
Photobiomodulation for Dry Age-related Macular Degeneration: A Literature Review

Photobiomodulation (PBM) is an approved treatment for numerous clinical indications and has been found to have significant positive impact in treatment of dry age-related macular degeneration. This literature review provides an overview of related peer-reviewed PBM publications including studies on the mechanism of action, preclinical research, and clinical studies of PBM treatment in dry age-related macular degeneration.

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Section I:

Photobiomodulation History & Mechanism of Action

1. Mitochondrial Dysfunction in Retinal Diseases

M Barot, MR Gokulgandhi and AK Mitra

The mitochondrion is a vital intracellular organelle for retinal cell function and survival. There is growing confirmation to support an association between mitochondrial dysfunction and a number of retinal degenerations. This review highlights the role of mitochondrial dysfunction originating from oxidative stress in the etiology of retinal diseases including diabetic retinopathy, glaucoma and age-related macular degeneration (AMD). Moreover, mitochondrial DNA (mtDNA) damage associated with AMD due to susceptibility of mtDNA to oxidative damage and failure of mtDNA repair pathways is also highlighted in this review. The susceptibility of neural retina and retinal pigment epithelium (RPE) mitochondria to oxidative damage with ageing appears to be a major factor in retinal degeneration. It thus appears that the mitochondrion is a weak link in the antioxidant defenses of retinal cells. This review will further summarize the prospective role of mitochondria targeting therapeutic agents for the treatment of retinal disease. Mitochondria based drug targeting to diminish oxidative stress or promote repair of mtDNA damage may offer potential alternatives for the treatment of various retinal degenerative diseases.

Barot et al. (2011). Mitochondrial Dysfunction in Retinal Diseases. Curr Eye Res, 12, 1069-77

2. The Nuts and Bolts of Low-level Laser (Light) Therapy

H Chung, T Dai, SK Sharma, YY Huang, JD Carroll and MR Hamblin

Soon after the discovery of lasers in the 1960s it was realized that laser therapy had the potential to improve wound healing and reduce pain, inflammation and swelling. In recent years the field sometimes known as photobiomodulation has broadened to include light-emitting diodes and other light sources, and the range of wavelengths used now includes many in the red and near infrared. The term "low level laser therapy" or LLLT has become widely recognized and implies the existence of the biphasic dose response or the Arndt-Schulz curve. This review will cover the mechanisms of action of LLLT at a cellular and at a tissular level and will summarize the various light sources and principles of dosimetry that are employed in clinical practice. The range of diseases, injuries, and conditions that can be benefited by LLLT will be summarized with an emphasis on those that have reported randomized controlled clinical trials. Serious life-threatening diseases such as stroke, heart attack, spinal cord injury, and traumatic brain injury may soon be amenable to LLLT therapy.

Chung et al. (2011). The Nuts and Bolts of Low-level Laser (Light) Therapy. Ann Biomed Eng, 2, 516-33A

3. Power Games

N Lane

Seventy-five years ago next month, Otto Warburg's star was at its zenith. The pioneering German biochemist delivered his Nobel address in December 1931. He described the ingenious experiments by which he had unmasked the enzyme responsible for the critical step of cell respiration, the process that turns the energy in chemical compounds into energy the cell can use. His work on respiration in the early 1930s nearly earned him a second Nobel, ultimately denied him by Hitler. Then his star began sinking. His ideas on the importance of cell respiration in cancer led many to dismiss him as a crank. And the rise of molecular genetics in the 1960s put such ideas into a far distant orbit. But now, Warburg's star is rising again. A new generation of researchers is returning to his ideas about respiration in cancer cells. Recent findings suggest that the enzyme he identified, cytochrome oxidase, is taking centre-stage in a new understanding of how the cell's energy metabolism affects health and diseases. And surprisingly they show that light has a profound effect on how the enzyme works – and could even be used to treat degenerative disease. To extract energy from molecules, the cell first breaks down glucose into simpler molecules via a process called glycolysis. It then feeds these molecules into energy-producing structures called mitochondria, which strip electrons from them to produce energy with the help of oxygen. As Warburg showed, cytochrome oxidase governs the last reaction in this process. Perhaps the most surprising aspect of the renaissance of Warburg's ideas is that the methods he used to make this discovery matter again. They exploit two chemical quirks: carbon monoxide (CO) can block respiration by binding to cytochrome oxidase in place of oxygen; and a flash of light can displace it, freeing up the site for oxygen to bind again.

