

Therapeutic Efficacy of Home-Use Photobiomodulation Devices: A Systematic Literature Review

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Abstract

Objective: Perform systematic literature review on photobiomodulation (PBM) devices used at home for nonesthetic applications.

Background: Home-use PBM devices have been marketed for cosmetic and therapeutic purposes. This is the first systematic literature review for nonesthetic applications.

Methods: A systematic literature search was conducted for PBM devices self-applied at home at least thrice a week. Two independent reviewers screened the articles and extracted the data. Treatment dosage appropriateness was compared to the World Association for Laser Therapy (WALT) recommendations. The efficacy was evaluated according to the relevant primary end-point for the specific indication.

Results: Eleven studies were suitable. Devices were applied for a range of indications, including pain, cognitive dysfunction, wound healing, diabetic macular edema, and postprocedural side effects, and were mostly based on near-infrared, pulsed light-emitting diodes with dosages within WALT recommendations. Regarding efficacy, studies reported mostly positive results.

Conclusions: Home-use PBM devices appear to mediate effective, safe treatments in a variety of conditions that require frequent applications. Conclusive evaluation of their efficacy requires additional, randomized controlled studies.

Keywords: photobiomodulation, low-level laser therapy, home use, self-applied, over the counter

Introduction

LIGHT THERAPY OR PHOTOBIMODULATION (PBM), previously referred to as low-level laser therapy (LLLT), is a nonthermal irradiation in the red to near-infrared (NIR) range of the electromagnetic spectrum. This low-risk, non-invasive technology is widely used for pain reduction, acceleration of wound healing, and treating a variety of inflammatory related conditions.¹

A practical problem that arises when initializing treatment with PBM is that it requires a large number of treatments early on, which translate into visiting the clinic two to three times a week. In certain medical conditions, it is recommended to receive daily treatments. This creates an obstacle for many patients who live far from a PBM clinic or those that are house bound. In such cases, availability of a home-use device would appear to provide an important advantage.²

Moreover, the rapidly escalating healthcare costs as a result of population aging with prolongation of periods with chronic disease and technological advancements have sparked a large number of applied initiatives for home-use devices.³ Governments are encouraging programs that support self-management from home, thereby reducing the load on the healthcare system.^{4,5} Home-use devices allow seniors, persons with disabilities or chronic health issues, and individuals recovering from injury, surgery, or illness to remain at their homes, which frequently turns out to be much more affordable than hospitalization or multiple ambulatory clinic visits.⁶

In the past two decades, a variety of over-the-counter, noninvasive home-use PBM devices have been marketed for cosmetic as well as therapeutic purposes. Indications for improving esthetics have included stimulating hair growth, reducing blemishes of acne, and reducing wrinkles. Reviews of devices primarily for esthetic purposes include the guide

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of Dodd et al.⁷ for home-use devices certified by the FDA for stimulation of hair growth, and those of Juhasz et al.⁸ and Hession et al.⁹ who reviewed available lasers and other intense light source home devices for a variety of dermatological indications. Approved indications for noncosmetic applications include, among others, temporary relief of pain, increasing blood flow, and accelerating herpes wound healing.

Clinicians in the PBM field advocate the home use of PBM devices for nonesthetic applications, both directly by consumers for chronic pain management and by physicians/institutions that lend out these devices for postprocedural side effect management.^{2,10–12} However, studies describing treatments with PBM devices at home for nonesthetic applications are scarce and we have failed to find a published review on this subject.

Therefore, the purpose of this study was to fill this gap and systematically review and summarize the literature describing the use of PBM at home for nonesthetic applications.

Methods

The review strategy was constructed according to Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) and the review protocol was registered in the international prospective register of systematic reviews, PROSPERO (CRD42018091415). The review methods were established before the conduct of the review.

Search strategy

A literature search for studies describing noncosmetic applications of PBM devices used at home was performed during December 2017 using PubMed and Embase without language or date restrictions. Because the nomenclature for PBM is so diverse, the formal search was preceded by a preliminary search to map the available literature and determine the optimal search strategy using THORgle, a noncommercial specialized database for PBM literature resources, which uses 72 alternative names for PBM and then filters and marks the false positives for exclusion. The THORgle, developed and maintained by James Carroll from Thor Photomedicine Ltd., can be accessed by personal communication. Following the preliminary search described above, the key words for the formal search were as follows:

(Photobiomodulation OR “Low level laser” OR “low energy laser” OR “low power laser” or “low intensity laser” or “low energy laser” OR LLLT OR “monochromatic near-infrared phototherapy” OR “narrow band light therapy”) AND (“home-use” OR “at home” OR “home device” OR “self-applied” OR “over-the-counter”).

Manual searches in relevant references were also conducted. Finally, conference abstracts from major PBM or laser conferences [World Association for Laser Therapy (WALT), North American Association for Laser Therapy (NAALT), American Society for Laser Medicine & Surgery (ASLMS), Laser Florence, and SPIE Photonics West] in the previous 2 years (2016–2017) were screened manually. Researchers in the field were contacted to identify potential articles and regarding the status of publication of relevant conference abstracts.

Inclusion criteria

- Prospective studies, case series, or case reports that contain reports of applications of PBM devices used for nonesthetic medical applications

- The device was used at least thrice a week at home by patient or caregiver

Exclusion criteria

- Primarily cosmetic indication, including hair growth, acne, antiaging, and wrinkle reduction
- Reviews or letters that contain no new/original data
- Trials that used over-the-counter devices at the clinic without home use
- Laser acupuncture
- Devices emitting blue light targeting bacteria or ultraviolet light for treatment of psoriasis

Study selection, evidence grading, and data extraction

Studies were screened initially by title and abstract according to the eligibility criteria. The full text of the studies that were found eligible was screened once more according to the eligibility criteria. The list of excluded articles with the reason for exclusion can be found in the Supplementary Data (see Supplementary Data at www.liebertpub.com/pho).

