The effectiveness of laser treatments for onychomycosis in adults in the community: a systematic review protocol

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Review question/objective
The objective of this review is to investigate if laser treatments can effectively treat onychomycosis of the nails in healthy adults living in the community. More specifically, the objectives are to identify:

wether the investigated experimental methods, modes and treatment regimens utilizing laser interventions, applied to adults (> 18 years) living in the community with at least one nail infected with onychomycosis, produce outcomes comparable to the current ‘gold standard treatment’ of oral terbinafine over a minimum 12-week treatment period.

Background
Onychomycosis (tinea unguium) is an extremely common and specific fungal infection caused by a keratinophilic dermatophyte Trichophyton rubrum that infects the nail plate, nail bed and matrix. Dermatophytes were present in 82% of onychomycosis isolates in an epidemiologic survey of superficial fungal infections and are the major causal agents of tinea pedis and onychomycosis. Traditionally, the term onychomycosis was used to describe nondermatophytic nail infection. Current research has shown that onychomycosis etiologically comprises of a suite of dermatophytic fungi, yeasts, saprophytic moulds and/or bacteria which colonize different ecological niches on a human. Onychomycosis prevalence has been estimated to be between 14-20% of the North American population and in the range of 3-22% in European countries. In 1999, Scher estimated a 2-18% incidence of onychomycosis in the global population. Due to the increasing numbers of immunocompromised individuals, extensive use of broad-spectrum antibiotics and chemotherapy, increasing numbers of older aged people and individuals engaged in
personal fitness programs utilizing public facilities, more recent research implicates onychomycosis caused by a fungus in about half of all nail infections worldwide. T. rubrum is the major pathogen in tinea unguium infection in most surveys with incidence rates reported between 68% to as high as 90% in Europe. The economic burden of treatment is high and the social impact on individuals is significant.

The incidence of dermatophytes and saprophytes isolated from infected individuals varies over geographic and demographic regions worldwide with onychomycosis skin infections reportedly affecting up to 30% of the adult population. The close relationship between tinea pedis and T. rubrum infection is well established and widely acknowledged. Hence it is necessary to confirm the diagnosis of the causal agent prior to starting a treatment regime.

Traditionally, testing involves fungal culture and direct microscopy techniques such as a KOH wet mount performed in an office-based situation or a laboratory. Samples are taken from the active areas of a lesion, mounted onto a glass slide with a 20% KOH solution and the solution is heated such that the epidermal cell keratin is dissolved and the fungal elements are left. Microscopic examination for septate or branching hyphae, budding cells and spores are evidence of fungal infection. Direct microscopy alone can result in false-negative results and the presence of nondermatophytes in culture specimens can further confound the identification of the causal organism. Cumulative evidence using direct microscopy techniques together with careful examination of a culture specimen provide unequivocal evidence of the causal agent.

More recently, the efficacy of periodic acid-Schiff (PAS) stain; which stains fungal wall glycoprotein, basement membrane material and mucosubstances bright red clearly delineating these elements from the pink-blue background used for testing, has been demonstrated. PAS is a very sensitive diagnostic test for onychomycosis in nail plate biopsy providing a definitive diagnosis of dermatophyte infection.

There are four recognized types of onychomycosis differentiated by infection pathway and clinical presentation.

Distal subungual onychomycosis (DSO) invades the distal nail plate progressing proximally to invade the nail bed and underside of the nail plate and is the most common form of onychomycosis caused by T. rubrum. Nails can become brittle, thickened, and discolored with pieces of nail breaking away.

White superficial onychomycosis (WSO) results in superficial infection of the nail plate indicated by the presence of ‘white islands’; it occurs mainly on toenails. As the infection consolidates, onycholysis can occur as the keratin breaks down.

T. rubrum colonization of the newly formed nail plate via the proximal nail fold, progressing distally with fingernails and toenails equally affected, is the least common form of onychomycosis in healthy adults; but is commonly isolated from immunocompromised individuals. Proximal subungual (white) onychomycosis (PSO) or (PSWO) is an early clinical marker for HIV.

Individuals who often have their hands in water or suffer from hyperhidrosis, and wear occlusive footwear can be infected with candidal onychomycosis, caused by Candida spp. Seventy percent of onychomycosis caused by yeast are attributed to Candida albicans. Total dystrophic onychomycosis (TDO) can be primarily due to chronic mucocutaneous candidiasis. One study on a geriatric
population suggested that mixed saprophytic infections may be more prevalent than the isolated
dermatophyte infection as the causal agent of onychomycosis. Onychomycosis is more likely to occur in the elderly and incidence is higher in males than females. Infections tend to increase in severity and prevalence (number of nails infected and area of nail affected) as individuals age, and are compounded by pre-existing health conditions such as diabetes, HIV, cancer and obesity.

