A BETTER LABEL FOR LASER THERAPY/ TISSUE VARIABILITY FACTORS IN PHOTOMEDICINE

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No matter what it is called, LASER THERAPY, or PHOTOMEDICINE THERAPY, is highly effective in resolving a plethora of disorders in the human body; some of the many terms used to describe laser therapy are:

- Photobiomodulation Therapy (PBMT);
- Photobiostimulation Therapy (PBST);
- Low Level Laser Therapy (LLLT);
- High Intensity Laser Therapy (HILT);
- Laser Therapy
- LED Therapy
- SLED Therapy
- Light Therapy
- Cold Laser Therapy
- and more

Most of the above terms are outmoded and represent outdated research and technology - most of this research is based on In Vitro studies that have no application in real-world environments. We propose that these terms and the thinking behind them be replaced by more inclusive, updated, and applicable science and terminology.

There is really no such thing as LLLT, HILT, PBMT, PBST and so on – these are just confusing ad hoc labels. There is only Biomedical Photonics, or Photomedicine, in all its formats, dosage levels, and applications. Laser Therapy is also a very important part of this integrative medicine modality

For ease of use, because it describes applied medicine using medical lasers in a much wider range of applications, and because “Laser Therapy” and all the other associated decades-old terminology are still struggling to gain widespread acceptance in the broader medical community, we propose the more relevant and widely accepted terms PHOTOMEDICINE, and PHOTOMEDICINE THERAPY be used in place of Laser Therapy and the other terms listed above.

Photomedicine Therapy vs. Laser Therapy

Otherwise known as Laser Therapy, Photomedicine, or Photomedicine Therapy is used for the relief of pain, to accelerate healing, decrease inflammation, to reverse autoimmune disorders, and so much more than laser therapy without the requisite medical and scientific knowledge. When laser energy is directed to targeted tissues, the energy penetrates deeply and is absorbed by mitochondria, the energy- producing part of a cell. This energy fuels many beneficial physiological responses resulting in the restoration of optimal cell morphology and function.

PHOTOMEDICINE THERAPY IS: LASER THERAPY, COMBINED WITH SCIENTIFIC AND MEDICAL KNOWLEDGE WITH PROPER APPLICATION

Photomedicine Therapy has been successfully used to treat a broad range of medical conditions, including musculoskeletal problems, arthritis, sports injuries, post-surgical wounds, diabetic ulcers, malfunctioning immune systems, dermatological conditions, and more.

The Primary Goal of Photomedicine Therapy is to stimulate targeted cells to perform natural functions at an enhanced rate. Targeted in chromophores, including hemoglobin and cytochrome c oxidase within the mitochondria, photomedicine treatments will aid in cellular respiration and reduce oxidative stress.

Unlike many pharmacological treatments that mask pain or only address the symptoms of disease, photomedicine therapy treats the underlying condition or pathology to promote healing. This means that photomedicine treatments can be more effective than pharmacology or standard laser therapy, include no side effects and include longer lasting benefits.

Other labels for Photomedicine also include Phototherapy and Biomedical Photonics

Biomedical Photonics is a new branch of physics that examines the behavior and properties of light and the interaction of light with organic matter. This emerging medical paradigm holds great promise for the future of medicine and is poised to experience explosive growth due to the noninvasive or minimally invasive nature and cost-effectiveness of photonic modalities in medical diagnostics and therapy.

Biomedical Applications:
Therapeutic
Medical Imaging (Tissue Clearing)
Shaped by Quantum Theory, Technology, and the Genomics Revolution

The integration of photonics, electronics, biomaterials, and nanotechnology holds great promise for the future of medicine. This topic has recently experienced an explosive growth due to the noninvasive or minimally invasive nature and the cost-effectiveness of photonic modalities in medical diagnostics and therapy.

PRIMARY TISSUE VARIABILITY FACTORS

This information deals with output power as a 'moving target' depending on what is called specific patient "tissue variability factors".