Evidence grading was assigned based on the Oxford Centre for Evidence-based Medicine Levels of Evidence. Both randomized and nonrandomized studies (i.e., case series/controls) were included. The latter were included because the medical applications described were hard to treat conditions [postprocedural oral anesthesia/paresthesia, cognitive dysfunction in Alzheimer patients, non-center involving diabetic macular edema (NCDME), and recalcitrant diabetic foot ulcers] or with a long follow-up (>5 years).

Data extracted included study design, clinical indication, description of the setting and participants, device used and its dosage parameters, treatment protocol—frequency, duration, and site of treatments—and the main findings of the article. If further information was required, the authors of original studies were contacted. The process of screening and data extraction was performed independently by each of the two authors. Disagreements were settled by discussion.

Result synthesis

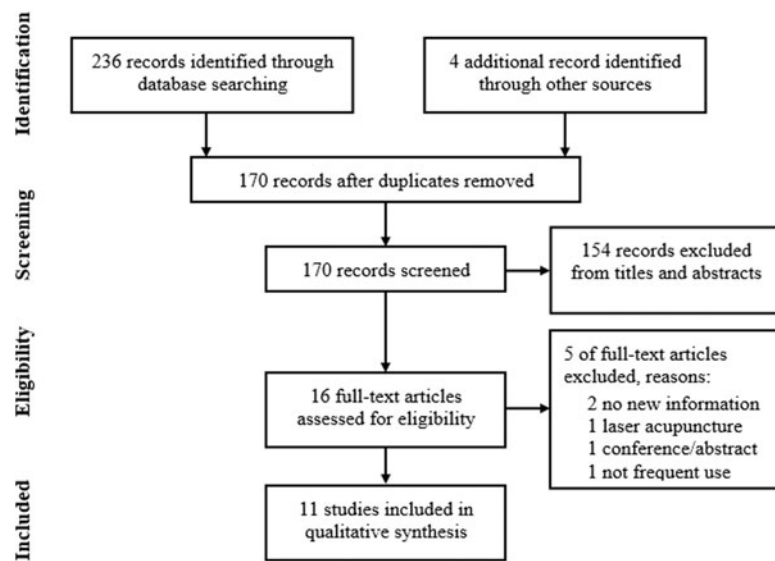
Device-related parameters, including light source [laser or light-emitting diodes (LEDs)], wavelength (red or NIR), power density, dosage, and pulsing frequencies, were grouped and the treatment dosage appropriateness was compared to the WALT recommendations (Joule per point or per area).¹³

Since the applications varied (pain, cognitive dysfunction, wound healing, diabetic macular edema, and postprocedural side effects), no single primary end-point for efficacy could be compared across all studies. Therefore, studies reporting similar indications were grouped and the efficacy of the device was evaluated according to the relevant primary end-point for the specific indication.

Minimizing risk of bias

We have used several methods to minimize risk of bias in this review: (1) the protocol was written before the beginning of the systematic search and was registered online at PROSPERO (CRD42018091415). (2) We adhered to the PRISMA guidelines while preparing reports of systematic reviews—the checklist can be found in the Supplementary

FIG. 1. Flow of systematic literature search.



Data.^{14,15} (3) In addition to searching the electronic databases, we manually searched conference abstracts for unpublished studies. (4) Search results were independently reviewed by two authors. (5) The level of evidence was graded with the Oxford Centre for Evidence-based Medicine Levels of Evidence since we included both randomized and nonrandomized studies. (6) Conflicts of interest were disclosed as required.

Results

Accountability

The results of the systematic literature search are presented in the flow diagram (Fig. 1). A total of 240 potentially relevant articles were identified by systematically searching in electronic databases, including 4 additional articles recommended by researchers in the field (of which Stelian et al.¹⁶ and Tang et al.¹⁷ were later included in the synthesis). After removal of duplicates, 170 records were screened for eligibility.

Appraisal of titles and abstracts according to the inclusion/exclusion criteria led to the exclusion of 154 studies for the following reasons: cosmetic indication ($n=54$); not home use ($n=36$); no new information (reviews and letters) ($n=22$); not human ($n=5$); and not relevant (not PBM, no connection to the topic) ($n=37$). Full texts of the remaining articles ($n=16$) were obtained for more detailed evaluation and a further five were excluded for the following reasons: no additional clinical information ($n=2$); laser acupuncture ($n=1$); abstract ($n=1$); and less than thrice a week ($n=1$). Finally, 11 studies were included in this review.

Table 1 includes the studies found in the literature review. These studies are mostly small- to medium-sized prospective studies or case series reporting the use of PBM devices at home. The largest studies are randomized controlled studies.

The medical indications varied and included pain and related symptoms,^{10,11,16,18} cognitive dysfunction,^{12,19} wound healing,^{20,21} NCDME,¹⁷ and postprocedural side effects.^{22,23} Because of the nature of the pathology, some of the appli-

cations were adjunctive to a medical procedure and hence recommended by a healthcare provider such as wound healing in diabetic foot ulcers, treatment of diabetic macular edema,¹⁷ and prophylaxis or treatment of side effects of a planned procedure,^{11,22,23} whereas the other indications could be patient initiated.

In addition to these studies, several relevant abstracts that were presented in the past 2 years were found by searching conference abstracts or were brought to our attention by colleagues in the field. These include the double-blind randomized control trial (RCT) by Hazez et al.²⁴ for treatment of diabetic foot ulcers, the double-blind RCT by Del Vecchio et al.²⁵ for treatment of temporomandibular joint-related pain in comparison to treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), and the pilot study by Goo et al.²⁶ for reducing symptoms related to menorrhagia.

In most studies, the devices used at home were consumer devices that could be bought over the counter (e.g., Virulite; B-cure diode laser; LumiPhase-R Compact; Intranasal and Neuro Veilight; WARP10; and MedX home),^{10-12,19,20,22,23} whereas in three studies, the devices were professional devices (e.g., Anodyne Therapy Professional System 480)^{18,21} or experimental devices (e.g., Amcor device)¹⁶ that are not designed for home use and require special guidance and/or treatment by a healthcare provider, but were nevertheless used at home at least thrice a week.

