

# The Clinical Pillars Paper

*Translating Science into Patient Outcomes*



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## **Aligning scientific research with best practices**

Randomized controlled trials have long been held up as the “gold standard” of clinical research, Multi Radiance Medical has performed over 30 studies since 2003.



## **Treating light as a photoceutical**

The combination of good evidence and virtually no side effects makes Multi Radiance Super Pulsed Lasers ideally suited to become the standard of care for all future pain treatments.



## **Translating scientific research into clinical practice**

Specific research based protocols complete with area of application, time, and total energy delivered are found in the second half of this monograph.



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### **Validating the Technology**

Multi Radiance Technology is composed of four individual wavelengths that span the therapeutic spectrum (blue, red, infrared). The Multi Radiance Medical proprietary core utilizes a combination of super pulsed 905 nm and 640 nm, 850-875 nm LEDs to create a synergistic effect that in turn regulates mitochondrial function. To maximize the clinical effect of the isolated and combined effects of the included wavelengths it is necessary to understand thermal time profiles (TTP), depth of penetration time profiles (DPTP), method of action, and the biphasic dose response curve.

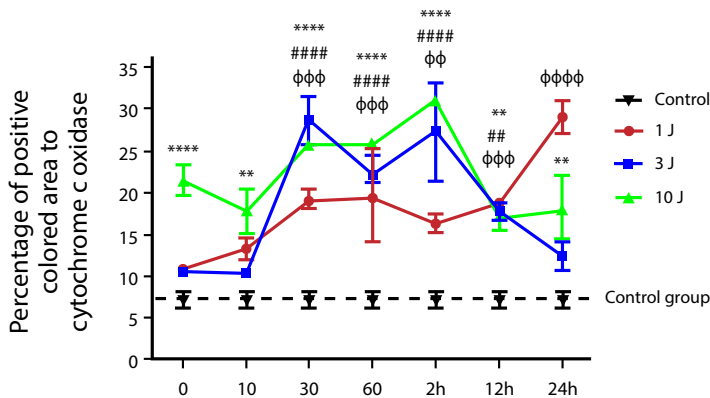
### **Optimizing Technology with Science**

Photothermal damage occurs when light energy deposition due to thermal deactivation occurs faster than thermal diffusion, and so the temperature of the target tissue rises.<sup>1</sup> This accentuates the rule that the positive photobiomodulation (PBM) effects are non-thermal<sup>2</sup> and negative effects have been linked with higher powered lasers that increase skin temperature.<sup>3</sup> The nanosecond pulses of the super pulsed laser attribute to the lack of accumulating skin temperature as noted by Grandinetti et al.<sup>4</sup> and to the beneficial effects of super pulsed laser therapy (SPLT).

Albuquerque-Pontes et al.<sup>5</sup> evaluated the simultaneous emission of multiple wavelengths on light penetration through the skin barrier. Individual, as well as combined, wavelengths were tested separately to establish the percentage of penetration or DPTP. A pattern of linearly increased penetration over time occurred, similar to the findings of Joensen et al.<sup>6</sup> Nearly 39% of the light from the surface penetrated through the dorsal skin; this was nearly double the predicted value calculated by the individual wavelengths. By improving the efficiency of penetration, a greater percentage of light energy is readily able to penetrate beneath the skin and minimizes the amount of energy being transformed into heat.

Friedmann et al.<sup>7</sup> identified the mechanism of pain relief following exposure to SPLT. A de-polymerization of the microtubules in C-fibers and A delta fibers due to oxidative stress from the electron transport chain acceleration interrupts neurogenic inflammation by inhibiting the release of substance P, calcitonin gene related peptide (CGRP) and neurokinin A. Cytochrome c oxidase (CCO) functions as the terminal constituent of the electron transport chain in the inner mitochondrial membrane, where it reduces molecular oxygen to water, allowing ATP production. Dysfunctional CCO promotes oxidative stress in many diseases.<sup>8</sup> Leal-Junior and Tomazoni<sup>9</sup> studied the effects of individual and combined combinations of three different wavelengths on intact skeletal muscle to identify the method of action behind this observed effect. After application of SPLT, an upregulation of CCO was noticed in a dose dependent manner, and activation lasted between 5 minutes and a full 24 hours following irradiation.

### Combined wavelengths



The biphasic dose response or Arndt-Schulz curve in PBM has been shown in both in vitro studies and in animal experiments.<sup>10</sup> Many studies often fail due to inadequate dosing.<sup>11</sup> This highlights the need to understand the values of this biphasic dose. A stimulatory dose is regarded as one that typically will reduce inflammation and stimulate tissue repair. Pain relief is typically achieved when larger doses of energy are applied to the tissue, creating a photophysical effect.<sup>12</sup> Antonialli et al.<sup>13</sup> conducted an experiment with humans to evaluate the biphasic dose response to skeletal muscle specifically with SPLT. Following an isokinetic exercise fatigue protocol, creatine kinase (inflammation) and VAS (pain) were measured for 96 hours in 40 male volunteers following a single exposure (250 Hz, 30 J) dose of SPLT. This experiment details the dose ranges from stimulatory (10 J to 30 J) to inhibitory (>50 J).

## Translating Science into Clinical Outcomes

Despite increasing interest in PBM therapy, with literally a new article published every other day, the practical aspects of clinical integration have remained slow. There is often a disconnect between laboratory procedures and clinical practice. This results in a breakdown of communication between researchers and clinicians that often ends in failed implementation of the positive observed outcome. The transfer and ultimately the translation of scientific findings need to align with the best practices.

Multi Radiance has trained its focus on translational research that challenges researchers in new ways, complementing enterprise and enhancing scientific progress for the interest and benefit of all. The ever-growing number of studies and research projects on super pulsed laser is now focused on the transfer or translation of clinical knowledge and peer-reviewed evidence to the practitioner to improve clinical outcomes.

For more details on these studies and Multi Radiance Technology, additional Pillars Papers are available from [www.multiradiance.com](http://www.multiradiance.com). Currently, there are three additional papers:

- **The Pillars Paper:** Details the laboratory and bench work that first validated and later optimized the multiple wavelength selections.
- **The Comparative Pillars Paper:** Separates PBM facts from fiction while explaining the difference between therapeutic laser devices.
- **The Veterinary Pillars Paper:** Explores the latest PBM evidence and expands on the clinical utility of SPLT in veterinary medicine to understand the potential value of therapeutic lasers.

## Introduction

The use of therapeutic lasers has experienced an explosive growth in several market segments including medical, dental, and veterinary. In 2020, the number of research studies has surpassed 6,500 on PubMed and continues to expand beyond its use in rehabilitation to include use as a novel and innovative means to enhance athletic performance and recovery. Low-level laser or most specifically non-thermal uses of lasers were found to have profound biological effects on

tissue including increased cell proliferation,<sup>14</sup> accelerating the healing process, promoting tissue regeneration, preventing cell death,<sup>15</sup> relief of pain<sup>16</sup> and anti-inflammatory activity.<sup>17</sup> This process is also known as photobiomodulation (PBM) and photobiomodulation therapy (PBMT).

The photobiological-photochemical phenomena are like photosynthesis carried out by plants. To enable the visible light of low energy to affect any living biological system, the energy-carrying photons must be absorbed by electrons belonging to a photoreceptor or chromophore of the target biological system.<sup>18</sup> One of the basic mechanisms of PBM is the stimulation of mitochondria,<sup>19</sup> which are thought to be a key target in the phototherapeutic mechanism of action acceleration of electron transfer by photons in the visible and near infrared region of the light spectrum<sup>20,21</sup> via the modulation of cytochrome c oxidase (CCO) activity. This stimulation leads to increased ATP production, modulation of reactive oxygen species, and induction of transcription factors.<sup>22</sup>

Therapeutic exposure to low levels of red and/or near infrared (NIR) light is commonly referred to as “low-level” because of its use of light at energy densities that are low compared to other forms of laser that are used for ablation, cutting, and thermally coagulating tissue.<sup>23</sup> Heat is a compounding limitation in achieving optimal phototherapeutic effects. As surface heating of the skin increases, the biological effect begins to decrease. Photothermal damage occurs when light energy deposition occurs faster than thermal diffusion, and the temperature of the target tissue rises.<sup>24</sup> This is especially true for highly pigmented skin.<sup>25</sup>

Most continuous wave lasers/LEDs and all high-powered Class 4 lasers produce a considerable amount of unwanted heat. Often scanning or non-contact treatments are used to mitigate heating, which affects the delivered dose and density of the therapy. Arany et al.<sup>26</sup> administered high-powered Class 4 lasers to determine the threshold at which laser absorption becomes phototoxic or cytotoxic. The conclusion was the accumulation of heat combined with the excessive release of ROS creates toxicity during Class 4 laser exposure. Mantineo et al.<sup>27</sup> notes that the temperature increases are more pronounced for 980 nm Class 4 than with any other wavelength due to the high absorption in water. This underpins the notion that Class 4 lasers do NOT

provide photobiostimulation as described by the North American Association of Photobiomodulation Therapy (NAALT) since the method of action for high-powered lasers is thermal tissue stimulation.

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Super pulsed laser (SPL) works differently than traditional high-powered lasers by generating extremely high-powered bursts of light at billionths-of-seconds durations. The result is a low thermal influence on the skin from maximizing the optimal dose to the target, creating a beneficial phototherapeutic effect that also could transit through the dermis much more efficiently to reach much deeper target tissue while maintaining the FDA/OSHA’s safest classification: Class 1.<sup>28</sup>

The United States Food and Drug Administration (FDA) recognizes devices with a non-thermal mechanism of action by the designation NHN for those devices that have been granted clearance as low-level therapeutic lasers. Most devices currently on the market are registered under the infrared exemption (ILY) and do not require clinical studies of effectiveness.

Non-thermal treatments are especially important when dealing with dark pigmented skin. The addition of pulsed red light (640-660 nm) and pulsed broadband infrared emitting diodes (850-875 nm) complete the therapeutic window, penetrating shallower tissue depths than the laser but providing additional photochemical (reducing inflammation) and photophysical (relieving pain) effects.<sup>29</sup>

## **The Pain Problem**

According to the Centers for Disease Control and Prevention, 50 million adults in the United States have chronic daily pain, with 19.6 million adults experiencing high impact chronic pain that interferes with daily life or work activities.<sup>30</sup> Patients with acute and chronic pain in the U.S. face a crisis because of significant challenges in obtaining adequate care, resulting in

profound physical, emotional, and societal costs. The cost of pain to the U.S. is estimated at between \$560 billion and \$635 billion annually.<sup>31</sup> At the same time, the country is facing an opioid crisis that, over the past two decades, has resulted in an unprecedented wave of overdose deaths associated with prescription opioids, heroin, and synthetic opioids.

