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Department of Skin and Venereal Diseases

Review of Device Based Treatment of Onychomycosis

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Summary of Thesis:

Review of Device Based Treatment of Onychomycosis

Aim: To review the device-based treatment methods used in the treatment of dermatophyte onychomycosis

Objectives:

1. To identify and describe device-based methods for the treatment of dermatophyte onychomycosis.
2. To analyse the effectiveness of laser monotherapy and combination treatment modalities for dermatophyte onychomycosis.
3. To provide an overview of photodynamic treatment methods (regimens, efficacy, outcomes) given to patients with dermatophyte onychomycosis.

Methods: The Medline (PubMed) electronic database was searched for studies published in the last ten years for device based treatment modality used in the treatment of onychomycosis and also studies implementing devices with other treatment modalities or comparing between them. The PRISMA guidelines were followed to carry out this review.

Results: a total of 20 clinical trials from 231 were identified and used to write this review after implementing inclusion and exclusion criteria. Analyzed interventions included different type of lasers, PDT and combination therapies. The results showed promising effect of these modalities although some contradictions were noticed. Nd:YAG and CO2 lasers are good treatment modality especially in patient who are unable to use systemic treatment. Combination therapy showed better results than individual treatment alone (oral or topical). PDT is good option in case of mild infection. Still more studies with larger population and longer follow up period should be conducted for us to be able to get better understanding of the efficacy of device based treatments
Conclusions:

- Nd:YAG and CO2 Lasers might be a good treatment option to treat onychomycosis especially in patients with contraindication for systemic antifungal treatment.
- Long pulsed lasers showed better results than short pulsed lasers.
- Combination therapy of long or short pulsed lasers with oral or topical treatment is superior to monotherapy alone.
- CO2 lasers can be used in treating onychomycosis but measures should be taken to decrease reinfection or coinfection rates as studies implemented this kind of lasers showed recurrence after some period of time.
- PDT can be useful in treating mild infection.
- Still more studies with larger population and longer follow up period should be conducted for us to be able to get better understanding of the efficacy of device based treatments (lasers and PDT).
**Abbreviations:**

ALA- aminolevulinic acid
CCR-clinical clearance rate
CER-clinical efficacy rate
DSO-Distal subungual onychomycosis
KOH-potassium hydroxide
MAL- methyl-aminolevulinic acid
MAL-PDT-Methyl aminolevulinate photodynamic therapy
MCR-mycological clearance rate
OSI-onychomycosis severity index
Nd: YAG -neodymium doped yttrium aluminum garnet
PAS-periodic acid–Schiff
PCR-Polymerase chain reaction
PDT – photodynamic therapy
pPDT- placebo PDT
PpIX- protoporphyrin IX
PSO-Proximal subungual onychomycosis
RCS-randomize control study
ROS-reactive oxygen species
WSO-White superficial onychomycosis
Terms:

OSI- classification method used to evaluate severity of infection by multiplying the score of the area involved (0-5) by the proximity of the infection to the matrix (0-5) and another 10 points are added if a patch of more than 2mm is present. Score is ranging between 0-35:

- Mild – 0-5
- Moderate-6-15
- Severe-16-35
Acknowledgement

I would like to thank my supervisor for her guidance and advice on this review. Her knowledge and experience within the field of dermatology helped me a great deal in completing this systematic review.

Conflict of interest

The author declares no conflicts of interest.
**Introduction:**

Onychomycosis is a common nail infection caused by dermatophyte, non-dermatophyte and yeasts. It is characterized by separation of the nail bed from the nail plate, inflammation and destruction of the normal nail anatomy[29] About half of the cases are caused by dermatophyte infections which include Trichophyton, Microsporum, and Epidermophton, with Trichophyton being the most common. [30]

According to new epidemiological studies that have been conducted in recent years Trichophyton nail infection prevalence throughout the world is estimated to be 5.5% .The high incidence of onychomycosis and it’s increasing rates can be attributed to increasing number of immunocompromised patients, increasing glucocorticoids usage, immunosuppressive agents, increasing numbers of systemic diseases such as diabetes, HIV, obesity etc. [31]  

**Onychomycosis can be classified into:**

Distal subungual onychomycosis (DSO) is the most common form, it involve invasion of the nail bed and underside of the nail plate beginning at the hyponychium and the spread of the infection proximally through the nail matrix. The most common microorganism to cause DSO is *Trichophyton rubrum*.