Light source, dosage parameters, and frequency of treatments

Light source. One consumer device (B-cure diode laser) and one experimental device (Amcor device) were lasers. The rest of the devices were composed of LEDs (Virulite; LumiPhase-R Compact; Intranasal and Neuro Veilight; WARP10; MedX home; and Anodyne Therapy Professional System 480).

Wavelengths. NIR is the most popular wavelength, although two devices were used exclusively with red light for skin treatment (Lumiphase-R)²⁷ and retina treatment

TABLE 1. STUDIES INCLUDED ACCORDING TO SYSTEMATIC SEARCH (ABOVE DASHED LINE) AS WELL AS ABSTRACTS (BELOW DASHED LINE), ORDERED BY PUBLICATION DATE

Study	Year	Design (Grade ^a)	Sample size	Application	Device
Merigo et al. ¹¹	2017	Case series (C)	3	Treating postprocedural oral anesthesia/paresthesia	B-cure diode laser (Good Energies, Haifa, Israel)
Saltmarche et al. ¹²	2017	Case series (C)	5	Improving cognitive dysfunction in Alzheimer patients	Vielight Neuro Alpha—intranasal applicator (Vielight, Inc., Toronto, Canada)
Fornaini et al. ¹⁰	2015	RCT (B)	24	Reducing pain related to temporomandibular disorder	B-cure diode laser (Good Energies)
Tang et al. ¹⁷	2014	Case series (C)	4	Reducing retinal thickness in diabetic retinal edema	WARP10 (Quantum Devices, Inc., Barneveld, WI)
Naeser et al. ¹⁹	2011	Case reports (C)	2	Improving cognitive dysfunction in TBI patients	MedX Home (MedX Health, Inc., Ontario, Canada)
Barolet and Boucher ²²	2010	Pilot RCT (C)	3	Prophylaxis of postscar revision side effects	LumiPhase-R Compact device (Opusmed, Montreal, Canada)
Barolet et al. ^{23,b}	2009	Pilot RCT (C)	14	Prophylaxis of postablative procedure side effects	LumiPhase-R Compact device (Opusmed)
Lavery et al. ¹⁸	2008	RCT (B)	69	Improving diabetic sensory neuropathy	Anodyne Therapy Professional System 480 (Anodyne Therapy, Tampa, FL)
Nather et al. ²¹	2007	Case series (C)	3	Healing recalcitrant diabetic foot ulcers	Anodyne Therapy Professional System 480 (Anodyne Therapy)
Hargate ²⁰	2006	RCT (B)	32	Reducing Herpes labialis lesions healing time	Virulite CS (Virulite LLC, Costa Mesa, CA)
Stelian et al. ¹⁶	1992	RCT (A)	50	Reducing knee pain	Experimental device (Amcor Ltd., Israel)
Hazeh et al. ²⁴	2017	RCT	19	Healing recalcitrant diabetic foot ulcers	B-cure diode laser (Good Energies)
Goo et al. ²⁶	2016	Pilot prospective	10	Reducing symptoms related to menorrhagia	Healite Mini (Lutronic Corp., Goyang, South Korea)
DeI Vecchio et al. ²⁵	2016	RCT	90	Reducing pain related to temporomandibular disorder	B-cure diode laser (Good Energies)

^aGrade of recommendation according to the Oxford Centre for Evidence-based Medicine—Levels of Evidence.

^bThis study was published as a full text in 2016.²⁷
RCT, randomized control trial; TBI, traumatic brain injury.

(WARP10)¹⁷, and two devices were used with both NIR and red light for transcranial treatment (MedX)¹⁹ and pain reduction (Amcor).¹⁶

Power density. According to specifications of the devices given by manufacturers (either directly or by dividing the total power by the beam size), the average power density ranged from 14 mW/cm² for the Vielight intranasal probe,¹² to 55 mW/cm² for the B-cure laser.^{10,11}

Dosage. As always in PBM studies, the dosage is the trickiest parameter, especially when pulsing is involved. Although in experimental systems, the dosage parameters are usually presented (e.g., the study by Stelian et al.¹⁶), consumer products consider some of the dosage parameters as proprietary information and therefore do not specify all the variables required to understand the actual dosage. Nonetheless, the total energy density per session ranged between 4 and 50 J/cm²,^{18,21,27} although most studies reported energy density to be in the range of 9–13 J/cm² per treatment point per session.^{10–12,19}

Pulsing. Almost all devices used pulsing as part of the protocol. The pulsing frequency varied from 100 Hz¹⁶ to 15 KHz.^{10,11} In the traumatic brain injury (TBI) case reports¹⁸ and in retina treatments,¹⁷ continuous wave (CW) mode was used.

Treatment frequency. Treatment frequency was mostly a single, daily, self-treatment regimen for up to 15 min per session. In four of the studies the protocol was different. In Nather et al.'s study,²¹ patients received treatments only thrice a week for 30 min per session. Using the same system, Lavery et al.'s patients¹⁸ received daily treatments for 40 min per session. In Tang's study, patients applied PBM twice a day for 88 sec per session. Finally, in the study by Hargate,²⁰ patients self-treated thrice a day for 3 min per session.

Treatment period. The total period in which the treatments were applied was dependent on the medical condition and ranged widely from a few days to several weeks for improvements to take place. Acute conditions such as herpes cold sores and postsurgical paresthesia/anesthesia required up to 1 week of treatment,^{11,20} whereas chronic conditions such as inflammatory-related pain^{10,16} or prophylaxis^{22,27} required a few weeks. Diabetic retinal treatments were applied daily during a period of 2–9 months.¹⁷ Some indications such as those involving transcranial/intranasal PBM required constant, daily treatments without which the symptoms were reported to regress to the original conditions.^{12,19}

Safety and efficacy of PBM at home

Table 2 includes detailed information of the studies found in the systematic literature search pertaining to patient characteristics, dosage parameters, treatment protocol, and the main findings.