Lane. (2006). Power games. Nature. 443, 901-3

4. Mechanisms of Low Level Light Therapy

MR Hamblin

The use of low levels of visible or near-infrared (NIR) light for reducing pain, inflammation and edema, promoting healing of wounds, deeper tissues and nerves, and preventing tissue damage has been known for almost forty years since the invention of lasers. Originally thought to be a peculiar property of laser light (soft or cold lasers), the subject has now broadened to include photobiomodulation and photobiostimulation using non-coherent light. Despite many reports of positive findings from experiments conducted in vitro, in animal models and in randomized controlled clinical trials, LLLT remains controversial. This likely is due to two main reasons; firstly, the biochemical mechanisms underlying the positive effects are incompletely understood, and secondly, the complexity of rationally choosing amongst a large number of illumination parameters such as wavelength, fluence, power density, pulse structure and treatment timing has led to the publication of a number of negative studies as well as many positive ones. In particular, a biphasic dose response has been frequently observed where low levels of light have a much better effect than higher levels.

Hamblin. (2006). Retrieved from <http://photobiology.info/Hamblin.html>

5. Low Intensity Light Stimulates Nitrite-Dependent Nitric Oxide Synthesis but Not Oxygen Consumption by Cytochrome C Oxidase: Implications for Phototherapy

KA Ball, PR Castello, RO Poyton

Cytochrome c oxidase (Cco) has been reported to be a receptor for some of the beneficial effects of low intensity visible and near-infrared light on cells and tissues. Here, we have explored the role of low intensity light in affecting a newly described function of Cco, its ability to catalyze nitrite-dependent nitric oxide (NO) synthesis (Cco/NO). Using a new assay for Cco/NO we have found that both yeast and mouse brain mitochondrial Cco produce NO over a wide range of oxygen concentrations and that the rate of NO synthesis increases as the oxygen concentration decreases, becoming optimal under hypoxic conditions. Low intensity broad-spectrum light increases Cco/NO activity in an intensity-dependent fashion but has no effect on oxygen consumption by Cco. By using a series of bandpass filters and light emitting devices (LEDs) we have determined that maximal stimulation of Cco/NO activity is achieved by exposure to light whose central wavelength is 590 ± 14 nm. This wavelength of light stimulates Cco/NO synthesis at physiological nitrite concentrations. These findings raise the interesting possibility that low intensity light exerts a beneficial effect on cells and tissues by increasing NO synthesis catalyzed by Cco and offer a new explanation for the increase in NO bioavailability experienced by tissue exposed to light.

Ball et al. (2011). Low Intensity Light Stimulates Nitrite-Dependent Nitric Oxide Synthesis but Not Oxygen Consumption by Cytochrome C Oxidase: Implications for Phototherapy. J Photochem Photobiol B. 102, 182-91

6. Photobiomodulation Directly Benefits Primary Neurons Functionally Inactivated by Toxins; Role of cytochrome c oxidase

MTT Wong-Riley, HL Liang, JT Eells, B Chance, MM Henry, E Buchmann, M Kane and HT Whelan

Far red and near infrared (NIR) light promotes wound healing, but the mechanism is poorly understood. Our previous studies using 670 nm light-emitting diode (LED) arrays suggest that cytochrome c oxidase, a photoacceptor in the NIR range, plays an important role in therapeutic photobiomodulation. If this is true, then an irreversible inhibitor of cytochrome c oxidase, potassium cyanide (KCN), should compete with LED and reduce its beneficial effects. This hypothesis was tested on primary cultured neurons. LED treatment partially restored enzyme activity blocked by 10–100 M KCN. It significantly reduced neuronal cell death induced by 300 M KCN from 83.6 to 43.5%. However, at 1–100 mM KCN, the protective effects of LED decreased, and neuronal deaths increased. LED significantly restored neuronal ATP content only at 10 M KCN but not at higher concentrations of KCN tested. Pretreatment with LED enhanced efficacy of LED during exposure to 10 or 100 M KCN but did not restore enzyme activity to control levels. In contrast, LED was able to completely reverse the detrimental effect of tetrodotoxin, which only indirectly down-regulated enzyme levels. Among the wavelengths tested (670, 728, 770, 830, and 880 nm), the most effective ones (830 nm, 670 nm) paralleled the NIR absorption spectrum of oxidized cytochrome c oxidase, whereas the least effective wavelength, 728 nm, did not. The results are consistent with our hypothesis that the mechanism of photobiomodulation involves the up-regulation of cytochrome c oxidase, leading to increased energy metabolism in neurons functionally inactivated by toxins.

