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

Thesis submitted in fulfillment of the requirements of the Master of Clinical Science,

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Abstract

Background

There is growing public interest in the application of laser therapy to common nail conditions such as onychomycosis, where traditional pharmaceutical options are long-term, expensive, messy and often unsuccessful, and suited to a limited demographic. Recent reviews highlighting the potential of laser therapies to offer effective, convenient, short duration treatment regimens have not demonstrated the effectiveness of different laser types and treatment modalities creating the need for further detailed research. This systematic review identifies, critically appraises, synthesises and presents the best available evidence for the effectiveness of laser treatments on onychomycosis of the nails in adults living in the community. The specific review question was: can laser treatment of onychomycotic nails produce outcomes comparable to the current 'gold standard' treatment of oral terbinafine over a minimum 12 week treatment period, for adults living in the community?

Methods

A three step search strategy for published and unpublished studies in English language, in the date range 1/1/1985 to 30/6/2013 resulted in nine studies being critically appraised by two independent reviewers using the Joanna Briggs Institute Meta Analysis of Statistics, Assessment and Review Instrument (MAStARI). Seven papers were included for data extraction and synthesis. The primary outcome was cure or clinical response defined by at least 3mm of clear nail growth in a three to 12 month period, or negative microscopy (periodic acid-Schiff [PAS] or potassium hydroxide [KOH] and negative mycological culture [mycological cure]). Complete cure was defined as totally clear nail with negative culture and microscopy (PAS or KOH).

Main Findings

There was a weak association that neodymium-doped yttrium aluminum garnet Nd:YAG 1064nm laser for the treatment of onychomycosis in adults could produce clear nail growth and a mycological cure in a 12 week period. Although there is a plethora of laser therapy options currently on the market, evidence is either of poor quality and a measurable effect cannot be identified, or is absent, to the point that it is not possible to objectively evaluate claims of benefit. Practitioners should be aware of there are significant gaps in the evidence, and that current evidence only supports Nd:YAG 1064nm laser therapy.

Interpretation

Before a new intervention is implemented, there should be clear evidence of benefit in direct head-to-head comparative studies against a known gold standard intervention. This systematic review found no such evidence related to most forms of laser therapy, and also an absence of evidence for many claims associated with laser therapy. While Nd:YAG 1064nm laser for the treatment of onychomycosis in adults is supported, multi center, randomised studies with good controls and adequate power that directly compare laser therapy against oral terbinafine are needed in order to determine the therapeutic effectiveness of laser therapy.

The objectives, inclusion criteria and methods of analysis for this review were specified in advance and documented in a protocol,[1] registration number CRD42013006731 in PROSPERO.[2]

Initial keywords used were: laser, light therapy, mycoses, onychomycosis, and *Trichophyton rubrum*.

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Chapter 1: INTRODUCTION

1.1 Context of the review

1.1.1 Onychomycosis

Traditionally, the term onychomycosis was used to describe nondermatophytic nail infection but has also been used as a more generic term to describe any fungal nail infection.[3, 4] Tinea unguium often referred to as onychomycosis, is an extremely common and specific fungal infection most frequently caused by keratinophilic dermatophytes *Trichophyton rubrum* with incidence rates reported between 68% to as high as 90% in Europe and/or *Trichophyton mentagrophytes* var. *interdigitalis* that infects the nail plate, nail bed and matrix.[5-9] Tinea unguium signs and symptoms can easily be confused with non-infected nail dystrophy due to skin diseases such as psoriasis, lichen planus, viral warts, dermatitis and the ageing process.[10] However, historically it is not uncommon for published research papers to use onychomycosis and tinea unguium almost as interchangeable terms giving rise to a lack of clarity regarding the infecting organisms.[4]

1.1.2 Dermatophytes, saprophytes, distribution and incidence

Dermatophytes are pathogenic fungi that grow on living tissue such as skin, mucous membranes, hair, nails, and other body surfaces whereas saprophytes are organisms such as yeasts, mouldy flora and fungi that live on dead organic matter. Dermatophytes are a homogenous group of keratinophilic fungi identified as the causative agents in the majority (90% of toenail and 50% of fingernail) of cutaneous infections and are the major causal agents of the skin infection, tinea pedis, and nail infection, onychomycosis.[4, 11-13] The close relationship between tinea pedis and *T.rubrum* infection is well established and widely acknowledged.[14, 15] *Trichophyton rubrum, Trichophyton mentagrophytes* var. *interdigitalis*, *Epiderophyton floccosum* and *T. tonsurans* are the most frequently isolated dermatophytes from skin scrapings and finger or toenail samples.[16, 17] Dermatophytes accounted for 82% of onychomycosis isolates in an epidemiologic survey of superficial fungal infections.[12]

More recent research has shown that onychomycosis etiologically comprises a suite of dermatophytic fungi (*Fusarium* spp., *Aspergillus* spp., *Alternaria*), saprophytic moulds such as *Scopulariopsis brevicaulis*, *Acremonium*, *Scytalidinum dimidiatum* and *Scytalidinium hyalinum* and/or bacteria which colonise different ecological niches on a human.[18] *Candida*

albicans and *Candida parapsilosis* are the most significant yeasts found to cause onychomycosis and paronychia.[17] The incidence of dermatophytes and saprophytes isolated from infected individuals varies over geographic and demographic regions worldwide with dermatophyte skin infections reportedly affecting up to 30% of the adult population.[11, 19, 20] However, dermatophytes may account for only 50% of onychomycotic nail infections.[11] Hence it is important to understand that the medical term onychomycosis refers to a chronic infection of the nails caused, in the main, by dermatophytes and *Candida* species.[17, 21]

1.1.2.1 Types of onychomycosis

There are four recognised types of onychomycosis differentiated by infection pathway and clinical presentation.[4, 22, 23] Distal subungual onychomycosis (DSO) or distal lateral subungual onychomycosis (DSLO) 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*.[4] Nails can become brittle, thickened and discoloured with pieces of nail breaking away.[4] White superficial onychomycosis (WSO) occurs mainly on toenails and is characterised by superficial localisation of fungi on the dorsal surface of the nail plate appearing as discrete 'white islands'.[22, 24] As the infection consolidates, onycholysis can occur as the keratin breaks down.[25] Proximal subungual (white) onychomycosis (PSO) or (PSWO) results from *T. rubrum* colonization of the newly formed nail plate via the proximal nail fold progressing distally, with fingernails and toenails equally affected. This is the least common form of onychomycosis in healthy adults but is commonly isolated from immunocompromised individuals.[22] Proximal subungual (white) onychomycosis is considered to be an early clinical marker for HIV infection; however, Tosti et al.[26] in their study of non-dermatophyte infections disagreed with this conjecture.[22, 27, 28]

Individuals who often have their hands in water or suffer from hyperhydrosis, 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*.[29] Total dystrophic onychomycosis (TDO) can be primarily due to chronic mucocutaneous candidiasis.[25]

1.1.2.2 Demographics, social and economic impact

The fact that the incidence of fungal nail infections are increasing is multifactorial. Detection methods are improving. There is a growing population of immunocompromised individuals who have increased susceptibility to infection, and an increasing number of elderly people. Across developed nations, there is an estimated 15-35% of population that will be aged over 65 years old by 2023.[30] In Australia, the number of individuals 65 years and over at 30 June 30 2004 was estimated at 2.6 million or 13% of the total population. This figure is estimated to rise to 27-31% by 2101.[31] Worldwide travel is more affordable and globally individuals are more mobile.[32] Climatic conditions and geographic location may affect the incidence and type of infection. Dermatophyte onychomycosis incidence is higher in temperate climate regions whereas yeasts, saprophytes and other non-dermatophyte infections may be more prevalent in tropical areas.[33] The incidence of onychomycosis attributed to dermatophyte infections has been estimated to be between two to eight percent in the western world. This estimate was contributed to by figures ranging between 14-20% of the North American population and 3-22% in European countries.[5, 34-36] In 1999, Scher [37] estimated a 2-18% incidence of onychomycosis in the whole world population and Thomas et al.[15] concurred with an estimate of 10%.

Advances in medical and pharmaceutical science together have contributed significantly to increased individual lifespan. There are increasing numbers of immunocompromised individuals and individuals undergoing invasive surgical procedures or receiving organ transplants who are reliant on the extensive use of broad-spectrum antibiotics and/or chemotherapy.[38] Onychomycosis is more likely to occur in the elderly.[39-42]

Onychomycotic infections tend to increase in severity and prevalence (number of nails infected and area of nail affected) as individuals age, accounting for 18.2% in individuals aged 60-79 years and approximately 50% of individuals over the age of 70 years.[15] Pre-existing health conditions such as diabetes, HIV infection, cancer and obesity compound the situation.[43-45] Gupta et al.[46] estimated 34% of individuals with diagnosed diabetes also have onychomycosis. Transmission of fungal infection can be from person to person but is more frequently attributed to contact with moist floor surfaces and individuals engaged in personal fitness programs utilising public facilities are considered at higher risk of infection.[6, 15, 47] Recent research implicates onychomycosis caused by a fungus in about half of all nail infections worldwide and incidence is higher in males than females.[15, 22, 48, 49]

Poor cosmetic appearance of nails can seriously impact an individual's employment prospects, personal relationships, self-esteem and lifestyle.[50, 51] In a multinational cross sectional study, Drake et al.[52] concluded that patients were physically and psychologically affected by onychomycotic nail infections and that there were demographic differences in the perceptions of the severity of the impact. Physicians tended to underestimate the pain associated with nail infections.[52] Onychomycotic toe nails which become very thick and malformed can significantly impact mobility and limit footwear choice.[29] Toenail infections can take many months to resolve, thus onychomycotic treatment is necessary to reduce pain, prevent infection spread and surmount physical limitations.[53]

In 1997 in the state of Victoria in Australia, the economic burden of treatment was demonstrated by a medication cost estimated at AUS$5 million.[20] The social impact on individuals was significant with an estimated 30% of podiatry treatments in Australia involving onychomycotic conditions.[20] In 1993 an estimated $US5 billion was spent on nail cosmetics in the USA.[20] Bessinger[54] reported that in 2010 the worldwide market for onychomycosis treatments was estimated at $US3.6 billion.

It must be noted that only 50% of dystrophic nails are caused by fungal infection.[55] Neither does isolating an organism mean that it is necessarily the causative infecting agent.[42, 56] Hence it is imperative to confirm the diagnosis of the causal agent prior to starting a treatment regimen.[11, 22, 49]

1.1.2.3 Microbiological identification techniques

Traditionally, fungal identification involves collection of an adequate sample which can then be used for light microscopy and mycological culture investigations. Both tests need to be positive for a definitive diagnosis of the infecting organism.[4, 16, 38] Microscopy in conjunction with culture growth on mycological agar growth medium is considered the diagnostic 'gold standard' for onychomycosis.[3]

1.1.2.3.1 Direct microscopy

Direct microscopy involves mounting samples taken from the active areas of a lesion onto a glass slide with a 10-20% potassium hydroxide (KOH) solution. The solution is heated such that the epidermal cell keratin is dissolved and the fungal elements are left. Enhancement of any fungal elements can be facilitated by the addition of a dye such as Calcofluor white to the KOH solution.[16] Another method incorporates dimethyl sulfoxide

with KOH a technique which provides more rapid clearing and maceration than KOH on its own, but specimens prepared in this manner must also be examined within 20 minutes for the presence of unstained refractive fungal components.[16] Microscopic examination for septate or branching hyphae, budding cells and spores are evidence of fungal infection.[49] Direct microscopy which follows a published standardized technique applied to nail fragments and incorporating subungual debris is a very sensitive test.[16, 57]

1.1.2.3.2 Mycological culture

Mycological culture involves the transfer of sample substrate onto a sterile laboratory agar growth medium utilising an aseptic technique. Generally Sabouraud's dextrose agar with cyclohexamide (5g/L) which suppresses growth of many saprophytic fungi and bacteria, and the antibiotic chloramphenicol (0.05g/L) are used.[16] Often a yellow-red indicator substance sensitive to acidity changes is included in the medium as dermatophytic fungi tend to produce alkaline metabolites. As the agar substrate absorbs these metabolites the acidity reduces producing a change in colour from yellow to red.[16] There are numerous nondermatophyte moulds that can also cause a substrate colour change; therefore identification requires microscopic examination and clinical mycological experience and expertise, otherwise false positive results could occur.[16]

1.1.2.3.3 Confounding factors for identification

Both direct microscopy and culture investigations in isolation can result in false-negative results [3] and the presence of nondermatophytes in culture specimens can further confound the identification of the causal organism.[3] The role of nondermatophytes in onychomycosis has been controversial.[9, 13] 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.[58]

Nondermatophytes can be common laboratory contaminants, or emerge as a result of poor sampling techniques. Cumulative evidence using direct microscopy techniques together with careful examination of a culture specimen, and sequential culture specimens, provide additional, unequivocal evidence of the causal agent.[4, 26]

1.1.2.3.4 Sampling techniques

Direct microscopic examination of skin or nail material is both cost effective and rapid; however it has been shown to produce false negatives in 5-15% of cases.[59-63] These arise due to fungal specimens consisting of visible but non-viable fungal elements which result in a KOH-positive but culture negative outcome.[16, 63] Where clinical indications are in contradiction of a negative culture result, repeat cultures should be undertaken.[16] KOH microscopy and fungal culture accuracy can range between 50% to 70% due to poor sample quality, collection techniques and contamination.[57, 59, 64-66] Even with correct and careful sampling and laboratory procedures, discrepancies can occur in about 30% of cases.[16, 63]

1.1.2.3.5 Sample types

Samples of nail clippings from the distal nail where any fungal elements may disintegrate or not be viable, present a well-documented risk of obtaining a false-negative microscopic result.[4, 16, 67-69] It is also possible for subungual scraping samples to yield very small numbers of fungal spores, easily overlooked, using direct microscopy but proving viable on the culture medium, thus yielding a KOH-negative but culture positive result.[63] Similarly, the type of sample is important. False negatives are more likely from large pieces of nail rather than much finer, particulate nail matter, including subungual debris, to ensure that every possible fungal niche is exposed and sampled.[16, 17]

1.1.2.3.6 Cumulative evidence

Nondermatophytes can be common laboratory contaminants, or emerge as a result of poor sampling techniques. Cumulative evidence using direct microscopy techniques together with careful examination of a culture specimen and sequential culture specimens provide additional unequivocal evidence of the causal agent.[4, 26]

1.1.2.3.7 Emerging technology

More recently the efficacy of periodic a 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.[66] PAS is a very sensitive diagnostic test for onychomycosis in nail plate biopsy providing a definitive diagnosis of dermatophyte infection.[66, 70, 71]

1.1.2.3.8 Defining recurrence and cure.

Recurrence is generally defined as the return of the disease within one year of treatment completion.[63] By implication, this definition suggests that although there may be a lack of clinical signs of disease at >12 months after completion of treatment, the initial treatment did not achieve a mycological cure.[63] However, if a new infection occurs at >12 months, reinfection is a more likely probability because there is the implication that the previous infection was cured, and now, there is a new infection.[63]

1.1.3 Current pharmaceutical treatment methods

The most commonly utilised current treatment methods for onychomycosis are topical and oral pharmaceuticals,[72] the former being less costly and causing less side effects than the latter. Current topical treatments include, for mild cases, nail lacquers amorolfine, ciclopirox and terbinafine spray, lotion and cream. In severe cases, systemic medications such as fluconazole, itraconazole, terbinafine and griseofulvin are prescribed.[19] Griseofulvin is less commonly prescribed these days as newer pharmaceuticals become available.

There are other oral and topical pharmaceutical preparations that are available to the public and a range of combination treatments that can be part of an individually tailored treatment regimen. This review is only addressing the most commonly and widely utilised treatments that have been widely researched.

