatment Secondary: Nail changes, nail growth, patient evaluation of treatment	group. Both treatment groups showed improvement in nail area affected compared to baseline (P<0.01) and there was no significant difference between groups (P value not reported). There was no significant difference between groups in the medical evaluation of treatment (P value not reported). There was no significant difference in cure and improvement between groups (P value not reported). Secondary: There were no significant differences in nail changes or nail growth between groups (P values not reported). There was no significant difference between groups in the patients' evaluation of treatment (P value not reported).
Honeyman et al[28] Terbinafine 250 mg daily for 4 months vs itraconazole 200 mg daily for 4 months Patients in both groups received placebo for an additional 8 months after initial therapy.	DB, DD, MC, PG, RCT Patients with toenail onychomycosis	N=179 12 months	Primary: Clinical response, mycological response, clinical global evaluation scores, effectively cured patient scores Secondary: Not reported	Primary: At the end of treatment (four months), mycological cure was similar for terbinafine and itraconazole (54.9 and 51.8%, respectively; P value not reported). At 12 months, the mycological cure was 95.3% for terbinafine and 84.3% for itraconazole (P=0.04). No significant differences in clinical response were observed between groups at month four or 12 (P>0.05). There was no significant difference in the clinical global evaluation at month four or 12 between groups when clinical cure was considered, though when clinical improvement was also considered, terbinafine showed significantly better scores (P<0.02). At four months, there was no difference in the proportion of patients considered

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				to be effectively cured patient, though at 12 months significantly more patients in the terbinafine group were considered effectively cured patient (95.3 and 75.7%, respectively; P<0.001). Secondary: Not reported
Gupta et al[29] Ciclopirox nail lacquer 8% topical solution applied to affected fingernail(s) and toenail(s) QD vs topical solution vehicle applied to affected fingernail(s) and toenail(s) QD Both study A and study B participants received either ciclopirox nail lacquer 8% topical solution or vehicle given QD.	2 DB, MC, PC, PG Patients aged 18 to 70 years with mild-to- moderate toenail onychomycosis caused by dermatophytes	N=560 48 weeks	Primary: Mycological cure rate (negative mycology), treatment success (≤10% nail involvement and negative mycology), treatment cure (clear nail and negative mycology) Secondary: Adverse effects	Primary: In study A, there was significant improvement in mycological cure in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (29% vs 11%, respectively; P<0.001). In study B, there was significant improvement in mycological cure in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (36% vs 9%, respectively; P<0.001). In study A, there was significant improvement in culture results in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (84% vs 37%, respectively; P<0.001). In study B, there was significant improvement in culture results in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (84% vs 44%, respectively; P<0.001). In study A, there was a statistically significant difference between ciclopirox and the vehicle in terms of treatment success (6.5% vs 0.9%, respectively; P=0.031). In study B, there was significant improvement in treatment success in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (12% vs 0.9%, respectively; P=0.001). In study A, there was no statistically significant difference between ciclopirox and the vehicle in terms treatment cure (5.5% vs 0.9%, respectively; P=0.059). In study B, there was significant improvement in treatment cure in patients treated with ciclopirox compared to patients receiving the vehicle throughout the 48-week treatment period (8.5% vs 0%, respectively; P=0.001). Secondary: In study A, adverse effects associated with ciclopirox compared to vehicle were