Poor cosmetic appearance of nails can seriously impact an individual’s employment prospects, personal relationships and general lifestyle. Onychomycotic toe nails which become very thick and malformed can significantly impact mobility and limit footwear choice. Onychomycotic infections tend to be long term (>12 months) and recalcitrant. Current therapies show poor efficacy with recurrence/reinfection rates around 25%.

The most commonly utilized current treatment methods are topical and oral pharmacotherapies, the former being less costly and causing less side effects than the latter. Oral medications can have side effects such as altered liver function. However, a 93% complete cure rate has been reported with a treatment regime of 250mg of terbinafine daily for seven days every three months. Treatment with oral terbinafine at the dosage of 250mg daily for twelve weeks resulted in a mycological cure rate between 77-82%, and a clinical cure rate of 60-70%. Terbinafine has been government approved for treatment of onychomycosis in all countries and is the current gold standard oral treatment.

Topical treatments for nail infections are problematic for several reasons. They require chemical penetration of the nail plate and bed to reach the target infected tissue, resulting in reported efficacy rates between 5% and 8%. A lengthy treatment period of three to 12 months is required and patients are generally non-compliant. Topical applications are not a treatment option for obese clients, individuals who are unable to reach their feet, and older individuals with poor eyesight and reduced manual dexterity. Thus there is need for more effective treatment options.

In recent years, device based non-invasive therapies such as laser, ultrasound, iotophoresis and photodynamic therapies have been applied to onychomycotic infections.

Compared to current pharmaceutical options, laser therapy offers a non-invasive, short-term treatment regime provided by a medical professional in a clinical setting; thereby reducing or eliminating negative patient experiences.

‘Laser’ is an acronym for ‘light amplification by stimulated emission of radiation’. Lasers produce coherent light that can be spot focused while maintaining very high irradiance. Lasers derive their name, and emit light with characteristics specific to the ‘lasing material’ that is activated. The light beam produced by a laser can be pulsed, pseudo-continuous or continuous, and has wavelengths in the ultraviolet, visible and infrared ranges for dermatological uses. Biological responses can be targeted precisely by the careful choice of light wavelength, pulse duration and fluence.

Laser application to the medical field did not flourish until the 1990s when it was discovered that solid state lasers that utilized the alexandrite crystal produced photons of 755-nm light in the near infrared spectrum, and quality switching enabled a pulse width range from 50-100ns.

Effective laser treatment relies on the theory of selective photothermolysis. Chromophores are substances which selectively absorb a particular light wavelength. Melanin, present in skin and...
Trichophyton species cell walls,\textsuperscript{57} absorbs the 1064 nm wavelength produced by the Q-switched Nd:YAG laser. Whereas the 532 nm wavelength of the Q-switched Nd:YAG laser is absorbed by the red chromophore xanthomegnin abundant in \textit{T. rubrum}.\textsuperscript{22,53,55,57} Each chromophore has a unique thermal relaxation time (TRT).\textsuperscript{58} The TRT of a substance is defined as the time taken for the object to cool after absorbing heat.\textsuperscript{59} This means that if the target chromophore is unable to cool faster than heat is delivered, then the target substance is hotter than its environment and is destroyed.\textsuperscript{55} In the case of fungi, this means that targeted laser treatment can be fungistatic.\textsuperscript{60} Conversely, heat is transferred to the surrounding environment if heat is delivered more slowly than the chromophore can cool.\textsuperscript{55,58} Essentially, as target size reduces, the TRT reduces, which in turn requires reduced laser pulse duration to confine the heat energy produced to the target tissue only.\textsuperscript{55} Advances in laser technology suggest that the longer wavelength of the neodymium-doped yttrium aluminum garnet (Nd:YAG) laser enables a deeper penetration of tissues and thus it can target fungal elements in the nail bed,\textsuperscript{51} specifically xanthomegnin.\textsuperscript{58} The Nd:YAG laser emits 1064-nm wavelength but can emit light at 1440-nm, 1320-nm and 940-nm wavelengths and has the capacity to be modified such that the beam can be continuous, Q-switched, long-pulsed or potassium titanyl phosphate (KTP) modes to emit a range of medically useful wavelengths.\textsuperscript{55}

The carbon dioxide, Nd:YAG, 870/930-nm combination and femtosecond infrared 800-nm lasers, Flash pumped short pulsed Nd:YAG 1064-nm, Nd:YAG 1320-nm, modelocked femtosecond pulse titanium sapphire lasers (Ti:Sapphire) laser, near infrared Diode lasers and low level laser light all offer the potential of an alternative to current pharmaceutical treatments for onychomycosis. Recently published reviews\textsuperscript{51,52,61} have highlighted the potential laser therapies have to offer effective, convenient, short duration treatment regimens, and the need for further detailed research; but have not systematically evaluated the effectiveness of different laser types and treatment modalities.

