For your convenience, Back Be Nimble's health care consultant has read and summarized how the use and efficacy of the Lumacare Duo Laser may relate to the content of this article.

FOR A QUICK REVIEW OF THE DEFINITION, THEORY AND USES FOR LOW LEVEL LASER LIGHT THERAPY (LLLT), SCAN THE YELLOW HIGHLIGHTED TEXT

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The Nuts and Bolts of Low-level Laser (Light) Therapy

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Abstract

Soon after the discovery of lasers in the 1960s it was realized that laser therapy had the potential to improve wound healing and reduce pain, inflammation and swelling. In recent years the field sometimes known as photobiomodulation has broadened to include light-emitting diodes and other light sources, and the range of wavelengths used now includes many in the red and near infrared. The term "low level laser therapy" or LLLT has become widely recognized and implies the existence of the biphasic dose response or the Arndt-Schulz curve. This review will cover the mechanisms of action of LLLT at a cellular and at a tissular level and will summarize the various light sources and principles of dosimetry that are employed in clinical practice. The range of diseases, injuries, and conditions that can be benefited by LLLT will be summarized with an emphasis on those that have reported randomized controlled clinical trials. Serious life-threatening diseases such as stroke, heart attack, spinal cord injury, and traumatic brain injury may soon be amenable to LLLT therapy.

Keywords: Low level laser therapy, Photobiomodulation, Mitochondria, Tissue optics, Wound healing, Hair regrowth, Laser acupuncture

INTRODUCTION AND HISTORY

Low level laser therapy (LLLT), also known as photobiomodulation, came into being in its modern form soon after the invention of the ruby laser in 1960, and the helium–neon (HeNe) laser in 1961. In 1967, Endre Mester, working at Semmelweis University in Budapest, Hungary, noticed that applying laser light to the backs of shaven mice could induce the shaved hair to grow back more quickly than in unshaved mice.[72] He also demonstrated that the HeNe laser could stimulate wound healing in mice.[70] Mester soon applied his findings to human patients, using lasers to treat patients with nonhealing skin ulcers.[69,71] LLLT has now developed into a therapeutic procedure that is used in three main ways: to reduce inflammation, edema, and chronic joint disorders[9,18,40]; to promote healing of wounds, deeper tissues, and nerves[24,87]; and to treat neurological disorders and pain.[17]

LLLT involves exposing cells or tissue to low levels of red and near infrared (NIR) light, and is referred to as "low level" because of its use of light at energy densities that are low compared to other forms of laser therapy that are used for ablation, cutting, and thermally coagulating tissue. LLLT is also known

as “cold laser” therapy as the power densities used are lower than those needed to produce heating of tissue. It was originally believed that LLLT or photobiomodulation required the use of coherent laser light, but more recently, light emitting diodes (LEDs) have been proposed as a cheaper alternative. A great deal of debate remains over whether the two light sources differ in their clinical effects.

Although LLLT is now used to treat a wide variety of ailments, it remains controversial as a therapy for two principle reasons: first, its underlying biochemical mechanisms remain poorly understood, so its use is largely empirical. Second, a large number of parameters such as the wavelength, fluence, power density, pulse structure, and timing of the applied light must be chosen for each treatment. A less than optimal choice of parameters can result in reduced effectiveness of the treatment, or even a negative therapeutic outcome. As a result, many of the published results on LLLT include negative results simply because of an inappropriate choice of light source and dosage. This choice is particularly important as there is an optimal dose of light for any particular application, and doses higher or lower than this optimal value may have no therapeutic effect. In fact, LLLT is characterized by a biphasic dose response: lower doses of light are often more beneficial than high doses.[38,85,105,108]

LASER–TISSUE INTERACTIONS

Light and Laser

Light is part of the spectrum of electromagnetic radiation (ER), which ranges from radio waves to gamma rays. ER has a dual nature as both particles and waves. As a wave which is crystallized in Maxwell’s Equations, light has amplitude, which is the brightness of the light, wavelength, which determines the color of the light, and an angle at which it is vibrating, called polarization. The wavelength (λ) of light is defined as the length of a full oscillation of the wave, such as shown in Fig. 1a

. In terms of the modern quantum theory, ER consists of particles called photons, which are packets (“quanta”) of energy which move at the speed of light. In this particle view of light, the brightness of the light is the number of photons, the color of the light is the energy contained in each photon, and four numbers (*X, Y, Z* and *T*) are the polarization, where *X, Y, Z* are the directions and *T* is the time.

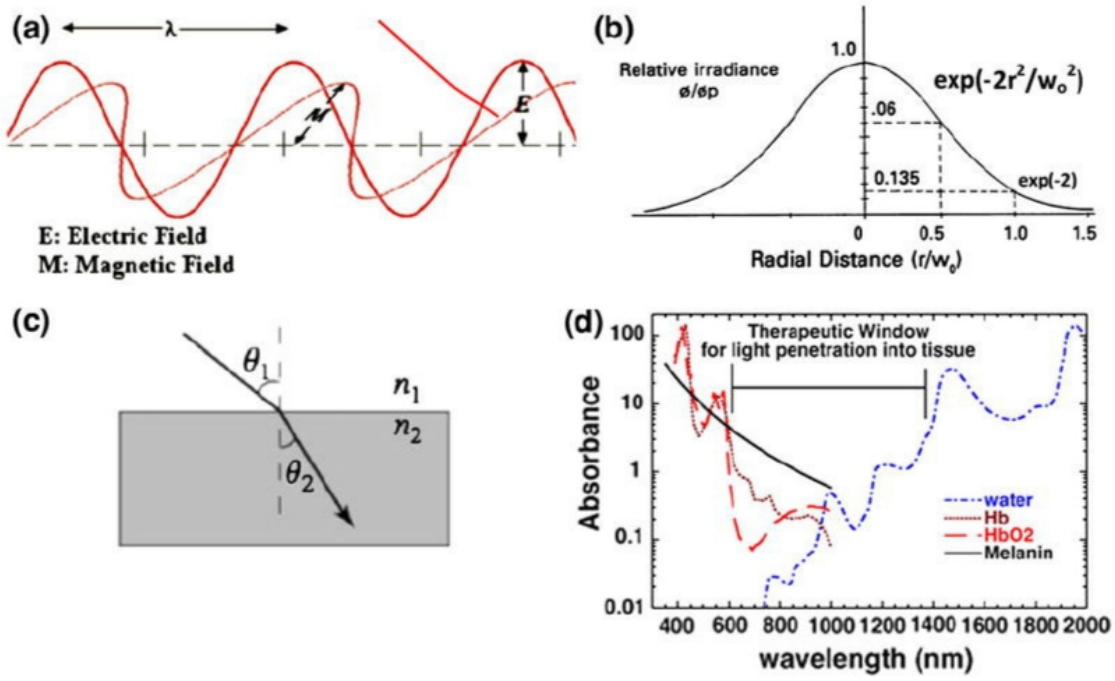

FIGURE 1

Basic physics of LLLT. (a) Light as an electromagnetic wave. (b) Gaussian laser beam profile. (c) Snellius' law of reflection. (d) Optical window because of minimized absorption and scattering of light by the most important tissue chromophores in the near-infrared spectral region.

A laser is a device that emits light through a process of optical amplification based on the stimulated emission of photons. The term "laser" originated as an acronym for light amplification by stimulated emission of radiation.[65] The emitted laser light is notable for its high degree of spatial and temporal coherence.

Spatial coherence typically is expressed through the output being a narrow beam which is diffraction-limited, often a so-called "pencil beam." Laser can be launched into a beam of very low divergence to concentrate their power at a large distance. Temporal (or longitudinal) coherence implies a polarized wave at a single frequency whose phase is correlated over a relatively large distance (the coherence length) along the beam. Lasers are employed in applications where light of the required spatial or temporal coherence could not be produced using simpler technologies.

Quite often, the laser beam is described as though it had a uniform irradiance (the power of the laser divided by the spot size). Most often, the laser beam assumes a Gaussian shape (that of a normal distribution), as shown in Fig. 1b.[118] There is a peak irradiance, and the irradiance decreases with distance from the center of the beam. This may be important in situations in which there are large variations in power. As power is increased, the irradiance in the tail of the Gaussian profile increases, and the distance of the critical threshold from the center of the beam becomes larger. For this type of profile, the spot size is often referred to as the $1/e^2$ radius, or diameter, of the beam; at this radial distance from the center of the beam, irradiation is lower by a factor of 0.135 ($1/e^2$) relative to the peak irradiance. About 85% of the power of the laser beam is present within the $1/e^2$ diameter.

Light Emitting Diodes (LED) A light-emitting diode (LED) is a semiconductor light source. Introduced

as a practical electronic component in 1962 early LEDs emitted low-intensity red light, but modern versions are available across the visible, ultraviolet and infrared wavelengths, with very high brightness. When a light-emitting diode is forward biased (switched on), electrons are able to recombine with electron holes within the device, releasing energy in the form of photons. This effect is called electroluminescence and the color of the light (corresponding to the energy of the photon) is determined by the energy gap of the semiconductor. An LED is often small in area (less than 1 mm^2), and integrated optical components may be used to shape its radiation pattern.[78]

Optical Properties of Tissue

When the light strikes the biological tissue, part of it is absorbed, part is reflected or scattered, and part is further transmitted.

Some of the light is reflected, this phenomenon is produced by a change in the air and tissue refractive index. The reflection obeys the law of Snellius (Fig. 1c), which states:

$$\frac{\sin\,\theta_1}{\sin\,\theta_2} = \frac{n_2}{n_1}$$

where θ_1 is the angle between the light and the surface normal in the air, θ_2 is the angle between the ray and the surface normal in the tissue, n_1 is the index of refraction of air, n_2 is the index of refraction of tissue.

Most of the light is absorbed by the tissue. The energy states of molecules are quantized; therefore, absorption of a photon takes place only when its energy corresponds to the energy difference between such quantized states. The phenomenon of absorption is responsible for the desired effects on the tissue. The coefficient μ_a (cm^{-1}) characterizes the absorption. The inverse, l_a, defines the penetration depth (mean free path) into the absorbing medium.

The scattering behavior of biological tissue is also important because it determines the volume distribution of light intensity in the tissue. This is the primary step for tissue interaction, which is followed by absorption. Scattering of a photon is accompanied by a change in the propagation direction without loss of energy. The scattering, similar to absorption, is expressed by the scattering coefficient μ_s (cm^{-1}). The inverse parameter, $1/\mu_s$ (cm), is the mean free path length until a next scattering event occurs.

Scattering is not isotropic. Forward scattering is predominant in biological tissue. This characteristic is described by the anisotropy factor *g*.*g* can have absolute values from 0 to 1, from isotropic scattering ($g = 0$) to forward scattering ($g = 1$). In tissue, *g* can vary from 0.8 to 0.99. Taking into account the *g* value, a reduced scattering coefficient, μ_s' (cm^{-1}), is defined as:

$$\mu_s' = \mu_s\,(1 - g)$$

The sum of μ_s and μ_a is called the total attenuation coefficient μ_t (cm^{-1}):

$$\mu_t = \mu_s + \mu_a$$

Light Distribution in Laser-irradiated Tissue

Most of the recent advances in describing the transfer of light energy in tissue are based upon transport theory.[13] According to transport theory, the radiance $L(\boldsymbol{R}, \boldsymbol{S})$ of light at position $\boldsymbol{R}$ traveling in the direction of unit vector $\boldsymbol{S}$ is decreased by absorption and scattering but it is increased by light that is scattered from $\boldsymbol{S'}$ direction into direction $\boldsymbol{S}$. Radiance is a radiometric measure that describes the amount of light that passes through or is emitted from a particular area, and falls within a given solid angle in a specified direction. Then, the transport equation which describes the light interaction is:

$$s \cdot \nabla L(\boldsymbol{r}, \boldsymbol{s}) = -(\mu_a + \mu_s) L(\boldsymbol{r}, \boldsymbol{s}) + \mu_s \int_{4\pi} p(\boldsymbol{s}, \boldsymbol{s'}) L(r, s') d\omega'$$

where $d\omega'$ is the differential solid angle in the direction $\boldsymbol{S'}$, and $p(\boldsymbol{S}, \boldsymbol{S'})$ is the phase function.

