·Review·

Photobiomodulation for the treatment of retinal diseases: a review

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Abstract

• **Photobiomodulation (PBM), also known as low level laser therapy, has recently risen to the attention of the ophthalmology community as a promising new approach to treat a variety of retinal conditions including age-related macular degeneration, retinopathy of prematurity, diabetic retinopathy, Leber´s hereditary optic neuropathy, amblyopia, methanol-induced retinal damage, and possibly others. This review evaluates the existing research pertaining to PBM applications in the retina, with a focus on the mechanisms of action and clinical outcomes. All available literature until April 2015 was reviewed using PubMed and the following keywords: "photobiomodulation AND retina", "low level light therapy AND retina", "low level laser therapy AND retina", and "FR/NIR therapy AND retina". In addition, the relevant references listed within the papers identified through PubMed were incorporated. The literature supports the conclusion that the low-cost and non-invasive nature of PBM, coupled with the first promising clinical reports and the numerous preclinical-studies in animal models, make PBM well-poised to become an important player in the treatment of a wide range of retinal disorders. Nevertheless, large-scale clinical trials will be necessary to establish the PBM therapeutic ranges for the various retinal diseases, as well as to gain a deeper understanding of its mechanisms of action.**

• **KEYWORDS:** photobiomodulation; low level laser therapy; age-related macular degeneration; retinopathy of prematurity; far-red to near-infrared; retinal degeneration; amblyopia; retinitis pigmentosa; methanol toxicity

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INTRODUCTION

The therapeutic qualities of red light had been known to mankind for centuries. In the current modern era, we refer to this practice as low level laser therapy, also known as photobiomodulation (PBM) and far-red to near-infrared (FR/NIR) light therapy. It consists of series of brief illumination with FR/NIR light (600-1000 nm) from a laser or a light emitting diode (LED). The long wavelengths allow for high tissue penetration and PBM therapy is currently applied to wound healing, reduction in neurologic pain, healing after peripheral nerve injury, stroke, and heart attacks. One of the most recent applications of PBM offers an innovative and non-invasive therapeutic approach to a host of challenging sight- threatening retinal conditions. Potential targets include age-related macular degeneration (AMD), retinopathy of prematurity (ROP), diabetic retinopathy, Leber's hereditary optic neuropathy, methanol-induced retinal damage, and possibly others. This review begins with a historical perspective on the role of PBM in medicine and its mechanisms. Later sections focus on the existing and future applications for the treatment of retinal diseases in both animal models and human subjects.

Photobiomodulation over the Centuries Red light had been valued in the practice of medicine since antiquity[1]. The utility of red light appears to be "re-discovered" at the end of the 18th century by Finsen [2-4] who later became to be known as the "father of contemporary phototherapy" for his astonishing achievements of curing skin disorders such as small blisters using red light and lupus vulgaris using UV light. These successes won him the 1903 Nobel Prize in Medicine and Physiology "in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science"[5].

It is believed that the medical usefulness of FR/NIR light had been "re-discovered" for a second time upon the invention of the laser in the 1960s[1,6]. It happened thanks to an unexpected research outcome where Mester *et al* [7] attempted to use laser-derived 694 nm light to induce skin cancer in mice. Prior to the experiment, the mouse fur atop the location where the light would be applied was shaved. To the researchers' surprise, the subsequent 694 nm light treatment not only failed to induce cancer but instead caused the fur to re-grow faster in the treated mice compared with the

untreated control. This was the first documented demonstration of "laser biostimulation" [6]. Ever since, the study and application of FR/NIR light had been of sustained interest in the medical community (recently reviewed by Chung *et al* [8], Rojas and Gonzalez-Lima [9], and Peplow *et al* [10]).

Over the years, the number of conditions amenable to PBM has greatly increased and their diversity is truly amazing, with the majority having been explored in both animal models and human patients. These range from wound healing, including diabetic ulcers [10-13] to pain control for neurologic neck pain[14] and pain from chronic joint disorders[15] to promotion of the regeneration and functional recovery of tissues with poor healing potential such as injured peripheral [16-17] and optical nerves [9,18], recovery following stroke [19] and other central nervous system damage such as traumatic brain injury [20]. Further, there are a number of applications of PBM to treat retinal disorders, which are the focus of this review and include AMD [21], diabetic retinopathy [22], and amblyopia [23], among many others. Although initially it was believed that the light used in PBM had to be coherent and polarized like light produced by the He-Ne laser, these properties are no longer considered essential such that devices containing LED arrays are now widely used in photo-medicine at only a fraction of the cost for a laser[1].

