Utilization of the 1064 nm Wavelength in Photobiomodulation: A Systematic Review and Meta-Analysis

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Abstract

Introduction: Photobiomodulation or low-level laser therapy (LLLT; < 0.5 W) has been used as a non-invasive treatment for various medical indications. Short (visible; 635-650 nm) and longer (invisible; 810-850 nm and 915-980 nm) near-infrared wavelengths have been commonly used, but power setting deficiencies or incorrect wavelength settings can cause negative outcomes. The 1064 nm wavelength as the longest wavelength is a relative newcomer in high-powered (> 0.5 W) laser photobiomodulation therapy (HPL-PBMT) with unique biophysical characteristics.

Methods: A comprehensive search of 2016-2021 PubMed, Google Scholar, and Cochrane databases for “photobiomodulation” restricted to clinical trials for patients with a medical diagnosis was done. “1064 nm” content was identified and restricted to high-powered lasers (> 0.5 watt). Cohen’s d was calculated for the effect size and the difference was determined as a measure of relative 1064 nm HPL-PBMT efficacy.

Results: The 22 independent studies meeting inclusion criteria focused on knee arthropathies, spine, shoulder/elbow, wound, gynecological, or osteoporosis with evaluation of pain, function, quality of life, range of motion (ROM), and anatomy. Pain was reduced with statistical significance (P < 0.05) in 90% of study assessments (n = 20) and 100% of studies focused on the knee (n = 6). Of 18 studies assessing functional outcome measures, 100% demonstrated statistically significant improvements. Follow-up assessments up to 6 months in 5 knee arthritis studies revealed long-term pain reduction after cessation of treatment. Improvements in wound healing, bone mineral density, and knee cartilage thickness were demonstrated. The largest effect sizes observed were pain reduction in knee arthritis (average Cohen’s d effect size = 2.46).

Conclusion: These studies have established that 1064 nm HPL-PBMT can effectively reduce pain, increase ROM, increase functional scores, and increase the quality of life for knee osteoarthritis and spinal disorders, with limitations. More studies are needed for clinical validation of single-trial data detecting changes in musculoskeletal conditions, cartilage thickness and bone density.

Keywords: Photobiomodulation; Musculoskeletal; Pain, Knee; Arthritis; Transcranial.

Introduction

Clinical trial studies evaluating the effectiveness of low-level (LLLT) laser photobiomodulation therapy (PBMT) have yielded inconsistent outcomes due to differences in laser parameter settings involving variable power levels, wavelength selection, light coherence, operation modes (pulsed versus continuous), beam sizes, and dosage depending on indications and specific patient populations. However, over the past 5 years, significant advances have been made, clarifying our understanding of which factors are most important for achieving reproducibly effective therapeutic outcomes.

Positive therapeutic outcomes can be dependent on the ability of laser light to penetrate and ultimately reach pathological tissues. As light transmits through tissue, it is lost by three processes: reflection, scattering, and absorption of light by water, melanin, or other chromophores. The depth of laser light penetration is dependent on the adjustable laser setting parameters of power density and wavelength. Multiple randomized controlled trials that directly compare low-power (< 0.5 W) and high-power (> 0.5 W) laser therapy have proven that high power can be required for efficacy. The highest power settings that can generate heat may need to be modified, depending on the condition being treated and the response of the patient. The upper limit of high-power laser settings to the patient can be modified in a number of ways, including faster movement of the treatment headpiece, administering therapy in pulsed light modes, using appropriate wavelength selection, and...
administration of specific cold or cryotherapy prior to laser therapy treatment.

Heat can be generated when light is absorbed by water or chromophores such as melanin - the predominant chromophore in skin. At the extreme, the high relative absorption by water, as with a carbon dioxide laser, which uses a light wavelength of 10,600 nm, results in flash boiling with tissue ablation, which is useful for surgical purposes. For photobiomodulation purposes, it is more desirable to consider wavelengths with characteristic minimal absorption of water and/or melanin, so there are both a reduction in heat generation and a greater depth of penetration at the high-power settings needed to reach deep tissue pathologies.\(^5,11-13\) The 810-830 nm wavelength has the lowest absorption of water of commonly used PBMT wavelengths\(^14\) (Figure S1,\(^15,16\) Supplementary file 1).

**Depth of Penetration**

Along the path of light from the source to the target pathologic tissue, there is at first higher absorption by melanin pigments in the skin, which is subtracted from deep tissue photobiomodulation delivery. Melanin represents a group of pigments in the skin that absorbs and reflects light and may be the most significant initial barrier to consider with respect to the depth of tissue photobiomodulation. Depending on the wavelength used, the upfront heat generated from absorption by melanin may be a dominant factor limiting the upper maximal limit of tolerable power intensity, particularly in darker pigmented individuals. The 1064 nm wavelength is distinguished as the longest wavelength that is routinely used.\(^17\) Eumelanin is the predominant melanin, and most significantly, 830 nm light is absorbed by eumelanin, but 1064 nm light is not.\(^5\) Accordingly, the initial melanin-generated heat produced with typical PBMT is no longer a concern with 1064 nm.

