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REVIEW

Photobiomodulation Using Light-Emitting Diode (LED) for Treatment of Retinal Diseases

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Abstract: Photobiomodulation (PBM) is a type of phototherapy that employs light-emitting diodes (LEDs) or low-power lasers to selectively administer specific wavelengths of visible light, ranging from 500 to 1000 nm, including near-infrared (NIR) wavelengths. LEDs are advantageous compared to lasers due to their ability to treat large areas at a lower cost, lack of tissue damage potential in humans, and reduced risk of eye-related accidents. The ophthalmology community has recently taken interest in PBM as a promising novel approach for managing various retinal conditions such as age-related macular degeneration, retinopathy of prematurity, retinitis pigmentosa, diabetic retinopathy, Leber's hereditary optic neuropathy, amblyopia, methanol-induced retinal damage, and potentially others. This review critically assesses the existing body of research on PBM applications in the retina, focusing on elucidating the underlying mechanisms of action and evaluating the clinical outcomes associated with this therapeutic modality.

Keywords: photobiomodulation, near-infrared, light emitting diode, age-related macular degeneration

Introduction

The therapeutic properties of red light have been widely recognized for many years. In contemporary times, this methodology is referred to as low-level laser therapy or photobiomodulation (PBM), specifically utilizing far-red to near-infrared (FR/NIR) light therapy. PBM involves the use of brief exposures to FR/NIR light (600–1000nm) emitted by a laser or light-emitting diode (LED). Due to the ability of longer wavelengths to penetrate tissues deeply, PBM therapy is currently being applied to facilitate wound healing, alleviate neurological pain, aid in recovery after peripheral nerve injuries, stroke, and heart attacks. A recent advancement of PBM is its innovative and non-invasive application for treating challenging retinal conditions that pose a threat to vision. Potential targets include age-related macular degeneration (AMD), retinopathy of prematurity (ROP), diabetic retinopathy, Leber's hereditary optic neuropathy, methanol-induced retinal damage, and potentially other related conditions.[1] This review presents a historical outlook on the role of PBM in the medical field, particularly concerning retinal diseases and their underlying mechanisms.

Photobiomodulation (PBM) therapy employs low-intensity light at specific wavelengths, primarily in the visible to near-infrared (NIR) range, to influence cellular processes. PBM has been used to treat various health conditions, including cognitive decline, wound healing, chronic skeletal muscle injury, and pain.[2]

PBM affects numerous cellular functions, such as gene expression, cellular growth, proliferation, survival, and differentiation.[3] The primary target for light absorption in the red-to-NIR region is cytochrome c oxidase (CcO), a key component of the mitochondrial electron transport pathway.[4] Activation of CcO initiates a series of biochemical reactions that result in increased production of adenosine triphosphate (ATP), decreased levels of reactive oxygen species (ROS), and enhanced antioxidant protection. These factors contribute to the restoration of cellular function.

Research suggests that PBM can regulate gene expression, activate transcription factors, modulate calcium signaling, and impact pathways associated with cell death, stress, and inflammation.[5–7]

The retina, which is highly dependent on energy and susceptible to mitochondrial dysfunction, represents a potential therapeutic target for PBM.[8] Preclinical studies have shown that PBM can reduce cell death, alleviate oxidative stress,

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and attenuate the immune response in retinal cells.[9] In animal models, PBM has demonstrated efficacy in reducing photooxidative stress,[10] hyperoxic stress,[11] retinopathy of prematurity,[6] and age-related changes in the retina.[12] These effects are mediated by the modulation of anti-inflammatory genes and proteins, resulting in a reduction of complement pathway mediators like C2a and C3a in the retina.[12–14]

Mechanisms of Action of Photobiomodulation (PBM)

Photobiomodulation (PBM) differs significantly from conventional laser medicine practices, which primarily rely on thermal mechanisms such as heating and burning. Instead of utilizing heat, PBM harnesses the photochemical conversion potential of low-intensity near-infrared (FR/NIR) light within the range of 630–1000 nm.[15–18]

Early studies in the late 1980s and 1990s shed light on the mechanism behind PBM, indicating that mitochondria serve as subcellular targets of FR/NIR light. It was proposed that a molecule called cytochrome C oxidase (CcO), situated inside the mitochondria, acts as the primary acceptor of light energy.[15–19]

CcO is responsible for transferring electrons from cytochrome C to molecular oxygen, which is the final step in the mitochondrial respiratory chain and crucial for cellular energy production. Further investigations into the action spectrum of FR/NIR light, which refers to the biological response based on wavelength, also supported CcO as the primary mediator of photoreceptor.[3,20]

Experiments conducted with HeLa cells, primary neurons, and rat retinas revealed the effects of PBM on CcO activity. For example, exposure to 670 nm light reversed the inhibitory impact of tetrodotoxin, a sodium channel blocker that can downregulate cytochrome C oxidase, in primary neuronal cells. Furthermore, PBM counteracted the toxic effects of formic acid on mitochondrial cytochrome C oxidase in rat retinas, resulting in improved vision outcomes.[20–22]

Stimulation of cytochrome C oxidase by FR/NIR light is believed to enhance energy production by mitochondria, increase metabolic rate, promote cell proliferation and migration.[23,24]

Moreover, investigations utilizing retinas from diabetic rodents have demonstrated that photobiomodulation (PBM) elicits a reduction in diabetes-induced inflammation or retinal vasculature.[25] Subsequently, cDNA microarray analysis conducted on human fibroblast cells exposed to red light revealed significant alterations in gene expression induced by PBM, including the upregulation of proteins constituting the mitochondrial respiratory chain and antioxidant genes.[26] Simultaneously, PBM was found to downregulate genes associated with apoptosis and stress response.[27,28]

PBM may also exert its effects by augmenting the bioavailability of nitric oxide (NO), stimulating its release from intracellular repositories like heme-containing proteins. Correspondingly, absorption measurements performed on HeLa cells by Karu[20] demonstrated that PBM induces NO dissociation from cytochrome C oxidase heme 3A under normal oxygen conditions.[4] As NO acts as an inhibitor of mitochondrial respiration, its separation from cytochrome C oxidase would reinstate mitochondrial oxygen consumption, subsequently enhancing energy production and promoting cellular metabolism. Additionally, the dissociated NO could serve as a signal for intracellular and extracellular hypoxia, diffusing out of the cell to function as a vasodilator and potentially triggering other undiscovered downstream effects. However, it is important to note that a study by Tang et al[25] failed to establish a connection to NO, as there was no change in NO concentration observed in cultured retinal cell lines (RGC5 and 661W) following PBM treatment. The beneficial impact of PBM on cell culture under high glucose stress conditions was diminished when the NO scavenger carboxy-PTIO was used, suggesting an NO-independent mechanism of action for PBM. Notably, a key caveat of the studies conducted by Karu and Tang[20,25] is that they employed different cell lines and experimental conditions.