1.1.3.1 Pharmacokinetics of topical treatments

Amorolfine belongs to the morpholine group of antifungal agents that inhibit two enzymes integral to the biosynthesis of ergosterol, a major component in fungal cell membrane.[73] Amorolfine is fungistatic through inhibiting cell growth, and fungicidal, promoting cell apoptosis against moulds, yeast, dermatophytes and nondermatophytes.[42]

Ciclopirox is a hydroxypyridone with multiple actions. Ciclopirox inhibits cytochromes by binding to trivalent metal cations (e.g. Fe^{3+}).[74] In addition it is known to reduce the activities of catalase and peroxidase, two enzymes vital to the mitochondrial electron transport process, as well as acting on nutrient uptake which in turn affects protein and nucleic acid synthesis. Thus Ciclopirox has fungicidal properties derived from its multiple actions.[74]

Terbinafine is an allylamine recommended for tinea pedis, and is promoted mainly for skin applications. This preparation is mainly fungicidal through its action of inhibiting fungal ergosterol synthesis at the squalene epoxidation stage, which leads to destruction of the

cell wall through disruption of the cell membrane.[74, 75] Terbinafine is fungicidal for dermatophytes but less effective against non-dermatophytes, such as yeast and *Candida* spp.[15]

1.1.3.2 Topical pharmaceutical treatments

Topical pharmaceutical treatments are available as lacquer, spray, lotion and cream. Topical treatment of any sort requires chemical penetration of the nail plate and bed to reach the target infected tissue.[72, 76] Topical treatment has difficulty maintaining a sustained concentration level in the nail substrate that is higher than the minimum inhibitory concentration required for the infecting fungus.[74]

Topical lacquers such as ciclopirox and amorolfine reduce transonychial water loss facilitating increased drug moiety in the nail plate.[15] This affords the active ingredient a longer contact period with the infected nail plate.[55] The lacquer film has the dual effect of improving hydration of the nail plate and potentially inducing the germination of dormant or drug-resistant fungal spores, thereby reducing the fungal infective load. Improved nail hydration helps eradicate and prevent recurrence of the infection by improving movement of the active ingredient through the diseased nail plate.[74]

Ciclopirox is a synthetic hydroxypyridone derivative with broad spectrum of efficacy against nondermatophytes moulds and yeasts in addition to dermatophytes.[77]

Mycological cure rates in the range of 29-36% using a daily application of 8% ciclopirox for up to 48 weeks has been reported.[75,78] Nail plate thinning is undertaken either by the patient or a health professional to optimise treatment efficacy. Side effects include burning sensations and puritis.[15] Ciclopirox is the only United States Federal Drug Administration (FDA) approved nail lacquer in the USA and is approved in more than 40 countries worldwide.[79]

Amorolfine is a phenyl-propyl morpholine derivative with broad-spectrum efficacy against dermatophytes and yeasts.[42, 80] Amorolfine is applied once or twice weekly until the nail re-grows (six months for fingernails and 12 months for toenails). Best results are achieved by thinning the diseased nail prior to the application of the lacquer. Applying 5% lacquer once a week for up to 24 weeks is reported to affect a 60-71% mycological cure in randomised clinical studies for onychomycosis. Treatment has no reported side effects except a rare case of chromonyhia.[15]

Amorolfine is approved for treatment of onychomycosis in Europe but not in the USA or Canada.

The pharmacokinetics of the allylamine terbinafine make it ideally suited to treating onychomycosis through its keratophilic and lipophilic properties.[79] Terbinafine reaches the nail plate by incorporating into newly forming nail within the nail matrix area and in addition diffuses from the nail bed to the nail plate. Terbinafine is available worldwide.[15] Recent new formulations of terbinafine as a nail lacquer and TDT-067 which is a topical formulation of terbinafine in a transfersome particle (a vesicle formed out of a lipid aggregate) show great promise for future treatment.[19] TDT- 067 treatment twice daily for 12 weeks with follow-up at 48 weeks recorded mycological cure rates of 90% at 12 weeks, 80% at 24 weeks and 38.5% at 48 weeks.[19]

1.1.4 Effectiveness of topical treatments

Topical treatments require chemical penetration of the nail plate and bed to reach the target infected tissue resulting in reported efficacy rates between 5% and 8%.[4, 72, 76, 81] A lengthy treatment period of three to 12 months is required and generally patients are non-compliant.[22, 72, 82] 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.

The main benefits of topical treatments for onychomycosis are the reduced risk of drug-to drug-interaction and fewer side effects compared to systemic treatment. They are a treatment choice for individuals unable to take the oral alternative.

Topical treatments are beneficial to treat cases of SWO and can be a treatment choice for DLSO if less than 50% of the nail is infected with no matrix involvement and also for situations where only three or four nails are infected.[15, 75]

There is strong evidence that allylamines are significantly more effective compared to other topical treatments with maximum benefit achieved at six weeks.[72] Read made best practice recommendations of a six-week treatment period using a topical agent containing an allylamine in the first instance or alternatively an azole for at least a four-week period.[83] (JBI Grade A [Appendix X].)

1.1.4.1 Oral systemic pharmaceutical treatments

Terbinafine, itraconazole and fluconazole became available to the public in the 1990s and are three main oral medications currently used to systemically treat onychomycotic infection.

1.1.4.2 Pharmacokinetics of oral treatments

Terbinafine belongs to the allylamine group of chemicals and inhibits the enzyme squalene epoxidase which is integral to the synthesis of ergosterol, a critical component of fungal cell membrane.[75] Accumulation of squalene initiates a biosynthetic pathway that is fungicidal, whereas depletion of ergosterol affords terbinafine its fungistatic activity against a range of yeasts and moulds.[40] Terbinafine is available in tablet or granule form.[84] Terbinafine is able to maintain a therapeutically active level within the nails, appearing in the stratum corneum within 24 hours of administration.[15] The mean active drug concentration remains in the body for up to three months post cessation of oral treatment.[15] Side effects include nausea, mild abdominal pain, diarrhea and rarely hepatotoxicity.[15]

Itraconazole and fluconazole both belong to the azole group of pharmaceuticals which inhibit the enzyme lanosterol 14 alpha-demethylase integral to the biosynthesis of ergosterol. This inhibition results in reduced levels of ergosterol and fungistatic activity.[75, 85]. Itraconazole is a highly lipophilic compound which tends to accumulate in skin and mucous membranes and is therefore usually administered on an intermittent schedule.[42] Itraconazole is licensed for onychomycosis in the USA at the rate of 200mg per day for three months.

Fluconazole has limited success in treating onychomycosis, and is used mainly for systemic candidiasis, but has the advantage of a once weekly treatment regimen.[15, 42] Dosage rates of 150mg or as high as 450mg per week only effect a cure rate in the range of 15-35%.[42] Fluconazole is licensed in many countries but not the USA. Fluconazole is available in tablets or oral suspension.[86] Azoles are fungistatic and have to be present in very high concentrations to be fungicidal.[15]

1.1.4.3 Effectiveness of oral systemic pharmaceutical treatments

Oral medications can have side effects such as altered liver function and manufacturers recommend a blood test for liver function pre- and post-treatment regimen.[15]

However, a 93% complete cure rate has been reported with a treatment regimen of 250mg of terbinafine daily for seven days every three months.[87] Treatment with oral terbinafine at the dosage of 250mg daily for 12 weeks resulted in a mycological cure rate of 94% and a clinical cure rate of 60-70%.[24, 88] Gupta et al. [81] undertook a meta-analysis of randomised controlled trials (RCTs) of systemic treatments for onychomycosis and concluded that terbinafine produced a mycological cure rate of 76%,(n=18 studies, 993 participants) which was higher than fluconazole (48%; n=3 studies, 167 participants), continuous itraconazole (59%; n=7 studies, 1131 participants), pulsed itraconazole (63%; n=6 studies, 318 participants) and griseofulvin (60%; n=3 studies, 131 participants).

Terbinafine has been government approved for treatment of onychomycosis in all countries[89] and is the current gold standard oral treatment,[19, 76] at the rate of 250mg per day for 12 weeks for toenail infection, and 250g per day for six weeks for fingernail infection.[75] Onychomycotic infections tend to be long term (>12 months) and frequently re-occur.[90] Current therapies show poor efficacy with recurrence/reinfection rates around 25%.[19, 90, 91]

1.1.4.4 Laser technology and potential medical applications

An ideal treatment should be available to the widest demographic, is cost effective, has no side effects, and is short term and effective. In recent years, device based non-invasive therapies such as laser, ultrasound, iotophoresis and photodynamic therapies have been applied to onychomycotic infections.[55, 82, 92-97] This review is focused on laser interventions for treatment of onychomycosis; therefore ultrasound, iotophoresis and photodynamic therapies will not be addressed any further. Compared to current pharmaceutical options, laser therapy offers a non-invasive, short-term treatment regimen provided by a medical professional in a clinical setting, thereby reducing negative patient experiences.[19]

1.1.4.5 Brief laser history

The following information is taken in the main from Lanigan.[94] '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 names 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.[82, 94, 98]

Laser technology began in the 1960s with Theodore H Maiman using ruby as a lasing medium, to produce high intensity flashes of light with a wavelength of 694nm.[99] During the 1960s ten different types of lasers were invented. These lasers utilised solid, gaseous, semi-conductor and liquid lasing media. In 1963 Dr Leon Goldman, 'the father of laser medicine', published the first scientific article on the use of laser in medicine and specifically his application of the ruby laser to pigmented skin lesions.[100] The 1960s also heralded the discovery of a process called Q-switching enabling ultra-short high energy laser pulses of nanoseconds (10^{-9}) duration to be produced. These energy pulses cause mechanical photo acoustic damage in target cells.

Laser application to the fields of medicine, surgery and dermatology did not flourish until 1983 when Anderson and Parrish[101] described their theory of selective photothermolysis which revolutionised laser therapy and the discovery of new materials enabled Q-switching to be further refined for dermatological applications.[102] Common terms used in laser technology are defined in Appendix I.

1.1.4.6 Types of lasers

1.1.4.6.1 Gas

Carbon dioxide lasers are gas lasers and were amongst the first developed. They operate in the thermal infrared range of 10μm and are ablative on biological tissue. A CO_2 laser has been utilised in experiments to treat onychomycosis.[103] However, they have been surpassed by advances in laser technology for medical applications.

1.1.4.6.2 Solid- State

The most versatile laser systems for medical applications are solid state lasers. The most common are the neodymium-doped yttrium aluminum garnet (Nd:YAG) laser and the titanium sapphire (Ti: Sapphire) laser.[93] The Nd:YAG emits light in the near infrared spectrum and the most common output wavelength is 1064nm. These lasers can be built in differing configurations to produce either continuous or short- or long-pulsed output. Long-pulsed lasers produce pulses in the millisecond (10^{-3}ms); whereas short-pulsed lasers, in the microsecond (10^{-6}μs).[104] Some solid-state lasers (ruby 694nm, alexandrite 755nm and Nd:YAG 1064nm) can be Q-switched for pulse durations in the nanosecond

(10^{-9}ns) range. Q switching is thought to destroy fungal hyphae. Lasers have been developed to also produce pulses in the femtosecond range (10^{-15}fs).[105] The Nd:YAG lasers are currently licensed in North America, the European Union, Canada and Australia for cosmetic applications.[93]

1.1.4.6.3 Diode

Diode lasers operate in the near-infrared range. They are small, portable and highly efficient and increasingly used for dermatology applications.[94] The dual wave-length (870/930nm) near infrared diode laser is postulated to stimulate the production of reactive oxygen species (ROS) and adenosine triphosphate (ATP), affecting the zinc dependent endopeptidases called matrix metalloproteinases (MMPs) noted for their ability to degrade extracellular matrix.[106]

The carbon dioxide, Nd:YAG, 870/930 nm combination and femtosecond infrared 800nm lasers, flash pumped short pulsed Nd:YAG 1064nm, Nd:YAG 1320nm, 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.

1.1.4.7 Potential laser treatment parameters for onychomycosis

Absorbed photons are able to produce chemical, mechanical and thermal changes in the target chromophore and surrounding tissues.[107] Effective laser treatment relies on the theory of selective photothermolysis which exploits the differences in energy absorption and thermal conductivity of the laser treatment between the target chromophore and the surrounding tissues.[108,110] Chromophores are substances which selectively absorb a particular wavelength of light. For example, melanin, present in skin[109] and *Trichophyton* species cell walls[107] absorb the 1064nm wavelength produced by the Q-switched neodymium-doped yttrium aluminum garnet Nd:YAG laser, whereas the 532nm wavelength of the Q switched Nd:YAG laser is absorbed by the red chromophore xanthomegnin, abundant in *T. rubrum*.[94, 107-109] Xanthomegnin is a fungal metabolite of *T rubrum* and is the major pigment which appears to give a fungal colony grown on a mycological media its rich red color on reverse.[53]

Each chromophore has a unique thermal relaxation time (TRT).[111] The TRT of a substance is defined as the time taken for the object to cool after absorbing heat.[112] This means that if

the target chromophore is unable to cool faster than heat is delivered, then the target substrate is hotter than its environment and is destroyed.[109] Conversely, heat is transferred to the surrounding environment if heat is delivered more slowly than the chromophore can cool.[109, 111] The fluence reaching the target after subtracting reflection and scattering has to be equal to or greater than the threshold fluence to achieve destruction of the target tissue.[105] 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.[98]

Advances in laser technology suggest that the longer wavelength of the (Nd:YAG) laser enables a deeper penetration of tissues and targeting of fungal elements in the nail bed.[82, 111] The Nd:YAG laser emits 1064nm wavelength but can emit light at 1440nm, 1320nm, 1120nm and 940nm wavelengths and has the capacity to be modified such that the beam can be continuous, Q-switched, long-pulsed or KTP modes to emit a range of medically useful wavelengths.[109] In the case of fungi this means that targeted laser treatment can potentially be fungicidal, using the Q-switched 532nm Nd:YAG laser targeting the chromophore xanthomegnin, which has peak absorption between 406nm and 555nm or using the same laser at the 1064nm wavelength where melanin is the targeted chromophore.[53, 92, 107]

1.1.4.8 Laser research for onychomycosis

The first reported laser therapy for onychomycosis utilised a carbon dioxide (CO_2) laser when Apfelberg et al.[113] reported treating nine cases of onychomycosis. This study reported six patients cleared of infection after one treatment, and two patients with recurrence. The veracity of this research is impossible to ascertain as there was no baseline confirmation of identification of the causal organism(s) or confirmation of clearance post treatment using either microscopy or culture samples with a suitable follow-up time frame. Unfortunately no operational parameters for the laser intervention were reported. The CO_2 laser is ablative and Borovoy et al.[103] exploited this function in a study employing laser fenestration to facilitate penetration of topical antifungal treatment through the nail to treat onychomycosis. The onychomycosis infection was confirmed via mycological culture in 200 participants. Nail plates were mechanically thinned prior to treatment. One CO_2 laser treatment was followed up with 12-18 months of topical antifungal cream. Participants were instructed to file nails regularly. Borovoy et al.[103]

reported complete clearance and no recurrence for 75% of participants after three years of follow-up. The dual wavelength 870-930nm diode laser in vitro demonstrated 100% eradication of bacteria, fungi and yeast.[92] Landsman et al[114] applied this dual wavelength laser to 26 mycologically confirmed infected toenails to achieve negative mycological cultures and at least 3mm of clear nail growth at four months in 39% of infected nails, representing a 77% clinical improvement, and a final 38% maintained negative culture and microscopy at nine months follow-up.

Numerous in vitro studies have experimented with a range of different light therapies and different wavelengths, from intense pulse light (IPL) 695-1000nm, erbium yttrium aluminum garnet laser (Er:YAG) at 2940nm, KTP 532nm plus Q-switched 532 and 1064nm Nd:YAG to pulsed diode laser 585nm, on an array of substrates including infected nail clippings, mycological culture of unidentified fungal species in addition to colonies of *T rubrum* [92, 107, 115, 116] A range of laser parameters such as laser spot size was also explored and results from these studies are at best directional with the in vitro study by Manevitch et al.[98] most definitive in producing complete fungal colony inhibition without causing structural nail plate damage utilising a mode-locked 800nm femtosecond (fs) infrared Ti: Sapphire laser.

1.2 Why this systematic review was undertaken

Treatment options using lasers for medically recognised conditions such as onychomycosis are the subject of growing interest; however their effectiveness has not been established. Published clinical trials utilising laser treatments for onychomycosis to date involve small numbers of participants and this systematic review of effectiveness of current laser treatments for onychomycotic infections of nails among adults living in the community provides an opportunity to examine these small studies collectively and provide information to assist medical professionals such as podiatrists, dermatologists and general practitioners develop client treatment plans.

Healthcare and scientific literature have a long tradition of narrative reviews, where experts in a field collate existing knowledge and publish their findings in the form of summaries on a specific topic to inform theory or draw conclusions. These styles of reporting are often referred to as literature review, critical review, narrative review, commentaries or expert opinion within the literature. [135,142]

Recently published literature on the emerging technologies of light-based therapies to treat onychomycosis illustrates these various styles of reporting and the complexity of the

information provided[93, 95, 97, 104, 117-129] These reviews have highlighted the potential of laser therapies 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.