It is important to understand that laser therapy dose effectiveness is dependent on a variety of patient tissue factors, all other variables being equal. Some of the biggest variables affecting photonic energy depth of penetration, absorption, and attenuation are listed below:

- Tissue Density: Adiposity Index vs BMI, Or Body Mass Index
- Tissue Structure: Cellular properties
- Tissue Permeability: (density of tissue structures); muscle, fat, nerve, ligament, bone, etc.
- Tissue Proximity: (depth of tissue (shallow vs. deep)
- Tissue Pigmentation: six levels, from white to black (Fitzpatrick Scale)
- Tissue Hydration: Hydrated or dehydrated (typical = Min. 54.8% to Max. 78.1%)
- Tissue Stress: Bio-behavioral factors that can induce cell damage (cortisol levels, etc.)
- Tissue Age: from atrophic to neoplastic
- Patient Immune System Function
- And more…

Low Level laser treatment may be adequate for the oral cavity and other shallow, deeply pigmented, moist, warm tissues - in most cases, a much higher level of energy is required for energy/tissue interactions (see Reciprocity Rule in Photobiology).

Laser light attenuates the further from the surface it penetrates, until it reaches a point at which the laser photon density is so low that no biological effect of the light can be measured. The biologically effective stimulatory depth photonic energy is dependent on the targeted tissues and varies according to the tissue factors listed above. Secondary and tertiary photobiomodulatory effects, as well as systemic effects, are additionally observed at greater tissue depths.

Primary, Secondary, and Tertiary Effects

Primary response is elicited when photons emitted by the laser reach the mitochondria and cell membranes of low-lying cells such as fibroblasts, where the photonic energy is absorbed by chromophores and is converted to chemical kinetic energy within the cell. Chromophores absorb photons with wavelengths between 700 and 1100 nanometers (NIR, or near infra-red), with those in the 790nm neighborhood being the deepest penetrating, as discussed earlier.

Secondary reactions lead to the amplification of the primary actions. A cascade of metabolic effects results in various physiological changes at the cellular level—such as changes in cell membrane permeability. Calcium is released from the mitochondria resulting in changes of intracellular calcium levels. This stimulates cell metabolism and the regulation of signaling pathways responsible for significant events required for tissue repair such as cell migration, RNA and DNA synthesis, cell mitosis, protein secretion, and cell proliferation.

Tertiary effects are induced at a distance from the cells in which the secondary events occur. Energized cells communicate with each other and with nonirradiated cells through increased levels of cytokines or growth factors. This intercellular communication results in an increase in the immune response with the activation of T-lymphocytes, macrophages, and

number of mast cells. An increase in the synthesis of endorphins and a decrease in bradykinin results in pain relief. Tertiary effects are the least predictable because they rely on intercellular interactions and vary according to tissue factor variables.

Treatment Dosage

Dosage refers to the amount of energy per unit area of tissue surface. Energy is measured in joules, the area in square centimeters and thus the dosage in joules per square centimeter, J/cm2. The power of a laser is the rate of energy delivery and is measured in watts, or milliwatts. One watt equals one Joule per second. Class IV therapy lasers have power output from 0.5 to 60Watts. As an example, a laser operating at 6 watts continuous wave would deliver 240 joules in one minute, and 120 J/min in pulsed mode set at a 50% duty cycle. If the treatment area was 50cm², the dosage would be 240J/50 cm², or 4.8 J/ cm² in continuous wave, and 2.4J/ cm² in pulsed mode at 50% output.

Biostimulation has been reported with doses from as low as 5J/ cm² to 300 J/ cm² (there is no ceiling dose in laser therapy). This wide range is explained by the vast differences in irradiating tissue cultures in a laboratory and treating a deep-lying condition in a clinical setting. Correct dosage is very complicated, as tissue factors must be considered, as well as wavelength, power density, type of tissue, condition of the tissue, acuteness or chronicity of the problem, pigmentation, treatment technique, etc. Nonetheless, there is a dosage window below which no biostimulation will occur, common with LLLT (Low Level Laser Therapy).

Numerous studies have supported the use of higher doses of laser irradiation. Substantial amounts of photonic energy applied at the surface will be reflected, absorbed, and scattered in the superficial tissues. If the target of laser therapy is several centimeters deep, a higher dose at the surface will be reduced to a moderate dose in the desired zone. At least 50% of the surface-applied energy will be lost, so a dosage of 10J/cm² would be diminished to 5J/cm² or less at a deep target site. This rate of diminishment decreases with higher output power levels.