In addition to the direct influence of PBM on gene expression and metabolic activity of photoreceptor cells, it is probable that neighboring cell types, particularly Müller cells, contribute to the favorable outcomes. Müller cells, acting as microglia in the retina, offer protection to photoreceptors.[29–32]

Albarracin and Valter[33] conducted a study on a rat model of light-induced retinal degeneration to investigate the effects of pre-treatment with 670 nm light. They observed that this pre-treatment resulted in beneficial changes in Müller cells, which are important supporting cells in the retina. These changes included the preservation of structural integrity, reduced stress response, and absence of gliosis.

The researchers also found that the pre-treatment maintained the normal metabolic state of Müller cells, as indicated by the continued expression of glutamine synthetase. This enzyme is crucial for clearing excess glutamate released by

photoreceptor cells. However, Müller cells can also contribute to retinal degeneration by producing free radicals and releasing pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF) and interleukin (IL-1).

Furthermore, early inflammatory changes in photoreceptor cells trigger immune responses that accelerate disease progression, and Müller cells play a key role in propagating this inflammation. Interestingly, Albarracin and Valter[31] discovered that pre-treatment with 670 nm light suppressed the upregulation of TNF in Müller cells and reduced the subsequent activation of NO synthase, an enzyme that produces the reactive radical nitric oxide (NO), which disrupts photoreceptor metabolism.[32]

In summary, significant progress has been made in understanding the mechanisms underlying the success of photobiomodulation (PBM). However, new signal transduction pathways are continually being explored, and there is still much to uncover in this complex puzzle.

Preclinical Studies Demonstrating the Use of 670 nm LED for the Treatment of Retinal Diseases

Photobiomodulation with 670 nm LED Enhances Retinal Wound Healing

The application of photobiomodulation to promote wound healing presents a promising approach for treating tissue injuries that could be adversely affected by more invasive methods. This is particularly relevant in the case of retinal or cerebral lesions, where photobiomodulation can serve as a primary or supplementary therapeutic intervention. For example, the use of laser beams may result in retinal injuries, and the prevalence of such injuries has been on the rise due to the increased utilization of lasers in military and industrial domains, with this trend expected to continue.[34]

Our research involved investigating laser-induced retinal injuries using a non-human primate model. Each experiment included one monkey subjected to laser treatment without LED therapy and another monkey receiving LED treatment (at a wavelength of 670 nm and an energy density of 4 J/cm2). A laser grid consisting of 128 spots was applied to the macula and perimacula regions of the central retina in the monkeys' right eyes. This grid induced grade I and II burns, affecting the photoreceptors and outer nuclear layer of the retina. To evaluate the functional condition of the retina, multifocal electroretinography (ERG) was performed.[34]

In the initial experiment, LED-treated monkeys underwent treatment at 1, 24, 72, and 96 hours after the injury caused by the laser. Both LED-treated and untreated monkeys exhibited a temporary increase in ERG amplitude shortly after the laser injury, but the increase was more pronounced in the LED-treated group. Assessment of the severity of the laser burn revealed a more than 50% improvement in retinal healing after one month in the LED-treated monkey compared to the untreated monkey. Furthermore, optical coherence tomography measurements demonstrated that the foveal retinal thickness in LED-treated animals remained consistent with pre-laser levels, while it was reduced by 50% in untreated animals. Notably, LED treatment prevented the loss of cytochrome oxidase staining in the lateral geniculate nucleus, indicating that the brain of LED-treated animals responded more effectively to visual input from the "healed" retina compared to untreated animals.[34]

LED Treatment Attenuates Mitochondrial Injury Induced by Methanol Intoxication

The study investigated the potential of using 670 nm light-emitting diode (LED) therapy to protect the retina against methanol-induced damage. Methanol toxicity leads to retinal and optic nerve injury, resulting in vision loss. The toxic byproduct of methanol metabolism, formic acid, is known to impair the crucial mitochondrial enzyme cytochrome oxidase. The researchers aimed to determine if exposure to monochromatic red radiation from 670 nm LED arrays could counteract the toxic effects of methanol-derived formic acid in a rodent model.

Using electroretinography to assess retinal function, the study found that three short treatments (2 minutes and 24 seconds each) with 670 nm LED therapy (4 J/cm2) at 5, 25, and 50 hours after methanol intoxication significantly reduced the harmful effects of methanol-derived formate on the retina during intoxication. Moreover, it greatly facilitated the recovery of retinal function following intoxication. Additionally, the LED treatment prevented histopathological changes induced by methanol-derived formate in the retina.

These findings establish a connection between the impacts of monochromatic red and near-infrared light on mitochondrial oxidative metabolism in laboratory experiments and their potential for protecting the retina in living

organisms. Based on these results, further investigation into the effectiveness of 670 nm LED therapy in treating retinal degenerative diseases is warranted.[35]

LED Therapy for the Treatment of Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a heterogeneous group of retinal dystrophies that lead to vision loss due to the degeneration of the retina. The majority of RP cases are caused by mutations in the rhodopsin gene, resulting in photoreceptor death. The exact mechanism behind this degeneration is not fully understood, but it is believed that the mutation alters the structure and function of rhodopsin. This alteration leads to misfolding of opsin proteins, which are responsible for binding to the cis-retinal chromophore. Misfolded opsins fail to adequately sequester the chromophore, leading to free radical reactions, oxidative stress, and increased vulnerability of photoreceptor cells to apoptosis.

In the study conducted by Eells et al[36] they investigated the effects of 670 nm LED treatment on the P23H-3 rat model, which mimics a rhodopsin mutation found in humans.[35] The researchers administered daily LED treatment for five days during the critical period of photoreceptor development in these rats. The LED array was positioned over the rats' heads at a distance of 2 cm, exposing both eyes. The treatment involved irradiation at 670 nm for 3 minutes, resulting in specific power intensity and energy density parameters.