Calculations of light distribution based on the transport equation require μ_S , μ_a, and p. To solve transport equation exactly is often difficult; therefore, several approximations have been made regarding the representation of the radiance and phase function. The approximate solutions of light distribution in tissue are dependent upon the type of light irradiation (diffuse or collimated) and the optical boundary conditions (matched or unmatched indexes of refraction).[16]

CELLULAR AND TISSULAR MECHANISMS OF LLLT

The precise biochemical mechanism underlying the therapeutic effects of LLLT are not yet well-established. From observation, it appears that LLLT has a wide range of effects at the molecular, cellular, and tissular levels. In addition, its specific modes of action may vary among different applications. Within the cell, there is strong evidence to suggest that LLLT acts on the mitochondria[27] to increase adenosine triphosphate (ATP) production,[43] modulation of reactive oxygen species (ROS), and the induction of transcription factors.[15] Several transcription factors are regulated by changes in cellular redox state. Among them redox factor-1 (Ref-[1]) dependent activator protein-1 (AP-1) (a heterodimer of c-Fos and c-Jun), nuclear factor kappa B (NF-κB), p53, activating transcription factor/cAMP-response element–binding protein (ATF/CREB), hypoxia-inducible factor (HIF)-1, and HIF-like factor.[15] These transcription factors then cause protein synthesis that triggers further effects down-stream, such as increased cell proliferation and migration, modulation in the levels of cytokines, growth factors and inflammatory mediators, and increased tissue oxygenation.[45] Figure 2 shows the proposed cellular and molecular mechanisms of LLLT.

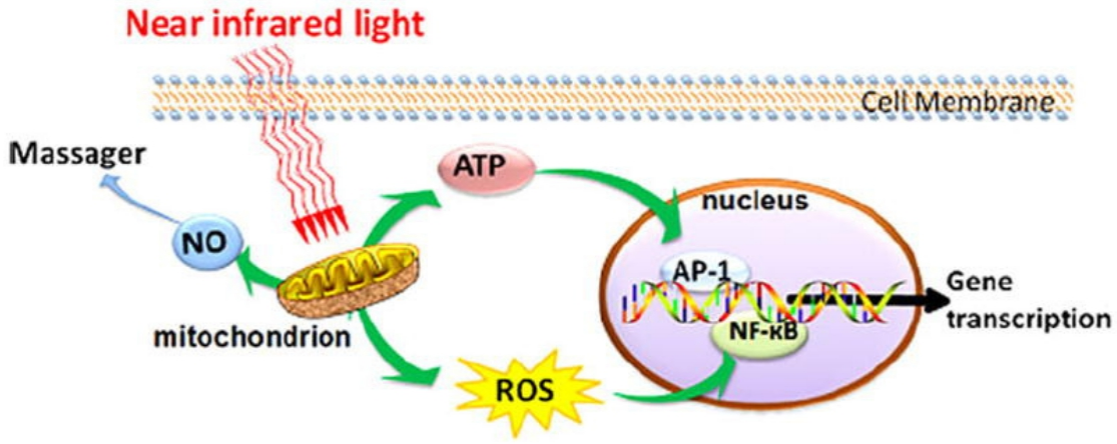

FIGURE 2

Cellular mechanisms of LLLT. Schematic diagram showing the absorption of red or near infrared (NIR) light by specific cellular chromophores or photoacceptors localized in the mitochondrial. During this process in mitochondria respiration chain ATP production will increase, and reactive oxygen species (ROS) are generated; nitric oxide is released or generated. These cytosolic responses may in turn induce transcriptional changes via activation of transcription factors (e.g., NF-κB and AP1).

Immune cells, in particular, appear to be strongly affected by LLLT. Mast cells, which play a crucial role in the movement of leukocytes, are of considerable importance in inflammation. Specific wavelengths of light are able to trigger mast cell degranulation,[22] which results in the release of the pro-inflammatory cytokine TNF-a from the cells.[115] This leads to increased infiltration of the tissues by leukocytes. LLLT also enhances the proliferation, maturation, and motility of fibroblasts, and increases the production of basic fibroblast growth factor.[31,67] Lymphocytes become activated and proliferate more rapidly, and epithelial cells become more motile, allowing wound sites to close more quickly. The ability of macrophages to act as phagocytes is also enhanced under the application of LLLT.

At the most basic level, LLLT acts by inducing a photochemical reaction in the cell, a process referred to as biostimulation or photobiomodulation. When a photon of light is absorbed by a chromophore in the treated cells, an electron in the chromophore can become excited and jump from a low-energy orbit to a higher-energy orbit.[42,108] This stored energy can then be used by the system to perform various cellular tasks. There are several pieces of evidence that point to a chromophore within mitochondria being the initial target of LLLT. Radiation of tissue with light causes an increase in mitochondrial products such as ATP, NADH, protein, and RNA,[83] as well as a reciprocal augmentation in oxygen consumption, and various *in vitro* experiments have confirmed that cellular respiration is upregulated when mitochondria are exposed to an HeNe laser or other forms of illumination.

The relevant chromophore can be identified by matching the action spectra for the biological response to light in the NIR range to the absorption spectra of the four membrane-bound complexes identified in mitochondria.[42] This procedure indicates that complex IV, also known as cytochrome *c* oxidase (CCO), is the crucial chromophore in the cellular response to LLLT.[44] CCO is a large transmembrane protein complex, consisting of two copper centers and two heme–iron centers, which is a component of the respiratory electron transport chain.[10] The electron transport chain passes high-energy electrons from electron carriers through a series of transmembrane complexes (including CCO) to the final electron

acceptor, generating a proton gradient that is used to produce ATP. Thus, the application of light directly influences ATP production by affecting one of the transmembrane complexes in the chain: in particular, LLLT results in increased ATP production and electron transport.[47,84]

The precise manner in which light affects CCO is not yet known. The observation that NO is released from cells during LLLT has led to speculation that CCO and NO release are linked by two possible pathways (Fig. 3). It is possible that LLLT may cause photodissociation of NO from CCO.[46,52] Cellular respiration is downregulated by the production of NO by mitochondrial NO synthase (mtNOS, a NOS isoform specific to mitochondria), that binds to CCO and inhibits it. The NO displaces oxygen from CCO, inhibiting cellular respiration and thus decreasing the production of ATP.[5] By dissociating NO from CCO, LLLT prevents this process from taking place and results in increased ATP production. An alternative or parallel mechanism to explain the biological activity of red or NIR light to release NO from cells or tissue is the following.[61,127] A new explanation has been recently proposed for how light increases NO bioavailability. [88] CCO can act as a nitrite reductase enzyme (a one electron reduction of nitrite gives NO) particularly when the oxygen partial pressure is low.[6] Ball *et al*. showed 590 ± 14 nm LED light stimulated CCO/NO synthesis at physiological nitrite concentrations at hypoxia condition.[6] The following reaction may take place:

$$NO_2^- + 2H^- + e^- (CCO) \rightarrow NO + H_2O$$

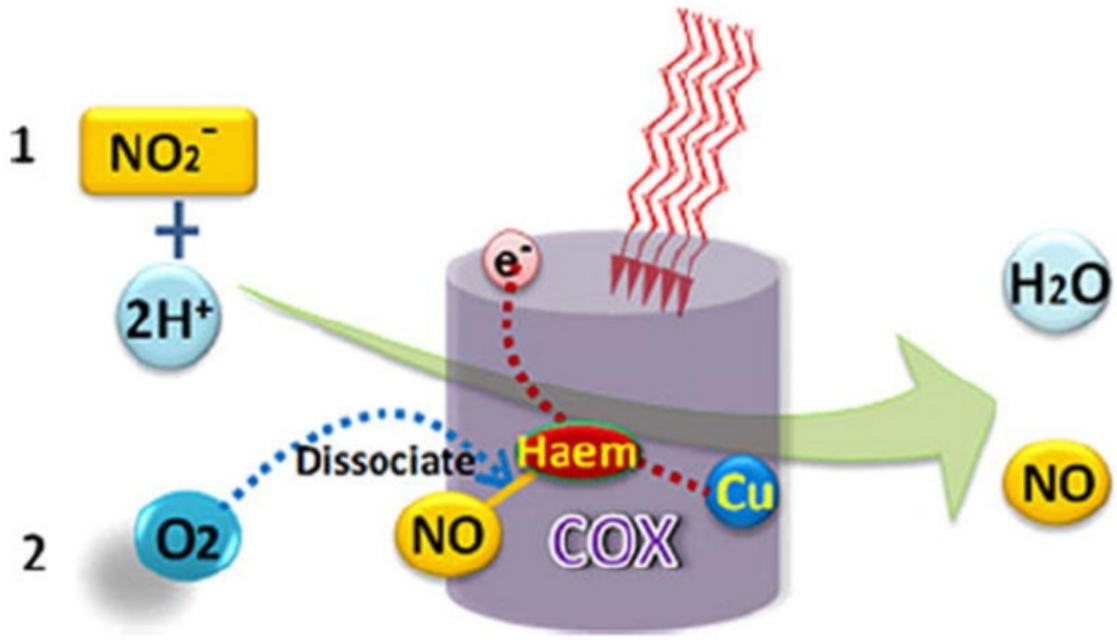

FIGURE 3

Two possible sources of nitric oxide (NO) release from cytochrome *c* oxidase (CCO). Path1 shows CCO can act as a nitrite reductase enzyme: Path 2 shows possible photo-dissociation of NO from CCO.

The influence of LLLT on the electron transport chain extends far beyond simply increasing the levels of ATP produced by a cell. Oxygen acts as the final electron acceptor in the electron transport chain and

is, in the process, converted to water. Part of the oxygen that is metabolized produces reactive oxygen species (ROS) as a natural by-product. ROS are chemically active molecules that play an important role in cell signaling, regulation of cell cycle progression, enzyme activation, and nucleic acid and protein synthesis. Because LLLT promotes the metabolism of oxygen, it also acts to increase ROS production. In turn, ROS activates transcription factors, which leads to the upregulation of various stimulatory and protective genes. These genes are most likely related to cellular proliferation,[76] migration,[32] and the production of cytokines and growth factors, which have all been shown to be stimulated by low-level light.[125,128]

The processes described above are almost certainly only part of the story needed to explain all the effects of LLLT. Among its many effects, LLLT has been shown to cause vasodilation by triggering the relaxation of smooth muscle associated with endothelium, which is highly relevant to the treatment of joint inflammation. This vasodilation increases the availability of oxygen to treated cells, and also allows for greater traffic of immune cells into tissue. These two effects contribute to accelerated healing. NO is a potent vasodilator via its effect on cyclic guanine monophosphate production, and it has been hypothesized that LLLT may cause photodissociation of NO, not only from CCO, but from intracellular stores such as nitrosylated forms of both hemoglobin and myoglobin, leading to vasodilation.[61]

LIGHT SOURCES AND DOSIMETRY

Currently, one of the biggest sources of debate in the choice of light sources for LLLT is the choice between lasers and LEDs. LEDs have become wide-spread in LLLT devices. Most initial work in LLLT used the HeNe laser, which emits light of wavelength 632.8-nm, while nowadays semi-conductor diode lasers such as gallium arsenide (GaAs) lasers have increased in popularity. It was originally believed that the coherence of laser light was crucial to achieve the therapeutic effects of LLLT, but recently this notion has been challenged by the use of LEDs, which emit non-coherent light over a wider range of wavelengths than lasers. It has yet to be determined whether there is a real difference between laser and LED, and if it indeed exists, whether the difference results from the coherence or the monochromaticity of laser light, as opposed to the non-coherence and wider bandwidth of LED light.

