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Applications of Photobiomodulation Therapy to Musculoskeletal Disorders and Osteoarthritis with Particular Relevance to Canada

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Abstract

Background: Musculoskeletal disorders caused by osteoarthritis (MSDs/OA) are a growing problem in the modern industrialized society in Canada. Overall aging of the general population and a progressive lack of exercise contribute to this alarming increase. Moreover, a range of chronic conditions including cardiovascular and mental diseases show significantly higher comorbidity with MSDs/OA. Conventional medical treatment for MSDs/OA includes nonsteroidal anti-inflammatory drugs and opiate pain killers. These drugs have major drawbacks such as a relative lack of efficacy, potential for addiction, and even death (Vioxx scandal). Photobiomodulation (PBM) was discovered over 50 years ago but has still not attained widespread acceptance by the medical community. This is partly due to uncertainty about the precise molecular mechanisms of action and a bewildering array of different wavelengths and dosimetric parameters employed in reported studies.
Objective: The goal of this review was to survey literature reports of PBM, also known as low-level laser therapy used for treatment of MSDs/OA, concentrating on the growth over time, different wavelengths employed, and application to different joints.
Methods: We searched the PubMed database for publication of study on PBM to treat the most common joints.
Results: We show that the field of PBM to treat MSDs/OA is expanding exponentially over the past 20 years. A trend has emerged over time for more power to achieve better effective treatments, and the understanding of the physiological effect of safe parameters has improved. There is, however, no consensus on the best set of parameters to treat a specific patient indication.
Conclusions: Finally, we highlight gaps in our knowledge and the barriers to further clinical trials. We suggest that the growing body of evidence indicating efficacy, and the almost total lack of side effects, should encourage continued clinical research to support clinical applications where better rehabilitation treatments are much needed.

Keywords: literature search, Canada, arthritis, photobiomodulation

Introduction

Musculoskeletal disorders caused by osteoarthritis

MUSCULOSKELETAL DISORDERS CAUSED by osteoarthritis (MSDs/OA) represent growing problems for the public health of our modern industrial society. Possible factors responsible for this increasing trend include increasing sedentary lifestyles, high incidence of obesity, and an overall increase in the aging of the population. MSDs/OA involve damage or disease that affects structural tissues, such as cartilage, ligaments, tendons, muscles, nerves, bones, and blood vessels. Common MSDs/OA conditions encompass the following indications: carpal tunnel syndrome, tendonitis, tendinosis, muscle strain, subacromial impingement syndrome (shoulder), epicondylitis (elbow), hip, knee OA, degenerative spinal disc disease, and a number of other embodiments of arthritis.

To illustrate the steadily increasing interest in MSDs within the medical community, Fig. 1 shows a graph of the growing number of MSDs publications cited in PubMed,

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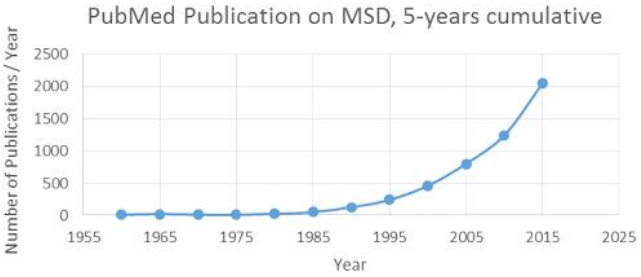

FIG. 1. Number of PubMed publications on MSDs in 5-year periods between 1960 and 2015. MSDs, musculoskeletal disorders.

from 1960 until 2015, in 5-year cumulative segments. A marked increase started to become apparent around 1990, correlating with increasing sedentary lifestyle and a rising demographic (the proportion of the baby boomer generation) reaching retirement age.[1] Figure 2 shows the increasing fraction of the Canadian population older than 65 years and the corresponding decrease in the population of children (0–14 years of age) from 1970 to 2030.

Cost of MSDs/OA in Canada is approximately $10 billion and rising

Over the past three decades, the increasing sedentary lifestyle is believed to explain why MSDs/OA now affects an increasingly younger population. With more people affected by MSDs/OA, and the overall increase in the aging population, the cost for treating MSDs in Canada is ~$10 billion,[2,3] and it continues to increase partly due to health care costs associated with drugs and orthopedic implants.

Pharmacological treatment of MSDs/OA and the problem with drugs

The mainstay of pharmaceutical treatment for pain in MSDs/OA has been nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs inhibit cyclooxygenase (also known as prostaglandin-endoperoxide synthase), an enzyme involved in arachidonic acid metabolism leading to the production of prostaglandins. The cyclooxygenase enzyme has two isoforms, COX1 and COX2. COX1 is involved in the protection of the stomach lining, whereas COX2 is more involved in triggering pain and inflammation.

NSAIDs are divided into two classes: nonspecific NSAIDs that inhibit both COX1 and COX2 (diclofenac, ibuprofen, naproxen, and aspirin), whereas there are also COX2-specific NSAIDs [celecoxib (Celebrex), valdecoxib (Bextra), and etoricoxib (Arcoxia)]. There was another COX2 inhibitor on the market called rofecoxib (Vioxx), but in 2004, it was pulled from the market by Merck amid lawsuits and implicated in causing between 88,000 and 139,000 heart attacks, 30–40% of which were fatal.[4] The total settlement costs were in excess of $5 billion. The so-called ''Vioxx scandal'' has tainted the whole subject of NSAIDs as therapeutic agents.[5] The Food and Drug Administration has since grouped all NSAIDs into a single class with similar warnings regarding skin, cardiovascular, renal, and gastrointestinal side effects.

