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Review

A seven-year human data analysis (2008-2015) of a near-infrared laser system for the treatment of onychomycosis

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ABSTRACT

Since the first United States Food and Drug Administration (FDA) clearance of a laser device for the treatment of onychomycosis in 2010, a large number of diverse laser systems have also gained clearance in the following five years. However, there has been very little follow-up data on the cleared systems concerning: (a) proposed anti-fungal mechanism of action for the devices, (b) retrospective studies post-approval and (c) suggested best practice therapy updates. This lack of follow-up data has been heavily criticized within the dermatology and podiatric communities. To answer these concerns, we herein present a 7-year review of all the available data (published and (un-published) for the 870 nm/930 nm Noveon laser system collected over the years 2008-2015. This review will discuss published human pilot data from 2008, published pivotal trial data from 2010, published retrospective data from the pivotal trial in 2012, and data from the 199-patient retrospective study published in 2014. This review also includes: (i) un-published data describing *in vivo* mycologic testing, (ii) un-published pivotal trial data measuring nail growth rates, and (iii) a discussion of *in vitro* published and human un-published reports describing antifungal potentiation with the Noveon laser. Finally, we give a series of suggestions and clinician advice for best clinical practices, based on these 7 years of data generation.

KEYWORDS: laser, onychomycosis, potentiation, topical antifungal

INTRODUCTION

The 870 nm/930 nm Noveon laser system is a dual wavelength, non-ablative, near-infrared diode system designed to use only the wavelengths 870 nm and 930 nm (+/- 1 nm). These wavelengths were chosen based on the work of Neuman *et al*. published in 1999 and 2002, where it was observed using a confocal laser microscope that these specific wavelengths would exclusively kill both eukaryotic and prokaryotic cells in a non-thermal environment. The mechanism of action was postulated by Neuman as occurring from the generation of singlet oxygen species created by the absorption of 870 nm/930 nm in unknown intracellular endogenous chromophores [1, 2].

In 2006 and 2007, Nomir Medical Technologies tested a prototype 870 nm/930 nm laser system against various Gm+ and Gm- bacterial species, dermatophytes, yeast, and mammalian fibroblasts *in vitro*. It was found that near-infrared photo-destruction with 870 nm/930 nm was possible against *Staphylococcus aureus*, *Escherichia coli*, *Trichophyton rubrum* and *Candida albicans* at physiologic temperatures. These experiments also revealed that bacterial, fungal and mammalian cellular redox pathways were all affected in a similar manner with the multiplexed 870 nm and 930 nm lasers, yet no harmful effect was observed in the mammalian fibroblasts, at the dosimetry necessary to kill the microbial species. It was postulated that the mechanism of action is an optically mediated mechano-transduction of cellular

redox pathways that decreases transmembrane potentials and increases reactive oxygen species. The full *in vitro* results confirming the unique antimicrobial nature of the 870 nm and 930 nm wavelengths were published in 2009. At that time, the putative absorptive chromophores were identified as Cytochrome C for 870 nm, and the C-H covalent bonds in long chain fatty acids of cell membranes for 930 nm. Table 1 is an abridged *in vitro* data set, from the antifungal photo-damage experiments in saline [3, 4].

Following the *in vitro* experimentation, the below-mentioned logic was presented to an investigational review board, based on which the human studies were approved and initiated;

(a) near-infrared photons do not carry enough energy to initiate photochemical reactions,

(b) near-infrared photons do not generate singlet oxygen and

(c) near-infrared photons do not cause mammalian cellular damage unless they are delivered at a high-enough intensity to cause thermal effects [5].

1. 2007-2008 antifungal human pilot studies

The first human tests were conducted to assess whether a lower dose of energy that would be tolerable to a human subject, would also show antifungal efficacy and translate into a viable human therapy for onychomycosis treatment. After (a) human thermal tolerance tests, and (b) cadaveric 870 nm/930 nm optical penetration tests in clear and mycotic nails, the following dosimetry was established with 1.5 cm flat-top projections. Table 2 and Figure 1 depict the actual dose calculations that follow the published guidelines for safe, non-ablative laser tissue interactions [6].

For the initial human antifungal mycology protocol, Sabourauds' dextrose agar (dextrose level (2%)) test plates were prepared with the antibacterial molecule chloramphenical (0.04 mg/ml) and the antifungal molecule cycloheximide (0.4 g/ml.) to preferentially select the dermatophyte *Trichophyton rubrum*. The dosimetry in Table 2 was then employed on the great toe and second toe of one foot of the patient as shown in Figure 2. The other foot was used as the control (Figure 2), and both

Table 1. *In vitro* dosimetry of *Trichophyton rubrum* and *Candida albicans* for photo-damage experiments. The samples were exposed to blended laser energy for 12 min 870 nm/930 nm exposures at physiologic temperatures and plated in triplicate. The laser exposures produced photo-inactivation of 100% of the colony forming units counted at 91 hours incubation versus control.

