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# Effective Treatments for Onychomycosis

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## Abstract

*Background: Onychomycosis is a highly prevalent nail infective disorder. Many treatments, with varied success rates and side effects, are used.*

*Objectives: To assess the most recommended treatment for Onychomycosis with the optimal cure rate and least severe side effects. Search Methods: PubMed, ProQuest, EBSCO Multisearch, and Google Scholar were used to gather information. Search terms such as “Onychomycosis,” and “Effective treatments for Onychomycosis” etc. were used.*

*Results: Effective treatments include oral, topical, nail avulsion, and laser treatments. Topical treatments have low cure rates and minimal side effects. Oral treatments have various side effects but the highest mycological and clinical cure rates. Laser treatments yield high cure rates and minimal to none side effects, but a small chance of recurrence of the Onychomycosis is possible.*

*Conclusion: For those who are not susceptible to adverse effects, Oral treatment is the recommended treatment. For individuals who have pre-existing conditions that may be harmed by adverse effects of medication, Laser should be the sought treatment. Topical treatments are not recommended due to its low efficacy rate.*

## Introduction

Onychomycosis, fungal infection, is the most ubiquitous nail infective disorder with a prevalence in males and elderly individuals. It is accountable for almost half of nail disorder consultations. Although traditionally harmless, Onychomycosis, if left untreated, can occasionally lead to more serious complications, especially in individuals with pre-disposing factors, such as diabetes, HIV-induced immunosuppression, and arterial disease (Piraccini, Alessandrini, 2015). Various researched treatments with high success rates are used to treat fungal nail infections. The Success of treatments is weighed by the clinical cure, which refers to the decreased deformity or discoloration of the nail, and mycological cure, which refers to the absence of fungus within the nail (Kreijkamp-Kaspers, Hawke, 2017). This study seeks to determine what is the most recommended treatment for Onychomycosis.

There are several forms of Onychomycosis. Distal and Lateral Subungual Onychomycosis (DLSO) is caused by fungus infecting the distal or lateral area of the nail (Kreijkamp-Kaspers, Hawke, 2017). It is characterized by a yellow-white detached nail plate and hardening of the skin, also known as hyperkeratosis. It is often associated with athletes’ foot, and occasional brown, black, or orange discoloration (Figure 1). A detached nail from the nail bed or white streaks on the nail are also common (Kreijkamp-Kaspers, Hawke, 2017). Superficial Onychomycosis (SO) occurs when fungus enters the nail plate and forms white opaque colonies in the form of raised grooves that can be easily rubbed off (Figure 2). This

form of Onychomycosis is also often associated with athlete’s foot. The most basic form of SO happens because of dermatophytes colonizing the outer layers of the nail without penetrating it. Endonyx Onychomycosis (EO) occurs when the fungal hyphae in the distal nail plate is permeated by fungus. The nail appears to be split in half lengthwise with possible discoloration (Figure 3) (Kreijkamp-Kaspers, Hawke, 2017). Proximal Subungual Onychomycosis (PSO) is caused by fungus originating in the proximal nail fold and spreading to the upper portion of the nail (Kreijkamp-Kaspers, Hawke, 2017). It causes a white area to appear under the lunula area of the nail along with periungual inflammation. It also causes bacterial paronychia and nail pustular psoriasis (Figure 4) (Piraccini, Alessandrini, 2015). Mixed Pattern Onychomycosis (MPO) occurs when different forms of Onychomycosis are present in the same patient, and

	Fungal Location	Toe/Nail Features
Distal Lateral Subungual Onychomycosis (DLSO)	Distal or lateral area of the nail is infected	Hyperkeratosis Discoloration of the nail Onycholysis Streaking
Superficial Onychomycosis (SO)	Nail surface is infected but the surrounding area is not	Striae on the nail
Endonyx Onychomycosis (EO)	Fungus permeates the fungal hyphae of the nail	Nail split lengthwise Discolored nail
Proximal Subungual Onychomycosis (PSO)	Originates in the proximal nail and spreads upward	White area appears under the lunula area of the nail Periungual inflammation Bacterial paronychia Nail pustular psoriasis
Mixed Pattern Onychomycosis (MPO)	Different forms of onychomycosis occur in the same person, possibly in the same nail	Features associated with whichever form of onychomycosis is present
Total Dystrophic Onychomycosis (TDO)	Occurring following other forms of onychomycosis, it is caused by different organisms entering the nail plate	Crumbled nail Thick and ridged nailbed

possibly even in the same nail. The final form of fungal nail infection is Total Dystrophic Onychomycosis (TDO), which follows other forms of Onychomycosis and is characterized by a crumbled nail with a thickened nail bed (Figure 5) (Kreijkamp-Kaspers, Hawke, 2017)

**Methods**

PubMed, ProQuest, Ebsco Multisearch, and Google Scholar were used to extract information. Terms such as “Onychomycosis” and “Effective Treatment for Onychomycosis” etc. were used.

