CLINICAL MANAGEMENT extra

Photobiomodulation Therapy for Wound Care: A Potent, Noninvasive, Photoceutical Approach

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GENERAL PURPOSE:

To provide background and examine evidence for the therapeutic application of light energy treatments for wound healing.

TARGET AUDIENCE:

This continuing education activity is intended for physicians, physician assistants, nurse practitioners, and nurses with an interest in skin and wound care.

LEARNING OBJECTIVES/OUTCOMES:

After completing this continuing education activity, you should be better able to:

1. Explain the basics of lasers, light-emitting diodes, and light-tissue interactions as they apply to photobiomodulation therapy.

2. Summarize the results of the authors' literature review of the evidence regarding the therapeutic applications of photobiomodulation treatments for wound healing.

ABSTRACT

OBJECTIVE: To provide background and examine evidence for the therapeutic applications of light energy treatments for wound healing.

METHODS: A search was performed in PubMed for peer-reviewed scientific articles published in the last 5 years using the search terms "photobiomodulation therapy" and "low-level laser therapy," and these terms combined with "wound," using a "human species" filter. This search yielded 218 articles on photobiomodulation therapy or low-level laser therapy and wounds. Of these, only articles on in vivo wound care using light treatments were specifically included in this review (n = 11).

RESULTS: The wound healing effects of low-dose laser treatments were first described over 50 years ago. Various doses ranging from 0.1 to 10 J/cm^2 and wavelengths ranging from 405 to 1,000 nm appear to provide therapeutic benefits for a broad range of chronic wounds. A range of light energy sources from LEDs to lasers have been used and have specific advantages and limitations. There is a lack of consensus on standardized treatment parameters such as wavelengths, dose, and therapeutic outcomes in the reviewed studies, preventing direct comparison and clinical protocol recommendation. An expert opinion based on ongoing research studies and reported literature is offered.

CONCLUSIONS: Noninvasive, economical, and multipurpose light devices are an attractive tool for wound management. However, there is an urgent need in the wound care community to develop optimal clinical protocols for use based on well-designed, rigorous clinical research studies.

KEYWORDS: LASER, LED, literature review, LLLT, low-level laser therapy, PBM, photobiomodulation therapy, wound healing

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INTRODUCTION

The use of light therapy dates back to ancient civilizations, going as far back as the ancient Egyptians and Indians, who used sunlight (heliotherapy) for healing and promoting health.[1] The therapeutic use of light energy was more fully appreciated in the late 19th century when a Danish physician-scientist, Niels Ryberg Finsen, demonstrated the benefits of red and blue light in the treatment of lupus vulgaris and was recognized with the 1903 Nobel Prize in Medicine and Physiology.[2] In 1960, the L.A.S.E.R. (Light Amplification by Stimulated Emission of Radiation) by Theodore Maiman was invented, based on theoretical work by Albert Einstein in 1917. This brought renewed attention to the therapeutic light energy field.[3,4] The monochromatic, coherent, and collimated nature of lasers led to immediate interest in their biologic effects. In 1967, Endre Mester,[5,6] a Hungarian physician-scientist, reported that low-dose laser treatments were capable of promoting wound healing and hair regrowth in mice. He termed this phenomenon *photostimulation* and went on to demonstrate the efficacy of this treatment in human patients with skin ulcers.[7]

EVOLUTION AND CURRENT CONSENSUS ON TREATMENT TERMINOLOGY

Several terms have been used to describe low-dose light treatments. The most popular include cold laser therapy and low-level laser therapy (LLLT). However, these are poor descriptors; there is no actual "cooling" during these treatments, and the terms "low" and "level" are vague. Moreover, there is considerable evidence for the utility of nonlaser devices in mediating these therapeutic benefits, indicating that the term "laser" is inaccurate. Hence, in 2014, the North American Association for Light Therapy and the World Association for Laser Therapy agreed by consensus to promote the term *photobiomodulation* (PBM) therapy as