A future development in LLLT devices will be the use of organic light emitting diodes (OLEDs). These are LEDs in which the emissive electroluminescent layer is a film of organic compounds which emit light in response to an electric current.[122] They operate in a similar manner to traditional semiconductor material whereby electrons and the holes recombine forming an exciton. The decay of this excited state results in a relaxation of the energy levels of the electron, accompanied by emission of radiation whose frequency is in the visible region.

The wavelengths of light used for LLLT fall into an “optical window” at red and NIR wavelengths (600–1070 nm) (Fig. 1d). Effective tissue penetration is maximized in this range, as the principal tissue chromophores (hemoglobin and melanin) have high absorption bands at wavelengths shorter than 600 nm. Wavelengths in the range 600–700 nm are used to treat superficial tissue, and longer wavelengths in the range 780–950 nm, which penetrate further, are used to treat deeper-seated tissues. Wavelengths in the range 700–770 nm have been found to have limited biochemical activity and are therefore not used. There are also reports of the effectiveness of wavelengths outside the range of absorption of NIR light by CCO. These wavelengths are in the near IR,[36] the mid-IR region including carbon dioxide laser (10.6 μm)[126] and also include broad band IR sources in the 10–50 μm range.[39] The chromophore in these situations is almost certainly water, possible present in biological membranes in some nanostructured form, that is different from bulk water allowing biological effects without gross heating of the tissue.[94,95] It is at present not clear at which wavelength CCO absorption ceases and water

absorption commences to be important.

Dosimetry

The power of light used typically lies in the range 1–1000 mW, and varies widely depending on the particular application. There is evidence to suggest that the effectiveness of the treatment varies greatly on both the energy and power density used: there appears to be upper and lower thresholds for both parameters between which LLLT is effective. Outside these thresholds, the light is either too weak to have any effect, or so strong that its harmful effects outweigh its benefits.

Response to LLLT changes with wavelength, irradiance, time, pulses and maybe even coherence and polarization, the treatment should cover an adequate area of the pathology, and then there is a matter of how long to irradiate for.

Dosimetry is best described in two parts,

1. Irradiation parameters (“the medicine”) see Table 1

TABLE 1

Irradiation parameters (the medicine).

Irradiation parameter	Unit of measurement	
Wavelength	nm	Light is packets of electromagnetic energy that also have a wave-like property. Wavelength is measure in nanometers (nm) and is visible in the 400–700 nm range. Wavelength determines which chromophores will absorb the light. LLLT devices are typically in the range 600–1000 nm as there are many peaks for cytochrome *c* oxidase in that range and clinical trials have been successful with them. There is some contention as wavelengths above 900 nm are probably more absorbed by water than CCO and excitation seems less likely so it introduces the possibility that maybe IR absorption by water in the phospholipid bilayers causes molecular vibration and rotation) sufficient to perturb ion channels alter cellular function
Irradiance	W/cm^2	Often called Power Density (technically incorrect) and is calculated as Power (W)/Area (cm^2) = Irradiance
Pulse structure	Peak power (W) Pulse freq (Hz) Pulse width (s) Duty cycle (%)	If the beam is pulsed then the Power reported should be the Average Power and calculated as follows: Peak Power (W) × pulse width (s) × pulse frequency (Hz) = Average Power (W). Pulses can be significantly more effective than CW[30] however, the optimal frequencies and pulse duration (or pulse intervals) remain to be determined
Coherence	Coherence length depends on spectral bandwidth	Coherent light produces laser speckle, which has been postulated to play a role in the photobiomodulation interaction with cells and sub-cellular organelles. The dimensions of speckle patterns coincide with the dimensions of organelles such as mitochondria. No definitive trials have been published to-date to confirm or refute this claim
Polarization	Linear polarized or zcircular polarized	Polarized light may have different effects than otherwise identical non-polarized light (or even 90° rotated polarized light). However, it is known that polarized light is rapidly scrambled in highly scattering media such as tissue (probably in the first few hundred μm). However, for the birefringent protein structures such as collagen the transmission of plane polarized light will depend on orientation. Several authors have demonstrated effects on wound healing and burns with polarized light[19,86,91]

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2. Time/energy/fluence delivered (“the dose”) see Table 2

TABLE 2

Irradiation time/energy/fluence ("dose").

Energy (Joules)	J	Calculated as: Power (W) × time (s) = Energy (Joules) This mixes medicine and dose into a single expression and ignores irradiance. Using Joules as an expression of dose is potentially unreliable as it assumes assumes a reciprocity relationship between irradiance and time [37,38]
Energy density	J/cm^2	Common expression of LLLT "dose" is Energy Density. This expression of dose again mixes medicine and dose into a single expression and is potentially unreliable as described above
Irradiation time	Seconds	Given the possible lack of reciprocity between irradiance and time [37,38] it is our view that the safest way to record and prescribe LLLT is to define the irradiation parameters ("the medicine") see Table 1, and then define the irradiation time (as the "dose").
Treatment interval	Hours, days or weeks	The effects of different treatment intervals is underexplored at this time though there is sufficient evidence to suggest that this is an important parameter. With the exception of some early treatment of acute injuries LLLT generally requires at least two treatments a week for several weeks to achieve clinical significance

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Dosimetry in LLLT is highly complicated. The large of number of interrelated parameters (see Table 1) has meant that there has not yet been a comprehensive study reported that examined the effect of varying all the individual parameters one by one, and it must be pointed out that it is unlikely there will ever be such a study carried out. This considerable level of complexity has meant that the choice of parameters has often depended on the experimenter's or the practitioner's personal preference or experience rather than on a consensus statement by an authoritative body. Nevertheless, the World Association of Laser Therapy (WALT) has attempted to provide dosage guidelines (http://www.walt.nu /dosage-recommendations.html).

Biphasic Dose Response

It is well established that if the light applied is not of sufficient irradiance or the irradiation time is too short then there is no response. If the irradiance is too high or irradiation time is too long then the response may be inhibited.[11,33,53] Somewhere in between is the optimal combination of irradiance and time for stimulation. This dose response often likened to the biphasic response known as "Arndt-Schulz Law",[68,105,116] which dates back to 1887 when Hugo Schulz published a paper showing that various poisons at low doses have a stimulatory effect on yeast metabolism when given in low doses[116] then later with Rudolph Arndt they developed their principle claiming that a weak stimuli slightly accelerates activity, stronger stimuli raise it further, but a peak is reached and that a stronger stimulus will suppress activity.[63] A more credible term better known in other areas of science and medicine is Hueppe's Rule. In 1896 Ferdinand Hueppe built on Hugo Schulz's initial findings by showing low dose

stimulation/high dose inhibition of bacteria by toxic agents. This is better known today by the term "hormesis" first coined in 1941 and first referenced in 1943,[63] which has subsequently been discussed multiple times in LLLT research.[34,38]

A graphical depiction of how the response to LLLT varies as a function of the combination of irradiance (medicine) and time (dose) is shown in Fig. 4, as a 3D model to represent the possible biphasic responses to the various combinations of irradiance and time or fluence.

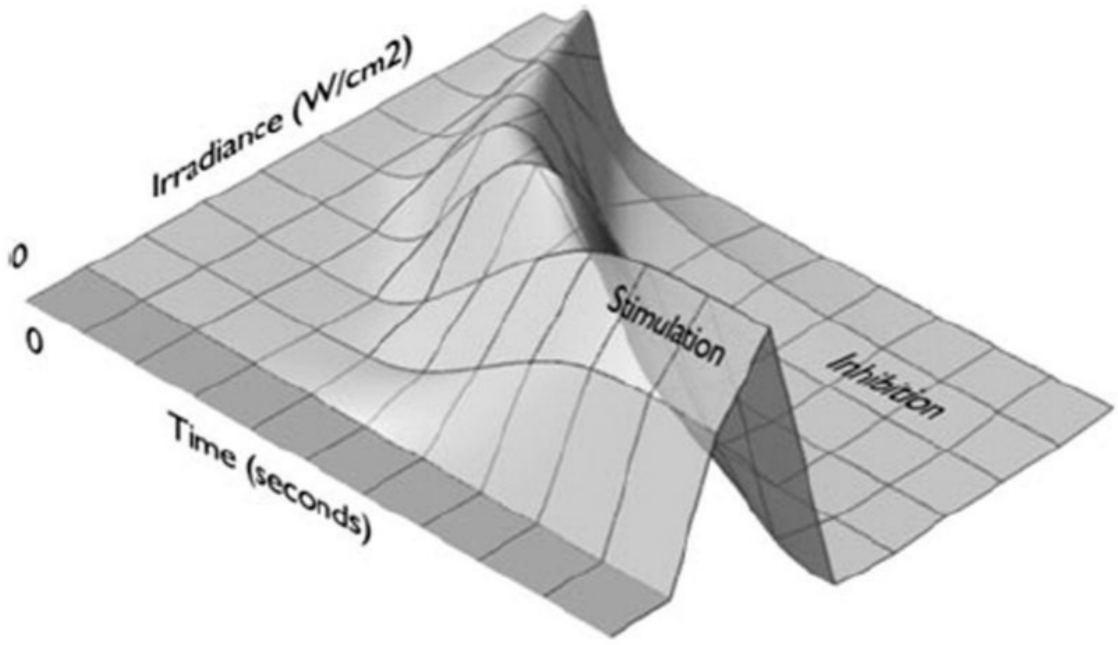

FIGURE 4

Biphasic dose response in LLLT. Three dimensional plot illustrating effects of varying irradiation time equivalent to fluence or irradiance on the biological response resulting in stimulation or inhibition.

SURVEY OF CONDITIONS TREATED WITH LLLT

LLLT is used for three main purposes: to promote wound healing, tissue repair, and the prevention of tissue death; to relieve inflammation and edema because of injuries or chronic diseases; and as an analgesic and a treatment for other neurological problems. These applications appear in a wide range of clinical settings, ranging from dentistry, to dermatology, to rheumatology and physiotherapy. Table 3 summarizes some of the published studies in animal models of diseases and conditions treated with LLLT. Table 4 summarizes some of the published clinical trials of LLLT.

TABLE 3

Pre-clinical studies on animals with low level light therapy for different conditions.