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
				mainly localized site reactions including erythema (4% vs 1%, respectively); tingling sensation, pain or intermittent burning (3% vs 2%, respectively); and changes in nail shape or color (2% vs 1%, respectively) (P values not reported). In study B, adverse effects associated with ciclopirox compared to vehicle were mainly localized site reactions including erythema (10% vs 2%, respectively); tingling sensation, pain or intermittent burning (0% vs 1%, respectively); and changes in nail shape or color (3% vs 3%, respectively) (P values not reported).
Elewski et al[30] (NCT01008033 NCT01007708) Efinaconazole QD vs vehicle QD	DB, MC, PC, PG, RCT Patients from 18 to 70 years of age with mild-to-moderate toenail DLSO without dermatophytomas or matrix involvement affecting ≥1 great toenail	Study 1: N=870 Study 2: N=785 48 weeks of double-blind treatment Four week post-treatment follow-up	Primary: Complete cure Secondary: Mycologic cure, complete or almost complete cure, treatment success, unaffected new toenail growth	Primary: The trials demonstrated complete cure at four weeks post-treatment in more efinaconazole-treated patients compared to vehicle-treated patients (study 1: 17.8% versus 3.3%; P<0.001, study 2: 15.2% versus 5.5%; P<0.001). Secondary: A greater proportion of efinaconazole-treated patients also experienced mycological cure, complete cure or almost complete cure, and treatment success compared to vehicle-treated patients (study 1: 55.2% versus 16.8%, 26.4% versus 7.0% and 35.7% versus 11.7%; P<0.001 for both endpoints, study 2: 53.4% versus 16.9%, 23.4% versus 7.5% and 31.0% versus 11.9%; P<0.001 for both endpoints). Unaffected new toenail growth was higher in efinaconazole-treated patients at 5.0 mm compared to 1.6 mm in vehicle-treated patients (P<0.001) in study 1, and 3.8 mm compared to 0.9 mm (P<0.001), respectively in study 2.
Maddin et al[5,31] (abstract and package insert) Itraconazole tablet 200 mg QD vs itraconazole two 100	MC, PC, RCT Patients with a diagnosis of distal and/or lateral subungual onychomycosis	N=791 52 weeks	Primary: Proportion of patients with a complete cure at 52 weeks, clinical cure, or mycological cure Secondary:	Primary: At week 52, 22.3% of patients in the Onmel 200 mg group had a complete cure compared to 1% in the placebo group (P value not reported). The mycological cure rate was 44% and 6% in the Onmel 200 mg group and placebo group respectively (P value not reported). The clinical cure rate was 26% and 3% in the Onmel 200 mg group and placebo group respectively (P value not reported).

Study and Drug Regimen	Study Design and Demographics	Sample Size and Study Duration	End Points	Results
mg capsules QD vs placebo			Not reported	Efficacy results comparing Onmel and generic itraconazole were similar however efficacy values were not reported. Secondary: Not reported

Drug regimen abbreviations: QD=once daily
Study abbreviations: CI=confidence interval, DB=double-blind, DD=double-dummy, MA=meta-analysis, MC=multicenter, OL=open-label, PC=placebo-controlled, PG=parallel-group, PRO=prospective, RCT=randomized controlled trial

Special Populations[#]

Table 4. Special Populations [1-8,35,36]

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
Ciclopirox	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. FDA approved for use in children ≥12 years of age.	No dosage adjustment is required.	No dosage adjustment is required.	B	Unknown; use with caution.
Efinaconazole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not reported; it appears as though no dose adjustment is required.	Not reported; it appears as though no dose adjustment is required.	C	Unknown; use with caution.
Griseofulvin	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. FDA approved for use in children ≥2 years of age.*	No dosage adjustment is required.	Not reported; use with caution. Contraindicated in patients with hepatocellular failure.	X	Unknown; due to potential for adverse effects, use is not reco-mmended in nursing mothers.
Itraconazole	Use with caution in elderly patients; transient or permanent hearing loss has been reported. Safety and efficacy in children have not been established.	Not reported, use with caution; it appears as though no dose adjustment is required.[†]	Not reported, use with caution; it appears as though no dose adjustment is required.[†]	C[‡]	Yes; percent not reported
Tavaborole	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	Not reported; it appears as though no dose adjustment is required.	Not reported; it appears as though no dose adjustment is required.	C	Unknown; use with caution
Terbinafine HCl	No evidence of overall differences in safety or	No dosage adjustment	Not reported; use is not	B	Yes; he ratio of terbinafine

Generic Name	Population and Precaution				
	Elderly/Children	Renal Dysfunction	Hepatic Dysfunction	Pregnancy Category	Excreted in Breast Milk
	efficacy observed between elderly and younger adult patients. Safety and efficacy in children have not been established.	required for CrCl ≥50 mL/min. Use in CrCl <50 mL/min is not reco-mmended.	recommended in patients with hepatic disease. Use in patients with hepatic cirrhosis is not recommended.		in milk to plasma is 7:1, use is not reco-mmended

CrCl=creatinine clearance, HCl=hydrochloride
*Reported for microcrystalline formulation only; not reported for ultra-microcrystalline formulation
†No adequate or well-controlled trials.
‡Use of itraconazole capsules (Sporanox®) and tablets (Onmel®) is contraindicated in pregnant patients or to women contemplating pregnancy.