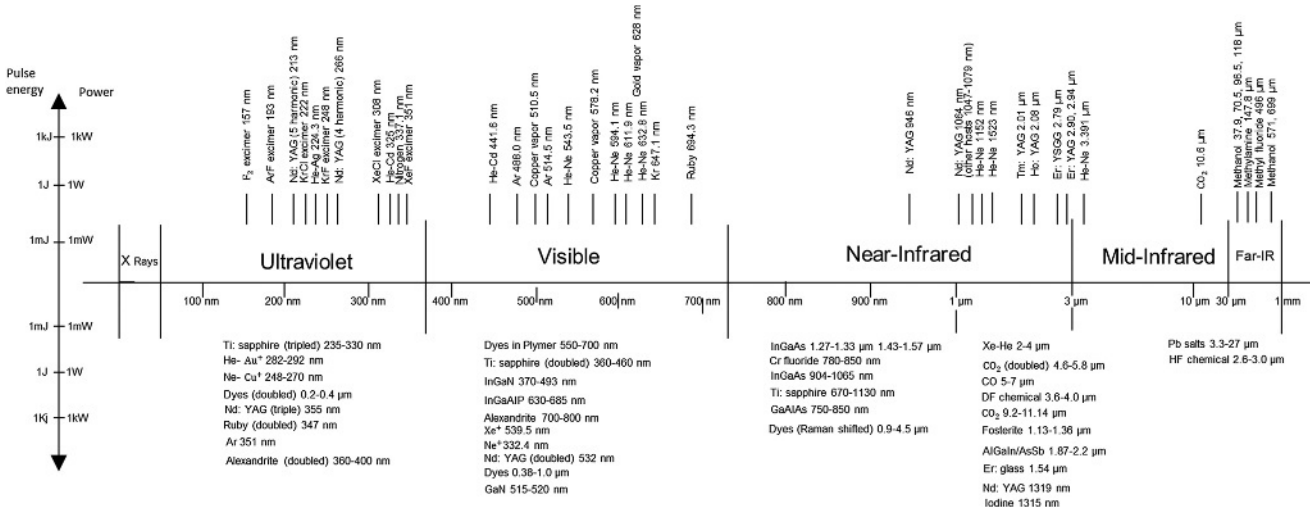
> *a form of light treatment that utilizes nonionizing forms of light sources, including lasers, light emitting diodes (LEDs) and broadband light, in the visible and infrared spectrum, involving a nonthermal process with endogenous chromophores eliciting photophysical (i.e., linear and nonlinear) and photochemical events at various biological scales. This treatment results in beneficial therapeutic outcomes including, but not limited to, the alleviation of pain or inflammation, immunomodulation, and promotion of wound healing and tissue regeneration.*[8]

DEVICES FOR PBM THERAPY

Significant improvements in laser technologies have enabled a dramatic reduction in footprint (size) and cost of laser technology since its invention in the 1960s. The early gas (helium-neon) or crystal (ruby, alexandrite) lasers have been largely replaced with newer, compact, and more economical semiconductor-based lasers (eg, gallium-aluminum-arsenide, aluminum gallium indium phosphide, indium gallium arsenide, and gallium-arsenide, among others).[9] This new semiconductor technology has also enabled the development of several newer wavelengths, spanning a broad range from ultraviolet to the far-infrared spectrum (Figure 1). In the 1990s, the introduction of solid-state, high-efficiency LEDs revolutionized the lighting industry, including biomedical applications of light.[10] The use of LEDs for PBM therapy has become more widespread, and its clinical efficacy has been clearly demonstrated.[11] However, there are several questions about the physical nature of LEDs and the precise biologic responses they elicit compared with lasers (Table 1). The clinical implications of coherence, polarization, half-width full-maximum, beam divergence, and

Figure 1.

VARIOUS COMMERCIAL LASER WAVELENGTHS USED IN CLINICAL APPLICATIONS[60]



the potential thermal interactions of various PBM devices on clinical safety and efficacy remain to be fully explored.[12–15]

LIGHT-TISSUE INTERACTIONS: A PHOTOCEUTICAL APPROACH TO PBM THERAPY

Light is a physical form of energy. To understand its therapeutic applications, a fundamental understanding of its biologic interactions is pertinent. A brief overview of light therapy terminology is presented (Table 2), and the reader is referred to more detailed descriptions of the physical phenomenon and characteristics of biologic tissue interactions.[11,16,17]

Whereas the high-power effects of lasers are well characterized, the low-power applications are still being investigated. Certain areas have benefitted from from fundamental explorations of visual phototransduction, sunlight and vitamin D metabolism, and melatonin and pineal gland biology of circadian rhythms. Various applications are being actively investigated, and some

Table 1.

COMPARISON OF LASER AND LED DEVICES USED FOR PBM THERAPY

Parameters	LED	LASER
Working principle	Electroluminance	Stimulated emission
Acronym	Light-emitting diode	Light amplification by stimulated emission of radiation
Response	Slower response	Faster response
Driving current	50–100 mA	5–40 mA
Nature of emitted light	Noncoherent, usually noncollimated, includes color shades (larger HWFM); nonpolarized	Coherent, collimated, monochromatic (very small HWFM); polarized
Junction area during manufacturing	Wide junction area	Narrow and small junction
Bandwidth range	10–50 THz	1–2 MHz
Power to light conversion efficiency	Approximately 20%	Approximately 70%
Numerical aperture of light beam	High	Extremely low
Costs and applications	Low cost, broader applications	High cost, specific application

Abbreviations: HWFM, half width of full maximum; PBM, photobiomodulation.

