# Low Level laser Therapy (LLLT) / Photobiomodulation (PBMT)

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# Introduction to Photobiomodulation (PBMT)

## What is PBMT?

Photobiomodulation (Formerly known as Low Level Light / Laser Therapy (LLLT)) is the application of light (usually a low power laser or LED) to promote tissue repair, reduce inflammation or induce analgesia. LLLT has been the subject of several systematic reviews for a range of musculoskeletal pathologies with favorable conclusions reported by The Lancet [1], BMJ [2], International Association for the Study of Pain [3] and the World Health Organization [4]. Unlike other many treatments LLLT is not an ablating or heating based therapy, it is more akin to photosynthesis.

The LLLT devices are typically in the red an near infrared spectrum. Sometimes pulsed and sometimes continuous beams are used. For acute and post operative pathologies as little as one session is all that is necessary but for chronic pain and degenerative conditions as many as ten sessions may be necessary. Whilst other wavelengths have similar effects they do not penetrate nearly so well as the red and near infrared range [5].

## Research:

To-date more than 400 randomized double blind placebo controlled clinical trials have been published with some professional guidelines suggesting LLLT is used as part of standard care, including :

World Health Organization (WHO) Task Force on Neck Pain systematic review [4]

The Lancet Systematic review of LLLT for Neck Pain [1]

International Association for the Study of Pain (IASP) fact sheets for Myofascial Pain Syndrome , osteoarthritis and neck pain [3]

British Medical Journal (BMJ) Systematic review and guidelines for treating tennis elbow [2]

American Physical Therapy Association (APTA) Systematic review and clinical practice guidelines for achilles tendinopathy: [8]

British Journal of Sports Medicine (BJSM) Systematic review for frozen shoulder [7]

European Society for Medical Oncology (ESMO) Clinical practice guidelines for oral mucositis [9]

Multinational Association for Supportive Cancer Care (MASCC) Clinical practice guidelines for oral mucositis [10]

## Applications

Arthropathies
Degenerative Disc Disease
Fractures
Lymphedema
Myofascial pain
Neuropathies
Rehabilitation
Soft tissue injuries
Tendinopathies

## Mechanism of Action

Most of the effects of LLLT can be explained by light absorption in the mitochondria [14-16]. Every cell in the body has lots of mitochondria (hundreds or thousands per cell). Mitochondria to make cellular energy (ATP) from oxygen and pyruvate. In stressed or ischemic tissues, mitochondria make their own nitric oxide (mtNO) [17-19] which competes with oxygen. The mtNO binds to Cytochrome c Oxidase (CcO) (the terminal enzyme in the electron transport chain) and displaces oxygen [20]. This displacement of oxygen has two negative effects; Reduced ATP synthesis

Increased oxidative stress (leading to inflammation via the inflammatory "master switch" NF-kB) [17-19, 21-23]. The effect of LLLT on hypoxic / stressed tissues can be described in several stages:

**Primary effect of LLLT: Absorption by cytochrome c oxidase**

Cytochrome c oxidase (CcO) absorbs red and near infrared light, the transfer of light energy by this enzyme triggers a series of downstream effects [14, 24-26].

**Secondary effect: Modulation of ATP, nitric oxide & reactive oxygen species**

Changes in ATP, reactive oxygen species and nitric oxide follow light absorption by CcO. These effects are redox state and dose dependent. In hypoxic or otherwise stressed cells it has been shown many times that following LLLT, nitric oxide is released, ATP is increased and oxidative stress is reduced [27-31].

**Tertiary effect: Downstream intracellular responses (gene transcription, and cellular signaling)**

The downstream effects of LLLT released nitric oxide, increased ATP and reduced oxidative stress are many. They are context and cell type specific. Either directly or indirectly these biochemical intermediates affect components in the cytosol, cell membrane, and nucleus that control gene transcription and subsequently cell proliferation, migration, necrosis and inflammation [27-31].

**Quaternary effect: Extracellular, indirect, distant effects**

Tissues that have not absorbed photons can also be affected indirectly via secretions from cells that have absorbed light. Cells in blood and lymph can be activated and they travel significant distances from the session area to have distant (systemic) effects [32]. These can be autocrine, paracrine, and endocrine effects (sometimes known as a "bystander" effects).