Of the 11 studies included in the systematic review, 10 reported positive results, and 1 reported no effect.¹⁸ One nonrelated adverse event was reported.¹⁷

Reducing inflammation-related joint pain

The studies by Stelian et al.¹⁶ and Fornaini et al.¹⁰ were double-blind, randomized controlled studies [in Stelian et al.'s study, the blinding was only vs. the NIR laser (presented in this study)]. The medical conditions that were treated with PBM were joint pains related to inflammation, including knee pain osteoarthritis¹⁶ and temporomandibular joint pain.¹⁰ Both studies reported significant pain reduction compared to sham irradiation following self-applied treatments [pain reduction (0=no pain to 10=worst possible pain), PBM vs. Sham: Fornaini 3.0 vs. 0.4; Stelian 3.9 vs. –0.1].

Stelian et al. also reported significant functional improvement in the irradiated group, but not in the sham-irradiated group as assessed using a disability index questionnaire. Furthermore, by following up the patients for at least 1 year after the end of treatment, the group found that the period from the end of the treatment until the patients required retreatment was much longer for patients who received PBM compared to the sham [time to retreatment, PBM (NIR) vs. Sham: 6.1 ± 3.2 vs. 0.53 ± 0.62 months].

Acceleration of wound healing

The objective in the studies by Hargate²⁰ and Nather et al.²¹ was to promote wound healing. While Hargate²⁰ treated acute wounds (cold sores on the lips) as a result of Herpes labialis, Nather et al.²¹ used PBM to treat chronic wounds on the feet of diabetic patients who did not respond to previous treatments. It is important to note that complete wound closure is an expected outcome for acute wounds such as cold sores, but not necessarily for diabetic foot wounds, which frequently lead to amputation. Both studies reported favorable results following 6 and 14–19 treatments, respectively.

In Hargate's double-blind RCT, the major finding was the significantly reduced time to complete healing (PBM vs. Sham: 6.3 ± 3.0 days vs. 9.4 ± 4.6 days, $p=0.048$) and accelerated crust formation (2.0 ± 1.2 vs. 2.9 ± 1.3, $p=0.059$). In Nather et al.'s study, the major finding was complete wound closure in two cases and reducing the size of the wound in the third case, which enabled complete closure with standard dressing 3 weeks later. The study by Hargate was a pivotal study that was the basis for obtaining FDA approval for the indication of accelerated treatment of Herpes labialis lesions on or around the lips (K083767).²⁸

Reducing symptoms related to abnormal sensation

The two studies aimed at treating symptoms related to abnormal sensation included a double-blind RCT by Lavery et al.,¹⁸ which used a professional system at home to improve peripheral sensation of diabetic patients, and the case series by Merigo et al.¹¹ using a consumer device to treat nerve-related complications—anesthesia and paresthesia—following oral and dental surgery.

The study by Lavery et al. was the largest published study found in this literature search and included 60 patients randomized to self-applied, 90, daily, active or sham treatments. This was the only study that did not report favorable results for at-home light therapy over sham intervention. In contrast, Merigo et al. reported full resolution of symptoms

TABLE 2. DETAILED INFORMATION PERTAINING TO PATIENT CHARACTERISTICS, DOSAGE PARAMETERS, TREATMENT PROTOCOL, AND THE MAIN FINDINGS: ORDERED BY YEAR OF PUBLICATION

Source	Patient characteristics	Dosage parameters	Study design and treatment protocol	Main finding
Merigo et al. ¹¹	Postsurgical anesthesia/paresthesia left lower lip, right lower lip, or lower cheek associated with surgical anesthesia, osteonecrosis (related to bisphosphonates), or implant surgery, respectively. The latter case not responding to pharmacological treatment. Age 55–63 years; M:F 1:2; n=3.	Laser: 808 nm, 250 mW peak power, 15 KHz, 3.75 J/min over 4.5 × 1.0 cm ² for 15 min per session, total fluence 12.5 J/cm ² . ^a	Daily self-application at home on area of paresthesia for 1–2 sessions for 15 min over the lower lip, chin, and the mental foramen for 1–3 weeks. No. of treatment: 3–21	Complete resolution of symptoms. No adverse events or side effects were reported.
Saltmarche et al. ¹²	Mild to moderately severe cognitive impairment, which was diagnosed with dementia or Alzheimer’s disease 6 months to 8 years before participation in the study. Age 72–90 years; M:F 4:1; n=5.	LEDs: Intranasal home device—810 nm, 14.2 mW/cm ² , pulsed 10 Hz, 25 min to a total of 10.7 J/cm ² .	Daily intranasal applications at home by patient or caregiver. This study included a 12-week treatment phase followed by a 4-week “no treatment” phase. During the treatment phase, patients received “neuro” treatments at the clinic once a week (twice a week in the first 2 weeks), in addition to the intranasal home use device. No. of treatment: 84	Significant improvement in the Mini-Mental state exam and Alzheimer Disease Assessment Scale (MMSE, <i>p</i> <0.003; ADAS-cog, <i>p</i> <0.023) that was manifested by clinical benefits, including increased function, better sleep, fewer angry outbursts, less anxiety, and less wandering. However, these benefits were partially lost during the 4-week “no-treatment” follow-up. No adverse events were reported.
Formaini et al. ¹⁰	Monolateral or bilateral temporomandibular joint disorder, with acute pain restricted to the joint area, associated with the absence of any muscle tenderness during palpation. Age 17–64 years; M:F 5:19; n=24.	Laser: See Merigo et al. ¹¹	Daily 15-min self-applications of active or sham treatment at home for 2 weeks on each side. No. of treatment: 14	Significant pain reduction in active group compared with sham after 1 week (pain reduction by VAS after 1 week, LLL vs. Sham: 2.7 ± 0.9 vs. 0.4 ± 1, <i>p</i> <0.0001), maintained at 2 weeks. No adverse events.
Tang et al. ¹⁷	NCDME identified clinically and confirmed using spectral domain OCT. Age 42–71, all males; n=4 (8 affected eyes).	LEDs: Array of 670 nm diodes over an area of 10 cm ² with power density of 50 mW/cm ² and a dose of 4.4 J/cm ² in 88 sec of treatment (time limit controlled by an internal timer). ^a	Twice a day through a closed eyelid, 88 sec per application over 1 eye with the other serving as control, for 2–9 months. No. of treatments 60–270	Significant reduction in macular thickening in regions corresponding to thickened areas (% change from before to after treatment in thickness: treated 20.0% ± 11.7% vs. untreated –3.0% ± 8.0%). One patient developed sectoral optic nerve hyperemia and edema in the treated eye, consistent with NAION, but this was deemed not related to the treatment because the patient was at risk for NAION before the study.