Mechanisms of Action of Photobiomodulation PBM is very different from the conventional use of photon energy in laser medicine where heating and burning are the prevailing mechanisms of action. Instead of relying on thermal activity, this new light therapy approach exploits the photochemical conversion potential of low-intensity FR/NIR (630-1000 nm) light.

The first insights into the mechanism of PBM came from studies in the late 1980s and 1990s that implicated mitochondria as the subcellular targets of FR/NIR[24-27]. It was proposed by Karu [28] that cytochrome C oxidase inside mitochondria serves as the primary photoacceptor. Cytochrome C oxidase is the enzyme that catalyzes the transfer of electrons from cytochrome C to molecular oxygen-the final step in the mitochondrial respiratory chain and essential for the sustained availability of energy inside cells. Further studies of the action spectrum of the FR/NIR light (defined as the biological response as a function of wavelength) also pointed towards cytochrome C oxidase as the main photoacceptor mediator[29-30]. Research in cell culture using HeLa cells [30-31], and primary neurons [32], demonstrated directly that PBM enhances the activity of cytochrome C oxidase. For instance, Wong-Riley *et al*[32] showed that 670 nm light completely reverses the ability of tetrodotoxin, which is a sodium channel blocker capable of indirect down-regulation of cytochrome C oxidase, to diminish this enzyme's activity in primary cultured neuronal cells. Also, PBM competed with potassium cyanide-an irreversible inhibitor of cytochrome C oxidase such that PBM's effectiveness to protect neurons from dying decreased with the increase of the potassium cyanide concentration. The hypothesis of cytochrome C oxidase being the primary target and effector of PBM is further supported by Eells *et al*'s [33] discovery that NIR light reverses the inhibitory and toxic effect of formic acid (the active metabolite in methanol intoxication), on mitochondrial cytochrome C oxidase in rat retinas, resulting in improved vision outcomes. The stimulation of cytochrome C oxidase by FR/NIR light is believed to lead to an increase in the energy production by mitochondria, increase in the metabolic rate, in cell proliferation and migration[6,34].

Further, *in vivo* studies using retinas from diabetic rats demonstrated that PBM leads to decrease in diabetes-induced inflammation or retinal vessels [35]. A cDNA microarray analysis of gene expression profiles in human fibroblast cells irradiated with red light showed that PBM causes marked changes in gene expression, including an upregulation in the proteins that comprise the mitochondrial respiratory chain and anti-oxidant genes[36]. At the same time, PBM was shown to cause a downregulation of genes implicated in apoptosis and the stress response.

PBM might also function by increasing the bioavailability of nitric oxide (NO) by prompting its release from intracellular stores such as heme-containing proteins [37-38]. Accordingly, absorption measurements from HeLa cells carried out by Karu *et al* [30] demonstrated that PBM leads to NO photo-dissociation from cytochrome C oxidase's heme 3A under normoxic conditions. Since NO functions as an inhibitor of the mitochondrial respiration, its dissociation from cytochrome C oxidase would restore mitochondria's oxygen consumption, which in turn should increase energy production and thus boost cellular metabolism. It is also conceivable, as pointed out by Poyton and Ball [39] in their review, that the dissociated NO could function both as a signal for hypoxia inside the cell and extracellularly where NO diffuses out of the cell and can function as a vasodilator and/or lead to potential additional and still-to-be-discovered downstream effects. However, it is necessary to mention that another study carried out by Tang *et al* [35] failed to demonstrate a link to NO as there was no change in the NO concentration in cultured retinal cell lines (RGC5 and 661W) after PBM treatment. Nor was the beneficial effect of PBM in cell culture, under high-glucose stress conditions, diminished by the NO scavenger carboxy-PTIO, indicating an NO-independent mode of action for PBM. Of course, the main caveat to the Karu *et al* [30] and Tang *et al* [35] studies is that they did not use the same cell line and experimental conditions.

In addition to the direct effect of PBM on the gene expression and metabolism of photoreceptor cells, it is likely that other cell types in the vicinity contribute to the beneficial outcomes. Namely, research has focused on Müller cells which function as microgia in the retina and offer protection to photoreceptors[40-43]. Albarracin and Valter[44] demonstrated that pre-treatment with 670 nm light (prior to damaging light exposure in the rat model of light-induced retinal degeneration) resulted in amelioration of the light damage-induced changes in Müller cells. These included: 1) protection of the structural integrity of Müller cells as visualized by anti-S100β staining; 2) weaker stress response, as demonstrated by weaker staining with vimentin; 3) the absence of gliosis, as shown by the absence of vimentin staining in the subretinal space. The normal metabolic state was maintained, as measured by the preserved expression of glutamine synthetase in Müller cells, which is paramount for the clearing of the excess glutamate released by nearby photoreceptors. On the other hand, Müller cells are known for the production of free radicals and the secretion of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFα) and interleukin (IL-1) in degenerating retinas. Also, early inflammatory changes in photoreceptors trigger immune responses that speed up the disease progression and Müller cells play a vital role in this inflammation propagation process. Interestingly, Albarracin and Valter [44] demonstrated that pre-treatment with 670 nm light in the light-induced model of retinal degeneration curbed the upregulation of TNFα in Müller cells and decreased the subsequent induction of NO synthase that produces the reactive radical NO-a major disruptor of photoreceptor metabolism[45].