The growing reluctance to prescribe NSAIDs has recently led to a corresponding growing tendency to prescribe opioid painkillers instead.[6] However, as it is now well known that there is a growing epidemic of deaths due to opioid overdoses, many of which started off with patients receiving legally prescribed opiate medications for painful conditions including MSDs/OA.[7]

Comorbidity correlation and the existence of a common pathway between cardiovascular disease and OA

The Australian Institute of Health and Welfare (AIHW) completed a report on arthritis and comorbidities.[8] A number of comorbid chronic conditions were observed in people with arthritis, including cardiovascular disease (CVD), back problems, mental health problems, asthma, diabetes, chronic

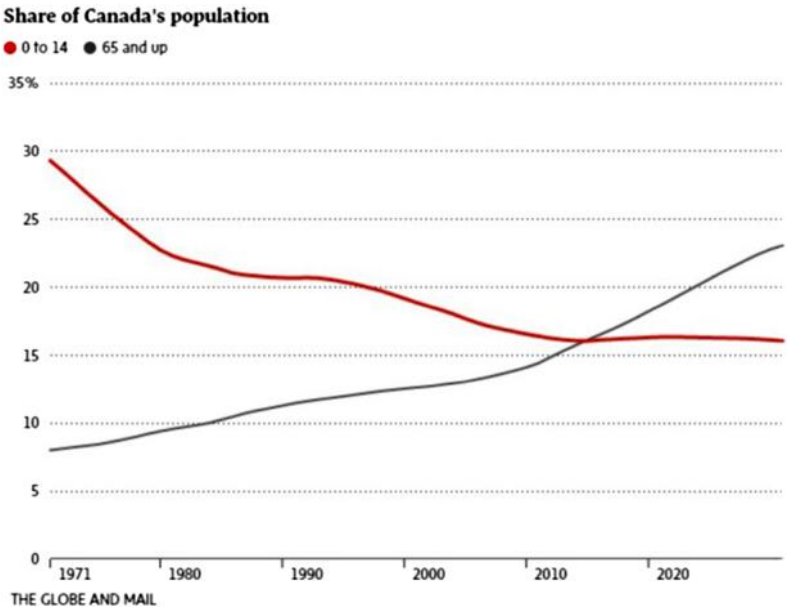

FIG. 2. Growth of senior population in Canada and corresponding decrease in children. Credit: The Globe and Mail, 2015. License #23506 granted.

obstructive pulmonary disease, and cancer, as shown in Fig. 3. Among these comorbid conditions, CVD dominates in general, but mental health dominates in the population aged 0–44 years. The study also observed that the trend of CVD is increasingly deteriorating for the younger population, which also correlates with higher occurrence of obesity.

The causal mechanisms at a cellular or molecular level that link OA and CVD are yet to be clearly established. For example, a meta-analysis by Wang et al.[9] observed that the statistical probability of CVD was significantly increased by 24% ($p<0.001$) in patients with OA compared with the general population. Although they stated that the underlying mechanisms behind the observed association between OA and CVD risks are not known, their meta-analysis suggested that there is strong evidence that OA is a significant risk factor for CVD. The study from the AIHW simply establishes a comorbidity between CVD and arthritis. However, Fernandes and Valdes[10] on common pathways for these diseases, in part inspired by the work of Rahman,[11,12] concluded that ''the data available to date also indicate that OA may be considered as an indirect cause of CVD by increasing walking disability and the use of analgesic medication such as NSAIDs.''

However, it is possible that there may exist a common pathophysiological mechanism leading to the development of both CVD and OA. This is based on the accumulation of age-related changes causing deregulation in pathways concerned with inflammation, cellular survival, and homeostasis. Endothelial dysfunction leads to stiffening and thickening of the arterial wall and an increased systolic blood pressure (hypertension). This leads to fibroblast proliferation, cardiac hypertrophy, decreased cardiac output, and inadequate tissue perfusion (ischemia). Tissue ischemia can reduce the supply of nutrients to cartilage and cause multiple bone infarcts and avascular necrosis characteristic of advanced OA.[10]

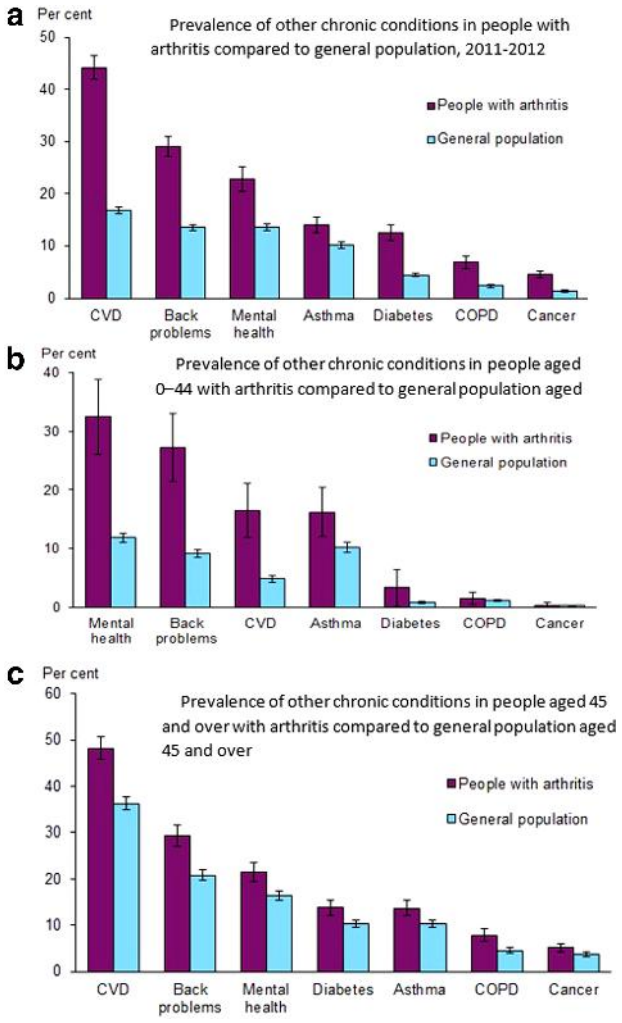

FIG. 3. Comparison of the prevalence of seven chronic conditions between population with arthritis compared with general population in 2011–2012. **(a)** Population as a whole, **(b)** stratified for people aged 0–44 years, and **(c)** stratified for people aged 45 years and older. Source: AIHW analysis of unpublished ABS Australian Health Survey, 2011–2012 (National Health Survey Component).[8] AIHW, Australian Institute of Health and Welfare.

Criteria of method for systematic reviews of the literature

This literature review aims to illustrate specific trends in the evolving field of photobiomodulation (PBM) to treating MSDs caused by OA, which we refer to as MSDs/OA herein. We built databases including published articles that span 41 years of research (1975–2016).