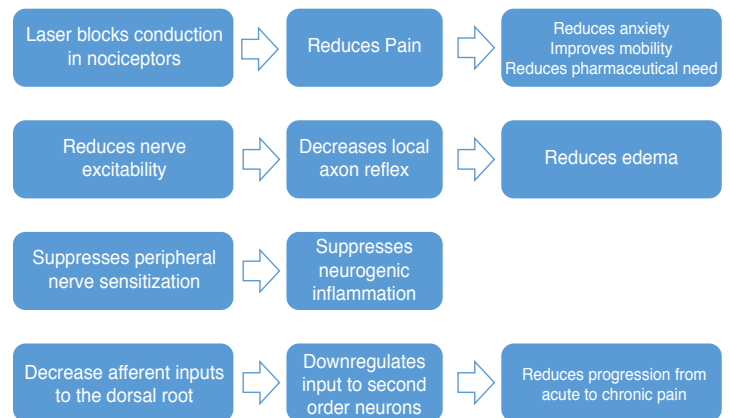
While pain care has grown more sophisticated, the most effective care still is not widely available. The use of light as a therapeutic alternative form of medicine to manage pain and inflammation has been proposed to fill this void. Super pulsed laser therapy (SPLT) offers a safe, drug-free, and side-effect-free method for pain relief, resolution of inflammation, and wound healing. Its efficacy is evidenced by the plethora of completed studies and clinical trials currently being performed to develop novel treatment for a variety of conditions in both human and veterinary medicine.

Super pulsed laser therapy offers a safe, drug-free, and side-effect-free method for pain relief, resolution of inflammation, and wound healing.

The nature of pain is widely misunderstood. Acute pain is the body's alarm system — it warns of potential harm. Acute pain initiates our defensive reactions to protect ourselves, such as jerking a hand away from a hot stove or triggering the fight-or-flight response to escape a threat. Pain caused by a physical injury normally resolves in a period of a few days to three months. Pain that lasts longer and interferes with daily functioning is known as chronic pain.

Pain is detected in the periphery by specialized receptors known as nociceptors. Nociceptors are stimulated by chemicals that are released during inflammation including prostaglandin E2 (PGE2), bradykinin, and Substance P. These chemicals positively alter resting nerve potential, making it easier to cause an action potential. Pain signals travel along specific nerve fibers, A $\delta$ -fibers (sharp localized pain) and C-fibers (diffuse pain), to the central spine (1st order neuron) where they enter the posterior horn of the spine after going through the posterior root ganglion.

The A $\delta$ -fibers release glutamate and C-fibers release substance P as they synapse with the second order neuron. The pain signal then crosses the spine and is then transmitted to the thalamus where it synapses one more time. The pain signal is finally transmitted to the sensory cortex where the brain compares it to other pain the person has experienced. One hundred percent of pain perception occurs in the brain. The level of pain that is perceived is partially based on how large the number of action potentials are that reach the sensory cortex. If the pain signal does not reach the brain or is decreased prior to reaching the brain, the perception of pain is decreased. The body has two pain modulation pathways that can dampen the pain signal: gate control and a descending pathway. Both pathways stimulate interneurons in the spine that release neurotransmitters (GABA and Enkephalin) resulting in the inhibition of the release of Glutamate and Substance P or preventing the threshold being reached in the second order neuron.



However, the opposite is also true; if the pain signal is amplified then the person will perceive a greater amount of pain. This is called sensitization, which occurs in various pain syndromes including fibromyalgia syndrome and results in chronic pain. As pain transitions from acute to chronic, the patient develops peripheral and central sensitization. This entails physiological changes that cause the pain signal from the periphery to be amplified at the spinal synapse prior to traveling up to the thalamus. The early stage is normal hyperalgesia caused by an increase in the glutamate and substance P receptor field both peripherally and centrally. This results in a more intense action potential that is perceived as a greater amount of pain for a smaller stimulus. This occurs because more receptors are stimulated causing a larger influx of positive ions

and causing a greater action potential. Additionally, the hypersensitive field increases to the area surrounding the injury. This is normal and will decrease to pre-injury levels as the tissue heals.

Late stage central sensitization occurs due to inadequate resolution of the injury and a continued stimulation of the nociceptors. The result is changes in the spinal synapse. Initially there is an increase in glutamate receptors. Additionally, spinal glial cells release inflammatory cytokines (PGE2, TNF- $\alpha$ , IL-6, IL-8) at the spinal level. These cause the amplification of the pain signal from the 1st order to the 2nd order neuron. Also, allodynia starts, which is essentially when a normal, non-painful stimulation results in pain. This occurs in individuals with complex regional pain syndrome (CRPS). Therefore, a low pain signal from the periphery results in a greater perception of pain. The final change of central sensitization is the destruction of the pain modulating interneurons. This results in a decrease in the body's own ability to modulate pain.

Pain is the most common reason for physician consultations in the United States<sup>32</sup> and the number one reason for missed work or school days is musculoskeletal pain. One out of three Americans is affected by chronic pain annually.<sup>33</sup> Pain caused by a physical injury normally resolves in a period of a few days to three months. Acute pain progresses into chronic pain when repeated or continuous nerve stimulation precipitates a series of altered pain pathways, resulting in central sensitization and impaired central nervous system mechanisms.<sup>34</sup>

Pain is the most common reason for physician consultations in the U.S. and the number one reason for missed work or school days is musculoskeletal pain.

Pain management is utilized for easing the suffering and improving the quality of life of those living with chronic pain. Pain sometimes resolves promptly once the underlying trauma or pathology has healed. Patients benefit most when their health providers utilize a multimodal approach combining different types of

therapies and when patients take on a significant role in optimal management of their own pain.

Over the past several decades, physicians have become increasingly willing to prescribe opioids to manage pain. Greater expectations for pain relief, aging population, obesity, and increase in frequency and complexity of surgery is creating the demand for better control of pain.<sup>35</sup> This escalating use of opioids has been accompanied by a sharp increase of over 250% in opioid-related mortality.<sup>36</sup>

The opioid crisis describes both the medical overuse and subsequent addiction by patients to opioid prescription and synthetic drugs. Opioid side effects include poor coordination, mood swings, depression, and anxiety combined with a dependence on the drugs. The damage to an individual can affect all facets of day-to-day life with the increased risk of fatal overdose. The question remains: why are opioids still being used as a healthcare modality?

Part of the complex reason is their efficacy as analgesics in comparison to alternative therapies. In the wake of the opioid crisis, research efforts have turned towards several non-pharmaceutical solutions to this issue. There is a growing need to implement novel pain modalities, such as super pulsed laser therapy, to reproduce the highly effective activity of opioids without the addictive and lethal side effects.

### **PBMT and Pain**

Pain has an unpleasant sensory and emotional experience associated with or resembling actual or potential tissue damage<sup>37</sup>. Most pain will resolve when the noxious stimulus is removed, inflammation has resolved, or the body has healed itself. However, pain may persist even after the resolute removal of the provoking stimulus and the apparent healing of the injury.

There are two well-recognized broad categories of pain: nociceptive and neuropathic. Nociceptive pain arises from various kinds of trouble in tissues reported to the brain by the nervous system, and pain typically changes with movement, position, and load. Neuropathic pain arises from damage to the nervous system itself, central or peripheral, either from disease or injury. The simplest neuropathies are mechanical insults but include anything that damages neurons, ranging from

multiple sclerosis to chemotherapy. Neuropathic pain is often more likely to lead to chronic pain, as nerves do not heal well. Obviously, these kinds of pain can and do overlap. Some medical problems, like injuries, can affect both nerves themselves and other tissues, causing both kinds of pain.

There is ample literature to support the relationship between persistent pain and functional disability. Pain was significantly associated with greater loss of function, highlighting the important real-world consequences of living with pain. Persistent pain often leads to the development of pain-limiting activities and if overlooked can develop into avoidance patterns. The so-called protective behavior that reduces the risk of future injury or pain will often increase pain, limit activity, and maintain pain and disability. This in turn can modify muscle patterns into overactivity as well as dysfunction that can set a person up for injury.<sup>38</sup> This is known as the Fear Avoidance Model.

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PBM has been shown to reduce inflammation and swelling, reduce pain, and promote healing for an array of musculoskeletal conditions. Several systematic reviews have identified strong evidence for lateral elbow tendinopathy (tennis elbow)<sup>39</sup> and tendinopathy,<sup>40</sup> acute pain,<sup>41</sup> osteoarthritis<sup>42</sup> and rheumatoid arthritis,<sup>43</sup> temporomandibular disorders,<sup>44</sup> myofascial trigger points and myofascial pain syndrome,<sup>45</sup> joint pain,<sup>46</sup> and cervical neck pain.<sup>47</sup>

Pain results when a stimulus causes action potentials to rapidly propagate along a nerve cell. These action potentials are primarily due to an expulsion of positively charged sodium ions (Na<sup>+</sup>) and an influx of potassium (K<sup>+</sup>) ions into the nerve cell altering the electrical potential across the membrane. Laser light is directly absorbed by receptors within the bi-lipid cellular membrane of nerve cells. Once absorbed, the laser light will increase the porosity of the cellular membrane, allowing for a reabsorption of sodium ions and expulsion of potassium ions across the cellular membrane to re-

balance the sodium-potassium pump and remove the pain signal at the source. The peak absorption of lipids is in the 905 nm to 910 nm range.<sup>48</sup> This specificity of absorption is targeted directly by the 905 nm super pulsed laser in Multi Radiance technology and is vital to the analgesic effects seen in clinical practice.

The direct effects of PBM are initially at the peripheral nerve endings of nociceptors, consisting of the thinly myelinated A $\delta$  and unmyelinated, slow-conducting C fibers, within the epidermis.<sup>49</sup> This will prevent the nerve from reaching threshold like how opioids cause post-synaptic inhibition.<sup>50</sup>

PBM applied with a sufficient dose of energy has an inhibitory effect on nerve action potentials that create analgesia in as little as 10 to 20 minutes following treatment<sup>51</sup>. When super pulsed laser is applied to peripheral nerves, de-polymerization of the microtubules in C-fibers and A $\delta$  fibers occur from oxidative stress resulting from the acceleration of the electron transport chain<sup>52</sup>. ATP and MMP (Mitochondrial Membrane Potential) is decreased, limiting Na<sup>+</sup>, K<sup>+</sup>, and ATPase which maintains normal electrophysiological balance of the nerve. This works to block pro-inflammatory mediators (PGE<sub>2</sub>, IL-6; TNF- $\alpha$ ) and blocks acetylcholine to eliminate muscle spasms. For chronic pain, the treatment must be done every 24 hours, as the microtubules regenerate and pain will return. The result is a decrease in stimulation of nociceptors in the periphery and a decrease in the pain being transmitted by C-fibers and A $\delta$  fibers.