One review published online in 2012, "Laser and light therapy for onychomycosis: a systematic review",[130] was found prior to conducting this research. The authors (Ledon et al) of that review were transparent in providing details of their search strategy and their search results concur with the systematic review search of the PubMed database by the author of this thesis reported in Glaser et al.[131] Literature reviews gather together relevant publications on a specific topic and can prove invaluable to assess the depth and breadth of a knowledge base pertinent to a specific topic. In addition it could be perfectly reasonable to restrict the search for relevant literature to one database as Ledon et al [130] have done. However, contemporary understanding of a systematic review of literature is that, more than one database has been searched for published literature and that grey literature sources have been searched for unpublished articles relevant to the topic. The literature sources (published and unpublished) to be searched and the search process are based on parameters outlined in an a priori protocol. It has been shown that studies that have a positive outcome are more likely to be published than those with negative results, thus the effects of a treatment tend to be overstated highlighting the need for critical appraisal.[132-134]

The strength of this systematic review lies in the application of the Joanna Briggs Institute System for the Unified Management, Assessment and Review of Information (JBI-SUMARI) software to develop an a priori protocol and the proven sound methodology of the Joanna Briggs institute Meta Analysis of Statistics Assessment and Review Instrument (MAStARI) applied to critically appraise and then extract the data from the included studies.

The objectives, inclusion criteria and methods of analysis for this review were specified in advance and documented in a protocol,[1] and registration number CRD42013006731 in PROSPERO.[2]

1.3 Statement of the review question

The objective of this systematic review was to identify, critically appraise, synthesise and present the best available evidence for the effectiveness of laser treatments on onychomycosis of the nails in adults living in the community.

The specific review question addressed was the following:

Can laser treatment of onychomycotic nails produce outcomes comparable to the current 'gold standard' treatment of oral terbinafine over a minimum 12-week treatment period for adults living in the community?

1.4 Overview of the science of evidence synthesis

Evidence-based medicine (EBM) and what has come to be known as evidence-based practice (EBP) or evidence-based healthcare (EBHC) began its evolution from empiricist and rationalistic philosophies predating the 19th century.[135] Hippocrates' observations regarding disease conditions are credited as the earliest formalization of the empiricist view in medical practice.[126] During the period of Enlightenment there was a movement away from blind acceptance of the authority of royalty or the church. Enlightened thinkers saw the individual as central in a world that could be objectively explained by use of verbal and numerical language to present the truth.[136] Remedies which were deduced from a traditional knowledge base and practitioners of other healing modalities or philosophic traditions who had not been trained in the newly developing universities were devalued and/or excluded.[126] Paradigms are inherently founded on action implications and power relationships.[137] Mainstream Medicine used the increasing success of science during the 17th and 18th century to consolidate a position of authority utilising a public perception of interdependence of science, competence and accountable practice.[126]

The underlying philosophy was that of Logical Positivism which embraced an objective reality where knowledge was advanced by means of data that could be directly verified in a logical process of empirical research or testing by independent observers applying inductive and deductive hypotheses based on a body of scientific theory.[138] Positivist research theory aims at controlling the physical world. It emphasises experimentation based on testing a theoretical hypothesis in a laboratory type setting, where the relations observed in the experiment are valid in that context, and the distance between the researcher/research process and the objects/subjects is maintained.[139, 140]

The positivist paradigm embraces a separation between facts and values. Psychologists were among the first social scientists to realise that the logical positivist paradigm

underpinning the quantitative experimental process would produce results with internal validity within a controlled/laboratory context but that these results could not be extrapolated to the multi-factorial environment of the external world where qualitative human foibles and variability make for a much more complicated and multilayered context.[136,141] This dissatisfaction with the Positivism paradigm highlighted a watershed in medical and social science research with a shift away from the dehumanised positivist empirical approach and towards Post positivism and research inclusiveness encompassing facts and values.[136] Despite some philosophical differences between the two paradigms, both approaches adopt a cause-effect approach to explain links between phenomena that can be identified, generalised and objectively studied by the detached researcher. Both paradigms firmly underpin quantitative research.[136] A realisation that no single approach was capable of providing sufficient information or understanding to proffer a valid solution to the understanding of a phenomenon heralds a new approach to the synthesis of research findings.[141]

1.4.1 Narrative synthesis

The scholarly traditional scientific review, which used a narrative format to summarise findings on a specific topic aimed at informing theory or drawing conclusions, contributed to advances in many areas of science. However, no matter how carefully the reviewer gathered the papers for review the limitations and potential for bias were ever present.[142] Contemporary medical, nursing and allied health publications have undergone a massive production increase which began in the late 20th century and continues to this day. This is apparent in print media and particularly online publications which may range from peer reviewed high quality research journals and databases to a plethora of quasi-medical sites offering generalised consumer information. As a result it is nearly impossible for practitioners to keep abreast with emerging/new primary research findings.[143] In addition, the endless range of publications makes it increasingly difficult to sift good quality research findings from a sea of plausible yet misleading, biased, industry-based, inadequately reported research findings.[143] Modern health professionals, policy makers and consumers require high quality information from a wide range of sources that will provide information on the feasibility, appropriateness, meaningfulness and effectiveness of large numbers of health-related interventions.[143, 144]

Sometimes the lack of expert input can lead to misunderstandings or may even create a false belief in essentially unreliable information which could potentially lead to health risks for the patients/consumers. Individual articles on a single topic could run into the many hundreds or even thousands.[143] Taken individually they may produce unclear or even confusing and contradictory findings. The reader has no real way of discerning whether findings from another country are applicable to their own circumstances. Valuable insights or findings may be presented in a language other than that of the consumer's and thus remain undiscovered.[143]

Thus traditional narrative synthesis has been plagued by publication and selection biases in addition to possibly the most serious flaw, i.e. the lack of any systematic method for assigning where the weight of the evidence lies.[140, 142] Too much weight can be given to large studies which are more likely to produce statistically significant results, while insufficient attention is paid to the quality of a study and the lack of differentiation between treatment effect sizes.[145] Thus a need for more structured critical exploration, evaluation and synthesis of relevant data to provide quality assessment and critique to inform practice is needed.

1.4.2 Method of synthesis

In 1976, Gene Glass introduced a new systematic method of searching literature, describing and combining study findings and presenting statistical analysis of combined study results through a method he called meta-analysis.[146] In contrast to a traditional narrative review, the statistical procedures of a meta-analysis provides a more objective assessment of the evidence, and a more precise estimate of effect size.[147, 148] Meta-analysis aims to make research synthesis an objective science as opposed to a subjective art.[145] The major contribution of Glass' new method is well described by Manchikanti et al. as 'the application of scientific strategies that limit bias by the systematic assembly, critical appraisal, and synthesis of all relevant studies on a specific topic.'[145(p819)] The statistical process of meta-analysis is usually the last step in a systematic review. By the late 1970s medical researchers were incorporating appropriate findings from behavioural and social sciences in addition to their empirical findings. Fifteen years later meta-analysis statistical methods are being re-evaluated, examined and published in conjunction with a growing realisation that RCTs are not the only form of empirical evidence appropriate to include in a systematic review.[149, 150]

The contemporary systematic review can be based entirely in quantitative or qualitative paradigms with a new emerging trend recognising the richness of incorporating both qualitative and quantitative evidence to inform EBHC.[151] Strategies for synthesising qualitative and quantitative evidence can range from the interpretive to the integrative respectively and employ an array of methods such as narrative summary, grounded theory, meta-ethnography case survey and Bayesian meta-analysis, depending on the type of question being addressed.[149, 150]

The systematic review differs significantly from a narrative review in that it is based on a carefully framed question and an a priori protocol which sets out the objective guidelines for its conduct, including details of the types of studies, population and context, intervention, comparator and outcomes which will be subject of the systematic review. The process of the systematic review aims specifically at minimising potential sources of biases arising through the researcher, publication, citation and selection or through risk of assessment.[140]

In systematic reviews all relevant published and unpublished evidence are gathered, and studies for inclusion are selected by applying the protocol guidelines, the methodological quality of each study is critically appraised by two independent reviewers, and the data extracted and synthesised. Results are summarised by application of a scientific methodology that is both explicit and transparent.[152] Transparency is vital to show no 'cross contamination' between the researcher and their chosen topic.[139] Conclusions should be drawn in a balanced and impartial manner to inform implications for practice and highlight any research gaps.

1.4.3 What constitutes best evidence

Healthcare has an inseparable association with evidence. Evidence underpins political decisions affecting healthcare policy and allocation of economic resources, which in turn directly affects institutional policy making, practitioner guidelines and ultimately evidence-based patient choice.[153] The debate about what constitutes best evidence in ongoing. Systematic reviewers gave credence to what Slavin[142] termed as 'best evidence' in an approach to excluding lower quality studies where sufficient higher quality studies existed as a method of evidence prioritising.[154] The importance of RCTs and the tacit designation of 'gold standard' evolved out of the concept of evidence having an inherent hierarchy.[134, 145] RCTs are designated top of the hierarchy of evidence and thus meta-analysis of RCTs

is deemed to provide an even higher level of evidence. Therefore properly conducted RCTs are much more likely to inform than mislead when deciding whether an intervention or treatment will do more good than harm.[126] Nevertheless the majority of medical research is observational with bias, lack of detail and poor reporting, making it very difficult to assess strengths or weaknesses of the studies, hindering generalisability of mixed results.[145] In some instances it is not possible to actually apply the principles of an RCT to answer a clinical question or assess the effectiveness of an intervention.[155] Other study designs such as quasi RCTs, cohort, cross sectional or descriptive case series may be all that are available as 'best evidence'.

Over time it became increasingly clear that 'best evidence' was subject to variable interpretation and that the quality of systematic reviews was in turn highly variable.[149] EBM and specifically EBHC have had to develop proformas for undertaking and reporting systematic reviews. Standard procedures have been developed with a view to providing transparency and rigour to all steps of the systematic review process (starting with the registration of an a priori protocol) and indeed research reporting in general, for example, the National Institute for Clinical Excellence (NICE),[156] Strengthening the Reporting of Observational Studies in Epidemiology (STROBE),[157] Preferred Reporting/Items for Systematic Reviews and Meta-Analyses (PRISMA)[158] Consolidated Standards of Reporting Trials (CONSORT).[159]

1.4.4 Different forms of evidence

Much recent assessment of progress and innovation in healthcare has resulted from utilising the outcomes of quantitative systematic reviews and meta-analyses However, quantitative evidence is only one form of evidence available to the health practitioner, a philosophical point raised by Sackett et al. proposing that 'The practice of evidence-based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research'.[135(p71)] This knowledge base aims to be holistic in its inclusiveness of evidence from scientific and non-scientific sources applied via the professional judgment of the clinician, with respectful consideration of patient preferences and the context in which the healthcare is being delivered.[160]

1.5 Methodological basis of the chosen approach to synthesis

This systematic review examining the effectiveness of laser therapy for onychomycosis in adults in a community setting was based on the Joanna Briggs Institute methodology assessing quantitative evidence for the effectiveness of an intervention, utilising the JBI-SUMARI software package incorporating the JBI comprehensive Review Management System (CReMS) and specifically the Meta Analysis of Statistics Assessment and Review Instrument (MAStARI) to critically appraise and then extract data from the included studies. Methodological quality in a JBI systematic review is determined by critical appraisal undertaken by two independent reviewers using standardised instruments.

In the first instance RCTs and quasi-RCTs were considered. None meeting the inclusion criteria were found. Cohort studies and descriptive case series studies have been included in this systematic review. These types of studies are considered to be less robust, lacking the experimental design element of random allocation to an intervention[145] and they rely on the association between changes in one characteristic or differences in an outcome, for example, the amount of clear nail growth post laser therapy. Nevertheless observational studies in a community setting provide useful data needed to assess the effectiveness of an intervention and have a long history of being applied to situations where exposures might cause injury or disease.[155] These studies have been included on the basis that they are the current 'best' evidence available. There have been numerous publications reporting on laser therapy for onychomycosis treatment but they are opinion based and often thinly disguised industry advertising and were not considered for inclusion.

The data extracted from seven included studies (two cohort and five case series) using MAStARI had significant heterogeneity. As a result, meta-analysis of the included studies was not undertaken due to the inherent biases and differences in study design, populations and the interventions measured outcomes and reporting. Thus the results and outcomes prescribed in the a priori protocol of this systematic review are reported in narrative form.

1.6 Definition of terms

The medical condition, onychomycosis (Tinea unguium), refers to a chronic infection of the finger or toenails caused, in the main, by the dermatophytes *Trichophyton rubrum*, *Trichophyton mentagrophytes* var. *interdigitalis, Epiderophyton floccosum, T tonsurans* and a suite of dermatophytic fungi (*Fusarium* spp., *Aspergillus* spp., *Alternaria* spp.), and saprophytic moulds such as *Scopulariopsis brevicaulis*, *Acremonium* spp, *Scytalidinum dimidiatum* and *Scytalidinium hyalinum* and yeasts, *Candida* species.[17, 21]

Chapter 2: THE SYSTEMATIC REVIEW PROTOCOL

This chapter provides a descriptive overview of the systematic review method, inclusion and exclusion criteria, search strategy, and the critical appraisal, data extraction and data synthesis processes.

2.1 Review question/objectives

The objective of this systematic review was to identify, critically appraise, synthesise and present the best available evidence for the effectiveness of laser treatments on onychomycosis of the nails in adults living in the community.

The specific review question addressed was the following:

Can laser treatment of onychomycotic nails produce outcomes comparable to the current 'gold standard' treatment of oral terbinafine over a minimum 12 week treatment period for adults living in the community?

2.2 Types of studies

Initially it was anticipated that there would be a small number of research papers due in part to the newness of the technology itself and the cost of laser equipment being prohibitive for many health practitioners. Therefore it was not unreasonable to anticipate that experimental designs would involve small numbers of participants, be statistically unsophisticated, and reflective of ease of recruiting, short time commitment and economic constraints. Thus finding RCTs or quasi RCTs was not anticipated. Nevertheless one RCT and a follow-up study were found.[114, 161] These were funded exclusively by Nomir Medical Technologies Inc. with the end points of the initial study 'specifically chosen to demonstrate clinical efficacy and safety.'[161(p169)] The lead author was contacted to seek clarification regarding the inclusion of participants with type 1 and type 2 diabetes and since the answer was in the affirmative this RCT and the follow-up study did not meet the inclusion criteria set out in the a prioiri protocol for this systematic review and were not considered further.

Prospective cohort studies and descriptive/case series studies were included in this systematic review. Cohort studies are observational in nature, identifying participants with a specific set of characteristics as a 'cohort' and providing a framework in which participants can be followed over time. Cohort studies can be utilised to measure changes

or outcomes over a time period and to relate these back to the initial start point. In the case of this review an example would be the amount of clear nail growth post laser therapy. Case series studies tend to be exploratory in nature, providing outcomes that are not necessarily definitive but pointing the way to new areas of research, assisting in the formulation of new hypotheses. This could be particularly useful and appropriate when investigating a new intervention such as laser therapy for the 'temporary increase of clear nail in onychomycosis'. There has been ongoing debate in relation to these types of studies being included in systematic reviews and particularly meta-analysis due to their susceptibility to a variety of biases. Shrier et al.[162] proposed the idea that well-conducted observational studies were not automatically more biased than well-conducted RCTs and that excluding observational studies a priori from systematic reviews ran counter to an evidence-based approach. Two cohort and five descriptive/case series studies were included in this systematic review because they are the current 'best' available evidence of laser therapy for onychomycosis in adults in the community.

2.3 Types of participants

Studies with males and females from any ethnicity and demographic living in the community were considered. There were various age cut-off points where individuals were designated adult for the purpose of participating in trials. This review considered individuals 18 years and over as adults, based on the legal adult age applied in Australia. In addition, laser therapy treatment can be dangerous and responsible health practitioners would be seeking informed consent prior to commencing a treatment regimen. Consideration was given to participants with either fingernail and/or toenail onychomycosis infection. Often individuals will demonstrate both fingernail and toenail fungal infection; however, all infections start with one presentation. Confirmation of the infecting organism was paramount for the reasons outlined in 1.1.2.2. Individuals with compromised immune systems and pregnant females were excluded because the full spectrum of the effects of laser therapy on biological tissues is currently speculative.

2.4 Types of interventions

Laser technology and its application to medical conditions is a rapidly expanding area and this systematic review aimed to be as inclusive of any laser technology applied to onychomycotic nail conditions as possible given these rapid advances.