The inclusion criteria for the *PBM database* were composed of searches performed on PubMed. The keywords criteria used in our PBM search include the following terms: ''Photobiomodulation,'' ''Low-level light therapy,'' ''Low-level laser therapy,'' ''HILT,'' ''High intensity laser therapy.'' The master database for our study uses the *PBM articles database*, but it only includes articles with keywords ''musculoskeletal disorder'' OR ''musculoskeletal disorders'' to produce a *Master Database* of PBM for MSD.

We analyzed the database to identify the trends for use of various specific wavelengths, and how the use changed over time. We classified the applications of PBM treatment to various MSDs/OA indications.

The *Master Database of PBM for MSD* was analyzed in terms of frequency of occurrence for wavelengths, along with a list of 47 discrete wavelength values (identified from their existence in the *Master Database*), ranging from 400 to 2000 nm. The resulting *Master Database* was then further divided into two ranges of time for date of publication: (1) an older period, over the date ranging from January 1, 1975, until December 31, 2004, and (2) a more recent period, over the date ranging from January 1, 2005, until January 17, 2017. The specific date was selected as the time boundary between the two time periods because it is the publication date of a research article by Brosseau et al.[13] that had a strong negative effect on the PMB field, as explained later in our article.

We also analyzed the *Master Database of PBM for MSD* against the most common MSDs/OA indications, after *limiting* inclusion to only the more recent publications of articles, dated from 2000 to 2016 period. We extracted the frequency of occurrence for most common indications, defined by limiting inclusion with a list of these specific

keywords: ''Ankle,'' ''Wrist,'' ''Elbow,'' ''Back,'' ''Pain,'' ''Shoulder,'' and ''Knee.'' This provides an estimate of research works using *PBM for MSDs/OA*, which typically aim to test and quantify the effectiveness of PBM applications for specified classes of MSDs/OA indications.

History of PBM and its scientific basis

Brief history of PBM

Phototherapy dates back to the early 20th century when Dr. Niels Finsen was awarded the Nobel Prize in Physiology or Medicine in 1903 for treating lupus vulgaris using an arc lamp. After the invention of the red ruby laser in 1960, a new therapy called ''low-level laser therapy'' (LLLT) or ''laser biostimulation'' was first discovered by Hungarian physician Endre Mester.

In 1967, Mester was experimenting on mouse and rat models to test whether lasers could cause cancer or alternatively whether they could treat cancer. Using a low-intensity laser, he made the serendipitous observation that laser radiation applied to areas of shaved skin on the back of mice caused the hair to grow back faster[14] (Fig. 4). Mester and co-workers also tested laser treatment for wound healing in diabetic patients with crural ulcers.[15]

Wound healing has continued to make slow but significant progress.[16] We refer to Cotler et al.[17] and a chapter by Hamblin[18] for a more detailed history of the PBM field.

Mechanisms of PBM

PBM therapy uses lasers or light-emitting diodes (LEDs) with specific properties (wavelength, total optical power, spot size, power density, pulse structure, and duration of exposure) to promote an increased activity of many processes involved in natural cellular metabolism. Most PBM devices deliver light in the visible red and/or near-infrared (NIR) regions of the spectrum. There have been several studies and reviews that have delved at some depth into the cellular and molecular mechanisms of PBM.[19–22] In the interests of space, we will only state here that the benefits of PBM stem from enhancement of the cellular activity, both in quality and in quantity, involving the mitochondria, membrane ion channels, reactive oxygen species, nitric oxide (NO), adenosine triphosphate (ATP), and cyclic-AMP in the activation of signaling pathways and cellular transcription factors.

Questions concerning PBM for MSDs/OA

A literature search of PubMed was conducted between November and December 2016 regarding the use of PBM for MSDs/OA. The search was stratified between two time periods: pre-2005 and post-2005. The goals of the search were to determine: (1) what the most common wavelengths are/were for PBM; (2) what disorders, especially which joints, were treated; and (3) has the use of PBM been increasing. The clinical studies were divided into double-blind, randomized controlled trials (DBRCT), series of case studies, and meta-analyses. The most common applications were knee OA, MSDs/OA conditions affecting other joints, and studies affecting musculoskeletal (MSK) tissue related to sports performance and recovery in athletes.

Mechanistic Studies

Fundamental mechanisms

One study that showed the effect of PBM on cell physiology was by Corral-Baques et al.[23] who tested a 655-nm diode laser on dog sperm and compared four groups that received energy doses of 0 (control), 4, 6, and 10 J/cm^2. The control group that did not get illumination had significantly different results than the irradiated group, and an optimal energy dose was consistently observed, thus showing that an optimized phototherapy dose improved the speed and motility of sperm cells *ex vivo*.

One question that is asked frequently is: ''how can one tell if it is the light that is responsible for the beneficial effect? Can a simple heat source do the same?'' Lanzafame et al.[24] designed an experiment using PBM in animal model of pressure ulcers to answer that question. The answer was a clear indication that it is light, not heat, that is responsible for the biological effect. They suggested that NO release was partly responsible for accelerated healing observed after PBM.

Two additional pathophysiological mechanisms have been proposed to explain why the observed benefits of phototherapy optimized for MSDs/OA should be given attention: these involve the pro-inflammatory therapeutic effects of PBM,[19] in the absence of inflammation, and the inhibition of oxidative stress of PBM,[20] when inflammation is present.

PBM in sports performance and recovery

PBM has been proven to be effective in enhancing sports performance and recovery. One study by Antonialli et al.[25]