The depth of penetration of both red and infrared wavelengths allows for easy targeting of the superficial peripheral nerve endings of nociceptors in the skin. Successful outcomes depend on good clinical skills linked with an understanding of the nature of the injury, mechanism of PBM effects, and the necessary energy needed to activate the desired effect. Treatment only requires transcutaneous application to deliver the adequate dose of light energy.

When managing pain, the area of injury is most often selected as a target. The dose response for Multi Radiance devices is 30 J to stimulate protective and anti-inflammatory responses, and 50 J or greater to block and inhibit pain. Therefore, the direct application of light with SPLT over the inflammation or area of pain is indicated with the appropriate dose. The emitter does not



require movements – and should be avoided to prevent dilution of the energy – as the Multi Radiance devices are skin and eye safe (Class 1M). As power increases the time may vary, new higher outputs with the ACTIV PRO devices can shorten the treatment application for less than 1 minute to modulate the inflammatory process and just 2 minutes to dampen pain.

These short times will allow other targets – other areas of pain, nerve roots, additional locations around a joint – to also be treated during the same session. By selecting multiple targets, the patient will experience faster and greater changes to their level of pain and healing.

### **Clinical Use of PBM**

For over fifty years, PBM has been shown to reduce inflammation and edema, induce analgesia, and promote healing in a range of musculoskeletal pathologies. PBM, especially when performed with super pulsed laser, is beneficial for pain relief and can accelerate the body's ability to heal itself. SPLT has a long history of strong scientific evidence, which supports its use in pain management.

Photobiomodulation, especially when performed with super pulsed laser, is beneficial for pain relief and can accelerate the body's ability to heal itself.

The use of SPLT has been studied for fibromyalgia,<sup>53</sup> temporomandibular disorder,<sup>54</sup> osteoarthritis,<sup>55</sup> non-specific knee pain<sup>56</sup> and also in management of pain after total hip replacements, which can have a direct impact on decreased use of pharmacologic agents, including NSAIDs and opioids.<sup>57</sup> SPLT has few side effects and is well-tolerated. Toward the end of 2018, PBM was presented as an innovative option to the U.S. Congress for addressing a domestic opioid-use epidemic. Subsequently, the Opioid Crisis Response was introduced in 2018, and would mandate the development and adoption of alternative pain treatments, such as PBM.<sup>58,59</sup> The combination of good evidence and virtually no side effects makes PBM ideally suited to become the standard of care for all future pain treatments.

### **Indications for Use**

As the technology evolves and the science unveils other mechanisms of action and biological effects, the use of photomedicine will continue to expand. Many Multi Radiance Medical super pulsed lasers are cleared for over-the-counter use (21 CFR 801 Subpart C) and indications include:

- the temporary relief of minor muscle and joint pain
- arthritis and muscle spasm
- relieving stiffness
- promoting relaxation of muscle tissue
- to temporarily increase local blood circulation where heat is indicated.

Other indications for SPLT by Multi Radiance Medical include:

- symptomatic relief and management of chronic, intractable pain
- adjunctive treatment for post-surgical and post-trauma acute pain
- adjunctive use in providing temporary relief of minor chronic neck and shoulder pain of musculoskeletal origin.

### **Treating Light as a Photoceutical**

PBM is a form of medicine that applies non-thermal forms of light energy to activate beneficial therapeutic outcomes. The dose or energy required to produce the phototherapeutic effect is one of the most crucial parameters in PBM to optimize. A dose refers to a specified amount of energy delivered in Joules J given in a single session. By contrast, the dosage is the suggested administration of light energy given over a specific period and how frequently it should be administered. Each of these three specific stages and symptoms are best treated with a different dose and rate of energy.

We often think of PBM as being either stimulatory (repair) or inhibitory (pain relief); this is defined as a bi-phasic dose. These effects are the direct result of the delivered dose. If an optimization study is not performed, the selection of doses in larger clinical trials can be nothing short of a random guess and may account for many of the unsuccessful outcomes in the literature and the very wide range of suggested doses from the World Association for Laser Therapy (WALT).<sup>60</sup>

Hampering the widespread adoption of PBM is the lack of consistent reliable doses due to device wavelength and power variability. There appears to be a range of doses that are influenced by power output, thermal profile, and depth of penetration. Understanding the dose response of each device studied allows for the design of larger, translational clinical trials that utilize the identified optimal parameters (wavelength, dose, treatment interval, etc.) to validate PBM for specific indications.

Multi Radiance Medical optimized the dose response for the combination of super pulsed laser, pulsing red and infrared LEDs, and static magnetic field from 2012-2014. These were measured in experiments that entailed dose escalation studies that evaluated the bi-phasic response of SPLT. Based upon the dose that has been documented by Antonialli et al. and further validated by De Marchi et al. and Machado et al., the dose response for Multi Radiance devices is 30 J to stimulate protective and anti-inflammatory responses and 50 J or greater to block and inhibit pain. The studies have since been peer-reviewed and published and a summary called The Pillars Paper is currently available from Multi Radiance Medical.

Multi Radiance Medical optimized the dose response for the combination of super pulsed laser, pulsing red and infrared LEDs, and static magnetic field from 2012-2014.

## **Translating Science into Clinical Success**

Multi Radiance Medical focuses on translational research that challenges researchers in new ways that complement enterprise and enhance scientific progress for the interest and benefit of all. The ever-growing number of studies and research projects on super pulsed laser is focused on the transfer or translation of clinical knowledge upon peer-reviewed evidence and is presented in the following studies.

**Knee Pain**  
**Osteoarthritis Pain**  
**Fibromyalgia**  
**TMD Pain and Dental Application of SPLT**  
**Neck, Shoulder, and Back Pain**  
**Diabetic Nerve Pain**  
**Summary of SPLT Effects on Pain**  
**Tissue Repair and Healing**  
**Comparative Modalities**  
**Chronic Obstructive Pulmonary Disease**  
**Genetic Disorders**  
**Cerebrovascular Disease**  
**Future Clinical Applications of PBMT**

## Knee Pain

Leal-Junior et al.<sup>61</sup> evaluated SPLT as an adjunct modality to standard care for non-specific acute and chronic pain. The study focused on clinical practice and suggested that although standard care (i.e., physical therapy or chiropractic therapy) is effective in treating knee pain, the addition of SPLT enhances clinical outcomes.

A total of 86 patients were recruited for a double-blind, randomized, placebo-controlled trial from five clinical sites (three chiropractic, one physical therapy, and one combination practice). All patients presented with either acute or chronic pain rated 30 or greater on the pain visual analogue scale (VAS) (0-100). The SPLT protocol consisted of 12 treatments in addition to standard rehabilitation exercises, given 3 times a week for four weeks. Energy was directed to the knee (250 Hz x 1 minute at 5 locations around the patella) as well as the lumbar spine (1000 Hz x 2 minutes to the affected side), inguinal lymphatics (1000 Hz x 2 min), and popliteal artery (50 Hz x 3 min). (Figure Leal, et al.)

Subjects completed a VAS measurement at six time points: baseline, treatment numbers 4, 7, 10, 12 (conclusion), and 30 days post follow-up. The SF-36<sup>®</sup> Health Survey was completed by subjects to measure their overall health pretreatment and includes eight domains: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. Scale scores for each of these eight health domains and two summary measures of physical and mental health (physical component summary and mental component summary) were analyzed.

The results demonstrated a decreasing trend in reported VAS pain scores in the active treatment group after treatment #7. VAS reached statistical significance at treatments 10 and 12 and resulted in a 50% improvement (15% greater than the placebo group) or one standard deviation improvement over the placebo group at treatment #12. This outcome was maintained in the follow-up phase when repeated VAS reporting was collected 30 days following the conclusion of the therapy.

Leal, et al Leal-Junior, E.C.P., Johnson, D.S., Saltmarche, A., & Demchak, T. (2014). Adjunctive use of combination of super-pulsed laser and light-emitting diodes phototherapy on nonspecific knee pain: double-blinded randomized placebo-controlled trial. *Lasers in medical science*, 29(6), 1839-1847.



de Paula Gomes de Paula Gomes CAF, Leal-Junior ECP, Dibai-Filho AV, et al. Incorporation of photobiomodulation therapy into a therapeutic exercise program for knee osteoarthritis: A placebo-controlled, randomized, clinical trial. *Lasers Surg Med*. 2018; 50(8): 819-828. doi:10.1002/lsm.22939



The placebo group also improved, and there was a clinically significant drop in VAS pain reported of 35%; however, statistical significance was not reached. This was expected as patients were receiving concurrent physical therapy/chiropractic care for their knee pain. The analyses of the SF-36 data demonstrated an increasing trend in physical component scores. SF-36 data demonstrated a statistically significant increase in physical functioning that was maintained through the 30-day follow-up visit.

This study suggests that although other therapies (physical therapy or chiropractic therapy) are effective in treating knee pain, the addition of PBM enhances

clinical outcomes regarding pain and physical functioning. Of note, approximately 40% of the total energy was delivered directly to the knee while the remaining 60% was divided between 3 other selected systemic targets: the L4 nerve root, inguinal lymph ducts, popliteal fossa. Treating the L4 nerve root possibly decreased transmission of the pain signal to the poster horn of the spine resulting in a lower transmission from the first order to second order neuron. The treatment to the inguinal lymph node was chosen to help decrease swelling. Treating the popliteal artery was designed to increase blood flow and oxygen to the knee to help with tissue healing and removal of cellular waste.

The target selection was based upon the Priority Principle, a dynamic methodology used for integrating SPLT into clinical practice by prioritizing the current physiological and functional needs of the patient and addressing different aspects of pain; for more information on Priority Principle, please visit [www.protocolbuild.com](http://www.protocolbuild.com). The local treatment applied energy to modulate the inflammation of the knee joint and the systemic targets activated lymphatic flow and improved circulation to the joint. An inhibitory dose was applied to the lumbar nerve distribution for the anterior knee to help provide analgesic pain relief. In combination, this helps to reduce both the source of inflammatory pain (the knee) and to reduce pain signals (at the spinal level).

Knee osteoarthritis (OA) is a chronic degenerative disorder related to aging notably with symptoms of joint pain and mobility.<sup>62</sup> Common symptoms are crepitus, swelling, subchondral bone proliferation, and synovitis.<sup>63</sup> de Paula Gomes et al.<sup>64</sup> investigated the effect of SPLT in combination with a therapeutic exercise program for individuals with knee osteoarthritis.