Disease	Parameters [ab]	Subject	Effect	References
Myocardial infarction	804 nm; 38 mW; 4.5 ± 0.1 mW/cm^2; 0.27 J/cm^2; CW, 1.5 × 3.5 mm	Rats	Reduced the loss of myocardial tissue	2
Myocardial infarction	635 nm, 5 mW, 6 mW/cm^2; 0.8 J–1 J/cm^2; CW; 0.8 cm^2; 150 s	Rats	The expression of multiple cytokines was regulated in the acute phase after LLLI	123
Myocardial infarction	804 nm; 400 mW 8 mW/cm^2; 0.96 J/cm^2; CW; 2 cm^2; 120 s	Rats and dogs	VEGF and iNOS expression markedly upregulated; angiogenesis and cardioprotection enhanced	113
Stroke	808-nm; .5 mW/cm^2; 0.9 J/cm^2 at cortical surface; CW; 300 μs pulse at 1 kHz; 2.2 ms at 100 Hz	Rabbits	The results showed that laser administered 6 h following embolic strokes in rabbits in P mode can result in significant clinical improvement and should be considered for clinical development	54
Stroke	808-nm; 7.5 mW/cm^2; 0.9 J/cm^2; 3.6 J/cm^2 at cortical surface; CW and 70 Hz, 4-mm diameter	Rats	LLLT issued 24 h after acute stroke may provide a significant functional benefit with an underlying mechanism possibly being induction of neurogenesis	81
TBI	808 ± 10 nm; 70 mW; 2230 mW/cm^2; 268 J/cm^2 at the scalp; 10 mW/cm^2; 1.2 J/cm^2 at cortical surface; CW; 2 mm^2	Rats	Single and multiple applications of transcranial laser therapy with 808-nm CW laser light appears to be safe in Sprague–Dawley rats 1 year after treatment	64
TBI	808-nm; 200 mW; 10 and 20 mW/cm^2; 1.2–2.4 J/cm^2 at cortical surface; 4 h post-trauma	Mice	LLLT given 4 h following TBI provides a significant long-term functional neurological benefit	82
TBI	660 nm or 780 nm, 40 mW; 3 J/cm^2 or 5 J/cm^2; CW; 0.042 cm^2 (3 s and 5 s) irradiated twice (3 h interval)	Rats	LLLT affected TNF-alpha, IL-1beta, and IL-6 levels in the brain and in circulation in the first 24 h following cryogenic brain injury	77
Spinal cord injury	830 nm; 100 mW; 30 mW/cm^2; 250 J/cm^2; CW, 0.028 cm^2	Rats	LLLT initiated a positive bone-tissue response, maybe through stimulation of osteoblasts. However, the evoked tissue response did not affect biomechanical or densitometric modifications	66
Spinal cord injury	810 nm; 1589 J/cm^2; 0.3 cm^2, 2997 s; daily for 14 days	Rats	Promotes axonal regeneration and functional recovery in acute SCI	120

Disease	Parameters [ab]	Subject	Effect	References
Arthritis	632.8 nm; 5 mW; 8 J/cm^2, CW; 2-mm diameter; 50 s; daily for 5 days	Rats	Laser reduced the intensity of the inflammatory process in the arthritis model induced by hydroxyapatite and calcium pyrophosphate crystals	92
Arthritis	632.8-nm; 3.1 mW/cm^2 CW, 1 cm diameter; 15 min; 3 times a week for 8 weeks	Rats	He–Ne laser treatment enhanced the biosynthesis of arthritic cartilage	59
Arthritis	810-nm; 5 or 50 mW/cm^2; 3 or 30 J/cm^2; CW; 4.5-cm diameter; 1, 10 or 100 min; daily for 5 days	Rats	Highly effective in treating inflammatory arthritis. Illumination time may be an important parameter	11
Wound healing	632.8-nm laser; 635, 670, 720 or 810-nm (±15-nm filtered lamp); 0.59, 0.79, and 0.86 mW/cm^2; 1, 2, 10 and 50 J/cm^2; CW; 3-cm diameter	Mice	635-nm light had a maximum positive effect at 2 J/cm^2. 820 nm was found to be the best wavelength. No difference between non-coherent 635 ± 15-nm light from a lamp and coherent 633-nm light from a He/Ne laser. LLLT increased the number of α-smooth muscle actin (SMA)-positive cells at the wound edge	20
Familial amyotropic lateral sclerosis (FALS)	810 nm; 140-mW; 12 J/cm^2; CW; 1.4 cm^2	Mice	Rotarod test showed significant improvement in the light group in the early stage of the disease. Immunohistochemical expression of the astrocyte marker, glial fibrilary acidic protein, was significantly reduced in the cervical and lumbar enlargements of the spinal cord as a result of LLLT	75

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[a]The light sources were all lasers unless LED is specifically mentioned.

[b]The laser parameters are given in the following order: wavelength (nm); power (mW), power density (mW/cm^2); energy (J); energy density (J/cm^2); mode (CW) or pulsed (Hz); spot size (cm^2); illumination time (sec); treatment repetition. In many cases, the parameters are partially unavailable.

TABLE 4

Clinical studies on patients with low level light therapy for different conditions.

Disease	Parameters [ab]	Subject	Effect	References
Myocardial infarction	632.8-nm, 5 mW; CW; 15 min; 6 days a week for 4 weeks on chest skin	39 patients	An improvement of functional capacity and less frequent angina symptoms during exercise tests	131
Stroke (NEST-1)	808-nm; 700 mW/cm^2 on shaved scalp with cooling; 1 J/cm^2 at cortical surface; 20 predetermined locations 2 min each	120 patients	The NEST-1 study indicated that infrared laser therapy has shown initial safety and effectiveness for the treatment of ischemic stroke in humans when initiated within 24 h of stroke onset	51
Stroke (NEST-2)	808-nm; 700 mW/cm^2 on shaved scalp with cooling; 1 J/cm^2 at cortical surface; 20 predetermined locations 2 min each	660 patients	TLT within 24 h from stroke onset demonstrated safety but did not meet formal statistical significance for efficacy. However, all predefined analyses showed a favorable trend, consistent with the previous clinical trial (NEST-1). Both studies indicate that mortality and adverse event rates were not adversely affected by TLT. A definitive trial with refined baseline National Institutes of Health Stroke Scale exclusion criteria is planned	130
Chronic TBI	9 × 635 and 52 × 870-nm LED cluster; 12-15 mW per diode; 500 mW; 22.2 mW/cm^2; 13.3 J/cm^2 at scalp (estimated 0.4 J/cm^2 to cortex); 2.1″ diameter	2 patients	Transcranial LED may improve cognition in chronic TBI patients even years after injury	79
Major depression and anxiety	810-nm, 250 mW/cm^2; 60 J/cm^2 on scalp; 2.1 J/cm^2 at cortical surface; CW; 4 cm^2; 240 s at each of 2 sites on forehead	10 patients	Significant improvement in Hamilton depression and anxiety scales at 2 weeks	96
Oral mucositis	830 nm; 150 mW; repeated every 48 h	16 patients	Immediate pain relief and improved wound healing resolved functional impairment that was obtained in all cases	12
Oral mucositis	830 nm; 15 mW; 12 J/cm^2; CW; 0.2 cm^2; daily for 5 days commencing at start of radio/chemotherapy	12 patients	The prophylactic use of the treatment proposed in this study seemed to reduce the incidence of severe oral mucositis lesions. LLLT was effective in delaying the appearance of severe oral mucosistis	58
Oral mucositis	660-nm; 10-mW; 2.5 J/cm^2, CW; 4 mm^2; daily for 5 days	75 patients	LLLT therapy was not effective in reducing severe oral mucositis, although a marginal benefit could not be excluded. It reduced radiation therapy interruptions in these head-and-neck cancer patients, which might translate into improved CRT efficacy	26

Disease	Parameters [ab]	Subject	Effect	References
Carpal tunnel syndrome (CTS)	830-nm; 60 mW; 9.7 J/cm^2; 10 Hz, 50% duty cycle, 10-min per day for 5 days a week	75 patients	Alleviate pain and symptoms, improve functional ability and finger and hand strength for mild and moderate CTS patients	14
Carpal tunnel syndrome (CTS)	632.8-nm; 9–11 J/cm^2; CW; 5 times/week for 3 weeks	80 patients	Effective in treating CTS paresthesia and numbness and improved the subjects' power of hand-grip and electrophysiological parameters	102
Carpal tunnel syndrome (CTS)	830-nm; 50 mW; 1.2 J/point; CW; 1 mm diameter. 2 min/point; 5 points across the median nerve trace; 5 times per week for 3 weeks	60 patients	LLLT was no more effective than placebo in CTS	110
Lateral epicondylitis (LE)	905 nm; 100 mW; 1 J/cm^2; 1000 Hz; 2 min; 5 days per week for 3 weeks	49 patients	No advantage for the short term; significant improvement in functional parameters in the long term	23
Lateral epicondylitis (LE)	904-nm; 25 mW, 0.275 J/point; 2.4 J/cm^2; pulse duration 200 nsec; 5000 Hz; 4-mm diameter 11 s/point; 3 times/week for 3 weeks	39 patients	LLLT in addition to exercise is effective in relieving pain, and in improving the grip strength and subjective rating of physical function of patients with lateral epicondylitis	50
Lateral epicondylitis (LE)	830 nm; 120 mW; CW; 5-mm diameter; 632.8 nm, 10 mW, CW; 2-mm diameter; 904 nm, 10 mW; pulsed; 2.5–4 J/point; 12 J/cm^2; 3–5 times/week for 2–5 weeks	324 patients	It was observed that under-and overirradiation can result in the absence of positive therapy effects or even opposite, negative (e.g., inhibitory) effects. The current clinical study provides further evidence of the efficacy of LLLT in the management of lateral and medial epicondylitis	103
Arthritis	830 nm, 50 mW; 10 W/cm^2; 6 J/point; 48 J/cm^2; CW, 0.5-mm^2; 2 times/week for 4 weeks	27 patients	Reduces pain in knee osteoarthritis and improves microcirculation	35
Arthritis	904-nm; 10 mW; 3 J/point; 3 J/cm^2; 200 nsec; 2500 Hz; 1 cm^2; 2 points 5 times/week for 2 weeks	90 patients	The study demonstrated that applications of LLLT in regardless of dose and duration were a safe and effective method in treatment of knee osteoarthritis	28
Leg ulcers	685 nm; 50 mW; 50 mW/cm^2; 10 J/cm^2; CW; 1 cm^2; 200 s; 6 times per week, for 2 weeks then every 2 days	23 patients	The study provided evidence that LLLT can accelerate the healing process of chronic diabetic foot ulcers, and it can be presumed that LLLT may shorten the time period needed to achieve complete healing	48

Disease	Parameters[ab]	Subject	Effect	References
Leg ulcers	685-nm; 200 mW; 4 J/cm^2	44 patients	No statistically significant differences in reduction of wound size	49

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[a]The light sources were all lasers unless LED is specifically mentioned.

[b]The laser parameters are given in the following order: wavelength (nm); power (mW), power density (mW/cm^2); energy (J); energy density (J/cm^2); mode (CW) or pulsed (Hz); spot size (cm^2); illumination time (sec); treatment repetition. In many cases, the parameters are partially unavailable.

Wound healing was one of the first applications of LLLT, when HeNe lasers were used by Mester *et al*. to treat skin ulcers.[69-71] LLLT is believed to affect all three phases of wound healing[111]: the inflammatory phase, in which immune cells migrate to the wound, the proliferative phase, which results in increased production of fibroblasts and macrophages, and the remodeling phase, in which collagen deposition occurs at the wound site and the extra-cellular matrix is rebuilt.