	<p><b>Figure 1</b> Distal Lateral Subungual Onychomycosis (DLSO). It is characterized by a yellow-white detached nail plate and hardening of the skin, also known as hyperkeratosis. It is often associated with discoloration of the nail and white streaks on the nailbed (Kreijkamp-Kaspers, Hawke, 2017).</p>
	<p><b>Figure 2</b> Superficial Onychomycosis occurs when fungus enters the nail plate and forms white opaque colonies in the form of raised grooves that can be easily rubbed off (Kreijkamp-Kaspers, Hawke, 2017)..</p>
	<p><b>Figure 3</b> Endonyx Onychomycosis- the nail appears to be split in half lengthwise with possible discoloration (Kreijkamp-Kaspers, Hawke, 2017)</p>
	<p><b>Figure 4</b> Proximal Subungual Onychomycosis causes a white area to appear under the lunula area of the nail along with periungual inflammation. It also causes bacterial paronychia and nail pustular psoriasis (Piraccini, Alessandrini, 2015).</p>
	<p><b>Figure 5</b> Total Dystrophic Onychomycosis is characterized by a crumbled nail with a thickened nail bed (Kreijkamp-Kaspers, Hawke, 2017).</p>

### Oral Treatment

One method currently used in treating fungal nails is an oral medication. The three most common ones prescribed are griseofulvin, terbinafine, and azoles. The drawback of this treatment method is that oral medications generally require long treatment periods and can cause various side effects. Because oral drugs can cause liver damage, patients must first undergo a liver function test to begin this form of treatment. Medication can be classified as fungistatic (inhibiting the growth of fungal cells), or fungicidal (directly causing cell death) (Kreijkamp-Kaspers, Hawke, 2017).

Griseofulvin, a fungistatic drug, was the first oral medication created to treat Onychomycosis. It disrupts the cell microtubules and is effective in fighting dermatophytes but ineffective at fighting yeast. The response rate of this drug is poor. Common side effects associated with Griseofulvin are allergic reactions, stomach disturbance, and nausea (Kreijkamp-Kaspers, Hawke, 2017).

The Azoles are a fungistatic class of medications. Common ones include Itraconazole and Ketoconazole, and they are given over the course of a few months. The growth of the fungus is halted by suppressing the synthesis of ergosterol in the cell membrane via the CYP51A1 enzyme. Side effects of the Azoles include nausea, bloating, diarrhea, and liver damage (Shirwaikar et. al. 2008).

Terbinafine, an allylamine drug, is the most recent oral medication created to treat Onychomycosis. As a fungicidal treatment, it acts as a non-competitive inhibitor for Squalene Epoxidase, the enzyme responsible for the conversion of Squalene to Ergosterol in the fungal membrane. This causes toxic levels of Squalene that make holes in the membrane, eventually killing the fungus (Kreijkamp-Kaspers, Hawke, 2017). Terbinafine requires an 8–12-week daily dose and can cause headaches and diarrhea (Shirwaikar et. al. 2008). Terbinafine has been demonstrated multiple times to be the most effective oral medication with the least severe side effects (Kreijkamp-Kaspers, Hawke, 2017).

To determine the effects of oral treatment, a randomized double-blind study was done contrasting two oral medications, terbinafine and itraconazole. The Terbinafine group, consisting of 186 patients, received a daily dose of 250 mg/day for 12 weeks, while the itraconazole group, also consisting of 186 patients, received 200 mg/day for 12 weeks. Clinical and mycological cures were assessed at weeks 4, 8, 12, 24, 36, and 48. At 48 weeks, negative mycology was achieved by 73% of patients in the Terbinafine group and 45.8% in the Itraconazole group. Clinical cures were attained by 76.2% in the Terbinafine group and 58.1% in the Itraconazole group (De Backer Et al, 1998).

Based on this study, the oral treatment seems to be an effective cure for Onychomycosis as the rates of mycological cure and clinical cure are high. Of the three most common ones, Terbinafine is the most recommended due to its efficacy and lack of side effects, but the Azoles and Griseofulvin have a high cure rate as well. Oral medication may be safest with younger children, as the older population is often on other medications and drug-drug interactions may occur (Leung et. el., 2020). Additionally, because adverse effects of medication are common amongst the immunosuppressed population, who are prone to onychomycosis, oral treatments should be avoided to ensure an effective and safe treatment.