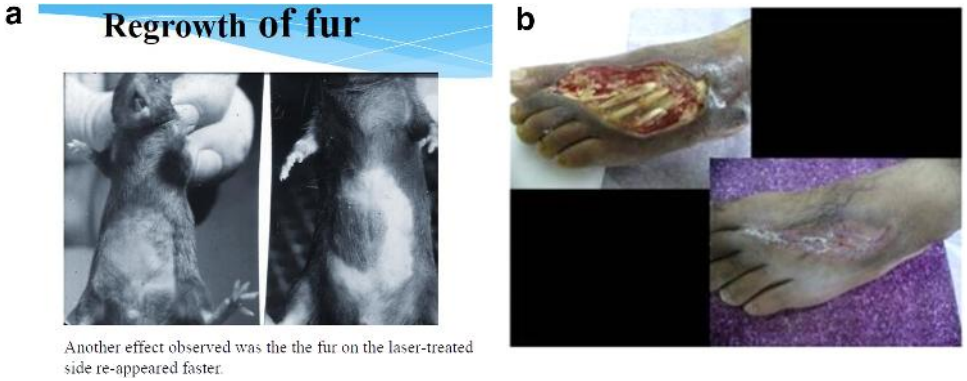

FIG. 4. Discoveries of Hungarian physician Endre Mester. **(a)** Faster hair regrowth on mice and **(b)** accelerated healing of diabetic wounds. Source: Permission to republish or display content granted by Springer-Verlag London (Order License ID: 4474751117139).[16]

evaluated the effects of PBM using different light sources on MSK performance and postexercise recovery, using a cluster of 12 diodes (4×905 nm lasers, 4×875 nm LEDs, and 4×670 nm LEDs) with total doses of 10, 30, and 50 J, or placebo over the quadriceps muscle. The 30 J dose showed the best results as it helped significantly increase performance, decreased delayed-onset muscle soreness, and improved biochemical markers related to MSK damage. The volunteers in this study were healthy males who were not trained before the study.

de Oliveira et al.[26] developed a protocol to examine what dose and optical power were best using an 810 nm laser on muscle performance of athletes. Four groups of professional soccer players received four different doses at a power of 200 mW (2, 6, and 10 J and a placebo group) in the pilot phase.

Then, the best dose from phase 1 was tested on all four groups at different optical powers (100, 200, and 400 mW and a placebo group). A similar protocol was further tested and validated in a study by Aver Vanin et al.[27] to investigate what dose was ideal for an 810 nm laser on muscle performance and postexercise recovery of athletes. Twenty-eight professional soccer players received three different doses at a power of 200 mW (10, 30, and 50 J). They concluded that the optimum dose was 50 J; therefore, the upper limit of the most beneficial dose was not reached in that study.

Dos Reis et al.[28] ran a double-blind placebo-controlled trial of PBM on quadriceps muscle performance and recovery in soccer players, before and after exercise, using an 830 nm laser. The athletes were divided into three groups: placebo, pre-fatigue laser, and post-fatigue laser. Using the laser on both the pre-fatigue and post-fatigue groups reduced serum lactate and creatine kinase (biomarkers for muscle fatigue), but the results in the post-fatigue laser group were more significant.

Wide Range of Optical Parameters Investigated in Studies of PBM for MSDs/OA

The availability of stable lasers at various wavelengths in the visible and NIR optical wavelengths has opened the door to numerous opportunities for experimental work in biomedicine, including PBM.

A literature search for the optimal parameters for wavelength or the best dosimetric measures does not produce a definite answer, but there is a trend toward certain better performing wavelengths and an increase in overall power levels.

The results of these searches show the frequency of publications at various wavelengths reported during two different time periods. In Fig. 5a, the frequency occurrence diagram for pre-2005 at various wavelengths shows 632.8, 635, 670, 780, 810, 830, 904, and 1064 nm as the wavelengths with the most publications.

Figure 5b by comparing pre-2005 and post-2005 illustrates the change with time concerning different wavelengths. The dominant wavelengths were as follows: 660, 670, 780, 808, 810, 830, 904, 980, and 1064 nm. The total number of publications grew nearly sevenfold between pre-2005 and post-2005.

PBM for MSDs/OA has met with an increasing level of success, but mostly empirical

PBM is a growing approach to improve healing and provide pain management for MSDs/OA. PBM has caught the attention of the medical establishment for nearly a decade but is only starting to slowly gain wide recognition. Figure 6a shows the history of publications of experimental LLLT and scientific PBM studies.

The field of PBM on MSDs has been improving rapidly over the past decade, regarding performance for pain reduction and supporting improved mobility. The use of DBRCT to investigate PBM has proven effectiveness of the intervention to treat MSDs in comparison to placebo with many reasonable protocols, especially those that included exercise with PBM.[29]

Starting in 2009, there was a novel implementation of phototherapy (that was originally invented in Italy) named ''high-intensity laser therapy'' (HILT). HILT has been studied to treat MSDs. The literature search on PubMed found growing studies mentioning HILT as of December 15, 2016; Fig. 6b lists the small, yet growing, number of publications discussing HILT.

PBM for MSDs/OA has been studied on a variety of joints

The search on PubMed produced 5618 publications of MSDs, as of December 15, 2016. We first combined MSD with our phototherapy keywords to obtain 273 results. Then, we looked at the most prevalent joints and anatomical regions divided into Ankle, Wrist, Elbow, Back Pain, Shoulder, and Knee.

Figure 7a shows the history of PBM publications, charted as a histogram for total MSD articles, and Fig. 7b shows specific MSD indications. The most common indications are knee issues, followed by shoulder problems and back pain.

PBM for the knees

In the view of many researchers, PBM is effective in conjunction with physiotherapy, as demonstrated by Alfredo et al.[30] on knee OA. Back in Hungary, Hegedus et al. observed that PBM is proven to be capable of reducing pain in knee OA, and he showed a correlation with improved microcirculation in the knees using thermography.[31]

There have been studies on MSD for the knees that were performed using HILT. One particular example of HILT was the work of Kheshie et al.[32] comparing HILT with LLLT to treat knee OA. The HILT used an Nd:YAG pulsed laser at 1064 nm, whereas the LLLT used a 830 nm laser. Both methods used the same dose of 1250 J. The study concluded that both LLLT and HILT were effective to treat knee OA and that exercise combined with LLLT or HILT was more effective than exercise plus placebo for pain reduction. Overall, exercise and HILT were most effective to increase function. Yet, details of the dose were not properly reported in terms of the total fluence (J/cm^2), and no detail was provided on the geometry of optical power delivery for both laser sources, which limited the value of the comparison.

