

[MOJ Orthop Rheumatol](#). Author manuscript; available in PMC 2016 Jun 9.

PMCID: PMC4743666

Published in final edited form as:

NIHMSID: NIHMS716157

[MOJ Orthop Rheumatol. 2015; 2\(5\): 00068.](#)

Published online 2015 Jun 9. doi: [10.15406/mojor.2015.02.00068](https://doi.org/10.15406/mojor.2015.02.00068)

## The Use of Low Level Laser Therapy (LLLT) For Musculoskeletal Pain

[Howard B Cotler](#),<sup>1,2,\*</sup> [Roberta T Chow](#),<sup>3</sup> [Michael R Hamblin](#),<sup>4,5,6</sup> and [James Carroll](#)<sup>7</sup>

<sup>1</sup>Gulf Coast Spine Care LTD, USA

<sup>2</sup>Laser Health Spa LLC, USA

<sup>3</sup>Brain and Spine Research Institute, University of Sydney, Australia

<sup>4</sup>Wellman Center for Photo medicine, Massachusetts General Hospital, USA

<sup>5</sup>Department of Dermatology, Harvard Medical School, USA

<sup>6</sup>Division of Health Sciences and Technology, USA

<sup>7</sup>Thor Photomedicine Ltd, UK

\* Corresponding author: Howard B Cotler, Owner and Medical Director, Laser Health Spa LLC, 1200 Binz Street, Suite 970 Houston, Texas, USA 77004, Tel: 713-523-8884; [Shamanhbc@yahoo.com](mailto:Shamanhbc@yahoo.com)

[Copyright notice](#) and [Disclaimer](#)

The publisher's final edited version of this article is available at [MOJ Orthop Rheumatol](#)

See other articles in PMC that [cite](#) the published article.

### Abstract

Go to:  Go to:

Pain is the most common reason for physician consultation in the United States. One out of three Americans is affected by chronic pain annually. The number one reason for missed work or school days is musculoskeletal pain. Currently accepted therapies consist of non-steroidal anti-inflammatory drugs, steroid injections, opiate pain medications and surgery, each of which carries their own specific risk profiles. What is needed are effective treatments for pain which have an acceptably low risk-profile. For over forty years, low level laser (light) therapy (LLLT) and LED (light emitting diode) therapy (also known as photobiomodulation) has been shown to reduce inflammation and edema, induce analgesia, and promote healing in a range of musculoskeletal pathologies. The purpose of this paper is to review the use of LLLT for pain, the biochemical mechanisms of action, the dose response curves, and how LLLT may be employed by orthopedic surgeons to improve outcomes and reduce adverse events.

With the predicted epidemic of chronic pain in developed countries, it is imperative to validate cost-effective and safe techniques for managing painful conditions which would allow people to live active and productive lives. Moreover the acceptance of LLLT (which is currently being used by many specialties around the world) into the armamentarium of the American health care provider would allow for additional treatment options for patients. A new cost-effective therapy for pain could elevate quality of life while reducing financial strains.

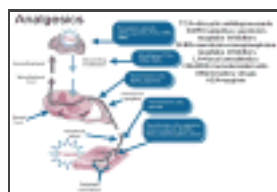
**Keywords:** Musculoskeletal, Pain, Low level laser therapy, Photobiomodulation, Injury repair

### Introduction

Go to:  Go to:

Musculoskeletal pain affects 116 million Americans annually at a cost of \$635 billion a year in medical bills, lost productivity and missed work or school [1,2]. All therapeutic treatments have their benefits, but also possess different side effects, risks and or complications. The current treatment for musculoskeletal pain includes modalities, immobilization, medications, chiropractic care, physical therapy, behavioral management, injections and/or surgery. These standard therapies have their particular associated risks/side effect profiles including peptic ulcers/gastric bleeding [3], systemic effects (cardiovascular) [4], infections (including epidural abscess) [5], narcotic dependency/addiction [6], deformities, neurologic deficits, and surgical complications [7]. The natural history of chronic pain is one of increasing dysfunction, impairment and possible disability.

The definition of pain by the “International Association for the Study of Pain” states: “Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [8]”. Withdrawal of the painful stimulus usually resolves pain promptly. Sometimes however, pain persists in spite of removal of the stimulus and even after healing of the body. Pain can also arise in the absence of any stimulus, disease or injury. Acute pain is considered to last less than thirty days, while chronic pain is of more than six months duration or as “pain that extends beyond the expected period of healing”. There are three different types of pain; nociceptive, neuropathic and central. The current medical treatment of pain or analgesics is directed at various steps of the pain pathways (Figure 1). Clinically, low level laser therapy (LLLT) can treat nociceptive [9] and neuropathic pain [10], while central pain has not yet been proven to be responsive to LLLT.



**Figure 1**

Site of analgesic action on the pain pathway.

## What is LLLT?

Low Level Laser Therapy (LLLT) sometimes known as Low Level Light Therapy or Photobiomodulation (PBM) is a low intensity light therapy. The effect is photochemical not thermal. The light triggers biochemical changes within cells and can be compared to the process of photosynthesis in plants, where the photons are absorbed by cellular photoreceptors and triggers chemical changes.