Adverse Drug Events

Table 5. Adverse Drug Events[1-8]

Adverse Event	Ciclopirox	Efinaconazole	Griseofulvin	Itraconazole	Tavaborole	Terbinafine HCl
Abdominal Pain	-	-	-	2	-	2.4
Albuminuria	-	-	-	1	-	-
Anorexia	-	-	-	1	-	-
Application site reaction	1	1.1 to 2.2	✔	-	1.3 to 2.7	-
Burning	1	-	-	-	-	-
Confusion	-	-	✔	-	-	-
Decreased libido	-	-	-	1	-	-
Diarrhea	-	-	✔	3	-	5.6
Dizziness	-	-	✔	2	-	-
Dyspepsia	-	-	-	-	-	4.3
Edema	-	-	-	4	-	-
Erythema	5	-	-	-	-	-
Epigastric distress	-	-	✔	-	-	-
Fatigue	-	-	✔	3	-	-
Fever	-	-	-	3	-	-
Flatulence	-	-	-	-	-	2.2
Headache	-	-	✔	4	-	12.9
Hypertension	-	-	-	3	-	-
Hypokalemia	-	-	-	2	-	-
Ingrown toenail	-	2.3	-	-	2.5	-
Insomnia	-	-	✔	-	-	-
Malaise	-	-	-	1	-	-
Nausea	-	-	✔	11	-	2.6
Oral thrush	-	-	✔	-	-	-
Pruritus	-	-	-	3	-	2.8
Rash	-	-	-	9	-	5.6
Somnolence	-	-	-	1	-	-
Taste disturbances	-	-	-	-	-	2.8
Upper				-		
Urticaria	-	-	-	-	-	1.1
Visual disturbances	-	-	-	-	-	1.1
Vomiting	-	-	✔	5	-	-

Contraindications

Table 6. Contraindications[1-8]

Contraindication	Ciclopirox	Efinaconazole	Griseofulvin	Itraconazole	Tavaborole	Terbinafine HCl
Coadministration with certain CYP 3A4 substrates				✔		
Coadministration with certain agents where absorption is regulated by P-gp				✔		
Congestive heart failure				✔		
Hepatocellular failure			✔			
Hypersensitivity to the drug or its components	✔		✔	✔		✔
Pregnancy			✔	✔		
Porphyria						
Ventricular dysfunction				✔		

Black Box Warning for itraconazole (Onmel®, Sporanox®)[5,6]

WARNING

Congestive Heart Failure, Cardiac Effects and Drug Interactions
If signs or symptoms of congestive heart failure occur during administration of itraconazole, continued itraconazole use should be reassessed. When itraconazole was administered intravenously to dogs and healthy human volunteers, negative inotropic effects were seen.

Drug Interactions
Coadministration of the following drugs is contraindicated with itraconazole: methadone, disopyramide, dofetilide, dronedarone, quinidine, ergot alkaloids (such as dihydroergotamine, ergometrine (ergonovine), ergotamine, methylergometrine (methylergonovine)), irinotecan, lurasidone, oral midazolam, pimozide, triazolam, felodipine, nisoldipine, ranolazine, eplerenone, cisapride, lovastatin, simvastatin and, in subjects with renal or hepatic impairment, colchicine. Coadministration with itraconazole can cause elevated plasma concentrations of these drugs and may increase or prolong both the pharmacologic effects and/or adverse reactions to these drugs. For example, increased plasma concentrations of some of these drugs can lead to QT prolongation and ventricular tachyarrhythmias including occurrences of torsades de pointes, a potentially fatal arrhythmia.

Warnings/Precautions

Table 7. Warnings and Precautions[1-8]

Warning/precaution	Ciclopirox	Efinaconazole*	Griseofulvin	Itraconazole	Tavaborole*	Terbinafine HCl
Coadministration with certain CYP3A4 inhibitors may result in cardiac dysrhythmias and/or sudden death	-	-	-	✔	-	-
Coadministration with calcium channel blockers; additive negative inotropic effects, use is contraindicated	-	-	-	✔	-	-
Congestive heart failure, peripheral edema, and pulmonary edema have been reported	-	-	-	✔	-	-
Do not administer to patients with congestive heart failure or evidence of ventricular dysfunction	-	-	-	✔	-	-
Hearing loss has been reported	-	-	-	✔	-	-
Hematologic effects (decrease in absolute lymphocyte counts) have been observed	-	-	-	-	-	✔
Hepatotoxic, including liver failure and death or transplant	-	-	-	✔	-	✔
Hepatotoxic, increases in AST, ALT, bilirubin and jaundice have been reported; may be serious and result in hospitalization or death.	-	-	✔	-	-	-
Itraconazole oral solution and capsules are not interchangeable	-	-	-	✔	-	-
Neuropathy has been reported	-	-	-	✔	-	-
Penicillium-related, cross-sensitivity may occur; known penicillium-sensitive patients have been treated with no response	-	-	✔	-	-	-
Photosensitivity has been reported	-	-	✔	-	-	-
Skin reaction, severe (Stevens-Johnson, toxic epidermal necrosis) and erythema multiforme have been reported	-	-	✔	-	-	✔
Smell disturbance including loss of smell has been reported, may resolve or be permanent. Discontinue use if taste disturbance occurs	-	-	-	-	-	✔