Proximal subungual onychomycosis (PSO) is the most infrequent type it occurs mostly in immunocompromised individuals. The infection invades proximally through the nailbed in the cuticle area and spreads distally. The infection can also be secondarily to trauma.

White superficial onychomycosis (WSO) is less common than DSO. It involves a direct inoculation of the fungi into the superficial nail plate. It can be easily recognized by its appearance on white spots which can coalesce and spreads as the infection progresses.

Total dystrophic onychomycosis refers to end stage nail disease. It is characterized by totally thick nail. [29]

Current treatment options include oral antifungal agents, which can be used alone or in combination with topical antifungal. Topical agents is usually not efficient if used as monotherapy ,therefore surgical or chemical debridement should be implemented as well to allow better penetration of the antifungal agent and better therapeutic results.[32]
Due to undesired side effects with oral antifungals such as headache, gastrointestinal upset and elevation of liver enzymes together with non-compliance with such medications, alternative treatment methods started to evolve. Laser therapy and photodynamic therapy became more popular due to their effectiveness and lack of systemic side effects. [2]

The most common used and FDA approved lasers are long pulsed neodymium doped yttrium aluminum garnet (Nd: YAG) 1064-nm laser, carbon-dioxide (CO2) laser, and near infrared diode laser.[33]

Photodynamic therapy (PDT) is another available alternative for the treatment of onychomycosis. PDT involves the use of a photosensitizer which then excited with light to generate reactive oxygen species (ROS). [2]

This thesis aims to evaluate and provide an updated review on the device based treatment of onychomycosis alone or in combination with oral or topical preparations, it efficacy and outcomes.
Aim and Objectives:

**Aim:** To review the device-based treatment methods used in the treatment of dermatophyte onychomycosis.

**Objectives:**

1) To identify and describe device-based methods for the treatment of dermatophyte onychomycosis.

2) To analyze the effectiveness of laser monotherapy and combination treatment modalities for dermatophyte onychomycosis.

3) To provide an overview of photodynamic treatment methods (regimens, efficacy outcomes) given to patients with dermatophyte onychomycosis

Materials and Methods:

This study was compiled using the “Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines”. Any original study, published in a reviewed journal, which examined the use of a laser technology or photodynamic therapy or a comparison between those methods to the standard of care in the treatment of onychomycosis was considered for inclusion. The primary outcome measure was efficacy, only including studies which employed microbiological or microscopical procedures to establish an initial diagnosis of the condition, and subsequently measured the outcome either by a repeated microbiological/microscopical assessment or measured changes in physical nail clearance following treatment.

A primary literature search was conducted using PubMed and search key words (onychomycosis) AND (laser OR photodynamic OR treatment OR UV light OR combination) in May 2018 and then repeated in December 2018. In addition, articles were searched by hand using reference lists of other relevant articles on device based treatment in onychomycosis. Initially, 231 articles were identified. Inclusion criteria are as follows: 1) Trichophyton onychomycosis clinical trials, published in the last
10 years (2008-2018), 2) studies employing laser or photodynamic therapy in the treatment of onychomycosis 3) the age of the subjects ranging from 18 to 65, 4) no other concomitant diseases except onychomycosis (diabetes, psoriasis etc.). Articles not written in English were excluded from this systematic review. After duplicate removal and abstract screen, 30 articles were found. These articles were subjected to full-text screen and 20 studies, are included in this systemic review.

Figure 1. Flow diagram of searching method

231 Records identified through database searching

228 Records after duplicates removed

228 Records screened

30 Full text articles assessed for eligibility

20 Studies included in systematic review

7 additional records identified by manual search of reference list of other publications.

198 records excluded based on exclusion criteria (language, animal study, older than 10 years)

10 not meeting inclusion criteria fully

7 additional records identified by manual search of reference list of other publications.
Literature review:

Description of device-based methods for the treatment of onychomycosis

1. Lasers

The primary mechanism in which lasers produce their effect is photothermic. Photothermic energy refers to light energy that converts into heat inside the affected tissue. The level of heat produced in this manner should be controlled to benefit the clearness of the infection without damaging the surrounding tissues. In order to achieve accumulation of heat inside the fungi without causing necrosis to the nail bed, the laser should be calibrated properly while taking in consideration different laser parameters. These parameters include wavelength, peak power, average power, spatial and temporal pulse format, pulse energy and spot size of the laser beam[1].