The double-blind, placebo-controlled trial studied 60 patients that were given either exercise, exercise + SPLT, or exercise + placebo SPLT. The Western Ontario and McMaster University Osteoarthritis Index (WOMAC) was selected as the primary outcome, with other measures of functional activity of the lower limbs with the Lower Extremity Functional Scale (LEFS), pain using Numerical Rating Pain Scale (NRPS), pressure pain threshold (PPT), muscle strength utilizing a portable dynamometer, and static balance by Functional Reach Test (FRT).

A total of 10 sessions, twice weekly for 50 minutes included: ten minutes of treadmill, squats, knee extension, hip adduction with exercise band, calf raises, and weight shifting. At the conclusion of each exercise session, each subject received active or placebo SPLT with the PainAway Laser. The laser targeted three areas: medial, lateral, and posterior knee. Treatment consisted of one minute per area, setting of 1000 Hz. This delivered 7.85 J and a total energy of 23.55 J per session.

**Knee Osteoarthritis Protocol: 1000 Hz  
x 1 minute per area = 7.85 J delivered  
per point**

The analysis found that there was a significant pain reduction of 48.7%, with the combination of exercise + SPLT for the NRPS compared to exercise alone and the exercise + placebo groups. The results validate those from Leal et al.<sup>65</sup> where the 50% reduction of pain was significant when SPLT was used in conjunction with other forms of rehabilitation including exercise. While no other outcomes demonstrated clinical significance, including functional aspects, it should be noted that the clinical trial did not employ the same targets from the previous study, nor did it treat any target other than the joint surface itself. This would be in line with the finding from Machado et al.<sup>66</sup> where only SPLT produced ergogenic effects when applied locally to muscles involved in physical activity and the resolution and reduction of arthritic pain is by strengthening surrounding supportive muscle of the knee joint.

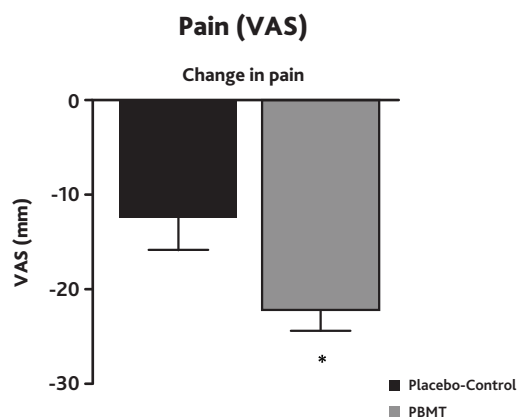
### **Osteoarthritis Pain**

Osteoarthritis (OA) degrades the articular cartilage and damages the subchondral bone. In advanced stages of OA, abnormal remodeling of cartilage and formation of osteophytes irreversibly destroy the affected joint. When conservative treatments fail or fail to manage pain, hip osteoarthritis results in the need for a total hip arthroplasty (THA). THA is known for being an extreme surgical procedure<sup>68</sup> and despite the improvement in post-surgical quality of life (QoL), the management of post-operative pain is inadequate.<sup>69</sup> There is a rapid accumulation of inflammation following THA. There is a high prevalence of persistent post-operative pain after total hip replacement.<sup>70</sup> Post-operative pain management

will likely include the use of NSAIDs for analgesia and this inherently carries its own cardiovascular risk even with short term usage.<sup>71</sup> PBM effects have been shown to be as effective as NSAIDs in managing the acute inflammation seen in joints,<sup>72</sup> but without the known side effects seen with medication.<sup>73</sup>

There is a rapid accumulation of inflammation following the repair and PBM has been shown to be effective in managing the acute inflammation seen in joints.<sup>74</sup> Langella et al.<sup>75</sup> evaluated the effect of 18 post-surgical hip arthroplasty (THA) patients in a randomized, double blind, placebo-controlled study. They evaluated the effects of a single intervention of super pulsed laser therapy (5000 Hz, 5 minutes, 40 J at 5 sites directly over the surgical incision) on pain and inflammation 8 to 12 hours post-surgery.

There is a high prevalence of persistent post-operative pain after total hip replacement.<sup>76</sup> The active SPLT group experienced significantly ( $p < 0.05$ ) decreased pain that was 82% greater than placebo immediately following surgery. This demonstrates the effectiveness of SPLT as an alternative to analgesic medication and offers a viable means of managing pain post-operatively. Pain management must last longer than what is available while in the hospital. At-home laser therapy is a safe and effective option that can be utilized during the early stages of rehabilitation to continue to help reduce pain.



Statistically significant ( $p > 0.03$ ) reduction in VAS. This change resulted in an immediate reduction of pain experienced by the patients following THA.

Additionally, modulation of the inflammatory process following the arthroplasty post-operatively was observed in the group treated with SPLT. Interleukin 8 (IL-8) is one of the major mediators of the inflammatory response. It is secreted by several cell types and attracts and activates neutrophils in inflammatory

regions<sup>77</sup>. The release of IL-8 was statistically reduced ( $p < 0.05$ ) and decreased IL-8 expression 12 times more than the placebo. The placebo treatment did not demonstrate any change ( $p > 0.05$ ).

Tumor necrosis factor alpha (TNF- $\alpha$ ) is a cell signaling protein (cytokine) involved in systemic inflammation and is one of the cytokines that make up the acute phase reaction. The dysregulation of TNF- $\alpha$  has been linked to rheumatoid arthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis.<sup>78</sup> In early stages of the inflammatory process, the increasing release of TNF- $\alpha$  stimulates both IL-6 and IL-8 following surgical intervention.<sup>79</sup> The findings indicate a statistically significant ( $p < 0.05$ ) decrease in serum levels of proinflammatory cytokine and measurements of TNF- $\alpha$  increased in the placebo group by 63% from baseline. By modulating TNF- $\alpha$  via SPLT, the patient will experience a less aggressive inflammatory process following the surgical procedure. This suggests that SPLT may also have an effect in modulating pain in these pathologies.

## Fibromyalgia

Fibromyalgia syndrome (FMS) is defined by the American College of Rheumatology (ACR) as a chronic widespread pain and tenderness in at least eleven of eighteen specific tender points<sup>80</sup> characterized by muscular tenderness, pain, fatigue, and cognitive difficulties.<sup>81</sup> It is not an inflammatory condition, nor does it lead to joint impairment or deformities.<sup>82</sup> The pathophysiology of chronic pain in patients with FMS is not completely understood,<sup>83</sup> but results obtained from research from previous decades implicate numerous factors, including changes in the brain and neural structure and function, muscular physiology, hormonal factors, and genetic influences.<sup>84</sup>

Patients with FMS may also present with symptoms such as sleep disorder, anxiety, depression,<sup>85,86</sup> difficulty with attention and concentration, as well as a range of gastrointestinal and somatosensory symptoms.<sup>87</sup> These symptoms often negatively affect a patient's quality of life by impacting their capacity, productivity, and family dynamics, and causing increased disability, absence from work, and decreased independence.<sup>88</sup>

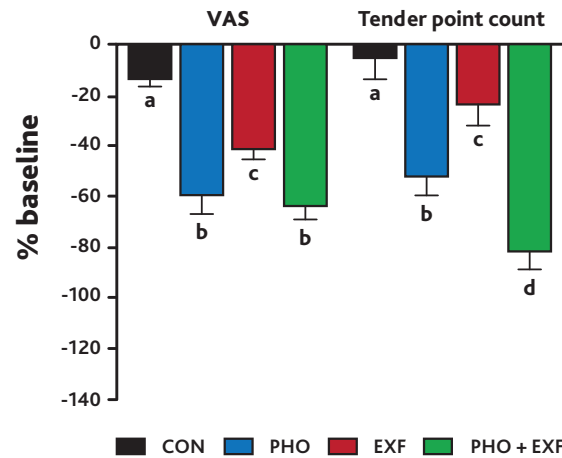
FMS is common worldwide; it affects approximately 2-8% of the general population<sup>89</sup> and presents a high-

er amount of diagnosis in females.<sup>90</sup> The economic impact of FMS is \$12-\$14 billion on indirect and direct costs plus \$31 billion in lost productivity. Fifteen percent of FMS patients are classified as disabled.<sup>91</sup> Some evidence shows that patients with FMS experience pain differently from the general population due to dysfunctional pain processing in the central nervous system<sup>92</sup>. The patient may exhibit a reduction in serotonin (neurotransmitter of the inhibitory descending system) and an increase of substance P (neuroexcitatory substance involved in the conduction of pain) in the central nervous system.<sup>93</sup> Despite increased knowledge about FMS, there is currently no cure for it.<sup>94</sup>

The main goal in managing FMS is pain control and improved function. This is often done by prescribing medications that are troublesome. It is a kitchen sink of different kinds of drugs, many of which can cause significant adverse events and side effects, especially when used in combination. The American College of Sports Medicine recommends exercise to treat FMS. However, one of the main barriers FMS patients have is pain catastrophizing, which means they do not exercise because they are afraid of the pain that will occur after they exercise. Demchak et al. published two case studies<sup>95, 96</sup> reporting positive results in treating patients with SPLT including a decrease in pain between 6-8 pain points, number of tender points (from 14 to zero), and Fibromyalgia Impact Questionnaire (FIQ) scores and an increase in function. FIQ is a common patient rated outcome measure used to determine the effect of FMS on a patient's life.

A larger clinical trial conducted by da Silva et al.<sup>97</sup> evaluated SPLT and exercise for managing pain and improving the quality of life of 160 women suffering from FMS. The study evaluated both short term (1 single session) and long-term (2 session per week for 10 weeks) and applied SPLT at 11 tender points for 300 s (40 J at 1000 Hz) per point. Exercise protocols included seven stretching exercises, TMJ exercises, and 30 min aerobic training on a treadmill at 75% age predicted max heart rate. Groups of patients were allocated into 2 different sessions: acute (1 session) and chronic (10 weeks, 2 times weekly) each with 4 groups: control, SPLT, Exercise, SPLT + Exercise. Algometry and VAS were used to evaluate the change in pain and FMS symptoms were evaluated utilizing the Fibromyalgia Impact Questionnaire (FIQ) and the Research Diagnostic Criteria (RDC). Any changes in the quality of life were to be assessed using the SF-36 survey.

During the single session, SPLT (alone) improved the pain threshold of 10 tender points (up to 20% greater) when compared to the control. However, for a single session there was no additional benefit in any of the SPLT + exercise group. Therapeutically, the effect is only acutely maintained and therefore repeated applications are indicated when managing FMS as the benefits of exercise therapy develop over time.