Table 2.
BASIC TERMINOLOGY FOR PBM TREATMENTS AND LIGHT-TISSUE INTERACTIONS

Parameter	Unit	Description
Wavelength	nm	Wavelength is a measurement of how far a photon will travel in one complete cycle; this can vary from ultrashort cosmic rays (femtometers) to radiofrequency (kilometers). Visible and infrared light are usually referred to in nanometers.
Energy	J	Each photon carries a discrete amount (quantum) of energy (E), where E = h V (E = energy, h = Planck constant, V = velocity). Therefore, a short wavelength = high-frequency and high-energy photons; a long wavelength = low-frequency and low-energy photons.
Fluence	J/cm^2	Refers to energy density, calculated as energy (J) delivered per unit area (cm^2)
Power	W	Power is the rate of delivery of the energy, 1 W = 1 J/s
Irradiance	W/cm^2	Refers to power density, calculated as power (W) over unit area (cm^2)
Continuous wave (CW)	—	Energy is transferred in a continuous mode, beam always "on"
Duty cycle	%	Amount of time light source is actually "on." A CW laser is always "on" 100% duty cycle
Pulsing	Peak power (W), pulse frequency (Hz), pulse width (s), pulse interval (s) and pulse train (s/min)	The energy transfer from a beam can be chopped or divided, and several parameters need to be reported: peak power is stated in watts; frequency is reported in hertz, which refers to number of pulses/s; a pulse width is duration the beam is turned on in seconds; a pulse interval is time pulse is off (s) and a pulse train is a series of pulse widths and gaps during single event (treatment). Average power (W) x of a pulsed beam is calculated as peak power (W) pulse width (s) x pulse frequency (Hz); this is especially important in dispersing thermal energy during treatment and preventing inadvertent damage.
Frequency	Hertz (Hz)	Refers to cycles/s, inversely related to wavelength as frequency (γ) = speed of light (c)/wavelength (λ). Therefore, a short wavelength = high frequency and a long wavelength = low frequency.
Chromophore	—	The part of the molecule that is responsible for its color; lasers are monochromatic (single color; peak wavelength).
Photon	—	An elementary particle of electromagnetic radiation that has no mass and can transfer energy.
Collimation	—	All beams are directed in a similar direction, and the overall beam diameter is small.
Coherence	—	Photons are vibrating in similar phase (space and time) and beam display properties of interference (constructive or destructive). High coherence enables precise, focused waveforms; lasers beams are inherently coherent and demonstrate constructive interference "speckles," whereas LEDs are noncoherent sources. The coherence of a laser beam is lost as it enters biologic tissue because of its heterogeneity.
Chromaticity	—	Refers to the luminous wave emitted of similar wavelength and energy; assessed as "band" representing half width of full maximum of a given wavelength; lasers are extremely narrow bands, allowing precise chromophore targeting while sparing adjacent tissue structures.
Polarization	—	Refers to the well-defined direction of electromagnetic field with respect to beam direction (photon); can be linear, circular, or elliptical; lasers are inherently polarized, whereas LEDs and broadband lights are not.

Abbreviations: LED, light-emitting diode; PBM, photobiomodulation.

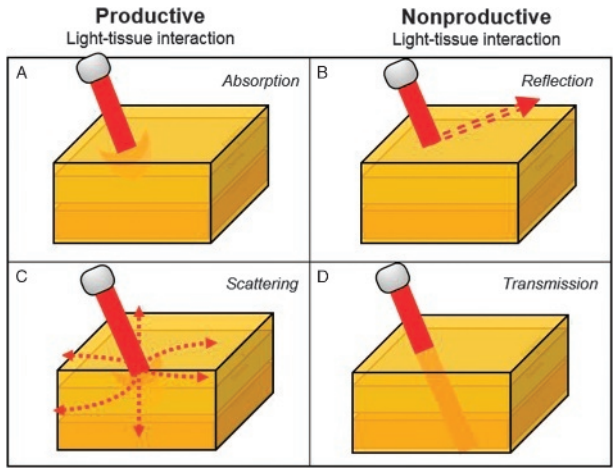
align well to conventional pharmaceutical approaches to biomedical therapies; therefore, the use of low-dose light therapeutics has been termed *photoceutical*.[18,19]