Critics of high-powered laser therapy claim damage will occur in the overlying healthy tissue. It is said that surface doses of 10J/cm² or more will be harmful. However, in the treatment of sick and injured tissue OR healthy, optimally functioning tissue, almost any dose can be used without noticeable macroscopic negative effects. This is the case in the use of surgical lasers which use very high power and energy densities for cutting, evaporating, and coagulating tissue. Adjacent to the destructive zone, very high levels of power density and dose also occur, but this is not found to be negative. In daily practice, thousands of clinicians are safely treating tens of thousands of patients daily with Class IV therapy lasers.

When treating with a GaAlAs diode laser, the current accepted dosages for tissue healing and/or chronic/acute pain ranges from around 10-12 J/cm² up to 300J/cm² DEPENDING ON TISSUE VARIABILITY FACTORS. Simple calculations show that if the condition being treated is lumbar pain, the area being treated could be 100cm² to 400cm², or even larger, especially if it is accompanied by radiculopathy. This equates to a total treatment dosage of 10,000 to 12,000 joules. If the treatment device was a low level or so-called super-pulse therapy laser, it could take several days to a week or more to administer appropriate dosages; however, a high-intensity Class IV therapy laser could accomplish the same dosage in less than 10 minutes!

The output wattage used with a Class IV therapy laser depends on a number of factors. A deeper target calls for a higher wattage so that a sufficient number of photons reach the target and produce the desired primary effects of photobiomodulation. For example, 18Watts would be used for lateral epicondylitis, 12Watts for cervical pain, and 30Watts for lumbar pain. Clinical judgment would prompt the laser therapist to adjust these numbers higher or lower.

Treatment Modes

Successful Photomedicine treatment is best delivered in a combination of continuous wave and various frequencies of pulsation. The human body tends to adapt to and become less responsive to any steady stimulus, so varying the pulsation rate will improve clinical outcomes. In pulsed, or modulated mode, the laser can operate at a duty cycle of 1% to 100% (CW) and the frequency of pulsation can be varied from 1 to 50,000 times per second, or Hertz (Hz). Empirical evidence has not clearly distinguished which frequencies are suitable for various problems, but there is a substantial body of anecdotal evidence to provide some guidance. Differing frequencies of pulsation produce unique physiological responses from the tissue, with optimal frequencies at 1Hz to 80Hz, and higher rates being more beneficial for deeper tissues.

Some Class IV therapy laser manufactures suggest the following:
- lower frequencies, from 2-10 Hz are shown to have an analgesic effect;
- mid-range numbers around 500 Hz are biostimulatory;

• pulse frequencies above 2,500 Hz have an anti-inflammatory effect; and
• frequencies above 5,000 Hz are anti-microbial and anti-fungal.15
There are no published research studies to support these conclusions, and evidence suggests they are simply random in nature.

Optimal Photomedicine therapy treatment would utilize several pulsed frequencies along with CW (continuous wave) over the course of a treatment plan to produce a combination of analgesia, anti-inflammatory effects, and biostimulation.

Effective clinical results come from a developed understanding of variable tissue factors that result in optimal treatment outcomes, rather than a reliance on unproven, outdated, manufacturer-sponsored theories based on biased in-vitro studies.

The Bunsen-Roscoe Law (BRL) of Reciprocity
http://www.photobiology.com/reviews/bunsen/index.htm

The Bunsen-Roscoe Law of Reciprocity states that specific biological effects are directly proportional to the total energy dose irrespective of the administered regime.

In Photomedicine, dosage is primarily the product of intensity and the duration of exposure; thus, the time required to deliver a certain dose is influenced by the intensity of the source and whether the exposure is continuous or fractionated (pulsed). This law is named after R. Bunsen and H. E. Roscoe, who, by their work in the 19th century opened a new field of research entitled Photochemistry. For photochemical reactions, it can be assumed that this law is valid only, at least within a certain dose range which must be individually defined for each reaction. However, responses of cells and tissues to electromagnetic radiation usually involve a sequence of interacting biological reactions, making a linear dose-time relationship less likely. Additionally, photosensitizing molecules might induce different cellular and molecular responses than does radiation alone.