(continued)

TABLE 2. (Continued)

Source	Patient characteristics	Dosage parameters	Study design and treatment protocol	Main finding
Naeser et al. ¹⁹	Closed head mTBI sustained in a motor vehicle accident 7 years before the treatment (patient 1) or sports and military related (patient 2). Age 52 and 59 years; M:F 0:2; n=2.	LEDs: Cluster of 633 and 870 nm diodes over an area of 5.35 cm in diameter with power density of 22.2 mW/cm ² and a dose of 13 J/cm ² . When applied to forehead, this is estimated to deliver 0.4 J/cm ² to the surface of the brain cortex.	Daily self-applications at home bilaterally and to midline sagittal areas using two LED clusters. Before home treatments, patient 1 received 7 months of weekly treatments at the clinic. Patient 2 began directly with daily home treatments. No. of treatment: 5 years daily	Improved cognitive functions: patient 1 improved focus time from 20 min to 3 h after 8 weeks of treatment. Patient 2 who was on medical disability returned to full work after 4 months of light treatments. However, regression appears if treatments are stopped for more than 1–2 weeks. Both patients were followed for at least 5 years and neither reported device-related adverse events.
Barolet and Boucher ²²	Bilateral abnormal scars requiring scar revision by CO ₂ surgery on both sides. Light treatment was given as prophylaxis to scar reformation. Age 27–57 years; M:F 1:2; n=3.	LEDs: 805 nm, 30 mW/cm ² , with a total fluence 27 J/cm ² per session.	Daily 15-min self-applications at home for 30 days on one side, while the other side served as control. No. of treatment: 30	Significant improvements on the active versus control side were seen by profile analysis of the scar, subjective grading, and Vancouver scar scale. No significant treatment-related adverse effects were reported.
Barolet et al. ²³	Photoaging treated by ablative skin rejuvenation. Light treatment was given as prophylaxis to side effects. Age 39–70 years; M:F 0:14; n=14.	LEDs: Red 660±10 nm pulsed 50 mW/cm ² for 160 sec accumulating to total fluence 4 J/cm ² . The spot size was 10×6 cm ² .	Daily self-applications at home over one side of the face (n=4) or both sides of the face (n=4) starting 2 days before procedure and then for 30 days after the procedure, or until redness resolved. In addition, a group of patients were treated on one side of the face at the clinic immediately after as well as 1, 2, 3, and 4 days postprocedure (n=3), and a group of patients was not treated with light (n=3). No. of treatment: 32	Significant reduction of erythema and edema mainly in the first few days after the procedure by blinded observer evaluation of treated versus untreated side. Moreover, by dermatoscopic measurement of erythema index (redness), home treatment as prophylaxis 2 days before the procedure resulted in greater erythema index reduction the first day after the procedure compared to treatment at the clinic beginning immediately after the procedure.
Lavery et al. ¹⁸	Diabetes and vibration perception threshold between 20 and 45 V. Age 65±2 years; M:F 17:43; n=60 (data for age and sex were reported separately for each group and pooled for this review).	LEDs: pads of 60 NIR (890 nm) gallium aluminum arsenide diodes providing 1.3 J/cm ² /min×40 min.	Daily 40-min self-applications at home of active or sham treatment for 90 days on the plantar aspect of the foot and both sides of the calf. No. of treatment: 90	No improvement in peripheral sensation, balance, pain, or quality of life compared to sham therapy.

(continued)

TABLE 2. (Continued)

Source	Patient characteristics	Dosage parameters	Study design and treatment protocol	Main finding
Nather et al. ²¹	Diabetic foot ulcer grade 2 that failed to heal after at least 1 month of standard therapy. Age 54–73 years; M:F 2:1; n = 3.	Pads of 60 NIR (890 nm) gallium aluminum arsenide diodes providing 1.3 J/cm ² /min × 30 min.	Thrice a week, 30-min applications by caregiver at home for up to 2 months. No. of treatment: 14–19	Complete closure of ulcers in combination with standard treatment. No adverse events were noted.
Hargate ²⁰	Cold sores on the lips and a history of recurrent orofacial herpes 2 (at least three episodes within the past year) (n = 32). No data about age or sex distribution reported.	LEDs: 1072-nm narrowband light from two LEDs with pulse frequency of 600 Hz and pulse width of 300 μs.	Thrice a day × 3 min per session for 2 days (6 sessions), self-application at home of active or sham treatment. No. of treatment: 6	Significant reduction in cold sore healing time (days to healing—active vs. sham: 6.3 ± 2.99 vs. 9.4 ± 4.58, p = 0.048), and reduction of time to crust formation (2.00 ± 1.21 vs. 2.88 ± 1.31, p = 0.059). No side effects were reported.
Stelian et al. ¹⁶	Degenerative osteoarthritis of the knee. Age 55–86 years; M:F 16:34; n = 50.	Laser: Red light—continuous wave 8 mW/cm ² and pulsed 100 Hz 34 mW/cm ² with total fluence 5.1 J/cm ² per treatment followed by infrared—continuous wave 11 mW/cm ² and pulsed 100 Hz 122 mW/cm ² with total fluence 5.1 J/cm ² with total energy of 5.6 J/cm ² per treatment.	Twice a day × 15 min per session (half-continuous wave and half pulsed) for 10 days, self-application at the nursing home of red, infrared, or sham treatment over both sides of the knee. No. of treatment: 20	Significant pain reduction as well as functional improvement in both red and NIR groups, but no pain reduction or functional improvement in sham group (pain reduction by VAS from baseline for red, NIR, sham: 3.2 vs. 3.9 vs. -0.1, p < 0.05; functional improvement by disability index questionnaire: 0.27 vs. 0.30 vs. 0.06, p < 0.05). The period from the end of treatment until the patients required retreatment was longer for red and infrared groups than for the placebo group (red 4.2 ± 3.0, infrared 6.1 ± 3.2, and sham 0.53 ± 0.62 months).