Sharma et al performed a comparative wavelength study of utility in photoacoustic imaging analysis, a rapidly emerging field of expanding utility that relies on the conversion of light energy to sound energy as first discovered by Alexander Graham Bell.\(^18\) The depth of penetration studies determined that the greatest depths of penetration were achieved by the 1064 nm laser with maximum permissible power settings as compared to 532 nm or 800 nm.\(^3\)

Basic research by Marshall and Vlkova compared the depth of penetration for commonly used PBMT wavelengths.\(^5\) First, they performed a literature-based analysis of reflection, refractive indices (scattering), absorption by water, and absorption by melanin with respect to commonly used wavelengths in PBMT. The researchers pointed out that the refraction index is 3x less for 1064 nm (1.5 cm\(^{-1}\)) light than for 810 nm (4.6 cm\(^{-1}\)) light and that general reflection, scattering, and absorption by melanin for wavelengths above 1000 nm are uniformly lower, while the 810 nm wavelength is the least absorbed by water. In subsequent experiments, investigators measured the depth of penetration through agarose-based tissue-mimicking media.\(^19\) Significantly, at high powers, the investigators determined that the relative energy detectable at 6.2 mm depths was the highest for 1064 nm (47%), followed by simultaneous 810 nm with 970 nm irradiation (37%), and lastly 810 nm (26%).\(^5\) The investigators concluded that wavelengths above 1000 nm have negligible absorption and reflection by melanin and that the 1064 nm wavelength has deeper penetration than 810 nm and 970 nm.

**Meta-analysis**

Understanding the clinical biophysics of 1064 nm HPL-PBMT is complicated, but ultimately what matters the most is to determine the optimal laser settings that provide the best clinical outcomes for specific indications. Towards this end, we performed a meta-analysis of all published clinical trials using high-powered 1064 nm wavelength-emitting lasers that was limited to published studies reported within the past 5 years of clinical trials.

**Methods**

**Search for Evidence and Article Selection**

This study conforms to all PRISMA guidelines and reports the required information accordingly. We performed a systematic review of the best evidence using Cochrane guidelines. Our structured question for this review was as follows in Figure 1. We searched the most important and appropriate electronic medical databases including PubMed, Cochrane library, and Google Scholar. We searched for the word “photobiomodulation” restricted to the years 2016-2021. The articles that were deemed to be irrelevant to the research objectives were excluded. After

![Figure 1. Search Results and Article Selection.](coverage.png)
collecting the full texts of articles which were related to the objectives of this study, the references of these articles were reviewed. The related references were identified, and their full texts were reviewed.

**Inclusion and Exclusion Criteria**

The inclusion criteria were (1) clinical trials, (2) use of high-powered lasers with power settings $>$ 0.5 W, (3) patients with a medical diagnosis, (4) comparison of high-powered lasers versus LLLT or placebo lasers or common backgrounds, and (5) use of outcome measures such as pain, range of motion (ROM), quality of life, cartilage thickness, disability indices, bone density, or gait. The exclusion criteria included (1) fundamental research or studies on animals, (2) controlled trials involving patients without a medical diagnosis, (3) review articles, (4) articles which did not have related statistical and clinical data.

**Statistical Analysis**

The significance level was set at $P < 0.05$. A statistical method was designed to measure the effect size specifically attributable to 1064 nm HPL-PBMT as compared to a common background. Cohen’s $d$ formula was used for the calculation of the effect size (ES). The standardized mean of group assessments made before and after treatment was divided by the pooled standard deviation.

$$ES = \frac{M \text{ time zero} - M \text{ follow up}}{SD \text{ pooled}}$$

The difference of effect sizes between two separate groups ($\pm$ 1064 nm HPL-PBMT) was calculated via the subtraction of the ES for each group as a metric for determining the relative efficacy specifically attributable to 1064 nm HPL-PBMT.

**Difference in effect size** = $ES_1 - ES_2$.

Interpretation was based on the values established by Cohen: small effect $\leq 0.2$, medium effect 0.2-0.8, and large effect $> 0.8$.

**Results**

The 22 studies meeting the criteria to be included in this meta-analysis have evaluated a variety of outcome measures including changes in pain, function, quality of life, ROM, and strength as well as anatomical structures (Table 1; see online Supplementary file 2, Table S1). Seven of the studies were double-blinded controlled trials. Thirteen of the studies were single-blinded controlled trials involving blinding either the practitioner or the assessor. No adverse events were reported in any studies except for one study involving patients diagnosed with hemophilic arthropathy, in which one patient experienced paresthesia at the application site and three others had nondescript adverse events, none of which were serious.

In all of these studies except one, statistically significant improvements were observed in one or more of these areas when comparing baseline measures to data collected at the end of treatment, with the probability value set at the standard $P < 0.05$. Twenty of the studies used pain as one of the outcome measures, with 19 studies using the visual analog scale (VAS) and one using the Present Pain Intensity Scale. 18 studies showed a statistically significant decrease in pain when comparing the baseline and after-treatment measures within the 1064 nm HPL-PBMT groups. Fourteen of those twenty studies also showed a statistically significant difference when they were compared (1064 nm HPL-PBMT vs control).

From those 20 studies, 13 examined long-term effects, lasting from 4 to 12 weeks after treatment. In 9 of those 13 studies, data showed that the statistically significant decreases in pain measures were still present in the 1064 nm HPL-PBMT groups. Similar data are found in a majority of the studies when considering other outcome measures. A considerable number of studies focused on the knee and spinal cord (6 each, 12 total), while 3 studies focused on the foot and 3 on the shoulder/arm for 18 controlled trial studies. The four remaining studies did not focus on musculoskeletal disorders: two wounds, one bone, and one primary dysmenorrhea. The greatest categorically favorable pain reduction responses were observed with the treatment of knee pathologies (see online Supplementary file 2, Table S1). One 2020 knee osteoarthritis study included measures of changes in knee cartilage from 3 different ultrasound aspects at 6 weeks after the cessation of treatment. High-powered 1064 nm PBMT caused a medium-to-large effect size when looking at changes in cartilage thickness from all three aspects, given that Cohen’s $|d| < 0.2$ = small effect, $0.2 < |d| < 0.8$ = medium effect, and $|d| > 0.8$ = large effect.