2.5 Comparators/context

Terbinafine has been government approved for treatment of onychomycosis in all countries and is the current gold standard oral treatment at the rate of 250mg per day for 12 weeks for toenail infection, and 250g per day for six weeks for fingernail infection (refer 1.1.4.3). [74] Terbinafine is a synthetic allylamine antifungal that is highly lipophilic in nature with a tendency to accumulate in skin, nails and fatty tissues.[15] Cytochromes P450 are a group of heme-thiolate monooxygenases present in the liver involved in an nicotinamide adenine dinucleotide phosphate (NADPH)-dependent electron transport pathway which oxidises a variety of structurally unrelated compounds, including steroids, fatty acids and xenobiotics, and contributes to the wide pharmacokinetics variability of the metabolism of drugs such as warfarin, diclofenac, phenytoin, tolbutamide and losartan.[40] Terbinafine inhibits ergosterol synthesis by inhibiting the fungal squalene monooxygenase (squalene 2, 3-epoxidase), an enzyme integral to the fungal cell wall synthesis pathway. The resultant high concentration of squalene and reduced amount of ergosterol are both thought to contribute to terbinafines' antifungal activity.[40, 76]

2.6 Types of outcomes

The primary outcome measures pertinent to this systematic review were cure or clinical response. A great deal of published research relating to treatment of onychomycosis has been bedeviled by a lack of clarity in defining exactly what is meant by cure. This systematic review defined 100% cure in accordance with the FDA guideline which is considered the best interim evidence of a new drug's efficacy, that is, negative KOH microscopy or PAS samples in conjunction with negative mycological culture results, in addition to 100% normal nail appearance. This is the strictest guideline for cure. However, there is a consensus that what is termed a mycological cure where there is negative KOH microscopy, or PAS samples and negative culture results, are adequate to claim cure. In the case of onychomycosis this arises from clinical knowledge that nails can remain malformed and imperfect in appearance as a result of external factors irrespective of any fungal involvement. Thus clinical response in this systematic review was defined in terms of a minimum of 3mm clear nail growth in a three to 12 month period or negative KOH microscopy, or PAS samples and negative culture results. The chosen rate of nail growth is within the range of expected nail growth for healthy adult males and females.

Secondary outcomes given consideration in this systematic review included:

- Compliance of participants which was assessed by their attending clinics for their treatments.
- Recurrence of infection identified by microscopy and or culture techniques for viable fungal elements at follow-up at six months and/or 12 months minimum time frame.
- Presence or absence of adverse effects. Adverse effects of interest included skin irritation (erythema) in the area adjacent to a treated nail, nail discolouration, onycholysis and periungual burning sensation.
- Client satisfaction with treatment.

2.7 REVIEW METHODS

2.7.1 Search strategy

The search strategy for this systematic review followed the standard procedures utilised by the Joanna Briggs Institute (JBI). Initially the JBI Database of Systematic Reviews and Implementation Reports and the Cochrane Current Controlled Trials Register were searched to ascertain if this or any similar previous systematic review had been undertaken or was planned. No other systematic review on the effectiveness of laser therapy for onychomycosis in adults living in the community was found. No other systematic reviews pertinent to this topic have been found since the completion of this research.

The search strategy utilised in this search aimed to find published and unpublished literature in the English language published between 1 January 1985 up to and including 30 June 2013. Laser technology is a new and rapidly advancing technology and this review was limited to publications in the date range of 1 January 1985 to 13 June 2013, on the assumption that it was highly unlikely that there would be relevant experimental data published prior to 1985. An initial search of MEDLINE/PUBMED and CINAHL was undertaken using the keywords laser, light therapy, mycoses, onychomycosis and *Trichophyton rubrum* followed by an analysis of the text words contained in the titles and abstracts, and of the index terms used to describe identified citations (Appendix III). A second search using all identified keywords and index terms was then undertaken across CINAHL, EMBASE, PUBMED, SCOPUS, PUBGET, Google Scholar, Web of Knowledge

and Web of Science databases. Appendix IV provides further details of the search strategy employed. Unpublished studies were searched for in MedNar, and ProQuest Database of Theses and Dissertations, and conference proceedings. Secondly, after scanning the citations returned from the databases, full text articles were retrieved for those abstract citations which appeared to match the inclusion criteria. Thirdly, the reference lists of all retrieved publications were searched to find any additional relevant papers. Eight authors of research presented as conference posters or abstracts were contacted to enquire about any unpublished data/studies; most did not reply. *ClinicalTrials.gov* register was searched for registered, ongoing, complete or incomplete trials and relevant authors contacted. One laser manufacturer was contacted for clarification of experimental methods for a published trial.

2.7.2 Assessment of methodological quality

Papers that met the inclusion criteria after examining the full text were taken through to the critical appraisal stage of the review process. These papers were assessed for methodological quality by two independent reviewers (HJG primary reviewer and either CL or KL) using the standardised critical appraisal instruments from the Joanna Briggs Institute MAStARI (Appendix V). Consistency between reviewers was maintained by adherence to the critical appraisal instrument descriptions. The standardised comparable cohort/case control studies appraisal instrument was applied to two cohort studies[163, 164] (Table 3.3) and the standardised descriptive/case series appraisal instrument was applied to seven case series studies. Five included studies[165-169] are presented in Table 3:4 and two excluded studies[170, 171] in Table 3:5. Both critical appraisal instruments include a total of nine questions to assess the validity of each study. Individual questions were rated as Yes, No, Unclear, or Not Applicable (N/A). Following each reviewer's independent appraisal, any discrepancies were identified by the primary reviewer (HJG) and discussed subsequently by both reviewers. Consensus was reached by discussion where differences in appraisal occurred and both reviewers were in agreement regarding studies, thus a third reviewer was not required to adjudicate.

The cohort study conducted by Zhang et al.[164] selected a cohort of patients from individuals attending the dermatology department of a hospital with an age range of 18-75 years, a disease duration range from two months to 15.5 years, and twice the number of females to males. There is clear selection bias and gender bias. Nevertheless it would be

reasonable to expect more females than males to attend for dermatology treatments, and the age range and disease duration are appropriate to indicate that the selected participants are representative of the population as a whole.

Participants were allocated randomly utilising the process of casting lots into two roughly equal groups and then the number of infected nails was assessed using the Scoring Clinical Index for Onychomycosis (SCIO) formula for assignment of individuals to sub groups A, B, and C. Allocation bias occurred as there was no blinding of participants or researchers either for the SCIO assessment and subsequent sub-group allocation. Utilising the SCIO does indicate that similar disease conditions prevailed.

Although problematic, the researchers endeavoured to minimise biases in selection of cases by ending up with comparable mean age, disease duration and number of infected nails to be treated per group. It was unclear if potential confounding factors were accounted for. The researchers used objective assessment criteria of treated nails at baseline and 8, 16 and 24 weeks. Follow-up time was rated U as it was unclear if the final assessment was actually carried out 24 weeks after the final stated treatment at 21days post baseline. Researchers stated that when adverse reactions occurred treatment was terminated, they excluded these cases from their calculated effective rate but included them in the occurrence rate of adverse reactions. This may account for what appear to be study discrepancies in the total numbers of nails in Table 4 in their article. There are no numbers given for adverse reactions per se; there is no clarity in the study design or execution. Experimental outcomes were measured using standard objective microscopic and fungal culture techniques. Statistical methods were appropriate, albeit expressed as percentages.

The cohort study by Nicolopoulos et al.[163] demonstrated selection, population and possibly gender bias. Their participants were not representative of the population as a whole as nail avulsion was a last resort treatment for long term or recalcitrant onychomycotic infection indicating that clients were at a similar disease point and the study participants were by inference individuals seeking treatment for an existing condition. There was no indication of the number of males or females in the cohort. This paper had discrepancies in participant numbers and the lead author was contacted to clarify several issues including number of participants in each treatment group. There were cultural/linguistic difficulties compromising this study's critical appraisal as the primary reviewer was unable to satisfactorily determine what the researchers intended in relation to minimising biases and

confounding factors in their study. The outcome of clear nail growth was assessed objectively with adequate follow-up carried out at six and 12 months post treatment. It was noted that the researchers reported three participants lost to follow-up with no reasons given and the outcomes for these participants were not described or included in the analysis. Nail re-growth was assessed by clinical examination which is a reliable methodology. The authors used Minitab software for analysis of variance which allows for comparisons between more than two groups and then applied a Tukey test method to assess where the significant group differences occurred. These are appropriate statistical tests for investigating these data.

The seven descriptive/case series studies[165-171] which underwent independent critical appraisal comprised populations selected from a client base attending five different dermatology clinics and one case study of an individual seeking treatment. In all studies there was no randomisation or pseudo randomisation of participants who were already clients seeking treatment of their own volition which in itself is source of a population bias. Therefore these samples were derived from selection bias in the first instance. Inclusion criteria were clearly defined for five studies[165-169] and not clearly defined for two studies.[67, 170]

The study by Hochman[165] identified nail thickness and potential reinfection as confounders but there were insufficient details to glean if their impact was actually assessed. Three studies stated their strategies for dealing with confounding factors such as nail thickness.[167-169] Two studies did not identify any confounding factors.[170, 171] All descriptive case series studies objectively assessed their outcomes.[165, 167-171] There were no comparator groups in any study. Follow-up time was unclear in the study by Dan et al.[171] All other studies had adequate follow-up time.[165-170] No participants were reported as withdrawing from any study with the exception of Dan et al.[171] where it was unclear if any participants withdrew. There was also lack of clarity surrounding outcome measurement and statistical analysis with regard to the study by Dan et al.[171] The study by Bunyaratavej et al.[170] used reliable outcome measures and statistical analysis was not applicable to outcomes for one participant. The remaining five studies[165-169] used reliable outcome measures and appropriate statistical analysis (percentages).

An appraisal score of 50 percent of answers in the affirmative for any appraisal instrument was considered sufficient to include the study. For all studies appraised a score of five Yes out of nine or more, using either appraisal instrument, was the yardstick for inclusion in this

review. Two case series studies scored less than five out of nine and were subsequently excluded from this review (Table 3:5).

All the appraised studies had varying degrees of internal experimental bias. Due to a persistent lack of clarity (across a large body of published research) by researchers reporting insufficient detail of the processes used by them to identify the infecting organism in suspected onychomycotic nail infection, clarity of inclusion criteria was deemed of paramount importance. Objective assessment of outcomes and adequate follow-up timing were also deemed highly important for a study to be included. See Appendix VII for studies excluded after appraisal and the reasons for their exclusion.

2.7.3 Data extraction

Data was extracted from papers included in the review using the standardised data extraction tool from JBI-MAStARI (Appendix VI). The data extracted included specific details about the interventions, populations, study methods and outcomes of significance to the review question and specific objectives. Data extraction was undertaken solely by the primary reviewer (HJG).

2.7.4 Data synthesis

Ideally, quantitative data would have been pooled for statistical meta-analysis using JBI-MAStARI. The interventions utilised the outcome measures reported and the statistical analysis of each study were examined and then compared. Two cohort studies and five case series studies researching laser therapies utilised differing treatment regimens, disparate participant populations and study designs, and reported on different outcomes and follow-up time frames. Due to the heterogeneity of included studies statistical pooling was not possible and the findings are presented in narrative form using tables and figures to aid in data presentation where appropriate.

Chapter 3: RESULTS

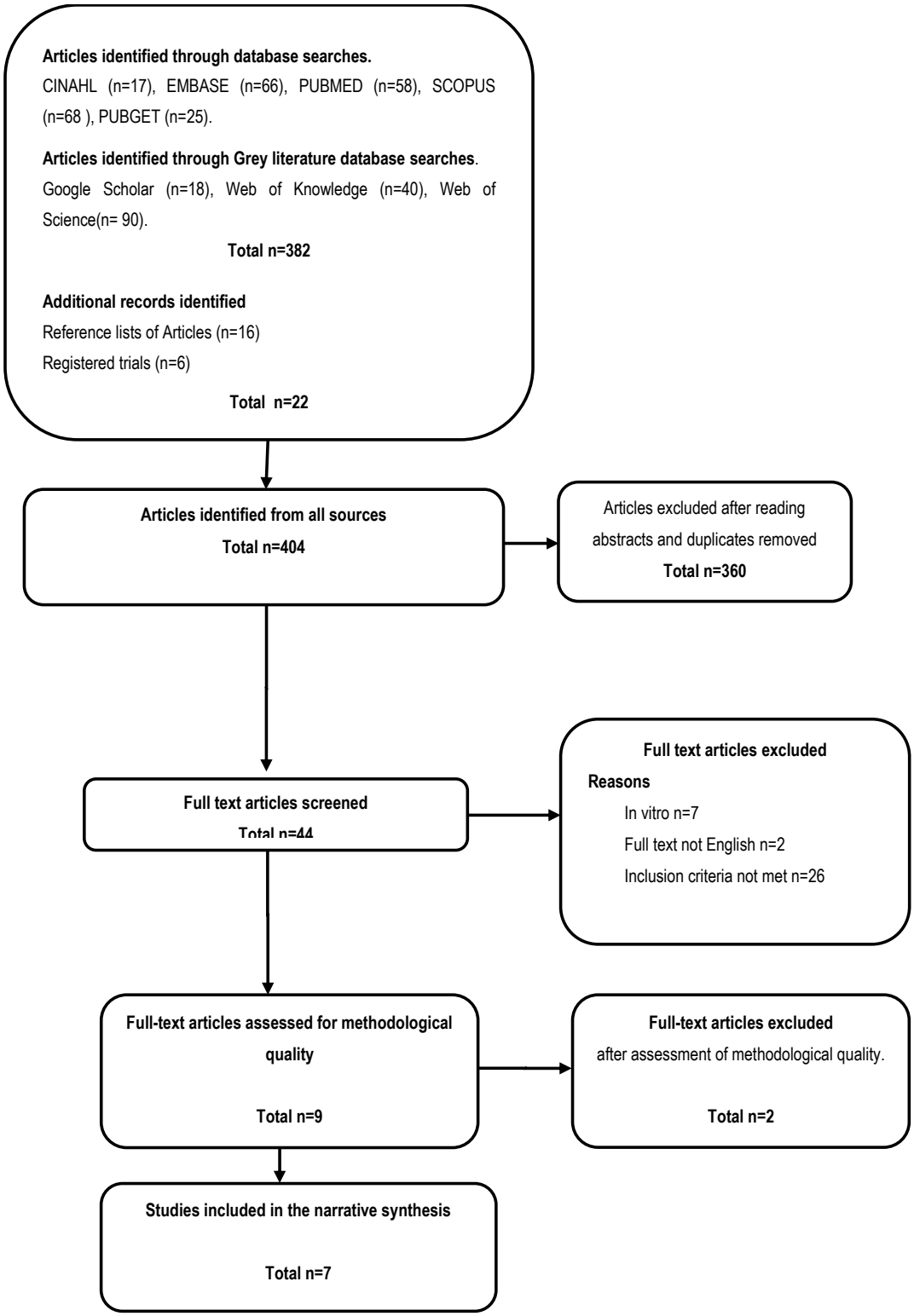
3.1 Description of studies

A comprehensive systematic literature search was undertaken following the three-step strategy outlined for the databases and grey literature sites named in the protocol.[1, 2] No additional studies were found searching MedNar or ProQuest Database of Theses and Dissertations and conference proceedings. One registered trial was found in the Cochrane Current Controlled Trial Register. A total of 382 citations were identified from the database searches (Figure 1). A further 22 were found through searching the reference lists giving an overall total of 404 citations. Three hundred and sixty citations were excluded after reading abstracts and removing duplicates. Forty-four full text articles were retrieved for detailed examination and, as a result, a further 35 were excluded because they failed to meet the inclusion criteria for this systematic review.

Nine studies were critically appraised for methodological quality by two independent reviewers and subsequently another two studies were excluded. Excluded studies together with the reasons for exclusion are presented in Appendix VII. A total of seven studies were included in the final analysis and their characteristics are presented in detail in Appendix VIII. These seven studies all investigated the effectiveness of laser treatment for onychomycosis using interventions including:

- Nd:YAG 1064nm laser with differing parameters of patterns of delivery, number of pulses per nail, spot size, fluence, pulse frequency, pulse duration, number of treatments per session, number of sessions and timing, pre-treatment and post treatment regimens.
- Carbon dioxide (CO_2) laser surgical removal of the onychomycosis nail plate and treatment of the nail bed and matrix with adjunct regimens of gallium aluminum arsenide (GaAlAs) 830nm diode laser, helium neon (HeNe) laser.

Figure 1: Flow diagram of search results and subsequent process of review



3.2 Search results

Seven studies with a total of 474 participants were included in this review. Two were prospective cohort studies and five were case series studies. All included studies were in the 1999-2013 date range.