A survey of the available literature on dose-time relationships in photobiology strengthen the view that the Bunsen-Roscoe law seems to be restricted to narrow limits for most photobiological reactions. With this knowledge it is surprising that the available information on the influence of radiation intensity is limited, and that in most experimental and clinical studies variations in radiation intensity are not included in the experimental setup (or simpler: are not studied). In photomedicine where endpoints such as therapeutic efficacy, carcinogenesis, immunosuppression and photoaging are of major importance, validity and failure of the BRL are either completely unknown, suppressed, or subject to speculation based on in-vitro-only studies, with the endpoint usually already predetermined.

In photomedicine, investigations into the molecular events underlying the differential effects of varying doses and intensities are necessary for a comprehensive understanding of the way living tissues respond to NIR radiation; in this regard to date, most investigations are limited to low-level energy and in-vitro environments because of a stubborn adherence to the stated Arndt-Schultz Rule.

Basic Laws of Photochemistry

The Grotthuss–Draper Law
http://www.newworldencyclopedia.org/entry/Photochemistry

“Only radiation absorbed in a system can produce a chemical change.”
The Grotthuss–Draper Law (also called the Principle of Photochemical Activation) states that only that light which is absorbed by a system can bring about a photochemical change. This law provides a basis for fluorescence and phosphorescence; the law was first proposed in 1817 by Theodor Grotthuss and in 1842, independently, by John William Draper.

Stark–Einstein Law
http://ccb.rutgers.edu/sites/default/files/coursefiles/courses_sp10/512/Handout_I_Photochemistry_I.pdf

“Number of activated molecules = number of quanta of radiation absorbed.”
The Stark–Einstein law is named after German-born physicists Johannes Stark and Albert Einstein, who independently formulated the law between 1908 and 1913, and is also known as the Photochemical Equivalence Law. It says that every

photon that is absorbed will cause a (primary) chemical or physical reaction; the photon = one unit of radiation; therefore, this is a single unit of EM radiation that is equal to Planck's constant (h) times the frequency of light. This quantity is symbolized by γ, hν, or ħω.

The Beer-Lambert Law

http://www.pci.tu-bs.de/aggericke/PC4/Kap_I/beerslaw.htm

The Beer-Lambert Law (or Beer's law) is the linear relationship between absorbance and concentration of an absorbing species. The general Beer-Lambert law is usually written as: A = a(lambda) * b * c
where A is the measured absorbance, a(lambda) is a wavelength-dependent absorptivity coefficient, b is the path length, and c is the analyte concentration. When working in concentration units of molarity, the Beer-Lambert law is written as: A = epsilon * b * c, where epsilon is the wavelength-dependent molar absorptivity coefficient with units of M -1 cm -1.

It is important to understand the orders of magnitude involved when it comes to therapeutic applications of photonic radiation. Far too often in photomedicine, generalized doses are conceived without a relative scale of comparative tissue interactions other than those initially achieved in-vitro; with energy often less than 5-10mW, dosages exist at or near the bottom of the U-shaped Dose Response Curve, illustrated by the oft-quoted Arndt-Schultz Rule (see below):

The Arndt-Schultz Rule

The Arndt-Schultz Rule, although enshrined as a ruling principle by LLLT proponents, was not derived for photomedicine and no longer applies even in pharmacology, for which it was originally derived. The Arndt–Schulz Rule or Schulz' Law is a claimed law concerning the effects of pharmacal, or poisons in various concentrations; it states that:

For every substance, small doses stimulate, moderate doses inhibit, large doses kill; in other words, highly diluted pharmacal or poisons enhance life processes, while strong concentrations may inhibit these processes or even terminate them.

The rule was named after Hugo Paul Friedrich Schulz and Rudolf Arndt, who originally formulated it in 1888; however, exceptions to the rule are so numerous that it cannot be considered a general law in pharmacology and has no application in photomedicine. For example, many paralyzing substances have no exciting effect in weak doses, and what constitutes a weak, medium or strong stimulus is highly individual, as pointed out by Arndt himself.

The Arndt-Schultz Rule is no longer cited in modern pharmacology texts, having been supplanted by the theory of hormesis; in addition, application of the Arndt-Schulz Rule in photomedicine never made sense.

Solar Irradiation

At the upper reaches of our atmosphere, the energy density of solar radiation is approximately 1,368 W/m2 (watts per square meter). At the Earth's surface, the energy density is reduced to approximately 1,000 W/m2 for a surface perpendicular to the Sun's rays at sea level on a sunny day.