ROM consistently increased in all 9 studies after treatment with 1064 nm HPL-PBMT. These included two studies focused on knee arthritis, five on various spinal diagnoses (lower back pain, herniation, cervical spondylosis, neck pain, lumbar disc protrusion), and two on shoulder/arm-related subacromial impingement syndrome.

Additional promising results showed significant improvement in various functional measures. The studies that did employ one or more measures of function used such scales as the European Quality of Life Survey (EuroQoL), the Oswestry Disability Index (ODI), the Neck Disability Index (NDI), the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the Quality of Life - Short Form 36 (SF-36) and the GAITRite System, among others. The various scales and indices were found to be valid and reliable in all studies. Some of the scales
take into account various aspects of general functioning such as mobility, self-care skills, common daily activities, pain, anxiety, and social functioning. The ODI and NDI look at functional disability levels related to pain, whereas the WOMAC looks at not only functional activities, such as using stairs, rising from sitting, standing, bending, walking, getting into and out of a car, and putting on and taking off socks, but also pain and stiffness. The

Table 1. Clinical Trial Studies Selected for Meta-analysis of 1064 nm Wavelength PBMT

| Categorical Reference | Groups | Laser Power (Watt, J/cm²) or Description | Treatment & Follow-up | PEDro Score | Outcome |
|-----------------------|--------|-----------------------------------------|-----------------------|-------------|---------|
| Knee osteoarthritis 33074393; 2020 | laser + ET n = 20 sham laser + ET n = 20 (double-blinded) | Analgesic: 12 W, 25 J/cm² for 3000 J; Biomodulatory: 12 W, 120 J/cm² for 3000 J | Treatment: 5 x/wk 2 wk Follow-up: EOT, 6 wk | 7 | Pain reduced (VAS & WOMAC) ROM increased Femoral cartilage thickness increased |
| Knee osteoarthritis 30178432; 2019 | laser n = 30 ET n = 30 CPT n = 30 (single-blinded) | 5W, 30Hz, 70% duty, 60 J/cm², 2400 J | Treatment: 3x/wk 12 wk Follow-up: EOT, 12 wk | 6 | Pain reduced Stiffness in knee reduced (WOMAC stiffness) ROM increased |
| Juvenile rheumatoid arthritis 30016193; 2018 | laser + ET n = 15 sham laser + ET n = 15 (double-blinded) | 3 kW peak power, 10.5 W average, 120-150 µs, 20-30 Hz, 10 J/cm², 60 cm² spot size, 15) per point to point points, 1500 total 8 m/s/session | Treatment: 3x/wk 4wk Follow-up: EOT, 12wk | 5 | Pain reduced Gate improved (GAITrite) |
| Knee Osteoarthritis 28078503; 2017 | laser + GCS + ET n = 23 GCS + ET n = 22 ET n = 22 (single-blinded) | Power level not described, 610 mJ/cm², 750 [knee total to both knees 8m/session | Treatment: 3/wk 12 wk Follow-up: EOT | 6 | Pain reduced Gate improved |
Table 1. Continued