The study findings showed that the LED treatment increased mitochondrial cytochrome oxidase activity, upregulated the production of antioxidant protective enzymes and cofactors, enhanced the production of neurotrophic factors, and prevented apoptotic cell death in the photoreceptors. These results have significant implications for the potential use of photobiomodulation in the treatment of retinal degenerative diseases. The research conducted with the P23H-3 rat model lays the groundwork for future clinical trials involving photobiomodulation in human patients. The obtained molecular, biochemical, and functional insights will provide crucial information necessary for comprehensive FDA approval of far-red to near-infrared LED devices for the treatment of retinal degenerative diseases.[35,36]

Antiangiogenic Activity of Photobiomodulation

Our research team recently conducted a study to investigate the effects of photobiomodulation (PBM) using a light-emitting diode (LED) on the vascular system. We utilized the chorioallantoic embryonic membrane of chicken eggs (CAM) as an experimental model and employed quantitative metrics to assess morphological changes.[37]

The PBM source used in our experiment was a phototherapy device equipped with a LED emitting light at a wavelength of 670 nm. Red light was applied at a distance of 2.5 cm from the CAM surface in different sessions of 90 seconds each (2x, 4x, or 8x), and we analyzed the vascular network topology using AngioTool software developed by the National Cancer Institute in the United States. To establish control groups, we treated one group with phosphate-buffered saline (PBS) and another with a bevacizumab solution (Avastin) known as the positive control (Beva).

We observed a decrease in the total length of blood vessels in both the Beva group (24.96 ± 67 12.85%) and the groups subjected to red light therapy at 670 nm - 34.66 ± 8.66% (2x), 42.42 ± 5.26% (4x), and 38.48 ± 6.96% (8x) compared to the control group. In particular, the incidence of 5.4 J/cm2 over 4 sessions (4x) resulted in a more regular vascular pattern. The reduction in vessel length was more pronounced in the groups exposed to a higher incidence of 670 nm red light (4x and 8x) (Figure 1).[37]

In conclusion, our study demonstrates that photobiomodulation can contribute to the reduction of blood vessel formation in the CAM and induce changes in the network topology. These findings suggest the potential application of this therapy in clinical studies involving patients with retinal diseases characterized by abnormal blood vessel growth, such as age-related macular degeneration (AMD).

Clinical Studies Demonstrating the Use of LED for the Treatment of Retinal Diseases

Photobiomodulation in Age-Related Macular Degeneration

Numerous clinical studies have examined the effectiveness and safety of Photobiomodulation (PBM) in individuals with dry age-related macular degeneration (AMD). Our research group assessed the immediate outcomes of retinal functional behavior in patients with dry AMD treated with PBM using a 670nm LED light source (this study included patients with

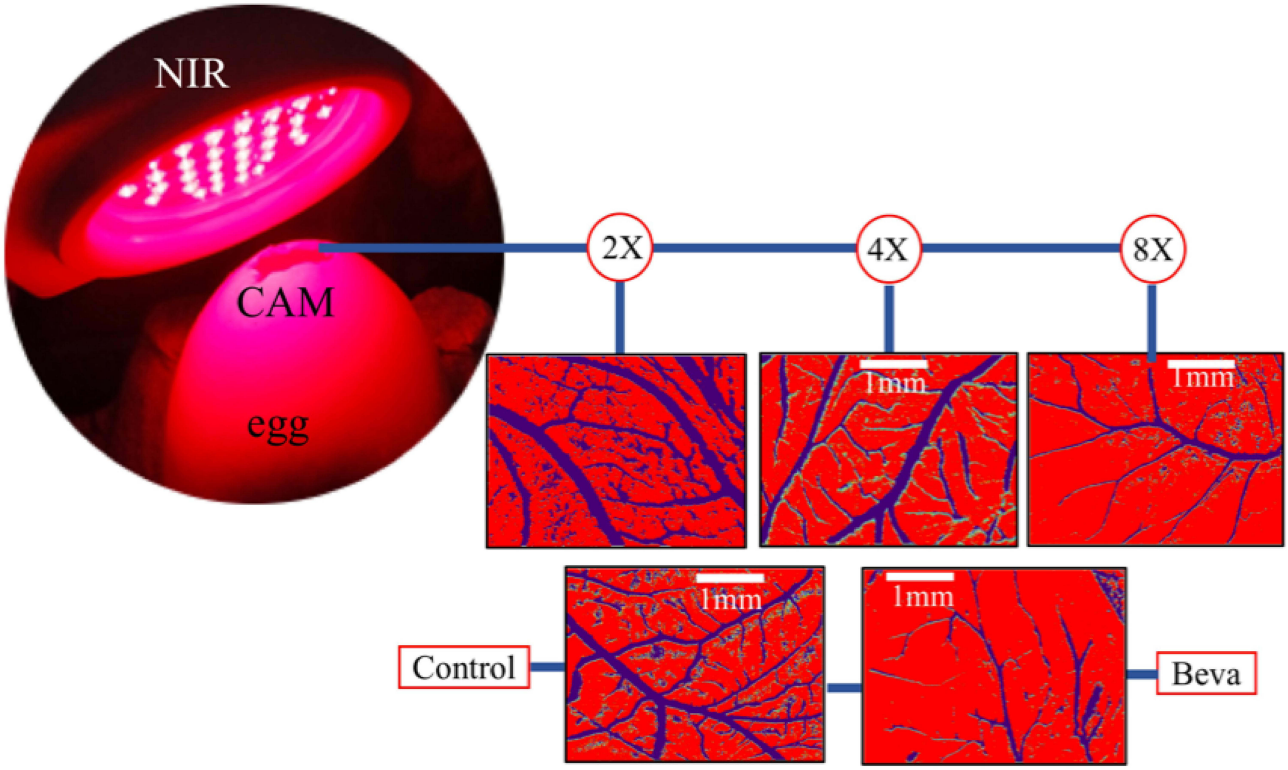

Figure 1 The upper part shows a sequence of 2, 4 and 8 applications of photobiomodulationPBM and the progressive decrease of the vascular network that is similar to the action of bevacizumab (below).
Notes: Reprinted from Dourado LFN, Siqueira RC, Alves AP, Paiva MRB, Agero U, Cunha Junior AS. Antiangiogenic activity of photobiomodulation in experimental model using chorioallantoic embryonic membrane of chicken eggs. Arq. Bras. Oftalmol. 2024;87(1):e2021–0524.[37]

drusen and also with geographic atrophy). A total of ten patients with dry AMD underwent nine PBM sessions, each involving exposure to a 670 nm LED light at a power density of 50 mW/cm2 for 88 seconds (Figure 2). The cumulative dose delivered per session was 4 J/cm2. The effects of therapy on best-corrected visual acuity (BCVA), retinal sensitivity, and the characteristics of the treated area were evaluated using various diagnostic tools such as multifocal electroretinography (ERG), optical coherence tomography (OCT), fluorescence retinography (FR), and autofluorescence (AF). Baseline measurements were compared with those obtained after nine PBM sessions, and statistical analyses were conducted using Chi-square and Student's t-tests with a significance level set at 0.05.[39]