### Topical Treatment

Another method used to treat fungal nail is topical therapy. Because toenails are generally non permeable, creams are not always effective because they are unable to get through the nail. Examples of commonly used creams include Efinaconazole and Tavaborole. A new topical method using nail lacquer has been recently introduced. The nail lacquers contain chemicals that aid the penetration of the nail and allow for more effective healing. The two main types of nail lacquers currently approved are ciclopirox and amorolfine. Ciclopirox lacquers disrupt the breakdown of toxic peroxides and the production of

	Classification	Method of Fungal	Side Effects
Griseofulvin	Fungistatic	Disrupts cell microtubules	Allergic reactions, stomach disturbance, and nausea
Azoles	Fungistatic	The synthesis of ergosterol is suppressed by CYP51A1 inhibition	Nausea, bloating, diarrhea, and liver damage
Terbinafine	Fungicidal	The synthesis of ergosterol is suppressed by squalene epoxidase inhibition	Headaches and Diarrhea

intracellular energy. It may also prevent nutrient uptake of the fungus which leads to fungal nutrient uptake resulting in exhaustion of amino acids and a reduction in protein synthesis. Side effects include rashes, nail irritation, discoloration, and ingrown toenail. On the other hand, an Amorolfine lacquer leads to cell death by inhibiting sterol biosynthesis. It is known to fight various forms of yeast, molds, and dermatophytes. After the amorolfine is applied to the nail, it rests on the nail for seven days and slowly penetrates the nail to reach the nail bed and heal the fungal infection. This treatment requires constant application until the fungus is completely removed, which averages nine to 12 months for toenails. Side effects, though rare, include itching, burning, inflammation, and irritation (Shirwaikar et. al. 2008).

To assess the efficacy of topical treatments, a research study measured the success rate of efinaconazole, a topical antifungal treatment. There were 62 patients, ages six through 16 years, in the study. The cream was administered once a day for 48 weeks, and patients were re-evaluated at 4 weeks post-treatment. At 12 weeks following the onset of treatment, 36.7 % of patients received a complete mycologic cure, and 65.0% reached a complete cure by the post-treatment follow-up (Eichenfield et. al. 2020).

To determine the efficacy of topical treatment, a 36-week sequential treatment of chemical nail avulsion, RV104A ointment, Ciclopirox cream, and Ciclopirox nail lacquer was compared with a 36-week treatment of Amorolfine. At 48 weeks, the mycological cure rate was 36.6% for the combination treatment and 12.7% for the amorolfine treatment. Clinical cure at week 48 was achieved by 53.5% of the patients in the sequential treatment group and 17% in the nail lacquer group (Paul et. al., 2013).

Topical treatments such as creams and nail lacquers do not appear to be effective treatments for onychomycosis. Low cure and clinical rates are associated with these interventions, and it relies heavily on the patient to comply with directions and remember instructions.

### **Nail Avulsion Treatment**

Nail avulsion, another treatment for Onychomycosis, involves removing part of the nail to access the infection site and treating the root, along with the nearby tissues with topical therapy. Chemical avulsion and surgical avulsion are two versions of this treatment. While surgical avulsion is more painful and is prone to risks such as hematomas and nail distortions, chemical avulsion is a highly tedious process. These treatments have high relapse rates and poor patient compliance, so they are generally not

performed unless other treatments have failed (Nayak, 2021).

Forty patients were treated for onychomycosis using a combined treatment of nail avulsion and topical therapy. Following the removal of the fungal nail, or part of it, the creams were to be applied daily. There were many dropouts or cases of non-compliance in the study, but 15 (56%) of the 27 remaining patients received a complete cure. On a follow-up visit, recurrence was noted on two patients. No side effects were noted in the study (Grover et. al, 2007).

This study confirms prior research which suggests that nail avulsion is not an effective treatment for onychomycosis. A low cure rate is associated with this method of treatment, and painful side effects are common.

### **Device-Based Treatments**

Device-based therapies are non-invasive treatments for Onychomycosis that have high success rates. One such treatment is lontophoresis, which applies a current and a charged drug to the infected nail bed. The flux rate of the drug administered is controlled by the device, and this treatment is sought after because of its high rate of nail permeability. Another example of a device-based therapy is ultrasound, which uses soundwaves to deliver drugs to the infection. This also has a successful rate of permeability. Photodynamic therapy is a recent device-based therapy that has been introduced. It involves the excitation of photosensitizing agents which create singlet oxygen that is responsible for the death of fungal cells. Aminolevulinic acid and methyl ester are two photosensitizing agents used for this process (Nayak, 2021).

Laser therapy, another device-based treatment, was developed using the principle of photothermolysis by targeting tissue in a designated area. A device sends a pulse of radiation to the infected area and kills the fungi. There are a few drawbacks of laser therapy, for example possible damage to the tissue if used at an extreme level. Laser therapy can also decrease collagen production, which provides structure in the tissue (Kushwaha et. al. 2015). Finally, the devices used for laser therapy are very expensive and are not covered by many insurances (Liddell, Rosen, 2015). There are several types of FDA-approved laser treatments utilized by podiatrists today.