| Categorical | Diagnosis Reference | Groups | 1064 nm Laser Session | Treatment & Follow-up | PEDro Score | Outcome |
|-------------|---------------------|--------|-----------------------|-----------------------|-------------|---------|
| Subacromial Impingement Syndrome | 334000012; 2021 | laser + exercise n = 32 | sham laser + exercise n = 31 (double-blinded) | 3 kW peak power, 360-1780 mJ/cm², 40 Hz, 2781 J total | Treatment: 5x/wk | 3wk | Follow-up: EOT, 12 wk | 8 | Pain reduced | ROM increased | Strength increased | Daily activity increased |
| | | | | 25 m/session | | |
| Shoulder Arm | Laser + MT + KT + EX n = 19 | ET n = 15 | KT + EX n = 20 | MT + KT + EX n = 16 (single-blinded) | 3 kW peak power; 5 mm spot diameter; 3 s phases: fast manual scanning 100 cm²/30s of the zones of muscular contracture, particularly trapezius, supraspinatus, and deltoid during shoulder abduction, for 1000 J/cm², 2nd phase 50 J to each of 4 trigger points; final phase with slow manual scanning 100 cm²/60 s to same first phase areas for 100 J total - 510, 610, and 710 mJ/cm² for a total of 2050 J. 30 m/session. | Treatment: 3x/15d | Follow-up: EOT | 6 | Pain reduced | (SPALDI) | Disability reduced | ROM increased |
| | Lateral epicondylitis | 29900938; 2016 | laser n = 31 | bandage n = 34 (double-blinded) | 75 s at 4 W for 6 J/cm² | Analgesic: targeting painful areas 4 sessions. Bistimulatory: 6x sessions 6 W 100-150 J/cm² 12 m/session | Treatment: 5x/wk | 2wk | Follow-up: 6 wk | 5 | Pain reduced, disability reduced, hand strength increased, and QoL improved |
| Foot | Calcaneal spur | 31478095; 2020 | laser + ET n = 21 | sham laser + ET n = 21 (double-blinded) | 3 kW peak power, 360-1780 mJ/cm², 150 ps, 10.5 W average power, 10-40 Hz, 0.2 cm² spot size, 1281 J total, 10 m/session. | Laser: 3x analgesic: 8 W, 75 s at 4 W for 6 J/cm² | Pain reduced, disability reduced, hand strength increased, and QoL improved |
| | | | | | Pain reduced, disability reduced, hand strength increased, and QoL improved |
| | Plantar fasciitis | 32513018; 2020 | laser n = 51 | LLLT n = 51 (single-blinded) | laser: 12 W, 120 J/cm², 3000 J total, 25 cm² spot, 7m/session | LLLT: 785 nm, 50 mW, 50-60 Hz, 4 J/cm², 140 J total, 35 cm² spot, 7 m/session | Treatment: 3x/wk | 8x 3wk | Follow-up: EOT, 4 wk | 8 | Improved pedographic measures |
| | Plantar fasciitis | 29627888; 2018 | laser n = 35 | LLLT n = 35 (single-blinded) | laser: 3x analgesic: 8 W, 75 s, 6 J/cm², 150 J total; 6x bio-stimulation: 30s, 6 W, 150 J/cm² dose LLLT: 904 nm, 240 mW, 5000 Hz, 0.16 W/cm², 160 s per session, 680 J total | Laser more effective than LLLT in the opinion of participants |
| Wound | Caesarian healing in diabetic women | 29706708; 2018 | laser n = 20 | sham laser n = 20 | 10.5 W, 0.5-1.8 J/cm², 10-40 Hz, 150 µs pulses 10-40 Hz, 150 J first phase, then 1 cm away from wound 20 J per each of 12 points, last phase same as first, but slow scanning | Treatment: 3x/wk | 6wk | Follow-up: EOT | 5 | Wound appearance improved |
| | Post-burn pruritus | 28233017; 2017 | laser n = 25 | sham laser n = 24 (double-blinded) | 3k W peak power, 0.5-1.8 J/cm², 150 µs pulses 10-15 Hz, 0.2 cm² spot size, 3000 J | Treatments per cycle for 3 cycles (3 mon) Follow-up: EOT, 12 wk | 10 | Itch severity reduced QoL improved Pain reduced (VAS) |
| Gynecological | Primary dysmenorrhea | 29184281; 2017 | laser n = 26 | PENF n = 26 (double-blinded) | 3 kW peak power, 810-1780 mJ/cm², 150 µs, 10-40 Hz, 880 J total | 3 treatments per cycle for 3 cycles (3 mon) Follow-up: EOT | 4 | Pain reduced Prostaglandins reduced |
| Bone | Osteoporosis & osteopenia by DEXA scan | 29068756; 2018 | laser + ET n = 25 | sham laser + exercise n = 25 | 10.5 W, 510-1780 mJ/cm², 150 µs pulses 10-30 Hz, spot size 0.2 cm², 3,000 J delivered 2x phases: fast scanning at 510, 610, and 710 mJ/cm² for 1500 J, then slow scanning 18 m/session | Treatment: 3x/wk | 24 wk | Follow-up: EOT, 1 yr | 2 | Lumbar bone mineral density improved |

GAITRite looks at functional gait parameters in an objective, quantifiable way. Of the 22 studies in this meta-analysis, 18 used some sort of functional outcome measure at baseline, at the end of treatment, and at long-term follow-up, which included 12 of the studies. All 18 studies showed statistically significant improvement in the various functional measures utilized when comparing baseline values to values at the end of treatment within HPL-PBMT groups, and the 12 studies with long-term follow-up continued to exhibit statistically significant improvement in function within the 1064 nm HPL-PBMT groups. When comparing results between 1064 nm HPL-PBMT and control groups, the positive trends continued for the most part. Of the 18 studies using a...
functional outcome measure, the 1064 nm HPL-PBMT
groups showed statistically significant improvement in
function when compared to the control groups in 15 of
those studies. Ten out of the 12 studies that looked at
long-term follow-up found those differences continued
with the 1064 nm HPL-PBMT groups outperforming the
control groups.

The three studies comparing high-powered 1064 nm to
lower-powered PBMT indicated that PBMT of a higher
power was required to achieve effectiveness. In one trial
involving patients with plantar fasciitis (PF), those treated
with 1064 nm high-powered PBMT exhibited better
outcomes than those treated with low-powered PBMT.4,38
Another study involving PF patients did not result in any
improvements after high- or low-powered PBMT.49 The
PF studies may be limited by the ability to identify the
target site to aim at the laser given that PF pain has the
potential to be referred to as neuronal pain.50 The third
study comparing high-powered 1064 nm PBMT to low-
powered PBMT showed benefits for both approaches in
the treatment of chronic lower back pain.46

Assessments performed after the cessation of treatment
helped determine whether the benefits were sustaining
and not merely transient effects. Fourteen studies
performed follow-up assessments ranging from 1 to
12 months. All five studies focused on knee arthritis
demonstrated a sustained reduction in pain with a large
effect, and follow-ups were performed for 6 weeks to 3
mos.24,26,31,33,34 One knee arthritis study detected increased
knee cartilage thickness with a large effect detectable 6
weeks after the cessation of treatment that was initially
performed for 3 weeks.24 Three spine-related diagnoses
had follow-up assessments.29,37,41 A large positive effect
was observed for the treatment of cervical spondylolisthesis
or lumbar disc protrusion, both 1 month after the cessation
of treatment, while no significant benefit was observed
for the treatment of lower lumbar disc degeneration.
No sustained benefit was observed with foot-related
treatments, calcaneal spur or PF after follow-up.