Different types of lasers exist in the field of dermatology aiming to treat onychomycosis

1.1 Nd:YAG lasers

The most commonly used type is Nd: YAG lasers. Its therapeutic effect is good. It can be used in elderly, immunosuppressed patients and even in patient with kidney and liver dysfunction as it lacks the systemic effect compered to oral therapy. Chromophores of fungal tissue absorb heat produced by the laser and shift it to the fungal tissue which eventually causes damage of the fungus. The temperature is set to be 40-50 °C which kills the fungal cell completely. [2]

Table 1 Nd:YAG lasers currently FDA approved for temporary increase in clear nail growth in patients with onychomycosis[3]

<table>
<thead>
<tr>
<th>Nd:YAG lasers</th>
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<tr>
<td>1,320-nm Nd:YAG</td>
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<tr>
<td>1,064-nm Nd:YAG long-pulsed</td>
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<tr>
<td>1,064-nm Nd:YAG Q-switched</td>
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<td>532-nm output mode Nd:YAG</td>
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</table>
1.2 CO2 lasers

Another type of laser used in the management of onychomycosis is fractional carbon-dioxide (CO₂) laser. This was the first laser applied in the field of dermatology. Its mechanism of action is based on a photothermal effect. The laser produces heat which converts the water inside the fungal tissue to steam, which causes swelling and increased pressure inside the fungal body. This pressure cause small pores to occur which also improve penetration of topical antifungal preparations into the nail bed. Bhatta et al. [2] reported 80% cure rate with fractional CO₂ laser combined with topical antifungal cream for 3 months with three sessions of laser treatment at 4-week intervals.

According to Arisa E.Ortiz et al. [4] many studies has been conducted throughout the years to investigate the optimal treatment setting as well as to understand which the most effective treatment regimen is. Further investigations still need to be done since the results are promising but not conclusive.

2. Photodynamic therapy (PDT)

Furthermore, in recent years photodynamic therapy (PDT) has emerged in the treatment of different skin diseases including onychomycosis. PDT combines light source and photosensitizer drug to penetrate deep into the nailbed in order to reach its therapeutic effect. [2]

PDT uses visible light to excite photosensitizing agents such as aminolevulinic acid (ALA) or methyl-aminolevulinic acid (MAL) to produce ROS which in turn causes selective tissue destruction. ALA and MAL are hydrophilic porphyrin precursors that saturate the heme pathway and produce protoporphyrin IX (PpIX). PpIX when combined with red light inhibit successfully Trichophyton species.[5]

3. UV-curable gels

The gels are composed of the diurethane dimethacrylate, ethyl methacrylate, 2-hydroxy-2-methylpropiophenone, combined with antifungal drug: amorolfine HCl or terbinafine HCl and an
organic liquid such as ethanol or NMP to serve as drug solvent. After application of the gel it is exposed to UVA lamp for 2 minutes, this leads to polymerization of the gel and formation of a thin film on its surface.

This glossy amorphous film on the surface of the nail is resistant to water and enables better drug release and ungual permeation. These gels have long residence on the nail which leads to increased compliance and the success of topical treatment.[6]

4. Combination therapies

The limited safety profile of oral antifungals, poor nail penetration of topical antifungal drugs, signals the need for new treatment options and therapeutic inventions. Combination therapies refers to the addition of one therapy to another in order to increase and improve treatment outcome by synergy, decreased fungal resistance and by applying two different mechanisms of action. Most combination therapies are based on improving drug delivery to the infected nail by applying adjunct chemical, mechanical or physical treatments (nail clipping, microporation, debridement, nail avulsion). Combined therapy are generally well tolerated with only transient discomfort, serves as a good alternative treatment for patients with contraindications to systemic antifungal agents.[7]

According to Kui Young Park et al. [8] at one randomized clinical trial which evaluated the clinical efficacy and safety of weekly applications of amorolfin 5% lacquer, either as a monotherapy (n = 64) or in combination with four 1064-nm Nd:YAG laser treatments (n = 64) over 16 weeks. At 16 weeks, the combined therapy group showed a significantly higher cumulative cure rate than the control group (71.9% vs. 20.3%, p < 0.0001).
**Effectiveness of laser monotherapy and combination treatment for onychomycosis**