Wong-Riley et al. (2005). Photobiomodulation Directly Benefits Primary Neurons Functionally Inactivated by Toxins; Role of cytochrome c oxidase. J Biol Chem. 280, 4761-71

7. Absorption of Monochromatic and Narrow Band Radiation in the Visible and Near IR by Both Mitochondrial and Non-Mitochondrial Photoacceptors Results in Photobiomodulation

S Passarella and T Karu

In addition to the major functions performed by in the cell, mitochondria play a major role in celllight interaction. Accordingly, it is generally accepted that mitochondria are crucial in cell photobiomodulation; however a variety of biomolecules themselves proved to be targets of light irradiation. We describe whether and how mitochondria can interact with monochromatic and narrow band radiation in the red and near IR optical regions with dissection of both structural and functional effects likely leading to photobiostimulation. Moreover, we also report that a variety of biomolecules localized in mitochondria and/ or in other cell compartments including cytochrome c oxidase, some proteins, nucleic acids and adenine nucleotides are light sensitive with major modifications in their biochemistry. All together the reported investigations show that the elucidation of the mechanism of the light interaction with biological targets still remains to be completed, this needing further research, however the light sensitivity of a variety of molecules strongly suggests that photobiomodulation could be used in both in photomedicine and in biotechnology.

Passarella et al. (2014). Absorption of Monochromatic and Narrow Band Radiation in the Visible and Near IR by Both Mitochondrial and Non-Mitochondrial Photoacceptors Results in Photobiomodulation. J Photochem Photobiol B. 140, 344-58

Section II:

Preclinical Studies Using Photobiomodulation

1. Treatment with 670 nm Light Up Regulates Cytochrome C Oxidase Expression and Reduces Inflammation in an Age-Related Macular Degeneration Model

R Begum, MB Powner, N Hudson, C Hogg and G Jeffery

Inflammation is an umbrella feature of ageing. It is present in the aged retina and many retinal diseases including age related macular degeneration (AMD). In ageing and in AMD mitochondrial function declines. In normal ageing this can be manipulated by brief exposure to 670 nm light on the retina, which increases mitochondrial membrane potential and reduces inflammation. Here we ask if 670 nm exposure has the same ability in an aged mouse model of AMD, the complement factor H knockout (CFH2/2) where inflammation is a key feature. Further, we ask whether this occurs when 670 nm is delivered briefly in environmental lighting rather than directly focused on the retina. Mice were exposed to 670 nm for 6 minutes twice a day for 14 days in the form of supplemented environmental light. Exposed animals had significant increase in cytochrome c oxidase (COX), which is a mitochondrial enzyme regulating oxidative phosphorylation. There was a significant reduction in complement component C3, an inflammatory marker in the outer retina. Vimetin and glial fibrillary acidic protein (GFAP) expression, which reflect retinal stress in Muller glia, were also significantly down regulated. There were also significant changes in outer retinal macrophage morphology. However, amyloid beta (Ab) load, which also increases with age in the outer retina and is pro-inflammatory, did not change. Hence, 670 nm is effective in reducing inflammation probably via COX activation in mice with a genotype similar to that in 50% of AMD patients even when brief exposures are delivered via environmental lighting. Further, inflammation can be reduced independent of Ab. The efficacy revealed here supports current early stage clinical trials of 670 nm in AMD patients

Begum et al. (2013). Treatment with 670 nm Light Up Regulates Cytochrome C Oxidase Expression and Reduces Inflammation in an Age-Related Macular Degeneration Model. PLoS One. 8, e57828