**Discussion**

Our systematic meta-analysis method is largely based on,
supported by, and confirmed by a previous meta-analysis
that focused on the beneficial effects of high-powered
laser photobiomodulation therapy on musculoskeletal
pain.5 In the previous analysis, investigators concluded
that HPL-PBMT can be an effective approach to pain
management. We also reached this conclusion and
extended these studies further by including newer
publications and focusing primarily on the determination
of the range and extent of any indications that responded
favorably to treatments using specifically the 1064 nm
wavelength of HPL-PBMT.

Of all anatomical musculoskeletal categories, the largest
amount of data obtained in our study involved the knee
(6 studies). Reductions in pain, increases in ROM, and
increased functionality were consistently observed. The
data conclusively support that HPL-PBMT with 1064
nm treatment can be highly efficacious in the reduction
of pain in knee arthritis with the potential for increasing
ROM, quality of life, and even cartilage growth.

The two trials which assessed cartilage thickness after
1064 nm HPL-PBMT were particularly impressive since
there are few, if any, known treatments that have been
able to demonstrably increase knee cartilage thickness.24,35
One trial did not detect significant changes in cartilage
thickness after performing treatments twice per week for 6
weeks; however, another trial that involved more frequent
daily treatments for just 2 weeks resulted in significantly
detectable increases in cartilage thickness, which was
detectable even 6 weeks after the cessation of treatment.
More studies are needed to determine the extent to
which high-powered PBMT is capable of increasing joint
cartilage thickness.

The large effect size seen repeatedly when treating
knee anatomicies may be in part due to the shorter depth
of light penetration that is required to reach pathologic
tissues in the knee. By contrast, anatomicies with greater
potential for referred nerve pain, including PF and spinal
diagnoses analyzed within this study, appear to be more
challenging to treat based on our analysis of the effect size
and under the particular 1064 nm HPL-PBMT treatment
settings that were used. Lumbar discs are chronically
weightbearing and no therapeutic benefit was seen after
the treatment of lumbar disc degenerative disease.37

Importantly, the improved outcome results observed
months after the cessation of treatment in multiple studies
with large effect sizes indicate that 1064 nm HPL-PBMT
can effectively stimulate healing beyond merely providing
transient symptomatic relief. Treatment reduced pain in
knee (5 studies), spine (2), and shoulder/arm (1) studies
and also stimulated increases in knee cartilage thickness,
improved quality of life, and improved functional
outcomes in assessments performed for times ranging
from 6 weeks to 3 months after the end of treatment.

This meta-analysis also confirms that 1064 nm HPL-
PBMT is also highly effective in promoting wound
healing.28,41 Significantly, wound healing is distinguished
as one of the simplest and unequivocal measurable PBMT
outcomes. Similar to wound healing, the effectiveness of
treating oral mucositis with PBMT is indiscernible, with
easily measurable outcomes and unequivocally positive
results. Oral mucositis routinely occurs in patients
undergoing hematopoietic stem cell transplantation or
radiotherapy ± chemotherapy and can cause extensive
pain and suffering. Photobiomodulation has proven to
be an effective drug-free treatment for cancer patients
undergoing the standard of care treatments.64

Owing in part to the clearly positive and reproducible
therapeutic results of PBMT, the prevention or treatment
of oral mucositis with PBMT is now the most universally accepted, recognized, and established guideline-directed PBMT-utilizing approach in photomedicine and is commonly covered by insurers.45, 46 Effective oral mucositis photobiomodulation is routinely performed with low-level light ≤ 100 mW because a negligible depth of tissue penetration is required to reach the targeted superficial highly-regenerating and circulating cells of the oral cavity.

By contrast, higher laser power settings are required to reach deeper tissue pathologies, and therefore, the outcome measures for the treatment of musculoskeletal disorders may not be as clear as those observed with overt oral mucositis outcomes. Studies examining low-powered PBMT have commonly led to inconsistent or negative outcomes when indications involve deeper tissue pathologies that absolutely require higher-powered lasers for the light to reach the target pathological tissues. This has an adverse effect on the field of medical PBMT and threatens to cause medical researchers to miss the identification of indications that are in fact highly responsive to the administration of high-powered photobiomodulation.

Safety Profile
In the twenty-two studies examined, 1064 nm HPL-PBMT caused no serious adverse events, and no significantly negative effects were observed across all outcome measures (Table S1). It is also impressive that there were no significantly negative effects observed after all of our measures, which is consistent with previous early analysis examining musculoskeletal pain.7 This demonstrates and supports the exceptional safety profile of high-powered photobiomodulation as a therapeutic approach.