In conclusion, great strides have been made towards understanding the mechanisms underlying PBM's success. Yet, ideas for the involvement of new signal transduction pathways are emerging each year and there are still many remaining pieces of the puzzle to be discovered.

Role of Photobiomodulation in Retinal Health –lessons Learned from Experimental Animal Models

Light-damage models of retinal degeneration and age-related macular degeneration The effects of PBM on the retina can be predicted using the known effects of PBM on other tissues and the mechanisms of retinal disease pathogenesis. In the case of AMD, Barron *et al*[46] demonstrated that cones in the aging human retina, and most prominently at the fovea, progressively accumulate mitochondrial DNA deletions and become more cytochrome C oxidase-deficient over time. Also, it is well known that inflammation, *via* complement activation, is associated with the pathogenesis of AMD. Since both mitochondria's health and the inflammatory state are influenced by PBM, it stood to reason that FR/NIR light could treat AMD. And indeed, this was proven by Qu *et al* [47] using the rat model of light-induced AMD that features tissue damage similar to AMD pathology in humans [48]. The retinal damage in the animals was ameliorated by 670 nm LED-derived light administered 3h prior to and at 0, 24, and 48h after the light damage, for 30min each for a total of 90 J/cm^2 energy density. This was demonstrated on the functional level with electro-retinogram (ERG) recordings where PBM ameliorated the decrease in the b-wave caused by the light damage. Also, there was a statistically significant decrease in cell loss as determined histopathologically *via* measurements of the outer nuclear layer (ONL) thickness.

In a study two years later, Rutar *et al* [49] demonstrated that much briefer treatments would suffice. In their mouse model of light-induced inflammatory retinal damage, pre-treatment with low-power 670 nm light for only 3min a day for 5d, delivering a total of 90 J/cm^2, followed by photoreceptor-damaging bright light, resulted in reduced immune reaction with lower expression of complement genes, fewer inflammatory cells in the subretinal space, and significantly less ONL thinning compared to untreated control animals. Similar results were obtained with pre-treatment or concurrent treatment with 670 nm light in albino rats whose retinas were injured by bright light [50]. In this latter study, in addition to the animals that received 670 nm light treatment prior to the light damage, there was a group that received the treatment after the light damage. The photoreceptor function in the second group was initially reduced, as measured by ERG recordings, but recovered by one month, thus providing hope for treating patients with advanced AMD pathology.

Further, the efficacy of FR/NIR phototherapy in AMD was demonstrated in a study of age-related retinal inflammation where aged mice were exposed to five 90s illuminations with 670 nm light over a 35d period, delivering a total of 18 J/cm^2. The treatment reduced the macrophage numbers as well as the inflammation markers TNF and complement component 3d[51].

The results from all the studies in animal models of AMD described in this section demonstrate the potential of PBM for ameliorating and even reversing retinal damage in this all too common condition among the elderly. The efforts to translate this approach to the bedside will be described later in this review.

Retinal damage in diabetes Diabetic retinopathy is a growing health concern, particularly in the developed countries where obesity keeps lowering the disease onset for type 2 diabetes. Yet, therapies aimed to preserve vision, such as laser photocoagulation, yield only a limited success and can themselves cause retinal damage. Fortunately, it might be possible to apply PBM to treat this condition, as was demonstrated in a pre-clinical study by Tang *et al*[35], using rats with streptozotocin-induced diabetes and in retinal cells exposed to harmful concentrations of glucose in their growth

media. PBM treatment of the rats consisted of whole-body irradiation with LED-derived 670 nm light for 240s, delivering 6.0 J/cm^2 per session, with one session per day for 9wk. Beneficial effects were observed on the functional, histological, and biochemical levels. These included statistically significant reduction in ganglion cell death and a 50% improvement of the photopic b wave ERG amplitude. Further, PBM reversed the diabetes-induced inflammatory state of the retina as demonstrated by reduction in leukostasis (the adherence of white blood cells to the retinal vascular walls) and in the expression of the intercellular adhesion molecule (ICAM)-1 adhesion molecule. Also, PBM led to a statistically significant inhibition of the diabetes-induced production of the oxidative-stress molecule superoxide and reversed the decrease in the anti-oxidant enzyme MnSOD. Interestingly, this study failed to detect an increase in the activity of cytochrome C oxidase in the retina, nor in their cultured retinal cells, which is in contradiction with the studies presented in the previous sections where cytochrome C oxidase was found to be the main target and effector of PBM. This controversy might open up the possibility for still unknown mechanisms of action of FR/NIR light.