**Long and Short-Pulsed Nd:YAG Lasers**

In recent years the application of laser therapy in the treatment of fungal infection has been increased. Laser treatment benefits seem to be related to its minimally invasive nature and lower number of sessions needed. Long pulsed Nd:YAG laser can penetrate deep into the tissue due to its long wavelength enabling effective inhibition of fungal growth. [9]

In 2011 a study conducted by L. Hochman et al. [10] aiming to evaluate efficacy of novel 0.65-millisecond pulsed Nd:YAG 1064-nm laser in treating onychomycosis, used 3 sessions of laser beams to 8 patients with PAS stain positive or culture positive onychomycosis. Each session was conducted with at least 3 weeks intervals. After 6 month mycological clearance was found in 7 out of 8 patients.

According to Kalokasidis et al. [11] in a prospective study with long Q-Switched Nd:YAG 1064 laser, 131 patients (94 females, 37 males) with confirmed onychomycosis by culture were treated with two sessions of laser therapy with one month interval. After 3 month follow up 95% of patients were mycologically cured. No statistically significant difference was observed between female and males.

S.H Moon et al. [12] aiming to demonstrate the efficacy of longed pulsed 1064-nm Nd:YAG laser, treated 13 patient with a total of 43 mycotic nails with five treatment sessions at 4 weeks interval. Of 43 infected nails, 4 achieved a complete cure (9.3%), 8 had excellent treatment outcomes with 80% clearence of the involves nail (18.6%) and 31 had good treatment outcomes with 50%-80% clearance (72%). Another study was conducted by G.Okan et al. [9] 30 patients were treated with long pulsed laser in a spiral pattern once a week for 4 weeks. At 6 month follow up mycological cure was achieved in 60% of patient of whom 89% were infected with Trichophyton. Complete clinical improvement was achieved in 47%, all of whom were infected with Trichophyton spp.

Short pulse lasers were on controversial discussion since it was approved by the FDA in 2010.[13] In a randomized controlled pilot study conducted by S.Karsai et al. [13] aiming to analyze the effect of short pulsed Nd:YAG lasers, 20 patients with a total of 82 with confirmed mycotic nails by lab tests were divided into 2 groups. The first group received four laser treatments every 4-6 weeks. The second group did not receive laser treatment. At 12 month follow up no mycological clearance was observed.
in any of the groups. No statistically significant difference was observed while comparing the OSI in both groups.

H.Hees et al. [14] compared short and long pulsed Nd:YAG lasers in a side comparison manner. 10 patients with both big toe nails infected were subjected to two treatment sessions: the left big toe was treated with long pulsed laser while the right big toe with short pulsed laser. OSI-Scores decreased for 3.8 ($p = 0.006$), 4.8 ($p = 0.0002$) and 2.9 points ($p = 0.04$) within 3, 6 and 9 months respectively. No statistically significant difference was observed between both treatment modalities.

**Long pulsed Nd:YAG laser combined with oral Terbinafine**

Terbinafine is the preferred oral antifungal in the treatment of onychomycosis based on recent meta-analysis due to its superior effect compared to other antifungals [7]. Its common side effects include headaches, gastrointestinal upset and rash[7]. To reduce systemic toxicity combination therapies can be used. Y.Xu at el. [19] compared the efficacy and safety of combined laser therapy with oral Terbinafine to oral therapy alone. 56 patients were divided into 3 groups: L (long pulsed laser), T (250 mg oral terbinafine) and L+T (both). Evaluation of MCR and CCR was done at 4, 8, 12, 16 and 24 weeks. MCR was 100% in the T + L group and was significantly lower in the T group and the L group. CCR in T+L group was significantly higher than in the other 2 groups.