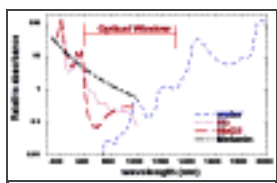
## History of LLLT

In 1903, Dr. Nils Finsen was awarded a Nobel Prize for his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation [11]. In 1960, Professor Maiman TH [12] built the first working red ruby laser [12], but it was not until 1967 when Mester E et al. [13,14] was able to demonstrate the phenomenon of “laser bio stimulation” [13,14]. In 1999, Whelan H et al. [15] presented his work on the medical applications of light emitting diodes (LED) for use on the NASA space station [15]. Subsequently over 400 Phase III randomized, double-blind, placebo-controlled trials have been published, with over 4000 laboratory studies of LLLT. (Pubmed.gov)

A laser is a device that generates light through a process of optical amplification based on the stimulated emission of electromagnetic radiation. There are four main classes of lasers as defined by the International Engineering Consortium (IEC standard 60825.) These classes indicate potential danger the radiation is to the eye.

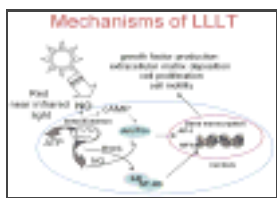
- a. Class 1/1M – CD player
- b. Class 2/2M – laser pointer
- c. Class 3R/3B – LLLT and CD and DVD writers
- d. Class 4 – Surgical laser

LLLT is the application of light (usually a low powered laser or LED typically power range of (10mW–500mW). Light with a wavelength in the red to near infrared region of the spectrum (660nm–905nm), is generally employed because these wavelengths have the ability to penetrate skin, and soft/hard tissues ([Figure 2](#)) and are proven in clinical trials to have a good effect on pain, inflammation and tissue repair. The power density (irradiance) is usually between  $5\text{W}/\text{cm}^2$  and is applied to an injury or to a painful site for 30–60 seconds a few times a week for several weeks. The result is a reduction of inflammation, pain relief and accelerated tissue regeneration. In most cases the lasers/LEDs used for LLLT emit a divergent beam (not focused or collimated) because collimation is lost in tissue, but as a consequence ocular risks are also diminished over distance.



[Figure 2](#)  
Tissue optical window.

### Mechanisms of LLLT ([Figure 3](#))



[Figure 3](#)  
Mechanisms of LLLT.

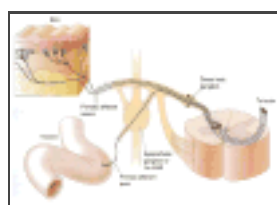
For low-power visible or near-infrared light to have an effect on a biologic system, the photon must be absorbed by electronic absorption bands belonging to a photon acceptor or chromophore (first law of photobiology) [16]. A chromophore is a molecule (or portion of a molecule) which imparts a color to a compound (e.g. chlorophyll, hemoglobin, myoglobin, cytochrome c oxidase, other cytochromes, flavin, flavoproteins or porphyrins) [17]. The “optical window” in a tissue describes a range of wavelengths where the penetration of light into tissue is maximized by employing red and near-infrared wavelengths [18]. The optimum wavelength has been estimated to be around 810 nm. Mitochondria are “the cellular power plants” in our cells and as such they convert food molecules and oxygen into energy (ATP) by oxidative phosphorylation. It has been proposed that cytochrome c oxidase (COX) is the primary photo-acceptor for the red-NIR wavelength range in mammalian cells [19]. Nitric oxide (NO) produced in mitochondria can inhibit respiration by binding to COX and displace oxygen especially in injured or hypoxic cells [20]. It is proposed that LLLT can photo-dissociate NO from COX and reverse the mitochondrial inhibition of respiration due to excessive NO binding [21]. The process of light mediated vasodilation was first described by RF Furchgott [22] in 1968, and his research on the biological properties of nitric oxide eventually led to the award of a Nobel Prize in 1998 [23]. LLLT is able to produce a shift in the overall cell redox potential in the direction of greater oxidation by increasing reactive oxygen species (ROS) and decreasing reactive nitrogen species (RNS) [24–30]. The long-term effects of LLLT are thought to be due to the activation of various transcription factors by the immediate chemical signaling molecules produce from mitochondrial stimulation by LLLT. The most important of these signaling molecules are thought to be ATP, cyclic-AMP, NO and ROS [16].

LLLT at low doses has been shown to enhance cell proliferation of fibroblasts [31–34], keratinocytes [35], endothelial cells [36] and lymphocytes [37,38]. The mechanism of proliferation is thought to result from photo-stimulation of the mitochondria leading to activation of signaling pathways and up regulation of transcription factors eventually giving rise to increases in growth factors [31,39–42]. LLLT can enhance neovascularization, promote angiogenesis and increase collagen synthesis to aid in the healing of acute [43] and chronic wounds [44–46]. It has been observed in many studies, that LLLT exhibits a biphasic dose response curve [47,48], where by lower doses of light are more effective than much higher doses. These low doses of light have demonstrated the ability to heal skin, nerves, tendons, cartilage and bones. This biphasic dose response curve may have important implications for LLLT for pain relief for the following reasons. Low-intensity LLLT stimulates mitochondria and raises mitochondrial membrane potential [49–51] and might be supposed to be more likely to increase metabolism and transport of action potentials in neurons rather than decrease it. However, much higher intensity LLLT produced by a focused laser spot acting on a nerve has the opposite effect, inhibiting mitochondrial metabolism in c-fibers and a-delta fibers and reducing mitochondrial membrane potential, thereby inducing a nerve blockade (see below).