Onychomycosis or tinea unguium – a fungal infection of the toenail
There was one 1064 nm HPL-PBMT study of note that did fulfill the criteria for inclusion in our meta-analysis, but that described the successful treatment of localized infectious disease. Onychomycosis is a common fungal toenail infection that can progress to an inability to walk or stand without disabling pain. Researchers reported that 1064 nm HPL-PBMT cured 11% of 56 patients with onychomycosis as compared to 21% cured when antifungal was used in combination with topical antifungal medication.47 The study did not meet the selection criteria for inclusion in our meta-analysis because it was an uncontrolled retrospective study. Nonetheless, the results support that more clinical trials are justified for consideration of the use of HPL-PBMT as a therapeutic approach, especially in the treatment of anatomically localized disease. Weber et al. pointed out that the approach is likely to be most useful for treating patients that are unable to tolerate systemic antifungals.

Table 2. Most Responsive Indications Limited to Studies With a Follow-up (Not Just End of Trial Assessment) and Prioritized From Top to Bottom Based on the Largest to Smallest Cohen’s d Effect Size

| Diagnosis                          | Laser Type | Power Settings          |
|-----------------------------------|------------|-------------------------|
| Knee arthritis4, 26, 32–34         | Nd:Yag     | 12 W average / 3 kW peak|
| Wound28, 31                        | Nd:Yag     | 10.5 W average / 3 kW peak|
| Spine29, 41 (cervical spondylosis, lumbar disc protrusion) | Nd:Yag | 12 W average / 3 kW peak|

Treatment Sites
One possible limitation of deep tissue HPL-PBMT studies is the challenge of properly aiming the laser given the potential for nerve-referred pain that is actually caused by distal pathologies. Missing the target pathology may be less likely to happen for the contained anatomy of the knee or toe (onychomycosis), so this may be part of the reason that knee outcomes are so universally positive in this analysis. By contrast, the less reproducibly positive outcomes observed involving the spine or PF foot pain may be improved with an appropriate aiming laser by the hands of a skilled and knowledgeable practitioner.

Multiple Applications
Our meta-analysis concludes that all three diagnoses listed in Table 2 can be effectively treated with high-powered 1064 nm PBMT to provide therapeutic benefits: knee arthritis, wound healing, and spinal disorders. High-powered 1064 nm PBMT had a large positive effect on all three conditions after follow-up assessment (Table 2). Treatment of chronic neck pain and non-specific lower back pain also resulted in a large reduction in pain, but assessment in these studies was limited because the assessment was only done at the end of treatment. Based on the analysis, the data predict that all of these spinal disorders can benefit from high-powered 1064 nm HPL-PBMT, but more clinical validation is needed to achieve recognition and acceptance by third party payors.

Conclusion
Our meta-analysis strongly supports that 1064 nm HPL-PBMT is a safe, tolerable, effective, and long-lasting therapeutic approach for the management of musculoskeletal pain. A specific application for the knee stood out with PBMT being extremely effective. Further clinical trials using high-power 1064 nm PBMT settings with continuous mode or pulse settings are needed to provide greater clinical validation of beneficially responsive non-superficial deeper tissue indications to achieve greater consensus and improved outcomes.

Ethical Considerations
Not applicable.

Conflict of Interests
CEV is the CEO of Aspen Laser with patent and pending patents.
Supplementary Materials

Supplementary file 1 contains Figure S1.
Supplementary file 2 contains Table S1.

References

1. Dompe C, Moncrieff L, Matys J, Grzech-Les niak K, Kocherova I, Bryja A, et al. Photobiomodulation-Underlying Mechanism and Clinical Applications. J Clin Med. 2020;9(6):1724. doi:10.3390/jcm9061724.

2. Salehpour F, Majdi A, Pazhuhi M, Ghasemi F, Khademí M, Pashazadeh F, et al. Transcranial Photobiomodulation Improves Cognitive Performance in Young Healthy Adults: A Systematic Review and Meta-Analysis. Photobiodermal Photomed Laser Surg. 2019;37(10):635-643. doi:10.1089/photob.2019.4673

3. Sharma AS, Srishiti, Periyasamy V, Pramanik M. Photoacoustic imaging depth comparison at 532-, 880-, and 1064- nm wavelengths: Monte Carlo simulation and experimental validation. J Biomed Optics. 2019;24(12):121904. doi:10.1117/1.JBO.24.12.121904.

4. Sommer AP, Schemper P, Pavlath AE, Försterling H-D, Mester AR, Trelles MA. Quantum biology of low level light therapy: death of a dogma. Ann Transl Med. 2020;8(7):440. doi:10.21037/atm.2020.03.159

5. Marshall RP, Vlkova K. Spectral Dependence of Laser Light on Light tissue Interactions and its Influence on Laser Therapy: An Experimental Study. Insights Biomed. 2020;5(1):1-4. doi:10.36648/2572-5610.4.4.66

6. Pruitt T, Parvez H, Wang X, Liu H. Investigation of 1064-nm Laser Fluence Within Tissue Phantoms for Better Prediction of Transcranial Photobiomodulation Depth. 2020. Paper presented at: Optical Tomography and Spectroscopy: 2020 Apr 20. Optical Society of America, doi:10.1364/TRANSLATIONAL.2020.JW3.A.29

7. Kaydok E, Orduhan B, Solum S, Karahan AY. Short-term Efficacy Comparison of High-intensity and Low-intensity Laser Therapy in the Treatment of Lateral Epicondylitis: A Randomized Double-blind Clinical Study. Arch Rheumatol. 2020;35(1):60-67. doi:10.5606/AchRheumatol.2020.7347

8. Orduhan B, Karahan AY, Kaydok E. The effect of high-intensity versus low-level laser therapy in the management of plantar fasciitis: a randomized clinical trial. Lasers Med Sci. 2018;33(6):1363-1369. doi:10.1007/s10103-018-2497-6