LLLT is believed to promote wound healing by inducing the local release of cytokines, chemokines, and other biological response modifiers that reduce the time required for wound closure, and increase the mean breaking strength of the wound.[8,32,73] Proponents of LLLT speculate that this result is achieved by increasing the production and activity of fibroblasts and macrophages, improving the mobility of leukocytes, promoting collagen formation, and inducing neovascularization.[31,60,67,80,90,104]

However, there is a lack of convincing clinical studies that either prove or disprove the efficacy of LLLT in wound healing. The results that are currently available are conflicting and do not lead to any clear conclusions. For example, Abergel *et al*. found that the 632.8 nm HeNe laser did not have any effect on the cellular proliferation of fibroblasts, while the 904 nm GaAs laser actually *lowered* fibroblasts proliferation.[1] In contrast, other studies noted an increase in proliferation of human fibroblasts exposed to 904 nm GaAs lasers,[85] rat myofibroblasts exposed to 670 nm GaAs lasers,[67] and gingival fibroblasts exposed to diode lasers (670, 692, 780, and 786 nm).[3] *In vivo* studies in both animal and human models show similar discrepancies. A study by Kana *et al*. claimed that treatment of open wounds in rats with HeNe and argon lasers resulted in faster wound closure.[41] Bisht *et al*. found a similar increase in granulation tissue and collagen expression in rats using the same treatment as Kana.[7] However, Anneroth *et al*. failed to observe any beneficial effects after laser treatment in a comparable rat model.[4] In human studies, Schindl *et al*. reported that application of a HeNe laser was beneficial in promoting wound healing in 3 patients,[99] whereas Lundeberg *et al*. found no statistically significant difference between leg ulcer patients treated with an HeNe laser and those treated with a placebo.[62]

The scarcity of well-designed clinical trials makes it difficult to assess the impact of LLLT on wound healing. Our task is further complicated by the difficulty in comparing studies, because of the large number of factors involved. In addition to the multiple parameters that must be adjusted to apply LLLT, such as the wavelength and power of the light, the effectiveness of the treatment also depends on many factors such as the location and nature of the wound, and the physiologic state of the patient. For example, impaired wound healing is one of the major chronic complications of diabetes,[25,89] and is thought to result from various factors, including decreased collagen production and impaired functionality of fibroblasts, leukocytes, and endothelial cells.[25,106] It has therefore been hypothesized

that LLLT could have beneficial effects in stimulating wound healing in diabetic patients.[98,100,124] Thus, in order to obtain a convincing verdict on the impact of LLLT on wound healing, we will require several large, randomized, placebo controlled, and double blind trials that compare the effects of LLLT on wounds that are as similar as possible. A greater understanding of the cellular and biochemical mechanisms of LLLT would also be useful in assessing these studies, as it would enable us to pinpoint exactly what criteria to use in determining the effectiveness of the therapy.

There appears to be more firm evidence to support the success of LLLT in alleviating pain and treating chronic joint disorders, than in healing wounds. A review of 16 randomized clinical trials including a total of 820 patients found that LLLT reduces acute neck pain immediately after treatment, and up to 22 weeks after completion of treatment in patients with chronic neck pain.[17] LLLT has also been shown to relieve pain because of cervical dentinal hypersensitivity,[93] or from periodontal pain during orthodontic tooth movement. [114] A study of 88 randomized controlled trials indicated that LLLT can significantly reduce pain and mprove health in chronic joint disorders such as osteoarthritis, patellofemoral pain syndrome, and mechanical spine disorders.[9] However, the authors of the study urge caution in interpreting the results because of the wide range of patients, treatments, and trial designs involved.

LLLT for Serious Diseases

LLLT is also being considered as a viable treatment for serious neurological conditions such as traumatic brain injury (TBI), stroke, spinal cord injury, and degenerative central nervous system disease.

Although traumatic brain injury is a severe health concern, the search for better therapies in recent years has not been successful. This has led to interest in more radical alternatives to existing procedures, such as LLLT. LLLT is hypothesized to be beneficial in the treatment of TBI. In addition to its effects in increasing mitochondrial activity and activating transcription factors, LLLT could benefit TBI patients by inhibiting apoptosis, stimulating angiogenesis, and increasing neurogenesis.[29] Experiments carried out with two mouse models indicated that LLLT could reduce the brain damaged area at 3 days after treatment, and treatment with a 665 nm and 810 nm laser could lead to a statistically significant difference in the Neurological Severity Score (NSS) of mice that had been injured by a weight being dropped onto the exposed skull.[121]

Transcranial LLLT has also been shown to have a noticeable effect on acute human stroke patients, with significantly greater improvement being seen in patients 5 days after LLLT treatment compared to sham treatment ($p < 0.05$, National Institutes of Health Stroke Severity Scale.)[51] This difference persisted up to 90 days after the stroke, with 70% of patients treated with LLLT having a successful outcome compared to 51% of control patients. The improvement in functional outcome because of applying transcranial LLLT after a stroke has been confirmed by studies in rat and rabbit models.[54,81]

Further experiments have tried to pinpoint the mechanism underlying these results. As expected, increased mitochondrial activity has been found in brain cells irradiated with LLLT,[54] indicating that the increased respiration and ATP production that usually follow laser therapy are at least partly responsible for the improvement shown in stroke patients. However, there is still the possibility that LLLT has other effects specific to the brain. Several groups have suggested that the improvements in patient outcomes are because of the promotion of neurogenesis, and migration of neurons.[81] This hypothesis is supported by the fact that the benefits of LLLT following a stroke may take 2–4 weeks to manifest, reflecting the time necessary for new neurons to form and gather at the damaged site in the brain.[21,101] However, the exact processes underlying the effects of LLLT in a stroke patient are still poorly understood.

LLLT has also been considered as a candidate for treating degenerative brain disorders such as familial amyotropic lateral sclerosis (FALS), Alzheimer's disease, and Parkinson's disease (PD).[75,129] Although only preliminary studies have been carried out, there are encouraging indications that merit further investigation. Michalikova *et al*. found that LLLT could reverse memory degradation and induce improved cognitive performance in middle-aged mice,[74] and Trimmer *et al*. found that motor function was significantly improved in human patients treated with LLLT in an early stage of FALS.[112]

Intravascular Laser Therapy

Intravenous or intravascular blood irradiation involves the *in vivo* illumination of the blood by feeding low level laser light generated by a 1–3 mW low power laser at a variety of wavelengths through a fiber optic inserted in a vascular channel, usually a vein in the forearm (Fig. 5a), under the assumption that any therapeutic effect will be circulated through the circulatory system[117] (see Fig. 5b). The feasibility of intravascular laser irradiation for therapy of cardio-circulatory diseases was first presented in the American Heart Journal in 1982.[57] The technique was developed primarily in Asia (including Russia) and is not extensively used in other parts of the world. It is claimed to improve blood flow and its transport activities, but has not been subject to randomized controlled trials and is subject to skepticism. Although it is at present uncertain what the mechanisms of intravascular laser actually are, and why it differs from traditional laser therapy; it has been hypothesized to affect particular components of the blood. Blood lipids (low density lipoprotein, high density lipoprotein, and cholesterol) are said to be "normalized"[56]; platelets are thought to be rendered less likely to aggregate thus lessening the likelihood of clot formation,[107] and the immune system (dendritic cells, macrophages and lymphocytes) may be activated.[109]

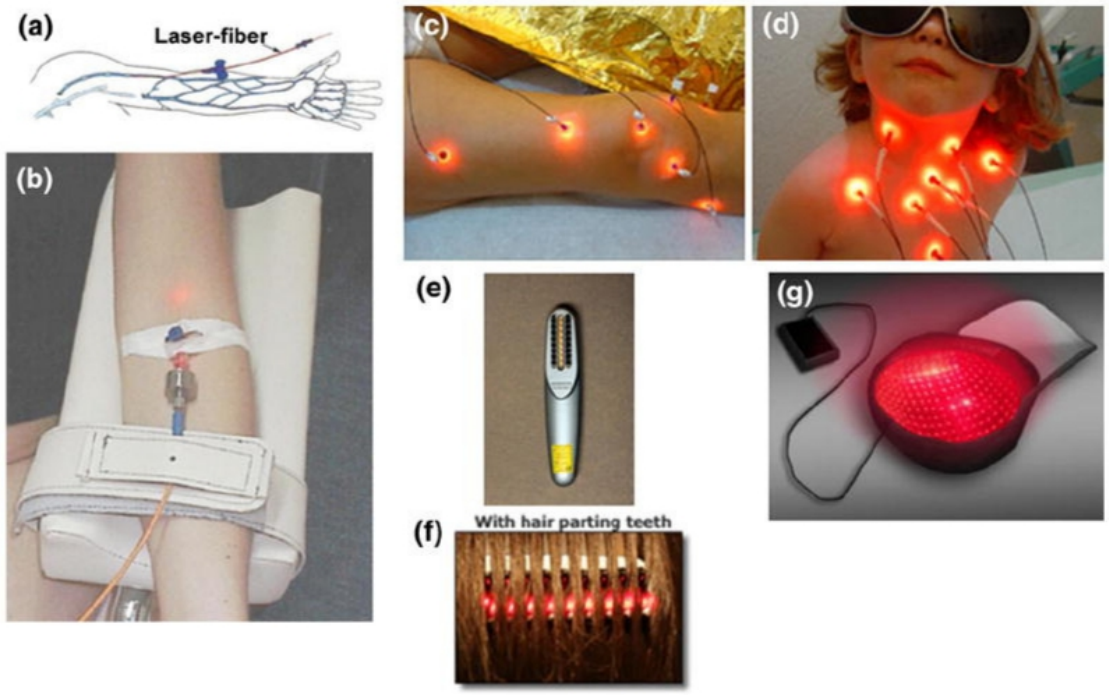

FIGURE 5

Some examples of LLLT devices and applications. (a and b) Intravascular laser therapy (Institute of Biological Laser therapy, Gottingen, Germany). (c and d) Laserneedle acupuncture system (Laserneedle GmbH, Glienicke-Nordbahn, Germany). (e and f) Lasercomb (Lexington Int LLC, Boca Raton, FL) for hair regrowth. (g) Laser cap (Transdermal Cap Inc, Gates Mills, OH) for hair regrowth.

Laser Acupuncture and Trigger Points

Low power lasers with small focused spots can be used to stimulate acupuncture points using the same rules of point selection as in traditional Chinese needle acupuncture.[119] Laser acupuncture may be used solely or in combination with needles for any given condition over a course of treatment. Trigger points are defined as hyperirritable spots in skeletal muscle that are associated with palpable nodules in taut bands of muscle fibers. They may also be found in ligaments, tendons, and periosteum. Higher doses of LLLT may be used for the deactivation of trigger points. Direct irradiation over tendons, joint margins, bursae etc. may be effective in the treatment of conditions in which trigger points may play a part. The Laserneedle system (see Figs. 5c, 5d) can be used to stimulate multiple acupuncture points or trigger points simultaneously.[97]

LLLT for Hair Regrowth

One of the most commercially successful applications of LLLT is the stimulation of hair regrowth in balding individuals. The photobiomodulation activity of LLLT can cause more hair follicles to move from telogen phase into anagen phase. The newly formed hair is thicker and also more pigmented. The Hairmax Lasercomb (Fig. 5e) was shown[55] to give a statistically significant improvement in hair growth in a randomized, double-blind, sham device-controlled, multicenter trial in 110 men with androgenetic alopecia and this led to FDA clearance for efficacy (FDA 510(k) number K060305). The teeth of the comb are supposed to improve the penetration of light though the existing hair to the

follicles requiring stimulation (Fig. 5f). Recently, a different LLLT device received FDA clearance in women suffering from androgenetic alopecia (FDA 510(k) numberK091496). This group of patients have fewer treatment options than men. In order to make the application of light to the head more user-friendly and increase patient compliance, companies have developed "laser caps" (Fig. 5g).

CONCLUSION AND OUTLOOK

Advances in design and manufacturing of LLLT devices in the years to come will continue to widen the acceptability and increase adoption of the therapy among the medical profession, physical therapists and the general public. While the body of evidence for LLLT and its mechanisms is still weighted in favor of lasers and directly comparative studies are scarce, ongoing work using non-laser irradiation sources is encouraging and provides support for growth in the manufacture and marketing of affordable home-use LED devices. The almost complete lack of reports of side effects or adverse events associated with LLLT gives security for issues of safety that will be required.