Retinopathy of prematurity Another major ophthalmic condition that had proven challenging to treat, particularly in the developing world, and which might benefit from FR/NIR phototherapy is ROP whose pathogenesis and treatment options were recently reviewed by Fulton *et al* [52]. The standard-of-care for premature infants in respiratory distress-oxygen supplementation, is believed to be the main culprit behind hyperoxia-induced retina damage. The mechanism involves the generation of reactive oxygen species which lead to inflammation and oxidative damage to DNA, including mitochondrial DNA, as well as damage to intracellular proteins and lipids. Photoreceptors are particularly vulnerable to these stresses, which eventually lead to photoreceptor cell death. Recent experiments by Natoli *et al* [53] using both mouse and rat models of ROP, where exposure to oxygen of newborn pups induced retinal damage, demonstrated that pre-treatment with 670 nm light reduces neovascularization, vaso-obliteration, retinal hemorrhages, and photoreceptor cell death. In another study, Albarracin *et al* [54] demonstrated that hyperoxia-induced photoreceptor loss in adult mice occurred simultaneously with an increased expression of the oxidative stress indicators acrolein and heme oxygenase (HMOX)-1, as measured by immunohistochemistry and quantitative reverse transcription-polymerase chain reaction (RT-PCR), respectively, as well as by an upregulation of pro-inflammatory complement C3 measured by quantitative RT-PCR. Pre-treatment with 670 nm light significantly reduced the expression of these stress markers as well as of complement C3, with the overall outcome being a slowing down of photoreceptor cell loss. These promising results in animal models could open a new avenue for exploration as biomedical researchers look for ways to prevent or cure ROP and its devastating visual and socioeconomic consequences in affected individuals and their families.

Methanol toxicity in the retina A further important application of FR/NIR phototherapy for the retina, as demonstrated in an animal model, is in the field of methanol intoxication. Here the mitochondrion comes in the spotlight again as the toxic metabolite formic acid inhibits cytochrome oxidase leading to the precipitous decline of mitochondrial function. Since the stimulation of cytochrome C oxidase is the suspected primary effect of FR/NIR phototherapy, it is not surprising that treatment with 670 nm light for 2.5min at 5, 25, and 50h after methanol poisoning was able to ameliorate the retinal damage in a rat model of methanol toxicity [33]. The animals in the treatment group featured both better functional (measured by ERG) and histopathological outcome and showed lack of retinal edema or swelling of photoreceptors' inner segments, all of which were prominent features in the non-treated group. The positive outcomes in this animal model study should encourage testing in humans in whom methanol poisoning leads to irreversible blindness.

Application of Photobiomodulation to Treat Retinal Diseases in Humans Inspired by the many positive outcomes in animal models, clinical investigators have begun to evaluate the usefulness of PBM for the treatment of retinal diseases in human subjects.

Age-related macular degeneration The first evidence for the application of PBM to treat AMD in humans became available in 2008 from a prospective study of 348 eyes of 203 patients where Ivandic and Ivandic [21] demonstrated improvement in visual acuity (VA) in patients with the dry and wet forms of AMD. Three hundred and twenty-eight eyes of 193 patients received four 40seconds-long transconjunctival irradiations over 2wk with 780 nm light from a semiconductor laser diode with 0.3 J/cm^2 delivered in the macular region during each treatment, with no adverse effects. Among the treated eyes, 146 had cataracts while 182 did not. The remaining 20 eyes of 10 patients received mock treatments and served as controls. The primary outcome VA improved in 97% of the treated patients who had cataracts by a mean of 2 lines (range 1-7 lines) and in 94.5% of the cataract-free patients by the same amount, with no change in VA in the few remaining treated eyes or in the controls. The VA improvement was accompanied by a decrease in metamorphosias, scotomas, and acquired dyschromatopsia. Also, in the sub-population of patients with wet AMD, PBM treatment reduced the edema and bleeding. The only drawback of this study was the disproportionately small control arm.