The spectrum of solar radiation reaching the Earth ranges from 290nm to more than 1,000,000nm and is divided as follows: 6.8% UV, 38.9% visible, and 54.3% near infrared radiation (NIR). Infrared constitutes the waveband longer than 760nm and up to 1mm and accounts for approximately 40% of the solar radiation reaching the ground at sea level.

Infrared energy has been divided into three bands: IR-A (760–1400 nm), IR-B (1400–3000 nm), and IR-C (3000 nm – 1 mm) (see below). IR radiation can penetrate the epidermis, dermis, and subcutaneous tissue to differing extents depending on the specific wavelength; exposure to IR is perceived as heat.

The strength of electromagnetic radiation depends on the energy of the individual particles or waves as well as the number of particles or waves present.

Electromagnetic radiation that has insufficient energy to completely remove electrons from atoms and molecules is referred to as non-ionizing radiation. Examples of this kind of radiation are visible light, infrared (NIR and FIR), and radio waves. Ionizing radiation has enough energy to remove tightly bound electrons from atoms, thus creating charged ions, and includes X-rays and gamma rays.

Ultraviolet (UV) radiation is intermediate between these two broad ranges; short-wavelength UV has enough energy to break chemical bonds and carry out photochemical reactions. Although the consequences of sun exposure on the skin have been extensively studied over the years, the impact of IR radiation has received far less attention than its UV counterpart, which is well known to cause skin cancer, photoaging, and immune suppression. Moreover, the solar IR-A (also called NIR) irradiance level is critical to trigger beneficial effects in the skin beyond which it becomes deleterious. Most studies reporting the detrimental effects of IR-A (upregulation of matrix metalloproteinase 1 or MMP-1) used artificial light sources far above the solar IR-A irradiance threshold.

Solar Irradiance Threshold of Therapeutic Energy

Solar irradiance is equal to the amount of energy (J, or Joules) delivered via sunlight to an area of the skin measured in CM^2; the solar irradiance threshold varies according to variable Tissue Factors listed below:

Wavelength	Irradiance/Power Density	Hourly Dosage
280nm – 400nm (UV)	6.4mW/CM^2	23J/CM^2 per hour
400nm – 700nm (visible)	46mW/CM^2	160J/CM^2 per hour
700nm – 3000nm (NIR, FIR)	48mW/CM^2	170J/CM^2 per hour

The wavelengths used in therapeutic photomedicine are in the visible and infrared range, typically:

635nm +/- 20nm	6.4mW/CM^2	21J/CM^2 per hour
810nm +/-20nm	4.3mW/CM^2	16J/CM^2 per hour
980nm +/- 20nm	2.7mW/CM^2	10J/CM^2 per hour

Therapeutic Window

(700nm – 1100nm)	33mW/CM^2	120J/CM^2 per hour

In other words, in one hour of sunlight, an exposed back would receive approximately 800,000J of therapeutic energy – orders of magnitude more than the minimal doses suggested by proponents of the Arndt-Schultz Rule. In addition, the same proponents neglect to consider basic rules of photomedicine – that tissue response is governed by the following Targeted Tissue Factors:

1. Tissue Mass: adiposity index or body mass index
2. Tissue Hydration: (fluid content) min. 54.8% to max. 78.1%
3. Tissue Structure: density/permeability of tissue structure
4. Tissue Proximity: (depth of tissue (shallow vs. deep)
5. Tissue Pigmentation: six levels, from white to black, according to Fitzpatrick Scale
6. Tissue Age: entropy, atrophy index
7. Tissue Stress: biobehavioral factors, allostasis vs. allostatic overload (acute vs. episodic or chronic stress and its effects on the human body)

Based on the above, it is logical to assume that effective treatment of mouth ulcers will require a much lower dosage than effective treatment of disc herniations or osteoarthritis of the knee joint, and effective dose ranges can be much higher than those suggested by proponents of the Arndt-Schultz Rule.