**Edema / Lymphatic flow**

There is good evidence that LLLT also improves lymphatic flow. A systematic review of eight clinical trials of LLLT for post mastectomy lymphoedema concludes that "There is moderate to strong evidence for the effectiveness of LLLT for the management of breast cancer related lymphedema" [33]. A controlled clinical trial on soccer players with second degree ankle sprains, found a significant reduction in edema volume for the laser group compared with placebo laser (both groups also had rest, ice, compression and elevation) [34]. A laboratory trial on Carrageenan-induced edema in the mouse paw found that treating lymph nodes alone was enough to reduce edema in the mouse paw [35]. The mechanism of action is unknown.

**Analgesia**

Analgesic effects are probably via a different mechanism from the increased ATP / reduced oxidative stress model described above. According to a systematic review of laser analgesia mechanisms by Chow et al [36], higher power density laser light > 300mW/cm$^2$, when absorbed by nociceptors, have an inhibitory effect on Aδ and C pain fibers. This high power density LLLT session slows conduction velocity, reduces amplitude of compound action potentials and suppresses neurogenic inflammation. Chow's own laboratory studies show that LLLT blocks anterograde transport of ATP-rich mitochondria in dorsal root ganglion neurons. Varicosities result from this inhibition, this is normally associated with disruption of microtubules. This effect is completely reversible and lasts only 48 hours [37-39]. More work is needed to fully understand the complete mechanism of action.

**Myofascial Trigger points**

Myofascial trigger points are palpable nodules in taut muscle bands and contraction of muscle fibers that lead to muscle spasms and limited joint movement. They are a component of several pain conditions, including migraine, tension-type headaches, temporomandibular disorder and neck pain. The motor end plate is central to the etiology of trigger points and EMG studies have shown abnormally high electrical activity over trigger points. Electrical activity is reduced after after LLLT and clinical studies have shown

that LLLT has immediate and cumulative effects on reducing pain [40-43], however the mechanism of action is not yet fully understood.

## LLLT PARAMETERS

For LLLT to be effective, the irradiation parameters (wavelength, power, power density, pulse parameters) need to be within certain ranges. If the wrong irradiation parameters are used or applied for the wrong amount of time, then session will be ineffective. If the power density is too low and / or the time is too short, then there is no significant effect. Alternatively, if the power density is too high and / or the session time is too long, then the benefit is lost and sometimes unwanted inhibitory effects occur [44-46].

Unfortunately, many researchers fail to accurately measure or even report some of these parameters. This is due, in part, to a poor appreciation of the relevance of these parameters and also because some of these measurements require expensive instrumentation that need to be operated by trained engineers or physicists [47].

Parameters should be considered in two parts: the 'medicine' and the 'dose'.

### MEDICINE

**Wavelength (nm)**

It is the structure of cytochrome c oxidase and its redox state that determines which wavelengths of light will be absorbed [14-16].. The optimum wavelength is not universally agreed, but most common LLLT devices used in dentistry are typically within the 600nm - 1000nm range. There are many absorption peaks for cytochrome c oxidase in that range, they penetrate tissues well, and many clinical trials have been successful with them.

**Power (W)**

The most common LLLT devices used in dentistry are in the range 50 - 200mW, but power density is just as important (if not more so), especially for large beam areas.

**Beam Area ($cm^2$)**

Beam area is required for calculating power density, but is difficult to measure and frequently misreported . Diode laser beams are typically not round (more often they are like an ellipse) and the beams are usually brighter in the middle and gradually weaken towards the edge (Gaussian distribution). This has been poorly understood by many researchers, errors are frequently made when reporting beam area. The aperture does not necessarily define the beam size, which should be measured using a beam profiler and reported at the $1/e^2$ point [47, 96].

**Power Density ($W/cm^2$)**

Power density is the product of Power (W)/beam area ($cm^2$). This parameter is frequently misreported due to difficulty with measuring beam area [47, 68]. Studies that have taken the trouble to measure beam power density carefully and taken measurements at the target depth report successful tissue repair and anti-inflammatory effects in the range of 5 - 55$mW/cm^2$ at the target [65-67]. Analgesia typically requires higher power densities; a systematic review of laboratory studies found power densities > 300 $mW/cm^2$ are necessary to inhibit nerve conduction in C-fibres and A-delta fibres [36]

**Pulse Structure (Peak Power (W), Pulse freq. (Hz), Pulse Width (s), Duty cycle (%))**

If the beam is pulsed, then the reported power should be the "Average Power" and calculated as follows: Peak Power (W) × pulse width (s) × pulse frequency (Hz) = Average Power (W). A review of the effect of pulses [64] concludes that "there was some evidence that pulsed light does have effects that are different from those of continuous wave light. However further work is needed to define these effects for different disease conditions and pulse structures." A subsequent study on traumatic brain injury in mice [63] showed

that 10Hz to be more effective than 100Hz or CW in reducing the neurological severity score.