Further support for PBM's usefulness in treating AMD patients stems from a prospective interventional case series of 18 eyes of 9 patients with dry AMD carried out by Merry G. *et al*, titled "Treatment of dry age-related macular degeneration with photobiomodulation" and presented at the 2012 ARVO Annual Meeting in Fort Lauderdale, FL. The PBM treatment there consisted of irradiation by the LED-based devices Warp 10 (Quantum Devices) at 670 nm, for 88s, delivering 4-7.7 J/cm^2 and Gentlewaves (Light Bioscience) at 590 and 790 nm, for 35s, delivering 0.1 J/cm^2 per treatment. All 18 eyes were treated sequentially with both devices each time for a total of 18 treatments (3 times per week for 6wk), with no adverse effects. There was statistically significant improvement in VA, by 1.5 lines on average, and in contrast sensitivity, with no changes on their third primary outcome-fixation stability.

Finally, a new US-based clinical trial is currently recruiting participants in order to study the potential benefit, tolerability, and safety of FR/NIR light therapy in adults with wet AMD ("Wet AMD Near Infrared Treatment Trial" administered by the New York Eye and Ear Infirmary at Mount Sinai). Hopefully, this trial will be able to address the drawbacks, such as insufficient controls, in prior studies.

Diabetic retinopathy After having demonstrated the beneficial effects of PBM in animal models of diabetes, Tang *et al* [22] translated the approach to human patients. In their internally controlled consecutive case series, 4 eyes of 4 patients with type 2 diabetes with non-center-involving diabetic macular edema (NCDME) underwent treatment with 670 nm light delivered by Warp 10 through a closed eyelid for 80s twice a day for 2-9mo, with total energy density of 25 J/cm^2. The second eye in each patient served as the internal control and was not treated. The treated eyes of all patients demonstrated statistically significant decrease in macular thickness by an average of 20% , while the non-treated eyes featured a slight increase in the thickness by 3% on average. One of the patients experienced sectoral optic nerve hyperemia and edema in their treated eye which was consistent with non-arteritic ischemic optic neuropathy (NAION). However, this occurrence might not have been related to the PBM treatment since prior to the study the patient had risk factors for NAION, including diabetes, hypertension, a small cup-to-disc ratio, a history of proliferative diabetic retinopathy treated with pan-retina photocoagulation 4y prior to study, and CDME treated 3y earlier with focal laser.

Tang *et al* 's [22] small case series is the first one to demonstrate a benefit of PBM to the patients with NCDME. Further investigations, using larger patient populations, will be necessary to establish the optimal treatment dose and duration, as well as identify and address potential safety concerns.

Amblyopia in adolescents and adults A well-known feature of amblyopia is that it becomes untreatable after the "critical period", which ends after the first-decade of life. Fortunately, there is evidence that amblyopia in older patients could benefit from PBM. This was demonstrated by Ivandic and Ivandic[23] in their patient-blinded placebo-controlled trial of adolescent and adult patients (age range of 13-72y and a mean of 46.8y) with pre-treatment BCVA of at most 20/30 (range of 20/30 to 20/400). Among the 231 treated eyes of 178 patients in that study, the cause for amblyopia was ametropia in 110 eyes and strabismus in the remaining 121 eyes. Of these, 20 eyes of 20 patients received mock treatment and served as controls. The other 211 eyes underwent 3-4 treatments over a 2-week period, for 30s each with 780 nm light emitted by a continuous-wave semi-conductor laser diode delivering 0.22 J/cm^2 per treatment. While there was no change in the VA among the control patients, the ones treated with PBM experienced a marked improvement. Of the patients with ametropia, 91% had an average increase in VA of 3 lines (range 1-7 lines) and of the patients with strabismus, 89% demonstrated VA improvements of 2.7 lines on average (range 1-7 lines). The beneficial effect was retained during the 6-month follow-up period. Moreover, one of the patients with strabismus and pre-treatment BCVA of 20/100 was followed for a total of 13 years during which 2 re-treatments were necessary to maintain the VA at the 20/25 level. However, it was noted that PBM led to more VA improvement in younger patients (less than 18y of age). Also, the increase in VA correlated with the pre-treatment baseline VA, where patients with severe ocular pathology, such as VA less than 20/200 or eccentric fixation, experienced little-to-no improvement. Overall, the Ivandic and Ivandic [23] study provides strong evidence for the application of PBM to treat amblyopia past the "critical period", with no therapy-related ocular or systemic side effects. In terms of the mechanism through which this treatment operates to improve VA in amblyopic eyes, the authors speculated that it might be similar to those at work in other retinal conditions, such as increase in cellular metabolism. Also, PBM might be stimulating inter-neuronal communication *via* promotion of synaptogenesis.