### LLLT in the treatment of pain

Acute orthopedic conditions such as sprains [52,53], strains, post-surgical pain, a whiplash injury [54], muscular back pain, cervical or lumbar radiculopathy [55,56], tendinitis [57,58] and chronic conditions such as osteoarthritis [59–64], rheumatoid arthritis, frozen shoulder [65], neck and back pain [56], epicondylitis [66], carpal tunnel syndrome [67,68], tendinopathy [69], fibromyalgia [70], plantar fasciitis [70], post tibial fracture surgery [9] and chronic regional pain syndrome are amenable to LLLT. Dental conditions producing pain such as orthodontic procedures [71], dentine hypersensitivity [72], and third molar surgery [73] respond well to treatment with LLLT. Neuropathic pain conditions can also be treated such as post herpetic neuralgia [74], trigeminal neuralgia (10), and diabetic neuropathy [75]. Due to the wide spectrum of conditions one would surmise that multiple mechanisms can operate to achieve pain relief.

The peripheral nerve endings of nociceptors, consisting of the thinly myelinated  $A\delta$  and unmyelinated, slow-conducting C fibers, lie within the epidermis. This complex network transduces noxious stimuli into action potentials. Moreover these nerve endings are very superficial in nature and thus are easily within the penetration depths of the wavelengths used in LLLT (Figure 4). The cell bodies of neurons lie within the dorsal nerve root ganglion, but the elongated cytoplasm (axons) of the neurons extends from the cell body to the bare nerve endings in the surface of the skin. The direct effect of LLLT are initially at the level of the epidermal neural network, but the effects move to nerves in subcutaneous tissues, sympathetic ganglia, and the neuromuscular junctions within muscles and nerve trunks.



**Figure 4**  
Afferent nerves.

LLLT applied with a sufficient level of intensity causes an inhibition of action potentials where there is an approximately 30% neural blockade within 10 to 20 minutes of application, and which is reversed within about 24 hours [76]. The laser application to a peripheral nerve does have a cascade effect whereby there is suppressed synaptic activity in second order neurons so that cortical areas of the pain matrix would not be activated.

Adenosine triphosphate (ATP) is the source of energy for all cells, and in neurons this ATP is synthesized by mitochondria while they are located in the dorsal root ganglion. These mitochondria are then transported along the cytoskeleton of the nerve by a monorail system of molecular motors. LLLT acts like an anesthetic agent, in that both LLLT and anesthetics have been shown to temporally disrupt the cytoskeleton for a matter of hours as evidenced by formation of reversible varicosities or beading along the axons, which in turn cause mitochondria to “pile up” where the cytoskeleton is disrupted [77]. The exact mechanism for this effect is unknown but it is not a thermal action. It has been shown that LLLT at the correct dose decreases mitochondrial membrane potential (MMP) in DRG neurons and that ATP production is then reduced [78] so perhaps the lack of ATP could be cause of this neural blockade. The most immediate effect of nociceptor blockade is pain relief which occurs in a few minutes and has been shown by the timed onset of a conduction blockade in somatosensory-evoked potentials (SSEPs) [76]. This inhibition of peripheral sensitization not only lowers the activation threshold of nerves but also decreases the release of pro inflammatory neuropeptides (i.e. substance P and CGRP). In persistent pain disorders this reduction of tonic input to activated nociceptors and their synaptic connections, leads to a long-term down-regulation of second-order neurons [78]. The modulation of neurotransmitters is a further possible mechanism of pain relief, as serotonin and endorphin levels have been shown to increase in animal models [79,80] and following laser treatment of myofascial pain in patients [81]. Thus LLLT can have short, medium and long term effects. Fast acting pain relief occurs within minutes of application, which is a result of a neural blockade of the peripheral and sympathetic nerves and the release of neuromuscular contractions leading to in a reduction of muscle spasms [82,83].

In the medium term there is a decrease of local edema and a reduction of inflammation within hours to days [84]. The action of LLLT in reducing swelling and inflammation has been well established in animal models as well as in clinical trials. The numbers of inflammatory cells has been shown to be reduced in joints injected with protease [85], in collagen-induced rheumatoid arthritis [86], and in acute pulmonary inflammation [87]. The expression levels of pro-inflammatory cytokines have been shown to be reduced by LLLT in burn wounds [88], in muscle cryo lesions [89] and in delayed type hypersensitivity [90]. The long term effects of LLLT occur within a week or two and can last for months and sometimes years as a result of improved tissue healing.

### **LLLT parameters**

For LLLT to be effective, the irradiation parameters (wavelength, power, power density, pulse parameters, energy density, total energy and time) need to be within certain ranges. The best penetrating wavelengths in the range of 760–850nm and may achieve a light density of  $5\text{mW}/\text{cm}^2$  at 5cm deep when the beam power is 1 Watt and surface density is  $5\text{W}/\text{cm}^2$ . There are four clinical targets for LLLT:

- a. The site of injury to promote healing, remodeling and reduce inflammation.
- b. Lymph nodes to reduce edema and inflammation.
- c. Nerves to induce analgesia.
- d. Trigger points to reduce tenderness and relax contracted muscle fibers.

Treatment times per point are in the range of 30 seconds to 1 minute. As little as one point may be treated in simple cases, but as many as 10 to 15 points may be treated for more complex dysfunction such as cervical or lumbar radiculopathy.