870 nm + 930 nm Output power (W)	Beam spot 1.5 cm diameter	Treatment time (Sec)	Energy density (J/cm^2)	Power density (W/cm^2)	Kill percentage
10.0 W	1.76 cm^2	720 Sec	4074 J/cm^2	5.68 W/cm^2	100%
11.0 W	1.76 cm^2	720 Sec	4500 J/cm^2	6.25 W/cm^2	100%

Table 2a. First laser exposure for human onychomycosis pilot study.

Parameters	Output power (W)	Beam spot (cm)	Area of spot (cm^2)	Time (sec)	Total energy (Joules)	Energy density (J/cm^2)	Power density (W/cm^2)
870 nm	1.5	1.5	1.77	250	375	212	0.85
930 nm	1.5	1.5	1.77	250	375	212	0.85
Combined	3.0	1.5	1.77	250	750	424	1.70

Table 2b. Second laser exposure for human onychomycosis pilot study.

Parameters	Output power (W)	Beam spot (cm)	Area of spot (cm^2)	Time (sec)	Total energy (Joules)	Energy density (J/cm^2)	Power density (W/cm^2)
930 nm	3.0	1.5	1.77	120	360	204	1.70

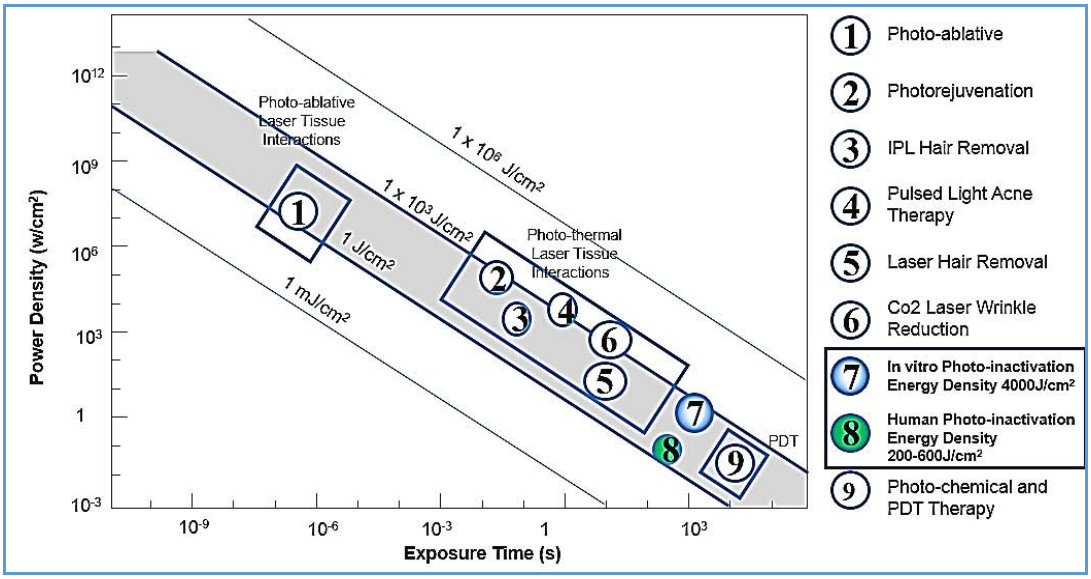

Figure 1. Triple logarithmic graph of laser tissue interactions by dose of energy. Note that the anti-fungal photo-inactivation dosimetry values are below thermal damaging energy density thresholds for laser energy. Y axis is the power density (irradiance), X axis is the laser exposure time in seconds, and the diagonal lines represent different energy densities or fluences [6].

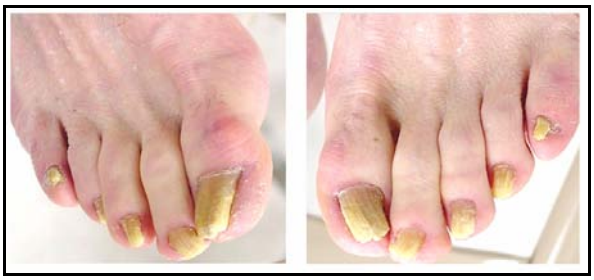

Figure 2. 67 year old male with onychomycosis present on all 10 toes for 30 years.