**Long Pulsed laser combined with oral itraconazole**

A self-controlled study by Y. Li at el. [20] divided patients into 2 groups: 21 in group A and 21 in group B. Group A included patients with mild-moderate fungal disease whereas group B with severe. Severity was determined by SCIO (scoring clinical index of onychomycosis). Each group was further divided into laser combined with itraconazole and to itraconazole alone. Laser therapy was given 7 times at 1 week interval. Itraconazole was administered orally 200 mg twice daily following 3 week rest. At the end of treatment the groups that received combination treatment showed better results than those who received oral treatment alone. These results were even more significant in group B in patients with more severe nail involvement. Authors concluded that for mild disease is better to use pure medication or combination therapy whereas in severe disease to use combination therapy.
**Short pulsed laser with Amolorfine nail lacquer**

In a randomized clinical trial by K. Park et al. [21] 128 patients with culture confirmed nail fungus were divided into two groups: one group received combination therapy with short pulsed laser and topical preparation while the other received topical treatment only. Four sessions of laser at 4 weeks interval was given to the test group, 5% amolorfine lacquer was given to all patients once a week for 16 weeks. The cumulative cure rate was significantly higher in the test group than in the control group with amorolfine only (71.88% vs. 20.31%, p<0.0001). At week 16, 81.25% of test patients gave "satisfied" or "very satisfied" responses while 23.44% of control patients gave those responses.

**Long pulsed Laser plus different topical antifungal**

In a randomized control study by T.Kim et al. [22] aiming to compare the outcome of combination treatment with antifungal alone, 56 patients were divided to three groups. T-topical naftifine HCL spray applied once daily for 24 weeks; L –laser only (2 laser sessions at 4 weeks interval); T+L both regimens combined. The response rates of the two laser-treated groups did not differ significantly (P > 0.05), but were significantly higher than those of the T group (P< 0.05). The cure rates were significantly higher in both laser-treated groups than in the T group at 24 weeks. In a retrospective by G.Weber et al. 27 patients received laser treatment alone while 29 patients received laser treatment plus topical antifungal (ciclopirox, or amorolfine ). Clinical improvement was observed in 56% in laser group and in 69% in combined group; complete healing with negative cultures was achieved in 11% of laser group vs.21% in laser +topical.[23]

**Long pulsed laser and topical terbinafine**

In order to compare effectiveness of each treatment R. El-Tatawy et al. [24] divided 40 females into two treatment groups; group A received 4 sessions of long pulsed laser at one week interval , group B applied topical terbinafine once daily for 6 month. The therapeutic endpoint consisted of clinical improvement which was evaluated at month 3 and 6 and mycological improvement. At 6 month follow up group A had 80% mycological clearance while in group B all patients still had positive cultures. In addition all patients in group A showed marked clinical improvement comparing to group B that had only mild to moderate improvement.
Fractional carbon dioxide (CO2) laser

Co2 lasers thought to enhance the penetration of topical antifungals into the nail and to directly kill the bacteria through its heating affect. [15][16]

Few clinical trials tried to show the efficacy of CO2 lasers and topical antifungals in treating nail onychomycosis:

CO2 laser combined with amorolfine cream

In 2014, E. Lim et al. [17] treated 24 patient with 3 sessions on ablative CO2 laser therapy follow by once daily application of topical amorolfine cream. At 3 month follow up 22 patients showed clinical response; 12 patients (50%) showed full response with negative microscopic findings. Only 2 patients showed no response at all.

CO2 laser combined with terbinafine cream

In a clinical trial by A.Bhatta et al. [16] 75 patients with mycotic nails received 3 sessions of laser therapy at 4 weeks interval followed by application of 1% terbinafine cream once daily for 3 month. At 3 month follow up 94.66% and 92% of the treated patients were potassium hydroxide and culture negative, respectively, after 3 months of treatment; only 84% and 80% were potassium hydroxide and culture negative, respectively, at 6 months of follow-up.

According to J.Shi et al.[18]30 patients received 12 sessions of laser therapy at 2 weeks interval in a period of 6 month combined with topical terbinafine application once daily for 6 month. At 1 and 3 month follow up after the last treatment mycological clearance rate(MCR) evaluated by microscopic examination was 77.42% (96 nails) and 74.19% (92 nails), respectively.