^aParameters from device specifications.

LED, light-emitting diode; mTBI, mild traumatic brain injury; NAION, nonarteritic ischemic optic neuropathy; NCDME, non-centered diabetic retinal edema; NIR, near infrared; VAS, Visual Analogue Scale.

following treatment in the 3 cases presented after as little as 3 and up to 21 daily treatments.

Prophylaxis of impaired healing or skin-related side effects

Both studies by Barolet and Boucher²² and Barolet²⁷ involved daily PBM irradiation as prophylaxis in conditions in which side effects are expected. In the first study, the objective was to prevent or reduce erythema and edema often associated with ablative cosmetic procedures,²⁷ and in the second study, the objective was to prevent or reduce scar formation in patients who previously had hypertrophic scars or keloids and were scheduled for scar removal procedures.²² Although the study groups in both trials were small, the split-face study design strengthened the results and enabled direct comparison of treated versus untreated sides by blinded evaluators.

In the first study,²⁷ the at-home PBM study group initiated self-treatments 2 days before ablative procedure and continued for 30 days after the procedure. The results were compared with a “clinic PBM” study group that received daily treatments 1–4 days after the procedure. The authors compared the effect of the treated to the untreated side in both groups and found that “at-home” treatment as prophylaxis resulted in much faster recuperation (erythema and edema reduction) in the first week on the LED-treated side compared to the clinic PBM group. In the second study, Barolet and Boucher²² presented a case series of three patients with bilateral scars that were removed surgically. The patients then initiated PBM self-treatment on the incision location on one side of the face, while the other side served as nonirradiated controls. Patients were followed up to 1 year postsurgery. Significant improvements in scar height as assessed macroscopically and by microtopography were reported at the PBM-treated side versus the nonirradiated side.

Reducing retinal thickness in diabetic retinal edema patients

Diabetes results in damage to the blood vessels. In the eye, this translates into leakage into the retina resulting in edema. In NCDME, the vision is not affected; however, this stage can deteriorate into centralized DME and with it, the gradual loss of vision. The extent of edema is measured by the thickness of the retina. Tang et al.¹⁷ applied PBM twice daily during 2–9 months to one of two eyes of four patients with NCMDE, while the other eye served as control. Significant reduction in macular thickness was reported in the PBM-treated eye, but not in the nontreated eye (20.0% ± 11.7% vs. –3.0% ± 8.0%). The authors reported an adverse event in one patient, but in their opinion, it was not related to the PBM treatment.

Improving cognitive function

Two studies using transcranial PBM, with or without intranasal at-home PBM, were found in the systematic review. Both had the objective of improving cognitive functions, but in very different medical conditions—TBI¹⁹ and dementia.¹² In the former,¹⁹ two cases of patients with TBI were reported to self-apply transcranial PBM treatments at home for up to 5 years. In the latter,¹² a case series of five

patients with varying degrees of Alzheimer-related dementia was presented. These patients received 12 weeks of transcranial PBM at the clinic once a week, but, in parallel, self-applied daily treatments at home with an intranasal PBM probe. A 4-week no-treatment phase followed the 12-week treatment phase. Both studies reported positive results in cognitive functions and behavioral parameters, but also stated that these benefits regressed if treatments were ceased.

Discussion

The results of this literature review show that PBM devices that are sold over the counter for home use are applied for a surprisingly wide range of applications with mostly positive results and without any reported adverse event (except of one possibly nonrelated). The devices are mostly based on LEDs in the NIR range of the spectrum, with pulsing, and with power and energy density within the range of WALT recommendations. In comparison to their clinical PBM counterparts, there are not many published studies using PBM devices at home, and those that are published are relatively small RCTs or small case series/reports.

From this review, and in accordance with the literature,²⁸ the parameters considered to be most important in evaluating the outcome of PBM studies were coherence, wavelength, power/energy density (irradiance and fluence), pulsing (or CW), treatment number, and frequency.

Coherence

Coherence is the property of light that enables the emitted photons to avoid complete scattering when initially penetrating the body, thereby reaching greater depth in the tissue. On this basis, it is generally accepted that LEDs are equally efficient as lasers for superficial use, and possibly for shallow structures, but that lasers are superior for deeper applications. Thus, clinical devices that have both LED probes and laser probes guide the users to apply LEDs for relatively superficial targets (wounds, lymph, and soft tissue), but to apply laser probes for deep targets (analgesia). Similarly, in this review, in applications that require reaching deeper structures such as for treatment of joint pain,¹⁰ the devices used were based on laser technology. However, most manufacturers use LEDs as the preferred light source. This is understandable in view of the stringent safety requirements by regulatory authorities regarding lasers, the advancement in technological aspects of LEDs, and their lower cost.