Results showed a significant improvement in BCVA, with an average decrease from 1.1 to 0.98 LogMAR ($p = 0.01$). The visual field examination revealed significant enhancements in mean deviation (−12.6% to −10.6%), standard deviation (10.54% to 9.89%), and index of deviation (56% to 60%) of background perimeter ($p = 0.02$, 0.03, and 0.02, respectively). No adverse events were reported during the follow-up period, and there were no abnormalities observed in OCT, ERG, FR, or AF findings.[39]

This short-term study demonstrates the potential of PBM as a safe and effective treatment option for improving visual acuity and macular perimetry in patients with dry AMD. Other studies using the multiwavelength approach have also shown statistically significant benefits on visual acuity, functional parameters, and disease morphology in patients with dry AMD.

The Valeda Light Delivery System, a PBM-based treatment specifically designed for ophthalmological use, has been approved as the first treatment for dry AMD. By utilizing multiple wavelengths (590 nm, 660 nm, and 850 nm), PBM targets different cellular outputs to improve clinical outcomes by stimulating cellular functions. Clinical trials have demonstrated that PBM can enhance vision and reduce drusen in patients with dry AMD (Figure 3).

The LIGHTSITE I pilot study conducted in 2018 investigated the effects of PBM in 30 subjects (46 eyes) with a diagnosis of dry AMD. The subjects were randomized into two groups: one received PBM treatment, and the other

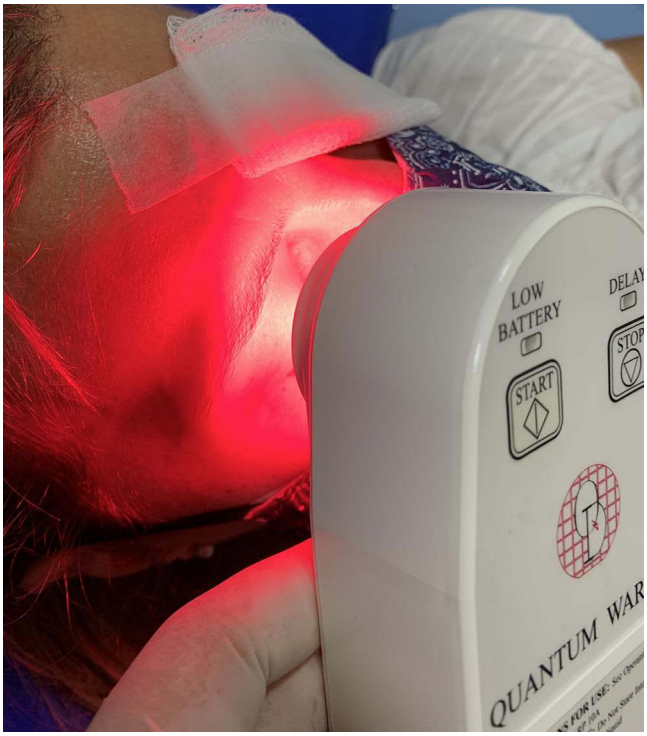

Figure 2 Quantum Devices WARP 10 is a high intensity, hand-held, portable, light-emitting diode (LED) device prototype used in our clinical study.

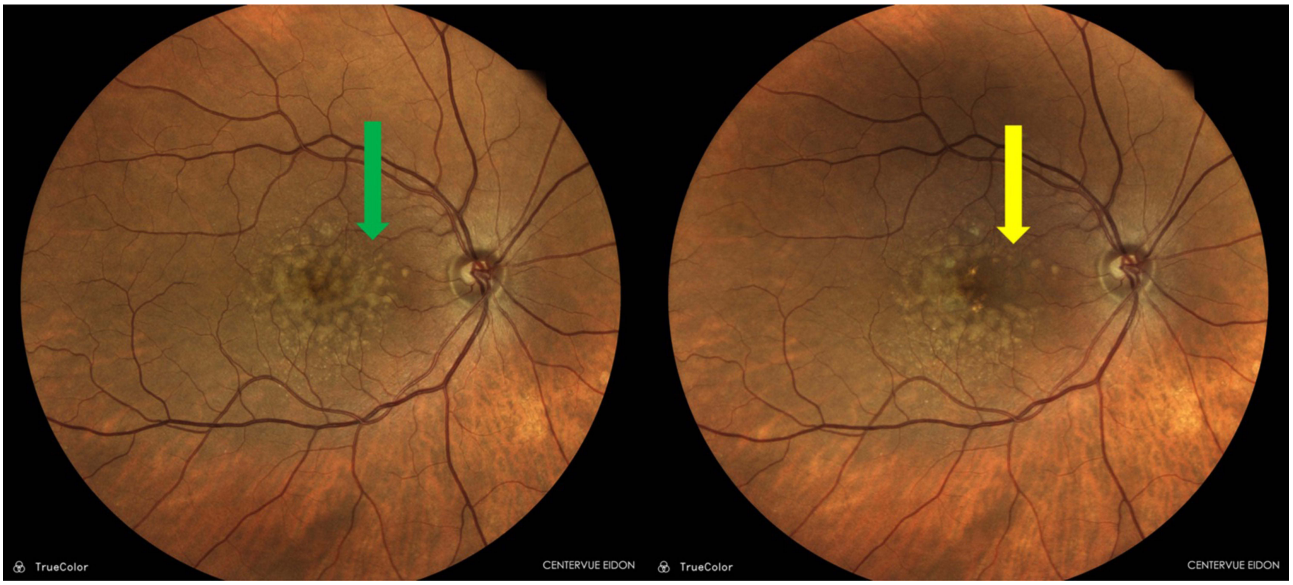

Figure 3 Patient underwent photobiomodulation therapy using the Valeda Light Delivery System and showed a reduction in drusen at the 1-year follow-up examination. Retinography showing the comparison before (green arrow) and after treatment (yellow arrow).