The BLR Dose Curve in Photomedicine

Based on solar irradiance threshold data, a more logical representation of the therapeutic dose curve in photomedicine would look like this:

Conclusion

Systematic clinical research into carefully designed studies will result in optimized higher-energy phototherapeutic regimens and dosages, with an improved therapeutic index, i.e. a maximized therapeutic benefit with minimized adverse reactions vs. the current LLLT standard, which represents minimal therapeutic benefit with minimal adverse reactions.

NOTE: We have drawn our conclusions from these and other similar studies found on the PubMed website: https://pubmed.ncbi.nlm.nih.gov/

A complete list of these studies can be found on http://advanmed.com

A meta-analysis of the efficacy of laser phototherapy on pain relief
http://www.ncbi.nlm.nih.gov/pubmed/20842007
Objective:
Laser phototherapy has been widely used to relieve pain for more than 30 years, but its efficacy remains controversial. To ascertain the overall effect of phototherapy on pain, we aggregated the literature and subjected the studies to statistical meta-analysis.
Conclusion:
Laser phototherapy effectively relieves pain of various etiologies; making it a valuable addition to contemporary pain management armamentarium

A meta-analysis of the efficacy of phototherapy in tissue repair
http://www.ncbi.nlm.nih.gov/pubmed/19698019
Objective:
The effect of phototherapy on tissue repair was determined by aggregating the literature and using statistical meta-analysis to analyze pertinent studies published between 2000 and 2007.
Conclusion:
These findings indicate that phototherapy is a highly effective form of treatment for tissue repair, with stronger supporting evidence resulting from experimental animal studies than human studies

Intricacies of dose in laser phototherapy for tissue repair and pain relief
https://www.ncbi.nlm.nih.gov/pubmed/19473073
Objective:
Inaccurate measurement and incorrect reporting of dosages are major shortcomings of phototherapy articles. As many as 30% of published reports in the field either lack relevant information needed to determine a dosage or report dosages that are altogether inaccurate. The high prevalence of dosage-related mistakes in published reports suggests that dosage determination errors are common among clinicians and other end-users. This special article is designed to advance understanding of the relevant parameters used in phototherapy for tissue repair and pain relief, particularly among clinicians and others who may not be completely familiar with the technology. I define and discuss five key parameters that influence dosage, including 1) radiant power, 2) radiant energy, 3) power density, 4) energy density, and 5) wavelength, and use hypothetical cases to demonstrate how factors such as beam spot size, size of lesion, mode of treatment (contact, noncontact, or scanning), frequency of treatment, dose per treatment, and cumulative dose affect dosages and treatment outcomes. The potential effects of patient-related factors, such as etiology, pathology, tissue optical density, depth of target tissue, and skin pigmentation are discussed concurrently and strategies are suggested to improve dosage determination.
Conclusion: Pending

Potential for Transcranial Laser Therapy to Treat Stroke, Traumatic Brain Injury, and Neurodegenerative Disease
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3128319/
Objective:
Transcranial Laser Therapy has shown many benefits in the treatment of TIA, Stroke Neurodegenerative conditions, and other injuries or diseases of the brain.
Conclusion:
TLT may be thought to be just in its infancy, but we believe the stage is set for rapid growth, especially in view of the massive and continuing failure of clinical trials of pharmaceuticals for many brain disorders and neurodegenerative diseases. As the population continues to age, and the epidemic of degenerative diseases of aging such as AD and other dementias continues to grow, TLT may make a real contribution to patient health. **Additional controlled studies with real and sham transcranial laser therapy are recommended.**

NEUROSCIENCE/ LASER THERAPY: Laser therapy boosts cognitive function following brain injury
https://www.bioopticsworld.com/articles/2011/05/neuroscience-low-level-laser-therapy-led-therapy-boosts-cognitive-function-following-brain-injury.html