Retinitis pigmentosa It might also be possible to apply PBM to treat RP, which is the most common cause of inherited retinal degeneration with non-syndromic prevalence of approximately 1 in 4000 [55-56]. The evidence for this is currently scarce and consists of a single case report of a 55-year-old patient with advanced bilateral retinitis pigmentosa (RP) whose VA prior to intervention was 20/50 bilaterally, with visual fields reduced to the central 5 degrees[57]. He was treated with transconjunctival illumination of the whole retina with 780 nm light, generated by a continuous-wave laser diode, for 40s for a total of 0.4 J/cm^2 per treatment,

Table 1 PBM sample delivery protocols from animal model studies

Retinal disease	Species	PBM delivery device	Mode of PBM application	Mode of disease induction	Pre-treatment	Concurrent treatment	Post-treatment
Model of AMD[44]	SD rats	LED array (λ=670nm)	At 2.5 cm distance from the eye	Light damage with 1000 lx for 24h	Once daily for 5d prior to light damage, 3min each, energy fluence of 9 J/cm^2	None	None
					Once on the day prior to light damage	Twice during the light-damage period	Once after the light-damage period
					None	None	Once daily for 5d, 3min each, at energy fluence of 9 J/cm^2
Model of diabetic retinopathy[35]	Lewis rats	LED array (λ=670nm)	Whole-body irradiation	Streptozoto-cin-induced diabetes	None	None	Once daily for 9wk, 240s each, at 6.0 J/cm^2 total energy density
Model of ROP[53]	New-born C57BL/6J mice or SD rats	LED array (λ=670nm)	At 2.5 cm distance from the eye	Oxygen-induced retinal damage over 5d (mice), 18d (rats)	None	Daily, 3min each, at 9 J/cm^2	None
Model of methanol toxicity[33]	SD rats	LED array (λ=670nm)	Whole-body irradiation	Methanol intoxication	None	None	2.5min sessions at 5, 25, and 50h after methanol poisoning, at 4 J/cm^2

λ: Wavelength; AMD: Age-related macular degeneration; SD: Sprague-Dawley; LED: Light-emitting diode; ROP: Retinopathy of prematurity.

Table 2 PBM sample delivery protocols from clinical trials

Type of retinal disease	λ (nm)	PBM delivery device	Mode of PBM Application	PBM regimen
AMD[21]	780	Semi-conductor laser diode	Transconjunctival irradiations	Twice per week for 2wk, 40s, at 0.3 J/cm^2 each
Diabetic retinopathy[22]	670	LED array	Through a closed eyelid	Twice a day for 2-9mo, 80s each, at 25 J/cm^2 total energy density
Amblyopia in adolescents and adults[23]	780	Semi-conductor laser diode	Applied to the macula by guiding the beam of the laser diode at 1 cm distance above the eyeball, with the eye in adduction	3-4 sessions over 2wk period, 30s each, at 0.22 J/cm^2 each
RP[57]	780	Continuous-wave laser diode	Transconjunctival illumination of the whole retina	Twice a week for 2wk, 40s, at 0.4 J/cm^2 each, repeated 5y later after a relapse

λ: Wavelength; AMD: Age-related macular degeneration; LED: Light-emitting diode; RP: Retinitis pigmentosa.

two times per week for 2wk. This resulted in VA improvement to 20/20 bilaterally and the regaining of normal visual field outer perimeters, although there remained a residual mid-peripheral circular scotoma. These gains in visual function were retained over the following 5y. However, the patient experienced a relapse at year 5 post-treatment with his visual function decreasing down to the pre-treatment level. A repetition of the 4-session PBM was able to restore the original vision gains and over the following 2y the patient underwent 17 more treatment sessions, on an as needed basis, in order to maintain the same VA.

Certainly, a larger study will be necessary to optimize the treatment protocol and gain a deeper understanding of the mechanism involved in the healing of retina succumbing to RP. Nevertheless, this very first report offers hope and will likely serve to spur more studies.

Delivery Protocols Being a rather new therapeutic approach for the treatment of retinal conditions, the experimental protocols for PBM delivery vary greatly. To illustrate this diversity, Tables 1 and 2 provide examples of successful regimen in animal model studies and clinical trials, respectively.

CONCLUSION

Given the promising pre-clinical results and the equally promising first few translations to human patients, we should expect a growth in the field of photobiomodulation applied to treat common retinal conditions such as age-related macular degeneration, retinopathy of prematurity, and diabetic retinopathy, as well as the many orphan disease variants of retinitis pigmentosa and possibly other retinal conditions. Nevertheless, much more work in human subjects as well as in animal models needs to be carried out in order to: 1) better understand the underlying mechanisms of how PBM helps cure and/or prevent retinal damage; 2) establish robust treatment protocols for the various applications; 3) identify and properly address potential harmful effects on the various tissues that get irradiated during PBM treatments. Currently, there are a number of challenges in the field. These include the large variety of potentially treatable ocular conditions and the wide range of treatment protocols being published in terms of wavelength, treatment session duration, and the total number of treatment sessions. These aspects make it harder to pull the available data into Meta-analyses for the purpose of developing standardized treatment guidelines. Also, most

of the available data stems from small clinical trials, case series, and reports, some of which lack proper controls. Nevertheless, if its usefulness can be established through large clinical trials, PBM would offer a non-invasive and inexpensive approach that is easy to deliver by medical providers, or even by patients themselves, to prevent or slow down the progress of retinal pathology.