received a sham treatment. The PBM treatment consisted of nine sessions delivered over three weeks. After each series of PBM treatments, the subjects exhibited an average gain of approximately four letters in best-corrected visual acuity (BCVA) immediately at months 1 and 7. About 50% of the PBM-treated subjects experienced an improvement of five or more letters, compared to only 13.6% in the sham-treated group at month 1. Statistically significant improvements were observed in contrast sensitivity, central drusen volume, central drusen thickness, and quality of life ($p < 0.05$). No serious

device-related adverse events were reported. Furthermore, the PBM-treated group with a favorable response (five or more letter improvement) showed a gain of eight letters after initial treatment and displayed earlier stages of AMD disease ($p < 0.01$).[40]

The LIGHTSITE II study conducted in 2021 was a scientific investigation carried out in multiple retinal centers across Europe. It was designed as a prospective, double-blind, randomized clinical trial involving patients diagnosed with intermediate dry age-related macular degeneration (AMD). The participants were divided into two groups: one receiving photobiomodulation (PBM) therapy and the other receiving a sham treatment, with a ratio of 2:1 between the two groups. PBM therapy was administered three times over a period of 10 months, with each session occurring every 4 months. The study included a total of 44 subjects, who had an average age of 74.1 years and had been living with dry AMD for an average of 3.7 years since diagnosis.

The results of the study revealed a statistically significant improvement in best-corrected visual acuity (BCVA) among the subjects receiving PBM therapy compared to those in the sham treatment group. Specifically, after 9 months from baseline, there was a notable increase in BCVA in the PBM-treated group (with a p-value of 0.01), whereas the sham-treated group only experienced a minimal gain of 0.5 letters. On average, the PBM group showed a vision benefit of approximately 4 letters at the 9-month mark, demonstrating the effectiveness of PBM therapy in improving visual outcomes for individuals with intermediate dry AMD.[38]

The LIGHTSITE III trial, a prospective, double-blind, randomized, multicenter clinical trial, was conducted at ten major retina centers in the US and involved 100 individuals with early to intermediate dry age-related macular degeneration (AMD). The eyes were treated with the Valeda system every four months. The last treatment was administered at 21 months, and the final follow-up visit occurred at 24 months. The primary efficacy endpoint was best-corrected visual acuity (BCVA). At 24 months, there were minimal safety risks and high patient adherence, with 80% of patients completing the trial. In the FBM-treated arm, there was a statistically significant improvement in visual acuity at month 21 after the last treatment, with sustained vision benefits throughout the trial, including at the 24-month endpoint.[41]

The analysis included 91 eyes in the FBM treatment group and 54 eyes in the sham treatment group in the modified intent-to-treat population with at least 1 post-treatment visit. The study initially demonstrated a statistically significant improvement in the primary outcome, BCVA, at 13 months in the FBM treatment group compared to the sham treatment group ($p = 0.02$). Now, a sustained average increase in ETDRS letter score >5.0 letters from baseline is reported at both the 13-month and 21-month timepoints in individuals with FBM-treated BCVA ($p < 0.0001$). The improvement in BCVA from baseline at 24 months in the FBM treatment group was significantly greater than in the placebo group, 5.9 vs 1.0 letters ($p = 0.0015$). Approximately 58% of eyes treated with FBM had a gain of >5 letters with an average gain of 8.5 + 0.5 letters.[41]

The ELECTROLIGHT study (2021) conducted further investigations into the effects of Photobiomodulation Therapy (PBM) on individuals with dry Age-Related Macular Degeneration (AMD), specifically analyzing its impact on electroretinography (ERG) outcomes, which serve as a quantitative measure of functional vision enhancement. The study discovered that after the completion of the initial nine PBM treatments, there was a 14.4% improvement in the Multiluminance ERG magnitude AUC compared to the baseline measurement. In the intention-to-treat population, a 9% improvement was observed at the 6-month mark. Additionally, a significant positive correlation ($P < 0.05$) between Multiluminance ERG and Best Corrected Visual Acuity (BCVA) was noted following the initial PBM treatment. Other studies have also reported positive correlations between Multiluminance ERG and fixed luminance ($R = 0.870$) as well as chromatic ERG outcomes ($R = 0.676$). At the 6-month follow-up, subjects demonstrated an approximate improvement of 12.8 ± 0.98 letters in BCVA compared to their baseline scores. Furthermore, the Mars contrast sensitivity (CS) exhibited improvements from baseline to month 6 at distances of 40 cm (0.202 log ± 0.02), 80 cm (0.197 log ± 0.02), and 120 cm (0.28 log ± 0.03). Currently, the LIGHTSITE III pivotal trial is underway in the United States, involving 100 patients diagnosed with intermediate dry AMD.[42]

Photobiomodulation in Retinal Vascular Diseases

An exploratory investigation employing the Valeda device and its multiwavelength Photobiomodulation (PBM) method enrolled 18 participants (30 eyes; unpublished data) with normal vision but indications of diabetic macular edema (DME). Following PBM treatment, approximately 28.6% of eyes exhibited resolution of intra-retinal fluid, while 40% of eyes displayed resolution of hard exudates. The central retinal thickness remained unchanged, measuring 302±58 µm at baseline and 296±47 µm after completion of the nine-session treatment cycle. No instances of phototoxicity, such as disruptions in the photoreceptor layers or retinal pigment epithelium, were observed during both treatment and a follow-up period of up to 16 months (unpublished data). Visual acuity remained steady at 0.1±0.1 logMAR. The majority of patients reported significant improvements in their subjective vision and quality of life.[43]

In a randomized study conducted by the DRCR Retina Network, the effectiveness of a single wavelength (690 nm) was assessed in patients with center-involved DME and normal vision. The study concluded that the single-wavelength approach, administered through a wearable home device, was well tolerated but did not exhibit superiority over a placebo in reducing central retinal thickness.[44]

A clinical investigation is currently underway to evaluate the impact of PBM using a Joovv device emitting red/infrared LED (660 nm and 810 nm) on patients with age-related macular degeneration (AMD) and DME/diabetic retinopathy.[44] Additionally, ongoing research explores the use of NIR PBM in cases of central or branch retinal vein occlusion.[2,45]