Participants were adults over the age of 18 (age range 18-75 years) with at least one fingernail or toenail diagnosed with onychomycosis by direct microscopy using KOH or PAS techniques and/or mycological culture. All studies were conducted in private dermatology clinics or hospital outpatient dermatology clinics, in northern hemisphere locations in China,[164] Greece,[163] Japan,[166] United States of America,[165] Serbia,[168, 169] and the Ukraine.[167]

The cohort studies by Zhang et al.[164] and Nicolopoulos et al.[163] included 33 participants in the age range of 18-75 years and 78 participants with a mean age of 56 years, respectively. Two case series studies, Hochman[165] and Kimura et al.[166] included participants with an age range of 48-91 years, (mean 66.6 years) and 37-88 years (mean 68 years) respectively, while in the case series studies by Kolodchenko,[167] Kozarev [169] and Kozarev 2011[168] the age ranges were 18-74 years, (mean 39.4 years) and 18-45 years, (no mean given) respectively. There were approximately double the number of females to males in two studies, Kolodchenko[167], and Kimura et al.[166] while in Hochman[165] there were three females and five males. Neither of Kozarev's studies[168, 169] provided gender breakdown data. Kolodchenkos' study[167] was the only one that noted Fitzpatrick skin types.[172]

One cohort study, Zhang et al.[164] and all five case series studies, Hochman,[165] Kimura et al.,[166] Kozarev,[169] Kozarev 2011[168] and Kolodchenko,[167] used Nd:YAG laser source with a 1064nm wavelength and various fluence, spot size, pulse duration and frequency settings. Zhang et al.[164] and three case series studies, Kozarev,[169] Kozarev 2011[168] and Kolodchenko,[167] used long pulsed Nd:YAG laser equipment. The remaining two case series studies, Hochman[165] and Kimura et al.,[166] used short pulsed Nd:YAG laser equipment. None of these six studies included a comparator or control group (Table 3:1).

Table 3:1 Summary of interventions for one cohort study and five case series studies using Nd:YAG 1064 nm

	Long-pulsed Nd:YAG			Short-pulsed Nd:YAG	
	Pinpointe ™Footlaser™	SP Dynamis Fotona, Slovenia	Dualis SP,Fotona, Slovenia	LightPod Neo™	Equipment loan from Cutera
STUDY	Zhang et al. [164]	Kolodchenko [167]	Kozarev [169] & Kozarev 2011[168]	Hochman[165]	Kimura et al [166]
INTERVENTION					
Photographs(months)	No	0, 3, 6,12	0, 6, 9,12	0, 2, 4-6	0, 1, 2, 3, 4, 5, 6
Fluence (J/cm^2)	240 - 324	35 - 40	35 - 40	223	14
Spot size (mm)	3	4	4	2	5
Pulse (ms)	30	35 - 40	35	0.65	0.3
Frequency (Hz)	1	Not stated	1	Not stated	5
Cooling	Not stated	Yes	Yes	None	None
Pattern	Spiral	Not stated	Spiral	Crisscross	Crisscross
Time taken/Tx	~6mins	Not stated	Not stated	~45secs/nail	1-2min/nail
Area treated	Nail plate	Nail plate +skin	Nail plate	Nail plate	Nail plate
Number of passes/Tx	3	2	3	2	2
Number of Tx	4 or 8	4	4	2 or 3	3,2,or,1
Timing of Tx (week)	1	1	1	3	4 or 8
Additional Tx	None	None	None	Topical Terbinafine	None
Client intervention	None	n=6 filed nails to thin	n=3 nails thinned with topical Tx (2010 study only)	Nail thinning and trimming	None

J/cm^2 Joules per centimetre squared: mm= millimetre: ms= millisecond: Hz= Hertz: Tx= treatment: sec=seconds: mins=minutes.

In the cohort study by Nicolopoulos et al.[163] all participants underwent CO_2 laser nail plate avulsion and were then allocated to groups A, B or C with different post-surgical treatment regimens. Table 3:2 summarises the reported number of participants in each treatment arm; however, there is more than one discrepancy in the text regarding the total number of participants, i.e. 73 or 78 and the total numbers receiving each treatment regimen, i.e. group A n=28 or 30, group B n=28 or 30, group C n=15 or 23. These may just be typographical errors that remained uncorrected. Three participants were lost to follow-up with no reasons given.

Table 3:2 Summary of interventions for cohort study by Nicolopoulos et al. [163]

	Group A n=28††	Group B n=27††	Group C n=23††
Post-surgery treatment	Terbinafine	GaAlAs, HeNe Low Level Laser	Placebo
Frequency of treatment	Daily until healing complete	2 weeks with a 3 day interval	NIL

†† Numbers of participants stated in Nicolopoulos et al.[163(Table 1,p183)]

Three case series studies, Hochman,[165] Kolodchenko[167] and Kozarev[169] addressed the issue of nail thickness. Hochman[165] encouraged all eight participants to file their nails to reduce nail thickness, and trim them to keep nail length to a minimum to maximize the penetration of the topical antifungal cream they were given to apply between laser treatments. Kolodchenko[167] had six participants with hyperkeratotic nails file their nails to reduce thickness to improve penetration of the laser beam. Kozarev[169] had three participants use a chemical pre-treatment on thick dystrophic nails to reduce nail thickness. All case series studies undertook a series of photographic records over a time range from 0 to 18 months. Neither cohort study[163, 164] reported taking photographs of participants nails prior to, during or after laser treatments. The characteristics of all included studies are presented in Appendix VIII.

3.3 Methodological quality

The critical appraisal scores for the two cohort studies, Zhang et al.[164] and Nicolopoulos et al.[163] are presented in Table 3.3. Studies scored six and five out of nine respectively when

critically appraised against the nine questions applicable to comparable cohort /case control studies.

Zhang et al.[164] provided details of gender, age and disease duration whereas Nicolopoulos et al.[163] did not. Zhang et al.[164] applied SCIO[173] to rate disease severity for every participant and although Nicolopoulos et al.[163] did not specifically state disease severity for participants, in clinical practice, surgical avulsion is generally only offered to clients with severe recalcitrant onychomycosis. Thus by implication, participants in this study are at the same disease stage.

Both cohort studies had selection bias as neither participants nor researchers were blinded when assigning participants to groups. It was unclear if confounding factors were taken into account by either study. Outcomes were measured using objective criteria, and there was a stated follow-up time minimum of six months for both studies, although Zhang et al.[164] was rated 'unclear' due to lack of clarity regarding timing between final treatment and follow-up commencing. Neither study described or included outcomes for people who withdrew. Outcomes were measured reliably and appropriate statistical analysis used in both studies.

Table 3:3 Critical appraisal scores for comparable cohort/case control studies

Study	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Zhang et al.[164]	Y	Y	Y	U	Y	U	N	Y	Y
Nicolopoulos et al. [163]	N	Y	U	U	Y	Y	N	Y	Y

Five case series studies Hochman,[165] Kimura et al.[166] Kolodchenko,[167] Kozarev,[169] and Kozarev 2011,[168] were critically appraised against the nine questions of the critical appraisal checklist for descriptive/case series (see Appendix V). Scores appear in Table 3:4.

All studies included populations of adult individuals over the age of 18 years who had been diagnosed with onychomycosis and were recruited from an existing patient/client base by the various researchers. All studies were internally biased, providing treatment to participants already seeking/being treated at a dermatology clinic. None of the studies

blinded participants or researchers to treatments or outcomes. There were a small number of participants in all studies. Hochman,[165] eight; Kimura et al.,[166]13; Kolodchenko,[167] 108; Kozarev,[169] 162; and Kozarev 2011[168] 72. There were no groups or subgroups involved and hence a description was superfluous. No participants were reported by any study to have withdrawn, thus inclusion of outcomes were not required. All included studies clearly defined their inclusion criteria. Kolodchenko[167] and Kimura et al.[166] included participants irrespective of disease severity. Kolodchenkos' study,[167] the 2010 study by Kozarev[169] and the follow -up study by Kozarev 2011[168] scored six out of nine against the critical appraisal criteria because the researchers clearly identified nail thickness as a confounding factor and implemented a treatment regimen to address this in their experimental design. Hochman[165] acknowledged variable nail thickness as a confounding factor but relied on participants' compliance to self-administer a nail thinning and trimming regimen to address the issue. All five studies utilised reliable measurement of outcomes and appropriate statistical analysis.

Table 3:4 Critical appraisal scores for five included descriptive/case series studies

Citation	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9
Hochman[165]	N/A	Y	U	Y	N/A	Y	N/A	Y	Y
Kimura et al.[166]	N/A	Y	N/A	Y	N/A	Y	N/A	Y	Y
Kolodchenko [167]	N/A	Y	Y	Y	N/A	Y	N/A	Y	Y
Kozarev 2010[169]	N/A	Y	Y	Y	N/A	Y	N/A	Y	Y
Kozarev 2011[168]	N/A	Y	Y	Y	N/A	Y	N/A	Y	Y

N/A= Not applicable, U=Unclear, Y=Yes, N=No

Two descriptive/case series studies Bunyaratavej et al.[170] and Dan et al.[171] scored three out of nine and one out of nine respectively when critically appraised against the nine questions for descriptive case series studies critical appraisal instrument (see Table 3.5).

Table 3:5 Critical appraisal scores for two excluded descriptive/case series

Bunyaratavej et al.[170]	N/A	N	N	Y	N/A	Y	N/A	Y	N/A
Dan et al.[171]	N/A	N	N	Y	N/A	U	U	U	U

These studies were shown to have a number of deficiencies highly likely to impact on study integrity and generalisability of results in relation to design, clinical context, appropriate patient population and description of the exposure/treatment, and were therefore excluded from further consideration (Appendix VII).

3.4 Overview of studies

3.4.1 Outcomes results data

For ease of reference, Table 3:6 summarises outcomes for the cohort studies by Zhang et al.[164] and Nicolopoulos et al.[163]

3.5 Primary outcomes

3.5.1 Cure or clinical response

Zhang et al.[164] assessed the effectiveness of their laser treatment according to four grades, defined as recovery (full-grown new nail with a smooth plate and bright colour with <5% defects), significant effect (≥60% newly grown nail), improvement (≥20% and <60% newly grown nail) and inefficacy (<20% newly grown nail). The recovery rate plus the significant effect rate were combined to arrive at the effective treatment rate. Zhang et al.[164] divided their 33 participants into two groups and then assigned the infected nails of the participants a disease severity rating according to SCIO.[173] The infected nails of participants in each group were then assigned to three sub-groups accordingly, A (II Degree 6 ≤SCIO <9), B (III Degree 9 ≤ SCIO <12), and C (IV Degree 12 ≤SCIO <15). Microscopic examination and culture samples from all 33 participants were assessed for fungal elements. Treatment group one received two laser treatments and treatment group two, one laser treatment. No statistically significant difference was found in the treatment effective rates between treatment groups one and two, and between treatment groups one and two or their subgroups (A, B, and C) (data not shown). The authors noted that

subgroup C (in both groups one and two) included >50% severe cases of onychomycosis, which might have influenced their results.

Table 3:6 Summary of outcomes for cohort studies by Zhang et al.[164] and Nicolopoulos et al.[163]

STUDY	OUTCOME	TIME (weeks)			
Zhang et al.[164]	CURE	0	8	16	24
	+ve microscopy % participants N=33	100	21	17	21
	+ve culture % participants N=33	36	12	15	8
	CLINICAL RESPONSE				
Zhang et al.[164]	Effective rate Mean % nails treated	Group 1 n=78	63	63	51
		Group 2 n=76	68	67(76)×	53
Nicolopoulos et al. [163]	Clinical examination of nails	Amount of clear new nail growth not reported at 6 or 12 months follow-up			

× Typographical error in Table 4 in the article[164]

Seventy-eight participants underwent CO_2 nail plate avulsion in the prospective cohort study by Nicolopoulos et al.[163] and were then assigned to three groups for post-operative interventions (Table 3:2). Clear nail growth was assessed at six and 12 months follow-up and based on clinical examination of nails. No measurement of nail growth was reported and there was no clarity regarding how the clinical examination was carried out. The reporting of statistical significance in relation to the final comparisons of groups is unclear. The researchers reported statistically significant difference between groups A (post-surgical topical antifungal medication, Terbinafine) and B (post-surgical low level laser treatment), ($P<0.005$) and between groups B and C (control group), ($P<0.005$) in terms of

measured mean healing time and pain score. They then reported no statistically significant difference between group A and control group C, but reported a significant p value, (P< 0.01)†. Several attempts have been made to seek clarification from the authors, and their response has failed to elucidate these discrepancies.

† Reported significance level taken directly from text of study.[163 (p183)]

Cure and clinical response results for case series studies by Hochman[165] and Kimura et al.[166] using short pulsed laser are presented in Table 3:7.

Hochman[165] reported seven participants had negative mycological culture results at 16 weeks demonstrating fungal eradication or cure. One participant had a positive culture result at 16 weeks which was attributed to overzealous nail thinning by the participant before and after laser treatments. Clear nail growth was assessed by means of visual nail inspection and comparison of photographs up to 40 weeks post treatment. Photographs of four participants only were included in the text, and no actual measurements of clear nail growth were reported

Kimura et al.[166] evaluated the preliminary data on the safety and efficacy of the sub millisecond Nd:YAG 1064nm laser in treating onychomycosis an average of 16 weeks post final treatment. The stated primary clinical endpoint was the overall improvement in onychomycosis as assessed by the level of clinical improvement in the appearance of the toenail and negative microscopic result if the toenail was completely clear. Kimura et al.[166] only assessed treated nails that showed 100% clear nail growth post treatment at 16 weeks using microscopy to demonstrate mycological cure. Clinical response was the overall improvement in the appearance of the nails measured by reduction of the Turbidity Score (Table 3:7).

Table 3:7 Summary of two case series studies Hochman[165] and Kimura et al.[166] using short pulsed Nd:YAG 1064 nm laser

STUDY	OUTCOMES	FOLLOW UP in weeks	
Hochman[165] N=8		16	40
	CURE -ve culture (number of participants n= 8)	7/8	
	CLINICAL RESPONSE Visual assessment via photographs of clear nail growth	no photos presented	4/8
	INEFFECTIVE +ve culture	1/8	
Kimura et al [166] N=13	CURE 100% clear nail growth plus -ve microscopy results (number of nails treated n=37)	19†/37	
	CLINICAL RESPONSE Overall improvement in Turbidity Moderate →Significant →Complete (number of nails treated n=37)	30/37	
	INEFFECTIVE/NO RESPONSE (number of nails treated n=37)	6/37	

†19 reported in the text (p499) but 18 in table 4 (p501)[166]

Summary of outcomes for three case series studies by Kolodchenko[167] Kozarev[169] and Kozarev 2011[168] using long pulsed Nd:YAG 1064 nm laser are presented in Table 3:8.

Kolodchenko[167] reported 89 participants as cured at 12 months follow-up. This figure included 80 with negative culture results and nine who showed clinical improvement. Clinical improvement, or clear nail growth, was evaluated from photographs taken at three, six and 12 months follow-up. Unfortunately neither the photographs nor any actual measurements of clear nail growth appeared in the text. Nineteen participants were non responsive to treatment. Kozarev claimed to have taken photographs at baseline, three,

six, nine and 12 months follow-up, but they did not appear in the study report, thus the amount of clear nail growth remains speculative.[169] At six months and 12 months all participants were fully cleared of fungal infections based on mycological culture and clinical evaluation. Kozarev's 2011 follow-up study reported 95.7% mycological clearance at three months, 98.8% clearance at six months and full clearance at 12 months.[168]

Table 3:8 Summary of three case series studies by Kolodchenko[167] Kozarev[169] and Kozarev 2011[168] using long pulsed Nd:YAG 1064nm laser

STUDY	OUTCOMES	Number of months			
Kolodchenko [167] N=108	**CURE** Mycological cure -ve Microscopy, -ve Culture	3	6	12	>12-30
		n=59	n=79	n=80	N/A
	CLINICAL RESPONSE Clear nail growth, visual and comparison with photos	n=12	n=12	n= 9	N/A
	INEFFECTIVE +ve for fungal elements	n=37	n=17	n=19	N/A
Kozarev [169] N=72	**CURE** Mycological cure -ve microscopy, -ve culture	n=69	n=72	n=72	N/A
	CLINICAL RESPONSE Clear nail growth, visual and comparison with photos	No measurement of clear nail growth stated. No photos attributed to study participants included in the text.			
	Fully clear nail plate, client assessment via phone call to 13 'cured' participants				100%
Kozarev 2011 [168] N=162	**CURE** Mycological cure -ve microscopy, -ve culture	95.7%	98.8%	100%	N/A
	CLINICAL RESPONSE Clear nail growth, visual and comparison with photos	No measurement of clear nail growth stated. No photos attributed to study participants included in the text.			
	Fully clear nail plate, client assessment via phone call to 46 participants				93.5% Unsure 6.5%
	INEFFECTIVE +ve for fungal elements	n=7 re-treated	n=2 re-treated	100%	

3.6 Secondary outcomes

3.6.1 Compliance

Apart from three participants in the cohort study by Nicolopoulos et al.[163] lost to follow-up with no reasons provided, all other participants in all the remaining included studies completed the experimental regimens.