Light-tissue interactions are broadly categorized into four processes: absorption, reflection, scattering, and transmission (Figure 2).[10] For the purposes of classifying therapeutic benefits, these interactions can be broadly divided into the productive (absorption and scattering, Figures 2A and B) or the nonproductive (reflection and transmission, Figures, 2C and D). The latter processes are exploited for various forms of optical imaging and spectroscopy. These interactions are determined by the physical properties of the light; for example, wavelength, pulsing, total energy and duration, and tissue composition determine the eventual therapeutic efficacy.[20–23]

Transmission is the noninteractive passage of a photon through biologic tissue. This is usually seen with high-energy photons and is not used directly for this therapy. Reflection can vary with the angle of the light beam, with the least reflection occurring when treatment beam is perpendicular to tissue.[20] Scattering is a result of the heterogeneity of biologic tissues. This process occurs when the incident photon changes its direction of propagation based on differences in refractive indices. Scattering enables the incident light to spread out but progressively reduces penetration, thereby limiting the depth of treatments. Among molecules, dermal collagen has been noted to be predominantly responsible for light scattering. The ability of the skin dermis to act as a turbid matrix results in scattering that approximates an inverse function of wavelength. This implies that shorter (eg, ultraviolet, visible) wavelengths have the greatest scattering, limiting the depth of penetration and increasing the possibility of absorption.

The effectiveness of light-tissue penetration in human skin is predominantly associated with the absorption spectra of three major biologic chromophores: melanin in the epidermis, hemoglobin (oxyhemoglobin and deoxyhemoglobin) in blood within the dermis, and water throughout tissues.[3,14] Blue (435–500 nm) wavelengths are absorbed by melanin, blood, and porphyrins, whereas red wavelengths (620–750 nm) penetrate deeper because it is subject to less absorption by blood and melanin. These major chromophores have the least impact (absorption) in the near-infrared (NIR, 750–950 nm) wavelengths, where water becomes more important. If there are no relevant wavelength-specific chromophores in the tissues, the photons pass through the tissue as total transmission (Figure 2D) without producing any biologic (nonproductive) effects.

Figure 2.
LASER-BIOLOGIC TISSUE INTERACTIONS THAT DETERMINE CLINICAL EFFECTIVENESS



Evoked biologic responses are a direct result of the transfer of physical light energy into a biochemical or biophysical change in tissues as the energy progressively attenuates to extinction.[20,24,25] Therefore, the penetration depth of a given light source is a result of not only its inherent wavelength-dependent photon energy (more for blue-red than NIR) but also the presence of relevant biologic chromophores (also more for blue-red than NIR), with the latter predominating. This essentially implies that effective light penetration is equal to the inverse of the wavelength-specific tissue absorption coefficient.

Because of this, the two popular PBM wavelengths used are red and NIR, although blue has been more recently explored.[14,15,26] Red and blue wavelengths are preferred (low penetration, high absorption) for treating superficial tissues, whereas NIR is preferred (low absorption, high penetration) to treat more deep-seated tissues (Figure 3).[8] More recently, research has delineated wavelength-specific responses from specific biologic chromophore absorption versus pure energy transfer responses (Rahman SU, et al, unpublished data, January 2019). Overall, careful examination of light-tissue interactions is critical to enable robust, reproducible clinical treatment parameters.

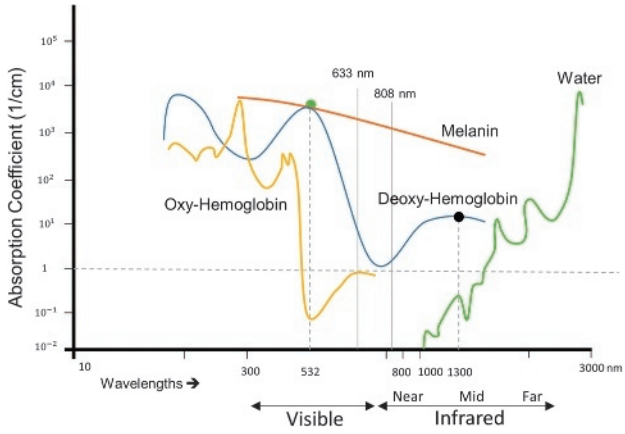
MOLECULAR MECHANISMS OF PHOTOBIOMODULATION THERAPY

It is increasingly apparent that light-biologic tissue interactions can evoke pathophysiologic (disease) and anatomy-specific responses. The four major biologic responses evoked by PBM include alleviation of pain and inflammation, a modulated immune response, and tissue healing and regeneration.[12] There are three PBM molecular mechanisms that appear to operate within discrete cellular compartments. First, and the most well-studied mechanism, is the absorption of specific wavelengths of light by a key enzyme of the respiratory chain within the mitochondria, cytochrome C oxidase (CCO). Seminal work[27,28] has demonstrated the action spectrum of CCO runs from the yellow through the red wavelengths (580–700 nm) with discrete peaks around 635 and 730 nm. Absorption of the incident photons by the CCO initiates a photochemical cascade increasing adenosine triphosphate (ATP) and reactive oxygen species (ROS) generation within the electron transport chain. This process involves interaction of ATP synthase with the coenzyme nicotinamide adenine dinucleotide and triggers the combination of inorganic phosphate with adenosine diphosphate to synthesize ATP.