CO2 laser with luliconazole cream

In a randomized, parallel group trial by B.Zhou et al. [15] 60 patient were divided into 2 groups; L group only received laser treatment (12 sessions at 2 weeks interval in a period of 6 month) and L+D received the same laser therapy protocol combined with once daily application of 1% luliconazole cream. Outcome measurements were clinical efficacy rate (CER) and mycological clearance rate (MCR). L+D group showed higher MCR (57.4% vs. 38.9%) and CER (69.6% vs.50.9%) comparing to L group.
Photodynamic Treatment methods

PDT based on methylene blue light

In order to determine the effectiveness of PDT in the treatment of moderate vs. severe onychomycosis, 22 immunocompetent patients were divided into 2 groups based on the severity of the infected nails in a study by L. Wallis et al. [25]. First group - 11 patients with severe disease, second group - 11 patients with mild to moderate disease. The treatment regimen included 6 months of MBLED/PD (Methylene blue - light emission diode) with 15 days interval between each session. The clinical and microbiological outcome was assessed after each session. At the last visit the clinical response rate was 100% in the moderate group compared to severe group which was only 63.3%.

Methyl aminolevulinate photodynamic therapy (MAL-PDT) vs placebo PDT(pPDT)

In a randomized control study by Y. Gilaberte et al. [26], 40 patients were divided into 2 treatment groups. 22 patients received 3 weekly sessions of MAL-PDT while 18 patients were treated with 3 weekly sessions of pPDT. Before each treatment the affected nails were softened with 40% urea ointment to enhance the penetration of the photosensitizer. Efficacy was evaluated at weeks 12, 24, 36. OSI was evaluated as primary end point and microbiological clearance as secondary end point. This study did not show significant differences between urea 40% + MAL-PDT and urea 40% + pPDT in the treatment of onychomycosis; although some results showed that it can be used as alternative treatment especially in non-dystrophic nails.

Aminolevulinic acid (ALA) PDT

In a signal center open trial by E. Sotiriou et al. [27] 30 patient with Trichophyton nail infection was treated with 20% ALA which was applied to the nail under occlusive dressing for 3 hours. Woods lamp was used to check for ALA induced protoporphyrins IX before applying red light. Treatment regimen included 3 sessions with 2 weeks interval between each session. Mycological and clinical evaluation was performed by the same investigators at 12 and 18 months. After one year 13 patients were cured (43.3%), at month 18, 11 patients of the previously cured still had persistent clearance (36.6%).
Methylene blue PDT vs. Fluconazole