The potential hazards are mostly ocular, as some LLLT devices are lasers, though increasingly LLLT devices have become LEDs. In most cases, LLLT devices emit divergent beams (not focused or collimated), so the ocular risk diminishes over distance. Manufacturers are obliged to provide the nominal ocular hazard distance (NOHD) within their user instructions. ANSI Z39.18 (2011) is the current definitive USA document on laser safety in healthcare environments ([www.ansi.org](http://www.ansi.org)) and IEC60825 is the International Standard. Part 8 provides guidelines for the safe use of laser beams on humans ([www.iec.ch](http://www.iec.ch)).

The North American Association for Laser Therapy conference in 2010 held a consensus meeting on safety and contraindications. Their main recommendations were:

- I. Eyes - Do not aim laser beams into the eyes and everyone present should wear appropriate safety spectacles.
- II. Cancer - Do not treat over the site of any known primary carcinoma or secondary metastasis unless the patient is undergoing chemotherapy when LLLT can be used to reduce side effects such as mucositis. LLLT however can be considered in terminally- ill cancer patients for palliative relief.
- III. Pregnancy- Do not treat directly over the developing fetus.
- IV. Epileptics - Be aware that low frequency pulsed visible light (<30Hz) might trigger a seizure in photosensitive, epileptic patients.

The adverse effects of LLLT have been reported to be no different from those reported by patients exposed to placebo devices in trials.

### **Orthopedic outcomes**

According to the more than 4000 studies on pub.med.gov, it can be concluded that the majority of laboratory and clinical studies have demonstrated that LLLT has a positive effect on acute and chronic musculoskeletal pain. Due to the heterogeneity of populations, interventions and comparison groups, this diversity means that every single study has not been positive. Pain is a very complex condition which presents in different forms with an interplay of mechanical, biochemical, psychological and socioeconomic factors. It is extremely challenging to compare LLLT to other treatments, and LLLT regimens are complicated by different lengths of treatment, all without standardization of wavelengths and dosages. Currently, there have been no long-term (greater than 2 year follow up) human clinical studies that have evaluated LLLT. The overall positive short term clinical studies in addition to strong laboratory studies should give the clinical confidence that LLLT may be beneficial for many individuals suffering from musculoskeletal pain, regardless of the cause. Consideration of evidence based treatment studies for LLLT has led to the determination that LLLT is classified as experimental/investigational by insurance companies (BCBSKS 2013), while the American Academy of Orthopedic Surgeons has no recommendations for or against its use. With FDA approval for temporary relief of muscle and joint pain, this underlines the need for further well-designed clinical studies.

### **Conclusion**

Go to:  Go to:

One has to be realistic about the therapeutic use of LLLT. The previous discussion has shown that LLLT is beneficial for pain relief and can accelerate the body's ability to heal itself. LLLT has a long history and strong basic science evidence, which supports its use in pain management. It has few side

effects and is well tolerated by the elderly. A laser or LED does not correct situations involving structural deficits or instabilities whether in bone or in soft tissue. Also, LLLT should only be used as an adjuvant therapy for pain relief in patients with neuropathic pain and neurologic deficits. Successful outcomes, like all medical management, depend on good clinical skills linked with an understanding of the nature of injury, inflammation, repair, pain, and the mechanism of laser and LED effects.

## Acknowledgments

Go to:  Go to:

Michael R Hamblin was supported by US NIH grant R01AI050875.

## Abbreviations

Go to:  Go to:

LED Light Emitting Diodes

LLLT Low Level Laser Therapy

PBM Photobiomodulation

NO Nitric Oxide

ATP Adenosine Triphosphate

ROS Reactive Oxygen Species

MMP Membrane Potential

## References

Go to:  Go to:

1. Johannes CB, Le TK, Zhou S, Johnston JA, Dworkin RH. The prevalence of chronic pain in United States adults: results of Internet-based survey. *J Pain*. 2010;11(11):1230–1239. [[PubMed](#)]
2. Gaskin DJ, Richard P. The economic costs of pain in the United States. *J Pain*. 2012;13(8):715–724. [[PubMed](#)]
3. Deeks ED. Fixed-dose ibuprofen/famotidine: a review of its use to reduce the risk of gastric and duodenal ulcers in patients requiring NSAID therapy. *Clin Drug Investig*. 2013;33(9):689–697. [[PubMed](#)]
4. Singh BK, Haque SE, Pillai KK. Assessment of nonsteroidal anti-inflammatory drug-induced cardiotoxicity. *Expert Opin Drug Metab Toxicol*. 2014;10(2):143–156. [[PubMed](#)]
5. Jones TF, Feler CA, Simmons BP, Melton K, Craig AS, et al. Neurologic complications including paralysis after a medication error involving implanted intrathecal catheters. *Am J Med*. 2002;112(1):31–36. [[PubMed](#)]
6. Argoff CE, Viscusi ER. The Use of Opioid Analgesics for Chronic Pain: Minimizing the Risk for Harm. *Am J Gastroenterol*. 2014;2(1):3–8. [[PubMed](#)]
7. Nasser R, Yadda S, Maltenfort MG, Harrop JS, Anderson DG, et al. Complication in spine surgery. *J Neurosurg Spine*. 2010;13(2):144–157. [[PubMed](#)]
8. Merskey H, Bagduk N. Classificaton of Chronic Pain. 2. International Association for the Study of

Pain (IASP) Task Force on Taxonomy, IASP Press; Seattle: 1994. Part III: Pain terms, a current list with definitions and notes on usage.