Long-term effect of phototherapy and exercise training on VAS scores and tender point numbers. Kruskal-Wallis test (post hoc Dunn) was applied in analysis. Different letters show significant differences among groups. Similar letters show no significant differences. Data are expressed as Δ%

This was observed in the 10-week session; SPLT only (80% reduction) and exercise only group (50% reduction) both had a significant reduction in the number of tender points compared to the control. There was a greater effect seen when SPLT + exercise was combined that demonstrated an additional 25% improvement over SPLT alone and 75% better reduction to exercise alone.

**Fibromyalgia: A 60 J dose per point delivered in 2 minutes has been optimized and validated in our most recently completed Fibromyalgia study using the MR5 ACTIV PRO LaserShower.**

Macfarlane et al.<sup>98</sup> evaluated 34 trials with a minimum of 2495 participants. There were 47 different exercise interventions, including aerobic that assisted with improvement in pain, and resistance training that identified significant improvement in pain and function.

The conclusion was that nearly all exercise was equally effective, and no evidence suggests a superiority of one over the other. The evidence for inclusion of exercise was strong (100% agreement). SPLT has been shown to improve exercise performance.<sup>99,100</sup> Therefore, the finding of a synergistic effect between the interventions is not surprising.

VAS is one of the most often used scales to evaluate pain perception. There was a large effect for both SPLT and exercise groups (nearly 50% greater than the placebo); however the SPLT and the SPLT + exercise groups experienced the greatest reduction in pain when compared to the control and exercise alone. When looking at the reduction in the number of tender points, it should be noted that the SPLT + exercise group significantly reduced the overall number of tender points and is the recommended protocol.

In the 10-week session, all FIQ, RDC, SF-36 and anxiety, sleep, depression, and fatigue scores were significantly different  $\Delta\%$  in the PHO + EXT group compared to the other groups. The assessment of fibromyalgia (FMS) is challenging because there are no biomarkers for this condition. Since 1991, the FIQ has been one of the most frequently used assessment tools in the evaluation of FMS and has been particularly useful as an outcome measure in FMS clinical trials.<sup>101</sup> The greatest impact was seen in the exercise alone and SPLT + exercise group. There was a marked reduction of FIQ scored by nearly 100%.

While the SPLT group also demonstrated beneficial outcomes, the greatest change was noted when both interventions were combined. Kuan et al.<sup>102</sup> performed a systematic review and meta-analysis on the use of PBM for FMS. The overall finding suggests PBM is a noninvasive, well-tolerated treatment for fibromyalgia to relieve discomfort, and the sub-analysis offers additional insight into the role of SPLT in FMS care. When comparing single wavelengths versus SPLT combined wavelength for FMS, the effect of SPLT was greater for the reduction of pain and the number of tender points as well as improvement in the severity of fatigue, stiffness, and anxiety. These outcomes describe the importance of a multi-faceted approach that includes both SPLT and an active therapy exercise program as suggested by the American College of Sports Medicine to improve FMS symptoms.<sup>103</sup>

## TMD Pain and Dental Application of SPLT

Temporomandibular disorders (TMD) are musculo-skeletal and neuromuscular conditions of the temporomandibular joint complex and surrounding muscles exhibiting pain or dysfunction, earache, headache, and facial pain. TMD affects up to 15% of adults, with a peak incidence at 20 to 40 years of age and most patients improve with a combination of noninvasive therapies, including pharmacotherapy and physical therapy.

Herpich et al.<sup>105</sup> evaluated the immediate and short-term effects of SPLT on 60 women with TMD. They measured the pain intensity, the pressure pain threshold (PPT), maximum vertical mandibular movement, and the electrical activity (EMG) of the masseter and temporal muscles were measured pre-treatment, immediately post, 24 h, and 48 h after SPLT treatment. There were four groups: 20 second dose of 1.4 J, 40 seconds dose of 2.8 J, 60 seconds of 7.86 J, and placebo control 0 J. Treatment was only performed extra-orally and administered to the anterior, middle, and posterior temporal muscle (three points) as well as the upper and lower masseter muscles (two points) bilaterally in all groups, totaling 10 points on each volunteer with a radiance area of 4 cm<sup>2</sup> per point.

**TMD Protocol: 1000 Hz x 60 seconds  
= 7.86 J per treatment point.**

Pain intensity decreased significantly with a median decrease of 2.2-2.7 pain points on a 10-point scale. The median decrease in pain was maintained for 48 h post treatment. The post-treatment evaluations in comparison to the pretreatment evaluation were observed in 1.4 J ([95% CI 1.35–3.85]) and 2.8 J ([95% CI 0.98–3.42]) especially after 48 hours and 7.86 J ([95% CI: 0.56–4.46]) especially after 24 hours, with a moderate effect size, but there was no effect on mouth range of motion, pressure pain threshold, or muscle activity as measured via EMG.

Herpich et al.<sup>106</sup> further evaluated the intraoral effects of bilateral SPLT of the lateral pterygoid muscle on TMD. Outcome measures included pain visual analog scale (VAS), mandibular ROM measured with digital calipers, and a functional scale. Two groups of 15



women were allocated into active or placebo SPLT in a randomized, sham-controlled, double blind clinical trial. Six sessions held 3 times a week for 2 weeks of 300 seconds or 40 J was applied to each lateral pterygoid muscle.

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Analyzing the outcomes, SPLT was found to be significantly more effective than sham for pain ( $p \leq 0.01$ ) and functioning ( $p \leq 0.04$ ). However, considering the minimal clinically important difference between 48 h (MD = -1.57, 95% CI - 3.10 to 2.32) and after six sessions (MD = -2.70, 95% CI - 4.22 to 1.18), the best effect was observed following the 6th visit. Mandibular ROM and function were not affected.

Herpich et al.'s first study may have demonstrated better outcomes from applying the SPLT to more muscles involved in TMD [anterior, middle, and posterior temporal muscle (three points) as well as the upper and lower masseter muscles (two points)], while the second study only treated the lateral pterygoid. While neither study demonstrated significant changes to the range of motion, the favorable outcomes in pain reduction support the inclusion of SPLT in the multimodal approach to treat TMD. Future treatments should continue to focus on less invasive modalities such as SPLT and consider including both protocols for the optimization of outcomes regarding pain reduction. As demonstrated, there is an effect with both intra- and extra-oral applications. This can lead to the use of some at-home laser therapy devices like the PainAway Laser to self-manage symptoms of TMD under a physician's guidance.

## Neck, Shoulder, and Back Pain

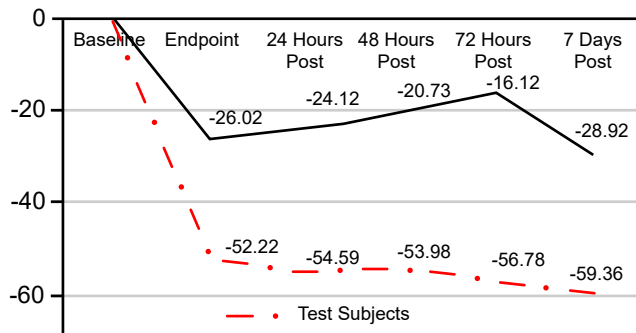
Spinal pain in the lumbar region (lower back) and cervical region (neck) are highly prevalent and are often the causes for many lost workdays. With a prevalence of 22-30% in patients worldwide, non-specific neck pain (NP) is one of the most common types of chronic pain, and nearly 67% of world's population will experience chronic non-specific neck pain at least once in their lives.<sup>107</sup>

Limited and poor range of cervical mobility as well as associated muscle weakness are common symptoms associated with chronic non-specific NP<sup>108</sup> and may be related to other conditions such as degenerative changes in the vertebra of the neck, shoulder trauma, and even depression or catastrophizing pain.<sup>109</sup> Symptom severity often improves within the first few weeks after the initial onset of pain; however, lingering pain and disability may persist for several months<sup>110</sup>. Patients with chronic pain and disability require heavy utilization of the healthcare system and prescriptive use of opioids and NSAIDs for pain relief.<sup>111</sup>

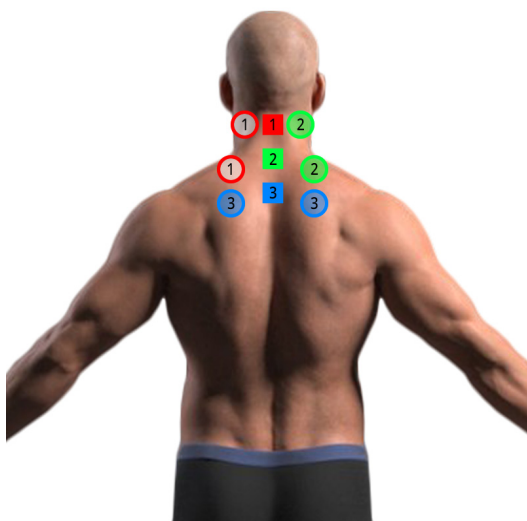
Casalechi et al. evaluated the effect of SPLT on 72 patients with chronic neck and shoulder pain. The SPLT was applied with slight pressure to nine locations of the cervical spine and upper shoulder regions and each received 3 minutes of energy (3000 Hz, 30 J). Treatment was performed twice weekly for three weeks. VAS results were statistically significant ( $p < 0.0001$ ). Neck and shoulder pain significant decreased in the

SPLT group by 52%-59% while the placebo group only decreased 16%-29%. The difference in proportion of study successes between procedure groups was found to be statistically significant at  $p < 0.00005$  and can be attributed to the efficacy of the application of the SPLT over a placebo device.

Change in neck/shoulder pain VAS across study duration by procedure group.



Additionally, it was noted that when analyzing the skin phenotype for the patients in this trial, Fitzpatrick Skin Type had no significant impact on the mean change in neck/shoulder pain VAS rating that occurred from baseline to study endpoint evaluation. This confirms the Grandinetti et al.<sup>112</sup> study stating skin pigmentation does not have a thermal impact on the skin and any beneficial outcomes seen clinically are based on PBM and not superficial tissue heating when using Multi Radiance Technology.



The significance in findings allowed for an indication of use for SPLT in the treatment of chronic neck and shoulder pain by the US FDA. The protocol targets not only the musculature of the upper shoulders and cervical spine but the cervical spine directly (3000

Hz for 3 minutes at each of the 6 muscle targets and 3 c-spine targets). It had been thought only the impacted area required energy, but overall, the inclusion of secondary targets, such as nerves, accessory muscle and blood vessels enhance the overall outcomes. It should be noted that photochemical changes following SPLT application may require between 48 and 72 hours to manifest.

**Neck and Shoulder Pain Protocol:**  
 3000 Hz x 3 minutes at each target =  
 30 J per target site  
 (see diagram).

Most low back pain (LBP) is the result of an injury, such as muscle sprains or ligament strains due to sudden movements or poor body mechanics while lifting heavy objects over time. These injuries can lead to inflammation which could include pain, swelling, and decrease in function. SPLT has demonstrated a positive modulatory effect on many inflammatory mediators, especially those causing pain and may be considered as an alternative therapy for LBP.