In a randomized control clinical trial by L. W. Figueiredo Souza et al.[28], 80 patients were divided into 2 treatment groups. Group A received placebo tablet and sessions of 2% methylene blue solution irradiated with light emission diode device (MBLED/PDT) while group B received 300 mg oral Fluconazole and placebo PDT. Clinical and microbiological cure was assessed at 1 and 12 month post treatment. Group A showed 90% clinical cure rate which was statistically significant (p<0.002). After 1 year the clinical cure rate reduced to 80%.
<table>
<thead>
<tr>
<th>Author</th>
<th>Study type</th>
<th>N of subjects</th>
<th>Intervention</th>
<th>Follow-up period</th>
<th>MCR</th>
<th>CCR</th>
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<td>Okan et al. [9]</td>
<td>Observational study</td>
<td>15</td>
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<td>6 month</td>
<td>60%</td>
<td>47%</td>
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<td>Kalokasidis et al. [11]</td>
<td>Prospective clinical study</td>
<td>131</td>
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<td>4-6 month</td>
<td>87.5%</td>
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<td>S.H Moon et al. [12]</td>
<td>Case series</td>
<td>13 (31)</td>
<td>1,064-nm long-pulsed Nd:YAG laser.</td>
<td>1 month after last treatment</td>
<td>9.4%</td>
<td>72% (50-80% improvement)</td>
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<td>Karsai et al. [13]</td>
<td>Prospective randomized controlled trial</td>
<td>20 (82)</td>
<td>short-pulsed 1064-nm Nd:YAG laser</td>
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<td>Pilot study</td>
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<td>short-pulsed Nd:YAG laser vs. long pulsed laser</td>
<td>9 month</td>
<td>20%</td>
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<td>Lim et al. [17]</td>
<td>Prospective clinical trial</td>
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<td>Study</td>
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<td>Bhatta et al. [16]</td>
<td>75 (365)</td>
<td>6 month</td>
<td>Fractional CO2 laser and 1% terbinafine liquor</td>
<td>92%</td>
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<td>Shi et al. [18]</td>
<td>30 (124)</td>
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<td>74.19%</td>
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<tr>
<td>Zhou et al. [15]</td>
<td>Randomized</td>
<td>6 month</td>
<td>L group- fractional carbon dioxide (CO2) laser and luliconazole 1% cream</td>
<td>57.4%</td>
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<tr>
<td></td>
<td>control study</td>
<td></td>
<td>L+D group- fractional carbon dioxide (CO2) laser</td>
<td>69.6%</td>
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<td>vs.</td>
<td>50.9%</td>
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<tr>
<td>Xu at el. [24]</td>
<td>53 (90)</td>
<td>24 weeks</td>
<td>T-oral terbinafine; L-long pulse YAG laser; T+L - both</td>
<td>100%</td>
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<td>Li et al. [20]</td>
<td>Self-</td>
<td>24 weeks</td>
<td>Group A(moderate) : divided to laser treatment alone or both laser and oral</td>
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<td>itraconazole</td>
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<tr>
<td></td>
<td>study</td>
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<td>Group B (severe) - further divided to both treatment</td>
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<td>Park et al.[21]</td>
<td>Randomized clinical trial</td>
<td>128</td>
<td>Group A-short pulsed YAG laser; Group B- 5% amorolfine nail lacquer once weekly</td>
<td>16</td>
<td>71.88% vs. 20.31%</td>
<td>81.25%</td>
</tr>
<tr>
<td>Kim et al.[22]</td>
<td>Randomized clinical trial</td>
<td>56</td>
<td>T-topical naftifine HCL spray; L - laser; T+L both topical naftifine and laser</td>
<td>24</td>
<td>15.2% vs. 22.5%</td>
<td>76% vs. 71.8% L+T</td>
</tr>
<tr>
<td>Weber et al.[23]</td>
<td>Retrospective study</td>
<td>56</td>
<td>27 patients – long pulsed laser; 29 patients – long pulsed laser + topical ciclopirox, or amorolfine</td>
<td>24</td>
<td>11% of laser group vs. 21% in combined group</td>
<td>56% in laser group and 69% in combined group</td>
</tr>
<tr>
<td>El-Tatawy et al.[24]</td>
<td>Randomized clinical trial</td>
<td>40</td>
<td>Group A- 4 sessions Nd-YAG laser; Group B- twice daily topical terbinafine for 6 months</td>
<td>6</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td>Wallis et al.[25]</td>
<td>open-label controlled clinical trial</td>
<td>22</td>
<td>Group A-severe onychomycosis; Group B-mild-onychomycosis</td>
<td>6</td>
<td>100% in the moderate</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>N</td>
<td>Treatments</td>
<td>Follow-up</td>
<td>Results</td>
<td></td>
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<tr>
<td>Gilaberte et al. [26]</td>
<td>Randomize</td>
<td>40</td>
<td>Group A - 3 weekly sessions of MAL-PDT + urea</td>
<td>36 weeks</td>
<td>53.85% vs. 41.56%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>control study</td>
<td></td>
<td>Group B - 3 weekly sessions of pPDT + urea</td>
<td></td>
<td>7.14% vs. 18.75%</td>
<td></td>
</tr>
<tr>
<td>Sotirioul et al. [27]</td>
<td>Open trial</td>
<td>30</td>
<td>20% ALA and red light</td>
<td>12 and 18 month</td>
<td>43.3%</td>
<td></td>
</tr>
<tr>
<td>Figueiredo Souza et al. [28]</td>
<td>Randomize</td>
<td>80</td>
<td>Group A - placebo tablet and sessions of 2% methylene blue solution</td>
<td>12 month</td>
<td>90%</td>
<td></td>
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<tr>
<td></td>
<td>control study</td>
<td></td>
<td>irradiation; Group B - 300 mg oral Fluconazole and placebo PDT</td>
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</tbody>
</table>
Discussion:

This review of published papers has yielded 20 studies investigating the use of lasers and PDT and combination of these modalities with oral or topical preparation in the treatment of onychomycosis. Sample sizes in all studies were generally small ranging from 8 to 131 patients, with four studies having 20 or fewer patients. The follow up lasted from 1 month till 18 month, with the majority of cases were followed for 6 month. The main outcomes used in the laser studies were negative microscopy, negative cultures, improvement in OSI and overall clinical improvement.

