A PHOTOCEUTICAL APPROACH TO TREATING FIBROMYALGIA

— A SCIENTIFIC MONOGRAPH —

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Dr. Demchak's main area of research is therapeutic modalities. He has 27 published manuscripts and 81 peer-reviewed presentations. He is currently a Full Professor at Indiana State University where his research interests include laser therapy treatments for fibromyalgia syndrome. He is also the founder, director and main clinician of Athletic Training Services at Wabash Valley Health Center.

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Dr. Leal's research expertise is photobiomodulation therapy in skeletal muscle disorders. A special interest has been developed in photobiomodulation research (low-level laser therapy and light emitting diode therapy) for skeletal muscle fatigue delaying, performance enhancement, injury prevention and recovery after strenuous physical activity, and more recently in progression delaying of muscular dystrophies.

According to Google Scholar, Dr. Leal-Junior has 191 scientific papers published, more than 130 of them in international peer-reviewed journals (indexed by Pubmed/Medline). He has presented more than 40 scientific papers at national and international congresses and in September 2011, Dr. Leal-Junior was awarded by NAALT with the Young Clinical Research Award in Phototherapy. He is a recipient of the Research Productivity Award given by the Brazilian Council of Research and Development. Currently he sits on the board of WALT – World Association for Laser Therapy as their Scientific Director.

A Photoceutical Approach to Treating Fibromyalgia
A Scientific Monograph

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Introduction

The use of therapeutic lasers has experienced an explosive growth in medical and veterinary markets: The number of published references on PubMed has surpassed 6,500 and continues at a pace of one new study daily. It is no longer considered an alternative therapy, but a non-pharmacological means of reducing pain.

The non-thermal photochemical-photophysical effects of light absorption cause increases in ATP production, modulation of reactive oxygen species, and induction of transcription factors[1] that increases cell proliferation.[2] This hastens the healing process, promotes tissue regeneration, and most importantly relieves pain[3] and inflammation.[4] Super pulsed laser therapy (SPLT), a unique form of light therapy, has demonstrated the ability to reduce pain in cases of knee osteoarthritis,[5,6] lumbar pain,[7] temporomandibular joint dysfunction,[8] following total hip replacement surgery,[9] non-specific knee injury,[10] and chronic neck/shoulder pain.[3]

SPLT has a long history of strong scientific evidence demonstrating analgesia across a range of musculoskeletal pathologies. It has few side effects, is well-tolerated, and may directly reduce use of pharmacologic agents, including NSAIDs and opioids.[9] With a profound effect on such a variety of painful clinical conditions, it has been suggested that SPLT may be beneficial for reducing pain associated with fibromyalgia syndrome.[11-14]

People with fibromyalgia experience chronic, all-over muscle and joint pain. Other symptoms include extreme fatigue and memory problems. Despite increased knowledge about fibromyalgia, there is currently no cause or cure.[15] People with fibromyalgia tend to be deeply sensitive to pain that would not bother most people. Some evidence shows that patients with fibromyalgia experience pain differently from the general population due to dysfunctional pain processing in the central nervous system.[16]

The purpose of this scientific monograph is to discuss the use of SPLT as a care option and recommend ideal treatment protocols for the management of fibromyalgia syndrome through an in-depth analysis of evidence and published literature.

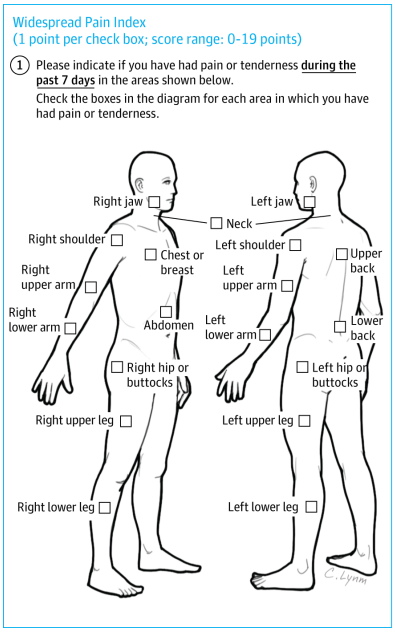
Fibromyalgia Syndrome

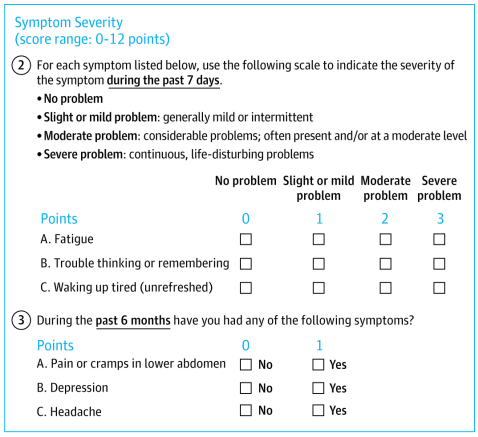
Fibromyalgia syndrome (FMS) is defined by the American College of Rheumatology (ACR) as chronic widespread pain and tenderness in specific tender points[17] characterized by muscular tenderness, pain, fatigue, and cognitive difficulties.[18] It is not an inflammatory condition, nor does it lead to joint impairment or deformities.[19] FMS is common worldwide; it affects approximately 2-8% of the general population.[20] Females are diagnosed three times higher than males.[21] Thirty-four percent of individuals with FMS spend $1,200-$12,000 per year above their insurance for healthcare. The average out-of-pocket expense for FMS patients with insurance is $5,310 annually. Between 15% and 25% of FMS patients receive disability. Overall economic impact of FMS is $12-$14 billion on indirect and direct costs plus $31 billion in lost productivity.[22]

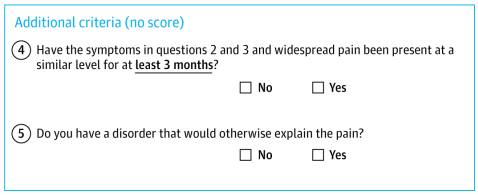
Diagnosis of Fibromyalgia Syndrome

Diagnostic criteria for FMS developed by the ACR in 2010 include the Widespread Pain Index (WPI) and two Symptom Severity Scales (SSS).[23] The WPI is the identification of areas where the patient felt pain over the last week from a list of 19 separate anatomical locations with a range of scores between 0 and 19.

The first SSS requires the patient to rate their fatigue, waking unrefreshed, and cognitive symptoms. The scale is 0-3 pts: 0 = no symptoms, 1 = slight symptoms, 2 = moderate symptoms, and 3 = severe symptoms.