Photobiomodulation Potential in Other Ophthalmic Indications

The photobiomodulation (PBM) technology has demonstrated anti-inflammatory and cell-protective effects, indicating its potential efficacy in various ophthalmic conditions, particularly those involving mitochondrial dysfunction as

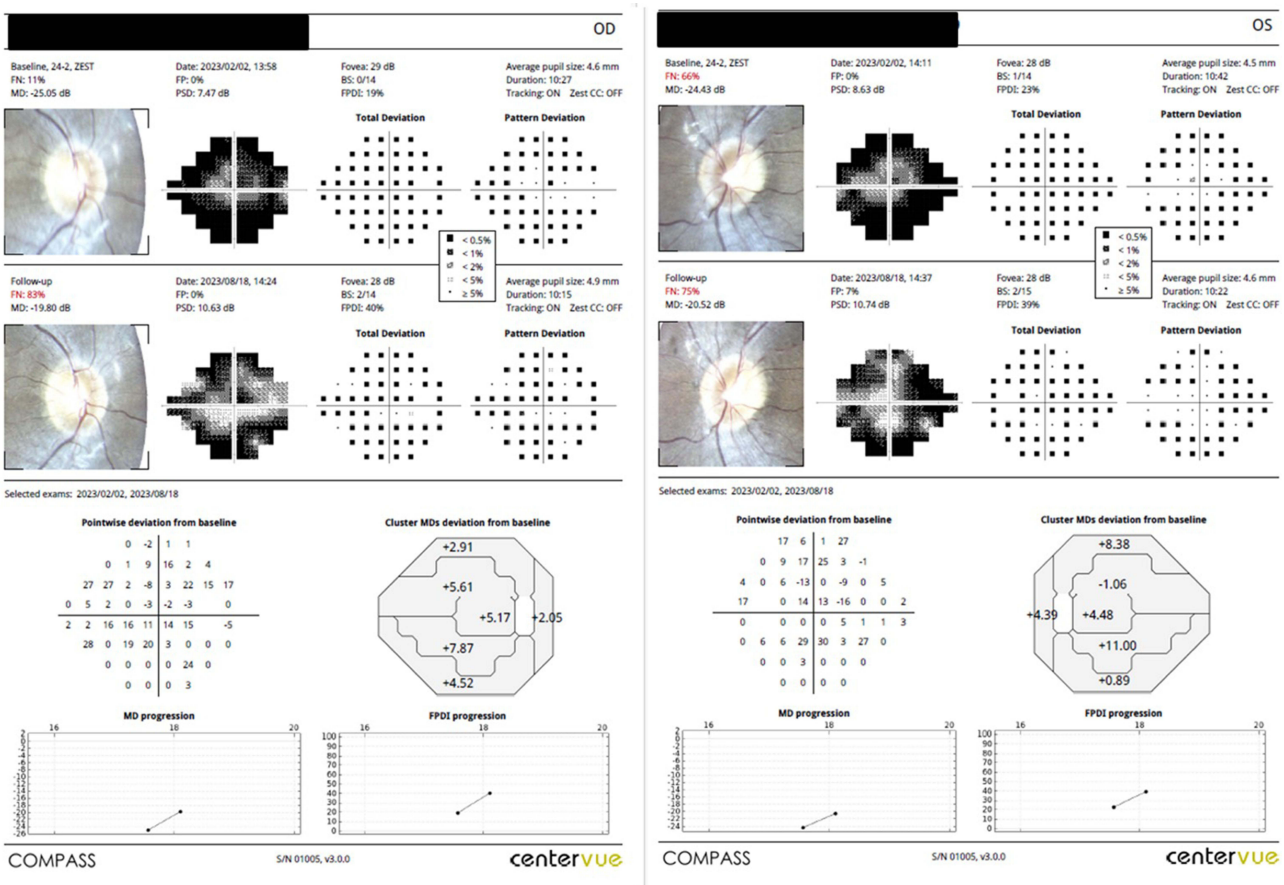

Figure 4 Patient with retinitis pigmentosa undergoing photobiomodulation therapy using the Valeda Light Delivery System and showing improvement in the visual field.

a contributing factor to disease progression. Neuronal damage is a significant component of numerous ophthalmic pathologies, for which no effective treatments currently exist. Leber hereditary optic neuropathy (LHON), an uncommon maternally inherited optic nerve disorder caused by specific mitochondrial DNA mutations, could potentially benefit from PBM therapy due to its impact on enhancing mitochondrial energy levels and function.[46,47] Similarly, many inherited retinal diseases are characterized by neurodegeneration and retinal atrophy, both of which may be attenuated through the application of PBM. Recent research has demonstrated the positive effects of PBM in Stargardt disease, a prevalent inherited macular degeneration disorder associated with mitochondrial dysfunction.[48] Benlahbib et al reported the use of photobiomodulation in cases of large soft druses and drusenoid pigment epithelial detachment.[49]

Additionally, a substantial body of scientific literature provides compelling evidence supporting the effectiveness of PBM in promoting wound healing, which may warrant exploration in ocular surgery and ocular injury cases.[50]

We are conducting a pilot study with patients affected by retinitis pigmentosa and have observed heterogeneous responses depending on the stage of the disease (data not yet published). In a specific case, one month after the 9-session protocol, the patient showed an improvement in visual field sensitivity 1 month after therapy (Figure 4).

Conclusion

Photobiomodulation (PBM) utilizing light-emitting diodes (LEDs) presents a promising and potent approach to modulate biological functions via low-power light wavelengths within the red to near-infrared spectrum. The metabolic processes of the eyes and neurons heavily depend on cytochrome c oxidase for energy production. PBM with LED technology has the ability to penetrate these specific tissues and aid in the recuperation of neurons affected by methanol intoxication, optic nerve trauma, neuropathy, retinal injuries, pigmentosa, and macular degeneration.[50] Thorough examination of animals and humans has not revealed any adverse effects. Hence, PBM using LEDs holds significant potential as a safe and efficacious method for various applications in the fields of ophthalmology and neurology in the foreseeable future.

Disclosure

The authors reports no conflicts of interest in this work.