2. Therapeutic Photobiomodulation for Methanol-Induced Retinal Toxicity

JT Eells, MM Henry, P Summerfelt, MTT Wong-Riley, EV Buchmann, M Kane, NT Whelan, and HT Whelan

Methanol intoxication produces toxic injury to the retina and optic nerve, resulting in blindness. The toxic metabolite in methanol intoxication is formic acid, a mitochondrial toxin known to inhibit the essential mitochondrial enzyme, cytochrome oxidase. Photobiomodulation by red to near-IR radiation has been demonstrated to enhance mitochondrial activity and promote cell survival in vitro by stimulation of cytochrome oxidase activity. The present studies were undertaken to test the hypothesis that exposure to monochromatic red radiation from light-emitting diode (LED) arrays would protect the retina against the toxic actions of methanol derived formic acid in a rodent model of methanol toxicity. Using the electroretinogram as a sensitive indicator of retinal function, we demonstrated that three brief (2 min, 24 s) 670-nm LED treatments (4 J/cm²), delivered at 5, 25, and 50 h of methanol intoxication, attenuated the retinotoxic effects of methanol derived formate. Our studies document a significant recovery of rod- and cone-mediated function in LED-treated,

methanol-intoxicated rats. We further show that LED treatment protected the retina from the histopathologic changes induced by methanol derived formate. These findings provide a link between the actions of monochromatic red to near-IR light on mitochondrial oxidative metabolism in vitro and retinoprotection in vivo. They also suggest that photobiomodulation may enhance recovery from retinal injury and other ocular diseases in which mitochondrial dysfunction is postulated to play a role. amenable to LLLT therapy.

Eells et al. (2003). Therapeutic Photobiomodulation for Methanol-Induced Retinal Toxicity. Proc Natl Acad Sci USA. 100, 3439-44

3. Photobiomodulation Directly Benefits Primary Neurons Functionally Inactivated by Toxins: Role of Cytochrome C Oxidase

MTT Wong-Riley, HL Liang, JT Eells, B Chance, MM Henry, E Buchmann, M Kane and HT Whelan

Far red and near infrared (NIR) light promotes wound healing, but the mechanism is poorly understood. Our previous studies using 670 nm light-emitting diode (LED) arrays suggest that cytochrome c oxidase, a photoacceptor in the NIR range, plays an important role in therapeutic photobiomodulation. If this is true, then an irreversible inhibitor of cytochrome c oxidase, potassium cyanide (KCN), should compete with LED and reduce its beneficial effects. This hypothesis was tested on primary cultured neurons. LED treatment partially restored enzyme activity blocked by 10–100 μM KCN. It significantly reduced neuronal cell death induced by 300 μM KCN from 83.6 to 43.5%. However, at 1–100 mM KCN, the protective effects of LED decreased, and neuronal deaths increased. LED significantly restored neuronal ATP content only at 10 μM KCN but not at higher concentrations of KCN tested. Pretreatment with LED enhanced efficacy of LED during exposure to 10 or 100 μM KCN but did not restore enzyme activity to control levels. In contrast, LED was able to completely reverse the detrimental effect of tetrodotoxin, which only indirectly down-regulated enzyme levels. Among the wavelengths tested (670, 728, 770, 830, and 880 nm), the most effective ones (830 nm, 670 nm) paralleled the NIR absorption spectrum of oxidized cytochrome c oxidase, whereas the least effective wavelength, 728 nm, did not. The results are consistent with our hypothesis that the mechanism of photobiomodulation involves the up-regulation of cytochrome c oxidase, leading to increased energy metabolism in neurons functionally inactivated by toxins.