This systematic review of effectiveness of current laser treatments for onychomycotic infections of nails among adults living in the community will provide information to assist medical professionals, such as podiatrists, dermatologists, and general practitioners, to develop their client treatment plan.

**Keywords**
laser, light therapy, mycoses, onychomycosis, \textit{Trichophyton rubrum}

**Inclusion criteria**

**Types of participants**

This review will consider studies that include males and females over the age of 18 years who have at least one nail with diagnosed onychomycosis using fungal culture, and direct microscopy, KOH method or periodic acid-Schiff (PAS). Males and females over the age of 18 years with diagnosed diabetes, HIV, cancer, transplant recipients and pregnant females will be excluded.

**Types of intervention(s)/phenomena of interest**

Studies that evaluate types of laser therapy for the treatment of onychomycosis including but not limited to; long pulse Nd:YAG laser, Flashlamp pumped short pulsed Nd:YAG 1064nm, 1320nm Nd:YAG laser,
modelocked femtosecond pulsed Ti:Sapphire laser, near infra-red Diode lasers, low level laser light treatment inclusive of dose duration and frequency.

**Types of outcomes**

This review will consider studies that include the following outcome measures:

Primary outcome is cure or clinical response.

Cure is defined as positive:

1. Clear nail growth (CNG) defined by at least 3mm growth in three to 12 months, or
2. No dermatophyte isolated from nail samples grown on a mycological culture medium, and
3. Absence of microscopically detectable fungal elements from nail samples treated with KOH, or
4. Absence of microscopically detectable fungal elements using PAS stain, or
5. 100% normal nail appearance in three to 18 months plus negative culture and microscopic results.

**Secondary Outcomes:**

Compliance rate measured by client attendance for treatments.

Recurrence as identified at follow-up at six and/or 12 months minimum timeframe.

Presence or absence of adverse effects. Adverse affects include skin irritation (erythema) adjacent to the treated nails, nail bed irritation, nail discoloration, onycholysis and periungal burning sensation.

Client satisfaction with treatment outcome.

**Types of studies**

This review will consider both experimental and epidemiological study designs including randomised controlled trials, non-randomised controlled trials, quasi-experimental, before and after studies, prospective and retrospective cohort studies, case control studies and analytical cross sectional studies for inclusion.

**Search strategy**

The search strategy aims to find both published and unpublished studies. A three-step search strategy will be utilised in this review. An initial limited search of MEDLINE and CINAHL will be undertaken followed by analysis of the text words contained in the title and abstract, and of the index terms used to describe the article. A second search using all identified keywords and index terms will then be undertaken across all included databases. Thirdly, the reference list of all identified reports and articles will be searched for additional studies. Studies published in English will be considered for inclusion in this review. Studies published from 1985 up to and including June 2013 will be considered for inclusion in this review as laser therapy applied to onychomycosis is a relatively new treatment and it is highly unlikely that there is any published literature relevant to this review that predates 1985.
The databases to be searched include:

CINAHL
EMBASE
PUBMED
SCOPUS
PUBGET
Cochrane Current Controlled Trials register for ongoing trials.
A hand search of podiatry journals not found in the electronic databases.
The search for unpublished studies will include:
MedNar, ProQuest database of Theses and Dissertations, conference proceedings, Google Scholar, Web of Knowledge and Web of Science.
Additionally, authors of papers identified through the above search strategy will be contacted to enquire about any unpublished data/studies. Contacting laser manufactures for reports of further published or unpublished trials will also be considered.

Initial keywords to be used will be: laser, light therapy, mycoses, onychomycosis, Trichophyton rubrum.

**Assessment of methodological quality**

Papers selected for retrieval will be assessed by two independent reviewers for methodological validity prior to inclusion in the review using standardised critical appraisal instruments from the Joanna Briggs Institute Meta Analysis of Statistics Assessment and Review Instrument (JBI-MAStARI) (Appendix 1). Any disagreements that arise between the reviewers will be resolved through discussion, or with a third reviewer.