We believe that LLLT will steadily progress to be better accepted by both the medical profession and the general public at large. The number of published negative reports will continue to decline as the optimum LLLT parameters become better understood, and as reviewers and editors of journals become aware of LLLT as a scientifically based therapy. On the clinical side, the public's distrust of big pharmaceutical companies and their products is also likely to continue to grow. This may be a powerful force for adoption of therapies that once were considered as "alternative and complementary," but now are becoming more scientifically accepted. LLLT is not the only example of this type of therapy, but needle acupuncture, transcranial magnetic stimulation and microcurrent therapy also fall into this class. The day may not be far off when most homes will have a light source (most likely a LED device) to be used for aches, pains, cuts, bruises, joints, and which can also be applied to the hair and even transcranially to the brain.

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Footnotes

CONFLICTS OF INTEREST James D. Carroll is the owner of THOR Photomedicine, a company which sells LLLT devices.

References

1. Abergel RP, Lyons RF, Castel JC, Dwyer RM, Uitto J. Biostimulation of wound healing by lasers: experimental approaches in animal models and in fibroblast cultures. *J Dermatol Surg Oncol.* 1987;13:127–133. [PubMed] [Google Scholar]

2. Ad N, Oron U. Impact of low level laser irradiation on infarct size in the rat following myocardial infarction. *Int J Cardiol.* 2001;80:109–116. [PubMed] [Google Scholar]

3. Almeida-Lopes L, Rigau J, Zangaro RA. Comparison of the low level laser therapy effects on cultured human gingival fibroblasts proliferation using different irradiance and same fluence. *Lasers Surg Med.* 2001;29:179–184. [PubMed] [Google Scholar]

4. Anneroth G, Hall G, Ryden H, Zetterqvist L. The effect of low-energy infra-red laser radiation on wound healing in rats. *Br J Oral Maxillofac Surg.* 1988;26:12–17. [PubMed] [Google Scholar]

5. Antunes F, Boveris A, Cadenas E. On the mechanism and biology of cytochrome oxidase inhibition by nitric oxide. *Proc Natl Acad Sci USA.* 2004;101:16774–16779. [PMC free article] [PubMed] [Google Scholar]

6. Ball KA, Castello PR, Poyton RO. Low intensity light stimulates nitrite-dependent nitric oxide synthesis but not oxygen consumption by cytochrome *c* oxidase: Implications for phototherapy. *J Photochem Photobiol B.* 2011;102:182–191. [PubMed] [Google Scholar]

7. Bisht D, Gupta SC, Mistra V. Effect of low intensity laser radiation on healing of open skin wounds in rats. *Indian J Med Res.* 1994;100:43–46. [PubMed] [Google Scholar]

8. Bisht D, Mehrortra R, Singh PA, Atri SC, Kumar A. Effect of helium-neon laser on wound healing. *Indian J Exp Biol.* 1999;37:187–189. [PubMed] [Google Scholar]

9. Bjordal JM, Couppe C, Chow RT, Tuner J, Ljunggren EA. A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders. *Aust J Physiother.* 2003;49:107–116. [PubMed] [Google Scholar]

10. Capaldi RA, Malatesta F, Darley-Usmar VM. Structure of cytochrome *c* oxidase. *Biochim Biophys Acta.* 1983;726:135–148. [PubMed] [Google Scholar]

11. Castano AP, Dai T, Yaroslavsky I, Cohen R, Apruzzese WA, Smotrich MH, Hamblin MR. Low-level laser therapy for zymosan-induced arthritis in rats: importance of illumination time. *Lasers Surg Med.* 2007;39:543–550. [PMC free article] [PubMed] [Google Scholar]

12. Cauwels RG, Martens LC. Low level laser therapy in oral mucositis: a pilot study. *Eur Arch Paediatr Dent.* 2011;12:118–123. [PubMed] [Google Scholar]

13. Chandrasekhar S. *Radiative transfer.* New York: Dover Publications; 1960. [Google Scholar]

14. Chang WD, Wu JH, Jiang JA, Yeh CY, Tsai CT. Carpal tunnel syndrome treated with a diode laser: a controlled treatment of the transverse carpal ligament. *Photomed Laser Surg.* 2008;26:551–557. [PubMed] [Google Scholar]

15. Chen AC-H, Arany PR, Huang Y-Y, Tomkinson EM, Saleem T, Yull FE, Blackwell TS, Hamblin MR. Low level laser therapy activates NF-κB via generation of reactive oxygen species in mouse embryonic fibroblasts. *Proc SPIE.* 2009;7165:71650–71659. [PMC free article] [PubMed] [Google Scholar]

16. Cheong WF, Prahl SA, Welch AJ. A review of the optical properties of biological tissues. *IEEE J Quantum Electron.* 1990;26:2166–2185. [Google Scholar]

17. Chow RT, Johnson MI, Lopes-Martins RA, Bjordal JM. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. *Lancet.* 2009;374:1897–1908. [PubMed] [Google Scholar]

18. Christie A, Jamtvedt G, Dahm KT, Moe RH, Haavardsholm E, Hagen KB. Effectiveness of nonpharmacological and nonsurgical interventions for patients with rheumatoid arthritis: an overview of systematic reviews. *Phys Ther.* 2007;87:1697–1715. [PubMed] [Google Scholar]

19. da Silva DF, Vidal BC, Zezell DM, Zorn TM, Nunez SC, Ribeiro MS. Collagen birefringence in skin repair in response to red polarized-laser therapy. *J Biomed Opt.* 2006;11:024002. [PubMed] [Google Scholar]

20. Demidova-Rice TN, Salomatina EV, Yaroslavsky AN, Herman IM, Hamblin MR. Low-level light stimulates excisional wound healing in mice. *Lasers Surg Med.* 2007;39:706–715. [PMC free article] [PubMed] [Google Scholar]

21. deTaboada L, Ilic S, Leichliter-Martha S, Oron U, Oron A, Streeter J, et al. Transcranial application of low-energy laser irradiation improves neurological deficits in rats following acute stroke. *Lasers Surg Med.* 2006;38:70–73. [PubMed] [Google Scholar]

22. el Sayed OS, Dyson M. Effect of laser pulse repetition rate and pulse duration on mast cell number and degranulation. *Lasers Surg Med.* 1996;19:433–437. [PubMed] [Google Scholar]

23. Emanet SK, Altan LI, Yurtkuran M. Investigation of the effect of GaAs laser therapy on lateral epicondylitis. *Photomed Laser Surg.* 2010;28:397–403. [PubMed] [Google Scholar]

24. Gigo-Benato D, Geuna S, Rochkind S. Phototherapy for enhancing peripheral nerve repair: a review of the literature. *Muscle Nerve.* 2005;31:694–701. [PubMed] [Google Scholar]

25. Goodson WH, Hunt TK. Wound healing and the diabetic patient. *Surg Gynecol Obstet.* 1979;149:600–608. [PubMed] [Google Scholar]

26. Gouvea de Lima A, Villar RC, de Castro G, Antequera R, Jr, Gil E, Rosalmeida MC, Federico MH, Snitcovsky IM. Oral mucositis prevention by low-level laser therapy in head-and-neck cancer patients undergoing concurrent chemoradiotherapy: a phase III randomized study. *Int J Radiat Oncol Biol Phys.* 2010 doi: 10.1016/j.ijrobp.2010.10.012. Epub ahead of print. [PubMed] [CrossRef] [Google Scholar]

27. Greco M, Guida G, Perlino E, Marra E, Quagliariello E. Increase in RNA and protein synthesis by mitochondria irradiated with helium-neon lase. *Biochem Biophys Res Commun.* 1989;163:1428–1434. [PubMed] [Google Scholar]

28. Gur A, Cosut A, Sarac AJ, Cevik R, Nas K, Uyar A. Efficacy of different therapy regimes of low-power laser in painful osteoarthritis of the knee: a double-blind and randomized-controlled trial. *Lasers Surg Med.* 2003;33:330–338. [PubMed] [Google Scholar]

29. Hashmi JT, Huang Y-Y, Osmani BZ, Sharma SK, Naeser MA, Hamblin MR. Role of low-level laser therapy in neurorehabilitation. *PM & R.* 2010;2:S292–S305. [PMC free article] [PubMed] [Google Scholar]

30. Hashmi JT, Huang YY, Sharma SK, Kurup DB, De Taboada L, Carroll JD, Hamblin MR. Effect of pulsing in low-level light therapy. *Lasers Surg Med.* 2010;42:450–466. [PMC free article] [PubMed] [Google Scholar]

31. Hawkins D, Abrahamse H. Biological effects of helium-neon laser irradiation on normal and wounded human skin fibroblasts. *Photomed Laser Surg.* 2005;23:251–259. [PubMed] [Google Scholar]

32. Hawkins D, Houreld N, Abrahamse H. Low level laser therapy (LLLT) as an effective therapeutic modality for delayed wound healing. *Ann NY Acad Sci.* 2005;1056:486–493. [PubMed] [Google Scholar]

33. Haxsen V, Schikora D, Sommer U, Remppis A, Greten J, Kasperk C. Relevance of laser irradiance threshold in the induction of alkaline phosphatase in human osteoblast cultures. *Lasers Med Sci.* 2008;23:381–384. [PubMed] [Google Scholar]

34. Hayworth CR, Rojas JC, Padilla E, Holmes GM, Sheridan EC, Gonzalez-Lima F. In vivo low-level light therapy increases cytochrome oxidase in skeletal muscle. *Photochem Photobiol.* 2010;86:673–680. [PubMed] [Google Scholar]

35. Hegedus B, Viharos L, Gervain M, Galfi M. The effect of low-level laser in knee osteoarthritis: a double-blind, randomized, placebo-controlled trial. *Photomed Laser Surg.* 2009;27:577–584. [PMC free article] [PubMed] [Google Scholar]

36. Hoffmann G. Principles and working mechanisms of water-filtered infrared-A (wIRA) in relation to wound healing. *GMS Krankenhhyg Interdiszip.* 2007;2:Doc54. [PMC free article] [PubMed] [Google Scholar]

37. Huang Y-Y, Chen AC-H, Carroll JD, et al. Biphasic dose response in low level light therapy. *Dose Response.* 2009;7:358–383. [PMC free article] [PubMed] [Google Scholar]

38. Huang YY, Sharma SK, Carroll JD, Hamblin MR. Biphasic dose response in low level light therapy—an update. *Dose Response.* 2011 in press. [PMC free article] [PubMed] [Google Scholar]

39. Huang CY, Yang RS, Kuo TS, Hsu KH. Phantom limb pain treated by far infrared ray. *Conf Proc IEEE Eng Med Biol Soc.* 2009;2009:1589–1591. [PubMed] [Google Scholar]

40. Jamtvedt G, Dahm KT, Christie A, Moe RH, Haavardsholm E, Holm I, Hagen KB. Physical therapy interventions for patients with osteoarthritis of the knee: an overview of systematic reviews. *Phys Ther.* 2008;88:123–136. [PubMed] [Google Scholar]

41. Kana JS, Hutschenreiter G, Haina D, Waidelich W. Effect of low-power density laser radiation on healing of open skin wounds in rats. *Arch Surg.* 1981;116:293–296. [PubMed] [Google Scholar]

42. Karu TI. Photobiological fundamentals of low-power laser therapy. *IEEE J Quantum Electron.* 1987;23:1703–1717. [Google Scholar]

43. Karu TI. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. *J Photochem Photobiol B.* 1999;49:1–17. [PubMed] [Google Scholar]

44. Karu TI, Afanas'eva NI. Cytochrome *c* oxidase as the primary photoacceptor upon laser exposure of cultured cells to visible and near IR-range light. *Dokl Akad Nauk.* 1995;342:693–695. [PubMed] [Google Scholar]