Knees have also been treated with laser acupuncture or laser-needle therapy (where a laser is applied to acupuncture points) that resulted in positive effects. One example was tested in a DBRCT by Yurtkuran et al.,[33] which showed significant improvement in pain and range of motion (ROM) in patients with knee OA and reduced swelling compared with the placebo laser. A single case study by Banzer et al.[34]

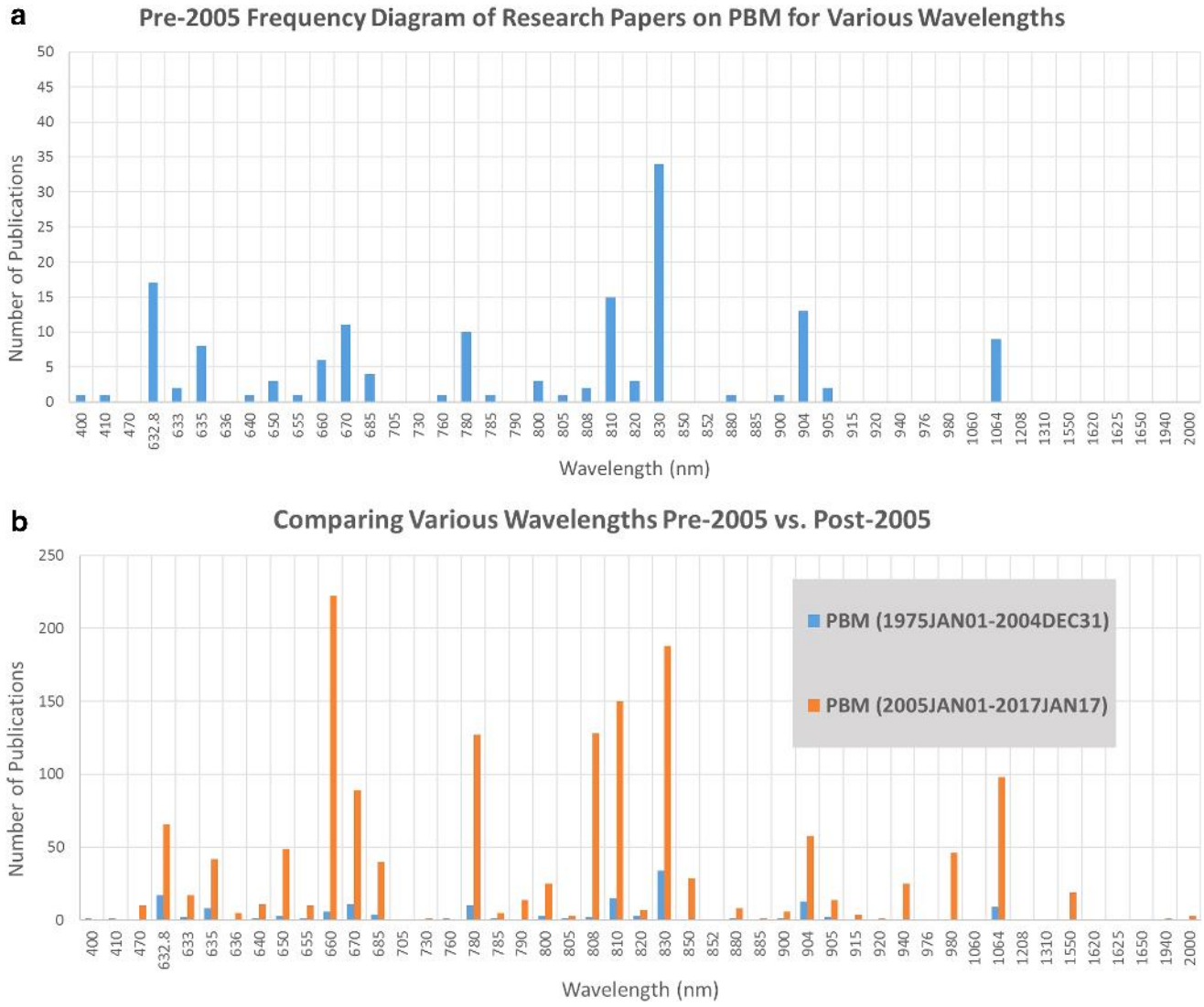

FIG. 5. Survey of different wavelengths used in PBM articles. **(a)** Between 1974 and 2004. **(b)** Between 2005 and 2017. PBM, photobiomodulation.

was performed on a 63-year-old patient with spontaneous osteonecrosis of the knee (SONK), with 685 and 885 nm laser needles used daily (60 min each) for 3 months. Magnetic resonance imaging (MRI) revealed complete healing of the knee 35 weeks after the treatment started, concluding that laser-needle therapy may be beneficial for treating SONK.

PBM for other joints

PBM has been tested on neck pain, such as the work of Konstantinovic et al.[35] performed on acute neck pain using a 905 nm laser. After 15 treatments[36] over the course of 3 weeks, the LLLT group experienced more effective short-term relief of arm pain and increased range of neck extension as opposed to the placebo group.

The same effects of reduced pain and increased ROM were experienced when Abrisham et al.[37] tested LLLT on subacromial syndrome in the shoulder with exercise, in comparison with exercise alone, and the results indicated that PBM with exercise has more effects on reducing shoulder pain than purely exercising. PBM has been proven to be more effective in pain reduction and increased ROM than ultrasound therapy for subacromial impingement syndrome,[38] low-back pain,[39] and carpal tunnel syndrome.[40]

Chronic low-back pain can also be effectively treated with PBM and exercise therapy,[41,42] and PBM has effective pain reduction on carpal tunnel syndrome.[43–45] A systematic review by Clijsen et al.[46] presented evidence that PBM is effective in pain reduction on MSDs, such as subacromial syndrome, knee OA, chronic low back pain, rheumatoid arthritis, and carpal tunnel syndrome.

PBM versus NSAIDs

NSAIDs are currently the treatment preferred by mainstream medicine for MSDs/OA. Studies should compare the effects of phototherapy with NSAIDs. While PBM can be as effective as NSAIDs to treat and reduce pain, the scientific clinical community needs proof that PBM has advantages over anti-inflammatory and pain-killing drugs.