9. Nesioonpour S, Mokmeli S, Vojdani S, Mohtadi A, Akhondzadeh R. The effect of low-level laser on post-operative pain after tibial fracture surgery: a double-blind controlled randomized clinical trial. *Anesth Pain Med.* 2014;4(3):e17350. [[PMC free article](#)] [[PubMed](#)]
10. Falaki F, Nejat AH, Dalirsani Z. The Effect of Low-level Laser Therapy on Trigeminal Neuralgia: A Review of Literature. *J Dent Res Dent Clin Dent Prospects.* 2014;8(1):1–5. [[PMC free article](#)] [[PubMed](#)]
11. Finsen NR. Nobel Lectures, Physiology or Medicine 1901–1921. Elsevier Publishing Company; Amsterdam, Netherlands: 1967.
12. Maiman TH. Stimulated optical radiation in ruby. *Nature.* 1960;187:493–494.
13. Mester E, Ludány G, Sellyei M, Szende B, Gyenes G, et al. Studies on the inhibiting and activating effects of laser beams. *Langenbecks Arch Chir.* 1968;322:1022–1027. [[PubMed](#)]
14. Mester E, Ludány G, Sellyei M, et al. The simulating effect of low power laser rays on biological systems. *Laser Rev.* 1:3.
15. Whelan HT, Smits RL, Buchman EV, Whelan NT, Turner SG, et al. Effect of NASA light-emitting diode irradiation on wound healing. *J Clin Laser Med Surg.* 2001;19(6):305–314. [[PubMed](#)]
16. Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, et al. The nuts and bolts of low-level laser (light) therapy. *Ann Biomed Eng.* 2012;40(2):516–533. [[PMC free article](#)] [[PubMed](#)]
17. Hamblin MR, Demidova-Rice TN. Cellular chromophores and signaling in LLLT. In: Hamblin MR, et al., editors. *Mechanisms for Low-Light Therapy II.* The International Society for Optical Engineering; Bellingham, Washington, USA: 2007.
18. Hamblin MR, Demidova TN. Mechanisms of low level light therapy - an introduction. In: Hamblin MR, et al., editors. *Mechanisms for Low-Light Therapy I.* Vol. 61001. The International Society for Optical Engineering; Bellingham, Washington, USA: 2006. pp. 1–12.
19. Wong-Riley MT, Liang HL, Eells JT, Chance B, Henry MM, et al. Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: role of cytochrome c oxidase. *J Biol Chem.* 2005;280(6):4761–4771. [[PubMed](#)]
20. Brown GC. Nitric oxide regulates mitochondrial respiration and cell functions by inhibiting cytochrome oxidase. *FEBS Lett.* 1995;369(2–3):136–139. [[PubMed](#)]
21. Lane N. Cell biology: power games. *Nature.* 2006;443(7114):901–903. [[PubMed](#)]
22. Ehrreich SJ, Furchgott RF. Relaxation of mammalian smooth muscles by visible and ultraviolet radiation. *Nature.* 1968;218(5142):682–624. [[PubMed](#)]
23. Martin W. Robert F Furchgott, Nobel laureate (1916–2009)--a personal reflection. *Br J Pharmacol.* 2009;158(3):633–637. [[PMC free article](#)] [[PubMed](#)]
24. Alexandrotou E, Yova D, Handries P, Keetsos D, Loukas S. Human fibroblast alterations induced by low power laser irradiation at the single cell level using confocal microscopy. *Photochem Photobiol Sci.* 2002;1(8):547–552. [[PubMed](#)]