The efficacy of laser treatment is dependent on several factors. Firstly, the wavelength of the light must be capable of penetrating many layers, such as the nail plate and underlying tissues. Therefore, the near-infrared spectrum is used in laser treatments as this light is found to be the most piercing. The pulse duration is another factor that affects the treatment. The span of the pulse must

be less than the thermal relaxation time of the target (the infection), which requires the laser systems to use relatively short pulse systems. The success of the laser is also dependent on the repetition rate of the system, which refers to the rate of the delivery of the pulses. A higher repetition rate allows for an increased pulse rate, which can speed up the treatment process. The diameter of the laser beam, known as the spot size, varies in length from 1mm to 10mm, and the size of the beam has different effects on the treatment. A smaller size beam will likely cause the laser to reach a greater surface area while the larger beams may speed up the treatment time. The fluence, which refers to the amount of energy pulsed into the target area, is the final factor affecting the laser treatment and it is generally an average calculated by the spot size and maximum pulse energy allowed (Gupta, Simpson, 2012).

There are several types of FDA-approved laser treatments utilized by podiatrists today. A long pulse laser system delivers long pulses to the infected area. The Fotona Dualis system is a long pulse laser system. In a clinical trial of this laser, 162 participants with confirmed onychomycosis were treated once a week for four consecutive weeks. At the follow up visits, which ranged from 12-18 months post-treatment, 100% of participants achieved mycological cures, and 93.5% reached clinical cures (Gupta, Simpson, 2012).

A short-pulse laser system is another form of laser treatment that delivers laser by the microsecond. The Pin-Pointe FootLaser, GenesisPlus, VARIA, and JOULE ClearSense are all examples that are on the market. There have been many studies done on these systems, which all yielded above 70% improvement of fungal nail (Gupta, Simpson, 2012).

A study on short-pulse laser divided 21 subjects with Onychomycosis into three groups: 1319 nm laser light, 1064 nm laser light, and broadband light. Four treatments spaced one week apart were given, and cultures were taken at one, three, and six-months following treatment. Patients reported mild to moderate discomfort and no unpleasant effects occurred. Determined by the six-month culture, 20 of the 21 patients reached mycological cure (Waibel et. al. 2013). This study may be confounded due to bias because an author of the study expressed, via a disclosure, a benefit in the production and usage of the specific laser used in the study (Lidell, Rosen, 2015).

Long-pulse and short-pulse lasers were compared in a trial consisting of 10 toenails with Onychomycosis. Cultures were taken prior to treatment and at the nine-month follow-up, and two independent evaluators rated the fungus using the Onychomycosis Severity Index (OSI).

Patients were also ordered to apply Ciclopirox daily to the infected area. Results showed no significant difference between the different laser systems and the lowest OSI level was seen at six months (Hees et. al. 2014). This study suggests a recurrence of the fungus at nine months.

The final form of laser systems used by current medical professionals is the Diode-laser system. This method can be done in a range of wavelengths and uses a semiconductor to deliver laser beams. The Noveon Laser uses a diode system and provides options of 870 and 930 nm (Gupta, Simpson, 2012). A clinical trial was performed on this system and measured the improvement of fungal nail in 26 infected toes. Treatment was administered on days 1, 14, 42, and 120, and follow up occurred on day 180. Results indicated that 85% of participants showed a decreased infection area, 65% displayed 3mm of clear nail growth, and 4 mm of clear nail growth was seen on 26% of the toes. This study provides objective proof of the improvement of the toenails, but the sample size is relatively small (Landsman et. al. 2010).

Jefferson et al., conducted a study that found diode laser therapy to be effective with little or no side effects. This study took samples of toenails from 3 independent clinical trials that used a dual-diode laser system. Results indicated that 67% of the toenails experienced more than 3mm of clear nail growth following the laser treatment, and 89% had increased clear nail growth at the six month follow up. No side effects were noted in any of the patients (Zang et. al. 2017).

Laser therapy demonstrates high cure rates for Onychomycosis. While all forms yield successful results, the long pulse laser seems to be the most effective in treating fungal nail. Although recurrence is a small possibility, laser treatment may be suggestable for patients with pre-existing conditions who cannot undergo other forms of Onychomycosis treatment due to its limited side effects.

### Discussion

Onychomycosis is a prevalent nail disorder affecting many people daily. While various forms of treatment are used, their treatment lengths, cure rates, and side effects must be taken into account. Topical remedies such as ointments and lacquers do not achieve clinically significant cure rates. Nail avulsion is a painful process and does not have a high efficacy. Oral treatments have the highest cure rate, but the common side effects prevent many people from using this treatment. For those without pre-existing conditions whose safety will not be compromised by its use, oral medication is the optimal course of treatment. Laser therapy, because of its high cure rate and lack of

side effects, is recommended as the gold standard of treatment for Onychomycosis for those who cannot tolerate the adverse effects of oral medications.

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