**Coherence**

Coherent light produces laser speckle, which has been postulated to play a role in the photobiomodulation interaction with cells and sub-cellular organelles. No definitive trials have been published to-date to confirm or refute this claim but it is clear that coherence is not required to have good clinical effects. [5]

### DOSE

Having established suitable irradiation parameters, they must be applied for adequate amount of time. If the wrong irradiation parameters are used or applied for the wrong irradiation time, then session will be ineffective [44, 45, 48, 49].

Energy (Joules) or energy density (fluence) ($W/cm^2$) is often referred to as "dose". These are different calculations and, on their own, are both potentially flawed methods of reporting this therapy. Table 2 shows the formulas and discusses the limitations.

**Energy (J)**

Calculated as: Power (W) x time (s)= Energy (Joules). Using Joules as an expression of dose is potentially unreliable as it assumes an inverse relationship between power and time and ignores power density.

**Energy Density (J/cm2)**

Calculated as: Power (W) x time (s) / beam area = Energy Density ($J/cm^2$). Using energy density as an expression of dose is also potentially unreliable, as it assumes an inverse relationship between power, time and power density.

**Irradiation time (s)**

Given the lack of reciprocity described above,the safest way to record and prescribe LLLT is to define the irradiation parameters, then define the irradiation time and not rely on the total energy or fluence applied.

**Treatment Interval (hours, days, or weeks)**

One session of acute injuries (or immediately post op) has clinically meaningful effects (though follow up session the next day may also be welcomed by the patient). For chronic non healing or chronic pain pathologies, LLLT typically requires two or three sessions a week for several weeks to achieve clinical significance.

## TREATMENTS

There are four common clinical targets for LLLT.

- The site of injury to promote healing, remodeling and reduce inflammation [52-56]
- Lymph nodes to help reduce edema and inflammation. [33, 35, 57]
- Nerves to induce analgesia [36, 37, 39, 58]
- Trigger points to reduce tenderness and relax contracted muscle fibers [40-43].

## SAFETY

LED products are considered safe and excluded from medical surveillance under Federal Law 21CFR 1040.10.

### Precautions

The North American Association for Laser Therapy conference 2010 held a consensus meeting on safety and contraindications: The main recommendations included:
CANCER - Do not treat over the site of any known primary carcinoma or secondary metastasis unless the patient is undergoing chemotherapy; it's use can be considered in terminally ill cancer patients for palliative relief.
PREGNANCY - Do not treat directly over a developing fetus (consequences unknown)
EPILEPTICS - Be aware that low frequency pulsed visible light (<30hz) might trigger a seizure in photosensitive epileptic patients. Make sure they cannot see any pulsing beams.

### Post Treatment Reactions

The Lancet review on neck pain [1] reported that "Half the studies obtained data for side-effects, with tiredness reported in the laser-treated group in three studies,42'46'" which was significant in one study"

A chronic joint disorder systematic review [41] reported: "In terms of side effects, six of the LLLT trials with optimal dose explicitly stated in their report that no adverse effects were observed. One trial reported an incident of transient adverse effects for one patient in each group.

## Conclusion

LLLT is a safe effective session for faster healing, better tissue remodeling, reduced inflammation and analgesia in a wide range of oral pathologies. It is drug free and relatively side-effect free and seems to work where pharmaceuticals do not [11-13, 60-62].

## Glossary

**Beam profiler**
An instrument for measuring the beam intensity distribution
**Laser speckle**
A random fuzzy looking pattern produced by coherent laser light. Technically speaking they are a random intensity pattern produced by the mutual interference of a set of wavefronts
**LED**
Light Emitting Diode. A narrow spectral width (one colour) semiconductor light source.
**Off-Label**
Use for a condition other than that for which it has been officially approved by a regulatory authority (e.g. FDA in USA, CE for Europe, Health Canada, TGA in Australia).
**Systematic Review**
A review in which research about a topic has been systematically identified, appraised and summarized.
**Tissue Remodeling**
The third phase of tissue repair after inflammation and cell proliferation

# About the Author

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- CEO of THOR Photomedicine Ltd www.thorlaser.com.
- A recognized authority on LLLT mechanisms of action, dose, dose rate effects and the measurement and reporting of parameters.
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