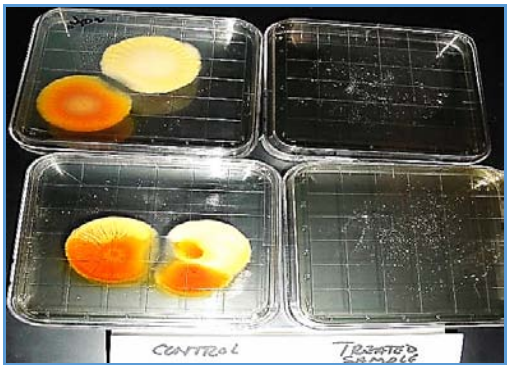

Figure 3. 9 days post laser therapy: White specks are nail shavings undissolved in the culture media.

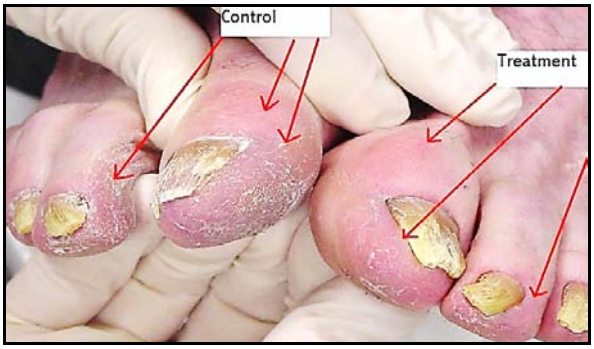

Figure 4. Reduced shedding of dermatophytes from treated nail to the paronychial areas, 3 days post 870 nm/930 nm irradiation on the treated toes.

underwent debridement and plating to establish positive *T. rubrum* culture.

Debridement-shavings from the treatment toes (post irradiation) and the control toes were plated on the agar plates described above. Figure 3 shows the classical *Trichophyton rubrum* growth apparent from the control shavings, and no growth can be seen from the shavings of the treatment toes 9 days post-procedure. Figure 4 depicts the treated and control toes of the same patient three days after treatment.

After three days, the treated toes clinically presented with reduced tinea pedis and scaling surrounding the nails. This improvement in the surrounding skin, coupled with the mycologic negative culture seen on the treated toenails, suggests a decontamination of the nail plate with the 870 nm/930 nm irradiation protocol. This improvement in the clinical tinea pedis, was likely the result of a lesser amount of shedding of dermatophytes to the surrounding paronychial areas, where before laser treatment, the infected nail was most likely acting as a reservoir for the fungus [7].

The concept of an infectious reservoir of fungi in mycotic nails was evaluated by Szepietowski *et al*. in 2006 [7]. In the Szepietowski analysis, the degree of mycotic nail infection, length of the infection, and existence of recurrent onychomycosis were the highest predictors of mycoses at distal sites, and Tinea pedis was the highest incidence of concomitant fungal infection. Szepietowski *et al*. suggested that toenail onychomycosis may exemplify a fungal reservoir that can seed and infect distant skin sites [7].

In late 2008, Nomir Medical performed the first investigational review board approved human pilot study with the Noveon technology for the treatment of onychomycosis, and the results were published in multiple venues [4, 8, 9]. In this pilot study, the great toes of seven patients with positive fungal cultures were irradiated with a uniform flat-top projection, four times (days 1, 7, 14 and 60) with 539 J/cm^2 of multiplexed 870 nm/930 nm energy. The flat-top projection was produced from a custom-fabricated micro-lens, and was chosen (vs a Gaussian projection) to achieve; (1) uniform dosimetry across the nails, and (2) an augmented internal fluence distribution to the deeper nail tissues.

The augmented internal fluence distribution is possible with large spot top-hat beam geometry, following the general equation {πr^2 * depth}, and relying on internal light scattering Monte Carlo effects [10]. After the second treatment on day 7 an over-the-counter (OTC) terbinafine spray was used only between the toes to suppress interdigital tinea pedis, and prevent possible re-infection [7].

The 2008 pilot study reported the following results:

(a) mycological negative cultures on day 60 for all patients

(b) experimental temperatures did not exceed 38 °C and

(c) no negative sequelae were recorded.

The fungal species that were cultured in these 7 patients were *Phaeoannellomyces*, *Trichophyton* and *Rhodotorula* [8, 9].