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REFERENCES

1 Karu TI. Effects of visible radiation on cultured cells. *Photochem Photobiol* 1990;52(6):1089-1098.

2 Finsen N. La Phototherapie. Paris: Carre ed Naud, Finsen Medicinske Lysinstitut de Copenhague; 1899.

3 Finsen NR. Of tadpoles and red rooms. *ASP News!* 1988;117:3.

4 Finsen NR. Electric lights & broken needles. *ASP News!* 1988-1989; 118.

5 "Physiology or Medicine 1903-Presentation Speech". *Nobelprize.org* Nobel Media AB 2014. Web. 24 Nov 2015.

6 Hamblin MR, Demidova TN. Mechanisms of low level light therapy. *Proc of Spie* 2006; 6140(6):1-12.

7 Mester E, Szende B, Gartner P. The effect of laser beams on the growth of hair in mice. *Radiobiol Radiother (Berl)* 1968;9(5):621-626.

8 Chung H, Dai T, Sharma SK, Huang YY, Carroll JD, Hamblin MR. The nuts and bolts of low-level laser (light) therapy. *Ann Biomed Eng* 2012;40 (2):516-533.

9 Rojas JC, Gonzalez-Lima F. Low-level light therapy of the eye and brain. *Eye & Brain* 2011;3:49-67.

10 Peplow PV, Chung TY, Baxter GD. Laser photobiomodulation of wound healing: a review of experimental studies in mouse and rat animal models. *Photomed Laser Surg* 2010;28(3):291-325.

11 Mester E, Nagylucskay S, Doklen A, Tisza S. Laser stimulation of wound healing. *Acta Chir Acad Sci Hung* 1976;17(1):49-55.

12 Mester E, Szende B, Spiry T, Scher A. Stimulation of wound healing by laser rays. *Acta Chir Acad Sci Hung* 1972;13(3):315-324.

13 Posten W, Wrone DA, Dover JS, Arndt KA, Silapunt S, Alam M. Low-level laser therapy for wound healing: mechanism and efficacy. *Dermatol Surg* 2005;31(3):334-340.

14 Chow RT, Johnson MI, Lopes-Martins RA, Bjordal JM. Efficacy of low-level laser therapy in the management of neck pain: a systematic review and meta-analysis of randomised placebo or active-treatment controlled trials. *Lancet* 2009;374(9705):1897-1908.

15 Bjordal JM, Couppe C, Chow RT, Tuner J, Ljunggren EA. A systematic review of low level laser therapy with location-specific doses for pain from chronic joint disorders. *Aust J Physiother* 2003;49(2):107-116.

16 Anders JJ, Geuna S, Rochkind S. Phototherapy promotes regeneration and functional recovery of injured peripheral nerve. *Neurol Res* 2004;26 (2):233-239.

17 Gigo-Benato D, Geuna S, Rochkind S. Phototherapy for enhancing peripheral nerve repair: a review of the literature. *Muscle Nerve* 2005;31 (6):694-701.

18 Assia E, Rosner M, Belkin M, Solomon A, Schwartz M. Temporal parameters of low energy laser irradiation for optimal delay of post-traumatic degeneration of rat optic nerve. *Brain Res* 1989;476 (2): 205-212.

19 Lampl Y, Zivin JA, Fisher M, Lew R, Welin L, Dahlof B, Borenstein P, Andersson B, Perez J, Caparo C, Ilic S, Oron U. Infrared laser therapy for ischemic stroke: a new treatment strategy: results of the NeuroThera Effectiveness and Safety Trial-1 (NEST-1). *Stroke* 2007;38 (6): 1843-1849.

20 Fitzgerald M, Hodgetts S, Van Den Heuvel C, Natoli R, Hart NS, Valter K, Harvey AR, Vink R, Provis J, Dunlop SA. Red/near-infrared irradiation therapy for treatment of central nervous system injuries and disorders. *Rev Neurosci* 2013;24(2):205-226.

21 Ivandic BT, Ivandic T. Low-level laser therapy improves vision in patients with age-related macular degeneration. *Photomed Laser Surg* 2008;26(3):241-245.