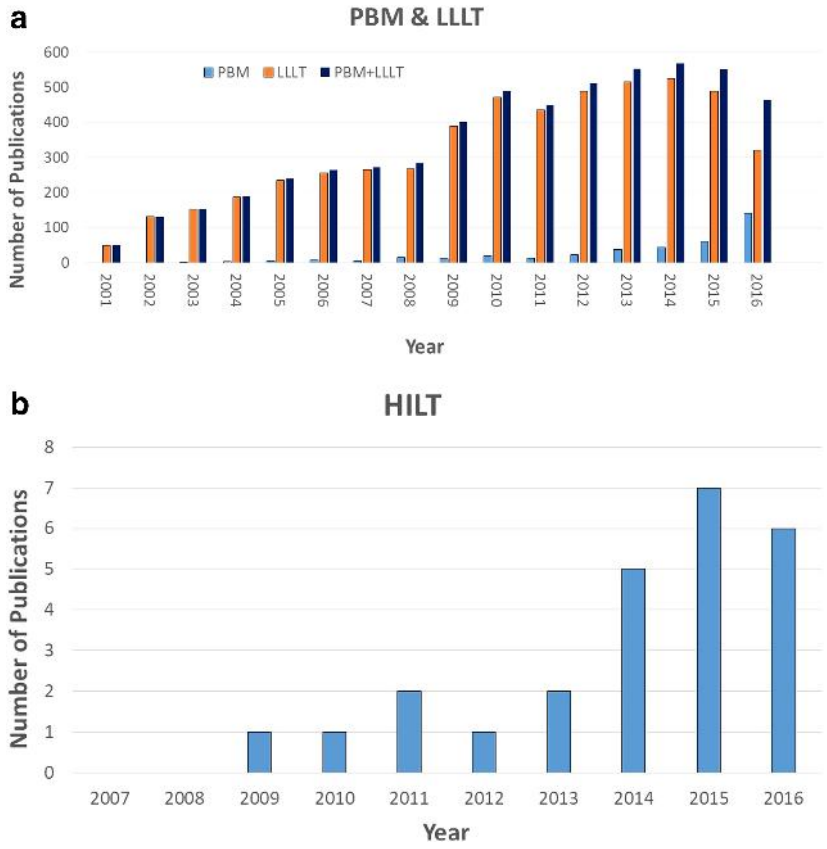

FIG. 6. Numbers of articles on different kinds of PBM. **(a)** Annual number of PubMed publications on PBM and LLLT between 2001 and 2016. **(b)** Annual number of PubMed publications on HILT between 2009 and 2016. LLLT, low-level laser therapy; HILT, high-intensity laser therapy.

To compare the effectiveness of NSAIDs against PBM requires understanding of the benefits and limitations of NSAIDs for treating MSDs. The leading European expert in PBM, Professor Jan Bjordal of the University of Bergen in Norway, tested the effects of opioids and NSAIDs in a meta-analysis of randomized placebo-controlled trials.[47]

The study found that the clinical effects of pharmaceuticals in knee OA were small and limited to only the first 2–3 weeks after the start of treatment. The pain relief effects, compared with the placebo, were smaller than patient-reported thresholds for clinical improvement. In addition to the fact that NSAIDs do not aim to cure MSDs, they have very limited effects on pain management, with no permanent benefits.

A number of publications co-written by Pinto Leal-Junior[48,49] have reported clinical studies on rats comparing the effects of PBM therapy and NSAIDs to treat MSDs/OA inflammation. They used animal models of rats that had intra-articular papain injections in their knees to induce knee OA to compare the effects of NSAIDs and PBM. In one study, both groups had similar effects on gene expression levels associated with inflammation, but PBM (and especially PBM combined with exercise) had better effects on the inflammatory process of OA compared with the rats administered with NSAIDs.

Future Research Directions

Gaps in the understanding of fundamental processes

There has been much progress in understanding how the fundamental processes of PBM work, but there are still many gaps in our knowledge required to completely define the optimum wavelength and energy dose for MSDs/OA treatment.

One of these knowledge gaps includes possible correlation between the calibrated surface irradiation (power density), modeling optical propagation into tissue, and calculating the actual energy deposited in the tissue. Another gap requires a deeper understanding of the photophysical and photobiological processes occurring inside the mitochondria of the cells and in the blood-irrigated tissues.

Yet, another gap involves a method to assess the physiological states of the treated tissues, to measure changes pre- and post-treatment, and possibly a system for real-time monitoring and feedback control.

Other gaps worth mentioning involve knowledge of optical scattering and photon diffusion, light-triggered NO release inside cells, biophotonic energy processes, pain management processes, tissue regeneration processes, cell-state-dependent processes, body size-dependent intensity and dosage variations, and the wavelength dependency of different biophotonic responses.

Problems in past clinical studies: lack of understanding of basic photobiology

Among the studies are inconsistencies regarding the extent of the benefits of PBM for treating MSDs, such as the work of Brosseau et al.,[13] who compared LLLT with a placebo LLLT to treat OA in the hands and concluded that LLLT was no better than placebo at reducing pain, stiffness, and improving functional status for patients with hand OA.