2. 2010 pivotal human onychomycosis study

In 2010, Landsman *et al*. [11] reported on a pivotal randomized controlled study with the Noveon laser to treat onychomycosis, with treatments occurring on days 1, 14, 42 and 120. Treatment dosimetry was the same as stipulated in Table 2, and after completion of the second treatment, OTC topical terbinafine 1% cream was applied only between the toes to control tinea pedis. All toes in this study were cultured and clear nail measurements were taken from standardized photographs. The treatment and control photographs were read and graded by blinded independent observers [11].

The results of this pivotal trial stated that 26 mycologically confirmed toes were treated (ten mild, seven moderate, and nine severe), and that all patients were examined on or about day 180. The blinded independent observers determined that;

(a) 85% of the treated toenails were improved by clear nail linear extent (P = 0.0015),

(b) 65% had at least 3 mm and 26% had at least 4 mm of clear nail growth and

(c) Of the 16 toes with moderate to severe involvement, ten (63%) improved, as shown by clear nail growth of at least 3 mm (P = 0.0112) [11].

3. Previously un-published nail growth rate data from the 2010 pivotal study

To further assess the clinical effects seen in the 2010 pivotal trial, Nomir Medical compared un-published nail growth rate data to a nail growth study by Yu *et al*. in 2004 [12]. The Yu *et al*. study measured growth rates of great toenails nails that had different levels of onychomycosis involvement, and the growth rates of these same nails after oral/systemic onychomycosis therapy.

He compared them with the control (non-infected) great toes of the same patient. In this study, Yu determined two different and very important facts:

1) The degree of difference between affected and unaffected great toenails with onychomycosis is

determined by the affected nail area; i.e. the larger the affected area, the slower the growth rate.

2) There are no differences in growth rate between healed great toenails with a history of onychomycosis and the opposite great toenails without a history of onychomycosis.

Essentially, Yu determined that 'different degrees of infection have different nail growth rates' and that nail growth rates return to normal with effective treatment.

When the Yu *et al.* data is examined with respect to the 'growth rate' data from the 2010 pivotal trial shown in Table 3, there is a direct association that can be seen. In the treated moderate and severely diseased toes that attained negative culture after the first two laser treatments (day 1 and day 14),

(a) increased clear longitudinal nail growth rate returned to normal by day 180 and

(b) increased clear area nail growth rate returned to normal by day 180.

The return to normal growth rate in treated moderate and severe mycotic toenails is consistent with the accelerated growth rate seen with the oral/systemic effective treatments by Yu *et al*. In contrast, yet equally important, is that the Noveon pivotal trial data shows no accelerated growth in the mild cases, as the nail bed and growth center matrix is not infected or injured to begin with, and is already growing at a normal rate.

These data speak in favor of negative mycology as the key to any successful onychomycosis therapy, independent of the method used to achieve it. This is most likely true because fungal keratinase is a proteolytic enzyme that will attack the disulfide (-S-S-) bond of the keratin amino acids and digest the nail, nail bed and matrix cells. When the fungi are killed, and therefore no longer producing keratinase, the nail begins to grow out in a clean manner, at a normal speed [13].

4. 2010 *in vitro* antifungal potentiation data

In 2010, Nomir Medical reported that Noveon laser pre-treatment of Methicillin resistant *Staphylococcus aureus* (MRSA) and multi-drug resistant *Escherichia coli in vitro*, led to the significant potentiation of erythromycin, tetracycline and ciprofloxacin in archived and modern clinical strains. Erythromycin, tetracycline and ciprofloxacin all succumb to efflux pumps in the plasma membranes, and the postulated mechanism of potentiation was an optically mediated reduction of plasma membrane potentials ($\Delta\Psi p$) that caused an attenuation of the energy-dependent efflux systems. When erythromycin and tetracycline were tested side-by-side to rifampin and trimethoprim, substantial potentiation was found for both the 1st generation macrolide and ketolide with the pre-irradiation of the MRSA colonies, yet no net benefit (beyond the laser photo-damage) was seen with rifampin and trimethoprim.

Table 3. Increased clear longitudinal nail growth and clear area nail growth rate in the moderate and severe cases that attained negative culture after the first 2 treatments.

Eligible toes – Day 180 **n = 37 Treated: 26 Control: 11**					
		MILD	**MODERATE**	**SEVERE**	**Total**
Negative culture average attained at day 14	Treated	50%	43%	67%	54%
	Control	25%	17%	0%	19%
Clear longitudinal growth average at day 180 (mm)	Treated	3.48	2.75	2.05	2.76
	Control	2.34	-0.18	-1.97	0.06
Clear area growth average at day 180 (mm^2)	Treated	12	6.7	16	11.6
	Control	11	-0.7	-133	-41

The lack of potentiation with the rifamycin and the dihydrofolate reductase inhibitor in MRSA is a result of the fact that the pathogen does not have $\Delta\Psi p$ or ATP-driven efflux pumps that act on rifampin and trimethoprim [14, 15]. These data led to further testing of the antimicrobial potentiation phenomenon *in vitro* with terbinafine and itraconazole resistant *Candida albicans* [16].