Warning/precaution	Ciclopirox	Efinaconazole*	Griseofulvin	Itraconazole	Tavaborole*	Terbinafine HCl
Taste disturbance including loss of taste has been reported, may resolve or be permanent. Discontinue use if taste disturbance occurs	-	-	-	-	-	✔
Topical use only; not for ophthalmic, oral or intravaginal use.	✔	-	-	-	-	-
Use on nails and immediately adjacent skin only.	✔	-	-	-	-	-

*No warnings and precautions reported

Drug Interactions

Common drug interactions are listed in Table 8. Refer to the manufacturer's FDA-approved label for a compressive list of all agents in which a drug-interaction exists.[1-8]

Table 8. Drug Interactions[1-8]

Generic Name	Interacting Medication or Disease	Potential Result
griseofulvin	oral contraceptives	Decreased effectiveness of oral contraceptives
itraconazole	CYP3A4 substrates	Increased plasma concentrations of CYP3A4 substrates.
itraconazole	P-gp substrates	Increased plasma concentrations of drugs in which gastric absorption is regulated by P-gp.
itraconazole	CYP3A4 inducers	Decreased plasma concentrations of itraconazole.
itraconazole	CYP3A4 inhibitors	Increased plasma concentrations of itraconazole,
itraconazole	antiarrhythmics (quinidine, dofetilide)	Prolonged QT interval; serious cardiovascular events may occur.
terbinafine HCl	CYP2D6 substrates	Increased plasma concentrations of CYP2D6 substrates.
terbinafine HCl	CYP2C9 and CYP3A4 inhibitors	Increased plasma concentration of terbinafine HCl.
terbinafine HCl	rifampin	Increased plasma concentration of terbinafine HCl.
terbinafine HCl	cimetidine	Decreased plasma concentration of terbinafine HCl.

CYP=cytochrome P450, P-gp=P=glycoprotein

Dosage and Administration

The FDA-approved doses for the treatment of onychomycosis are listed in Table 9. Refer to the manufacturer's product-specific label for additional dosage information.[1-8]

Table 9. Dosing and Administration[1-8,33,34]

Generic Name	Adult Dose	Pediatric Dose	Availability
Ciclopirox	Onychomycosis (finger, toe): Topical solution: apply to affected finger or toes QD at bedtime or eight hours before washing	Onychomycosis (finger, toe): > 12 years of age: see adult dosing	Topical solution: 8%
Efinaconazole	Onychomycosis (toe): Topical solution: apply to affected toenails QD for 48 weeks	Safety and efficacy in children have not been established.	Topical solution: 10%
Griseofulvin microcrystalline	Onychomycosis (finger): Oral suspension, tablet: 1,000 mg/day for at least four months Onychomycosis (toe): Oral suspension, tablet: 1,000 mg/day for at least six months Tinea Capitis, Tinea Corporis, Tinea Cruris: Oral suspension, tablet: 500 mg/day for two to six weeks	Onychomycosis and other tinea infections: > 2 years of age: 20 mg/kg/day (max 1,000 mg/day)	Oral Suspension: 125 mg/5 mL Tablet: 500 mg