The second SSS requires patients to identify somatic symptoms they suffered over the previous week from a list of 40 symptoms. The second SSS is scored overall 0-3; 0 = no symptoms, 1 = few symptoms, 2 = moderate number of symptoms, and 3 = a great deal of symptoms. There is no guideline for defining how many symptoms have to be checked to equal moderate or a great deal.

The patient must meet the following three conditions to be diagnosed with FMS:

1. WPI score ≥ 7 and SS score ≥ 5 OR WPI score from 3-6 and SS score ≥ 9
2. Symptoms have been present at a similar level for at least 3 months
3. The patient does not have a disorder that would otherwise explain the pain

There are several outcome measures used to monitor the severity of the symptoms associated with FMS and the impact on health and activities of daily living (ADL) of patients. The measures can be used to determine treatment effectiveness. The Fibromyalgia Impact Questionnaire (FIQ)[22] is the most widely used patient-rated outcome measure. The FIQ is designed to determine the impact of FMS on the person's life over the previous week. It is divided into two parts; the first part of the FIQ is used to determine the impact of FMS on the person's ADL including shopping, driving, housework, yard work, and visiting others. The second part includes rating of overall pain level and pain level when active, effect on energy level and stiffness, and anxiety and depression. The overall score for FIQ is out of 100 points.

Other measures include simply tracking the number of tender points, similar to the WPI. Additionally, clinicians and researchers use pressure algometry to measure the amount of pressure they need to apply to a tender point to elicit pain. Other measures focus only on pain including the Brief Pain Index (pain previous 24 hours and current pain) and the Pain Catastrophizing Scale. Pain catastrophizing is the magnification of the threat of a pain stimulus. The person's perception of their inability to prevent or treat pain-related thoughts in anticipation of, during, or following a painful event affects pain catastrophizing. Patients tend to do one of three things that magnify their pain: ruminate (think about pain), magnify, or feel helpless to manage their pain. For example, a person with fibromyalgia may not want to exercise because they are anticipating the increase in pain after they exercise. One reason they choose not to exercise is because they do not have an effective treatment to manage their pain. This may change if the patient has an effective pain treatment available.

Etiology of Fibromyalgia Syndrome

The cause of FMS is not known but seems to be multifaceted. There is evidence to support several physiological symptoms normally reported by FMS patients including widespread pain at specific tender points, feeling of cold near tender points, and fatigue. One working theory is that multiple levels of the nervous system are involved from increased amplification of neural input, increased Sympathetic Nervous System (SNS) input resulting in vasoconstriction in areas of tender points, and an increase in neural activity in specific areas of the brain.[24]

Pain at specific tender points may be a combination of increased nociceptive input[24,25] and decreased blood flow.[24,26,27] Vasoconstriction of blood vessels in the area of tender points has been established by several researchers. A decrease in blood flow could be caused by overactive SNS input[24] in combination with excessive peptidergic sensory innervation,[27] which includes an increase in Aδ and C fibers. The increase in Aδ fibers may contribute to the pain pressure allodynia associated with tender points.[27] Additionally, the increase in Type C nociceptor hyperactivity could be associated with the constant pain.[25] Vasoconstriction leads to ischemia specifically in the area of the tender point. This is thought to produce myalgia partially due to a decrease in energy production of the cells and degenerative muscle damage.[24]

Overactivity of the SNS is thought to be one possible cause of the vasoconstriction,[24] which is similar to other chronic pain syndromes including amplified musculoskeletal pain syndrome (AMPS) and complex regional pain syndrome (CRPS).[28] Additionally, there is evidence to support central sensitization also occurs, which is the amplification of neural input, mainly along pain fibers, that leads to the increased perception of pain. FMS patients have increased activation of the insula cortex, which is one part of the brain that interprets pain signals.[29]

Treatment of Fibromyalgia Syndrome

The first line of treatment for pain is medication. The FDA has approved three drugs to treat fibromyalgia syndrome: the antidepressants duloxetine (Cymbalta) and milnacipran (Savella), plus the anti-seizure medicine pregabalin (Lyrica). Cymbalta prevents norepinephrine and serotonin reuptake in the posterior horn of the spine. These neurotransmitters stimulate the encephalin interneuron, resulting in the increased release of encephalin, which is the body's natural opiate. Basically, it keeps the descending modulating pain pathway active. Lyrica (pregablin) blocks calcium channels at the afferent axon terminal, therefore inhibiting the pain neurotransmitters from being released into the posterior horn synapse. These medications effectively reduce FMS pain by half in approximately 10% of the FMS patients who use them. In other words, these medications only work for 10% of the FMS patients.[30] In addition to being ineffective, these medications have several potential side effects including nausea, dizziness, somnolence, headaches, and potential to increase suicidal thoughts.[30]

The American College of Sports Medicine (ACSM) recommends exercise for FMS patients. There is sufficient evidence that exercise has a positive effect in reducing WPI and tender points and increasing function.[31-33] Evcik et al. reported a decrease in FIQ and pain for both at-home exercise programs and aquatic therapy.[34] Exercise is also effective in treatment of other chronic pain syndromes including AMPS.[35-37] Exercising counteracts many of the suspected causes of FMS pain. Blood flow increases to working muscles and skin and enkephalin is released to the whole body.

Honda et al. published a meta-analysis of randomized control trials using various physical agents to treat FMS.[38] Overall, Honda et al. reported Transcutaneous Electrical Stimulation (TENS),[39] Pulsed Electromagnetic Fields (PEMF),[40] and Balneotherapy[41] treatments were effective in decreasing pain in FMS patients.[38] Balneotherapy (mineral baths) decreased the number of tender points 5.2 ± 1.7.[41-44] Additionally, balneotherapy decreased FIQ (mean=17.82 ± 9.83) and pain VAS (mean=2.92 ± 1.23) in FMS patients. TENS[39] and PEMF[40] also decreased pain between 2 and 4 points and PEMF decreased FIQ by 33.5 points. The Honda et al.[38] meta-analysis also showed PBM was effective in decreasing the number of tender points, FIQ, and pain.

Laser and Light Therapy in Fibromyalgia Treatment

Light is crucial for supporting the fundamentals of life and maintaining the surrounding environment. Breakthroughs in light technology continue to revolutionize the medical industry. The idea that exposure to light could stimulate or regulate biological functions was once considered "alternative" because it seemed too simple for mainstream acceptance. Hampering the widespread adoption of photobiomodulation (PBM) is the lack of consistent reliable doses due to device wavelength and power variability; determining optimal parameters of light (wavelength, power, frequency of treatment) is a difficult task. It can require years of optimization to demonstrate reproducible results.