The purpose of the *C. albicans* experiment was to determine if a sub-lethal dose of the Noveon laser would potentiate sub-minimum inhibitory concentrations (MICs) of Terbinafine and Itraconazole against a resistant fungal strain. *Candida albicans* ATCC 14053 was irradiated *in vitro* with 8640 J/cm^2 over 30 minutes in saline, and the samples were then plated in quintuplicate (against control) on sub-MICs of terbinafine (0.5 ug/ml) and itraconazole (0.5 ug/ml).

With both itraconazole and terbinafine, the combination of sub-lethal 870 nm/930 nm energy and antifungal sub-MICs killed ~85% more colony forming units (CFU) than the sum of the individual activities of each treatment alone. These data confirm a correlation of synergy of the antifungal molecules with the 870 nm/930 nm light therapy *in vitro* with *Candida albicans*. In addition, there was a statistically significant difference in CFU distribution between control and experimental colonies (terbinafine $P = 0.0143$, and itraconazole $P = 0.0090$). It was postulated that;

(a) the observed antifungal synergy resulted from a photo-biological attenuation of ATP-dependent macromolecular synthetic pathways, via disruption of mitochondrial $\Delta\Psi$ and endogenous generation of reactive oxygen species (ROS), and

(b) this phenomenon could potentially be exploited in human antifungal therapy [16].

There is also a strong possibility that efflux pumps in the resistant candida were photo-biologically attenuated with the 870 nm/930 nm energy in a similar manner to the attenuation that was shown with MRSA and *E. coli* [14, 15, 17].

5. 2012: A 270-day clinical and mycological review of the 2010 pivotal onychomycosis study

In 2012, Landsman and Robbins [18] reviewed the 270-day clinical and mycological data from the 2010 pivotal onychomycosis study and found that 38% of the treated population had negative culture and negative microscopy at day 270, qualifying as 'mycological cures'. These mycological cures even occurred in severe disease. They also reported by direct inspection from day 180 to day 270 that 35% of the treated cases (those with available day 270 pictures) continued to improve [11, 18].

6. 2014: A 199-patient retrospective study of Noveon onychomycosis therapy

In 2014, the results of a 199-patient retrospective study that included full clinical topical antifungal homecare regimens for tinea pedis were published [19]. This study using the commercial Noveon Nail Laser included 199 subjects (687 toes) from 12 different treatment sites across the United States. The top-line data was reported as follows:

(a) 95% of patients showed improvement in their onychomycosis from baseline

(b) there was an 87% reduction in visible infection, measured and recorded as toes originally assigned to the 'severe' category that improved to the mild or moderate disease category

(c) 32% of toes achieved a 'complete cure' with no visible sign of infection

(d) there were no adverse effects reported

Figure 5 shows a case from the retrospective trial, involving treatment with the commercial Noveon unit and 'hands-free' automated toe-clips.

The increased efficacy seen in the retrospective trial is most likely the result of two factors:

1) All affected toes on a given foot were treated instead of just the halux

2) Full OTC homecare topical antifungal regimens for tinea pedis were given to all patients, unlike the pivotal study, to prevent reinfection of the nails

When these data are examined with respect to the analysis of Szepietowski *et al.*, the increased clinical efficacy that was seen is logical [7]. To further understand the critical necessity of a homecare regimen with any onychomycosis therapy, Daniel *et al*. in 2006, discussed the necessity of complete fungal eradication from the 'pedal reservoir' to prevent chronic fungal infections [20]. Also, as

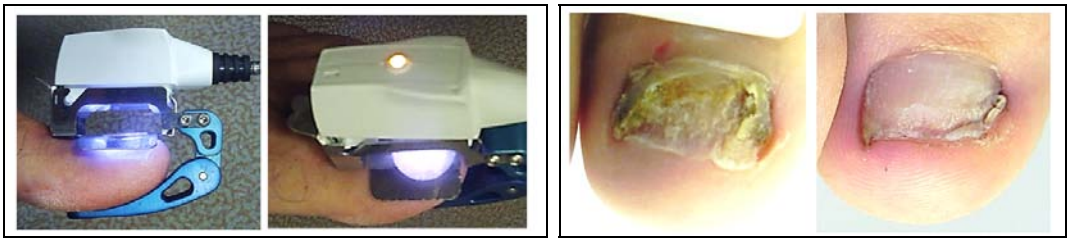

Figure 5. Mycotic toes treated with the Noveon in the retrospective study.

far back as 1957, Strauss and Kligman suggested that, "There is no need to look for an exogenous source of infection from direct or indirect contact with other persons. The nearest and most abundant source is within the foot itself" [21].