Generic Name	Adult Dose	Pediatric Dose	Availability
	Tinea Pedis: Oral suspension, tablet: 1,000 mg/day for four to eight weeks		
Griseofulvin ultra-microcrystalline	Onychomycosis (finger): Tablet: 750 mg/day for at least four months Onychomycosis (toe): Tablet: 750 mg/day for at least six months Tinea Capitis, Tinea Corporis, Tinea Cruris: Tablet: 375 mg/day for two to six weeks Tinea Pedis: Tablet: 750 mg/day for four to eight weeks	Onychomycosis and other tinea infections: >2 years of age: 15 mg/kg/day (max 750 mg/day)	Tablet: 125 mg 250 mg
Itraconazole	Onychomycosis (finger): Capsule: two treatment pulses, each one consisting of 200 mg BID for one week separated by a three-week period Onychomycosis (toe): Capsule, tablet: 200 mg QD for 12 weeks	Safety and efficacy in children have not been established.	Capsule: 100 mg Tablet: 200 mg
Tavaborole	Onychomycosis (toe): Topical solution: apply to affected toenails QD for 48 weeks	Safety and efficacy in children have not been established.	Topical solution: 5%
Terbinafine HCl	Onychomycosis (finger): Tablet: 250 mg QD for six weeks Onychomycosis (toe): Tablet: 250 mg QD for 12 weeks	Safety and efficacy in children have not been established.	Tablet: 250 mg

Drug regimen abbreviations: BID=twice daily, QD=once daily
*Not indicated for the treatment of onychomycosis

Clinical Guidelines

Table 10. Clinical Guidelines

Clinical Guideline	Recommendations
European Academy of Dermatology and Venereology: **Onychomycosis Treatment Guidelines (2005)**[32]	• Prior to initiating treatment, it is important that the diagnosis be confirmed and the etiological agent identified. • Topical monotherapy is indicated when the matrix area is not involved. Topical treatment is also suitable for patients who are reluctant to take oral medications or have swallowing difficulties. The only case in which it is not recommended is if nail penetration may be suboptimal. • Oral antifungal drugs are generally considered to be more effective than topical treatments. However, they are accompanied by a higher risk of systemic adverse effects and drug interactions. • Oral monotherapy (terbinafine, itraconazole, or fluconazole) or combined oral and topical (nail lacquer) is recommended when 1) at least 50% of the distal nail plate is involved; 2) the nail matrix area is involved; 3) mycological criteria such as the causative agent or agents are known and oral agents can target specific fungi; 4) topical drugs are not indicated when topical drug transport is suboptimal; and 5) oral or combined therapy is also recommended in cases of nail matrix area involvement. • Combination therapy with systemic and topical treatments may be considered when a large portion of the nail plate is affected (>50%), when the nail matrix is involved, and in cases of treatment failure. • Griseofulvin is associated with the poorest mycological cure rate (<30%) and is rarely used. Terbinafine is associated with the highest mycological cure rate (77 to 100%).
British Association of Dermatologists: **Guidelines for the Treatment of Onychomycosis (2003)**[33]	• Both topical and oral agents are available for the treatment of fungal nail infection. The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. • Systemic therapy is almost always more successful than topical treatment, which should only be used in superficial white onychomycosis, possibly very early distal and lateral subungual onychomycosis, or when systemic therapy is contraindicated. • Both terbinafine and itraconazole have been shown to be more effective than griseofulvin in dermatophyte onychomycosis and the optimal choice of treatment lies between terbinafine and itraconazole. • Terbinafine is more effective than itraconazole for dermatophyte infection of the nails and should be first-line treatment. Itraconazole may be considered a second-line treatment. • Expected cure rates vary and range from 80 to 90% for fingernail infections and 70 to 80% for toenail infections.

Conclusions

Onychomycosis is a progressive infection of the nail bed which may extend into the matrix or plate, leading to destruction, deformity, thickening and discoloration. Agents approved for the treatment of onychomycosis include ciclopirox (Penlac®), itraconazole tablets (Onmel®) and capsules (Sporanox®), griseofulvin microsize (Grifulvin V®) and ultramicrosize (GRIS-PEG®), tavaborole (Kerydin®), and terbinafine HCl (Lamisil®).[1-8] Generally speaking, systemic therapy with terbinafine HCl or itraconazole has been shown to be more effective in treating onychomycosis of the toe or fingernail compared to the griseofulvin products; however, there are several studies that found itraconazole to be just as effective as terbinafine HCl.[9-28] Treatment guidelines have not been updated recently and do not include the newer agents, but state oral therapy is preferred, with topical therapy being useful in combination with an oral product.[32-33] Oral therapy with terbinafine HCl or itraconazole is significantly shorter duration than local therapy or treatment with oral griseofulvin. Therapy with oral terbinafine HCl or itraconazole lasts up to eight weeks maximum, opposed to 48 week or longer with local therapy or with griseofulvin. However, drug interactions may limit the use of oral agents as both terbinafine HCl and itraconazole have significant drug interactions. Ciclopirox and griseofulvin are approved in pediatric patients (age ≥12 years and ≥2 years, respectively).[1-8]

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