Photoceuticals: Light as Medicine

A new theoretical perspective has emerged that considers light energy as a form of medicine. Light can be prescribed in the same manner as pharmacological agents. It is possible to optimize the desired biological effect to achieve a predictable response. This anticipated therapeutic response requires the right composition of light (wavelength) administered at the correct dose (time and power) with the correct dosage (frequency of application).

The process of optimization has been attempted through trial and error, supplemented with the previous experience, knowledge, and wisdom of the technology. 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 to validate PBM for specific indications. If a pharmaceutical is used to diagnose, treat, or prevent disease and for restoring, then a photoceutical is a device that delivers an optimized dose of light energy to repair, restore, or alter biological processes for a specific indication of use. When taking into consideration the photoceutical approach, the understanding that light is composed of different and unique wavelengths of varying energies underpins how the desired biological effects are observed following light exposure. This approach can determine the optimal dose (specified amount of energy taken at one time) and the dosage (the prescribed administration of a specific amount, number, and frequency of doses over a specific period). Multi Radiance Medical optimized the dose response for the multiwavelength combination from 2012-2014. The studies have since been peer-reviewed and published and a summary called The Pillars Paper is currently available upon request from Multi Radiance Medical.

Therefore, a photoceutical light-emitting device delivers optimized doses of light energy using curated wavelengths and the ideal frequency of exposure to significantly impact treatment effectiveness, improve the quality of life, and support the continuum of care system (CoCS) over the life span.

Understanding the Mechanism of Action

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.[45] 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, and the energy needed to activate the desired effect. Treatment only requires transcutaneous application to deliver the adequate dose of light energy.

One of the basic mechanisms of PBM is the stimulation of mitochondria,[46] which are thought to be a key target in the phototherapeutic mechanism of action acceleration of electron transfer by photons in the vis-

ible and near infrared region of the light spectrum[47,48] via the modulation of cytochrome c-oxidase (CCO) activity. This stimulation leads to increased adenosine triphosphate (ATP) production, modulation of reactive oxygen species (ROS), release of nitric oxide, and induction of transcription factors.[1]

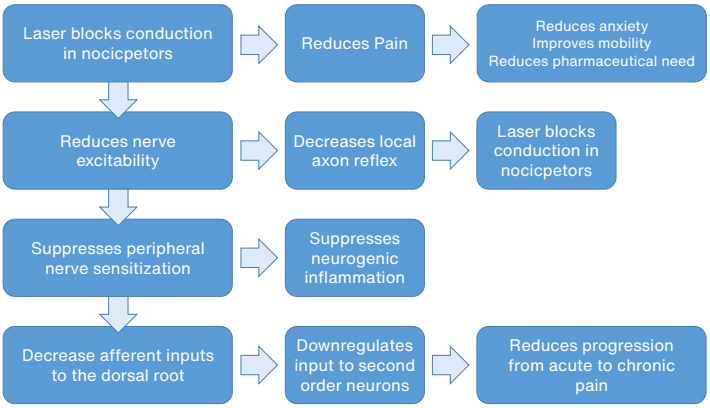
The photobiological effects are biphasic in nature.[49] A low dose of light energy (based upon power, penetration, density, and time) is recognized as providing a stimulatory effect in the tissue. Increased ATP production provides energy for cellular processes as well as a release of low levels of ROS and nitric oxide.[49] Nitric oxide causes vasodilation effects on blood vessels and stimulates the dissociation of oxygen from hemoglobin, resulting in increased blood flow and oxygen availability to the tissues.[50]

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+) and an influx of potassium (K+) ions into the nerve cell, altering the electrical potential across the membrane. The peak absorption of lipids is in the 905 nm to 910 nm range.[51]

A larger dose of light energy (usually in the near infrared wavelength) results in inhibitory effects that clinically decrease or inhibit pain.[49] 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 rebalance the sodium-potassium pump and remove the pain signal at the source.

Treatments that apply a sufficient dose of energy have an inhibitory effect on nerve action potentials, creating analgesia in as little as 10 to 20 minutes following treatment.[52] When super pulsed laser is applied to peripheral nerves, de-polymerization of the microtubules in C-fibers and Aδ fibers occurs from oxidative stress resulting from the acceleration of the electron transport chain.[53] ATP and Mitochondrial Membrane Potential (MMP) are decreased, limiting Na+, K+, and ATPase that maintain normal electrophysiological balance of the nerve. This works to block pro-inflammatory mediators (PGE2, IL-6; TNF-α), and blocks acetylcholine to eliminate muscle spasms. For chronic pain, the treatment must be done every 48-72 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 Aδ fibers.

Nociceptor Blockade from PBM



The Effect of Photoceuticals on Fibromyalgia Pain

There are two observable effects noted following photoceutic exposure that may impact the possible etiology of FMS. First, transcutaneous exposure of oxyhemoglobin to light (photohemotherapy) can induce vasodilation and oxygen dissociation.[50] Applying the energy to tender points may increase the blood flow to the area, counteracting the local ischemic effects and promoting healing over time. There is blockage of neural transmission of pain by inhibiting Aδ and C nociceptors after the absorption of energy. Treatment directed to the active tender points could decrease the fast pain associated with added pressure to the tender points. Additionally, the overall constant pain associated with C nociceptors could also be reduced.

To provide additional analgesia, treatments for pain should also include treating the nerve roots and trunks associated with the active tender points.[54] Targeting the posterior spine root ganglion may have an effect on decreasing central sensitization.[54] There is evidence supporting the treatment of the sympathetic nervous system (SNS) through stellate ganglion block. Studies using traditional medication stellate ganglion blocks have decreased pain and increased blood flow in the arms of FMS patients.[55,56] PBM can effectively be used to block stellate ganglion and might be used to treat FMS in a similar fashion.