Tomazoni et al.<sup>113</sup> sought to evaluate the acute effects of a single PBMT on systemic levels of inflammatory mediators in chronic LBP patients. Nine locations were selected in the low back: six spinal musculature locations with 1000 Hz to the for 3 minutes (30 J) and three directly to the lumbar spine with 3000 Hz for 3 minutes (30 J) were treated. Blood was taken pre-treatment and 15 minutes post-treatment; pain VAS data was also collected at the same time points. There were no statistically significant decreases in VAS or TNF- $\alpha$  and IL-6 levels. However, there was an effect ( $p < 0.04$ ) on PGE2 levels which decreased by approximately 50% in the SPLT group and only approximately 23% in the placebo group. PGE2 is a pro-inflammatory mediator that helps depolarize nociceptors. Therefore, a decrease in PGE2 should result in a decrease in pain.

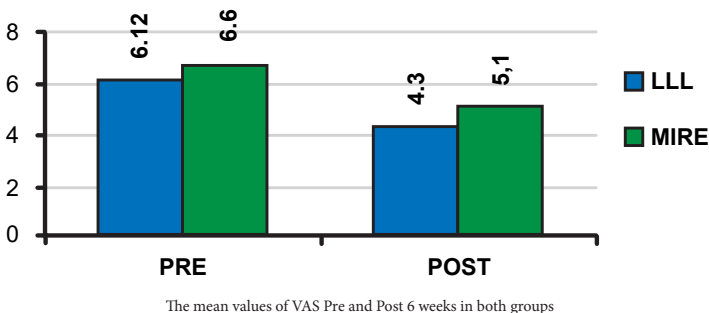
**Low Back Pain: 1000 Hz x 3 minutes =  
 10 J per spinal musculature point; 3000  
 Hz x 3 minutes = 30 J per lumbar spine  
 point.**

Additionally, there appears to be a difference in the effects of SPLT on TNF $\alpha$  levels because of acute versus chronic injury. Langella et al. reported a decrease in TNF- $\alpha$  within 10-minutes post-SPLT after hip arthroplasty surgery. This type of surgery would be considered an acute injury. Tomazoni et al. tested the effects of SPLT in a chronic injury and did not find a decrease in TNF- $\alpha$  at 15 min post-treatment.

## Diabetic Nerve Pain

Diabetic peripheral neuropathy (DPN) is a painful and common complication of diabetes. Approximately 50% of all cases will develop neuropathic pain caused by a primary lesion from a persistent hyperglycemic state or dysfunctions in the nervous system. Diabetic sensorimotor polyneuropathy associated with DPN is thought to contribute to impaired balance, altered gait patterns, and increased risk of falling.

Abdelhameed<sup>114</sup> compared the effects of SPLT and LED (infrared) therapy on pain, sensation, balance, and lower limb blood flow with 40 male patients with painful DPN. The patients had painful peripheral neuropathic symptoms for greater than or equal to 6 months and type 2 diabetes associated with duration. Baseline measurements of pain, cutaneous sensation, Doppler flow meter, and static stability assessments were taken prior to being given either intervention that were administered twice a week for six weeks. The Multi Radiance Medical TQ Solo<sup>®</sup> was applied to an area of pain along the sole or dorsum of each foot for 5 minutes.



The significant improvements in the reduction of pain by the patients in this study were 42% ( $p < 0.001$ ); for patients in the SPLT group, this is considered a clinically relevant change. This can be attributed to the analgesic effects seen in SPLT and related to the local release of neurotransmitters such as nitric oxide and increased ATP production and anti-inflammatory cytokines. It has been discovered that 905 nm near-infra-

red photoenergy can be highly effective in improving circulation and, subsequently, muscle performance. It was concluded from this study that SPLT can improve painful symptoms in patients with diabetic neuropathy.

## Summary of SPLT Effects on Pain

Overall, SPLT decreases acute and chronic musculoskeletal pain as well as FMS and diabetic neuropathic pain. Based on the studies presented, the combination of SPLT and exercise has a synergistic effect for decreasing pain and increasing function. SPLT decreases the inflammatory cytokines PGE2, TNF- $\alpha$ , and IL-8, which are related to acute and chronic inflammation and pain. These same inflammatory cytokines are part of inflammatory diseases including rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, inflammatory bowel disease, and psoriasis. Therefore, SPLT may also be effective in treating these pathologies.

## Tissue Repair and Healing

There are several well-documented effects of PBMT in promoting wound healing.<sup>116</sup> Chronic wounds often do not heal in less than 3 months and do not proceed through the normal reparative process.<sup>117</sup> These wounds usually lack tissue integrity, have residual inflammation, and are infected.<sup>118</sup>

The most common wound care complication is infection. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection is caused by a type of staph bacteria that have become resistant to many antibiotics used to treat ordinary staph infections. MRSA may have a significant impact on a vulnerable patient's overall health and well-being, including delayed wound healing. Serious complications are more likely with MRSA as the infection may not be readily treated due to the limited range of effective antibiotics available. Schnedeker et al.<sup>119</sup> measured the in vitro bactericidal activity of 465 nm blue light on MRSA. Samples were treated with 250 mW of 465 nm for 900 s (56.25 J/cm<sup>2</sup>), 1800 s (112.5 J/cm<sup>2</sup>), and 3600 s (225 J/cm<sup>2</sup>). There was a significant decrease in colony count with blue light irradiation at all doses for MRSA ( $P = 0.0006$ ) in a dose-dependent manner. Blue light therapy can suppress the growth of MRSA and enhance decolonization at the 30- and 60-minute doses. Therefore, blue light therapy should be considered as a non-pharmacological treatment for MRSA.

**MRSA Protocol: 465 nm blue light at 250 mW for 30-60 minutes delivering 112 – 225 J/cm<sup>2</sup>**

Diabetes mellitus-associated impaired wound healing severely affects life quality of patients with diabetes mellitus, leading to prolonged hospitalization and lower limb amputations.<sup>120</sup> Diabetic foot ulcers (DFU) and chronic venous ulcers (CVU) are cutaneous lesions that are complicated to treat and heal. Traditional therapies, including local debridement and antibiotics, are frequently unsuccessful and result in pain and loss of function. Landau et al.<sup>121</sup> evaluated the combined effect of topical hyperbaric oxygen and SPLT for the treatment of chronic ulcers.

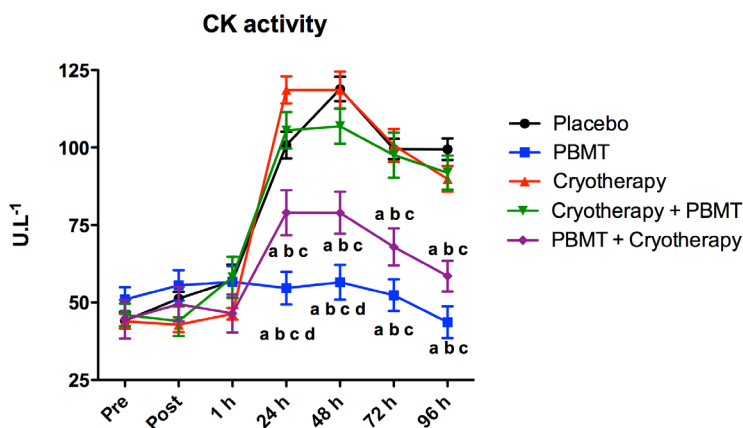
They reported a pain reduction in small non-surgical necrotic areas on their feet within 10-20 visits seen twice weekly and given 10 minutes of SPLT. There was a high proportion of success with closure, even when the DFU patients had co-morbidities of peripheral artery disease and peripheral neuropathy. In a covariant group of 20 patients received SPLT alone for varicose vein ulcers, all were resolved within 3 months.

### Comparative Modalities

In clinical practice, it is not uncommon for modalities to be administered as a monotherapy or as an adjunct to other modalities or treatments. It is often necessary to choose between the application of multiple therapeutic agents to optimize the limited available time with a patient. Therefore, a greater understanding of the most effective therapeutic agents or combination of modalities for a given condition is necessary to optimize the clinical decision-making process. We have already demonstrated the positive effects of combining SPLT and exercise.

One of the most widely utilized therapeutic interventions is cryotherapy. Despite the lack of scientific evidence for its use related to recovery, cryotherapy remains a popular means of reducing delayed onset muscle soreness (DOMS) and minimizing muscular damage following exercise or sport. de Paiva et al.<sup>122</sup> evaluated the effects of cryotherapy and super pulsed laser therapy after high-intensity exercise. The dou-

ble-blind, placebo-controlled clinical trial recruited 50 healthy male volunteers who were randomized into five groups (PBMT, cryotherapy, cryotherapy + PBMT, PMBT + cryotherapy, or placebo) that evaluated exercise performance (maximum voluntary contraction (MVC)), delayed onset muscle soreness (DOMS), and muscle damage (creatine kinase (CK)). The dose was 1000 Hz for 5 minutes at six different locations of the quadriceps; there was 39 J delivered per location or 234 J total.



CK activity. Values are mean and error bars are standard error of the mean (SEM). Letter a indicates the significant difference compared to placebo (p<0.05), letter b indicates the significant difference compared to cryotherapy (p<0.05), letter c indicates the significant difference compared to cryotherapy + PBMT (p<0.05), and letter d indicates the significant difference compared to PBMT + cryotherapy (p<0.05)

**Muscle Recovery Protocol: 1000 Hz x 5 minutes = 39 J per point (6 points total = 234 J delivered)**

All outcomes were measured at baseline; immediately after; and at 1, 24, 48, 72, and 96 hours.

Treatments were applied immediately after, 24, 48, and 72 hours post-exercise. The outcomes revealed that the SPLT intervention when applied alone improved MVC above baseline levels, decreased DOMS and mitigated the increase in CK concentrations (p < 0.05) within 24 hours post-treatment when compared to all other treatments. The results indicate that MVC returns to baseline and possibly slightly greater than baseline with SPLT and based on the CK concentration, the SPLT prevented further muscle damage.

The combination of SPLT followed by cryotherapy resulted in improvements in the outcome measures; however, these improvements were less than the SPLT only group. Cryotherapy as mono-treatment and cryotherapy + SPLT outcomes followed the same course as

the placebo ( $p > 0.05$ ), meaning these treatments did not have a therapeutic effect.