Wong-Riley et al. (2005). Photobiomodulation Directly Benefits Primary Neurons Functionally Inactivated by Toxins: Role of Cytochrome C Oxidase. J Biol Chem. 280, 4761-71

4. Low-Intensity Far-Red Light Inhibits Early Lesions That Contribute to Diabetic Retinopathy: In Vivo and In Vitro

J Tang, Y Du, CA Lee, R Talahalli, JT Eells and TS Kern

Treatment with light in the far-red to near-infrared region of the spectrum (photobiomodulation [PBM]) has beneficial effects in tissue injury. We investigated the therapeutic efficacy of 670-nm PBM in rodent and cultured cell models of diabetic retinopathy. Studies were conducted in streptozotocin-induced diabetic rats and in cultured retinal cells. Diabetes-induced retinal abnormalities were assessed functionally, biochemically, and histologically in vivo and in vitro. We observed beneficial effects of PBM on the neural and vascular elements of retina. Daily 670-nm PBM treatment (6 J/cm²) resulted in significant inhibition in the diabetes induced death of retinal ganglion cells, as well as a 50% improvement of the ERG amplitude (photopic b wave responses) (both $P < 0.01$).

To explore the mechanism for these beneficial effects, we examined physiologic and molecular changes related to cell survival, oxidative stress, and inflammation. PBM did not alter cytochrome oxidase activity in the retina or in cultured retinal cells. PBM inhibited diabetes-induced superoxide production and preserved MnSOD expression in vivo. Diabetes significantly increased both leukostasis and expression of ICAM-1, and PBM essentially prevented both of these abnormalities. In cultured retinal cells, 30-mM glucose exposure increased superoxide production, inflammatory biomarker expression, and cell death. PBM inhibited all of these abnormalities. PBM ameliorated lesions of diabetic retinopathy in vivo and reduced oxidative stress and cell death in vitro. PBM has been documented to have minimal risk. PBM is noninvasive, inexpensive, and easy to administer. We conclude that PBM is a simple adjunct therapy to attenuate the development of diabetic retinopathy.

Tang et al. (2013). Low-Intensity Far-Red Light Inhibits Early Lesions That Contribute to Diabetic Retinopathy: In Vivo and In Vitro. Invest Ophthalmol Vis Sci. 54, 3681-90

5. Photobiomodulation reduces photoreceptor death and regulates cytoprotection in early states of P23H retinal dystrophy

DK Kirk, S Gopalakrishnan, H Schmitt, B Abroe, M Stoehr et al.

Irradiation by light in the far-red to near-infrared (NIR) region of the spectrum (photobiomodulation, PBM) has been demonstrated to attenuate the severity of neurodegenerative disease in experimental and clinical studies. The purpose of this study was to test the hypothesis that 670 nm PBM would protect against the loss of retinal function and improve photoreceptor survival in a rodent model of retinitis pigmentosa, the P23H transgenic rat. P23H rat pups were treated once per day with a 670 nm LED array (180 sec treatments at 50 mW/cm²; fluence 9 joules/cm²) (Quantum Devices Inc., Barneveld WI) from postnatal day (p) 16-20 or from p10-20. Sham-treated rats were restrained, but not exposed to NIR light. The status of the retina was determined at p22 by assessment of mitochondrial function, oxidative stress and cell death. In a second series of studies, retinal status was assessed at p30 by measuring photoreceptor function by ERG and retinal morphology by Spectral Domain Optical Coherence Tomography (SD-OCT). 670 nm PBM increased retinal mitochondrial cytochrome oxidase activity and upregulated the retina's production of the key mitochondrial antioxidant enzyme, MnSOD. PBM also attenuated photoreceptor cell loss and improved photoreceptor function. PBM protects photoreceptors in the developing P23H retina, by augmenting mitochondrial function and stimulating antioxidant protective pathways. Photobiomodulation may have therapeutic potential, where mitochondrial damage is a step in the death of photoreceptors.

Kirk et al. Photobiomodulation reduces photoreceptor death and regulates cytoprotection in early states of P23H retinal dystrophy. Proc. SPIE 8569, Mechanisms for Low-Light Therapy VIII, 85690F (5 March 2013); <https://doi.org/10.1117/12.981791>