45. Karu TI, Kolyakov SF. Exact action spectra for cellular responses relevant to phototherapy. *Photomed Laser Surg.* 2005;23:355–361. [PubMed] [Google Scholar]

46. Karu TI, Pyatibrat LV, Afanasyeva NI. Cellular effects of low power laser therapy can be mediated by nitric oxide. *Lasers Surg Med.* 2005;36:307–314. [PubMed] [Google Scholar]

47. Karu TI, Pyatibrat LV, Kalendo GS. Irradiation with He-Ne laser increases ATP level in cells cultivated in vitro. *J Photochem Photobiol B.* 1995;27:219–223. [PubMed] [Google Scholar]

48. Kaviani A, Djavid GE, Ataie-Fashtami L, Fateh M, Ghodsi M, Salami M, Zand N, Kashef N, Larijani B. A randomized clinical trial on the effect of low-level laser therapy on chronic diabetic foot wound healing: a preliminary report. *Photomed Laser Surg.* 2011;29:109–114. [PubMed] [Google Scholar]

49. Kokol R, Berger C, Haas J, Kopera D. Venous leg ulcers: no improvement of wound healing with 685-nm low level laser therapy. Randomised, placebo-controlled, double-blind study. *Hautarzt.* 2005;56:570–575. [PubMed] [Google Scholar]

50. Lam LK, Cheing GL. Effects of 904-nm low-level laser therapy in the management of lateral epicondylitis: a randomized controlled trial. *Photomed Laser Surg.* 2007;25:65–71. [PubMed] [Google Scholar]

51. Lampl Y, Zivin JA, Fisher M, Lew R, Welin L, Dahlof B, Borenstein P, Andersson B, Perez J, Caparo C, Ilic S, Oron U. Infrared laser therapy for ischemic stroke: a new treatment strategy: results of the Neuro-Thera Effectiveness and Safety Trial-1 (NEST-1) *Stroke.* 2007;38:1843–1849. [PubMed] [Google Scholar]

52. Lane N. Cell biology: power games. *Nature.* 2006;443:901–903. [PubMed] [Google Scholar]

53. Lanzafame RJ, Stadler I, Kurtz AF, Connelly R, Peter TA, Sr, Brondon P, Olson D. Reciprocity of exposure time and irradiance on energy density during photoradiation on wound healing in a murine pressure ulcer model. *Lasers Surg Med.* 2007;39:534–542. [PubMed] [Google Scholar]

54. Lapchak PA, Salgado KF, Chao CH, Zivin JA. Transcranial near-infrared light therapy improves motor function following embolic strokes in rabbits: an extended therapeutic window study using continuous and pulse frequency delivery modes. *Neuroscience.* 2007;148:907–914. [PubMed] [Google Scholar]

55. Leavitt M, Charles G, Heyman E, Michaels D. HairMax LaserComb laser phototherapy device in the treatment of male androgenetic alopecia: a randomized, double-blind, sham device-controlled, multicentre trial. *Clin Drug Invest.* 2009;29:283–292. [PubMed] [Google Scholar]

56. Lebed'kov EV, Tolstykh PI, Marchenko LF, Turkina TI, Krivikhin VT. The effect of the laser irradiation of the blood on its lipid and phospholipid components in diabetes mellitus. *Voen Med Zh.* 1998;319:37–38. 95. [PubMed] [Google Scholar]

57. Lee G, Ikeda RM, Dwyer RM, Hussein H, Dietrich P, Mason DT. Feasibility of intravascular laser irradiation for in vivo visualization and therapy of cardiocirculatory diseases. *Am Heart J.* 1982;103:1076–1077. [PubMed] [Google Scholar]

58. Lima AG, Antequera R, Peres MP, Snitcosky IM, Federico MH, Villar RC. Efficacy of low-level laser therapy and aluminum hydroxide in patients with chemotherapy and radiotherapy-induced oral mucositis. *Braz Dent J.* 2010;21:186–192. [PubMed] [Google Scholar]

59. Lin YS, Huang MH, Chai CY. Effects of helium-neon laser on the mucopolysaccharide induction in experimental osteoarthritic cartilage. *Osteoarthr Cartil.* 2006;14:377–383. [PubMed] [Google Scholar]

60. Loevschall H, Arenholt-Bindeslev D. Effect of low level diode laser irradiation of human oral mucosa fibroblasts in vitro. *Lasers Surg Med.* 1994;14:347–354. [PubMed] [Google Scholar]

61. Lohr NL, Keszler A, Pratt P, Bienengraber M, Warltier DC, Hogg N. Enhancement of nitric oxide release from nitrosyl hemoglobin and nitrosyl myoglobin by red/near infrared radiation: potential role in cardioprotection. *J Mol Cell Cardiol.* 2009;47:256–263. [PMC free article] [PubMed] [Google Scholar]

62. Lundeberg T, Malm M. Low-power HeNe laser treatment of venous leg ulcers. *Ann Plast Surg.* 1991;27:537–539. [PubMed] [Google Scholar]

63. Martius F. Das Amdt-Schulz Grandgesetz. *Munch Med Wschr.* 1923;70:1005–1006. [Google Scholar]

64. McCarthy TJ, De Taboada L, Hildebrandt PK, Ziemer EL, Richieri SP, Streeter J. Long-term safety of single and multiple infrared transcranial laser treatments in Sprague-Dawley rats. *Photomed Laser Surg.* 2010;28:663–667. [PubMed] [Google Scholar]

65. McGuff PE, Bushnell D, Soroff HS, De-terling RA., Jr Studies of the surgical applications of laser (light amplification by stimulated emission of radiation) *Surg Forum.* 1963;14:143–145. [PubMed] [Google Scholar]

66. Medalha CC, Amorim BO, Ferreira JM, Oliveira P, Pereira RM, Tim C, Lirani-Galvao AP, da Silva OL, Renno AC. Comparison of the effects of electrical field stimulation and low-level laser therapy on bone loss in spinal cord-injured rats. *Photomed Laser Surg.* 2010;28:669–674. [PubMed] [Google Scholar]

67. Medrado AR, Pugliese LS, Reis SR, Andrade ZA. Influence of low level laser therapy on wound healing and its biological action upon myofibroblasts. *Lasers Surg Med.* 2003;32:239–244. [PubMed] [Google Scholar]

68. Mester E, Mester AF, Mester A. The biomedical effects of laser application. *Lasers Surg Med.* 1985;5:31–39. [PubMed] [Google Scholar]

69. Mester E, Nagylucskay S, Doklen A, Tisza S. Laser stimulation of wound healing. *Acta Chir Acad Sci Hung.* 1976;17:49–55. [PubMed] [Google Scholar]

70. Mester E, Spiry T, Szende B, Tota JG. Effect of laser rays on wound healing. *Am J Surg.* 1971;122:532–535. [PubMed] [Google Scholar]

71. Mester E, Szende B, Spiry T, Scher A. Stimulation of wound healing by laser rays. *Acta Chir Acad Sci Hung.* 1972;13:315–324. [PubMed] [Google Scholar]

72. Mester E, Szende B, Tota JG. Effect of laser on hair growth of mice. *Kiserl Orvostud.* 1967;19:628–631. [Google Scholar]

73. Meyers AD. Lasers and wound healing. *Arch Otolaryngol Head Neck Surg.* 1990;116:1128. [PubMed] [Google Scholar]

74. Michalikova S, Ennaceur A, van Rensburg R, Chazot PL. Emotional responses and memory performance of middle-aged CD1 mice in a 3D maze: effects of low infrared light. *Neurobiol Learn Mem.* 2008;89:480–488. [PubMed] [Google Scholar]

75. Moges H, Vasconcelos OM, Campbell WW, Borke RC, McCoy JA, Kaczmarczyk L, Feng J, Anders JJ. Light therapy and supplementary Riboflavin in the SOD1 transgenic mouse model of familial amyotrophic lateral sclerosis (FALS) *Lasers Surg Med.* 2009;41:52–59. [PubMed] [Google Scholar]

76. Moore P, Ridgway TD, Higbee RG, Howard EW, Lucroy MD. Effect of wavelength on low-intensity laser irradiation-stimulated cell proliferation in vitro. *Lasers Surg Med.* 2005;36:8–12. [PubMed] [Google Scholar]

77. Moreira MS, Velasco IT, Ferreira LS, Ariga SK, Barbeiro DF, Meneguzzo DT, Abatepaulo F, Marques MM. Effect of phototherapy with low intensity laser on local and systemic immunomodulation following focal brain damage in rat. *J Photochem Photobiol B.* 2009;97:145–151. [PubMed] [Google Scholar]

78. Moreno I, Sun CC. Modeling the radiation pattern of LEDs. *Opt Express.* 2008;16:1808–1819. [PubMed] [Google Scholar]

79. Naeser MA, Saltmarche A, Krengel MH, Hamblin MR, Knight JA. Improved cognitive function after transcranial, light-emitting diode treatments in chronic, traumatic brain injury: two case reports. *Photomed Laser Surg.* 2011;29:351–358. [PMC free article] [PubMed] [Google Scholar]

80. Noble PB, Shields ED, Blecher PD, Bentley KC. Locomotory characteristics of fibroblasts within a three-dimensional collagen lattice: modulation by a Helium/Neon soft laser. *Lasers Surg Med.* 1992;12:669–674. [PubMed] [Google Scholar]

81. Oron A, Oron U, Chen J, Eilam A, Zhang C, Sadeh M, Lampl Y, Streeter J, DeTaboada L, Chopp

M. Low-level laser therapy applied transcranially to rats after induction of stroke significantly reduces long-term neurological deficits. *Stroke.* 2006;37:2620–2624. [PubMed] [Google Scholar]

82. Oron A, Oron U, Streeter J, de Taboada L, Alexandrovich A, Trembovler V, Shohami E. Low-level laser therapy applied transcranially to mice following traumatic brain injury significantly reduces long-term neurological deficits. *J Neurotrauma.* 2007;24:651–656. [PubMed] [Google Scholar]

83. Passarella S, Casamassima E, Molinari S, Pastore D, Quagliariello E, Catalano IM, Cingolani A. Increase of proton electrochemical potential and ATP synthesis in rat liver mitochondria irradiated in vitro by helium-neon laser. *FEBS Lett.* 1984;175:95–99. [PubMed] [Google Scholar]

84. Pastore D, Greco M, Petragallo VA, Passarella S. Increase in H^+/e^- ratio of the cytochrome *c* oxidase reaction in mitochondria irradiated with helium-neon laser. *Biochem Mol Biol Int.* 1994;34:817–826. [PubMed] [Google Scholar]

85. Pereira AN, Eduardo Cde P, Matson E, Marques MM. Effect of low-power laser irradiation on cell growth and procollagen synthesis of cultured fibroblasts. *Lasers Surg Med.* 2002;31:263–267. [PubMed] [Google Scholar]

86. Pinheiro AL, Pozza DH, Oliveira MG, Weissmann R, Ramalho LM. Polarized light (400–2000 nm) and non-ablative laser (685 nm): a description of the wound healing process using immunohistochemical analysis. *Photomed Laser Surg.* 2005;23:485–492. [PubMed] [Google Scholar]

87. Posten W, Wrone DA, Dover JS, Arndt KA, Silapunt S, Alam M. Low-level laser therapy for wound healing: mechanism and efficiency. *Dermatol Surg.* 2005;31:334–340. [PubMed] [Google Scholar]

88. Poyton RO, Ball KA. Therapeutic photobio-modulation: nitric oxide and a novel function of mitochondrial cytochrome *c* oxidase. *Discov Med.* 2011;11:154–159. [PubMed] [Google Scholar]