9. Ezzati K, Laasko E-L, Saberi A, Youssefzadeh Chabok S, Nasiri E, Bakhshayesh Eghbali B. A comparative study of the dose-dependent effects of low level and high intensity photobiomodulation (laser) therapy on pain and electrophysiological parameters in patients with carpal tunnel syndrome: a randomized controlled trial. Eur J Phys Rehabil Med. 2020; 56(6):733-740. doi:10.23736/S1973-9087.19.05835-0

10. Henderson TA, Morries LD. Near-infrared photonic energy penetration: can infrared phototherapy effectively reach the human brain? Neuropsychiatr Dis Treat. 2015;11:2191-2208. doi:10.2147/NIDT.S78182

11. Simpson CR, Kohl M, Essenpreis M, Cope M. Near-infrared optical properties of ex vivo human skin and subcutaneous tissues measured using the Monte Carlo inversion technique. Phys Med Biol. 1998;43(9):2465-2478. doi:10.1088/0031-9155/43/9/003

12. Esnouf A, Wright PA, Moore JC, Ahmed S. Depth of penetration of an 850 nm wavelength low level laser in human skin. Acupunct Electrother Res. 2007;32(1-2):81-86. doi:10.3727/0360129077815844165

13. Calderhead RG. Photobiological Basics of Photostimulation and Phototherapy. HA NMI Medical Publishing; 2011.

14. Toselli F, Bodechtel J, eds. Imaging Spectroscopy: Fundamentals and Prospective Applications. Springer Netherlands; 1992.

15. Splinter R, Hooper BA, Hooper BA. An Introduction to Biomedical Optics. CRC Press; 2006. doi:10.1201/9781420011838

16. Wang P, Li T. Which wavelength is optimal for transcranial low-level laser stimulation? J Biophotonics. 2019;12(2): e201800173. doi:10.1002/jbio.201800173

17. Steinberg I, Huland DM, Vermesh O, Frostig HE, Tummers WS, Gambhir SS. Photoacoustic clinical imaging. Photoacoustics. 2019;14:77-98. doi:10.1016/j.pacs.2019.05.001

18. Mustari A, Nishidate I, Wares MdA, et al. Agarose-based Tissue Mimicking Optical Phantoms for Diffuse Reflectance Spectroscopy. J Vis Exp. 2018;(138):57578. doi:10.3791/57578

19. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2nd edition. Routledge; 1988.

20. Brand A, Bradley MT, Best LA, Stoica G. Multiple trials may yield exaggerated effect size estimates. J Gen Psychol. 2011;138(1):1-11. doi:10.1080/00221309.2010.520360

21. Yilmaz M, Erogul S, Dundar U, Toktas H. The effectiveness of high-intensity laser therapy on pain, range of motion, functional capacity, quality of life, and muscle strength in subacromial impingement syndrome: a 3-month follow-up, double-blinded, randomized, placebo-controlled trial. Lasers Med Sci. 2021. doi:10.1007/s10103-020-03224-7

22. Yesil H, Dundar U, Toktas H, Eyvaz N, Yesil M. The effect of high intensity laser therapy in the management of painful calcaneal spur: a double blind, placebo-controlled study. Lasers Med Sci. 2020;35(4):841-852. doi:10.1007/s10103-019-02870-w

23. Akaltun MS, Altingdag O, Turan N, Gunsoy S, Gur A. Efficacy of high intensity laser therapy in knee osteoarthritis: a randomized controlled study. Clin Rheumatol. 2020; 40(5):1989-1995. doi:10.1007/s10067-020-05469-7

24. Thabet AAE-M, Elsodany AM, Battecha KH, Alshehri MA, Refaat B. High-intensity laser therapy versus pulsed electromagnetic field in the treatment of primary...
26. El-Shamy SM, Alayat MSM, Abdelgailil AA, Alshehri MA. Long-Term Effect of Pulsed Nd:YAG Laser in the Treatment of Children with Juvenile Rheumatoid Arthritis: A Randomized Controlled Trial. *Photomed Laser Surg.* 2018;36(8):445-451. doi:10.1089/pho.2018.4444

27. Alayat MS, Mohamed AA, Helal OF, Khaled OA. Efficacy of high-intensity laser therapy in the treatment of chronic neck pain: a randomized double-blind placebo-control trial. *Lasers Med Sci.* 2016;31(4):687-94. doi:10.1007/s10103-016-1910-2

28. Ebid AA, Ibrahim AR, Omar MT, El Baky AMA. Long-term effects of pulsed high-intensity laser therapy in the treatment of post-burn pruritus: a double-blind, placebo-controlled, randomized study. *Lasers Med Sci.* 2017;32(3):693-701. doi:10.1007/s10103-017-2172-3

29. Venosa M, Rominanili E, Padua R, Cerciello S. Comparison of high-intensity laser therapy and combination of ultrasound treatment and transcutaneous nerve stimulation in patients with cervical spondylosis: a randomized controlled trial. *Lasers Med Sci.* 2019;34(5):947-953. doi:10.1007/s10103-018-2682-7

30. Yilmaz M, Taraki D, Taraki E. Comparison of high-intensity laser therapy and combination of ultrasound treatment and transcutaneous nerve stimulation on cervical pain associated with cervical disc herniation: A randomized trial. *Complement Ther Med.* 2020;49:102295. doi:10.1016/j.ctim.2019.102295