Reactive species are short-lived chemical intermediaries that readily chemically interact with biologic molecules.[29] They play critical roles in cell signaling, regulation of cell cycle progression, enzyme activation, and nucleic acid and protein synthesis. Because

Figure 3.

ABSORPTION SPECTRUM FOR VARIOUS BIOLOGIC CHROMOPHORES THAT AFFECT TISSUE RESPONSES TO SPECIFIC LIGHT WAVELENGTHS[61]



The major individual chromophores are noted; although many other biologic elements are known (eg, porphyrins, cryptochromes), their precise spectral characteristics remain to be carefully investigated.

oxygen is a predominant electron acceptor in the electron transport chain, the common ROS include hydrogen peroxide, superoxide, and nitric oxide. In specific cell types (eg, endothelium and cardiac myocytes), small amounts of nitric oxide complexed with CCO are released following light absorption.[30,31]

A second PBM mechanism focuses on light-modulated cell membrane receptors and transporters such as the opsins, transient receptor potential V1, and aryl hydrocarbon receptor.[32–34] Absorption of light results in modulation of several key ions such as calcium (Ca^{2+}), protons (H^+), and Na^+/K^+ between the cytosol and extracellular matrix that play key roles in cellular physiology. This specific mechanism is particularly relevant for the analgesic and inflammation modulation responses noted with PBM therapy.

Finally, the third extracellular mechanism has been recently described by the authors,[35] involving activation of a multifaceted growth factor, transforming growth factor β (TGF-β), which acts on several cell types in a context-dependent manner. Researchers observed that PBM-induced ROS was sensed by a redox-sensitive methionine that leads to a change in the latent TGF-β1 conformation, resulting in its activation.

These three mechanisms provide a robust biologic rationale for PBM interventions in specific pathophysiologic contexts. However, several other PBM mechanisms that are relevant to specific anatomical (eg, wounds on limbs vs mucosa) or disease-specific (eg, venous vs diabetic wounds) pathologies are being actively investigated.

PBM THERAPY FOR WOUND HEALING

There are several well-documented effects of PBM therapy in promoting wound healing.[36,37] Among the PBM mechanisms outlined previously, extracellular activation of TGF-β1 appears to be a central wound healing pathway because of its potent effects on a large range of cells in the wound milieu, including hemostasis (platelet-derived TGF-β) and inflammatory cells (macrophage-derived TGF-β) and its prominent role on the extracellular matrix (latent TGF-β–binding protein-associated TGF-β1 sequestered in the matrix).

Direct effects of PBM on pain and inflammatory mediators such as histamine, serotonin, bradykinin, and prostaglandins have been documented.[38] Further, PBM treatments can promote epithelial migration and proliferation, endothelial migration and organization for angiogenesis, inflammatory infiltration, macrophage phagocytoses, immune surveillance, fibroblast matrix synthesis, and wound contraction, among other things.[12] Recent studies have highlighted the efficacy of PBM treatments to promote epithelial cell functions, especially their basal colony-forming units (stem/progenitor cells) that not only can aid re-epithelialization but also promote regeneration of skin appendages such as glands and hair follicles.[32,39]

There is also now a better understanding of PBM effects on cell lineage-specific responses and maximal dose thresholds that is enabling precise clinical dosing.[40,41] The PBM dose delivery with a small laser spot size versus multiple diodes or large LED arrays requires careful attention to dosimetry that can have a dramatic effect on healing responses (Figure 4).[12,42]

Literature Search

On August 17, 2018, authors searched the MeSH terms "PBM" (photobiomodulation therapy) and "LLLT" (low-level laser therapy) and the combination of these with "wound" on PubMed using a filter for studies in humans published in the last 5 years. This exercise was not directed at a comprehensive literature review on PBM and wounds; the 5-year time limit was focused on combining research on current PBM technologies, sound therapeutic rationale, and the current understanding of this treatment modality. Of 218 articles resulting from the search based on these parameters, 11 relevant articles were selected that directly addressed the use of PBM/LLLT applications in chronic wounds. All articles focusing on either surgical debridement or photodynamic therapy that represented higher-powered or thermal effects were excluded.

Search results are discussed here under individual wound types based on increasing complexity of wound etiopathogenesis and treatments with PBM therapy. A specific emphasis is placed on device parameters and clinical delivery protocols, followed by expert author opinion based on both ongoing research and clinical studies.