**Data collection**

Data will be extracted from papers included in the review using the standardised data extraction tool from JBI-MAStARI (Appendix 2). The data extracted will include specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives.

**Data synthesis**

Quantitative data will, where possible be pooled in statistical meta-analysis using JBI-MAStARI. All results will be subject to double data entry. Effect sizes expressed as odds ratios (for categorical data) and weighted mean differences (for continuous data) and their 95% confidence intervals will be calculated for analysis. Heterogeneity will be assessed statistically using the standard Chi-square and also explored using sensitivity analysis. Subgroup analyses based on population and intervention differences, study quality and different study designs included in this review will be considered where appropriate. Where statistical pooling is not possible the findings will be presented in narrative form including tables and figures to aid in data presentation where appropriate.
Conflicts of interest

None to declare

Acknowledgements

Secondary Reviewer Ms Michelle Hodgkiss
References


18. Einarson TR, Gupta AK, Shear NH, Arikian S. Clinical and economic factors in the treatment of


38.Gupta AK, Fleckman P, Baran R. Ciclopirox nail lacquer topical solution 8% in the treatment of toenail


Appendix I: Appraisal instruments

MAStARI appraisal instrument

### JBI Critical Appraisal Checklist for Randomised Control / Pseudo-randomised Trial

<table>
<thead>
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<th>Yes</th>
<th>No</th>
<th>Unclear</th>
<th>Not Applicable</th>
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<tbody>
<tr>
<td>1.</td>
<td>Was the assignment to treatment groups truly random?</td>
<td>☐</td>
<td>☐</td>
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<td>2.</td>
<td>Were participants blinded to treatment allocation?</td>
<td>☐</td>
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<td>3.</td>
<td>Was allocation to treatment groups concealed from the allocator?</td>
<td>☐</td>
<td>☐</td>
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<td>4.</td>
<td>Were the outcomes of people who withdrew described and included in the analysis?</td>
<td>☐</td>
<td>☐</td>
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<td>5.</td>
<td>Were those assessing outcomes blind to the treatment allocation?</td>
<td>☐</td>
<td>☐</td>
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<td>6.</td>
<td>Were the control and treatment groups comparable at entry?</td>
<td>☐</td>
<td>☐</td>
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<td>7.</td>
<td>Were groups treated identically other than for the named interventions?</td>
<td>☐</td>
<td>☐</td>
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<td>8.</td>
<td>Were outcomes measured in the same way for all groups?</td>
<td>☐</td>
<td>☐</td>
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<td>9.</td>
<td>Were outcomes measured in a reliable way?</td>
<td>☐</td>
<td>☐</td>
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<td>10.</td>
<td>Was appropriate statistical analysis used?</td>
<td>☐</td>
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**Overall appraisal:** Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion):

________________________________________________________________________

________________________________________________________________________

________________________________________________________________________
## JBI Critical Appraisal Checklist for Descriptive / Case Series

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<tr>
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<td>Was study based on a random or pseudo-random sample?</td>
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<td>2.</td>
<td>Were the criteria for inclusion in the sample clearly defined?</td>
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<td>3.</td>
<td>Were confounding factors identified and strategies to deal with them stated?</td>
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<td>4.</td>
<td>Were outcomes assessed using objective criteria?</td>
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<td>5.</td>
<td>If comparisons are being made, was there sufficient descriptions of the groups?</td>
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<td>6.</td>
<td>Was follow up carried out over a sufficient time period?</td>
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<td>7.</td>
<td>Were the outcomes of people who withdrew described and included in the analysis?</td>
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**Overall appraisal:**  Include □  Exclude □  Seek further info □

Comments (Including reason for exclusion)

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Appendix II: Data extraction instruments

MAStARI data extraction instrument

**JBI Data Extraction Form for Experimental / Observational Studies**

Reviewer: ____________________ Date: ____________________

Author: ____________________ Year: ____________________

Journal: ____________________ Record Number: ____________________

**Study Method**

- RCT [ ]
- Quasi-RCT [ ]
- Longitudinal [ ]
- Retrospective [ ]
- Observational [ ]
- Other [ ]

**Participants**

Setting

Population

**Sample size**

Group A: ______________

Group B: ______________

**Interventions**

Intervention A

Intervention B

**Authors Conclusions:**

**Reviewers Conclusions:**
Study results

Dichotomous data

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Continuous data

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