22 Tang J, Herda AA, Kern TS. Photobiomodulation in the treatment of patients with non-center-involving diabetic macular oedema. *Br J Ophthalmol* 2014;98(8):1013-1015.

23 Ivandic BT, Ivandic T. Low-level laser therapy improves visual acuity in adolescent and adult patients with amblyopia. *Photomed Laser Surg* 2012; 30(3):167-171.

24 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.

25 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.

26 Bakeeva LE, Manteifel 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.

27 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.

28 Karu TI. Photobiology of Low-Power Laser Therapy. United Kingdom: The Universities Press (Belfast) Ltd;1989.

29 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.

30 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. *J Photochem Photobiol B* 2005;81(2):98-106.

31 Karu TI, Pyatibrat LV, Afanasyeva NI. A novel mitochondrial signaling pathway activated by visible-to-near infrared radiation. *Photochem Photobiol* 2004;80(2):366-372.

32 Wong-Riley MT, Liang HL, Eells JT, Chance B, Henry MM, Buchmann E, Kane M, Whelan HT. Photobiomodulation directly benefits primary neurons functionally inactivated by toxins: role of cytochrome c oxidase. *J Biol Chem* 2005;280(6):4761-4771.

33 Eells JT, Henry MM, Summerfelt P, Wong-Riley MT, Buchmann EV, Kane M, Whelan NT, Whelan HT. Therapeutic photobiomodulation for methanol-induced retinal toxicity. *Proc Natl Acad Sci U S A* 2003;100(6): 3439-3444.

34 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.

35 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.

36 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.

37 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.

38 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.

39 Poyton RO, Ball KA. Therapeutic photobiomodulation: nitric oxide and a novel function of mitochondrial cytochrome c oxidase. *Discov Med* 2011; 11(57):154-159

40 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.

41 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.

42 Norenberg MD. Distribution of glutamine synthetase in the rat central nervous system. *J Histochem Cytochem* 1979;27(3):756-762.

43 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.

44 Albarracin R, Valter K. 670 nm red light preconditioning supports Müller cell function: evidence from the white light-induced damage model in the rat retina. *Photochem Photobiol* 2012;88(6):1418-1427.

45 Zhang J, Snyder SH. Nitric oxide stimulates auto-ADP-ribosylation of glyceraldehyde-3-phosphate dehydrogenase. *Proc Natl Acad Sci U S A* 1992;89(20):9382-9385.

46 Barron MJ, Johnson MA, Andrews RM, Clarke MP, Griffiths PG, Bristow E, He LP, Durham S, Turnbull DM. Mitochondrial abnormalities in ageing macular photoreceptors. *Invest Ophthalmol Vis Sci* 2001;42 (12): 3016-3022.

47 Qu C, Cao W, Fan Y, Lin Y. Near-infrared light protect the photoreceptor from light-induced damage in rats. *Adv Exp Med Biol* 2010; 664:365-374.

48 Rutar M, Provis JM, Valter K. Brief exposure to damaging light causes focal recruitment of macrophages, and long-term destabilization of photoreceptors in the albino rat retina. *Curr Eye Res* 2010;35(7):631-643.

49 Rutar M, Natoli R, Albarracin R, Valter K, Provis J. 670-nm light treatment reduces complement propagation following retinal degeneration. *J Neuroinflammation* 2012;9:257.

50 Albarracin R, Eells J, Valter K. Photobiomodulation protects the retina from light-induced photoreceptor degeneration. *Invest Ophthalmol Vis Sci* 2011;52(6):3582-3592.

51 Kokkinopoulos I, Colman A, Hogg C, Heckenlively J, Jeffery G. Age-related retinal inflammation is reduced by 670 nm light via increased mitochondrial membrane potential. *Neurobiol Aging* 2013;34(2):602-609.

52 Fulton AB, Hansen RM, Moskowitz A, Akula JD. The neurovascular retina in retinopathy of prematurity. *Prog Retin Eye Res* 2009;28 (6): 452-482.

53 Natoli R, Valter K, Barbosa M, Dahlstrom J, Rutar M, Kent A, Provis J. 670nm photobiomodulation as a novel protection against retinopathy of prematurity: evidence from oxygen induced retinopathy models. *PLoS One* 2013;8(8):e72135.

54 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;14:125.

55 Boughman JA, Conneally PM, Nance WE. Population genetic studies of retinitis pigmentosa. *Am J Hum Genet* 1980;32(2):223-235.

56 Humphries P, Kenna P, Farrar GJ. On the molecular genetics of retinitis pigmentosa. *Science* 1992;256(5058):804-808.

57 Ivandic BT, Ivandic T. Low-level laser therapy improves vision in a patient with retinitis pigmentosa. *Photomed Laser Surg* 2014;32(3):181-184.