PBM THERAPY FOR CHRONIC WOUNDS

Chronic wounds are defined as wounds that do not heal for at least 180 days (3 months) and do not proceed through the normal reparative process.[43] These wounds usually present with lack of tissue integrity and volume, pain, and persistent inflammation and are often infected.[44] The initiating injury in these wounds can vary from physical (pressure, burns, or radiation), chemical, electrical, or immunologic injuries that all result in persistent tissue damage. Literature searches for individual clinical presentations of chronic wounds based on inciting injury are described in the following sections.

Burn Wounds

In a recent case series by de Oliveira et al,[45] low-dose LED therapy (658 nm red) of varying doses and duration was performed to treat second- and third-degree burn wounds. A total of five cases were included in a double-blind, placebo-controlled (contralateral limb, device switched off) study. The treatment device consisted of a cluster of 12 LEDs with peak power of 40 mW, beam size of 0.13 cm^2, and an irradiance of 0.31 W/cm^2. The probe was protected by a translucent film and placed perpendicular to, and in contact with, the skin. The investigators used digital imaging, visual analog scores, and histologic analyses of debrided tissues to assess healing outcomes. All subjects reported less pain and pruritus after PBM treatments, with reduced inflammatory exudate and fibrin with improved re-epithelialization and granulation tissue organization compared with contralateral control sites.[45]

Expert Opinion. Despite significant heterogeneity among subjects, the investigators reported therapeutic benefits with a single wavelength (red) LED device. Although this device was a 12-LED cluster probe, the authors note treatment limitations of adequately covering large wound surface areas uniformly. Methods to optimize these delivery protocols have been suggested and are being developed, specifically accounting for dosing per unit area (tissue surface irradiance) and treatment time. Interestingly, various doses tested in this study showed some efficacy, and careful calibration in future studies should be investigated.

Venous Ulcers

Vitse et al[46] recently undertook a prospective, randomized, double-blind, placebo-controlled human clinical study with 24 subjects. The study was designed with two groups; there were no significant differences between subject characteristics in terms of age, gender, or wound parameters. Both groups received standard wound care including debridement of necrotic tissue, hydrating wound dressings, daily application of compression (30 mm Hg), support stockings, and nutrition counseling. The investigators used a 635-nm (red) laser consisting of three diodes at 17.5-mW output power each, with an irradiance of 2.46 mW/cm^2 for 20-minute treatments, resulting in a total fluence of 2.95 J/cm^2. Treatments were repeated twice a week for 12 weeks. As controls, the investigators used a sham treatment device indistinguishable from the treatment device to both the subject and treatment-performing investigator. Wounds were assessed at 2 and 12 weeks with arterial blood flow measurements (laser Doppler), pain score (visual analog scale 0–100), record of pain medications taken, and digital photography (laser planimetry). Results included reduced pain in PBM-treated wounds at 4 and 12 weeks. However, there was no significant statistical significance ($P > .05$) compared with the placebo group.[46]

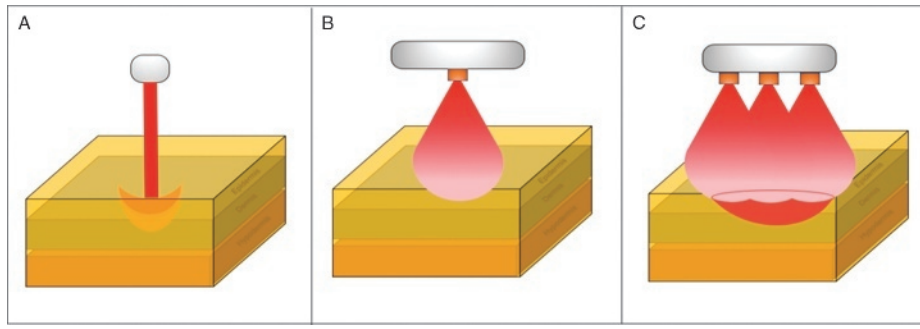
Expert Opinion. The positive results in this study appear to arise from the reduced sample size and researchers choosing low-responding/nonresponding wounds (ulcer areas 30% following a week of routine wound care). Further, the PBM protocol lacks several key descriptors (delivery details, coverage of wound surfaces), and the dosing appears to be rather inadequate (low irradiance-fluence, lack of adequate repetitions). Optimization of these parameters in future studies, along with routine venous wound management approaches, could promote PBM therapy as a potent adjuvant in venous ulcer care.[47] Further, specific emphasis on dose and wavelength from laboratory studies demonstrating the ability of PBM treatments to modulate endothelial biology could be very informative.[48]