Photoceutical Treatment of Fibromyalgia Syndrome

The main goal in managing FMS is pain control and improved function. Yeh et al.[57] performed a systematic review and meta-analysis on the use of light for FMS. The overall finding suggests laser therapy is a non-invasive, well-tolerated treatment for fibromyalgia to relieve discomfort, and the sub-analysis offers additional insight into the role of super pulsed laser (SPL) in FMS care. In a separate systematic review and meta-analysis of physical agents used to treat FMS, Honda et al. demonstrated a similar efficacy.[38] There is significance of using light as a photoceutical for the treatment of FMS to reduce tender point count, decreasing FMS impact on the patient's life, and pain.[38,57]

The majority of research using light to treat FMS has focused on treatment of the tender points, with the main outcomes of decreasing the overall number of tender points and pain. There are 18 identified tender points associated with fibromyalgia. These points closely match the ACR WPI points. Additionally, many of the studies also measured the impact of FMS on the patient's life using the FIQ. Changes in the patient's function would be reflected in a decrease in the overall FIQ score. Some of the studies combined PBM with other interventions including exercise, stretching and tape. PBM treatment effects for FMS are summarized in the table at the end of this paper. There are differences in the effects of PBM on FMS, which may be due to the type of light-emitting device used. The summary of the research studies is divided between continuous single-wavelength emitters and SPL multi-wavelength emitters. The table at the end contains a summary of the published research on the effects of PBM and FMS.

Early Treatment Outcomes with Single-Wavelength Devices

Four studies using continuous wave PBM specifically measured changes in number of tender points. The average decrease in the number of tender points across studies was 4.89±2.8. [58-61] Most of these studies used a treatment dose between 2 Joules (J) and 4 J per tender point. Changes in FIQ scores were monitored by four authors with the mean decreases of 18±7.79.[59-62] However, the authors did not specify which part of the FIQ caused the change in score. It is unknown if the subjects had increased ADLs, changed pain ratings, fatigue, or psychological factors. There is a large variability in changes in FIQ scores between studies.

Overall pain changes are the main outcome of most PBM and fibromyalgia studies. However, researchers have used different measurement instruments, so it is difficult to compare the results between studies. Ruaro et al.[61] used the McGill pain questionnaire and reported a decrease of 12.9 points. Armagan et al.[59] used a myalgia score and reported a decrease of 5 points. Gur et al.[58,60] reported a 1.8- and 1.24-point decrease in pain respectively using a 10-point VAS scale. None of the researchers reported complete resolution of the pain for their subjects over the course of the studies.

Matsutani et al.[63] studied the effects of PBM combined with a stretching program. They reported a pain ⇩2.9 for the PBM + stretch and ⇩2.7 for the stretch-only group, suggesting the stretching alone had the same effect on pain as PBM. Germano Marciel et al[64] studied the effects of PBM + exercise. However, they treated the quadriceps, hamstrings, and calves of the FMS patients instead of the tender points. The number of tender points only decreased by one, while the FIQ decreased by 54 points in PBM + exercise and 47 in the Placebo PBM + exercise groups. These results indicate that exercise has a positive impact on FIQ scores, but not number of tender points. Additionally, it indicates that location of PBM treatment is important to have an effect on FMS pain and number of tender points.

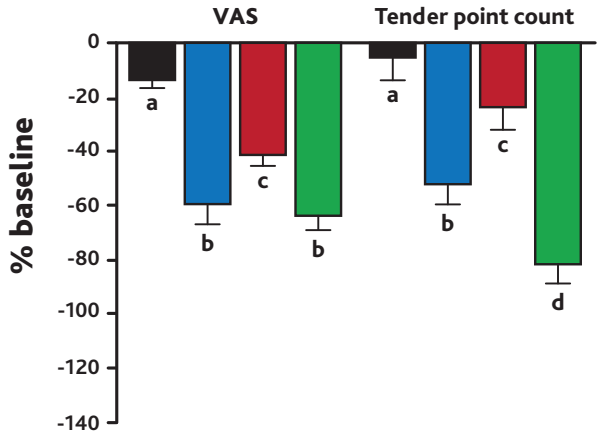
Super Pulsed Laser and Multi-Wavelength Studies

The following published studies treated FMS patients with multi-wavelength emitters (905 nm SPL; 875 nm IR; 670 nm red). Two published case studies[12,13] reported positive results in treating FMS patients. Moore and Demchak treated an FMS patient two days per week for two weeks using a treatment dose of 16 J per active tender point. The patient reported an average pain decrease of 3.5 immediately post-treatment. The total number of tender points (⇩ 8) and FIQ score (⇩ 59) decreased after two weeks of treatment. In a different case study, Demchak et al.[12] trained a patient to treat themselves with a multi-wavelength laser device (Pain-Away) at home. The patient treated each active tender point daily (16 J/pt) as needed. The patient reported a

complete abatement of all tender points (14 to 0) and pain (8 to 0) after four consecutive days of treatment.

Due to the impact of SPLT in these two case studies and ACSM guidelines suggesting exercise to treat FMS, da Silva et al.[14] evaluated the effect of SPLT + exercise for managing pain and improving the quality of life in FMS sufferers. The study included 160 women suffering from FMS and it evaluated both short-term (one session) and long-term (two sessions per week for 10 weeks) effects of SPLT and/or exercise. Patients were allocated into two different sessions: acute (one session) and chronic (10 weeks, two times weekly) each with four groups: control, SPLT, exercise, SPLT + exercise. Pain pressure threshold was measured using algometry at each tender point. Pain was measured using a VAS 10-cm scale. Both measures were used to evaluate the changes in pain. FMS symptoms were evaluated utilizing the FIQ and the Research Diagnostic Criteria (RDC). Changes in the quality of life were assessed using the SF-36 survey. SPLT was applied at 11 tender points for 300 seconds (40 J at 1000 Hz). Exercise protocols included seven stretching exercises, TMJ exercises, and 30-minute aerobic training on a treadmill at 75% age-predicted maximum heart rate.

During the single session, SPLT increased pain pressure threshold for 10 (50%) of the 20 tested points. When SPLT was combined with exercise, 80% of the tender points were affected. However, exercise alone only affected one out of 20 points (5%). This outcome suggests that in the single session there was no additional benefit of adding exercise to the SPLT.



Long-term effect of phototherapy and exercise training on VAS scores and tender point numbers. Kruskal-Wallils 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%.

After 10 weeks of treatment, pain decreased for the treatment groups as follows: SPLT ⇩65%, exercise ⇩45%, and SPLT+ exercise ⇩70%.

There was a large effect for both SPLT and exercise groups; however, the SPLT and the SPLT + exercise groups experienced the greatest reduction in pain when compared to the control and exercise groups alone. When looking at the reduction in the number of tender points, SPLT decreased by 50% and the exercise group decreased 25%; however, the combination of SPLT + exercise had a synergistic effect resulting in an 85% decrease in tender points.