3.6.2 Recurrence

Recurrence was noted by Zhang et al.[164] between two and four months after treatment, in five nails of three patients from group one and five nails of two patients in group two. The recurrence rate for all participants was not reported. Two participants infected with *T. rubrum* did not show any treatment effect at all during the treatment period or at any period post treatment in this study. However, the authors noted that both fungal microscopic examination and culture rates yielded more positives at 24 weeks than at eight weeks. Mycological effect was assessed by fungal microscopic examination for infective units and fungal culture growth before treatment and at eight, 16, and 24 weeks. Nicolopoulos et al.[163] reported recurrence of onychomycosis in three (non-compliant) patients who did not use Chlorhexidine disinfectant or the topical antifungal medication, Terbinafine, post-operatively. There is no mention of Chlorhexidine as part of the post-operative regimen in the 'method' section of this study. Thus it is unclear which participants used it and in what context.

Hochman[165] noted one participant had a positive culture result at 16 weeks which was attributed to overzealous nail thinning by the participant before and after laser treatments. Kimura et al.[166] reported a lack of response in six out of 37 nails treated. Neither Hochman[165] or Kimura et al.[166] reported on recurrence. Kolodchenko[167] re-treated 37 individuals found to be positive for fungal elements at three months. After the second treatment 17 participants remained non-responsive while two other participants became re-infected in the six to 12 months follow-up period. It is unclear if the six participants in Kolodchenkos' study[167] who thinned their nails by filing were included in the group of nine participants reported to have achieved only a 30-50% clinical improvement and never achieved mycological sterilization, and/or were included in the total number of 19 cases reported as non-responsive to treatment.[167] Ten non-responders had onychomycosis caused by mouldy floras identified as *Aspergillus niger* and *Candida* spp. Kolodchenko[167]

claimed to have cured four out of ten cases of *Candida* spp and zero out of three *Aspergillus niger* infection, in contrast to Kozarev[169] who claimed to have eradicated both these organisms.

Kolodchenko[167] utilised telephone interviews 18 months after treatment to ask 13 'cured' participants if their nails were clear and healthy in appearance. Thirteen reported remaining free of fungal infection, by visual inspection of their treated nails, 18 months after laser treatment.

Both of Kozarevs' studies[168, 169] reported complete clearance at 12 months and that laser treatment regimens were repeated for a small number of participants at three and six months. There were three participants in Kozarevs' study[169] who used a topical preparation to thin dystrophic nails and there were three participants who needed re-treatment at three months. Unfortunately there is no way of knowing, from the results presented, if these participants were one and the same. A very small number, 13/72 of the 'cured' participants, were contacted post 12 months follow-up by Kozarev.[169] Kozarev 2011[168] reported 12-18 months follow-up phone calls to 46 of the 'cured' participants, and 93.5% reported having fully clear nail plates and 6.55% were unsure if their nail plates were completely clear. However, none of the three studies, Kolodchenko[167] Kozarev[169] and Kozarev 2011,[168] reported specifically on recurrence.

3.6.3 Adverse effects

All studies reported no serious adverse side effects. Hochman[165] noted a temporary darkening under the nails of two clients which resolved several weeks after treatment. Kozarev 2011[168] reported a slight yellowish discolouration of nails post laser treatment. The number of affected participants was not reported, nor were further comments regarding this side effect. In addition, there was no mention if participants were concerned about the yellowish discolouration.

3.6.4 Participant satisfaction

The cohort studies by Zhang et al.[164] and Nicolopoulos et al.[163] assessed participant satisfaction. Zhang et al.[164] used four categories: not satisfied, generally satisfied, satisfied, and very satisfied. Four participants were not satisfied, six generally satisfied, 16 satisfied and seven very satisfied. Nicolopoulos et al.[163] assessed patient satisfaction in terms of time to heal and pain levels using a pain score ranging from ten as most severe pain, to

zero equaling no pain. Mean pain figures for each treatment group, A, B, and C, were reported as ten, four and nine respectively.

Hochman[165] and Kimura et al.[166] reported verbal responses of mild, easily tolerated discomfort. Kolodchenko[167] recorded 38 participants with no pain, 61 with mild pain and nine with medium pain. Kozarev[169] required participants to fill out a questionnaire after each treatment to evaluate the pain level on a five-point scale where zero was no pain, one mild pain, two moderate pain, three severe pain and four intolerable pain. These results were collated and averaged to give an overall figure of 26.39% of participants who had no pain (zero), 45.8% mild pain (one), 27.78% moderate pain (two) and no participants with severe (three) or intolerable pain (four). The only case series study to report on participant satisfaction was Kozarev[169] who reported all participants as satisfied with the treatment. In the follow-up study, Kozarev 2011[168] interviewed 46 participants who reported having no problems with their nails after treatment; however, this study did not report explicitly on participant satisfaction.

3.7 Review findings

There is a weak association by underpowered studies (JBI levels of evidence 3c cohort study with a control group,[163] 3e for observational study without a control,[164] and 4c for case series[165-169] [see Appendix IX]) that using a Nd:YAG 1064nm laser for the treatment of onychomycosis in adults over the age of 18 years living in the community could result in some clear nail growth in a 12-week period. This outcome may be more artifact than effect of intervention due to naturally occurring nail growth rates, improved participant foot hygiene practices and adjunct treatments such as nail thinning, topical antiseptic and/or antifungal application.

Chapter 4: DISCUSSION AND CONCLUSIONS

This chapter discusses the effect of the various laser interventions on outcome measures. The strengths and limitations of this review and implications for practice and research are discussed.

4.1 General discussion

The objective of this systematic review was to identify, critically appraise, synthesise and present the best available evidence for the effectiveness of laser treatments on onychomycosis of the nails in adults living in the community.

The specific review question addressed was the following:

Can laser treatment of onychomycotic nails produce outcomes comparable to the current 'gold standard' treatment of oral terbinafine over a minimum 12-week treatment period for adults living in the community?

The findings of this systematic review indicate that laser therapy has the potential to produce a result equivalent to the current 'gold standard' of oral terbinafine over a minimum 12-week treatment period. A mycological cure result of negative microscopy and culture results at 12 weeks was reported by three studies and at 16 weeks by one study.[167-169,164] Two studies reported a clinical cure at 16 weeks post laser treatment.[165, 166] Laser avulsion surgery may result in a clear new nail plate at 12 months.[163]

The sample sizes were very small and the lack of clarity, accuracy and transparency in reporting results together with the lack of blinding of researchers or participants during selection, allocation, intervention treatment and assessment of outcomes mean that the risk of bias for all included studies is high and the integrity of internal validity questionable.

The results from the included studies demonstrate that laser therapy can be applied to finger and toenail infections with a mycological etiology. All the included studies variously reported improvement in nail appearance, eradication of *T rubrum* and/or mouldy flora, and that there were no adverse side effects. None of the included studies however provided any reliable quantitative evidence to substantiate these claims.

It is not possible to attribute the reported outcomes of mycological cure in 12 or 16 weeks or even clinical response of clear nail growth solely to the laser intervention in any of the included studies. This is due to all the included studies utilising adjunct treatments, ranging from nail thinning via mechanical or chemical means, topical antifungal treatment, client

education regarding foot hygiene and most significant, variations in laser operational parameters on an ad hoc basis in the treatment regimen.

The included studies had very small numbers of participants and there was no mention of any duplicate/replicate samples being taken or assessed so as to test either the accuracy of sample collection and processing or to test any inter or intra operator error. Hochman[165] and Kozarev[169] both sent samples to an independent laboratory for mycological culture for growth and identification of the infecting organism(s).

Details of the method of sample collection were generally lacking. Timing of taking nail clippings for mycological examination from participants who used topical anti-fungal treatments pre- and post laser therapy could be a serious confounding factor as topical Terbinafine may be residual for up to seven days after treatment.[17, 174]

Utilising the amount of clear nail growth as a parameter for cure must be applied with caution as fungal infective elements indiscernible to the naked eye can remain lying deep within the cornified layer. This may suggest that the one participant who had a positive culture result at 16 weeks in the study by Hochman[165] where this was attributed to keeping the nails excessively thin, many have in fact been merely the participant who 'mined' into the residual infection in the cornified layer.

It has also been well documented that even if cure had been achieved, the appearance of the nail plate may have well remained disfigured or discoloured due to underlying etiology, or trauma.[15, 20] Thus, while it was very useful to have participants' feedback on comfort or pain of the actual laser intervention, it was interesting that not one included study addressed participant satisfaction with nail plate aesthetics. It would also have been very enlightening to have subgroup analysis for the participants who were deemed to have thick nails requiring extra treatments prior to receiving the laser intervention. There was also no mention of assessing participants for peripheral neuropathy or vascular insufficiency prior to inclusion in any study.

Clarity in reporting was lacking, with results for individuals mixed with results for infected nails and there was no way of matching an individual to their infected nails and the result of the laser treatment per individual.[164] Claims made were not always commensurate with the evidence presented, for example, in a trial where the age range was 18-45 years,[169] it does not seem reasonable for the author to conclude from the results presented that the method was useful for the 'broadest range of patients, especially the elderly '.[169(p7)]

Also, there were several instances of inconsistencies with the number of participants, treatments received and statistical significance, compounding interpretation of results from the included studies.[163, 164, 166, 167]

Both cohort studies, Zhang et al.[164] and Nicolopoulos et al.,[163] reported recurrence in very short time-frames of two-four months and ≤12 months respectively, which would generally be considered far more likely to be re-emergence of the original infection. One of the case series studies, Kozarev 2011,[168] attempted to gain some measure of recurrence/reinfection by telephoning participants 12-30 months after treatment; however, only a very small number of participants were contacted. None of the remaining studies reported in a meaningful way on recurrence or reinfection. Therefore the long term efficacy of laser treatment for onychomycosis remains unanswered.

4.1.1 Study population

The generalisability of the results from any of the included studies to the broader population was very limited. Three studies, Zhang et al., Kimura et al. and Kolodchenko,[164, 166, 167] had roughly twice the number of female to male participants, which may well have been a fair reflection of female:male ratio of a population presenting to a dermatology clinic. However, historically greater numbers of males are infected. Both Kozarev and Kozarev 2011[168, 169] provided no gender breakdown and had a relatively young age range in 18-45 years, as did Zhang et al.[164] (average age 48.8 years) which could be indicative of the effectiveness of laser therapy for a younger age range but limited the generalisability of these results to the documented increasing aging global population in the >50 years age range where severity and incidence are a significant evolving problem. On the other hand, studies by Nicolopoulos et al.[175] Hochman[165] and Kimura et al.[166] had a mean population age in the mid-fifties to late sixties, but the sample sizes were too small to extrapolate outcomes to a wider population.

The numbers of nails infected whether they were hand or foot digits, and specifically which digit and type of mycotic infection, would also appear to be of no real relevance to the reported outcome of clinical improvement. Essentially everyone who was treated showed some clear nail growth, according to the researchers. No quantifiable data was provided.

4.1.2 Laser intervention

Considering all the apparent variations in laser operational parameters, the number of treatments, the timing of treatments and the delivery patterns, it is interesting that no reliably quantifiable outcome was reported by any study that would lead one to believe any specific set of laser operational parameters to be superior to any other treatment regimen for onychomycotic nail infections in adults living in the community.

4.1.3 Comparator and outcomes

The included studies demonstrated a mycological cure at 12 and 16 weeks and a clinical cure at 16 weeks post treatment. These outcomes are comparable to reported results from treatment by Terbinafine. However, the evidence is tenuous at best with follow-up times bordering on the minimum required to assess if it really is a cure or reinfection or a continuing infection from the existing status quo.

4.1.4 Patient satisfaction

There are two main factors that make it surprising that none of the researchers mention considering/surveying their participants specifically on nail aesthetics.

1. The vast amount of published literature derived from surveys carried out in the northern hemisphere which clearly describes the significant impact poor nail appearance has on an individual's psychological and physical health, their socio-economic prospects and mobility.
2. Lasers have only been given approval for the 'temporary increase of clear nail in onychomycosis' by the FDA which is clearly a cosmetic guideline and not at all therapeutic.

The participant's voice is totally lost if the question isn't asked in the first place. The contextual propriety of laser treatment for clear nail growth remains unknown from the participant's viewpoint while the researcher pursues a purely therapeutic application of laser therapy.

In addition, although patients are reported to have signed informed consent documents,[166, 167, 169] there is no specific mention of counseling regarding potential serious adverse outcomes except[167] of laser treatment such as nail discolouration, subungual hematoma and nail growth abnormalities. Nail discolouration was reported by Kozarev 2011 but phone-calls at follow-up did not report on this.[168]

4.1.5 Effectiveness of CO_2 laser nail ablation and adjunct laser treatment to reduce healing time and pain experience

Nail avulsion is an acceptable therapy for clients who have had recurrent long-term onychomycotic infections. Clinical follow-up over a six-month period to assess new clear nail growth is reasonable. It would possibly be quite enlightening to apply the dual laser therapy post conventional nail avulsion surgery to investigate if healing times and pain scores can be positively affected. Otherwise the application of post-surgical laser treatments over an extended period would seem to be burdensome both time-wise and financially to the consumer. Nevertheless laser nail avulsion could provide a useful alternative to conventional surgical techniques for consumers unable or unwilling to tolerate anesthesia.

4.2 Review limitations

This review was limited to full text studies in English as the majority of laser instruments evolved from 'cold war' weapons research reported in English.[176] Lockwood and White (2012)[177] note that limiting studies included in a review by date and language must be undertaken with great caution, and other researchers found that outcomes from meta-analyses where language restriction was applied produced different results from those where language restriction was not applied.[178] Two case series studies where the full text was in other languages were excluded.[179, 180] (Figure1)

Laser technology is a new and rapidly advancing technology and this review was limited to publications in the date range of 1 January 1985 to 13 June 2013, on the assumption that it was highly unlikely that there would be relevant experimental data published prior to 1985. The veracity of this assumption was borne out of finding only one potentially relevant reference pre-dating 1985.[113] This study would have been excluded on the basis of not meeting other pertinent inclusion criteria outlined in the a priori protocol. In addition laser manufacturers did not gain approval from the American based Food and Drug Administration (FDA) of laser treatment for dermatological conditions and for the 'temporary increase of clear nail in onychomycosis' until 2009/2010 (reported in Gupta and Simpson[93]).

Other limitations of this systematic review were the small number of studies that met the inclusion criteria and in addition, the majority of studies were underpowered case series

studies. The limited number of studies and the low power of the studies found highlight the need for well-designed quality research into laser therapy for onychomycosis.

Data from unpublished trials is indispensable in evidence synthesis to minimise publication bias[181] and are integral to the inclusiveness and completeness of the systematic review process.[153] Several trials had been registered with the *ClinicalTrial.gov* site that would appear pertinent to this review.[182-186] The results were undisclosed, unavailable or considered by the researchers themselves to have major flaws and be invalid.[184] Potentially relevant research was also reported in newspaper articles or publications designed to provide generalist information on emerging technologies or techniques to health professionals and members of the public. Authors of the articles and the researchers whose research work was reported were contacted, with no replies forthcoming. Doshi and Jones[181] elucidate the differences in data sets available to the systematic reviewer and government agencies, even when both have access to the same clinical trials.[181] These same authors also illustrate (Figure 2, p7) how raw data can be transformed in a less than transparent process into multiple reports of very different levels of detail and length, for example, abstracts or posters and reports to specialist groups such as 'white papers'. Hees et al.[115] note that publication bias or 'top drawer syndrome' is likely to affect the number of laser studies without significant findings being withheld from journal publication and that researchers themselves are loathe to submit research that does not have significant results. Nevertheless, where authors fail to respond to requests for further details regarding their research, it leaves the systematic reviewer and indeed the research world, as a whole, the poorer.

Two very recent publications, one by Bristow[187] and the other by Gupta and Simpson,[120] differ significantly in methodology from this comprehensive systematic review. Neither study evolves out of an a-priori protocol based on a clearly defined question. Thus there is a lack of transparency regarding the review process. In addition the literature on which the conclusions are based is not subjected to critical appraisal by independent reviewers.