89. Raskin P, Marks JF, Burns H, Plumer MD, Siperstein MDL. Capillary basement membrane within diabetic children. *Am J Med.* 1975;58:365–375. [PubMed] [Google Scholar]

90. Reddy GK, Stehno-Bittel L, Enwemeka CS. Laser photostimulation accelerates wound healing in diabetic rats. *Wound Repair Regen.* 2001;9:248–255. [PubMed] [Google Scholar]

91. Ribeiro MS, Da Silva DF, De Araujo CE, De Oliveira SF, Pelegrini CM, Zorn TM, Zezell DM. Effects of low-intensity polarized visible laser radiation on skin burns: a light microscopy study. *J Clin Laser Med Surg.* 2004;22:59–66. [PubMed] [Google Scholar]

92. Rubio CR, Cremonezzi D, Moya M, Soriano F, Palma J, Campana V. Helium-neon laser reduces the inflammatory process of arthritis. *Photomed Laser Surg.* 2010;28:125–129. [PubMed] [Google Scholar]

93. Sandford MA, Walsh LJ. Thermal effects during desensitisation of teeth with gallium-aluminium-arsenide lasers. *Periodontology.* 1994;15:25–30. [Google Scholar]

94. Santana-Blank L, Rodriguez-Santana E. The interaction of light with nanoscopic layers of water may be essential to the future of photobiomodulation. *Photomed Laser Surg.* 2010;28(Suppl 1):S173–S174. [PubMed] [Google Scholar]

95. Santana-Blank L, Rodriguez-Santana E, Santana-Rodriguez K. Theoretic, experimental, clinical bases of the water oscillator hypothesis in near-infrared photobiomodulation. *Photomed Laser Surg.* 2010;28(Suppl 1):S41–S52. [PubMed] [Google Scholar]

96. Schiffer F, Johnston AL, Ravichandran C, Polcari A, Teicher MH, Webb RH, Hamblin MR. Psychological benefits 2 and 4 weeks after a single treatment with near infrared light to the forehead: a pilot study of 10 patients with major depression and anxiety. *Behav Brain Funct.* 2009;5:46.

[PMC free article] [PubMed] [Google Scholar]

97. Schikora D. Laserneedle acupuncture: a critical review and recent results. *Med Acupunct.* 2008;20:37–42. [Google Scholar]

98. Schindl A, Heinze G, Schindl M, Pernerstorfer-Schon H, Schindl L. Systemic effects of low-intensity laser irradiation on skin microcirculation in patients with diabetic microangiopathy. *Microvasc Res.* 2002;64:240–246. [PubMed] [Google Scholar]

99. Schindl A, Schindl M, Pernerstorfer-Schon H. Low intensity laser irradiation in the treatment of recalcitrant radiation ulcers in patients with breast cancer–long-term results of 3 cases. *Photodermatol Photoimmunol Photomed.* 2000;16:34–37. [PubMed] [Google Scholar]

100. Schindl A, Schindl M, Schon H, Knobler R, Havelec L, Schindl L. Low-intensity laser irradiation improves skin circulation in patients with diabetic microangiopathy. *Diabetes Care.* 1998;21:580–584. [PubMed] [Google Scholar]

101. Shen J, Xie L, Mao XO, Zhou Y, Zhan R, Greenberg DA, Jin K. Neurogenesis after primary intra-cerebral hemorrhage in adult human brain. *J Cereb Blood Flow Metab.* 2008;28:1460–1468. [PMC free article] [PubMed] [Google Scholar]

102. Shooshtari SM, Badiee V, Taghizadeh SH, Nematollahi AH, Amanollahi AH, Grami MT. The effects of low level laser in clinical outcome and neurophysiological results of carpal tunnel syndrome. *Electromyogr Clin Neurophysiol.* 2008;48:229–231. [PubMed] [Google Scholar]

103. Simunovic Z, Trobonjaca T, Trobonjaca Z. Treatment of medial and lateral epicondylitis–tennis and golfer's elbow—with low level laser therapy: a multicenter double blind, placebo-controlled clinical study on 324 patients. *J Clin Laser Med Surg.* 1998;16:145–151. [PubMed] [Google Scholar]

104. Skinner SM, Gage JP, Wilce PA, Shaw RM. A preliminary study of the effects of laser radiation on collagen metabolism in cell culture. *Aust Dent J.* 1996;41:188–192. [PubMed] [Google Scholar]

105. Sommer AP, Pinheiro AL, Mester AR, Franke RP, Whelan HT. Biostimulatory windows in low-intensity laser activation: lasers, scanners, and NASA's light-emitting diode array system. *J Clin Laser Med Surg.* 2001;19:29–33. [PubMed] [Google Scholar]

106. Spanheimer RG, Umpierrez GE, Stumpf V. Decreased collagen production in diabetic rats. *Diabetes.* 1988;37:371–376. [PubMed] [Google Scholar]

107. Stebliukova IA, Khairetdinova NB, Belov AM, Kakitelashvili NA. Effects of low-energy laser irradiation on platelet aggregation in cerebrovascular disorders. *Sov Med.* 1989;(3):77–80. [PubMed] [Google Scholar]

108. Sutherland JC. Biological effects of polychromatic light. *Photochem Photobiol.* 2002;76:164–170. [PubMed] [Google Scholar]

109. Tadakuma T. Possible application of the laser in immunobiology. *Keio J Med.* 1993;42:180–182. [PubMed] [Google Scholar]

110. Tascioglu F, Degirmenci NA, Ozkan S, Mehmetoglu O. Low-level laser in the treatment of carpal tunnel syndrome: clinical, electrophysiological, and ultrasono-graphical evaluation. *Rheumatol Int.* 2010 doi: 10.1007/s00296-010-1652-6. Epub ahead of print. [PubMed] [CrossRef] [Google Scholar]

111. Thomas DW, O'Neill ID, Harding KG, Shepherd JP. Cutaneous wound healing: a current perspective. *J Oral Maxillofac Surg.* 1995;53:442–447. [PubMed] [Google Scholar]

112. Trimmer PA, Schwartz KM, Borland MK, DeTaboada L, Streeter J, Oron U. Reduced axonal transport in Parkinson's disease cybrid neurites is restored by light therapy. *Mol Neurodegener.* 2009;4:26. [PMC free article] [PubMed] [Google Scholar]

113. Tuby H, Maltz L, Oron U. Modulations of VEGF and iNOS in the rat heart by low level laser therapy are associated with cardioprotection and enhanced angiogenesis. *Lasers Surg Med.* 2006;38:682–688. [PubMed] [Google Scholar]

114. Wahl G, Bastanier S. Soft laser in postoperative care in dentoalveolar treatment. *ZWR.* 1991;100:512–515. [PubMed] [Google Scholar]

115. Walsh LJ, Trinchieri G, Waldorf HA, Whitaker D, Murphy GF. Human dermal mast cells contain and release tumor necrosis factor-alpha which induces endothelial leukocyte adhesion molecule-1. *Proc Natl Acad Sci USA.* 1991;88:4220–4224. [PMC free article] [PubMed] [Google Scholar]

116. Webb C, Dyson M, Lewis WH. Stimulatory effect of 660 nm low level laser energy on hypertrophic scar--derived fibroblasts: possible mechanisms for increase in cell counts. *Lasers Surg Med.* 1998;22:294–301. [PubMed] [Google Scholar]

117. Weber MH, Fussgänger-May TW. Intravenous laser blood irradiation. *German J Acupunct Rel Tech.* 2007;50:12–23. [Google Scholar]

118. Welch AJ, Torres JH, Cheong WF. Laser physics and laser-tissue interaction. *Tex Heart Inst J.* 1989;16:141–149. [PMC free article] [PubMed] [Google Scholar]

119. Whittaker P. Laser acupuncture: past, present, and future. *Lasers Med Sci.* 2004;19:69–80. [PubMed] [Google Scholar]

120. Wu X, Dmitriev AE, Cardoso MJ, Viers-Costello AG, Borke RC, Streeter J, Anders JJ. 810 nm wavelength light: an effective therapy for transected or contused rat spinal cord. *Lasers Surg Med.* 2009;41:36–41. [PubMed] [Google Scholar]

121. Wu Q, Huang YY, Dhital S, Sharma SK, Chen AC, Whalen MJ, Hamblin MR. Low level laser therapy for traumatic brain injury. *Proc SPIE.* 2010;7552:755201–755206. [Google Scholar]

122. Xiao L, Chen Z, Qu B, Luo J, Kong S, Gong Q, Kido J. Recent progresses on materials for electrophos-phorescent organic light-emitting devices. *Adv Mater.* 2011;23:926–952. [PubMed] [Google Scholar]

123. Yang Z, Wu Y, Zhang H, Jin P, Wang W, Hou J, Wei Y, Hu S. Low-level laser irradiation alters cardiac cytokine expression following acute myocardial infarction: a potential mechanism for laser therapy. *Photomed Laser Surg.* 2011;29:391–398. [PubMed] [Google Scholar]

124. Yu W, Naim JO, Lanzafame J. Effects of photostimulation on wound healing in diabetic mice. *Lasers Surg Med.* 1997;20:56–63. [PubMed] [Google Scholar]

125. Yu HS, Wu CS, Yu CL, Kao YH, Chiou MH. Helium-neon laser irradiation stimulates migration and proliferation in melanocytes and induces repigmentation in segmental-type vitiligo. *J Invest Dermatol.* 2003;120:56–64. [PubMed] [Google Scholar]

126. Zand N, Ataie-Fashtami L, Djavid GE, Fateh M, Alinaghizadeh MR, Fatemi SM, Arbabi-Kalati F. Relieving pain in minor aphthous stomatitis by a single session of non-thermal carbon dioxide laser irradiation. *Lasers Med Sci.* 2009;24:515–520. [PubMed] [Google Scholar]

127. Zhang R, Mio Y, Pratt PF, Lohr N, Warltier DC, Whelan HT, Zhu D, Jacobs ER, Medhora M, Bienengraeber M. Near infrared light protects cardiomyocytes from hypoxia and reoxygenation injury

by a nitric oxide dependent mechanism. *J Mol Cell Cardiol.* 2009;46:4–14. [PMC free article] [PubMed] [Google Scholar]

128. Zhang Y, Song S, Fong CC, CTsang CH, Yang Z, Yang M. cDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light. *J Invest Dermatol.* 2003;120:849–857. [PubMed] [Google Scholar]

129. Zhang L, Xing D, Zhu D, Chen Q. Low-power laser irradiation inhibiting Abeta25–35-induced PC12 cell apoptosis via PKC activation. *Cell Physiol Biochem.* 2008;22:215–222. [PubMed] [Google Scholar]

130. Zivin JA, Albers GW, Bornstein N, Chippendale T, Dahlof B, Devlin T, Fisher M, Hacke W, Holt W, Ilic S, Kasner S, Lew R, Nash M, Perez J, Rymer M, Schellinger P, Schneider D, Schwab S, Veltkamp R, Walker M, Streeter J. Effectiveness and safety of transcranial laser therapy for acute ischemic stroke. *Stroke.* 2009;40:1359–1364. [PubMed] [Google Scholar]

131. Zycinski P, Krzeminska-Pakula M, Peszynski-Drews C, Kierus A, Trzos E, Rechcinski T, Figiel L, Kurpesa M, Plewka M, Chrzanowski L, Drozdz J. Laser biostimulation in end-stage multivessel coronary artery disease–a preliminary observational study. *Kardiol Pol.* 2007;65:13–21. discussion 22–13. [PubMed] [Google Scholar]