The debate regarding the importance of coherence is especially relevant for transcranial PBM, where light is expected to penetrate through the skull (and scalp, periosteum, meninges, and dura on the way) to reach the cortical surface of the brain.²⁹ The intranasal approach is one of the methods used to circumvent this problem where the light penetrates through the cribriform plate of the ethmoid bone (sieve like—with many holes), reaching subcortical and cortical structures of the limbic system related to Alzheimer’s disease. This approach is used in Saltmarche et al.’s study for treatment of mild to moderate Alzheimer patients, wherein an intranasal LED probe was placed inside the nostril with a clip.¹²

Wavelength

The wavelength used in most studies found in this review was NIR that is associated with greater depth of penetration. In agreement with this approach, Barolet²⁷ used only red LEDs for strictly superficial use, on unhampered skin, whereas when an incisional wound with a possibly forming scar was involved, the same author used a different version of the device with NIR wavelength.²² NIR was used also by Hargate²⁰ and Nather et al.²¹ for wound healing that involved both acute and chronic wounds, respectively, and by Fornaini et al.¹⁰ for reducing joint pain. It is interesting that in Naeser et al.'s study,¹⁹ the consumer device used for treating TBI had both red and NIR wavelengths.

Although most studies that use PBM for transcranial applications use NIR wavelengths exclusively to maximize penetration,²⁹ Naeser et al. postulates that a possible mechanism of action of PBM in TBI is by stimulating blood flow through the emissary veins located on the scalp surface. In their study, red wavelength was shown to stimulate blood flow and improve erythrocyte deformability, thereby justifying its use in addition to NIR. The other study found in this review in which both red and NIR were used was Stelian et al.'s study,¹⁶ in which PBM was used for reducing knee pain. The authors in the latter study did not relate to the specific effects of red versus NIR wavelength for this application. Tang et al.¹⁷ used red LEDs based on their previous pre-clinical studies.

Irradiance and fluence

The irradiance and fluence range reported in the studies found in this review were not large—14–55 mW/cm² and 4–50 J/cm². Most of the devices in this review are within the range of irradiance and fluence shown in other studies with their clinical counterparts.

Both studies dealing with joint pain in this review^{10,16} used the suggested dose by the WALT (780–860 nm lasers: 50–500 mW, minimal effective dose 4 J/point), and the beneficial outcome of both studies in pain [reduction of 3–3.9 corresponding to 30–39 mm in the Pain Visual Analogue Scale (VAS)] was similar to that found in a systematic review by Bjordal et al. for pain for joint disorders³⁰ [pain reduction of 29.8 mm (95% CI: 18.9–40.7) in favor of the active PBM groups].

Acceleration of wound healing is one of the first indications that PBM was used for, and one of the most thoroughly studied.³¹ In this review, we have found one study in which PBM was used to treat acute herpes labialis and another for diabetic recalcitrant use. PBM was shown to accelerate HSV-1-related wound healing and reduce recurrence rate in a clinical setting in several studies using a wide fluence range of 2,³² 4.5,³³ and 48 J/cm².³⁴ Hargate²⁰ did not disclose the fluence of the device and therefore it is not possible to compare them with the previous studies.

Regarding recalcitrant diabetic wounds, although many *in vitro* and *in vivo* studies evaluated the use of PBM for this indication in various models, only a few high-quality clinical studies can be found in the published literature. According to these, 4 J/cm² seems to be an effective fluence on points over the periphery of the wound that is covered with skin, whereas a much lower dose should be applied directly over the open wound.³⁵ In the study by Nather et al.,²¹ pads

that emit uniform light over the entire diabetic wounds were used with fluence of 1.3 J/cm² during 40 min, which adds up to a total dose of 52 J/cm². This is much higher than what was reported previously.

PBM prophylaxis for impaired healing was previously studied in patients undergoing surgery for inguinal hernias using a clinical device. Improvement in macroscopic appearance and reduction in scar thickness were reported following 13 J/cm² in NIR, but not in controls.³⁶ However, Barolet and Boucher²² used 27 J/cm² in NIR with a home-use device for the same indication in patients prone to scar formation, and reported beneficial outcomes compared to the control side. PBM was shown previously to decrease erythema and edema postablative procedures in a clinical setting with less than 1 J/cm² using one device³⁷ and up to 60 J/cm² in another.³⁸ In Barolet's study,²⁷ 4 J/cm² was used as prophylaxis for erythema and edema postablative procedure with a successful outcome.

PBM treatment for iatrogenic sensory aberration of the inferior alveolar was previously reported in the clinical setting in two separate clinical studies^{39,40} using a GaAlAs 820 nm laser, with irradiance of 5 mW/cm² and an energy dose of 6 J per point. The authors in both studies reported improvement in sensory function after completion of a 20-session protocol. In Merigo et al.'s study presented in this review,¹¹ the authors used PBM for the same indication with similar parameters—808 nm wavelength and energy dose of 5 J per point—and reported complete resolution of symptomatology after 3–21 treatments.

The rationale for treating diabetic neuropathy with PBM was to improve blood flow, thereby reducing symptoms of neuropathy. The double-blind RCT by Lavery et al.¹⁸ was planned to confirm or reject the findings of a retrospective cohort study by Powell et al.⁴¹ that followed 252 patients treated for the same symptoms, who received the same light treatment at the clinic until reversal of the symptoms and then continued the light therapy treatment at home. Powell et al. reported 78% reduction in falls and reversal of peripheral neuropathy within 1 month, which remained a year later.

In contrast, in the study by Lavery et al., no positive results of the light system were found over the controls that received sham irradiation with heat pads. This discrepancy is possibly due to the fact that Lavery et al.'s study did not select for patients who already had reversal of symptoms like Powell and changed the protocol to include heat as sham control, as well as to include only home treatments without sessions at the clinic.