25. Chen AC, Arany PR, Huang YY, Tomkinson EM, Sharma SK, et al. Low level laser therapy activates NF-kB via generation of reactive oxygen species in mouse embryonic fibroblasts. *PLOS One*. 2011;6(7):e22453. [[PMC free article](#)] [[PubMed](#)]
26. Grossman N, Schneid N, Reuveni H, Halevy S, Lubart R. 780 nm low power diode laser irradiation stimulates proliferation of keratinocyte cultures: involvement of reactive oxygen species. *Lasers Surg Med*. 1998;22(4):212–218. [[PubMed](#)]
27. Lavi R, Shainberg A, Friedmann H, Shneyvays V, Rickover O, et al. Low energy visible light induces reactive oxygen species generation and stimulates an increase of intracellular calcium concentration in cardiac cells. *J Biol Chem*. 2003;278(42):40917–40922. [[PubMed](#)]
28. Lubart R, Eichler M, Lavi R, Friedman H, Shaimberg A. Low-energy laser irradiation promotes cellular redox activity. *Photomed Laser Surg*. 2005;23(1):3–9. [[PubMed](#)]
29. Pal G, Dutta A, Mitra K, Grace MS, Romanczyk TB, et al. Effect of low intensity laser irradiation with human skin fibroblast cells using fiber-optic nano-probes. *J Photochem Photobiol B*. 2007;86(3):252–261. [[PubMed](#)]
30. Zhang J, Xing D, Gao X. Low-power laser irradiation activates Src tyrosine through reactive oxygen species –mediated signaling pathway. *J Cell Physiol*. 2008;217(2):518–528. [[PubMed](#)]
31. Lubart R, Wollman Y, Friedmann H, Rochkind S, Laulicht I. Effects of visible and near infrared lasers on cell cultures. *J Photochem Photobiol B*. 1992;12(3):305–310. [[PubMed](#)]
32. Yu W, Naim JO, Lanzafame RJ. The effect of laser irradiation on the release of bFGF from 3T3 fibroblasts. *Photochem Photobiol*. 1994;59(2):167–170. [[PubMed](#)]
33. Vinck EM, Cagnie BJ, Cornelissen MJ, Declercq HA, Cambier DC. Increased fibroblast proliferation induced by light emitting diode and low power laser irradiation. *Lasers Med Sci*. 2003;18(2):95–99. [[PubMed](#)]
34. Frigo L, Fávero GM, Lima HJ, Maria DA, Bjordal JM, et al. Low-level laser irradiation (InGaAlP-660 nm) increases fibroblast cell proliferation and reduces cell death in a dose-dependent manner. *Photomed Laser Surg*. 2010;28(Suppl 1):S151–S156. [[PubMed](#)]
35. Basso FG, Oliveira CF, Kurachi C, Hebling J, Costa CA. Biostimulatory effect of low-level laser therapy on keratinocytes in vitro. *Lasers Med Sci*. 2013;28(2):367–374. [[PubMed](#)]
36. Szymanska J, Goralczyk K, Klawe JJ, Lukowicz M, Michalska M, et al. Phototherapy with low-level laser influences the proliferation of endothelial cells and vascular endothelial growth factor and transforming growth factor-beta secretion. *J Physiol Pharmacol*. 2013;64(3):387–391. [[PubMed](#)]
37. 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(1):8–12. [[PubMed](#)]
38. Agaiby AD, Ghali LR, Wilson R, Dyson M. Laser modulation of angiogenic factor production by T-lymphocytes. *Lasers Surg Med*. 2000;26(4):357–363. [[PubMed](#)]
39. Stadler I, Evans R, Kolb B, Naim JO, Narayan V, et al. In vitro effects of low-level laser irradiation at 660 nm on peripheral blood lymphocytes. *Lasers Surg Med*. 2000;27(3):255–256. [[PubMed](#)]

40. Saygun I, Nizam N, Ural AU, Serdar MA, Avcu F, et al. Low-level laser irradiation affects the release of basic fibroblast growth factor (bFGF), insulin-like growth factor-I (IGF-I), and receptor of IGF-I (IGFBP3) from osteoblasts. *Photomed Laser Surg.* 2012;30(3):149–154. [[PubMed](#)]
41. Esmaeelinejad M, Bayat M. Effect of low-level laser therapy on the release of interleukin-6 and basic fibroblast growth factor from cultured human skin fibroblasts in normal and high glucose mediums. *J Cosmet Laser Ther.* 2013;15(6):310–317. [[PubMed](#)]
42. de Sousa AP, Paraguassú GM, Silveira NT, de Souza J, Cangussú MC, et al. Laser and LED phototherapies on angiogenesis. *Lasers Med Sci.* 2013;28(3):981–987. [[PubMed](#)]
43. Chen CH, Tsai JL, Wang YH, Lee CL, Chen JK, et al. Low-level laser irradiation promotes cell proliferation and mRNA expression of type I collagen and decorin in porcine Achilles tendon fibroblasts in vitro. *J Orthop Res.* 2009;27(5):646–650. [[PubMed](#)]
44. Usumez A, Cengiz B, Oztuzcu S, Demir T, Aras MH, et al. Effects of laser radiation at different wavelengths (660, 810, 980, and 1,064 nm) on mucositis in an animal model of wound healing. *Lasers Med Sci.* 2014;29(6):1807–1813. [[PubMed](#)]
45. Yu W, Naim JO, Lanzafame RJ. Effects of photostimulation on wound healing in diabetic mice. *Lasers Surg Med.* 1997;20(1):56–63. [[PubMed](#)]
46. Dadpay M, Sharifian Z, Bayat M, Bayat M, Dabbagh A. Effects of pulsed infra-red low level-laser irradiation on open skin wound healing of healthy and streptozotocin-induced diabetic rats by biomechanical evaluation. *J Photochem Photobiol B.* 2012;111:1–8. [[PubMed](#)]
47. Woodruff LD, Bounkeo JM, Brannon WM, Dawes KS, Barham CD, et al. The efficacy of laser therapy in wound repair: a meta-analysis of the literature. *Photomed Laser Surg.* 2004;22(3):241–247. [[PubMed](#)]
48. Huang YY, Chen AC, Carroll JD, Hamblin MR. Biphasic dose response in low level light therapy. *Dose Response.* 2009;7(4):358–383. [[PMC free article](#)] [[PubMed](#)]
49. Huang YY, Sharma SK, Carroll J, Hamblin MR. Biphasic dose response in low level light therapy - an update. *Dose Response.* 2011;9(4):602–618. [[PMC free article](#)] [[PubMed](#)]
50. Huang YY, Nagata K, Tedford CE, Hamblin MR. Low-level laser therapy (810 nm) protects primary cortical neurons against excitotoxicity in vitro. *J Biophotonics.* 2014;7(8):656–664. [[PMC free article](#)] [[PubMed](#)]
51. Huang YY, Nagata K, Tedford CE, McCarthy T, Hamblin MR. Low-level laser therapy (LLLT) reduces oxidative stress in primary cortical neurons in vitro. *J Biophotonics.* 2013;6(10):829–838. [[PMC free article](#)] [[PubMed](#)]
52. Sharma SK, Kharkwal GB, Sajo M, Huang YY, De Taboada L, et al. Dose response effects of 810 nm laser light on mouse primary cortical neurons. *Lasers Surg Med.* 2011;43(8):851–859. [[PMC free article](#)] [[PubMed](#)]
53. Alayat MS, Atya AM, Ali MM, Shosha TM. Long-term effect of high-intensity laser therapy on the treatment of patients with chronic back pain: a randomized blinded placebo-controlled trial. *Lasers Med Sci.* 2014;29(3):1065–1073. [[PubMed](#)]
54. Stergioulas A. Low-level laser treatment can reduce edema in second degree ankle sprains. *J Clin*