In the 10-week session, all FIQ, RDC, SF-36, anxiety, sleep, depression, and fatigue scores were significantly decreased in exercise, SPLT, and SPLT + exercise groups. While SPLT and exercise groups demonstrated beneficial outcomes, the greatest change was noted when both interventions were combined. These outcomes describe the importance of a multi-faceted approach that includes both SPLT and an active therapeutic exercise program to improve FMS symptoms.

The combination of SPLT + exercise provided the greatest effect on the severity of pain and number of tender points (SMD: 5.20; 95% CI, 3.85-6.55 and SMD: 7.02; 95% CI, 5.29-8.76, respectively) and the secondary outcome of fatigue (SMD: 1.35; 95% CI, 0.65-2.04). Simply, a confidence interval (CI) is a way to compare the effect of the different treatments on FMS and how well the outcomes represent the FMS population. These outcomes suggest that effects seen in the SPLT + exercise group were more greatly pronounced and will likely yield the most clinically relevant outcomes. As reported in the knee pain and osteoarthritis studies, combining SPLT with exercise results in a synergistic effect.

The most recent clinical study utilized an MR5 ACTIV PRO® LaserShower, however it did not add exercise to the treatment protocol. The laser treatment consisted of a 60 J dose, utilizing 1000 Hz for 2 minutes on each active tender point three days per week for three weeks. The number of tender points decreased from 15 to 7 (⇩ 52%), which is similar to da Silva. Additionally, FIQ score decreased by 44 points in the active PBM group, which is 20 points greater than the decrease reported by Vayvay and 2.4 times greater than the average FIQ decrease (x=18) reported in all other PBM

and fibromyalgia studies. Pain was measured using a VAS scale, and the average decrease in pain for active PBM was 4.3. Gur et al. only reported a decrease of 1.8 in both studies. Based on this data, it appears that treating with a multi-wavelength super pulsed laser has a greater effect on tender point count, FIQ scores, and pain than single-wavelength continuous emitters.

Optimizing Photoceutical Effects for Light-Based Treatments

Effectiveness of PBM treatments varied greatly between research studies. The following treatment parameters may have resulted in differences in outcomes: treatment location, dose per treatment location, type of emitter (multi-wavelength and super pulsed), and the combination of PBM and exercise.

Treatment location
The majority of studies treated the patients' identified tender points. The only exception was Germano Maciel[64] who followed the PBM performance enhancement protocol for increasing strength and treated the quadriceps, hamstrings, and calves instead of tender points. As a result, Germano Maciel reported no difference between exercise and PBM + exercise groups in number of tender points. All other studies reported a decrease in number of tender points. Treatment to the tender points makes sense due to the decrease in blood flow to these points associated with FMS. PBM stimulates the release of nitric oxide which causes vasodilation, thereby increasing blood flow. Additionally, PBM may be decreasing the nociceptive input from the C and Aδ fibers.

Dose
Most of the randomized, controlled PBM studies (77%) utilized a dose of 2-4 J per tender point.[58-64] The outcomes for PBM-only treatments were a 4.89±2.8 decrease in tender points across studies,[58-61] a 18±7.7959-62 decrease in FIQ scores, and a decrease of 1.5 in pain VAS.[58,60] The two published case studies treated each active tender point with a dose of 16 J. The decreases in tender points (⇩8 & ⇩13), FIQ (⇩44 & ⇩59), and acute pain VAS (⇩3.5) were greater than that seen in studies using a lower dose.[12,13] However, a large randomized, controlled trial is needed first to optimize the dose and second to determine effectiveness. Da Silva et al. used a 40 J dose/tender point; however, only percent change in FIQ and tender points were reported, therefore their outcomes cannot be compared to other studies.[14] The MR5 ACTIV PRO LaserShower treatment consisted of a 60 J dose to active tender points resulting in a decrease in tender points, FIQ, and pain.

Devices
The Yeh et al.[57] meta-analysis showed that a combination of SPL and a multi-wavelength emitter was more effective than single-wavelength PBM treatments for FMS. The single-wavelength continuous wave PBM treatments only penetrated the skin to a certain level due to wavelength. Therefore, these treatments only affected the etiological causes of FMS symptoms that are associated with that level of penetration. Additionally, continuous wave PBM devices may increase temperature, which has a negative effect on the PBM outcomes. SPL works differently than traditional continuous wave lasers by generating very 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. This allows the clinician to provide a higher treatment dose, creating a beneficial phototherapeutic effect. Additionally, SPL allows for greater penetration through the dermis, which results in a more efficient dose and the ability to treat deeper target tissue. Based on the etiology of FMS, multiple wavelengths could be effective in treating different causes of FMS. The SPL emitters were used in the case studies, da Silva et al., and clinical trial which utilized multiple wavelengths.

Clinical Trial Summary

A clinical study titled "A double-blind, placebo-controlled randomized evaluation of the effect of the MR5™ ACTIV PRO LaserShower (FibroLux) for the temporary relief of pain associated with fibromyalgia," was conducted to determine if the treatment effect of the FibroLux is greater than placebo for the temporary relief of pain associated with fibromyalgia.

Study Design
The study was a prospective placebo-controlled, randomized, double-blind, parallel group, multi-center design conducted across three test sites.

Subjects
Ninety (90) subjects were enrolled and completed the study: 45 subjects were randomized to the active treatment group and 45 subjects were randomized to the placebo group. Subjects were females aged 25 to 60 years with an ovulatory cycle, body mass index ≥ 18.5 kg/m², a baseline Visual Analog Scale (VAS) pain rating of ≥ 50 or a score on the Fibromyalgia Impact Questionnaire (FIQ) ≥ 50, and a diagnosis of fibromyalgia per the current American College of Rheumatology (ACR) criteria with symptoms present for greater than three months. The study was restricted to inclusion of female subjects to represent the predominant patient population with fibromyalgia that is determined to be 90% female and to present differently in males. Subjects were excluded from study participation if they had diabetes mellitus; uncontrolled hypertension; malignant tumors; dengue, Zika, or chikungunya in recent years; arthritis; chronic fatigue syndrome; lupus; auto-immune disease; psychiatric illness; hypersensitivity to light; participation in regular exercise; a physical injury in the past 6 months; a pacemaker; or were pregnant.