Pressure Ulcers

In a well-designed study, Taradaj et al[49] performed a single-blind, randomized clinical study to assess the effects of three common wavelengths to treat pressure ulcers. Their study recruited 71 subjects and placed them in four groups: (1) placebo (routine standard of wound care and laser treatments with device switched off), (2) 658 nm (red laser), (3) 808 nm (NIR laser), and (4) 940 nm (NIR laser). All groups received routine care for their pressure wounds including daily wound irrigations with a 0.9% physiologic saline solution and 1% hydrophilic silver sulfadiazine cream along with adapted footwear, self-care, and the prevention of disabilities.[50] Wound areas were assessed with planimetry using an NIR camera. The lasers were used at a power output of 50 mW with a spot size of 0.1 cm^2 for an effective fluence of 4 J/cm^2 at the tissue surface. Treatments were performed with a scanner 50 cm from the wound surface with a movement frequency at 20 Hz along the ordinate axis and 0.5 Hz along the abscissa axis. All groups were homogenous in all participant characteristics. Their results noted that the 658-nm laser treatment was most effective (70% closure, $P < .05$) at promoting wound closure. In contrast, the 808- and 940-nm laser treatments (31% and 30% closure, respectively) did not appear to improve healing rates significantly compared with the placebo group (28% closure).[49]

Figure 4.

THE DIFFERENCES BETWEEN LASER (A), SINGLE-LED (B), OR MULTIPLE-LED ARRAY (C) ILLUMINATION OF BIOLOGIC TISSUES[62]



While the laser beam is shown as a coherent and collimated beam that loses these properties when it enters the tissues, the LEDs have a noncoherent, divergent beam that inherently lacks these characteristics. Nonetheless, both light sources have been shown to generate therapeutic PBM responses. The LED array emphasizes the increased beam intensity (which partly overcomes LED lack of tissue penetration) and larger area of tissue coverage that significantly improves its utility compared with the more efficient laser PBM device.

Expert Opinion. The use of a scanning mode with the limited spot size of lasers requires consistent technique to effectively deliver care. This study did a good job of outlining the methods used and represents an effective starting point to develop a more rigorous protocol.[46] Unfortunately, a lack of attention to several PBM treatment parameters has resulted in inconsistent outcomes that are of questionable utility in clinical practice guidelines.[50] Attention to both single treatment dosing (time, power density, and wound coverage pattern) and repetitions (per week and total number of treatments) can further improve future clinical outcomes. Recent evidences have observed specific (but not all) biologic responses appear to respond therapeutically when lower power (energy per photon) of NIR wavelength lasers is compensated with higher visible wavelengths (red photons). Researchers should take care to avoid the thermal effects of NIR and direct attention to their increased tissue penetration. The use of other wavelengths (eg, blue), as mentioned by Taradaj et al,[49] could be helpful to manage pain and infections.

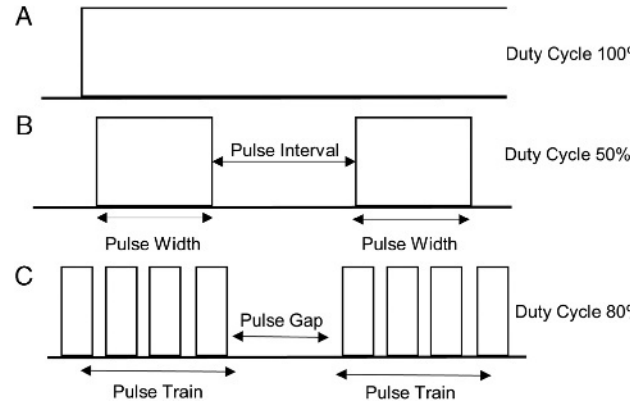
Diabetic Foot Ulcers

In a randomized controlled study by Feitosa et al[51] in 2015, 16 subjects with uncontrolled diabetes and diabetic foot ulcers were divided into two groups. Both groups received routine wound care treatments, whereas one group was also treated with a 30-mW laser at 632.8 nm for a fluence of 4 J/cm^2. Each treatment lasted 80 seconds and was repeated three times a week for 4 weeks. Wounds were assessed by digital imaging, and a visual analog pain score was used. Their results demonstrated a statistically significant ($P < .05$) reduction in wound size and pain scores in PBM-treated wounds at 12 and 30 days compared with controls.[51]

In a study by Mathur et al,[52] 30 controlled subjects with diabetes (fasting blood sugar 200 mg/dL) with at least one diabetic foot ulcer persisting for 6 weeks were treated with a 660-nm laser at 50 mW/cm^2 for 60 seconds daily for 15 days. The investigators assessed wounds with laser Doppler imaging, anterior brachial index, and digital wound imaging. They noted a significant improvement in PBM-treated wounds (30%–50%, $P < .05$) in a majority of subjects compared with minimal changes in the control group.[52]

Figure 5.