References

1. Geneva II. Photobiomodulation for the treatment of retinal diseases: a review. *Int J Ophthalmol*. 2016;9(1):145–152. doi:10.18240/ijo.2016.01.24
2. Munk MR, Valter K. Photobiomodulation in age-related macular degeneration. *Retin Physician*. 2022;19:36–39.
3. Karu T. Primary and secondary mechanisms of action of visible to near-IR radiation on cells. *J Photochem Photobiol B*. 1999;49(1):1–17. doi:10.1016/S1011-1344(98)00219-X
4. Poyton RO, Ball KA. Therapeutic photobiomodulation: nitric oxide and a novel function of mitochondrial cytochrome c oxidase. *Discov Med*. 2011;11(57):154–159.
5. Cardoso LM, Pansani TN, Hebling J, de Souza Costa CA, Basso FG. Photobiomodulation of inflammatory-cytokine-related effects in a 3-D culture model with gingival fibroblasts. *Lasers Med Sci*. 2020;35(5):1205–1212. doi:10.1007/s10103-020-02974-8
6. Natoli R, Valter K, Barbosa M, et al. 670nm photobiomodulation as a novel protection against retinopathy of prematurity: evidence from oxygen-induced retinopathy models. *PLoS One*. 2013;8(8):e72135. doi:10.1371/journal.pone.0072135
7. Benson P, Kim JY, Riveros C, Camp A, Johnstone DM. Elucidating the time course of the transcriptomic response to photobiomodulation through gene co-expression analysis. *J Photochem Photobiol B*. 2020;208:111916. doi:10.1016/j.jphotobiol.2020.111916
8. Lock JH, Irani NK, Newman NJ. Neuro-ophthalmic manifestations of mitochondrial disorders and their management. *Taiwan J Ophthalmol*. 2021;11(1):39–52. doi:10.4103/tjo.tjo_68_20
9. Lu YZ, Natoli R, Madigan M, et al. Photobiomodulation with 670 nm light ameliorates Müller cell-mediated activation of microglia and macrophages in retinal degeneration. *Exp Eye Res*. 2017;165:78–89. doi:10.1016/j.exer.2017.09.002
10. Albarracin R, Eells J, Valter K. Photobiomodulation protects the retina from light-induced photoreceptor degeneration. *Invest Ophthalmol Vis Sci*. 2011;52(6):3582–3592. doi:10.1167/iovs.10-6664
11. Albarracin R, Natoli R, Rutar M, Valter K, Provis J. 670 nm light mitigates oxygen-induced degeneration in C57BL/6J mouse retina. *BMC Neurosci*. 2013;14(1):125. doi:10.1186/1471-2202-14-125
12. Begum R, Powner MB, Hudson N, Hogg C, Jeffery G. Treatment with 670 nm light up regulates cytochrome C oxidase expression and reduces inflammation in an age-related macular degeneration model. *PLoS One*. 2013;8(2):e57828. doi:10.1371/journal.pone.0057828
13. Saliba A, Du Y, Liu H, et al. Photobiomodulation mitigates diabetes-induced retinopathy by direct and indirect mechanisms: evidence from intervention studies in pigmented mice. *PLoS One*. 2015;10(10):e0139003. doi:10.1371/journal.pone.0139003
14. Rutar M, Natoli R, Albarracin R, Valter K, Provis J. 670-nm light treatment reduces complement propagation following retinal degeneration. *J Neuroinflammation*. 2012;9(1):257. doi:10.1186/1742-2094-9-257
15. Hilf R, Murant RS, Narayanan U, Gibson SL. Relationship of mitochondrial function and cellular adenosine triphosphate levels to hematoporphyrin derivative-induced photosensitization in R3230AC mammary tumors. *Cancer Res*. 1986;46(1):211–217.