Looking at the results of studies evaluating the different type of lasers there is no consensus if its use is really effective. This can be resulting from different strategy of patient’s selection or different tests that was used to diagnose the infection in the first place. Some studies relied on only one diagnostic test \[11\][17][19]while others used few diagnostic tests to confirm onychomycosis.\[9-10][12-16][18][20-28]Another problem that arises is related to the definition of “cure” or “treatment effectiveness”, some studies used clinical improvement\[20\] as the only measure to show effectiveness while other use few treatment end points to evaluate effectiveness. One study evaluated effectiveness using patient satisfaction scale which can be problematic \[21\] as each individual assess severity differently according to his point of view. The OSI was a commonly used scale which evaluates the amount of nails involved \[13\] \[14\] \[20\][26]. Some studies didn’t use visual score and mostly relied on negative cultures and microscopy. In addition, when reviewing different treatment regimens involving lasers there are many discrepancies between different studies. Each study use different laser wavelengths and different number of sessions. These discrepancies also can disturb the conclusion considering laser treatment. The average follow up period lasted 6 month which may be too short considering the slow nail growth rate which can change the treatment results. The human nail grows approximately 1 mm/month and it is slower in older individuals and in infected nail. Due to this maybe a longer follow up period should be considered in order to better evaluate efficacy of treatment; however, prolonging the follow up period increase the risk of reinfection and coinfection. These two should be evaluated in determining the follow up duration. Another topic to discuss is related to the thickness of the nail and the severity of the infection i.e. if the nail is dystrophic or not. Some studies implemented nail debridement using mechanical or chemical measures before treatment initiation in order to get better results and increase penetration into the nail bed. Non dystrophic nails had better results than dystrophic once. Only one study compare short pulsed laser to long pulsed laser in the treatment of dystrophic nails and the results were not statistically significant. \[14\]
While reviewing combination therapy the results were more conclusive and uniform. All studies show better outcomes in the combination group than in the control, [19-24] it may be due to the fact that two different measures were taken with different mechanisms of action; furthermore the addition of topical/oral therapy can also prevent co-infection or reinfection. It is difficult to determine which combination treatment is superior due to different measures that were taken during the clinical trial. Some studies used topical antifungal [21-24] while others used oral drugs. [19-20] The clinical diagnosis also differed: some studies used culture and microscopies while others used microscopy alone. The clinical outcome evaluation consisted of different endpoints, some used negative cultures and KOH testing, some implemented OSI measurements and others used patient’s satisfaction scale. One study compared long pulsed laser to topical terbinafine which presented mycological clearance in laser group while in control group still were positive cultures after 6 month. [24]

Not many clinical trials were conducted to evaluate the efficacy of photodynamic therapy. From the studies published only two were randomized clinical trials. [26][28] These studies showed that there was a positive therapeutic effect for the use of PDT in the treatment of onychomycosis. The positive aspect in treating onychomycosis with PDT is related to the absence of systemic side effects. The reported local side effects were mild local discomfort and burning sensation which mostly were well tolerated without the need of additional intervention. [25-28] Most of the trials used nail softener such as urea on the nail before treating with light in order to achieve better penetration of the photosensitizer. One study showed that the severity of the disease had a direct impact on the treatment efficacy, as the severity was milder the clinical outcome was superior. [25] Most of the studies have reported a good clinical and microbiological cure rate but the percentage were seen to decrease on follow-up. [27][28] The reason for it might be related to the decrease penetrance of the photosensitizer, reinfection or not optimal treatment protocol. As the studies show promising results there is still a need for more clinical trials to make a fine conclusion on PDT treatment efficacy.
Conclusions:

- Nd: YAG and CO2 Lasers might be a good treatment option to treat onychomycosis especially in patients with contraindication for systemic antifungal treatment.
- Long pulsed lasers showed better results than short pulsed lasers.
- Combination therapy of long or short pulsed lasers with oral or topical treatment is superior to monotherapy alone.
- CO2 lasers can be used in treating onychomycosis but measures should be taken to decrease reinfection or coinfection rates as studies implemented this kind of lasers showed recurrence after some period of time.
- PDT can be useful in treating mild infection.
- Still more studies with larger population and longer follow up period should be conducted for us to be able to get better understanding of the efficacy of device based treatments (lasers and PDT).


10. Becker C, Bershow A. Laser therapy. Dermatology Online J UC Davis Peer [Internet]. 2013;19:32–3. Available from: http://escholarship.org/uc/item/0js6z1kw Keywords:


33. Figueiredo Souza LW, Souza SVT, Botelho ACC. Randomized controlled trial comparing