4.3 Review strengths

The strength of this comprehensive systematic review lies in the development and publication of an a priori protocol where population, intervention comparator and outcomes, and inclusion and exclusion criteria are clearly defined. Literature searching for published and unpublished material follows the PRISMA guidelines. Additionally the included studies

underwent critical appraisal for sources of bias by two independent reviewers utilising the JBI-MAStARI instruments.

4.4 Implications for practice

A new intervention should clearly demonstrate it can produce results at least as good as the current 'gold standard' treatment regimen. This conclusion could not be reached with any confidence on the basis of the data synthesised from the studies included in this systematic review.

The current 'gold standard' treatment of oral terbinafine 250mg/day daily for three or four months was based on a body of research which has been developed since the 1980s as new pharmaceutical products became available.[40] This research incorporated a wide-ranging demographic in different geographic locales and included numerous randomised controlled placebo based comparative clinical trials. Bell-Syer et al.[188] conducted a systematic review of oral treatments for fungal infections which included 12 randomised controlled trials involving 700 participants. In addition, Crawford and Hollis[72] identified 67 randomised controlled trials in their systematic review and concluded that terbinafine was the most effective topical treatment for onychomycosis. Thus both oral and topical terbinafine interventions are backed by a significant body of rigorous scientific research. Therefore recommendations arising from this systematic review would concur with the existing evidence that terbinafine is the most effective treatment for fungal nail infections. Terbinafine remains the treatment of choice until further robust research into laser therapies demonstrates outcomes at the very least comparable to the current 'gold standard' (Grade of Recommendation B, see Appendix X).

4.5 Implications for research

Onychomycosis is a serious, escalating problem worldwide, and new interventions such as laser treatments are worthy of sound scientific investigation that addresses clearly defined questions with systematic and rigorous methods involving comparative high quality studies with adequate experimental design and robustness to produce a body of new knowledge.

One of the benefits of case series studies is the fact that they are very useful in being directive, raising new ideas or approaches to future research into a given topic. This is very much the case arising from the data synthesised from two cohort studies and five case

series studies by the author of this thesis reported in the systematic review by Glaser et al.[131]

4.5.1 Future quantitative investigations

The actual mode of laser action on fungi and living human tissue remains a topic of speculation and research. Currently laser treatments are being promoted as largely cosmetic which is exactly as the FDA approved them in the first instance. In the long-term it may be shown that a different type of laser system utilising different wavelengths is required to affect a complete cure. Different chromophores may need to be targeted to achieve fungal eradication. Alternatively laser therapy may be most effective as an adjunct treatment to systemic or topical antifungal therapy.

One area of future research could involve elucidating a balance point between an emerging intervention/technology such as laser and the current 'gold standard' to provide onychomycosis treatments to a broader demographic than pharmaceuticals alone.

Firstly, the effectiveness of any laser intervention has to be established one way or the other. This will require a well conducted RCT experimental design where participants and researchers are blinded to allocation, treatments and outcome measuring. Recruitment of an adequate population of participants needs to be done from multiple centres to derive meaningful statistical analysis. Fungal infection needs to be confirmed by direct microscopy techniques and culture. Ideally a three-armed RCT comparing laser treatment with an inactive control/placebo light treatment, and an oral terbinafine regimen with no adjunct treatments could be conducted. There needs to be follow-up timing of 12 months minimum to ascertain cure, reinfection or recurrence with confidence and a demonstration of 100% clear new nail growth. Repeat mycological examination utilising microscopy and culture should be performed at follow-up. Clear nail growth rates need to be quantitatively measured and reported.

Since the effects of laser therapy on living tissue are still open to speculation it would be inadvisable to include pregnant woman and immunocompromised individuals. Well conducted randomised studies with good controls and adequate statistical value are the best way to assess the effectiveness of an intervention. Until this research is done the effectiveness of laser therapy for onychomycosis remains unknown.

4.5.1.1 Peripheral neurovascular parameters

It would be useful to incorporate measurement of blood pressure at the toe level prior to commencing any laser treatment as compromised blood perfusion has been implicated in reduced nail growth rates. In addition individuals can have reduced blood flow to the extremities for a variety of medical reasons, diagnosed or latent, and blood pressure is easily measured and would provide useful adjunct information, especially in light of the increased incidence and severity of onychomycosis in an aging demographic and the associated loss of peripheral circulatory patency. For similar reasons standard peripheral neuropathic tests should be incorporated. In fact tests for loss of nerve function are probably very important as experimental participants need to be able to detect/perceive heat and pain. No participant is going to tell you about pain they cannot feel.

4.5.1.2 Nail growth rate

Nail growth rates should be measured for all participants. The included systematic review studies do not provide reliable quantifiable nail growth data and it is an important parameter worthy of investigation. Worldwide there is a paucity of studies investigating nail growth data for any demographic. It is possible that there is a stimulatory effect of laser therapy on nail growth but once again this remains speculative without statistically sound data for comparison. Therefore this study is worth carrying out irrespective of laser therapy.

4.5.1.3 Diet controlled type 2 diabetes

A further experimental RCT with the above criteria but including measurement of toe pressures and peripheral nerve tests on individuals with diet controlled diabetes type 2 diagnosed could prove informative to offering laser interventions to this particular demographic.

4.5.1.4 Mechanical nail interventions

In a clinical setting podiatrists employ the practice of debriding, trimming and thinning gryphotic nails for client comfort with or without any mycological infection. As a rule the treated nails grow out over time with nice clear nail plate growth. To the author's knowledge there are no published or unpublished experimental studies of any design

detailing an optimal treatment regimen for this practice. The current treatment regimen relies on the clinical expertise and experience of the podiatrist.

Another RCT investigation/experiment could investigate mechanical nail thinning and infected nail area reduction of mycotic nails with linear clear nail growth measured over a 12-month period.

4.5.1.5 Potential qualitative investigations

Most clients are concerned with nail aesthetics and just want the quickest way to be rid of the offending condition. An extensive and comprehensive quality of life survey on the effects of onychomycosis could be undertaken in South Australia. Any RCT to test effectiveness of a laser intervention should also specifically include patient satisfaction with treatment regimen and nail aesthetics as outcomes.

4.5.1.6 Effectiveness of foot hygiene education

Since the spread of onychomycosis is closely associated to the adoption of occlusive footwear worldwide, the significance of these options could be further explored. The effectiveness of preventative patient education programs to improve foot and shoe hygiene is another area poorly reported in the southern hemisphere.

While the scenarios for experimental investigation raised in points 4.5.1.1 to 4.5.1.6 are not specifically designed to test the effectiveness of laser intervention per se they have arisen as ideas for future research areas from the systematic review based on the Joanna Briggs Institute methodology assessing quantitative evidence for the effectiveness of an intervention, utilising the JBI-SUMARI software package incorporating the JBI Comprehensive Review Management System (CReMS) and specifically MAStARI to critically appraise and then extract the data from two cohort and five case series studies.

4.6 Conclusions

There was a weak association that Nd:YAG 1064nm laser for the treatment of onychomycosis in adults could produce clear nail growth and a mycological cure in a 12-week period or a clinical cure in a 16-week period. Although there is a range of laser therapy options currently available, evidence is either of poor quality and it was not possible to identify a measurable effect, or is absent, such that claims of benefit cannot be

objectively evaluated. Practitioners should be aware of these gaps in the evidence, and that current evidence only supports Nd:YAG 1064nm laser therapy.

Prior to implementing a new intervention, there should be clear evidence of benefit in direct head-to-head comparative studies against a known 'gold standard' intervention. This systematic review found no such evidence related to different forms of laser therapy and also found a lack of evidence for many of the claims associated with laser therapy. While Nd:YAG laser therapy for the treatment of onychomycosis in adults living in the community is supported, multicenter, randomised studies with good controls and adequate value that directly compare laser therapy against oral terbinafine are needed in order to determine the therapeutic effectiveness of laser therapy for onychomycosis.

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Appendix I: Laser terminology

- Photons

The photons or packets of energy which form a laser beam can be absorbed reflected, scattered or transmitted by any surface. Photons act by transferring their energy to matter which absorbs them. The substrate which absorbs the photon energy is called a chromophore.[102]

- Chromophores

Chromophores in the case of skin can be endogenous such as melanin or exogenous such as tattoo pigment. Without a target chromophore the laser beam of photons will pass through the tissue producing no effect whatsoever. Thus it is vital to select and target a chromophore in or as near as possible to the target tissue. [105]

- Scattering, reflection, absorption (what happens to photons)

Skin has many layers and the process of photon reflection can occur at every interface. In addition endogenous structures in skin lack homogeneity resulting in scattering. In instances of increased scattering, absorption is increased and the depth of penetration is reduced.

- Energy

Energy is proportional to the number of photons and is measured in Joules expressed as J. The power of a laser is the rate of energy delivery measured in watts (W) where one watt is equal to one joule (J) per second.[105] The Power and Time factors are variable. The amount of energy delivered per unit area is called fluence.[104]

- Fluence

Fluence is measured in Joules per square centimetre and expressed as J/cm^2. Greater scattering in tissue has been shown to occur the smaller the laser beam spot size. Thus a larger laser beam spot diameter will penetrate tissue to a greater depth. However, the depth of the target chromophore and the power generation of the laser system are also integral components in choosing a beam spot size.

- Wavelength

Wavelength is the distance measured in the direction of propagation between two points in the same phase of consecutive wave cycles. [105]

Essentially a short wavelength delivers high frequency, high energy photons. Thus the shorter the pulse power, the higher the laser's peak power output.[104] A long wavelength delivers a relatively low frequency and low energy photons.[105]

Appendix II: Systematic review protocol

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: whether the investigated experimental methods, modes and treatment regimens utilising 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.[1]

Dermatophytes were present in 82% of onychomycosis isolates in an epidemiologic survey of superficial fungal infections[2] and are the major causal agents of tinea pedis and onychomycosis.[1,2]

Traditionally, the term onychomycosis was used to describe nondermatophytic nail infection.[3] 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.[4]

Onychomycosis prevalence has been estimated to be between 14-20% of the North American population5 and in the range of 3-22% in European countries.[6-8] In 1999, Scher[9] estimated a 2-18% incidence of onychomycosis in the global population.

Due to the increasing numbers of immunocompromised individuals, extensive use of broad-spectrum personal fitness programs utilising public facilities,[11] more recent research implicates onychomycosis caused by a fungus in about half of all nail infections worldwide.[12-14] *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.[6,11,15-17] The economic burden of treatment is high[18] and the social impact on individuals is significant.[19,20]

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.[1,21,22] The close relationship between tinea pedis and *T.rubrum* infection is well established and widely acknowledged.[23,24] Hence it is necessary to confirm the diagnosis of the causal agent prior to starting a treatment regime.[1,13,14]

Traditionally, testing involves fungal culture and direct microscopy techniques[3,10] such as a KOH wet mount performed in an office-based situation or a laboratory.[13,14] 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.[14] Direct microscopy alone can result in false-negative results[25] and the presence of nondermatophytes in culture specimens can further confound the identification of the causal organism.[25] Cumulative evidence using direct microscopy techniques together with careful examination of a culture specimen provide unequivocal evidence of the causal agent.[3]

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.[26] PAS is a very sensitive diagnostic test for onychomycosis in nail plate biopsy[27,28] providing a definitive diagnosis of dermatophyte infection.[26]

There are four recognised types of onychomycosis13 differentiated by infection

pathway and clinical presentation.[3]

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*.[3] Nails can become brittle, thickened, and discoloured with pieces of nail breaking away.[3]

White superficial onychomycosis (WSO) results in superficial infection of the nail plate indicated by the presence of 'white islands'; it occurs mainly on toenails.[13,29] As the infection consolidates, onycholysis can occur as the keratin breaks down.[30]

T. rubrum colonisation 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.[13] Proximal subungual (white) onychomycosis (PSO) or (PSWO) is an early clinical marker for HIV.[13,31,32]

Individuals who often have their hands in water or suffer from hyperhydrosis, and wear occlusive footwear can be infected with candidal onychomycosis, caused by Candida spp.[33] Seventy percent of onychomycosis caused by yeast are attributed to *Candida albicans*.[33] Total dystrophic onychomycosis (TDO) can be primarily due to chronic mucocutaneous candidiasis.[34] 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.[35]

Onychomycosis is more likely to occur in the elderly[36,37] and incidence is higher in males[38] than females. Infections tend to increase in severity and prevalence (number of nails infected and area of nail affected) as individuals age,[24] and are compounded by pre-existing health conditions such as diabetes,[39] HIV,[40] cancer and obesity.[41]

Poor cosmetic appearance of nails can seriously impact an individual's employment prospects, personal relationships and general lifestyle.[42,43] Onychomycotic toe nails which become very thick and malformed can significantly impact mobility and limit footwear choice.[33] Onychomycotic infections tend to be long term (>12 months) and recalcitrant. Current therapies show poor efficacy with recurrence/reinfection rates around 25%.[21,44]

The most commonly utilised current treatment methods are topical and oral pharmacotherapies;[45] the former being less costly and causing less side effects than the latter. Oral medications can have side effects such as altered liver function.[24]

However, a 93% complete cure rate has been reported with a treatment regime of 250mg of terbinafine daily for seven days every three months.[46] 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%.[47,48] Terbinafine has been government approved for treatment of onychomycosis in all countries[49] and is the current gold standard oral treatment.[21,34]

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,[45] resulting in reported efficacy rates between 5% and 8%.[3,50] A lengthy treatment period of three to 12 months is required [45] and patients are generally non-compliant[13,51]

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.[52]

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.[52]

'Laser' is an acronym for 'light amplification by stimulated emission of radiation'.[53] Lasers produce coherent light that can be spot focused while maintaining very high irradiance.[53] Lasers derive their name, and emit light with characteristics specific to the 'lasing material' that is activated.[53] 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.[53] Biological responses can be targeted precisely by the careful choice of light wavelength, pulse duration and fluence.[51,53,54]

Laser application to the medical field did not flourish until the 1990s when it was discovered that solid state lasers that utilised the alexandrite crystal produced photons of 755-nm light in the near infrared spectrum;[55] and quality switching[55] enabled a pulse width range from 50-100ns.[56]

Effective laser treatment relies on the theory of selective photothermolysis.[22] Chromophores are substances which selectively absorb a particular light wavelength. Melanin, present in skin[22,55] and *Trichophyton* species cell walls,[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 *T. rubrum*.[22,53,55,57] Each chromophore has a unique thermal relaxation time (TRT).[58] The TRT of a substance is defined as the time taken for the object to cool after absorbing heat.[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.[55] In the case of fungi, this means that targeted laser treatment can be fungistatic.[60]

Conversely, heat is transferred to the surrounding environment if heat is delivered more slowly than the chromophore can cool.[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.[55] Advances in laser technology suggest that the longer wavelength of the neodymium-doped yttrium aluminium garnet (Nd:YAG) laser enables a deeper penetration of tissues and thus it can target fungal elements in the nail bed,[51] specifically xanthomegnin.[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.[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[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, *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 discolouration, onycholysis and periungual 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 I omitted to avoid repetition; refer Appendix V). 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 II omitted to avoid repetition; refer Appendix VI).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 reviewers: Associate Professor Craig Lockwood and Dr Karolina Lisy
This systematic review forms part of a submission for a Masters of Clinical Science and the secondary reviewers will only be used for the critical appraisal stage of the

review.