6. Near-Infrared Photobiomodulation in Retinal Injury and Disease

JT Eells, S Gopalakrishnan and K Valter

Evidence is growing that exposure of tissue to low energy photon irradiation in the far-red (FR) to near-infrared (NIR) range of the spectrum, collectively termed “photobiomodulation” (PBM) can restore the function of damaged mitochondria, upregulate the production of cytoprotective factors and prevent apoptotic cell death. PBM has been applied clinically in the treatment of soft tissue injuries and acceleration of wound healing for more than 40 years. Recent studies have demonstrated that FR/NIR photons penetrate diseased tissues including the retina. The therapeutic effects of PBM have been hypothesized to result from intracellular signaling pathways triggered when FR/NIR photons are absorbed by the mitochondrial photoacceptor molecule, cytochrome c oxidase, culminating in improved mitochondrial energy metabolism, increased cytoprotective factor production and cell survival. Investigations in rodent models of methanol-induced ocular toxicity, light damage, retinitis pigmentosa and age-related macular degeneration have demonstrated the PBM attenuates photoreceptor cell death, protects retinal function and exerts anti-inflammatory actions.

Eells et al. (2016). Near-Infrared Photobiomodulation in Retinal Injury and Disease. Adv Exp Med Biol. 854, 437-41

Section III:

Clinical Studies of Photobiomodulation Treatment in Dry AMD

1. Low-Level Laser Therapy Improves Vision in Patients with Age-Related Macular Degeneration

BT Ivandic and T Ivandic

The objective of this study of a case series was to examine the effects of low-level laser therapy (LLLT) in patients with age-related macular degeneration (AMD). AMD affects a large proportion of the elderly population; current therapeutic options for AMD are limited, however. In total, 203 patients (90 men and 113 women; mean age 63.4 + 5.3 y) with beginning (“dry”) or advanced (“wet”) forms of AMD (n = 348 eyes) were included in the study. One hundred ninety three patients (mean age 64.6 + 4.3 y; n = 328 eyes) with cataracts (n = 182 eyes) or without cataracts (n = 146 eyes) were treated using LLLT four times (twice per week). A semiconductor laser diode (780 nm, 7.5 mW, 292 Hz, continuous emission) was used for transconjunctival irradiation of the macula for 40 sec (0.3 J/cm²) resulting in a total dose of 1.2 J/cm². Ten patients (n = 20 eyes) with AMD received mock treatment and served as controls. Visual acuity was measured at each visit. Data were analyzed retrospectively using a t test. LLLT significantly improved visual acuity (p = 0.00001 versus baseline) in 162/182 (95%) of eyes with cataracts and 142/146 (97%) of eyes without cataracts. The prevalence of metamorphopsia, scotoma, and dyschromatopsia was reduced. In patients with wet AMD, edema and bleeding improved. The improved vision was maintained for 3–36 mo after treatment. Visual acuity in the control group remained unchanged. No adverse effects were observed in those undergoing therapy. In patients with AMD, LLLT significantly improved visual acuity without adverse side effects and may thus help to prevent loss of vision.

Ivandic et al. (2008). Low-Level Laser Therapy Improves Vision in Patients with Age-Related Macular Degeneration. Photomed Laser Surg. 26, 241-5

2. TORPA I: Treatment of dry Age-related Macular Degeneration with Photobiomodulation

GF Merry, R Devenyi, R Dotson, S Markowitz and S Reyes

To evaluate if Photobiomodulation (PBM) can affect vision in patients with dry Age-Related Macular Degeneration (AMD). Prospective interventional case series. Near Infra Red (NIR) and yellow wavelengths of low powered light were applied to eyes with AMD in serial consecutive treatments. Included were patients with dry AMD, 50 years or older and with visual acuity between 20/20 - 20/200. Primary outcome measures selected were change in visual acuity, contrast sensitivity and fixation stability. The treatment protocol was completed in 18 eyes (9 patients). Visual Acuity (p<0.0001) and contrast sensitivity (p<0.0001) at cycles/degree and (p<0.0032) at 1.5 cycles/degree were positive and significant. There were no significant changes in fixation stability parameters. PBM proves to be beneficial for improvement of vision and contrast sensitivity and a safe treatment for dry AMD in this pilot study. Larger studies are warranted to validate the findings from this study.

Merry et al. (2012) Treatment of dry Age-related Macular Degeneration with Photobiomodulation. Presented at The Association for Research and Vision in Ophthalmology (Fort Lauderdale). May 7.

3. Photobiomodulation for the Treatment of Retinal Diseases: A Review

I Geneva

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. 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.