16. Karu T, Pyatibrat L, Kalendo G. Irradiation with He-Ne laser increases ATP level in cells cultivated in vitro. *J Photochem Photobiol B*. 1995;27(3):219–223. doi:10.1016/1011-1344(94)07078-3
17. Bakeeva LE, Manteĭfel VM, Rodichev EB, Karu TI. Formation of gigantic mitochondria in human blood lymphocytes under the effect of an He-Ne laser. *Mol Biol (Mosk)*. 1993;27(3):608–617.
18. Manteifel V, Bakeeva L, Karu T. Ultrastructural changes in chondriome of human lymphocytes after irradiation with He-Ne laser: appearance of giant mitochondria. *J Photochem Photobiol B*. 1997;38(1):25–30. doi:10.1016/S1011-1344(96)07426-X
19. Karu TI. *Photobiology of Low-Power Laser Therapy*. United Kingdom: The Universities Press (Belfast) Ltd; 1989.
20. Karu TI, Pyatibrat LV, Kolyakov SF, Afanasyeva NI. Absorption measurements of a cell monolayer relevant to phototherapy: reduction of cytochrome c oxidase under near IR radiation. *Photomed Laser Surg*. 2005;81(2):98–106.
21. Karu TI, Pyatibrat LV, Afanasyeva NI. A novel mitochondrial signaling pathway activated by visible-to-near infrared radiation. *Photochem and Photobiol*. 2004;80(2):366–372.
22. Wong-Riley MT, Liang HL, Eells JT, et al. Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: role of cytochrome c oxidase. *J Biol Chem*. 2005;280(6):4761–4771. doi:10.1074/jbc.M409650200
23. Eells JT, Henry MM, Summerfelt P, et al. Therapeutic photobiomodulation for methanol-induced retinal toxicity. *Proc Natl Acad Sci*. 2003;100(6):3439–3444. doi:10.1073/pnas.0534746100
24. Lovschall H, Arenholt-Bindslev D. Low level laser therapy effect on mitochondrial rhodamine 123 uptake in human oral fibroblasts in vitro. *Lasers Life Sci*. 1998;8:101–116.
25. Tang J, Du Y, Lee CA, Talahalli R, Eells JT, Kern TS. Low-intensity far-red light inhibits early lesions that contribute to diabetic retinopathy: in vivo and in vitro. *Invest Ophthalmol Vis Sci*. 2013;54(5):3681–3690. doi:10.1167/iovs.12-11018
26. Zhang Y, Song S, Fong CC, Tsang CH, Yang Z, Yang M. cDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light. *J Invest Dermatol*. 2003;120(5):849–857. doi:10.1046/j.1523-1747.2003.12133.x
27. Lohr NL, Keszler A, Pratt P, Bienengraber M, Warltier DC, Hogg N. Enhancement of nitric oxide release from nitrosyl hemoglobin and nitrosyl myoglobin by red/near infrared radiation: potential role in cardioprotection. *J Mol Cell Cardiol*. 2009;47(2):256–263. doi:10.1016/j.yjmcc.2009.03.009
28. Shiva S, Gladwin MT. Shining a light on tissue NO stores: near infrared release of NO from nitrite and nitrosylated hemes. *J Mol Cell Cardiol*. 2009;46(1):1–3. doi:10.1016/j.yjmcc.2008.10.005
29. Rattner A, Nathans J. The genomic response to retinal disease and injury: evidence for endothelin signaling from photoreceptors to glia. *J Neurosci*. 2005;25(18):4540–4549. doi:10.1523/JNEUROSCI.0492-05.2005
30. Joly S, Lange C, Thiersch M, Samardzija M, Grimm C. Leukemia inhibitory factor extends the lifespan of injured photoreceptors in vivo. *J Neurosci*. 2008;28(51):13765–13774. doi:10.1523/JNEUROSCI.5114-08.2008
31. Norenberg MD. Distribution of glutamine synthetase in the rat central nervous system. *J Histochem Cytochem*. 1979;27(3):756–762. doi:10.1177/27.3.39099
32. Linser P, Moscona AA. Induction of glutamine synthetase in embryonic neural retina: localization in Müller fibers and dependence on cell interactions. *Proc Natl Acad Sci U S A*. 1979;76(12):6476–6480. doi:10.1073/pnas.76.12.6476
33. Albarracin R, Valter K. 670 nm red light preconditioning supports Muller cell function: evidence from the white light-induced damage model in the rat retina. *Photochem Photobiol*. 2012;88(6):1418–1427. doi:10.1111/j.1751-1097.2012.01130.x
34. Whelan HT, Wong-Riley MT, Eells JT, VerHoeve JN, Das R, Jett M. DARPA soldier self care: rapid healing of laser eye injuries with light-emitting diode technology. *NATO RTO-MP-HFM*. 2005;109:1–18.
35. Eells JT, DeSmet KD, Kirk DK, et al. Photobiomodulation for the treatment of retinal injury and retinal degenerative diseases. In: Waynant R, Tata DB, editor. *Proceedings of Light-Activated Tissue Regeneration and Therapy Conference. Lecture Notes in Electrical Engineering*. Vol. 12. Springer; 2008.
36. Yu D, Cringle S, Valter K, Walsh N, Lee D, Stone J. Photoreceptor death, trophic factor expression, retinal oxygen status and photoreceptor function in the P23H Rat. *Invest Ophthalmol Vis Sci*. 2004;45(6):2013–2019. doi:10.1167/iovs.03-0845
37. Dourado LFN, Siqueira RC, Alves AP, Paiva MRB, Agero U, Cunha Junior AS. Antiangiogenic activity of photobiomodulation in experimental model using chorioallantoic embryonic membrane of chicken eggs. *Arq Bras Oftalmol*. 2024;87(1):e2021–0524. doi:10.5935/0004-2749.2021-0524
38. Markowitz SN, Devenyi RG, Munk MR, et al. A double-masked, randomized, sham-controlled, single-center study with photobiomodulation for the treatment of dry age-related macular degeneration. *Retina*. 2020;40(8):1471–1482. doi:10.1097/IAE.0000000000002632
39. Siqueira RC, Belíssimo LM, Pinho TS. Short-term results of photobiomodulation using light-emitting diode light of 670 nm in eyes with age-related macular degeneration. *Photobiomodul Photomed Laser Surg*. 2021;39(9):581–586. doi:10.1089/photob.2021.0005
40. Merry GF, Munk MR, Dotson RS, Walker MG, Devenyi RG. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration. *Acta Ophthalmol*. 2017;95(4):e270–e277.
41. Modi Y, Russell MW, Singh RP, Tedford C. Clinical Trial Download: Lightsite III-24-month Photobiomodulation Results. Noninvasive treatment could slow progression in intermediate AMD. *Retinal Physician*. 2023;20:47–48.
42. Perich L, Montzka D, Munk M, et al. Improvement of visual function and electroretinography following photobiomodulation (Valeda light delivery system) treatment in dry age-related macular degeneration subjects (ELECTROLIGHT) (final analysis). Poster presented at: EURETINA; September 9–12, 2021; virtual meeting; 2021.
43. Inken S, Schwahn H, Munk MR, et al. Non-invasive treatment of early diabetic macular edema by multi-wavelength photobiomodulation with the Valeda light delivery system. *Invest. Ophthal Vis Sci*. 2021;62(8):1066.
44. Kim JE, Glassman AR, Josic K, et al.; DRCR Retina Network. A randomized trial of photobiomodulation therapy for center-involved diabetic macular edema with good visual acuity (Protocol AE). *Ophthalmol Retina*. 2022;6(4):298–307. doi:10.1016/j.oret.2021.10.003
45. Near-infrared light photobiomodulation treatment for retinal vein occlusion macular oedema (NIRVO); ClinicalTrials.gov identifier: NCT04847869; 2021. Available from: https://clinicaltrials.gov/ct2/show/NCT04847869. Accessed April 25, 2022.
46. Leruez S, Amati-Bonneau P, Verny C, et al. Mitochondrial dysfunction affecting visual pathways. *Rev Neurol (Paris)*. 2014;170(5):344–354. doi:10.1016/j.neurol.2014.03.009
47. Bagli E, Zikou AK, Agnantis N, Kitsos G. Mitochondrial membrane dynamics and inherited optic neuropathies. *In Vivo*. 2017;31(4):511–525.

48. Scalinci SZ, Valsecchi N, Pacella E, Trovato Battagliola E. Effects of photo-biomodulation in Stargardt disease. *Clin Ophthalmol*. 2022;16:85–91. doi:10.2147/OPTH.S344378
49. Benlahbib M, Cohen SY, Torrell N, et al. Photobiomodulation therapy for large soft drusen and drusenoid pigment epithelial detachment in age-related macular degeneration: a single-center prospective pilot study. *Retina*. 2023;43(8):1246–1254. doi:10.1097/IAE.0000000000003805
50. Kuffler DP. Photobiomodulation in promoting wound healing: a review. *Regener Med*. 2016;11(1):107–122. doi:10.2217/rme.15.82