7. 2014: FDA clearance with new indication language

In March 2014, as a result of the pivotal clinical trial data and submitted retrospective data from the 199-patient retrospective analysis, the Noveon laser was granted a new FDA clearance for the treatment of onychomycosis. The 2014 clearance language states: "The Noveon® is indicated for the temporary increase in clear nail in patients with onychomycosis (e.g., dermatophytes – *Trichophyton rubrum* and *T. mentagrophytes*) only when used together with topical antifungal drug therapies approved to treat the accompanying tinea pedis and/or approved to treat onychomycosis".

This new clearance language is the first to recognize that:

(1) a patient's tinea pedis must also be treated to see sustained improvement in onychomycosis, as tinea pedis treatment prevents re-infection of the nails [7, 20, 21-23], and

(2) laser treatment should concurrently be performed with topical onychomycosis therapies.

This new clearance language is significant in two respects. First, from an infectious disease perspective, the indication has evolved to recognize tinea pedis as a major etiology for onychomycosis [20, 21]. Second, it takes into account not only the published *in vitro* antifungal potentiation data as being relevant, but also the published retrospective study data, clearly correlating that antifungal homecare amplifies the 870 nm/930 nm optical onychomycosis treatment [24].

8. 2013-2015 anecdotal reports concerning: (a) oral antifungal potentiation in non-responsive (laser) therapy of onychomycosis, and (b) antagonistic effects of oil-based topical antifungals on laser therapy

In 2013, Gupta *et al*., in a lengthy review of the literature, searched the PubMed, EMBASE and CENTRAL data bases for clinical trials on fluconazole monotherapy for culture-proven dermatophyte onychomycosis, and analyzed fluconazole doses, cure rates and duration of therapy. Gupta found that the optimal dose and regimen for therapy in the treatment of dermatophyte onychomycosis was 150 mg weekly for more than 6 months. They found no evidence of increased efficacy resulting from weekly doses up to 450 mg [25]. With this data in mind, the following regimen (Table 4) was formulated and suggested to clinicians who requested dosing recommendations for non-responsive laser cases, based on the published *in vitro* anti-fungal potentiation data with the Noveon system. This regimen was suggested to clinicians to be dispensed in the week before each laser treatment.

The regimen was recommended in the week before each laser treatment in a Noveon therapy

Table 4. Oral fluconazole regimen suggested to clinicians for non-responsive laser cases, which is to be added to a second round of laser therapy in the week before each laser exposure.

Fluconazole	Day	Laser treatment
150 mg	1	NA
150 mg	3	NA
150 mg	5	NA
0	7	Yes

schedule, and represents only 16% of what was recommended by Gupta as an optimal time (24 weeks) of oral therapy [25].

The group of clinicians that followed this oral fluconazole regimen reported that the intermittent dosing of the patient for the 7 days before each laser therapy with the Noveon laser greatly improved the efficacy of the laser in re-treatment of those cases that did not respond to the laser alone, the first time.

If one were to analyze this anecdotal clinical data through the principal of parsimony (i.e. choose the simplest scientific explanation that fits the evidence), one would simply look for the published *in vitro* and *in vivo* antibiotic potentiation data with 870 nm/930 nm, and the published *in vitro* and retrospective antifungal potentiation data [14-16, 19]. However, the correlation between the prior published data and the clinical anecdotal reports of enhanced efficacy in onychomycosis therapy does not prove causation. A controlled study needs to be performed with the modified oral fluconazole regimen alone vs the laser/fluconazole combination to show a true causation for potentiation in non-responding cases.

While the clinicians observing success may be tempted to state *post hoc ergo propter hoc* (after this, therefore because of this), at present there is not enough data to simply affirm causation. However, if onychomycosis cases treated with the Noveon laser that are classified as 'non-responders' to the laser alone later on show enhanced response with the combined therapy in a completed trial, it would be a very large step forward for the treatment of the most difficult cases of this disease.

Therefore, the following can be appropriately stated:

(a) Given prior published *in vitro* and *in vivo* studies concerning documented antibiotic and antifungal potentiation, the concept of this phenomenon also working on a clinical level against onychomycosis is credible *a priori*, and

(b) The antifungal potentiation phenomenon has a scientifically acceptable rationale [26].