While cryotherapy exhibits some effects on inflammatory events at a cellular and physiological level after acute tissue damage, overall, the evidence-supporting cryotherapy as a recovery modality is insufficient. Therefore, the use and effectiveness of cryotherapy as recovery strategy must be questioned. Based on these outcomes, it is suggested that treating with SPLT post high-intensity training will result in a faster recovery for the participants.

## **Chronic Obstructive Pulmonary Disease**

Skeletal muscle fatigue is characterized by decreased muscle capacity to generate or maintain power production during muscle activity. During physical activity, decreased circulating oxygen contributes to muscle fatigue from the increased consumption of oxygen required to maintain muscle function. Miranda et al.<sup>123</sup> assessed pre-exercise SPLT on muscle performance during a progressive cardiopulmonary treadmill exercise test to evaluate the effects on oxygen consumption and muscle fatigue.

Twenty untrained male volunteers performed a standardized progressive cardiopulmonary exercise test on a treadmill with a fixed inclination of 1% until exhaustion. A total of 17 sites on each lower limb (9 on the quadriceps, 6 on the hamstrings, and 2 on the gastrocnemius muscles) were delivered a dose of 30 J per site.

**COPD: 30 J per site. (9 on the quadriceps, 6 on the hamstrings, and 2 on the gastrocnemius muscles)**

When applied before a progressive cardiopulmonary exercise test on a treadmill, SPLT increased the distance covered ( $P < .001$ ) and time until exhaustion on the cardiopulmonary test ( $P < .001$ ). Pulmonary ventilation was greater ( $P = .004$ ) and the score for dyspnea was lower ( $P < .001$ ) after active SPLT than after placebo. The responder analysis showed improvements after active PBMT in the distance covered during the test in 80% ( $n = 16$ ) of volunteers and the time until exhaustion for 85% of volunteers ( $n = 17$ ). This means that SPLT can enhance performance in 80% to 85% of

people who use SPLT for ergogenic effects.

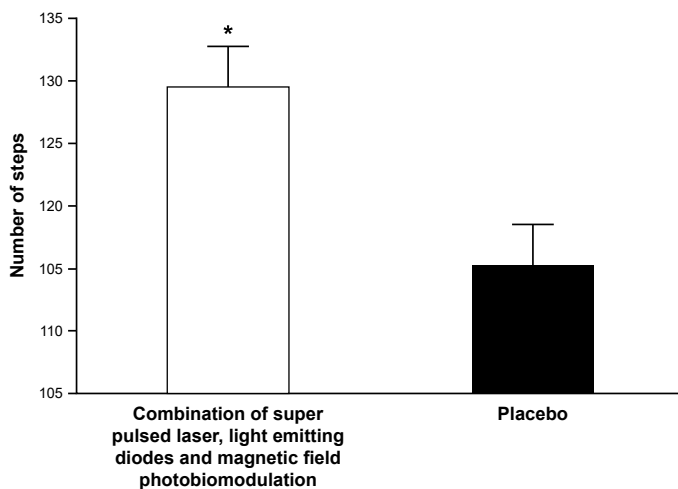
During mild to moderate exercise at a steady pace, pulmonary ventilation increases linearly with oxygen consumption and carbon dioxide production. An increase in tidal volume and respiratory rate causes pulmonary ventilation to increase under these conditions. Given the muscles' need for increased oxygen and energy during exercise, cardiorespiratory changes occur. The main cardiorespiratory changes during exercise are increased pulmonary ventilation and increased supply of oxygen to the muscles. Therefore, muscle fatigue during strenuous exercise is often accompanied by shortness of breath. SPLT may improve muscle strength, increase aerobic capacity, reduce dependence on glycolytic metabolism, and protect muscle from lactate during activity.

Chronic obstructive pulmonary disease (COPD) is a pulmonary pathological disorder that significantly affects peripheral muscle strength and endurance. Progression of the disease reduces peripheral muscle function and alters metabolism. Gosselink et al.<sup>124</sup> documented that reduced quadriceps muscle strength was a predictor of reduced maximum oxygen uptake ( $VO_2$ ) in patients suffering from COPD. Peripheral muscle dysfunction in patients with COPD is characterized by a reduction in the proportion of oxidative fibers and an increase in the proportion of glycolytic fibers, changes in bioenergetics (attenuation of mitochondrial enzyme activity), and decapillarization (loss of capillary density).



Based on the results of their prior study with healthy volunteers, Miranda et al.<sup>125</sup> evaluated the acute effects of SPLT on isokinetic performance in 13 stable patients (no change in plan of care in the preceding 4 weeks) with moderate COPD. Peripheral muscular fatigue is often observed with COPD, and SPLT has been observed to improve muscular fatigue. A single dose of SPL was administered to the femoral quadriceps muscle of patients with COPD, and maximum voluntary isometric contraction (MVIC), peak torque (PT), and total work (TW) of the non-dominant lower limb were measured.

There were statistically significant increases for PT ( $p=0.003$ ) and TW after application of SPLT when compared to placebo ( $p=0.005$ ). Significant differences were also found for MVIC ( $p=0.000$ ), sensation of dyspnea ( $p=0.003$ ), and fatigue in the lower limbs ( $p=0.002$ ). The researchers concluded that SPLT administered to the femoral quadriceps muscle of patients with COPD improved labored breathing, increased the PT by 20.2% and the TW by 12%, and decreased muscle fatigue in the lower limbs.



Miranda et al.<sup>126</sup> further evaluated the effects of SPLT on quadriceps muscle performance, exercise tolerance, and metabolic variables in patients with COPD utilizing 6-minute stepper test (6MST). The 6MST is commonly used to evaluate the course of exercise tolerance of in/outpatient rehabilitation. Twenty-one patients with COPD completed the 6MST protocol over 2 weeks and were given SPLT or placebo before each session at 17 sites (30 J dose per location) of each lower limb. The administration of the SPLT significantly increased the number of steps ( $p=0.000$ ), perception of breathlessness ( $p=0.000$ ), and lower limb fatigue ( $p=0.001$ ).

Both studies on COPD showed a profound effect following a brief exposure to multi-wavelength light on muscle fatigue and dyspnea. These outcomes would become the basis for the current clinical trial for use of SPLT to improve critical care of COVID-19 ventilated patients. The Ministry of Health in Brazil has approved an international group of researchers lead by Dr. Ernesto Leal-Junior to collect data on the effect of SPLT on ventilated ICU patients suffering from the novel coronavirus. The hope of the trial is to demonstrate daily application of SPLT can improve ventilation and the immune response while decreasing inflammation and the length of hospitalization. Successful outcomes may allow SPLT to become a part of the critical care solution for the future treatment of COVID-19 patients.

## Genetic Disorders

Duchenne muscular dystrophy (DMD) is a genetic disorder associated with mutations in the dystrophin gene. DMD is characterized by progressive muscle degeneration and weakness due to the changes of a protein called dystrophin that protects muscles from mechanical stresses during muscle contraction. DMD symptom onset is in early childhood, usually between ages 2 and 3. The disease primarily affects boys, but in rare cases it can affect girls.<sup>127</sup> In Europe and North America, the prevalence of DMD is approximately 6 per 100,000 individuals.

Inflammatory and immune responses are central to the pathogenesis of DMD. The most common pharmacological treatment of DMD is prescribed glucocorti-

coids.<sup>128</sup> However, long term use of corticosteroids has demonstrated serious side effects, causing the treatment to be interrupted.<sup>129</sup> Albuquerque-Pontes et al.<sup>130</sup> analyzed the cytoprotective effects of SPLT to delay dystrophy progression in mdx mice, the most widely used animal model for DMD research. The goal was to optimize the therapeutic dose ranges and document possible side effects from the therapy and evaluate functional performance, muscle morphology, and gene and protein expression of dystrophin.

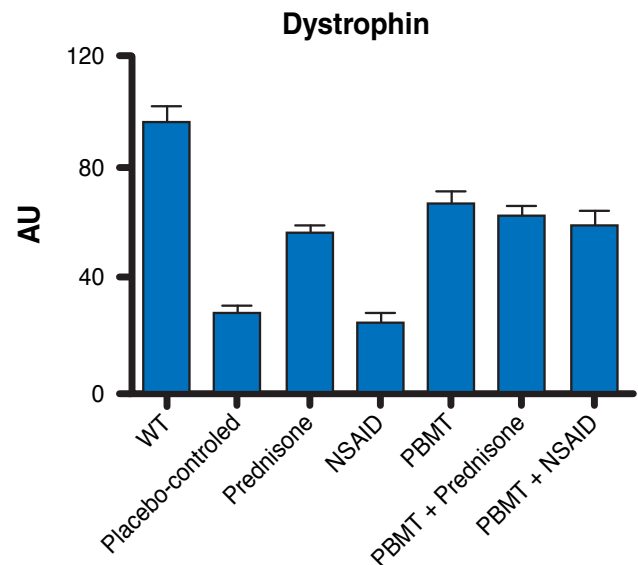
The study design included five groups of animals: wild type (untreated, normal controls), mdx (placebo control), mdx (1 J dose), mdx (3 J dose) and mdx (10 J). The SPLT was applied in direct contact with the tibialis anterior muscle (bilaterally) for 14 weeks, 3 times per week.

Functional performance recorded the number of repetitions the mouse would stair climb until fatigue and was significantly improved ( $p < 0.001$ ) with the 10 J dose. Muscle tissue degeneration, characterized by the decrease in size and number of muscle fibers, increased central nuclei positioning and nuclei clustering, was improved by all doses, with better outcomes with the 3 and 10 J. Gene expression (3 J  $p < 0.01$  and 10 J  $p < 0.01$ ) and protein expression (3 J  $p < 0.001$  and 10 J  $p < 0.05$ ) of dystrophin was significantly increased with doses when compared to placebo-control group. The continued application of SPLT over the 14 weeks demonstrated the ability to coax dystrophin production out of the cell's own disabled gene.

The use of SPLT has emerged as a novel area of DMD research. Tomazoni et al.<sup>131</sup> further evaluated the effects of SPLT and pharmacological therapy (glucocorticoids and non-steroidal anti-inflammatory drugs) in mdx mice. Seven groups were analyzed in the trial: wild type (normal control), mdx + placebo, mdx + 10 J SPLT, mdx + prednisone, mdx + NSAID, mdx SPLT 10 J + Prednisone, and mdx SPLT 10 J + NSAID.

The use of SPLT demonstrated consistent morphological improvement ( $p < 0.0001$ ) in decreasing the positioning of the nuclei at the center of the muscle fibers, nuclear clusters, and maintaining the number and size of muscle fibers compared to the mdx placebo control. Both treatments with prednisone and SPLT applied alone or combined were effective in protecting muscular morphology. The NSAID group showed fewer changes when compared to the SPLT and prednisone groups and was

less effective than the SPLT in preserving the morphological changes during disease progression.