31. Angelova A, Ilieva EM. Effectiveness of High Intensity Laser Therapy for Reduction of Pain in Knee Osteoarthritis. *Pain Res Manag.* 2016;2016:9163618. doi:10.1155/2016/9163618

32. El-Shamy SM, Abdelaal AAM. Efficacy of pulsed high-intensity laser therapy on pain, functional capacity, and gait in children with haemophilic arthropathy. *Disabil Rehabil.* 2018;40(4):462-468. doi:10.1080/09638288.2016.1261416

33. Alayat MSM, Aly THA, Elsayed AEM, Fadil ASM. Efficacy of pulsed Nd:YAG laser in the treatment of patients with knee osteoarthritis: a randomized controlled trial. *Lasers Med Sci.* 2017;32(3):503-511. doi:10.1007/s10103-017-2141-x

34. A Nazari A, Moezy A, Nejati P, Mazaherinejad A. Efficacy of high-intensity laser therapy in comparison with conventional physiotherapy and exercise therapy on pain and function of patients with knee osteoarthritis: A randomized controlled trial with 12-week follow up. *Lasers Med Sci.* 2019;34(3):505-516. doi:10.1007/s10103-018-2624-4

35. Salli A, Akkurt E, İzki AA, Şen Z, Yılmaz H. Comparison of High Intensity Laser and Epicondylitis Bandage in the Treatment of Lateral Epicondylitis. *Arch Rheumatol.* 2016;31(3):234-238. doi:10.5606/ArchRheumatol.2016.5793

36. Pekyavas NO, Baltaci G. Short-term effects of high-intensity laser therapy, manual therapy, and Kinesio taping in patients with subacromial impingement syndrome. *Lasers Med Sci.* 2016;31(6):1133-1141. doi:10.1007/s10103-016-1963-2

37. Taradaj J, Rajfur K, Shay B, Rajfur J, Ptaszkowski K, Walewicz K, et al. Photobiomodulation using high- or low-level laser irradiations in patients with lumbar disc degenerative changes: disappointing outcomes and remarks. *Clin Interv Aging.* 2018;13:1445-1455. doi:10.2147/CIA.S168094.

38. Abdelbasset WK, Nambi G, Alsubaia SF, Abodonya AM, Saleh AK, Ataalla NN, et al. A Randomized Comparative Study between High-Intensity and Low-Level Laser Therapy in the Treatment of Chronic Nonspecific Low Back Pain. *Evid Based Complement Alternat Med.* 2020;2020:1350281. doi:10.1155/2020/1350281.

39. Alayat MSM, Abdel-Kafy EM, Thabet AAM, Abdel-Malek AS, Ali TH, Header EA. Long-Term Effect of Pulsed Nd-YAG Laser Combined with Exercise on Bone Mineral Density in Men with Osteopenia or Osteoporosis: 1 Year of Follow-Up. *Photomed Laser Surg.* 2018;36(2):105-111. doi:10.1089/pho.2017.4328

40. Narusevicute D, Kubilius R. The effect of high-intensity versus low-level laser therapy in the management of plantar fasciitis: randomized participant blind controlled trial. *Clin Rehabil.* 2020;34(8):1072-108. doi:10.1177/0269215520929073

41. Chen L, Liu D, Zou L, Huang J, Chen J, Zou Y, et al. Efficacy of high intensity laser therapy in treatment of patients with lumbar disc protrusion: A randomized controlled trial. *J Back Musculoskelet Rehabil.* 2018;31(1):191-196. doi:10.3233/BMR-170793.

42. Alshami AM, Souvlis T, Coppieters MW. A review of plantar heel pain of neural origin: differential diagnosis and management. *Man Ther.* 2008;13(2):103-111. doi:10.1016/j.math.2007.01.014

43. Thabet AAE-M, Mahrán HG, Ebid AA, Alshehri MA. Effect of pulsed high intensity laser therapy on delayed caesarean section healing in diabetic women. *J Phys Ther Sci.* 2018;30(4):570-575. doi:10.1589/jpts.30.570

44. THOR Photomedicine Ltd. *Annette Quinn - Oral Mucositis Academy of Laser Dentistry* 2016. YouTube. Accessed April 16, 2021. [https://www.youtube.com/watch?v=xU5_9169dbw](https://www.youtube.com/watch?v=xU5_9169dbw)

45. Zadik Y, Arany PR, Fregnaní ER, Bossi P, Antunes HS, Bensadoun RJ, et al. Systematic review of photobiomodulation for the management of oral mucositis in cancer patients and clinical practice guidelines. *Support Care Cancer.* 2019;27(10):3969-3983. doi:10.1007/s00520-019-04890-2

46. Cold Laser and High-Power Laser Therapies - Medical Clinical Policy Bulletins | Aetna. Accessed October 14, 2020. [http://www.aetna.com/cpb/medical/data/300_399/0363.html](http://www.aetna.com/cpb/medical/data/300_399/0363.html)

47. Weber GC, Firouzi P, Baran AM, Bökülu E, Schrumpf H, Buhrner BA, et al. Treatment of onychomycosis using a 1064-nm diode laser with or without topical antifungal therapy: a single-center, retrospective analysis in 56 patients. *Eur J Med Res.* 2018;23(11):53. doi:10.1186/s40001-018-0340-y. doi:10.1186/s40001-018-0340-y