9. Antagonistic effects of oil-based topicals for onychomycosis on Noveon laser therapy

Every clinical report that Nomir Medical has received since 2013 concerning oil-based topical antifungals for onychomycosis has described their antagonistic effects on 870 nm/930 nm laser onychomycosis therapy. The use of oils has been reported to decrease laser efficacy, and the secession of these products with laser re-treatment has universally resulted in the return to normal treatment efficacy, with Noveon onychomycosis therapy.

Oils are used as delivery vehicles for antifungal molecules such as tolnaftate, that come in solution (mineral oil or jojoba oil), which are classified as emollients [27]. Podiatric patients use oil emollients specifically to keep skin moist. The terms 'emollient' and 'moisturizer' can be used interchangeably as oils 'trap the water in the skin' [28]. Using emollients as a vehicle for antifungal drug delivery for onychomycosis is a debatable concept, as excessive moisture is one of the causative etiologies for onychomycosis [29].

It may be that the antagonistic effects of oils that the clinicians are reporting are based on their moisture enhancing function, thereby:

(a) keeping the biofilm component of mycotic nails and dermatophytomas moist and preserving fungal resistance mechanisms [30-32], and

(b) keeping the conidia of the dermatophytes moist, and assisting them in protection against the environmental stress of desiccation, and heat from the laser [33].

Finally, there could be a reflection or refraction of the laser energy away from the mycotic nail that is impregnated with the oil, thereby decreasing the laser treatment dose based on the reflective and refractive index of the oil being used [34].

CONCLUSION

Based on seven years of studies and clinical data, the following are the 'Best Practice Recommendations' for clinicians utilizing the Noveon Laser system for the treatment of onychomycosis:

1) Identify fungus as the causative agent before treatment through culture, periodic acid–Schiff stain, or polymerase chain reaction [35, 36].

2) Debride nails and immediately begin a twice daily topical home care treatment (azole liquid-based topical antifungals twice/day) on the feet and nails of the patients, ten days before first laser therapy [37].

3) Explain the homecare procedures to all patients, especially those who are less educated. Carefully describing the importance of the antifungal homecare regimen is critical to ensuring treatment success [38].

4) Encourage the patients to use anti-fungal product in their shoes [39].

5) Avoid oil-based antifungals for laser patients [28-34].

6) For non-responsive cases, treat a second time with a modified oral fluconazole regimen and laser therapy, as fluconazole is a proven safe oral antifungal at the dosages described, and there are anecdotal reports for potentiation with 870 nm/930 nm therapy [40].

7) As it has been shown that even topical cationic dyes do not penetrate dermatophytoma biofilms in severely mycotic nails, debriding nails and immediately beginning the modified oral fluconazole regimen (at the outset of 870 nm/930 nm laser onychomycosis therapy) for the most severe cases should be beneficial to the therapy [41].

CONFLICT OF INTEREST STATEMENT

Dr. Eric Bornstein is the Chief Science Officer and Chief Medical Officer of Nomir Medical Technologies, the inventor of the 870 nm/930 nm phototherapy device. Dr. Bornstein is employed by Nomir and retains stock in the company. Dr. Annette Joyce utilizes a Noveon laser in her podiatric practice, and is a consultant for Nomir Medical Technologies.