Laser Med Surg. 2004;22(2):125–128. [[PubMed](#)]

55. Konstantinovic LM, Cutovic MR, Milovanovic AN, Jovic SJ, Dragin AS, et al. Low-level laser therapy for acute neck pain with radiculopathy: a double-blind placebo-controlled randomized study. *Pain Med.* 2010;11(8):1169–1178. [[PubMed](#)]

56. Draper WE, Schubert TA, Clemmons RM, Milse SA. Low-level laser therapy reduces time to ambulation in dogs after hemilaminectomy: a preliminary study. *J Small Anim Pract.* 2012;53(8):465–469. [[PubMed](#)]

57. 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(9705):1897–1908. [[PubMed](#)]

58. Lopes-Martins RA. Tendinitis, an open avenue for low-level laser therapy. *Photomed Laser Surg.* 2014;32(7):369–370. [[PubMed](#)]

59. Marcos RL, Arnold G, Magnenet V, Rahouadj R, Magdalou J. Biomechanical and biochemical protective effect of low-level laser therapy for Achilles tendinitis. *J Mech Behav Biomed Mater.* 2014;29:272–285. [[PubMed](#)]

60. Okuni I, Ushigome N, Harada T, Ohshiro T, Musya Y, et al. Low level laser therapy (lllt) for chronic joint pain of the elbow, wrist and fingers. *Laser Ther.* 2012;21(1):15–24. [[PMC free article](#)] [[PubMed](#)]

61. Alghadir A, Omar MT, Al-Askar AB, Al-Muteri NK. Effect of low-level laser therapy in patients with chronic knee osteoarthritis: a single-blinded randomized clinical study. *Lasers Med Sci.* 2014;29(2):749–755. [[PubMed](#)]

62. Bjordal JM, Johnson MI, Lopes-Martins RA, Bogen B, Chow R, et al. Short-term efficacy of physical interventions in osteoarthritic knee pain. A systematic review and meta-analysis of randomised placebo controlled trials. *BMC Musculoskelet Disord.* 2007;8:51. [[PMC free article](#)] [[PubMed](#)]

63. Leal-Junior EC, Johnson DS, Saltmarche A, Demchak T. Adjunctive use of combination of super-pulsed laser and light-emitting diodes phototherapy on nonspecific knee pain: double-blinded randomized placebo-controlled trial. *Laser Med Sci.* 2014;29(6):1839–1847. [[PubMed](#)]

64. Hamblin MR. Can osteoarthritis be treated with light? *Arthritis Res Ther.* 2013;15(5):120. [[PMC free article](#)] [[PubMed](#)]

65. Kheshie AR, Alayat MS, Ali MM. High-intensity versus low-level laser therapy in the treatment of patient with knee osteoarthritis: a randomized controlled trial. *Lasers Med Sci.* 2014;29(4):1371–1376. [[PubMed](#)]

66. Jain TK, Sharma NK. The effectiveness of physiotherapeutic interventions in treatment of frozen shoulder/adhesive capsulitis: a systematic review. *J Back Musculoskelet Rehabil.* 2014;27(3):247–273. [[PubMed](#)]

67. 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(3):145–151. [[PubMed](#)]