Objective:
Research newly published in Photomedicine and Laser Surgery (doi:10.1089/pho.2010.2814) details the first case reports documenting improved cognitive function in chronic traumatic brain injury (TBI) patients treated with transcranial light-emitting diodes (LEDs), and concludes that controlled studies are warranted. The study reports the application of red and near-infrared LEDs, applied transcranially to forehead and scalp areas of two patients. The studies used MedX Health's (Mississauga, ON, Canada) model 1100 LED console device, a cluster-head of 2.1 inches in diameter containing 52 near-infrared (870 nm) and nine red (633 nm) diodes for a total optical output power of 500 mW (±20%) continuous wave.
Conclusion:
Patient 1 began the low-level laser therapy (LLLT) seven years after closed-head TBI from a motor vehicle accident, at a time when her ability for sustained attention (computer work) was just 20 minutes. After eight weekly treatments (applied bilaterally for between 5 and 13 minutes), her sustained attention time increased to three hours. She has now performed nightly home treatments for five years. Patient 2 had a history of closed-head trauma (sports/military and recent fall), and magnetic resonance imaging showed frontoparietal atrophy. When she began the LED treatment, she had been on medical disability for five months. After four months of nightly LED treatments at home, she was able to discontinue medical disability and return to working full-time. Neuropsychological testing after nine months of LED treatment indicated significant improvement in executive function (inhibition, inhibition accuracy) and memory, as well as reduction in post-traumatic stress disorder. These patients' cognitive gains decreased if they stopped treatment for one to two weeks, and returned when treatment was restarted. The findings will provide a basis for future therapeutic use of phototherapy, according to Raymond J. Lanzafame, editor-in-chief of Photomedicine and Laser Surgery. "The development of novel therapies to restore function after neurologic injury, stroke, or disease is an increasingly important goal in medical research as a result of an increase in non-fatal traumatic wounds and the increasing prevalence of dementias and other degenerative disorders in our aging population," he explains.

Transcranial laser stimulation improves human cerebral oxygenation
https://www.ncbi.nlm.nih.gov/pubmed/26817446
Objective:
Transcranial laser stimulation of the brain with near-infrared light is a novel form of non-invasive photobiomodulation or low-level laser therapy (LLLT) that has shown therapeutic potential in a variety of neurological and psychological conditions. Understanding of its neurophysiological effects is essential for mechanistic study and treatment evaluation. This study investigated how transcranial laser stimulation influences cerebral hemodynamics and oxygenation in the human brain in vivo using functional near-infrared spectroscopy (fNIRS).
Results:
In both experiments, transcranial laser stimulation induced an increase of oxygenated hemoglobin concentration (Δ[HbO2]) and a decrease of deoxygenated hemoglobin concentration (Δ[Hb]) in both cerebral hemispheres. Improvements in cerebral oxygenation were indicated by a significant increase of differential hemoglobin concentration (Δ[HbD] = Δ[HbO2] - Δ[Hb]). These effects increased in a dose-dependent manner over time during laser stimulation (10 minutes) and persisted after laser stimulation (6 minutes). The total hemoglobin concentration (Δ[HbT] = Δ[HbO2] + Δ[Hb]) remained nearly unchanged in most cases.
Conclusion:
Near-infrared laser stimulation applied to the forehead can transcranially improve cerebral oxygenation in healthy humans.

Low-level laser therapy for wound healing: mechanism and efficacy
https://www.ncbi.nlm.nih.gov/pubmed/15841638
Objective:
In examining the effects of LLLT on cell cultures in vitro, some articles report an increase in cell proliferation and collagen production using specific and somewhat arbitrary laser settings with the helium neon (HeNe) and gallium arsenide lasers, but none of the available studies address the mechanism, whether photothermal, photochemical, or photomechanical, whereby LLLT may be exerting its effect. Some studies, especially those using HeNe lasers, report improvements in surgical wound healing in a rodent model; however, these results have not been duplicated in animals such as pigs, which have skin that more closely resembles that of humans. In humans, beneficial effects on superficial wound healing found in small case series have not been replicated in larger studies.
Conclusion:

To better understand the utility of laser therapy in cutaneous wound healing, good clinical studies that correlate cellular effects and biologic processes are needed. Future studies should be well-controlled investigations with rational selection of lasers and treatment parameters. In the absence of such studies, the literature does not appear to support widespread use of LLLT in wound healing at this time. Although applications of high-energy (10-100 W) lasers are well established with significant supportive literature and widespread use, conflicting studies in the literature have limited low-level laser therapy (LLLT) use in the United States to investigational use only. Yet LLLT is used clinically in many other areas, including Canada, Europe, and Asia, for the treatment of various neurologic, chiropractic, dental, and dermatologic disorders. To understand this discrepancy, it is useful to review the studies on LLLT that have, to date, precluded Food and Drug Administration approval of many such technologies in the United States. The fundamental question is whether there is sufficient evidence to support the use of LLLT. (LLLT, or Low Level Laser Therapy does not recognize Primary Tissue Variability Factors, and is therefore ineffective.