REFERENCES

1. Neuman, K. C., Chadd, E. H., Liou, G. F., Bergman, K. and Block, S. M. 1999, Biophysical Journal, 77(5), 2856-2863.
2. Neuman, K. C. 2002, Single Molecule Study of RNA Polymerase Transcription Under Load, Doctoral dissertation, Princeton University.
3. Bornstein, E. S and Michelon, M. 2009, Abstract presented at American Society for Laser Medicine and Surgery, National Harbor, Maryland.
4. Bornstein, E., Hermans, W., Gridley, S. and Manni, J. 2009, Photochemistry and Photobiology, 85(6), 1364-1374.
5. Lim, H. W. 1993, Clinical Photomedicine (Vol. 6), CRC Press, Chapter 1.
6. Boulnois, J. 1986, Lasers in Medical Science, 1(1), 47-66.
7. Szepietowski, J. C., Reich, A., Garlowska, E., Kulig, M. and Baran, E. 2006, Archives of Dermatology, 142(10), 1279-1284.
8. Bornstein, E., Robbins, A. and Michelon, M. 2008, Abstract presented at: New Cardiovascular Horizons, September 10-13, New Orleans, LA.
9. Bornstein, E. S. 2009, J. Am. Pod. Med. Assoc., 99(4), 348-352.
10. Klavuhn, K. G. 2000, Illumination geometry: the importance of laser beam spatial characteristics. Laser Hair Removal Technical Note No. 2, Coherent Medical, Pleasanton, Ca.
11. Landsman, A. S., Robbins, A. H., Angelini, P. F., Wu, C. C., Cook, J., Oster, M. and Bornstein, E. S. 2010, J. Am. Pod. Med. Assoc., 100(3), 166-177.
12. Yu, H. J., Kwon, H. M., Oh, D. H. and Kim, J. S. 2004, Clinical and Experimental Dermatology, 29(4), 415-418.
13. R. K. S. Kushwaha and J. Guarro (Eds.). Biology of Dermatophytes and other Keratinophilic Fungi. Revista Iberoamericana de Micología, Bilbao, 2000, 86-92.
14. Bornstein, E., Gridley, S., Wengender, P. and Robbins, A. 2010, Photochemistry and Photobiology, 86(3), 617-627.
15. Bornstein, E. 2014, Trends in Photochemistry & Photobiology, 16, 35-45.
16. Bornstein, E. and Gridley S. 2010, Future strategies for the control of fungal diseases, Edinburgh UK. Aug 1-6.
17. Prasad, R. and Rawal, M. K. 2014, Frontiers in Pharmacology, 5, 1-13.
18. Landsman, A. and Robbins, A. 2012, Journal of the American Podiatric Medical Association, 102(2), 169-171.
19. Bornstein, E. 2014, Podiatry Management, 33(6), 137.
20. Daniel C. Ralph and Nathaniel J. Jellinek. 2006, Archives of Dermatology, 142(10), 1344-1346.
21. Strauss, J. S. and Kligman, A. M. 1957, AMA Archives of Dermatology, 76(1), 70-79.

22. Perea, S., Ramos, M. J., Garau, M., Gonzalez, A., Noriega, A. R. and Del Palacio, A. J. 2000, Clin. Microbiol., 38, 3226-3230.
23. Zaias, N. and Rebell, G. J. 1996, Am. Acad. Dermatol., 35, S17-S20.
24. Evans, E. G. 2001, Br. J. Dermatol., 145(Suppl. 60), 9-13.
25. Gupta, A. K., Drummond-Main, C. and Paquet, M. 2013, Journal of Dermatological Treatment, 24(1), 75-80.
26. Musiol, R., Mrozek-Wilczkiewicz, A. and Polanski, J. 2014, Current Medicinal Chemistry, 21(7), 870-893.
27. Patravale, V. B. and Mandawgade, S. D. 2008, International Journal of Cosmetic Science, 30(1), 19-33.
28. Kelechi, T. J. and Stroud, S. 2004, Adv. Nurse Pract., 12, 67-84.
29. André, J. and Achten, G. 1987, International Journal of Dermatology, 26(8), 481-490.
30. Burkharta, C. N., Burkhart, C. G. and Gupta, A. K. 2002, Journal of the American Academy of Dermatology, 47(4), 629-631.
31. Costa-Orlandi, C. B., Sardi, J. C. O., Santos, C. T., Fusco-Almeida, A. M. and Mendes-Giannini, M. J. S. 2014, Biofouling, 30(6), 719-727.
32. Chandra, J., Kuhn, D. M., Mukherjee, P. K., Hoyer, L. L., McCormick, T. and Ghannoum, M. A. 2001, Journal of Bacteriology, 183(18), 5385-5394.
33. Leng, W., Tao, L., Rui, L., Jian, Y., Candong, W., Wenliang, Z. and Qi, J. 2008, BMC Genomics, 9, 303.
34. Jiusheng, L. 2010, Applied Spectroscopy, 64(2), 231-234.
35. Reisberger, E. M., Abels, C., Landthaler, M. and Szeimies, R. M. 2003, British Journal of Dermatology, 148(4), 749-754.
36. Faggi, E., Pini, G., Campisi, E., Bertellini, C., Difonzo, E. and Mancianti, F. 2001, Journal of Clinical Microbiology, 39(9), 3382-3385.
37. Westerberg, D. P. and Voyack, M. J. 2013, American Family Physician, 88(11), 762-770.
38. Kyle, J. A. 2013, US Pharm., 38(6), 51-54.
39. Feuilhade de Chauvin, M. 2012, Journal of the European Academy of Dermatology and Venereology, 26(7), 875-878.
40. Smith, S. W., Sealy, D. P., Schneider, E. and Lackland, D. 1995, Southern Medical Journal, 88(12), 1217-1220.
41. Souza, L., Simone, V. and Carvalho Botelho, A. 2014, Anais brasileiros de dermatologia, 89(1), 184-186.