Across all subjects, the average age was 45.24 years. Subjects were predominantly Caucasian (43%) and Hispanic (44.44%). Subjects spanned the range of Fitzpatrick Skin Types I through VI, with Fitzpatrick Skin Type III being the most prevalent (44.44% of subjects). At study entry, subject average tender point count (TPC) was 15.25, average Visual Analog Scale (VAS) pain rating was 77.76, and average total Fibromyalgia Impact Questionnaire (FIQ) score was 78.61.

Study Procedures
Subjects received nine treatment administrations with the FibroLux (active or placebo) to self-identified tender points across a three-week period: three treatments per week, each treatment two to three days apart. Subjects agreed to use only the medications, treatments, and therapies determined by the study investigator during the individualized medication stabilization phase of the study to relieve any fibromyalgia pain, as needed, throughout study participation.

Primary Endpoint
The aim of the study was to determine if the treatment effect of the FibroLux for the active treatment group was greater than that for the placebo treatment group. The study was predetermined to be considered a success if, using the Intent-To-Treat (ITT) analysis, the primary endpoint was statistically significant at the 0.05 level.

Primary efficacy outcome measure was predefined as the difference in the proportion of subjects between active and control groups who achieved a clinically meaningful and statistically significant decrease in tender point count of 20% or greater at study endpoint, defined as end of the three-week treatment administration phase, relative to baseline, defined as the evaluation occurring before the first treatment administration. Overall study success was predefined as a 30% or greater difference in the proportion of individual subject successes between treatment groups. As each enrolled randomized subject in the clinical study completed all study visits and procedures, only the primary intent-to-treat (ITT) analysis was performed.

Of the subjects who received the active treatments with the FibroLux, 86.67% met the individual subject success criteria compared with 48.89% of placebo group subjects. The difference of 37.78% in individual subject successes between treatment groups, in favor of the active treatment group, exceeded the pre-determined criteria of a 30% difference ($p<0.0005$).

Secondary Endpoints

Tender Point Count (TPC)
The mean decrease in TPC from study baseline to endpoint for active group subjects was 8.00 points compared with 2.71 points for subjects in the placebo group, a 5.29-point difference in mean change in TPC between treatment groups in favor of active treatment group subjects.

Visual Analog Scale (VAS)
Mean pain ratings on the 0-100 Visual Analog Scale (VAS) decreased 42.84 points for active treatment group subjects and 17.98 points for placebo treatment group subjects, a difference of 24.86 points in favor of active treatment group subjects.

Total Score on the Fibromyalgia Impact Questionnaire (FIQ)
Mean total score on the FIQ decreased 35.79 points for active treatment group subjects and 20.83 points for placebo treatment group subjects, a difference of 14.96 points in favor of active treatment group subjects.

Subject Satisfaction
At study endpoint evaluation, 80% of subjects in the active treatment group reported being "very satisfied" with the study outcome compared with 51% of subjects in the placebo treatment group.

Adverse Events
Adverse events were reported by 17.78% of subjects treated with the active device and 13.33% of subjects treated with the sham device. Reported adverse events were slight increases in pain/tension (3 actively treated subjects and 5 sham treated subjects), itching/scratching, spasms, redness at the treatment site, drowsiness, headache, and blurred vision. Each was determined to be mild and either unrelated or potentially related to the study treatment. No adverse event required any intervention nor resulted in a subject withdrawing or being withdrawn from the study, and each fully and satisfactorily resolved by study completion.

Conclusion
Collectively, the study results demonstrated that the FibroLux delivers a safe and effective treatment for reducing fibromyalgia pain when administered three times a week over a consecutive three-week period.

SPL + Exercise
It is understood that exercise has a positive effect on decreasing FMS symptoms and improving function.[14,30,32-34,62-65] There appears to be a synergistic benefit of combining PBM and exercise. However, this synergistic benefit appears to be dependent on treatment location, dose, and exercise type. Da Silva[66] reported a greater decrease in both tender points and FIQ over the course of the study for the PBM + exercise group than in the PBM or exercise-only groups using a 40 J dose over each tender point. Vayvay[62] reported similar decreases in the PBM + exercise and exercise-only group using 2 J per tender point. Germano Maciel[64] reported no difference between exercise and PBM + exercise groups in number of tender points but treated only the legs.

Translation of Research into Clinical Practice

One of the main symptoms preventing FMS patients from exercising is pain or the catastrophizing of pain. However, PBM is effective in decreasing pain associated with FMS. Additionally, there is a synergistic effect in utilizing PBM + exercise.

Based on the current research, the following treatment is recommended for FMS using PBM: use an SPL multi-wavelength emitter at least two days per week in conjunction with an exercise program, with a suggested dose between 16 and 40 J per active tender point. There appears to be a cumulative effect, therefore treating consecutive days may increase the benefits.
The effectiveness of exercise-only and PBM + exercise appeared to depend on the exercise performed and the location of the PBM treatments. Several exercise programs have been effective in treating FMS, but not all exercise modes have had a synergistic effect with PBM. Strength training exercises have been effective in improving function in female FMS patients.[32] Whole-body stretching programs effectively reduced pain, but adding PBM to the stretching program did not change the outcomes.[63] Combining aerobic exercise with neuromuscular and neuromotor exercise was effective in treating FMS. da Silva utilized a combined whole-body stretching program with 30 minutes of aerobic exercise (75% of age-predicted maximum heart rate) and reported positive outcomes for exercise alone and PBM alone.[66] However, the greatest effect occurred when PBM was combined with the stretching and aerobic exercise program.

Ideal treatment progression would start with PBM (MW-SPL) for the first week of treatment, then add in the aerobic exercise after the patient understands that PBM treatment is effective in decreasing their pain. Clinicians should monitor the effectiveness of treatments using the FIQ and a tender point count or WPI. This will allow the clinician to adjust the treatment as needed. It is also suggested using the ACR diagnostic criteria every month to determine overall effectiveness of treatment on WPI and Somatic symptom scores.

Conclusion

Fibromyalgia syndrome is a common and costly condition that causes chronic widespread pain, fatigue, and cognitive difficulties. Between 2-8% of the general population are affected by fibromyalgia and the overall economic impact of this condition totals $12-$14 billion in indirect and direct costs plus $31 billion in lost productivity.

With no known cause or cure, first-line treatments for fibromyalgia include three FDA-approved drugs that have been shown to be effective in only 10% of patients while carrying the risk of several serious side effects like nausea, headaches, and increased suicidal thoughts. Exercise is also recommended, though some fibromyalgia patients may avoid exercise in fear of the intense pain that may follow.