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Appendix III: Logic grid for searching

Laser therapy	Onychomycosis	Age groups
Laser*[tw] OR light[tw]	Onychomycos*[tw] OR ((fungi[mh] OR fung*[tw] OR yeast*[tw] OR yeasts[mh] OR candida[tw] OR mycoses[tw]) AND (nail[tw] OR nails[tw] OR toenail*[tw])) OR tinea ungui*[tw] OR trichophyton[tw]	Child*[tw] OR adolesce*[tw]

Appendix IV: Search strategy

PUBMED Search Strategy	28/7/13
1. Laser*[tw]	206549
2. light[tw]	456086
3. Laser*[tw] OR light[tw]	637033
4. Onychomycos*[tw]	2961
5. fungi[mh]	284711
6. fung*[tw]	220519
7. yeast*[tw]	149018
8. candida[tw]	51315
9. mycoses[tw]	19866
10. tinea ungui*[tw]	276
11. trichophyton[tw]	6333
12. 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11	422277
13. nail[tw]	16216
14. nails[tw]	19787
15. toenail*[tw]	1690
16. 13 OR 14 OR 15	28906
17. 12 AND 16	2528
18. 3 AND 17	94
19. Child*[tw]	1824737
20. adolesce*[tw]	1564020
21. 19 OR 20	2617259
22. 18 NOT 21	84
FILTERS: Date range 1-1-1985 to 30-6-2013, Human, English language	
Total of papers	84
Filter by date	77
Filter by human	63
Filter by English	58
Keep #1, #2,#5,#8,#18,#19,#56. Total number of papers 7	

Appendix V: MAStARI appraisal instruments

JBI Critical Appraisal Checklist for Descriptive / Case Series

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

	Yes	No	Unclear	Not Applicable
1. Was study based on a random or pseudo-random sample?	☐	☐	☐	☐
2. Were the criteria for inclusion in the sample clearly defined?	☐	☐	☐	☐
3. Were confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
4. Were outcomes assessed using objective criteria?	☐	☐	☐	☐
5. If comparisons are being made, was there sufficient descriptions of the groups?	☐	☐	☐	☐
6. Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7. Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8. Were outcomes measured in a reliable way?	☐	☐	☐	☐
9. Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info ☐

Comments (Including reason for exclusion)

JBI Critical Appraisal Checklist for Comparable Cohort/ Case Control

Reviewer _____ Date _____

Author _____ Year _____ Record Number _____

		Yes	No	Unclear	Not Applicable
1.	Is sample representative of patients in the population as a whole?	☐	☐	☐	☐
2.	Are the patients at a similar point in the course of their condition/illness?	☐	☐	☐	☐
3.	Has bias been minimised in relation to selection of cases and of controls?	☐	☐	☐	☐
4.	Are confounding factors identified and strategies to deal with them stated?	☐	☐	☐	☐
5.	Are outcomes assessed using objective criteria?	☐	☐	☐	☐
6.	Was follow up carried out over a sufficient time period?	☐	☐	☐	☐
7.	Were the outcomes of people who withdrew described and included in the analysis?	☐	☐	☐	☐
8.	Were outcomes measured in a reliable way?	☐	☐	☐	☐
9.	Was appropriate statistical analysis used?	☐	☐	☐	☐

Overall appraisal: Include ☐ Exclude ☐ Seek further info. ☐

Comments (Including reason for exclusion)

Appendix VI: MAStARI data extraction instruments

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

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Continuous data

Outcome	Intervention ( ) number / total number	Intervention ( ) number / total number

Appendix VII: Excluded studies

Bunyaratavej SC, Muanprasart K, Thanomkitti L, Matthapan R, Wanitphakdeedecha S, Eimpunth S and Manuskiatti W. (2013). Successful treatment of onychomycosis caused by Scytalidium dimidiatum by long-pulsed 1064 nm Nd:YAG laser and combination of laser treatment and 5% amorolfine nail lacquer: A case report. J Am Acad Dermatol 2013 68(4): AB130-AB130.

Reason for exclusion: Scored 3/9 when assessed against the nine questions of the JBI critical appraisal instrument for Descriptive/Case series studies.

Dan MB, Chen NJ, Chao CY. Clinical studies of Nd:YAG laser and Chinese herbal medicine in treatment of patients with Tinea unguium. International Conference on Photodynamic Therapy and Laser Medicine.1993; 1616: 420-422.

Reason for exclusion: Scored 1/9 when assessed against the nine questions of the JBI critical appraisal instrument for Descriptive/Case series studies.

Appendix VIII: Characteristics of included studies

Study	Methods	Participants	Intervention A	Intervention B	Notes
Hochman LG.[165]	Descriptive/Case Series Study	Average age 66.6 years (range 48-91). 5 males and 3 females. 11 participants who had dystrophic nails clinically consistent with fungal infection screened but only 8 had confirmation of fungal infection n=4 by culture all processed by a commercial laboratory or n=4 PAS staining. 7 had infections of their toenails and one had	Infected nails photographed. Then laser treatment began. Nd:YAG 1064-nm (LightPod Neo; Aerolase, Tarrytown, NY, USA) fluence 223J/cm2, 2mm spot, 0.65-ms pulse no cooling sprays, gels or topical anesthetics used. Crisscross treatment pattern. One vertical pass and horizontal pass to cover the entire nail		Nails were thinned by clients, a highly variable proposition. An antifungal was also used between treatments which could have confounded the results by increasing the number of positive outcomes. It would not be possible to estimate how effective the laser treatment has truly been.

		an infected fingernail.	surface. 45 seconds or less /nail/treatment. Subjects had either 2 or 3 treatments spaced at least 3 weeks apart. Antifungal cream given to all clients after each treatment to be applied daily to the nails to prevent reinfection. Cultures were obtained from nail samples taken after second or third treatment session. Efficacy assessed by repeat culture and photographic inspection.		

			Photographs at baseline, second and third treatment session then during follow-up visits 4-6 or more months after the final treatment.		
Kimura U, Takeuchi, K, Kinoshita A, Takamori K, Hiruma M, Suga Y. [166]	Descriptive/Case Series Study	Average age 68 years (range 37-88) 4 Males & 9 Females. 9 DLSO= 25 toenails, 2 TDO=5 toenails,1PSO=1 toenail and 1 TDO=2 & same client SWO=6 toenails. Diagnosis of fungal infection confirmed with KOH direct microscopic examination. Total of	Only toenails with clinical evidence of infection at baseline were treated. Sub-millisecond 1064-nm Nd:YAG laser fluence 14J/cm2 5mm spot diameter pulse time 300microsec (0.3ms) repetition rate of 5 Hz. Treatment 100-200 pulses to the great		Laser intervention is almost identical to Hochman except the spot size is larger ie 5mm.and there were no adjunct treatments such as topical antifungal cream between laser treatments.

		37 affected toenails.	toenail and 20-100 pulses to the 2-5 toenails. No cooling sprays, gels or topical anaesthetics. Criss cross pattern one vertical and one horizontal pass. Treatment time 1-2 minutes/toenail. 7 subjects treated 3 times. 5 subjects treated twice, 1 subject treated once. Treatments were 4 and/or 8 weeks apart. Standardised photographs taken at baseline and 4, 8, 12, 16, 20 and 24 week		

			time points using digital SLR camera (EOS7D Canon K.K. Tokyo, Japan).		
Kolodchenko and Baetul YV.[167]	Descriptive/Case Series Study	Average age 39.4 years (range 18-74) 70 females and 38 males. Fitzpatrick skin types 1-111. 96 DSO, 2 Endonyx, 3 PSO, 7 TDO. 8 patients with T. rubrum, 17 T mentagrophytes, 10 Candida spp 3 Aspergillus niger. 108 patients with a total of 312 infected nails. Patients had laboratory confirmed nail infection	Laser 1064-nm Nd:YAG (SP Dynamis, Fotona, Slovenia) Fluence 35-40J/cm2 Pulse duration 35 msec and 4mm spot. Two passes with a two minute interval applied to every infected nail. No post-op care prescribed, all patients given advice on the prevention of reinfection at home. 4		Authors acknowledged the poor effectiveness of the laser treatment against mouldy flora, and comorbidity (psoriasis) and that their sample size was very small. Patient pain/discomfort reported as mild/easily tolerated.

		of varying severity. Patients had between one and eleven nails affected. 102 patients with infected toenails and 6 patients with fingernails infected.	sessions of treatment with an interval of 7 days between. Laser applied to the entire nail as well as surrounding skin. Cryo 6 Zimmer, Germany used to provide air cooling during laser treatment.		
Kozarev J.2011[168]	Descriptive/Case Series Study	162 participants with 413 infected nails.	VSP 1064-nm Nd:YAG laser (Dualis SP; Fotona, Slovenia) 4mm spot size, pulse duration 35ms, pulse rate 1Hz. Spiral pattern to irradiate entire nail surface.		Although the author states that the same method as the 2010 publication are used there appears to be a lack of clarity in the frequency of treatments. The

			One session, 3 passes across each nail. Follow-ups at 3, 6 and12 months. Mycological check-up at 3 and 6 months and clinical nail evaluations at 12 months. Telephone follow-ups of 46 patients that took place at 12-18 months,18-24,24-30 and > 30months after treatment		paper reads as if there was only one laser session. There is no indication of numbers with thick dystrophic nails which might have required the pre-treatment previously described, no the numbers of clients with different types of onychomycotic infection, no gender or age information. In the 2010 study Kozarev reports effective treatment of Candida infection which other authors

					have not achieved. It would have been very useful to have greater detail of diagnosis for onychomycosis. Author does report yellowing of nails and mild-moderate heat sensation but there is no indication via follow-up phone interviews if the discoloration was an issue for the clients long-term.
Kozarev J and Vizintin Z. 2010[169]	Descriptive/Case Series Study	Age range 18-45 years.110 initially screened but only 72	Photographs using consistent camera settings, lighting and		Author conclusions very broad and sweeping especially

		patients with 194 affected nails tested positive for fungal infection, using KOH microscopy and laboratory culture examination. Participants had to have one or more toe nail and/or finger nail infected.38=DSO, 6=TDO, 22=PSO and 6=Endonyx onychomycosis. 37 patients with T. rubrum, 22 T.mentagrophytes, 10 Candida spp and 3 Aspergillus niger. 3 patients had thick dystrophic nails which	nail position were taken at baseline, 6, 9 and 12 months follow up visits. 6VSP 1064-nm Nd:YAG laser (Dualis SP; Fotona, 6 Slovenia) fluence 35-40J/cm2, 4mm spot size, pulse duration 35ms, pulse rate 1Hz. Laser beam applied in a spiral pattern to irradiate the entire nail plate plus and then a 2 minute pause =one pass. This was repeated twice more to give a total of three passes. Total therapy		since no elderly patients were included in this trial.

		were pre-treated.	consisted of 4 sessions at weekly intervals. No local anesthesia, analgesic, prophylactic antibiotics or antiviral given to any patient post operatively. Cold air cooling applied to area during laser treatment (Cry06, Zimmer, Germany used). 3 patients had thick dystrophic nails which were pre-treated for three nights with a preparation including 40% urea, 20%		

			anhydrous lanolin, 5% white wax, and 35% white petrolatum under occlusion. The temperature increase of the nail plate was measured during treatment for the first few patients only, using FLIR Thermal Imager and TheraCAM Researcher Pro2.8.		
Nicolopoulos CS, Tsioutis V, Nicolopoulos NS, Giannoudis PV.[163]	Comparable Cohort/Case Control Studies	78 with a mean age of 56 years with clinical and culture diagnosis of T rubrum/mentagrophytes and Candida albicans.	30 patients treated using CO2 (LaserLabs CY) procedure. Plus topical Terbinafine post-surgery until	15 patients had the CO2 surgery only. Surgical procedure for all participants involved mechanical debridement of nail	Surgical avulsion of the nail plate for onychomycotic infections is a significantly aggressive treatment.

		Classified as distal subungual onychomycosis	healing complete. Another 28 patients treated using CO2 (LaserLabs CY) procedure plus low level laser therapy (GaAlAs-60mW, 830NM, 0.2cm2 spot size diode laser, LaserLabs, CY/HeNe-1.5mW,632NM, 0.2cm2 spot size, continuous laser Siberbauer, Austria)830NM applied for 10s (~4J.cm2) to centre of nail wound. Then probe of He-Ne laser (632 NM) applied for	to nail bed level CO2 laser positioned in the center of the surgery field set at 7 watts, 1mm spot size (power density ~700watts/cm2). Laser beam directed at the level of the nail bed to vapourize superficial tissue and fungus. Fungus in the nail root removed by using the laser beam at an angle under the eponychium to the matrix. Surgical site dressed with Silver Sulphadiazine1%w/w	

			3.5min to the surrounding skin at 4 perimeter points (average energy density ~2J/cm2 per point) for 2 weeks with 3 day interval.	and covered with Melolin. Redressed two days later when the other treatments (i.e. Lamisil or low level laser were introduced before the dressings were reapplied.	
Zhang RN, Wang DK, Zhuo FL, Duan XH, Zhang XY, Zhao JY.[164]	Comparable Cohort/Case Control Studies	Average age 48.8 years (range 22-75). 10 males and 23 females. Duration of disease range 2 months - 30 years (mean duration 15.5 years). Mycological microscopic examination and fungal	Patients randomly assigned to group by casting lots. Three sub groups established according to SCIO. A(11 degree,<6SCIO<9), B (111 degree, (<SCIO<12) and C(1V degree,	Patients randomly assigned to group by casting lots. Three sub groups established according to SCIO. A(11 degree,<6SCIO<9), B (111 degree, (<SCIO<12) and	Results biased by subgroup C including almost twice the number of patients to the other two subgroups with severe cases accounting for >50% of included cases. Although satisfactory

		culture used to confirm infection of nails. 12 strains of fungi identified, including 11 *T. rubrum* and 1 *Candida albicans*. Total number of affected nails 154 with a mean of 4.7 nails/person. 18 fingernails and 136 toenails.	12<SCIO<15) Nd:YAG 1064nm 240-324J/cm2 fluence, 30ms pulse duration, 3mm spot size 1Hz frequency. Spiral pattern to cover entire nail plate. Each session comprised 3 passes across the nail plate with 2 minute pauses between passes. A full course of treatment consisted of four sessions executed on days 0, 7, 14 and 21. This group had 2 courses of treatment.(8	C(1V degree, 12<SCIO<15) Nd:YAG 1064nm 240-324J/cm2 fluence, 30ms pulse duration, 3mm spot size 1Hz frequency. Spiral pattern to cover entire nail plate. Each session comprised 3 passes across the nail plate with 2 minute pauses between passes. A full course of treatment consisted of four sessions executed on days 0, 7, 14 and 21. This group had one	results are reported the microscopic and fungal cultures rate showed increased positives at 24 weeks compared to 8 weeks after treatment.

			sessions)	course of treatment.(four sessions).	

Appendix IX: Joanna Briggs Institute Levels of Evidence

The New JBI Levels of Evidence and Grades of Recommendation are now being used for all JBI documents as of the 1st of March 2014.

Levels of Evidence - Effectiveness

Level 1 – Experimental Designs	Level 1.a – Systematic review of Randomized Controlled Trials (RCTs)
	Level 1.b – Systematic review of RCTs and other study designs
	Level 1.c – RCT
	Level 1.d – Pseudo-RCTs
Level 2 – Quasi-experimental Designs	Level 2.a – Systematic review of quasi-experimental studies
	Level 2.b – Systematic review of quasi-experimental and other lower study designs
	Level 2.c – Quasi-experimental prospectively controlled study
	Level 2.d – Pre-test – post-test or historic/retrospective control group study
Level 3 – Observational – Analytic Designs	Level 3.a – Systematic review of comparable cohort studies
	Level 3.b – Systematic review of comparable cohort and other lower study designs
	Level 3.c – Cohort study with control group
	Level 3.d – Case – controlled study
	Level 3.e – Observational study without a control group
Level 4 – Observational – Descriptive Studies	Level 4.a – Systematic review of descriptive studies
	Level 4.b – Cross-sectional study
	Level 4.c – Case series
	Level 4.d – Case study
Level 5 – Expert Opinion and Bench Research	Level 5.a – Systematic review of expert opinion
	Level 5.b – Expert consensus
	Level 5.c – Bench research/ single expert opinion

Appendix X: New JBI Grades of Recommendation

Developed by the Joanna Briggs Institute Levels of Evidence and Grades of Recommendation Working Party October 2013

JBI Grades of Recommendation

Grade A

A 'strong' recommendation for a certain health management strategy where (1) it is clear that desirable effects outweigh undesirable effects of the strategy; (2) where there is evidence of adequate quality supporting its use; (3) there is a benefit or no impact on resource use, and (4) values, preferences and the patient experience have been taken into account.

Grade B

A 'weak' recommendation for a certain health management strategy where (1) desirable effects appear to outweigh undesirable effects of the strategy, although this is not as clear; (2) where there is evidence supporting its use, although this may not be of high quality; (3) there is a benefit, no impact or minimal impact on resource use, and (4) values, preferences and the patient experience may or may not have been taken into account.

The FAME scale (Feasibility, Appropriateness, Meaningfulness and Effectiveness) may help inform the wording and strength of a recommendation.

F – Feasibility; specifically:

. What is the cost effectiveness of the practice?

. Is the resource/practice available?

. Is there sufficient experience/levels of competency available?

A – Appropriateness; specifically:

. Is it culturally acceptable?

. Is it transferable/applicable to the majority of the population?

. Is it easily adaptable to a variety of circumstances?

M – Meaningfulness; specifically:

. Is it associated with positive experiences?

. Is it not associated with negative experiences?

E – Effectiveness; specifically:

. Was there a beneficial effect?

. Is it safe? (i.e. is there a lack of harm associated with the practice?