Evaluation Of Laser Therapy In Reducing Diabetic Polyneuropathy Related Pain And Sensorimotor Disorders
http://acta.tums.ac.ir/index.php/acta/article/view/4395

Objective:

Over the past three decades physicians have used light level laser therapy (LLLT) for the management and the treatment of diabetic peripheral neuropathy and have obtained results that calls for further investigations. This study aimed to investigate the effectiveness of LLLT in treatment of pain symptoms in patients with diabetic polyneuropathy. In this study 60 patients with diabetic peripheral neuropathy were matched based on their sex, age, BMI, type of diabetes, duration of diabetes, and duration of pain, and randomized to case and control groups based on their established scores on the visual analog scale (VAS) and the Toronto clinical scoring system (TCSS). Cases received laser therapy with wavelength of 78 nm and 2.5 j/cm2 two times a week, each time for 5 min, for one month. During the same period, controls received sham laser therapy. Comparing the differences between the two groups' VAS and TCSS mean scores before the intervention with that of the 2 weeks and 4 weeks after the intervention we were able to see a statistically significant difference between the two groups ($P<0.05$). On the other hand, when we compared their VAS and TCSS mean scores 4 weeks and 2 weeks after the intervention we did not find any statistically significant difference between the two groups. We achieved the same results when we examined cases' and controls' pre and post VAS and TCSS scores independent from each other; no improvement in the assessment based on their 2 and 4 weeks comparisons tests. Laser therapy resulted in improved neuropathy outcomes in diabetic patients who received it relative to the group that received sham therapy, evaluating before and after LLLT assessments.

Conclusion:

Further studies are needed to test types of lasers, as well as different dosage and exposure levels required in different phase of neuropathic care, so as to obtain reproducible results.

The molecular mechanisms of the antimicrobial properties of laser processed nano-particles
https://www.research.manchester.ac.uk/portal/files/68670907/FULL_TEXT.PDF

Objective:

Microbial resistance to the current available antibiotics is considered a global health problem, especially for the Multi-Drug Resistant pathogens (MDR) including methicillin resistant Staphylococcus aureus. Recently nanoparticles (NPs) have been involved in variety of antimicrobial applications due to their unique properties of antibacterial effects. However, the molecular mechanisms behind their antibacterial activity are still not fully understood.

Conclusion:

In this study, we produced silver Ag NPs (average size 27 nm) and silverTitanium Ag-TiO2 NPs (average size 47 nm) using picosecond laser ablation. Our results showed that both laser NPs had obvious size-dependent antibacterial activity. The laser Ag NPs with a size of 19 nm and Ag-TiO2 NPs with a size 20 nm presented the highest bactericidal effect. The laser generated Ag and Ag-TiO2 NPs with concentrations 20, 30, 40, and 50 µg/ml showed strong antibacterial effect against three bacterial strains: E. coli, P. aeruginosa, and S. aureus, and induced the generation of reactive oxygen species (ROS), lead to cell membrane interruption, lipid peroxidation, DNA damages, glutathione depletion and the eventual cell death. Both types of laser NPs at two concentrations (2.5 and 20 µg/ml) showed low cytotoxicity to the in vitro cultured five types of human cells originated from the lung (A549), kidney (HEK293), Liver (HepG2), skin (HDFc) and blood vessel cells (hCAECs). The antibacterial activity of the laser generated Ag and Ag-TiO2 NPs had lasted for over one year depending on the degree of air exposure and storage conditions. Frequent air exposure increased particle oxidation and reduced the antibacterial durability of the laser generated Ag NPs. The laser generated Ag NPs had lower antibacterial activity when stored in cold compared to that

stored at room temperature. The antibacterial activity of laser generated Ag and Ag-TiO2 NPs were also compared with four types of commercial based-silver wound dressings (Acticoat TM, Aquacel® Ag, Contreet ® Foam, and Urgotul® SSD) against E. coli to inform future application in this area. In conclusion, laser generated Ag and Ag-TiO2 NPs have strong bactericidal effect and low toxicity to human cells which could be a type of promising antibacterial agents for future hygiene and medical applications.