In the last decade, PBM was applied to treat a variety of retinal diseases in humans after demonstrating beneficial effects in various animal models.⁴² One of the suggested mechanisms for this beneficial effect was presented in a study using long-term daily administration of brief application of 670 nm light in diabetic mice. It was shown that PBM treatment significantly inhibited the diabetes-induced leakage and degeneration of retinal capillaries, as well as the reduction in visual function in diabetic mice.⁴³ All clinical studies for ophthalmology-related studies used very brief treatments (40–80 sec). However, except the study by Tang et al.,¹⁷ which used continuous red LEDs 4.4 J/cm² twice daily at home, the rest of the studies used NIR lasers 0.2–0.4 J/cm² twice to thrice a week at the clinic for a limited

number of sessions with NIR lasers⁴² or multi-wave devices with both red and NIR.⁴⁴

Finally, in human transcranial PBM studies applied for neurological disorders, the irradiance and fluence regularly used in the clinic are in the range of 10–70 mW/cm² and 10–30 J/cm², respectively.²⁹ Both studies found in this review used devices that emitted irradiation in the lower end of these ranges with 14.2 and 22 mW/cm², and 10.7 and 13 J/cm² for Saltmarche et al.¹² and Naeser et al.,¹⁹ respectively.

Pulsing

Pulsing is not yet part of the WALT recommendations.¹³ Nevertheless, most home-use devices found in this review applied pulsing in their treatment protocols. It is widely accepted that by using pulsed photons, accumulative tissue heating is avoided during the pulse OFF time (referred to as the “quench period”), thereby enabling a deeper penetration while using higher power densities compared to CW protocol.⁴⁵ The added safety value of low-frequency pulsing is widely used in high-power lasers for ablative applications, where low frequencies up to 10 Hz are regularly used to avoid overlap of pulses that may result in thermal damage.

However, in PBM, the objective is not ablation and therefore peak power is lower, hence the frequency of pulses used may be higher. The added value of higher pulse frequencies may pertain to entrainment or synchronization (or resonance) of biological or chemical reactions, respectively, in response to light.⁴⁶ For example, microsecond pulsing patterns were found to be superior to millisecond pulsing for collagen production in human primary fibroblasts,⁴⁷ and while 100 Hz was found to be the best frequency for proliferation, 600 Hz was the best for oxidative bursts in human HEP-2 cells.⁴⁸ In the devices found in this review, the safety consideration may explain the choice of 100 Hz pulse frequency,¹⁶ and the specific pulsing effect may explain the added value of 15 KHz^{10,11} pulse frequency. It should be noted that some consumer devices use continuous irradiation, most notably the 670 nm LED device WARP10.^{17,49}

Treatment frequency

Home treatments are especially relevant when frequent sessions are required. Such situations can occur for a limited amount of time, for example, as an adjunct to periodontal therapy as suggested in the recent editorial by Tuner,² for postprocedural pain/inflammation control,¹¹ or as prophylaxis for skin side effects or impaired healing.^{22,27} In such situations, clinics or hospitals sometimes lend out home devices for patients for 2–4 weeks following procedures until pain/inflammation is resolved (G. Ross and C. Fornaini, pers. comm.).

Other conditions require treatments at home because traveling to the clinic is difficult and daily treatments are required for an indefinite amount of time, for example, in case of cognitive impairment,^{12,19} or when dealing with chronic joint pain on the background of rheumatism.¹⁶ Another situation that requires frequent sessions is when the medical condition is characterized by recurring condition such as with Herpes²⁰ or as suggested by Cassano et al.⁵⁰ for treatment of depression, in the study in which they used a transcranial PBM consumer device at the clinic for treat-

ment of major depressive disorder⁵⁰ or other neurobehavioral deficits.²⁹

Number of publications

PBM consumer devices are widely used, both directly by patients and by physicians/institutions that lend out these devices for postprocedural pain management. Nonetheless, it is surprising to find such a small number of studies designed to confirm their efficacy. We found only four studies that were double-blind RCTs. The remaining were small pilot studies or case series/reports.

There are several potential reasons for the paucity of publications. The major reason is of course financial. Clinical studies are expensive and cannot be conducted without significant funding. Many companies that have tried to design and distribute home-use devices have gone out of business because of the high cost of regulatory requirements and advertisement (personal communications). This situation limits the funding for basic and clinical studies that could have been provided by the companies—as is common in the pharmaceutical industry or in the cosmetics field for consumer devices.

Unfortunately, competitive grant money for studies with consumer devices is an even rarer occurrence. According to acknowledgments, affiliations, disclosures, or other listings in the studies found in this review, only one study was funded by competitive grant money,¹⁹ three were industry sponsored,^{12,20,22} and three received complimentary devices for use during the study.^{10,18,21} The lack of funding explains the limited size of the studies, which further lends to their reduced credibility that translates frequently to unwillingness to reimburse by the leading insurers.

Therefore, in order for the scientific and clinical community to appropriately evaluate the efficacy and benefits of consumer PBM devices, support for additional well-planned, adequately powered, controlled studies is an absolute necessity.

In addition, it will be of great value if physicians will publish their experience as retrospective case series or conduct open-label studies for those patients who receive devices for postprocedural applications. Companies selling PBM consumer devices can gather information on long-term safety and efficacy results by conducting postmarketing surveys or through testimonials. It is understood that such reports may be prone to bias; however, until appropriate funding for large-scale clinical studies with long-term follow-up will be available, such sharing of information is crucial for validation of this promising technology.

The limitations of this systematic review were mainly due to the small number of studies included and the variability in study design.

Conclusions

At-home PBM devices, sold over the counter, have good potential for effective and safe treatments in a variety of medical conditions requiring frequent sessions. However, appropriate evaluation of the efficacy and benefits of what appears to be very promising consumer PBM devices, requires additional, randomized, adequately powered, controlled studies, the support for which must be reprioritized by the relevant commercial and scientific institutions.

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Authors' Contributions

L.G.: Review concept and design; literature search and selection, data extraction and methodological quality assessment, data analysis and interpretation, and drafting and revision; and review of treatment parameters; N.N.H.: Literature search and selection, data extraction and methodological quality assessment, data analysis and interpretation, and drafting and revision. Both authors read and approved the final article.

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