Geneva. (2016). Photobiomodulation for the Treatment of Retinal Diseases: A Review Int J Ophthalmol. 9, 145-52

4. TORPA II: Photobiomodulation Reduces Drusen Volume and Improves Visual Acuity and Contrast Sensitivity in Dry Age-Related Macular Degeneration

GF Merry, MR Munk, RS Dotson, MG Walker and RG Devenyi

To evaluate the efficacy of photobiomodulation (PBM) treatment for patients with dry age-related macular degeneration (AMD). Assessments on 42 eyes with dry AMD (age related eye disease study (AREDS) 2-4) were conducted. Multiwavelength light emitting diode (LED) light comprising of yellow (590 nm), red (670 nm) and near-infrared (790 nm) bandwidths was applied to subjects' eyes for a treatment course of 3 weeks. Outcome measures were changes in best-corrected visual acuity (BCVA), contrast sensitivity (CS), drusen volume and central drusen thickness. Significant improvement in mean BCVA of 5.90 letters ($p < 0.001$) was seen on completion of the 3-week treatment and 5.14 letters ($p < 0.001$) after 3 months. Contrast sensitivity improved significantly (log unit improvement of 0.11 ($p = 0.02$) at 3 weeks and 3 months (log unit improvement of 0.16 ($p = 0.02$) at three cycles per degree. Drusen volume decreased by 0.024 mm³ ($p < 0.001$) and central drusen thickness was significantly reduced by a mean of 3.78 μ m ($p < 0.001$), while overall central retinal thickness and retinal volume remained stable. This is the first study demonstrating improvements in functional and anatomical outcomes in dry AMD subjects with PBM therapy. These findings corroborate an earlier pilot study that looked at functional outcome measures. The addition of anatomical evidence contributes to the basis for further development of a non-invasive PBM treatment for dry AMD.

Merry et al. (2017). Photobiomodulation Reduces Drusen Volume and Improves Visual Acuity and Contrast Sensitivity in Dry Age-Related Macular Degeneration. Acta Ophthalmol. 95, e270-e277

5. LIGHTSITE I: A Double-Masked, Randomized, Sham-Controlled, Single-Center Study with Photobiomodulation for the Treatment of Dry Age-Related Macular Degeneration

SN Markowitz, RG Devenyi, MR Munk, CL Croissant, SE Tedford, R Rückert, MG Walker, BE Patino, L Chen, M Nido and CE Tedford.

The LIGHTSITE I study investigated the efficacy and safety of Photobiomodulation (PBM) treatment in subjects with dry age-related macular degeneration (AMD). Thirty subjects (46 eyes) were treated with the Valeda™ Light Delivery System wherein subjects underwent two series of treatments (3x per wk for 3-4 wks) over one year. Outcome measures included Best-Corrected Visual Acuity (BCVA), Contrast Sensitivity (CS), microperimetry, Central Drusen Volume (CDV) and Drusen Thickness (CDT), and Quality of Life (QoL) assessments. PBM-treated subjects showed a BCVA mean letter score gain of 4 letters immediately following each treatment series at month 1 (M1) and M7. Approximately 50% of PBM-treated subjects showed improvement of ≥ 5 letters versus 13.6% in sham-treated subjects at M1. High responding subjects (> 5 letters improvement) in the PBM-treated group showed a gain of 8 letters post initial treatment ($p < 0.01$) and exhibited earlier stages of AMD disease. Statistically significant improvements in CS, CDV, CDT and QoL were observed ($p < 0.05$). No device-related adverse events were reported. PBM treatment statistically improved clinical and anatomical outcomes with more robust benefits observed in subjects with earlier stages of dry AMD. Repeated PBM treatments are necessary to maintain benefits. These pilot findings support previous reports and suggest the utility of PBM as a safe and effective therapy in subjects with dry AMD.

Markowitz et al., (2019). LIGHTSITE I: A Double-Masked, Randomized, Sham-Controlled, Single-Center Study with Photobiomodulation for the Treatment of Dry Age-Related Macular Degeneration. *Retina*. Advance online publication. doi: 10.1097/IAE.0000000000002632.2019.



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