68. Fusaku Y, Asanyvalai T, Saensri P, Thengwittayaporn S. Low-level laser therapy with a wrist splint to treat carpal tunnel syndrome; a double-blinded randomized controlled trial. *Lasers Med Sci*. 2014;29(3):1279–1287. [[PubMed](#)]
69. Lazovic M, Ilic-Stojanovic O, Kocic M, Zivkovic V, Hrkovic M, et al. Placebo-controlled investigation of low-level laser therapy to treat carpal tunnel syndrome. *Photomed Laser Surg*. 2014;32(6):336–344. [[PubMed](#)]
70. Tumilty S, Munn J, McDonough S, Hurley DA, Basford JR, et al. Low level laser treatment of tendinopathy: a systematic review with meta-analysis. *Photomed Laser Surg*. 2010;28(1):3–16. [[PubMed](#)]
71. Jastifer JR, Catena F, Doty JF, Stevens F, Coughlin MJ. Low-level laser therapy for the treatment of chronic planta fasciitis: a prospective study. *Foot Ankle Int*. 2014;35(6):566–571. [[PubMed](#)]
72. Li FJ, Zhang JY, Zeng XT, Guo Y. Low-level laser therapy for orthodontic pain: a systematic review. *Lasers Med Sci* 2014 [[PubMed](#)]
73. Hashim NT, Gasmalla BG, Sabahelkheir AH, Awooda AM. Effect of the clinical application of the diode laser (810 nm) in the treatment of dentine hypersensitivity. *BMC Res Notes*. 2014;7:31. [[PMC free article](#)] [[PubMed](#)]
74. Saber K, Chiniforush N, Shahabi S. The effect of low level laser therapy on pain reduction after third molar surgery. *Minerva Stomatol*. 2012;61(7–8):319–322. [[PubMed](#)]
75. Knapp DJ. Postherpetic neuralgia: case study of class 4 laser therapy intervention. *Clin J Pain*. 2013;29(10):e6–e9. [[PubMed](#)]
76. Bashiri H. Evaluation of low level laser therapy in reducing diabetic polyneuropathy related pain and sensorimotor disorders. *Acta Med Iran*. 2013;51(8):543–547. [[PubMed](#)]
77. Baxter GD, Walsh DM, Allen JM, Lowe AS, Bell AJ. Effects of low intensity infrared laser irradiation upon conduction in human median nerve in vivo. *Exp Physiol*. 1994;79(2):227–234. [[PubMed](#)]
78. Chow RT, David MA, Armati PJ. 830 nm laser irradiation induces varicosity formation, reduces mitochondrial membrane potential and blocks fast axonal flow in small and medium diameter rat dorsal root ganglion neurons: implications for the analgesic effects of 830 nm laser. *J Peripher Nerv Syst*. 2007;12(1):28–39. [[PubMed](#)]
79. Klein T, Magerl W, Hopf HC, Sandkühler J, Treede RD. Perceptual correlates of nociceptive long-term potentiation and long-term depression in humans. *J Neurosci*. 2004;24(4):964–971. [[PubMed](#)]
80. Hagiwara S, Iwasaka H, Okuda K, Noguchi T. GaAlAs (830 nm) low-level laser enhances peripheral endogenous opioid analgesia in rats. *Lasers Surg Med*. 2007;39(10):797–802. [[PubMed](#)]
81. Erthal V, da Silva MD, Cidral-Filho FJ, Santos AR, Nohama P. ST36 laser acupuncture reduces pain-related behavior in rats: involvement of the opioidergic and serotonergic systems. *Lasers Med Sci*. 2013;28(5):1345–1351. [[PubMed](#)]
82. Carrasco TG, Guerisoli LD, Guerisoli DM, Mazzetto MO. Evaluation of low intensity laser therapy in myofascial pain syndrome. *Cranio*. 2009;27(4):243–247. [[PubMed](#)]

83. Olavi A, Pekka R, Pertti K, Pekka P. Effects of the infrared laser therapy at treated and non treated trigger points. *Acupunct Electrother Res.* 1989;14(1):9–14. [[PubMed](#)]
84. Carati CJ, Anderson SN, Gannon BJ, Piller NB. Treatment of postmastectomy lymphedema with low-level laser therapy: A double blind, placebo-controlled trial. *Cancer.* 2003;98(6):1114–1122. [[PubMed](#)]
85. Pillar NB, Thelander A. Treating chronic post mastectomy lymph edema with low level laser therapy: a cost effective strategy to reduce severity and improve the quality of survival. *Laser Therapy.* 1995;7:163–8.
86. Guo H, Luo Q, Zhang J, Lin H, Xia L, et al. Comparing different physical factors on serum TNF-alpha levels, chondrocyte apoptosis, caspase-3 and caspase-8 expression in osteoarthritis of the knee in rabbits. *Joint Bone Spine.* 2011;78(6):604–610. [[PubMed](#)]
87. Alves AC, de Carvalho PT, Parente M, Xavier M, Frigo L, et al. Low-level laser therapy in different stages of rheumatoid arthritis: a histological study. *Lasers Med Sci.* 2013;28(2):529–536. [[PubMed](#)]
88. Mafra de Lima F, Villaverde AB, Salgado MA, Castro-Faria-Neto HC, Munin E, et al. Low intensity laser therapy (LILT) in vivo acts on the neutrophils recruitment and chemokines/cytokines levels in a model of acute pulmonary inflammation induced by aerosol of lipopolysaccharide from *Escherichia coli* in rat. *J Photochem Photobiol B.* 2010;101(3):271–278. [[PubMed](#)]
89. Gupta A, Keshri GK, Yadav A, Gola S, Chauhan S, et al. Superpulsed (Ga-As, 904 nm) low-level laser therapy (LLLT) attenuates inflammatory response and enhances healing of burn wounds. *J Biophotonics.* 2014 9999 (9999) [[PubMed](#)]
90. Assis L, Moretti AI, Abrahão TB, Cury V, Souza HP, et al. Low-level laser therapy (808 nm) reduces inflammatory response and oxidative stress in rat tibialis anterior muscle after cryolesion. *Lasers Surg Med.* 2012;44(9):726–735. [[PMC free article](#)] [[PubMed](#)]
91. Oliveira RG, Ferreira AP, Côrtes AJ, Aarestrup BJ, Andrade LC, et al. Low-level laser reduces the production of TNF-alpha, IFN-gamma, and IL-10 induced by OVA. *Lasers Med Sci.* 2013;28(6):1519–1525. [[PubMed](#)]