In addition to managing other types of pain, evidence shows that using super pulsed laser therapy (SPLT) is an effective, non-invasive, drug-free method for treating fibromyalgia pain. Inhibitory doses of SPLT can relieve pain when applied at active tender points and decrease central sensitization when targeting the posterior spine root ganglion. Additionally, the overall impact of fibromyalgia syndrome was reduced with SPLT.

Like a pharmaceutical, a photoceutical delivers an optimized dose of light energy to repair, restore, or alter biological processes for a specific indication of use. Through years of peer-reviewed research and trials, Multi Radiance Medical has determined the optimal dose (specified amount of energy taken at one time) and the dosage (prescribed amount, number, and frequency of doses over a specific period) for effective SPLT.

The MR5 treatments resulted in a 2 times greater decrease in number of tender points and 2.4 times greater decrease in pain and FIQ scores. Treating with an SPL multi-wavelength emitter reduced the impact of FMS 2.4 times more than other PBM treatments using single-wavelength continues devices. This means the patients were able to complete ADL at a higher rate compared to prior treatments.

Additionally, after a recent clinical trial demonstrating it as a safe and effective treatment, the FDA cleared the FibroLux therapeutic laser for adjunctive use in the temporary relief of pain associated with fibromyalgia.

Based on research studies and meta-analyses evaluating various types and combinations of laser therapy and exercise, the following photoceutical treatment is recommended for fibromyalgia syndrome: use a super pulsed laser multi-wavelength emitter at least two days per week in conjunction with an aerobic exercise program, with a suggested dose between 16 J and 40 J per active tender point. Treating consecutive days may increase the benefits due to a cumulative effect, and SPLT helps decrease the pain to encourage the patient to continue exercise.

With virtually no side effects and minimal contraindications, super pulsed laser therapy should be considered a viable treatment option for managing fibromyalgia pain.

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Appendix

This data show that the use of monowavelength PBM as an adjunct to exercise (which is the gold standard treatment for fibromyalgia) does not promote any additional benefit, since it just led to a non-significant decrease of 0.59 in the number of tender points when compared to exercise alone. On the other hand, the use of multiple wavelengths and different light sources synergistically as an adjunct to exercise promotes a significant decrease of 7.02 on the number of tender points when compared to exercise alone.

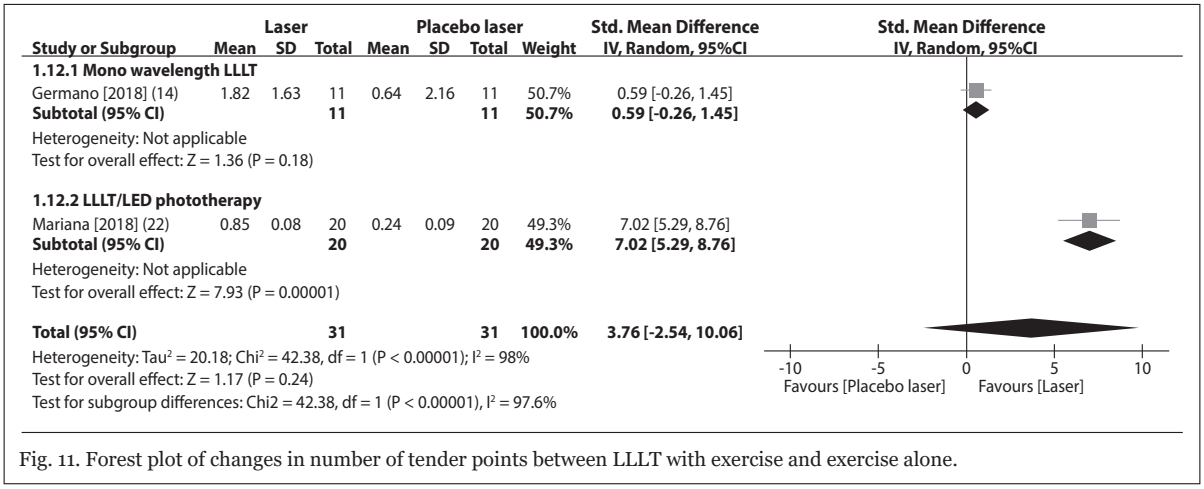


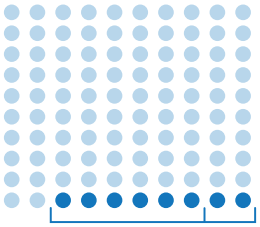
Fig. 11. Forest plot of changes in number of tender points between LLLT with exercise and exercise alone.

Yeh SW, Hong CH, Shih MC, Tam KW, Huang YH, Kuan YC. Low-Level Laser Therapy for Fibromyalgia: A Systematic Review and Meta-Analysis. Pain Physician. 2019 May;22(3):241-254. PMID: 31151332.

Fibromyalgia Syndrome (FMS)

Fibromyalgia syndrome (FMS) is defined by the American College of Rheumatology (ACR) as a chronic widespread pain and tenderness in specific tender points[1] characterized by muscular tenderness, pain, fatigue, and cognitive difficulties[2]. The FibroLux laser has been FDA cleared for adjunctive use in the temporary relief of pain associated with fibromyalgia (K212189)

Adult Population



2 - 8% affected

(3) FDA Drugs

Effectively reduces pain by half but in only 10% of the patients who use them

Out of Pocket Expenses

Patient average out of pocket expense with insurance was $5,310 annually

Photoceutical

A non-pharmological treatment that promotes healing by reducing the inflammation that causes nerve irritation and provokes pain

Tender Points

FibroLux reduced the amount of tender points by 52%.

Pain (VAS)

FibroLux reduced the amount of pain by 53%.