THE MODES OF LIGHT SOURCE OPERATIONS CAN BE CONTINUOUS (A) OR PULSED (B, C).



The pulsing characteristics are defined by the pulse duration (width), reported in seconds; pulse intervals, reported in seconds; and pulse frequency (number of pulses per second, in Hz). In more sophisticated pulsing sequences, especially in ultrafast pulses (nanoseconds, picoseconds, or femtoseconds), a series of pulses termed the pulse train are followed by a pulse gap. This is usually reported as time (eg, picoseconds). The duty cycle refers to the time the beam is on during entire treatment. For a continuous wave, this is 100%, although it can vary significantly with pulsing regimens as noted here.

In another study, Carvalho et al[53] examined the utility of combining essential fatty acids (EFAs) as a wound dressing along with PBM treatments. They recruited 32 subjects with controlled diabetes (fasting blood sugar 150–350 mg/dL) and placed them into one of four groups: (1) control (no interventions), (2) EFAs alone, (3) PBM alone, or (4) PBM-EFA treatments. They obtained similar laser Doppler imaging, anterior brachial indices, visual analog scale pain scores, and digital wound imaging where they observed a statistically significant reduction ($P < .05$) in pain and wound area in the PBM and PBM-EFA groups compared with controls and EFAs alone.[53]

Finally, Ruh et al[54] investigated the potential benefits of PBM therapy in a case series with eight subjects with diabetes who were immobilized for at least 12 months and presented with pressure ulcers (grades II-IV). They performed PBM treatments with a 100-mW laser at 660 nm for 12 seconds per point, with each point 2 cm apart for total fluence of 2 J/cm^2. Treatments were performed daily for 12 days; wounds were analyzed clinically, and tissues were collected for mRNA analyses for cytokine profiles. Their results demonstrated significant improvements in wound areas following PBM treatments that correlated with increased prohealing factors including vascular endothelial growth factor (angiogenesis) and TGF-β (matrix and epithelial closure), whereas TNF-α (inflammation) levels were reduced. These results indicate that the clinical improvements noted with PBM treatments appear to correlate with tissue factors representing improved healing responses.[54]

Expert Opinion. The two major points highlighted in these studies are that attention to the clinical protocol should be based on underlying pathology (metabolic, inflammation, or neurological) as well as optimized delivery regimens.[38] Direct assessment of "tissue surface irradiance" provides a more reliable delivery parameter than average power of the unit, irradiance at probe output, or distance-to-target measurements.[55] Changes in molecular markers offer further objective assessment of wound healing responses, strengthening the evidence for any therapeutic benefits.[56]

CONCLUSIONS

This brief literature review indicates the benefits of PBM therapy for various types of wounds. There are several studies on the therapeutic efficacy of PBM therapy for oral mucositis, ultraviolet skin damage, and radiation dermatitis that were outside the scope of this review.[42,57–59]

A major limitation noted in this review was the wide range of PBM clinical protocols among studies with respect to wavelength, dose, and delivery that prevent a rigorous consensus. Understanding the photobiologic mechanisms of PBM using correct wavelengths is critical for optimal clinical light treatment parameters for desired therapeutic medical and biological outcomes. Nonetheless, within the limits of the presented studies, the clinical benefits noted could serve as templates for development of more rigorously designed clinical studies to evaluate PBM therapy in wound healing.

Attention to treatment costs such as purchase and maintenance of PBM equipment should be balanced with potential improved clinical efficacy and the benefits of lowered care costs. Further, the access to wound care afforded by this nonpharmacologic intervention could also be specifically evaluated. Among various avenues for further development of PBM technologies, a photoceutical approach to validating pharmacodynamics, pharmacokinetics, and clinical safety and efficacy seems most attractive. Targeting robust, objective outcomes, especially molecular biomarkers, will enable PBM therapy to become a potent modality for wound management in the future.

PRACTICE PEARLS

- Promotion of wound healing was among the first observed benefits of low-dose light treatments (photobiomodulation therapy). There is now growing evidence from well-designed controlled human studies for this specific application.
- Discrete wavelengths and light dose can be used to promote specific phases of wound healing.
- There are now well-understood molecular mechanisms mediating the use of low-dose light therapies.
- Light treatment parameters can be tailored to specifically account for both anatomical and pathophysiologic responses, including device settings and treatment delivery approaches.
- As with most current therapies, the biologic target and disease etiology must be addressed for maximal reproducible therapeutic benefit from these treatments.

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