In addition, the treatments with SPLT ( $p = 0.0005$ ), SPLT + prednisone ( $p = 0.0048$ ), and SPLT + NSAID ( $p = 0.0021$ ) increased dystrophin protein expression compared to placebo-control group. However, in the functional performance, the SPLT presented better results compared to glucocorticoids ( $p < 0.0001$ ). In contrast, the use of NSAIDs did not appear to add benefits.

The results demonstrated that glucocorticoids and SPLT preserve muscle morphology and increase the protein expression of dystrophin. Interestingly, both groups improved on the functional performance assessment from baseline as well. The Prednisone group ( $p < 0.01$ ) and SPLT group ( $p < 0.0001$ ) both showed a significantly increased number of repetitions; however, the SPLT group was significantly ( $p < 0.0001$ ) greater than all other groups.

Future SPLT trials in human may help preserve muscular morphology by reducing inflammatory and oxidative stress. With minimal side effects, it may be a promising non-pharmacological treatment for treating Duchenne muscular dystrophy in the future.

## Cerebrovascular Disease

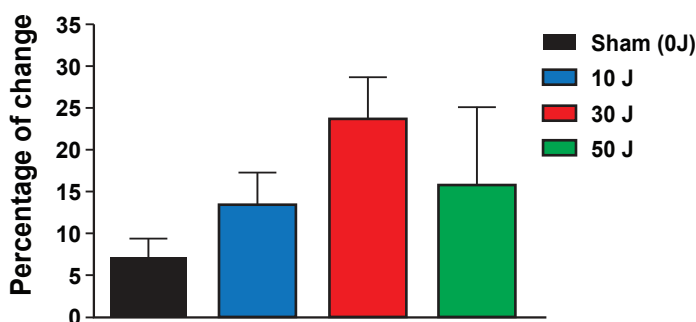
Cerebrovascular accidents (strokes) are among the main causes of disability and death in the adult population worldwide.<sup>132</sup> A stroke occurs when the flow of

oxygen-rich blood to a portion of the brain is interrupted. Without oxygen, brain cells begin to die after a few minutes. Symptoms occur in the parts of the body that these brain cells control. Examples of stroke symptoms include sudden weakness; paralysis or numbness of the face, arms, or legs (paralysis is an inability to move); trouble speaking or understanding speech; and trouble seeing.

The impaired limb function affects the ability to maintain postural and motor control, leading to impaired gait, loss of balance, and reduced functional mobility.<sup>133</sup> Reduction in functional mobility fosters inactivity that can lead to an increased risk of cardiac events or recurrent stroke and poor quality of life. It is vital to enhance muscle strength, mobility and balance early following the post-stroke period to improve the likelihood of a successful recovery.

Casalechi et al.<sup>134</sup> sought to evaluate the effects of SPLT on the functional mobility of stroke survivors. The cross-over, triple blind, placebo-controlled study recruited 10 patients diagnosed with hemiparesis stemming from an ischemic or hemorrhagic stroke. SPLT was applied to nine sites of the knee extensors, six sites on the knee flexors and two on the plantar flexors bilaterally with 10 J, 30 J, or 50 J at 250 Hz or placebo during the cross-over phases of the trial.

**Change in six-minutes walking test**



The functional outcome measures were the 6-min walk test (6MWT) and the Timed Up and Go (TUG) test. During the 6MWT, patients walk, beginning from standing, at a self-selected pace without running for six minutes back and forth along a 10-m track. The distance was recorded, and significant improvements ( $p < 0.05$ ) were found in 30 J per site dose as compared to the baseline evaluation. The TUG test measures simple movements and balance. The goal is to get up from sitting, walk a 3-m distance and return to a seated

position on the chair. The times were recorded, and significant improvements were also found using a total energy per site of 30 J per site compared to sham and baseline ( $p < 0.05$ ).

There remains an urgent need to identify cost-effective, evidence-based interventions for reducing falls and related injuries in stroke patients.<sup>135</sup> Falls are common after stroke, with between 14% and 65% of stroke survivors experiencing falls while in hospital<sup>136</sup> and up to 73% of stroke survivors experiencing a fall in the first 6 months after discharge home.<sup>137</sup> SPLT has not demonstrated changes in balance or stability; however, it has demonstrated beneficial effects on improving muscle strength and functional ability in stroke survivors which is key to preventing further injury post-stroke.

### **Future Clinical Applications of PBMT**

Multi Radiance Medical is currently conducting research in numerous new fields, including but not limited to ophthalmology, neurology, and immunology. The company is also seeking FDA approvals for several unique musculoskeletal conditions that will most likely go through the DeNovo process. As is the standard for research, Multi Radiance Medical seeks first to prove safety and efficacy and then continue the research to optimize the dose and adapt the technology to meet the need.

### **Conclusion**

Super pulsed laser therapy offers a safe, drug-free, and side-effect-free method for pain relief of both acute and chronic injuries. The benefits are increased regarding function when SPLT is combined with therapeutic exercise. Additionally, SPLT is beneficial for preventing or treating MRSA, speeding up wound healing, increasing function in COPD and stroke patients, and decreasing recovery post high-intensity exercise. SPLT is a promising new treatment for Duchenne muscular dystrophy as well.

SPLT could be a safe at-home treatment when a pre-programmed device is utilized. Its efficacy is evidenced by the plethora of completed studies and clinical trials currently being performed to develop novel treatment for a variety of conditions in both human and veterinary medicine.



This clinical monograph has sought to translate extensive research into clinical practice. In addition to this static publication, Multi Radiance Medical continues to sponsor monthly webinars on Laser Therapy University ([www.lasertherapyu.org](http://www.lasertherapyu.org)), hold regional and national seminars, publish monthly newsletters, and conduct live clinical support available during normal business hours.

The company continues to conduct research worldwide and is always open to discussions with clinicians or institutions that share the same vision of commercializing laser and LED technology that will help improve the human (and veterinary) condition. Multi Radiance Medical thanks readers for continued interest and support and looks forward to new advancements in the future of photobiomodulation therapy.

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Douglas Johnson has over 25 years in the clinical practice and serves as the Senior Vice President, Clinical and Scientific Affairs at Multi Radiance Medical and Chief Science Officer at PhotoOpTx. He is involved in numerous research studies involving photobiomodulation that focus on human performance enhancement and rehabilitation. His present area of research involves evaluating the effects of photobiomodulation on neurodegenerative diseases and diabetes.

Named as a clinical advisor to Laser Therapy U, Mr. Johnson attended Wayne State University and The University of Detroit-Mercy where he earned a Summa Cum Laude Bachelor of Science degree in Sports Medicine in 1994. Johnson is current a fellow of the Laboratory of Phototherapy and Innovative Technology, Sao Paulo, Brazil.

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Timothy J. Demchak graduated from The Ohio State University in 2001 with his Doctorate degree in Exercise Physiology. He also attended Ball State University where he earned a Master of Science degree in Biomechanics and a bachelor's degree from Manchester University. A certified Graston Technique specialist and instructor, Dr. Demchak has been a Certified Athletic Trainer since 1994, and practices clinically.

Dr. Demchak's main area of research is therapeutic modalities. He has 25 published manuscripts and 78 peer-reviewed presentations, and additionally has participated in seven webinars on Laser Therapy U. He is currently a Full Professor at Indiana State University and his research interests include laser therapy treatments for fibromyalgia syndrome, migraines, trigeminal neuralgia, and vertigo. He is also the founder, director, and main clinician of Athletic Training Services at Wabash Valley Health Center.

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Ernesto Leal-Junior has a bachelor's degree in Physical Therapy, Master's degree in Biomedical Engineering, and he defended his PhD thesis in 2010 at University of Bergen - Norway. In 2012 he finished his Post-Doctoral internship at Department of Pharmacology of University of Sao Paulo. He is Full Professor at Nove Julho University in Sao Paulo (Brazil) since 2010, where he is the head of Laboratory of Phototherapy and Innovative Technologies in Health (LaPIT) and supervises several Post-doctoral fellows, Ph.D. candidates and master's degree students. Since 2018 he is acting as Visiting Professor at University of Bergen (Norway), and since 2013 he acts as lead researcher for Multi Radiance Medical.

Currently Dr. Leal-Junior has over 120 scientific papers in the photobiomodulation field published in international peer-reviewed journals (indexed in Pubmed/Medline). He has published 40 randomized clinical trials (RCTs) to the date, becoming the researcher that has authored more RCTs on photobiomodulation in the world.

Since January 2015, Dr. Leal-Junior is a recipient of the Research Productivity Award given by Brazilian Council of Research and Development. He has been granted by government research agencies and by private companies with more than USD 3,000,000 in grants and scholarships.

## **Abbreviations List**

6MST - 6-minute stepper test	Na <sup>+</sup> - sodium ions
6MWT - 6-minute walk test	NIR - near infrared
ACR - American College of Rheumatology	NM – nanometer, wavelength
ATP - adenosine triphosphate	NP – neck pain
CCO - cytochrome c-oxidase	NRPS - numerical rating pain scale
CI - confidence interval	NSAID – non-steroidal anti-inflammatory drug
CGRP - calcitonin gene related peptide	OA - osteoarthritis
CK - creatine kinase	PBM - photobiomodulation
COPD - chronic obstructive pulmonary disease	PBMT - photobiomodulation therapy
CVU - chronic venous ulcers	PL - placebo
DFU - diabetic foot ulcers	PPT - pressure pain threshold
DMD - Duchenne muscular dystrophy	PT - peak torque
DOMS - delayed onset muscle soreness	QoL - quality of life
DPN - diabetic peripheral neuropathy	RCT – randomized controlled trials
DPTP - depth of penetration time profile	RDC - research diagnostic criteria
FDA - Food and Drug Administration	SPL - super pulsed laser
FIQ - fibromyalgia impact questionnaire	SPLT - super pulsed laser therapy
FM - fibromyalgia	THA - total hip arthroplasty
FRT - functional reach test	TMD - temporomandibular disorders
Hz - hertz	TTP - thermal time profile
ICU - intensive care unit	TNF - tumor necrosis factor
IL-6 or IL-8 - interleukin 6 or 8	TUG - timed up and go
J - joule	TW - total work
K <sup>+</sup> - potassium ions	VAS - visual analog scale
LED - light-emitting diode	VO <sub>2</sub> - maximum oxygen uptake
LEFS - lower extremity functional scale	WALT - World Association for Laser Therapy
MMP - mitochondrial membrane potential	WOMAC - Western Ontario and McMaster University
MRSA - methicillin-resistant staphylococcus aureus	Osteoarthritis Index
MVIC or MVC - maximum voluntary isometric contraction	Δ% - mean difference
	Aδ - A-delta

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