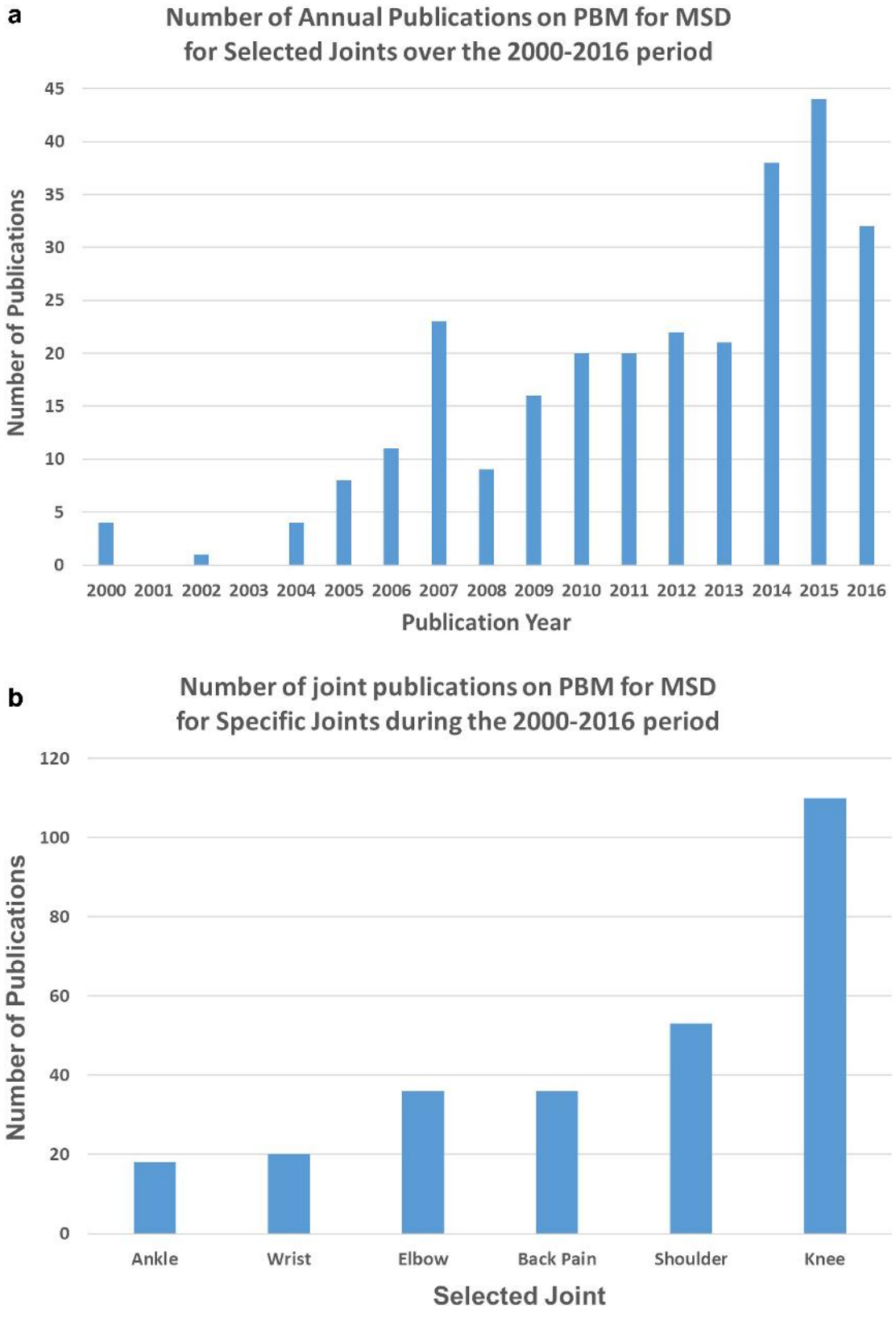

FIG. 7. PBM articles for MSDs. **(a)** Number of annual publications on PBM for MSDs in total (ankle, wrist, elbow, back, shoulder pain, and knee) during the period from 2000 to 2016. **(b)** Number of publications on PBM for MSDs for specific different joints (ankle, wrist, elbow, back, shoulder, and knee) during the period from 2000 to 2016.

This is an example where incorrect assumptions led science in the wrong direction.

A critical article by Hode and Tuner[50] in 2006 discussed the negative results from the work of Brosseau et al.[13] and pointed out that only a minute amount of total energy was indeed absorbed by the tissue. This is now known that the energy used then was not sufficient to produce the necessary photochemical processes in cell's mitochondria.

Inconsistencies are an important issue in the field of PBM. According to Khan and Arany,[51] the likely causes for the inconsistencies are the following: (a) ''the complexity of the biophotonics interactions with biological systems'' and (b) ''a lack of understanding of the precise molecular mechanisms mediating its therapeutic responses.'' They also pointed out weaknesses in laser dosimetry as a cause for the inconsistencies in a majority of negative PBM studies; the PBM literature has often reported laser irradiance (laser power over area) at the laser probe tip. This practice is inaccurate, misleading, and could be an important cause of inconsistencies in the field.

To be precise and complete, PBM treatment of MSDs/OA must include:

(a) Physical patient data, such as transverse area and depth of the treatment area, patient skin reflectance, and depth of volume to be treated.
(b) Physical illumination parameters: wavelength, pulse structure, illumination beam size and shape, intensity (mW/cm^2), wavelength (nm), optical bandwidth (nm), peak and average total power (W), and duration and frequency of treatment.

The determination calculation of a total dose (fluence) in J/cm^2 at the skin surface is essential. But ultimately, what is most important is the total energy deposited in the treated tissues. The first law of photochemistry says that there must be optical energy absorbed; therefore, it is the deposited energy density (energy per volume, e.g., in J/cm^3) that ends up in the mitochondria that needs quantification. The connection between skin surface dose and deposited energy in the targeted tissues to be treated is a not a trivial one, but a crucial one to be obtained, if we want PBM to proceed in a method which is most rational, systematic, and provides quantitative scientific method.

Discussion

Bringing a fresh new perspective

Redefining the health care equation for treating MSDs/OA

The article by Brosseau et al.[13] in 2005 weighed heavily on formal opinions of highly regarded medical advisory groups, such as the Cochrane Collaboration and Osteoarthritis Research Society International (OARSI), because some of the authors were members of the committee on LLLT.

Dr. Jan Magnus Bjordal noted, in his editorial in *Photomedicine and Laser Surgery* in 2015,[52] that a strong bias still exists against PBM in these medical advisory groups, which are otherwise considered to be neutral and unbiased in assessing medical treatments. Dr. Bjordal suggested that the lack of openness indicates conflict of interests in editorial board members for the Musculoskeletal Group of the Cochrane Collaboration, which appears to also affect the OARSI.

Despite the growing body of evidence in favor of PBM and LLLT for the management of MSDs/OA pain, the OARSI has decided to omit all references to this physical therapy method in its 2014 report. This is likely due to significant number of published studies that have been deemed to be of low scientific quality and to record unsubstantiated claims and lack of control in LLLT equipment industry.

Unfortunately, because LLLT can still be deemed a fringe medical therapy, these negative past events from a few players (providers and clinical researchers) in phototherapy has created negative prejudice and additional challenges for PBM to make progress toward medical acceptance. It is unfortunate, especially since there have been no side effects reported for PBM; while the opposite is certainly true when one considers conventional pharmaceutical solutions.

Considering the recent fact that many drugs are compiling the problem of health care with addiction or accelerated degeneration of diseases, there is a growing sense that a call to action is needed. One can hope that awareness of this problem and anticipation to resolve it with the more effective means that the offering of PBM will motivate a meaningful call to action.

Initiative to reduce cost of clinical research on humans

Much is yet to be learned regarding the role of phototherapy in the biology of cells and complex model systems. For humans, clinical trials are needed, and costs are always limiting factors for execution of human clinical trials. PBM has been disadvantaged by the fact that companies in the PBM field have only a tiny fraction of the resources that are available to large pharmaceutical companies who can spend millions of dollars on large clinical trials.