FIQ Score

45% reduction in Fibromyalgia Impact Questionnaire score

Treatment Protocol

Use emitter 3 days per week in conjunction with 30 minutes of exercise, and a 60 joule dose

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Author	PBM Tx	Interventions	Dose / Site	Tx Sites	Tx Freq	Outcomes
Armagan et al. (2006)32. Armagan O, Tascioglu F, Ekim A, Oner C. Long-term efficacy of low level laser therapy in women with fibromyalgia: A placebo-controlled study. J Back Musculoskelet. 2006;19(4):135-140. doi:Doi 10.3233/Bmr-2006-19405	830 nm	PBM Placebo PBM	2J/ TP	TP	5d/wk x 2 weeks (10 total)	Tender points: PBM ⇩1.18 : PL ⇩1.06 FIQ: PBM ⇩7 : PL ⇩1.75 Myalgia Score: PBM ⇩ 5.5: PL ⇩ 1.56
Demchak et al.. Case Study 39. Demchak T, Taylor B, Christian M. Using Low-Level Light Therapy to Successfully Treat Fibromyalgia Syndrome: Case Report. Practical Pain Mangement. 2018;18(8):49-53; 66.	905 nm SPL; 875 nm IR; 670 nm Red	PBM Case Study	16 J/ Tender point	Active TP	4 days in a row (4 total)	Tender points: PBM ⇩13 FIQ: PBM ⇩ 44 Pain: VAS ⇩ 8
Germano Maciel et al.. (2018) 41.Germano Maciel D, Trajano da Silva M, Rodrigues JA, et al. Low-level laser therapy combined to functional exercise on treatment of fibromyalgia: a double-blind randomized clinical trial. Lasers Med Sci. Dec 2018;33(9): 1949-1959. doi: 10.1007/s10103-018-2561-2	808 nm	PBM + Exercise PL PBM + Exercise	4J location	Quad (8pts); hamstrings (6 pts) & Calf (3 pts) bilaterally	3d/wk x 8 weeks (24 total)	Tender points: PBM+ Ex⇩1.82: Ex ⇩0.64 FIQ: PBM+ Ex ⇩52.4: PL + Ex ⇩47.69
Gur et al.. (2002)31. Gur A, Karakoc M, Nas K, Cevik R, Sarac J, Demir E. Efficacy of low power laser therapy in fibromyalgia: a single-blind, placebo-controlled trial. Lasers Med Sci. 2002;17(1):57-61. doi:10.1007/s101030200010	904 nm	PBM Placebo PBM	2 J /TP	Active TP	5d/wk x 2 weeks (10 total)	Tender points: PBM ⇩6.55 : PL ⇩4.15 Pain: PBM ⇩1.82: PL ⇩ 1.04
Gur et al.. (2002)34. Gur A, Karakoc M, Nas K, Cevik R, Sarac J, Ataoglu S. Effects of low power laser and low dose amitriptyline therapy on clinical symptoms and quality of life in fibromyalgia: a single-blind, placebo-controlled trial. Rheumatol Int. Sep 2002;22(5):188-93. doi:10.1007/s00296-002-0221-z	904 nm	PBM Placebo PBM Amitriptyline	2 J/TP	Active TP	5d/wk x 2 weeks (10 total)	Tender points: PBM ⇩7.52: PL ⇩3.9 : A ⇩5.45 FIQ: PBM ⇩23.25: PL ⇩9.64 : A: ⇩ 17.95 Pain: PBM ⇩1.24 : PL ⇩ 1.00 : A: ⇩ 0.81
Matsutani et al. (2007) 36.Matsutani LA, Marques AP, Ferreira EA, et al. Effectiveness of muscle stretching exercises with and without laser therapy at tender points for patients with fibromyalgia. Clin Exp Rheumatol. May-Jun 2007;25(3):410-5.	830 nm	PBM +Stretch Stretch	3J/ TP	17 TP	2d/wk x 5 wks (10 total)	Pain: PBM + Stretch: ⇩ 2.9 : Stretch ⇩ 2.7
Moore & Demchak Case Study38. Moore J, Demchak T. Treatment of Fibromyalgia Syndrome with Low Level Laser Therapy: A Case Report. Int J Athl Therapy and Athl Train. 2012;18(2):24-28.	905 nm SPL; 875 nm IR; 670 nm Red	PBM Case Study	16 J/ TP	Active TP	2d/wk x 2 wks (4 total)	Tender points: PBM ⇩8 FIQ: PBM ⇩ 59
Ruaro et al. (2014)33. Ruaro JA, Frez AR, Ruaro MB, Nicolau RA. Low-level laser therapy to treat fibromyalgia. Lasers Med Sci. Nov 2014;29(6):1815-9. doi:10.1007/s10103-014-1566-8	670 nm	PBM & Placebo PBM	4J/ TP x 4 spots 1 cm of tender point 16J/point?	17 TP	3d/wk x 4 wks (12 Total)	Tender points: PBM ⇩7.3 : PL ⇩ 1.4 FIQ: PBM ⇩ 18.6: PL 5.2 McGill Pain Questionnaire: PBM ⇩12 : PL ⇩4.9
Da Silva et al.. (2017)42. da Silva MM, Albertini R, de Carvalho Pde T, et al. Randomized, blinded, controlled trial on effectiveness of photobiomodulation therapy and exercise training in the fibromyalgia treatment. Laser Med Sci. 2017;33(2):343-351.	905 nm SPL; 875 nm IR; 670 nm Red	Control PBM PBM + Exercise PL PBM + Exercise	39.3 J/ pt.	10 specific locations bilaterally 20 total points	2d/wk x 10 wks (20 Total)	Tender Points: C: ⇩15% PBM: ⇩57%: PBM+E ⇩85%; PL-PBM + Ex: ⇩25% FIQ: C: ⇩1% PBM:⇩8% PBM+E: ⇩25%; PL + Ex ⇩25% Pain: C: ⇩15% PBM: ⇩60% PBM+E: ⇩70%; PL + Ex: ⇩45%
Vayvay et al. (2016)35. Vayvay ES, Tok D, Turgut E, Tunay VB. The effect of Laser and taping on pain, functional status and quality of life in patients with fibromyalgia syndrome: A placebo- randomized controlled clinical trial. J Back Musculoskelet Rehabil. 2016;29(1):77-83. doi:10.3233/BMR-150600	850 nm	PBM + Exercise PL PBM + Exercise PL PBM + Tape	2J / tender point	18 TP	5d/wk x 3 wks (15 total)	FIQ: PBM+ Ex ⇩23.75 : PL + Ex ⇩16.17; Tape + Exercise 19.73 SF36: PBM+ Ex ⇩11.53 : PL + Ex ⇩5.73; Tape + Exercise 6.73
MRM MR5 Study	905 nm SPL; 875 nm IR; 670 nm Red	Active PBM Inactive PBM	60J/Active Tender point	Dependent on active tender points	3d/wk x 3 Weeks (9 total)	Tender points: PBM ⇩8.0 : PL ⇩2.71 FIQ: PBM ⇩35.79 : PL ⇩20.93 Pain: PBM ⇩4.3 : PL ⇩1.8

nm= nanometers; J= Joules; TP= Tender point; PL= Placebo; Ex= Exercise; A=Amitriptyline

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