Technologies enabling a more rapid and effective metrology of the human biometrics could bring significant cost reductions for clinical trials if the technology delivers precision and convenience at low cost. For example, the upcoming availability of new digital technologies for metrology (e.g., ROM and biometrics) could be factors that are likely to spur advances toward cheaper and faster clinical trials. These advances can support the rise and use of new physical therapy, such as phototherapy, to become on par with pharmaceutical solutions currently dominating the pain market for MSDs/OA.

PBM for MSDs/OA targets pain management for physical rehabilitation

The currently established medical practice has a standard prognosis for patients diagnosed with arthritis or OA: it can only get worse and that the disease process is irreversible. As of 2016, current medical wisdom in America views arthritis as an incurable disease of old age and that one must endure it with some symptomatic help from drugs. Meanwhile, the search for disease modifying OA drugs sought

by big pharma has proved to be elusive for the past four decades.

We hypothesize that drugs may not in fact be the solution; and recent studies have often proven that drugs actually exacerbate the problem, causing further degeneration into a chronic condition. We suggest that arthritis treatment could benefit from biological modeling on healthy individuals; strangely, this is rarely discussed.

It has been reported[53] that phototherapy can be used in combination with physiotherapy exercise to effectively reduce chronic pain in the majority of cases especially in the short term. The added capability of phototherapy to promote tissue healing can enhance physical rehabilitation and may lead to the resolution of MSDs/OA in the longer term.

The field of PBM as a growing therapeutic method for a wide array of applications

Since 2005, there have been an increasingly large number of research articles that have reported success using phototherapy to treat various joint indications of MSDs/OA (Fig. 7a, b), where knee OA represent a dominant number of cases. Although PBM cannot replace orthopedic surgery when needed, and it is likely to be useful to treat pain symptoms postsurgery[54] and promote tissues healing.

However, the author poses that the value of PBM resides in its preventive capability via early intervention for MSDs/OA. It can be shown that PBM can prevent the advance of degenerative disease MSDs/OA, and workers are investigating possibilities to reverse and to heal the damage of MSDs/OA. Physical therapy treatment approaches with a perspective toward rehabilitation looks promising.

Although this work focuses mainly on chronic MSDs/OA problems, applications also grew in numbers to enhance endurance and improve speed of postexercise recovery[28] and for treating acute pain.[55] Other areas of possible interest include wound healing,[56] traumatic brain injuries,[57] and dentistry to name a few. This illustrates the breadth of applications of PBM for improving health.

Phototherapy is still not recognized by mainstream medical practice in any major European countries, such as United Kingdom, Scandinavia, Germany, France, Spain, and Italy. The cost of formal clinical trials has held back the PBM field. Even if formal designs for clinical protocols have greatly improved, funds to carry out the studies have often not been made available due to prejudices and negative bias from the past.

Key area of improvements for translational research into physical rehabilitation practice

One issue in the application of PBM technologies that has hindered progress, both in the market and in research, is safety consideration. Laser eye safety requires the use of eye protection (laser safety goggles) for Class IIIB (5–500 mW) and Class IV (>500 mW) lasers. Moreover, most PBM lasers require skin contact and the risk of transmission of skin diseases may dissuade some volunteers and will add technical costs for disinfecting equipment between treatments as required for infection control.[58]

There was a relatively large increase in both the number of research articles and the range of different wavelengths used in the research articles (Fig. 5a, b). The plethora of wavelengths, pulse structures, delivery methods, and equipment contributes to the complexity of the field. In most cases, the laser application relies on the operator to some extent for repeatability of patient treatment. Yet, published treatments can be performed by different operators, on different patients, using different lasers.

A few recurrent points have caused debate by many critics,[59] regarding limitation in documenting the experimental parameters in PBM studies, and the consequence on the publication's quality. The most common criticism from optical physicists and photobiology experts is the apparent lack of understanding of the fundamental photophysical and photochemical processes of light propagation and energy absorption that are key to affect a biological response. This led to an incomplete description of experimental treatment conditions.

It can become difficult for an educated scientist, concerned with fairness and precision, to compare work between studies. It is virtually impossible to compare outcomes between otherwise similar studies if the precise relationship between optical energy parameters (wavelength, intensity, power, etc.) and the resulting biological response is not sufficiently well documented. The contribution to growth in PBM knowledge is limited if one cannot carefully analyze and compare between works.

The optical energy being delivered to the patient needs to be more precisely controlled and must be delivered in a reproducible and documented manner. The first law of photochemistry and photobiology[60,61] needs to be applied correctly that sufficient light (number of photons) must get to the tissue being treated to expect an effect. At this time, some reports have deficiencies in this area, and few reports attempt to assess the actual amount of energy (J/cm^3) deposited in the volume of tissue being treated.

Pain is a symptom; while the goal of analgesics has been to mute the symptom, the greater potential of PBM for treating MSDs/OA resides in its capability for tissues healing. The PBM approach makes most sense in the perspective of a rehabilitation treatment based on physical therapy that includes physical exercise. Therefore, measuring health improvements should go beyond pain metrics and should be based on mobility metrics and their improvement over time.

Considering the complexity of the situation, it will likely take a large amount of data to resolve the uncertainty and to close the gap of knowledge in a satisfactory manner. Therefore, like any other physical science, accumulating evidence derived from empirical data will eventually lead to consensus. In the meantime, this accumulated body of empirical evidence shows that phototherapy is safe and effective to manage pain.[62] It is imperative, in our view, that we start to implement these methods despite the present imperfect knowledge but knowing that the treatments and parameters are safe and effective. The more quality data are collected, the greater the opportunity for further analysis, using modern big data processing methods.

Big data in phototherapy must be acquired in the most precise and meaningful way possible. We need to accumulate a large body of precise and complete factual knowledge of PBM in patients and treatment outcomes in pain management and improved functionality. The purpose of this work was to motivate the systematic definition and implementation of standards of practice for PBM treatment of MSDs/OA. We need to work on acquiring a body of quality

data to evaluate progress toward patient rehabilitation, as we work to provide effective short-term pain treatments.

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Author Disclosure Statement

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